Pan-sarcoma multi-omic analysis identifies sarcoma subtypes with immunogenic potential

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Background

- Immune checkpoint inhibitors (ICI) have limited efficacy against soft tissue sarcomas (STS)
- Response to ICI are seen both in individual sarcoma subtypes and in individual patients with otherwise resistant subtypes
- Traditional biomarkers for ICI responsiveness (i.e. PD-L1, TMB) have been insufficient for differentiating which patients with STS will benefit from ICI[1]
- Upregulation of the T cell inflamed score (TIS)[2], an 18 gene expression signature reflective of an active tumor immune microenvironment (TME), has been associated with a response to ICI across multiple solid tumors
- We sought to investigate the prevalence of a high TIS across a large cohort of soft tissue sarcomas

Methods

- Next-generation sequencing of DNA (592 gene panel or whole exome) and RNA (whole transcriptome) was performed on 3605 sarcoma patient samples, representing 45 histologic subtypes, submitted to a CLIA-certified laboratory (Caris Life Sciences, Phoenix, AZ)
- TIS was calculated as an 18 gene weighted coefficient composite value from transcriptomic data[2]
- The Microenvironment Cell Populations-counter tool was used to quantify immune cell populations[3]
- TMB-High (≥ 10 mutations/Mb); PD-L1+ (SP142; 2+|5% = positive)
- Results were compared to NGS data from melanoma (n=1255), a representative immunogenic tumor type. High TIS was defined as a score within the upper quartile of melanoma TIS (>5.5).
- P-values were adjusted for multiple hypothesis testing

Table 1. Distribution of Sarcoma Subtypes included in the study.

Sarcoma Subtype	Abbreviation	N samples
Overall	**Overall**	**3605**
Gastrointestinal Stromal Tumor	GIST	524
Uterine Leiomyosarcoma	ULMS	454
Sarcoma, NOS	SARCNOS	421
Leiomyosarcoma	LMS	345
Pleomorphic Sarcoma	PLSARC	192
Dedifferentiated Liposarcoma	DDLS	148
Angiosarcoma (non-Cutaneous)	ANGS-nonCUT	133
Spindle Cell Sarcoma	SCSARC	97
High-Grade Endometrial Stromal Sarcoma	HGESS	82
Uterine Carcinosarcoma/Uterine Malignant Mixed Mullerian Tumor	UCS	75
Synovial Sarcoma	SYNS	71
Solitary Fibrous Tumor/Hemangiopericytoma	SFT	64
Malignant Peripheral Nerve Sheath Tumor	MPNST	59
Liposarcoma	CHS	52
Chondrosarcoma	RMS	51
Rhabdomyosarcoma	CHDM	49
Chordoma	LIPO	47
Undifferentiated Uterine Sarcoma	UUS	46
Myxofibrosarcoma	MFS	43
Osteosarcoma	OS	39
Myxoid/Round-Cell Liposarcoma	MRLS	37
Desmoid/Aggressive Fibromatosis	DES	36
Low-Grade Endometrial Stromal Sarcoma	WDLS	35
Uterine Sarcoma, Other	LGESS	35
Uterine Adenosarcoma	OUSARC	35
Well-Differentiated Liposarcoma	ARMS	35
Desmoplastic Small-Round-Cell Tumor	ES	32
Angiosarcoma (Cutaneous)	ANGS-CUT	30
Ewing Sarcoma	PECOMA	30
Fibrosarcoma	FIBS	24
Perivascular Epithelioid Cell Tumor	EHAE	24
Uterine Sarcoma/Mesenchymal	USARC	22
Epithelioid Hemangioendothelioma	PLLS	22
Pleomorphic Liposarcoma	PT	21
Phyllodes Tumor of the Breast	RCSNOS	19
Round Cell Sarcoma, NOS	UELMS	18
Uterine Epithelioid Leiomyosarcoma	IMT	17
Inflammatory Myofibroblastic Tumor	DDCHS	17
Dedifferentiated Chondrosarcoma	HPCCNS	16
Alveolar Rhabdomyosarcoma	DSRCT	15
Clear Cell Sarcoma	CCS	15
Hemangiopericytoma of the Central Nervous System	ARMS	15
Myxoid Chondrosarcoma	MYCHS	14
Epithelioid Sarcoma	ERMS	13
Embryonal Rhabdomyosarcoma	EPIS	13
Pleomorphic Rhabdomyosarcoma	PLRMS	12
Angiosarcoma (Unclear)	ANGS-Unclear	11

Results

Figure 1. TIS score distributions by sarcoma subtypes

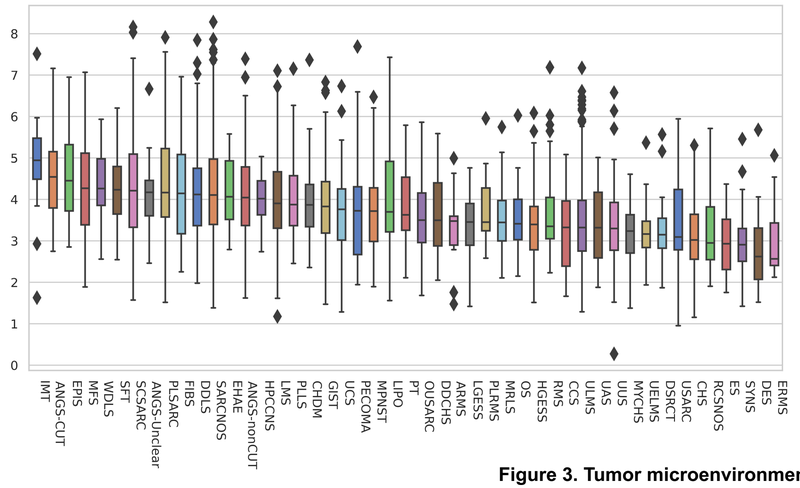


Figure 2. Proportion of TIS scores within Melanoma (MM) TIS score Quartiles by sarcoma subtype

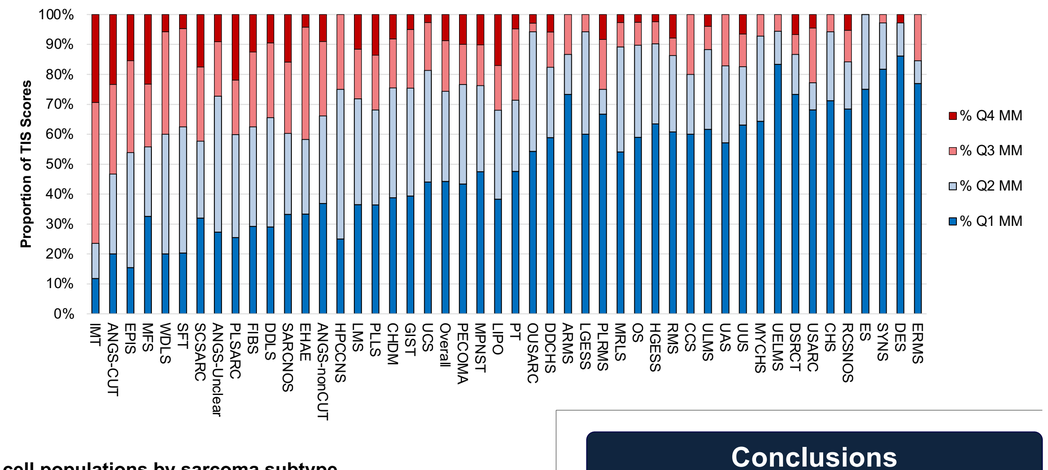


Figure 3. Tumor microenvironment cell populations by sarcoma subtype

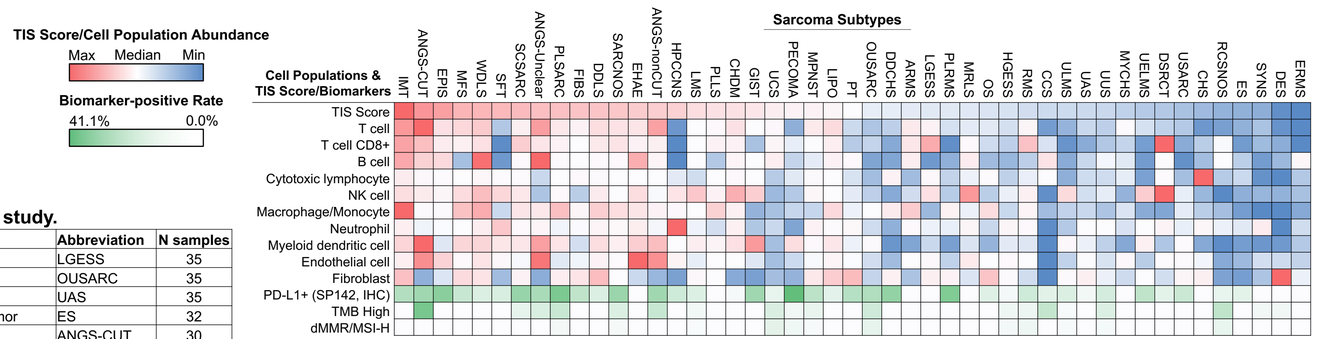
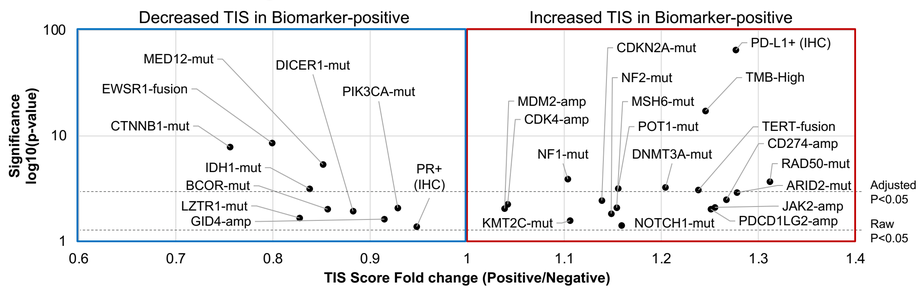


Figure 4. Biomarker association with TIS Scores



Biomarker-positive = mutated (mut), copy number amplified (amp), fusion-positive, IHC+, or TMB-High samples
Biomarker-negative = wild type, IHC-, or TMB-Low samples

Conclusions

- We found high median TIS and/or significant proportions of samples with a high TIS in sarcoma subtypes with previously demonstrated responsiveness to ICI, including MFS, PLSARC, LPS, and ANGS, while unresponsive tumor types such as RMS, DES, SYNS, and ES had low TIS.
- We further identified subtypes with high TIS but limited prior clinical data supporting ICI use, such as IMT, EPIS, MPNST, SFT, and PEComa.
- Our results warrant prospective exploration of TIS as a predictive biomarker for ICI use in sarcoma.

1. Keung EZ et al. *Clin Cancer Res* 2020;26:1258–66.
2. Cristescu R et al. Science 2018; 362(6411).
3. Becht E et al. Genome Biol. 2016;17(1):218.

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