540046: Racial Disparities in Endometrial Cancer Survival Persist After Molecular Classification

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Background

- Black/African American (BAA) patients with endometrial cancer (EC) have 2x mortality rate vs. White patients
- ProMisE molecular classification (MC) is now standard for risk stratification
- Previous studies demonstrate that racial disparities in EC persist even when controlling for histology

Critical Question:

Do racial disparities in EC survival persist after controlling for molecular subtype?

Methods

Cohort

- N=10,162 EC samples (BAA n=2,410; White n=7,752) from Caris Life Sciences®

Molecular classification

- NGS (NextSeq/NovaSeq) for ProMisE classification:
  - POLE-mt (ultramutated)
  - MSI-H (hypermutated)
  - TP53-mt (copy number high)
  - NSMP (no specific molecular profile; TP53-wt)
- RNA sequencing (NovaSeq) for transcriptomic profiling

Analysis

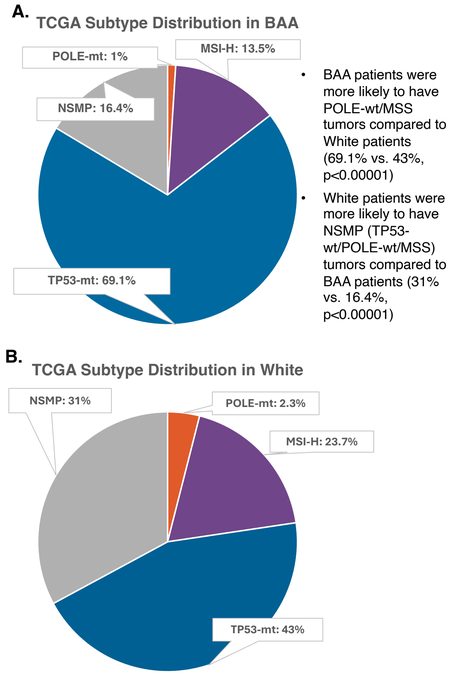
- Overall survival (OS) calculated from tissue collection to last contact using Cox proportional hazards models
- Gene set enrichment analysis performed to assess pathway-level differences

Results

Table 1. Demographics

Characteristic	BAA	White	p-value
N	2,410	7,752	
Age, median (range)	67.0 (21 - 90+)	69.0 (18 - 90+)	<0.001
Histology, N (%)			<0.001
Carcinosarcoma	17.7% (426/2410)	10.3% (797/7752)	
Clear Cell Carcinoma	3.5% (84/2410)	2.7% (213/7752)	
Endometrioid Carcinoma	18.9% (455/2410)	35.9% (2786/7752)	
Serous	32.3% (778/2410)	19.6% (1517/7752)	
Other	27.7% (667/2410)	31.5% (2439/7752)	
Biopsy Site, N (%)			0.003
Primary	77.6% (1871/2410)	73.6% (5704/7752)	
Metastatic	21.4% (515/2410)	25.4% (1967/7752)	
Unclear	1.0% (24/2410)	1.0% (81/7752)	
Ethnicity, N (%)			0
Hispanic or Latino	1.5% (37/2410)	5.8% (448/7752)	
Not Hispanic or Latino	58.9% (1419/2410)	89.6% (6943/7752)	
Unknown	39.6% (954/2410)	4.7% (361/7752)	
Prior Carboplatin, N (%)			0.004
Yes	12.3% (297/2410)	10.6% (820/7752)	
Prior Radiation, (%)			0.001
Yes	13.3% (321/2410)	16.2% (1259/7752)	

Figure 1. ProMisE classification by race



- BAA patients were more likely to have POLE-wt/MSS tumors compared to White patients (69.1% vs. 43%, p<0.00001)
- White patients were more likely to have NSMP (TP53-wt/POLE-wt/MSS) tumors compared to BAA patients (31% vs. 16.4%, p<0.00001)

Table 2. Molecular differences by race and classifier

Biomarker	TP53-mt			NSMP		
	BAA %	White %	Δ%	BAA %	White %	Δ%
ARID1A-mt	4.47	10.3	-5.83	32.8	48.9	-16.1
CTNNB1-mt	NS	NS	-	31.1	40.2	-9.1
FGFR2-mt	0.6	2.94	-2.34	3.29	11.3	-8.01
PIK3CA-mt	23.1	36.6	-13.5	NS	NS	-
PIK3R1-mt	9.58	15.4	-5.82	17.9	35	-17.1
PTEN-mt	6.83	15.7	-8.87	40.4	66.9	-26.5
PPP2R1A-mt	15.5	23.8	-8.3	NS	NS	-
CDKN2A-del	NS	NS	-	22	13.7	8.3
CDKN2B-del	NS	NS	-	13.7	5.45	8.25
MTAP-del	NS	NS	-	18.8	8.92	9.88
ER+	NS	NS	-	62.6	76	-13.4
PR+	NS	NS	-	53.1	67.4	-14.3

Figure 3. Immune pathways are downregulated in BAA vs White patients across all ProMisE classifiers by pre-ranked GSEA

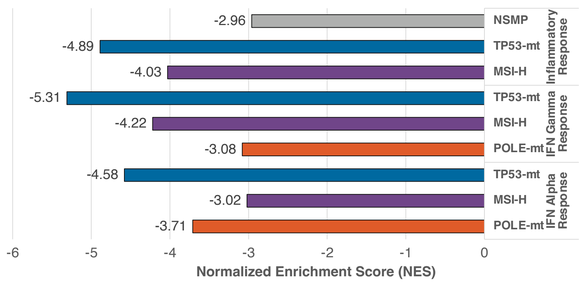
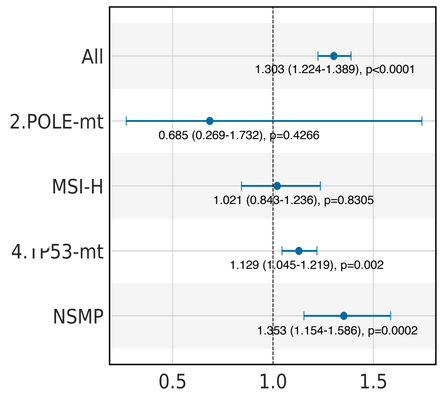
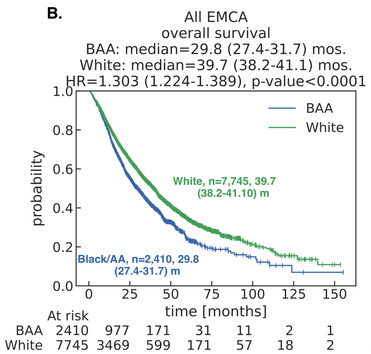
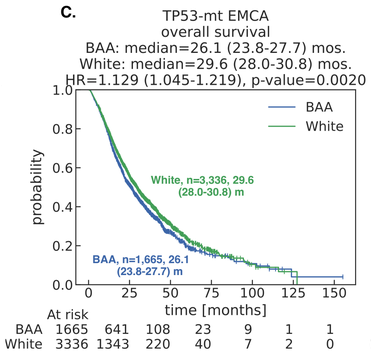


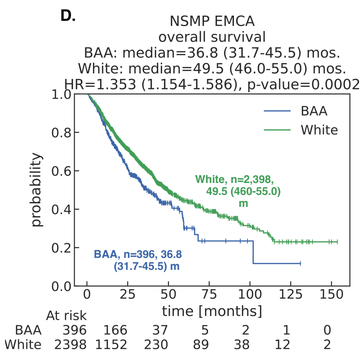
Figure 2. Real-world OS by race across ProMisE classifiers

A. [Univariate] Forest Plot showing survival by TCGA Subtype









KEY TAKEAWAYS:

- ✓ **Racial disparities in endometrial cancer persist after controlling for ProMisE molecular classification**
- ✓ BAA patients were more likely to develop TP53mt tumors, but the **survival disparity was largest in the NSMP group**
- ✓ BAA and White patients show **differential expression of known prognostic mutations and immune features** even within the same molecular subtype
  - Existing classification schemas may overlook important biological heterogeneity
  - Downregulation of immune-related pathways in BAA patients may affect immunotherapy response

- Across EC, BAA patients had shorter OS (29.8 vs 39.7 months (m); HR: 1.303 (1.224-1.389), p<0.0001).
- BAA patients had worse OS in the NSMP cohort (36.8 vs 49.5m; HR 1.35 (1.15-1.59), p<0.001) and TP53-mt cohort (26.1 vs 29.6 m; HR 1.13 (1.05-1.22), p=0.002).
- Race was not associated with differences in OS in POLE-mt (NR vs 51.4 m, p=0.4266) and MSI-H (44.4 vs 45.9 m, p=0.8305).

Figure 4. Post-Pembrolizumab/Dostarlimab survival by race across ProMisE classifiers

A. [Univariate] Forest Plot showing post-Pembro/Dostar survival by TCGA Subtype