

Predictive gene signature for trabectedin efficacy in advanced soft-tissue sarcoma: A Spanish group for research in sarcoma (GEIS) study

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BACKGROUND: Predictive biomarkers of trabectedin represent a clinical unmet need to support the rational selection of this drug in the advanced soft-tissue sarcomas (STS) setting.¹ A few potential predictive biomarkers of trabectedin had been described in previous studies, including ERCC1, BRCA1, and HMGA1, among others²⁻⁶; however, they are based mostly on the analysis of single selected molecular factors. We presented here a predictive transcriptomic-based signature for trabectedin efficacy in STS.

METHODS: A total of 140 patients with advanced STS (at diagnosis or at any time from then on), with paraffin tumor block available, with at least 2 lines of treatment in advanced disease (one of them trabectedin) were included in this study. Gene expression was evaluated by direct transcriptomics, using HTG EdgeSeq Oncology Biomarkers Panel (HTG Molecular Diagnostics, Inc.; Tucson, AZ, USA). Raw counts were normalized to transcripts per million (TPM). Univariate Cox regression analysis was performed to find genes significantly associated with PFS and only those genes with significantly different curves were further retained (P < 0.05). These remaining genes were used as input to build a gene expression signature, using a multivariate Cox regression applying a Lasso penalty. Risk scores were calculated by multiplying the expression of every gene with its corresponding Cox regression coefficient.

RESULTS:

Table 1. Patient demographics

	N (%)		N (%)
Gender		Grade	
Male	65 (46)	1	18 (13)
Female	75 (54)	2	33 (24)
Stage at diagnosis		3	83 (59)
Localized	114 (81)	Not available	6 (4)
Metastatic	26 (19)	Location	
Sarcoma subtype		Somatic	93 (66)
Leiomyosarcoma	44 (31)	Visceral	47 (34)
Liposarcoma	32 (23)	Median follow up from diagnostic (months)	45
Synovial sarcoma	14 (10)	Median follow up from trabectedin line (months)	12
Undifferentiated pleomorphic sarcoma	14 (10)	Median Age, years (range)	51 (17-79)
Other	36 (26)		

Takeaway messages:

- Our study identified a new 29-gene-based signature that significantly predicts trabectedin efficacy in STS patients.
- Prospective validation of this predictive gene signature is warranted.

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Table 2. Relevance of each gene in the predictive gene-based signature or trabectedin efficacy

Gene	PFS Coefficient*	Gene	PFS Coefficient*
NES	0.2095511	PDGFA	0.0738301
HMGA1	0.1174332	HMGB3	0.1364676
NTRK2	-0.1103706	BOC	-0.0567087
TUBB3	0.0054917	CA12	-0.0392118
MGST1	-0.0013439	MAP2K4	0.0763498
KPNA2	0.1683102	GAS6	-0.0050561
TLR3	-0.0450361	LTBR	-0.0182079
ZHX2	-0.0019279	CDKN2A	-0.0016390
FST	-0.0024324	A2M	-0.0781384
FANCB	0.0875522	FGF18	-0.0085375
SLC7A5	0.0401899	CACNB2	-0.0728624
NCK2	0.1708447	PSMD2	0.0666337
DUSP10	0.0210266	NF1	-0.0361881
CACNA1C	-0.0612329	DMD	-0.0088567
FANCA	0.0212150		

*Positive coefficients are associated with worse PFS.

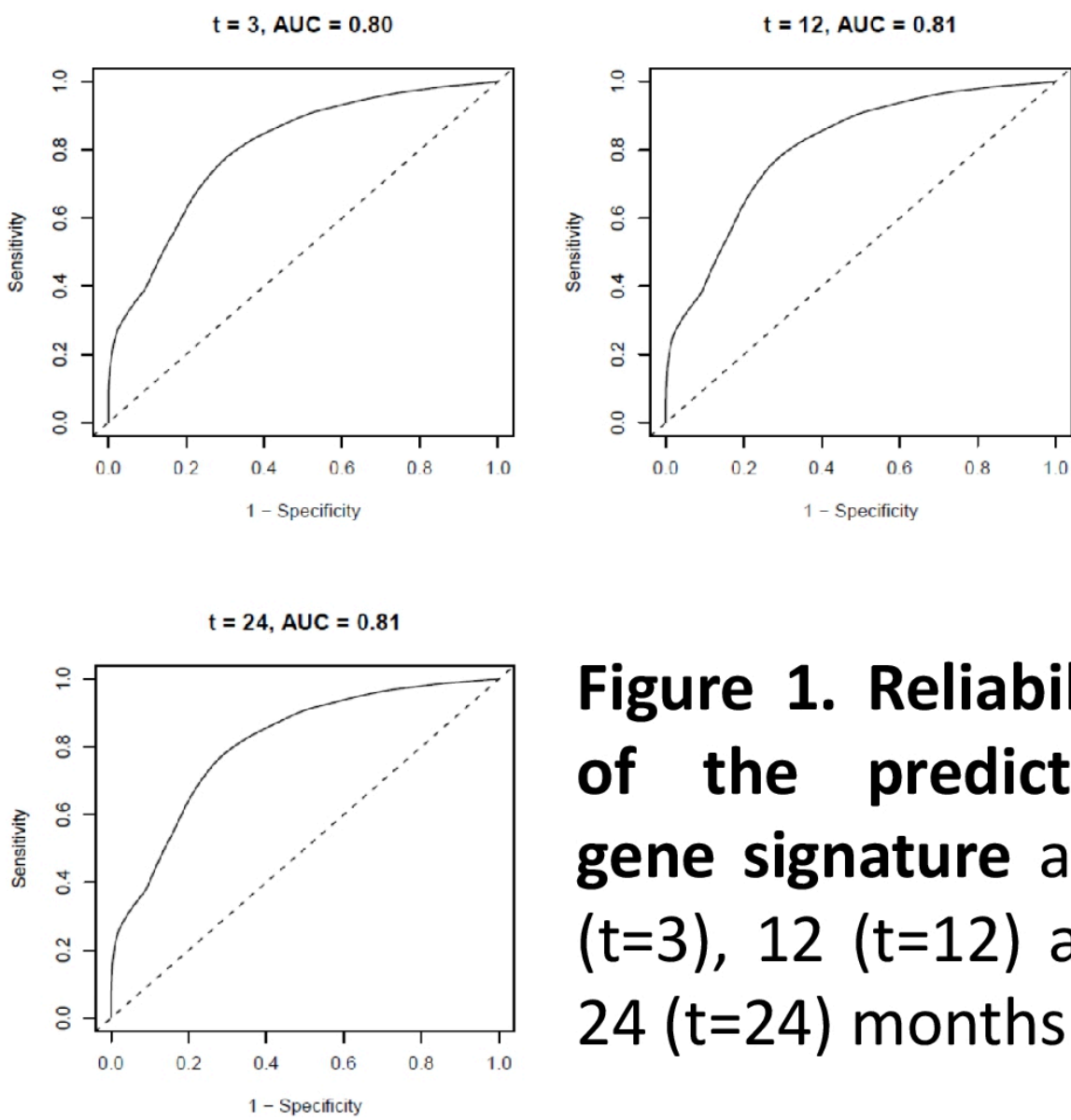


Figure 1. Reliability of the predictive gene signature at 3 (t=3), 12 (t=12) and 24 (t=24) months

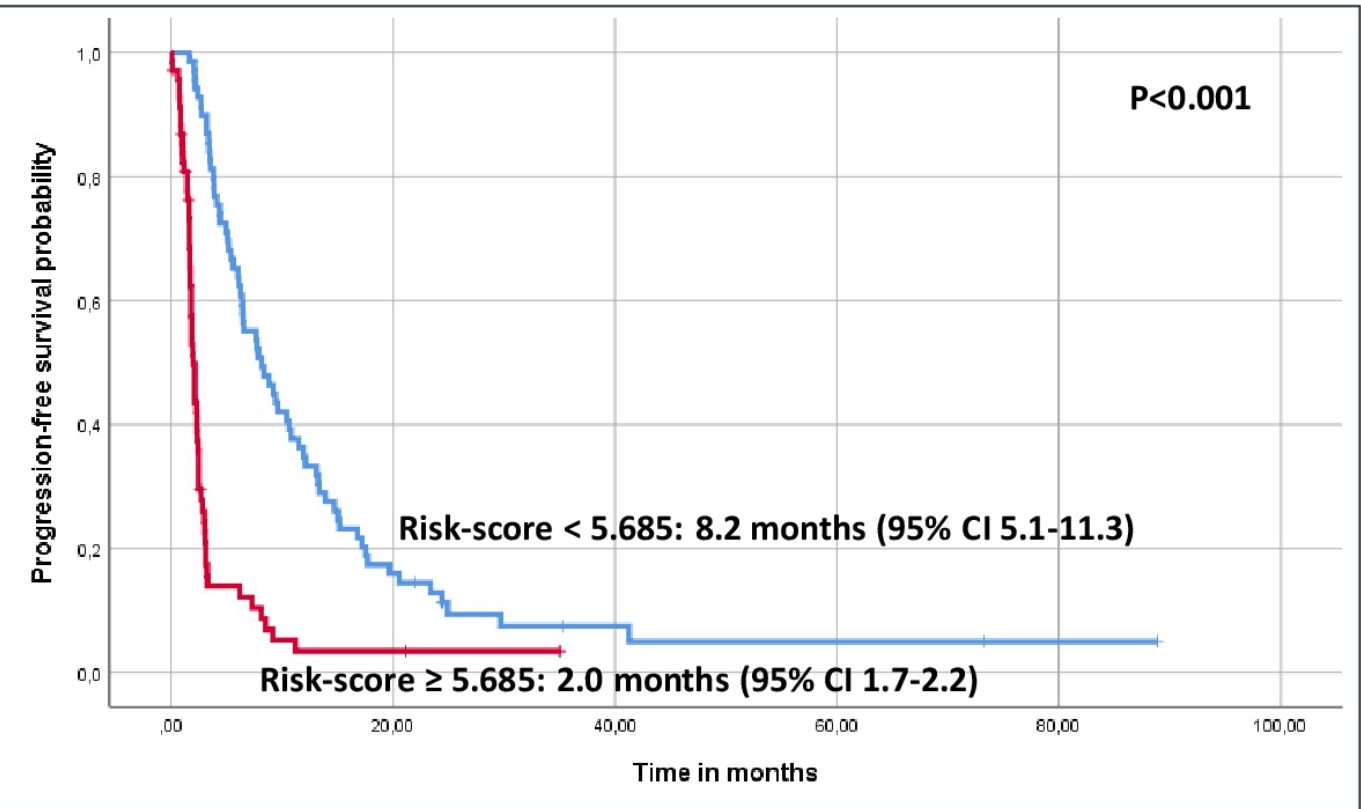


Figure 2. Survival analysis for trabectedin progression-free survival. The risk-score cut-off used was 5.685.

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