

High *MUC16* Expression Is Associated With Poor Real-World Overall Survival in Patients With High-Grade Serous Ovarian Carcinoma

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Objective

The aim of this analysis was to assess the potential prognostic association between real-world overall survival (rwOS) and mucin 16 (*MUC16*) mRNA expression and CA125 protein level in patients with high-grade serous ovarian carcinoma (HGSOC)

Conclusions

- » In this real-world analysis of samples from patients with HGSOC, high tumor *MUC16* expression at metastatic diagnosis was prognostically associated with poor rwOS
- Eastern Cooperative Oncology Group performance status (ECOG PS) and *BRCA* mutation status were also independent prognostic factors for rwOS
- Results were similar in the treatment-naïve subpopulation, with age at diagnosis as an additional independent predictor of survival
- » Consistent with prior studies,^{8,9} high circulating CA125 was associated with poor prognosis in patients with heavily pretreated HGSOC
- Age at diagnosis and ECOG PS were also independently associated with rwOS in this population
- » These findings support *MUC16* as a potential prognostic biomarker and therapeutic target in HGSOC
- » HWK-016, a next-generation antibody-drug conjugate that targets the non-shed extracellular domain of *MUC16*, is being evaluated in a phase 1 trial in patients with solid tumors, including advanced or metastatic ovarian cancer (NCT07470853)¹⁰

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

Background

- » Mucin 16 (*MUC16*) is a cell-surface glycoprotein that contributes to cancer progression through its roles in promoting tumor cell proliferation, metastasis, and immune evasion^{1,2}
- *MUC16* undergoes proteolytic cleavage and sheds cancer antigen 125 (CA125), a widely used serum biomarker, into the bloodstream. The non-shed extracellular domain of *MUC16* remains expressed on the surface of tumor cells^{1,2}
- » *MUC16* is overexpressed in approximately 80% of epithelial ovarian cancers and has relatively low expression in normal tissue.^{1–3} A robust concordance between *MUC16* mRNA expression and protein level has been observed in ovarian cancer⁴
- *MUC16* expression is 3- to >100-fold higher than that of clinically validated and emerging antibody-drug conjugate targets, including *SLC34A2* (sodium-dependent phosphate transport protein 2B [NaPi2b]; 3-fold), *PTK7* (protein tyrosine kinase 7; 4-fold), *ERBB2* (human epidermal growth factor receptor 2 [HER2]; 4-fold), *FOLR1* (folate receptor alpha [FRα]; 4-fold), *TACSTD2* (trophoblast cell-surface antigen 2 [TROP2]; 5-fold), *VTCN1* (B7-H4; 15-fold), *CDH6* (15-fold), and *CLDN6* (126-fold)⁵
- » High-grade serous ovarian carcinoma (HGSOC) is the most common histologic subtype of ovarian cancer, accounting for approximately 70% of all cases⁶
- Most patients with HGSOC are diagnosed with advanced-stage disease, resulting in poor outcomes and 5-year survival rates of only 30–40%,^{6,7} highlighting the need for improved prognostic biomarkers and therapeutic strategies
- » *MUC16* expression remains high in HGSOC, irrespective of disease stage or platinum-sensitivity status^{4,8}
- CA125 protein abundance is also high in HGSOC, increasing in parallel with advancing disease stage,⁴ and has been linked with poor survival outcomes^{8,9}

Methods

- » De-identified multimodal data from a real-world database (Tempus AI, Inc.) were used to analyze real-world overall survival (rwOS) by tumor *MUC16* mRNA expression—quantified as log₂(transcripts per million [TPM]+1)—and serum/plasma CA125 protein level (U/mL) in patients with HGSOC
- Analyses were based on tumor biopsies collected within 30 days of the date of first metastasis, and on serum/plasma samples collected within 14 days prior to the start of first-line (1L) and second- or later-line (2L+) therapy
- Tumor samples were stratified by median *MUC16* expression (low [<median] vs high [≥median])
- A cutoff of 70 U/mL, corresponding to 2 × the upper limit of normal (ULN) in patients with cancer, was used to define low (≤70 U/mL) and high (>70 U/mL) serum/plasma CA125 groups
- » The associations between rwOS and *MUC16* mRNA expression and CA125 protein level were analyzed using a Cox proportional hazards model, adjusted for age at diagnosis, Eastern Cooperative Oncology Group performance status (ECOG PS), surgery outcome (residual disease, no residual disease, or not eligible for surgery/unknown), and International Federation of Gynecology and Obstetrics (FIGO) or American Joint Committee on Cancer (AJCC) stage
- *MUC16* analyses were additionally adjusted for tumor purity, biopsy site, *BRCA* status, homologous recombination deficiency (HRD) status, and *FOLR1* status

Results

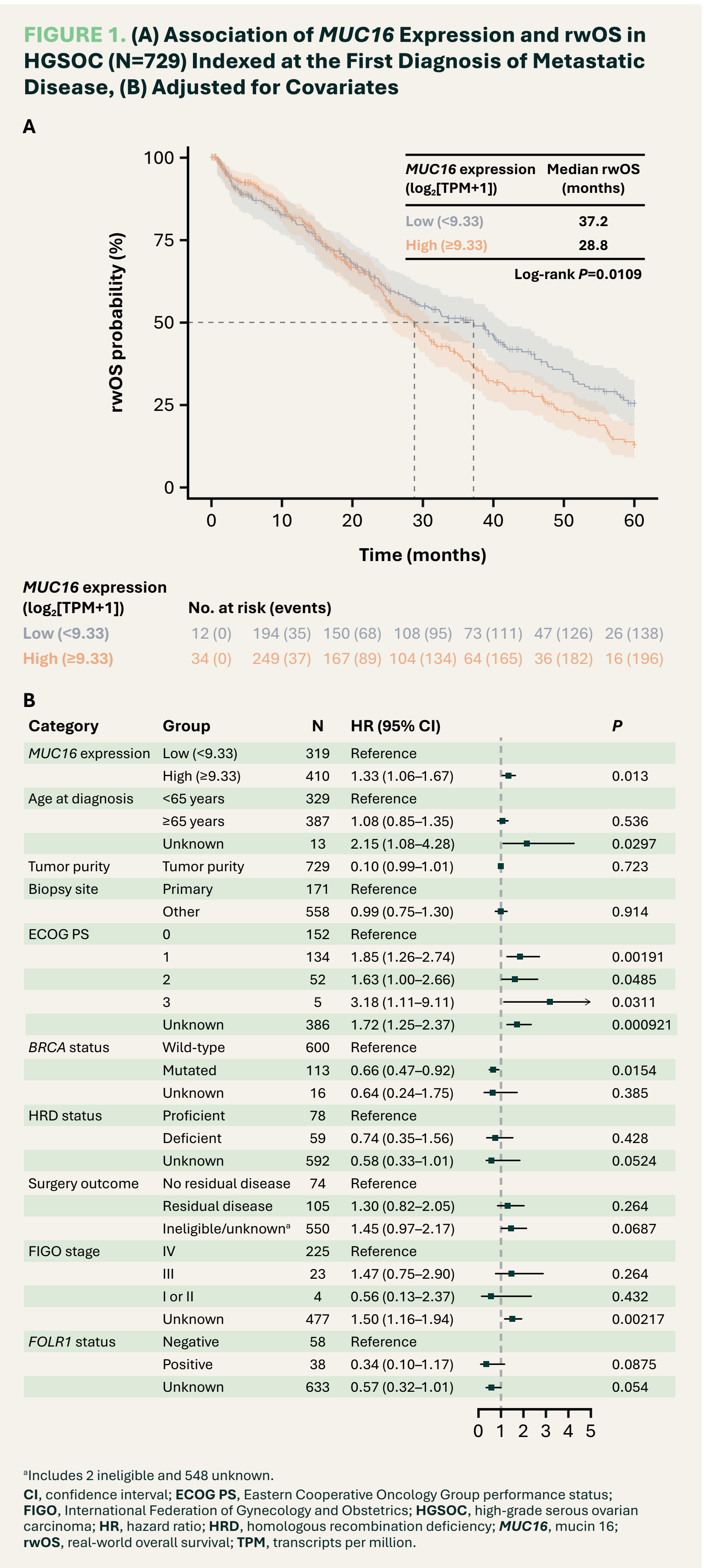
ASSOCIATION BETWEEN *MUC16* EXPRESSION AND rwOS

- » Based on a median *MUC16* expression (log₂[TPM+1]) of 9.33, tumor samples from 729 patients with HGSOC were stratified into low (<9.33; n=319) and high (≥9.33; n=410) *MUC16* expression groups
- This median cutoff aligns closely with the empirical immunohistochemistry (IHC) concordance threshold (log₂[TPM+1] of 9.07, corresponding to ≥50% cell positivity at ≥2+/3+ IHC staining intensity)
- Baseline patient demographics and disease characteristics are shown in **Table 1**
- » Median rwOS was significantly shorter in tumor samples from patients with high versus low *MUC16* expression, indexed at the first diagnosis of metastatic disease (median, 28.8 vs 37.2 months; log-rank *P*=0.0109) (**Figure 1A**)
- » In a multivariate analysis adjusting for age at diagnosis, tumor purity, biopsy site, ECOG PS, *BRCA* status, HRD status, surgery outcome, FIGO stage, and *FOLR1* status, *MUC16* expression remained prognostically associated with rwOS (hazard ratio [HR] 1.33 [95% confidence interval (CI) 1.06–1.67]; *P*=0.013) (**Figure 1B**)
- Other variables independently associated with rwOS were ECOG PS (1 vs 0: HR 1.85 [95% CI 1.26–2.74], *P*=0.00191; 2 vs 0: HR 1.63 [95% CI 1.00–2.66], *P*=0.0485) and *BRCA* mutation status (HR 0.66 [95% CI 0.47–0.92]; *P*=0.0154)
- » Among the subset of tumor samples from patients who were treatment naïve at first metastatic diagnosis (n=356), median rwOS remained significantly shorter with high (n=207) versus low (n=149) *MUC16* expression (median, 33.8 vs 49.8 months; log-rank *P*=0.0178) (data not shown)
- Similar to the overall population at metastatic diagnosis, *MUC16* expression remained prognostically associated with rwOS in the multivariate analysis (HR 1.69 [95% CI 1.15–2.48]; *P*=0.00719), and ECOG PS (2 vs 0: HR 2.23 [95% CI 1.05–4.76]; *P*=0.0377) and *BRCA* mutation status (HR 0.52 [95% CI 0.27–0.98]; *P*=0.0428) were independently associated with rwOS; in the treatment-naïve population, age at diagnosis was also independently prognostic for rwOS (≥65 vs <65 years: HR 1.75 [95% CI 1.17–2.63]; *P*=0.00674)

TABLE 1. Baseline Demographics and Disease Characteristics in Patients With HGSOC, Stratified by *MUC16* Expression and Indexed at the First Diagnosis of Metastatic Disease

Characteristic, n (%) ^a	Patients with HGSOC, indexed at the first diagnosis of metastatic disease (N=729)	
	Low <i>MUC16</i> expression (<9.33 log ₂ [TPM+1]) (n=319)	High <i>MUC16</i> expression (≥9.33 log ₂ [TPM+1]) (n=410)
Age at diagnosis		
<65 years	128 (40)	201 (49)
≥65 years	184 (58)	203 (50)
Unknown	7 (2)	6 (1)
Treatment history		
Treatment naïve	149 (47)	207 (50)
Treatment exposed	111 (35)	131 (32)
Prior to 1L	3 (1) ^b	2 (<1)
After 1L	77 (24)	73 (18)
After 2L / 3L / 4L+	16 (5) / 4 (1) / 6 (2)	22 (5) / 9 (2) / 13 (3)
Unknown line of therapy	5 (2)	12 (3)
Unknown	59 (18)	72 (18)
Biopsy site		
Primary	80 (25)	91 (22)
Other	239 (75)	319 (78)
ECOG PS		
0	67 (21)	85 (21)
1	62 (19)	72 (18)
2	20 (6)	32 (8)
3	3 (1)	2 (<1)
Unknown	167 (52)	219 (53)
BRCA status		
Wild-type	267 (84)	333 (81)
Mutated	41 (13)	72 (18)
Unknown	11 (3)	5 (1)
HRD status		
Proficient	36 (11)	42 (10)
Deficient	20 (6)	39 (10)
Unknown	263 (82)	329 (80)
Surgery outcome		
No residual disease	36 (11)	38 (9)
Residual disease	44 (14)	61 (15)
Ineligible/unknown	1 (<1) / 238 (75)	1 (<1) / 310 (76)
FIGO stage		
I or II	3 (1)	1 (<1)
III	11 (3)	12 (3)
IV	96 (30)	129 (31)
Unknown	209 (66)	268 (65)
<i>FOLR1</i> status		
Negative	23 (7)	35 (9)
Positive	15 (5)	23 (6)
Unknown	281 (88)	352 (86)

^aWhere percentages do not sum to 100%, this is due to rounding. ^bIncludes two patients with unknown treatment status.
1L, first line; **2L**, second line; **3L**, third line; **4L+**, fourth line or later line; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **FIGO**, International Federation of Gynecology and Obstetrics; **HGSOC**, high-grade serous ovarian carcinoma; **HRD**, homologous recombination deficiency; ***MUC16***, mucin 16; **TPM**, transcripts per million.



ASSOCIATION BETWEEN CA125 PROTEIN LEVEL AND rwOS

- » Based on a cutoff of 70 U/mL (2 × ULN), samples from 560 patients with HGSOC indexed prior to the start of 2L+ therapy were stratified into high (>70 U/mL; n=383) and low (≤70 U/mL; n=177) serum/plasma CA125
- Baseline patient demographics and disease characteristics are shown in **Table 2**

TABLE 2. Baseline Demographics and Disease Characteristics in Patients With HGSOC, Stratified by Serum/Plasma CA125 Level and Indexed Prior to the Start of 2L+ Therapy

Characteristic, n (%) ^a	Patients with HGSOC, indexed prior to the start of 2L+ therapy (N=560)	
	Low serum/plasma CA125 (≤70 U/mL) (n=177)	High serum/plasma CA125 (>70 U/mL) (n=383)
Age at diagnosis		
<65 years	100 (56)	211 (55)
≥65 years	74 (42)	165 (43)
Unknown	3 (2)	7 (2)
Metastatic status		
Primary	61 (34)	118 (31)
Metastatic	65 (37)	179 (47)
Unknown	51 (29)	86 (22)
Line of therapy		
2L	92 (52)	154 (40)
3L	34 (19)	96 (25)
4L+	51 (29)	133 (35)
ECOG PS		
0	33 (19)	78 (20)
1	29 (16)	73 (19)
2+	2 (1)	20 (5)
Unknown	113 (64)	212 (55)
Surgery outcome		
No residual disease	39 (22)	73 (19)
Residual disease	34 (19)	91 (24)
Ineligible/unknown	2 (1) / 102 (58)	4 (1) / 215 (56)
AJCC stage^b		
4	71 (40)	208 (54)
Unknown	106 (60)	175 (46)

^aWhere percentages do not sum to 100%, this is due to rounding. ^bPatients with AJCC stage 1–3 disease were excluded from the analysis due to small sample sizes.
2L+, second line or later line; **AJCC**, American Joint Committee on Cancer; **CA125**, cancer antigen 125; **ECOG PS**, Eastern Cooperative Oncology Group performance status; **HGSOC**, high-grade serous ovarian carcinoma.

- » Median rwOS was significantly shorter in patients with high versus low serum/plasma CA125 prior to the start of 2L+ therapy (median, 15.1 vs 31.4 months; log-rank *P*=1.54×10⁻⁷) (**Figure 2A**)
- » In a multivariate analysis adjusting for age at diagnosis, ECOG PS, surgery outcome, and AJCC stage, serum/plasma CA125 remained prognostically associated with rwOS (high vs low: HR 1.85 [95% CI 1.44–2.37]; *P*=1.42×10⁻⁶) (**Figure 2B**)
- Variables that were independently associated with rwOS were age at diagnosis (≥65 vs <65 years: HR 1.40 [95% CI 1.12–1.75]; *P*=0.00318) and ECOG PS (2+ vs 0: HR 2.03 [95% CI 1.20–3.43]; *P*=0.00822)
- » Similarly, among tumor samples indexed prior to the start of 1L therapy (n=757), those from patients with high (n=629) versus low (n=128) serum/plasma CA125 were correlated with significantly shorter median rwOS (median, 34.2 months vs not reached; log-rank *P*=1.68×10⁻⁷), and they remained prognostically associated with rwOS in multivariate analysis (high vs low: HR 1.94 [95% CI 1.34–2.81]; *P*=0.000453) (data not shown)
- In the multivariate analysis, age at diagnosis was also independently associated with rwOS (≥65 vs <65 years: HR 1.59 [95% CI 1.28–1.97]; *P*=2.75×10⁻⁵)

FIGURE 2. (A) Association of Serum/Plasma CA125 and rwOS in HGSOC (N=560) Indexed Prior to the Start of 2L+ Therapy, (B) Adjusted for Covariates

