Estrogen and progesterone receptors are associated with improved survival and increased immunogenicity in uterine carcinosarcoma

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2021 ASCO ANNUAL MEETING

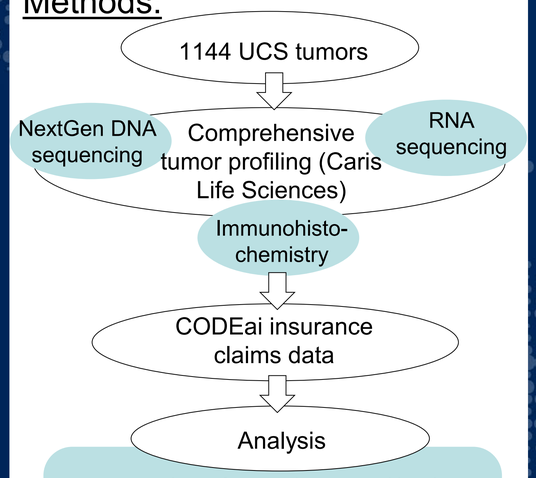
Background:

- Recent data has shed light on molecular profiles of uterine carcinosarcoma (UCS) but few have correlated molecular profiles with prognosis.
- In a preliminary data analysis, we found that hormone receptors (HR)—estrogen receptor (ER) and progesterone receptor (PR)—expression was associated with improved OS.

Objective:

Investigate the molecular profile differences between ER+/- and PR +/- tumors.

Methods:

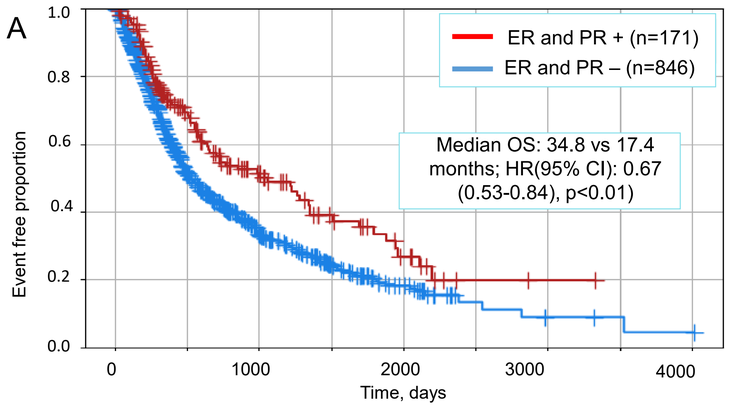


- Statistical significance determined by chi-square and Wilcoxon rank sum test.
- p values adjusted for multiple comparisons (q) to be <0.05
- Survival calculated using CodeAI data

Figure 1: Flowchart describing methods

Results:

A



B

Biomarker	N	Median OS (months)	P-value
PR+	208	25.4	< 0.05
PR-	953	18.7	
ER+	277	29.4	<0.05
ER-	885	17.3	

Figure 2: HR receptor positive status was associated with improved median OS in UCS. (A) Median OS of ER and PR positive tumors. (B) Breakdown of ER+ vs ER - tumors and PR + vs PR – tumors by median OS in months.

	Molecular Alteration	ER+ (%)	ER- (%)	Q-value	PR+ (%)	PR- (%)	Q-value
Gene (Mut/High Expression)	TP53	71.6	83.1	0.01	68.3	83.1	<0.01
	PTEN	33.5	13.8	<0.01	36.1	14.7	<0.01
	Androgen Receptor	41.4	9.3	<0.01	36.2	12.3	<0.01
	PR or ER	64.4	3.5	<0.01	85.3	10.4	<0.01
	JAK1	9.7	3.0	0.04	11.8	3.1	0.01
	CTNNB1	12.2	1.4	<0.01	15.7	1.4	<0.01
	ARID1A	63.6	42.5	0.226	71.2	41.9	0.012
	ATRX	7.9	1.6	0.192	10.8	1.4	0.02
Pathway	TP53	71.4	82.1	0.02	68.5	82.1	<0.01
	WNT	19.5	5.8	<0.01	23.8	5.8	<0.01
	PI3K	61.0	48.9	0.06	62.2	49.4	0.05
	HR Pathway	8.9	4.7	0.32	11.5	4.6	0.03
	DNA Damage Sensors	6.5	2.8	0.217	8.7	2.6	<0.01
	Chromatin Remodeling	40.4	27.8	0.125	43.4	28.2	0.04

Table 1: ER and PR positive tumors have distinct molecular profiles compared to their negative counterparts.

KEY FINDINGS:

HR+ tumors have distinct molecular profiles from HR- tumors and appear to be more immunogenic by way of more frequent MSI-H status, TMB-H, increased infiltrating regulatory T-cells and IDO1 expression

- Suggests possible benefit with immune-oncology therapy and may contribute to the observed improved OS
- More data are needed to determine if HR status is a marker of response to IO therapy

Figure 3: Markers of response to immuno-oncology therapy in HR+/- tumors. Both (A) ER and (B) PR positive tumors had significantly higher MSI and TMB.

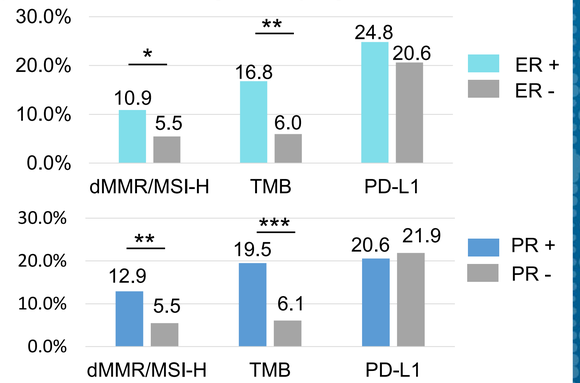


Table 2: Immune microenvironment of PR + tumors by immune cell fraction. T regulatory cells were significantly higher in both ER+ and PR + tumors compared to ER – and PR -. Immune checkpoint genes had higher expression in HR+ tumors (significantly higher for IDO).

Significance markers: * q<0.05; ** q<0.01; *** q<0.001

Marker		PR-	PR+	Q-value	ER-	ER+	Q-value
IC Gene (median TPM, normalized to median TPM in PR-/ER-)	CD80	1	0.7177	1	1	1.132	1
	CD86	1	1.1504	1	1	1.356	0.875
	CD274	1	1.1746	1	1	1.458	0.238
	CTLA4	1	1.2223	1	1	1.359	1
	HAVCR2	1	1.0705	1	1	1.088	1
	IFNG	1	1.5896	1	1	1.668	0.409
	IDO1	1	1.9437	0.034	1	2.258	0.001
	LAG3	1	1.2193	1	1	1.299	1
	PDCD1	1	1.2193	1	1	1.133	1
	PDCD1LG2	1	1.2806	1	1	1.484	0.394
Immune Cell Fraction (%)	B cell	5.84%	5.71%	1	5.93%	5.51%	1
	Macrophage M1	0.63%	1.26%	1	0.55%	1.44%	0.136
	Macrophage M2	4.20%	4.77%	1	3.98%	5.00%	0.076
	Monocyte	0.00%	0.00%	0.036	0.00%	0.00%	0.240
	Neutrophil	2.51%	2.73%	1	2.44%	2.93%	1
	NK cell	3.49%	2.98%	0.667	3.50%	3.04%	0.378
	CD4+ T Cells	0.00%	0.00%	1	0.00%	0.00%	1
	CD8+ T Cells	0.00%	0.00%	1	0.00%	0.00%	1
	Tregs	0.59%	1.18%	0.010	0.55%	1.22%	0.002
	Myeloid dendritic cell	3.63%	3.27%	1	3.66%	2.94%	1