Pazopanib or methotrexate–vinblastine combination chemotherapy in adult patients with progressive desmoid tumours (DESMOPAZ): a non-comparative, randomised, open-label, multicentre, phase 2 study

Maud Toulmonde, Marina Pulido, Isabelle Ray-Coquard, Thierry Andre, Nicolas Isambert, Christine Chevreau, Nicolas Penel, Emmanuelle Bompas, Esma Saada, François Bertucci, Celeste Lebbe, Axel Le Cesne, Patrick Soulie, Sophie Piperno-Neumann, Stephen Sweet, Fabiola Cecchi, Todd Hembrough, Carine Bellera, Michèle Kind, Amandine Crombe, Carlo Lucchesi, François Le Loarer, Jean-Yves Blay, Antoine Italiano

Summary

Background Desmoid tumours are locally aggressive tumours associated with substantial morbidity. No systemic treatments are approved for this disease, with methotrexate–vinblastine the only chemotherapy regimen assessed in a clinical trial setting to date. VEGF overexpression is a common feature in aggressive desmoid tumours. Pazopanib is an oral antiangiogenic agent targeting VEGF receptors 1, 2, and 3, platelet-derived growth factor receptor-like protein (PDGFR) α and β, and c-KIT tyrosine kinases. We aimed to assess antitumour activity and safety of targeted therapy or combination chemotherapy in progressive desmoid tumours.

Methods DESMOPAZ was a non-comparative, randomised, open-label, phase 2 trial conducted at 12 centres from the French Sarcoma Group. We enrolled adults (≥18 years) with progressive desmoid tumours, normal organ function and centrally documented progressive disease according to Response Evaluation Criteria in Solid Tumors version 1.1 based on two imaging assessments obtained within less than a 6-month interval. Participants were randomly assigned (2:1) to oral pazopanib 800 mg per day for up to 1 year or to an intravenous regimen combining vinblastine (5 mg/m² per dose) and methotrexate (30 mg/m² per dose), administered weekly for 6 months and then every other week for 6 months. Randomisation was stratified according to inclusion centre and tumour location. The primary endpoint was the proportion of patients who had not progressed at 6 months in the first 43 patients who had received one complete or two incomplete cycles of pazopanib. This endpoint was also assessed as a prespecified exploratory endpoint in all patients who had received one complete or two incomplete cycles of methotrexate–vinblastane. Safety analyses were done for all patients who received at least one dose of allocated treatment. This trial was registered with ClinicalTrials.gov, number NCT01876082.

Findings From Dec 4, 2012, to Aug 18, 2017, 72 patients were enrolled and randomly assigned (n=48 in the pazopanib group; n=24 in the methotrexate–vinblastine group). Median follow-up was 23·4 months (IQR 17·1–25·5). 46 patients in the pazopanib group and 20 patients in the methotrexate–vinblastine group were assessable for activity. In the first 43 patients assessable for the primary endpoint in the pazopanib group, the proportion of patients who had not progressed at 6 months was 83·7% (95% CI 69·3–93·2). The proportion of patients treated with methotrexate–vinblastine who had not progressed at 6 months was 45·0% (95% CI 23·1–68·5). The most common grade 3 or 4 adverse events in the pazopanib group were hypertension (n=10, 21%) and diarrhoea (n=7, 15%) and in the methotrexate–vinblastine group were neutropenia (n=10, 45%) and liver transaminitis (n=4, 18%). 11 patients (23%) had at least one serious adverse event related to study treatment in the pazopanib group, as did and six patients (27%) in the methotrexate–vinblastine group.

Interpretation Pazopanib has clinical activity in patients with progressive desmoid tumours and could be a valid treatment option in this rare and disabling disease.

Funding GlaxoSmithKline and Novartis.

Introduction

Desmoid tumours are rare, locally aggressive tumours with an unpredictable natural history, which mostly affect individuals aged between 15 and 60 years. Despite their infiltrative growth pattern and high propensity for local recurrence, some of these tumours can stop growing or even regress without any intervention. Although surgery has been standard treatment for decades, studies have suggested the benefit of front-line watchful waiting after diagnosis to avoid unnecessary invasive treatment.[1,2] However, about a third of patients with desmoid tumours will have progressive or highly

Lancet Oncol 2019; 20: 1263–72

Published **Online** June 19, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30276-1

See **Comment** page 1190

Department of Medicine (M Toulmonde MD, Prof A Italiano MD), **Clinical and Epidemiology Department and Clinical Investigation Centre, INSERM** (M Pulido MSc, C Bellera PhD), **Department of Radiology** (M Kind MD, A Crombe MD), **Bioinformatics Unit** (C Lucchesi PhD), **and Department of Pathology** (F Le Loarer MD), **Institut Bergonié, Bordeaux, France; University of Bordeaux, Bordeaux, France** (Prof A Italiano); **Department of Medicine, Centre Léon Bérard, Lyon, France** (Prof I Ray-Coquard MD, Prof J-Y Blay MD); **Department of Medical Oncology, Hôpital Saint-Antoine, Paris, France** (Prof T Andre MD); **Department of Medicine, Centre George-Francois Leclerc, Dijon, France** (N Isambert MD); **Department of Medicine, Oncopole, Toulouse, France** (C Chevreau MD); **Department of Medicine, Centre Oscar Lambret, Lille, France** (Prof N Penel MD); **Department of Medicine, Institut de Cancérologie de l'Ouest, Nantes, France** (E Bompas MD); **Department of Medicine, Centre Antoine Lacassagne, Nice, France** (E Saada MD); **Department of Medicine, Institut Paoli Calmettes, Marseille, France** (F Bertucci MD); **Department of Dermatology, Hôpital Saint-Louis, France** (C Lebbe MD); **Department of Medicine, Gustave Roussy,Villejuif, France** (A Le Cesne MD); **Department of**

Medicine, Institut de Cancérologie de l'Ouest, Angers, France (P Soulie MD); **Department of Medicine, Institut Curie, Paris, France** (S Piperno-Neumann MD); **and NantOmics, Rockville, MD, USA** (S Sweet PhD, F Cecchi PhD, T Hembrough PhD)

Correspondence to: Prof Antoine Italiano, Institut Bergonié, Department of Medicine, 33000, Bordeaux, France
a.italiano@bordeaux.unicancer.fr

Research in context

Evidence before this study

We searched PubMed with the terms "desmoid tumor" OR "fibromatosis" AND "clinical trial" NOT "review" for clinical trials done in humans published in English up to Dec 31, 2018. We identified 11 citations that reported results from clinical trials conducted according to the ethical guidelines and principles of the International Declaration of Helsinki. Of these 11 citations, two included outcomes for the methotrexate–vinblastine chemotherapy regimen, five included outcomes after treatment with a tyrosine kinase inhibitor, and one reported results from radiotherapy. The remaining three citations reported data from hormonal therapy or miscellaneous agents. Only one of these studies was randomised. None of the studies included only patients with confirmed progressive disease at inclusion according to Response Evaluation Criteria in Solid Tumors (RECIST).

Added value of this study

Current guidelines recommend chemotherapy for aggressively growing, symptomatic or even life-threatening desmoid tumours. Our results show that pazopanib, a multi-tyrosine kinase inhibitor already approved for the management of advanced soft-tissue sarcomas, induced responses in patients with progressive desmoid tumour, resulting in a proportion of patients with 6-months non-progression of 84%.

Implications of all the available evidence

The DESMOPAZ trial is the first randomised trial assessing systemic therapy in confirmed progressive desmoid tumour. Patients included in this study had aggressive desmoid tumours. Our results confirm that multityrosine kinase inhibitors, notably those targeting angiogenesis, such as pazopanib, compare favourably with chemotherapy in terms of safety and activity in patients with desmoid tumours and could be a valid therapeutic option.

symptomatic disease, or both, and need therapeutic intervention. Several pharmacological treatments, such as hormonal therapy (eg, tamoxifen), non-steroidal anti-inflammatory drugs (NSAIDs), tyrosine-kinase inhibitors (TKIs), such as imatinib[3–5] or sorafenib,[6] and cytotoxic chemotherapy[7–16] have been associated with clinical benefit in patients with progressive or recurrent desmoid tumours. However, evidence concerning the role of these systemic approaches is scarce and mainly based on small, single-centre case series. The combination of intravenous methotrexate and vinblastine is the only conventional systemic regimen assessed in a clinical trial setting, with encouraging efficacy and acceptable safety profile, notably in the paediatric and adolescent and young adult population in which it is widely used.[7,15] Proportions of patients achieved an objective response and disease stabilisation were 40% and 60%, respectively, in the first trial, and 19% and 50% in the second trial. However, the weekly intravenous regimen required multiple outpatient visits, possibly impeding the patients' daily activities, and was associated with myelotoxicity.

See Online for appendix

VEGF overexpression has been identified as a common feature in desmoid tumours, especially in recurrent aggressive cases.[17] Retrospective data have shown promising results in 26 patients treated with the TKI sorafenib.[6] Pazopanib is an oral TKI targeting VEGF receptors 1, 2, and 3, PDGFRα and β, and c-KIT tyrosine kinases that is already approved for the management of soft-tissue sarcomas.[18] We aimed to assess the activity and safety of pazopanib and combination methotrexate–vinblastine in patients with progressive desmoid tumours.

Methods

Study design and participants

DESMOPAZ is a non-comparative, randomised, open-label, multicentre, phase 2 trial for which patients were recruited from 12 centres from the French Sarcoma Group (appendix p 2). Patients were eligible if they were aged at least 18 years and had histologically confirmed desmoid tumours after central review; Eastern Cooperative Oncology Group (ECOG) performance status 0–1; adequate renal, hepatic, and cardiac functions; and any type and number of previous treatments. Blood tests included assessment of blood cell count, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, albumin, bilirubin, creatinine, and urea nitrogen. A washout period of 14 days for previous treatment was mandatory. Key exclusion criteria included previous treatment with pazopanib or methotrexate–vinblastine. All patients had centrally documented progressive disease according to RECIST 1.1 based on two imaging assessments obtained within less than a 6-month interval. Archived formalin-fixed, paraffin-embedded samples of tumour tissue were mandatorily collected at baseline, and an on-treatment tumour biopsy at cycle 2 was optional. As required by the French regulations, the protocol was centrally approved by a central institutional review board (the Comité de Protection des Personnes Sud-Ouest et Outre Mer III, Bordeaux, France), which reviewed the appropriateness of the clinical trial protocol as well as the risks and benefits to study participants. The protocol is available in the appendix. All patients provided written, informed consent.

Randomisation and masking

Eligible patients were randomly assigned (2:1) to receive either pazopanib or a regimen combining methotrexate and vinblastine, with a web-based randomisation system (TenAléa software) at the central sponsor site. Once the randomisation was completed, the investigator received an automated email confirmation with the group of treatment allocated. Randomisation was stratified according to inclusion centre and tumour location (limbs and girdles *vs* other). A minimisation randomisation method was used to avoid substantial imbalance between the groups. Patients and investigators were not masked to treatment allocation.

Procedures

After inclusion and screening, patients received pazopanib 800 mg per day orally for up to 1 year, or intravenous methotrexate (30 mg/m²) plus vinblastine (5 mg/m²), once a week for 6 months and then every 2 weeks for 6 months. Treatment was continued until progression, unacceptable toxicity, investigator's decision, patient consent withdrawal, or for a maximum of 1 year. Crossover was permitted after central confirmation of progression. Safety was monitored by assessing all adverse events continuously through the study, graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0. Laboratory assessments were done at baseline, week 2, week 4, and every 4 weeks afterwards. Pazopanib and methotrexate–vinblastine dose adjustments in case of adverse events were planned in the protocol guidelines. Tumour lesions were assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 at baseline within 14 days before the first dose of pazopanib or methotrexate–vinblastine, and every 12 weeks until disease progression or the start of another treatment. MRI was used for head and neck, limbs, or trunk wall lesions, whereas CT scan was used for internal trunk lesions. All responses had to be confirmed by repeating imaging at a minimum of 4 weeks from the first observation. Primary endpoint assessment was based on centrally blinded reviewed radiological data. Quality of life and pain modification were assessed at baseline, every 4 weeks during the first 3 months and every 12 weeks thereafter, at progression, and the study end. Tumour samples were collected centrally at Institut Bergonié for the post-hoc proteomic analysis at the end of recruitment.

Outcomes

The primary endpoint was the the proportion of patients who had not progressed at 6 months defined as the percentage of patients remaining alive and progression-free at 6 months as per RECIST 1.1 after the day of randomisation.

Secondary endpoints were safety by CTCAE version 4.0; best overall response, defined as the best response obtained from the start of treatment to the time of progression (complete response, partial response, stable disease, or progressive disease as per RECIST 1.1); 1-year and 2-year progression-free survival; overall survival; health-related quality of life (HRQOL) assessed at each cycle with European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaires; and pain intensity assessed at each cycle with Brief Pain Inventory forms.[19,20] Progression-free survival was defined as the time from the start of randomisation to the time of progression or death from any cause, whichever occurs first. Patients alive and progression free were censored at the date of the last follow-up. Overall survival was defined as the time from the start of randomisation to the time of death from any cause or last patient contact. Pharmacokinetics testing of pazopanib and pharmacogenomics was planned and the results will be reported elsewhere.

For the **TenAléa** see https://prod.tenalea.net/gso/dm/

Statistical analysis

A two-stage Simon's design[21] was used. Considering the following hypothesis of a favourable true proportion of

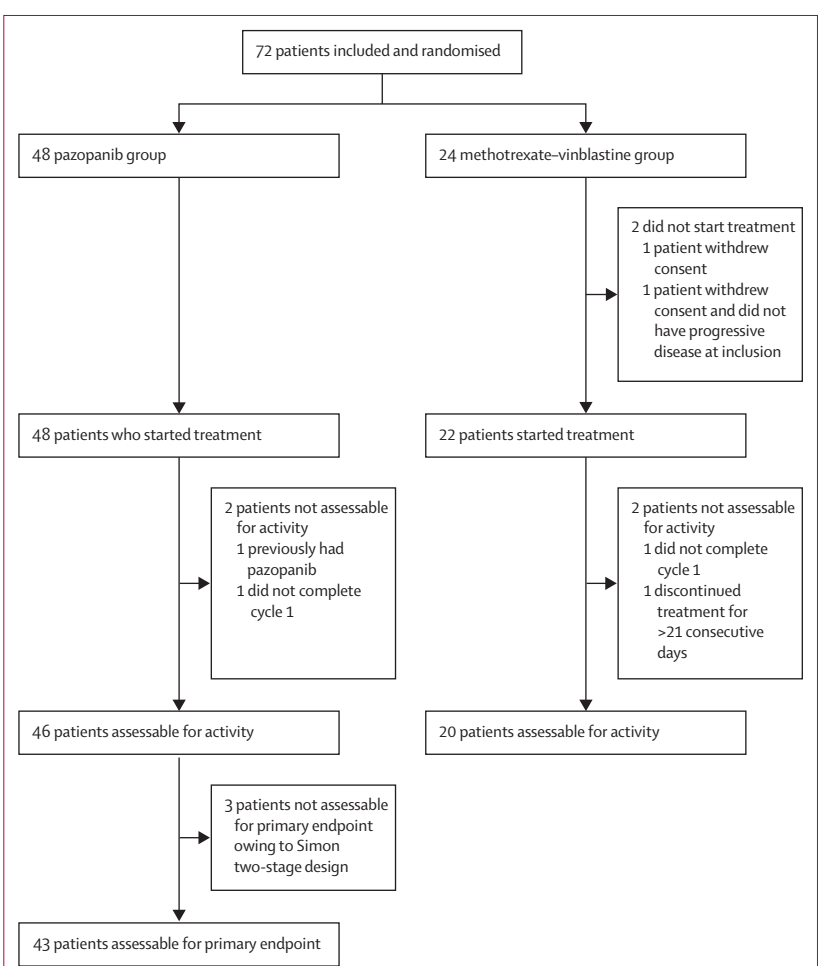

Figure 1: **Trial profile**

	Pazopanib (n=48)	Methotrexate and vinblastine (n=24)
Median age (range)	35 (18–78)	42 (21–79)
Sex		
Female	31 (65%)	15 (63%)
Male	17 (35%)	9 (38%)
Performance status (ECOG)		
0	34 (71%)	18 (75%)
1	14 (29%)	6 (25%)
Location		
Limbs and girdles	27 (56%)	9 (38%)
Internal trunk or mesenteric	13 (27%)	13 (54%)
Trunk wall	7 (15%)	2 (8%)
Head and neck	1 (2%)	0
Mutational status		
CTNNB1 T41A	15 (31%)	10 (42%)
CTNNB1 S45P	9 (19%)	4 (17%)
CTNNB1 S45F	8 (17%)	2 (8%)
APC gene	6 (13%)	2 (8%)
No mutation identified	6 (13%)	3 (13%)
Unknown	4 (8%)	3 (13%)
Gardner's syndrome		
Yes	7 (15%)	4 (17%)
No	41 (85%)	20 (83%)
Previous treatment		
Hormonal therapy*	11 (23%)	2 (8%)
Tyrosine kinase inhibitor†	3 (6%)	2 (8%)
Chemotherapy‡	4 (8%)	0
COX2 inhibitor	27 (56%)	13 (54%)
Surgery	22 (46%)	8 (33%)
Radiotherapy	7 (15%)	1 (4%)
Number of previous systemic treatment lines		
0	11 (23%)	6 (25%)
1	17 (35%)	13 (54%)
2	13 (27%)	1 (4%)
3	7 (15%)	4 (17%)

Data are n (%), unless otherwise stated. ECOG=Eastern Cooperative Oncology Group. *Luteinising hormone-releasing hormone agonist, tamoxifen. †Imatinib. ‡Liposomal doxorubicin, vinblastine, methotrexate, melphalan.

Table 1: **Baseline characteristics**

patients who had progression at 6 months of 80%, a null of 60%, a type I error rate α of 5%, a β of 20%, and a 2:1 randomisation, 43 assessable patients were needed in the pazopanib group and 22 patients in the methotrexate–vinblastine group. Following the inclusion of the first 11 assessable patients, if seven patients or fewer were progression free at 6 months, the study would be terminated early. Otherwise, a second group of 32 patients would be recruited. If at the end of recruitment, at least 31 of the 43 first assessable patients were progression free at 6 months, pazopanib would be considered to have significant antitumour activity in desmoid tumours. Each group was analysed independently. No formal statistical comparison was done between groups. All enrolled patients who received at least one dose of pazopanib or methotrexate–vinblastine were eligible for safety analyses and constituted the safety population. The activity population included all patients who met eligibility criteria and had received at least one complete cycle or two incomplete cycles of treatment. The primary endpoint was assessed on the first 43 assessable patients of the pazopanib group. Secondary endpoints were assessed on the patients from the efficacy population. The median follow-up was calculated by means of the reverse Kaplan-Meier method. Endpoints were reported with their 95% CIs, as well as the medians for overall survival and progression-free survival. Survival endpoints (overall survival and progression-free survival) were analysed by means of the Kaplan-Meier method. Quantitative variables were described by the median and range, and qualitative variables were described by the frequency and percentage. For HRQOL assessment, a minimum change between baseline and cycle 6 of 10 points was considered clinically meaningful.[22] Exploratory, post-hoc proteomic analyses of pretreatment tumour samples were done in line with previous work from Kim and colleagues[23] (appendix p 1) with the aim to identify a proteomic signature predictive of response to pazopanib. Statistical analyses were done with SAS (version 9.2). This study was registered with ClinicalTrials.gov, number NCT01876082.

Role of the funding source

The data were collected with the sponsor data-management system and were analysed and interpreted by representatives of the sponsor in collaboration with the investigators. MT, MP, CB, and AI had access to the raw data. The funders of the study(GlaxoSmithKline and Novartis) had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all of the data and had final responsibility to submit for publication.

Results

From Dec 4, 2012, to Aug 18, 2017, 72 patients were randomly assigned. Two patients were excluded in the methotrexate–vinblastine group after randomisation—one patient who withdrew consent and one who had previously received pazopanib—and 70 started treatment (figure 1).

The median age was 40 years (range 18–79), and two-thirds of the patients were women (table 1). In the pazopanib group, half of the tumours were located in the limbs or girdles, and 15% originated from the trunk wall; half of the patients in the methotrexate–vinblastine group had internal trunk or mesenteric disease. Three-quarters of patients had already received systemic treatment, with a median of one (IQR 0–3) previous line.

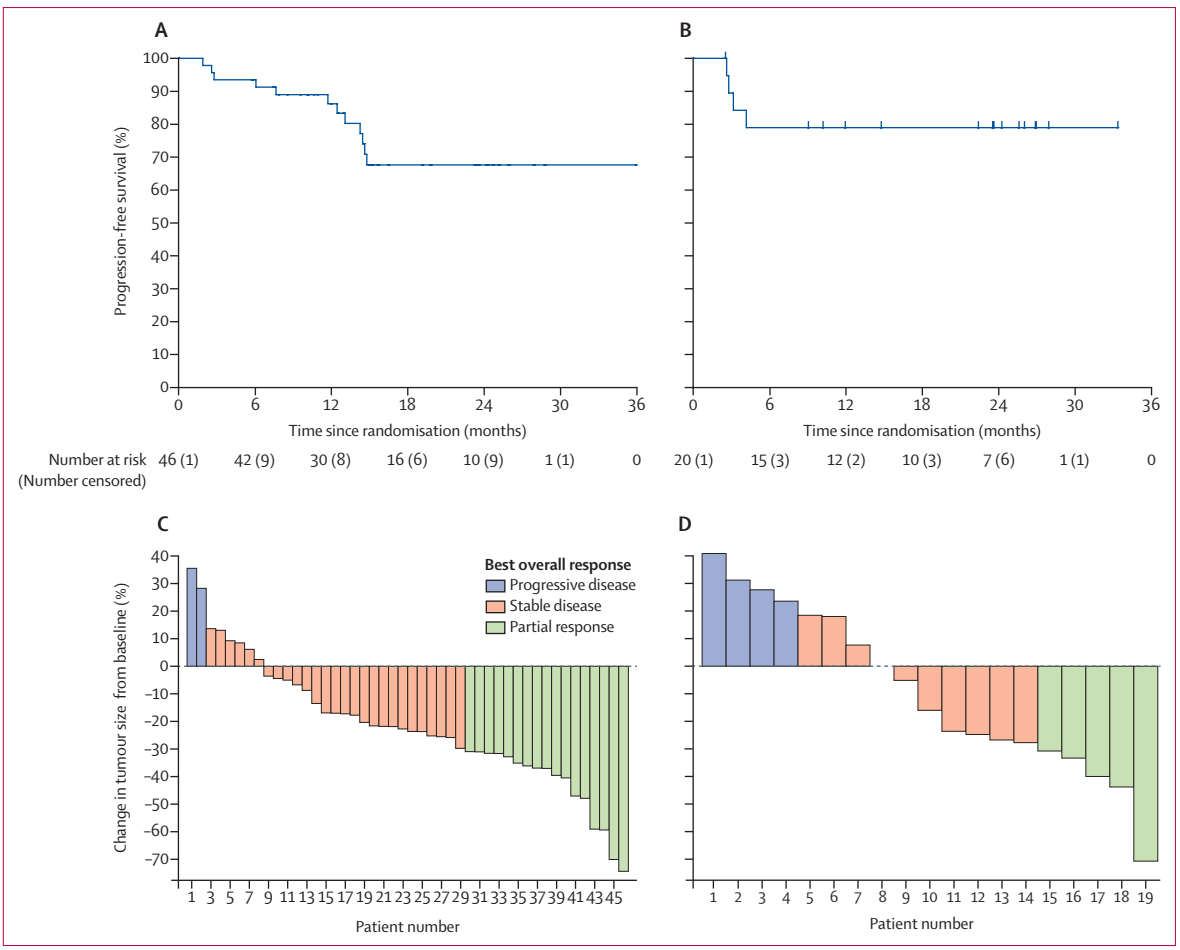

Figure 2: **Overall response and progression-free survival**
(A) Progression-free survival in the pazopanib group (n=46). (B) Progression-free survival in the methotrexate–vinblastine group (n=20). (C) Best overall response of 46 patients included in the pazopanib group. (D) Best overall response of 19 patients included in the methotrexate-vinblastine group (one patient had no radiological assessment available).

The median follow-up was 23·4 months (IQR 17·1–25·5 months). 25 (52%) of 48 patients in the pazopanib group and five (23%) of the 22 patients in the methotrexate–vinblastine group completed the planned 1-year treatment schedule. The reasons for stopping study treatment before the planned completion were disease progression for six (13%) of 48 patients in the pazopanib group and six (27%) of 22 patients in the methotrexate–vinblastine group, unacceptable adverse event for four (8%) patients in the pazopanib group and five (23%) patients in the methotrexate–vinblastine group, and other reasons for one (2%) patient in the pazopanib group and three (14%) patients in the methotrexate–vinblastine group (appendix p 3). Eight patients crossed over after progression: two patients from the pazopanib to the methotrexate–vinblastine group and six from the methotrexate–vinblastine to the pazopanib group.

Four patients were not eligible for activity assessment; therefore 66 patients were included in the activity analysis: 46 in the pazopanib group of whom the first 43 patients were included in the primary endpoint analyses, and 20 patients in the methotrexate–vinblastine group, of whom one patient had no radiological assessment available for response. 36 of the first 43 patients eligible and assessable for activity in the pazopanib group were free of progression after central review at 6 months; the proportion of patients who had not progressed at 6 months was 83·7% (95% CI 69·3–93·2). In a prespecified exploratory analysis, nine 45·0% (23·1–68·5) of 20 patients had not progressed at 6 months in the methotrexate–vinblastine group.

The median progression-free survival was not reached for either group. The 1-year progression-free survival was 85·6% [95% CI 70·7–93·2] and the 2-year progression-free survival was 67·2% [95% CI 49·0–81·9] in the pazopanib group, and both were 79·0% [95% CI 53·2–91·5] in the methotrexate–vinblastine group (figure 2A and B). One patient in the pazopanib group died 9 months after treatment completion from sepsis, which was deemed not related to the study drug.

	Pazopanib group (n=48)			Methotrexate and vinblastine group (n=22)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Fatigue	36 (75%)	3 (6%)	0	14 (64%)	1 (5%)	0
Diarrhoea	31 (65%)	7 (15%)	0	7 (32%)	0	0
Nausea and vomiting	(54%)	0	0	16 (73%)	0	0
Headache	19 (40%)	1 (2%)	0	3 (14%)	0	0
Palmar–plantar syndrome	16 (33%)	1 (2%)	0	0	0	0
Anorexia	16 (33%)	0	0	4 (18%)	0	0
Mucositis oral	13 (27%)	0	0	7 (32%)	0	0
Dysgeusia	13 (27%)	0	0	2 (9%)	0	0
Hypertension	12 (25%)	9 (19%)	1 (2%)	0	0	0
ASAT or ALAT increase	10 (21%)	2 (4%)	0	2 (9%)	3 (14%)	1 (5%)
Hypothyroidism	10 (21%)	0	0	0	0	0
Arthralgia	9 (19%)	0	0	0	0	0
Myalgia	8 (17%)	0	0	4 (18%)	1 (5%)	0
Abdominal pain	8 (17%)	0	0	1 (5%)	0	0
Skin hypopigmentation	8 (17%)	0	0	0	0	0
Alopecia	6 (13%)	0	0	4 (18%)	0	0
Dry skin	6 (13%)	0	0	0	0	0
Other gastrointestinal	5 (10%)	1 (2%)	0	0	0	0
Gastrointestinal pain	4 (8%)	1 (2%)	0	3 (14%)	0	0
Other investigations	4 (8%)	1 (2%)	0	1 (5%)	2 (9%)	0
Neutropenia	3 (6%)	3 (6%)	1 (2%)	2 (9%)	9 (41%)	1 (5%)
Bilirubin increase	3 (6%)	0	0	2 (9%)	0	0
Other hepatobiliary	2 (4%)	1 (2%)	0	2 (9%)	3 (14%)	0
Paraesthesia	2 (4%)	0	0	5 (23%)	1 (5%)	0
Constipation	2 (4%)	0	0	8 (36%)	0	0
Anaemia	0	1 (2%)	0	5 (23%)	0	0
Thromboembolic event	0	1 (2%)	0	0	0	0

Data are n (%). ALAT=alanine aminotransferase. ASAT=aspartate aminotransferase. Treatment-related adverse events that were reported in either study group in more than 5% of patients for grade 1–2 and any for grades 3 and 4 are shown; no deaths due to adverse events were reported; patients could have >1 adverse event. Other investigations were thyroid-stimulating hormone and lactate dehydrogenase concentrations.

Table 2: **Treatment-related adverse events during the treatment period**

All the patients but one from the pazopanib group (died at 12·5 months) were still alive at time of study analysis. Median overall survival was not reached in each group. 2-year, 3-year, and 4-year overall survival were the same in the pazopanib group (97·3%, 95% CI [82·3–99·6] and 100% (95% CI not applicable) in the methotrexane–vinblastine group, respectively.

In the pazopanib group, most patients had a decrease in tumour size (figure 2C). 17 (37·0% [95% CI 23·2–52·5]) of 46 patients in the pazopanib group had a partial response as best overall response according to RECIST version 1.1, 27 (58·7% [95% CI 43·2–73·0]) had stable disease, whereas two (4·4% [95% CI 0·1–14·8]) had progressive disease (one patient who had Gardner's syndrome and one who had a wild-type-*CTTNB1* mesenteric tumour [figure 2C]).

11 (55%) of 20 patients in the methotrexate–vinblastine group had a detectable decrease in tumour size (figure 2D). Five patients (25% [95% CI 8·7–49·1]) had a partial response as best overall response according to RECIST version 1.1, whereas ten patients had stable disease (50% [95% CI 27·2–72·8]) and four had progressive disease (20% [95% CI 5·7–43·7]; figure 2D).

70 patients were evaluated for safety. Treatment-related adverse events that were reported in either study group in more than 5% of patients for grade 1–2 and any for grades 3 and 4 are shown in table 2. 27 (56%) of the 48 patients in the pazopanib group and 17 (77%) of the 22 patients in the methotrexate–vinblastine group had at least one grade 3 or 4 adverse event. The most common grade 3 or 4 adverse events in the pazopanib group were hypertension (n=10, 21%) and diarrhoea (n=7, 15%) and in the methotrexate–vinblastine group were neutropenia (n=10, 45%) and liver transaminitis (n=4, 18%). 11 patients (23%) in the pazopanib and six patients (27%) in the

methotrexate–vinblastine group had at least one serious adverse event related to study treatment (appendix p 2).

Adverse events led to dose modification in 35 (73%) or definitive treatment discontinuation in four (8%) of 48 patients in the pazopanib group and to dose modification in 17 (77%) or definitive treatment discontinuation in five (23%) of 22 patients in the methotrexate–vinblastine group (appendix p 3). In the pazopanib group, these were mainly grade 2–3 diarrhoea, grade 2 fatigue, and grades 2–3 hypertension. In the methotrexate–vinblastine group, these were grade 3 hepatobiliary disorders, grade 4 neutrophil count decrease, and grade 3 musculoskeletal disorders. Four patients in each group definitively stopped treatment because of toxicity related to the study drug. These were one grade 3 hypertension, one grade 3 thromboembolic event, one grade 2 uterine haemorrhage, and one grade 2 bilirubin increase in the pazopanib group, and one grade 2 infusion site extravasation, one grade 3 hepatobiliary disorder, one grade 2, and one grade 3 paresthesia in the methotrexate–vinblastine group.

In the analysis of HRQOL, the global health status between baseline and cycle 6 was considered stable in the pazopanib group, associated with a clinically meaningful decrease in pain intensity. In the methotrexate–vinblastine group, the global health status between baseline and cycle 6 decreased from baseline more than 10 points and the patients with available data at cycle 6 reported a meaningful decrease in emotional functioning without modification in pain intensity (tables 3, 4).

Overall, 28 patients had tumour material available for post-hoc proteomics analyses, 21 in the pazopanib group and seven in the methotrexate–vinblastine group. Patients from the pazopanib group were classified into three groups according to tumour shrinkage RECIST scoring (appendix pp 1–2). Hierarchical clustering identified a set of peptides with differential expression significantly associated with an objective response to pazopanib (RECIST-response ≥–0·3) compared with a no response (figure 3).

	Pazopanib group		Methotrexate and vinblastine group	
	Baseline (n=44)	Cycle 6 (n=41)	Baseline (n=19)	Cycle 6 (n=6)
Global health status	67 (50–83)	67 (50–75)	67 (42–83)	50 (73–80)
Physical functioning	93 (77–100)	87 (73–93)	87 (73–100)	80 (67–100)
Emotional Functioning	75 (54–88)	83 (67–100)	100 (83–100)	67 (17–50)
Pain	33 (17–67)	17 (0–33)	33 (0–50)	33 (44–67)
Fatigue	28 (6–56)	44 (33–56)	22 (11–44)	44 (0–17)

EORTC QLQ=European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Data are median (IQR).

Table 3: **Health-related quality of life using the EORTC QLQ-C30 questionnaire (100-point scale)**

	Pazopanib group		Methotrexate and vinblastine group	
	Baseline (n=32)	Cycle 6 (n=24)	Baseline (n=15)	Cycle 6 (n=4)
Worst pain	6·5 (5–8)	5 (4–7)	5 (3–8)	4 (3–6)
Least pain	2 (1–4)	1·5 (0–3)	1 (0–2)	0 (0–0·5)
Average pain	6 (4–6)	3 (2–5·5)	4 (2–5)	3 (2–5·5)
Treatment associated pain relief (%)	50% (30–60)	70% (45–80)	50% (20–60)	40% (40–40)

Data are median (IQR).

Table 4: **Pain intensity assessments using the Brief Pain Inventory (10-point scale)**

Discussion

To our knowledge, the DESMOPAZ trial is the first non-comparative randomised trial in confirmed progressive desmoid tumours. Patients included in this study had aggressive desmoid tumours: three-quarters of patients had already received systemic treatment and all had progressive disease according to RECIST in the 6 months before inclusion in the study, and we found that 83·7% (95% CI 69·3–93·2) of patients treated with pazopanib had not progressed at 6 months.

Owing to the absence of a randomised trial in desmoid tumours, physician choice of a systemic treatment for patients with desmoid tumours is often driven by empirical experience. A couple of prospective studies and several retrospective studies have assessed chemotherapy for symptomatic patients.[7–16] Because of concerns about use of cytotoxic drugs with potential late toxic effects, such as liposomal doxorubicin in young patients, alternative non-chemotherapeutic options have been explored in desmoid tumours. The first TKI investigated in patients with desmoid tumours was imatinib, which showed low clinical activity, with tumour shrinkage in less than 10% of patients as reported in two clinical trials.[4,5] Sorafenib was the first multitargeted TKI with activity reported in patients with desmoid tumours. A retrospective series reported partial response in 25% of patients, and imaging features of increased fibrosis and decreased cellularity in up to 92% of them.[6]

Pazopanib is the only multitargeted TKI approved for the management of soft-tissue sarcomas.[18] Retrospective data were reported on its promising activity in desmoid tumours.[24–26] The DESMOPAZ study confirms that pazopanib has meaningful clinical activity in desmoid tumours, with the proportion of patients who had not progressed at 6 months of more than 80% in a population of patients with very poor prognosis. Moreover, most responses in the pazopanib group were early, with clinically meaningful improvements in clinical symptoms such as pain and emotional functioning, as shown on EORTC QLQ-C30 assessments. Notably, incidence of mucositis, an adverse event associated with pain, was not higher in the methotrexate–vinblastine group than in the pazopanib group. In desmoid tumors, drug activity is frequently associated with an early increase in tumour heterogeneity on MRI with the occurrence of necrotic and fibrotic processes

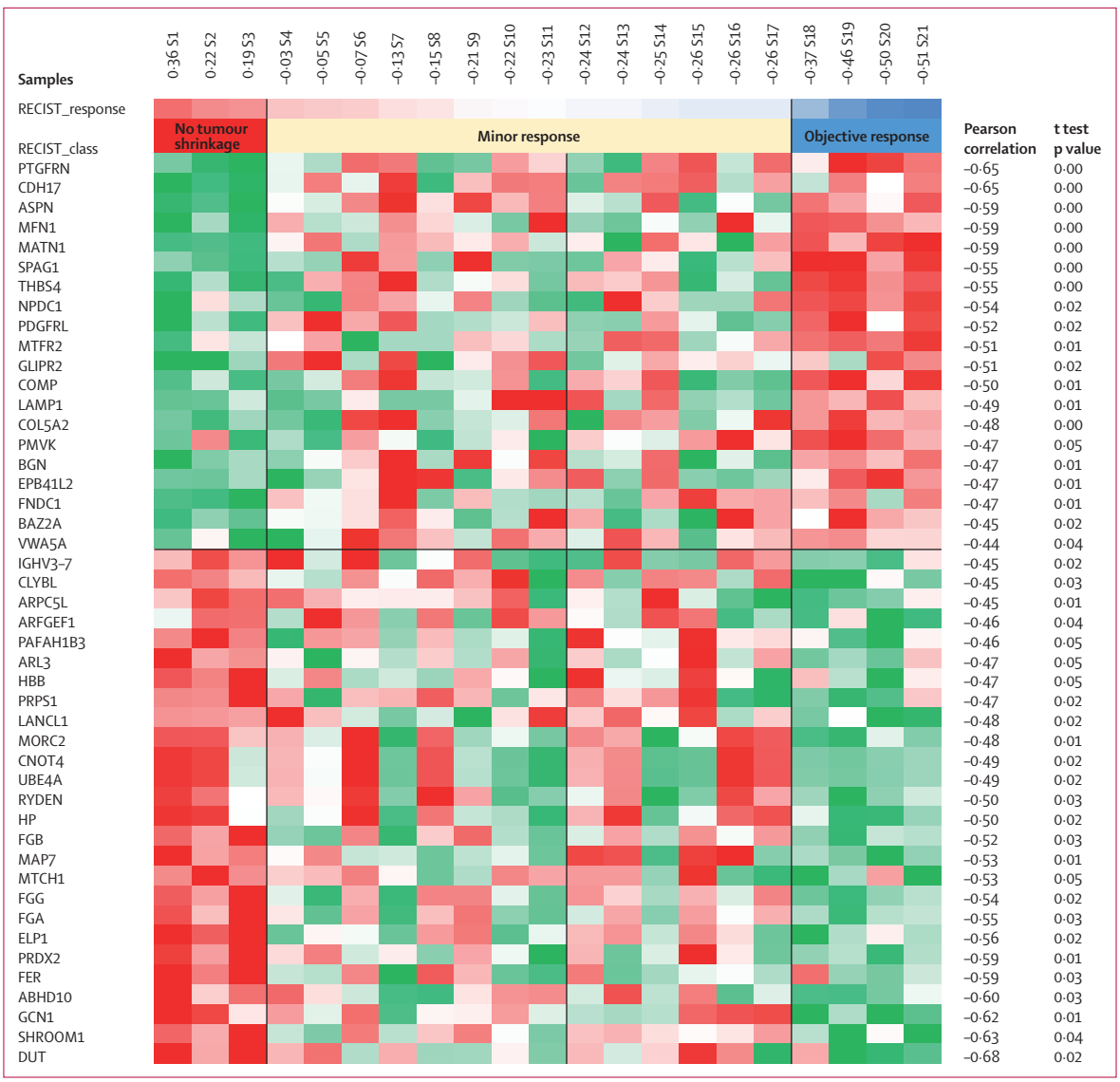

Figure 3: **Protein expression profiling associated with RECIST-response scoring for patients in the pazopanib group (n=21)**
The second row reports RECIST-response numerical values, and the third row reports RECIST-response classes: no tumour shrinkage, objective response (reduction in tumour size of more than 30%), and minor response (reduction in tumour size between −1 and −29%). Samples are sorted into columns by increasing RECIST-response numerical value. The 46 proteins significantly differentially expressed between no tumour shrinkage and objective response RECIST tumour classes are shown. Red indicates overexpression and green indicates underexpression on a gradient scale. Proteins are sorted into rows by increasing Pearson standard correlation between the protein expression value and RECIST-response numerical value. Pearson standard correlation values and *t* test p values are given for each protein differentially expressed between the no tumour shrinkage and the objective response desmoid tumour class.

together with a decrease in active cellular component, despite the longest diameter being considered stable according to conventional RECIST. In this regard, the use of RECIST to establish the radiological response has certainly underestimated the real antitumour activity of pazopanib. Dedicated criteria for the radiological assessment of desmoid tumours should certainly be designed, considering changes in textural and shape quantitative features (ie, delta radiomics) on standardised MRI protocols, including T2 and contrast-enhanced T1-weighted imaging.[27]

The proportion of patients who had not progressed at 6 months after treatment with methotrexate–vinblastine was 45·0% (95% CI 23·1–68·5). Albeit limited by small numbers, progression-free survival at 1 year and 2 years in the methotrexate–vinblastine group was 79·0%, indicating potential sustained activity in some patients. A slight decrease between 1-year and 2-year progression-free survival in the pazopanib group suggests that longer treatment could be proposed in some patients, such as those with remaining active tumour residue on MRI. This remains

to be tested in a future trial with endpoints dedicated to radiomics.

Altogether, the results of the DESMOPAZ trial are in line with those of the ALLIANCE A091105 trial, which included 87 patients with unresectable desmoid tumours.[28] In the ALLIANCE A091105 trial, patients were randomly assigned (2:1) to receive oral sorafenib at 400 mg or placebo. In that study, 33% (95% CI 20–48) of patients achieved a partial response with sorafenib and 20% (8–38) with placebo, and 1-year progression-free survival was 89% (80–99) with sorafenib compared with 46% (32–67) with placebo. Importantly, progression according to RECIST was not mandatory for inclusion in the ALLIANCE A091105 trial, as it was in the DESMOPAZ trial. About 40% of patients had disease that was effectively progressive at inclusion according to RECIST, and tumour regression was also observed in the placebo group, confirming the unpredictable nature of desmoid tumours, and the importance of carefully evaluating the need for therapeutic intervention that is associated with potential side-effects. Three other important differences can be highlighted between the DESMOPAZ and the ALLIANCE A091105 trials: in the DESMOPAZ study, the diagnosis of desmoid tumour was centrally reviewed by a group of expert pathologists, which is crucial given the high rate of misdiagnosis (up to 33%) in the community setting;[29] imaging was centrally reviewed by blinded independent radiologists at baseline to confirm disease progression, and during treatment to assess activity outcomes in order to control bias from errors in progression assessments; and three-quarters of patients had been already treated with systemic therapy, with 21% having received two or more previous lines in the methotrexate–vinblastine group and 42% having received two or more previous lines in the pazopanib group. Conversely, in the ALLIANCE A091105 trial, only a third of patients had received previous systemic treatment (41% in the placebo group and 36% in the sorafenib group) and more than half of patients were newly diagnosed (51% in the placebo group and 54% in the sorafenib group).

Overall, the toxicity of pazopanib was manageable and the toxicity profile of methotrexate–vinblastine in line with previous studies,[7,15] with less grade 3–4 neutropenia and anaemia. However, dose reductions were frequent and similar in both groups (73% in the pazopanib group and 77% in the methotrexate–vinblastine group). Despite these findings, however, pazopanib resulted in meaningful clinical activity. Of note, in the ALLIANCE A091105 trial, sorafenib was administered at the 400 mg daily dose, which is 50% of the recommended licensed daily dose. Despite the lower dose used dose interruptions occurred in 65% of the patients. Altogether, these data advocate for an upfront use of an adapted dose of pazopanib in this specific population.

The mechanism of action of multityrosine kinase inhibitors such as pazopanib or sorafenib in desmoid tumours is not known. A post-hoc proteomic analysis of pretreatment samples allowed the identification of several proteins significantly overexpressed in patients with an objective response to pazopanib compared with patients with no objective response. Differentially expressed proteins in patients with an objective response were involved in angiogenesis regulation and various processes such as cell-to-cell and cell-to-matrix interactions, cellular proliferation, migration, adhesion and attachment, vascular inflammation, including notably thrombospondin-4 and platelet-derived growth factor receptor-like protein. Importantly, among the most differentially expressed proteins in the responding patient group were PDGF receptor-like protein and thrombospondin-4. Sustained expression and phosphorylation of PDGFR alpha and PDGFR beta on immunohistochemistry have been reported in aggressive desmoid tumours, and this is believed to occur within an autocrine or paracrine loop mediated by cyclo-oxygenase-2 overexpression and deregulation of the APC–β-catenin signalling pathway.[30] Thrombospondin-4 is an important proangiogenic factor that contributes to tumour growth via TGF-β pathway activation, which mediates Wnt/β-catenin signalling in desmoid tumours.[31,32]

This study has limitations. It was a non-comparative, randomised trial, therefore precluding direct comparison of the chemotherapy regimen with pazopanib. Baseline tumour biopsies were optional, and only a small number of samples were available for exploratory proteomics analysis, the results of which remain hypothesis-generating. There was also no pharmacokinetics data reported on pazopanib. Such data could help adapt the dosing of pazopanib and improve safety profile. Blood samples collection for pharmacokinetics analysis were planned in the protocol, and results will be reported at a later stage.

Randomised clinical trials in very rare diseases such as desmoid tumours are usually considered challenging. The DESMOPAZ study focused on a very rare condition and completed accrual in the expected time. This was made possible thanks to the involvement of patient advocacy groups in the design of the study and the unique nature of the French Network for diagnosis and management of patients with mesenchymal tumours.

In conclusion, the primary objective of this study was reached. Pazopanib has clinical activity in patients with progressive desmoid tumours and might be considered a valid treatment option in this rare and disabling disease.

Contributors

AI and CB conceived and designed the study. MT, IR-C, TA, NI, CC, NP, EB, ES, FB, CL, ALC, PS, SP-N, J-YB, AI provided study material or treated patients. All authors collected and assembled data. MT, MP, SS, FC, TH, CL, AI developed the tables and figures. MT, MP, AI did the literature search and wrote the report. MK, AC, FLL, J-YB provided study material or treated patients. All authors were involved in the critical review of the manuscript and approved the final version.

Declaration of interests

CC reports personal fees from Ipsen, Novartis, Pfizer, and Bristol-Myers Squibb. CL reports research grants, personal fees, and non-financial

support from Amgen, Bristol-Myers Squibb, MSD, Roche, Novartis, Pierre Fabre, Sanofi, Merck Serono, Pfizer, and Incyte. SS was an employee of Nantomics during the study. FC was an employee of Nantomics during the study. TH is an employee of Nantomics. J-YB reports research grants, personal fees, and non-financial support from Bayer, GlaxoSmithKline, and Novartis. AI has declared research grand and personal fees from Ipsen, Novartis, Bayer, Bristol-Myers Squibb, Epizyme, Immune Design, Daiichi Sankyo, and MSD. All other authors declare no competing interests.

Data sharing

Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures, and appendices will be shared with investigators whose proposed use of the data has been approved by an independent review committee (learned intermediary) identified for this purpose and beginning 12 months and ending 36 months following article publication. Proposals may be submitted up to 36 months following article publication to the corresponding author.

Acknowledgments

This study was sponsored by Institut Bergonié, and funded by GlaxoSmithKline and Novartis (Novartis acquired pazopanib from GlaxoSmithKline in 2016). We thank all patients, caregivers, and families who contributed to the study, as well as members of SOS Desmoide for involvement in designing and relaying information about the study.

For the **study** see http://www.sos-desmoide.asso.fr

References

1 Kasper B, Baumgarten C, Garcia J, et al. An update on the management of sporadic desmoid-type fibromatosis: a European consensus initiative between sarcoma patients EuroNet (SPAEN) and European Organization for Research and Treatment of Cancer (EORTC)/soft tissue and bone sarcoma group (STBSG). *Ann Oncol* 2017; **28:** 2399–408.

2 Penel N, Le Cesne A, Bonvalot S, et al. Surgical versus non-surgical approach in primary desmoid-type fibromatosis patients: a nationwide prospective cohort from the French sarcoma group. *Eur J Cancer* 2017; **83:** 125–31.

3 Mace J, Biermann JS, Sondak V, et al. Response of extraabdominal desmoid tumors to therapy with imatinib mesylate. *Cancer* 2002; **95:** 2373–79.

4 Penel N, Le Cesne A, Bui BN, et al. Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): an FNCLCC/French sarcoma group phase II trial with a long-term follow-up. *Ann Oncol* 2011; **22:** 452–57.

5 Chugh R, Wathen JK, Patel SR, et al. Efficacy of imatinib in aggressive fibromatosis: results of a phase II multicenter Sarcoma alliance for research through collaboration (SARC) trial. *Clin Cancer Res* 2010; **16:** 4884–91.

6 Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of sorafenib against desmoid tumor/deep fibromatosis. *Clin Cancer Res* 2011; **17:** 4082–90.

7 Azzarelli A, Gronchi A, Bertulli R, et al. Low-dose chemotherapy with methotrexate and vinblastine for patients with advanced aggressive fibromatosis. *Cancer* 2001; **92:** 1259–64.

8 Constantinidou A, Jones RL, Scurr M, Al-Muderis O, Judson I. Pegylated liposomal doxorubicin, an effective, well-tolerated treatment for refractory aggressive fibromatosis. *Eur J Cancer* 2009; **45:** 2930–04.

9 Gega M, Yanagi H, Yoshikawa R, et al. Successful chemotherapeutic modality of doxorubicin plus dacarbazine for the treatment of desmoid tumors in association with familial adenomatous polyposis. *J Clin Oncol* 2006; **24:** 102–05.

10 Meazza C, Bisogno G, Gronchi A, et al. Aggressive fibromatosis in children and adolescents: the Italian experience. *Cancer* 2010; **116:** 233–40.

11 Patel SR, Evans HL, Benjamin RS. Combination chemotherapy in adult desmoid tumors. *Cancer* 1993; **72:** 3244–47.

12 Skapek SX, Hawk BJ, Hoffer FA, et al. Combination chemotherapy using vinblastine and methotrexate for the treatment of progressive desmoid tumor in children. *J Clin Oncol* 1998; **16:** 3021–27.

13 Weiss AJ, Horowitz S, Lackman RD. Therapy of desmoid tumors and fibromatosis using vinorelbine. *Am J Clin Oncol* 1999; **22:** 193–95.

14 Reich S, Overberg-Schmidt US, Buhrer C, Henze G. Low-dose chemotherapy with vinblastine and methotrexate in childhood desmoid tumors. *J Clin Oncol* 1999; **17:** 1086.

15 Skapek SX, Ferguson WS, Granowetter L, et al. Vinblastine and methotrexate for desmoid fibromatosis in children: results of a pediatric oncology group phase II Trial. *J Clin Oncol* 2007; **25:** 501–06.

16 Garbay D, Le Cesne A, Penel N, et al. Chemotherapy in patients with desmoid tumors: a study from the French sarcoma group (FSG). *Ann Oncol* 2012; **23:** 182–86.

17 Matono H, Tamiya S, Yokoyama R, et al. Abnormalities of the Wnt/beta-catenin signalling pathway induce tumour progression in sporadic desmoid tumours: correlation between beta-catenin widespread nuclear expression and VEGF overexpression. *Histopathology* 2011; **59:** 368–75.

18 van der Graaf WT, Blay JY, Chawla SP, et al. Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2012; **379:** 1879–86.

19 Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singapore* 1994; **23:** 129–38.

20 Aaronson NK, Ahmedzai S, Bergman B, et al. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; **85:** 365–76.

21 Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989; **10:** 1–10.

22 Osoba D, Rodrigues G, Myles J, Zee B, Pater J. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998; **16:** 139–44.

23 Kim YJ, Sweet SM, Egertson JD, et al. Data-independent acquisition mass spectrometry to quantify protein levels in FFPE tumor biopsies for molecular diagnostics. *J Proteome Res* 2019; **18:** 426–35.

24 Agresta L, Kim H, Turpin BK, et al. Pazopanib therapy for desmoid tumors in adolescent and young adult patients. *Pediatr Blood Cancer* 2018; **65:** e26968.

25 Szucs Z, Messiou C, Wong HH, et al. Pazopanib, a promising option for the treatment of aggressive fibromatosis. *Anticancer Drugs* 2017; **28:** 421–26.

26 Martin-Liberal J, Benson C, McCarty H, Thway K, Messiou C, Judson I. Pazopanib is an active treatment in desmoid tumour/aggressive fibromatosis. *Clin Sarcoma Res* 2013; **3:** 13.

27 Lambin P, Leijenaar RTH, Deist TM, et al. Radiomics: the bridge between medical imaging and personalized medicine. *Nat Rev Clin Oncol* 2017; **14:** 749–62.

28 Gounder MM, Mahoney MR, Van Tine BA, et al. Sorafenib for advanced and refractory desmoid tumors. *N Engl J Med*. 2018; **25:** 2417–28.

29 Penel N, Coindre JM, Bonvalot S, et al. Management of desmoid tumours: A nationwide survey of labelled reference centre networks in France. *Eur J Cancer*. 2016; **58:** 90–96.

30 Signoroni S, Frattini M, Negri T, et al. Cyclooxygenase-2 and platelet-derived growth factor receptors as potential targets in treating aggressive fibromatosis. *Clin Cancer Res* 2007; **13:** 5034–40.

31 Varghese S, Braggio DA, Gillespie J, et al. TGF-beta and CTGF are mitogenic output mediators of Wnt/beta-catenin signaling in desmoid fibromatosis. *Appl Immunohistochem Mol Morphol* 2017; **25:** 559–65.

32 Muppala S, Xiao R, Krukovets I, et al. Thrombospondin-4 mediates TGF-beta-induced angiogenesis. *Oncogene* 2017; **36:** 5189–98.