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Original article

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A double-blind placebo-controlled randomized phase 2 trial assessing the activity and safety of regorafenib in non-adipocytic patients previously treated with both chemotherapy and pazopanib

RUNNING TITLE: Regorafenib and pazopanib in sarcoma

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ABSTRACT

Background

Metastatic soft tissue sarcomas (STS) management remains an unmet medical need. We assessed the activity and safety of regorafenib in patients with metastatic non-adipocytic STS who were previously treated with both chemotherapy and pazopanib.

Patients and Methods

This double-blind, placebo-controlled, multicenter comparative randomized phase-II trial included patients with histologically proven advanced and inoperable STS. Patients receiving placebo were offered optional cross-over for centrally confirmed disease progression. Primary endpoint was centrally-reviewed RECIST-based progression-free survival (PFS), analyzed on the intent-to-treat dataset. In total, 24 events were required for 90% power, hazard ratio (HR)=0.33 (median PFS, 3.6 versus 1.2 months), and 1-sided $\alpha=0.1$. (ClinicalTrials.gov, NCT01900743).

Results

From December 2015 to October 2017, 37 patients were randomized; 18 to regorafenib and 19 to placebo. Thirteen patients assigned to placebo switched to regorafenib after progression. Median follow-up was 27.2 months (95%-confidence interval [CI]: 24.4–not reached). We observed a significant PFS-benefit of regorafenib compared to placebo (adjusted HR=0.33; 95%-CI, 0.15–0.74; $p=0.0007$ median PFS=2.1 versus 1.1 months, respectively), and a large and nearly significant OS-benefit despite the cross-over (adjusted HR=0.49; 95%-CI, 0.23–1.06; $p=0.007$; median OS=17.8 versus 8.2 months). Before cross-over, the most common grade-3 or higher adverse events were lymphopenia (5 versus 1, respectively), diarrhea (4 versus 0), dyspnea (3 versus 1), skin toxicity (3 versus 0), arterial hypertension (2 versus 0), and increased transaminases (2 versus 0).

Conclusion

The present study demonstrated a meaningful clinical anti-tumor activity with regorafenib in heavily pretreated patients with non-adipocytic STS.

KEYWORDS: Angiogenesis; pazopanib; soft tissue sarcoma; randomized phase 2 trial; regorafenib.

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Author Contributions

NP and MCLD designed and supervised the trial and wrote the paper; NP, MCLD, and JW analyzed the data and contributed to the trial design. All other authors supervised clinical patient management, reviewed and approved the paper.

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INTRODUCTION

Soft tissue sarcomas (STS) account for about 1% of adult cancers [1] and include four major histological groups (liposarcoma, leiomyosarcoma, synovial sarcoma and other sarcomas) [2]. At localized stage, surgery, often with (neo)-adjuvant radiation therapy for larger tumors, is the mainstay of treatment. The role of neoadjuvant chemotherapy is still debated. Nevertheless, at least 40% of patients develop recurrent or metastatic disease. For metastatic disease, for decades, the standard of care has been doxorubicin [3,4]. Beyond the doxorubicin (+/- ifosfamide)-based chemotherapy, most currently approved chemotherapy agents (pazopanib [5], trabectedin [6]) provide improvement in progression-free survival (PFS) that does not translate into an overall survival (OS) advantage. On the contrary, eribulin provides an OS improvement in liposarcoma (13.5 versus 11.5 months) with no impact on PFS [7]. However, with currently approved treatment options, the OS of patients at metastatic stage remains poor with a median of approximately 18 months in most recent studies [8]. Metastatic STS management still represents an unmet medical need.

Excluding some rare histological STS subtypes (such as alveolar soft part sarcoma) [9], immunotherapy does not seem to have achieved a breakthrough in STS management [10]. On the contrary, there is a growing body of evidence that large-spectrum tyrosine kinase inhibitors play a critical role in refractory-sarcoma management; regarding the positive results of a large international phase 3 trial pazopanib becomes one of the standards of care in doxorubicin-refractory non-adipocytic soft tissue sarcoma [5; 11]. In a large randomized phase 2 trial, regorafenib demonstrated also significant improvement of PFS in chemotherapy-refractory non-adipocytic sarcomas (3.7 versus 1.0 months) [12]. Furthermore, compared to placebo, regorafenib also improved PFS in chemotherapy-refractory osteosarcoma [13] (4.0 versus 1.0 months). In a large phase 3 trial, regorafenib demonstrated significant improvement of PFS in imatinib- and sunitinib-refractory GIST compared to placebo (4.8 versus 0.9 months). Although regorafenib is an active drug in

refractory sarcoma, especially in sunitinib-refractory GIST; however, its activity in patients with STS after exposure to pazopanib remains an open question.

To determine the activity of regorafenib in pazopanib-pretreated metastatic non-adipocytic STS, we conducted a double-blind, placebo-controlled comparative phase 2 trial assessing the efficacy and safety of regorafenib in this population.

PATIENTS AND METHOD

Study design and participants

REGOSARC was a double-blinded, placebo-controlled, multicenter, French and Austrian comparative randomized phase 2 trial assessing the activity and safety of regorafenib in several STS cohorts. We report here the results of the fifth cohort focused on pazopanib-pre-treated metastatic non-adipocytic STS. Patients were randomly assigned to either treatment with regorafenib or matched placebo. Treatment was administered until one of the following events occurred: confirmed progressive disease according to Response Evaluation Criteria in Solid Tumours (RECIST v.1.1) by central radiological review, unmanageable or unacceptable toxicity, death, patient's refusal of treatment, or investigator's opinion. Noteworthy, patients allocated to the placebo arm were offered to be treated with regorafenib if centrally confirmed disease progression occurred (according to RECIST 1.1).

The study was approved by the ethical and regulatory committee (French Ethical Committee ["Comité de Protection des Patients Nord-Ouest IV"; date of approval March 21, 2013], and Austrian Ethical Committee ["Ethik Kommission Medizinische Universität Wien; n° 1376/2013] and the French and Austrian Drug Agencies ("Agence Nationale de Sécurité du Médicament"; date of approval March 8, 2013). All study procedures were conducted in accordance with the International Conference on Harmonisation (ICH) Harmonized Tripartite Guideline on Good Clinical Practice. Signed informed consents

were obtained from all study participants before registration. This study is registered with ClinicalTrials.gov, NCT01900743.

Eligible patients were required to have histologically proven advanced and inoperable STS with intolerance or failure of doxorubicin-based chemotherapy, intolerance to or failure of pazopanib, and at least one unidimensionally or bidimensionally measurable lesion according to RECIST v.1.1, documentation of progression before study entry (according to the investigator judgement), ≥ 18 years old, an Eastern Cooperative Oncology Group (ECOG) performance status ≤ 1 , and with normal hematological (absolute neutrophil count $\geq 1,500/\text{mm}^3$; platelets $\geq 100,000/\text{mm}^3$; hemoglobin ≥ 9.0 g/dL; International Normalized Ratio ≤ 1.5 times of upper limit of normal [ULN]), normal renal function (normal spot urine analysis, serum creatinine $\leq 1.5 \times \text{ULN}$, and glomerular filtration rate (GFR) ≥ 30 ml/min/1.73 m²), normal liver function (aspartate transaminase and alanine transaminase $\leq 2.5 \times \text{ULN}$ ($\leq 5.0 \times \text{ULN}$ for patients with liver involvement of their cancer), bilirubin $\leq 1.5 \times \text{ULN}$ and alkaline phosphatase $\leq 2.5 \times \text{ULN}$ [$\leq 5 \times \text{ULN}$ with liver involvement of their cancer]), and normal pancreatic function (amylase or lipase $\leq 1.5 \times \text{ULN}$).

Main exclusion criteria included more than four lines of systemic treatment for metastatic STS (with a wash-out period of 3 weeks), liposarcoma, and some specific histological subtypes (GIST, soft tissue Ewing sarcoma, alveolar, or embryonal rhabdomyosarcoma), primary bone sarcoma, prior treatment with regorafenib, and contraindication to regorafenib (i.e. active cardiac disease, uncontrolled hypertension, arterial or venous thrombotic events ...etc). Central pathological review was done by the pathology experts at the "Réseau de Relecture en Pathologie des Sarcomes" in France. Grading was based on "Fédération Nationale des Centres de Lutte contre le Cancer » score (FNCLCC) [14].

Randomization and masking

Balanced 1:1 randomization was done centrally by Oscar Lambret Cancer Center

Research Unit Staff using computer-generated permuted blocks of four patients.

Randomization was stratified by country (France/Austria) and histological subtypes (leiomyosarcoma/synovial sarcoma/ other non-adipocytic sarcoma).

Patients, investigators, and radiologists in charge of the central radiological review were all blinded. Treatment allocation remained masked until confirmed disease progression.

Procedures

Patients were randomly assigned to receive oral regorafenib 160 mg (4 tablets of 40 mg once daily for 3 weeks on/1 week off) or placebo, plus best supportive care. Best supportive care included any method to preserve the comfort and dignity of the patients and excluded any disease-specific anti-neoplastic agents. Dose interruptions and/or dose reductions recommendations have been previously described [15]. Other procedures have been previously described [15]

Outcomes

The primary endpoint of this phase 2 trial was PFS, defined as the time between randomization and first evidence progression, according to RECIST 1.1 with central radiological review, or death from any cause. Secondary efficacy endpoints included: ratio of time to progression under regorafenib to time to progression under previous treatment (“growth modulation index”), best tumor response rate, and OS. Adverse events (AEs) were graded according to the NCI-CTC v.4.0.

Statistical analysis

PFS, OS, and time to progression were estimated by the Kaplan-Meier method from the date of randomization. Cox models were used to estimate the hazard ratios (HR) and 95%-confidence intervals (95%-CI) associated with the treatment effect (regorafenib versus placebo) after testing for the proportional hazards assumption with the scaled Schoenfeld residual method. Patients without tumor progression or death at the time of the final analysis were censored at their last date of follow-up. Study cut-off for all analyses was April 01, 2019. The primary analysis was based on a multivariable Cox model, adjusted for the following pre-specified factors: histology and number of prior lines of systemic treatment. A post-hoc analysis was performed adjusted also for the grading, to control for a possible confounding factor.

In this comparative trial, statistical assumptions were $PFS_0=1.2$ months (expected PFS with placebo), $PFS_1=3.6$ months (expected PFS with regorafenib), 1-sided $\alpha=0.1$ and $\beta=0.10$. Therefore, 24 confirmed disease progression were required, leading to a maximal sample size of 44 participants.

All efficacy endpoints (PFS, OS, best response, and growth modulation index) were analyzed in the intent-to-treat population (main analysis). Per protocol analysis was also performed, excluding patients with a major protocol deviation.

The occurrence of AEs (whatever the cause), was analyzed in the safety population, including all patients who had started the study treatment. For each type of AE, the worst grade observed across the entire treatment duration before cross-over were tabulated by treatment arm.

All tests were two-sided. Statistical analyses were conducted using STATA/SE version 13.1 statistical software (StataCorp, LP, College Station, TX).

Role of the funding source

Employees of the funder participated in the development of the trial design. The two academic groups (French Sarcoma group and Sarcoma Platform Austria) conducted data collection, monitoring, analysis, and interpretation. The first manuscript draft was initially written by the study-coordinator (NP) with independent medical writer assistance. All co-authors subsequently provided input and approval to submit for publication. The authors assume responsibility for the completeness and integrity of the data, the study fidelity to the protocol, and statistical analysis. The corresponding author had full access to all of the data and the final responsibility for the decision to submit for publication

RESULTS

From December 2015 to October 2017, 37 were randomized in this cohort in 11 French Sarcoma Centers (Table 1; Figure 1). The enrolment was prematurely closed (37 out of 44 planned patients, 84%) because the required number of events was reached (24 patients with centrally confirmed disease progression). One patient was not eligible because the primary tumor location was the bone (major deviation). Patient characteristics are summarized in Table 1. Most baseline characteristics were well balanced between treatment arms, nevertheless there was a nearly significant excess of grade 3 by FNCLCC

grading of STS in the placebo arm compared to the regorafenib arm (10/13, 77% versus 5/14, 36%, among the 27 informative patients, Fisher exact test, $p=0.054$, Table 1). All patients had been treated with chemotherapy and pazopanib. In both arms, the median number of prior treatment lines for metastatic disease was 3 (range, 2–6). All patients received the allocated treatment. At the cut-off date (April 1, 2019), disease progression was documented and centrally confirmed in all cases. All patients were included in the intent-to-treat population as well as in the safety population.

The median follow-up was 27.2 months (interquartile range, IQR: 25.7–30.9 months). At the time of the analysis, disease progression had been reported in all patients, and 29 patients had died; 12 and 17 in the placebo and regorafenib arm, respectively. The predefined primary objective of superiority was met since there was a significant PFS-benefit in the regorafenib arm compared to the placebo: adjusted-HR=0.33, 95%-CI: 0.15–0.74, $p=0.007$, with a median PFS of 2.1 months (95%-CI: 1.5–3.8) versus 1.1 month (95%-CI: 0.9–1.8) in the regorafenib and the placebo arm, respectively (Table 2, Figures 2A and 2C). There was also a nearly significant improvement in OS: adjusted HR=0.49, 95%-CI: 0.23–1.06, $p=0.07$, with median OS of 17.8 (95%-CI: 9.7–27.0) versus 8.2 (95%-CI: 6.0–16.0) months, respectively (Figure 2B). Results were relatively stable in the post-hoc analyses adjusted for histological grade. However point estimates and p-values have to be interpreted with caution as ten patients were excluded from this analysis due to missing data for the grade. Growth modulation index was found to be superior or equal to 1.3 in 22% of patients treated with regorafenib (4/18) and 5% of patients treated with placebo (1/19). No patient achieved an objective response under the study treatment.

At the time of the analysis, all patients had stopped the study treatment. The median duration of regorafenib treatment was 5.2 months (range, 0.6–19.4 months) and the median duration of placebo administration was 1.6 month (range, 0.6–10.0 months). In the regorafenib arm, the causes of permanent discontinuation of treatment were: disease

progression (15/18, 83%) and severe AE in 3 cases (3/18, 17%; including grade 3 arterial hypertension, gastric perforation, and grade 3 heart failure, 1 case each).

In the regorafenib arm, the median relative dose-intensity was 0.88 (range, 0.37–1.00).

The relative dose-intensity was below 0.8 in 7 patients (39%). In 8 out of 18 patients allocated to regorafenib arm, investigators maintained regorafenib beyond disease progression as defined by RECIST 1.1 and by blinded central radiological review. This was either because of the clinical benefit (N=3) or because the date of progression, defined at the central review, was earlier than the date of progression, defined by the treating physician (N=5) (Figure 2C). After progression, 11 of the 18 patients from the regorafenib arm received another systemic treatment (chemotherapy) versus 17 of the 19 patients of the placebo arm, including 13 who received regorafenib (post-progression cross-over).

Safety data were presented for the 37 enrolled patients. The maximum grade of AEs by patient and by arm were as follows: grade 1 in 1/19 (5%) and 1/18 (5%) patients assigned to placebo and regorafenib arm, respectively. Grade 2 in 11/19 (58%) and 0/18 patients assigned to placebo and regorafenib arm, respectively. Grade 3 in 5/19 (26%) and 12/18 (66%) patients assigned to placebo and regorafenib arm. Grade 4 in 1/19 (5%) and 5/18 (27%) patients assigned to placebo and regorafenib arm, respectively. Grade 5 in 1/19 (5%, general physical health deterioration leading to death, due to disease progression) and 0/18 patients assigned to placebo and regorafenib arm, respectively. The number of patients with serious AEs (irrespective of causality) was 5/19 (26%) and 13/18 (72%) in the placebo and regorafenib arm, respectively. Table 3 detailed all the reported AEs, classified or not as related to the study drug. The safety profile observed in the regorafenib arm was in accordance with prior findings. Before cross-over, the most common grade-3 or higher adverse events were lymphopenia (5 versus 1, respectively), diarrhea (4 versus 0), dyspnea (3 versus 1), skin toxicity (3 versus 0), arterial hypertension (2 versus 0), anemia (1 versus 0), and increased transaminases (2 versus 0).

DISCUSSION

In non-adipocytic STS patients pre-treated with pazopanib, regorafenib was an active drug improving the PFS (Table 1; Figure 2A). The treatment was manageable, without unexpected toxicity (Table 2), and with a median relative dose-intensity of 88%.

Our study showed regorafenib to be active after exposure to pazopanib in heavily pre-treated patients (PFS of 2.1 months versus 1.1 month). Pazopanib and regorafenib are both multi-kinase inhibitors; however, their targets differ, and this could explain the activity of regorafenib in patients previously exposed to pazopanib. For example, in cell-free assays, regorafenib seems to display more marked effects on vascular endothelial growth factor receptor 2 (IC₅₀ 4.2 nM versus 30 nM) and platelet-derived growth factor receptors- β (IC₅₀ 22 nM versus 84 nM) compared to pazopanib [16,17]. Nevertheless, the precise mechanism of action of both pazopanib and regorafenib in STS remain poorly understood. Furthermore, we did not have predictive factors to enable the selection of properly responding patients. From a pragmatical and clinical point of view, in the current trial, most of the patients exposed to pazopanib had discontinued pazopanib because of disease progression (32/37, 86%) and not because of toxicity (4/37, 11%). Regarding the median duration of prior exposure to pazopanib (6.3 months, range 1.0-21.7), most of the patients enrolled in this trial were truly resistant/refractory to pazopanib. Thus, regorafenib was not a “me-too” treatment in this clinical setting and provides clinical benefit in pazopanib-refractory/resistant sarcoma.

The apparent overall survival benefit must be interpreted with caution, especially after the failure of Olaratumab phase 3 trial [18] whereas randomized phase 3 trial was so promising [19]. To our knowledge, until now, there were only 2 clinical trials conducted in such population, associated with statistically significant improvement in OS. In a large phase 3 trial, Schöffski et al. demonstrated significant improvement in OS in liposarcoma

or leiomyosarcoma treated with eribulin (n=228) compared to those treated with dacarbazine (n=224), with 13.5 months versus 11.5 months, respectively (HR=0.77, p=0.0169). In planned sub-group analysis, this advantage was observed in liposarcoma (HR=0.51, [0.35–0.75]) and not in leiomyosarcoma (HR=0.93, [0.71 –1.20]). In this trial, eribulin was not associated with PFS improvement compared to dacarbazine, with 2.6 and 2.6 months, respectively (HR=0.88, [0.71–1.09], p=0.23) [7]. In a randomized phase 2 trial, Garcia-del-Muro et al. compared the activity of gemcitabine-dacarbazine (n=58) with gemcitabine alone (n=54). Median PFS was 4.2 versus 2.0 months (HR, 0.58; 95%-CI, 0.39–0.86; p=0.005) while median OS was 16.8 versus 8.2 months (HR, 0.56; 95%-CI, 0.36–0.90; p=0.014) [20]. But this finding was not confirmed later by appropriate superiority-designed phase 3 trial. In the current trial, despite optional cross-over, we found that there was a non-statistically significant but clinically relevant improvement in OS: 8.2 versus 17.8 months (p=0.07). The current trial was not designed to demonstrate OS benefit (Table 1; Figure 2B), since optional cross-over was allowed and the sample size was limited. Therefore, this finding must be interpreted with caution. OS advantage must be confirmed by an appropriate trial.

This study had several limitations. We observed that 4 out of 37 patients were enrolled in the trial whereas eligibility criteria were not met. However only one case was reviewed as a major protocol deviation (patient with a bone sarcoma, excluded for the per protocol analysis).. Another limitation is that we observed a nearly significant imbalance of the histological grade distribution between randomized groups; however, results were relatively stable in the post-hoc multivariable analyses controlling for this possible confounding factor. Unfortunately, the grade was missing for 10 patients reducing the number of patients in the post-hoc multivariable analysis (Table 2). Lastly, we did not record quality of life in this study, so we are not able to score the magnitude of clinical benefit as recommended by ESMO [21]. The sample size was limited but appropriate to

formally analyze the primary endpoint (PFS). The median PFS with regorafenib was about 2.1 months, which appeared disappointing. However, the study population was heavily pre-treated and most of the patients had already received the approved drugs for STS management (pazopanib, doxorubicin, trabectedin, Ifosfamide, and dacarbazine in 100%, 97%, 54%, 38%, and 35% of cases, respectively).

Regorafenib warrants formal superiority phase 3 trial in both chemotherapy and pazopanib-refractory non-adipocytic soft tissue sarcoma. However, to the best of our knowledge, this confirmatory trial is not planned yet.

Conflict of interests

NP and JYB received research funding from Bayer HealthCare SA. ALC declares personal fees from Novartis, PharmaMar, Pfizer, Lilly, and Ariad, outside the submitted work. OM reports personal fees from Roche, personal fees from Pfizer, personal fees from Novartis, personal fees from Bayer, personal fees from Amgen, personal fees from Astra-Zeneca, personal fees from BMS, outside the submitted work. All other authors declare that they have no conflicts of interest.

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Table 1 – Baseline characteristics and efficacy endpoints

Characteristics	Placebo (N=19)	Regorafenib (N=18)
Baseline characteristics		
Gender		
Men	5 (26%)	4 (22%)
Women	14 (74%)	14 (78%)
Age (in years)		
Median	60	61
Extreme values	36-76	41-71
ECOG-PS		
0	8 (42%)	9 (50%)
1	11 (58%)	8 (44%)
Missing		1 (6%)
Histological subtypes		
Leiomyosarcoma	11 (58%)	13 (72%)
Synovial sarcoma	1 (5%)	0
Other sarcomas, including	7 (37%)	5 (28%)
- Undifferentiated pleomorphic sarcoma	3 (16%)	3 (17%)
- Angiosarcoma	3 (16%)	0
- Solitary fibrous tumor	0	2 (11%)
- Spindle cell osseous sarcoma ^(a)	1 (5%)	0
FNCLCC Grading		
- Grade 1	0	2 (14%)
- Grade 2	3 (23%)	7 (50%)
- Grade 3	10 (77%)	5 (36%)
- Missing data	6	4
Time interval between diagnosis and inclusion (months)		
Median	39.8	44.0
Extreme values	19.4-151.9	13.2-308.2
Primary sites		
- Soft tissue	13 (68%)	10 (56%)
- Uterus	6 (32%)	7 (39%)
- Bone	0	1 (5%)
Metastasis		
- Lung	13 (68%)	16 (88%)
- Liver	9 (47%)	8 (44%)
- Bone	4 (21%)	6 (33%)
- Peritoneum	2 (10%)	6 (33%)
Prior lines		
- 2	2 (10%)	7 (39%)
- 3	8 (42%)	6 (33%)
- 4	7 (37%)	4 (22%)
- 5 ^(b)	1 (5%)	1 (5%)
- 6 ^(b)	1 (5%)	0
Previous systemic treatments (excluding pazopanib)		
- Doxorubicin	19 (100%)	17 (94%)
- Ifosfamide	11 (58%)	3 (16%)
- Trabectedin	11 (58%)	9 (50%)
- Dacarbazine	7 (37%)	6 (33%)
- Gemcitabine	9 (48%)	11 (61%)
- Taxane	2 (10%)	2 (11%)
- Cyclophosphamide	3 (15%)	1 (5%)
- Other	0	2 (11%)
Prior exposure to pazopanib		
Yes	19 (100%)	18 (100%)
Pazopanib as last line prior to enrollment	10 (52%)	11 (61%)
Duration in months: Median (Range)	8.2 (1.0-21.7)	5.8 (1.3-19.9)
Reason for pazopanib discontinuation		
- Physician decision	1 (5%)	0
- Toxicity	1 (5%)	3 (17%)
- Progression	17 (90%)	15 (83%)

(a) The patient with a spindle cell osseous sarcoma was classified as a major deviation to eligibility criteria. This patient is included in the main analysis (intent-to-treat) but is excluded from the per protocol analysis

(b) Three patients had received more than 4 prior lines of treatment. These deviations to eligibility criteria were classified as minor deviations. These patients are included in all analyses.

Table 2 – Efficacy endpoints

Endpoints	Placebo Arm <i>N=19</i>		Regorafenib Arm <i>N=18</i>		P-value
Overall survival (OS)					
Events	17		12		
Median OS (months) (95%CI)	8.2	(6.0 – 16.0)	17.8	(9.7 – 27.0)	
3 months-OS rate (95%CI)	89%	(64 – 97)	88%	(61 – 97)	
6 months-OS rate (95%CI)	79%	(53 – 91)	83%	(55 – 94)	
12 months- OS rate (95%CI)	37%	(16 – 57)	65%	(38 – 82)	
HR (95%CI)-ITT	1 (Ref)		0.49 (95%CI: 0.23 – 1.03)		0.058
Adjusted HR (IC95%)-ITT ^(a)	1 (Ref)		0.49 (95%CI: 0.23 – 1.06)		0.07
Post-hoc Adjusted HR (95%CI)-ITT ^(c)	1 (Ref)		0.37 (95%CI: 0.11 – 1.17)		0.09
HR (95%CI)-Per protocol ^(b)	1 (Ref)		0.48 (95%CI: 0.22 – 1.03)		0.058
Progression-free survival (PFS)					
Events	19		18		
Median PFS (months) (95%CI)	1.1 m	(0.9 – 1.8)	2.1	(1.5 – 3.8)	
3 months-PFS rate (95%CI)	5%	(0 – 21)	33%	(14 – 54)	
6 months-PFS rate (95%CI)	-	-	22%	(7 – 43)	
12 months-PFS rate (95%CI)	-	-	6%	(0 – 22)	
Unadjusted HR (95%CI)-ITT	1 (Ref)		0.31 (95%CI: 0.15 – 0.67)		0.0023
Adjusted HR (95%CI)-ITT ^(a)	1 (Ref)		0.33 (95%CI: 0.15 – 0.74)		0.007
Post-hoc Adjusted HR (IC95%)-ITT ^(c)	1 (Ref)		0.39 (95%CI: 0.12 – 1.28)		0.12
HR (95%CI)- Per protocol ^(b)	1 (Ref)		0.32 (95%CI: 0.15 – 0.69)		0.0031
Best responses (according to the treating center evaluation)					
Complete response	0	0%	0	0%	
Partial response	0	0%	0	0%	
Stable disease	8	42%	13	72%	
Progressive disease ^(d)	11	58%	5	28%	
Growth Modulation Index, GMI patients with GMI >1.33 (%)	1	5%	4	22%	-

OS: overall survival

CI: confidence interval HR: Hazard ratio

ITT: Intent to treat

PFS: progression-free survival

- (a) Primary analysis: Model adjusted for histology (Leiomyosarcoma vs. other sarcoma, one patient with synovial sarcoma was considered as other sarcoma for this analysis), number of prior lines of systemic treatment (<4 vs. 4+)
- (b) One patient from the placebo arm was excluded in per protocol analysis (patient with an osseous spindle cell sarcoma). Results of the per protocol analysis were similar to intent to treat
- (c) Post-hoc analysis: Model adjusted for histology (Leiomyosarcoma vs. other sarcoma, one patient with synovial sarcoma was considered as other sarcoma for this analysis), number of prior lines of systemic treatment (<4 vs. 4+) and histological grade (1 and 2 vs 3). Ten cases are excluded in this analysis due to missing data for the grade: six in placebo arm and four in regorafenib arm.
- (d) Including one patient who died of progression before the first tumor evaluation. His best response was considered as progression disease although no RECIST evaluation could be performed.

Table 3 – Adverse events per arm before cross-over (classified as related or not to study treatment)

Adverse Event Category	Placebo arm N=19		Regorafenib arm N=18	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	19 (100%)	3 (16%)	17 (94%)	6 (33%)
Anemia	19 (100%)	0	17 (94%)	1 (6%)
Leucopenia	19 (100%)	0	17 (94%)	0
Lymphopenia	16 (84%)	1 (5%)	15 (83%)	5 (28%)
Neutropenia	1 (5%)	0	3 (17%)	1 (6%)
Thrombocytopenia	3 (16%)	0	6 (33%)	0
Other ⁽¹⁾	2 (11%)	2 (11%)	0	0
Cardiac disorders	2 (11%)	1 (5%)	3 (17%)	1 (6%)
Cardiac failure	0	0	1 (6%)	1 (6%)
Chest pain	2 (11%)	1 (5%)	2 (11%)	0
Ear and labyrinth disorders	0	0	3 (17%)	0
Dizziness	0	0	2 (11%)	0
Hearing impairment	0	0	2 (11%)	0
Endocrine disorders	2 (11%)	0	1 (6%)	0
Hyperparathyroidism	1 (5%)	0	0	0
Hypothyroidism	1 (5%)	0	1 (6%)	0
Eye disorders	0	0	1 (6%)	0
Visual impairment	0	0	1 (6%)	0
Gastrointestinal disorders	10 (53%)	2 (11%)	15 (83%)	6 (33%)
Abdominal pain	5 (26%)	0	6 (33%)	0
Diarrhoea	5 (26%)	0	10 (56%)	4 (22%)
Constipation	3 (16%)	1 (5%)	5 (28%)	0
Nausea	1 (5%)	1 (5%)	3 (17%)	0
Vomiting	4 (21%)	0	6 (33%)	0
Stomatitis	4 (21%)	0	8 (44%)	0
Dysgeusia	0	0	2 (11%)	0
Dyspepsia	3 (16%)	0	3 (17%)	0
Dysphagia	0	0	2 (11%)	0
Ascites	1 (5%)	0	0	0
Gastric perforation	0	0	1 (6%)	1 (6%)
Other ⁽²⁾	0	0	2 (11%)	1 (6%)
General disorders	11 (58%)	3 (16%)	18 (100%)	4 (22%)
Asthenia	9 (47%)	0	13 (72%)	1 (6%)
Anorexia	4 (21%)	0	8 (44%)	0
Weight loss	0	0	4 (22%)	1 (6%)
General condition deterioration	2 (11%)	2 (11%)	1 (6%)	1 (6%)
Pain	5 (26%)	1 (5%)	12 (67%)	2 (11%)
Fever	0	0	3 (17%)	1 (6%)
Oedema peripheral	1 (5%)	0	1 (6%)	0
Other ⁽³⁾	1 (5%)	0	0	0
Hepatobiliary disorders	0	0	2 (11%)	1 (6%)
Cholecystitis	0	0	1 (6%)	0
Jaundice	0	0	1 (6%)	1 (6%)
Infections ⁽⁴⁾	4 (21%)	0	7 (39%)	2 (11%)

Adverse Event Category	Placebo arm N=19		Regorafenib arm N=18	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	n (%)	n (%)	n (%)	n (%)
Injury	1 (5%)	1 (5%)	2 (11%)	0
Investigation / metabolism	19 (100%)	5 (26%)	17 (94%)	8 (44%)
Transaminases increased	8 (42%)	0	8 (44%)	2 (11%)
Alkaline phosphatase increased	14 (74%)	0	8 (44%)	0
Gamma-glutamyltransferase increased	2 (11%)	2 (11%)	0	0
Hyperbilirubinemia	1 (5%)	0	6 (33%)	1 (6%)
Amylase increased	0	0	1 (6%)	0
Lipase increased	0	0	5 (28%)	2 (11%)
Blood creatinine increased	6 (32%)	0	5 (28%)	0
Hypoalbuminaemia	5 (26%)	0	9 (50%)	0
Triglycerides increased	0	0	2 (11%)	1 (6%)
Hypoglycaemia	0	0	2 (11%)	1 (6%)
Hyperglycaemia	5 (26%)	0	10 (56%)	1 (6%)
Hyponatraemia	6 (32%)	1 (5%)	5 (28%)	0
Hypokalaemia	2 (11%)	0	4 (22%)	1 (6%)
Hyperkalaemia	4 (21%)	1 (5%)	5 (28%)	2 (11%)
Hypocalcaemia	2 (11%)	0	4 (22%)	0
Hypercalcaemia	4 (21%)	1 (5%)	2 (11%)	0
Hypophosphataemia	1 (5%)	1 (5%)	6 (33%)	1 (6%)
Musculoskeletal and connective tissue disorders	6 (32%)	0	7 (39%)	0
Musculoskeletal pain ⁽⁵⁾	6 (32%)	0	7 (39%)	0
Nervous system disorders ⁽⁶⁾	1 (5%)	0	4 (22%)	1 (6%)
Psychiatric disorders ⁽⁷⁾	4 (21%)	0	5 (28%)	0
Renal and urinary disorders	2 (11%)	0	4 (22%)	0
Proteinuria	2 (11%)	0	3 (17%)	0
Chromaturia	0	0	1 (6%)	0
Reproductive system and breast disorders	0	0	1 (6%)	0
Vaginal mucositis	0	0	1 (6%)	0
Respiratory, thoracic and mediastinal disorders	5 (26%)	1 (5%)	11 (61%)	3 (17%)
Dyspnoea	4 (21%)	1 (5%)	7 (39%)	3 (17%)
Dysphonia	0	0	4 (22%)	0
Pulmonary hypertension	1 (5%)	0	0	0
Other ⁽⁸⁾	1 (5%)	0	5 (28%)	1 (6%)
Skin and subcutaneous tissue disorders	3 (16%)	0	10 (56%)	3 (17%)
Hand foot skin reaction	1 (5%)	0	7 (39%)	2 (11%)
Rash	1 (5%)	0	4 (22%)	1 (6%)
Alopecia	0	0	3 (17%)	0
Other ⁽⁹⁾	3 (16%)	0	6 (33%)	1 (6%)
Vascular disorders	4 (21%)	0	10 (56%)	3 (17%)
Arterial hypertension	0	0	6 (33%)	2 (11%)
Haemorrhage ⁽¹⁰⁾	3 (16%)	0	8 (44%)	0
Pulmonary embolism	0	0	1 (6%)	1 (6%)
Other ⁽¹¹⁾	1 (5%)	0	0	0

- (1) "Blood and lymphatic system disorders. Other" include Leukocytosis, Platelet count increase.
- (2) "Gastrointestinal disorders. Other" include Haemorrhoids, Intestinal disorder
- (3) "General disorders. Other" include Discomfort
- (4) "Infections" include Bronchopulmonary infection, Catheter-related infection, Viral gastroenteritis, Flu syndrome, Upper respiratory tract infection, Urinary tract infection
- (5) "Musculoskeletal pain" include Arthralgia, Arthromyalgia, Back pain, Myalgia, Muscle spasms, Arthrosis
- (6) "Nervous system disorders" include Encephalopathy, Memory impairment, Peripheral sensory neuropathy, Somnolence
- (7) "Psychiatric disorders" include Anxiety, Depression, Insomnia, Mental disorders
- (8) "Respiratory, thoracic and mediastinal disorders. Other" include Cough, Pleural effusion
- (9) "Skin and subcutaneous tissue disorders. Other" include Acne, Dry skin, Hair colour changes, Pruritus, Radiodermatitis, Desquamation, Urticaria.
- (10) "Hemorrhage" include Epistaxis, Haematuria, Hemoptysis, Metrorrhagia, Rectal hemorrhage, Hematoma, Ecchymosis
- (11) "Vascular disorders. Other" include Superior vena cava syndrome

Figures legends

Figure 1 – Patients disposition.

Figure 2

Figure 2A – Progression-free survival

Kaplan-Meier estimates of the probability of progression in all randomly assigned patients to treatment with regorafenib or placebo.

Figure 2B - Overall survival

Kaplan-Meier estimates of the probability of death in all randomly assigned patients to treatment with regorafenib or placebo.

Figure 2C- Swimmer Plot

Swimmer plot with each bar representing the survival time from the start of this study for one patient. This graph indicates, for each patient, the central review progression, the duration treatment in this regorafenib arm, the crossover in the placebo arm and the patient's condition (dead or alive). The orange bar represents the leiomyosarcoma (LMS) and the blue bar represents the other sarcoma (Oth-S). The only patient with a synovial sarcoma was considered as other sarcoma for this graphical representation.



