MULTI-OMIC ANALYSIS OF 1,001 GIST TUMORS REVEALS IMMUNE ENRICHED SUBTYPES

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30th Anniversary

2025 ANNUAL MEETING

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Immune Checkpoint Inhibitors (ICI) have limited efficacy in GIST

What we know molecularly:

- Distinct molecular subtypes of GIST (*KIT*, *PDGFRA*, *SDH*-deficient, *NF1*, *BRAF*)
- Immunosuppressive TIME (Low CD8+ T cell, M2 macrophage dominant)
- Inflammation signatures correlate with high-risk features

What we know clinically:

- Immunogenicity is rare, hard to predict, with prior studies limited in sample size
- ICI predictor in carcinomas are not well studied in sarcomas

Opportunity:

- Can we leverage a published ICI signature of sensitivity using multiomic GIST data to define clinically meaningful cohorts?

Blay JY, et al. *Nat Rev Dis Primers*. 2021.
Zhao R, et al. *Cell Prolif*. 2019.
Wei ZW, et al. *EBioMedicine*. 2020.
Seligson ND, et al. *J Immunother Cancer*. 2024.
Roulleaux Dugage M, et al. *Front Immunol*. 2021.

Methods

Data source:
* Tempus AI, multi-modal database
* 1,001 samples, 926 GIST unique patients
* Sequenced between 2010-2024

Gene signature: Immune Profile Score (IPS)
* Predict outcomes in ICI-treated solid tumors
* Validated in >3,300 patients
* IPS-High: longer survival across 16 cancers
* Outperformed PD-L1, TMB, and MSI alone

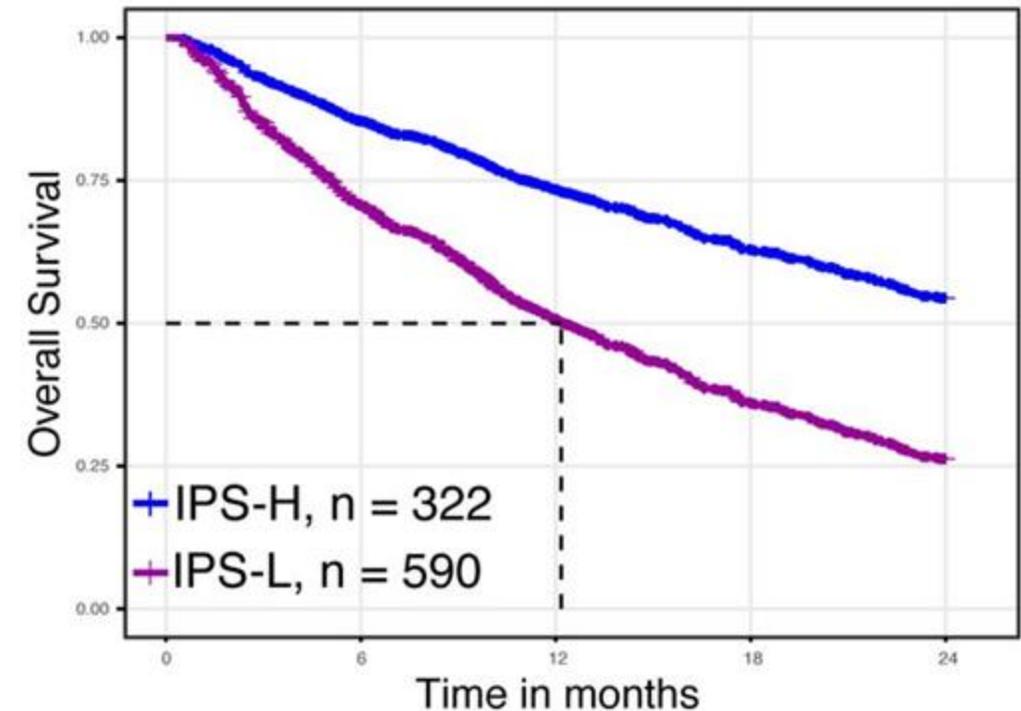| Pathology Cohort (N = 1,001)	
Age at diagnosis	62 years
Sex (Male)	54%
Metastatic Disease	375 (37%)
Tissue Site	
Stomach/Esophagus	331 (33%)
Small Intestine	213 (21%)
Other sites	457 (46%)
DNA Alterations	
KIT	789 (79%)
Exon 11	518 (52%)
Exon 9	102 (10%)
Other/Multiple	169 (17%)
PDGFRA	89 (9%)

IPS Identifies ICI Sensitive Cohorts in Carcinomas

Development and validation of the Immune Profile Score (IPS), a novel multiomic algorithmic assay for stratifying outcomes in a real-world cohort of patients with advanced solid cancer treated with immune checkpoint inhibitors

Alia D Zander,[1] Rossin Erbe,[1] Yan Liu,[1] Ailin Jin,[1] Seung Won Hyun,[1] Sayantoni Mukhopadhyay,[1] Ben Terdich,[1] Mario G Rosasco,[1] Nirali Patel,[1] Brett M Mahon,[1] A Kate Sasser,[1] Michelle A Ting-Lin,[1] Halla Nimeiri,[1] Justin Guinney,[1] Douglas Adkins,[2] Matthew Zibelman,[3] Kyle A Beauchamp,[1] Chithra Sangli,[1] Michelle M Stein,[1] Timothy Taxter,[1] Timothy Chan,[4] Sandip P Patel,[5] Ezra E W Cohen[1]
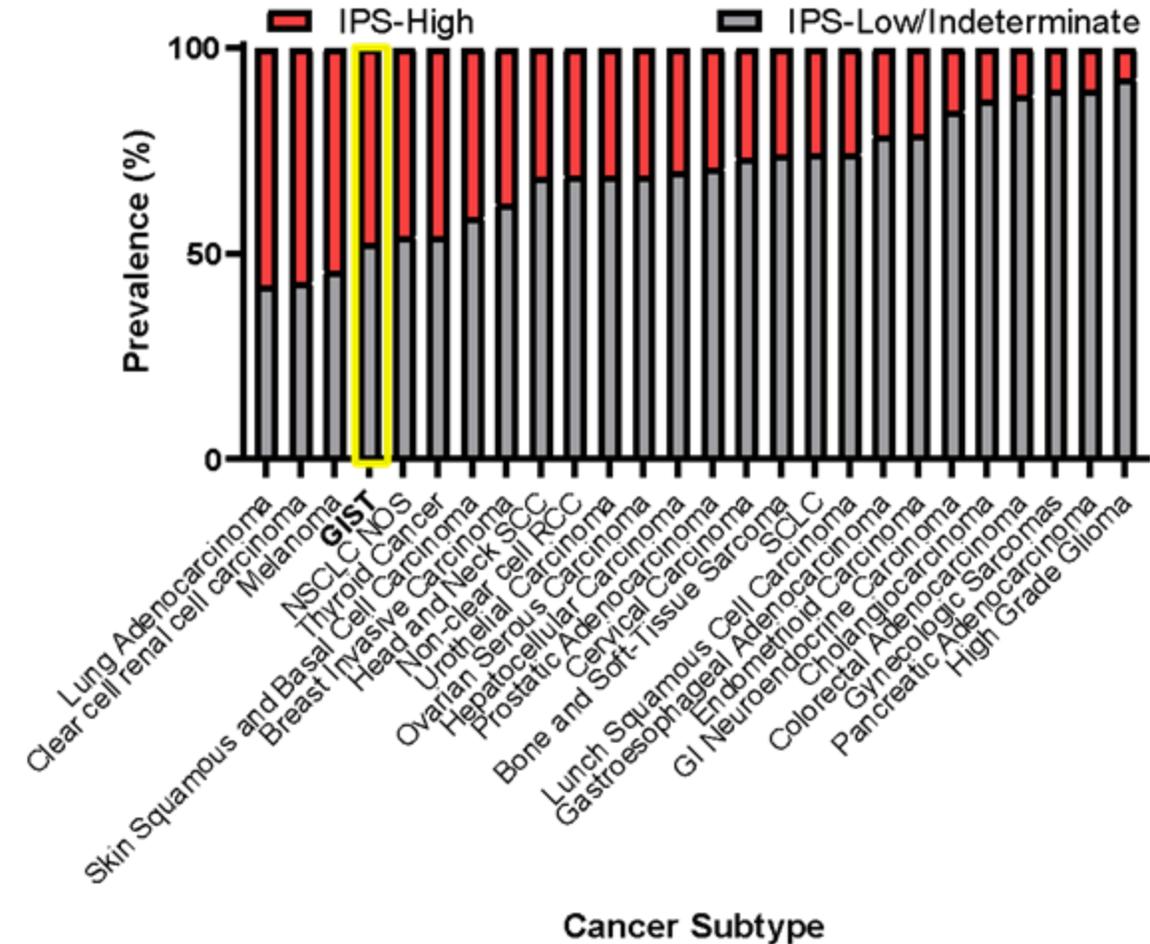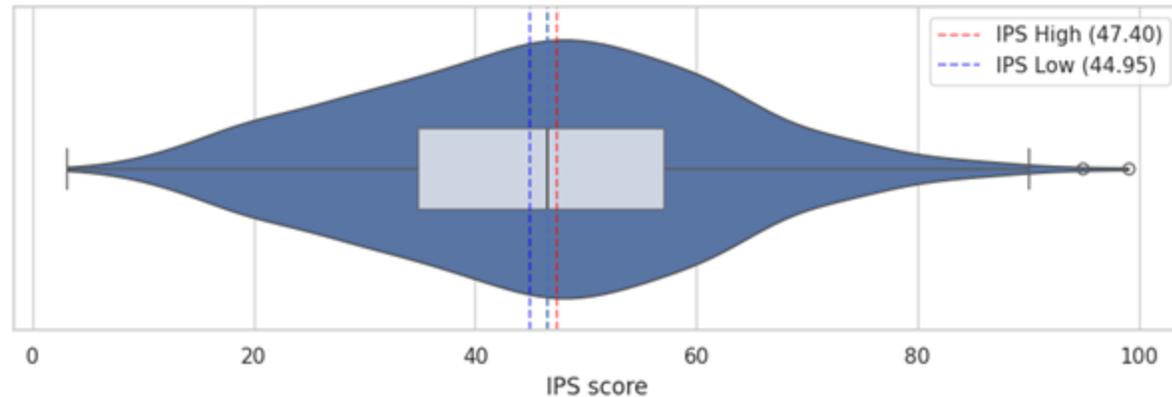
Biological role	IPS feature
Immune inflammation in tumor	CD74, Meta-analysis literature signature, SPP1, CXCL9, CD40
T cell exhaustion/ inhibition	CD276, CD274, IDO1, PDCD1LG2
Neoantigen burden	TMB
Tumor immune resistance	gMDSC signature, Tempus immune exhaustion signature

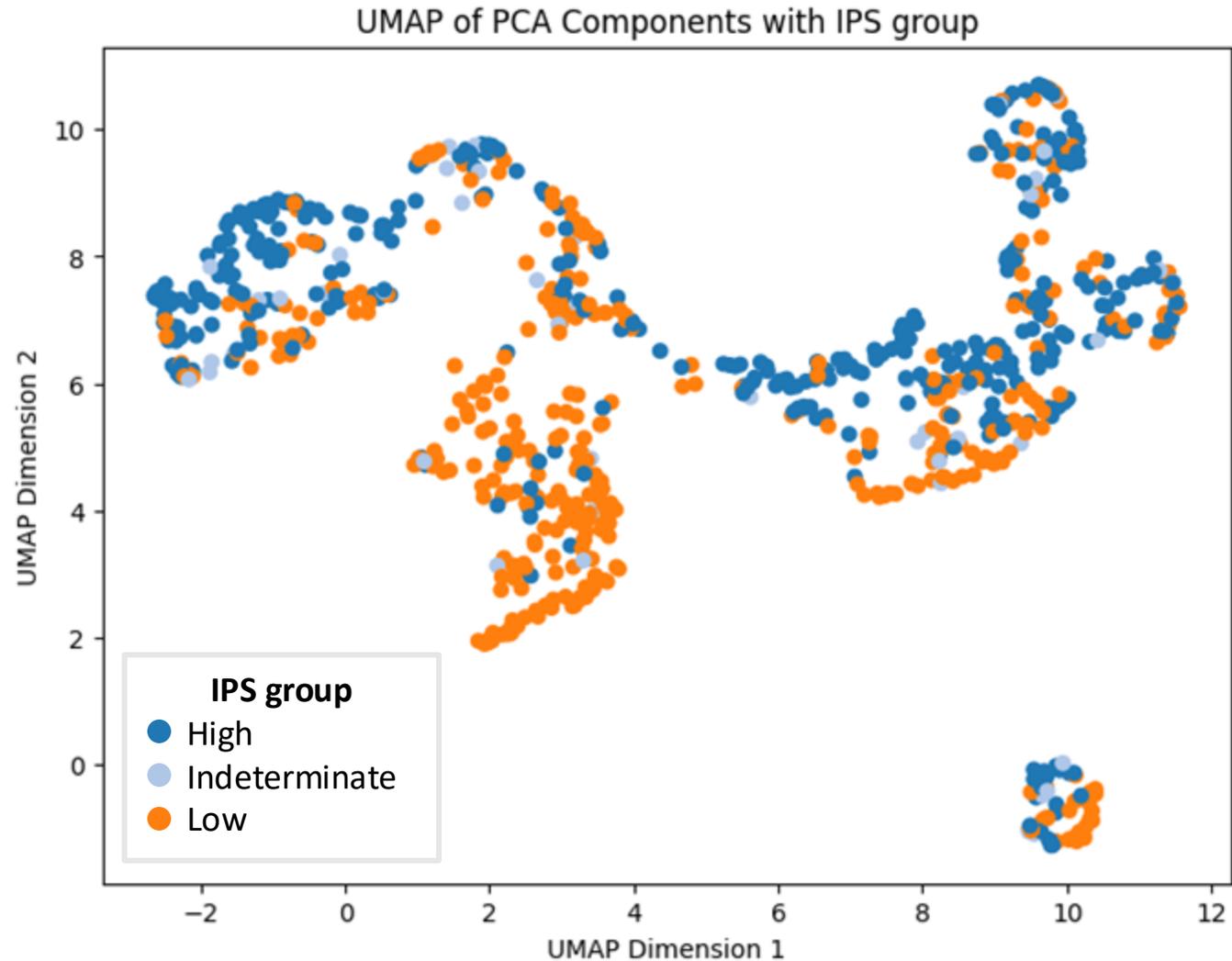**Overall Survival Following 1st Line ICI**

IPS-H, n = 322
IPS-L, n = 590

Zander AD, et al. *J Immunother Cancer*. 2025.

High Prevalence of IPS-H in GIST

GIST: 47.4% IPS-H; 46.5% IPS-L

Zander AD, et al. *J Immunother Cancer*. 2025.

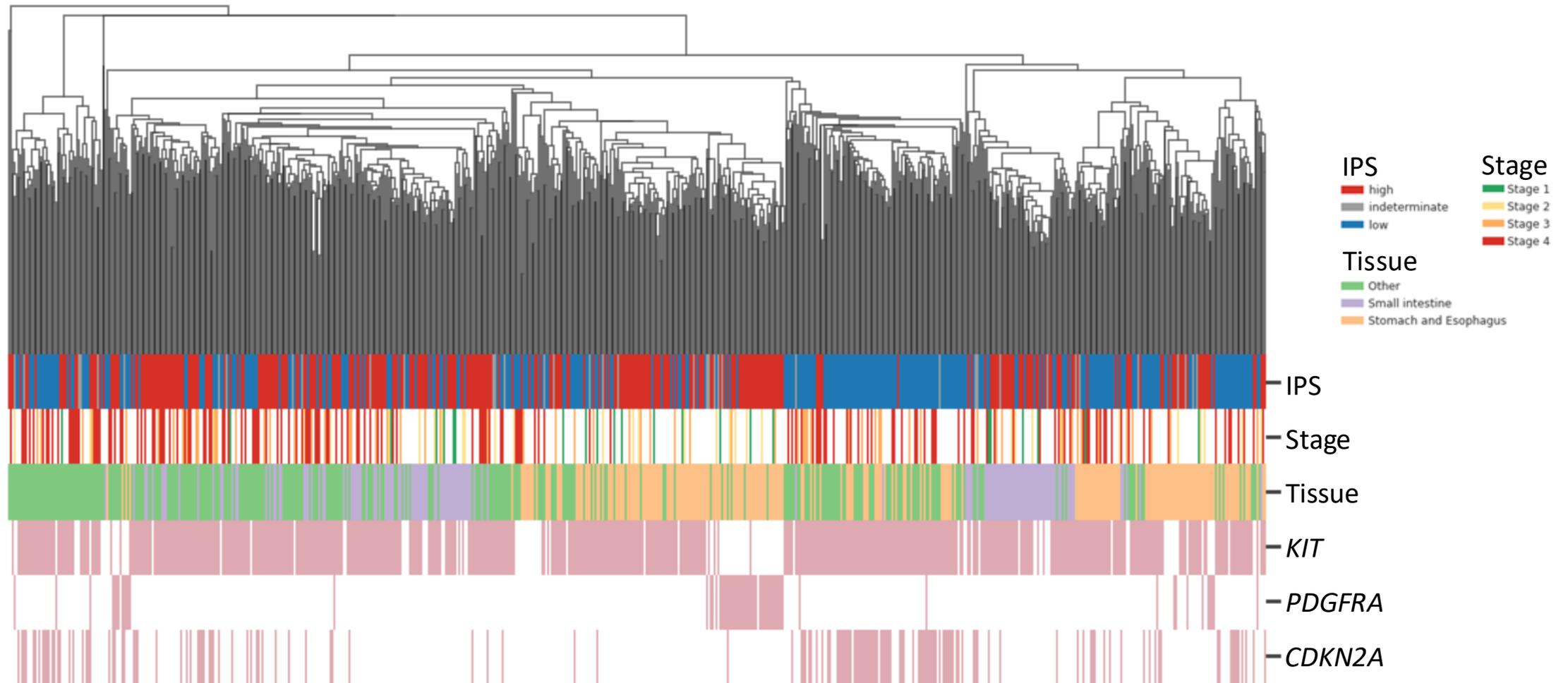# IPS-High GIST Cluster Into Distinct Subsets

UMAP of PCA Components with IPS group

IPS-High is Associated With Site and Stage
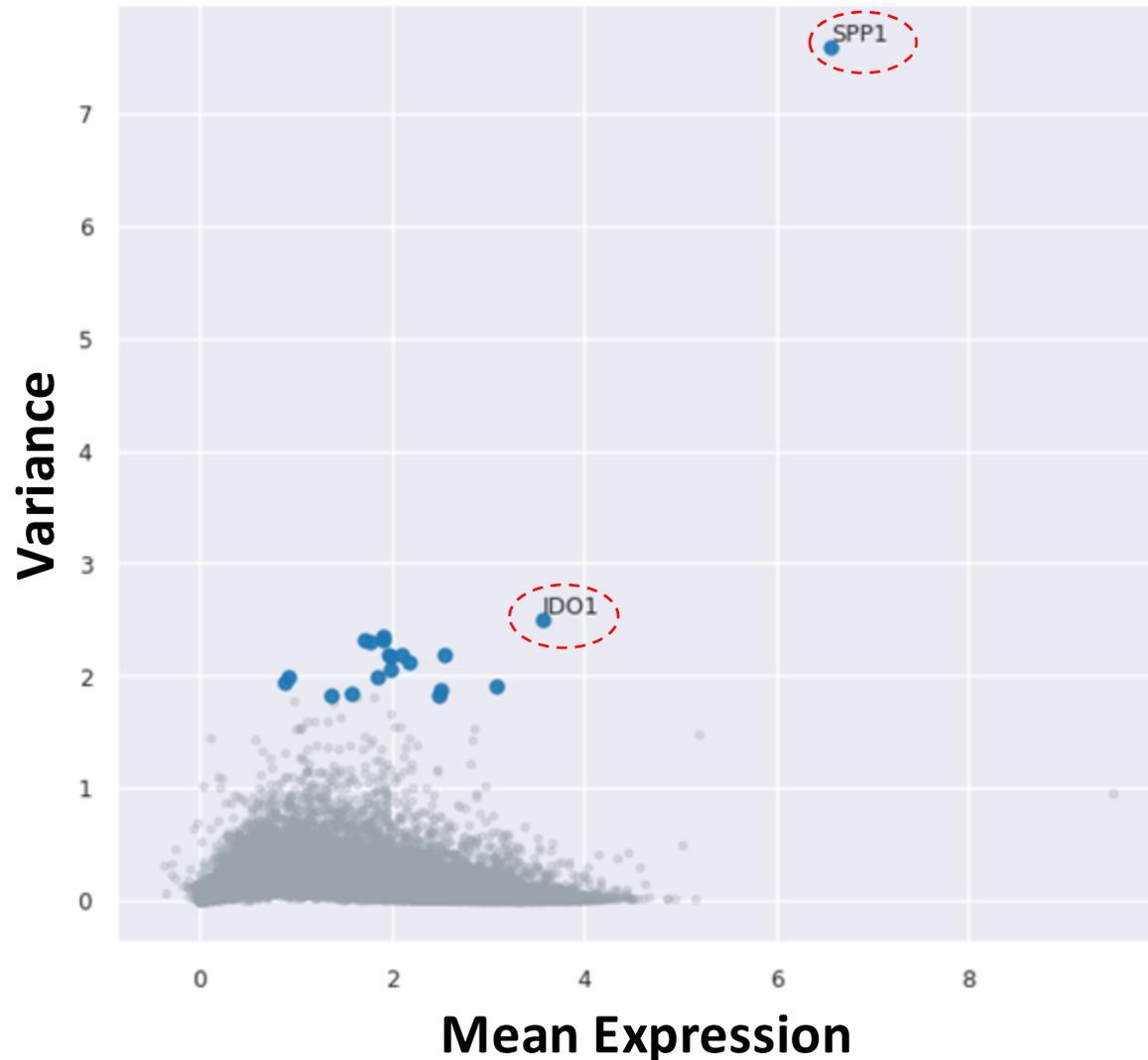
		IPS-H	IPS-L/ Indeterminate	p Value
Site	Stomach/ Esophagus	46.8%	53.2%	0.01
	Small Intestine	57.3%	42.7%	
Stage	1-3	55.0%	45.0%	0.005
	4	37.3%	62.7%	
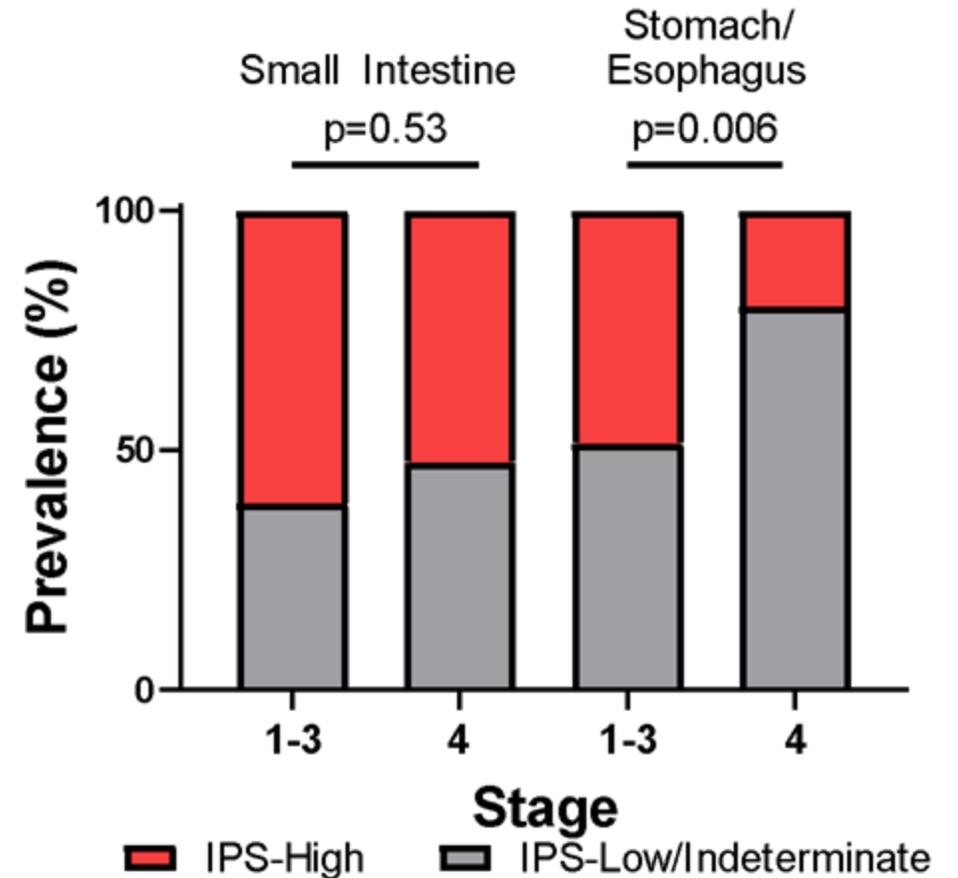
# IPS-H is associated with *PDGFRA, KIT* alterations

IPS signature genes *SPP1* and *IDO1* are noteworthy in GIST
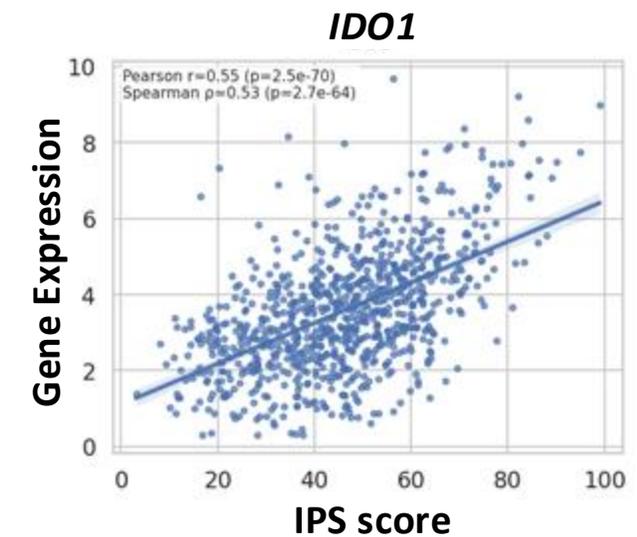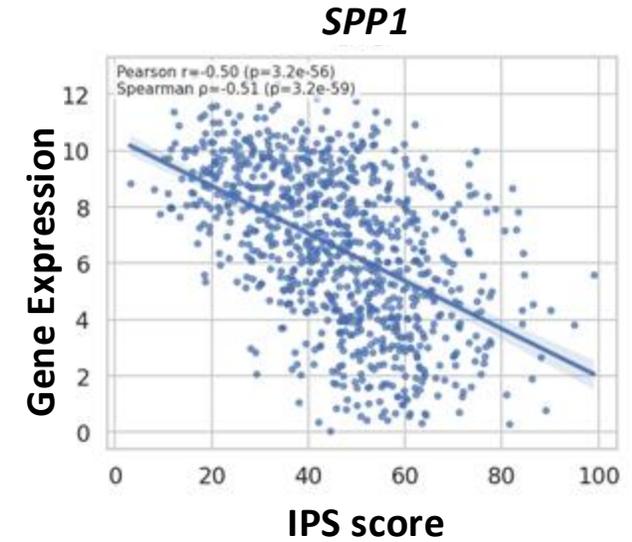
Conclusion

- Largest multi-omic evaluation of GIST patients to date
- Clinical and molecular biomarkers associated with a validated ICI signature
- Initial validation of immunosuppressive microenvironment
- Further studies required to confirm these findings
  - Integrated multi-omic analysis
  - TIME analysis
  - Clinical outcomes
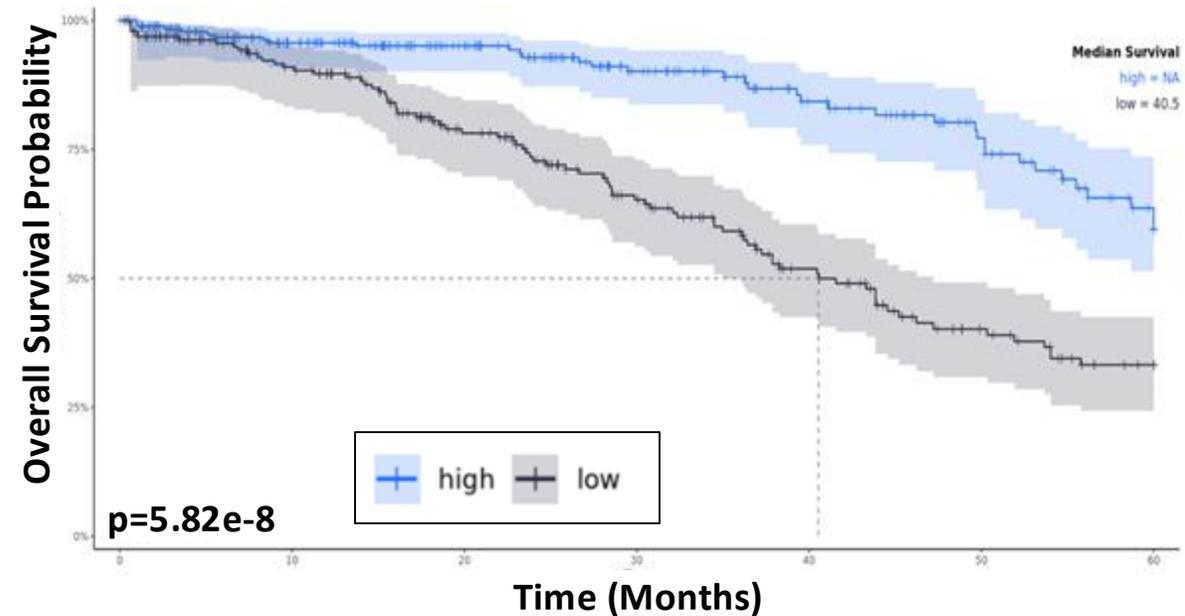
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