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ORIGINAL RESEARCH

Regorafenib in patients with relapsed advanced or metastatic chordoma: results of a non-comparative, randomised, double-blind, placebo-controlled, multicentre phase II study

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Background: REGOBONE multicohort study explored the efficacy and safety of regorafenib for patients with advanced bone sarcomas; this report details the cohort of patients with relapsed advanced or metastatic chordoma.

Methods: Patients with relapsed chordoma progressing despite 0-2 prior lines of systemic therapy, were randomised (2 : 1) to receive regorafenib (160 mg/day, 21/28 days) or placebo. Patients on placebo could cross over to receive regorafenib after centrally-confirmed progression. The primary endpoint was the progression-free rate at 6 months (PFR-6) (by RECIST 1.1). With one-sided α of 0.05, and 80% power, at least 10/24 progression-free patients at 6 months (PFR-6) were needed for success.

Results: From March 2016 to February 2020, 27 patients were enrolled. A total of 23 patients were assessable for efficacy: 7 on placebo, 16 on regorafenib, 16 were men, median age was 66 (32-85) years. At 6 months, in the regorafenib arm, 1 patient was not assessable, 6/14 were non-progressive (PFR-6: 42.9%; one-sided 95% CI = 20.6) 3/14 discontinued regorafenib due to toxicity; and in the placebo arm, 2/5 patients were non-progressive (PFR-6: 40.0%; one-sided 95% CI = 7.6), 2 were non-assessable. Median progression-free survival was 8.2 months (95% CI 4.5-12.9 months) on regorafenib and 10.1 months (95% CI 0.8 months-non evaluable [NE]) on placebo. Median overall survival rates were 28.3 months (95% CI 14.8 months-NE) on regorafenib but not reached in placebo arm. Four placebo patients crossed over to receive regorafenib after centrally-confirmed progression. The most common grade $\geq$3 regorafenib-related adverse events were hand-foot skin reaction (22%), hypertension (22%), pain (22%), and diarrhoea (17%), with no toxic death.

Conclusion: This study failed to show any signal of benefit for regorafenib in patients with advanced/metastatic recurrent chordoma.

Key words: recurrent/metastatic chordoma, regorafenib

INTRODUCTION

Chordoma is a rare bone tumour arising from the persistent notochordal elements. The disease develops in the spine (sacrum 50% and bones from the mobile spine 20%) and in the skull base (30%).[1] It is an indolent malignancy that progresses slowly, but exhibits strong local aggressiveness and often develops as huge masses that compress vital nerves and blood vessels.[2] Local relapse has extremely poor survival rates and local control is rarely achievable. Possible salvage treatment can include surgery and/or radiation therapy, and/or radiofrequency ablations (RFA), and/or

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systemic treatment, balancing morbidity, quality of life and expected disease control.[3] Approximately 30% of patients with chordoma will develop metastases, usually late in the natural history of the disease, and mostly after local recurrence.[1] For oligometastatic disease, surgery, RFA or stereotactic radiation therapy can be considered in selected cases. Metastatic patients have a poor prognosis and no standard systemic treatment is universally accepted. Chemotherapy is inactive and is generally not recommended.[1]

Early clinical data have suggested some potential activity of multikinase inhibitors with anti-vascular endothelial growth factor (VEGF) activity, such as sorafenib and sunitinib, in patients with bone sarcomas.[4,5] Regorafenib is an orally bioavailable multikinase inhibitor targeting tumour cells, vasculature, and the tumour microenvironment. It blocks the activity of multiple protein kinases, including those involved in the regulation of tumour angiogenesis (VEGFR-1, -2, and -3, and TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, and BRAFV600E), and the tumour microenvironment [platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR)].[6] Regorafenib has demonstrated antitumour activity in pretreated metastatic non-adipocytic soft tissue sarcoma,[7] a population for which pazopanib has also demonstrated activity in prolonging progression-free survival (PFS).[8] The French Sarcoma Group designed this investigator-initiated clinical trial, called REGOBONE, to explore the activity of regorafenib in progressive advanced/metastatic chordoma as well as other primary bone sarcomas tested in separate parallel cohorts. Compared with placebo, regorafenib also improved PFS in progressive chemotherapy-refractory metastatic osteosarcoma (4.0 versus 1.0 months) in the REGOBONE osteosarcoma cohort[9]; the subsequent chondrosarcoma cohort reported some antitumour acitivity.[10] The objective of the present study was to explore the potential antitumour activity of regorafenib in patients with progressive advanced, recurrent and/or metastatic disease.

PATIENTS AND METHODS

Study design and participants

REGOBONE, an investigator-initiated signal-seeking trial, is a basket study of five parallel independent cohorts of different metastatic bone sarcoma histopathological subtypes. Parallel cohorts assessed the activity and safety of regorafenib or placebo, using a randomised, non-comparative, double-blind, placebo-controlled phase II trial design. We present here the results of the chordoma cohort.

The study was approved by an ethical and regulatory committee (French Ethical Committee, Comité de Protection des Personnes Sud Méditerrannée 1, approved on 26 March 2014). All patients provided written informed consent before enrolment. The trial is registered in the European Clinical Trials Register database (EudraCT N°: 2013-003910-42) and at ClinicalTrials.gov (NCT02389244). To participate in the chordoma cohort, eligible patients were required to have histological diagnosis of chordoma, and objective disease progression within 6 months before study entry measured by RECIST v1.1, both confirmed by a centralised review, as well as measurable disease by RECIST v1.1 not amenable to curative intent, and previously treated with 0-2 prior systemic regimens (either chemotherapy or targeted therapy) for relapsed/recurrent disease. Central radiological review was done by an independent radiologist. The complete list of other eligibility criteria, along with the protocol, are described and available on line (http://www.unicancer.fr/protocole-regobone). Patients were randomly assigned (2 : 1) to receive either oral regorafenib or matched placebo. After centrally-confirmed disease progression (according to RECIST 1.1), patients initially randomised to placebo were offered cross over to open-label regorafenib. Central pathological review was done by an expert bone sarcoma pathologist from the 'Réseau de Relecture en Pathologie des Sarcomes Osseux' in France.[11]

Registration and randomisation (2 : 1) were centralised via a web-based system (IWRS) using permuted blocks design provided by an independent partner (ATLANSAT). Patients, pharmacists, investigators, radiologist in charge of central radiological review, site study teams, and sponsor were all blinded to the allocated treatment. Treatment allocation was masked until centrally-confirmed disease progression. Patients were randomly assigned to receive best supportive care combined with either regorafenib 160 mg orally (four tablets of 40 mg once daily, 3 weeks on and 1 week off), or matched placebo tablets. Best supportive care included any method to preserve the comfort and dignity of the patients and excluded any disease-specific antineoplastic agents. Dose interruptions and/or dose reduction recommendations have been previously described.[9]

The primary endpoint was the progression-free rate at 6 months (PFR-6), defined as the proportion of patients without disease progression at 6 months, after confirmation by central radiological review according to RECIST 1.1. Secondary endpoints included: PFS per modified RECIST v1.1, objective response rate, overall survival (OS), duration of overall response, and safety/tolerability. PFS was measured from the date of randomisation until the date of confirmed radiological progression or death from any cause, whichever occurred first.

For patients who were event free at the time of the analysis, PFS was censored at the time of the final adequate tumour assessment. Centrally assessed progression was used for the analysis. OS was defined as the time from randomisation to the date of death from any cause and censored at the date of final contact for patients alive. Objective response to treatment corresponded to proportion of patients with complete or partial response as best response from randomisation. Duration of response, which applies only to responders, was measured from the time of first documented response (complete response or partial

response) until the first documented disease progression or death. Patients who died from causes other than progression were censored at the date of death.

Statistical analysis

When the REGOBONE study was designed there was a paucity of published data regarding PFS of patients with metastatic/recurrent chordoma following failure of prior targeted therapy or chemotherapy for progressing relapsed disease. Therefore, we chose PFR-6 as the primary endpoint. Using a similar design as for the other REGOBONE cohorts, we calculated the sample size by A'Hern single stage design for phase II trials similar to a Fleming phase II design but assuming an exact binomial distribution.[12] The sample size for chordomas cohort was calculated as follows: a lower limit of 40% progression-free patients or less would mean that the regorafenib did not warrant further investigation in this setting. A sample size of 23 patients provided 80% power to reject the null hypothesis with a one-sided, type 1 error of 5%, with 10 successful patients being the lower cut-off. To account for a possible non-assessable patient rate of 5%, an additional patient was required in the experimental group (total 24 patients). A sample size of eight assessable patients was required in the placebo arm. No comparative hypothesis was formulated and no statistical comparison between the control and experimental arms was planned.

Thereby, the primary endpoint and all other efficacy outcomes were analysed by modified intention to treat, including all patients who initiated blinded study drug treatment, with no major protocol violation. Major protocol violations were defined as deviations that could potentially affect efficacy analysis, including patients not meeting important inclusion or exclusion criteria.

The occurrence of adverse events was analysed in the safety population, defined as all confirmed chordoma patients who received at least one dose of the intended treatment. The severity of the adverse event was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 4.0. The percentage of progression-free patients at 8 weeks was calculated in each arm with their respective 95% confidence interval (CI). PFS and OS were estimated using the Kaplan—Meier method. We used SAS (version 9.4) for all analyses.

RESULTS

From March 2016 to March 2020, 27 patients were accrued and randomised in this cohort (Figure 1). Four patients were excluded from efficacy analysis; three in the regorafenib arm and one in the placebo arm. One was excluded because the diagnosis of chordoma was not histologically confirmed by central review, two were non-progressive at inclusion, and one withdrew consent before starting treatment. In total, 23 patients with histologically confirmed progressive advanced or metastatic chordoma constitute the population for efficacy analysis: 16 patients were initially randomised to regorafenib and 7 to placebo. The patient without confirmed chordoma histology and the patient who withdrew consent before starting treatment are also removed from the safety population ($n = 25$).

As described in Table 1, the baseline characteristics of 23 chordoma patients were well balanced between the two arms except for a small imbalance in age, and in the higher number of patients with metastatic disease in the regorafenib arm, but with patients with a better PS at study entry.

As expected in chordoma, the majority of patients had unresectable recurrent disease, with mainly prior surgery and or radiation therapy. Approximately 30% of patients in both arms received any previous systemic therapy. Imatinib was the only systemic therapy ever given to the seven patients with any history of systemic treatment before study entry; no patient received any other systemic treatment before study entry.

At 6 months after study start for all participants, the primary study end-point (progression-free rate at 6 months with RECIST 1.1, PFR-6) was not met at the planned analysis: 6/14 patients were progression-free at 6 months on regorafenib (40.0%; 95% CI = 20.6) but 10 would have been required for a 'success', 5 patients progressed per RECIST, and 3 patients discontinued regorafenib for toxicity (one due to uncontrolled hypertension, one for epigastralgia, and one for gastrointestinal bleeding). Concerning these three patients, two progressed within 6 months after stopping regorafenib and the last one started a new treatment 5 months after stopping regorafenib and was alive 10 months after stopping regorafenib. Two patients progressed with early clinical deterioration within 2 months and therefore were non-assessable at 6 months for primary study end-point (PFR-6).

In the placebo arm, 2/5 patients were progression-free at 6 months (40.0%; 95% CI = 7.6). Two patients were non-assessable at 6 months for the primary study end-point; one patient withdrew consent at 2 months without disease progression, and one patient stopped for early clinical progression at 2.2 months and started a new treatment.

At the time of the analysis, the median follow-up of alive patients was 22 months (minimum 1.9, maximum 36.3 months), 11 deaths were notified, 3 under placebo (43%) and 8 under regorafenib (50%), all due to disease progression. Median PFS was 8.2 months (4.5-12.9 months) in the regorafenib arm and 10.1 months (95% CI 0.8 months-NE) in the placebo arm. Figure 2 shows the PFS curves per blinded central review. Four out of seven (57%) placebo patients crossed over to receive regorafenib after centrally-confirmed progression. Three patients with disease progression on placebo did not switch to regorafenib for the following reasons; one withdrew his consent, one died within 2 months after progression, and one was non-eligible to cross over to regorafenib.

Median OS was 28.3 months (95% CI 14.8 months-NE) for patients randomised to regorafenib and was not achieved in the placebo arm, with OS rates at 12 months of 88% (95% CI 59% to 97%) on regorafenib and 67% (95% CI 19% to 90%) on placebo. Figure 3 shows the OS curves, including the four of seven (57%) placebo patients who crossed over to open-label regorafenib.

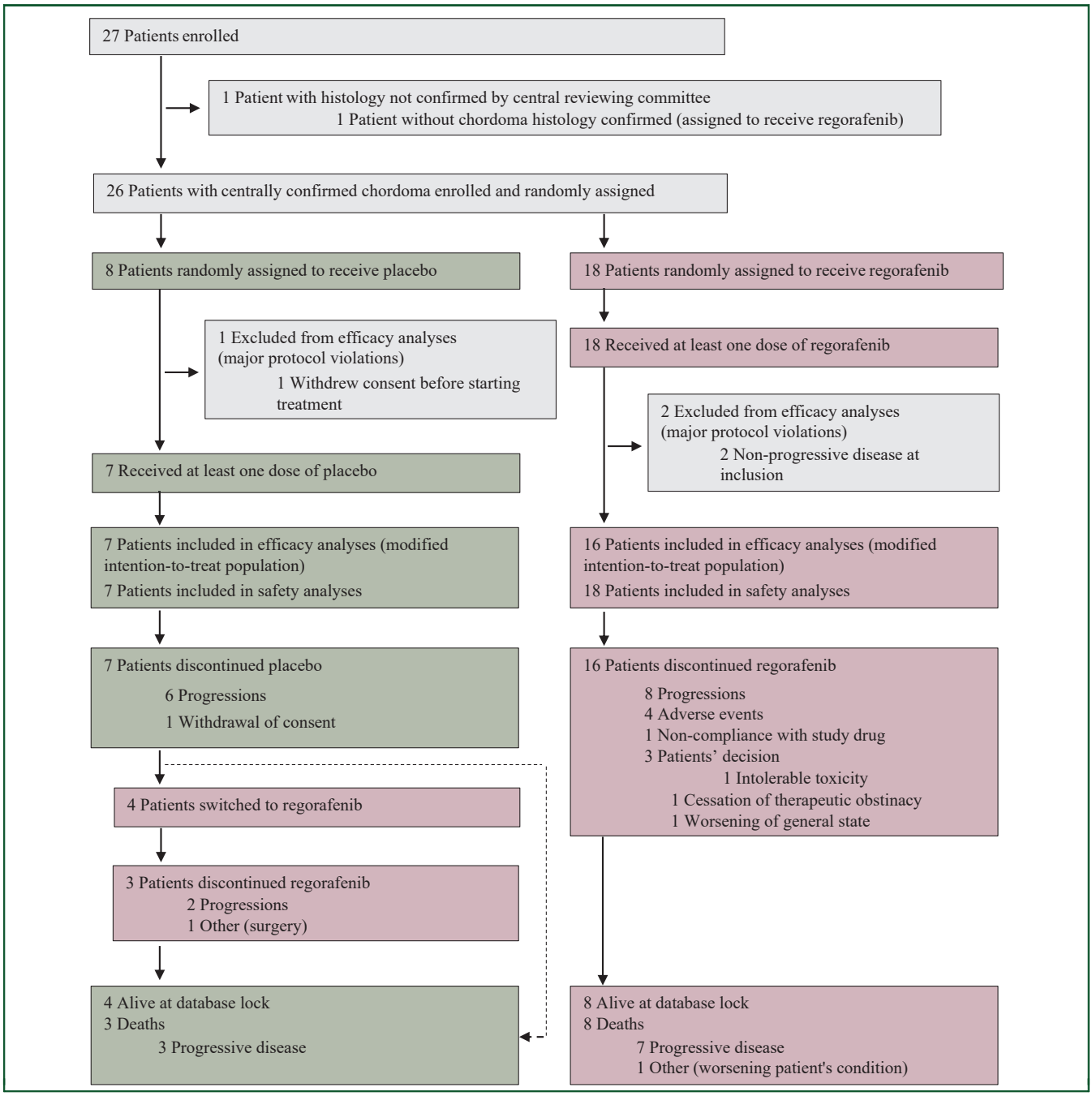

Figure 1. Study population – consort diagram.

The swimmer plots (Supplementary Figure S1, in Appendix A, available at https://doi.org/10.1016/j.esmoop.2023.101569) show the initial PFS and PFS after crossover for the 10 patients initially randomised to the placebo arm who subsequently received open-label regorafenib.

The median treatment duration was 5.2 months (minimum-maximum 0.5-34.2) on regorafenib, and 2.2 months (minimum-maximum 0.7-13.6) on placebo. Transient treatment discontinuation occurred in 11 (68.8%) of 16 patients in the regorafenib arm, and in 3 out of 7 (43%) on placebo. Dose reductions, all for toxicity, were reported in 11 out of 16 patients (68.8%) in the regorafenib arm, and in 1 out of 7 (14%) patients in the placebo arm. Regorafenib was reduced by one dose level to 120 mg/day for 6 patients (37.5%) and to 80 mg/day for 5 patients (31.3%), whereas placebo was reduced by one dose level for 1 patient only.

Safety data for the two groups until optional crossover are shown in Table 2. The most common regorafenib-related grade $\geq$3 adverse events were hand-foot skin reaction (22%), hypertension (22%), pain (22%) and diarrhoea (17%), with no toxic death. Five treatment-related serious adverse events occurred in three patients on regorafenib (one acute pancreatitis, two cholecystitis, one lung disorder (pulmonary infection), and in one patient (14.3%) on

Table 1. Patient and tumour characteristics

(*n*, %)		Placebo (*n* = 7)	Regorafenib (*n* = 16)	Excluded from efficacy analysis (*n* = 2)
Age (median, IQR), years		54 (32-70)	67.5 (33-85)	47.5 (47-48)
Sex	Male	5 (71)	11 (68.7)	1 (50.0)
	Female	2 (28.6)	5 (31.3)	1 (50.0)
ECOG PS	0	2 (28.6)	7 (43.8)	1 (50.0)
	1	5 (71.4)	9 (56.2)	1 (50.0)
Primary site	Sacrum/coccyx	4	8	1
(*n*)	Skull	2	5	0
	Spine	1	6	1
Metastatic disease		1 (14.3)	6 (37.5)	2 (100)
Locally advanced		6 (85.7)	10 (62.5)	0 (0.0)
Main sites of metastases	Lung/pleura	1 (14.3)/0 (0)	4 (25)/1 (6.3)	2 (100)/0 (0)
	Bone/lymph nodes	0 (0)/1 (14.3)	3 (18.8)/0 (0)	0 (0)
Prior treatment				
For primary T	Surgery/radiation	6 (85.7)/5 (71.4)	14 (87.5)/15 (93.8)	1 (50)/2 (100)
Prior systemic TRT	YES/NO	2 (28.6)/5 (71.4)	5 (31.3)/11 (68.7)	0 (0)/2 (100)
% Of prior imatinib		2 (28.6)	5 (31.3)	0 (0)

ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; T, tumor; TRT, treatment.

placebo (epilepsy). End of treatment due to adverse events occurred in three (18.7%) patients on regorafenib as mentioned above.

DISCUSSION

Previously published data from the osteosarcoma cohorts of the REGOBONE multicohort trial and from osteosarcoma SARC024 study indicated activity of regorafenib in delaying progression with that subtype of bone sarcomas.[9,13] In this small, non-comparative chordoma cohort, however, the target for success in the primary end-point (PFR-6) was not achieved. According to the study design criteria for success, 10 out of 16 progression-free patients at 6 months in the regorafenib arm according to RECIST 1.1 would have been necessary to consider this study successful, whereas only 6/14 (40%) patients remained free of disease progression at the 6 months timepoint in the trial. This study is negative and fails to show any signal of benefit for regorafenib in patients with progressive locally advanced or metastatic incurable chordoma. Moreover, the median PFS rate on regorafenib was 8.2 months and 10.1 months on placebo, and OS curves overlapped greatly in this small study.

This study shows that a placebo-controlled, randomised study by a cooperative academic group is feasible and acceptable even in this very rare disease. To our knowledge

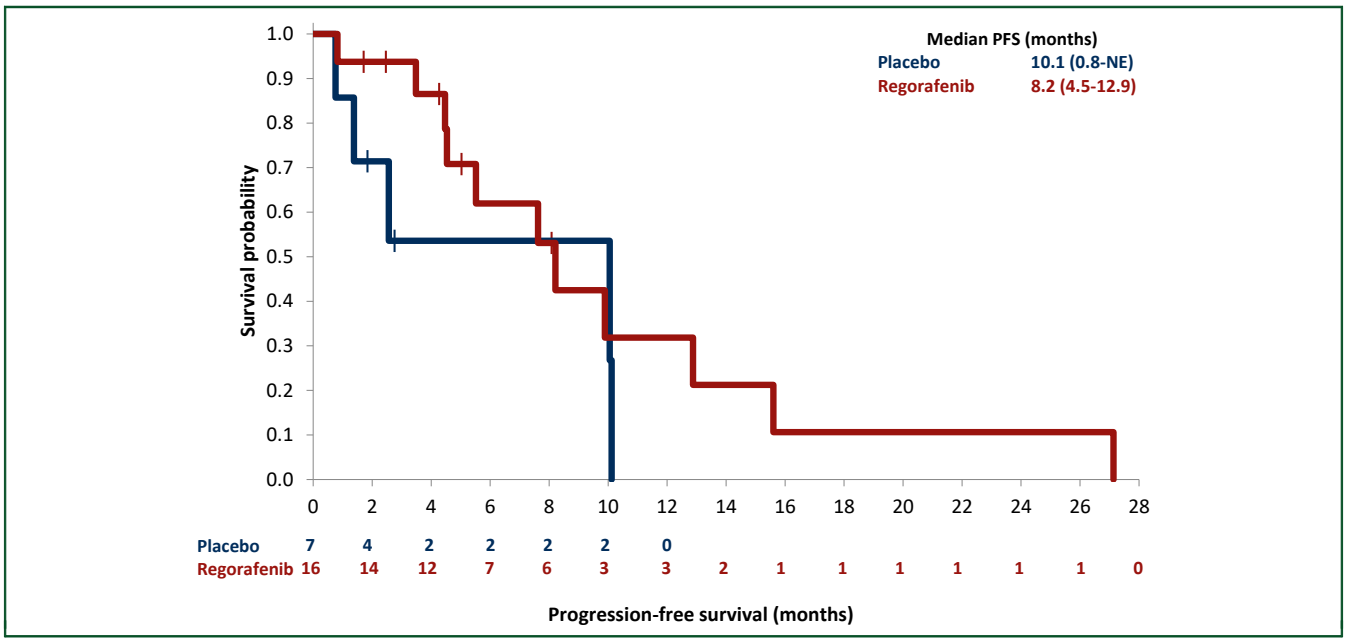

Figure 2. Progression free survival (primary endpoint per blinded central review).

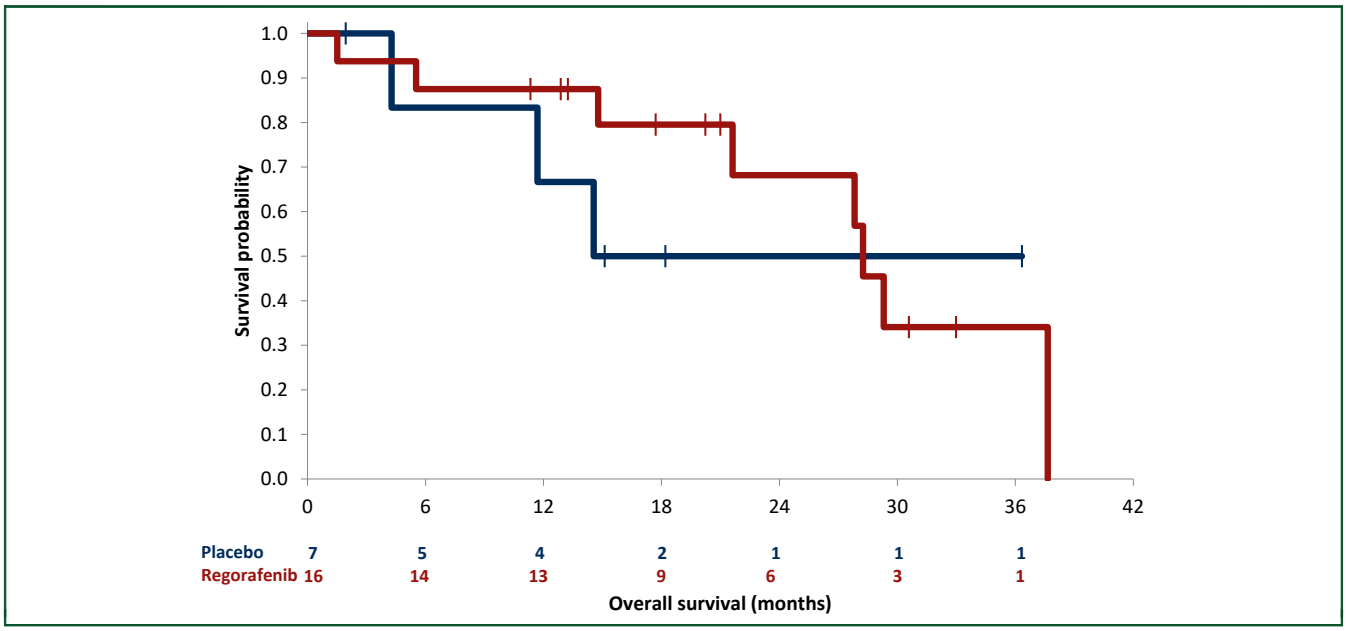

Figure 3. **Overall survival including 83% of placebo patients who crossed over to regorafenib.**

this REGOBONE study is the only randomised trial carried out in chordoma patients, with the aim of evaluating any preliminary signal of activity with a multikinase inhibitor (regorafenib) versus placebo.

The indications for molecular targeted therapies in chordoma patients are largely based on very small prospective clinical trials, limited retrospective studies, and especially case reports in particular with imatinib and erlotinib (an EGFR inhibitor).[14-21]

There are only a few prospective single arm phase II studies that have been conducted in recurrent/progressive patients with chordomas; with a specific tyrosine kinase inhibitor, as imatinib alone[14] or combined with an mTOR inhibitor (everolimus[15]), with EGFR inhibitor (lapatinib[16]) or with multikinase inhibitors with anti-VEGF activity (sorafenib, dasatinib, sunitinib).[17-19] In these prospective phase II studies, the median PFS rates reported on treatment were 9.2 months with imatinib alone, 6.3, 8, and 8.5 months with dasatinib,[18] lapatinib,[16] and sunitinib,[19] respectively, 14 months with imatinib plus everolimus combination,[15] and not reached with sorafenib.[17] The median OS rates (when reported) were 25 months with lapatinib, 35 months with imatinib, 47 months for imatinib plus everolimus combination, and not reached with sorafenib.[14-17] There is uncontrolled evidence that molecular targeted therapies (imatinib, sorafenib, sunitinib, dasatinib) can be beneficial in advanced chordoma in terms of PFS.

The efficacy and safety of any molecular targeted therapy regimen in chordoma patients, as well as any speculation regarding potential underlying molecular mechanisms, lack adequately powered systematic investigation. There appears to be insufficient activity to build upon future combinations with regorafenib for chordoma, without more relevant understanding of the biology of these tumours in potentially sensitive subsets of patients.

Regorafenib required dose modification when initiated at full dose (160 mg per day) in 68% of patients. The overall safety profile of regorafenib was as expected but led to early treatment discontinuations for a significant proportion of this group of patients who were older than patients in placebo arm.

The present study has some limitations, since it was statistically non-comparative, done in only one country, and included a small number of patients. Our results confirm that patients with advanced chordoma can have a variable clinical course.

At this time, there is still no truly optimal standard therapy for patients with progressive/relapsed chordoma after disease-progression following local treatment. New treatment options are urgently needed for this rare and poorly understood disease, with poor prognosis in case of locoregional or distant recurrence. Recently, the immune checkpoint inhibitor, pembrolizumab, was associated with potential activity in recurrent progressive pretreated chordoma, with 1-year PFS and OS rates of 31% and 76.6%, respectively, in the French Acsé Pembrolizumab study done in 34 patients, with median PFS still not achieved.[22] Immunotherapy approaches may therefore warrant further evaluation in a large prospective trial in first-line systemic therapy for chordoma relapse.

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Table 2. Adverse events per treatment group before crossover

	Regorafenib								Placebo							
	n = 18								*n* = 7							
	1-2		3		4		Any grade		1-2		3		4		Any grade	
Blood and lymphatic system disorders, *n* (%)																
Anaemia	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Thrombocytopenia	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Gastrointestinal disorders, *n* (%)																
Abdominal distension	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Abdominal pain	5	(27.8)	1	(5.6)	0		6	(33.3)	1	(14.3)	0		0	1	(14.3)	
Constipation	6	(33.3)	0		0		6	(33.3)	1	(14.3)	0		0	1	(14.3)	
Diarrhoea	5	(27.8)	3	(16.7)	0		8	(44.4)	2	(28.6)	0		0	2	(28.6)	
Dyspepsia	3	(16.7)	0		0		3	(16.7)	1	(14.3)	0		0	1	(14.3)	
Dysphagia	1	(5.6)	2	(11.1)	0		3	(16.7)	1	(14.3)	0		0	1	(14.3)	
Gastrointestinal disorder	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Nausea	5	(27.8)	0		0		5	(27.8)	3	(42.9)	0		0	3	(42.9)	
Pancreatitis acute	0		0		1[a]	(5.6)	1	(5.6)	0		0		0	0		
Stomatitis	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Vomiting	4	(22.2)	1	(5.6)	0		5	(27.8)	1	(14.3)	0		0	1	(14.3)	
General disorders, *n* (%)																
Pain																
Asthenia	12	(66.7)	2	(11.1)	0		14	(77.8)	4	(57.1)	0		0	4	(57.1)	
Chills	2	(11.1)	0		0		2	(11.1)	1	(14.3)	0		0	1	(14.3)	
General physical health deterioration	2	(11.1)	0		0		2	(11.1)	0		1	(14.3)	0	1	(14.3)	
Mucositis	3	(16.7)	0		0		3	(16.7)	0		0		0	0		
Pain	8	(44.4)	4	(22.2)	0		12	(66.7)	4	(57.1)	0		0	4	(57.1)	
Xerosis	1	(5.6)	0		0		1	(5.6)	0		0		0	0		
Hepatobiliary disorders, *n* (%)																
Bilirubin increase	3	(16.7)	0		0		3	(16.7)	0		0		0	0		
Cholecystitis	0		0		1[a]	(5.6)	1	(5.6)	0		0		0	0		
Cholecystitis acute	1[a]	(5.6)	0		0		1	(5.6)	0		0		0	0		
Infections and infestations, *n* (%)																
Corona virus infection	1	(5.6)	0		1	(5.6)	2	(11.1)	0		0		0	0		
Cystitis	0		0		0		0		0		1	(14.3)	0	1	(14.3)	
Infection	1	(5.6)	2	(11.1)	0		3	(16.7)	0		0		0	0		
Investigations, *n* (%)																
Blood alkaline phosphatase	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Blood bilirubin increased	3	(16.7)	0		0		3	(16.7)	0		0		0	0		
Transaminases increased	2	(11.1)	0		1	(5.6)	3	(16.7)	0		0		0	0		
Weight decreased	6	(33.3)	0		0		6	(33.3)	0		0		0	0		
Metabolism and nutrition disorders, *n* (%)																
Anorexia	7	(38.9)	0		0		7	(38.9)	0		1	(14.3)	0	1	(14.3)	
Hypokalaemia	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Hypophosphataemia	1	(5.6)	1	(5.6)	0		2	(11.1)	0		0		0	0		
Musculoskeletal and connective tissue disorders, *n* (%)																
Muscle spasms	4	(22.2)	0		0		4	(22.2)	0		0		0	0		
Myalgia	3	(16.7)	0		0		3	(16.7)	1	(14.3)	0		0	1	(14.3)	
Nervous system, *n* (%)																
Disturbance in attention	0		0		0		0		1	(14.3)	0		0	1	(14.3)	
Dysaesthesia	4	(22.2)	0		0		4	(22.2)	0		0		0	0		
Dysgeusia	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Epilepsy	0		0		0		0		0		1[a]	(14.3)	0	1	(14.3)	
Extensor plantar response	1	(5.6)	0		0		1	(5.6)	0		0		0	0		
Memory impairment	0		0		0		0		1	(14.3)	0		0	1	(14.3)	
Neuropathy peripheral	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Sciatica	1	(5.6)	0		0		1	(5.6)	1	(14.3)	0		0	1	(14.3)	
Psychiatric disorders, *n* (%)																
Anxiety	1	(5.6)	0		0		1	(5.6)	1	(14.3)	0		0	1	(14.3)	
Renal and urinary disorders, *n* (%)																
Proteinuria	1	(5.6)	1	(5.6)	0		2	(11.1)	0		0		0	0		
Urinary retention	0		0		0		0		1	(14.3)	0		0	1	(14.3)	
Urinary tract disorder	2	(11.1)	0		0		2	(11.1)	0		0		0	0		
Respiratory, thoracic, and mediastinal disorders, *n* (%)																
Cough	1	(5.6)	0		0		1	(5.6)	1	(14.3)	0		0	1	(14.3)	
Dysphonia	2	(11.1)	1	(5.6)	0		3	(16.7)	0		0		0	0		

Continued

Table 2. Continued

	Regorafenib								Placebo					
	n = 18								*n* = 7					
	1-2		3		4		Any grade		1-2		3		4	Any grade
Dyspnoea	2	(11.1)	1	(5.6)	0		3	(16.7)	1	(14.3)	0		0	1 (14.3)
Lung disorder	0		0		1[a]	(5.6)	1	(5.6)	0		0		0	0
Skin and subcutaneous tissue disorders, *n* (%)														
Alopecia	2	(11.1)	1	(5.6)	0		3	(16.7)	0		0		0	0
Hand and foot skin reaction	7	(38.9)	4	(22.2)	0		11	(61.1)	0		0		0	0
Other skin toxicity	8	(44.4)	1	(5.6)	0		9	(50.0)	0		0		0	0
Pain of skin	2	(11.1)	0		0		2	(11.1)	0		0		0	0
Vascular disorders, *n* (%)														
Hot flush	0		0		0		0		1	(14.3)	0		0	1 (14.3)
Hypertension	6	(33.3)	4	(22.2)	0		10	(55.6)	1	(14.3)	0		0	1 (14.3)

[a]One patient had a related serious adverse event.

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ROLE OF THE FUNDER

The funder had no role in study design, data collection, monitoring, analysis, and interpretation or writing of the report. Once the trial has been designed, UNICANCER, as the sponsor for the study, in collaboration with the French Sarcoma Group, was responsible for all aspects of the trial.

DISCLOSURE

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