

# Imatinib for progressive and recurrent aggressive fibromatosis (desmoid tumors): an FNCLCC/French Sarcoma Group phase II trial with a long-term follow-up

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**Background:** Imatinib evaluated as a new treatment option in patients with recurrent or established progressive aggressive fibromatosis/desmoid tumor (AF/DT).

**Patients and methods:** Forty patients with unresectable and progressive symptomatic AF/DT were treated with imatinib (400 mg/day for 1 year) in a Simon's optimal two-stage phase II study ( $P_0 = 10\%$ ,  $P_1 = 30\%$ ,  $\alpha = 5\%$ ,  $\beta = 10\%$ ). The primary end point was non-progressive at 3 months (RECIST).

**Results:** The study population consisted of 28 women and 12 men, with a mean age of 41 (range 20–72 years). Most of the primary sites were extra-abdominal (24, 54.5%). Familial adenomatous polyposis was observed in six (15%) cases. The median follow-up was 34 months. Imatinib toxicity was similar to that previously reported in literature. Tumor assessment was validated by a central independent radiology committee for 35 patients. At 3 months, one (3%) complete and three (9%) partial confirmed responses were observed. The non-progression rates at 3, 6 and 12 months were, respectively, 91%, 80% and 67%. The 2-year progression-free and overall survival rates were 55% and 95%, respectively. Two patients with mesenteric AF/DT died from progressive disease.

**Conclusion:** Imatinib is active in the treatment of recurrent and progressive AF/DT, providing objective response and long-term stable disease in a large proportion of patients.

**Key words:** aggressive fibromatosis, desmoid tumor, imatinib, phase II trial

## introduction

Aggressive fibromatosis, also known as desmoid tumor (AF/DT), is a rare fibroblastic proliferative disease affecting about two to four persons per million per year [1]. It presents as a locally aggressive tumor with unpredictable behavior; while it may remain indolent in some patients, it may also cause patient death in a significant proportion of cases [2]. AF/DTs may occur in the context of a predisposing genetic condition, Gardner's syndrome, characterized by germline mutations of the APC gene [3]. Approximately 50% of AF/DTs occur in the extremities, other main locations being the trunk wall and mesentery [4, 5].

At diagnosis, surgery is the treatment of reference but local relapses are frequent [4–8]. In the absence of consensual guidelines, treatment of these local relapses is a clinical dilemma. Previous reports of treatments in the medical literature provide inconsistent tumor control data: iterative surgery, radiotherapy, treatment with tamoxifen, low-dose chemotherapy and conventional doxorubicin-based regimen [4–8]. Recently, a watch-and-wait policy consisting of systemic treatment as opposed to surgery proposed by several authors has resulted in prolonged progression-free survival in a substantial proportion of patients [9]. Decision making is therefore particularly difficult in such situations because of the unpredictable behavior of this tumor. Spontaneous stabilizations or regressions are regularly seen and 'watchful waiting' could thus be considered as a reasonable option [9].

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However, several sites (mesenteric and basi-cranial locations) may be life threatening in the event of progression and require active treatment. Moreover, surgery or radiotherapy may cause significant sequelae [1] without controlling the disease. Therefore, new treatment options that could stabilize AF/DT need to be evaluated [10].

Imatinib (STI571, Gleevec), a tyrosine kinase inhibitor with selectivity for c-kit, platelet-derived growth factor receptor (PDGFR)- $\alpha$ , PDGFR- $\beta$  and macrophage colony-stimulating factor, has dramatically modified the treatment and outcome of patients with gastrointestinal stromal tumor [11], unresectable dermatofibrosarcomas [12] and other solid tumors such as advanced pigmented villonodular synovitis [13].

Previous studies have also reported activity of imatinib in patients with AF/DT [14–16]. Therefore, we conducted a multicenter clinical phase II trial to evaluate the efficacy and tolerability of imatinib in patients with proven relapsing or progressive AF/DT with long-term follow-up.

## patients and methods

### study design

Enrolled patients were at least 18 years old with histologically proven and progressive AF/DT that was measurable or assessable by computed tomography (CT) scan or magnetic resonance imaging (MRI) and not amenable to radiotherapy or non-mutilating surgery. Prior systemic therapy for AF/DT was allowed. Additional inclusion criteria were as follows: contraception both during and 3 months after imatinib treatment, adequate hematologic function (granulocytes  $> 1000/\mu\text{l}$  and platelets count  $> 100\,000/\mu\text{l}$ ), adequate liver function [total bilirubin  $< 1.5 \times$  the upper limit of normal (ULN), alanine aminotransferase and aspartate aminotransferase  $< 2.5 \times$  ULN], adequate renal function (creatinine  $< 2.5 \times$  ULN). Diagnosis of AF/DT was confirmed by the French Sarcoma Group network of pathologists.

Exclusion criteria included the following: pregnant or breast-feeding patients, a previous history of cancer, significant hepatic cytolysis or cholestasis, severe underlying comorbid disease that could alter compliance, concomitant treatment with non-steroidal anti-inflammatory drugs (except for pain relief), chemotherapy or hormonotherapy.

Patients received 400 mg of imatinib daily until progression according to RECIST [17] or unacceptable toxicity that precluded further treatment. Patients with progressive AF/DT at a daily dose of 400 mg could undergo dose escalation to 800 mg daily (400 mg twice daily) at the discretion of the investigator. Dose reductions were planned according to the occurrence and recurrence of grade 2/3 toxic effects. The maximum duration of treatment at 400 mg was planned to be 12 months even in the event of non-progression. However, dose escalation to 800 mg after a first progression was planned to last 6 months. Therefore, imatinib exposure could range from 12 to 18 months, depending on the moment the progression occurred (Figure 1).

Study investigations were carried out after approval by Lyon Ethics Committee (Comité Consultatif de Protection des Personnes se Prêtant à une Recherche Biomédicale, date of approval: 25 May 2004) and the French National Agency for Human Investigations (Agence Française de Sécurité Sanitaire des Produits de Santé, date of approval: 11 March 2004). Written informed consent was obtained from each patient.

### evaluation during study and response assessment

During the study, patients underwent clinical, hematological and biological evaluations on day 1, 15, 30, 60, 90, 180 and thereafter every 3 months.

Toxic effects were graded according to the National Cancer Institute—Common Toxicity Criteria (version 3.0).

Disease was assessed by comparing unidimensional tumor measurements (CT scan or MRI) on pre- and per-treatment imaging studies (at days 90 and 180 and thereafter every 3 months). Response was assessed according to RECIST [17]. An independent panel of third-party radiologists reviewed selected imaging studies to verify entry criteria (progressive disease) and all imaging was done during the study medication treatment period to ensure consistent unbiased application of RECIST.

### statistical analysis

The primary end point was non-progressive disease rate (including stable disease, complete and partial responses according to RECIST) at 3 months. The number of patients was calculated with a Simon optimal two-stage design [18]. The study required 35 assessable patients (18 at first step and 17 at second step) to decide with a 5% type I error and a 90% power whether the non-progressive disease proportion  $P$  was less than or equal to  $P_0 = 10\%$  or greater than or equal to  $P_1 = 30\%$ . According to the Simon design, imatinib could be considered as effective if at least seven non-progressive patients were observed at the end of the second stage (7/35). Planned accrual was 40 patients in order to allow for 10% of ineligible or untreated patients. Secondary end points included non-progressive disease rate at 12 months, response rate at 3 and 12 months, progression-free survival and overall survival. Progression-free survival was defined as the time from inclusion to the date of progression or death or censored at the last follow-up. Overall survival was defined as the time from inclusion to the date of death due to any cause. Survival functions were calculated by the method of Kaplan–Meier [19]. Median follow-up was calculated using a reverse Kaplan–Meier estimate [20]. Comparisons of survival curves used univariate Cox model. All analyses were conducted using the SAS software version 9.1.

## results

### patient characteristics

Forty patients were included from September 2004 to October 2005 in 15 French Sarcoma Group centers. The mean age was 41 (range 20–72 years). There were 28 women (70%) and 12 men (30%). WHO performance status (PS) was documented in 37 cases: PS = 0 in 27 cases (73%), PS = 1 in 9 cases (24%) and PS = 2 in 1 case (3%). The tumor was multifocal in four cases (10%). Most of primary locations were extra-abdominal: 24/44 (54%). The most frequent primary locations were the abdominal wall in seven cases (15%), the mesentery in nine cases (20%) and head and neck in four cases (9%). Familial adenomatous polyposis was documented in six patients (15%). The patients had previously undergone the following treatments: surgery (34 cases, 85%), hormonal therapy (18 cases, 45%), non-steroidal anti-inflammatory drugs (12 cases, 30%), radiotherapy (9 cases, 23% with a median dose of 50 Gy) and chemotherapy (8 cases, 20%). Thirty-three enrolled patients (85%) had symptomatic disease with radiological evidence for progressive disease. Six patients presented with locally advanced AF/DT requiring mutilating surgery.

### treatment

The treatment was administered at a dose of 400 mg/day in all patients. The median duration of treatment was 12 months (range 1–35). Dose escalation was up to 600 mg/day in one case (2%) and up to 800 mg/day in eight cases (20%). Dose

reduction was necessary in six patients treated with 400 mg/day and in two patients treated with 800 mg/day. Twenty patients (50%) stopped treatment before the planned 1-year period of treatment because of progression (nine cases), grade 3 extra-hematological toxicity (four cases), patient refusal (six cases) and investigator's decision (one case).

**efficacy**

The primary end point was the response rate at 3 months after central radiological review that was possible in 35 cases. We observed 1 complete response, 3 partial responses, 28 cases of stable disease and 3 of progressive disease. The complete response was observed in the chest wall and is maintained at the time of writing ( $\geq 62$  months). The three partial responses were observed in axillary (one case), abdominal (one case) and mesenteric (one case) presentations with a duration of 6,  $\geq 9$  and  $\geq 27$  months, respectively. The non-progression rate at 3 months was therefore 32/35 [91% {95% confidence interval (CI): 77–96}]. The non-progression rate at 3 months was 26/29 (89%) for patients with previous progressive disease and 6/6 (100%) for patients requiring mutilating surgery. The non-progression rates at 6, 9 and 12 months were, respectively, 28/35 (80%), 20/29 (69%) and 14/21 (67%) (Table 1). After dose escalation, a second progression occurred in 8 of 10 cases after a 12-month median time of transient stable disease (range 2–30). The progression-free survival rate at 12 months was significantly lower among patients previously treated with radiotherapy (56% versus 71%; see Table 2).

**toxic effects**

Imatinib therapy was well tolerated by this population and toxicity was manageable in most cases. No grade 4 toxicity was

seen. Grade 3 toxicity was seen in 18 patients (45%), including rash (four cases), abdominal pain (four cases), vomiting (three cases), nausea (two cases), diarrhea (two cases), myalgia (two cases, including one case with rhabdomyolysis) and asthenia (two cases). The toxic effects leading to premature dropout of treatment were as follows: pruritis associated with myalgia and rhabdomyolysis (one case), myalgia (one case), vomiting (one case) and increase in transaminases (one case). One case of a secondary cancer, a clear cell renal carcinoma, was diagnosed 9 months after starting imatinib treatment.

**survival**

The median progression-free survival time was 25 months, with a median follow-up time of 34 months. The 2-year progression-free and overall survival rates were 55% (95% CI 39–69) and 95% (95% CI 82–99), respectively. Two deaths occurred due to progressive mesenteric AF/DT (Figures 2 and 3).

**discussion**

This study, the largest published, provides data with long-term follow-up and includes patients with documented evidence of progressive disease before imatinib treatment.

This is of particular clinical interest as the treatment of recurrent AF/DT remains debatable [10], partly due to the variable nature of the disease course. Surgery, which is often iterative, could be avoided in some patients experiencing spontaneous regressions or long-lasting periods of stabilization [9, 21, 22]. Watchful waiting would seem to be a reasonable option if the tumor is in a non-life-threatening location. While radiotherapy remains an underused option [10, 23], numerous systemic treatments, including non-steroidal anti-inflammatory

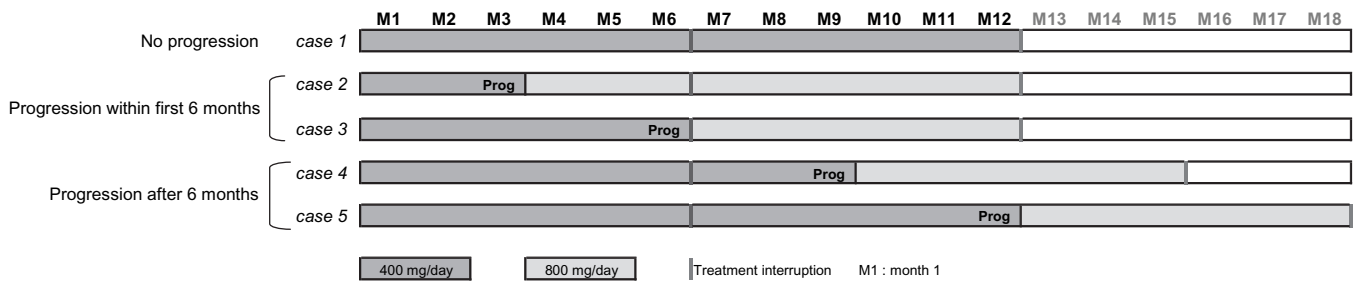


Figure 1. Treatment schedule

Table 1. Efficacy of imatinib (400 mg/day) for recurrent or progressive aggressive fibromatosis/desmoid tumors

		Assessment by investigator (n = 40)	Central blinded radiological review (n = 35)
Objective response at 3 months (RECIST)	Complete response	1 (2.5%)	1 (2.9%)
	Partial response	2 (5.0%)	3 (8.6%)
	Stable disease	30 (75.0%)	28 (80.0%)
	Progressive disease	5 (12.5%)	3 (8.6%)
	Not evaluable	2 (5.0%)	–
	Not centrally reviewed	–	5/40 (12.5%)
Non-progression rate	At 3 months	32/35 (91.5%)	At 12 months
	At 6 months	28/35 (80.0%)	14/21 (66.7%)
	At 12 months	14/21 (66.7%)	

**Table 2.** Predictive factors for progression-free survival under imatinib

Variables	Event free at 12 months (%)	Hazard ratio	95% CI	P
Gender				
Men	68			0.80
Women	67	0.80	0.47–2.65	
Age (years)				
<40	59			0.34
≥40	74	0.67	0.30–1.53	
Size (mm)				
<88	63			0.43
≥88	75	0.71	0.31–1.66	
Mesenteric AF/DT				
No	69			0.62
Yes	63	1.28	0.48–3.47	
Previous surgery				
No	83			0.21
Yes	65	2.53	0.59–10.8	
Previous radiotherapy				
No	71			<b>0.04</b>
Yes	56	2.46	1.03–5.90	
Previous treatment with non-steroidal anti-inflammatory drugs				
No	77			0.17
Yes	56	1.77	0.78–4.03	
Previous hormonal therapy				
No	71			0.14
Yes	58	1.89	0.81–4.38	
Previous chemotherapy				
No	72			0.18
Yes	50	1.89	0.74–4.81	

drugs, tamoxifen and chemotherapy, are often used but with inconsistent clinical benefit [10]. Imatinib is the best evaluated systemic treatment in this large armamentarium [15, 16, 22] and the results of three phase II trials are now available. Heinrich et al. reported a first phase II study evaluating 800 mg of imatinib daily in 19 patients with advanced AF/DT. They observed a long-lasting stable disease (>18 months) in 3 cases and a stable disease in 13 cases [15]. The same author reported a second multi-tumor phase II trial evaluating imatinib at a dose of 400 mg/day and including 20 patients with life-threatening AF/DT. The response rate was available in 17 cases, including two cases of partial responses and eight cases of stable disease [16]. In both studies, whatever the dose of imatinib, the median time to progression was 9 months.

The phase II study we report here confirms the efficacy of imatinib (400 mg/day) for patients with AF/DT failing local treatment. Three months after the beginning of treatment, we observed three confirmed partial responses and one confirmed complete response. The non-progression rates at 3, 6 and 12 months were, respectively, 90%, 80% and 67% in the per-protocol population. The median time to progression was 25 months. Excluding one case of severe rhabdomyolysis [21], the tolerability profile was similar to previously reported data [24, 25]. After the study period, a dose escalation to 800 mg/day provided one second complete response at 27 months.

Nevertheless, imatinib cannot be considered as standard treatment in relapsed AF/DT but rather as a new option that will need to be integrated to the large armamentarium. Lev et al. have recently reported that 10 of 13 patients treated with tamoxifen experienced partial response and 12 of 14 patients treated with chemotherapy experienced objective response (including one complete response) [10]. Chemotherapy (doxorubicin and dacarbazine) has been prospectively evaluated by Gega et al. [8]. In seven patients with familial adenomatous polyposis and deep unresectable intra-abdominal AF/DT, three complete and four partial responses were seen, with an impressive median time to progression of 74 months [8]. The optimal sequence of these various systemic treatments is unknown. However, it would now be useful to assess the precise risk/benefit profile of imatinib in randomized clinical trials even if such trials are complex to design and challenging to conduct. The following study designs could be considered: (i) A discontinuation design in patients experiencing long-lasting non-progressive disease could establish the benefit of prolonged treatment [20]. However, while this design is particularly appropriate to evaluate targeted therapies, it is probably only reasonable for patients with non-life-threatening AF/DT. In the present phase II, the protocol stipulated that imatinib was discontinued after 1 year and two third of our patients were free of progression at this time. (ii) A classical phase III comparative trial would actually be the best way to definitely establish the superiority of a new therapeutic option. Unfortunately, there is no consensual treatment of recurrent AF/DT that could constitute a standard of care. Moreover, most of AF/DT patients referred to comprehensive cancer centers have been heavily pretreated exhausting in most cases the classic therapeutic options. Another challenge lies in the calculation of the sample size to better estimate the median time to progression under the treatment chosen as standard of care. Unfortunately, available data are scarce in this setting [8, 10] and sample size calculation would undoubtedly require an international collaborative study due to the rarity of AF/DT.

Identifying which imatinib-sensitive tyrosine kinase is involved could represent a key step in further clinical research approaches. Immunoblotting and immunohistochemistry evaluations of four cases included in the Heinrich phase II trial evaluating 400 mg/day of imatinib showed a strong positivity for c-Kit and PDGFR- $\beta$  and negativity for PDGFR- $\alpha$ , tyrosine-phosphorylated-c-Kit, phosphorylated-PDGFR- $\alpha$  or - $\beta$  [15]. Moreover, no activating mutation was found in c-Kit, PDGFR- $\alpha$  or - $\beta$  [15]. In their phase II study evaluating 800 mg/day of imatinib, immunoblotting analyses showed strong expression of PDGFR- $\beta$  in all seven cases and absence of expression of c-Kit and PDGFR- $\alpha$  [16]. Similarly to their previous study, no activating mutations were found in c-Kit, PDGFR- $\alpha$  or - $\beta$  [15]. Mutations in APC were found in 16 of 19 cases but were not correlated to imatinib response [16]. In the same study, Heinrich et al. reported a correlation between median time to progression and plasma level of PDGFR- $\beta$  [16]. These data suggest that (i) overexpression of PDGFR- $\beta$  without activating mutation could be the target involved in the AF/DT response to imatinib and (ii) plasma level of PDGFR- $\beta$  could be used as a surrogate marker. These hypotheses need to be confirmed in a large cohort of patients [26]. We are currently performing

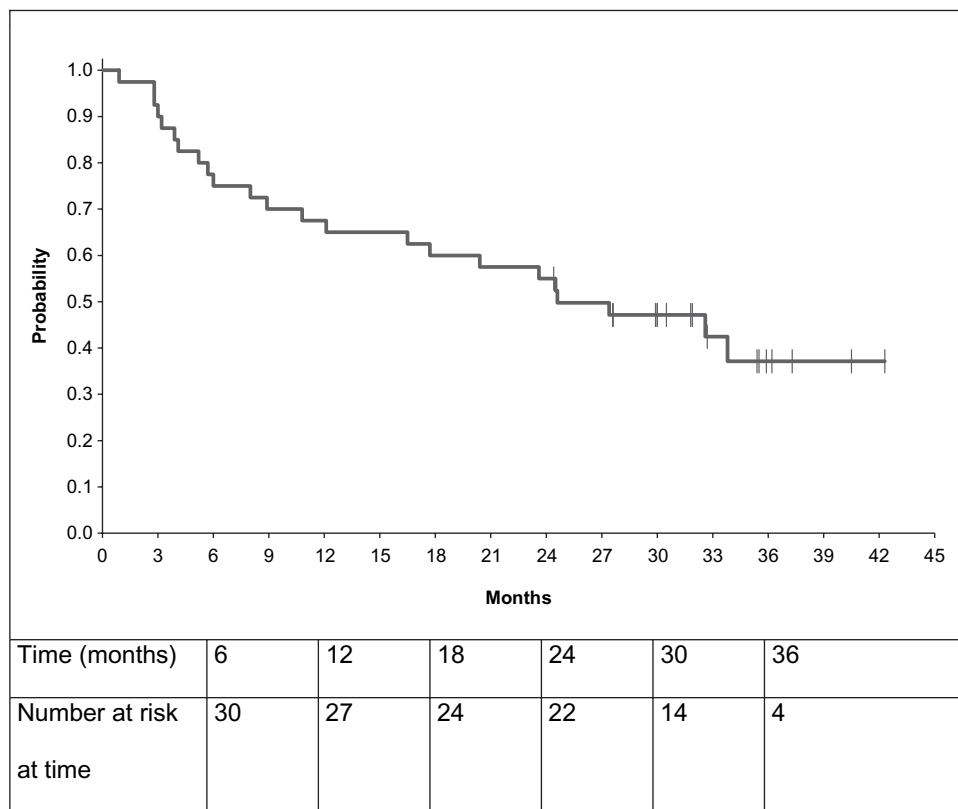


Figure 2. Progression-free survival curve.

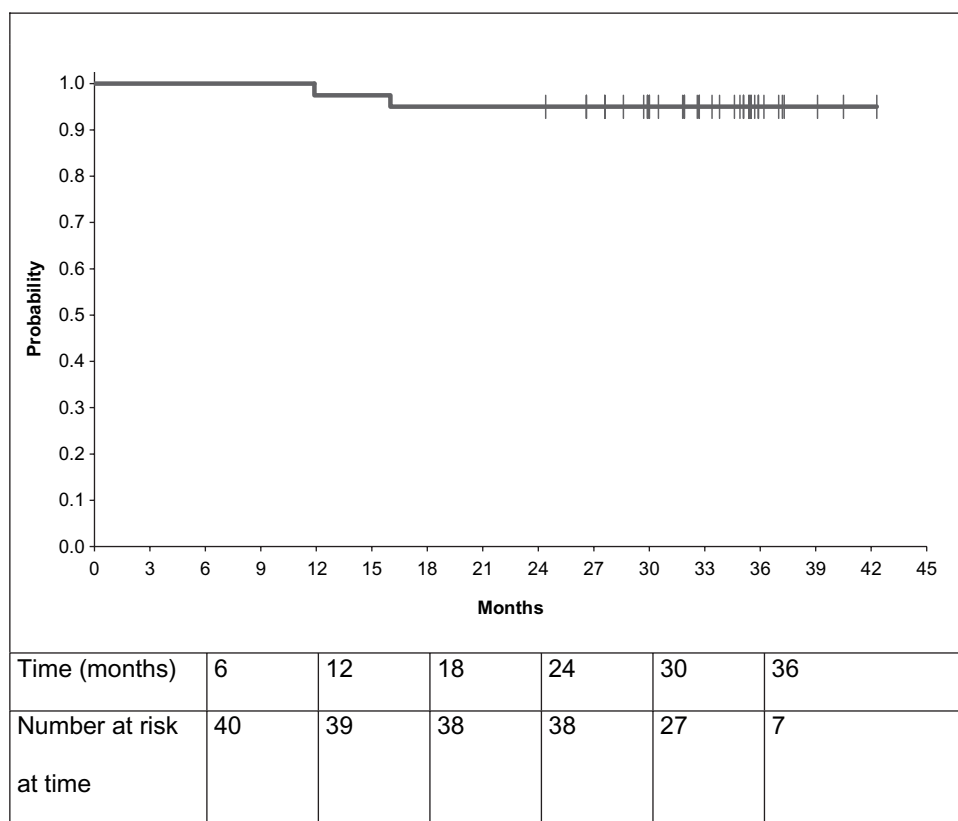


Figure 3. Overall survival curve.

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biological studies on plasma and tumor specimens collected during the study to better identify the tyrosine-kinase-dependent pathway implied in AF/DT.

To conclude, in spite of the challenges in providing conclusive data due to the very low incidence of this disease, this study supports previous findings that imatinib may be considered as an option in the treatment of recurrent AF/DT. Further clinical trials with translational studies are required to clearly identify the target and better characterize the position of this drug in the sequencing of treatment.

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