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**Pazopanib or combination chemotherapy in adult patients with progressive desmoid tumors: a randomized, open label, multicentre phase 2 study**

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## **ABSTRACT**

**Background:** Desmoid tumors (DT) are locally aggressive tumors with potential significant morbidity. There is no approved systemic treatment for this disease. Methotrexate/vinblastine (MV) is the only chemotherapy regimen assessed in a clinical trial setting to date. VEGF overexpression is a common feature in aggressive DT. Pazopanib is an oral antiangiogenic agent targeting VEGFR1, 2, and 3, PDGFR $\alpha$  and  $\beta$  and c-KIT tyrosine kinases. We report the first randomized trial assessing a targeted therapy or combination chemotherapy in progressive DT.

**Methods:** DESMOPAZ is a non-comparative, randomized, open label phase 2 trial conducted in 12 centers in France, including patients older than 18 years with progressive DT, that assessed the efficacy and safety of pazopanib 800 mg/day orally continuously, or a regimen combining vinblastine (5 mg/m<sup>2</sup>/dose) and methotrexate (30 mg/m<sup>2</sup>/dose), both administered by intravenous injection weekly for 26 weeks and every other week for 26 weeks. A two-stage Simon's design was used. Randomization was stratified according to inclusion center and tumor location (limbs and girdles versus other). A minimization randomization method has been used to avoid significant imbalance between the arms. The primary endpoint was the 6-month non-progression rate (NPR) in the eligible and assessable population, defined as all patients who had received one complete or two incomplete cycles of treatment. Safety analyses were performed in all patients who received at least one dose of allocated treatment. **Clinical Trial Registration:** *NCT01876082*

**Findings:** From December 2012 to August 2017, 72 patients were recruited (pazopanib arm: 48; MV arm: 24). The median follow up was 23.4 months [95% CI: 20.5-24.2]. Forty-six in the pazopanib arm and 20 in the MV arm were assessable for efficacy. In the first 43 patients assessable for the primary endpoint in the pazopanib arm, the 6-month NPR was 83.7% [95% CI:

69.3-93.2]. It was 45% [95% CI: 23.1-68.5] in the MV arm. The most common grade 3 or 4 adverse events in the pazopanib arm were hypertension (n=10, 21%) and diarrhea (n=7, 15%) in the pazopanib and neutropenia (n=10, 45.5%) and liver transaminitis (n=4, 18.5%) in the MV arm, respectively. Eleven patients (22.9%) and 6 patients (27.3%) had at least one serious adverse event related to study treatment in the pazopanib and MV arms respectively.

***Interpretation:*** Pazopanib has clinical activity in patients with progressive DT and can be considered a valid treatment option in this rare and disabling disease.

This study was sponsored by Institut Bergonié and funding support was provided by GlaxoSmithKline and Novartis (Novartis acquired Pazopanib from GlaxoSmithKline in 2016).

## **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 methotrexate-vinblastine chemotherapy regimen, five included outcomes after treatment with a tyrosine kinase inhibitor, and one reported results from radiation therapy. The remaining three citations reported data from hormonal therapy or miscellaneous agents. Only one of these studies was randomized. None of them included only patients with confirmed progressive disease at inclusion according to RECIST.

### ***Added value of this study***

A hallmark of desmoid tumors is their unpredictable natural history. Many of them tend to regress spontaneously. However, a small subset of patients has desmoid tumors characterized by an aggressive outcome leading to severe pain, functional impairment and, more rarely, a life-threatening condition. Current guidelines recommend chemotherapy for aggressively growing, symptomatic or even life-threatening desmoid tumors. Our results show that pazopanib, a multi-tyrosine kinase inhibitor already approved for the management of advanced soft-tissue sarcomas, induces RECIST partial response in 17 (37%) of 46 patients with progressive desmoid tumor, resulting in a proportion of patients with 6-months non-progression of 83.7%. This proportion was 45% for patients treated with combination chemotherapy.

#### ***Implications of all the available evidence***

The DESMOPAZ trial is the first randomized trial assessing systemic therapy in truly progressive desmoid tumor. Patients included in this study had desmoid tumor characterized by an aggressive behavior: Three quarters of patients had already received systemic treatment and all had progressive disease according to RECIST within an interval of less than 6 months before inclusion in the study. Our results confirm that multi-tyrosine kinase inhibitors, notably those targeting angiogenesis such as pazopanib compare favorably with chemotherapy in terms of safety and effectiveness in patients with desmoid tumors and should be considered as a valid therapeutic option.

## **ARTICLE**

### **INTRODUCTION**

Desmoid tumors (DT) are rare, locally aggressive tumors affecting individuals mostly between the ages of 15 and 60 years, with an unpredictable natural history. Indeed, despite their infiltrative growth pattern and high propensity for local recurrence, some of these tumors may stop growing or even regress without any intervention. Although surgery has been the standard of treatment for decades, recent studies have suggested the benefit of front-line watchful waiting after diagnosis to avoid unnecessary mutilating treatment.<sup>1,2</sup> However, about one-third of patients with DT will have progressive and/or highly symptomatic disease and need therapeutic intervention. Several pharmacological treatments, such as hormonal therapy (e.g., tamoxifen), nonsteroidal anti-inflammatory drugs (NSAIDs), tyrosine kinase inhibitors (TKI), such as imatinib<sup>3-5</sup> or sorafenib,<sup>6</sup> and cytotoxic chemotherapy<sup>7-16</sup> have been associated with clinical benefit in patients with progressive and/or recurrent DT. However, evidence concerning the role of these systemic approaches is scarce and mainly based on small single-center case series. The combination of intravenous (IV) 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 pediatric and AYA (adolescent and Young Adults) population where it is widely used.<sup>7,15</sup> Objective response and disease stabilization proportions were 40% and 60% in the first, and 19% and 50% in the second trial, respectively. However, the weekly IV regimen required multiple outpatient visits, possibly impeding the patients' daily activities, and was associated with myelotoxicity.

VEGF overexpression has been identified as a common feature in DT, especially in recurrent aggressive cases. Retrospective data have shown promising results in 26 patients treated with TKI sorafenib.<sup>6</sup> Pazopanib is an oral TKI targeting VEGFR1, 2, and 3, PDGFR $\alpha$  and  $\beta$  and c-KIT tyrosine kinases that is already approved for the management of soft-tissue sarcomas.<sup>18</sup> DESMOPAZ is a non-comparative, randomized, multicenter phase 2 trial designed to assess the efficacy and safety of pazopanib or methotrexate-vinblastine in patients with progressive DT.

## **METHODS**

### ***Study design and participants***

The DESMOPAZ phase 2 trial involved 13 centers from the French Sarcoma Group.

Patients were eligible if they were at least 18 years of age and had histologically confirmed DT after central review, ECOG Performance status 0-1, adequate renal, hepatic and cardiac functions (see Study synopsis, appendix page 4), and any type and number of previous treatment. Blood tests included assessment of blood cell count, alanine transaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), albumin, bilirubin, creatinine, urea nitrogen. A washout period of 14 days for previous treatment was mandatory (see Study synopsis, appendix page 7). Key exclusion criteria included previous treatment with pazopanib or MV (see Study synopsis, appendix page 6-8). 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 FFPE samples of tumor tissue were mandatorily collected at baseline, and an on-treatment tumor biopsy at Cycle 2 was optional. As required by the French regulation, the protocol was centrally approved by a central IRB (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. All patients provided written informed consent.

### ***Randomization and masking***

Eligible patients were randomly assigned using a 2:1 ratio to receive either pazopanib or a regimen combining methotrexate-vinblastine, respectively. Upon investigator's request and after confirmation of all eligibility criteria, eligible patients were randomly assigned between the two arms of treatment by a web-based randomisation system (TenAléa software, <https://prod.tenalea.net/gso/dm/>) centralized at the sponsor site. Once the randomization was completed, the investigator received an automatic confirmation by email with the arm of treatment allocated. Randomization was stratified according to inclusion center and tumor location (limbs and girdles versus other). A minimization randomization method has been used to avoid significant imbalance between the arms. Patients and investigators were not masked to treatment allocation.

### ***Study procedures***

After inclusion and screening, patients received pazopanib 800 mg/day orally continuously, or methotrexate (30 mg/m<sup>2</sup>) + vinblastine (5 mg/m<sup>2</sup>), IV, 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 NCI-CTCAE v.4.0. Laboratory assessments were performed at baseline week 2, week 4 and every four weeks afterwards. Pazopanib and methotrexate-vinblastine dose adjustments in case of adverse events

were planned in the protocol guidelines Tumor lesions were assessed according to RECIST v1.1 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.

### ***Outcomes***

The primary endpoint was the 6-month nonprogression rate (NPR) defined as the percentage of patients remaining alive and progression-free at 6 months as per RECIST 1.1 after the day of randomization.

Secondary endpoints included safety by CTCAE v4.0, best overall response (BOR), defined as the best response obtained from the start of treatment to the time of progression between complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) as per RECIST 1.1; 1-year and 2-year progression-free survival (PFS); overall survival (OS); health-related quality of life (HRQoL) and pain intensity assessed at each cycle with EORTC QLQ-C30 questionnaires and Brief Pain Inventory (BPI) forms, respectively.<sup>19,20</sup> PFS was defined as the time from the start of treatment 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. OS was defined as the time from the start of treatment to the time of death from any cause or last patient contact. For HRQoL assessment, a minimal change of 10 points was

considered clinically meaningful.<sup>21</sup> Pharmacokinetics of pazopanib were planned and results will be reported at a later date.

### *Statistical Analysis*

A two-stage Simon's design<sup>23</sup> was used. Considering the following hypothesis of a favorable true 6-month nonprogression rate of  $H_1=80\%$ , a null rate of  $H_0=60\%$ , a type I error rate  $\alpha=5\%$ , a  $\beta=20\%$  and a 2:1 randomization, 43 assessable patients were needed in the pazopanib arm and 22 patients in the methotrexate-vinblastine arm. Following the inclusion of the first 11 assessable patients, if  $\leq 7$  patients were progression free at 6 months, the study would be terminated early. Otherwise, a second group of 32 subjects would be recruited. If at the end of recruitment,  $\geq 31$  among the 43 first assessable patients were progression free at 6 months, pazopanib would be considered to have significant anti-tumor activity in DT. Each arm was analyzed independently. No formal statistical comparison was performed between arms. 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 efficacy population included all subjects 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 43 first assessable patients of the pazopanib arm. Secondary endpoints were assessed on the patients from the efficacy population. The median follow-up was calculated using the reverse Kaplan-Meier method. Endpoints were reported with their 95% confidence interval, as well as the median survival rates for OS and PFS. Survival endpoints (OS and PFS) were analysed using the Kaplan-Meier method. Quantitative variables were described using the median and range, and qualitative variables were described using frequency and percentage. Exploratory post-hoc proteomic analyses of pretreatment tumor samples were performed in line with previous work from Kim et al.<sup>22</sup> (Webappendix pages 1)

with the aim to identify a proteomic signature predictive of response to pazopanib. Statistical analyses were performed using SAS version 9.2 software (SAS Institute, North Carolina, USA).

This study was registered with ClinicalTrials.gov number NCT01876082.

### ***Role of the funding source***

The study was sponsored by Institut Bergonié (Bordeaux, France). The data were collected using the sponsor data-management system and were analyzed and interpreted by representatives of the sponsor in collaboration with the investigators. MT, MP, CB and AI had access to the raw data.

All the authors contributed to and reviewed the data reported, verified that the study was conducted in fidelity to the study protocol, edited and approved the final manuscript submitted for publication, and vouched for the completeness of the data set and integrity of the analysis.

The funding sources (GlaxoSmithKline and Novartis) played no role in the design of this study and did not play any role during its execution, analysis, interpretation of the data, or decision to submit results. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

## **RESULTS**

From 4 December 2012 to 18 August 2017, 72 patients were randomized. Two patients were excluded - one patient who withdrew consent and one who had previously received pazopanib - and 70 started treatment (Fig. 1). The median follow up was 23.4 months [95% CI: 20.5-24.2].

Characteristics of patients included in the study are described in Table 1. The median age was 40 years, and two-thirds were women. In the pazopanib arm, half of the tumors were located in the limbs or girdles, and one-third originated from the trunk wall, whereas half of the patients from

the methotrexate-vinblastine arm had internal trunk/mesenteric disease. Three-quarters of patients had already received systemic treatment, with a median number of one previous line.

Among the 70 treated patients, 25 (52%) of the 48 patients from the pazopanib arm and five (23%) of the 22 patients from the methotrexate vinblastine arm completed the planned 1-year treatment schedule. The reasons for stopping study treatment before the planned completion were as follows: disease progression for six (12%) and six (27%) patients, unacceptable adverse event for four (8%) and five (23%) patients, and other reasons for four (8%) and five (23%) patients, in the 48 patients of the pazopanib arm and the 22 patients of the methotrexate-vinblastine arm, respectively (Webappendix page 2). Eight patients crossed over after progression: two patients from the pazopanib to methotrexate-vinblastine arm and six from the methotrexate-vinblastine to pazopanib arm.

Four patients were not eligible for efficacy assessment; therefore 66 patients were included in the efficacy analysis: 46 in the pazopanib arm of whom the 43 first patients were included in the primary endpoint analyses, and 20 patients in the methotrexate-vinblastine arm, of whom one patient had no radiological assessment available for response., Thirty-six of the 43 first patients eligible and assessable for efficacy in the pazopanib arm were free of progression after central review at 6 months, leading to a proportion of patients with 6-month nonprogression of 83.7% [95% CI: 69.3-93.2].

The proportion of patients achieving 6-month nonprogression in the methotrexate-vinblastine arm was 45.0% [95% CI: 23.1-68.5].

In the pazopanib arm, most patients had a decrease in tumor size (Fig. 2A). Seventeen (37.0% [95% CI: 23.2-52.5]) of 46 patients in the pazopanib arm had a PR as BOR according to RECIST v1.1, 27 (58.7% [95% CI: 43.2-73.0]) had SD, whereas two (4.4% [95% CI: 0.1-14.8])

had PD (one 62-year-old man with a Gardner syndrome and one 37-year-old man with a wild-type-*CTTNB1* mesenteric tumor (Fig. 2A)).

Eleven (58%) of 20 patients in the methotrexate-vinblastine arm exhibited a detectable decrease in tumor size (Fig. 2B). Five patients (25% [95% CI: 8.7-49.1]) had a PR as BOR according to RECIST v1.1, whereas ten patients had SD (50% [95% CI: 27.2-72.8]) and four had PD (20% [95% CI: 5.7-43.7]) (Fig. 2B).

The median PFS was not reached for both arms. The one-year PFS and two-year PFS were 85.6% [95% CI: 70.7-93.2] and 67.2% [95% CI: 49-81.9] in the pazopanib arm, and both 79% [95% CI: 53.2-91.5] in the methotrexate-vinblastine arm, respectively (Fig. 2C and D). One patient died in the pazopanib arm, 9 months after treatment completion, from a sepsis not related to study drug.

Considering HRQoL evaluation, the global health status between baseline and cycle 6 was considered stable in the pazopanib arm, and there was also a trend toward improvement in emotional functioning, associated with a meaningful decrease in pain intensity. In the methotrexate-vinblastine arm, the global health status between baseline and cycle 6 decreased from more than 10 points and the patients with available data at cycle 6 reported a meaningful decrease in cognitive functioning without modification in pain intensity (Tables 2 and 3).

Seventy 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 grade 3 and 4 are shown in Table 4. The most common adverse events in the pazopanib arm were fatigue and diarrhea. Twenty-seven (56%) of the 48 patients in the pazopanib arm and 17 (77%) of the 22 patients in the methotrexate-vinblastine arm had at least one grade 3 or 4 adverse event, respectively. Eleven patients (22.9%) and 6 patients (27.3%) had at least one serious adverse

event related to study treatment in the pazopanib and MV arms respectively. (supplementary table 2).

Adverse events led to dose modification or definitive treatment discontinuation in 35 (73%) and 3 (8%) of 48 patients in the pazopanib arm and in 17(77%) and 4 (18%) of 22 patients in the methotrexate-vinblastine arm respectively (Supplementary Table 3) In the Pazopanib arm, these were mainly grade 2-3 diarrhea, grade 2 fatigue, and grade 2-3 hypertension (HT). In the methotrexate-vinblastine arm, these were grade 3 hepatobiliary disorders, grade 4 neutrophil count decrease and grade 3 musculoskeletal disorders. Four patients in each arm definitively stopped treatment for a toxicity related to study drug. These were one grade 3 HT, one grade 3 thromboembolic event, one grade 2 uterine hemorrhage and one grade 2 bilirubin increase in the pazopanib arm, and one grade 2 infusion site extravasation, one grade 3 hepatobiliary disorder, one grade 2 and one grade 3 paresthesia in the methotrexate-vinblastine arm, respectively.

Overall, 28 patients had tumor material available for proteomics analyses, 21 in the pazopanib arm and seven in the methotrexate-vinblastine arm. Patients from the pazopanib arm were classified into 3 groups according to tumor shrinkage RECIST scoring (Webappendix pages 1-2). Hierarchical clustering identified a set of peptides with differential expression significantly associated with an objective response to pazopanib (RECIST-response  $\geq -0.3$ ) compared with a nonobjective 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 (THBS4) and Platelet-derived growth factor receptor-like protein (PDGFR-L) (Fig. 3).

## **DISCUSSION**

To our knowledge, the DESMOPAZ trial is the first non-comparative randomized trial in truly progressive DT. Patients included in this study had DT characterized by an aggressive behavior: Three quarters of patients had already received systemic treatment and all had progressive disease according to RECIST within an interval of less than 6 months before inclusion in the study. This trial is positive, with 83.7% of patients achieving 6-month non-progression with pazopanib.

Due to the lack of a randomized trial in DT, physician choice of a systemic treatment for patients with DT is often driven by empirical experience. A couple of prospective studies and several retrospective studies have assessed chemotherapy for symptomatic patients.<sup>7-16</sup> Because of concerns using cytotoxic drugs with potential late toxic effects such as liposomal doxorubicin in young patients, alternative nonchemotherapeutic options have recently been explored in DT. The first TKI explored in patients with DT was Imatinib, which showed only limited clinical activity, with tumor shrinkage in less than 10% of patients as reported in two clinical trials.<sup>4,5</sup> Sorafenib was the first multitargeted TKI with activity reported in patients with DT. A retrospective series reported PR in 25% of patients, and imaging features of increased fibrosis and decreased cellularity in up to 92% of them.<sup>6</sup>

Pazopanib is the only multitargeted TKI approved for the management of soft-tissue sarcomas.<sup>18</sup> Retrospective data were reported on its promising activity in DT.<sup>25-26</sup> The DESMOPAZ study confirms that pazopanib has meaningful clinical activity in DT, with a 6-month NPR of more than 80% in a very poor-prognosis population of patients. Moreover, most responses in the pazopanib arm were early, with rapid improvement in clinical symptoms such as pain and emotional functioning as shown on EORTC QLQ-C30 assessments. Of note, incidence of mucositis, an adverse event associated with pain, was not higher in the methotrexate-

vinblastine arm. Importantly, we also observed an early increase in tumor heterogeneity on the MRIs of patients on treatment, with the occurrence of necrotic and fibrotic processes 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 determine the radiological response has certainly underestimated the real anti-tumor activity of pazopanib. Dedicated criteria for the radiological assessment of DT should certainly be designed, considering changes in textural and shape quantitative features (i.e., delta-radiomics) on standardized MRI protocols including T2 and contrast-enhanced T1-weighted imaging.<sup>27</sup>

The NPR was 45% in the patients treated with methotrexate-vinblastine. Interestingly, albeit limited by small numbers, PFS at one and two year in the methotrexate-vinblastine arm settled at 79% [53.2-91.5], indicating potential prolonged activity in some patients. We also observed a slight decrease between 1-year and 2-year PFS in the pazopanib arm, suggesting that longer treatment could be proposed in some patients. These could be patients with remaining active tumor residue on MRI. This remains to be tested in a future trial with endpoints dedicated to radiomics.

Altogether, results of the DESMOPAZ trial are in line with those of the ALLIANCE A091105 trial, which included 87 patients with unresectable DT.<sup>28</sup> Patients were randomized 2:1 to receive oral sorafenib at 400 mg or placebo. In this study, 33% of patients achieved a PR with sorafenib and 20% with placebo, and the one-year PFS rate was 89% with sorafenib compared with 46% with placebo. Importantly, progression according to RECIST was not mandatory for inclusion in the ALLIANCE A091105 trial, as it was in the DESMOPAZ trial. Indeed, about 40% were effectively progressive at inclusion according to RECIST, and tumor regression was also observed in the placebo arm, confirming the unpredictable nature of DT, and the importance

to carefully evaluate 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 (i) the diagnosis of desmoid tumor 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<sup>29</sup> (ii) imaging were centrally reviewed by blinded independent radiologists at baseline to confirm disease progression, and during treatment to assess efficacy outcomes in order to control bias from errors in progression assessments (iii) three quarter of patients had been already treated with systemic therapy, with 21% and 42% having received 2 or more previous lines in the methotrexate vinblastine and the pazopanib arm, respectively. Conversely, in the ALLIANCE A091105 trial only one third of patients had received previous systemic treatment (41% in the placebo arm and 36% in the sorafenib arm) and more than half of patients were newly diagnosed (51% and 54%, respectively).

Overall, the toxicity of pazopanib was manageable and the toxicity profile of methotrexate-vinblastine in line with previous studies,<sup>7,15</sup> with yet less grade 3-4 myelotoxicity. However, dose reductions were frequent and rates equal in both arms. Despite this, 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 that, 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 multi-tyrosine kinase inhibitors such as pazopanib or sorafenib in DT is not known. 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. Importantly, among

the most differentially expressed proteins in the responding patient group were PDGFR-L and THBS4. Sustained expression and phosphorylation of PDGFRA and PDGFRB on IHC have been reported in aggressive DT, and this is believed to occur within an autocrine/paracrine loop mediated by COX-2 overexpression and deregulation of the APC/ $\beta$ -catenin signaling pathway.<sup>30</sup> THBS4 is an important pro-angiogenic factor that contributes to tumor growth via TGF- $\beta$  pathway activation, which mediates Wnt/ $\beta$ -Catenin signaling in DT.<sup>31,32</sup>

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

Performing a randomized clinical trial in very rare diseases such as DT is usually considered as a real challenge. The DESMOPAZ study focused on a very rare condition and completed accrual in expected time. This was made possible thanks to 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 tumors.

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

Contributors

Conceived and designed the study: AI, CB

Provided study material or treated patients: MT, IRC, TA, NI, CC, NP, EB, ES, FB, CL, ALC, PS, SPN, JYB, AI

Collected and assembled data All authors

Developed the tables and figures MT, MP, SS, FC, TH, CL, AI

Did the literature search wrote the report: MT, MP, AI

All authors were involved in the critical review of the manuscript and approved the final version.

Declaration of interests: Mrs Fabiola CECCHI was an employee of Nantomics at the time of study conduction and analysis. Pr Jean-Yves BLAY has declared research grant, personal fees and non-financial support from Bayer, GSK and Novartis. Mr Todd HEMBROUGH is an employee of Nantomics. . Dr Christine CHEVREAU has declared personal fees from IPSEN, NOVARTIS, PFIZER and BMS. Pr Antoine ITALIANO has declared research grand and personal fees from IPSEN, Novartis, Bayer, BMS, Epizyme, Immune Design, Daiichi and MSD. Pr Celeste LEBBE has declared research grand, personal fees and non-financial support from Amgen, BMS, MSD, Roche, Novartis, Pierre Fabre, Sanofi, Merck Serono, Pfizer and Incyte. Mr Stephen SWEET was an employee of Nantomics at the time of study conduction and analysis.

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#### Data sharing statement

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 the corresponding author.

#### Conflict of interest statement

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## TABLES

**Table 1.** Patient characteristics at baseline (N=72)

	<b>PZ (n=48)</b>		<b>MV (n=24)</b>		<b>Total (N =72)</b>	
	n	%	n	%	n	%
Median age (range)	35 (18-78)		42 (21-79)		40 (18-79)	
Sex						
<b>Female</b>	31	65%	15	63%	46	64%
<b>Male</b>	17	35%	9	37%	26	36%
Performance status (ECOG)						
<b>0</b>	34	71%	18	75%	52	72%
<b>1</b>	14	29%	6	25%	20	28%
Location						
<b>Limbs and girdles</b>	27	<b>56%</b>	9	38%	36	<b>50%</b>
<b>Internal trunk/mesenteric</b>	13	27%	13	<b>54%</b>	26	<b>36%</b>
<b>Trunk wall</b>	7	15%	2	8%	9	13%
<b>Head and neck</b>	1	2%			1	1%
Mutational status						
<b>CTNNB1 T41A</b>	15	31.2%	10	41.7%	25	34.7%
<b>CTNNB1 S45P</b>	9	18.7%	4	16.7%	13	18%
<b>CTNNB1 S45F</b>	8	16.7%	2	8.3%	10	13.9%
<b>APC gene</b>	6	12.5%	2	8.3%	8	11.1%
No mutation identified	6	12.5%	3	12.5%	9	12.5%
Unknown	4	5.5%	3	12.5%	7	9.7%
Gardner syndrome						
<b>Yes</b>	7	15%	4	17%	11	15%
<b>No/NA</b>	41	85%	20	83%	61	85%
Previous treatment						
<b>Hormonal therapy<sup>1</sup></b>	11	22.9%	2	8.3%	13	18%
<b>Tyrosine kinase inhibitor<sup>2</sup></b>	3	4.2%	2	8.3%	5	7%
<b>Chemotherapy<sup>3</sup></b>	4	8.3%	0	0%	4	5.5%
<b>COX2 inhibitor</b>	27	56.2%	13	54.1%	15	20.8%
<b>Surgery</b>	22	45.8%	8	33.3%	30	41.7%
<b>Radiotherapy</b>	7	9.7%	1	4.1%	8	11.1%
Number of previous systemic treatment lines						
<b>0</b>	11	23%	6	25%	17	23.6%
<b>1</b>	17	35%	13	54%	30	41.7%
<b>2</b>	13	27%	1	4%	14	19.4%
<b>3</b>	7	15%	4	17%	11	15.3%

<sup>1</sup> LHRH agonist, tamoxifen; <sup>2</sup> imatinib; <sup>3</sup> liposomal doxorubicin, vinblastine, methotrexate, melphalan

Table 2. Health-related Quality of Life using the EORTC QLQ-C30 questionnaire								
	Pazopanib Arm				MV arm			
	Baseline (N= 44)		Cycle 6 (N = 41)		Baseline (N= 19)		Cycle 6 (N = 6)	
<b>HRQoL</b> (100 point scale)	Median	(Q1-Q3)	Median	(Q1-Q3)	Median	(Q1-Q3)	Median	(Q1-Q3)
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)

Table 3. Pain Intensity assessments using the BPI form								
	Pazopanib Arm				MV arm			
	Baseline (N= 32)		Cycle 6 (N = 24)		Baseline (N= 15)		Cycle 6 (N = 4)	
<b>BPI</b> (10-point scale)	Median	(Q1-Q3)	Median	(Q1-Q3)	Median	(Q1-Q3)	Median	(Q1-Q3)
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)

Table 4. Treatment-related Adverse Events during the treatment period (N = 70)

	<b>PZ (n=48)</b>						<b>MV (n=22)</b>					
<b>Common adverse event</b>	<b>G1/2</b>		<b>G3</b>		<b>G4</b>		<b>G1/2</b>		<b>G3</b>		<b>G4</b>	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)

Fatigue	36	(75)	3	(6)	0	(0)	14	(64)	1	(4.5)	0	(0)
Diarrhea	31	(65)	7	(15)	0	(0)	7	(32)	0	(0)	0	(0)
Nausea and vomiting	26	(54)	0	(0)	0	(0)	16	(73)	0	(0)	0	(0)
Headache	19	(40)	1	(2)	0	(0)	3	(14)	0	(0)	0	(0)
Palmar-plantar syndrome	16	(33)	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)
Anorexia	16	(33)	0	(0)	0	(0)	4	(18)	0	(0)	0	(0)
Mucositis oral	13	(27)	0	(0)	0	(0)	7	(32)	0	(0)	0	(0)
Dysgeusia	13	(27)	0	(0)	0	(0)	2	(9)	0	(0)	0	(0)
Hypertension	12	(25)	9	(19)	1	(2)	0	(0)	0	(0)	0	(0)
ASAT/ALAT increase	10	(21)	2	(4)	0	(0)	2	(9)	3	(14)	1	(4.5)
Hypothyroidism	10	(21)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Arthralgia	9	(19)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Myalgia	8	(17)	0	(0)	0	(0)	4	(18)	1	(4.5)	0	(0)
Abdominal pain	8	(17)	0	(0)	0	(0)	1	(4.5)	0	(0)	0	(0)
Skin hypopigmentation	8	(17)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Alopecia	6	(13)	0	(0)	0	(0)	4	(18)	0	(0)	0	(0)
Dry skin	6	(13)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Other gastrointestinal	5	(10)	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)
Gastrointestinal pain	4	(8)	1	(2)	0	(0)	3	(14)	0	(0)	0	(0)
Other investigations	4	(8)	1	(2)	0	(0)	1	(4.5)	2	(9)	0	(0)
Neutrophil count decrease	3	(6)	3	(6)	1	(2)	2	(9)	9	(41)	1	(4.5)
Bilirubin increase	3	(6)	0	(0)	0	(0)	2	(9)	0	(0)	0	(0)
Other hepato-biliary	2	(4)	1	(2)	0	(0)	2	(9)	3	(14)	0	(0)
Paresthesia	2	(4)	0	(0)	0	(0)	5	(23)	1	(4.5)	0	(0)
Constipation	2	(4)	0	(0)	0	(0)	8	(36)	0	(0)	0	(0)
Anemia	0	(0)	1	(2)	0	(0)	5	(23)	0	(0)	0	(0)
Thromboembolic event	0	(0)	1	(2)	0	(0)	0	(0)	0	(0)	0	(0)

## FIGURE LEGENDS

**Figure 1. DESMOPAZ study flow chart (N = 72).**

**Figure 2A. Best overall response of patients included in the pazopanib arm (N = 46).**

PD: progressive disease; SD: stable disease; PR: partial response.

**Figure 2B. Best overall response of patients included in the methotrexate- vinblastine arm (N = 19\*).**

*(\*One patient with no radiological assessment available)*

PD: progressive disease; SD: stable disease; PR: partial response.

**Figure 2C. Progression-free survival in the pazopanib arm (N=46).**

**Figure 2D. Progression-free survival in the methotrexate-vinblastine arm (N=20).**

**Figure 3. Protein expression profiling associated with RECIST-response scoring for patients in the pazopanib arm (N= 21).**

The second row reports RECIST-response numerical values, and the third row reports RECIST-response classes: “no tumor shrinkage”, “objective response” (reduction in tumor size > -30%) and “minor response” (reduction in tumor size between -1 and -29%)

Samples are sorted into columns by increasing RECIST-response numerical value.

The 46 proteins significantly differentially expressed between “no tumor shrinkage” and “objective response” RECIST tumor classes are shown. Proteins are sorted into rows by increasing Pearson standard correlation between the protein expression value and RECIST-response numerical value.

The green, white and red palette represents protein values that are respectively lower, equal or higher in the “no tumor shrinkage” than the “objective response” desmoid tumor class.

The last two columns report Pearson standard correlation values and t-test p-values for each protein differentially expressed between the “no tumor shrinkage” and the “objective response” desmoid tumor class.





