Transcriptomic signatures (sig.) associated with markers of immune and angiogenic sensitivity in Clear Cell Renal Cell Carcinoma (ccRCC) with sarcomatoid/rhabdoid features

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Background:

Predictive biomarkers for optimal treatment selection in RCC are lacking. Gene expression profiling (GEP) studies have identified angiogenic and immune sig. with potential predictive value in patients (pts) with advanced ccRCC. We aimed to update the findings of a large multi-institutional database (Barata, ASCO-GU 21), with a focus on tumors with sarcomatoid/rhabdoid features.

Methods:

- Whole transcriptome sequencing was performed for ccRCC patient samples submitted to a commercial CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ).
- Genomic signature were identified by tumor GEP and hierarchical clustering based on the validated 66-gene signature (D'Costa et al, 2020);
- Samples from both primary tumors and metastatic sites were included.
- Histology reflects both local and central pathology review

Results:

- Final analysis included 506 pts [median age 62 (range 19-90), 69.8% men] with ccRCC based on tissue samples from kidney (50%), lung (11.4%), bone (8.5%), liver (4.3%) or other sites (25.6%).
- GEP sig. stratified samples into angiogenic (23.5%), mixed (53.2%) and T-effector subgroups (23.3%).

Table 1 – Baseline patient and tumor characteristics

Characteristic	All cases	'Angiogenic' subgroup	'Mixed' subgroup	'T-effector' subgroup	P-value (Test) 'Angio' vs 'T-eff'
Total, N cases (% of total)	506 (100%)	119 (23.5%)	269 (53.2%)	118 (23.3%)	--------
Median Age, years (SD)	62 (11.1)	64 (11.3)	63 (11.2)	60 (10.5)	**0.0044**
- Age Range, years	19-90	19-90	28-86	38-83	(Mann-Whitney U)
Female/Male, N cases	153/353	52/67	73/196	28/90	**0.0012**
- (% Female/% Male)	(30.2%/69.8%)	(43.7%/56.3%)	(27.1%/72.9%)	(23.7%/76.3%)	(Chi-square)
Metastatic/Primary, N cases	255/251	66/53	130/139	59/59	0.3997
- (% Metastatic/% Primary)	(50.5%/49.5%)	(55.5%/44.5%)	(48.3%/51.7%)	(50.0%/50.0%)	(Chi-square)

- **Tumors expressing an angiogenic sig**. were more commonly found in pancreatic/small bowel metastases (p=0.01), older pts (p=0.004) and associated with *PBRM1* mutations and endothelial cell population abundance.

Figure 1 – Distribution of Subtypes by Specimen Site

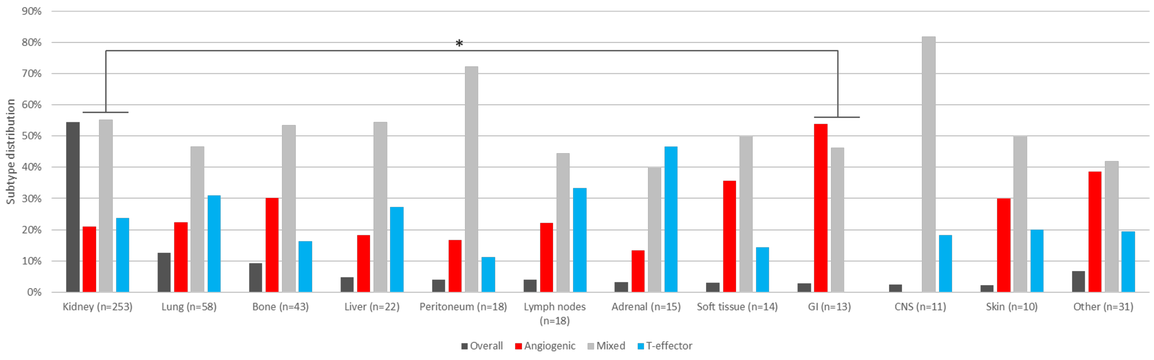
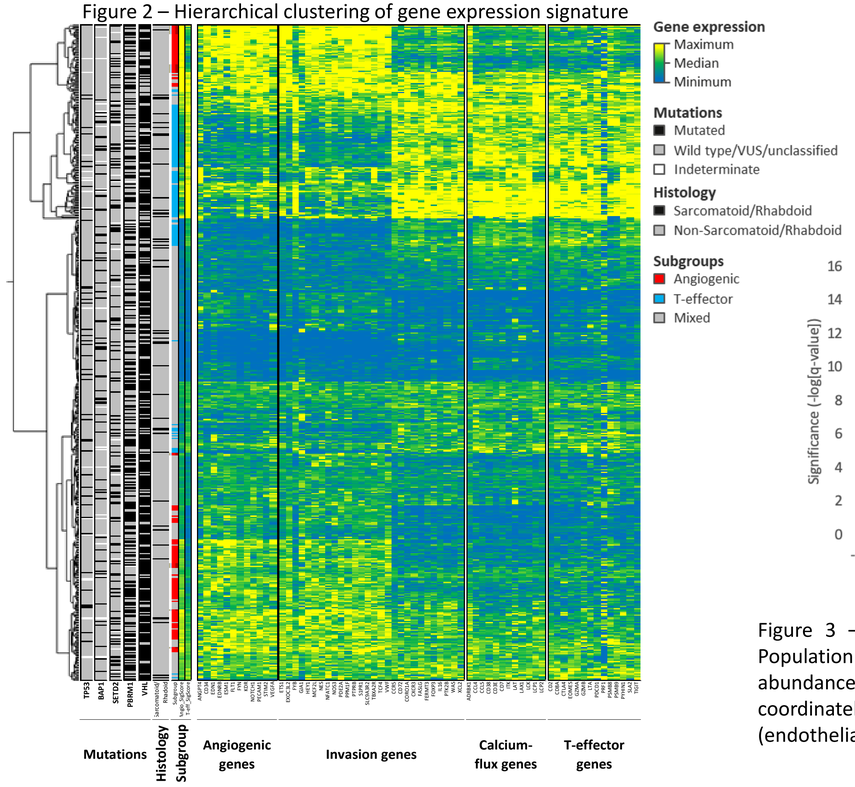


Figure 2 – Hierarchical clustering of gene expression signature



- **A subset of tumors (8.5%) with sarcomatoid and/or rhabdoid features** had a higher prevalence of the T-effector (48.8%) compared to angiogenic (7.0%) sig. and associated with increased immune cell population abundance and immune checkpoint gene expression: T cells (p=0.03), cytotoxic lymphocytes (p=0.04), CTLA4 (p=0.02), LAG3 (p=0.001) and PDCD1 (p=0.004).

Table 2 – Baseline patient and tumor characteristics - **ccRCC with sarcomatoid/rhabdoid**

Characteristic	All cases	'Angiogenic' subgroup	'Mixed' subgroup	'T-effector' subgroup	P-value (Test) 'Angio' vs 'T-eff'
Total, N cases (% of total)	43 (100%)	3 (7.0%)	19 (44.2%)	21 (48.8%)	--------
Median Age, years (SD)	59 (13.5)	49 (18.9)	59 (12.9)	60 (12.2)	0.0806
- Age Range, years	19-83	19-54	34-77	38-83	(Mann-Whitney U)
Female/Male, N cases	18/25	1/2	9/10	8/13	0.8734
- (% Female/% Male)	(41.9%/58.1%)	(33.3%/66.7%)	(47.4%/53.6%)	(38.1%/61.9%)	(Chi-square)
Metastatic/Primary, N cases	6/37	0/3	2/17	4/17	0.4076
- (% Metastatic/% Primary)	(14.0%/86.0%)	(0.0%/100.0%)	(10.5%/89.5%)	(19.0%/81.0%)	(Chi-square)

Results:

- **T-effector sig. tumors** were found more frequently in men (p=0.0012), kidney biopsies (p=0.001), associated with immunotherapy markers [dMMR/MSI (p=0.0293), TMB (P=0.0292), PD-L1 (P<0.0001)], immune cell population abundance and checkpoint gene expression, as well as *BAP1* (p<0.0014), *NF2* (p=0.0295) and *TP53* (p=0.0162) alterations.

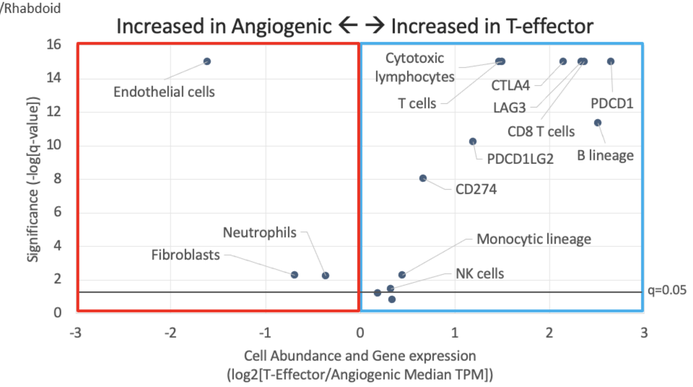
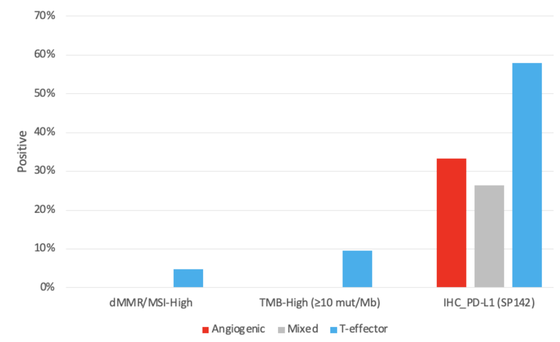


Figure 3 – Analysis of ccRCC tumor microenvironment by Microenvironment Cell Population (MCP)-counter. Immune cell population (e.g. T cells, cytotoxic lymphocytes) abundance and immune checkpoint genes (e.g. *PDCD1*, *CD274*, *CTLA4*, *LAG3*) were coordinately increased in the T-effector subgroup, while stromal cell population (endothelial cells, fibroblasts) abundance was increased in the Angiogenic subgroup.

Figure 4 – Immunotherapy marker association in **ccRCC with sarcomatoid/rhabdoid features**



Conclusions:

- Our updated real-world dataset confirms the presence of distinct RCC genomic sig. potentially associated with clinically meaningful markers of immune and angiogenic sensitivity.
- Prospective validation of these GEPs in therapeutic RCC clinical trials are warranted.