Curr. Treat. Options in Oncol. (2021) 22: 61
DOI 10.1007/s11864-021-00858-9

Skin Cancer (T Ito, Section Editor)

Current Management of Angiosarcoma: Recent Advances and Lessons From the Past

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Published online: 7 June 2021

This article is part of the Topical Collection on *Skin Cancer*

Keywords Angiosarcoma · Angiosarcoma Project · Immunotherapy

Opinion statement

Despite their rarity, angiosarcomas are one of the most aggressive soft tissue sarcomas. Management can often be challenging due to their location and infiltrative nature. A multidisciplinary treatment approach is always warranted, but the recurrence remains high even for localized tumors despite multimodality treatment. In the metastatic setting, cytotoxic chemotherapies, targeted therapies, and, more recently, immunotherapy are used. The sequence of systemic therapies remains currently a topic of active investigation. Over the last couple of years, there have been significant advances in understanding angiosarcoma biology, most notably via patient-driven initiatives like the Angiosarcoma Project. The knowledge derived from such translational work has led to identifying potential biomarkers of response to treatments and exploring new therapeutic avenues. More clinical trials are underway to expand treatment options and improve patient outcomes.

Introduction

Angiosarcomas are highly aggressive, exceedingly rare sarcomas representing less than 1% of all sarcomas [1]. The neoplastic cells exhibit endothelial differentiation and are of vascular or lymphatic origin. Angiosarcoma can develop throughout the body and occur at any age but is most commonly diagnosed in adults aged 60–70 years old [2]. More than half of angiosarcomas are cutaneous, with the most common involved area being the head and neck region, particularly the scalp [3]. The remaining angiosarcomas can arise from the breast, soft tissues, bones, and visceral organs such as the liver and spleen [3].

Most angiosarcomas arise spontaneously, but there are certain well-described risk factors. Radiation therapy is an established risk factor for developing angiosarcomas, namely radiation-associated angiosarcomas, in any radiation-exposed body area [4]. Chronic lymphedema is also associated with angiosarcomas and is called Steward-Treves syndrome [4, 5]. Various carcinogens and chemicals such as vinyl chloride and thorium dioxide have been associated with the development of hepatic angiosarcomas [4]. Several genetic syndromes have also been recognized as risk factors for angiosarcomas, including neurofibromatosis, Maffucci syndrome, germline *BRCA1* or *BRCA2* mutations, and Klippel-Trenaunay syndrome [4].

The treatment of angiosarcomas depends on the stage and location. Surgical resection remains the mainstay of therapy in localized disease, although it can often be challenging to achieve negative margins due to the infiltrative nature of the disease. Even with resection, the local and distant recurrence rates are high. In metastatic disease, systemic cytotoxic chemotherapy can induce responses, although the duration is typically short, and eventually, most patients succumb to the disease [6].

Herein we highlight the most clinically relevant updates on angiosarcomas published in the last 2 years. We also provide a brief overview of updated treatment approaches in localized and metastatic settings.

Recent advances

Knowledge of disease biology and clinical features

Despite the rarity of angiosarcomas, there have been fundamental advances in unveiling angiosarcoma biology in the last couple of years. The progress in understanding the disease has had treatment implications and was translated into early clinical trials. The Angiosarcoma Project (ASC project), a patient-driven research initiative, is the most notable example [7••]. The ASC project generated and published tumor genomic and germline data and clinical data collected directly from patients throughout the United States. More than 300 patients were registered in 18 months, and 47 tumor samples from 36 patients were subjected to whole-exome sequencing. The angiosarcomas were classified into eight subclassifications: primary breast, cardiac, bladder, lung, HNFS (head, neck, face, scalp), abdominal area, cutaneous RAAS (radiation-associated angiosarcoma), and angiosarcoma of the spleen [7••].

From the genomic data, the most frequently mutated genes were *TP53* (25%), *KDR* (22%), and *PIK3CA* (21%). The KDR and TP53 mutations were mutually exclusive, with 89% of the *KDR* gene mutations observed in primary breast angiosarcomas, and 82% of the *TP53* mutations noted in the non-primary breast angiosarcomas [7••]. The *PIK3CA* alterations were also more commonly found in the primary breast angiosarcomas (9/18 samples) vs. 1/29 non-primary breast angiosarcomas. Notably, preclinical data on some of the *PIK3CA* mutations noted in this cohort (Arg88Gln, Pro124Leu, and Gly914Arg) showed cell dependency on *PIK3CA*, suggesting potential activity of PIK3a inhibition.

Next, the tumor mutation burden (TMB) was reported for all the sequenced samples. The HNFS angiosarcomas had a significantly higher median TMB than the other angiosarcoma subtypes (20.7 mutations per megabase vs. 2.8). All the HNFS samples with high TMB (≥ 10) had the UV light-dominant mutational signature suggesting that high TMB is caused by UV damage from sun exposure, similarly to melanoma. This signature was only found in HNFS samples [7••]. When subjected to mutational signature analysis, angiosarcomas had a high probability of genomic variations secondary to CpG island demethylation except for HNFS samples, which were impacted by the UV light, similarly to melanoma and other skin malignancies [8].

These results were concordant with another recently published study on angiosarcomas, where 18 samples were subjected to multiomic analysis [9]. The majority of those patients had HNFS angiosarcoma (N = 13/18), and a distinct UV signature was seen in six out of the 13 patients. These tumors also harbored the highest TMB compared to the remaining tumors [9]. Gene expression profiles of those tumors identified three distinct clusters; cluster 3 was the most active in immune-related pathways with the highest tumor inflammation signature (TIS) scores. As expected, HNFS angiosarcomas were dominant in clusters 1 and 3, frequently with UV-related DNA damage with strongly enriched immune cell types in cluster 3 [9].

Another recent study shed more light on the biology of angiosarcomas by studying the genome-wide DNA methylation patterns of 36 samples across four different clinical subtypes of angiosarcoma–radiation-associated, UV-associated, soft tissue, and visceral angiosarcoma [10]. DNA methylation reflects the cell of origin and the changes in gene expression. The clinical subtypes correlated with four distinct clusters. The UV and radiation associated fell into two distinct groups, suggesting two different subtypes within each histology [10]. Overall, the cluster in which both the UV and radiation-associated angiosarcoma fell had, as expected, a higher number of chromosomal abnormalities. Interestingly, the patients with angiosarcoma in the cluster with higher chromosomal instability had more favorable survival [10]. MGMT methylation, which may predict sensitivity to alkylating agents, was found in 19% of angiosarcomas, none of which was either radiation or UV associated [10].

Other noteworthy developments include a meta-analysis which characterized the incidence and course of secondary angiosarcomas in the context of chronic lymphedema or radiation. One hundred forty-eight studies were included, with a total of 229 patients [11]. The majority of angiosarcomas were in the breast (83 patients) and extremities (72 patients), and 72.5% of patients were female. These secondary angiosarcomas have distinct features, including the latency of presentation, which ranges from 2 to 50 years after the treatment of the primary carcinoma, and their incidence mainly in older patients with an average age of diagnosis of 65 years [11]. Another important aspect of secondary angiosarcomas is their presentation, often appearing as nonspecific skin changes such as erythematous rash or bluish skin discoloration, making diagnosis particularly challenging [11]. Traditional imaging modalities such as PET/CT or MRI can also be nonspecific or negative particularly in cutaneous presentations. In all instances, clinical examination while maintaining a high index of suspicion is vital in diagnosis. Prevention of postoperative lymphedema and early diagnosis of secondary angiosarcomas constitute the best management and offer the best chances for favorable outcomes.

Clinical studies

The European Musculoskeletal Oncology Society (EMSOS) reported a large retrospective study on bone angiosarcomas, an exceedingly rare type of angiosarcoma, representing less than 1% of all bone tumors [12]. As with other non-osteogenic bone sarcomas, the management is controversial and largely not standardized due to their rarity. The EMSOS included 80 patients with primary bone angiosarcomas treated across nine institutions in Europe. Metastatic disease was present in 44% of patients at the time of diagnosis, higher than other bone sarcomas [12]. As expected, there was variability in the types of chemotherapy received, with 33% of patients receiving osteosarcoma-based regimen and the remaining receiving soft tissue sarcoma regimens: adriamycin/ifosfamide (22%), Paclitaxel (17%), and gemcitabine (11%). The response rates in patients with metastatic disease who received adriamycin/ifosfamide doublet vs. osteosarcoma-based regimen were similar [12]. The 5-year overall survival was 41% for localized and 8% for metastatic disease [12]. For patients with localized disease, the 5-year progression-free survival was better in those who received adjuvant chemotherapy than those who did not (49% vs. 33%, respectively).

Localized disease

The standard treatment for localized angiosarcoma remains surgical resection with adequate margins. However, the involved anatomic region may frequently constitute the disease unresectable. This is particularly true in HNFS angiosarcomas, where a large area of the scalp may be involved with no clear margins. Angiosarcomas originating from large vessels or the heart also represent a challenge, and resection is often not feasible. Secondary angiosarcomas are typically treated similarly to primary angiosarcomas.

There is no definitive data based on randomized studies supporting improvement in PFS and/or OS with systemic chemotherapy in this setting. However, given the high recurrence and metastatic rates of localized angiosarcomas [13], additional treatment modalities such as systemic chemotherapy and/or radiation are implemented to improve survival or to create surgical options for initially unresectable disease. A few retrospective studies were published last year regarding the use of systemic chemotherapy in the localized setting.

Neoadjuvant chemotherapy may potentially facilitate surgical resection by decreasing the tumor's size and eradicate the micrometastatic disease. A recent review reported the outcomes of six retrospective studies and 18 case reports that included patients with localized angiosarcoma who received chemotherapy before or after surgical resection [14]. The chemotherapy regimens used across these studies included gemcitabine with docetaxel, doxorubicin with ifosfamide, doxorubicin, ifosfamide, and Paclitaxel alone [14]. For the patients with cutaneous angiosarcoma, the addition of neoadjuvant chemotherapy had no survival benefit but also did not lead to a detrimental delay in surgical resection [14]. For cardiac angiosarcomas, though, the addition of neoadjuvant chemotherapy did improve surgical resection. For the remaining angiosarcoma subtypes, no definitive conclusions were feasible due to data and histologic type heterogeneity. It is essential to be noted that the overall response rate to

neoadjuvant chemotherapy was reported to be as high as 88%, particularly for the HFNS angiosarcomas [14].

A recent retrospective analysis of patients with localized angiosarcoma treated across EORTC (European Organization for Research and Treatment of Cancer) sites reported the outcomes of 86 patients — 43 received treatment in the neoadjuvant, 27 in the adjuvant setting, and 16 in both settings [15]. Almost one-third of the patients had breast angiosarcomas, and 69.4% of them were radiation-associated angiosarcomas. One-fourth of patients received neoadjuvant chemotherapy followed by resection. The most commonly used regimen was Paclitaxel (35.6%), followed by doxorubicin and ifosfamide (11.9%) and gemcitabine/docetaxel (10.2%). Other regimens included docetaxel alone (8.5%), gemcitabine alone (8.5%), doxorubicin, and Paclitaxel (3.4%), and others [15]. The median PFS and OS for all patients from diagnosis were 1.4 and 4.9 years, respectively [15]. Given the variety of the treatments used and heterogeneity of the included patient population, subgroup analyses were not performed, and thus, conclusions on therapeutic approaches cannot be made.

The role of concurrent chemotherapy with Paclitaxel and radiation in patients with localized cutaneous angiosarcoma was also recently explored [16•]. The treatment course of 57 patients was reviewed; 22 patients received chemoradiation (CRT), and 35 received other treatment modalities (non-CRT) [16•]. In the CRT cohort, concurrent Paclitaxel with radiation was given as definitive therapy in 13 (59.1%) patients and neoadjuvant prior to resection in 9 (40.9%) patients. In the non-CRT cohort patients, the majority of patients received chemotherapy and surgery (31.4%) and surgery with radiation (28.6%) [16•]. No significant difference was observed in the 2-year local control, distant control, or PFS between the two cohorts. The 2-year OS was, however, significantly higher for patients in the CRT group vs. in the non-CRT, 94.1% vs. 71.6% ($p = 0.033$), respectively. Patients in the CRT group who received surgery as well had a 2-year OS of 100% [16•]. A phase II study of concurrent Paclitaxel with radiation is currently recruiting patients to validate these findings (NCT03921008).

Metastatic disease

Systemic therapy is the cornerstone of treatment for metastatic angiosarcoma. Although there is no established first-line standard of care regimen, several chemotherapy and targeted agents are highly effective in this disease. However, metastatic angiosarcoma is incurable, and long-term survival is uncommon for most angiosarcoma subtypes.

Chemotherapy

The most commonly used agents in the upfront treatment of metastatic angiosarcoma are either anthracycline or taxane-based regimens. No sufficient evidence and no head-to-head comparison to support either as the first-line regimen exist, and thus, they are used sequentially in practice. Anthracycline-based regimens are the most commonly used first-line treatment in most advanced soft tissue sarcomas. Their efficacy in angiosarcoma is similar to other sarcoma types. The response rate (RR) of 108 patients with angiosarcoma

treated with anthracycline-based regimens was 25% in a pooled analysis of patients treated in 11 EORTC trials [17]. The median PFS and OS were 4.9 and 9.9 months, respectively. The combination of doxorubicin with ifosfamide led to longer PFS than doxorubicin alone (HR 0.53, 95% CI 0.33–0.86; $p = 0.010$) for angiosarcoma patients [17].

The efficacy of pegylated doxorubicin (PLD) in sarcomas is generally limited, except for specific soft tissue sarcoma subtypes like desmoid tumors. Several small retrospective studies have shown the potential activity of PLD in angiosarcoma, and it may be an option in patients who cannot tolerate more intensive chemotherapy. The most extensive study on this included a study of 21 patients with angiosarcoma who received PLD and had a RR of 33% [18].

Paclitaxel has a particular activity in angiosarcomas and is often used in the first or second-line setting. Its efficacy was demonstrated in the phase II ANGIOTAX study in which 30 patients with angiosarcoma were included and showed RR of 19% with median PFS and OS 4 and 8 months, respectively [19]. Retrospective studies have also demonstrated the efficacy of Paclitaxel in treatment-naïve or pretreated patients [20, 21].

Gemcitabine, in combination with docetaxel, is a typical second-line regimen in the management of advanced soft tissue sarcomas. Whereas there is no prospective study on this combination in metastatic angiosarcoma, in a retrospective study of 25 patients treated with gemcitabine alone, RR was 64% with a median PFS and OS or 7 and 17 months, respectively [22]. The combination of gemcitabine with nab-paclitaxel (albumin-bound Paclitaxel) was also recently explored in a retrospective cohort of patients with soft tissue sarcomas [23]. Three out of the 17 patients had angiosarcoma, with one achieving complete response with PFS of 12 months, one partial response with PFS of 7 months, and one stable disease with PFS of 8 months [23]. Given the overall better toxicity profile of nab-paclitaxel over Paclitaxel, it may offer an alternative with similar efficacy. Further studies to investigate this combination in soft tissue sarcomas and in angiosarcomas are warranted.

Similar to taxanes, eribulin interferes with microtubule polymerization and is currently approved for patients with metastatic liposarcoma who have received a prior anthracycline-based regimen. In light of angiosarcomas' sensitivity to taxanes, a prospective observational study of eribulin was recently reported and included 25 patients with cutaneous angiosarcoma who had progressed to taxanes [24]. Five patients (20%) achieved a partial response with a median PFS and OS of 4 and 8.6 months, respectively [24]. Given the less neurotoxicity of eribulin compared to taxanes, this agent may offer a treatment option after progression to taxanes, especially for patients not eligible for an anthracycline-based regimen.

The efficacy of oral Paclitaxel in combination with encequidar, a novel adenosine triphosphate (ATP)-binding cassette (ABC) transporter P-gp inhibitor, was recently investigated in a phase II trial of patients with unresectable cutaneous angiosarcoma who had not received prior taxane therapy [25]. The inhibition of the P-gp prevents cytotoxic agents' efflux from the epithelial cells to the gastrointestinal tract leading to higher oral bioavailability and efficacy of the chemotherapy. Out of the 22 evaluable patients, 6 achieved complete response (27.3%), 5 partial response (22.7%), and 11 stable disease (50%). The median PFS was 36 months, and OS at 52 weeks was 92% [25]. The median age of patients included in that study was 75 years old, making those results

particularly notable, given the favorable side effect profile of the combination [25].

Targeted agents

Vascular endothelial growth factor (VEGF) and VEGF receptors are overexpressed in angiosarcomas [26–28], targeting that pathway has been appealing. Bevacizumab, an antibody against VEGF, has been studied in the treatment of angiosarcomas in a phase II study of 23 patients with modest results — only 2/23 patients achieved PR, and 11 had stable disease [29]. When combined with Paclitaxel in the ANGIOTAX PLUS trial, the RR was only 28% compared to 45.8% in the combination and monotherapy with Paclitaxel, respectively [30]. When bevacizumab was combined with gemcitabine/docetaxel in a single-arm phase II study, of the five patients with angiosarcoma, four had tumor reductions, and three had a partial response [31]. Whether the chemotherapy backbone in combination strategies with bevacizumab affects its activity needs further investigation in larger prospective studies.

Some multi-targeted tyrosine kinase inhibitors (TKIs) can have activity against VEGF and have been explored in angiosarcoma. Pazopanib is a TKI approved in soft tissue sarcomas that progressed on anthracycline-based regimens. In angiosarcoma, a modest benefit was observed in retrospective studies with median PFS in the range of 3 months and no significant responses [32]. This modest activity was also seen in phase II prospective study on pazopanib in patients with angiosarcoma, which accrued 29 patients overall [33]. Among the evaluable patients, the best response was stable disease in 12 patients. Stable disease was seen more frequently in patients with cutaneous angiosarcoma (25%) vs. visceral angiosarcoma (8.3%) [33]. Tumor amplifications of members of the VEGFR family such as *VEGFR2* (*KDR*) and *VEGFR3* (*FLT4*) have been reported to confer sensitivity particularly to pazopanib and may potentially guide treatment selection for those patients [34].

Another TKI, regorafenib that has activity against VEGF and is approved in the treatment of gastrointestinal stromal tumors, showed some preliminary activity in the few patients with angiosarcoma who were included in the REGOSARC phase II trial [35]. An angiosarcoma-specific phase II trial included 31 patients with metastatic and locally advanced disease [36]. This trial also showed modest results, similar to pazopanib — median PFS and OS of 3.55 and 11.4 months, respectively [36]. RR was 14.29% with one confirmed complete response, two partial responses, and 12 stable diseases [36].

Endoglin is a surface receptor postulated to mediate resistance to pazopanib. An antibody to endoglin (TRC105) was tested in combination with pazopanib vs. pazopanib alone in a phase III trial (TAPPAS) in 123 patients with advanced angiosarcoma [37]. The addition of TRC105 did not demonstrate activity when combined with pazopanib [37]. The median PFS was similar in both arms, 4.3 vs. 4.2 months in the pazopanib alone vs. pazopanib/TRC105, respectively [37].

Immunotherapy

The anti-PD1 (programmed death 1) checkpoint inhibitor, pembrolizumab, was approved for tumors with high TMB (≥ 10 mutations/megabase) regardless of histology based on the KEYNOTE-158 study [38]. Hence, immunotherapy can be a treatment option for angiosarcomas with high TMB, particularly the

HNFS subset. Before this approval, the activity of checkpoint inhibitors in angiosarcomas had been reported in the literature with promising results. Within the ASC project cohort, three out of ten patients with HNFS angiosarcoma were treated with Pembrolizumab [7••]. Two had high TMB, and both had a durable response to pembrolizumab after having refractory disease to standard therapies [7••]. We and others have also reported cases of patients with angiosarcoma treated with checkpoint inhibition either with anti-PD-1/PD-L1 or anti-CTLA-4 agents. Responses have been reported primarily in cutaneous angiosarcomas and less frequently in radiation-associated breast angiosarcoma [39, 40•, 41–43]. This activity was also shown in the phase 2 DART trial (NCT02834013), which studied the efficacy of nivolumab/ipilimumab in rare tumors and included a cohort of patients with metastatic or unresectable angiosarcoma. Sixteen patients with angiosarcoma were enrolled; 3 out of 9 patients with cutaneous angiosarcoma and 1 with radiation-associated breast angiosarcoma had responses [44]. Additional studies explicitly focused on angiosarcoma and immunotherapy alone or in combination with chemotherapy, tyrosine kinase inhibitors, or oncolytic virus (T-VEC) are currently underway (NCT04607200, NCT04339738, NCT03921073, NCT03512834).

Conclusion

The treatment landscape of angiosarcomas is slowly changing primarily due to our better understanding of this heterogenous sarcoma. Patient advocacy and participation in clinical trials are vital in expanding the treatment options and ultimately improving outcomes. Clinical trials based on translational work have the most potential to truly make an impact and advance the field in such rare diseases.

Declarations

Conflict of interest

Vaia Florou declares that she has no conflict of interest.

Breelyn A. Wilky has received compensation from SpringWorks and Deciphera for service as a consultant.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- • Of importance
- •• Of major importance

1. Antonescu C. Malignant vascular tumors—an update. Mod Pathol. 2014;27:S30–8.
2. Lahat G, Dhuka AR, Hallevi H, Xiao L, Zou C, Smith KD, et al. Angiosarcoma: clinical and molecular insights. Ann Surg. 2010 Jun;251(6):1098–106.
3. Mark RJ, Poen JC, Tran LM, Fu YS, Juillard GF. Angiosarcoma: a report of 67 patients and a review of the literature. Cancer. 1996;77(11):2400–6.

4. Young RJ, Brown NJ, Reed MW, Hughes D, Woll PJ. Angiosarcoma. Lancet Oncol. 2010 Oct;11(10):983–91.
5. Gaballah AH, Jensen CT, Palmquist S, Pickhardt PJ, Duran A, Broering G, et al. Angiosarcoma: clinical and imaging features from head to toe. Br J Radiol. 2017;90(1075):20170039.
6. Florou V, Wilky BA. Current and future directions for angiosarcoma therapy. Curr Treat Options in Oncol. 2018;19(3):14.
7.•• 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–.

Results of the highly impactful Angiosarcoma Project in terms of expanding the knowledge on angiosarcoma at the tumor genomic level.

8. Boichard A, Wagner MJ, Kurzrock R. Angiosarcoma heterogeneity and potential therapeutic vulnerability to immune checkpoint blockade: insights from genomic sequencing. Genome Med. 2020;12(1):61.
9. Chan JY, Lim JQ, Yeong J, Ravi V, Guan P, Boot A, et al. Multiomic analysis and immune profiling reveal distinct subtypes of human angiosarcoma. J Clin Invest. 2020;130(11):5833–46.
10. Weidema ME, van de Geer E, Koelsche C, Desar IME, Kemmeren P, Hillebrandt-Roeffen MHS, et al. DNA methylation profiling identifies distinct clusters in angiosarcomas. Clin Cancer Res. 2020;26(1):93–100.
11. Co M, Lee A, Kwong A. Cutaneous angiosarcoma secondary to lymphoedema or radiation therapy — a systematic review. Clin Oncol. 2019 Apr;31(4):225–31.
12. Palmerini E, Leithner A, Windhager R, Gosheger G, Boye K, Laitinen M, et al. Angiosarcoma of bone: a retrospective study of the European Musculoskeletal Oncology Society (EMSOS). Sci Rep. 2020;10(1):10853.
13. Fayette J, Martin E, Piperno-Neumann S, Le Cesne A, Robert C, Bonvalot S, et al. Angiosarcomas, a heterogeneous group of sarcomas with specific behavior depending on primary site: a retrospective study of 161 cases. Ann Oncol. 2007;18(12):2030–6.
14. Heinhuis KM, IJzerman NS, van der Graaf WTA, Kerst JM, Schrage Y, Beijnen JH, et al. Neoadjuvant systemic treatment of primary angiosarcoma. Cancers (Basel). 2020;12(8):2251.
15. Constantinidou A, Sauve N, Stacchiotti S, Blay J-Y, 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.
16.• Roy A, Gabani P, Davis EJ, Oppelt P, Merfeld E, Keedy VL, et al. Concurrent paclitaxel and radiation therapy for the treatment of cutaneous angiosarcoma. Clin Transl Radiat Oncol. 2021:114–20.

First report on efficacy of concurrent chemoradiation in localized cutaneous angiosarcoma, that may change the standard approach in this setting if findings are confirmed in the ongoing phase II study.

17. 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. 2014;50(18):3178–86.
18. D'Angelo SP, Munhoz RR, Kuk D, Landa J, Hartley EW, Bonafede M, et al. Outcomes of systemic therapy for patients with metastatic angiosarcoma. Oncology. 2015;89(4):205–14.
19. 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. 2008;26(32):5269–74.
20. Schlemmer M, Reichardt P, Verweij J, Hartmann JT, Judson I, Thyss A, et al. Paclitaxel in patients with advanced angiosarcomas of soft tissue: a retrospective study of the EORTC soft tissue and bone sarcoma group. Eur J Cancer. 2008;44(16):2433–6.
21. Fata F, O'Reilly E, Ilson D, Pfister D, Leffel D, Kelsen DP, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. Cancer. 1999;86(10):2034–7.
22. 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. 2012;23(2):501–8.
23. Tian Z, Zhang F, Li P, Wang J, Yang J, Zhang P, et al. Albumin-bound paclitaxel and gemcitabine combination therapy in soft tissue sarcoma. BMC Cancer. 2020;20(1):698.
24. Fujisawa Y, Fujimura T, Matsushita S, Yamamoto Y, Uchi H, Otsuka A, et al. The efficacy of eribulin mesylate for patients with cutaneous angiosarcoma previously treated with taxane: a multicentre prospective observational study. Br J Dermatol. 2020 Nov 26;183(5):831–9.
25. Ravi V, Wagner M, Chen TW-W, Loong HHF, Mennel RG, Yen C-C, et al. A phase II study of oraxol in the treatment of unresectable cutaneous angiosarcoma. J Clin Oncol. 2020;38(15_suppl):11517.
26. Hamerlik P, Lathia JD, Rasmussen R, Wu Q, Bartkova J, Lee M, et al. Autocrine VEGF–VEGFR2–Neuropilin-1 signaling promotes glioma stem-like cell viability and tumor growth. J Exp Med. 2012;209(3):507–20.
27. Itakura E, Yamamoto H, Oda Y, Tsuneyoshi M. Detection and characterization of vascular endothelial growth factors and their receptors in a series of angiosarcomas. J Surg Oncol. 2008;97(1):74–81.
28. Zietz C, Rössle M, Haas C, Sendelhofert A, Hirschmann A, Stürzl M, et al. MDM-2 oncoprotein overexpression, p53 gene mutation, and VEGF up-regulation in angiosarcomas. Am J Pathol. 1998;153(5):1425–33.
29. Agulnik M, Yarber JL, Okuno SH, von Mehren M, Jovanovic BD, Brockstein BE, et al. An open-label,

multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol. 2013;24(1):257–63.
30. 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. 2015;33(25):2797–802.
31. Dickson MA, D'Adamo DR, Keohan ML, D'Angelo SP, Carvajal RD, Gounder MM, et al. Phase II trial of gemcitabine and docetaxel with bevacizumab in soft tissue sarcoma. Sarcoma. 2015;2015:532478.
32. 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 (Madr). 2017;56(1):88–92.
33. von Mehren M, Litwin S, Ravi V, Schuetze S, Movva S, Agulnik M, et al. Multicenter phase II trial of pazopanib (P) in patients with angiosarcoma (AS). J Clin Oncol. 2019;37(15_suppl):11039.
34. Ravi V, Sanford EM, Wang W-L, Ross JS, Ramesh N, Futreal A, et al. Antitumor response of VEGFR2- and VEGFR3-amplified angiosarcoma to pazopanib. J Natl Compr Canc Netw. 2016;14(5):499–502.
35. Mir O, Brodowicz T, Italiano A, Wallet J, Blay JY, Bertucci F, et al. Safety and efficacy of regorafenib in patients with advanced soft tissue sarcoma (REGOSARC): a randomised, double-blind, placebo-controlled, phase 2 trial. Lancet Oncol. 2016;17(12):1732–42.
36. Agulnik M, Robinson SI, Okuno SH, Siontis B, Attia S, Kocherginsky M, et al. Multicenter, open-label phase II study of daily oral regorafenib for chemotherapy-refractory, metastatic and locally advanced angiosarcoma. J Clin Oncol. 2020;38(15_suppl):11561.
37. Jones R, Ravi V, Brohl AS, Chawla SP, Ganjoo K, Italiano A, et al. Results of the TAPPAS trial: An adaptive enrichment phase III trial of TRC105 and pazopanib (P) versus pazopanib alone in patients with advanced angiosarcoma (AS). Ann Oncol [Internet]. 2019 Oct;30:v683.
38. Marabelle A, Fakih M, Lopez J, Shah M, Shapira-Frommer R, Nakagawa K, et al. Association of tumour mutational burden with outcomes in patients with advanced solid tumours treated with pembrolizumab: prospective biomarker analysis of the multicohort, open-label, phase 2 KEYNOTE-158 study. Lancet Oncol. 2020;21(10):1353–65.
39. 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.
40.• Florou V, Espejo Freire A, Goel N, Rosenberg AE, Wilky BA, Trent JC. Safety and efficacy of immune checkpoint inhibitors in patients with angiosarcoma. In: CTOS Annual Meeting. 2019.

First case series describing the use and efficacy of immune checkpoint inhibitors in patients with angiosarcoma.

41. Sindhu S, Gimber LH, Cranmer L, McBride A, Kraft AS. Angiosarcoma treated successfully with anti-PD-1 therapy—a case report. J Immunother cancer. 2017;5(1):58.
42. Momen S, Fassihi H, Davies HR, Nikolaou C, Degasperi A, Stefanato CM, et al. Dramatic response of metastatic cutaneous angiosarcoma to an immune checkpoint inhibitor in a patient with xeroderma pigmentosum: whole-genome sequencing aids treatment decision in end-stage disease. Mol Case Stud. 2019;5(5):a004408.
43. Hamacher R, Kämpfe D, Reuter-Jessen K, Pöttgen C, Podleska LE, Farzaliyev F, et al. Dramatic response of a PD-L1–positive advanced angiosarcoma of the scalp to pembrolizumab. JCO Precis Oncol. 2018;16(2):1–7.
44. Wagner M, Othus M, Patel S, Ryan C, Sangal A, Powers B, et al. 795 A 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. 2020;8(Suppl 3):A843.

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