#11544: Characterizing patterns of mTORC1 activation across sarcomas using single-sample gene set enrichment analysis (ssGSEA) and a national biomarker database

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Background

- The mTOR pathway is a central signaling circuit in many tumors and contributes to cell growth
- The phase III SUCCEED trial (2012) showed statistically significant—but clinically minimal—difference in PFS with the mTOR inhibitor (mTORi) ridaforolimus after chemo response, but didn't stratify by molecular findings
- The AMPECT trial (2021) showed activity of nab-sirolimus in PEComa, especially in *TSC2*-mut tumors

Goal

Identify sarcomas by subtype/mutational status that have evidence of mTORC1 activation (mTORC1-act) and may derive benefit from mTOR inhibition

Methods

Sarcoma samples at Caris (n=3757) → RNA seq → gene expression profile → Downloaded Hallmark mTORC1 signaling gene set from mSigDB → Performed gene set variation analysis (GSVA), a variation on ssGSEA → Real-world OS, HR by Cox proportional hazards → Validation using TCGA (n=265)

Activation of the mTOR pathway, as measured by gene expression, is more common in some sarcoma subtypes (especially UPS) and can be both prognostic and possibly predictive of response to mTOR inhibitors

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Figure 1. mTORC1 signaling GSVA scores (Caris)

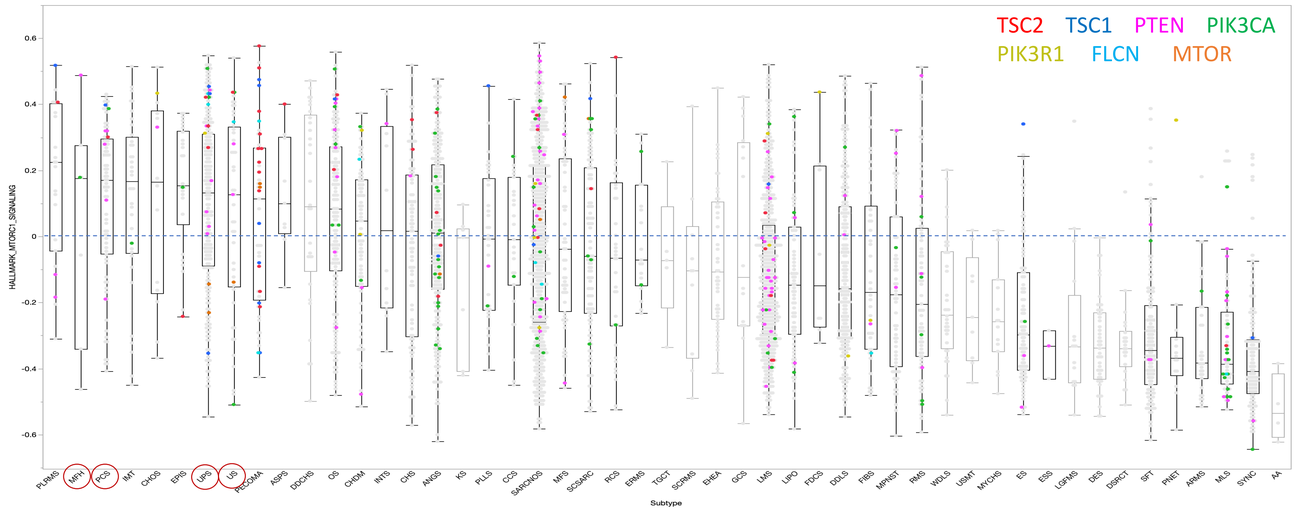


Fig 2. mTORC1 GSVA scores (TCGA)

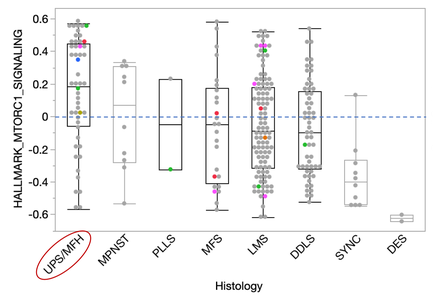


Fig 3. Survival by mTORC1-act (Caris)

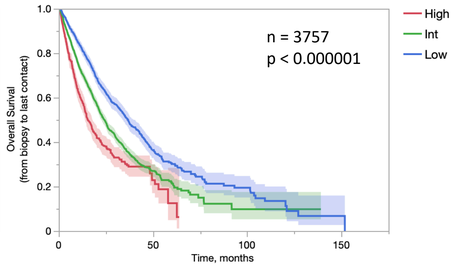
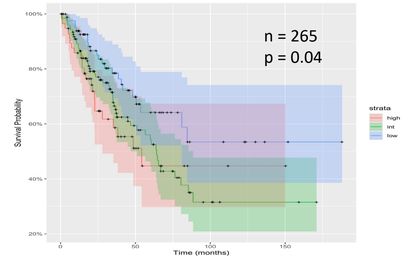


Fig 4. Survival by mTORC1-act (TCGA)



Results

- Among positive/highest mTORC1-act scores (expected): PEComa (median=0.114), osteosarcoma (OS) (median=0.084) (**Fig 1**)
- High mTORC1-act in UPS/MFH (median=0.132/0.176), IMT (median=0.167), epithelioid sarcoma (EPIS) (median=0.155) (**Fig 1**)
- In PEComa, TSC2 alterations associated with mTORC1-act (p=0.036), but TSC1 alterations not (p=0.63); aligns with responses in AMPECT
- Strongest predictor of mTOR-act = histology (p<0.00001) > mutations in *TSC2* (p<0.001) > *TSC1* (p=0.002) > *PTEN* (p=0.01) > *PIK3R1* (p=0.02)
- Prognosis (Caris): Pan-sarcoma OS lower with high mTORC1-act scores (15.4 months) < intermediate (24.2) < low (36.8) (p<0.000001) (**Fig 3**)
- TCGA (validation): highest mTORC1-act score in UPS/MFH (median=0.185), similar trends in other subtypes compared with Caris (**Fig 2**)
- Prognosis (TCGA): Pan-sarcoma OS lower with high mTORC1-act scores (22.8 months) < intermediate (33.5) < low (34.9) (p=0.04) (**Fig 4**)
- ★ Findings support this as method to identify mTORC1-act, related prognosis, and potential candidates for targeted therapies in sarcomas

Future directions

- Delineate responses to therapies based on mTORC1-act
- Explore gene expression as a biomarker for sarcoma patients
- Clinical trial of mTORi in select sarcoma population

References

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