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Sarcomas

Activity of Pazopanib and Trabectedin in Advanced Alveolar Soft Part Sarcoma

Silvia Stacchiotti,[a] Olivier Mir,[b] Axel Le Cesne,[b] Bruno Vincenzi,[c] Alexander Fedenko,[d] Robert G. Maki,[e,f] Neeta Somaiah,[g] Shreyaskumar Patel,[g] Mehedi Brahmi,[h] Jean Y. Blay,[h] Kjetil Boye,[i] Kirsten Sundby Hall,[i] Hans Gelderblom,[j] Nadia Hindi,[k] Javier Martin-Broto,[k] Hanna Kosela,[l] Piotr Rutkowski,[l] Antoine Italiano,[m] Florence Duffaud,[n,o] Eisuke Kobayashi,[p] Paolo G. Casali,[a] Salvatore Provenzano,[a] Akira Kawai[p]

[a]Cancer Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; [b]Cancer Medicine, Gustave Roussy Cancer Campus, Université Paris-Saclay, Villejuif, France; [c]Medical Oncology, University Campus Bio-Medico, Rome, Italy; [d]N.N. Blokhin Russian Cancer Research, Moscow, Russian Federation; [e]Monter Cancer Center, Northwell Health, Lake Success, New York, USA; [f]Cold Spring Harbor Laboratory, Cold Spring Harbor, New York, USA; [g]Department of Sarcoma Medical Oncology, MD Anderson Cancer Center, Houston, Texas, USA; [h]Cancer Medicine, Centre Léon Bérard, Lyon, France; [i]Department of Oncology, Norwegian Radium Hospital, Oslo University Hospital, Oslo, Norway; [j]Department of Medical Oncology, Leiden University Medical Center, Leiden, The Netherlands; [k]Department of Medical Oncology, Biomedicine Research Institute (IBIS), University Hospital Virgen del Rocio, Sevilla, Spain; [l]Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland; [m]Institut Bergonié, Bordeaux, France; [n]Service d'Oncologie Médicale Chu la Timone, Marseille, France; [o]Aix Marseille Université (AMU), Marseille, France; [p]Musculoskeletal Oncology and Rehabilitation Medicine, National Cancer Center, Tokyo, Japan

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Sarcoma • Alveolar soft part sarcoma • Trabectedin • Pazopanib • Chemotherapy

Abstract

Background. Alveolar soft part sarcoma (ASPS) is an exceedingly rare and orphan disease, without active drugs approved in the front line. Pazopanib and trabectedin are licensed for sarcoma treatment from second-line, but very little and contradictory data are available on their activity in ASPS. Lacking ongoing and/or planned clinical trials, we conducted a multi-institutional study involving the reference sites for sarcoma in Europe, U.S., and Japan, within the World Sarcoma Network, to investigate the efficacy of pazopanib and trabectedin.

Materials and Methods. From May 2007, 14 of the 27 centers that were asked to retrospectively review their databases had identified 44 advanced ASPS patients treated with pazopanib and/or trabectedin. Response was evaluated by Response Evaluation Criteria in Solid Tumors 1.1. Progression-free survival (PFS) and overall survival (OS) were computed by Kaplan-Meier method.

Results. Among 30 patients who received pazopanib, 18 were pretreated (13 with other antiangiogenics). Response was evaluable in 29/30 patients. Best responses were 1 complete response, 7 partial response (PR), 17 stable disease (SD), and 4 progressions. At a 19-month median follow-up, median PFS was 13.6 months (range: 1.6–32.2+), with 59% of patients progression-free at 1 year. Median OS was not reached.

Among 23 patients treated with trabectedin, all were pretreated and evaluable for response. Best responses were 1 PR, 13 SD, and 9 progressions. At a 27-month median follow-up, median PFS was 3.7 months (range: 0.7–109), with 13% of patients progression-free at 1 year. Median OS was 9.1 months.

Conclusion. The value of pazopanib in advanced ASPS is confirmed, with durable responses, whereas the value of trabectedin appears limited. These results are relevant to defining the best approach to advanced ASPS. ***The Oncologist*** 2018;23:62–70

Implications for Practice: This retrospective study, conducted among the world reference centers for treatment of sarcoma, confirms the value of pazopanib in patients with advanced alveolar soft part sarcoma (ASPS), with dimensional and durable responses, whereas trabectedin shows a limited activity. Alveolar soft part sarcoma is resistant to conventional cytotoxic chemotherapy. Pazopanib and trabectedin are licensed for treatment of sarcoma from second line; in the lack of prospective clinical trials, these results are relevant to defining ASPS best management and strongly support initiatives aimed at obtaining the approval of pazopanib in the front line of the disease.

Correspondence: Silvia Stacchiotti, M.D., Fondazione IRCCS Istituto Nazionale Tumori, via Venezian 1, Milan, Italy. Telephone: 390223902803; e-mail: silvia.stacchiotti@istitutotumori.mi.it Received April 11, 2017; accepted for publication June 20, 2017; published Online First on July 28, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0161

Introduction

Alveolar soft part sarcoma (ASPS) is a rare soft tissue sarcoma (STS) that carries a specific t(X;17)(p11;q25), involving a ASPSCR1-transcription factor E 3 (TFE3) fusion [1, 2]. The natural history of this tumor is characterized by an indolent behavior, coupled with a paradoxical high metastatic rate. As a result, most patients eventually require medical therapy. Although conventional anthracycline-based chemotherapy is inactive in this disease [1, 3–5], ASPS was reported to be sensitive to antiangiogenic agents like sunitinib, cediranib, and, more recently, anlotinib [6–10]. These antiangiogenic agents can induce dimensional responses and durable disease control in 35% and 60% of patients, respectively, across different published studies. Unfortunately, none of these drugs are approved for the treatment of ASPS, and no active agents have regulatory approval in the front line.

Trabectedin and pazopanib are among the medical agents licensed for treatment of STS from second line after failure to anthracyclines, but data on their activity in patients affected by ASPS are scant. Trabectedin is a marine-derived product characterized by a complex and unique mechanism of action, affecting multiple key processes in tumor cell replication and death [11], and targeting tumor microenvironment [12, 13]. Trabectedin approval in STS is based on the results of two trials carried out in adult patients with a diagnosis of liposarcoma or leiomyosarcoma after failure of prior conventional chemotherapy [14, 15]. In the first study, one trabectedin regimen was superior to another (with evidence of a longer progression-free survival [PFS] in favor of a 24-hour infusion regimen, as compared with a 3-hour infusion schedule) [14]. In the other study, trabectedin was superior to dacarbazine in the same histologies in terms of PFS, although not in terms of overall survival (OS) [15].

Pazopanib is an antiangiogenic agent, inhibiting vascular endothelial growth factor receptors (VEGFR) 1–3, that was initially investigated in sarcoma within a phase 2 trial published by Sleijfer and colleagues in 2009 [16, 17]. In the phase 3 study in nonadipocytic STS that followed the phase 2 trial, the median PFS was 4.6 months for pazopanib, compared with 1.6 months for placebo, with an OS of 12.5 months versus 10.7 months [18].

In patients affected by ASPS, there are few case reports stating that trabectedin can achieve the stabilization of the tumor without evidence of tumor shrinkage. Unfortunately, those reports did not detail if treated patients were progressive or not before starting the drug [19–21]. Conversely, Nakamura and colleagues recently described 4 Response Evaluation Criteria in Solid Tumors (RECIST) responses of 12 (33%) ASPS patients treated with pazopanib [22], while a study from Korea noted 1 response among 6 ASPS patients treated with the drug within a prospective trial that was unfortunately closed early due to slow accrual (Clinicaltrials.gov reference NCT02113826) [23].

Due to the rarity of ASPS and the lack of prospective trials, we conducted a retrospective multi-institutional case-series analysis among reference centers for treatment of STS, with the support of the World Sarcoma Network, to investigate the activity and the efficacy of trabectedin and pazopanib in advanced ASPS patients. The results presented herein are important to refine the best clinical management of the disease in the metastatic setting.

Materials and Methods

We considered all consecutive patients with locally advanced and/or metastatic ASPS treated with trabectedin (group A) and/or pazopanib (group B), in front or further lines, outside clinical trials, from May 2007 to November 2016. Patients were treated at 14 international reference centers for treatment of STS from Europe, U.S., and Japan, selected among 27 institutions that were asked to review their databases within the World Sarcoma Network effort. Only cases in which diagnosis of ASPS was histologically proven and confirmed by each institutional pathologist were included in the study. All patients provided a written informed consent to the treatment with trabectedin and/or pazopanib. Approval by each Institutional Review Board was also required.

Treatment

Patients in group A received intravenous trabectedin, at a starting dose ranging from 1.3–1.5 mg/m^2 - (at investigator's discretion, with a maximum dose of 2.6 total mg per cycle), given in 24-hour continuous infusion, with glucocorticoid premedication, every 3 weeks, until progression or toxicity.

Patients in group B were administered pazopanib orally, at the dose of 800 mg per day (either 800 mg oral daily or 400 mg twice a day), continuously, until progression or toxicity.

Clinical Assessment

Performance status, biochemistry, and blood count were evaluated at baseline and monitored throughout the study period. Adverse events were recorded. Disease status was assessed by whole body computed tomography (CT) scan and/or a CT/magnetic resonance imaging (MRI) of the sites of disease at baseline and then repeated every 2–3 months, at the discretion of the treating physician.

Efficacy Assessment

Response to treatment was assessed by RECIST, version 1.1 [24]. Overall survival and PFS were estimated on SAS University Edition software (SAS Institute, Cary, NC, https://www.sas.com/en_us/home.html) and survival analyses were conducted by the Kaplan-Meier method. Patients without evidence of progression and interrupting treatment with trabectedin (group A) and with pazopanib (group B) for any reason were censored at the last follow-up. Patients alive or lost to follow-up were censored at the last contact.

Results

We retrospectively identified 23 patients treated with trabectedin (group A) and 30 patients treated with pazopanib (group B). Four patients were treated sequentially with trabectedin and pazopanib and are included in both groups. Tables 1 and 2 summarize patient characteristics and clinical findings.

Group A: Trabectedin

All patients completed their treatment (22 progressive; 1 other) and all were evaluable for response. Mean age was 32 (range: 19–48) years. Performance status was $\leq$ 3 in all cases. All patients, except for one who was treated for a locally advanced tumor, had metastatic disease. Twenty-one of 23 patients had received at least 1 prior line of medical therapy before starting

Table 1. Patient characteristics and clinical findings for patients treated with trabectedin (group A)

Patient ID	Sex	Age	ASPL-TFE3	Primary site	Past medications	Evidence of PD	Response	Reason for withdrawal	PFS (months)	OS (months)	AEs
1[a]	M	33	Y	Leg	Epirubicin, ifosfamide, cyclophoshamide, sunitinib, pazopanib	Y	SD	PD	7.2	12.5+	N
2[a]	M	40	Y	Arm	Sunitinib, crizotinib, pazopanib	Y	PD	PD	0.7	4.5+	N
3	M	41	Y	Thigh	Crizotinib, pazopanib	Y	PD	PD	2.3	2.9+	N
4	F	32	UNK	Leg	Sunitinib	Y	PR	PD	20.5	27+	N
5	M	51	UNK	Thigh	N/A	UNK	SD	PD	4.2	20.2	N
6	F	29	Y	Pelvis	N/A	UNK	SD	PD	4.3	59.7+	N
7	F	31	UNK	Thigh	Gemcitabine, imatinib, bevacizumab, dacarbazine	Y	SD	PD	4.6	17.4	N
8	M	28	Y	Leg	Doxorubicin	Y	SD	PD	4.4	6.1	Anemia
9	M	26	UNK	M. psoas	Doxorubicin, ifosfamide, dacarbazine, gemcitabine, docetaxel	Y	PD	PD	2.4	18.9	N
10[a]	F	27	UNK	Thigh	Sunitinib, crizotinib	Y	SD	PD	3.7	17.1	Brain haemorrhage (not drug related), anemia
11[a]	M	43	UNK	Leg	Doxorubicin, ifosfamide, pazopanib	UNK	SD	PD	6.4	9	Neutropenia
12	M	34	N	Trunk	Doxorubicin	UNK	SD	Patient's choice	17.6	23.8	Diarrhea, neutropenia
13	M	31	UNK	Thigh	Cisplatin, ifosfamide, gemcitabine, dacarbazine, pazopanib, sunitinib, imatinib	Y	PD	PD	1.2	18.1+	N
14	F	19	UNK	Leg	Epirubicin, ifosfamide, gemcitabine, dacarbazine	Y	PD	PD	1.9	6.7	N
15	F	16	UNK	Thigh	Vinorelbine, cyclophosphamide	Y	SD	Complete remission after lung metastasectomy	109+	109+	Anemia
16	M	30	Y	Thigh	Doxorubicin, ifosfamide, sunitinib	UNK	SD	PD	3.5	5.2	N
17	M	40	UNK	Thigh	Doxorubicin, ifosfamide, sunitinib	UNK	PD	PD	2.1	3.3	N
18	M	31	Y	Thigh	Doxorubicin, sunitinib, sorafenib	UNK	PD	PD	2.1	4.6	N
19	F	48	Y	Forearm	Doxorubicin, ifosfamide, sunitinib	UNK	SD	PD	3.4	4.8	Transaminitis
20	M	21	UNK	Knee	Doxorubicin, sunitinib	UNK	SD	PD	5.4	9.1	N
21	M	33	Y	Thigh	Doxorubicin, ifosfamide	UNK	PD	PD	2.4	3.3	N
22	M	23	Y	Pelvis	Doxorubicin, sunitinib	UNK	SD	PD	3.7	5.2	Transaminitis, rhabdomyolysis
23	F	35	Y	Thigh	Doxorubicin, ifosfamide, sunitinib	UNK	PD	PD	2.3	4.8	N

[a]Patients treated with both trabectedin and pazopanib.

Abbreviations: AE, adverse event; F, female; ID, identification; M, male; N, no; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; UNK, unknown; Y, yes.

Table 2. Patient characteristics and clinical findings for patients treated with pazopanib (group B)

Patient ID	Sex	Age	ASPL-TFE3	Primary site	Past medications	Evidence of PD	Response	Reason for withdrawal	PFS (months)	OS (months)	AEs
24[a]	M	39	Y	Arm	Sunitinib, crizotinib	Y	SD	PD	6.2	7.7	N
25	F	29	Y	Retroperitoneum	Sunitinib, crizotinib, doxorubicin	Y	PR	N/A	13.1	13.1	N
26[a]	M	32	Y	Leg	Epirubicin, ifosfamide, cyclophosphamide, sunitinib, crizotinib	Y	SD	AE	3.5	17.9	Asthenia, anorexia
27	F	23	Y	Leg	Crizotinib, sunitinib	Y	PR	N/A	6.2	6.2	N
28	M	39	Y	Leg	Epirubicin, ifosfamide, sunitinib, crizotinib	N	SD	N/A	5.6	5.6	N
29	M	41	Y	Thigh	Crizotinib	Y	SD	PD/AE	4.3	12.9	Flu-like symptoms
30	F	22	Y	Retroperitoneum	Cyclophosphamide	UNK	PR	PD	8.7	12.5	N
31	M	32	Y	Thigh	Sunitinib, crizotinib	Y	CR	N/A	15.2	15.2	N
32	M	34	UNK	Thigh	(8 lines) N/A	UNK	UNK	N/A	2.3	2.3	N
33	M	26	UNK	Thigh	N/A	UNK	SD	PD	15.0	31.8	N
34	F	34	UNK	Tongue	Sunitinib	UNK	SD	PD	12.2	28.0	N
35	M	25	UNK	Thigh	Doxorubicin, ifosfamide, gemcitabine, docetaxel	UNK	SD	PD	13.6	24.9	N
36	F	23	UNK	Thigh	N/A	UNK	SD	PD	15.0	19.4	N
37	M	28	Y	Liver	Cediranib	UNK	SD	PD	10.1	27.1	Blurred vision
38	F	26	UNK	Left thigh	N/A	UNK	SD	PD	4.8	4.8	N
39[a]	F	28	UNK	Thigh	Sunitinib, crizotinib, trabectedin	Y	SD	PD	1.6	9.6	Complication from response
40	M	29	Y	Calf	Sunitinib, crizotinib	Y	SD	N/A	11.8	11.8	N
41[a]	M	43	UNK	Leg	Doxorubicin, ifosfamide	UNK	SD	PD	7.0	15.0	N
42	F	68	Y	Mediastinum	Doxorubicin, gemcitabine, docetaxel	UNK	PR	PD	15.0	28.6	N
43	M	51	UNK	Leg	Doxorubicin, gemcitabine	UNK	PD	PD	3.3	9.0	Transaminitis
44	F	22	UNK	Thigh	N/A	UNK	PR	N/A	3.6	3.6	N
45	F	32	UNK	Thigh	N/A	Y	PR	AE	32.2	32.2	Hypertension
46	M	34	UNK	Thigh	N/A	Y	SD	PD	16.1	31.2	N
47	F	35	UNK	Neck	N/A	N	SD	PD	19.9	29.6	N
48	F	32	UNK	Leg	N/A	Y	SD	PD	14.9	28.8	N
49	F	32	UNK	Thigh	N/A	Y	PR	AE	26.4	26.4	Meningitis
50	F	35	UNK	Forearm	N/A	N	PD	PD	14.4	19.0	N
51	M	35	UNK	Shoulder	Sunitinib	Y	SD	PD	13.5	16.2	N
52	F	35	UNK	Retroperitoneum	N/A	N	PD	PD	5.9	26.1	N

(continued)

Table 2. (continued)

Patient ID	Sex	Age	ASPL-TFE3	Primary site	Past medications	Evidence of PD	Response	Reason for withdrawal	PFS (months)	OS (months)	AEs
53	M	33	UNK	Thigh	Sunitinib, gemcitabine, docetaxel	UNK	PD	PD	1.7	2.1	N
24	M	39	Y	Arm	Sunitinib, crizotinib	Y	SD	PD	6.2	7.7	N
25	F	29	Y	Retroperitoneum	Sunitinib, crizotinib, doxorubicin	Y	PR	N/A	13.1	13.1	N
26	M	32	Y	Leg	Epirubicin, ifosfamide, cyclophosphamide, sunitinib, crizotinib	Y	SD	AE	3.5	17.9	Asthenia, anorexia
27	F	23	Y	Leg	Crizotinib, sunitinib	Y	PR	N/A	6.2	6.2	N
28	M	39	Y	Leg	Epirubicin, ifosfamide, sunitinib, crizotinib	N	SD	N/A	5.6	5.6	N
29	M	41	Y	Thigh	Crizotinib	Y	SD	PD/AE	4.3	12.9	Flu-like symptoms
30	F	22	Y	Retroperitoneum	Cyclophosphamide	UNK	PR	PD	8.7	12.5	N

[a]Patients treated with both trabectedin and pazopanib.

Abbreviations: AE, adverse event; CR, complete response; F, female; ID, identification; M, male; N, no; N/A, not applicable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; UNK, unknown; Y, yes.

trabectedin >1 line in 17 patients). The information on the evidence of progression before trabectedin initiation was available in 11 cases, all progressive.

Starting dose of trabectedin was 1.2, 1.3, and 1.5 mg/m^2 in 4, 5, and 14 cases, respectively, administered every 3 weeks. Median number of cycles administered was four. Overall, trabectedin toxicity was as expected and was fairly well tolerated [grade (G) $\geq$ 3 non-hematologic toxicity 4; G $\geq$ 3 hematologic toxicity 5]. None of the patients had to definitively stop their treatment due to toxicity. In all patients, toxicity resolved upon holding trabectedin.

Response

Best RECIST responses with trabectedin were 1 partial response (PR), 13 stable disease (SD), and 9 progressive disease (PD), for an overall response rate (ORR) of 4.3%.

At a 27-month median follow-up, the median OS was 9.1 months, with 16 patients dead at the time of the present analysis (Fig. 1A). Median PFS by RECIST was 3.7 months (range: 0.7–109; Fig. 2A), with 13% of patients progression-free at 12 months.

Group B: Pazopanib

At the time of the present analysis, 23 patients had completed the treatment with pazopanib (19 progression; 4 toxicity), while 7 (23%) were still on therapy. Twenty-nine of 30 patients were evaluable for response.

Mean age was 33 (range: 22–68) years. Performance status was 0–2 in all patients. All patients had metastatic disease. Twelve patients were treatment-naïve at the time of starting pazopanib, and 18 were pretreated with at least 1 previous regimen. Thirteen (43%) patients had already received another antiangiogenic drug before starting pazopanib. The evidence of progression before starting pazopanib was documented in 13 out of 17 cases for which this information was available, and the remaining 4 patients were stable.

All patients started pazopanib at the dose of 800 mg/day, except for three patients who received 600 mg/day. Median number of cycles was 12 (range: 2–33). Pazopanib was fairly well tolerated (G $\geq$ 3 non-hematologic toxicity: 6; G $\geq$ 3 hematologic toxicity: 0). Four patients definitively stopped pazopanib due to side effects. In all patients, toxicity resolved upon pazopanib discontinuation.

Response

Best response to pazopanib by RECIST was: 1 complete response (CR), 7 PR, 17 SD, and 4 PD (Fig. 3), for an ORR of 27%. Notably, three patients responded to pazopanib after failure of another antiangiogenic agent (Fig. 4).

The median OS was not reached at the time of this analysis (Fig. 1B). At a 19-month median follow-up, the median PFS by RECIST was 13.6 months (range: 1.6–32.2+). The PFS at 12 months was 59% (Fig. 2B).

Progression-free survival analysis stratified by the extent of the response showed a significantly better outcome in patients achieving a RECIST CR and/or PR (8 cases) in comparison with those who had only an SD (17 cases; median PFS: not reached vs. 13.5 months, respectively; median OS: not reached) or a PD (4 cases; median PFS: 4.6 months; median OS: not reached; Fig. 5). A comparison between patients naïve to and pretreated with other antiangiogenics showed a trend towards a better PFS in untreated patients (median PFS: 14.4 vs. 12.2 months, respectively; supplemental online Fig. 1).

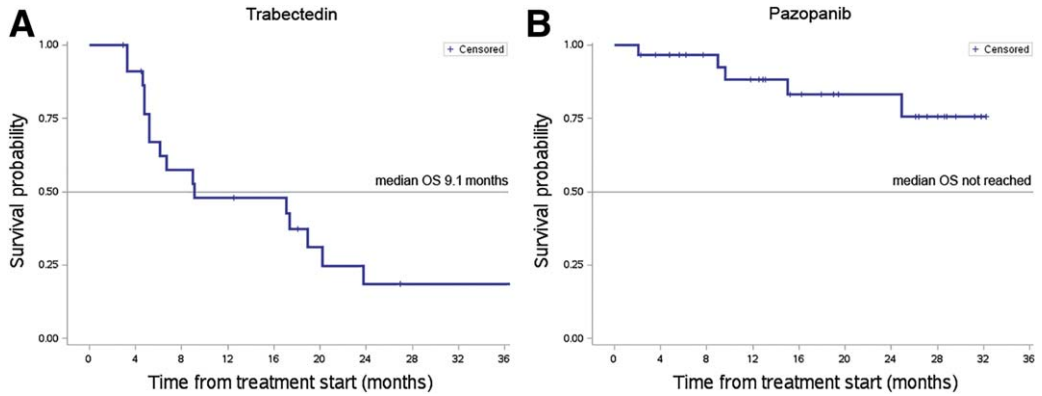

Figure 1. Overall survival curve of patients treated with trabectedin and with pazopanib. At a 27-month median follow-up, the median OS of patients treated with trabectedin **(A)** was 9.1 months (range: 2.9–109). At a 19-month median follow-up, the median OS of patients treated with pazopanib **(B)** was not reached (range: 2.1–32.2).

Abbreviation: OS, overall survival.

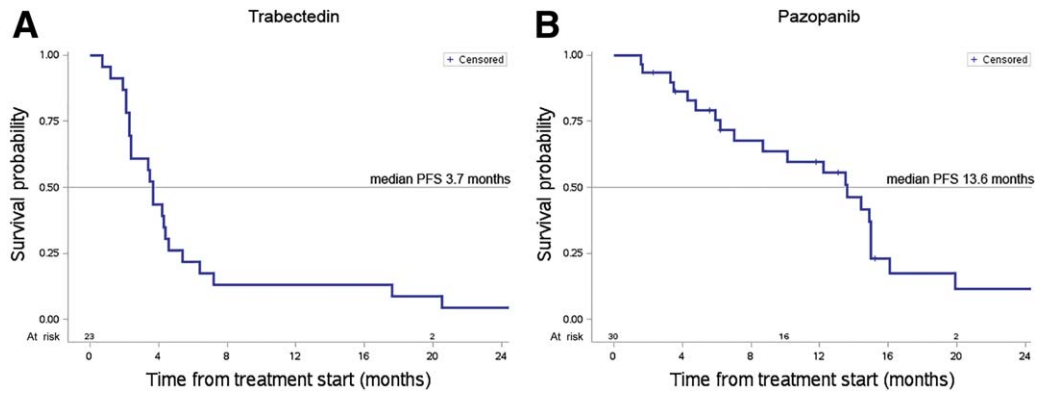

Figure 2. Progression-free survival curve of patients treated with trabectedin and with pazopanib. At a 27-month median follow-up, the median PFS by Response Evaluation Criteria in Solid Tumors (RECIST) was 3.7 months (range: 0.7–109) for patients treated with trabectedin **(A)**. In the group of patients treated with pazopanib **(B)**, the median PFS by RECIST was 13.6 months (range: 1.6–32.2) as evaluable at a median follow-up of 19 months.

Abbreviation: PFS, progression-free survival.

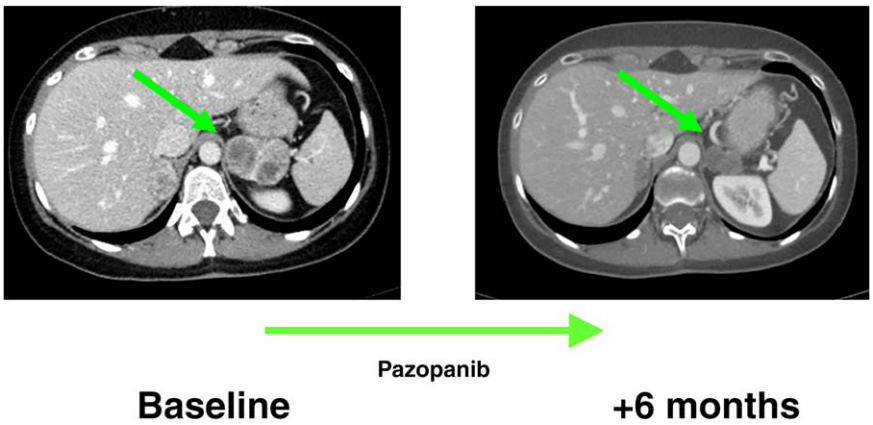

Figure 3. Response to pazopanib. Axial, contrast-enhanced computed tomography scans in a patient affected by intra-abdominal metastasis from an alveolar soft part sarcoma of the lower limb, at baseline and after six cycles of treatment with pazopanib, when a Response Evaluation Criteria in Solid Tumors partial response was achieved.

Discussion

Our multi-institutional retrospective study collected the two largest series currently available of patients affected by advanced and/or metastatic ASPS and treated with trabectedin or pazopanib, including 30 and 23 cases, respectively. This study confirms the activity of pazopanib in patients with advanced ASPS, with 27% ORR by RECIST, a median PFS of 13.6 months, and 59% of patients progression-free at 12 months. Responses to pazopanib were also detectable in 3 of 13 patients with secondary resistance to other antiangiogenics. By contrast, the

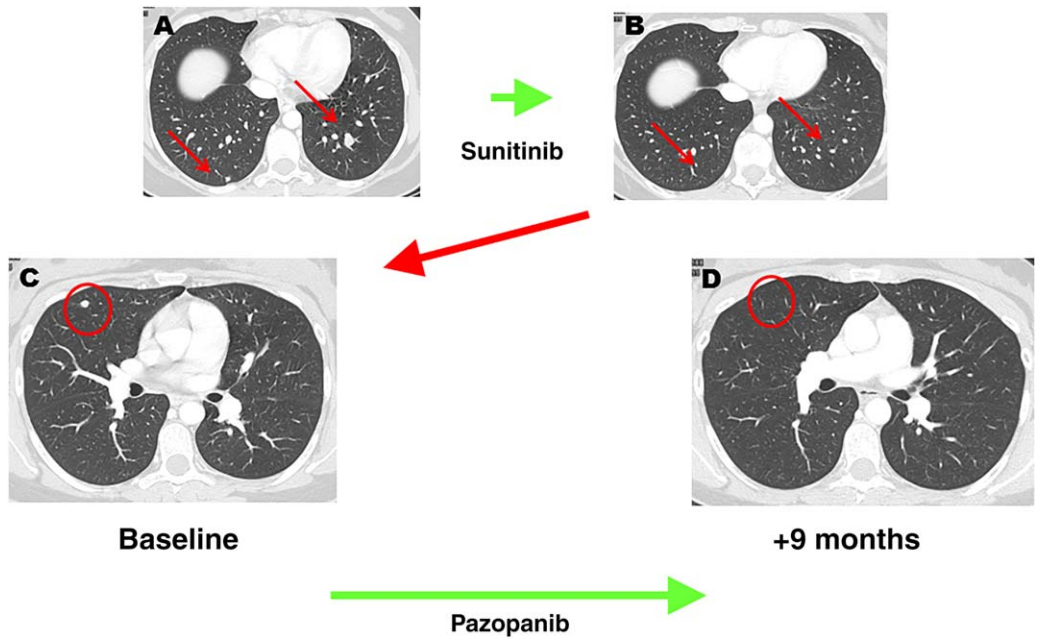

Figure 4. Response to pazopanib after secondary resistance to sunitinib. Axial, contrast-enhanced computed tomography scans in a patient affected by lung metastases from a retroperitoneal alveolar soft part sarcoma. **(A, B)**: The initial response to sunitinib followed by a secondary progression marked by the appearance of new lung lesions (**C**, red circle). **(D)**: Afterward, patient was started on pazopanib with a new response.

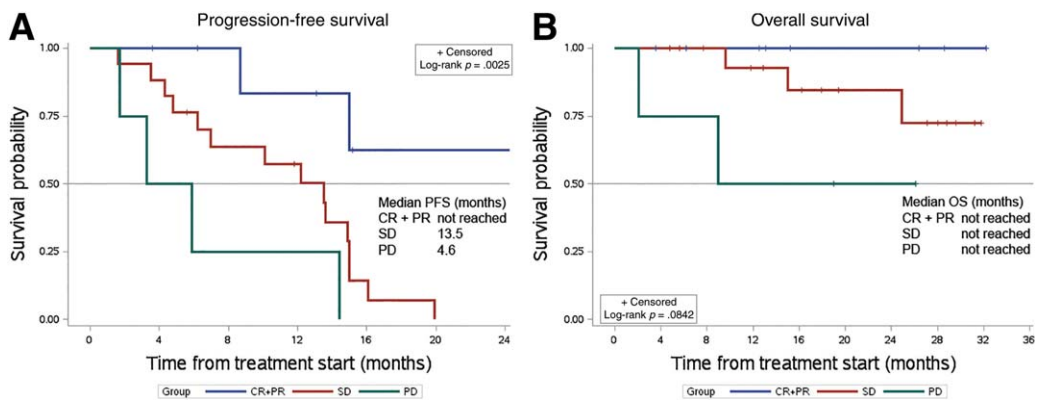

Figure 5. Progression-free survival and OS analysis stratified by the extent of Response Evaluation Criteria in Solid Tumors (RECIST) response. Patients whose best response was a CR or a PR by RECIST were grouped together (group A, CR/PR patients: 8, blue line in the graph) and compared with those who showed an SD (group B, SD patients: 17, red line) and those who progressed (group C, PD patients: 4, green line). **(A)**: Median PFS (range) was not reached (3.6–32.2), 13.5 months (1.6–19.9), and 4.6 months (1.7–14.4) in group A, B, and C, respectively. **(B)**: Median OS was not reached in all groups, with all patients of group A alive at the time of the present analysis (blue line).

Abbreviations: CR, complete response; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

value of trabectedin in this series looked limited, with only a single RECIST response (ORR 4.3%), a 3.7-month median PFS, and 13% of patients free from progression at 12 months.

Alveolar soft part sarcoma is an extremely rare disease. Its rarity makes it challenging to conduct prospective clinical trials, as the premature closure of a Korean study on pazopanib due to lack of recruitment recently demonstrated [23]. This confirms that collaborative efforts are of major importance. With all the limitations of a retrospective study, our case-series analysis provides new information on the activity of two agents that are available for STS in daily clinical practice.

The activity of trabectedin appeared limited, once more underscoring the low sensitivity of ASPS to cytotoxics. Compared with available reports [19–21], in our series trabectedin did not achieve prolonged disease control in most patients, with only three cases remaining stable while under treatment for $>$ 12 months. Of course, one should consider the high proportion of heavily pretreated patients.

By contrast, our study confirms the role of antiangiogenics in ASPS. Of note, unfortunately, none of the agents with antiangiogenic activity tested in ASPS so far are approved for treatment of the disease in the front line, and pazopanib is the only antiangiogenic drug formally registered for treatment of STS, after failure on anthracycline. The results of a randomized trial on cediranib in ASPS will be available soon and, if positive, will possibly pave the way to the registration of another active drug for this tumor. The antitumor effect of pazopanib in this series was somewhat inferior to what has been reported on sunitinib and cediranib, both in terms of ORR (27% for pazopanib vs. 35%–60% for cediranib and sunitinib) and duration of response

(13-month median PFS in case of pazopanib vs. 15–19 months with sunitinib in different series) [6–9, 26]. One can provide only tentative explanations. Forty percent of patients in our series had been previously treated with another antiangiogenic agent and this may have limited, at least in part, the effect of pazopanib, although mechanisms of resistance to antiangiogenics in ASPS are unknown and could not be investigated retrospectively in this multi-institutional series. In fact, a trend towards a better outcome was detected in our study when the PFS of patients pretreated with pazopanib before starting pazopanib was compared with the PFS of those naïve to antiangiogenic agents (median PFS 12.2 vs. 14.4 months). On the other hand, three patients included in our study responded to pazopanib after failure on other antiangiogenic agents. This observation confirms that, at least in some cases, the evidence of resistance to a given antiangiogenic does not prevent the activity of another drug of the same class. Conversely, the different spectrum of targets inhibited by various antiangiogenics could be responsible for a different degree of antitumor effect. In particular, sunitinib has a broader kinase profile compared with pazopanib, which is a "purer" antiangiogenic drug. Sunitinib has activity against platelet derived growth factor receptor (PDGFR)a, PDGFRb, KIT, VEGF receptors 1–3 (VEGFR1–3), fms-like tyrosine kinase 3 (FLT3), and, notably, macrophage colony-stimulating factor receptor 1 (MCSFR1) [26], whereas pazopanib is a more selective VEGF-signaling inhibitor [16]. Overall, the mechanisms underlying the response to sunitinib, cediranib, anlotinib, and pazopanib in ASPS remain under evaluation. The antiangiogenic effect of this class of agents may well target the peculiar vasculature of ASPS [1], sustained by the translocation-related activation of the lactate pathway, as described by Goodwin et al. [27]. In addition to their antiangiogenic impact, a direct antitumor effect due to the inhibition of VEGFR, PDGFR, and rearranged during transfect (RET) expressed by the tumor cells was described [8]. Finally, Kummar et al. intriguingly showed on tumor biopsies from eight patients treated with cediranib that the antitumor effect of this agent induced the downregulation of genes related to myeloid infiltrate and vasculogenesis [7]. Myeloid infiltration has also been proved by another group, which showed the presence of myeloid cells both along the tumor vessels and interspersed within the tumor cells [28–30]. The role of tumor-infiltrating myeloid cells in the formation and maintenance of abnormal blood vessels in tumors is well known [31]. These observations suggest an immunomodulatory role of this class of drugs in addition to the antiangiogenic and direct antitumor effect that could be enhanced when agents with a greater activity against MCSFR1, such as sunitinib, are administered. These data also suggest that immunomodulation could play a role in this sarcoma type, and that combination of immunotherapeutic agents such as immune checkpoint inhibitors and antiangiogenic agents may be worth exploring, as is being done in ongoing clinical trials.

Conclusion

These data confirm that pazopanib is active in patients with advanced ASPS, whereas the value of trabectedin seems to be limited. Collaborative efforts are of major importance in improving the management of people with very rare sarcoma subtypes. In an extremely rare disease where cytotoxics are clearly ineffective, we believe that antiangiogenics should be available for clinical use as first-line medical options.

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Author Contributions

Conception/design: Silvia Stacchiotti, Axel Le Cesne, Robert G. Maki, Shreyaskumar Patel, Jean Y. Blay, Hans Gelderblom, Javier Martin-Broto, Piotr Rutkowski, Paolo G. Casali, Akira Kawai

Provision of study material or patients: Silvia Stacchiotti, Olivier Mir, Axel Le Cesne, Bruno Vincenzi, Alexander Fedenko, Robert G. Maki, Neeta Somaiah, Shreyaskumar Patel, Mehedi Brahmi, Jean Y. Blay, Kjetil Boye, Kirsten Sundby Hall, Hans Gelderblom, Nadia Hindi, Javier Martin-Broto, Hanna Kosela, Piotr Rutkowski, Antoine Italiano, Florence Duffaud, Eisuke Kobayashi, Paolo G. Casali, Salvatore Provenzano, Akira Kawai

Collection and/or assembly of data: Silvia Stacchiotti, Olivier Mir, Axel Le Cesne, Bruno Vincenzi, Alexander Fedenko, Robert G. Maki, Neeta Somaiah, Shreyaskumar Patel, Mehedi Brahmi, Jean Y. Blay, Kjetil Boye, Kirsten Sundby Hall, Hans Gelderblom, Nadia Hindi, Javier Martin-Broto, Hanna Kosela, Piotr Rutkowski, Antoine Italiano, Florence Duffaud, Eisuke Kobayashi, Paolo G. Casali, Salvatore Provenzano, Akira Kawai

Data analysis and interpretation: Silvia Stacchiotti, Olivier Mir, Axel Le Cesne, Bruno Vincenzi, Alexander Fedenko, Robert G. Maki, Neeta Somaiah, Shreyaskumar Patel, Mehedi Brahmi, Jean Y. Blay, Kjetil Boye, Kirsten Sundby Hall, Hans Gelderblom, Nadia Hindi, Javier Martin-Broto, Hanna Kosela, Piotr Rutkowski, Antoine Italiano, Florence Duffaud, Eisuke Kobayashi, Paolo G. Casali, Salvatore Provenzano, Akira Kawai

Manuscript writing: Silvia Stacchiotti, Olivier Mir, Axel Le Cesne, Bruno Vincenzi, Alexander Fedenko, Robert G. Maki, Neeta Somaiah, Shreyaskumar Patel, Mehedi Brahmi, Jean Y. Blay, Kjetil Boye, Kirsten Sundby Hall, Hans Gelderblom, Nadia Hindi, Javier Martin-Broto, Hanna Kosela, Piotr Rutkowski, Antoine Italiano, Florence Duffaud, Eisuke Kobayashi, Paolo G. Casali, Salvatore Provenzano, Akira Kawai

Final approval of manuscript: Silvia Stacchiotti, Olivier Mir, Axel Le Cesne, Bruno Vincenzi, Alexander Fedenko, Robert G. Maki, Neeta Somaiah, Shreyaskumar Patel, Mehedi Brahmi, Jean Y. Blay, Kjetil Boye, Kirsten Sundby Hall, Hans Gelderblom, Nadia Hindi, Javier Martin-Broto, Hanna Kosela, Piotr Rutkowski, Antoine Italiano, Florence Duffaud, Eisuke Kobayashi, Paolo G. Casali, Salvatore Provenzano, Akira Kawai

Disclosures

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