HER2 in Endometrioid Endometrial Adenocarcinoma (E-EMCA): Defining Incidence, Molecular Profiles, and Outcomes

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Background:

- Currently, immunohistochemistry (IHC) for HER2 in Endometrioid Endometrial Cancer (E-EMCA) is not standard of care
- We aimed to establish the correlation of HER2 transcript to IHC expression in the much more frequently tested uterine serous carcinoma (USC)
- We applied the threshold calculated in USC to E-EMCA and compared molecular and immune profiles among HER2+ and HER2- E-EMCA tumors, which may affect response to targeted therapy

Methods:

- 1462 E-EMCA tumors were analyzed using NGS (592, NextSeq; WES, NovaSeq) and WTS (NovaSeq) (Caris Life Sciences, Phoenix, AZ)
- PD-L1 was tested by IHC (SP142, ≥1%)
- Microsatellite instability (MSI) was tested by FA, IHC and NGS
- TMB was measured by totaling somatic mutations per tumor (TMB-H: ≥10 mutations/MB)
- LOH cut-off was ≥ 16%
- HER2+ cut-off by WTS was determined by Receiver Operator Characteristic (ROC) analysis in USC tumors by comparing to HER2 IHC/CISH results and ERBB2 WTS expression using 2018 Breast Cancer ASCO/CAP Guidelines
- Immune cell infiltrates were calculated by Quantiseq
- Real world overall survival (OS) was extracted from insurance claims data and calculated using Kaplan-Meier survival curves for molecularly defined cohorts from tissue collection to last contact
- Significance was determined using chi-square and Mann-Whitney U test and adjusted for multiple comparisons
  - *(q-value <0.05), p<0.05 but q>0.05 was considered a trend*

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Results

Figure 1. Determining ERBB2 mRNA cut-off in E-EMCA using 2018 HER2 Breast Cancer ASCO/CAP guidelines applied to USC

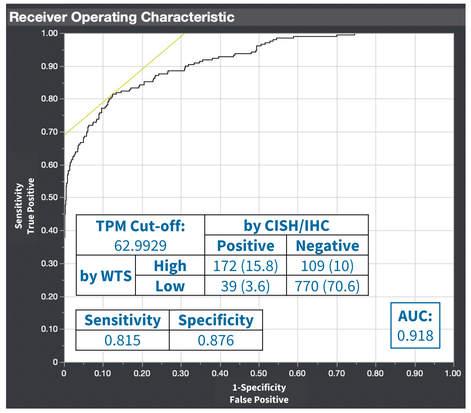


Figure 2. HER2+ positivity in E-EMCA, as determined by WTS.

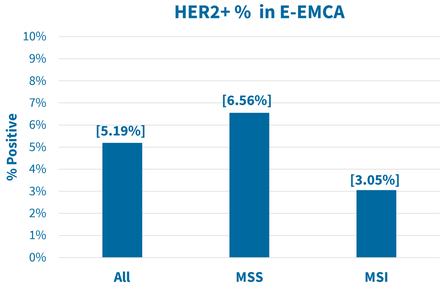


Table 1. Basic patient demographics.

E-EMCA	All	All		MSS		MSI-H	
		HER2+	HER2-	HER2+	HER2-	HER2+	HER2-
N	1462	76 (5.20)	1386 (94.8)	59 (6.56)	840 (93.4)	17 (3.05)	540 (96.9)
Age, median (range)	64 (26-90)	68 (41-90)	64 (26-90)	69 (41-90)	61 (26-90)	66 (54-85)	67 (28-90)
Site							
Primary	1224 (83.7)	62 (81.6)	1162 (83.8)	50 (84.7)	709 (84.4)	12 (70.6)	449 (83.1)
Metastatic	232 (15.9)	14 (18.4)	218 (15.7)	9 (15.3)	128 (15.2)	5 (29.4)	88 (16.3)
Unclear	6 (0.41)	0 (0)	6 (0.43)	0 (0)	3 (0.36)	0 (0)	3 (0.56)

Table 2. Mutational Landscape of HER2+/- E-EMCA.

	Biomarker	All	MSS	MSI
Cell Cycle	CCND1			
Chromatin Remodeling	ASXL1			
	KMT2D			
	NSD1			
Fanconi Anemia	FANCL			
HR	BAP1			
	BRCA1			
mRNA Splicing	SF3B1			
MYC	MAX			
NOTCH	FBXW7		*	
PI3K	AKT1			
	PIK3R1	*		
	PTEN	****	****	
RTK RAS	FGFR2			
	PTPN11			
TP53	TP53	****	****	
WNT	CTNNB1	*	**	
	RNF43			
	CTCF			
	JAK1			
	LOH	****	****	
	U2AF1			

Table 3. IO-related Biomarkers in HER2+/- E-EMCA.

Biomarker		All	MSI	MSS
IO-related Biomarkers	dMMR/MSI-H			
	PD-L1 (SP142)			
	TMB-H			

Table 4. IHC Markers in HER2+/- E-EMCA.

Biomarker		All	MSI	MSS
IHC	ER	*		*
	Her2/Neu	*		*
	PR	****		****

Legend:

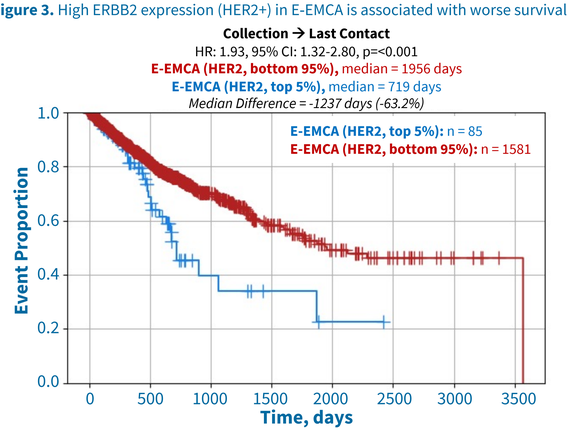
Decrease (q<0.05)
Decrease (p<0.05, q>0.05)
Neutral (No clear trend)
Increase (p<0.05, q>0.05)
Increase (q<0.05)

* <0.05
** <0.01
*** <0.001
**** <0.0001

Table 5. IHC Markers in HER2+/- E-EMCA.

Immune Microenvironment		All	MSS	MSI
Immune Checkpoint Gene Expression (Median TPM)	CD80	**	**	
	CD86		*	
	CD274			*
	CTLA4			
	HAVCR2	**	**	
	IFNG			
	IDO1			
	LAG3		*	
	PDCD1			
	PDCD1LG2	**	**	
Immune Cell (%)	B cell			
	Macrophage M1			
	Macrophage M2			*
	Monocyte			**
	Neutrophil	****	****	
	NK cell			
	T cell CD4+			*
	T cell CD8+			
	Tregs	****		*
	Myeloid Dendritic	**	**	
Immune and Molecular Signatures	T-Cell Inflamed	***	*	
	IFN	***		
	MPAS	****	****	****

Figure 3. High ERBB2 expression (HER2+) in E-EMCA is associated with worse survival.



Study Highlights

- We determined a cut-off of ≥ 62.99 TPM for HER2+ with a sensitivity of 81.5%, specificity of 87.6% and AUC of 0.918 in USC *(Fig 1)*
- When the 62.99 TPM cut-off is applied to E-EMCA, 76 of 1462 (5.2%) E-EMCA tumors were HER2+ *(Table 1)*
- HER2+ tumors had fewer mutations (mt) in *PI3KR1*, *PTEN* and *CTNNB1* but higher mts in *TP53* and more frequent LOH (q<0.05) *(Table 2)*
- HER2+ tumors had a trend towards decreased MSI-H status (22.4% vs 39.1%; p=0.003, q=0.058) and TMB-H (25.4% vs 41.5%; p=0.007, q=0.084) *(Table 3)*
- MSS HER2+ E-EMCA had a similar mutational profile compared to all HER2+ tumors; MSI-H HER2+ E-EMCA had a trend towards higher DDR pathway gene mts compared to MSI-H HER2- EMCA tumors *(Table 2)*
- HER2+ tumors had increased Dendritic cell (3.84% vs 2.97%) but decreased Neutrophil (2.66% vs 5.20%) & T-reg (1.38% vs 2.07%) infiltration (q<0.01) *(Table 5)*
- HER2+ tumors had higher immune checkpoint gene expression of *CD80*, *HAVCR2* and *PDCD1LG2* (q<0.01), and increased T-cell inflamed and MAPK activation score (q<0.01) *(Table 5)*
- MSS HER2+ E-EMCA tumors had a similar immune profile when compared to all HER2+ tumors; MSI-H HER2+ E-EMCA tumors had increased Treg infiltration and MAPK activation score *(Table 5)*
- Median OS was significantly worse for HER2+ pts compared to HER2- (64.3 vs. 23.6 months, HR: 1.93(1.32-2.80), p<0.001) *(Fig 3)*

Conclusion:

- Using a WTS cutoff from USC, 5% of E-EMCA are HER2+ and showed distinct molecular and immune profile compared to HER2- tumors
- HER2+ confers a worse OS compared to HER2- tumors
- Furthermore, HER2+ tumors demonstrate an immune hot phenotype suggesting that immunotherapy may be a potential therapeutic option