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► **To cite this version:**

Matthieu Roulleaux-Dugage, Antoine Italiano. New immunotherapy strategies for patients with sarcomas: highlights from the 2023 ASCO annual meeting. *Journal of Hematology and Oncology*, 2023, 16, 10.1186/s13045-023-01486-6 . hal-04431492

HAL Id: hal-04431492

<https://hal.science/hal-04431492>

Submitted on 1 Feb 2024

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EDITORIAL

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New immunotherapy strategies for patients with sarcomas: highlights from the 2023 ASCO annual meeting

Matthieu Roulleaux-Dugage² and Antoine Italiano^{1,2,3*}

Abstract

Immunotherapy has revolutionized cancer treatment, but currently, immuno-oncology agents have not been approved for patients with soft tissue sarcomas. However, there is growing evidence suggesting that immunotherapy could be an effective therapeutic strategy for this group of diseases. Here, we reviewed the latest advances of immunotherapy trials from the 2023 American Society of Clinical Oncology Annual Meeting, including some novel and encouraging combination regimens. Further research is still needed to fully understand the optimal use of these agents in sarcoma treatment.

Considering the recent advancements in immune checkpoint inhibitors (ICIs), there remains limited and controversial human data supporting the effectiveness of immunotherapy in soft tissue sarcomas (STS) based on the current clinical trials.

A recent analysis of pooled data from nine clinical trials investigating ICIs in sarcomas, comprising 384 patients, revealed an overall objective response rate (ORR) of 15.1% [1]. However, when excluding alveolar soft-part sarcoma, a rare subtype highly responsive to PD-1/PD-L1 monoclonal antibodies, the ORR dropped to 9.8% [1].

During the latest American Society of Clinical Oncology (ASCO) meeting, several studies presented combination therapeutic strategies which aimed at improving response rates to ICIs (Table 1). Three studies explored the combination of ICI with different chemotherapy regimens.

Reichardt et al. reported the findings of the NITRA-SARC study, which investigated the safety and efficacy of a regimen combining the cytotoxic agent trabectedin and the PD1 antagonist nivolumab in patients with advanced STS [2]. The study rationale was based on preclinical data suggesting that trabectedin could enhance the activity of immune-modulating agents by influencing the tumor microenvironment and reducing tumor-associated macrophages [3]. Trabectedin has shown synergistic effects with PD1 inhibition in preclinical models [4]. Forty-three patients with L-sarcomas and 49 patients with other sarcomas were enrolled. Safety was manageable, with the most frequent grade 3/4 adverse events being leucopenia, anemia, nausea, vomiting, and increased liver enzymes. The overall response rate was 10.9% (10% for cohort A and 13% for cohort B). Median progression-free survival (PFS) and overall survival (OS) for cohort A were 5.5 months (95% CI 2.2–11.3) and 18.7 months (95% CI 13.7–31.3), respectively. For cohort B, median PFS and OS were 2.3 months (95% CI 1.8–2.6) and 5.6 months (95% CI 3.5–8.6), respectively. However, the observed activity in this study did not surpass the expected outcomes with trabectedin alone.

Wilky et al. presented the results of a phase 2 study that investigated the combination of doxorubicin with

*Correspondence:

Antoine Italiano

a.italiano@bordeaux.unicancer.fr

¹ Department of Medicine, Institut Bergonié, 229 Cours de l'Argonne, 33000 Bordeaux, France

² DITEP, Gustave Roussy, Villejuif, France

³ Faculty of Medicine, University of Bordeaux, Bordeaux, France



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Table 1 Clinical trials investigating immunotherapy-based regimens in patients with advanced soft-tissue sarcomas (ASCO 2023)

Reference	Population	Line	Phase	Intervention	n	ORR—n (%)	mPFS (months)	mOS (months)	Safety results
7	LMS	First line	Ib	Doxorubicin 75mg/m ² D1 + DTIC 400mg/m ² D1-D2 + Nivolumab (240mg/360mg) D2 q3w for 6 cycles Followed by Nivolumab q3w 1 year as maintenance	16	9 (56.2%)	8.7	–	20% G3 Anemia 30% G3-4 Neutropenia 5% (n = 1) G3 Febrile neutropenia
5	All	First or Second line (no prior anthracycline/CB)	II	Balsitlimab (αPD-1) 300mg q3w for 2 years Zalifrelimab (αCTLA-4) 1 mg/kg q6w 4 cycles Doxorubicin 75mg/m ² q3w 6 cycles start at C1 (stage 2, n=14) or C2 (stage 1, n= 19)	33	10 (33.3%)	5.6	14.5	12% G3 + irAE (2 colitis)
13	LMS	First or Second line (no prior anthracycline)	Ib	TTH-621 (αCD47 IgG1) 0.2mg/kg D1, D8—q3w Doxorubicin 75mg/m ² q3w up to 6 cycles	23	5 (21.7%)	–	–	8.7% G3 + Anemia 43.5% G3 + Neutropenia 4.3% (n = 1) G3 + Febrile neutropenia 4.3% (n = 1) G3 + pancreatitis
10	All	Second line and beyond	II	Arm A: cabozantinib 60 mg daily vs Arm B: Cabozantinib 40 mg daily + Ipilimumab (1 mg/kg) + Nivolumab (3 mg/jg) q3w for 4 cycles Followed by Cabozantinib 40 mg daily plus Nivolumab 480 mg q4w 1 year as maintenance	Arm A: 36 Arm B: 69	Arm A: 2 (6%) Arm B: 7 (11%)	Arm A: 3.75 Arm B: 5.36	Arm A: 22.6 Arm B: not reached	15.9% G3 Liver enzymes increase
8	Angiosarcomas	Previously treated with taxanes (ICB and VEGFR-TKI naive)	II	Nivolumab 480mg q4w Cabozantinib 40mg daily	22	13 (59.0%)	9.6	NR	36.4% G3 + TRAE

zalifrelimab (a CTLA-4 inhibitor) and balstilimab (a PD1 inhibitor) in patients with advanced STS [5]. Doxorubicin has been shown to induce immunogenic cell death (ICD), triggering an immune response against dead-cell antigens and facilitating tumor antigen presentation and T-cell activation [6]. The study hypothesized that combining doxorubicin with zalifrelimab and balstilimab would improve the 6-month progression-free survival (PFS) rate compared to historical doxorubicin. Thirty patients with various STS types were enrolled, and four patients (12%) experienced grade 3/4 immune-related adverse events (colitis, pancreatitis, diabetic ketoacidosis, hypertriglyceridemia, hypothyroidism). The 6-month non-progression rate was 46.4% (95% CI 28–66), failing to reach the study's objective of 63%.

Martin-Broto et al. reported the efficacy and safety data of a combination of nivolumab with the doxorubicin/dacarbazine chemotherapy regimen [7]. The rationale for this study was like the one reported by Wilky et al., based on doxorubicin's potential to induce immunogenic cell death and synergize with PD1 targeting [6]. Thirty-six patients with advanced leiomyosarcomas were included, with 16 patients evaluable for efficacy. Safety was acceptable, with 15% of patients experiencing grade 3/4 neutropenia. Nine patients achieved an objective response, six had stable disease, and one had progressive disease. The median PFS was 8.7 months (95% CI 7.9–9.3).

In addition to chemotherapy combinations, studies have reported safety and efficacy data for combining ICIs with tyrosine kinase inhibitors. Grilley-Olson et al. presented the results of the Alliance A091902 study, a phase 2 study investigating the combination of nivolumab with cabozantinib in patients with advanced angiosarcomas who had previously failed taxane-based chemotherapy [8]. Previous evidence suggested that angiosarcomas might be more responsive to immune checkpoint inhibition [9]. Targeting angiogenesis with a multi-tyrosine kinase inhibitor and an ICI represented therefore a promising strategy for this subtype. Twenty patients participated in the study, and the combination was well-tolerated, with the most frequent treatment-related adverse event being hypertension. The objective response rate was 59%, with durable responses and a median PFS of 9.6 months (5.4-NR).

Cabozantinib was also combined with nivolumab and ipilimumab in a randomized phase 2 study comparing this combination to cabozantinib alone [10]. Sixty-nine patients were randomized to the combination arm, and 36 received cabozantinib monotherapy. The combination arm observed seven objective responses (11%), while the monotherapy arm had two (6%). The median PFS was 5.3 months (95% CI 4.1–11) for the combination and 3.5 months (95% CI 1.1–7.7) for monotherapy ($p=0.016$).

The median OS was 22.6 months (95% CI 14.8-NA) for the combination and not reached (9.6-NA) for monotherapy ($p=0.42$). Notably, among the 19 patients from the cabozantinib monotherapy arm who were allowed to cross over to the combination arm, seven showed tumor shrinkage, suggesting at least an additive effect of the combination with nivolumab and ipilimumab.

Apart from immune checkpoint inhibition, other immune targets hold therapeutic potential for sarcomas. STS often exhibit heavy infiltration by tumor-associated macrophages (TAM) [11]. Additionally, STS, including leiomyosarcomas, express high levels of CD47, which suppresses phagocytic activity and enables tumor cells to evade immune-mediated clearance [12]. Movva et al. presented the results of a phase 2 study investigating TTI-621 in combination with doxorubicin in patients with advanced leiomyosarcomas [13]. Doxorubicin has been shown to promote tumor cell phagocytosis by inducing preapoptotic translocation of calreticulin to the cell surface [14]. Preclinical studies demonstrated enhanced anti-tumor activity and increased macrophage-mediated killing with the combination of doxorubicin and CD47-targeted antibodies [15]. TTI-621 is a recombinant soluble fusion protein that combines the Fc region of human IgG1 with the CD47 binding domain of human SIRP α , overriding CD47-mediated inhibition of phagocytosis and providing pro-phagocytic stimulation. Twenty-three patients were enrolled in the study, and the most frequent treatment emergent adverse events included neutropenia, anemia, and thrombocytopenia. Notably, five patients (21.7%) achieved an objective response.

It is crucial to emphasize that all these studies included patients without utilizing any biomarker-based selection strategy. While certain histological subtypes, such as undifferentiated pleomorphic sarcomas or de-differentiated liposarcomas, have shown anecdotal responses and potential sensitivity to treatment [9, 16], the current biomarker for immunotherapy in several epithelial tumors, PD-L1 expression, is not relevant for STS. Although PD-L1 expression of $\geq 1\%$ in tumor cells was observed in over 15% of patients, it did not demonstrate a clear correlation with clinical benefits [1]. Furthermore, the tumor mutation burden was generally low across all histological subtypes, with a median burden of fewer than two mutations per megabase [17].

Recent data have suggested that the presence of tertiary lymphoid structures (TLS) may serve as a relevant strategy to identify patients with advanced STS who are more likely to benefit from immune checkpoint inhibition [18]. However, TLS are present in only 20% of STS cases. Therefore, investigating combination strategies to convert “cold tumors” into “hot tumors” and enhance their sensitivity to ICIs is of paramount importance.

The studies presented at ASCO explored combinations of immune-oncology agents with various drugs, including cytotoxic agents and VEGFR inhibitors. However, the main limitation of these studies is that almost all of them were single-arm and/or did not include analysis of sequential blood or tissue samples. Except for the study investigating the combination of nivolumab plus cabozantinib in angiosarcomas [8], the response and survival rates observed were similar to those seen with the current standard of care. Unfortunately, the absence of sequential tumor biopsies and randomization hinders drawing definitive conclusions regarding the influence of these combinations on the tumor microenvironment and their potential correlation with clinical benefits.

Acknowledgements

Not applicable.

Author contributions

AI drafted the manuscript. MRD prepared the table. All authors participated in the process of revising the manuscript. All authors read and approved the final manuscript.

Funding

The study is supported by a grant of the Agence Nationale de la Recherche "ANR-21-RHUS-0010".

Declarations

Ethics approval and consent to participate

This is not applicable for this summary.

Consent for publication

This is not applicable for this summary.

Competing interests

The authors declare no competing interests.

Received: 20 July 2023 Accepted: 24 July 2023

Published online: 08 August 2023

References

- Italiano A, Bellera C, D'Angelo S. PD-1/PD-L1 targeting in advanced soft-tissue sarcomas: a pooled analysis of phase II trials. *J Hematol Oncol*. 2020;13(1):55.
- Reichardt P, Andreou D, Flörcken A, Groß T, Richter S, Kessler T, Kortüm M, Schmidt CA, Kasper B, Wardelmann E, Benedict A, Sookthai D, Wilhelm Mueller D, Pink D. Efficacy and safety of nivolumab and trabectedin in pretreated patients with advanced soft tissue sarcomas (STS): Results of a phase II trial of the German Interdisciplinary Sarcoma Group (GISG-15, NitraSarc). *J Clin Oncol* 2023;41(16_suppl): 11500.
- Germano G, Frapolli R, Belgiovine C, Anselmo A, Pesce S, Liguori M, et al. Role of macrophage targeting in the antitumor activity of trabectedin. *Cancer Cell*. 2013;23:249–62.
- Ratti C, Botti L, Cancila V, Galvan S, Torselli I, Garofalo C, et al. Trabectedin overrides osteosarcoma differentiative block and reprograms the tumor immune environment enabling effective combination with immune checkpoint inhibitors. *Clin Cancer Res*. 2017;23:5149–61.
- Wilky B, Maleddu A, Mailhot A, Cartwright C, Gao D, Tellez CM, Powers K, Kemp L, Therrien N, Patel JM, Elan Grossman J, O'Day S, Elias AD. A single-arm, open-label phase 2 trial of doxorubicin plus zalifrelimab, a CTLA-4 inhibitor, with balstilimab, a PD-1 inhibitor, in patients with advanced metastatic soft tissue sarcomas. A single-arm, open-label phase 2 trial of doxorubicin plus zalifrelimab, a CTLA-4 inhibitor, with balstilimab, a PD-1 inhibitor, in patients with advanced metastatic soft tissue sarcomas. *J Clin Oncol* 2023;41(16_suppl): 11501.
- Kepp O, Senovilla L, Vitale I, Vacchelli E, Adjemian S, Agostinis P, Apetoh L, Aranda F, Barnaba V, Bloy N, Bracci L, Breckpot K, Brough D, Buqué A, Castro MG, Cirone M, Colombo MI, Cremer I, Demaria S, Dini L, Eliopoulos AG, Faggioni A, Formenti SC, Fučíková J, Gabriele L, Gaipal US, Galon J, Garg A, Ghiringhelli F, Giese NA, Guo ZS, Hemminki A, Herrmann M, Hodge JW, Holdenrieder S, Honeychurch J, Hu HM, Huang X, Illidge TM, Kono K, Korbelik M, Krysko DV, Loi S, Lowenstein PR, Lugli E, Ma Y, Madeo F, Manfredi AA, Martins I, Mavilio D, Menger L, Merendino N, Michaud M, Mignot G, Mossman KL, Multhoff G, Oehler R, Palombo F, Panaretakis T, Pol J, Proietti E, Ricci JE, Riganti C, Rovere-Querini P, Rubartelli A, Sistigu A, Smyth MJ, Sonnemann J, Spisek R, Stagg J, Sukkurwala AQ, Tartour E, Thorburn A, Thorne SH, Vandenabeele P, Velotti F, Workenhe ST, Yang H, Zong WX, Zitvogel L, Kroemer G, Galluzzi L. Consensus guidelines for the detection of immunogenic cell death. *Oncoimmunology*. 2014;3(9): e955691.
- Martin Broto J, Diaz Beveridge R, Moura D, Ramos R, Martinez-Trufero J, Carrasco-Garcia I, Lopez-Pousa A, Gonzalez-Billalabeitia E, Gutierrez A, Cruz Jurado J, Ana Sebio, Ana Herrero Heras, Claudia Maria Valverde Morales, Nadia Hindi ImmunoSarc2: A Spanish Sarcoma Group (GEIS) phase Ib trial of doxorubicin and dacarbazine plus nivolumab in first line treatment of advanced leiomyosarcoma. *J Clin Oncol* 2023;41(16_suppl): 11502.
- Grilley-Olson JE, Allred JB, Schuetze S, Davis EJ, Wagner MJ, Stewart Poklepovic A, Waechter B, Riedel RF, WELLIVER MX, Berg SA, George S, Robinson SI, Googe PB, D'Angelo SP, Schwartz GK. A multicenter phase II study of cabozantinib + nivolumab for patients (pts) with advanced angiosarcoma (AS) previously treated with a taxane (Alliance A091902). *J Clin Oncol* 2023;41(16_suppl): 11503.
- D'Angelo SP, Mahoney MR, Van Tine BA, Atkins J, Milhem MM, Jahagirdar BN, et al. Nivolumab with or without ipilimumab treatment for metastatic sarcoma (Alliance A091401): two open-label, non-comparative, randomised, phase 2 trials. *Lancet Oncol*. 2018;19(3):416–26.
- Van Tine BA, Eulo V, Toeniskoetter J, Ruff T, Luo J, Kemp L, Moreno Tellez C, Weiss MC, Hirbe AC, Frederick Meyer C, Elias AD, Diamond M, Hartner LP, Bui N, Ganjoo KN, Maki RG, Wilky BA. Randomized phase II trial of cabozantinib combined with PD-1 and CTLA-4 inhibition versus cabozantinib in metastatic soft tissue sarcoma. *J Clin Oncol* 2023;41(17_suppl): LBA11504.
- Kostine M, Braire-de Bruijn IH, Cleven AHG, Vervat C, Corver WE, Schilham MW, Van Beelen E, van Boven H, Haas RL, Italiano A, Cleton-Jansen AM, Bovée JVMG. Increased infiltration of M2-macrophages, T-cells and PD-L1 expression in high grade leiomyosarcomas supports immunotherapeutic strategies. *Oncoimmunology*. 2017;7(2): e1386828.
- Willingham SB, Volkmer JP, Gentles AJ, Sahoo D, Dalerba P, Mitra SS, Wang J, Contreras-Trujillo H, Martin R, Cohen JD, Lovelace P, Scheeren FA, Chao MP, Weiskopf K, Tang C, Volkmer AK, Naik TJ, Storm TA, Mosley AR, Edris B, Schmid SM, Sun CK, Chua MS, Murillo O, Rajendran P, Cha AC, Chin RK, Kim D, Adorno M, Raveh T, Tseng D, Jaiswal S, Enger PØ, Steinberg GK, Li G, So SK, Majeti R, Harsh GR, van de Rijn M, Teng NN, Sunwoo JB, Alizadeh AA, Clarke MF, Weissman IL. The CD47-signal regulatory protein alpha (SIRPα) interaction is a therapeutic target for human solid tumors. *Proc Natl Acad Sci USA*. 2012;109(17):6662–7.
- Movva S, Druta M, Davis LE, Monga V, Milhem MM, Bailey HH, Chugh R, Bruns I, Allgood VE, Chawla SP. Safety and clinical activity of TTI-621 in combination with doxorubicin in patients with unresectable or metastatic high-grade leiomyosarcoma: Results from the low-dose expansion cohort. *J Clin Oncol* 2023;41(16_suppl): 11508.
- Obeid M, Tesniere A, Ghiringhelli F, Fimia GM, Apetoh L, Perfettini JL, Castedo M, Mignot G, Panaretakis T, Casares N, Métivier D, Larochette N, van Endert P, Ciccocanti F, Piacentini M, Zitvogel L, Kroemer G. Calreticulin exposure dictates the immunogenicity of cancer cell death. *Nat Med*. 2007;13(1):54–61.
- Feliz-Mosquea YR, Christensen AA, Wilson AS, Westwood B, Varagic J, Meléndez GC, Schwartz AL, Chen QR, Mathews Griner L, Guha R, Thomas CJ, Ferrer M, Merino MJ, Cook KL, Roberts DD, Soto-Pantoja DR. Combination of anthracyclines and anti-CD47 therapy inhibit invasive breast cancer growth while preventing cardiac toxicity by regulation of autophagy. *Breast Cancer Res Treat*. 2018;172(1):69–82.

16. Tawbi HA, Burgess M, Bolejack V, Van Tine BA, Schuetze SM, Hu J, et al. Pembrolizumab in advanced soft-tissue sarcoma and bone sarcoma (SARC028): a multicentre, two-cohort, single-arm, open-label, phase 2 trial. *Lancet Oncol.* 2017;18(11):1493–501.
17. Trabucco SE, Ali SM, Sokol E, Schrock AB, Albacker LA, Chung J, et al. Frequency of genomic biomarkers of response to immunotherapy in sarcoma. *JCO.* 2018;36(15_suppl):11579.
18. Italiano A, Bessedé A, Pulido M, Bompas E, Piperno-Neumann S, Chevreaux C, Penel N, Bertucci F, Toulmonde M, Bellera C, Guegan JP, Rey C, Sautès-Fridman C, Bougouïn A, Cantarel C, Kind M, Spalato M, Dadone-Montaudie B, Le Loarer F, Blay JY, Fridman WH. Pembrolizumab in soft-tissue sarcomas with tertiary lymphoid structures: a phase 2 PEMBROSARC trial cohort. *Nat Med.* 2022;28(6):199–206.

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