Sorafenib for Patients with Advanced Angiosarcoma: A Phase II Trial from the French Sarcoma Group (GSF/GETO)

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ABSTRACT

Background. Angiosarcomas account for <2% of all soft tissue sarcomas. This subtype is one of the most aggressive forms of soft tissue sarcoma. The prognosis for angiosarcoma patients in the advanced phase remains poor with current cytotoxic agents (progression-free survival [PFS] time of ~4 months and overall survival [OS] time of ~8 months). We investigated the antitumor activity of sorafenib in patients with metastatic or advanced angiosarcomas in a phase II trial.

Methods. We conducted a stratified phase II trial. The primary endpoint was the progression-free rate (PFR) at 9 months according to the Response Evaluation Criteria in Solid Tumors. A two-stage design (optimal Simon design) was used. Patients received sorafenib (400 mg twice daily) for 9 months until unacceptable toxicity or tumor progression. Central pathological and radiological reviews were performed. Data on stratum A (superficial angiosarcoma) and stratum B (visceral angiosarcoma) are currently available.

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This trial is registered with ClinicalTrials.gov (identifier, NCT00874874).

Findings. Strata A and B recruited 26 and 15 patients, respectively. The median age was 63 years (range, 31–82 years), with 17 male and 24 female patients. Fourteen cases arose in irradiated fields. Thirty patients (73.0%) had been pretreated with conventional chemotherapy. No unexpected toxicity occurred. The PFR at 9 months was 3.8% in stratum A and 0.0% in stratum B. The median PFS times were 1.8 months and 3.8 months, respectively, whereas the

median OS times were 12.0 months and 9.0 months, respectively. No responses were observed in chemotherapy-naïve patients, whereas a 40% tumor control rate and 23% response rate were observed in the pretreated population. In this cohort, no activating mutation of the *KDR* gene (exons 15, 16, 24) was detected.

Interpretation. Sorafenib showed limited antitumor activity in pretreated patients only, for both visceral and superficial angiosarcoma, but tumor control was of short duration. *The Oncologist* 2012;17:260–266

INTRODUCTION

Angiosarcomas account for <3% of all adult soft tissue sarcomas, but they encompass a heterogeneous group of tumors with variable histological characteristics [1]. Most of angiosarcomas are high-grade tumors [1–5]. Angiosarcomas are heterogeneous, with a large spectrum of clinical (skin and scalp angiosarcoma, angiosarcoma arising in irradiated fields, Stewart-Treves syndrome, hepatic angiosarcoma related to occupational causes, etc.) and histological (epithelioid forms, low-grade angiosarcoma mimicking benign vascular lesions) forms [1–5]. In some cases, the differential diagnosis with other vascular or vascularized sarcomas (such as epithelioid hemangioendothelioma, hemangiopericytoma, and malignant solitary fibrous tumor) is very difficult, and in the setting of a clinical trial, this requires a central pathological review [6]. The prognosis of angiosarcoma patients remains very poor. Fifteen percent of patients present with metastasis at the time of diagnosis [2]. The 5-year overall survival (OS) rate for nonmetastatic cases is only 30%–40% because of the high incidence of metastatic spread [2]. The median OS duration at the metastatic stage is ~8 months. Doxorubicin-based or weekly paclitaxel regimens may provide short-lasting tumor control, with a typical median progression-free survival (PFS) time of ~4 months [2, 7, 8]. Metastatic angiosarcoma is considered an orphan disease [2, 7, 8].

In very recent years, numerous studies have explored the biology of angiosarcoma. The most important recent findings highlight the crucial role of proangiogenic growth factors and their receptors in angiosarcoma [9–14]. In vitro studies have demonstrated that the mRNA and proteins of vascular growth factors and receptors are overexpressed in angiosarcoma cell lines: vascular endothelial growth factor (VEGF)-A, VEGF-C, VEGF receptor (VEGF-R)1, VEGF-R3, vascular permeability factor (VPF), FLT-A, KDR (VEGF-R2), and v-ets erythroblastosis virus E26 oncogene homolog 1 (ETS-1) [9–14]. VEGF and VEGFRs are overexpressed at an early stage in angiosarcoma development [9]. Itakura et al. [11] showed that VEGF-A was overexpressed in 32 of 34 human angiosarcoma cases, VEGF-C was overexpressed in four of 34 cases, VEGF-R1 was overexpressed in 22 of 34 cases, and VEGF-R3 was overexpressed in 27 of 34 cases. Recently Antonescu et al. [13] reported on strong KDR (VEGF-R2) expression in primary breast angiosarcoma and angiosarcoma arising in the irradiated chest wall. An increase in the activating phosphorylation of transduction cascade proteins (mitogen-activated protein kinase) depending on Raf has been established for angiosarcoma [12]. Lahat et al. [14] found overexpression of

VEGFRs and intracellular second messengers (p-AKT, phosphorylated 4E binding protein 1, and eukaryotic translation factor 4E) in a series of 68 human angiosarcoma cases. VEGF and VEGFR pathways constitute a potential target for treatment of angiosarcoma.

Sorafenib, a small molecule B-RAF and VEGFR inhibitor, is a logical candidate for treatment of angiosarcoma. Maki et al. [15] explored the activity of sorafenib in patients with advanced soft tissue sarcomas through a multistrata phase II trial. In the “vascular sarcoma” stratum (including 33 angiosarcoma and four epithelioid hemangioendothelioma patients), sorafenib provided some objective responses (five of 37) and a 6-month PFS rate of ~30%. In light of these facts, a phase II trial focusing on angiosarcoma with systematic central pathological review and molecular analysis was initiated to better estimate the activity of sorafenib.

PATIENTS AND METHODS

Study Population and Eligibility Criteria

The patients considered for this study were required to be ≥18 years of age. All had histologically proven angiosarcoma, reviewed by an independent pathologist (Y.M.R.), with metastasis or locally advanced stage not amenable to radiotherapy or curative-intent surgery after multidisciplinary decision making. Any prior systemic treatment for angiosarcoma was allowed. Measurable or assessable disease with computed tomography scan was required as per the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 [16]. Additional key eligibility criteria were as follows: histologically proven angiosarcoma, locally advanced angiosarcoma not amenable to surgery, or metastatic angiosarcoma; at least one lesion measurable according to the RECIST, version 1.1; no brain or meningeal metastasis; no more than two prior lines of chemotherapy (whatever the indication); a World Health Organization performance status score ≤2; and WBC ≥3,000/mm³, platelet count ≥100,000/mm³, hemoglobin level ≥9 g/dL, international normalized ratio and activated partial thromboplastin time ≤1.5× the upper limit of normal (ULN), liver transaminases ≤1.5× ULN, total bilirubin ≤1.5× ULN, serum creatinine ≤1.5× ULN, and amylase and lipase ≤1.5× ULN. Regarding angiosarcoma arising in irradiated fields, inclusion was allowed when there was any clinical argument suggesting a possible recurrence of the prior cancer treated with radiotherapy. The present report is focused on the first

two strata. Two strata are still recruiting: stratum C (malignant solitary fibrous tumor, hemangiopericytoma, and epithelioid hemangioendothelioma) and stratum D (chordoma).

Treatment

Patients received a starting dose of sorafenib of 400 mg orally twice daily, continuously until intolerable toxicity, tumor progression, or withdrawal of informed consent. Dose reduction to 400 mg orally daily and then to 200 mg orally daily was permitted for patients experiencing severe toxicities (grade 3 or recurrent grade 2 toxicities).

Study Endpoints

The primary endpoint was the 9-month progression-free rate (PFR). The secondary endpoints were (a) safety and toxicity assessed according to National Cancer Institute Common Toxicity Criteria (version 3.0), (b) the response rate at 3, 6, and 9 months, (c) for pretreated patients, the growth modulation index (time to progression with sorafenib divided by time to progression with the previous line), (d) the OS duration, and (e) the median time to progression.

During the study, patients underwent clinical, hematologic and biological evaluation at baseline, day 1, day 7, day 15, day 30, day 60, day 120, day 180, and day 270. Disease was assessed by comparing unidimensional tumor measurements (computed tomography scan) on imaging studies before and during treatment at 3, 6, and 9 months. We assessed response according to the RECIST, version 1.1. An independent third-party radiologist (L.L.) reviewed selected imaging studies to verify all imaging performed during the treatment period with the trial drug to ensure consistent, unbiased application of the RECIST.

Sample Size Calculation and Statistical Analysis

We hypothesized that sorafenib could not provide an objective response but could provide long-lasting disease stabilization. The 9-month PFR appeared to be a reasonable and unquestionable criterion to capture this drug effect. The number was calculated using a Simon two-stage design. We defined two strata: stratum A included all forms of superficial angiosarcoma (skin, scalp, soft tissue, and breast angiosarcoma), whether it was de novo or arose in an irradiated field. Stratum B included all forms of bone or visceral angiosarcoma. The statistical assumption was based on the results of a previous trial investigating weekly paclitaxel in angiosarcoma patients [7]. The 9-month PFR was 12.7% with weekly paclitaxel [7]. We calculated the sample size with the following assumptions: $P_0 = 12.7\%$ (corresponding to a 4-month PFR of 40%) and $P_1 = 31.7\%$ (corresponding to a 4-month PFR of 60%). In stratum A, α was fixed at 10% and β was fixed at 5%. In stratum B, α was fixed at 8% and β was fixed at 19%. The atypical α and β values used in stratum B take into account the rarity of visceral angiosarcomas. In stratum A, 26 patients were to be included in the first stage; the second stage was to be opened if at least three successes were seen. In this stratum, sorafenib would be considered as an active treatment if at least nine of 44 successes were seen. In stratum B, 15 patients were to be included in the first stage. The second stage was to be opened if at least two successes were seen.

Sorafenib would be considered as an active treatment if at least six of 24 successes were seen.

Objective response was assessed among the assessable population ($n = 41$). The Kaplan–Meier method was used to calculate the time to progression and OS time. The survival time and time to progression were both defined from the start of treatment, to the date of death or last follow-up for OS and to the date of progression or death or censoring at the last follow-up for time to progression. Both were classed among the intent-to-treat population. Safety was assessed in all patients having received ≥ 2 weeks of treatment ($n = 39$).

Biological Correlative Study

Four single nucleotide polymorphisms (SNPs) of *VEGFA* (rs2010963, rs833061) and *KDR* (rs2305948, rs1870377) were selected based on the mechanism of action of sorafenib and their previous association with angiogenesis inhibitor efficacy or toxicity in other tumor models [17, 18]. Exons 15, 16, and 24 of *KDR* were also screened for the presence of activating mutations that had been associated with sensitivity to sorafenib and sunitinib in vitro [13]. Tumor DNA was extracted from paraffin-embedded tissue. Genotyping was obtained by direct sequencing. Protocols are available on request.

Ethical and Regulatory Considerations

This study was conducted after approval by the regional ethics committee (Comité de Protection des Patients Nord-Ouest III; date of approval, June 16, 2009) and after declaration to the French Health Products Safety Agency (Agence Française de Sécurité Sanitaire et des Produits de Santé, June 1, 2009). The study was registered in the European Clinical Trials Register (EudraCT number 2007–004651–10) as well as on the ClinicalTrials.gov Web site (identifier, NCT00874874) [19]. Informed consent was obtained from each patient.

RESULTS

Patient Characteristics

From June 2008 to June 2009, 41 patients (17 men and 24 women) were enrolled in 13 centers. All were eligible. Twenty-six angiosarcomas were superficial (stratum A) and 15 were visceral (stratum B). In stratum A, the primary sites were the breast ($n = 10$), the upper limbs ($n = 5$), the lower limbs ($n = 4$), the head and neck ($n = 3$), the chest wall ($n = 3$), and the abdominal wall ($n = 1$). In stratum B, the primary sites were the heart ($n = 4$), the spleen ($n = 2$), the pulmonary artery ($n = 2$), the bone ($n = 2$), the bladder ($n = 1$), the duodenum ($n = 1$), the colon ($n = 1$), and the liver ($n = 1$). Patient characteristics at baseline are described in Table 1. The median age was 65 years (range, 31–82 years) in stratum A and 55 years (range, 19–80 years) in stratum B.

Safety and Toxicity

Safety was assessable in 39 patients (two patients did not receive sorafenib). The median duration of treatment was 58 days (range, 0–328+ days). Nineteen patients required dose reduction and 17 patients required transient drug discontinua-

Table 1. Patient characteristics at baseline

Characteristic	Stratum A n (%)	Stratum B n (%)	Total n (%)
n	26	15	41
Men	8 (31.0)	9 (60.0)	17 (41.0)
Women	18 (69.0)	6 (40.0)	24 (59.0)
Angiosarcoma arising in irradiated field	13 (50.0)	1 (7.0)	14 (34.0)
Associated lymphedema	6 (23.0)	—	—
FNCLCC grade 1	0 (0.0)	0 (0.0)	0 (0.0)
FNCLCC grade 2	7 (27.0)	1 (7.0)	8 (19.5)
FNCLCC grade 3	9 (34.5)	6 (40.0)	15 (36.5)
Grade not assessable	10 (38.5)	8 (53.0)	18 (44.0)
Epithelioid angiosarcoma	9 (35.0)	4 (26.5)	13 (31.0)
Presence of metastasis	19 (73.0)	14 (93.5)	33 (80.5)
Lung metastasis	8 (30.5)	9 (60.0)	17 (41.5)
Liver metastasis	3 (11.5)	5 (33.0)	8 (19.5)
Bone metastasis	2 (7.5)	7 (46.5)	9 (22.0)
WHO PS score 0	9 (34.5)	5 (33.0)	14 (34.0)
WHO PS score 1	11 (42.5)	7 (46.5)	18 (44.0)
WHO PS score 2	6 (23.0)	3 (20.5)	9 (22.0)
Chemotherapy-naïve patients	7 (27.0)	4 (27.0)	11 (27.0)
Patients having received one line	11 (42.0)	5 (33.0)	16 (39.0)
Patients having received two lines	8 (31.0)	6 (40.0)	14 (34.0)
Pretreatment with doxorubicin	14 (54.0)	10 (66.0)	24 (58.5)
Pretreatment with weekly paclitaxel	8 (31.0)	5 (33.0)	13 (31.5)

Abbreviations: FNCLCC, Fédération Nationale des Centres de Lutte Contre le Cancer; PS, performance status; WHO, World Health Organization.

tion. The causes of definitive treatment discontinuation were: nonrelated pulmonary embolism (one case), toxicity (five cases), and tumor progression (33 cases). For the five patients requiring treatment discontinuation because of toxicity despite per protocol drug reduction and optimized supportive care, the observed toxicities were: grade 4 acute pancreatitis (one case) and grade 3 asthenia and grade 3 skin toxicities with or without grade 3 mucositis (four cases). No toxic death was notified. Table 2 lists the maximum toxicity observed per patient.

Activity: Primary Endpoint

Response was assessable for 23 patients in stratum A and 13 patients in stratum B (Table 3). The overall response rates were 14.6% at 4 months and 0% at 9 months. The overall nonprogression rates were 24.4% at 4 months and 2.4% at 9 months. In stratum A, 26 patients were included in the first step. Because only

Table 2. Maximum treatment-related toxicity (n = 39)

Toxicity	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Hand-foot syndrome	5 (13)	6 (15)	0
Other skin reaction	15 (38)	6 (15)	0
Mucositis	13 (33)	2 (5)	0
Anemia	2 (5)	3 (8)	0
Thrombocytopenia	1 (2)	0	0
Neutropenia	0	0	0
Fatigue	6 (15)	6 (15)	0
Lost of appetite	1 (2)	0	0
Vomiting	4 (10)	0	0
Diarrhea	7 (17)	6 (15)	0
Abdominal pain	3 (8)	0	0
Constipation	1 (2)	1 (2)	0
Acute pancreatitis	0	0	1 (2)
Arthromyalgia	4 (10)	2 (5)	0
Bleeding	2 (5)	3 (8)	0
Arterial hypertension	2 (5)	1 (2)	0
Left ventricular function drop	0	1 (2)	0

National Cancer Institute Common Toxicity Criteria, version 4, grade 2–4 adverse events in all patients. Incidence of maximal toxicity considered by investigator as possibly, probably, or definitely related to sorafenib.

one of them experienced stable disease at 9 months, the opening of the second stage was not allowed. In stratum B, 15 patients were enrolled. Because only one patient experienced stable disease at 9 months, opening of the second stage was not allowed. The predefined level of activity was not reached in either stratum.

Other Activity Endpoints

The median PFS intervals were 1.8 months in stratum A and 3.8 months in stratum B (Fig. 1). The median PFS times were 2.0 months in chemotherapy-naïve patients and 1.9 months in pretreated patients (Fig. 2). The median OS times were 12.0 months in stratum A and 9.0 months in stratum B (Fig. 3). The median OS times were 9.0 months in pretreated patients and 9.7 months in chemotherapy-naïve patients. OS and PFS times were in the range of those observed in the AngioTax study [7] (Figs. 1 and 3).

Correlative Biological Studies

Tumor material was available for 27 patients. For exons 15, 16, and 24 of *KDR*, sequences were interpretable in 19, 15, and 22 cases, respectively. No mutation in *KDR* was detected. For the four SNPs rs2010963, rs833061, rs2305948, and rs1870377, sequences were interpretable for 22, 24, 22, and 18 cases, respectively. All patients but three were homozygous for the common allele. One patient showed a variation previously not reported in exon 6 of *VEGFA* (D349N) and two patients showed a heterozygous genotype for the rs1870377 *KDR* SNP (Q472H).

Table 3. Response rates

	At day 60	At day 120	At day 180	At day 290
Stratum A, superficial angiosarcoma (<i>n</i> = 26)				
Disease status				
Not assessable	6	4	3	3
Progressive disease	14	16	19	22
Stable disease	4	2	1	1
Partial response	1	2	1	0
Complete response	1	2	2	0
Overall response rate, %	7.7	15.4	11.5	0
Overall non-progression rate, %	23.0	23.0	15.4	3.8
Strata B, visceral angiosarcoma (<i>n</i> = 15)				
Disease status				
Not assessable	2	2	2	2
Progressive disease	7	9	12	13
Stable disease	4	2	1	0
Partial response	2	2	0	0
Complete response	0	0	0	0
Overall response rate, %	13.3	13.3	0	0
Overall nonprogression rate, %	40.0	26.6	6.6	0
Strata A and B (<i>n</i> = 41)				
Overall response rate, %	9.8	14.6	7.3	0
Overall non-progression rate, %	29.3	24.4	12.2	2.4
Chemotherapy-naïve patients (<i>n</i> = 11)				
Disease status				
Not assessable	3	3	3	3
Progressive disease	5	7	8	8
Stable disease	3	1	0	0
Partial response	0	0	0	0
Complete response	0	0	0	0
Overall response rate, %	0	0	0	0
Overall nonprogression rate, %	27.2	9.0	0	0
Pretreated patients (<i>n</i> = 30)				
Disease status				
Not assessable	2	2	2	2
Progressive disease	16	19	23	27
Stable disease	5	3	2	1
Partial response	6	4	1	0
Complete response	1	2	2	0

(continued)

Table 3. (Continued)

	At day 60	At day 120	At day 180	At day 290
Overall response rate, %	23.0	20.0	10.0	0
Overall nonprogression rate, %	40.0	30.0	16.7	3.3
Metastatic angiosarcoma (<i>n</i> = 33)				
Disease status				
Not assessable	5	5	5	5
Progressive disease	16	20	24	27
Stable disease	7	4	2	1
Partial response	4	2	0	0
Complete response	1	2	2	0
Overall response rate, %	15	12	6	0
Overall nonprogression rate, %	36	24	12	3
Locally advanced angiosarcoma (<i>n</i> = 8)				
Disease status				
Not assessable	0	0	0	0
Progressive disease	5	6	7	8
Stable disease	1	0	0	0
Partial response	2	2	1	0
Complete response	0	0	0	0
Overall response rate, %	25	25	12.5	0
Overall nonprogression rate, %	37.5	25	12.5	0

Figure 1. Progression-free survival times in stratum A and stratum B, with the progression-free survival times observed in the AngioTax study as a reference [7].**DISCUSSION**

Angiosarcoma is a rare sarcoma with a high risk for relapse [1, 4, 5]. Following metastatic development, the prognosis remains poor with all available cytotoxic agents. Because of the

Figure 2. Progression-free survival times in patients with and without prior chemotherapy (CT).

Figure 3. Overall survival times in stratum A and stratum B, with the overall survival times observed in the AngioTax study as a comparison [7].

possible contribution of VEGF and KDR (VEGF-R2) in angiosarcoma [9–14], we conducted a stratified phase II trial investigating sorafenib as a treatment for advanced angiosarcoma. Because of their different behaviors, superficial angiosarcoma and visceral angiosarcoma were analyzed in separate strata. A third stratum, including epithelioid hemangioendotheliomas and hemangiopericytoma/malignant solitary fibrous tumors, is still accruing.

Until now, few agents have been demonstrated to have significant activity in patients with advanced angiosarcoma. In the largest retrospective study ($n = 149$), the median OS duration was 11 months [8]. There are few active drugs. A doxorubicin-based regimen as a first-line treatment ($n = 71$) provided a complete response in six cases (8.4%) and a partial response in 16 cases (22.5%) [8]. The activity of a doxorubicin-based regimen has been confirmed in many retrospective studies [1, 2, 8], with a median PFS interval close to 6 months. Weekly paclitaxel as a first-line treatment ($n = 47$) provided a complete response in eight cases (17.5%) and a partial response in 13 cases (28.0%) [8]. The activity of weekly paclitaxel was established in a formal phase II trial [7] and confirmed by many other retrospective studies [3, 20, 21], with a median PFS interval of 4–6 months.

The primary endpoint in this study was the PFR at 9 months, but <5% of the patients achieved this primary endpoint (Table 3, Figs. 1 and 2). Even though the eligibility criteria did not formally include the criterion “progressive disease at entry,” this study illustrates that metastatic and locally advanced angiosarcomas are very aggressive entities. Nevertheless most patients in the present study had previously been exposed to chemotherapy (30 of 41, 73.1%), especially to doxorubicin-based regimens (24 of 41, 58.3%) and weekly paclitaxel (13 of 41, 31.7%) (Table 1). Sixteen patients (39.0%) had been exposed to one line of chemotherapy and 14 patients had been exposed to two or more lines of chemotherapy (34.0%) (Table 1). In light of these facts, the validity of a primary endpoint based on a fixed time point assessment appears debatable, because it does not take into account the aggressiveness and the accelerated spreading observed after exposure to subsequent treatment lines. Nevertheless, the activity was actually similar for both superficial and visceral angiosarcoma (Table 3, Figs. 1 and 3). Sorafenib was inactive in chemotherapy-naïve patients (Table 3), whereas confirmed objective responses, including complete responses, were observed in pretreated patients (Table 3, Fig. 2). The 3-month and 6-month PFRs for pretreated patients were, respectively, 35% and 16%, within the range of those observed with active agents according to the Soft Tissue and Bone Sarcoma Group of European Organization for Research and Treatment of Cancer [22, 23]. This suggests that patients with angiosarcoma previously exposed to chemotherapy could benefit from sorafenib treatment. Nevertheless, we were not able to identify any predictive factor for clinical benefit (Table 3). The nature of observed toxicity with sorafenib was as expected, without any specific toxicity (no bleeding) or toxic death (Table 2). Nevertheless, in this study population of patients heavily pretreated with chemotherapy, the rates of dose reduction because of toxicity (48.7%), transient drug discontinuation as a result of toxicity (43.6%), and definitive drug discontinuation for nonmanageable toxicity (12.8%) were higher than those reported for patients pretreated with other tyrosine kinase inhibitors.

Other antiangiogenic agents were evaluated as treatment for vascular sarcoma (angiosarcoma and epithelioid hemangioendothelioma) in two previous phase II trials. One trial investigated the activity of bevacizumab alone (15 mg/kg every 3 weeks). Some preliminary results were presented at the American Society of Clinical Oncology Annual Meeting in 2009. Twenty-six patients were assessable for response, with three partial responses (three to 16 cycles) and 13 cases of stable disease (three to 22 cycles) [24]. Maki et al. [15] reported on the activity of sorafenib in 40 patients with vascular sarcoma: the response rate was 13%, the 3-month PFS rate was 64%, the 6-month PFS rate was 31%, the median PFS time was 4 months, and the median OS duration was 15 months.

Antonescu et al. [13] recently showed that only 10% of angiosarcomas display activating mutations in *KDR*. Furthermore, in vitro studies have demonstrated that angiosarcomas with mutated *KDR* are highly sensitive to sorafenib. We explored the correlation between genotype and activity and tolerance. Nevertheless, the enrolled population was very homogeneous. In the present series, we did not find any *KDR* mutation (in exons 15, 16, and 24); this could explain the limited activity observed. All

patients but three were homozygous for the common allele of *KDR* SNPs. The heterozygous patients did not experience any specific toxicity (in particular, there was an absence of severe arterial hypertension and hand-foot syndrome, as previously reported [17, 18]). One patient showed a variation previously not reported in exon 6 of *VEGFA* (D349N). In that case, the observed PFS interval was 220 days (7.3 months).

Sorafenib did not reach the predefined level of activity and provided stable disease of limited duration for patients with advanced and pretreated angiosarcoma. New studies are required to better target the subpopulation of patients benefiting from this treatment.

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AUTHOR CONTRIBUTIONS

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See the accompanying commentary on pages 154–156 of this issue.