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New Molecular Insights, and the Role of Systemic Therapies and Collaboration for Treatment of Epithelioid Hemangioendothelioma (EHE)

Silvia Stacchiotti, MD[1,*]
William Tap, MD[2]
Hugh Leonard[3]
Nadia Zaffaroni, PhD[4]
Giacomo G Baldi, MD[5]

Address
[*,1]Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale Dei Tumori, Via G. Venezian 1, 20133 Milan, Italy
Email: silvia.stacchiotti@istitutotumori.mi.it
[2]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York City, USA
[3]Chair of Trustees of the EHE Rare Cancer Charity UK, Charity Number 1162472, Kingston-Upon-Thames, UK
[4]Department of Experimental Oncology, Fondazione IRCCS Istituto Nazionale Dei Tumori, Milan, Italy
[5]Department of Medical Oncology, Santo Stefano Hospital, Prato, Italy

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Opinion statement

Epithelioid hemangioendothelioma (EHE) is an ultra-rare, translocated vascular sarcoma. EHE can have different clinical presentations from indolent to rapidly evolving cases, behaving as a high-grade sarcoma. Serosal effusion and systemic symptoms such as fever and severe pain are known as adverse prognostic factors; however, outcome prediction at disease onset remains a major challenge. In spite of its rarity, an international collaborative effort is in place with the support of patient advocates to increase the knowledge of

EHE biology, develop new treatment options, and improve patient access to new active medications. Currently, systemic therapies are indicated only for patients suffering from progressive and/or symptomatic disease and in patients with a high risk of organ dysfunction. Standard systemic agents available so far for treatment of sarcomas, and in particular anthracycline-based chemotherapy, have marginal activity in EHE. On this background, EHE patients should be always considered for clinical study when available. The MEK inhibitor trametinib has been recently investigated prospectively in advanced EHE showing some activity, but the publication of the full dataset is still awaited to better interpret the results. Besides, there are data on response to antiangiogenics such as sorafenib and bevacizumab and, from retrospective studies, interferon, thalidomide, and sirolimus. Unfortunately, none of these agents is formally approved for EHE patients and access to treatments varies greatly between countries causing a huge disparity in patient care from one country to another.

Introduction

Epithelioid hemangioendothelioma (EHE) is an ultra-rare vascular sarcoma, accounting for < 0.5 cases/1,000,000/year. It often presents with multifocal spread (> 50% of cases), with the lung/pleura, liver, and bone being the typical involved sites [1•, 2••, 3]. EHE affects patients of all ages; it is most common after the second decade of life with a slight predominance in females [3]. Approximately 90% of EHE cases are molecularly characterized by a t(1;3) (p36.3;q25) translocation that leads to a *WW Domain Containing Transcription Regulator 1* (*WWTR1*)—also called transcriptional coactivator with PDZ-binding motif (*TAZ*)—and *Calmodulin Binding Transcription Activator 1* (*CAMTA1*) fusion gene [4•]. A minority of patients (about 10%) are characterized by a t(X;11) (p11;q22) translocation that leads to fusion of *Yes-associated protein 1* (*YAP*) and *Transcription Factor Binding To IGHM Enhancer 3* (*TFE3*) genes [5]. In addition, a few EHE cases mainly associated with cardiac involvement showed variant WWTR1 fusions, including *WWTR1-MAML WWTR1-ACTL6A*, and fusions where no *WWTR1* partner was identified [6]. Intriguingly, the prognostic role of the fusion subtype is still a matter of debate, even though the presence of the *WWTR1-CAMTA1* fusion was recently reported to correlate with a worse 5-year overall survival (OS) compared to *YAP1-TFE3* (59% versus 86%) [7•].

EHE can have different clinical presentations with indolent cases also in the metastatic stage of disease that remain asymptomatic and stable over long periods of time, cases with a radiological slowly progressive disease, and patients affected by a rapidly evolving variant, which behaves as a high-grade sarcoma, often associated with inflammatory symptoms burden (tumor-related pain, fever, fatigue, and weight loss) and serosal invasion/effusion [2••, 8•]. As a result, the patient's outcome is variable, with a 5-year survival ranging between 20 and 70% [7•, 9].

Outcome prediction at disease onset remains a major challenge, although serosal effusion, presence of systemic symptoms such as fever, weight loss, and pain, and a high mitotic count are known as adverse prognostic factors [7•, 8•]. Notably, pain affecting EHE patients can be severe and very difficult to treat, as the effect of opioids commonly used in cancer pain is unfortunately largely unsatisfactory. Recently, a consensus paper on the optimal treatment strategy in patients with EHE drafted by the sarcoma community of experts and EHE patient representatives was published [2••], proposing active surveillance as the up-front strategy for advanced asymptomatic or slowly progressive disease and medical treatment for advanced symptomatic and/or progressive cases.

In this review, we summarize data on the systemic therapies available for medical treatment of EHE and the biological background supporting their use and the opening of pathways to new potential treatment options for the disease.

Molecular background and preclinical data

Molecular alterations in EHE

YAP and *WWTR1* (also called *TAZ*) genes, which are involved in the two, mutually exclusive translocations that can be found in EHE, are downstream effectors in the Hippo pathway, a signaling cascade involved in both tumor suppressive and oncogenic processes and are identified as oncogenes [10]. Specifically, they are transcriptional co-activators that lack DNA binding domains but interact with DNA binding transcription factors, such as TEAD1-4, for driving transcription. *TAZ-CAMTA1* and *YAP-TFE3* drive transcriptomic profiles that are different from full-length YAP/TAZ transcriptomes due to the ability of both fusion proteins to simultaneously hyperactivate a TEAD-based transcriptional program and modulate the euchromatin landscape through the interaction with the YEATS2 and ZZZ3 components of the ATAC complex in human cell lines [11]. Additional studies in NIH3T3 mouse embryonic fibroblasts transformed with the *TAZ-CAMTA1* gene fusion identified CTGF as a tumorigenic transcriptional target of *TAZ-CAMTA1*. CTGF was found to sustain the anchorage-independent proliferation of transformed cells by binding to integrin αIIbβ3 and to deregulate the Ras-MAPK signaling cascade [12]. Importantly, pharmacological inhibition of MAPK signaling by trametinib impaired the growth of NIH3T3 transformed cells both in vitro and following xenotransplantation in mice. Such preclinical findings provided the rationale for developing a clinical trial with trametinib in EHE patients (NCT03148275).

The NGS-based search for additional genomic aberrations carried out in 49 EHE patients with a confirmed *TAZ-CAMTA1* gene fusion showed the presence of a secondary pathogenic genomic variant in about 50% of cases. Commonly altered genes included *CDKN2A/B*, *RB1*, *APC*, and *FANCA* and were more frequently detected in patients with advanced-stage disease [13].

Preclinical models to study EHE biology and develop treatment strategies

The unequivocal demonstration that *TAZ-CAMTA1* is sufficient to generate EHE in vivo has been provided by two recent studies aimed at generating genetically engineered mouse models (GEMM) of the disease. Using an overexpression system with expression based on a Tet-Off approach, Driskill et al. showed that *TAZ-CAMTA1* expression in endothelial cells induced an angiogenic and regenerative-like transcriptional program and was sufficient to support the formation of vascular tumors with the distinctive features of EHE in the lungs of mice [14]. Moreover, *TAZ-CAMTA1* was found to require the TEAD family of transcription factors to drive tumorigenesis while the disruption of the TAZ-CAMTA1-TEAD interaction, as well as the ectopic expression of a dominant-negative TEAD, inhibited *TAZ-CAMTA1*-mediated transformation of endothelial cells.

Seavey et al. generated a conditional knock-in mouse model in which the wild-type *WWTR1(TAZ)* locus is converted into a *WWTR1(TAZ)-CAMTA1* locus through the utilization of a flip-excision cassette and Cre-recombinase [15]. These mice develop EHE tumors, mostly located on the diaphragm surface and involving retroperitoneal organs, such as pancreas and kidney, which fully reproduce the histological features of human EHE, express key EHE markers, and show significant enrichment of the human EHE gene set.

To assess whether *CDKN2A* loss, which is the most common secondary genomic variant in clinical EHE [13], cooperates with the *TAZ-CAMTA1* gene fusion to promote EHE progression, the same research group intercrossed their EHE GEMM model with a *CDKN2A* conditional knockout mouse allele [16]. Loss of CDKN2A enhanced the tumorigenicity of EHE in vivo and enabled the generation of EHE cell lines through disaggregation of tumors explanted from mice. Treatment of cells with an inhibitor of the YAP/TAZ-TEAD interaction markedly inhibited proliferation, thus highlighting the potential of TEADs as novel therapeutic targets for EHE, which is also supported by the availability of TEAD inhibitors that have already entered phase 1 clinical trials in other tumor histologies, including IAG933 700 (NCT04857372, Novartis), IK-930 (NCT05228015, Ikena Oncology), and VT3989 701 (NCT04665206, Vivace Therapeutics).

We recently reported the first patient-derived xenograft (PDX) model generated from a patient suffering from an aggressive clinical variant of EHE, presenting with systemic symptoms [17]. The PDX fully reproduces the originating clinical tumor in terms of histo-morphology, presence of the *TAZ-CAMTA1* gene fusion, and overall transcriptomic profile. The PDX model was initially used to comparatively assess the activity of drugs currently approved for clinical use in EHE, such as doxorubicin, and drugs used off-label, such as sirolimus. Doxorubicin showed almost negligible activity while sirolimus induced 69–81% tumor volume inhibition, as a function of drug dose. Consistent with in vivo results, sirolimus was more active than doxorubicin also on the in vitro cell line established from the EHE PDX.

The PDX model was also used to evaluate the drug effect on the expression/release of GDF-15, the cytokine that was found overexpressed in the serum of patients with the most aggressive variant of EHE compared to those with indolent disease [17]. Circulating levels of human GDF-15 were present in the blood of EHE PDX but not in healthy mice or mice with pleomorphic sarcoma xenotransplants. Moreover, GDF-15 was lower in EHE PDX treated with sirolimus compared to solvent. Consistently, sirolimus treatment reduced the amounts of GDF-15 released from the EHE cell line.

Overall, results from these studies indicate the relevance of GEMM and PDX models (i) for assessing the activity of anticancer drugs, as well as (ii) for identifying and pre-clinically validating novel therapeutic targets and, in the case of PDXs, also novel circulating biomarkers.

Clinical and molecular prognostic factors in EHE

Although molecularly well defined by the presence of the *WWTR1-CAMTA1* fusion, EHE is characterized by extreme variability in clinical behavior with a wide spectrum of different disease presentations, growth rates, and evolution, from indolent to very aggressive disease [18].

Pathological risk factors for worse outcomes have been also described, including increased mitotic activity (>3 mitotic figures/50 high-power fields (HPF)), grading, and size (>3.0 cm) [19].

Clinical risk factors for worse outcomes include tumor-related symptoms such as weight loss, pain, cough, hemoptysis, and signs like pleural effusions and anemia [9, 20, 21]. Notably paraneoplastic symptoms are uncommon in soft tissue sarcoma other than EHE, representing a peculiar clinical feature for this tumor type. The mechanism behind pleural involvement or refractory tumor-related pain in EHE is still unknown and the prognostic role of inflammatory and hormonal circulating biomarkers is currently under investigation [17]. Clinicopathologic and molecular findings were recently correlated with survival in a large cohort of 93 translocation-positive EHE [7•]. Eighty-three patients with *WWTR1-CAMTA1* fusion positive and 10 patients with *YAP1-TFE3* fusion positive EHE were retrospectively identified. Patients with EHE with *WWTR1-CAMTA1* fusion had a less favorable outcome compared to the *YAP1-TFE3* subset with a 5-year overall survival of 59% versus 86%, respectively. This series also confirmed that patients with pleural disease had the worst outcome, with only 22% of patients with pleural involvement still alive at 5 years.

Systemic therapies in EHE

As agreed by the community of experts, and due to the heterogeneity of the clinical presentations and prognosis, the use of systemic therapies in patients with EHE is usually to be considered only in advanced progressive patients after an initial period of observation and/or in the presence of tumor-related symptoms or when there is a high risk of organ dysfunction [2••].

Unfortunately, none of the compounds currently approved for the treatment of sarcomas showed unequivocal clinical activity in the disease, and data available on potentially effective systemic agents are often limited to case reports or small single-institution series, frequently reporting on patients whose pathological diagnosis was not molecularly confirmed and without details on the evidence of disease progression before starting their antitumor therapy. This, along with the dramatic clinical variability of EHE and poorly defined outcome measures to show meaningful clinical activity of a drug, makes it challenging to interpret anecdotal experiences and data from retrospective series, meta-analyses, and even retrospective and small prospective studies. Due to EHE rarity, comparative, prospective, and randomized studies

were never conducted in this tumor type and it is unlikely that they will ever be run, at least until new methodological approaches will be implemented and accepted by regulatory bodies. In addition, we still miss data to understand whether access to systemic treatment in metastatic patients aimed at stabilizing the disease and/or ameliorating symptoms as early as possible can prevent a worse prognosis. Finally, the disease pattern of progression, often marked by the appearance of serosal effusion and thickness, which can happen without the evidence of new lesions and/or the growth of already known nodular metastases, cannot be adequately captured by RECIST nor other dimensional criteria commonly used to assess response to medical agents in clinical trials, thus making it very challenging to demonstrate the activity of drugs in spite of the evidence of clinical improvement and the stopping of tumor growth.

Data of activity are available to antiangiogenics [22–26], interferon [27], thalidomide [28], and mammalian target of rapamycin (mTOR) inhibitors [29, 30, 31••] and more recently the MEK-inhibitor trametinib [32••].

Table 1 summarizes the data from the main prospective and retrospective studies on systemic treatments available for EHE.

In 2021, the World Sarcoma Network, a collaborative group involving several sarcoma reference centers worldwide, collected the largest series of patients with EHE treated with systemic agents [33••]. This was a retrospective study. However, with the lack of prospective trials, this is the best level of evidence available so far on the efficacy of the approved and most commonly used agents for treatment of advanced sarcomas. This study included 73 EHE cases, all molecularly confirmed (i.e., only *WWTR1-CAMTA1* or *YAP1-TFE3* fusion positive cases were included in the analysis), affected by advanced disease, diagnosed from 2000, and treated with systemic agents (33 patients treated with anthracycline-based chemotherapy, 11 with weekly paclitaxel, 12 with pazopanib, 15 with interferon, and 27 with other agents). Anthracycline-based chemotherapy showed marginal activity, with an overall response rate (ORR) assessed retrospectively by RECIST of 3%, a median progression-free survival (m-PFS) of 5.5 months, and 30% PFS at 12 months, which was consistent with findings from other series [34]. These results, representing the few other data available in the literature on anthracyclines in EHE, do not currently support their routine use in this tumor type as agreed upon by an expert community 2••. Although, the m-PFS of adriamycin in EHE overlaps with that seen in other STS, the ORR is lower and these data did not control for the often-indolent behavior of some of the EHE subtypes as disease progression was not qualified prior to starting chemotherapy. Similar results were seen with weekly paclitaxel, with a 9% ORR, a m-PFS of approximately 3 months, and 32% PFS at 12 months. While waiting for other confirmatory prospective data, chemotherapy is still considered in patients affected by the more aggressive variant of the disease with no other options available 2••.

Interferon resulted in an ORR of 7% and a m-PFS of 8.9 months, longer than that seen with other agents (27, 35, 36). In this series, pazopanib did not achieve any objective response, m-PFS was of approximately 3 months (interquartile range, IQR, 2.1–7.1), and 12-month PFS was 17% 33••. Other anecdotal objective responses to pazopanib were reported by Kollàr et al. with

Table 1. Summary of prospective and retrospective data available on systemic treatments in EHE

	Study type	Drug	Patients (*N*)	Age range (yrs)	Prior progression before treatment start	ORR	m-PFS (months)
Schuetze SM et al CTOS Annual Meeting 2022	Phase II	Trametinib	44	22–81	Y	9.4% (4 PR)	8.4
Chevreau C et al Cancer 2013	Phase II	Sorafenib	15	31–76	Y	13.3% (2 PR)	6.0
Agulnik M et al Ann Oncol 2013	Phase II	Bevacizumab	7	18–94	N	29% (2 PR)	9.0
Frezza AM et al Cancer Med 2021	Retrospective	Anthra-based Paclitaxel Pazopanib Interferon	33 11 12 15	34–61 33–68 42–58 41–50	Y:19 – N:14 Y:6 – N:5 Y:10 – N:2 Y:12 – N:3	3% (1 PR) 9% (1 PR) 0% 7% (1 PR)	5.4 2.8 2.8 8.9
Kollar A et al Acta Oncologica 2017	Retrospective	Pazopanib	10	47 (median)	Y	20% (2 PR)	26
Stacchiotti S et al Ann Surg Oncol 2016	Retrospective	Sirolimus	17	22–68	Y	6% (1 PR)	12
Stacchiotti S et al Cancer 2021	Retrospective	Sirolimus	37	40–53	Y	11% (4 PR)	13
Engel ER et al J Pediatr Hematol Oncol. 2019	Retrospective	Sirolimus	6	7–16	Y	50% (4 PR)	22
Riou et al J Am Soc Clin Oncol 2012	Retrospective	Sirolimus	1	20	Y	PR	NE
Cohen et al Clin Cancer Res 2012	Phase I	Sirolimus	1	Adult	Y	PR	NE
Cournoyer et al Pediatr Blood Cancer 2020	Retrospective	Sirolimus	8	2–26	Y	25% (2 PR)	NE

ORR, overall response rate; *m-PFS*, median progression-free survival; *Y*, yes; *N*, no; *NE*, not evaluated; *PR*, partial response

2 partial responses within the 10 patients with EHE treated with pazopanib in the EORTC retrospective series in vascular sarcomas (23). In addition to pazopanib, which is the only antiangiogenic drug currently approved for the treatment of pre-treated advanced soft tissue sarcoma, bevacizumab was investigated prospectively in locally advanced/metastatic EHE in 7 patients within a phase II study, showing a RECIST ORR of 29%, with 57% stable disease (SD), and a m-PFS of 9.7 months (25). In another phase II study of sorafenib including 15 cases of progressive advanced EHE, this agent achieved 2 RECIST partial responses (PR) and 5 SD, and a 9-month PFR of 31% (24).

Based on preclinical data (12), a phase II, single-arm trial (NCT03148275) with the MEK-inhibitor trametinib was conducted by the Sarcoma Alliance for Research through Collaboration (SARC) collaborative group in the USA in a population of 42 progressive and/or symptomatic patients with advanced EHE and the results were recently preliminarily presented at the Connective Tissue Oncology Society (CTOS) 2022 annual meeting 32••, showing a 9.4% RECIST ORR (i.e., 4/42 patients, 2 of them being however fusion negative), a m-PFS of 8.4 months, 30% PFR at 12 months, and a 2-year survival rate of 41%. Interestingly, the authors reported a significant reduction in pain intensity and global pain scores after 4 weeks of treatment. However, further details and a better definition of responsive patients are needed to direct the clinical application of trametinib in the disease. In addition, the final analysis should also evaluate the specific impact of treatment in the 18 patients who had lung/pleural disease, and if the observed m-PFS was in patients with more indolent liver/lung disease. The full dataset and future development plans to make trametinib available to EHE patients are awaited.

Another drug of interest in EHE is the mTOR inhibitor, sirolimus (30, 31••). Although investigated only retrospectively and not formally approved in this indication, sirolimus is one of the antitumor agents considered more effective in EHE and more often administered worldwide 2••. The first reports of activity date back to 2012 by Riou and Cohen, who described a major response lasting 16 months in a patient affected by EHE within a Maffucci's syndrome and another response to sirolimus in a prospective phase 1 study of this agent in advanced solid tumors lasting more than 3 years, respectively (37, 38). Stacchiotti et al. initially presented in 2016 a first retrospective series of 18 patients with advanced, molecularly confirmed, and progressive EHE treated with sirolimus within the Italian Rare Cancer Network, describing 1 RECIST PR and 12 SD with a m-PFS of 12 months (30). These results were updated in 2021 on a larger number of patients, with a RECIST ORR of 4/37 (11%), a m-PFS of 13 months (range 3.7–NE), and a 12-month PFS of 54%, at a median follow-up (m-FU) of 41.5 months (IQR 23.9–56.8 months) 31••. Of interest, 2 out of 13 patients with serosal effusion in this series remained progression-free for about 12 months. Moreover, 4 of 5 patients who discontinued sirolimus without evidence of progression experienced PD after sirolimus discontinuation and all of them achieved a new disease stabilization after rechallenging sirolimus, as described in one case in Fig. 1. Eventually, the activity of sirolimus was described by Engel in a population of pediatric EHE patients, with 4 PR of 6 patients retrospectively identified (29).

Based on these data and the preclinical results in support of the role of mTOR inhibition in EHE, sirolimus is prioritized as one of the preferred

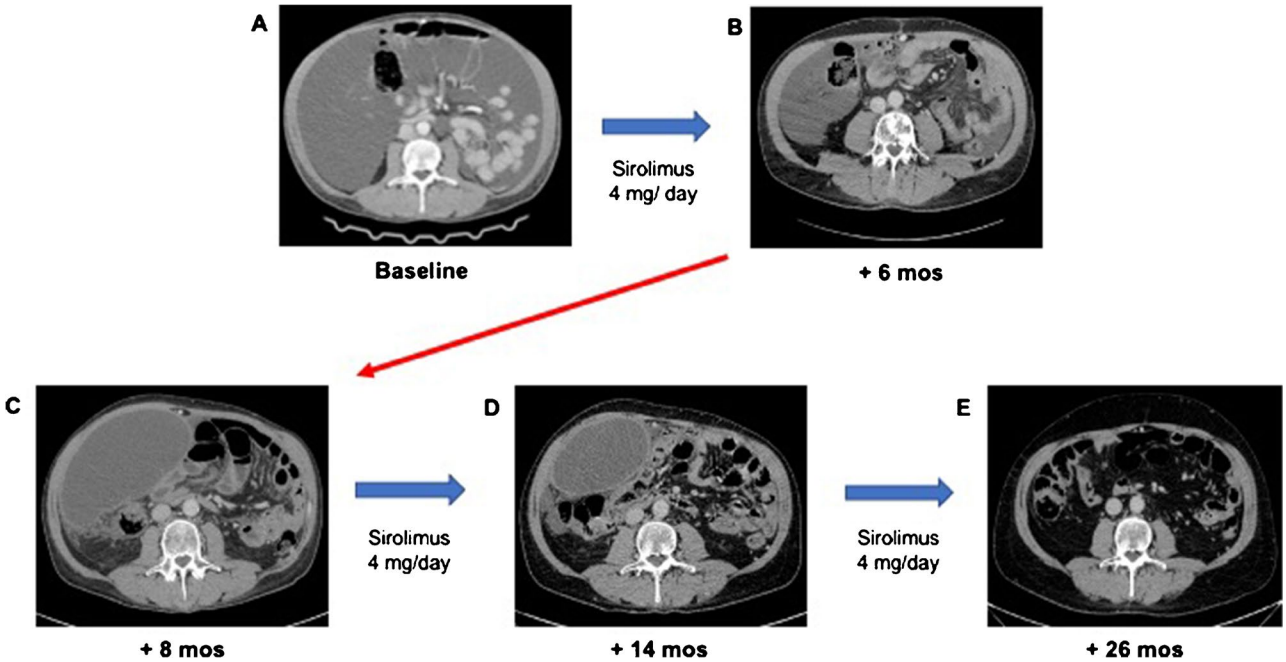

Fig. 1 Computed tomography scan (venous phase after contrast medium) of a EHE patient with liver, lung, bone metastases and symptomatic peritoneal effusion. **A, B,** Response to sirolimus after 6 months of treatment. **C,** Interval progression with increase of peritoneal effusion, worsening of general condition and pain, and increase in analgesics intake, observed after 2 months from sirolimus discontinuation, due to a non-drug–related adverse event. **D, E,** New response after sirolimus rechallenge, maintained for more than 2 years, with resolution of symptoms and discontinuation of the analgesics

options for advanced and progressive or symptomatic EHE patients (2••). It is however still left to define if a higher dose of sirolimus is needed for patients with the more aggressive variant of the disease. Of course, as sirolimus is not formally labeled for EHE, the access to this agent and other potentially active drugs in EHE varies greatly across all countries and regions, with huge disparities in the way EHE patients are treated around the world.

Data on anti-programmed death-1 (PD-1) drugs in EHE are limited and currently do not allow the provision of any advice on their use for EHE patients outside clinical studies. To our knowledge, available data are limited to a series of 4 EHE patients treated with PD1-based therapy published by Rosenbaum et al., with prolonged disease stabilization. This report does not provide any information on the evidence of progression of the disease before the start of treatment to allow interpretation of the role of PD-1 inhibition in disease stabilization. However, patients with EHE are now being included in many trials studying immunotherapy in sarcomas. For example, a single-arm European phase Ib/II trial (IMMUNOSARC, NCT03277924) is currently investigating the combination of nivolumab with sunitinib in selected soft tissue and bone sarcoma histotypes, including EHE (39). Final results of this and other trials are awaited to understand if EHE is responsive to checkpoint inhibitors, alone or in combination.

Interestingly, celecoxib, a non-steroidal anti-inflammatory drug (NSAIDs), was also reported to have some antitumor effect, with 4 patients achieving a partial regression described so far (40).

When available, EHE should be considered for enrollment in clinical trials, starting from frontline. Among others, a pilot phase II study with eribulin, an anti-mitotic drug inhibitor of microtubule dynamics, is currently ongoing in the USA enrolling angiosarcoma and EHE patients (NCT03331250), while, based on the molecular profile of EHE, a new and promising treatment opportunity is represented by the recently started prospective trials on TEAD inhibitors in solid tumors, including EHE (NCT04857372, NCT05228015, NCT04665206).

Conclusions and future perspectives

Although standard, formally approved medical therapy for treatment of patients of any age affected by progressive and symptomatic EHE is still missing starting from the frontline, a huge effort to better understand the biology of EHE and identify new targets and prognostic and predictive factors is currently ongoing worldwide, thanks to the ongoing collaboration between the sarcoma community of experts, basic scientists, patients advocates, and other stakeholders. In particular, the collaboration with the EHE Group, comprising a number of sister EHE advocacy organizations across the globe, is providing sarcoma physicians and researchers with access to the global EHE patient community, ensuring that patients are completely involved in most initiatives on the disease and providing ongoing support with funding of preclinical and clinical research.

This led to the document, "Epithelioid hemangioendothelioma, an ultra-rare cancer: a consensus paper from the community of experts" that has tried for the first time to define what should currently be the optimal care of this tumor and to harmonize the treatment of the disease, and increase the awareness of how specifically it deserves to be approached (2••). This collaboration and worldwide commitment are leading to the opening of prospective registries and clinically prospective studies specifically focusing on EHE, despite EHE rarity. Productive and committed collaboration is also fostering the discussion with European and US regulatory bodies to try to eliminate the barriers that patients and clinicians often face when dealing with rare and ultra-rare tumors, and which we believe will lead to and allow fundamentally better care for EHE patients in the coming years.

Compliance with Ethical Standards

Conflict of Interest

None of the authors has any interest to report directly related to this manuscript.
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Human and Animal Rights and Informed Consent
All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

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