



Pazopanib for treatment of advanced malignant and dedifferentiated solitary fibrous tumour: a multicentre, single-arm, phase 2 trial

Javier Martin-Broto, Silvia Stacchiotti, Antonio Lopez-Pousa, Andres Redondo, Daniel Bernabeu, Enrique de Alava, Paolo G Casali, Antoine Italiano, Antonio Gutierrez, David S Moura, Maria Peña-Chilet, Juan Diaz-Martin, Michele Biscuola, Miguel Taron, Paola Collini, Dominique Ranchere-Vince, Xavier Garcia del Muro, Giovanni Grignani, Sarah Dumont, Javier Martinez-Trufero, Emanuela Palmerini, Nadia Hindi, Ana Sebio, Joaquin Dopazo, Angelo Paolo Dei Tos, Axel LeCesne, Jean-Yves Blay, Josefina Cruz

Summary

Background A solitary fibrous tumour is a rare soft-tissue tumour with three clinicopathological variants: typical, malignant, and dedifferentiated. Preclinical experiments and retrospective studies have shown different sensitivities of solitary fibrous tumour to chemotherapy and antiangiogenics. We therefore designed a trial to assess the activity of pazopanib in a cohort of patients with malignant or dedifferentiated solitary fibrous tumour. The clinical and translational results are presented here.

Methods In this single-arm, phase 2 trial, adult patients (aged ≥ 18 years) with histologically confirmed metastatic or unresectable malignant or dedifferentiated solitary fibrous tumour at any location, who had progressed (by RECIST and Choi criteria) in the previous 6 months and had an ECOG performance status of 0–2, were enrolled at 16 third-level hospitals with expertise in sarcoma care in Spain, Italy, and France. Patients received pazopanib 800 mg once daily, taken orally without food, at least 1 h before or 2 h after a meal, until progression or intolerance. The primary endpoint of the study was overall response measured by Choi criteria in the subset of the intention-to-treat population (patients who received at least 1 month of treatment with at least one radiological assessment). All patients who received at least one dose of the study drug were included in the safety analyses. This study is registered with ClinicalTrials.gov, number NCT02066285, and with the European Clinical Trials Database, EudraCT number 2013-005456-15.

Findings From June 26, 2014, to Nov 24, 2016, of 40 patients assessed, 36 were enrolled (34 with malignant solitary fibrous tumour and two with dedifferentiated solitary fibrous tumour). Median follow-up was 27 months (IQR 16–31). Based on central radiology review, 18 (51%) of 35 evaluable patients had partial responses, nine (26%) had stable disease, and eight (23%) had progressive disease according to Choi criteria. Further enrolment of patients with dedifferentiated solitary fibrous tumour was stopped after detection of early and fast progressions in a planned interim analysis. 51% (95% CI 34–69) of 35 patients achieved an overall response according to Choi criteria. Ten (29%) of 35 patients died. There were no deaths related to adverse events and the most frequent grade 3 or higher adverse events were hypertension (11 [31%] of 36 patients), neutropenia (four [11%]), increased concentrations of alanine aminotransferase (four [11%]), and increased concentrations of bilirubin (three [8%]).

Interpretation To our knowledge, this is the first trial of pazopanib for treatment of malignant solitary fibrous tumour showing activity in this patient group. The manageable toxicity profile and the activity shown by pazopanib suggests that this drug could be an option for systemic treatment of advanced malignant solitary fibrous tumour, and provides a benchmark for future trials.

Funding Spanish Group for Research on Sarcomas (GEIS), Italian Sarcoma Group (ISG), French Sarcoma Group (FSG), GlaxoSmithKline, and Novartis.

Copyright © 2018 Elsevier Ltd. All rights reserved.

Introduction

A solitary fibrous tumour is a ubiquitous soft-tissue tumour with a pronounced haemangiopericytoma-like vascular pattern and thick collagen bands exhibiting immunoreactivity for CD34.¹ Pathologists distinguish between typical and malignant solitary fibrous tumour mainly on the basis of mitotic count (≤ 4 or >4 mitoses per 10 high power fields [hpf]), necrosis, and nuclear pleomorphism. The latest WHO classification still

preserves these terms.¹ However, the clinical behaviour of these tumours is difficult to anticipate, and both subtypes can develop metastases. Additionally, solitary fibrous tumour with an abrupt transition to high-grade sarcoma, the so-called dedifferentiated solitary fibrous tumour, represents the most aggressive subtype within the spectrum of solitary fibrous tumours.² Three different research groups identified *NAB2-STAT6* gene fusion in chromosome 12 as characteristic of solitary fibrous

Lancet Oncol 2019; 20: 134–44

Published Online
December 18, 2018

[http://dx.doi.org/10.1016/S1473-2045\(18\)30676-4](http://dx.doi.org/10.1016/S1473-2045(18)30676-4)

See Online/Comment page 14

Department of Medical Oncology (J Martin-Broto MD, N Hindi MD), Department of Pathology (E de Alava MD, M Biscuola MD), and Clinical Bioinformatics Area, Fundación Progreso y Salud (M Peña-Chilet PhD, J Dopazo PhD), University Hospital Virgen del Rocío, Sevilla, Spain; Institute of Biomedicine of Sevilla, Sevilla, Spain (J Martin-Broto, E de Alava, D S Moura PhD, J Diaz-Martin PhD, M Taron PhD, N Hindi); Adult Mesenchymal and Rare Tumor Unit, Department of Cancer Medicine (S Stacchiotti MD, P G Casali MD) and Soft Tissue and Bone Pathology, Histopathology and Pediatric Pathology Unit, Department of Diagnostic Pathology and Laboratory Medicine (P Collini MD), Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; Department of Medical Oncology, Sant Pau Hospital, Barcelona, Spain (A Lopez-Pousa MD, A Sebio MD); Department of Medical Oncology, University Hospital La Paz, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain (A Redondo MD); Musculoskeletal Imaging Section, University Hospital La Paz, Madrid, Spain (D Bernabeu MD); CIBERONC, Madrid, Spain (E de Alava, M Biscuola); Department of Oncology, Institut Bergonié, Bordeaux, France (Prof A Italiano MD); Department of Hematology, University Hospital

Research in context

Evidence before this study

We searched PubMed for all case series or trials that involved systemic treatment of advanced solitary fibrous tumours, published in English or Spanish between Jan 1, 1980, and Jan 31, 2018. Terms used for the search were "solitary fibrous tumor", "hemangiopericytoma", "advanced", "metastatic", "systemic treatment", "doxorubicin", "anthracycline", "antiangiogenic", "sunitinib", "pazopanib", "series", and "trial". Five retrospective and monocentric case series focusing on systemic treatment for solitary fibrous tumour were identified, and no clinical trial was found. There were two case series with chemotherapy, two with molecular targeted therapy, and one with a combination of chemotherapy and antiangiogenic agents. The series collected a heterogeneous population of patients with solitary fibrous tumour, who had received a range of radiological assessments.

Added value of this study

This trial provides a benchmark for pazopanib efficacy in terms of overall response, progression-free survival, and overall

survival in the specific cohort of patients with malignant solitary fibrous tumour. To our knowledge, this first trial of pazopanib for treatment of malignant solitary fibrous tumour confirmed our prespecified assumptions about pazopanib activity and informed aspects of central pathology review, central radiology review, and translational research which contribute to increasing knowledge about antiangiogenic activity in solitary fibrous tumour.

Implications of all the available evidence

The antiangiogenic drug pazopanib is active in advanced malignant solitary fibrous tumour. Choi criteria resulted in better detection of pazopanib activity compared with RECIST. Pazopanib should be included as first option of systemic treatment for advanced malignant solitary fibrous tumour, in the next European Society for Medical Oncology clinical guidelines in soft-tissue sarcoma. Ongoing clinical trials already incorporate antiangiogenic agents in this entity, in combination with other compounds, such as anti-PD-1 inhibitors.

tumours. This fusion replaces a repressor domain (*NAB2*) with a transactivation domain (*STAT6*), resulting in a transcriptional activator through the early growth response pathways.³⁻⁵ Nuclear expression of *STAT6* has consequently emerged as a highly sensitive and specific immunomarker for solitary fibrous tumours.⁶

Most solitary fibrous tumours are localised at diagnosis, most frequently in abdominal and thoracic cavities, followed by limbs. The risk of metastases ranges between 35% and 45% in series with a long follow-up.^{7,8} Several research groups propose a risk classification on the basis of some clinicopathological factors common to all solitary fibrous tumour subtypes as a more rational approach, instead of distinguishing between typical and malignant solitary fibrous tumour subtypes.^{9,10} Still, the absence of prospective trials in solitary fibrous tumour is a hindrance to understanding whether clinical behaviour of typical or malignant solitary fibrous tumour is different even in advanced disease.

Systemic therapeutic options in advanced solitary fibrous tumour have consisted of chemotherapy and antiangiogenic drugs, the results of which have been published in several retrospective analyses.¹¹⁻¹⁶ For most cases, the best responses obtained following RECIST criteria were stabilisation of disease.^{11,12,17} In studies that included patients with dedifferentiated solitary fibrous tumours who were treated with chemotherapy, partial responses were seen in up to 20% of cases.¹³ It is noteworthy that patients treated with antiangiogenics had a higher overall response (measured by Choi criteria) and longer progression-free survival and overall survival than patients treated with chemotherapy. However, data from chemotherapy and antiangiogenics are not fully comparable; series on chemotherapy usually report results of

first-line therapy, so reports include pretreated patients. This has an effect on overall survival as the expected survival for first-line therapy is longer than for further-line therapy.¹⁴⁻¹⁶

Preclinical evidence has shown different efficacy of different antiangiogenic drugs in the treatment of solitary fibrous tumours, at least in studies that included models of dedifferentiated solitary fibrous tumour.¹⁸ Taking into account the lower activity of chemotherapy compared with antiangiogenic drugs, the relevance of response criteria to measure the effect of systemic treatment, the sensitivity of solitary fibrous tumours to different antiangiogenic agents, and the absence of prospective trials that include solitary fibrous tumours, we designed a single-arm, phase 2 trial to investigate the activity of the antiangiogenic pazopanib in solitary fibrous tumour. A multinational effort was thus activated by Italian, French, and Spanish sarcoma groups. The clinical and translational results of the cohort of patients with malignant and dedifferentiated solitary fibrous tumour are presented here. Other cohorts of this trial, which are beyond the scope of this Article, include patients with typical solitary fibrous tumour (still in recruitment phase) and patients with extraskeletal myxoid chondrosarcoma.

Methods

Study design and participants

In this single-arm, phase 2 trial, adult patients (aged ≥ 18 years) with diagnosis of metastatic or unresectable malignant or dedifferentiated solitary fibrous tumour at any location, who had progressed (by RECIST and Choi criteria) in the previous 6 months, were enrolled at 16 tertiary hospitals with expertise in sarcoma care in Spain, Italy, and France. Other relevant inclusion criteria

Son Espases, Palma, Balearic Islands, Spain (A Gutierrez MD); Department of Pathology (D Ranchere-Vince MD) and Department of Medical Oncology (Prof J-Y Blay MD), Centre Léon Bérard, Université Claude Bernard Lyon, Lyon, France; Catalan Institute of Oncology, Barcelona, Spain (X Garcia del Muro MD), Institut d'Investigació Biomèdica de Bellvitge, University of Barcelona, Barcelona, Spain (X Garcia del Muro); Sarcoma Unit, Division of Medical Oncology, Candiolo Cancer Institute, FPO, IRCCS, Candiolo, Italy (Giovanni Grignani, MD); Department of Medical Oncology, Gustave Roussy Cancer Campus, Villejuif, France (S Dumont MD, A LeCesne MD); Department of Medical Oncology, University Hospital Miguel Servet, Zaragoza, Spain (J Martinez-Trufero MD); Chemotherapy Unit, Istituto Ortopedico Rizzoli, Bologna, Italy (E Palmerini MD); Department of Medicine, University of Padua School of Medicine, Padua, Italy (Prof A P Dei Tos MD); and Department of Medical Oncology, University Hospital of Canarias, Tenerife, Spain (J Cruz MD)

Correspondence to: Dr Javier Martin-Broto, LAB 215, Instituto de Biomedicina de Sevilla (IBIS), Sevilla 41013, Spain
jmartin@mustbesevilla.org

were histological confirmation by central pathology review at national level, ECOG performance status of 0–2, estimated life expectancy of eligible patients of 3 months or longer, measurable disease according to Choi and RECIST criteria, adequate bone marrow function (haemoglobin >10 g/dL, absolute neutrophil count $\geq 1.5 \times 10^9$ cells per L, platelet count $\geq 100\,000$ cells per mm^3), adequate hepatic function (alanine and aspartate aminotransferases ≤ 2.5 times the upper limit of normal [ULN] concentrations, total bilirubin ≤ 1.5 times the ULN concentrations, creatine phosphokinase ≤ 2.5 times the ULN concentrations), adequate renal function (serum creatinine ≤ 1.5 mg/dL), and normal left ventricular ejection fraction. Patients had to provide written, informed consent before study-specific procedures or assessments were made and had to be willing to comply with treatment and follow-up. Informed consent was obtained before the start of the screening process.

Some relevant exclusion criteria were previous treatment with antiangiogenic drugs; pregnancy; breastfeeding; previous radiotherapy in target lesions; history of another malignancy (except for non-melanomatous skin carcinoma or in-situ carcinoma, or unless the patient had been disease-free for at least 10 years); clinically significant gastrointestinal abnormalities that might increase the risk for gastrointestinal bleeding; corrected QT interval greater than 480 ms; poorly controlled hypertension; history of cerebrovascular accident including transient ischemic attack, pulmonary embolism, or untreated deep venous thrombosis within the past 6 months (patients with recent deep venous thrombosis who had been treated with anticoagulant drugs for at least 6 weeks were eligible); evidence of active bleeding; diagnosis of severe cardiac disease; infections; any serious or unstable pre-existing medical, psychiatric, or other condition that could interfere with patient's safety, provision of informed consent, or compliance to study procedures; or participation in another trial in the previous 14 days or five half-lives of a drug before recruitment to the present study. The group of patients with dedifferentiated solitary fibrous tumour was terminated on the basis of a lack of efficacy discovered at a planned interim analysis. Procedures were done in accordance with guidelines established by the local ethics committee from each hospital, and in accordance with the Declaration of Helsinki. Approval from the ethics committee of each participating centre was obtained before study initiation. The study protocol is available online.

Procedures

Patients received pazopanib 800 mg once daily, taken orally without food, at least 1 h before or 2 h after a meal. Dose reductions were planned according to the drug brochure. If dose reduction of pazopanib was necessary because of toxicity, the dose would be reduced stepwise by 200 mg at each step. If the toxicity was abated with

reduction of the dose and dose re-escalation was considered safe by the investigator, the pazopanib dose would then be increased stepwise back to the pre-event dose, by 200 mg increments at each step, after monitoring for 10–14 days at each dose level to ensure that toxicity did not recur or worsen. Treatment with pazopanib was continued until any of the following events occurred: disease progression according to Choi criteria, unacceptable toxicity, withdrawal of consent, the patient was considered by the investigator or the sponsor to be non-compliant with the requirements of the protocol, or a delay in pazopanib administration was longer than 3 weeks.

Central pathology review at national level was mandatory before accrual. The pathology criteria applied for malignant solitary fibrous tumour classification included a mitotic count greater than 4 mitoses per 10 high power fields (hpf), and tumour necrosis, nuclear pleomorphism, or both. Positive immunohistochemistry results for STAT6, and positive RT-PCR or fluorescence in situ hybridisation results for *NAB2-STAT6* fusion were also recommended for central pathology review (appendix). The same criteria were applied for classification of dedifferentiated solitary fibrous tumours. Areas of high-grade sarcoma with an abrupt transition to areas of solitary fibrous tumour defined the dedifferentiated subtype. Immunohistochemistry was done on representative formalin-fixed paraffin-embedded tissue sections with anti-STAT6 polyclonal antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA). Strong STAT6 expression in more than 50% of nuclei was considered a positive result (appendix pp 1–2). Supranational pathology review occurred after accrual and included a comprehensive review of fusions—including *NAB2-STAT6* fusions—by next generation sequencing (appendix pp 1–2). Radiological assessments of the target and non-target lesions were done every 8 weeks by CT scan. Tumour density was determined by measuring CT attenuation coefficient in Hounsfield units (HU); a region of interest was drawn around the margin of the entire tumour using the arterial and portal phases.¹⁹ Central radiology review was compulsory and performed at least at the time of interim analysis and at the time of the end of the study. All centres had to upload the CT scans anonymously to a web-based imaging platform. Laboratory assessments (liver, kidneys and other metabolic tests, haematology, coagulation tests, urinalysis for proteinuria, thyroid function tests, and pregnancy tests) were done at baseline and at least on a monthly basis. Hepatic function was monitored more closely, at baseline and in weeks 3, 5, 7, 9, 12, and 16 of treatment. For translational research, biomarker analyses were done on formalin-fixed paraffin-embedded tumour tissue before treatment. Gene expression analyses (appendix pp 1–2) were done with the Immuno-Oncology assay (HTG Molecular Diagnostics, Tucson, AZ, USA). This assay was selected on the basis of the hypothesis that immunomodulation could have a crucial role in pazopanib activity. Samples were grouped according to patients' median progression-free survival.

See Online for appendix

For the study protocol see
<http://grupogeis.org/es/actividad-cientifica/ensayos-clinicos/ensayos-abiertos>

The low-risk group (better prognosis) was made up of patients with a progression-free survival higher than the median (5·6 months); the high-risk group (worse prognosis) comprised those patients with progression-free survival lower than the median.

Adverse events were graded according to CTCAE v4.0 and were monitored on a weekly basis for the first month, and then at least once every 4 weeks.

Outcomes

The primary endpoint was the proportion of patients who achieved an overall response (complete or partial) measured using Choi criteria. Secondary endpoints were progression-free survival, overall survival, clinical benefit, overall response according to RECIST version 1.1, and toxicity profile according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE v4.0). Progression-free survival was assessed by median time and measured from treatment start date until progression or death and overall survival was measured from treatment start date until death. Patients who had reached complete response, partial response, or stable disease during 6 months or more and were presenting clinical improvement of symptoms were considered as having experienced clinical benefit. Central pathological review and correlation of response with biomarkers analysed in the accompanying translational study were protocol-prespecified exploratory endpoints.

Statistical analysis

Sample size was estimated with Simon's optimal two-stage design. For an α value of 0·1 and power of 0·80, we estimated an overall response of 40% as H_0 and 60% as H_1 . In the first stage of the trial, 23 patients were to be enrolled, from which at least 12 patients were to have at least partial responses according to Choi criteria. If this occurred, a maximum of 31 evaluable patients would be treated in a second stage of the trial. To reject the null hypothesis, at least 16 responses according to Choi criteria out of 31 patients were needed. Patients who had provided written informed consent and had a centrally confirmed diagnosis of malignant solitary fibrous tumour formed the intention-to-treat population. Overall survival and progression-free survival was measured with the intention-to-treat population. The per-protocol population was defined as the subset of the intention-to-treat population with measurable disease at study entry (as per Choi and RECIST criteria). Patients in this population also received at least one month (one cycle) of treatment and had at least one radiological assessment. Otherwise the patient was not considered assessable (the exception was early progression or death, for which patients were included). The primary endpoint (overall response according to Choi criteria) was measured in the per-protocol population. Safety analyses were done in patients who received at least one dose of the study drug.

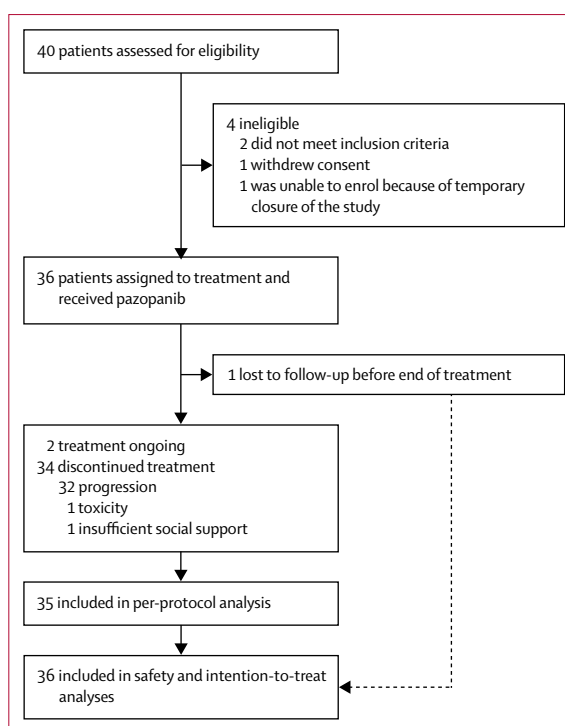


Figure 1: Trial profile

For variables with binomial distributions, frequencies and percentages were calculated with their corresponding 95% CIs. To compare categorical variables, Fisher's exact or χ^2 tests were used where applicable. The following clinicopathological factors were analysed as categorical variables in univariate analysis: age (categorised according to the median value), primary tumour size at diagnostic time, tumour burden (sum of the maximum diameter of all the target lesions at the baseline), ECOG performance status, mitotic number, tumour site (visceral or somatic), nuclear pleomorphism, presence of necrosis, and occurrence of grade 3–4 hypertension. Time-to-event variables (overall survival and progression-free survival) were measured from the date of therapy onset and were estimated according to Kaplan-Meier survival analysis. Comparisons between the variables of interest were done with the log-rank test. Multivariate analyses with the variables that appeared to be significant in the univariate analyses were done according to the Cox proportional hazard regression model. The validity of proportional hazard assumption was verified by adding a time-dependent variable to each model to confirm that the hazard ratio for each covariate did not increase or decrease over time. All p values reported were two-sided, and significance was defined as a p value lower than 0·05. The software package used for statistical analysis was SPSS Statistics (version 20).

Best response (partial and complete responses), according to Choi and RECIST criteria, measured from the time of obtaining the best response were analysed

	All patients (n=36)
Age (years)	62 (44–74)
Sex	
Female	21 (58%)
Male	15 (42%)
Eastern Cooperative Oncology Group performance status	
0	58%
1	36%
2	6%
Location of primary tumour	
Thorax	11 (31%)
Abdomen	11 (31%)
Extremities	6 (16%)
Meninges	5 (14%)
Other	3 (8%)
Median time from diagnostic time to metastasis appearance (months)	18 (3–68)
Histology	
Malignant	34 (94%)
Dedifferentiated	2 (6%)
Nuclear pleomorphism	17 (47%)
Primary tumour size at diagnosis (mm)	80 (35–114)
Median mitotic count (per 10 high power fields)	7 (4–11)
Mitoses (per 10 high power fields)	
<6	10 (29%)
6–10	16 (45%)
>10	9 (26%)
Median of the sum of all target lesions per patient (mm)	83 (48–130)
Type of advance disease	
Metastatic	94%
Locally advanced	6%
Previous systemic therapies	12 (33%)
Two lines of chemotherapy	3 (8%)
Doxorubicin and dacarbazine followed by dacarbazine	2 (5%)
VAC/IE followed by cisplatin and pemetrexed	1 (3%)
One line of chemotherapy	8 (22%)
Doxorubicin	5 (14%)
Dacarbazine	1 (3%)
Doxorubicin and dacarbazine	1 (3%)
Vincristine, adriamycin, and cyclophosphamide	1 (3%)
Sunitinib	2 (6%)
Imatinib	1 (3%)

Data are n (%) or median (IQR). VAC/IE=combination chemotherapy using vincristine, adriamycin, cyclophosphamide alternating with ifosfamide and etoposide.

Table 1: Baseline characteristics

univariantly, with respect to progression-free survival and overall survival.

To measure performance at baseline, negative control probes were used as quality control, as described previously.²⁰ Median progression-free survival was taken as grouping criteria for bioinformatics translational analyses (appendix p 2). If significantly different expressed genes had been found by HTG Molecular Immuno-oncology assay, then they were included in a univariate and multivariate analysis, along with other clinical-pathological

factors. As *ISG15* and *BCL2* were the genes with significant differences in expression, they were included in the univariate and multivariate analysis. The optimal cut-point value to discriminate between high expression and low expression was calculated with reference to the overall survival receiver operating characteristics (ROC) curve. For *ISG15* expression the area under curve (AUC) was 0·62, and for *BCL2* the AUC was 0·66.

This study is registered with ClinicalTrials.gov, number NCT02066285, and with the European Clinical Trials Database, EudraCT number 2013-005456-15.

Role of the funding source

This trial has been sponsored and designed by GEIS along with the collaboration of ISG and FSG. GlaxoSmithKline and Novartis partially supported expenses for organisational management of the trial's clinical research, as well as for drug supply and shipping. The funders had no role in data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

From June 26, 2014, to Nov 24, 2016, 40 patients with advanced and progressing solitary fibrous tumour were assessed for eligibility (figure 1). 36 patients were enrolled in the study (34 with malignant tumour and two with dedifferentiated tumour). The clinical cutoff for the final data analyses was March 1, 2018. At that time, two (6%) of 36 patients were still receiving treatment and 34 (94%) of 36 patients had discontinued pazopanib: 32 (89%) because of progression, one (3%) because of toxicity (grade 3 hypertension), and one (3%) because of insufficient social support (figure 1). One patient was lost to follow-up before the end of treatment.

35 patients were included in the per protocol population and 36 patients were included in the intention-to-treat and safety populations. A total of 293 1-month cycles of treatment were given to the 36 enrolled patients, with a median of 5·5 cycles per patient (IQR 3–12·5). The median dose intensity for pazopanib was 98% (IQR 81–100). 21 (58%) of 36 patients had dose interruptions and ten (28%) had dose reductions. At baseline, 12 (33%) of 36 patients had received previous systemic therapy; 11 (31%) had received at least one line of chemotherapy, and three (8%) had been treated with previous targeted therapies (table 1).

Based on central radiology review (interim analysis and at the time of clinical cutoff for the final data analysis), 18 (51%) of 35 patients had partial responses, nine (26%) had stable disease, and eight (23%) had progressive disease according to Choi criteria; whereas two (6%) of 35 patients had partial responses, 21 (60%) had stable disease, and 12 (34%) had progressive disease according to RECIST. Thus, the overall response of 35 patients was 51% (95% CI 34–69) according to Choi criteria and 6%

(95% CI 0–14) according to RECIST criteria. The median decrease in tumour density from baseline was 28% (IQR 4 to 45; figure 2). Discrepancies between central and local radiological assessment according to Choi were found in seven patients; five patients considered to have partial responses by central assessment were assessed as having stable disease by local assessment and two were considered to have partial responses or stable disease by central assessment, but progressive disease by local assessment. None of the cases that had been considered partial responses or stable disease by local assessment were changed to progressive disease when centrally assessed.

At a median follow-up period of 27 months (13–31), 32 (91%) of 35 patients had events of progression according to Choi, 25 (71%) had events of progression according to RECIST in central review, and there were ten (29%) deaths. Median progression-free survival of all 36 patients was 5.57 months (95% CI 4.51–6.62) based on Choi criteria by central review, and 5.57 months (4.29–6.84) based on RECIST by central review (figure 3). Median overall survival was not reached, and overall survival at 24 months was 73% (95% CI 58–88; figure 3). Median progression-free survival was 8.47 months (3.34–13.60) for responding patients and 3.53 months (95% CI 0.75–6.31) for non-responding patients according to Choi criteria ($p=0.001$). Likewise, those patients obtaining partial response, according to Choi criteria had a significantly better 24-month overall survival than did progressing patients (figure 3, appendix p 2). The accrual of dedifferentiated solitary fibrous tumour was not allowed after early and fast progression was observed at 0.57 and 1.73 months in two patients. The two patients who had previously been treated with sunitinib were sensitive to pazopanib, showing a progression-free survival according to Choi of 10.80 and 4.47 months. The patient with 4.47 months of progression-free survival was lost to follow-up before end of treatment.

Prespecified univariate analyses of clinicopathological factors showed that lower mitotic count significantly correlated with better progression-free survival ($p<0.0001$) and overall survival ($p<0.0001$), and tumour size significantly correlated with progression-free survival ($p=0.038$; table 2). Age was not a prognostic factor in progression-free survival and overall survival. Best response according to Choi and RECIST, measured from the time of best response, significantly correlated with progression-free survival and overall survival (appendix p 2). Nevertheless, Choi criteria were better than RECIST criteria for differentiating patients in progressive disease with worse overall survival; median overall survival of patients with progressive disease according to Choi was 4.5 months (95% CI 0–10.5) and 2-year overall survival was 25% (0–55; $p<0.0001$), while median overall survival of patients with progressive disease according to RECIST was 6.5 months (0–27.4) and 2-year overall survival was 31% (0–62; $p=0.007$; appendix p 2). Median overall survival of patients who had progressive disease according to

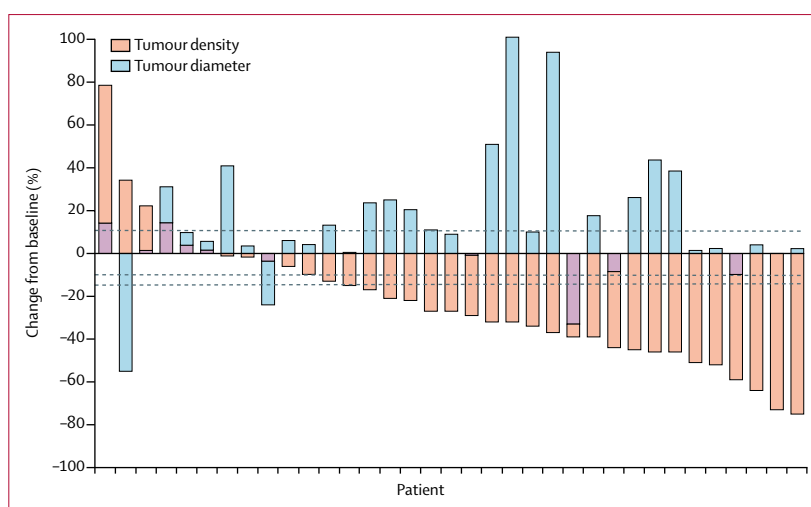


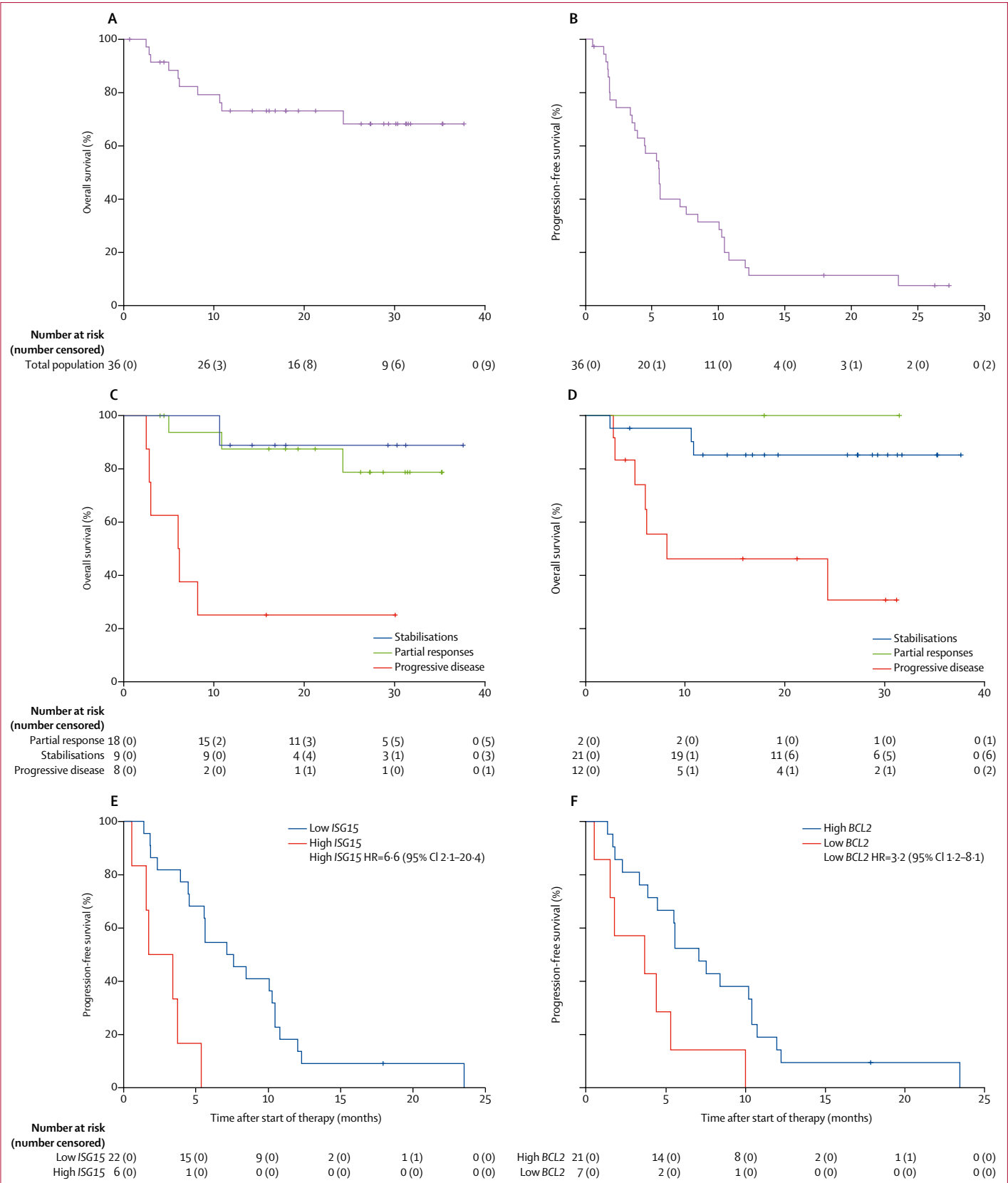
Figure 2: Response to treatment by patient according to Choi criteria

All patients in the per-protocol population shown ($n=35$). Tumour diameter was measured in mm and tumour density was measured in Hounsfield units. The dashed lines represent +10% of diameter increase, -10% of diameter decrease, -15% density decrease (Choi criteria cutoffs). Purple bars are overlaps.

RECIST but partial responses according to Choi was 24.3 months (0–53.2).

There were no deaths related to adverse events. The most frequent secondary adverse events related to treatment of any grade observed in the 36 patients were hypertension (24 [67%]), increased alanine aminotransferase concentrations (20 [56%]), increased aspartate aminotransferase concentrations (17 [47%]), fatigue (17 [47%]), diarrhoea (17 [47.2%]), weight loss (14 [39%]), nausea (ten [28%]), and increased bilirubin concentrations (ten [28%]; table 3). The most frequent type of haematological toxicity was neutropenia (13 [36%]). No febrile neutropenia was observed. The most frequent grade 3 or higher adverse events were hypertension (11 [31%] of 36 patients), neutropenia (four [11%]), increased concentrations of alanine aminotransferase (four [11%]), and increased concentrations of bilirubin (three [8%]). Four (11%) patients had pazopanib-related serious adverse events: two (6%) patients had grade 3 elevations in aminotransferases, one (3%) patient had ileitis, and one (3%) had tonsil abscesses. All patients completely recovered from their side-effects without intervention. Clinical benefit will be reported in a separate paper.

Confirmation of diagnosis by central pathology review at national level resulted in 13 (36%) patients with more than 4 mitoses per 10 hpf; 11 (31%) of 36 patients with more than 4 mitoses per 10 hpf and nuclear pleomorphism; six (17%) patients with more than 4 mitoses per 10 hpf and necrosis; three (8%) patients with more than 4 mitoses per 10 hpf, nuclear pleomorphism, and necrosis; one (3%) patient with nuclear pleomorphism and necrosis; and two (6%) patients with pleomorphism only. Cellularity was not always reported in central pathology review at national level, but in central pathology review at supranational review 25 (78%) of 32 patients



had hypercellularity. Central pathology review at supranational level confirmed malignant solitary fibrous tumour on the basis of mitotic count in 27 (78%) of 32 patients with enough available formalin-fixed paraffin-embedded tissue sections. The remaining five (14%) patients had a mitotic count lower than 4 per 10 hpf, and in three patients (8%) pleomorphism was present. The low mitotic count in these five patients could have been caused by insufficient quantity of tumour sample in these five cases. Nuclear immunostaining for STAT6 was positive in 34 (94%) of 36 patients. Additionally, a fusion was detected by next generation sequencing in 29 (94%) of 31 patients who had given a tumour sample (tissue from five patients was not available for fusion analysis after supranational pathological review). The most frequent fusion breakpoints were *NAB2* exon 4–*STAT6* exon 2 in nine (29%) of 31 patients and *NAB2* exon 6–*STAT6* exon 16/17 in 12 (39%) of 31 patients (appendix pp 2–3). The two (6%) patients with fusion-negative samples had their samples examined by the study reviewer pathologists (EdA, PC, and DR-V) and an external expert pathologist (APDT). Based on morphology, one patient was eventually diagnosed with malignant solitary fibrous tumour, but for the other patient there was no consensus for dedifferentiated solitary fibrous tumour. Both fusion-negative samples were positive for STAT6 by fluorescence in situ hybridisation.²¹

For the translational analyses, gene expression analyses quantitatively measured the expression of 549 genes involved in the innate and adaptive immune response to cancer. Based on bioinformatics analyses of the RNA transcripts, 30 genes with the most significant difference in expression between patients with worse and better progression-free survival were recorded (appendix p 3). Among these, only *ISG15* and *BCL2* showed significant prognostic relevance for both progression-free survival and overall survival in the univariate analyses. High expression of *ISG15* had a worse median progression-free survival (1.7 months [95% CI 0–3.9] vs 7.1 months [4.5–9.8], $p<0.0001$) and worse 2-year overall survival (20% [95% CI 0–55] vs 86% [71–100], $p<0.0001$; table 2; figure 3). However, high expression of *BCL2* was associated with better median progression-free survival (7.1 months [4.8–9.4] vs 3.7 months [0–8.6]; $p=0.012$) and a better 2-year overall survival (85% [CI 69–100] vs 34% [0–72]; $p=0.001$; table 2; figure 3). In the multi-

	Median progression-free survival (months; n=36)	p value	24-month overall survival (%; n=36)	p value
Age (years)				
0–62	7.6 (1.7–13.5)	0.37	72% (51–93)	0.85
>62	4.5 (2.9–6)	..	74% (52–96)	..
Primary tumour size at diagnosis (mm)				
0–50	5.6 (2.2–9.1)	0.038	84% (68–100)	0.17
>50	3.5 (2.6–4.5)	..	54% (27–81)	..
Eastern Cooperative Oncology Group performance status				
0	5.6 (3.8–7.4)	0.42	85% (70–100)	0.23
1	4.5 (0.9–8)	..	55% (26–84)	..
2	1.8	..	50% (0–100)	..
Mitoses (per 10 high power fields)				
<6	5.6 (0–12.7)	<0.0001	90% (71–100)	<0.0001
6–10	5.6 (2.6–8.7)	..	94% (82–100)	..
>10	1.7 (1.6–1.8)	..	13% (0–37)	..
Tumour burden				
Low	5.6 (5.5–5.8)	0.2	87% (69–100)	0.06
High	5.4 (3.1–7.6)	..	62% (39–84)	..
Tumour site				
Visceral	5.6 (5.2–5.9)	0.19	79% (62–95)	0.39
Somatic	4.5 (0–10.5)	..	60% (30–90)	..
Pleomorphism				
Yes	4.5 (2.9–6.2)	0.4	82% (64–100)	0.27
No	5.6 (5.4–5.8)	..	62% (36–89)	..
Necrosis				
No	5.6 (3.2–8)	0.08	80% (63–98)	0.29
<10%	3.4 (0.7–6.1)	..	67% (29–100)	..
>10%	3.9 (0–12)	..	50% (1–99)	..
Hypertension grade 3–4				
Yes	3.9 (0.9–9)	0.15	67% (36–97)	0.9
No	5.6 (5.2–5.9)	..	75% (58–92)	..
ISG15 expression*				
Low	7.1 (4.5–9.8)	<0.0001	86% (71–100)	<0.0001
High	1.7 (0–3.9)	..	20% (0–55)	..
BCL2 expression*				
Low	3.7 (0–8.6)	0.012	34% (0–72)	0.001
High	7.1 (4.8–9.4)	..	85% (69–100)	..

Data are n (95% CI) or n% (95% CI). *Tumour samples were available for 28 patients.

Table 2: Univariate analyses of clinicopathological factors according to progression-free survival and overall survival

Figure 3: Malignant solitary fibrous tumour survival analysis

(A) Overall survival in the intention-to-treat population. (B) Progression-free survival according to Choi criteria in the intention-to-treat population. Subgroup analysis of overall survival according to Choi (C) or RECIST (D) criteria by response outcome in the per-protocol population. (E) Progression-free survival according to Choi criteria by *ISG15* gene expression. (F) Progression-free survival according to Choi criteria by *BCL2* gene expression. The optimal cutoff value to discriminate between high and low expression of *ISG15* and *BCL2* was calculated with reference to the overall survival receiver operating characteristic curve. For *ISG15* expression the area under curve was 0.62, and for *BCL2* expression the area under curve was 0.66. HR=hazard ratio.

variate analysis, *ISG15* expression was the only independent prognostic variable that was significant for both progression-free survival and overall survival (table 4).

Discussion

In this phase 2 trial, we found that 18 (51%) of 35 patients had partial responses to pazopanib according to Choi criteria and central radiology review, which suggests that pazopanib has activity in the treatment of malignant solitary fibrous tumour. Moreover, the 28% decrease in median tumour density, median progression-free survival

	Any grade (n=36)	Grade 1-2 (n=36)	Grade 3 (n=36)	Grade 4 (n=36)
Haematological toxicity				
Neutropenia	13 (36%)	9 (25%)	4 (11%)	0
Leucopenia	12 (33%)	11 (31%)	1 (3%)	0
Lymphocytopenia	11 (31%)	11 (31%)	0	0
Thrombocytopenia	10 (28%)	10 (28%)	0	0
Anaemia	7 (19%)	6 (17%)	1 (3%)	0
Leucocytosis	1 (3%)	1 (3%)	0	0
Non-haematological toxicity				
Hypertension	24 (67%)	13 (36%)	11 (31%)	0
Increased alanine aminotransferase concentration	20 (56%)	16 (44%)	3 (8%)	1 (3%)
Increased aspartate aminotransferase concentration	17 (47%)	15 (42%)	2 (6%)	0
Fatigue	17 (47%)	15 (42%)	2 (6%)	0
Diarrhoea	17 (47%)	15 (42%)	2 (6%)	0
Weight loss	14 (39%)	13 (36%)	1 (3%)	0
Nausea	10 (28%)	10 (28%)	-	0
Increased bilirubin concentration	10 (28%)	7 (19%)	3 (8%)	0
Increased alkaline phosphatase concentration	8 (22%)	7 (19%)	1 (3%)	0
Skin or hair hypopigmentation	8 (22%)	7 (19%)	1 (3%)	0
Increased gamma-glutamyltransferase concentration	7 (19%)	5 (14%)	2 (6%)	0
Oral mucositis	7 (19%)	6 (17%)	1 (3%)	0
Anorexia	6 (17%)	6 (17%)	0	0
Vomiting	5 (14%)	5 (14%)	0	0
Headache	5 (14%)	5 (14%)	0	0
Abdominal pain	5 (14%)	5 (14%)	0	0
Hypothyroidism	5 (14%)	5 (14%)	0	0
Hyperkalaemia	5 (14%)	5 (14%)	0	0
Hyponatraemia	4 (11%)	4 (11%)	0	0
Decreased albumin concentration	4 (11%)	3 (8%)	1 (3%)	0
Palmar-plantar erythrodysesthesia	4 (11%)	4 (11%)	0	0
Dysgeusia	4 (11%)	4 (11%)	0	0
Skin and subcutaneous tissue disorders	2 (6%)	2 (6%)	0	0
Sinus bradycardia	2 (6%)	2 (6%)	0	0
Alopecia	2 (6%)	2 (6%)	0	0
Dry mouth	2 (6%)	2 (6%)	0	0

Data are n (%). No grade 5 adverse events were reported. The table includes grade 1 or 2 adverse events occurring in at least 5% of patients and grade 3 or 4 events in all patients.

Table 3: Adverse events

of 5·6 months, 6-month progression-free survival of 40%, and 2-year overall survival of 73% in previously progressing patients (albeit being secondary endpoints in this study), suggest activity of pazopanib in patients who have advanced, malignant disease. Previously published data on treatment of advanced malignant solitary fibrous tumour has only been from retrospective analyses. Park and colleagues¹¹ retrospectively analysed the clinical outcomes of 18 patients with solitary fibrous tumour who received conventional chemotherapy; 16 (89%) patients had stabilisations and two (11%) had progressive disease according to RECIST. Median progression-free survival was

4·6 months, 6-month progression-free survival was 28%, and 2-year overall survival was 48%. Likewise, Stacchiotti and colleagues¹³ observed six (20%) partial responses and a median progression-free survival of 4 months according to RECIST, in 30 evaluable patients treated either with anthracycline monotherapy or anthracycline and ifosfamide. 6-month progression-free survival was 20%, and median overall survival was 11 months. Our study outcomes are comparable in terms of overall response and progression-free survival to a retrospective analysis of patients treated with sunitinib. Stacchiotti and colleagues¹⁴ observed 14 (48%) partial responses, five (17%) stabilisations, and ten (35%) progressive disease according to Choi criteria in 29 evaluable patients diagnosed with malignant or dedifferentiated solitary fibrous tumour who were treated with sunitinib. Median progression-free survival was 7 months and 6-month progression-free survival was 45%. However, the median overall survival of 16 months was shorter than in our study, possibly because of the higher proportion of patients with dedifferentiated solitary fibrous tumour in the study, as compared with our study. Maruzzo and colleagues¹⁵ collected prospective data on the clinical outcomes of 11 patients with advanced solitary fibrous tumour treated with pazopanib and evaluable by Choi, reporting five (46%) patients had partial responses, four (36%) had stabilisations, and two (18%) had progressive disease. Median progression-free survival was 4·7 months and 6-month progression-free survival was 44·9%. The results by Maruzzo and colleagues¹⁵ are also consistent with those observed in the present study, except that the median overall survival of 13·5 months was also shorter. Finally, Park and colleagues¹⁶ published a retrospective analysis of 14 patients with solitary fibrous tumour treated with temozolomide plus bevacizumab, showing seemingly better outcomes than in our study. They observed 11 (79%) patients had partial responses, two (14%) had stabilisations, and one (7%) had progressive disease according to Choi criteria. Median progression-free survival was 9·7 months, 6-month progression-free survival was 78·6%, and median overall survival was 24 months. The patients did have more favourable characteristics; seven patients had localised tumours and at least three had typical solitary fibrous tumours. Altogether, previously published data from retrospective analyses support the use of pazopanib in advanced malignant solitary fibrous tumour. Additionally, our prospective trial, gives us a benchmark for overall response, progression-free survival, and overall survival for pazopanib in the treatment of advanced malignant solitary fibrous tumour.

Because of the low incidence of advanced solitary fibrous tumour (<1 case per million), clinical research is challenging and is complicated by the fact that solitary fibrous tumour presents as localised in more than 90% of cases,^{8,12} so surgery is the cornerstone. The multinational effort of this present study, with a careful selection of specialised sarcoma centres in three countries, not only met the accrual goal in a reasonable period (less than

2.5 years), but also enabled the recruitment of patients with specific solitary fibrous tumour variants. Typical, malignant, and dedifferentiated solitary fibrous tumour are thought to be different subtypes within the spectrum of solitary fibrous tumour, with different pathological features and clinical behaviour.^{9,12,22} As this distinct biological behaviour could also be translated into the metastatic setting, we considered a more rational approach and planned to explore pazopanib treatment of distinct subtypes in different cohorts. Although we have not made comparisons between cohorts (the advanced typical solitary fibrous tumour cohort is still in recruitment phase), tumour size of the primary tumour and mitotic count at diagnosis have displayed potential prognostic relevance in the cohort of patients with metastatic malignant or dedifferentiated solitary fibrous tumour for progression-free survival and overall survival. Both variables have been recognised as prognostic factors in localised disease for metastasis-free and disease-specific survival rates,⁸ but interestingly, these variables also have a prognostic role in the metastatic setting according to our data (table 2).

Analysis of different variants of solitary fibrous tumour separately was also convenient. The recruitment of patients with dedifferentiated solitary fibrous tumour was stopped after acknowledging an early and fast progression in two patients. This finding is in alignment with observations in preclinical and retrospective clinical studies, in which dedifferentiated solitary fibrous tumour had a more aggressive clinical course and was more sensitive to chemotherapy than malignant solitary fibrous tumour and hardly sensitive to pazopanib.^{13,18,23} On the other hand, dedifferentiated solitary fibrous tumour was reported to be less sensitive to sunitinib than malignant solitary fibrous tumour, with 36% of partial responses and stabilisations observed in patients with dedifferentiated solitary fibrous tumour compared with 79% of partial responses and stabilisations observed in patients with malignant solitary fibrous tumour according to Choi criteria.¹⁴

Cellularity, nuclear pleomorphism, and especially mitotic count were the pathological features most extensively applied for classifying solitary fibrous tumours as malignant in our series (in line with previous publications).^{24,25} We detected fusions in 94% of patients, the most frequent being *NAB2* exon-6 *STAT6* exon 16/17 in 39% of patients. Over-fixation might have caused the negative fusion result in two (6%) cases. In the largest published case series, the presence of fusions ranged between 55% and 100%, and the most frequent breakpoint varied by study.³⁻⁵

In our study, *ISG15* overexpression significantly correlated with worse progression-free survival and overall survival; moreover, *ISG15* expression was the only independent prognostic factor for overall survival and progression-free survival in our multivariate analyses. This prognostic correlation has also been identified at the mRNA or protein level.^{26,27} *ISG15* is a ubiquitin-like protein

	Progression-free survival		Overall survival	
	Hazard ratio (95% CI)	p value	Hazard ratio (95% CI)	p value
Mitosis (<10 vs ≥10 per 10 high power fields)	1.39 (0.39–4.92)	0.61	1.84 (0.25–15.60)	0.55
Primary tumour size at diagnosis (<5 cm vs ≥5 cm)	1.95 (0.84–4.52)	0.12	..	..
<i>BCL2</i> expression	0.73 (0.17–3.08)	0.67	0.31 (0.03–3.34)	0.34
<i>ISG15</i> expression	6.61 (2.14–20.43)	0.001	10.73 (2.22–51.82)	0.003

Table 4: Multivariate analyses of clinicopathological factors according to progression-free survival and overall survival

that has been associated with cancer survival, response, and stemness, and its overexpression has been observed in different cancers. *ISG15* overexpression has also been related to increased drug resistance.²⁶ *ISG15* expression should be measured at protein level, and the predominant fraction of *ISG15* (conjugated or free) in malignant solitary fibrous tumour should be investigated. We found that overexpression of *BCL2* significantly correlated with better progression-free survival and overall survival in our study. Although it is true that a correlation between high *BCL2* expression and better prognosis has been described in some tumours,²⁸ the underlying mechanism remains unclear. Whether it is related to autophagy inhibition by BCL-2 preventing the resistance of antiangiogenic agents such as pazopanib deserves further investigation.²⁹ In fact, loss of BCL-2 by immunohistochemistry has already been described as a marker of solitary fibrous tumour progression towards a dedifferentiated form.³⁰

Although median progression-free survival was the same with local or central assessment, there were some discrepancies that led to results being worse than they would have otherwise been. Two patients stopped early because of local radiological assessment, but during central assessment they were not considered as having progressive disease; this might have been a limitation of the study. For this trial, central rather than local radiological assessment was used for analysis.

In summary, findings from this single-arm, phase 2 trial suggest that pazopanib has activity in advanced malignant solitary fibrous tumour. In terms of overall response, progression-free survival, and overall survival, and acknowledging the biases of historical comparisons, pazopanib seems to compare favourably to historical controls with solitary fibrous tumour treated with chemotherapy. To our knowledge, this is the first phase 2 trial of pazopanib for treatment of malignant solitary fibrous tumour and provides a benchmark for future trials. The data on post-protocol therapies are being prospectively collected and will offer valuable information regarding the sequential use of antiangiogenic agents in solitary fibrous tumour. The prognostic role of *ISG15* and BCL-2 will be functionally validated and comparatively analysed with the typical solitary fibrous tumour cohort once accrual has been completed.

Contributors

JM-B and SS did the study conception and design. JM-B, SS, AL-P, AR, PGC, AI, XGdM, GG, JM-T, EP, NH, AS, AL, J-YB, and JC collected and assembled the data. JM-B, DB, EdA, AG, DSM, MP-C, JD-M, MB, MT, PC, DR-V, SD, JD, and APDT did data analysis and interpretation. JM-B, SS, ALP, AR, DB, EdA, PGC, AI, AG, DSM, MP-C, JD-M, MB, MT, PC, DR-V, XGdM, GG, SD, JM-T, EP, NH, AS, JD, APDT, AL, J-YB, and JC took part in manuscript writing. JM-B, SS, AL-P, AR, DB, EdA, PGC, AI, AG, DSM, MP-C, JD-M, MB, MT, PC, DR-V, XGdM, GG, SD, JM-T, EP, NH, AS, JD, APDT, AL, J-YB, and JC took part in the final approval of manuscript.

Declaration of interests

JM-B declares research support from Novartis, Pharmamar, and EISAI, and honoraria from Novartis, Lilly, and Pharmamar. SS declares research support from Novartis and Pfizer and advisory role fees from Bayer. AR declares advisory role fees from Pharmamar, Lilly, Novartis, Amgen, AstraZeneca, Tesaro, and Roche, and research funding from Pharmamar, Roche and EISAI. PC declares research support, advisory fees, and honoraria from Novartis and Pfizer. DSM declares research support from EISAI and Pharmamar. XGdM declares personal fees from Pfizer, Lilly, EISAI, Pharmamar, and BMS. GG declares advisory fees from Pharmamar and honoraria from Novartis, Bayer, and EISAI. EP declares personal fees from Amgen, Daiichi Sankyo and Lilly, and non-financial support from Pfizer, Pharmamar, Takeda, Lilly, and BMS. AL declares honoraria from Pfizer, Novartis, Bayer, Lilly, Pharmamar, Nanobiotics, and Amgen. J-YB declares research support and honoraria from GlaxoSmithKline, Novartis, and Bayer. JC declares research support from Novartis and honoraria from Novartis, Lilly, Roche, Pierre Fabre, Pharmamar, EISAI and AstraZeneca. All other authors declare no competing interests.

Acknowledgments

We would like to thank GEIS, ISG, and FSG for sponsoring the study. GlaxoSmithKline and Novartis partially supported expenses for organisational management of the trial's clinical research, as well as for shipping and supply of the drug. J-YB and FSG were supported by NETSARC, RREPS, RESOS, INTERSARC LYRIC/LYRICAN, EuroSARC (FP278742), and EURACAN. We would like to thank Patricio Ledesma, Martina Piccinini, Celeste Cagnazzo, Gabriella Dinoi, and Julien Gautier for clinical trial management and Vivienne Birch for the English language editing. We would also like to thank the radiologist Carlo Morosi.

References

- Fletcher CDM, Bridge JA, Hogendoorn P, Mertens F. WHO classification of tumours of soft tissue and bone. Lyon: IARC Press, 2013.
- Mosquera JM, Fletcher CD. Expanding the spectrum of malignant progression in solitary fibrous tumors: a study of 8 cases with a discrete anaplastic component—is this dedifferentiated SFT? *Am J Surg Pathol* 2009; **33**: 1314–21.
- Robinson DR, Wu YM, Kalyana-Sundaram S, et al. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. *Nat Genet* 2013; **45**: 180–85.
- Chmielecki J, Crago AM, Rosenberg M, et al. Whole-exome sequencing identifies a recurrent NAB2-STAT6 fusion in solitary fibrous tumors. *Nat Genet* 2013; **45**: 131–32.
- Mohajeri A, Tayebwa J, Collin A, et al. Comprehensive genetic analysis identifies a pathognomonic NAB2/STAT6 fusion gene, nonrandom secondary genomic imbalances, and a characteristic gene expression profile in solitary fibrous tumor. *Genes Chromosomes Cancer* 2013; **52**: 873–86.
- Doyle LA, Vivero M, Fletcher CD, Mertens F, Hornick JL. Nuclear expression of STAT6 distinguishes solitary fibrous tumor from histologic mimics. *Mod Pathol* 2014; **27**: 390–95.
- O'Neill AC, Tirumani SH, Do WS, et al. Metastatic patterns of solitary fibrous tumors: a single-institution experience. *AJR Am J Roentgenol* 2017; **208**: 2–9.
- Demico EG, Park MS, Araujo DM, et al. Solitary fibrous tumor: a clinicopathological study of 110 cases and proposed risk assessment model. *Mod Pathol* 2012; **25**: 1298–306.
- Demico EG, Wagner MJ, Maki RG, et al. Risk assessment in solitary fibrous tumors: validation and refinement of a risk stratification model. *Mod Pathol* 2017; **30**: 1433–42.
- van Houdt WJ, Westerveld CM, Vrijenhoek JE, et al. Prognosis of solitary fibrous tumors: a multicenter study. *Ann Surg Oncol* 2013; **20**: 4090–95.
- Park MS, Ravi V, Conley A, et al. The role of chemotherapy in advanced solitary fibrous tumors: a retrospective analysis. *Clin Sarcoma Res* 2013; **3**: 7.
- DeVito N, Henderson E, Han G, et al. Clinical characteristics and outcomes for solitary fibrous tumor (SFT): a single center experience. *PLoS One* 2015; **10**: e0140362.
- Stacchiotti S, Libertini M, Negri T, et al. Response to chemotherapy of solitary fibrous tumour: a retrospective study. *Eur J Cancer* 2013; **49**: 2376–83.
- Stacchiotti S, Negri T, Libertini M, et al. Sunitinib malate in solitary fibrous tumor (SFT). *Ann Oncol* 2012; **23**: 3171–79.
- Maruzzo M, Martin-Liberal J, Messiou C, et al. Pazopanib as first line treatment for solitary fibrous tumours: the Royal Marsden Hospital experience. *Clin Sarcoma Res* 2015; **5**: 5.
- Park MS, Patel SR, Ludwig JA, et al. Activity of temozolomide and bevacizumab in the treatment of locally advanced, recurrent, and metastatic hemangiopericytoma and malignant solitary fibrous tumor. *Cancer* 2011; **117**: 4939–47.
- Le Cesne A, Ray-Coquard I, Duffaud F, et al. Trabectedin in patients with advanced soft tissue sarcoma: a retrospective national analysis of the French Sarcoma Group. *Eur J Cancer* 2015; **51**: 742–50.
- Stacchiotti S, Tortoreto M, Baldi GG, et al. Preclinical and clinical evidence of activity of pazopanib in solitary fibrous tumour. *Eur J Cancer* 2014; **50**: 3021–28.
- Choi H, Charnsangavej C, Faria SC, et al. Correlation of computed tomography and positron emission tomography in patients with metastatic gastrointestinal stromal tumor treated at a single institution with imatinib mesylate: proposal of new computed tomography response criteria. *J Clin Oncol* 2007; **25**: 1753–59.
- Chadly DM, Best J, Ran C, et al. Developmental profiling of microRNAs in the human embryonic inner ear. *PLoS One* 2018; **13**: e0191452.
- Alla R, Luo S, Helman E, et al. Fix the fixation: effect of formalin fixation on targeted sequencing, variant calling and gene expression. AACR Annual Meeting 2016; New Orleans, LA; April 16–20. Abstract 3616.
- Thway K, Ng W, Noujaim J, Jones RL, Fisher C. The current status of solitary fibrous tumor: diagnostic features, variants, and genetics. *Int J Surg Pathol* 2016; **24**: 281–92.
- Stacchiotti S, Saponara M, Frapolli R, et al. Patient-derived solitary fibrous tumour xenografts predict high sensitivity to doxorubicin/dacarbazine combination confirmed in the clinic and highlight the potential effectiveness of trabectedin or eribulin against this tumour. *Eur J Cancer* 2017; **76**: 84–92.
- England DM, Hochholzer L, McCarthy MJ. Localized benign and malignant fibrous tumors of the pleura. A clinicopathologic review of 223 cases. *Am J Surg Pathol* 1989; **13**: 640–58.
- Vallat-Decouvelaere AV, Dry SM, Fletcher CD. Atypical and malignant solitary fibrous tumors in extrathoracic locations: evidence of their comparability to intra-thoracic tumors. *Am J Surg Pathol* 1998; **22**: 1501–11.
- Chen RH, Du Y, Han P, et al. ISG15 predicts poor prognosis and promotes cancer stem cell phenotype in nasopharyngeal carcinoma. *Oncotarget* 2016; **7**: 16910–22.
- Bektas N, Noetzel E, Veeck J, et al. The ubiquitin-like molecule interferon-stimulated gene 15 (ISG15) is a potential prognostic marker in human breast cancer. *Breast Cancer Res* 2008; **10**: R58.
- Abdel-Fatah TM, Perry C, Dickinson P, et al. Bcl2 is an independent prognostic marker of triple negative breast cancer (TNBC) and predicts response to anthracycline combination (ATC) chemotherapy (CT) in adjuvant and neoadjuvant settings. *Ann Oncol* 2013; **24**: 2801–07.
- Selvakumaran M, Amaravadi RK, Vasilevskaia IA, O'Dwyer PJ. Autophagy inhibition sensitizes colon cancer cells to antiangiogenic and cytotoxic therapy. *Clin Cancer Res* 2013; **19**: 2995–3007.
- Collini P, Negri T, Barisella M, et al. High-grade sarcomatous overgrowth in solitary fibrous tumors: a clinicopathologic study of 10 cases. *Am J Surg Pathol* 2012; **36**: 1202–15.