Biological processes associated with the efficacy of sunitinib plus nivolumab in soft-tissue sarcoma: correlative studies of the IMMUNOSARC trial of Spanish (GEIS) and Italian (ISG) sarcoma groups

#1536

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Background

- **Soft-tissue sarcomas (STS)** are a group of rare, life-threatening, malignant tumors for which more efficient therapeutic options are necessary.
- Cancer immunotherapy has emerged as an active therapeutic option for several types of solid cancers.
- **IMMUNOSARC** was a European, single arm, non-randomized, open label, prospective phase Ib/II trial testing the **double inhibition of angiogenesis (sunitinib) and PD-1/PD-L1 axis (nivolumab) in bone and STS**.
- Since angiogenesis promotes immunosuppression, the combination therapy seeks **to convert a cold into an inflamed microenvironment**.
- The trial met its primary endpoint for STS, with **48% of patients free of progression at 6 months (m)**.[1]
- Part of the results from the **correlative studies** are herein presented.

Methods

- Sixty-eight adult patients with selected subtypes of sarcoma have been enrolled during three years.
- 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).
- Differential gene expression was analyzed according to 6-m progression-free survival (PFS). A negative binomial generalized linear model was applied, using edgeR R/Bioconductor package. Functional enrichment analysis was performed using enrichR package and Gene Ontology (GO) database.

Results

Table 1. First ten differentially expressed genes taking into account 6-m PFS rate.

	logFC	PValue
DLGAP5	1,09729	0,00002
AURKB	0,97972	0,00002
NR4A3	-1,93734	0,00003
MAOB	-2,20566	0,00003
WHSC1	0,87751	0,00008
NUF2	0,93483	0,00010
ABHD2	-1,62988	0,00011
CDC20	1,33925	0,00013
ECT2	1,12292	0,00013
NUSAP1	1,10916	0,00015
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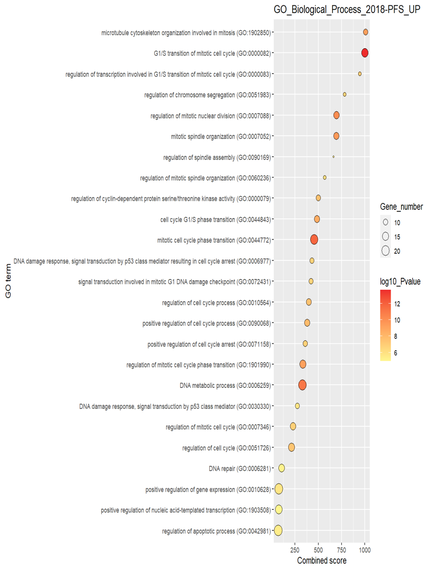

Figure 1. GO analysis showing Biological Processes associated to selected up-regulated genes taking into account 6-m PFS rate.

Figure 2. GO analysis showing Biological Processes associated to selected down-regulated genes taking into account 6-m PFS rate.

Table 2. First ten differentially expressed genes taking into account Overall Survival (OS).

	logFC	PValue
PLA2G2A	3,48814	0,00001
ALDH1A1	-2,41818	0,00004
ITGA8	-1,75482	0,00008
TICAM1	0,74314	0,00028
NR4A3	-1,67382	0,00033
FAM105A	-1,00283	0,00034
S100B	2,46255	0,00036
PDGFB	-0,84179	0,00037
PDGFD	-1,48592	0,00038
CHAD	-2,86794	0,00047
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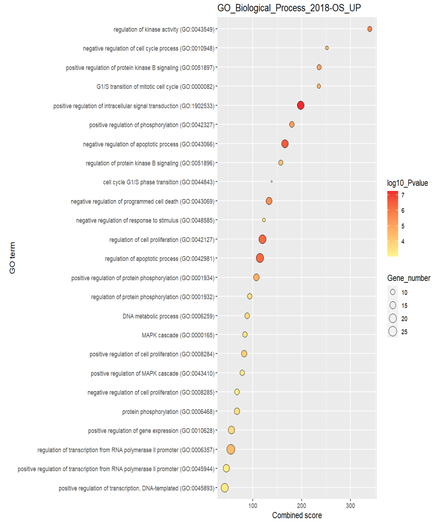

Figure 3. GO analysis showing Biological Processes associated to selected up-regulated genes taking into account OS.

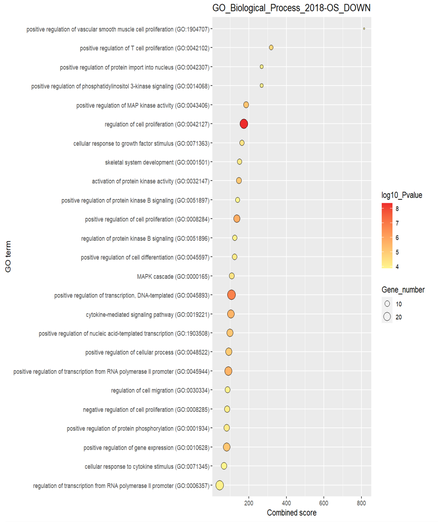

Figure 4. GO analysis showing Biological Processes associated to selected down-regulated genes taking into account OS.

Conclusions

- **DNA damage repair (DDR) and cell cycle-related processes seemed to be associated with worse outcome to immunotherapy-based schemes.**
- **Further studies are warranted to understand the potential added value of cell cycle inhibitors or DDR-targeted therapies to immunotherapy.**

Acknowledgments

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Disclosures

SL has nothing to disclose.

References

1.Martin-Broto J, Hindi N, Grignani G, et al. Nivolumab and sunitinib combination in advanced soft tissue sarcomas: a multicenter, single-arm, phase Ib/II trial. J Immunother Cancer. 2020 Nov;8(2):e001561.

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