Antibody-drug conjugate (ADC) biomarker targets in endometrial cancer (EC): Molecular characterization and implications for therapeutic decision-making

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Background:

Given the evolving landscape of ADCs, we evaluated expression of emerging ADC targets in EC and compared expression patterns across molecular subgroups (POLE mutated [POLEm], MSI-high [MSI-H], TP53-mutated [TP53m] or No Specific Molecular Profile [NSMP]) defined by the Proactive Molecular Risk Classifier for Endometrial Cancer.

Methods:

- Tumors were analyzed by DNA and RNA sequencing and immunohistochemistry (IHC) for select proteins (Caris Life Sciences, Phx, AZ)
- ER+ defined as % staining ≥ 1%
- Statistics were calculated by Mann-Whitney U test and adjusted for multiple comparisons ($q < 0.05$)
- Expression was split into top quartile (H) and bottom quartile (L)
- Overall survival (OS) was obtained from insurance claims data and calculated from first treatment to last contact
- Hazard ratios (HR) were calculated by Cox proportional hazards with p-values by log-rank tests.

Results

Table 1. Demographics.

Age, median (range)	67.0 (18 - 90+)
Histology, N (%)	
Carcinosarcoma	11.6% (1598/13731)
Clear Cell Carcinoma	2.9% (392/13731)
Endometrioid Carcinoma	34.1% (4685/13731)
Serous	21.0% (2886/13731)
Other	30.4% (4170/13731)
Race, N (%)	
AAPI	2.6% (353/13731)
BAA	17.6% (2410/13731)
White	56.5% (7752/13731)
Other	3.4% (465/13731)
Unknown	20.0% (2751/13731)
Ethnicity, N (%)	
Hispanic or Latino	7.8% (1076/13731)
Not Hispanic or Latino	70.8% (9728/13731)
Unknown	21.3% (2927/13731)
Genetically Inferred Ancestry, N (%)	
AFR (African)	20.5% (2811/13720)
AMR (American Indigenous)	8.3% (1141/13720)
CSA (Central South Asia)	1.2% (171/13720)
EAS (East Asian)	3.0% (417/13720)
EUR (European)	66.6% (9143/13720)
MID (Middle Eastern)	0.3% (37/13720)
OCE (Oceanian)	0.0% (0/13720)

Figure 1. ProMise Classifier

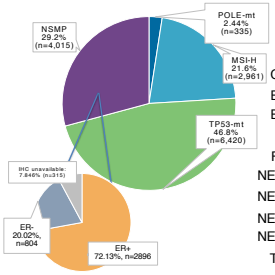
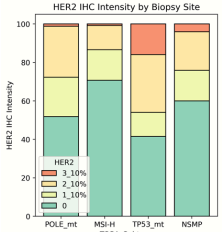


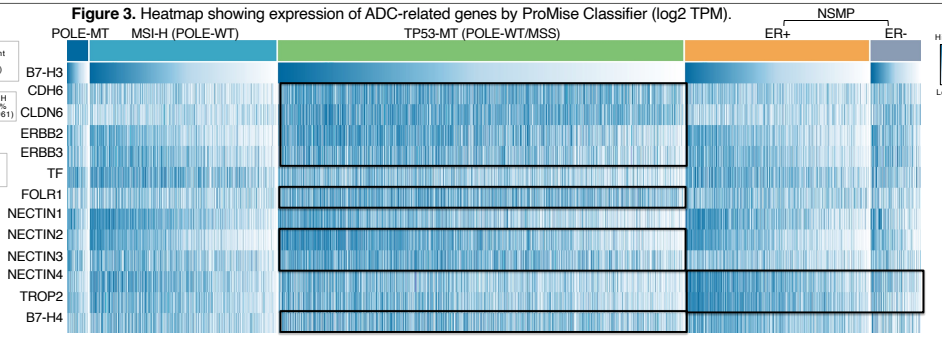
Figure 2. IHC HER2 across Classification.



- HER2+ by IHC was highest in TP53m tumors compared to POLEm, MSI-H, and NSMP (15.9% vs 1.2% vs 0.8% vs 4.0%; p<0.05)

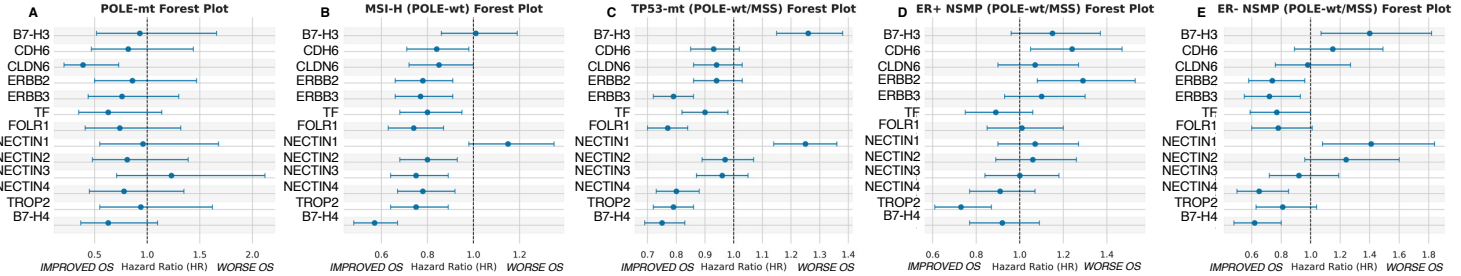
HER2	POLE-mt	MSI-H	TP53-mt	NSMP
0	43 (51.81)	347 (70.67)	1326 (41.53)	430 (59.97)
+1 and >=10%	17 (20.48)	78 (15.89)	398 (12.46)	114 (15.9)
+2 and >=10%	22 (26.51)	62 (12.63)	960 (30.07)	144 (20.08)
+3 and >=10%	1 (1.2)	4 (0.81)	509 (15.94)	29 (4.04)

Figure 3. Heatmap showing expression of ADC-related genes by ProMise Classifier (log2 TPM).



- TP53m tumors had the highest RNA expression of CDH6, B7-H4, CLDN6, ERBB3, ERBB2, FOLR1, NECTIN2 and NECTIN3; NSMP tumors had the highest expression of TROP2 and NECTIN4 relative to other subtypes (highlighted by black boxes in Figure 3)
- Compared to all solid tumors, TP53m EC had the highest median RNA expression of B7-H4 and second highest of CLDN6 and FOLR1 (not shown)

Figure 4. Forest plot showing HR (95% CI) of the prognosis of -H and –L ADC genes by ProMise Classifier.



- Assessing the prognostic effect of ADC targets by subtype, POLEm CLDN6-H tumors had improved OS compared to CLDN6-L (HR 0.39, p=0.003) (Fig 4A)
- In MSI-H tumors, TROP2-H, CDH6-H, B7-H4-H, CLDN6-H, ERBB3-H, ERBB2-H, FOLR1-H, TF-H and NECTIN2-4-H was associated with improved OS (HR 0.57-0.84, p<0.05) (Fig 4B)
- In TP53m tumors, TROP2-H, B7-H4-H, FOLR1-H, HER3-H, TF-H and NECTIN4-H was associated with improved OS (HR: 0.75-0.90, p<0.05) and NECTIN1H and B7-H3H with worse OS (HR: 1.26, p<0.001) (Fig 4C)
- In ER+ NSMP tumors, TROP2-H had improved OS (HR: 0.73, p<0.05) and ERBB2-H and CDH6-H had worse OS (HR: 1.24-1.29, p<0.05) (Fig 4D)
- In ER- NSMP tumors, B7-H4-H, ERBB3-H, ERBB2-H and NECTIN4-H had improved OS (HR: 0.62-0.74, p<0.05) and B7-H3-H and NECTIN1-H had worse OS (HR: 1.40, p=0.01) (Fig 4E)

Conclusions: Expression of ADC targets differs by molecular subtype with varying associations with OS in EC patients. Focusing future clinical trials on EC subsets with high biomarker expression will be critical to efficiently developing novel targeted therapeutics.

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