European Journal of Cancer 207 (2024) 114188

Contents lists available at ScienceDirect

European Journal of Cancer

journal homepage: www.ejcancer.com

The challenge of running trials in advanced angiosarcoma: A systematic review of the literature from EORTC/STBSG to guide the development of angiosarcoma-specific trials

Armelle Dufresne [a,*], Lars H. Lindner [b], Jana Striefler [c], Bernd Kasper [d], Winan Van Houdt [e], Saskia Litiere [f], Sandrine Marreaud [f], Jean-Yves Blay [a], Lorenzo D'Ambrosio [g], Silvia Stacchiotti [h]

[a] Centre Leon Berard Cancer Center, Lyon, France
[b] LMU Klinikum, Munchen, Germany
[c] University Cancer Center, Hamburg, Germany
[d] Mannheim Cancer Center, Mannheim, Germany
[e] Netherland Cancer Institute, Amsterdam, the Netherlands
[f] EORTC Headquarters, Brussels, Belgium
[g] University of Turin, Orbassano, Italy
[h] National Insitute of Tumors, Milan, Italy

ARTICLE INFO

Keywords:
Advanced angiosarcoma
Chemotherapy
Tyrosine kinase inhibitor
Immune therapy
Biomarkers
Clinical trial design

ABSTRACT

Introduction: While available systemic treatments have modest long term efficacy in advanced angiosarcoma, immunotherapy represents an interesting new therapeutic opportunity. To establish its benefit, it is required to conduct a clinical trial assessing its efficacy and toxicity compared to standard treatments.
Material and methods: This is a literature review from PubMed search.
Results: Several systemic treatments (chemotherapy and TKI) are currently used in advanced angiosarcoma with ORR ranging from 12.5 to 68 % and PFS from 2 to 7 months. However, few randomized trials, mainly phase II, has been conducted to compare these treatments. While most centers propose doxorubicin containing regimens or paclitaxel in 1st or 2nd line, a high heterogeneity of regimens administered in this setting is observed even across sarcoma specialized centers with no consensual standard treatment. Encouraging signals of immunotherapy activity have been reported in angiosarcoma from several retrospective and phase II studies assessing anti-PD1 either alone or in combination with anti CTLA4 or TKI. Although cutaneous and head and neck location seems to benefit more from immunotherapy, response may be observed in any angiosarcoma subtype. In sarcoma in general and AS in particular, no biomarker has been clearly established to predict the efficacy of immunotherapy: high tumor mutational burden and presence of tertiary lymphoid structures are under assessment.
Discussion: Even essential, developing a randomized clinical trial in AS struggles with the heterogeneity of the disease, the lack of consensual standard regimen, the uncertainty on optimal immunotherapy administration and the absence of established predictive biomarkers.
Conclusion: International collaboration is essential to run randomized trial in advanced AS and asses the efficacy of immune therapy in this rare and heterogeneous disease.

1. Introduction

Angiosarcoma (AS) is a rare and highly aggressive malignant mesenchymal tumour, originating from vascular endothelial cells and accounting for approximately 2–4 % of soft tissue sarcomas (STS) [1]. Patients present with metastatic disease at diagnosis in 20–45 % of cases; in addition, half of patients presenting with localized disease will suffer of metastatic relapse despite an optimal local treatment. In the metastatic setting, the chances of cure are low and treatments consist of palliative systemic therapies [chemotherapy and tyrosine kinase

* Correspondence to: Centre Leon Berard, 28 rue Laennec, 69008 Lyon, France.
E-mail address: armelle.dufresne@lyon.unicancer.fr (A. Dufresne).

https://doi.org/10.1016/j.ejca.2024.114188
Received 14 May 2024; Received in revised form 17 June 2024; Accepted 18 June 2024
Available online 29 June 2024

inhibitors (TKI)] with limited efficacy leading to a median (m-) overall survival (OS) ranging from 6 to 16 months [2].

AS may develop at any anatomical location, superficial or deep, as a primary event or secondary to exposure to etiologic factors like radiation [3]. Biologically, AS are genomic and karyotype complex sarcomas lacking recurrent chromosomal changes. The clinical and biological heterogeneity and rarity of AS are major hurdles to the development of more efficient and data-driven treatments.

The activity of immunotherapy (IO) is limited in unselected STS, ongoing clinical trials aim to identify criteria of patients selection on biomarkers or histotypes. Signals of efficacy of anti-PD1/PD-L1 based IO have recently been reported in retrospective and prospective studies in advanced AS. Prospective clinical trials are warranted to better define which patients with advanced AS would benefit most from IO.

The objective of this work is to analyze the literature and provide structured data on the efficacy of standard treatments for advanced AS, most recent data on efficacy of IO, and biomarkers of immune response to provide the background for the discussion on how to develop IO in this disease.

2. Material and methods

MEDLINE was searched through PubMed to perform the collection of all English articles published between January 2005 and January 2023 on the topic. Terms used for the selection were "angiosarcoma, advanced, metastatic, systemic treatment, chemotherapy, tyrosine kinase inhibitors, immune therapy, retrospective studies, prospective studies, phase II/III clinical trials, translational studies, immune biomarkers".

We decided to report here the results of prospective trials and retrospective studies assessing efficacy of systemic agents in the advanced setting.

3. Results

3.1. Efficacy of available systemic treatments in advanced AS

There is a high diversity of systemic treatments used in AS including anthracyclines, taxanes, gemcitabine, ifosfamide and cyclophosphamide, and antiangiogenics such as pazopanib, or among off-label agents i.e. sorafenib [4]. Unfortunately, no randomized phase III trials have directly compared these treatments.

In 2014, Young *et al.* analysed data from 108 adult AS enrolled in 11 prospective EORTC clinical trials (9 randomized and 2 non-randomized) to compare anthracycline sensitivity between AS and other sarcoma types [5]. The efficacy in AS was similar to that observed in STS in general with an overall response rate (ORR) of 25 %, m- progression free survival (PFS) of 4.9 months [95 % confidence interval (CI) 3.7–6.1] and m-OS of 9.9 months (95 % CI 8.3–12.3).

Sensitivity of AS to weekly paclitaxel was reported in 2008 from the ANGIO-TAX trial (NCT00217607) [6]. This phase II, single-arm, multicentric French study included 30 adult patients with advanced AS. The ORR at 2 months, i.e. the study primary end-point, was 18 %. ORR was 18 % and 19 % at 4 and 6 months, respectively, with a m-PFS and OS of 4 and 8 months. No difference in OS was observed when comparing the 10 patients with RT-associated AS with the 20 patients with de novo AS, probably due to the small sample size.

The ANGIOTAX+ study was a randomized non-comparative, multicentric French phase II study (NCT01303497) to investigate bevacizumab plus paclitaxel versus paclitaxel alone [7]. Fifty adult advanced AS were randomized, 24 in the arm of paclitaxel alone. The location of primary AS was balanced between the 2 groups. Despite non-comparative in nature, this study showed superimposable results between the 2 arms. In the control arm, m-PFS was 6.6 months with a 45.8 % RECIST ORR at 3 months and a m-OS of 19.5 months.

Sorafenib was investigated in a phase II study including 145 STS, among which 40 AS [8]. In the AS cohort m-PFS was 3.8 months (95 % CI 2.8–5.5 months), with 5/6 PR by RECIST and m-OS of 14.9 months. Sorafenib was then assessed in a phase II clinical trial in 2 cohorts of advanced AS: 26 patients with superficial AS (including 14 radiation-associated AS (RAAS)) and 15 visceral AS) [9]. The m-PFS was 1.8 and 3.8 months, respectively, whereas the m-OS was 12.0 and 9.0 months, respectively.

The only randomized phase III trial in this indication compared pazopanib to TRC105 + pazopanib [10]. The study failed to demonstrate an improvement in PFS but show randomized study are feasible. Table 1 lists main results of these prospective trials. Table 2 lists main results of several retrospective trials.

3.2. Current immune therapy approaches in AS

In a prospective, multicenter, single-arm phase II study (SWOG S1609) 16 advanced AS were treated with double immune checkpoint blockade (ICB) anti-CTLA-4 and anti-PD-1 [15]. Ipilimumab and nivolumab were administered in 9 and 7 patients with cutaneous and non-cutaneous AS, respectively. RECIST ORR was 25 % (3/5 with scalp/face AS). The 6-month PFS was 38 % (95 %CI 20–71 %). There were 68.8 % immune-related adverse events (irAE), thereof 2 (12.5 %) grade 3 or 4 irAEs (ALAT/ASAT increase and diarrhea) reported. One/7 patients with high TMB and 2/3 patients with high PDL1 expression achieved a PR.

Another multicenter, single-arm phase II study of nivolumab and cabozantinib evaluated 21 patients with advanced AS (Alliance A091902) [JCO.2023.41.16_suppl.11503]. All patients received prior taxanes and 24 % had also received prior anthracycline. At a 11.2 months m-follow-up, 13/21 patients responded (11 RECIST PR, 2 CR), for a 62 % ORR. Responses were seen in patients with primary cutaneous disease. m-PFS was 9.6 months (95 % CI 5.3-NR), and m-OS 20.5 months (95 % CI 14.4-NR). Grade 3 hypertension was observed in 10 % of the cases.

Similar PFS rates were reported in a retrospective analysis from the MD Anderson Cancer Center [16]. Twenty-five patients with AS who received pembrolizumab monotherapy were identified. Patients were pretreated with at least 2 lines of systemic chemotherapy. RECIST ORR was 18 % and 6-month PFS was 6.2 months. No difference in PFS was seen according to primary tumor location (56 % cutaneous and 44 % visceral). The m-OS for the entire population was 23.0 (95 % CI 14.3 – 40.7) months, with a longer OS for cutaneous than for visceral AS (40.7 vs 15.1 months).

Shorter PFS rates were found in a retrospective analysis of 35 patients from the Memorial Sloan Kettering Cancer Center with different immunotherapeutic approaches: ICB monotherapy (anti-PD-1 or anti-PD-L1), ICB combination therapy (anti-CTLA-4 + anti-PD-1) and ICB in combination with innovative immunomodulation therapies [17]. Indeed, the m-PFS and m-OS were 11.9 (95 % CI 7.4 - 31.9) and 42.5 (95 % CI 19.6 – 114.2) weeks, respectively. Thirteen patients (37 %) had a PFS $\geq$ 16 weeks. Clinical factors associated with longer PFS and OS were ICB plus other therapy regimens and cutaneous head and neck (H&N) AS.

A case series of 7 AS patients treated with ICB was reported from the Miami – Sylvester Comprehensive Cancer Center, thereof 5 patients with cutaneous AS and 2 with breast AS [18]. Treatments were either pembrolizumab + axitinib (n = 1), anti-CTLA-4 (n = 2) and pembrolizumab (n = 4). RECIST ORR was 71 % (5/7) at 12 weeks. At the time of the report, 3/7 patients have progressed with a m-PFS of 3.4 months. No $\geq$ grade 2 toxicities were reported.

A few AS patients (n $\leq$ 5) among other STS subtypes were also included in phase II studies with durvalumab plus tremelimumab (anti-PD-L1 + anti-CTLA-4) [19] as well as in a phase II study with the IDO1 inhibitor epacadostat plus pembrolizumab [20]. In both studies, AS patients did not achieve remarkable responses, but the limited number of patients prevents the possibility to derive definitive conclusions.

Table 1
Efficacy of available systemic treatments in advanced AS from prospective studies.

Reference	Methodology	Population	Regimen	ORR	Survival
Penel 2008[6]	Phase II	30 locally advanced/metastatic AS33 % RAAS,20 % superf,	Paclitaxel 80 mg/m^2,63 % 1st line36 % 2nd line	18 % at 2 m	PFS 4mOS 8 m
Ray Coquard2015 [7]	Randomised Phase II	50 locally advanced/metastatic AS 50 % RAAS, 66 % superf/34 % visceral	Weekly paclitaxel 90 mg/m^2 (+/- Beva)	45,8 %	PFS 6,6mOS 19,5 m
Maki2009[8]	Phase II	40 advanced AS1st to 4th line	Sorafenib	12,5 %	PFS 3,8mOS 14,9 m
Ray Coquard 2012 [9]	Phase II	41 advanced AS34 % RAAS	Sorafenib27 % 1st line	23 %	PFS ≈ 2mOS ≈ 9 m
Jones2022[10]	Phase III	114 advanced AS50 % cutaneous28 % 1st line	Pazopanib	13 %	PFS 4.3mOS 7.7 m
			Pazopanib + TRC105	5 %	PFS 4.2mOS 10.9 m

Table 2
Efficacy of available systemic treatments in advanced AS from retrospective studies.

Reference	Methodology	Population	Regimen	ORR	Survival
Young 2014[5]	Pooled analysis of 11 prospective trials	108 AS,10 % cutaneous	Anthracyclin-based regimen,1st line	25 %	PFS 4,9mOS 9,9 m
Italiano 2012 [11]	Retrospective	117 advanced AS, 1st lineDoxo arm: 7 % cutaneous, 36 % RAASWeekly pacli arm: 33 % cutaneous, 28 % RAAS	Doxorubicin	29,5 %	PFS 3 m OS 5,5 m
			Weekly paclitaxel	53 %	PFS 5,8mOS 10,3 m
Stacchiotti 2012 [12]	Retrospective	25 advanced AS	Gemcitabine	68 %	PFS 7mOS 17 m
Watson2023 [13]	Retrospective	42 advanced AS 90 % in ≥ 2nd line	Gemcitabine	38 %	PFS 5.4mOS 9.9 m
Kollar2017[14]	Retrospective + pooled analysis of 2 prospective trials	40 advanced AS	Pazopanib	20 %	PFS 3mOS 9,9 m

RAAS: radiation-associated AS; m: months

Finally, at ASCO 2024 Annual Meeting, results from 3 prospective studies with IO in AS were presented. A phase II trial reported a 50 % ORR and 6 months m-PFS among 32 AS patients treated with paclitaxel plus avelumab as first line treatment (Kim, #11512). In a randomized phase II trial, paclitaxel was compared to paclitaxel with nivolumab: the combination failed to improve m-PFS or ORR. A strong signal for efficacy of the combination arm was reported in scalp/face tumor location (Grilley-olson, #11514). The anti-PD1 Cemiplimab was administered to 18 AS patients and led to 27.8 % ORR at week 24 with m-DOR of 6.2months. Of note, 2 patients had complete response, both secondary AS (1 UV-associated and 1 radiotherapy-associated). Two out of 3 patients TMB-high had partial response at week 24. (Van Ravensteijn #11513). Table 3.

3.3. Biomarker of immunotherapy efficacy

Available biomarker data in AS primarily consists of case series, with few phase I or II IO studies.

3.3.1. Tumor mutational burden (TMB)

The Angiosarcoma Project [21] analyzed 338 self-registered patients with any AS subtype. TMB was determined in 47 samples with a median of 3.3 muts/Megabase (MB) and was significantly higher in H&N AS vs non-H&N tumors (20.7 and 2.8 muts/MB, respectively). Two patients with H&N TMB-high AS who had received off-label anti PD1 therapy showed durable responses even after discontinuation of treatment. Analysis of TMB was part of the case series of Espejo-Freire *et al.* examining genomic biomarkers in 143 cases (44 H&N, 31 breast, 28 visceral, 16 extremity, 11 cutaneous, and 13 unknown origin) AS [22]. TMB was high (>10 muts/MB) in 26 % of cases, reaching 64.4 % of the H&N AS cohort and < 15 % in other locations. Chan *et al* analyzed 68 AS retrospectively combining next-generation sequencing, gene expression profiling, and multiplex immunohistochemistry [23]. M-TMB of the whole cohort was 1.95 mut/MB (range 0.06–7.16), whereas m-TMB in patients with cutaneous H&N AS was 5.04 mut/MB. In another retrospective study including 35 AS (among which 14 H&N AS), with administration of at least 1 dose of ICB, Rosenbaum *et al* reported a longer PFS in cutaneous H&N AS compared to others (17.9 vs 10 weeks) [17]. In this population, the m-TMB was 3.7 mut/MB (range 0–35.4).

Table 3
Publications assessing the efficacy of IO in advanced AS.

Reference	Methodology	Population	Regimen	ORR	Survival
Wagner2021	Phase II	16 advanced(9 cutaneous, 7 non-cutaneous)	Ipilimumab + Nivolumab	25 %(PR in 3/5 H&N AS)	6 m PFS: 38 %
Grilley-Olson 2023	Phase II	21 advanced(12 cutaneous, 1 liver, 2 breast, 6 other)	Nivolumab + Cabozantinib	62 %(7/12 with cutaneous and 6/9 with non-cutaneous)	PFS 9.6 mOS 20.5 m
Ravi2022	Retrospective	25 advanced(56 % cutaneous, 44 % visceral)	Pembrolizumab	18 %DCR 59 %	PFS 6.2 m(cutaneous 4.7 mvisceral 6.2 m) OS 72.6 m
Rosenbaum 2022	Retrospective	35 advanced	ICB aloneICB combination, ICB plus other		PFS 11.9 weeksOS 42.5 weeks
Florou2019	Retrospective	7 advanced(5 cutaneous,2 breast)	Pembrolizumab (n = 4)+ Axitinib (n = 1),+ CTLA-4 inhibitor (n = 2)	71 %	PFS 3.4 m

DCR: Disease control rate, ICB: Immune Checkpoint Blockade

There was no statistically significant correlation between TMB and PFS or OS. Van Ravensteijn *et al.* analyzed 79 primary and 178 secondary AS (RT-associated, UV-associated, Stewart Treves syndrome) [24]. M-TMB was 3.2 and 3.9 mut/MB in primary and secondary AS, respectively. TMB-high (≥10 muts/MB) was reported in 6 (12 %) samples: 3 UV-associated, 2 visceral, and 1 non-UV-associated skin AS. The case series of Florou *et al* included 7 patients receiving 5 to 14 doses of ICB [18]. Complete response was seen in 1 patient with cutaneous AS and TMB-low (0.09 mut/MB). Two other patients with cutaneous AS and TMB-high (15 and 12 mut/MB, respectively) showed a PR.

3.3.2. PD1/PD-L1 expression

Tomassen *et al* analyzed PD1/PD-L1 expression in 165 AS [25]. High PD1/PD-L1 expression was reported in soft tissue (40 %), UV associated (18 %), and visceral (17 %) AS. Moreover, a particularly high PD1 expression (38 %) was observed in RAAS. The case series of 143 AS by Espejo-Freire also detected differences regarding PD-L1 expression according to the site of origin: 21.8 % in the whole cohort, 33.1 % in H&N, 23.1 % in visceral, 10.3 % in breast, 14.3 % in extremity, and 11.1 % in cutaneous AS [22].

3.3.3. TLS, TIL, MSI, signature

The presence of tertiary lymphoid structures (TLS) is a promising predictive biomarker of response to IO in STS. No AS was included in the PEMBROSARC clinical trial which investigated the activity of pembrolizumab in STS and showed a correlation between response and mature TLS presence [26]. In the immunohistochemical analysis of TIL by van Ravensteijn, a significantly higher density of CD3 + T cells, CD4 +T helper cells, CD8 + cytotoxic T cells and FoxP3 + T regulatory cells was observed in secondary AS compared to primary AS [24]. T cell density was higher in UV-associated AS than in RAAS and in non UV-associated skin AS. The rate of MSI-high cases in AS ranges from 0 % to 2.3 %, especially in H&N AS [17,22,24], MSI seems not to be a relevant biomarker. Various commercial and academic clusters and genetic signatures for AS have been studied. Their methods of analysis are diverse, focusing on microenvironment, methylation profile, UV mutational signature etc. However, at present none of them represents a clear biomarker for efficacy of IO in AS.

4. Discussion

Establishing the efficacy of current treatments for advanced AS overall and within specific patient subgroups is essential to design future studies in the disease.

Most of chemotherapy regimens available for treatment of STS demonstrated a certain level of efficacy in advanced AS, even though the lack of randomized studies makes a consensual standard 1st or 2nd line therapy difficult to establish. The retrospective study from EORTC [4] reports 16 different systemic treatment regimen administered in neo adjuvant setting in 59 patients across sarcoma centers, reflecting the lack for consensual standard treatment.

Even if no IO agents are currently approved for treatment of STS in Europe, preliminary data available so far suggest that IO is a promising treatment option and deserves to be investigated further in the disease. Cutaneous and H&N location seems to benefit more from IO, although responses may be observed in any location of AS. Currently, the results of prospective trials are available, in addition to a few small retrospective case series, but available data do not allow to differentiate the efficacy between anti PD1/PD L1 and anti CTLA4, as monotherapy or in combination to other IO, to chemotherapy or to TKI.

To improve IO strategy in sarcoma and in AS in particular, accurate patient selection is crucial, based on clinical and/or biomarkers, as seen in other cancers. However, the scarcity and heterogeneity of data jeopardize the possibility at present to derive definitive conclusions on their predictive impact for IO efficacy. TMB-high and presence of mature TLS appear to be the most promising biomarkers so far. It's interesting to note a tendency for higher efficacy of IO in H&N location/TMB-high/UV-associated AS.

Demonstrating a benefit from a new treatment over a standard one by randomized trial remains, in principle, the gold standard for authorities to justify new drug approval. This is particularly challenging in advanced AS; this literature review nicely demonstrates that if running prospective trials, randomized or not, in this indication is feasible, the interpretation of data is limited by the rarity and heterogeneity of the disease. Health authorities have to take into account those limits in orphan diseases. To run a randomized trial to establish IO as a new treatment in advanced AS, international community will have to 1/ agree on a consensual control arm and the expected most efficient experimental arm, 2/ plan a stratification to take into consideration the heterogeneity of disease presentation (de novo vs secondary), disease extent (locally advanced versus metastatic), primary tumor site (cutaneous vs breast vs visceral vs others), 3/ include ancillary studies to investigate predictors of response such as TMB, PD1/PDL1 expression, mature TLS presence and TILs, 4/ define the most relevant endpoints. This effort can only be considered through international collaboration. Even if successful by addressing the above scientific questions, the major challenges will be enrolling patients and getting approval within a reasonable timeframe in absence of adjusted rules for new drugs in rare cancers. Currently, from the diagnosis to the implementation of new treatments, the chance of being cured remains imbalanced between rare and common cancers.

5. Conclusion

Several systemic agents are available for treatment of advanced AS. However, prognosis of patients affected by advanced AS remains poor and there is an urgent need for the approval of new effective treatments. Recent preliminary data suggest that IO might be a new, very interesting option. Notably, IO activity looks different across different AS subtypes and clinical predictive factors and biomarkers still need to be identified: running randomized clinical trial of IO in AS is feasible taking into consideration several obstacles. Beyond AS, this discussion highlights the challenges clinical research has to deal with when aiming at getting patients access to innovative drugs in rare and heterogeneous disease like STS in general.

Funding

No funding was obtained for this research.

CRediT authorship contribution statement

Armelle Dufresne: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Formal analysis, Conceptualization. **Lars H. Lindner:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Formal analysis, Conceptualization. **Jana Striefler:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Methodology, Formal analysis, Conceptualization. **Bernd Kasper:** Writing – review & editing, Validation, Methodology, Conceptualization. **Winan Van Houdt:** Writing – review & editing, Validation, Methodology, Conceptualization. **Saskia Litiere:** Writing – review & editing, Validation, Methodology, Conceptualization. **Sandrine Marreaud:** Writing – review & editing, Validation, Methodology, Conceptualization. **Jean-Yves Blay:** Writing – review & editing, Validation, Methodology, Conceptualization. **Lorenzo D'Ambrosio:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Silvia Stacchiotti:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization.

Declaration of Competing Interest

Armelle Dufresne, Jana Striefler, Bernd Kasper, Saskia Litiere, Sandrine Marreaud: these authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

References

[1] de Pinieux G, Karanian M, Le Loarer F, Le Guellec S, Chabaud S, Terrier P, et al. Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. PloS One 2021;16(2):e0246958.

[2] Gronchi A, Miah AB, Dei Tos AP, Abecassis N, Bajpai J, Bauer S, et al. Soft tissue and visceral sarcomas: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol J Eur Soc Med Oncol 2021;32(11):1348–65.

[3] Salminen SH, Sampo MM, Böhling TO, Tuomikoski L, Tarkkanen M, Blomqvist CP. Radiation-associated sarcoma after breast cancer in a nationwide population: increasing risk of angiosarcoma. Cancer Med 2018;7(9):4825–35 (Sep).

[4] Constantinidou A, Sauve N, Stacchiotti S, Blay JY, Vincenzi B, Grignani G, et al. Evaluation of the use and efficacy of (neo)adjuvant chemotherapy in angiosarcoma: a multicentre study. ESMO Open 2020;5(4):e000787 (Aug).

[5] Young RJ, Natukunda A, Litière S, Woll PJ, Wardelmann E, van der Graaf WTA. First-line anthracycline-based chemotherapy for angiosarcoma and other soft tissue sarcoma subtypes: pooled analysis of eleven European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group trials. Eur J Cancer Oxf Engl 1990 2014;50(18):3178–86.

[6] Penel N, Bui BN, Bay JO, Cupissol D, Ray-Coquard I, Piperno-Neumann S, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX study. J Clin Oncol J Am Soc Clin Oncol 2008;26(32):5269–74.

[7] Ray-Coquard IL, Domont J, Tresch-Bruneel E, Bompas E, Cassier PA, Mir O, et al. Paclitaxel given once per week with or without bevacizumab in patients with advanced angiosarcoma: a randomized Phase II trial. J Clin Oncol J Am Soc Clin Oncol 2015;33(25):2797–802.

[8] Maki RG, D'Adamo DR, Keohan ML, Saulle M, Schuetze SM, Undevia SD, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. J Clin Oncol J Am Soc Clin Oncol 2009;27(19):3133–40.

[9] Ray-Coquard I, Italiano A, Bompas E, Le Cesne A, Robin YM, Chevreau C, et al. Sorafenib for patients with advanced angiosarcoma: a phase II trial from the French Sarcoma group (GSF/GETO). Oncologist 2012;17(2):260–6.

[10] Jones RL, Ravi V, Brohl AS, Chawla S, Ganjoo KN, Italiano A, et al. Efficacy and safety of TRC105 plus pazopanib vs pazopanib alone for treatment of patients with advanced angiosarcoma: a randomized clinical trial. JAMA Oncol 2022;8(5):740–7.

[11] Italiano A, Cioffi A, Penel N, Levra MG, Delcambre C, Kalbacher E, et al. Comparison of doxorubicin and weekly paclitaxel efficacy in metastatic angiosarcomas. Cancer 2012;118(13):3330–6.

[12] Stacchiotti S, Palassini E, Sanfilippo R, Vincenzi B, Arena MG, Bochicchio AM, et al. Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network. Ann Oncol J Eur Soc Med Oncol 2012;23(2):501–8.

[13] Watson S, Verret B, Ropert S, Adam J, Bahleda R, Briand S, et al. Single-agent gemcitabine in patients with advanced, pre-treated angiosarcoma: a multicenter, retrospective study. Cancer Med 2023;12(3):3160–6.

[14] Kollár A, Jones RL, Stacchiotti S, Gelderblom H, Guida M, Grignani G, et al. Pazopanib in advanced vascular sarcomas: an EORTC Soft Tissue and Bone Sarcoma Group (STBSG) retrospective analysis. Acta Oncol Stock Swed 2017;56(1):88–92.

[15] Wagner MJ, Othus M, Patel SP, Ryan C, Sangal A, Powers B, et al. Multicenter phase II trial (SWOG S1609, cohort 51) of ipilimumab and nivolumab in metastatic or unresectable angiosarcoma: a substudy of dual anti-CTLA-4 and anti-PD-1 blockade in rare tumors (DART). J Immunother Cancer 2021;9(8):e002990.

[16] Ravi V, Subramaniam A, Zheng J, Amini B, Trinh VA, Joseph J, et al. Clinical activity of checkpoint inhibitors in angiosarcoma: a retrospective cohort study. Cancer 2022;128(18):3383–91.

[17] Rosenbaum E, Antonescu CR, Smith S, Bradic M, Kashani D, Richards AL, et al. Clinical, genomic, and transcriptomic correlates of response to immune checkpoint blockade-based therapy in a cohort of patients with angiosarcoma treated at a single center. J Immunother Cancer 2022;10(4):e004149.

[18] Florou V, Rosenberg AE, Wieder E, Komanduri KV, Kolonias D, Uduman M, et al. Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of seven patients from a single institution. J Immunother Cancer 2019;7(1):213.

[19] Somaiah N, Conley AP, Parra ER, Lin H, Amini B, Solis Soto L, et al. Durvalumab plus tremelimumab in advanced or metastatic soft tissue and bone sarcomas: a single-centre phase 2 trial. Lancet Oncol 2022;23(9):1156–66.

[20] Kelly CM, Qin LX, Whiting KA, Richards AL, Avutu V, Chan JE, et al. A phase II study of epacadostat and pembrolizumab in patients with advanced sarcoma. Clin Cancer Res J Am Assoc Cancer Res 2023;29(11):2043–51.

[21] Painter CA, Jain E, Tomson BN, Dunphy M, Stoddard RE, Thomas BS, et al. The angiosarcoma project: enabling genomic and clinical discoveries in a rare cancer through patient-partnered research. Nat Med 2020;26(2):181–7.

[22] Espejo-Freire AP, Elliott A, Rosenberg A, Costa PA, Barreto-Coelho P, Jonczak E, et al. Genomic landscape of angiosarcoma: a targeted and immunotherapy biomarker analysis. Cancers 2021;13(19):4816.

[23] Chan JY, Lim JQ, Yeong J, Ravi V, Guan P, Boot A, et al. Multiomic analysis and immunoprofiling reveal distinct subtypes of human angiosarcoma. J Clin Invest 2020;130(11):5833–46.

[24] van Ravensteijn SG, Versleijen-Jonkers YMH, Hillebrandt-Roeffen MHS, Weidema ME, Nederkoorn MJL, Bol KF, et al. Immunological and genomic analysis reveals clinically relevant distinctions between angiosarcoma subgroups. Cancers 2022;14(23):5938.

[25] Tomassen T, Weidema ME, Hillebrandt-Roeffen MHS, van der Horst C, et al. Analysis of PD-1, PD-L1, and T-cell infiltration in angiosarcoma pathogenetic subgroups. Immunol Res 2022;70(2):256–68.

[26] Italiano A, Bessede A, Pulido M, Bompas E, Piperno-Neumann S, Chevreau C, et al. Pembrolizumab in soft-tissue sarcomas with tertiary lymphoid structures: a phase 2 PEMBROSARC trial cohort. Nat Med 2022;28(6):1199–206.