Characterizing the genomic landscape of malignant perivascular epithelioid cell family of tumors (PEComa-FT) in a real-world population using the Foundation Medicine genomic database

Daniel S. Lefler, MD

2024 ANNUAL MEETING

Disclosures

- Aadi – advisory board honorarium

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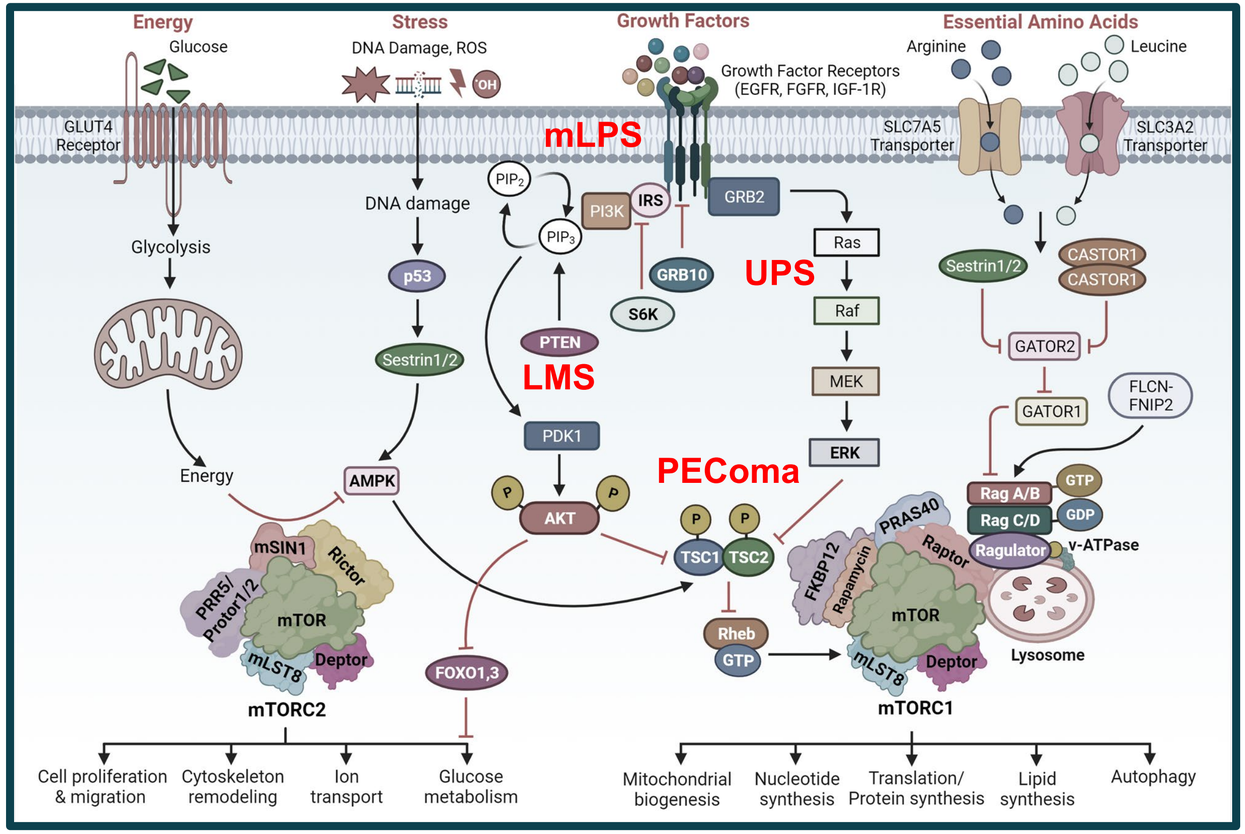
The mTOR pathway in sarcoma

- Central signaling pathway(s) involved in multiple biological processes; complex upstream + extensive downstream signaling
- Roles demonstrated in osteosarcoma, leiomyosarcoma, and other STS → SUCCEED trial using ridaforolimus
- Evidence of activation may provide prognostic and predictive information, such as differential responses to chemo- and immunotherapies (abstract # 1854955)



Panwar et al., Sig Transduct Target Ther 2023

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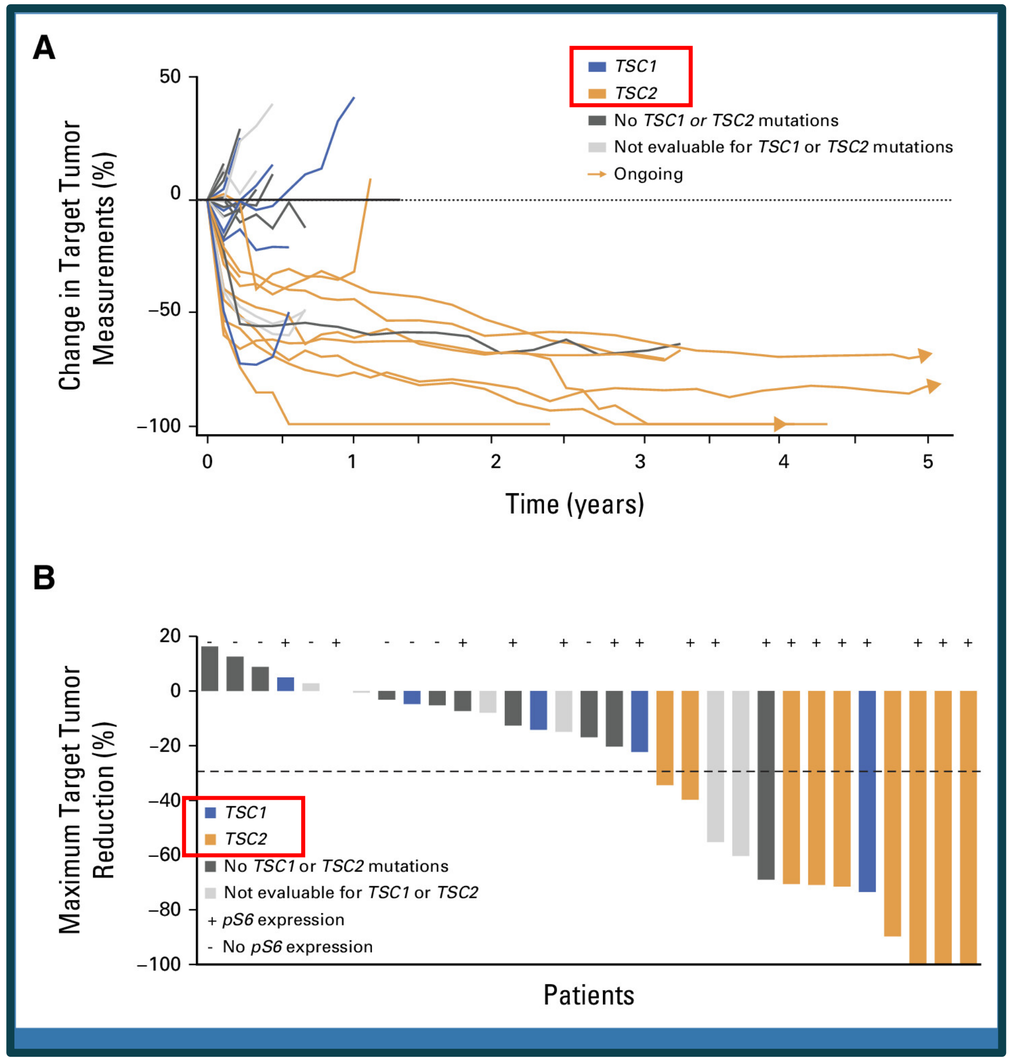
Malignant PEComa: successful targeting of mTOR

- *nab*-sirolimus is a modified, intravenous rapamycin analog with high intratumoral accumulation and strong mTOR inhibition
- The AMPECT trial demonstrated activity of *nab*-sirolimus in patients with PEComa
- ORR 38.7%, mDOR 39.7 months, mOS 53.1 months; AEs: mucositis, cytopenias, fatigue, rash, GI sx
- Greatest benefit was seen in patients with *TSC1* and *TSC2* inactivating alterations
- Related tumors include AML and LAM



Wagner et al., JCO 2024

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What is the landscape of gene alterations in the PEComa family of tumors (PEComa-FT)?

With what frequency are genes involved in mTOR signaling/activation altered in PEComa-FT, including and beyond *TSC1* and *TSC2*?

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Methods: mTOR gene alterations in PEComa-FT

- Next-generation tumor-only sequencing (NGS) was performed on unique samples from patients with advanced cancers (August 2014 to July 2023) using FoundationOne®Heme and FoundationOne® CDx assays and analyzed using the FoundationInsights™ web-based platform.

- Included patients with PEComas and its related family of tumors, including angiomyolipoma (AML) and lymphangioleiomyomatosis (LAM)

- Frequency and pathogenicity of gene alterations, tumor mutational burden (TMB), microsatellite instability (MSI) status, and demographics at the time of NGS in PEComa-FT samples were characterized.

- The frequencies of alterations of genes involved in canonical mTOR signaling were evaluated

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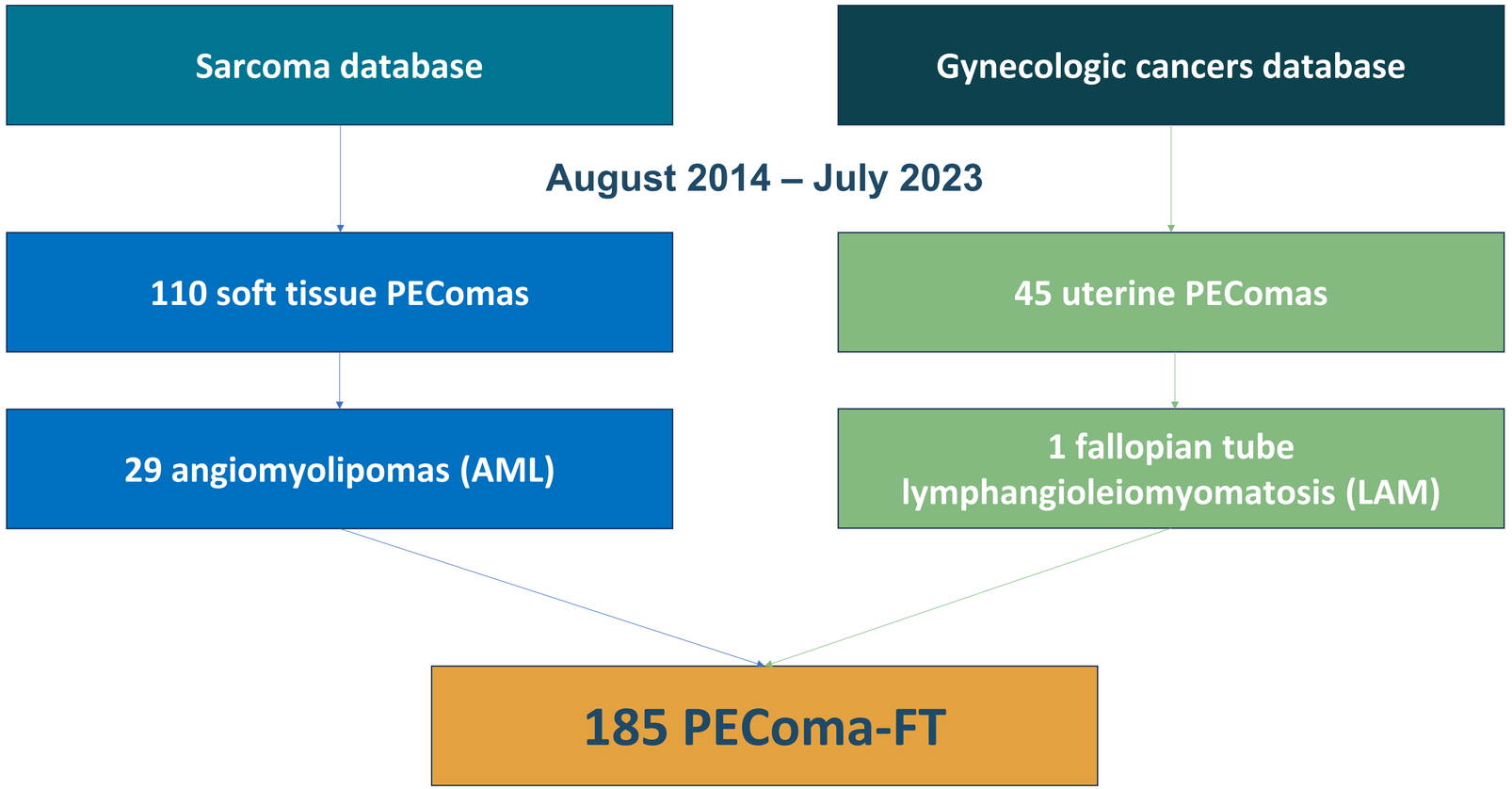
Results: mTOR gene alterations in PEComa-FT



Of 185 patients:

146 (78.9%) female
87 (47.0%) age 51-70
4 (2.1%) pediatric

TMB-low: 173/179 (96.7%)

MSS: 166/169 (98.2%)

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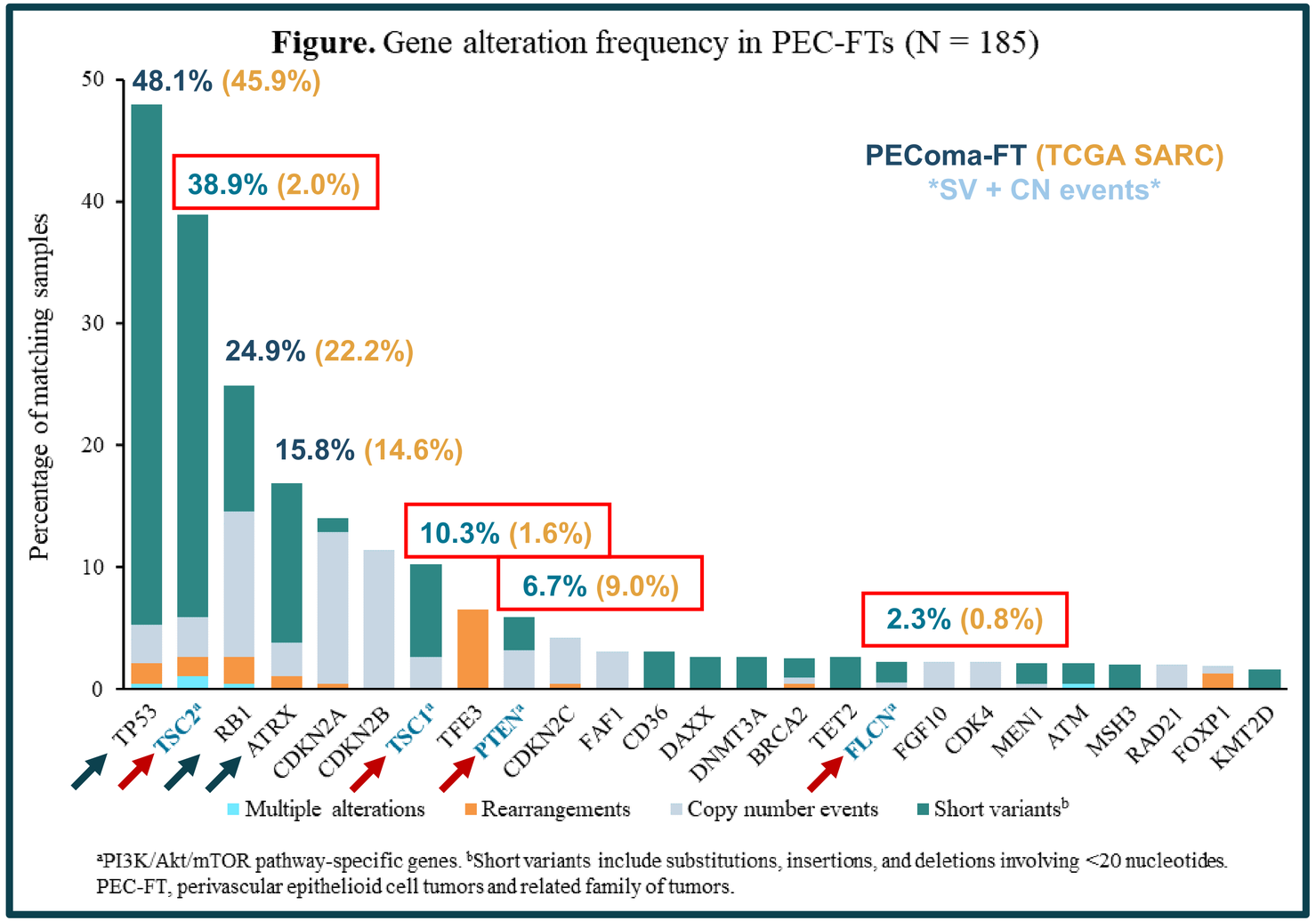
Results: mTOR gene alterations in PEComa-FT



Genes commonly altered in soft tissue sarcomas

Genes known to be involved in mTOR signaling

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Results: mTOR gene alterations in PEComa-FT

Table. Enrichment for PI3K/Akt/mTOR pathway alterations in PEC-FT samples

	PEC-FT Samples (N = 185)			
Gene	**All Alterations (%)**	**Short Variants (%)**	**Copy Number Events (%)**	**Rearrangements (%)**
AKT2	0.5	0.5	0	0
FBXW7	1.1	1.1	0	0
FLCN	2.3	1.7	0.6	0
MTOR	1.6	1.6	0	0
PIK3C2G	0.5	0.5	0	0
PTEN	5.9	2.7	3.2	0
RICTOR	1.6	0	1.6	0
STK11	0.5	0	0	0.5
TSC1	10.3	7.6	2.7	0
TSC2	38.9	33.0	3.2	1.6
Cumulative frequency of PI3K/Akt/mTOR pathway alterations			**63.2%**	**+ 4.3% (8) PEComas with *TFE3* rearrangements**

AMPECT 16.1 29.0

No alterations present in AKT1, AKT3, INPP4B, PIK3C3 PIK3CA, PIK3CD, PIK3CG, PIK3R1, PIK3R2, or RPTOR among PEC-FT samples.
PEC-FT, perivascular epithelioid cell tumors and related family of tumors.

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Takeaways, limitations, and future directions

- This is the largest (n=185) genomic characterization of PEComa-FT using real-world data
- Many of the most common genes mutated/deleted in soft tissue sarcomas are found altered at similar frequencies in PEComa-FT (*e.g., TP53, RB1, ATRX*)
- PEComa-FT are enriched for mTOR pathway gene alterations: *TSC1/2* in 49% of cases + another 10-20% exhibit other mutations, deletions, or fusions (*TFE3*)
- *Limitations*: genes included in FoundationOne® assay, other biomarkers (IHC), histopathological diagnosis not centrally reviewed, no clinical outcomes
- Further study is warranted re: PEComa-FT's molecular biology-histopathology relationship
- Some alterations may be "more important" than others for mTOR pathway activation; quantifying this may guide efforts in therapeutic targeting

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