Molecular determinants of response to immune-oncology therapy in uterine carcinosarcoma

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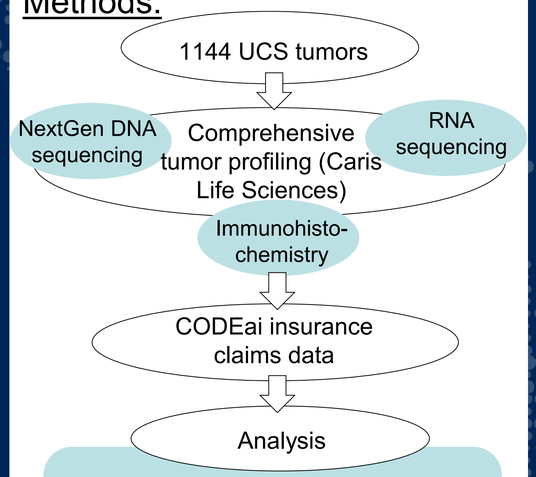
Background:

- Uterine carcinosarcomas (UCS) are rare tumors with a poor prognosis
- UCS has not traditionally been included in endometrial cancer (EC) clinical trials and treatment options are limited
- Immune-oncology (IO) therapy has shown promise UCS, but it is unknown which patients benefit most

Objective:

Identify immunogenic markers in UCS and explore treatment response to IO therapy

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:

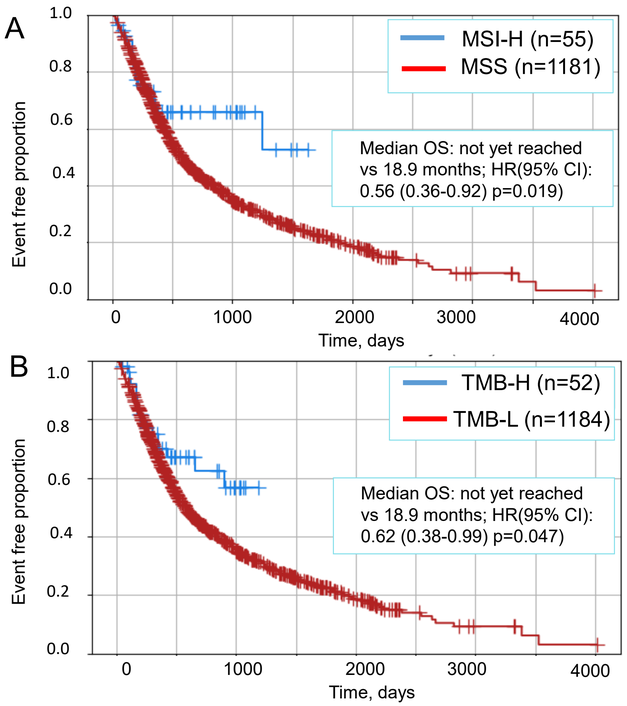
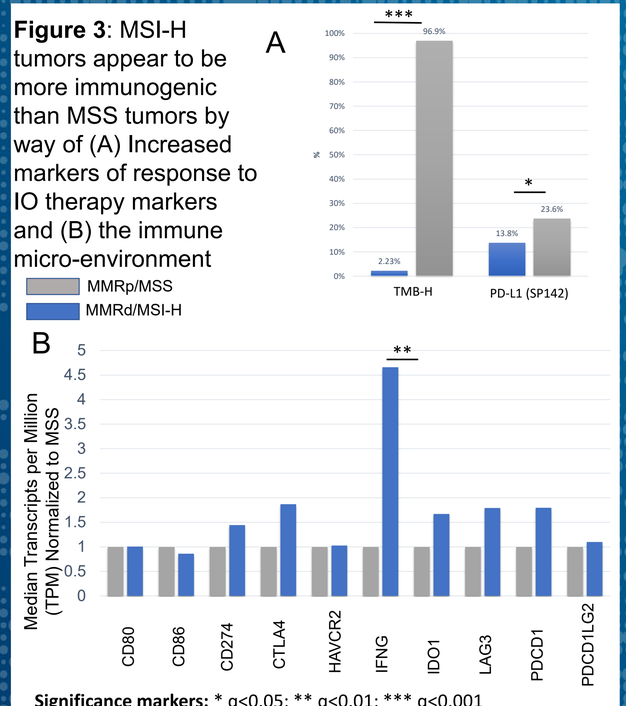


Figure 2: High Microsatellite Instability (MSI-H) (A) and high tumor mutational burden (TMB-H) (B) are associated with improved survival in uterine carcinosarcoma.

Table 1: MSI and MSS tumors have distinct molecular profiles

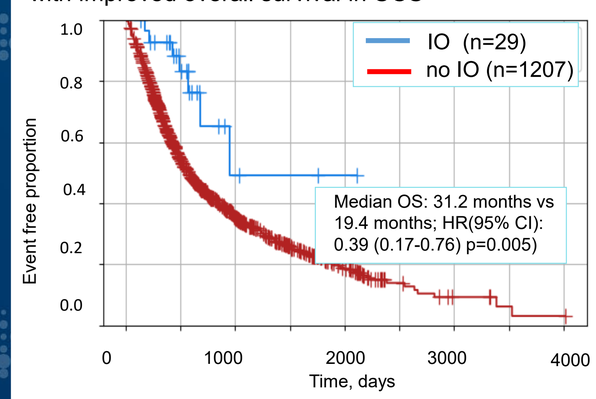
	Molecular Alteration	MMRd/MSI-H	MMRp/MSS	Adjusted p-value
Gene	TP53	43.6%	86.5%	< 0.01
	ARID1A	91.1%	36.6%	< 0.01
	PIK3CA	54.4%	28.7%	< 0.01
	PTEN	86.0%	14.4%	< 0.01
	PIK3R1	30.6%	10.2%	< 0.01
	RB1	23.1%	5.27%	< 0.01
	NF1	22.5%	4.56%	0.01
	KMT2D	48.0%	4.50%	< 0.01
	KMT2C	22.7%	4.27%	< 0.01
Pathway	TP53 Pathway	42.1%	85.6%	< 0.01
	PI3K	93.0%	54.0%	< 0.01
	RTK RAS	57.9%	33.2%	< 0.01
	Chromatin Remodeling	96.1%	25.4%	< 0.01
	WNT	52.6%	7.67%	< 0.01
	HR Pathway	23.2%	4.92%	< 0.01
	DNA Damage Sensors	17.5%	3.84%	< 0.01
	TNF-alpha Signaling	9.80%	1.49%	0.03
	Hedgehog Signaling	9.26%	0.41%	<0.01

Figure 3: MSI-H tumors appear to be more immunogenic than MSS tumors by way of (A) Increased markers of response to IO therapy markers and (B) the immune micro-environment



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

Figure 4: Treatment with IO therapy is associated with improved overall survival in UCS



KEY FINDINGS:

- IO therapy is associated with improved survival in UCS
- MSI and TMB are markers of improved OS in patients with UCS
- dMMR/MSI-H tumors have a distinct molecular profile compared to MMRp/MSS tumors, and appear to be more immunogenic, which could contribute to the improved survival seen in patients who received IO therapy