#11539: Deciphering the molecular landscape and the tumor microenvironment of Perivascular Epitheloid Cell Neoplasm (=PEComa)

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Background & Aim:

- PEComa is a rare mesenchymal neoplasm composed of perivascular epithelioid cells. Due to its rarity, diagnosis is challenging, and no standardized treatment guidelines have been established.
- A part of PEComas showed a benefit upon nab-sirolimus treatment (Wagner AJ et al, ASCO 2019)
- A subgroup of PEComas are characterized by a loss of function mutation in TSC1/2.
- In the majority the molecular landscape and the composition of the tumor microenvironment (TME) remain largely unclear.
- We conducted this study to elucidate the genetic landscape of PEComas.

Patients & Methods:

- Thirty-five PEComa specimens were centrally analyzed at the Caris Life Sciences laboratory.
- NextGen DNA sequencing (NextSeq, 592 gene panel or NovaSeq, whole-exome-sequencing), whole-transcriptome RNA sequencing (NovaSeq) and immunohistochemistry (Caris Life Sciences, Phoenix, AZ) were performed.
- Gene expression profiling (GEP) was performed by unsupervised hierarchical clustering.
- RNA deconvolution analysis was performed using the Microenvironment Cell Populations (MCP)-counter method to quantify immune cell populations.

Results:

Figure 1: Most common mutations detected were *TP53* (47%), *ATRX* (32%), *TSC1/2* (11%/29%) and *MSH3* (17%). *TP53* mutations occurred less frequently (25 vs 60%, p=0.055) in *TSC1/2*-mutated (*TSC1/2-mt*) compared to *TSC1/2*-wildtype (*TSC1/2*-wt) tumors.

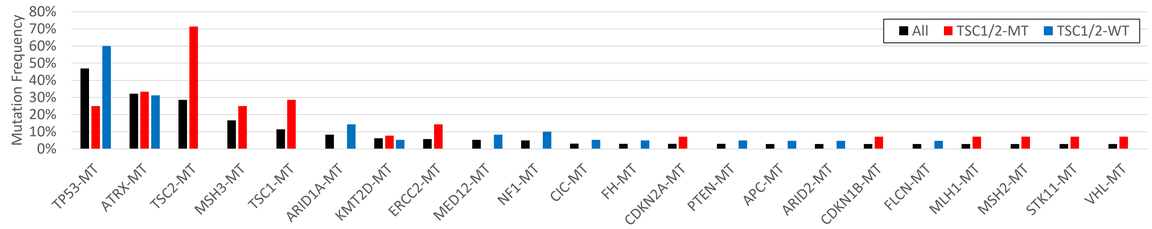


Figure 2: PEComas associated with high or low PI3K-AKT-mTOR pathway signalling.

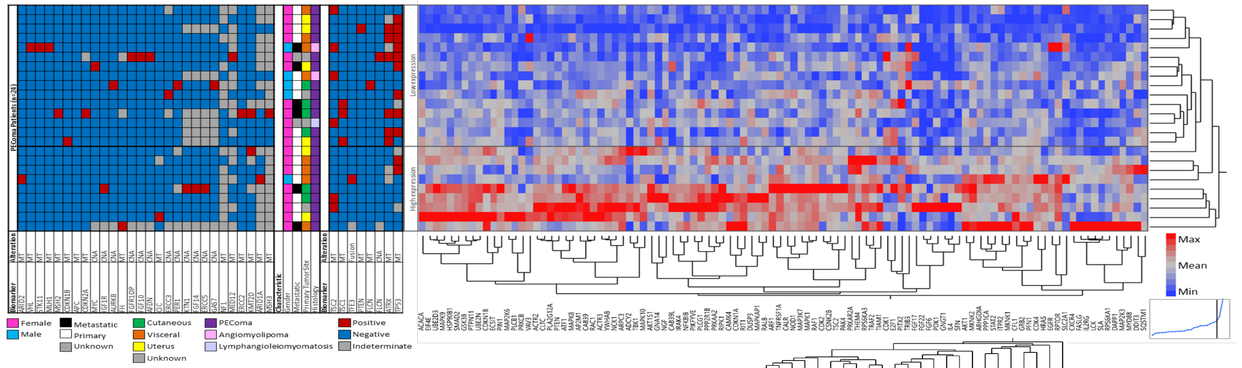
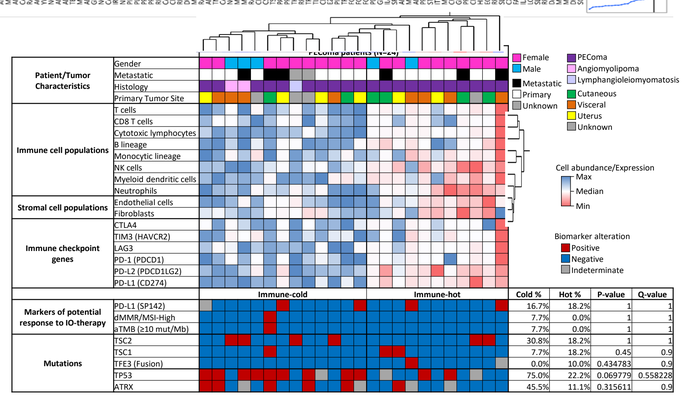


Figure 3: TMEs were characterized by a significant increase of NK cells and fibroblasts, as well as a relevant decrease of $CD8^+$ T cells and B cells. dMMR/MSI-H and TMB-H were rare (2.9%, n=1 each). PD-L1 expression was observed in 21.9% (n=7) of patients.



	Cold %	Hot %	P-value	Q-value
PD-L1 (SP142)	16.7%	18.2%	1	1
dMMR/MSI-High	7.7%	0.0%	1	1
bTMB (≥10 mut/Mb)	7.7%	0.0%	1	1
TSC2	30.8%	18.2%	1	1
TSC1	7.7%	18.2%	0.45	0.9
TFE3 (Fusion)	0.0%	10.0%	0.434783	0.9
TP53	75.0%	22.2%	0.069779	0.558228
ATRX	45.5%	11.1%	0.315611	0.9

CONCLUSIONS:

1) PEComas are characterized by a heterogeneous molecular landscape with a high prevalence of *TSC1/2* mutations.
2) Only a subset of *TSC1/2*-mt PEComas were associated with an up-regulation of the PI3K-Akt-mTOR pathway.
3) This might explain why not all patients showed a benefit when using mTOR inhibitors.

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