Prognostic value of *EZH2* expression for immunotherapy-based schemes in advanced soft-tissue sarcoma: A translational research from Spanish Group of Research on Sarcoma (GEIS)

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BACKGROUND

Immunotherapy-based treatments had shown to be active in several solid tumors, including in selected subtypes of sarcomas. IMMUNOSARC (NCT03277924) is a phase Ib/II trial [from Spanish (GEIS) and Italian (ISG) sarcoma groups], that tested the combination of nivolumab (anti-PD-1 inhibitor) plus sunitinib (anti-angiogenic agent) in advanced sarcomas. Among the 65 soft-tissue sarcoma (STS) patients (pts) enrolled, 48% were free of progression at 6 months, meeting the trial's primary endpoint.[1] EZH2 is the catalytic subunit of the Polycomb Repressive Complex 2 and it has been described to play an important role in the transcriptional repression of genes involved in T-cell migration and T-cell-mediated anti-tumor activity. The aim of this study was to explore the value of EZH2 gene expression as potential prognostic biomarker of the activity of immunotherapy-based schemes.

METHODS

- Sixty-four adult patients with selected subtypes of sarcoma have been enrolled during three years in the IMMUNOSARC clinical trial.
- Paraffin tumor blocks were prospectively collected at baseline (before Sunitinib initiation).
- Direct transcriptomics was performed using HTG Molecular Oncology Biomarker panel (HTG Molecular Diagnostics, Inc.; Tucson, AZ, USA).
- Data was normalized with DESeq2 and the cut-off of *EZH2* expression was calculated with MAXSTAT R package.
- *EZH2* gene expression was correlated with patient outcome.

RESULTS

	N (%)
Gender	
Male	38 (59%)
Female	26 (41%)
Extension at baseline	
Locally advanced	4 (6%)
Metastatic	60 (94%)
ECOG at baseline	
0	30 (47%)
1	34 (53%)
Sarcoma subtype	
Alveolar soft-part sarcoma	7 (11%)
Angiosarcoma	7 (11%)
Clear cell sarcoma	11 (17%)
Epithelioid sarcoma	7 (11%)
Extraskeletal myxoid chondrosarcoma	4 (6%)
Solitary fibrous tumor	7 (11%)
Synovial sarcoma	11 (17%)
Undifferentiated Pleomorphic Sarcoma	10 (16%)
Median Age, years (range)	40 (19-78)
Median *EZH2* expression in read counts (range)	884.79 (297.60-11231.55)

Table 1. Patient's characteristics , n=64

Gene	MAXSTAT Cut-off
EZH2	570.15 read counts

Table 2. MAXSTAT cut-off calculated for *EZH2* expression.

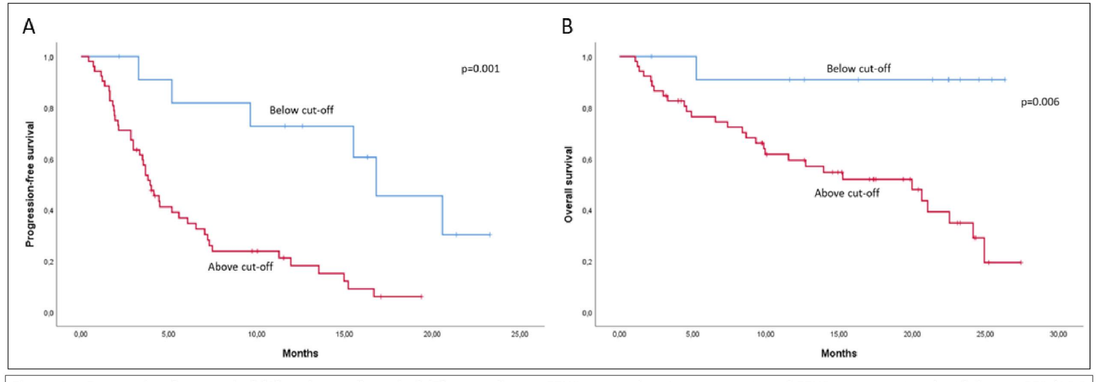

Figure 1 – Progression-free survival (A) and overall survival (B), according to EZH2 expression. Low expression of EZH2 was associated with better PFS (16.8 months vs. 3.9 months; p=0.001) and better OS (NR vs. 20.0 months; p=0.006).

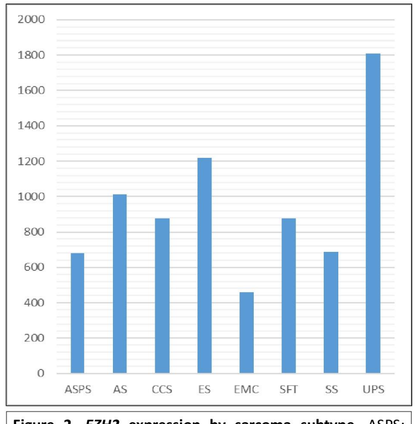

Figure 2. *EZH2* expression by sarcoma subtype. ASPS: alveolar soft-part sarcoma; AS: angiosarcoma; CCS: clear cell sarcoma; ES: epithelioid sarcoma; ECM: extraskeletal myxoid chondrosarcoma; SFT: solitary fibrous tumor; SS: synovial sarcoma and UPS; undifferentiated pleomorphic sarcoma.

CONCLUSIONS

- *Low expression of EZH2 was associated with better outcome in advanced STS patients treated with immunotherapy-based schemes.*
- *These results might support the rationale for the combination of EZH2 inhibitors with immune-modulating agents for future studies.*

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