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Original Research

Activity of axitinib in progressive advanced solitary fibrous tumour: Results from an exploratory, investigator-driven phase 2 clinical study

S. Stacchiotti [a,*], N. Simeone [b], S. Lo Vullo [c], C. Morosi [d], F.G. Greco [d], A. Gronchi [e], M. Barisella [f], P. Collini [f], N. Zaffaroni [g], G.P. Dagrada [f], A.M. Frezza [a], L. Mariani [c], P.G. Casali [a,h]

[a] *Medical Oncology Unit 2, Medical Oncology Department, Fondazione IRCCS Istituto Nazione dei Tumori, Milan, Italy*
[b] *Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[c] *Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[d] *Radiology Department, Fondazione IRCCS Istituto Nazione dei Tumori, Milan, Italy*
[e] *Sarcoma Unit, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[f] *Diagnostic Pathology and Laboratory Medicine Department, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*
[g] *Molecular Pharmacology Unit, Department of Experimental Oncology and Molecular Medicine, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*
[h] *Medical Oncology and Hemato-Oncology Department, University of Milan, Milano, Italy*

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Abstract ***Background:*** To explore the activity of axitinib in advanced solitary fibrous tumour (SFT).

Patients and methods: In this investigator-driven phase II study on axitinib in advanced and progressive SFT, patients received axitinib, 5 mg bis in day (BID), until progression or limiting toxicity. Pathologic diagnosis was centrally reviewed, distinguishing malignant SFT (M-SFT) and high-grade/dedifferentiated SFT (HG/D-SFT) subtypes. The primary end-point was the overall response rate (ORR) by Choi criteria (Choi). Secondary end-points were response by Response Evaluation Criteria in Solid Tumours (RECIST), progression-free survival (PFS) and overall survival (OS).

Results: From April 2015 and October 2017, 17 eligible patients entered the study (metastatic: 17; SFT subtype: 13 M-SFT, 4 HG/D-SFT; prior treatment: 9 antiangiogenics, 5 cytotoxics). All patients were evaluable for response. The best Choi response was seven partial response (PR) (ORR, 41.2%), six stable disease (SD) and four progressions. Choi-ORR was 54% (7/13) when only M-SFTs were considered. Four of seven responsive patients were pretreated

* *Corresponding author*: Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milan, Italy. Fax: +390223902404.
E-mail address: silvia.stacchiotti@istitutotumori.mi.it (S. Stacchiotti).

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with pazopanib. No responses were detected in HG/D-SFT. Best RECIST response was one PR (5.9%), 14 SD and two progressions. Toxicity was as expected. Median Choi-PFS was 5.1 (interquartile range [IQR]: 2.5–14.8) months. Median Choi-PFS was 14.8 (IQR: 5.1–18.0) and 2.8 (IQR: 2.0–5.9) months for patients responsive and non-responsive by Choi, respectively ($p = 0.0416$). At a 14.4-month median follow-up, median OS was 25.3 months.

Conclusion: This study showed that axitinib is active in progressive advanced SFT. One-half of patients carrying the malignant variant of the disease responded, with a >12-month median progression arrest. Responses were better detected with Choi and seen even in patients resistant to other antiangiogenics. Tolerability was good.

1. Introduction

Solitary fibrous tumour (SFT) is a rare sarcoma that can arise at any site of the body but often affects serosae [1]. Previously known as hemangiopericytoma, SFT is characterised by the presence of the *NAB2-STAT6* fusion gene that leads to the nuclear expression of the transcription factor STAT6, regarded today as an important marker for differential diagnosis [2]. Morphology, necrosis and mitotic index allow SFT subclassification into three variants, which are unified by the presence of *NAB2-STAT6* translocation. They include 'classic' SFT subtype, i.e. a very low-risk tumour; 'malignant' SFT (M-SFT) (>4 mitosis/10 high-power field and/or necrosis and high cellularity), which is usually a low-/intermediate-risk tumour but can behave similarly to a high-grade tumour when the mitotic rate increases and 'high-grade/dedifferentiated' SFT (HG/D-SFT), that can lose the classic SFT morphology and the immunophenotypical markers like CD34 and even the nuclear expression of STAT6, with possible misdiagnoses [3]. SFT has a low tendency towards recurrence after complete resection, but a higher metastatic rate (40%) is observed in case of HG/D-SFT [4,5].

The outcome in patients with advanced disease is still unsatisfactory, as the disease cannot be cured. The overall response rate (ORR) to anthracycline-based chemotherapy, which is standard front-line treatment for soft tissue sarcoma (STS), is low (approximately 10%). Interestingly, there are suggestions pointing to a greater activity in patients with more aggressive variants [6–8].

The activity of antiangiogenic agents in SFT has been explored since 2010. First reports focused on bevacizumab combined to temozolomide and on sunitinib [9–11]. Then, results were provided with pazopanib, which was initially evaluated retrospectively and whose activity has been recently confirmed within a prospective phase II study [12,13].

Axitinib is an oral antiagiogenic drug active against vascular endothelial growth factor (VEGFR) −1, −2, −3, platelet-derived growth factor β (PDGRF-β) and c-KIT, currently approved for treatment of renal carcinoma. Axitinib is being evaluated in soft-tissue sarcomas (STS) within a British trial, whose results are still pending (NCT01140737). There are preclinical data suggesting axitinib activity in SFT patient-derived xenograft models, although its effect in the HG/D-SFT subtype looked limited [14]. No clinical data in STF are nowadays available.

Therefore, starting from April 2015, at the Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy (INT), we decided to carry out an exploratory phase 2, investigator-initiated clinical study on axitinib in patients with advanced SFT (EudraCT number: 2013-005596-40). Its results are reported herein.

2. Patients and methods

This is an Italian, single-arm, investigator-initiated, phase II clinical study in adult patients affected by a progressive, advanced SFT. Pathologic diagnosis was centrally determined, distinguishing M-SFT and HG/D-SFT. Main inclusion criteria were pathological diagnosis of SFT, advanced disease, centrally confirmed evidence of progression by Choi in the 6 months before entering the study; Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤2; discontinuation of any other medical cancer therapy for at least 4 weeks before staring the study drug.

The study was conducted at INT. The institutional review board approved the study. All patients gave their written informed consent.

2.1. Study design and statistical analysis

Descriptive statistics and frequency tabulation were used to summarise patient and tumour characteristics.

The primary end-point was ORR by Choi [15,16]. With a planned sample size of 16 patients, the trial was powered to detect an ORR of ≥30% and to exclude a ORR of ≤5%, alpha and beta error levels being fixed at 10%. Secondary end-points were response rate by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, overall survival (OS), progression-free survival (PFS) by Choi and RECIST, clinical benefit rate (CBR) by Choi. ORR was defined as the proportion

of patients who achieved complete response (CR) or partial response (PR), while CBR was considered as the proportion of patients who achieved CR or PR or stable disease (SD) for ≥6 months. Corresponding 95% confidence intervals (95%-CIs) were calculated based on the binomial distribution.

PFS and OS curves were estimated using the Kaplan–Meier method and compared using log-rank tests. Times to event occurrence were computed from the date of treatment start to the date when the event was recorded or censored at the date of last follow-up assessment in event-free patients. All treated patients were evaluable, and therefore there was no need to distinguish intention-to-treat and per-protocol populations.

2.2. Pathological assessment

Before starting treatment, tumour samples obtained at the time of primary tumour and of the last disease recurrence were centrally reviewed. All cases were classified as classic SFT, M-SFT or HG/D-SFT according to the World Health Organisation classification and more recent literature criteria [1,3]. Immunoprofile assessment was performed by using the following antibodies and dilutions: STAT6 (Rabbit Poly, Santa Cruz; 1:400), CD34 (PBEnd/10, DAKO; 1:100) and Ki-67 (Mib-1, DAKO; 1:400), bcl2 (124, DAKO; 1:500). Antigen retrieval was made at 95C with 5 mM pH 6 citrate buffer for 6 min (CD34, bcl2) or 15 min (Ki-67). UltraVision Quanto Detection System horseradish peroxidase (HRP) (Thermo Fisher Scientific, Kalamazoo, MI) was used as detection system according to manufacturer's protocol. For Ki-67, the proportion of expressing cells was scored as three categories: low: 0–10%, moderate: 11–30% and high: >30%.

2.3. Treatment

Patients received oral axitinib, 5 mg bis in day (BID), continuously, until progression or unacceptable toxicity. Treatment was withheld for haematologic toxicity G ≥ 3 and non-haematologic toxicity G ≥ 2, and it was resumed after recovery to haematologic toxicity G ≤ 2 or non-haematologic toxicity G ≤ 1. Patients had a regular physical examination and a complete blood count/serum chemistry evaluation. All patients were evaluated at baseline with whole-body computed tomography (CT) and magnetic resonance imaging (MRI) and/or CT of the tumour site(s). Adverse events (AEs) were graded according to the US National Cancer Institute Common Toxicity Criteria, version 4.0.

2.4. Response assessment

Response was assessed by CT and/or MRI, according to Choi and RECIST 1.1, after 4 weeks from treatment start, then every 2 months. All patients had to be evaluated using the same technique (MRI or CT). As for Choi, PR was defined as a ≥10% decrease in tumour size and/or ≥15% decrease in tumour density (venous phase) on CT or ≥15% decrease in contrast enhanced on Turbo Spin Echo T1 weighted images at MRI compared with baseline, irrespective of any increase in tumour size, given the absence of new lesions. Stable disease (SD) was classified when criteria for partial response (PR) or progressive disease (PD) were not met. PD was defined by the presence of a ≥10% increase in tumour size and without evidence ≥15% decrease in tumour density or in case of a new lesion.

2.5. Role of the funding source

The study was an investigator-initiated study. Pfizer provided axitinib and was informed of the results. The corresponding author had the final responsibility for the decision to submit the article for publication and wrote the manuscript in cooperation with all the other authors. The company had no role in writing or revising the manuscript.

3. Results

Between April 2015 and October 2017, 18 patients were enrolled, 17 started the experimental treatment (1 screening failure), and all of them were evaluable for response. Supplementary Fig.1 shows the CONSORT recruitment-tracking flowchart.

Median follow-up time was 14.4 months (interquartile range [IQR]: 11.7–28.5). Fifteen patients completed their treatment, two are still receiving axitinib at the time of writing this article. Reasons for discontinuation were progression (14 patients) and others (1).

Table 1 summarises patient characteristics. Nine patients (52.9%) were pretreated with antiangiogenic agents (7 pazopanib; 2 sunitinib). Thirteen (76.5%) cases were M-SFT, and four (23.5%) were HG/D-SFT. All cases were positive for nuclear STAT6. The centralised review of the radiologic assessment (CT or MRI) was performed before entering this study, and signing the informed consent showed a Choi progression in 6 months before starting axitinib in all patients (12 patients progressing while on another treatment, 5 while on active surveillance). In addition, the study baseline radiologic evaluation also confirmed Choi progression in the last 6 months in all cases.

3.1. Antitumour activity

All patients who entered the study were evaluable for response by Choi and RECIST.

Best Choi response was PR, SD and PD in 7 (41.2%), 6 (35.3%) and 4 (23.5%) patients, respectively, with a Choi-ORR of 41.2% (95%-CI: 18.4–67.1%). PR were observed in 4/9 (44.4%) patients pretreated with

Table 1
Patients characteristics.

Characteristics			Entire series (N = 17)	
			N	%
Sex	Male		11	64.7
	Female		7	35.2
Age, *years*	Median		53	
	IQR		34–76	
Primary tumour site	Meninges		4	23.5
	Pleura		4	23.5
	Retroperitoneum		4	23.5
	Pelvis		2	11.7
	Other		3	17.6
Tumour extent at the time of study entry	Locally advanced		0	0
	Metastatic		17	100
ECOG PS	0		12	70.6
	1		5	29.4
	2		0	0
Prior medical TX	No		9	53
	Yes		8	47
		Cytotoxic chemo	*5*	*29.4*
		Antiangiogenic tx	*9*	*52.9*
		Pazopanib	*7*	*41.2*
		Sunitinib	*2*	*11.7*
Nuclear STAT6 (IHC)	Negative		0	0
	Positive		17	100
SFT subtype	M-SFT		13	76.5
	HG/D-SFT		4	23.5
Evidence of Choi progression in the 6 months prior to start axitinib	No		0	0
	Yes		17	100

N: number; IQR: interquartile range; ECOG PS: Eastern Cooperative Oncology Group performance status; SFT: solitary fibrous tumour; M-SFT: malignant solitary fibrous tumour; HG/D-SFT: high-grade/dedifferentiated solitary fibrous tumour; TX: therapy; IHC: immunohistochemistry.

antiangiogenics. None of the four patients with HG/D-SFT responded to axitinib. Choi-ORR was 54% (7/13) by considering only M-SFT. Best response by RECIST was one PR (5.9%), 14 SD (82.4%) and two PD (11.8%). Fig. 1 shows a response and a progression to axitinib. Fig. 2 shows the waterfall-plots of the best changes in tumour diameter and in tumour density.

Choi-CBR was 52.9% (95%-CI: 27.8–77.0%). RECIST-CBR was 52.9% (95%-CI: 27.8–77.0%).

Median Choi-PFS was 5.1 (IQR: 2.5–14.8) months, with 9- and 12-month PFS estimates of 35.3% (95%-CI: 18.5–67.2%) and of 35.3% (95%-CI: 18.5–67.2%), respectively (Fig. 3). Median PFS for patients responsive by Choi was 14.8 (IQR: 5.1–18.0) months, while was 2.8 (IQR: 2.0–5.9) months ($p = 0.0416$) for patients without evidence of response. Median PFS by Choi was 6 and 2.5 months for M-SFT and D-SFT, respectively. Six-month Choi-progression free rate (PFR) was 46.2% (95%-CI: 25.7–83.0) for M-SFT and 25.0% (95%-CI: 4.6–100.0) for D-SFT.

Median RECIST-PFS was 9.4 (IQR: 2.5–31.0) months (Supplementary Fig.2), with 9- and 12-months PFS estimates of 52.9% (95%-CI: 33.8–82.9%) and 47.1% (95% CI: 28.4–77.9), respectively. Six-month RECIST-PFR was 69.2% (95%-CI: 48.2–99.5) for M-SFT and 25.0% (95%-CI: 4.6–100.0) for D-SFT.

Median OS was 25.3 (IQR: 15.4–31.0) months (Fig. 4). Median OS for patients responsive by Choi was 31.0 (IQR: 25.3–31.0) months while for patients without evidence of response was 15.4 (IQR: 10.3–not estimated) months ($p = 0.1050$).

3.2. Drug delivery and toxicity

Overall, axitinib was well tolerated. Toxic effect was as expected. Main non-haematologic toxicity included fatigue (8 cases, G1-2), hypertension (14, G1-2) and mucositis (7, G1-2). Eight patients (47.1%) temporarily discontinued their treatment at least once due to toxicity; in all cases, toxic effect resolved upon discontinuation. Neither G3/G4/G5 toxicity nor clinically significant haematologic toxicities were observed.

4. Discussion

This investigator-initiated, exploratory phase 2 study shows that axitinib is active in patients with advanced malignant-variant SFT, with possibly durable responses that are usually non-dimensional (and are thus detectable by Choi criteria). In fact, in a population of 17 advanced SFT, treated with axitinib for a progressive disease, the Choi ORR (i.e., the study primary end-

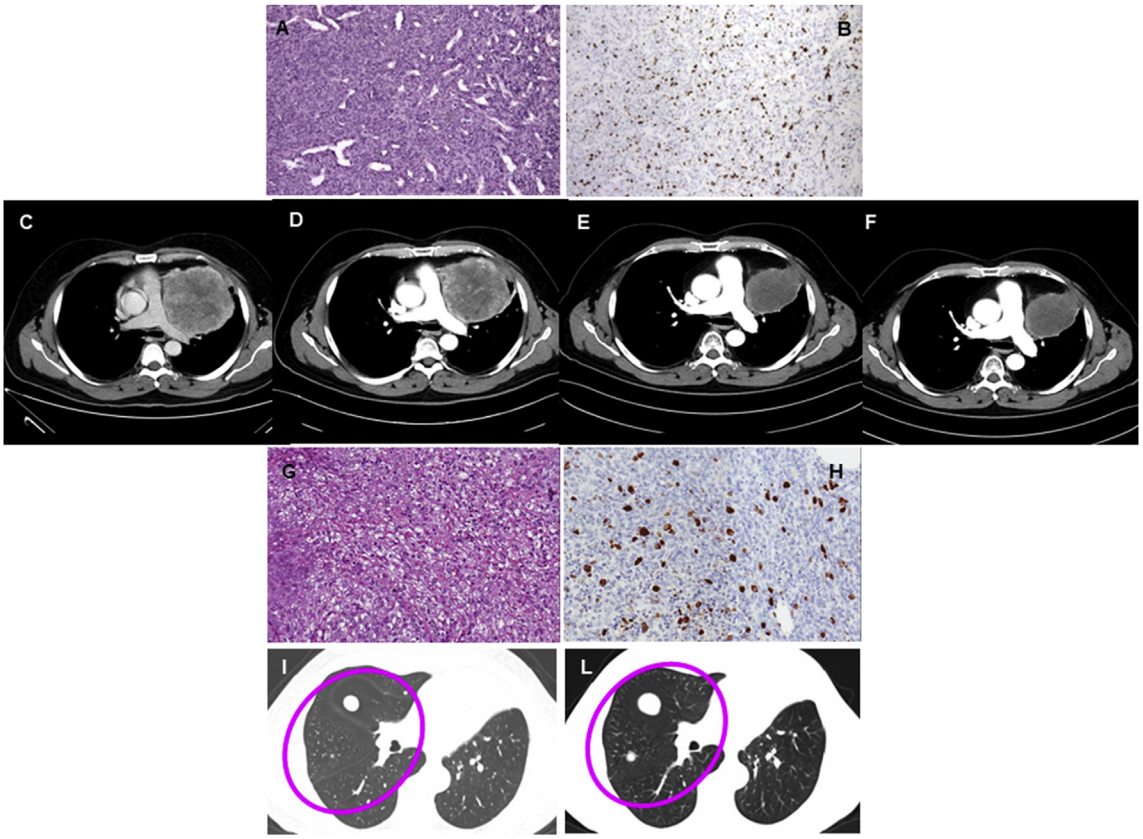

Fig. 1. **Response to axitinib in two SFTs metastatic to the lung.** Case 1, tumour morphology was consistent with an M-SFT (A: hematoxylin-eosin staining; B: MIB1). CT scans (venous phase) showed a paracardiac lesion at baseline (C) and after 1, 12, 18 (D, E, F) months of axitinib, with >15% decrease in tumour density (baseline: 60 HU; after 18 months: 24 HU) and >30% decrease in tumour size (baseline: 110 mm; after 18 months: 82 mm), consistent with a Choi and RECIST response. In Case 2, morphology was consistent with a HG/D-SFT (G: hematoxylin-eosin staining shows pleomorphic features and a high mitotic rate; H: high MIB1). CT detected a new lesion at the first response assessment (L) compared to baseline (I), i.e. a Choi and RECIST progression. M-SFT: malignant solitary fibrous tumour; HG/D-SFT: high-grade/dedifferentiated solitary fibrous tumour; CT: computed tomography; RECIST: Response Evaluation Criteria in Solid Tumours; HU, Hounsfield Unit.

point) was 41.2%, with only one patient achieving a RECIST PR. Choi responses were observed also in 4/7 patients refractory to a prior antiangiogenic. The median PFS was 5.1 and 9.4 months by Choi and RECIST, respectively. However, in patients responsive by Choi, the median PFS was 14.8 (IQR: 5.1–18.0) months. Axitinib was well tolerated, with no cases of G3 side-effects nor definitive interruption due to toxicity.

This study, the first with axitinib, though limited in size, showed a response rate by Choi in the same range as with pazopanib, i.e., the only antiangiogenic approved in STS and the only assessed not only retrospectively [12,17] but also prospectively in the disease [13]. In fact, the Choi-ORR was slightly lower for axitinib compared with what observed with pazopanib in the prospective trial (41 versus 51%) but was 54% if calculated, excluding HG/D-SFT. Notably, the Choi-ORR observed with pazopanib in the retrospective studies published so far is also consistent (ranging between 45 and 50%) [12,17].

The advent of molecularly targeted agents has made the evaluation of tumour response more complex. Several studies have reported the lack of shrinkage in responding tumours and raised concerns of significant underestimation of responses using RECIST. In GIST responding to imatinib, the degree of contrast enhancement on CT can decrease greatly compared with the baseline regardless of whether tumours shrink [15]. These observations led to the definition of Choi that resulted more accurate in predicting disease-specific survival than RECIST. On the other side, there are known limitations of Choi, especially in terms of reproducibility. Interestingly, all studies published so far on molecular-targeted treatments in SFT (pazopanib, bevacizumab, sunitinib, sorafenib, dasatinib) showed a disease stabilisations by RECIST as best response in most cases while a higher ORR was seen when Choi was applied [9–11,17,18]. Therefore, we decided to select Choi ORR as primary end-point to better describe tumour behaviour while under treatment and looking

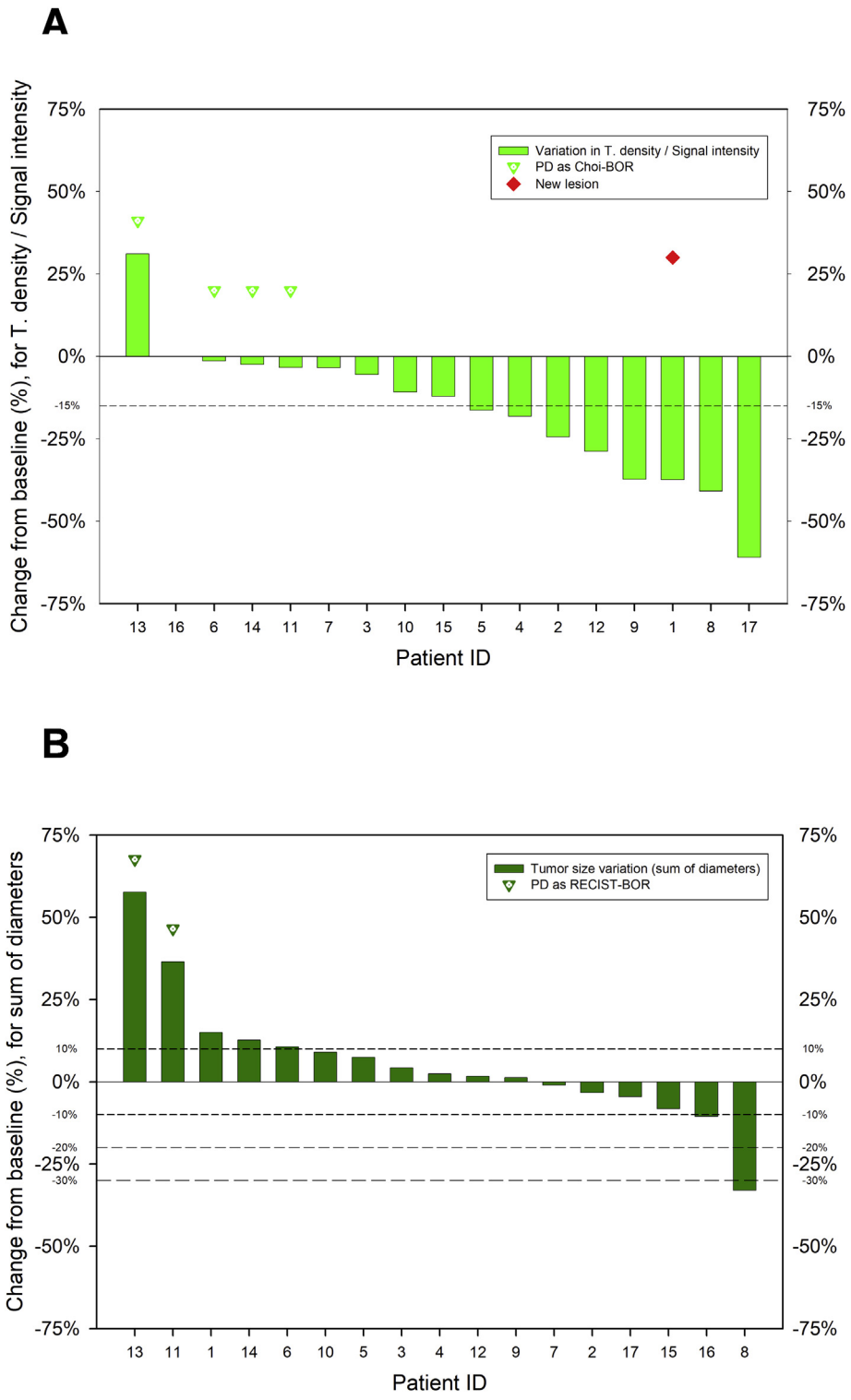

Fig. 2. **Waterfall-plots of best changes in tumour density/signal intensity and in tumour size.** A: best changes in tumour density/signal intensity of the target lesions. The red diamond indicates the presence of a new lesion (i.e. a disease progression in spite of a >15% decrease in tumour density). B: shows the best changes in the sum of the maximum tumour diameters. The green arrows indicate patients with RECIST progression as best response. RECIST: Response Evaluation Criteria in Solid Tumours. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

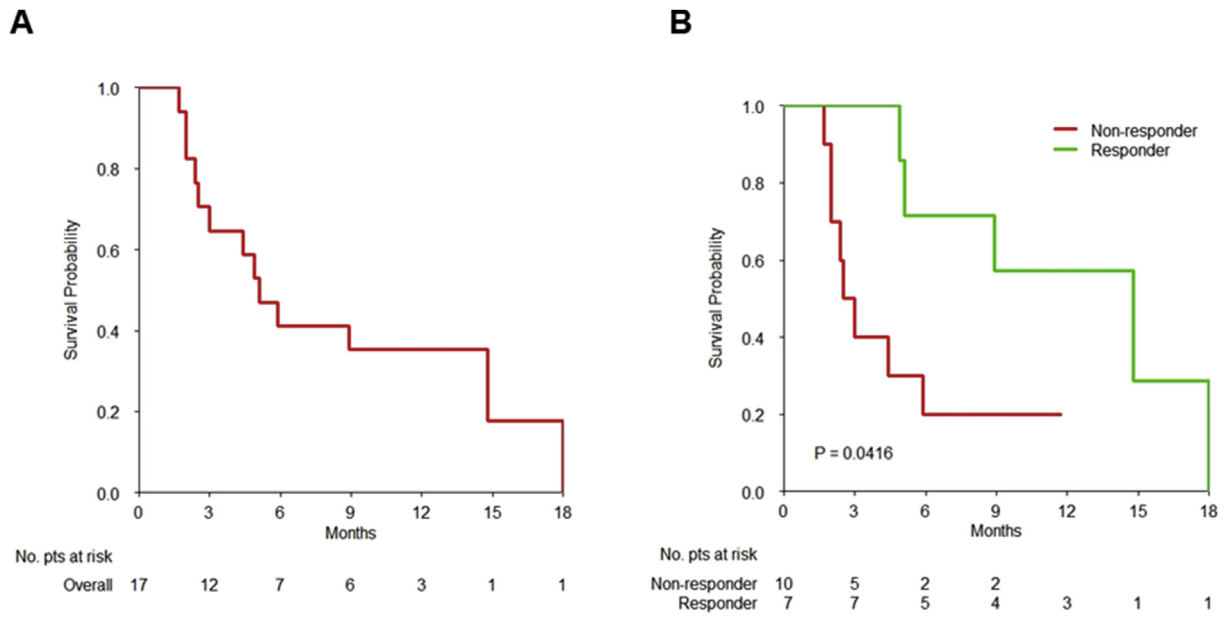

Fig. 3. **Choi-PFS.** A: PFS of the whole study population (median Choi-PFS: 5.1 months). B: PFS for patients responsive and non-responsive by Choi (median Choi-PFS for responsive patients versus non-responsive patients: 14.8 versus 2.8 months). PFS: progression-free survival.

for a better correlation between the response and the clinical outcomes.

While in SFT antiangiogenics documented non-dimensional responses in most responsive cases, dimensional responses to antiangiogenics have been observed in a distinct proportion of alveolar soft part sarcomas and extraskeletal myxoid chondrosarcoma [19,20]. On the other end of the spectrum, antiangiogenics and ,in particular, pazopanib have a lower activity in histologies such as synovial sarcoma and leiomyosarcoma, in terms of both RECIST and non-RECIST responses [21]. This distribution of response rates and patterns in STS histologies is intriguing. It stresses further the need to explore the activity of new agents across STS histologies by using RECIST as well as non-RECIST criteria. On the other hand, we may speculate that it has to do with discrepant mechanisms of action of these drugs across STS. This may be suggested also by the fact that in this study, we could detect responses to axitinib even in patients refractory to other antiangiogenics (4 of 7). Of course, all these drugs

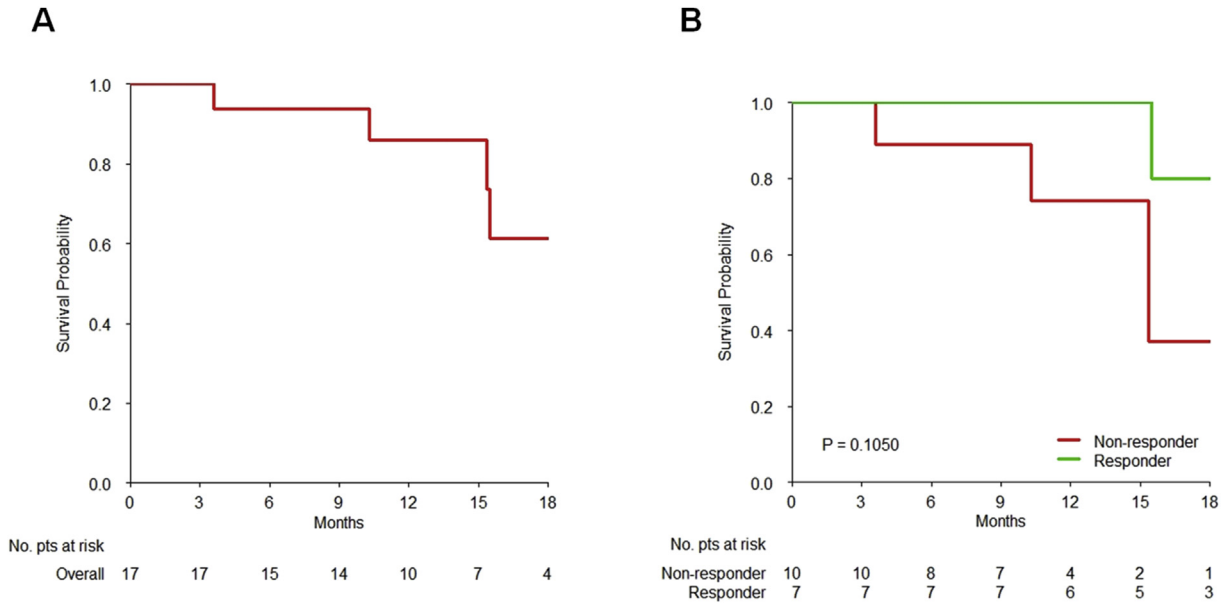

Fig. 4. **Overall Survival.** A: whole study population OS (median OS: 25.3 months). B: OS for patients responsive and non-responsive by Choi (median OS in responsive patients 31.0 versus 15.4 months in non-responsive patients). OS: overall survival.

share antiangiogenic properties but are also multityrosine kinase inhibitors and possibly immunomodulators. This is a potential area for further investigations, biologically and pathologically.

In our study, axitinib was active only in the malignant variant of SFT because no responses were seen in the four patients enrolled with HG/D-SFT. Of course, this is a very small number of patients. However, the same observation was also made in the pazopanib study [13]. Indeed, one may easily speculate that chemotherapy is more active in the HG/D-SFT [5,6,22]. An Italian phase 2 study aimed at assessing the antitumour effect of doxorubicin plus dacarbazine (DTIC) and of trabectedin is ongoing (NCT03023124), and an analysis by pathologic subtype is foreseen. Of notice, histological progression is a possible event in SFT, and patients starting with a low-grade tumour may develop a high-grade disease later in their clinical history. In this study, the pathologic central review was performed in all cases, and the SFT subtype was defined according to the morphologic appearance detectable at the last histologic assessment available.

Although consistent to what was found with pazopanib, the observed median PFS to axitinib was limited, averaging 5 months [13]. However, disease control was significantly longer in responsive patients, with a median Choi-PFS for patients responsive by Choi of 14.8 months compared with 2.8 months in patients without evidence of response. This translated in a trend towards a better survival for responsive cases (e.g. median OS 31.0 versus 15.4 months in patients without evidence of response). All patients were progressing on study entry. In other words, a tumour response to antiangiogenics may be clinically relevant, given the disease setting.

In conclusion, in this small study, one-half of patients with a non–high-grade progressive M-SFT treated with axitinib had a median progression arrest higher than 1 year. Responses were seen also in patients resistant to other antiangiogenics. Tolerability was good. All this may be clinically relevant. The extreme rarity of this histology makes it questionable whether further evidence in support may be provided through future studies.

Conflict of interest statement

S.S. had advisory roles in Bayer, PharmaMar, received speaker's honoraria from PharmaMar and institutional funding from sponsored studies: Bayer, Novartis, Pfizer, PharmarMar.

F.A.M. received institutional funding from sponsored studies: Bayer, Novartis, Pfizer, PharmaMar.

G.A. had advisory roles in and received honoraria from PharmaMar and institutional funding from sponsored studies: PharmaMar.

C.P.G. received honoraria from Pfizer, PharmaMar and institutional funding from sponsored studies: Bayer, Novartis, Pfizer, PharmaMar.

All remaining authors have declared no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2018.10.024.

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