Cutaneous Angiosarcomas: Molecular Pathogenesis Guides Novel Therapeutic Approaches

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Summary
Cutaneous angiosarcoma (CAS) is a highly aggressive cancer with a poor prognosis. Primary, spontaneous CAS (pCAS) and secondary, post-irradiation- or lymphedema-associated CAS (sCAS) are clinically, but also molecularly distinct. Myc amplification/overexpression is a characteristic, although not exclusive feature of sCAS, while loss of TP53 selectively occurs in pCAS. Detailed molecular analyses with modern multi-omics approaches have revealed that both pCAS and sCAS exhibit considerable molecular heterogeneity. Affected genes and their molecular regulators including a plethora of microRNAs may serve as future drug targets. Furthermore, pCAS could be subdivided into clusters with high tumor mutational burden and/or high tumor inflammation signatures providing a rationale for the stratification of pCAS patients in future immunotherapeutic clinical studies. Development of novel treatment regimens guided by these molecular alterations, however, cannot fully keep up with the pace of their discovery due to the low incidence of the disease. Nevertheless, beyond conventional surgery and chemoradiotherapy, clinical trials investigating novel treatment options have been initiated including targeted therapies against VEGF and VEGFR1–3 such as bevacizumab and pazopanib, and β-adrenoreceptor blockers such as propranolol. Finally, immunotherapies are being developed including immune checkpoint inhibitors pembrolizumab and nivolumab as well as anti-RANKL antibody denosumab.

Epidemiology and Clinical Manifestations
Angiosarcoma (AS) is a rare soft tissue sarcoma. Angiosarcoma accounts for approximately 1% of all soft tissue sarcomas, and the incidence is 0.01–0.05 per 100,000 persons per year [1]. Angiosarcoma can occur on the skin and in different other organs (breast, thyroid, lung, liver, kidney, heart), with cardiac AS possibly being a special form. In addition to the organ of manifestation, a distinction is made between primary and secondary AS (Table 1). Primary AS occur sporadically and are predominantly localized in the skin (60%). Primary cutaneous angiosarcoma (pCAS) is a highly malignant tumor of the elderly patient with an age peak of 60–70 years. Classically, pCAS occurs on sun-damaged skin of the scalp and face, while the trunk (25%) and the extremities (15%) are less frequently involved. People with lighter skin types are more frequently affected and among Asian patients, involvement of the scalp and face is even more common (95%). With a ratio of 2 : 1, men are more frequently affected than women. Clinically, predictive factors for a poor prognosis of pCAS are age (> 70 years), tumor size (> 5 cm), tumor location (capillitium), resection with positive margins, and advanced stage.

Clinical presentation of pCAS is variable depending on the extent and the stage of the disease making early detection difficult. Most commonly, erythematous plaques and patches are found (Figure 1a), but pCAS can also occur as circumscribed erythema, purpuric lesions, and livid-to-bluish-brownish plaques or nodules (Figure 1b), as well as morphea-like or hyperkeratotic lesions (Figure 1c). In the course of the disease ulceration of the plaques and tumor nodules may develop. Differential diagnosis may be difficult merely on clinical
grounds and may vary with location. Primarily, other benign or malignant vascular lesions may be considered. However, the development of malignant vascular tumors on the basis of a congenital hemangioma or of congenital vascular malformations such as a portwine stain is extremely rare [2]. As an example, for a special location, pCAS may occur on the nose, evoking an array of differential diagnoses such as rosacea with development of rhinophyma, Morbihan’s disease, lupus pernio, Kaposi’s sarcoma on the nose or primary cutaneous acral CD8+ T-cell lymphoma (Figure 1b).

Secondary CAS (sCAS) comprises lymphedema-associated sCAS and post-irradiation sCAS (Figure 2a–c). Chronic lymphedema-associated sCAS most often occurs after radical mastectomy or axillary lymph node dissection, a condition first described by Stewart and Treves in 1948 (so-called Stewart-Treves syndrome). However, lymphedema-associated sCAS can also arise on any other type of chronic lymphedema. Typically, lymphedema-associated sCAS presents with livid-erythematous plaques with cutaneous or subcutaneous nodules. Conversely, post-irradiation sCAS most

| Location                      | Lymphedema-associated sCAS | Post-radiation sCAS |
|-------------------------------|-----------------------------|---------------------|
| Head, neck, and scalp         | Extremities, breast, trunk  | Breast, chest wall  |
| Clinical presentation         | Livid-erythematous plaques and cutaneous and subcutaneous nodules | Red-brownish papules and nodules on erythematous livid-brown plaques |
| Causation                     | Lymphedema after mastectomy or axillary lymph node dissection or any other chronic lymphedema | Mastectomy and subsequent radiation of mammary carcinoma |
| Histogenesis                  | Blood vascular or lymphatic EC | Blood vascular or lymphatic EC |
| Lead molecular alteration     | Loss of tumor suppressor gene TPS3 | over-expression/amplification of Myc oncogene |
| Molecular patterns            | MAP kinase pathway – KRAS, HRAS, NRAS, BRAF, MAPK1, NF1 | KIT, FLT4, RET, UNC5A, CTLA4, ISRL2, ICOS, RAB17, RASGRP3, CDKN2C, HRAS, PDGFRB |
| Others: PTPRB/VE-PTP (inhibitor of VEGFR1–3), PLCG1, NTSR-1, ANKRDS1, CDKN2A |
| Fusion gene: NUP160-SCL43A3   | |
| Clusters (multi-Omics and immunoprofiling) | Cluster 1: high TMB/UV signature; low TIS; Cluster 3: high TMB/UV signature; high TIS | Cluster 2: low TMB; low TIS |
| Surgical management           | Complete resection with wide excisional margins | Complete resection with wide excisional margins |
| Chemotherapy                  | Metastatic or locally advanced AS | Metastatic or locally advanced AS |
| Radiotherapy                  | Adjuvant | Adjuvant |
| Prognosis                     | Poor | Poor |

Abbr.: TMB, tumor mutational burden; TIS, tumor inflammation signature.
commonly arises after mastectomy and subsequent radiation because of a mammary carcinoma. Therefore, post-irradiation sCAS localizes primarily to the breast, the chest wall, or sporadically to the flank, axilla, groin, shoulder, and rather rarely to the leg. Clinically, red-brownish papules and nodules develop on erythematous-to-livid-brownish plaques. In addition, ulceration may also develop. Because of increasing numbers of breast-conserving surgery and concomitant radiotherapy, the incidence of post-irradiation sCAS is rising. As differential diagnosis to post-irradiation sCAS, atypical vascular lesions (AVL) have to be considered. Atypical vascular lesions mimic low-grade post-irradiation sCAS occurring in the same group of patients. Differential diagnosis between AVL and post-irradiation sCAS is challenging because of overlapping histological features, especially in small biopsies. Upon resection, up to 50 % of AVL lesions turn out to contain post-irradiation sCAS. In contrast to post-irradiation sCAS, however, AVL typically take a benign course, with true progression of AVL to post-irradiation sCAS of less than 10 % [3].

**Histogenesis**

Angiosarcoma and CAS are malignant vascular tumors (Figure 3a) thought to derive from blood vascular or lymphatic endothelial cells. The true cell of origin of the diverse forms of AS and CAS, however, hitherto remains elusive. This is due to the fact that endothelial cells (EC) may undergo transdifferentiation from one type of endothelial cells to another or may assume a pathological state of endothelial differentiation; in addition, lineage specificity of blood vascular versus lymphatic endothelial marker genes is not sufficient upon immunohistochemical analysis to allow clear-cut attribution to one or the other type of endothelium. A prime example for pathological endothelial transdifferentiation is Kaposi’s sarcoma. In Kaposi’s sarcoma, human herpesvirus (HHV)8 induces lymphatic reprogramming of blood vascular EC with a pathological mixture of 70 % lymphatic and 30 % blood vascular endothelial genes being expressed in the transdifferentiated EC [4]. For AS or CAS, however, similar approaches to dissect the cell of origin have not yet been described.
On the contrary, immunohistochemical detection of vascular endothelial markers has been widely applied in AS and CAS (Figure 3b, c). Markers used include CD31 (Figure 3b) and ERG staining both blood vascular and lymphatic EC alike, CD34 staining subtypes of blood vascular EC and weakly lymphatic EC, Fli-1 being strongly expressed by blood vascular EC, as well as Prox-1, podoplanin (Figure 3c), VEGFR3 and Lyve-1 selectively expressed in normal lymphatic versus blood vascular EC (Table 2). In addition, these EC marker genes frequently show lineage infidelity as they are expressed, for example, in stem cells (CD31, CD34), myeloid cells (CD31, Lyve-1), epithelial cells (Prox-1, podoplanin) or other tumors (Fli-1). Therefore, the results of studies with these markers in benign and malignant vascular neoplasms were inconclusive so that categorization of AS into classical, “blood vascular” versus “lymphatic” subtypes was abandoned. By contrast, Mankey and collaborators identified expression of multiple lymphatic EC markers in ten out of 49 cases of AS and CAS and re-introduced the concept of angiosarcoma with lymphangiosarcomatous differentiation/lymphangiosarcoma. In their study, however, lymphatic EC marker genes were expressed also by 41–69 % of the other AS/CAS cases [5]. Counter-intuitively, these “lymphangiosarcoma” cases were not lymphedema-associated sCAS cases, but clinically represented pCAS of the head and scalp. Recently, complexity has risen even further by the identification of cases categorized as “lymphatic-type angiosarcoma with prominent lymphocytic infiltrate” [6]. Therefore, it remains controversial at present whether “lymphatic-type” angiosarcomas can be clearly differentiated clinically or by histology/immunohistochemistry from “classical” angiosarcoma of presumptive blood vascular origin, and whether such differentiation has prognostic and therapeutic significance.

**Molecular Pathogenesis**

**MYC**

In general, the pathogenesis of CAS is not resolved. Molecularly, CAS seems to be heterogeneous. High-level amplification on chromosome 8q24.21 and strong overexpression of Myc exclusively in sCAS were seminal findings [7] underscoring that the pathogenesis of pCAS and sCAS is different. Meanwhile, Myc amplification/overexpression has also been detected in some cases of pCAS; however, the significance of these findings remains to be elucidated [8]. Amplification/overexpression of Myc can reliably be detected by fluorescent in situ hybridization (FISH) or immunohistochemistry, and analysis of Myc amplification/overexpression aids in the differential diagnosis of sCAS versus AVL, the latter usually being Myc-negative [3]. Novel findings indicate that upregulation of Myc is further induced by upstream signaling pathways.

![Figure 3](image-url) Hematoxylin-eosin stain (HE) and vascular immunohistochemistry of pCAS. Angiosarcoma histology (HE) (a), AS immunohistochemistry, CD-31 (b), AS immunohistochemistry D2-40 (c).
Notably, the so-called atypical Protein kinase C lambda/iota (aPKC\(\lambda\)) is strongly overexpressed in Myc-positive sCAS. aPKC\(\lambda\) is a key regulator of cell polarity important in many epithelial tissues and carcinoma pathogenesis, but it also controls endothelial cell proliferation. aPKC\(\lambda\) phosphorylates the endothelial transcription factor FoxO1 at Ser218 inactivating its DNA binding site. In pCAS, FoxO1 Ser218 is no longer able to bind and activate the promoter of micro-RNA miR-34c whose normal function is to suppress Myc expression [9]. This cascade of molecular alterations altogether results in overexpression of Myc (Figure 4). Notably, aPKC\(\lambda\) also upregulates PD-L1 [10]. While directly targeting Myc is a challenging task in cancer, aPKC\(\lambda\) inhibitors as well as miR-34c mimetics that pharmacologically mimic the role of natural miR-34c may be developed into sCAS/AS drugs in the future.

**microRNAs**

In addition to miR-34c, miRNAs seem to play an ever-increasing role in AS (Table 3). miR-17-92 was shown to be significantly up-regulated in the context of Myc up-regulation in sCAS, but not in pCAS. miR-17-92 up-regulation cause down-regulation of thrombospondin-1, a potent endogenous inhibitor of angiogenesis [11]. Angiosarcoma-derived miR-126 and miR-214 have been shown to represent biomarkers of AS released into the circulating plasma via microvesicles from AS cells; miR-126 controls Egfl7, a modulator of angiogenesis [12]. Similarly, miR-210 is down-regulated in AS and targets Ephrin A3 known to modulate (tumor) angiogenesis [13]. In another study, miR-222-3p was shown to be up-regulated, while miR-497-5p, miR-378-3p, and miR-483-5p were down-regulated in AS. miR-222-3p targets vascular endothelial zinc finger (VEZF)1, a regulator of vascular integrity and angiogenesis. Down-regulation of miR-497-3p led to marked up-regulation of intermediate conductance calcium-activated potassium channel KCa3.1; KCa3.1 mediates endothelial proliferation and angiogenesis. Application of TRAM-34, a KCa3.1 inhibitor, or of a miR-497-5p mimetic inhibited proliferation of angiosarcoma cell lines in vitro and reduced tumor growth in a xenotransplant model in vivo [14]. Finally, biallelic loss of Dicer1, an enzyme indispensable for microRNA synthesis, drives development of highly aggressive angiosarcomas [15]. Therefore, antagoniRs or miR
mimetics may have high potential as future drugs against angiosarcoma, especially sCAS and AS.

A plethora of mutated, dysregulated, dysfunctional genes

Besides Myc and miRs, pCAS and sCAS show distinct mutational profiles (Table 1). While sCAS exhibits mutations in KIT, FLT4, RET, UNC5A, CTLA4, ISRL2, ICOS, RAB17, and RASGRF3, pCAS contains mutations in TP53 as well as in several proteins of the MAP kinase pathway such as KRAS, HRAS, NRAS, BRAF, MAPK1, and NF1. Furthermore, pCAS harbors mutations in PTTRB/VE-P, PLCG1, NTSR-1, ANKRD1, and CDKN2A as well as the fusion gene NUP160-SCL43A3 [16–19]. Notably, TP53 loss of function and Myc amplification/overexpression occur in

| microRNA  | Regulation of expression in AS | Putative target(s) | Regulation of target(s) | Function | AS subtype |
|-----------|---------------------------------|---------------------|-------------------------|----------|------------|
| miR-17-92 (11) | Up-regulated | Thrombospondin-1 | Down-regulated | Inhibitor of angiogenesis | sCAS |
| miR-34c (6) | Down-regulated | Myc | Up-regulated | Oncogene | sCAS |
| miR-126 (8) | Up-regulated | DNA-methyltransferase-1 (Dnmt1) | Down-regulated | As biomarker, released into the circulation in extracellular vesicles; hypomethylation-associated activation of egfl7, a regulator of angiogenesis | N. d. |
| miR-210 (10) | Down-regulated | Ephrin A3 | Up-regulated | Modulation of (tumor) angiogenesis | N. d. |
| miR-214 (8) | Up-regulated | N. d. | N. d. | As biomarker, released into the circulation in extracellular vesicles; angiocrine mediator of exosome-induced angiogenesis | N. d. |
| miR-222-3p | Up-regulated | Peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α), vascular endothelial zinc finger (VEZF)1, phosphodieste- terase 3 (PDE3) | Down-regulated | Regulation of energy metabolism, vascular integrity and angiogenesis | N. d. |
| miR-378-3p (9) | Down-regulated | Unknown | N. d. | N. d. | N. d. |
| miR-483-5p (9) | Down-regulated | Unknown | N. d. | N. d. | N. d. |
| miR-497-5p (9) | Down-regulated | Intermediate conductance calcium-activated potassium channel KCa3.1 | Up-regulated | Endothelial proliferation and angiogenesis | N. d. |
| Dicer (12) | Bi-allelic loss | N. a. | N. a. | Synthesis of microRNA; genetic engineered deficiency in endothelial cells drives development of hepatic as | Hepatic AS |

Abbr.: n. d., no date; n. a., not applicable.
an almost mutually exclusive manner in pCAS and sCAS, respectively. Regarding MAP kinase pathway involvement, Dai and collaborators have reported development of RET mutant pCAS during BRAF inhibitor therapy indicating that paradoxical activation of the MAP kinase pathway upon treatment with BRAF inhibitors may not only cause squamous cell carcinomas and keratoacanthomas, but occasionally also pCAS [20]. Functionally, PTPRB/VE-PTP is of special relevance as it inhibits the vascular endothelial growth factor (VEGF) receptor tyrosine kinases (VEGFR1–3). VEGFR1–3 are strongly overexpressed in AS [21] as is Ang2 receptor Tie2 [22] and both receptor tyrosine kinase systems may be appropriate targets for treating AS. Survivin and the Hippo signaling pathway may also be potential therapeutic targets in pCAS [23]. In addition, Notch1 has been described as a potential tumor suppressor gene especially in CAS, but also AS from other sites [24]. Confirming these findings, Notch1 silencing in liver endothelial cells led to hepatic angiosarcomas [25].

Tumor mutational burden and tumor inflammation signatures

Only recently, Chan JY and collaborators [26] systematically broadened molecular dissection of AS by employing a multi-omics approach and immunoprofiling. Molecular distinction between pCAS (clusters 1 and 3) and sCAS (cluster 2) was confirmed by their study. pCAS was subdivided into two clusters with low (cluster 1) or high (cluster 3) tumor inflammation signatures (TIS), respectively. In both clusters 1 and 3, approx. 50 % of cases show UV mutational signatures and high tumor mutational burden (TMB) (Table 1). Cluster 3 with high TMB and high TIS scores provides the rationale for immune checkpoint inhibitor (ICI) immunotherapy supported by the dramatic response of a metastatic pCAS to ICI therapy in a patient with xeroderma pigmentosum [27].

Standard of Care

Surgery

Complete resection with wide excisional margins is the primary approach in the treatment of CAS (R0 resection) [28]. Resection, especially R0 resection, was shown to be the most effective procedure to increase the 5-year survival rate [29] and positive resection margins were correlated with poor prognosis [29]. However, tumor-free surgical margins are indeed achieved in only 20–50 % of patients and despite R0 resection the prognosis of patients especially with tumors > 5 cm remains dismal, due to local recurrences [30–32]. In addition, there is no widely accepted clear-cut definition of wide excision or of the size of clinically determined or histopathologically controlled safety margins. Deep excisional margins are also not well defined. If not infiltrated, it is generally accepted to resect the fascia to achieve R0 resection; if infiltrated, the structures underlying the fascia such as portions of the muscle or the periosteum must also be resected to achieve R0 status. In pCAS of the scalp and even more so of the face, surgical R0 resection is often not possible due to the limitations enforced by the anatomical localization. As a consequence, local recurrence rates after surgical treatment of CAS are generally high [31, 32].

In addition to radical surgery, palliative surgery to reduce tumor burden and maintain quality of life is used primarily in patients with very extensive tumor involvement and poor prognosis. A special form of palliative surgery is electrochemotherapy (ECT). Recently, Campana and collaborators reported a European registry-based cohort study on ECT for advanced CAS. ECT was well tolerated and produced sustained response rates with minimal side effects [33].

Radiotherapy

To reduce local recurrence, postoperative radiotherapy with an irradiation dose of > 70 Gy has been reported to be effective in terms of local control of the tumor [34]. Currently, radical resection followed by postoperative radiotherapy is the treatment of choice for local, well-demarcated cases of CAS. In general, multimodality therapy comprising surgical intervention plus postoperative radiation significantly improves local tumor control, disease-specific survival, and overall survival [32]. In contrast to postoperative radiotherapy, primary radiotherapy has mostly been applied to inoperable patients with CAS, but reliable study data are lacking.

Chemotherapy

As prognosis of CAS, especially with tumors > 5 cm, is poor even after conventional treatment with surgery (R0) and radiotherapy, alternative treatment options have been studied, i.e., chemoradiotherapy. Fujisawa and collaborators reported that first line chemoradiotherapy with taxane is superior to surgery and postoperative radiotherapy, especially when followed by maintenance chemotherapy [35]. The most commonly used taxanes in the therapy of AS are paclitaxel and docetaxel. Recently, nab-paclitaxel, a novel 130 nm albumin particle-bound (nab) formulation of paclitaxel with improved pharmacokinetics, was successfully used in a patient with metastasized CAS [36]. Several other chemotherapeutic agents are also available for the treatment of CAS such as doxorubicin, ifosfamide and gemcitabine. Gemcitabine is used both as a single agent and in combination with docetaxel. In addition to taxanes, trabectedin is a novel DNA-binding agent approved for the second-line treatment of soft tissue
sarcomas including AS; however, trabectedin is only moderately effective in AS [28]. Another novel drug with potential benefit for CAS is eribulin mesylate. Eribulin is a cytostatic drug that targets microtubules to prevent tumor cell proliferation. Recently, the results of a first observational study on the efficacy of eribulin mesylate as second-line treatment in patients with CAS were published [37]. Response rates were promising (14–20 %) making eribulin mesylate a potential candidate for second-line treatment in CAS after taxane therapy.

**Novel treatment options**

**Targeted therapies**

As AS is a vascular tumor and as vascular endothelial growth factor (VEGF) receptors have been shown to be overexpressed in CAS, VEGF and VEGFR inhibitors or multi-tyrosine kinase inhibitors are potential drug targets in CAS. Bevacizumab, a VEGF inhibitor, has been shown to be effective as monotherapy in AS [38]. However, in combination with paclitaxel chemotherapy, bevacizumab offered no additional benefit [39]. Therefore, bevacizumab could be a therapeutic option for second-line treatment of CAS following paclitaxel.

In contrast, pazopanib is a multi-tyrosine kinase inhibitor targeting VEGF-R1–3, platelet growth factor receptor (PDGF-R) and c-Kit. Pazopanib has been shown to be effective in patients with AS in a large retrospective analysis [40]. Ogata and collaborators reported that pazopanib slows progression in taxane-resistant CAS [41]. On the contrary, Kitamura and collaborators did not find a difference in CAS patients treated with or without pazopanib [42]. In a single institution study, the overall response rate to pazopanib (800 mg daily, high dose) in CAS patients was 60 % [43]. To clarify these discrepancies, a single-arm trial of pazopanib in patients with paclitaxel-pretreated patients with pCAS is currently conducted.

As the non-selective β-adrenergic receptor blocker propranolol was found to be highly effective in severe hemangiomas of infancy, it seemed a reasonable approach to investigate propranolol also in CAS especially in respect to few side effects. Several case reports have confirmed this notion. In addition, Pasquier and collaborators successfully treated a series of seven patients [44], and Amaya and collaborators successfully treated nine patients with AS with propranolol [45]. At present, the efficacy of propranolol in CAS is studied in a neoadjuvant trial.

**Immunotherapies**

As already discussed, the multi-omics analysis and immunoprofiling study by Chan and collaborators provides a rationale for the use of immune checkpoint inhibitor (ICI) therapies in patients with pCAS [26]. The highest probability for a good response rate may be ascribed to cluster three patients with high TIS, especially in combination with high TMB as assessed immunohistochemically by cyclobutane pyrimidine dimer staining (50 % of cluster 3 patients). Cluster 1 pCAS patients with low TIS, but high TMB could also be considered to profit from ICI treatment (50 % of cluster 1 patients). Currently, only limited information is available regarding the clinical value of ICI therapy in CAS. Florou and collaborators treated seven patients with CAS with different ICI regimens resulting in a 71 % overall response rate [46]. Apart from this study, only three case reports describe positive responses to ICI in CAS. In contrast to the scarcity of clinical studies, several immunohistochemical analyses of the expression of immune checkpoint molecules such as PD-1 and PD-L1 in tissue sections have been published with contradictory results regarding prognosis [10, 47–49]. Therefore, further studies are needed to clarify the relevance of ICI therapy in CAS.

In addition to ICI therapy, IL-2 therapy was studied in CAS in combination with radiotherapy and revealed an overall survival of 36.2 months [50]. In the following years, IL-2 therapy was described to be successfully used in several case reports. More recently, long-term remissions were achieved in patients with prior IL-2 therapy by maintenance treatment with pazopanib [51] and by protracted intralesional IL-2 therapy [52].

Finally, the RANK–RANKL pathway may be an additional immune target in CAS. Maeda and collaborators treated bone metastases in a patient with CAS with denosumab, a monoclonal antibody targeting RANK, and showed strong up-regulation of RANK and RANKL on malignant endothelial cells of AS tissue specimens [53]. Notably, the RANK–RANKL pathway is involved not only in immune stimulation, but also in regulation of angiogenesis. Therefore, combination therapies of ICI therapies and targeted therapies could be beneficial in CAS and should be further evaluated in clinical studies. Table 4 summarizes the recent clinical studies in CAS, while Figure 3 provides a flowchart of recommended therapies for the different stages of CAS.

**Concluding Remarks**

Despite the achievements described here, progress in the molecular pathogenesis and in the establishment of evidence-based treatment modalities for CAS is too slow to meet the urgent clinical needs of the patients who succumb to this highly aggressive cancer with a still dismal prognosis. We therefore strongly advocate to join forces in a structured effort of collaboration and to form an international study group for the advancement of molecular research and treatment of CAS.
Table 4 Article on the treatment options of CAS (published 2015-2021).

| Reference          | Indication        | Treatment regimen                  | Sex | Age (in years) | Study design                  | Number of patients | Key findings                                                                 |
|--------------------|-------------------|------------------------------------|-----|----------------|-------------------------------|--------------------|-----------------------------------------------------------------------------|
| Trofymenko O et al. [54] | N/a               | Surgery                            | N/a | N/a            | Retrospective, multicentric   | 624                | Only surgery – esp. when ensuring negative margins – is predictive for improved OS (Hazard ratio: 0.44; 95% confidence interval: 0.31–0.63) |
| Scholtz J et al. [55]  | First-line        | Surgery                            | F   | 83             | Case report                   | 1                  | N/a                                                                         |
| Choi JH et al. [56]  | First-line        | Surgery                            | M: 3 | Ø 75,7         | Retrospective, unicentric     | 3                  | N/a                                                                         |
| Sanada T et al. [57]  | First-line        | Definitive brachytherapy (45–60 Gy) | F: 3 | Ø 82,1         | Retrospective, unicentric     | 9                  | N/a                                                                         |
| Suzuki G et al. [58]  | First-line        | Radiotherapy (60–100 Gy)           | F: 5 | Ø 77           | Retrospective, unicentric     | 14                 | mOS: 31 months                                                               |
| Ito T et al. [59]    | First-line        | Radiotherapy (45–85 Gy)            | N/a | N/a            | Retrospective, unicentric     | 31                 | N/a                                                                         |
| Ito T et al. [59]    | First-line        | Chemotherapy with taxane (docetaxel, paclitaxel) | N/a | N/a            | Retrospective, unicentric     | 19                 | mOS: 62.2 months 5 y RF: 34.9%                                               |
| Kajihara I et al. [60] | First- & second-line | Chemotherapy, biweekly Gemcitabine monotherapy | F:1 | 60             | Case report                   | 1                  | CR                                                                          |
| Kajihara I et al. [61] | Second-line       | S-1/docetaxel, chemotherapy        | F:1 | 70             | Case report                   | 1                  | PR                                                                          |
| Fujisawa Y et al. [37] | Second-line & third-line | Eribulin                            | F: 4 | Ø 74           | Prospective, multicentric     | 25                 | mOS: 8.6 months PFS: 3 months                                                |
| Fujimura T et al. [62] | Second-line      | Eribulin                            | F: 1 | Ø 73           | Case series                   | 3                  | N/a                                                                         |
| Liu D et al. [63]    | Second-line       | Paclitaxel, PDT: 20 % 5-ALA, Surgery | F   | 49             | Case report                   | 1                  | CR                                                                          |
| Campana LG et al. [33] | Second-line      | ECT (electrochemotherapy)          | F: 13 | Ø 76           | Prospective, multicentric     | 20                 | CR: 40 % (8/20); PR: 40 % (8/20); SD: 15 % (3/20); PD: 5 % (1/20)           |
| Ihara H et al. [64]  | First-line        | CCRT concurrent chemoradiation with maintenance chemotherapy | N/a | N/a            | Retrospective, unicentric     | 9                  | 3 y OS: 75 % 3 y PFS: 55 %                                                  |

Continued
| Reference | Indication | Treatment regimen | Sex | Age (in years) | Study design | Number of patients | Key findings |
|-----------|------------|-------------------|-----|----------------|--------------|-------------------|--------------|
| Roy A et al. [65] | First-line Concurrent paclitaxel-based chemoradiotherapy | F: 7 M: 15 | N/a | Retrospective, multicentric | 22 | 2 y OS: 94.1% |
| Oashi K et al. [66] | N/a | Multimodal therapy (surgery or non-surgery or group + chemotherapy or radiation or both) | N/a | N/a | Retrospective, unicentric | 23 | 5 y OS: 28.6% mOS: 38 months |
| Herrscher H et al. [67] | First-line Multimodal therapy (neo-adjuvant chemotherapy + radiation) | M: 1 | Ø 72 | Case report | 67 | 3 | CR |
| Chow TL et al. [68] | First-line Multimodal therapy (surgery + radiotherapy or chemotherapy + radiation) | M: 3 | Ø 72 | Retrospective, unicentric | N/a | 3 | CR |
| Cassidy RJ et al. [69] | Multimodal therapy (surgery + postoperative chemotherapy or chemoradiation + surgery) | N/a | Ø 72 | Retrospective, unicentric | N/a | N/a | 3 | mOS: 34 months |
| Mullins B et al. [70] | First-line Multimodal therapy (surgery + adjuvant radiation therapy or neoadjuvant chemoradiation + surgery) | N/a | Ø 72 | Retrospective, unicentric | N/a | N/a | 3 | CR |
| Andrá C et al. [71] | N/a | Multimodal therapy (surgery + postoperative radiation therapy) | N/a | N/a | Retrospective, unicentric | N/a | N/a | 40 | 5 y OS: 46% 5 y RF: 19% |
| Patel S et al. [72] | N/a | Multimodal therapy (combination of surgery, radiation therapy and/or chemotherapy) | N/a | N/a | Retrospective, unicentric | N/a | N/a | 40 | 5 y OS: 46% 5 y RF: 19% |
| Ye J et al. [73] | First-line Multimodal therapy (surgery + chemotherapy + anti-angiogenic therapy) | M: 1 | Ø 72 | Case report | 67 | 3 | mOS: 38 months |
### Table 4 Continued.

| Reference             | Indication            | Treatment regimen                                      | Sex  | Age (in years) | Study design               | Number of patients | Key findings                           |
|-----------------------|-----------------------|--------------------------------------------------------|------|----------------|---------------------------|-------------------|----------------------------------------|
| Pasquier E et al. [44] | First- & second- & third-line | β-blocker and vinblastine-based metronomic chemotherapy | F: 2 | Ø 53           | Retrospective, unicentric | 7                 | CR: 14 % (1/7) PR: 43 % (3/7)            |
| Amaya CN et al. [45]  | Second-line           | β-blocker (propranolol, carvedilol) in combination with anti-cancer treatment regimen | F: 6 | N/a            | N/a                       | 9                 | PFS: 9 months OS: 36 months              |
| Chow W et al. [74]    | Second-line           | β-blocker, systemic therapy, radiation                 | M    | N/a            | Case report               | 1                 | PR                                     |
| Heinhuis KM et al. [75]| First-line            | Neoadjuvant propranolol                                 | N/a  | N/a            | Neoadjuvant trial, Prospective | 14                | Neoadjuvant trial on the efficacy of propranolol mono-therapy |
| Ray-Coquard IL et al. [39]| First- & second-line | Paclitaxel alone (Arm A) Paclitaxel + bevacizumab (Arm B) | F: 38 M: 11 Arm A: Ø 65,5 Arm B: Ø 66 | Retrospective, multicentric | n = 24, arm A n = 25, arm B total: 49 | A: mOS: 19.5 months, PFS: 6.6 months B: mOS: 15.9 months, PFS: 6.6 months |
| Darr-Foit S et al. [76]| First-line            | Paclitaxel, bevacizumab + radiation                     | M    | 69             | Case report               | 1                 | PR                                     |
| Ogata D et al. [41]   | Second-line           | Pazopanib                                               | F: 3 | Ø 72,8         | Retrospective, unicentric | 5                 | PR: 40 % (2/5)                          |
| Kitamura S et al. [42]| First- & second-line  | Pazopanib                                               | F: 2 | Ø 79,6         | Retrospective, multicentric | 8                 | PD: 75 % (6/8) SD: 25 % (2/8) PFS: 1.81 months OS: 14.13 months |
| Kollár A et al. [40]  | First-, second-, third-line | Pazopanib                                               | N/a  | N/a            | retrospective             | 40                | CR: 0 PR: 20 % (8/40) SD: 17,5 % (7/40) PD: 57,5 % (23/40) |
| Fujiwara S et al. [43]| First- & second-line  | Pazopanib                                               | F: 2 | Ø 74,7         | Case series               | 10                | CR: 10 % (1/10) PR: 50 % (5/10) SD: 10 % (1/10) PD: 30 % (3/10) |

Continued
To identify reports on the treatment of CAS published in 2015–2021, a systematic search was performed in PubMed using the following term: ((cutaneous angiosarcoma|ti) OR Angiosarcoma of the head and neck|ti) OR angiosarcoma of the scalp|ti) AND (therapy|Title/Abstract) OR treatment|Title/Abstract) AND (“2015.01.01”[Date - Create]): “2021.03.21”[Date - Create]). Study selection and data extraction were then performed applying the following criteria: inclusion: publications in German or English, prospective or retrospective studies, controlled clinical trials, randomized clinical trials, case reports; exclusion: published in a language other than German or English, animal studies, letters to the editor, expert opinions, practice guideline, guidelines, meta-analyses, pure systematic reviews. Only the potentially most relevant studies were included in the table; studies relevant to the treatment of CAS, e.g. studies including AS and CAS patients, but not identified by the search algorithm were also included in the table.

**Abbr.**: F, female; m, male; N/a, not available; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; OS, overall survival; PFS, progression free survival; RF, recurrence free survival; mOS, median overall survival; 5 y OS, 5 year OS; 5 y RF, 5 year RF; 2 y OS, 2 year OS; 3 y OS, 3 year OS; 3 y PFS, 3 year PFS.

| Reference       | Indication          | Treatment regimen                                                                 | Sex | Age (in years) | Study design                      | Number of patients | Key findings                                                                 |
|-----------------|---------------------|------------------------------------------------------------------------------------|-----|----------------|-----------------------------------|--------------------|------------------------------------------------------------------------------|
| Oashi K et al. [77] | Second-line         | Pazopanib in patients pretreated with paclitaxel                                  | N/a | N/a            | Single arm confirmatory trial, multicentric | Plan to recruit 30 | Evaluation of the efficacy and safety of pazopanib as a second-line treatment in patients pretreated with paclitaxel |
| Ji G et al. [78] | Third-line          | Apatinib                                                                           | M   | 74             | Case report                       | 1                  | PR                                                                            |
| Watanabe M et al. [51] | First-line         | Pazopanib after prior interleukin2                                                 | M: 2| Ø 71           | Case series                       | 2                  | PFS: 9.5 months OS: 37 months                                                |
| Gebhardt C et al. [52] | Second-line        | Second-line interleukin 2                                                         | F   | 75             | Case report                       | 1                  | CR                                                                            |
| Florou V. et al. [46] | Second- & third-line | Pembrolizumab alone (or + Axitinib), AGEN1884 (CT-LA4-inhibitor)               | F: 5| Ø 66,1         | Case series                       | 7                  | PR: 57 % (4/7) CR: 4% (1/7) PD: 29% (2/7)                                    |
| Sindhu S et al. [79] | Second-line         | Anti-PD1 antibody pembrolizumab                                                   | M   | 63             | Case report                       | 1                  | PR                                                                            |
| Hofer S et al. [80] | Third-line          | Anti-PD1 antibody nivolumab                                                       | F   | 81             | Case report                       | 1                  | CR                                                                            |
| Momen S et al. [27] | Fourth-line         | Anti-PD1 antibody pembrolizumab                                                   | M   | 32             | Case report                       | 1                  | CR                                                                            |

Table 4 Continued.
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References

1. Conic RRZ, Damiani G, Frigerio A et al. Incidence and outcomes of cutaneous angiosarcoma: A SEER population-based study. J Am Acad Dermatol 2020; 83: 809–16.
2. Iga N, Endo Y, Fujisawa A et al. Possible association between cutaneous angiosarcoma of the scalp and nuchal salmon patch. J Dermatol 2013; 40: 1049–50.
3. Motaparthi K, Lauer SR, Patel RM et al. MYC gene amplification by fluorescence in situ hybridization and MYC protein expression by immunohistochemistry in the diagnosis of cutaneous angiosarcoma: Systematic review and appropriate use criteria. J Cutan Pathol. 2021; 48(4): 578–86.
4. Hong YK, Foreman K, Shin JW et al. Lymphatic reprogramming of blood vascular endothelium by Kaposi sarcoma-associated herpesvirus. Nat Genet 2004; 36: 683–5.
5. Mankey CC, McHugh JB, Thomas DG et al. Can lymphangiosarcoma be resurrected? A clinicopathological and immunohistochemical study of lymphatic differentiation in 49 angiosarcomas. Histopathology 2010; 56: 364–71.
6. Martinez AP, Zapata M, North PE et al. Lymphatic-type “angiosarcoma” with prominent lymphocytic infiltrate. Am J Surg Pathol 2020; 44: 271–9.
7. Manner J, Radlwimmer B, Hohenberger P et al. MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. Am J Pathol 2010; 176: 34–9.
8. Shon W, Sukov WR, Jenkins SM et al. MYC amplification and overexpression in primary cutaneous angiosarcoma: a fluorescence in-situ hybridization and immunohistochemical study. Mod Pathol 2014; 27: 509–15.
9. Riddell M, Nakayama A, Hikita T et al. aPKC controls endothelial growth by modulating c-Myc via FoxO1 DNA-binding ability. Nat Commun 2018; 9: 5357.
10. Kawamura A, Kawamura T, Riddell M et al. Regulation of programmed cell death ligand 1 expression by atypical protein kinase C lambda/iota in cutaneous angiosarcoma. Cancer Sci 2019; 110: 1780–9.
11. Italiano A, Thomas R, Breen M et al. The miR-17-92 cluster and its target THBS1 are differentially expressed in angiosarcomas dependent on MYC amplification. Genes Chromosomes Cancer 2012; 51: 569–78.
12. Heishima K, Mori T, Ichikawa Y et al. MicroRNA-214 and microRNA-126 are potential biomarkers for malignant endothelial proliferative diseases. Int J Mol Sci 2015; 16: 23377–91.
13. Nakashima S, Jinnin M, Kanemaru H et al. The role of miR-210, E2F3 and ephrin A3 in angiosarcoma cell proliferation. Eur J Dermatol 2017; 27: 464–71.
14. Chen Y, Kuang D, Zhao X et al. miR-497-5p inhibits cell proliferation and invasion by targeting KCa3.1 in angiosarcoma. Oncotarget 2016; 7: 58148–61.
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15 Hanna JA, Drummond CJ, Garcia MR et al. Biallelic Dicer1 Loss Mediated by aP2-Cre Drives Angiosarcoma. Cancer Res 2017; 77: 6109–18.
16 Murali R, Chandramohan R, Möller I et al. Targeted massively parallel sequencing of angiosarcomas reveals frequent activation of the mitogen activated protein kinase pathway. Onco-target 2015; 6: 36041–52.
17 Shimozono N, Jinnin M, Masuzawa M et al. NUP160-SLC43A3 is a novel recurrent fusion oncogene in angiosarcoma. Cancer Res 2015; 75: 4458–65.
18 Behjati S, Tarpey PS, Sheldon H et al. Recurrent PTPRB and PLCG1 mutations in angiosarcoma. Nat Genet 2014; 46: 376–9.
19 Ronchi A, Cozzolino I, Zito Marino F et al. Primary and secondary cutaneous angiosarcoma: Distinctive clinical, pathological and molecular features. Ann Diagn Pathol 2020; 48: 151597.
20 Dai J, Knder CA, Chu EY et al. Development of RET mutant cutaneous angiosarcoma during BRAF inhibitor therapy. J Cutan Pathol 2017; 44: 1053–6.
21 Itakura E, Yamamoto H, Oda Y et al. Detection and characterization of vascular endothelial growth factors and their receptors in a series of angiosarcomas. J Surg Oncol 2008; 97: 74–81.
22 Hasenstein JR, Kasmerchak K, Buehler D et al. Efficacy of Tie2 receptor antagonism in angiosarcoma. Neoplasia 2012; 14: 131–40.
23 Tsuneki M, Kinjo T, Mori T et al. Survivin: A novel marker and potential therapeutic target for human angiosarcoma. Cancer Sci 2017; 108: 2295–305.
24 Panse G, Chrisinger JS, Leung CH et al. Clinicopathological analysis of ATRX, DAXX and NOTCH receptor expression in angiosarcomas. Histopathology 2018; 72: 239–47.
25 Dill MT, Rothweiler S, Djonov V et al. Disruption of Notch induces vascular remodeling, intussusceptive angiogenesis, and angiosarcomas in livers of mice. Gastroenterology 2012; 142: 967–77.e2.
26 Chan JY, Lim JQ, Yeong J et al. Multimodal analysis and immunoprofiling reveal distinct subtypes of human angiosarcoma. J Clin Invest 2020; 130: 5833–46.
27 Momen S, Fassihi H, Davies HR 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. Cold Spring Harb Mol Case Stud 2019; 5(5): a004408.
28 Vogt T, Müller CSM, Melchior P et al. Si-Leitlinie Kutane Angiosarkome – Update 2021. AWMF online. 2021/01/01 Edition, 2021.
29 Shin JY, Roh SG, Lee NH et al. Predisposing factors for poor prognosis of angiosarcoma of the scalp and face: Systematic review and meta-analysis. Head Neck 2017; 39: 380–6.
30 Pawlik TM, Paulino AF, McGinn CJ et al. Cutaneous angiosarcoma of the scalp: a multidisciplinary approach. Cancer 2003; 98: 1716–26.
31 Abraham JA, Hornicek FJ, Kaufman AM et al. Treatment and outcome of 82 patients with angiosarcoma. Ann Surg Oncol 2007; 14: 1953–67.
32 Guadagnolo BA, Zags CK, Araujo D et al. Outcomes after definitive treatment for cutaneous angiosarcoma of the face and scalp. Head Neck 2011; 33: 661–7.
33 Campana LG, Kis E, Bottyán K et al. Electrochemotherapy for advanced cutaneous angiosarcoma: A European register-based cohort study from the International Network for Sharing Practices of electrochemotherapy (InspECT). Int J Surg 2019; 72: 34–42.
34 Hata M. Radiation therapy for angiosarcoma of the scalp: total scalp irradiation and local irradiation. Anticancer Res 2018; 38: 1247–53.
35 Fujisawa Y, Yoshino K, Kadono T et al. Chemoradiotherapy with taxane is superior to conventional surgery and radiotherapy in the management of cutaneous angiosarcoma: a multicentre, retrospective study. Br J Dermatol 2014; 171: 1493–500.
36 André F, Frischhut N, Walder A et al. Combined nab-paclitaxel and irradiation for large cutaneous angiosarcoma of the face and scalp with pulmonary metastases. J Dtsch Dermatol Ges 2020; 18: 754–7.
37 Fujisawa Y, Fujimura T, Matsuhashita S 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; 183: 831–9.
38 Aguilnik M, Yarber JL, Okuno SH et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. Ann Oncol 2013; 24: 257–63.
39 Ray-Coquard IL, Domont J, Tresch-Bruneel E 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: 2797–802.
40 Kollár A, Jones RL, Stacchiotti S et al. Pazopanib in advanced vascular sarcomas: an EORTC Soft Tissue and Bone Sarcoma Group (STBSG) retrospective analysis. Acta Oncol 2017; 56: 88–92.
41 Ogata D, Yanagisawa H, Suzuki K et al. Pazopanib treatment slows progression and stabilizes disease in patients with taxane-resistant cutaneous angiosarcoma. Med Oncol 2016; 33: 116.
42 Kitamura S, Yanagi T, Inamura Y et al. Pazopanib does not bring remarkable improvement in patients with angiosarcoma. J Dermatol 2017; 44: 64–7.
43 Fujisawa S, Nakano E, Nakamura K et al. Pazopanib as a potential chemotherapy for cutaneous angiosarcoma: A case series of 10 patients from a single institution. J Dermatol 2020; 47: e273–e74.
44 Pasquier E, André N, Street J et al. Effective management of advanced angiosarcoma by the synergistic combination of propranolol and vinblastine-based metronomic chemotherapy: a bench to bedside study. EBioMedicine 2016; 6: 87–95.
45 Amaya CN, Perkins M, Belmont A et al. Non-selective beta blockers inhibit angiosarcoma cell viability and increase progression-free- and overall-survival in patients diagnosed with metastatic angiosarcoma. Oncoscience 2018; 5: 109–19.
46 Florou V, Rosenberg AE, Wieder E et al. Angiosarcoma patients treated with immune checkpoint inhibitors: a case series of
seven patients from a single institution. J Immunother Cancer 2019; 7: 213.

47 Gambichler T, Koim S, Wrobel M et al. Expression of programmed cell death proteins in kaposi sarcoma and cutaneous angiosarcoma. J Immunother 2020; 43: 169–74.

48 Honda Y, Otsuka A, Ono S et al. Infiltration of PD-1-positive cells in combination with tumor site PD-L1 expression is a positive prognostic factor in cutaneous angiosarcoma. Oncoimmunology 2017; 6: e1253657.

49 Shimizu A, Kaira K, Okubo Y et al. Positive PD-L1 expression predicts worse outcome in cutaneous angiosarcoma. J Glob Oncol 2017; 3: 360–9.

50 Ohguri T, Imada H, Nomoto S et al. Angiosarcoma of the scalp treated with curative radiotherapy plus recombinant interleukin-2 immunotherapy. Int J Radiat Oncol Biol Phys 2005; 61: 1446–53.

51 Watanabe M, Nakai K, Iwaki Y et al. Successful long-term treatment with pazopanib after prior interleukin-2 therapy in patients with metastatic cutaneous angiosarcoma of the scalp. Dermatol Ther 2020; 33: e14007.

52 Gebhardt C, Ziegler B, Stadler S et al. Complete remission of treatment-refractory advanced angiosarcoma of the scalp by protracted intralesional interleukin-2 therapy. Br J Dermatol 2015; 172: 1156–8.

53 Maeda T, Kitamura S, Yanagi T. RANK-RANKL signalling pathway contributes to disease progression in cutaneous angiosarcoma: a case report with an immunohistochemical review and in vitro experiments. J Eur Acad Dermatol Venereol 2020; 34: e834–e37.

References 54–80 can be found online.