

Durable and Treatment-Agnostic *MUC16* Expression in Ovarian Cancer Supports Targeted Antibody-Drug Conjugate Development

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Objective

This analysis aimed to assess the expression of mucin 16 (*MUC16*) and other antibody-drug conjugate (ADC) targets before and after standard-of-care treatments in ovarian cancer

Conclusions

- » *MUC16* expression is highly stable over time across standard-of-care therapies for ovarian cancer, with lower treatment-associated variability than other ADC targets, indicating low susceptibility to therapy-induced modulation
 - High and stable *MUC16* expression was observed in both unpaired and paired tumor samples before and after treatment with standard-of-care therapies
- » As *MUC16* is not downregulated by standard-of-care treatments, *MUC16*-directed ADCs may be suitable for use both in combination with standard early-line platinum-based treatment and in the relapsed setting
- » HWK-016, a next-generation ADC targeting the non-shed extracellular domain of *MUC16*, is currently being evaluated in a phase 1 clinical trial in patients with advanced/metastatic solid tumors, including ovarian cancer (NCT07470853)⁸

Background

- » Approximately 70% of patients with ovarian cancer relapse and progress to platinum-resistant disease after treatment with standard-of-care platinum-based chemotherapy¹
- » The development of targeted therapies, such as antibody-drug conjugates (ADCs), has improved outcomes for patients with platinum-resistant ovarian cancer, with the ADC mirvetuximab soravtansine achieving an objective response rate of 42% in folate receptor alpha (FRα)-high tumors²
 - However, prognosis remains poor for patients with tumors that do not carry actionable biomarkers¹
- » Mucin 16 (*MUC16*), a cell-surface glycoprotein involved in tumor cell proliferation and immune evasion, is associated with poor prognosis in patients with ovarian cancer^{3,4}
 - *MUC16* is an attractive therapeutic target due to its tumor-selective protein and mRNA enrichment, with concordance between mRNA expression and protein abundance⁵; it also demonstrates robust expression across histologic subtypes of ovarian cancer, irrespective of platinum-sensitivity status⁵
- » HWK-016 is an investigational, next-generation ADC that selectively binds to the non-shed extracellular domain of *MUC16*; it comprises a monoclonal antibody conjugated to a novel topoisomerase inhibitor (CPT116) via a stable, cleavable linker that enhances intracellular delivery and limits systemic exposure⁶
- » Paired biopsies from patients with ovarian cancer pre- and post-ADC exposure have shown changes in expression of target proteins, including reduced expression of FRα, human epidermal growth factor receptor 2 (HER2), and cadherin 6 (CDH6)⁷
 - This underscores the importance of identifying the most appropriate ADC for patients based on tumor biomarker status at the time of treatment initiation

Methods

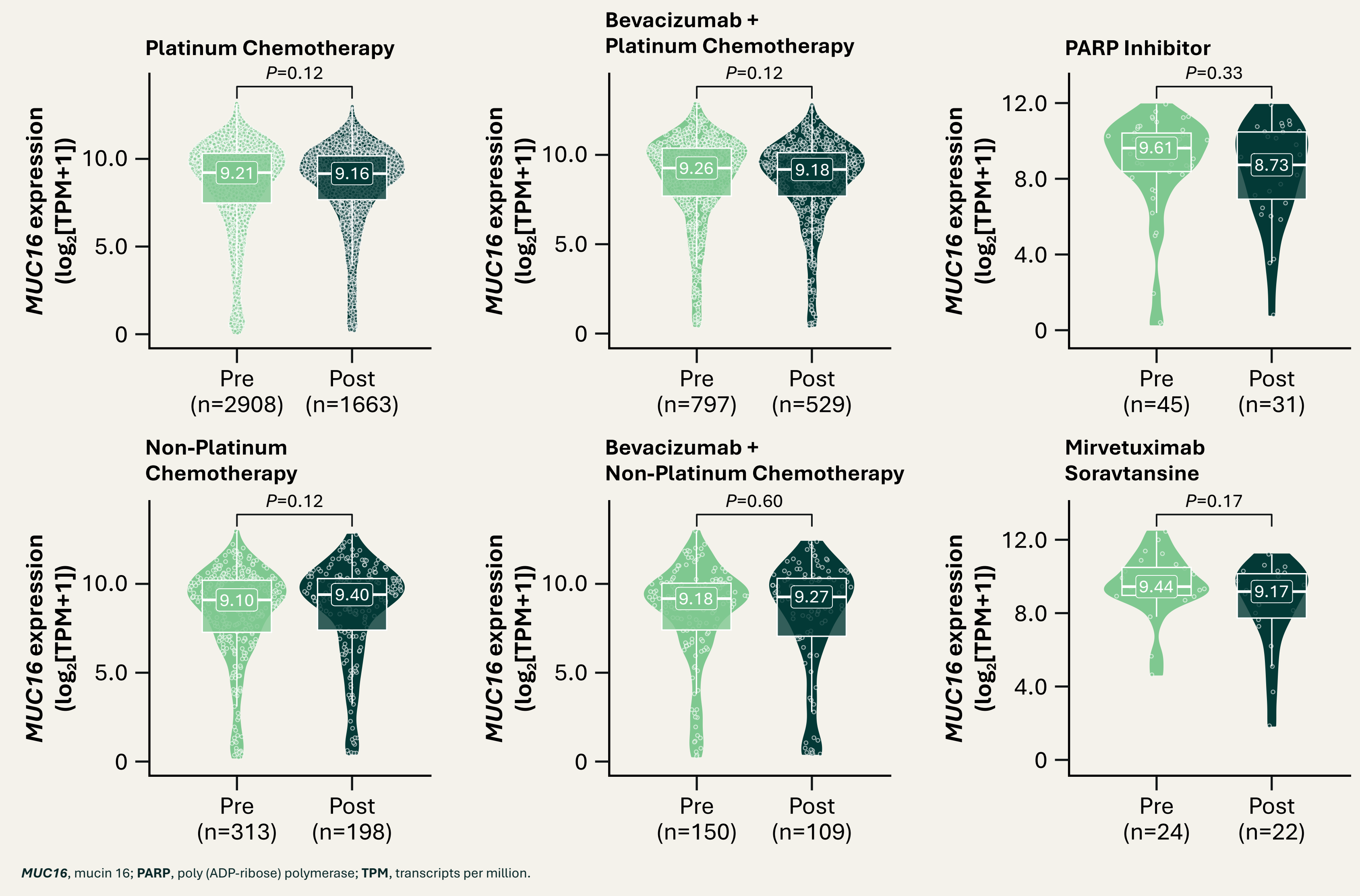
- » De-identified RNA-sequencing and treatment data from a real-world database (Tempus AI, Inc.) were used to explore expression of *MUC16* and other potential ADC targets in pre- versus post-treatment tumor biopsy samples from patients with ovarian cancer
 - Pre-treatment samples were collected within 365 days prior to start of treatment; post-treatment samples were collected 14–730 days after start of treatment
 - Analyses were carried out separately for unpaired and paired samples, which formed non-overlapping sample sets
 - Additional adjusted analyses were performed (multiple linear regression for unpaired samples; linear mixed-effects model for paired samples), which controlled for tumor purity, age, line of therapy, biopsy site, platinum-sensitivity status, and metastatic status; adjusted analyses for *FOLR1* (FRα) expression before and after mirvetuximab soravtansine treatment excluded biopsy site and metastatic status due to limited sample size
- » Median *MUC16* mRNA expression was quantified as log₂(transcripts per million [TPM]+1)
 - Pre- to post-treatment changes in expression were analyzed using the Wilcoxon test and delta medians were calculated

Results

EFFECT OF STANDARD-OF-CARE TREATMENTS ON *MUC16* EXPRESSION IN OVARIAN CANCER TUMOR SAMPLES

- » The analysis included 5293 ovarian cancer tumor samples (unpaired, n=4939; paired, n=354)
- » *MUC16* expression (log₂[TPM+1]) remained stable after most standard-of-care treatments (**Figure 1**)
 - Among unpaired samples, changes in pre- versus post-treatment median *MUC16* expression (log₂[TPM+1]) in unadjusted (**Figure 1**) and adjusted analyses, respectively, were –0.05 and –0.13 with platinum chemotherapy (median, 9.21 vs 9.16), –0.08 and –0.17 with bevacizumab plus platinum chemotherapy (median, 9.26 vs 9.18), –0.88 and +0.11 with a poly (ADP-ribose) polymerase (PARP) inhibitor (median, 9.61 vs 8.73), +0.30 and +0.34 with non-platinum chemotherapy (median, 9.10 vs 9.40), +0.09 and +0.18 with bevacizumab plus non-platinum chemotherapy (median, 9.18 vs 9.27), and –0.27 and –1.62 with mirvetuximab soravtansine (median, 9.44 vs 9.17)
 - Among paired samples, changes in pre- versus post-treatment median *MUC16* expression in unadjusted and adjusted analyses, respectively, were –0.65 and –0.48 with platinum chemotherapy (median, 9.21 vs 8.56; n=165), and –0.21 and –0.86 with bevacizumab plus platinum chemotherapy (median, 8.85 vs 8.64; n=62) (data not shown)
- » Treatment-associated effect sizes were consistently small, with median *MUC16* expression (log₂[TPM+1]) range, 8.56–9.61 remaining closely aligned with the target positivity threshold (log₂[TPM+1] of 9.07, corresponding to ≥50% cell positivity at ≥2+/3+ immunohistochemistry [IHC] staining intensity). At the lowest median bound (8.56), *MUC16* expression corresponded to ≥40% IHC positivity

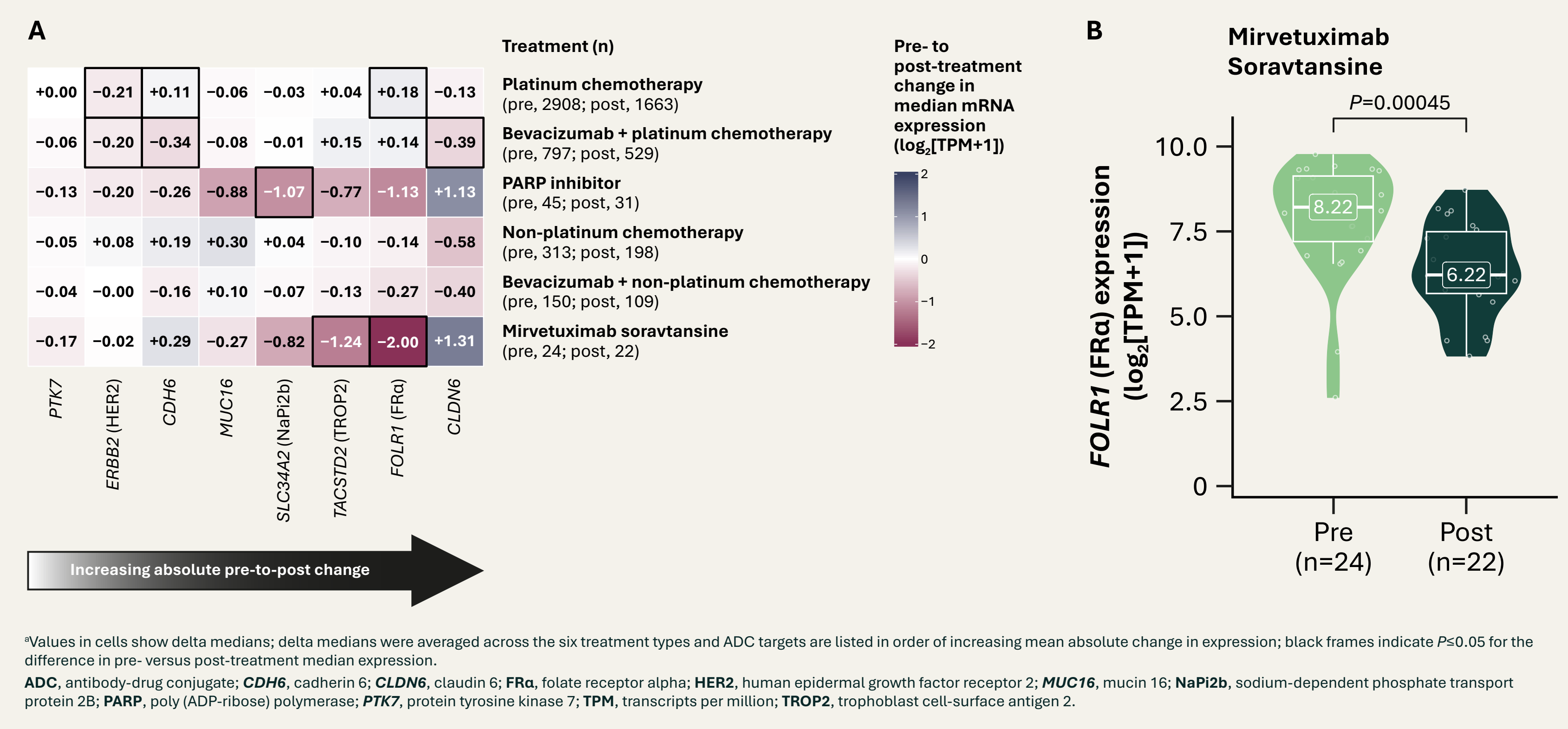
FIGURE 1. Change in *MUC16* mRNA Expression Pre to Post Treatment With Standard-of-Care Therapies in Ovarian Cancer (Unpaired Samples; Unadjusted Analysis)



EXPRESSION OF *MUC16* AND OTHER ADC TARGETS BEFORE AND AFTER STANDARD-OF-CARE TREATMENTS

- » In an unadjusted analysis of unpaired samples (n=4939), pre- versus post-treatment expression (log₂[TPM+1]) of other ADC targets—including *FOLR1* (FRα), *TACSTD2* (trophoblast cell-surface antigen 2 [TROP2]), and *SLC34A2* (sodium-dependent phosphate transport protein 2B [NaPi2b])—showed greater variation in treatment-associated expression compared with *MUC16* across standard-of-care therapies (**Figure 2A**)
 - In the adjusted analysis, pre- to post-treatment changes in median expression of these ADC targets remained more variable than those of *MUC16* across standard-of-care therapies (data not shown)
- » There was a significant reduction in expression of *FOLR1* (FRα) following treatment with the FRα-targeted ADC mirvetuximab soravtansine (**Figure 2B**)
 - The pre- versus post-mirvetuximab soravtansine change in *FOLR1* (FRα) expression (log₂[TPM+1]) was –2.00 (median, 8.22 vs 6.22; P=0.00045); however, sample sizes were small (pre-treatment, n=24; post-treatment, n=22)

FIGURE 2. Pre- Versus Post-Treatment Changes in Expression of (A) *MUC16* and Other ADC Targets in Ovarian Cancer Across Standard-of-Care Therapies^a and (B) *FOLR1* (FRα) With Mirvetuximab Soravtansine (Unpaired Samples; Unadjusted Analyses)



REFERENCES

1. Li H, et al. *Genes Dis.* 2025;13:101801.
2. Moore KN, et al. *N Engl J Med.* 2023;389:2162–74.
3. Giamouglannis P, et al. *Carcinogenesis.* 2021;42:327–43.
4. Yang N, et al. *BMC Cancer.* 2025;25:294.
5. Matulonis UA, et al. Presented at the SGO Annual Meeting on Women's Cancer 2026. Poster #1515.
6. Keegan KS, et al. Presented at the AACR Annual Meeting 2026. Abstract #1324.
7. Lee YJ, et al. *J Clin Oncol.* 2026;44(16_suppl):5594.
8. Moore KN, et al. Presented at the ESMO Gynaecological Cancers Congress 2026. Poster #1671IP.

ACKNOWLEDGMENTS and DISCLOSURES

This study was sponsored by Whitehawk Therapeutics, Morristown, NJ, USA. Medical writing assistance was provided by Farhana Burnett, PhD, CMPP, of Twist Medical, and funded by Whitehawk Therapeutics.

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Kathleen N. Moore reports funding to her institution from Clovis, Genentech, GSK, Lilly, PTC Therapeutics, and Verastem; royalties/license from UpToDate; consulting fees from Aadi, Abbvie, AstraZeneca, BioNTech, Blueprint pharma, Caris, Corcept, Daiichi, Duality, Eisai, Genentech/Roche, GSK, Immunogen, Iovance, Janssen, Lilly, Merck, Mersana, Novartis, Novocure, Pharma®, Regeneron, Schrodinger, Takeda, VBL Therapeutics, Verastem, Zentalis, and Zymeworks; payment or honoraria from AstraZeneca, Great Debates and Updates, GSK, Immunogen, Medscape, PRIME, and RTP; travel expenses from AstraZeneca and BioNTech; and serving as a GOG P Associate Director.

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