Efficacy and safety of regorafenib in adult patients with metastatic osteosarcoma: a non-comparative, randomised, double-blind, placebo-controlled, phase 2 study

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Summary

Background Regorafenib has proven activity in patients with pretreated gastrointestinal stromal tumours and colorectal and hepatocellular carcinoma. We designed REGOBONE to assess the efficacy and safety of regorafenib for patients with progressive metastatic osteosarcoma and other bone sarcomas. This trial comprised four parallel independent cohorts: osteosarcoma, Ewing sarcoma, chondrosarcoma, and chordoma. In this Article, we report the results of the osteosarcoma cohort.

Methods In this non-comparative, double-blind, placebo-controlled, phase 2 trial, patients aged 10 years or older with histologically confirmed osteosarcoma whose disease had progressed after treatment with one to two previous lines of chemotherapy for metastatic disease and an Eastern Cooperative Oncology Group performance status of 0 or 1 were enrolled. Patients were randomly assigned (2:1) to receive either oral regorafenib (160 mg/day, for 21 of 28 days) or matching placebo. Patients in both groups also received best supportive care. Randomisation was done using a web-based system and was stratified (permuted block) by age at inclusion (<18 *vs* ≥18 years old). Investigators and patients were masked to treatment allocation. Patients in the placebo group, after centrally confirmed progressive disease, could cross over to receive regorafenib. The primary endpoint was the proportion of patients without disease progression at 8 weeks. Analyses were done by modified intention to treat (ie, patients without any major entry criteria violation who initiated masked study drug treatment were included). All participants who received at least one dose of study drug were included in the safety analyses. This study is registered with ClinicalTrials.gov, number NCT02389244, and the results presented here are the final analysis of the osteosarcoma cohort (others cohorts are ongoing).

Findings Between Oct 10, 2014, and April 4, 2017, 43 adult patients were enrolled from 13 French comprehensive cancer centres. All patients received at least one dose of assigned treatment and were evaluable for safety; five patients were excluded for major protocol violations (two in the placebo group and three in the regorafenib group), leaving 38 patients who were evaluable for efficacy (12 in the placebo group and 26 in the regorafenib group). 17 of 26 patients (65%; one-sided 95% CI 47%) in the regorafenib group were non-progressive at 8 weeks compared with no patients in the placebo group. Ten patients in the placebo group crossed over to receive open-label regorafenib after centrally confirmed disease progression. 13 treatment-related serious adverse events occurred in seven (24%) of 29 patients in the regorafenib group versus none of 14 patients in the placebo group. The most common grade 3 or worse treatment-related adverse events during the double-blind period of treatment included hypertension (in seven [24%] of 29 patients in the regorafenib group *vs* none in the placebo group), hand–foot skin reaction (three [10%] *vs* none), fatigue (three [10%] *vs* one [3%]), hypophosphataemia (three [10%] *vs* none), and chest pain (three [10%] *vs* none). No treatment-related deaths occurred.

Interpretation Regorafenib demonstrated clinically meaningful antitumour activity in adult patients with recurrent, progressive, metastatic osteosarcoma after failure of conventional chemotherapy, with a positive effect on delaying disease progression. Regorafenib should be further evaluated in the setting of advanced disease as well as potentially earlier in the disease course for patients at high risk of relapse. Regorafenib might have an important therapeutic role as an agent complementary to standard cytotoxic chemotherapy in the therapeutic armamentarium against osteosarcoma.

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Introduction

Treatment options for osteosarcomas, especially in the setting of metastatic or unresectable disease, are very scarce. Following failure of standard first-line therapy for osteosarcoma, patients who relapse present a challenging treatment dilemma. In general, patients with osteosarcomas have a poor prognosis following recurrence or metastatic spread of the disease, and thus represent a

Research in context

Evidence before this study

We searched PubMed for clinical trials published in English from Jan 1, 2005, to July 31, 2018, that assessed the activity of regorafenib in patients with recurrent, metastatic, and/or unresectable osteosarcoma (excluding gastrointestinal stromal tumours and soft tissue sarcoma) previously treated with conventional chemotherapy. We used the terms "osteosarcoma", "tyrosine kinase inhibitors", "antiangiogenic kinase inhibitors", and "regorafenib". To the best of our knowledge, no previous trial assessing the activity of regorafenib in this population has been published. Preliminary evidence for the activity of sorafenib, another multikinase inhibitor, alone or combined with everolimus has been reported in this clinical setting. Two non-randomised, phase 2 studies reported a median progression-free survival of 4 months (95% CI 7–8) with sorafenib and of 5 months (95% CI 2–7) with sorafenib and everolimus. However, no randomised, placebo-controlled trial has assessed the efficacy of sorafenib versus placebo in recurrent metastatic or unresectable osteosarcoma.

Added value of this study

Although the current trial was statistically non-comparative, this placebo-controlled study suggests that patients with osteosarcoma treated with regorafenib have an extended progression-free survival relative to patients with osteosarcoma who were randomly allocated to placebo.

Implications of all the available evidence

Regorafenib shows clinical activity in adult patients with metastatic osteosarcoma where no other therapies have proven to be effective, and thus warrants further clinical exploration in patients with metastatic unresectable osteosarcoma. A phase 2 trial in the USA assessing regorafenib in patients with osteogenic sarcoma, liposarcomas, Ewing or Ewing-like sarcoma, and rhabdomyosarcoma has recently completed enrolment (NCT02048371).

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severe unmet medical need. No standardised treatment options exist in terms of the choice of second-line chemotherapy or the use of investigational drugs.[1] In European Society for Medical Oncology and National Comprehensive Cancer Network osteosarcoma guidelines, there is no single agreed standard of care for recurrent metastatic osteosarcoma following first-line chemotherapy.[2,3] Although the most active chemotherapy regimen of high-dose methotrexate, doxorubicin, and cisplatin with or without ifosfamide or mifamurtide can eradicate subclinical metastases in the first-line setting, it rarely cures unresectable osteosarcoma.[4]

Some second-line and later-line treatments have been investigated, but only marginal activity has been documented.[5–7] Phase 2 trials and retrospective analyses have reported responses to second-line or later-line treatments (eg, cyclophosphamide and etoposide, gemcitabine and docetaxel, or pemetrexed), with objective responses achieved in 3–29% of patients and a median progression-free survival of less than 4 months.[5–7] Increased knowledge of the oncogenic pathways in osteosarcoma pathogenesis and the advent of targeted therapies have prompted investigation of drugs aimed at several signalling pathways. Numerous small molecule kinase inhibitors (eg, imatinib) and monoclonal antibodies (eg, trastuzumab) have been tested in addition to standard chemotherapy,[8] as well as bevacizumab and drugs targeting IGF-1R alone[9–11] or combined with mTOR inhibitors.[10] Although none of these agents showed substantial activity in patients with advanced or recurrent high-grade osteosarcoma, some biomarkers such as phospho-ERK1/2 were correlated with growth, survival, neo-angiogenesis, and metastatic potential of high-grade osteosarcoma.[12,13] Despite a somatic mutation rate higher than that of any other paediatric cancer, responses to checkpoint inhibitors in osteosarcoma have been disappointingly low so far. In the recently reported SARC028 trial,[14] only one of the 22 patients with osteosarcoma who received single-agent pembrolizumab achieved a partial response per Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) and progression-free survival at 8 weeks was low at 24%. Given these poor results, patients with recurrent or metastatic osteosarcoma should be considered for investigational approaches in an attempt to develop novel effective strategies for care.

There is a relatively strong biological rationale for angiogenesis inhibition in osteosarcomas. Circulating VEGF and VEGFR levels correlate with the extent of disease and patient prognosis in osteosarcomas.[15] Preclinical data suggest that inhibition of angiogenic pathways in established vasculature can attenuate growth of osteosarcomas in vitro and in vivo.[12,16] Early clinical data also suggest activity of VEGFR-inhibiting kinase inhibitors such as sorafenib and sunitinib in patients with bone sarcomas.[17,18] However, both these agents also inhibit other signalling kinases, including KIT, PDGFR, and, to a lesser extent, RET and FGFR1; it remains unclear whether antiangiogenesis inhibition or a spectrum of kinase inhibition might explain any activity from these relatively non-selective kinase inhibitors.

Grignani and colleagues reported promising results from a phase 2 trial of sorafenib alone in patients with pretreated recurrent osteosarcoma.[19] In 35 treated patients, the proportion who achieved clinical benefit (partial response, minor response, or stable disease) was 29% (ten of 35 patients) at 6 months, and 4-month progression-free survival was 46% (95% CI 28–63).[19] In a second phase 2 trial, the addition of everolimus to sorafenib did not substantially change the low proportion of objective responses (10% in Grignani and colleagues' study of

sorafenib alone[19] *vs* 14% with the addition of everolimus[20]). Although the combination slightly prolonged duration of response to 5 months compared with 4 months with sorafenib alone, the 6-month progression-free survival of 45% was less than the prespecified threshold of activity (6-month progression-free survival of ≥50%) that was the limit to consider activity worthy of further research in a phase 3 trial.[20]

In addition to drugs targeting the VEGFR pathway, other cellular signalling pathways have also been evaluated for potential new osteosarcoma treatments, including the mTOR pathway.[12] This approach was based on models which showed that many sarcomas, including osteosarcomas,[12] activate the mTOR pathway as a compensatory stress response to exposure to other tyrosine kinase inhibitors.[21] However, as previously noted, clinical trials combining sorafenib and everolimus have not yielded promising results in osteosarcoma.[20]

Regorafenib is an orally bioavailable multikinase inhibitor targeting tumour cells, vasculature, and the tumour microenvironment. It blocks the activity of several protein kinases, including those involved in the regulation of tumour angiogenesis (VEGFR-1, VEGFR-2, and VEGFR-3, and TIE2), oncogenesis (KIT, RET, RAF-1, BRAF, and BRAFV600E), and the tumour microenvironment (PDGFR and FGFR).[22] In a phase 1 trial of regorafenib,[23] one of the three patients who achieved an objective response had an advanced pretreated osteosarcoma. Regorafenib has shown efficacy and manageable toxicity in the treatment of refractory colorectal carcinomas as well as gastrointestinal stromal tumours in three phase 3 trials, leading to approval by regulatory authorities worldwide for those indications.[24–26] Regorafenib has also shown antitumour activity in pretreated metastatic or advanced non-adipocytic soft tissue sarcoma[27]—a setting in which pazopanib, another antiangiogenic kinase inhibitor, has also demonstrated activity in prolonging progression-free survival.[28] The objective of the present study was to explore the antitumour activity of regorafenib in patients with progressive recurrent osteosarcoma after failure of conventional chemotherapy.

Methods

Study design and participants

For the **protocol** see http://www.unicancer.fr/protocole-regobone

The French Sarcoma Group (FSG) designed this investigator-initiated, non-comparative, randomised, double-blind phase 2 clinical trial, REGOBONE, as a basket study of four parallel independent cohorts of different histological subtypes of metastatic bone cancers, to assess the activity and safety of regorafenib. The REGOBONE trial is a signal-seeking study. Patients were enrolled in the following cohorts based on disease histopathology: osteosarcoma, Ewing sarcoma of bone, chondrosarcoma, and chordoma. In each parallel cohort, patients were randomly assigned (2:1) to receive either oral regorafenib or matching placebo. Enrolment in the osteosarcoma cohort completed first, while the other three cohorts are continuing to accrue. In this Article, we present the results of the randomised phase 2 trial in the cohort of patients with metastatic osteosarcoma.

Eligible patients were required to have a histological diagnosis of osteosarcoma (confirmed by central pathological review by an expert pathologist from the Réseau de Relecture en Pathologie des Sarcomes Osseux in France[29]) and objective disease progression within 3 months prior to study entry measured by RECIST v1.1, both confirmed by central review, as well as measurable disease by RECIST v1.1. Patients had to have disease that was not amenable to treatment with curative intent, and had to have been previously treated with one to two lines of chemotherapy for metastatic disease, with at least 4 weeks since their last chemotherapy (6 weeks in the case of nitrosoureas and mitomycin C), immunotherapy, or any other pharmacological treatment and/or radiotherapy. Initially, only adult patients (aged ≥18 years) were eligible; however, the study was amended on Sept 19, 2016, to allow accrual of patients aged 10 years and older. Eligible patients also had to have an adequate performance status (adults: Eastern Cooperative Oncology Group [ECOG] performance status of 0–1; children aged >12 years: a score of ≥60% on the Karnofsky performance scale; children aged ≤12 years a score of ≥60% on the Lansky scale), a body surface area of at least 1·30 m², and a life expectancy of longer than 3 months. Additionally, patients had to have adequate bone marrow function (absolute neutrophil count ≥1·5×10⁹ cells/L, platelets ≥100×10⁹/L, haemoglobin concentration ≥9 g/dL), normal renal function (serum creatinine ≤1·5×upper limit of normal [ULN], glomerular filtration rate ≥30 mL/min per 1·73 m² according to the modified diet in renal disease abbreviated formula, and normal spot urine analysis), normal liver function (aspartate aminotransferase and alanine aminotransferase ≤2·5×ULN [or ≤5·0×ULN for patients with liver involvement of their cancer], bilirubin ≤1·5×ULN, and alkaline phosphatase ≤2·5×ULN [or ≤5×ULN in those with liver involvement of their cancer]), and normal pancreatic function (lipase ≤1·5×ULN) to be eligible. Patients who had previously received VEGF inhibitor treatment and those with clinically relevant cardiovascular disease (eg, active symptomatic cardiac disease, uncontrolled hypertension, and arterial or venous thromboembolic events) were not eligible. The complete list of other eligibility criteria is available in the online protocol.

The study protocol was approved by an ethical and regulatory committee (French Ethical Committee, Comité de Protection des Personnes Sud Méditerrannée 1; approved on March 26, 2014) and by the French Drug Agency (Agence Nationale de Sécurité du Médicament; approved on May 2, 2014). All study procedures were done in accordance with the International Council for Harmonisation tripartite guideline on good clinical practice. One study amendment (protocol V6, June 29, 2016) added the possibility to enrol children. The amendment was approved by the ethics committee on July 13, 2016, and

by the French Drug Agency on Sept 19, 2016. All patients (or the parents or legal representatives of patients aged 10–17 years) provided written, informed consent before enrolment. An independent data monitoring committee monitored the safety during the study (with an interim analysis of safety planned once after half the patients were included).

Randomisation and masking

Registration and randomisation were centralised via a web-based system (IWRS) using a permuted block design provided by an independent partner (ATLANSAT, Rezé, France). ATLANSAT was in charge of generating the randomisation lists for each cohort and was not involved in the data analysis. A unique kit number was allocated to each treatment package (one package containing three bottles of regorafenib or placebo tablets), allowing maintenance of double-blind masking in the study. Once randomisation had been performed by the participating site through the IWRS, an automatic email, stipulating the treatment kit number to provide the patient with, was sent directly to the pharmacy's site. After the study amendment allowing the inclusion of patients between 12 and 17 years old, randomisation was stratified by age at inclusion (<18 years *vs* ≥18 years). Patients, investigators, pharmacists, site study teams, the pathologist in charge of histological confirmation, the radiologist in charge of central radiological review, and the sponsor were all masked to treatment allocation, and treatment allocation remained masked until centrally confirmed disease progression.

Procedures

Patients were randomly assigned (2:1) to receive best supportive care combined with either regorafenib 160 mg orally per day (four tablets of 40 mg once daily), in a 3 weeks on and 1 week off schedule (ie, treatment given for 21 of 28 days), or matching placebo tablets. This dose and schedule of regorafenib were chosen because it is the standard dose and schedule approved by regulatory authorities worldwide for two other diseases (gastrointestinal stromal tumours and colorectal carcinoma). For children aged 10–17 years with a body surface area of at least 1·30 m², regorafenib was to be administered in the same schedule at a dose of 82 mg/m² per day (the recommended phase 2 dose of single-agent regorafenib given in a paediatric dose-escalation phase 1 study [NCT02085148]). Best supportive care included any method to preserve the comfort and dignity of the patients and excluded any disease-targeting antineoplastic agent, such as any kinase inhibitor, chemotherapy, radiotherapy, or surgical intervention.

Dose interruptions or dose reductions were required if any of the following adverse events was observed: grade 2 or 3 hand–foot reactions; grade 3 arterial hypertension (despite appropriate antihypertensive treatment); grade 3 increases in the concentration of alanine transferase, aspartate aminotransferase, or bilirubin; and any grade 4 toxicity. Dose reductions were implemented in 40 mg (one tablet) increments, with 80 mg being the lowest recommended daily dose.

Treatment was administered until one of the following events occurred: confirmed progressive disease according to RECIST v1.1 (with real-time confirmation by independent central radiological review);[30] unacceptable toxicity (according to investigator judgment); death; patient's refusal of treatment; or investigator's decision. Patients receiving placebo were offered optional crossover to regorafenib once disease progression was confirmed by centralised review.

At baseline, the following procedures were done: a physical examination; thoracic and abdominal CT scan; full blood count, coagulation, hepatic function, and biochemistry tests; thyroid function tests; urine analysis; and echocardiography or multigated acquisition scan. Physical examination and assessment of adverse events were done on days 1 and 14 during the first two cycles, then on day 1 of each cycle until cycle 6, and then every two cycles until the end of treatment. Hepatic function was assessed weekly during the first two treatment cycles and then on day 1 of each cycle until the end of study treatment. Haematology (full blood count) was assessed on days 1 and 14 during the first two cycles, and then on day 1 of each cycle until the end of study treatment. Biochemistry was assessed on day 1 of cycles 1–6 and then every second cycle until the end of treatment. Treatment-related adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0, during the on-treatment period (defined as the period from the time of first dose of study medications up to 30 days of the last dose).

Serial tumour size assessment by CT imaging was done every 4 weeks for the first 4 months (day 1 of cycles 1–4) and then every 8 weeks (every second cycle) until the end of study treatment. For patients in the placebo group who crossed over to receive open-label regorafenib after centrally confirmed disease progression and unblinding, disease restaging was resumed at the original schedule (ie, every 4 weeks for the first 4 months, and then every 8 weeks [every second cycle]) until the end of study drug treatment.

All patients entered the follow-up period 30 days after discontinuation of study treatment (regorafenib or placebo). Patients were to enter the follow-up period regardless of the reason for study drug discontinuation and vital status was to be updated every 3 months for 18 months.

Outcomes

The primary endpoint was the proportion of patients without disease progression at 8 weeks. Secondary endpoints were: progression-free survival, which was assessed centrally according to modified RECIST v1.1

(measured from the date of randomisation until the date of confirmed radiological progression or death from any cause, whichever occurred first); objective responses (the proportion of patients who achieved a complete or partial response as their best response since randomisation, according to modified RECIST v1.1, overall survival (defined as the time from randomisation until the date of death from any cause); duration of overall response (only measured in responding patients, and defined as the time from first documented response until first documented disease progression or death); disease control at 6 months (the proportion of patients who had a best response of complete response, partial response, or stable disease at 6 months according to RECIST v1.1); the proportion of patients who were progression free at 3 and 6 months; time to progression (defined as the delay from the date of randomisation to the date of the first progression), growth modulation index (ratio of time to progressive disease under regorafenib to time to progression under previous treatment); and safety and tolerability. In patients in the placebo group who crossed over to regorafenib after disease progression, progression-free survival was measured from the date of crossover, and was both assessed by the investigators and confirmed by central review.

Statistical analysis

When the REGOBONE study was designed, there was a paucity of published data regarding the progression-free survival of patients with osteosarcoma following failure of standard treatments. At the same time, reported objective responses to chemotherapy after methotrexate, doxorubicin, and cisplatin with or without ifosfamide varied widely, making this endpoint unsuitable in patients with advanced and unresectable high-grade osteosarcoma. Therefore, we chose progression-free survival as the primary endpoint. We calculated the sample size by A'Hern single-stage design for phase 2 trials, which is similar to a Fleming phase 2 design but assumes an exact binomial distribution.[31]

When we designed REGOBONE, the published literature reported a median progression-free survival with an inactive drug (cylcophosphamide and etoposide, gemcitabine and docetaxel, or pemetrexed) of about 6 weeks for osteosarcoma[5–7] and that an active drug should at least double this median to be considered of interest. Notably, no comparative progression-free survival data were available for placebo, because of the absence of published randomised placebo-controlled trials. These hypotheses about median progression-free survival translated into a 67% non-progression rate at 8 weeks defined as the expected efficacy in the experimental (regorafenib) group. A lower limit of 40% non-progressive patients or less would mean that regorafenib did not warrant further investigation in this setting. A sample size of 23 patients would provide 80% power to reject the null hypothesis with a one-sided, type I error of 5%, with 14 successful patients being the lower cutoff point for decision making. 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 12 evaluable patients was required in the placebo group, according to the 2:1 randomisation ratio. After the study amendment that allowed the inclusion of children, we expected to include at least six children or adolescents to have sufficient data in the paediatric population.

No comparative hypothesis was formulated and no statistical comparison between the control and experimental group was planned. The placebo group was only included to check the similarity between the enrolled patients and historical controls with respect to clinical outcome when given standard treatments. Thereby, the primary endpoint and all other efficacy outcomes were analysed by modified intention to treat, including all patients who initiated study drug treatment, with no major protocol violations. Major protocol violations were defined as deviations that could potentially affect the efficacy analysis, including patients not meeting important inclusion or exclusion criteria (eg, non-progressive disease at inclusion, or without measurable target lesions). All patients who received at least one dose of the intended study drug (regorafenib or placebo) were included in the safety analyses.

The percentages of patients who were progression-free at 8 weeks in each group were calculated with their respective 95% CIs (which were one-sided due to the Fleming design). Progression-free survival and overall survival were estimated using the Kaplan-Meier method, and were described in terms of median or specific timepoint estimation in each group, along with the associated two-sided 95% CIs for the estimates. For patients who were event free at the time of the analysis, progression-free survival was censored at the time of the final adequate tumour assessment. Overall survival was censored at the date of final contact for patients alive. For the time-to-progression endpoint, patients who died from causes other than progression were censored at the date of death. We used SAS (version 9.4) for all analyses. This study is registered with ClinicalTrials.gov, number NCT02389244.

Role of the funding source

Bayer Healthcare SAS (Loos, France) supplied regorafenib and placebo tablets and provided funding to UNICANCER. Bayer Healthcare had no role in study design, data collection, monitoring, analysis, and inter pretation or writing of the report. Once the trial had been designed, UNICANCER, as the sponsor for the study, in collaboration with the French Sarcoma Group were responsible for all aspects of the trial. All authors were involved in writing and reviewing the publication. FD and SC had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Oct 10, 2014, and April 4, 2017, 43 adult patients were enrolled from 13 French comprehensive cancer centres (appendix p 1) and randomly assigned 2:1 to receive regorafenib or placebo (figure 1). These 43 patients represent the population for safety analysis (figure 1). Five patients (two in the placebo group and three in the regorafenib group) were not included in the full analysis set because of major protocol violations: four patients without documented progressive disease at inclusion (two in each group) and one patient with no measurable lesion at inclusion (in the regorafenib group); these five patients were not included in the modified intention-to-treat efficacy analysis. Two patients who were initially enrolled in the REGOBONE chondrosarcoma cohort had their diagnoses changed to osteosarcoma after central histological review (one of whom was randomly assigned to regorafenib and the other to placebo); data from both these patients were incorporated into the osteosarcoma cohort. In total, 38 adult patients with histologically confirmed advanced osteosarcoma constituted the population for efficacy analysis: 26 patients randomly assigned to regorafenib and 12 to placebo. No patient remained on treatment at the time of this analysis (figure 1).

The baseline characteristics of patients were well balanced between the two groups (table 1) except for a small imbalance in sex and ECOG performance status. The median age of the patients was 33 years (IQR 22–50). Only adult patients were enrolled despite the study amendment which allowed the accrual of patients older than 10 years. Most patients (34 [79%] of 43) had only one previous chemotherapy regimen for metastatic disease at inclusion. All patients who were included in the efficacy evaluable population, except one with locally advanced disease in the regorafenib group, had metastatic measurable disease. As expected with osteosarcoma, distant metastases were mainly in the lung and bone. Most patients had received the three most common drugs used for treating adults with osteosarcoma; doxorubicin, cisplatin, and ifosfamide. High-dose methotrexate had also been given to ten (23%) of 43 of the patients overall. At the time of the analysis, the median follow-up of patients who were alive was 31·6 months (IQR 24·1–33·6).

The primary study endpoint was met at the planned analysis at 8 weeks of follow-up: in the regorafenib group, 17 (65%) of 26 patients were without disease progression at 8 weeks, whereas all patients in the placebo group had progressive disease at 8 weeks. Two partial responses were recorded in the regorafenib group, with durations of response of 6·2 and 12·9 months. No responses were recorded in the placebo group.

At the time of analysis (after data cutoff on April 18, 2018), all 26 patients in the regorafenib group and all 12 patients in the placebo group had progressed, and 33 (87%) of 38 patients had died (21 [81%] of 26 patients in the regorafenib group *vs* all 12 [100%] in the placebo group). Disease progression was the cause of most of these deaths, except for one death in the placebo group which was attributed to toxicity (alteration of the patient's general state due to cancer).

Median progression-free survival was 16·4 weeks (95% CI 8·0–27·3) in the regorafenib group and 4·1 weeks (3·0–5·7) in the placebo group (table 2, figure 2). This difference in progression-free survival was maintained over time, as shown by the results for progression-free survival at 12 and 24 weeks (table 2). Median overall survival was 11·3 months (95% CI 5·9–23·9) in patients

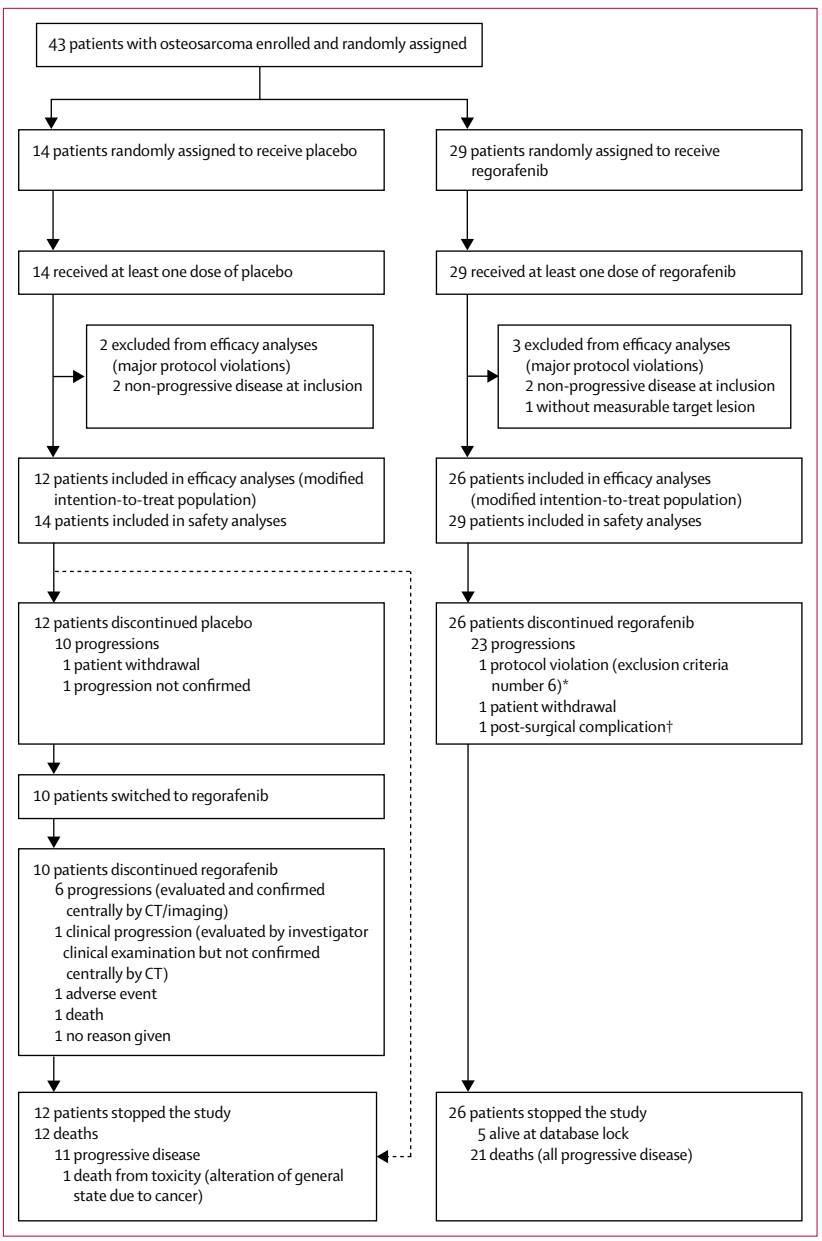

Figure 1: **Trial profile**

*Arterial or venous thrombotic or embolic events such as cerebrovascular accident (including transient ischaemic attacks), deep vein thrombosis, or pulmonary embolism within the last 6 months before randomisation. †Local infection after surgery to treat knee arthritis.

See Online for appendix

	Regorafenib group (n=26)	Placebo group (n=12)	Excluded from efficacy analysis (n=5)
Age, years	32 (21–50)	40 (29–43)	30 (23–43)
Sex			
Male	19 (73%)	5 (42%)	4 (80%)
Female	7 (27%)	7 (58%)	1 (20%)
ECOG performance status			
0	12 (46%)	2 (17%)	2 (40%)
1	14 (54%)	10 (83%)	2 (40%)
Unknown	0	0	1 (10%)
Presence of metastases			
No (locally advanced disease)	1 (4%)	0	2 (40%)
Yes	25 (96%)	12 (100%)	3 (60%)
Sites of metastases*			
Lung	24 (92%)	10 (83%)	2 (40%)
Bone	6 (23%)	3 (25%)	0
Lymph node	3 (12%)	4 (33%)	0
Pleural	3 (12%)	1 (8%)	0
Previous lines of chemotherapy for metastatic disease			
1	21 (80%)	10 (83%)	3 (60%)
2	5 (20%)	2 (17%)	2 (40%)
0	0	0	0
Previous treatment at entry			
Doxorubicin	26 (100%)	12 (100%)	2 (40%)
Ifosfamide	24 (92%)	12 (100%)	3 (60%)
Cisplatin	25 (96%)	11 (92%)	1 (20%)
High-dose methotrexate	7 (27%)	3 (25%)	0
Etoposide	21 (81%)	5 (42%)	1 (20%)
Gemcitabine or docetaxel	3 (12%)	2 (16%)	0
Oral cyclophosphamide	3 (12%)	1 (8%)	2 (40%)

Data are median (IQR) or n (%). ECOG= Eastern Cooperative Oncology Group. *Patients could have more than one metastasis.

***Table 1*: Baseline characteristics**

	Regorafenib group (n=26)	Placebo group (n=12)
Non-progressive disease at 8 weeks	17 (65%; 95% CI 47–)*	0
Response at 8 weeks		
Complete response	0	0
Partial response	2 (8%)	0
Stable disease	15 (58%)	0
Progressive disease	9 (35%)	12 (100%)
Median progression-free survival, weeks	16·4 (95% CI 8·0–27·3)	4·1 (95% CI 3·0–5·7)
Progression-free survival at 12 weeks	62% (95% CI 40–77)	0
Progression-free survival at 24 weeks	35% (95% CI 17–52)	0

Data are n (%) unless otherwise specified. *One-sided 95% CI (due to the Fleming design).

***Table 2*: Efficacy outcomes**

who received regorafenib and 5·9 months (1·3–16·4) in those randomly assigned to placebo (figure 3); notably the confidence intervals are overlapping in this small cohort. Following the centralised confirmation of progressive disease, ten of 12 patients initially randomly assigned to placebo crossed over to open-label regorafenib. Two patients in the placebo group did not cross over to regorafenib: one withdrew from the study and died within 4 weeks, and one died within 16 days of study entry, before any tumour evaluation could be done and without centrally confirmed progressive disease. One patient in the placebo group stopped treatment because of investigator-defined progression, which was not confirmed centrally. Because this patient died from progressive disease within 14 days after treatment withdrawal, they were censored at his date of death (rather than at their last tumour assessment) for the progression-free survival analysis. This death was considered as an event in the analysis of progression-free survival after crossover. The only patient censored in analysis of progression-free survival after crossover was a patient who stopped treatment for toxicity without any tumour evaluation after the end of treatment.

The progression-free survival curves after initial randomisation to either regorafenib or placebo, as well as the progression-free survival results of the ten patients who crossed over to open-label regorafenib, are presented in the appendix (p 2). Median progression-free survival in the patients who crossed over to regorafenib was 19·4 weeks (95% CI 3·6–27·7).

The swimmer plots (appendix p 3) show the initial progression-free survival and progression-free survival after crossover for the ten patients initially randomised to placebo who subsequently received open-label regorafenib. The plots show that rapid disease progression on placebo was slowed by the introduction of regorafenib. The waterfall plots in figure 4 and in the appendix (p 4) show the tumour responses obtained on blinded treatment and on open-label regorafenib. The results of the growth modulation index will be reported in a separate publication.

Treatment administration, including details of treatment duration and dose reductions, is presented in table 3. In the efficacy evaluable population, no patient permanently discontinued study treatment because of adverse events. Transient discontinuation, defined as any dose delay or dose hold, occurred in 12 (46%) of 26 patients initially assigned to regorafenib and in one (8%) of 12 patients initially assigned to placebo. A transient interruption of treatment for toxicity was reported in nine (35%) of 26 patients in the regorafenib group and none in the placebo group. Dose reductions were reported in ten (38%) of 26 patients initially assigned to regorafenib versus one (8%) of 12 patients initially assigned to placebo (patient decision to reduce dose from 160 to 120 mg). These dose reductions were all because of adverse events. All dose reductions in the regorafenib group were because of non-haematological toxicities, namely hand–foot syndrome (n=5), erythema (n=2), hyperbilirubinaemia (n=1), diarrhoea (n=1), and lipase increase (n=1). In the five patients excluded from the efficacy analysis, one patient in the regorafenib group had a dose reduction because of toxicity (diarrhoea, vomiting, and palmar–plantar syndrome) and one had a

transient treatment discontinuation decided by the patient (in the placebo group). The outcomes of the five excluded patients (duration of treatment, overall response rate, and progression-free survival) are presented in the appendix (p 5).

In the safety population, 13 treatment-related serious adverse events occurred in seven (24%) of 29 patients in the regorafenib group versus none of 14 patients in the placebo group. All these treatment-related serious adverse events in the regorafenib were at least grade 3 severity, and were hypertension (n=3), hypophosphataemia (grade 4; n=1 and grade 3; n=2), hand–foot skin reaction (n=2), transaminases increase (n=1), lipase increase (n=1), blood alkaline phosphatase increase (n=1), epilepsy (n=1), and haemothorax (n=1).

Table 4 shows the safety results in the two groups until optional crossover in the 43 patients who received treatment. The most common grade 3 or worse treatment-related adverse events during the double-blind period in the regorafenib group included hypertension (in seven [24%] of 29 patients), hand–foot skin reaction (in three [10%] patients), fatigue (in three [10%]), hypophosphataemia (in three [10%]), and chest pain (in three [10%]). There were no treatment-related deaths reported in either treatment group. No unexpected adverse events were reported.

Discussion

Our results provide evidence for activity of regorafenib in the treatment of metastatic osteosarcoma in adult patients, after failure of previous chemotherapy. Based on the non-progression rate at 8 weeks of 65% in the regorafenib group compared with 0% for those initially randomly assigned to placebo, this non-comparative signal-seeking study met its primary endpoint.

We chose progression-free survival rather than objective response as our primary endpoint because tumour shrinkage in the calcified lesions of advanced osteosarcoma might not accurately reflect the true antitumour activity, since either calcifications or necrosis can occur in the absence of tumour shrinkage.[19] Since 2008, the expert osteosarcoma community has favoured the use of progression-free survival as a more efficient and reliable endpoint than objective response in phase 2 trials in recurrent osteosarcoma, in which both disease progression at any site and death from any cause are considered as events. This approach has been recently supported by the reanalysis of eight recent negative Children's Cancer Group, Pediatric Oncology Group, and Children's Oncology Group phase 2 trials in the past 10 years,[1] although the authors used the term event-free survival for what is usually referred to as progression-free survival.[32,33] When we designed the REGOBONE study in 2013, there was no consensus on the optimal duration of progression-free survival on which to judge the trial outcome as positive or negative. Recently Lagmay and colleagues,[1] recommended that progression-free survival longer than 4 months be considered a metric to judge a positive outcome for single-arm phase 2 trials of patients with measurable metastatic or unresectable osteosarcoma. According to this recommendation, with a median progression-free survival of 16 weeks with regorafenib, our study provides evidence of the activity of regorafenib in this setting. Although we did not calculate

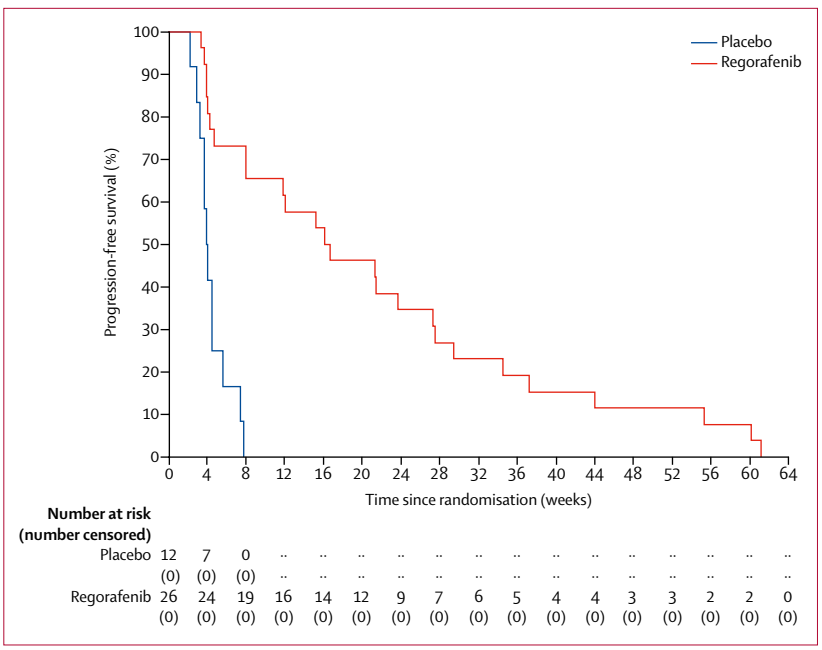

Figure 2: **Progression-free survival, according to blinded central review**

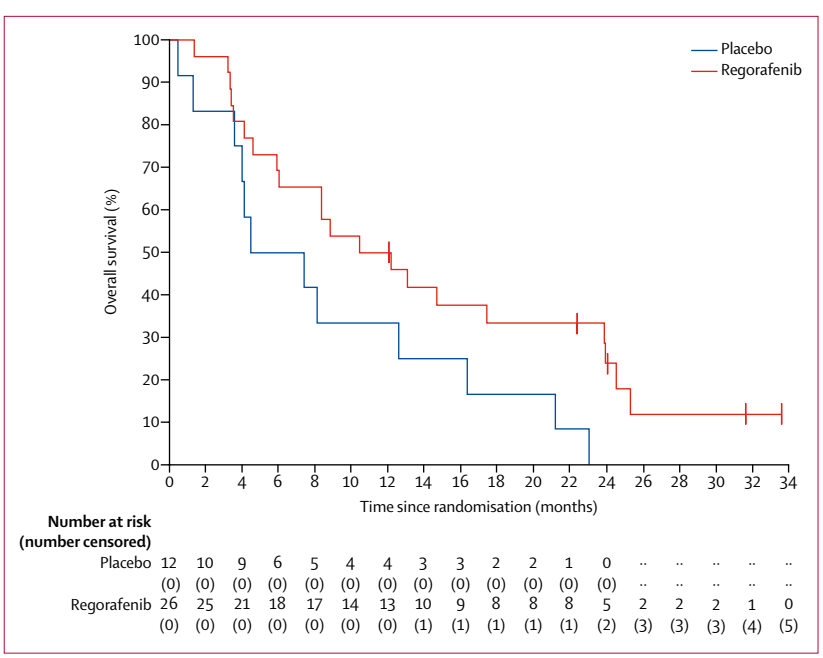

Figure 3: **Overall survival**
The figure includes the ten (83%) of 12 patients in the placebo group who crossed over to regorafenib (they are represented in the placebo group on the figure). Vertical lines denote censored patients.

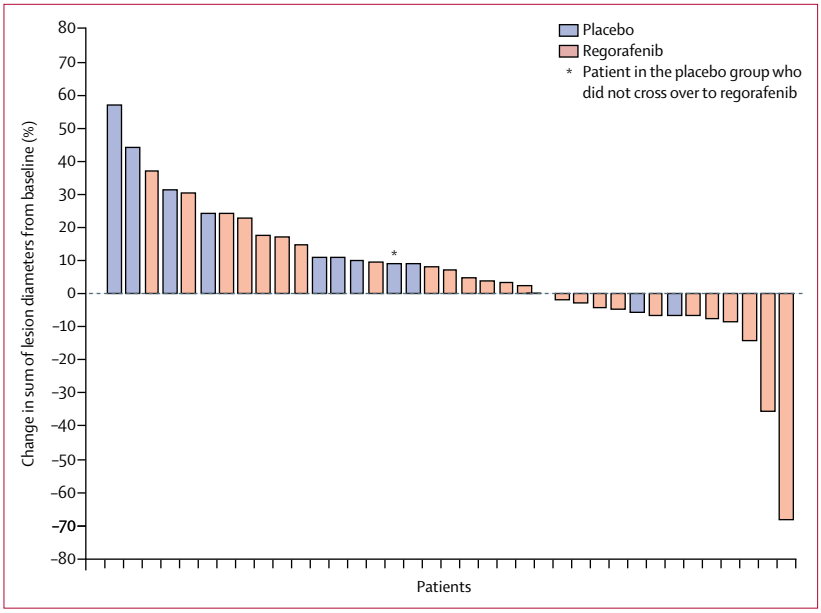

Figure 4: **Waterfall plot of best responses (reductions in sum of lesion diameters from baseline)**
The figure shows best change from randomisation in sum of lesions diameters (%) in the two treatment groups before crossover. Only 37 of 38 patients are shown on the figure; one patient in the placebo group died 16 days after treatment initiation before any tumour evaluation.

	Regorafenib			Placebo (n=12)	Patients excluded from efficacy analysis (n=5)
	Initially assigned to regorafenib (n=26)	Received regorafenib after switch from placebo (n=10)	Subtotal (all patients who received regorafenib; n=36)		
Duration of treatment, months	3·4 (2·1–7·6)	3·9 (1·6–6·3)	3·4 (1·6–7·0)	1·1 (0·9–1·3)	4·5 (1·0–5·3)
Dose reduction					
No	16 (62%)	6 (60%)	22 (61%)	11 (92%)	4 (80%)
Yes	10 (38%)	4 (40%)	14 (39%)	1 (8%)	1 (20%)
Reduction to dose level −1 (120 mg/day, for 3 of 4 weeks)	7 (27%)	2 (20%)	9 (25%)	1 (8%)	0
Reduction to dose level −2 (80 mg/day, for 3 of 4 weeks)	3 (11%)	2 (20%)	5 (14%)	0	1 (20%)

Data are median (IQR) or n (%).

Table 3: **Treatment administration**

any p values in our non-comparative signal-seeking study, the difference between the two progression-free survival curves is of interest, especially since the confidence intervals do not overlap.

We extensively debated our study design when planning this trial, and we respect the fact that determination of the optimal trial design to seek an efficacy signal of new drugs in advanced osteosarcoma and other bone sarcomas is challenging. We note that leaders in the osteosarcoma community have posited uncontrolled phase 2 trials as sufficient to determine signals of efficacy, including work by Lagmay and colleagues.[1] However, we also recognise that this idea might still be controversial beyond the community of osteosarcoma experts. Rather than doing a single-arm phase 2 trial, in which the basal hypothesis cannot be checked, we decided to add a placebo group in our study in order to address the critique that selection bias might drive the results noted with regorafenib. The placebo group was only included to check the outcomes between the enrolled patients and expectations from historical patient series with respect to clinical outcome obtained with standard treatments. We feel that this design was justified and adds to the ability to believe the outcomes showing some efficacy with regorafenib in this disease. The potential for patients to cross over from placebo to unblinded study drug at progression in this trial makes the randomised, phase 2 trial more acceptable to physicians, patients, and ethical review committees, who are appropriately cautious especially when children are enrolled in blinded randomised placebo-controlled trials. The frequent serial disease evaluation (every 4 weeks) in both groups during the first 4 months in this study also enabled investigators to detect progression early and to respond rapidly by offering patients initially allocated to the placebo group crossover to regorafenib after centrally confirmed disease progression. For all these reasons, our investigative team believes that this study as designed (and as approved by the French regulatory and ethical authorities) was ethically sound and fully appropriate for a signal-seeking trial. Of course, the crossover design also compromises the ability to assess the clinical effect—if any—on overall survival. Central review of scans was done online in a relatively real-time manner to confirm progression before any unblinding and consideration of crossover.

We also note that there is great heterogeneity of patients with osteosarcoma in any phase 2 study population (eg, sensitive *vs* refractory disease to first-line treatment; first *vs* subsequent relapses; local *vs* metastatic relapse; and resectable *vs* unresectable recurrent or metastatic disease). We felt that this fact further justifies our choice of a randomised phase 2 trial design, especially when using progression-free survival as the primary endpoint, while also noting that it is more feasible to accrue an adequate sample size in rare diseases in smaller randomised phase 2 designs than in large definitive phase 3 trials.[34] Blinded randomised trials might further avoid bias of relapse over-estimation in any control group.[32]

Our results are in accordance with those of single-arm phase 2 studies by Grignani and colleagues in relapsed and unresectable osteosarcoma, which reported a median progression-free survival of 4 months (95% CI 2–5) with sorafenib alone, and of 5 months (2–7) with sorafenib

	Regorafenib group (n=29)				Placebo group (n=14)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders								
Anaemia	7 (24%)	0	0	0	1 (7%)	0	0	0
Lymphopenia	4 (14%)	1 (3%)	0	0	0	0	0	0
Thrombocytopenia	3 (10%)	0	0	0	0	0	0	0
Gastrointestinal disorders								
Diarrhoea	11 (38%)	2 (7%)	0	0	1 (7%)	0	0	0
Nausea	7 (24%)	0	0	0	5 (36%)	0	0	0
Constipation	9 (31%)	2 (7%)	0	0	0	0	0	0
Abdominal pain	7 (24%)	0	0	0	0	0	0	0
Dry mouth	5 (17%)	0	0	0	1 (7%)	0	0	0
Vomiting	4 (14%)	0	0	0	1 (7%)	0	0	0
Stomatitis	4 (14%)	0	0	0	0	0	0	0
General disorders and administration site conditions								
Fatigue	23 (79%)	3 (10%)	0	0	6 (43%)	1 (7%)	0	0
Mucosal inflammation	9 (31%)	0	0	0	1 (7%)	0	0	0
Chest pain	3 (10%)	3 (10%)	0	0	1 (7%)	0	0	0
Fever	7 (24%)	0	0	0	0	0	0	0
Investigations								
Weight decreased	10 (35%)	0	0	0	0	1 (7%)	0	0
Blood alkaline phosphatase increase	5 (17%)	2 (7%)*	0	0	1 (7%)	0	0	0
Lymphocyte count decreased	5 (17%)	0	0	0	0	1 (7%)	0	0
Transaminases increased	5 (17%)	1 (3%)*	0	0	0	0	0	0
Blood bilirubin increased	5 (17%)	0	0	0	0	0	0	0
Gamma-glutamyltransferase phosphatase increase	5 (17%)	0	0	0	0	0	0	0
Hyperbilirubinaemia	2 (7%)	1 (3%)	0	0	0	0	0	0
Lipase increase	0	1 (3%)*	0	0	0	0	0	0
Metabolism and nutrition disorders								
Decreased appetite	9 (31%)	1 (3%)	0	0	0	1 (7%)	0	0
Hypophosphataemia	2 (7%)	2 (7%)†	1 (3%)†	0	0	0	0	0
Hypokalaemia	0	2 (7%)	0	0	0	1 (7%)	0	0
Musculoskeletal and connective tissue disorders								
Muscle spasms	5 (17%)	0	0	0	0	0	0	0
Back pain	4 (14%)	0	0	0	0	0	0	0
Myalgia	1 (3%)	0	0	0	0	1 (7%)	0	0
Muscle atrophy	0	0	0	0	0	1 (7%)	0	
Nervous system disorders								
Headache	7 (24%)	0	0	0	1 (7%)	0	0	0
Dysgeusia	3 (10%)	0	0	0	0	0	0	0
Epilepsy	0	1 (3%)*	0	0	0	0	0	0
Anxiety	5 (17%)	0	0	0	0	0	0	0
Renal and urinary disorders								
Proteinuria	7 (24%)	0	0	0	1 (7%)	0	0	0
Respiratory, thoracic, and mediastinal disorders								
Dysphonia	9 (31%)	0	0	0	1 (7%)	0	0	0
Dyspnoea	7 (24%)	1 (3%)	0	0	2 (14%)	0	0	0
Cough	5 (17%)	0	0	0	2 (14%)	0	0	0
Pleural effusion	0	2 (7%)	0	0	0	0	0	0
Haemothorax	0	1 (3%)*	0	0	0	0	0	0
Respiratory distress	0	0	0	1 (3%)	0	0	0	0

(Table 4 continues on next page)

	Regorafenib group (n=29)				Placebo group (n=14)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous page)								
Skin and subcutaneous tissue disorders								
Hand–foot skin reaction	12 (41%)	3 (10%)†	0	0	1 (7%)	0	0	0
Other skin toxicity	12 (41%)	1 (3%)	1 (3%)	0	2 (14%)	0	0	0
Vascular disorders								
Hypertension	5 (17%)	7 (24%)‡	0	0	2 (14%)	0		0

Data are n (%). *One patient had a related serious adverse event. †Two patients had a related serious adverse event. ‡Three patients had a related serious adverse event. Several related serious adverse events could have occurred in one patient.

Table 4: **Adverse events (before crossover)**

and everolimus.[19,20] Other phase 2 trials in refractory osteosarcoma have reported low overall responses and short progression-free survival. For example, the combination of cixutumumab and temsirolimus led to six (11%) of 54 patients achieving an overall response, with a median progression-free survival of 6 weeks (95% CI 5·9–12),[10] while in the R1507 study of the monoclonal antibody to IGF-1R, only two (5%) of 38 patients achieved an overall response and 12-week progression-free survival was 17% (95% CI 11·2–22·6).[11]

Given its short duration of administration before disease progression occurred, we do not believe that the previous exposure to placebo significantly affected the impact of open-label regorafenib after crossover. Additionally, the fact that the median progression-free survival is approximately the same after crossover from placebo to regorafenib as in the patients initially randomly assigned to regorafenib further serves as confirmation of the clinical activity of regorafenib.

We do not believe one can make subtype-specific conclusions from this small non-comparative study, and the potential confounding impact of inter-patient variations in disease behaviour cannot be definitively ruled out. However, the conclusion that regorafenib itself, rather than disease-specific behaviour, is the cause for the delay in progression of disease is also supported by the data from the patients initially randomly assigned to placebo after crossover to open-label regorafenib, in whom the rapid disease progression on placebo was slowed by the introduction of regorafenib.

Furthermore, our study showed a particularly clinically meaningful result in that a third of these patients with metastatic disease remained free from progression at 6 months in the regorafenib group. Apart from Grignani and colleagues' phase 2 trial[20] combining sorafenib and everolimus, which reported an impressive 6-month progression-free survival of 45%, to our knowledge, no other osteosarcoma trial has reported such prolonged duration of disease control following failure of standard chemotherapy in adult patients. Moreover, the median progression-free survival of 16 weeks in the group initially randomly assigned to regorafenib and of 19 weeks in the patients initially assigned to placebo who crossed over to open-label regorafenib in our study confirms a positive effect of this agent in controlling disease progression.

Even if time-to-progression after crossover were equivalent to that observed for patients initially randomly assigned to receive regorafenib, this placebo group consists only of 12 patients, including two who died before crossover. This fact might explain the observed trend in overall survival between the two groups. Moreover, the confidence intervals of the overall survival curves are large and overlap each other in this small non-comparative study. We note the consistency in our trial with previous results from others testing similar multikinase inhibitors in patients with metastatic osteosarcoma: the median overall survival of 11·3 months (95% CI 5·9–23·9) in the regorafenib group of our trial is very similar to the median overall survival of 10 months (8–15) in the previously reported phase 2 study of sorafenib and everolimus.[20] While still regrettably short-lived, we believe that these overall survival durations are both clinically meaningful for patients and might potentially add to any other benefits derived from other conventional agents available to treat osteosarcoma in this relapsed and refractory setting.

Early clinical data suggest activity of VEGFR-inhibiting kinase inhibitors such as sorafenib and sunitinib in patients with bone sarcomas.[17,18] All these agents, similar to regorafenib, inhibit several signalling kinases, including KIT, PDGFR, and, to a lesser extent, RET and FGFR1; however, whether antiangiogenesis inhibition or a range of other kinase inhibitory activities might explain activity from these relatively non-selective kinase inhibitors remains unclear.

This study also confirms that metastatic osteosarcoma is a very aggressive disease, with a median progression-free survival of only 4 weeks in the placebo group—worse than our null hypothesis of 6 weeks as expected. We did not record any unexpected toxicity in this trial, and the overall toxicity and safety of regorafenib were as expected and quite acceptable and manageable. We note that regorafenib might not be tolerable at the full dose (160 mg per day) in a large fraction of patients, and our data suggest that patient-specific dose modification to deliver a dose tailored to each individual patient tolerance

(since dose modifications were allowed in our trial) might represent a clinically beneficial dosing strategy.

This trial was not stratified by sex, since this is not a proven prognostic nor predictive factor for treatment outcomes in recurrent osteosarcoma after failure of conventional chemotherapy. Although there was a slight imbalance in sex between the two groups, we do not believe this to be a major concern in this non-comparative trial. Given the trial's non-comparative design and small size, no statistical test across sex would have any power to assess this, and we do not believe there is any biological reason to think that this imbalance affected the outcomes in any meaningful way. We also acknowledge the small imbalance in ECOG performance status between the two groups, amplified by the small sample size in the placebo group. This small non-comparative trial was not stratified for that variable, but this is not viewed as a major concern given the known variations in assessment of ECOG status across these close ranges (ECOG status 0 or 1) in this non-comparative trial. Patients with ECOG status 2 were not included in the trial to minimise the potential confounding effects of inter-patient clinical heterogeneity, given the small trial size. In terms of previous chemotherapy, we note that the role of ifosfamide in osteosarcoma remains controversial, but in France this agent has been studied in the first-line treatment of adult osteosarcoma patients in a recent national French Osteosarcoma protocol (OS2006),[35] which probably explains the relatively high percentage of patients with previous ifosfamide treatment.

Our study does have some limitations. This trial was statistically non-comparative, done in only one country, on a small number of patients, and recruited adult patients with osteosarcoma only; accrual in paediatric patients could not be accomplished. We would have liked to have seen accrual in paediatric patients, but the early use of placebo probably discouraged participation. These factors mean that the generalisability of our study's findings to other populations of osteosarcomas might be debatable. Additionally, since regorafenib is a multikinase inhibitor, with antiangiogenic and other activities, it is impossible to determine whether one target of inhibition is driving the antitumour activity more than another. The anti-VEGFR or the anti-PDGFR activities might be important, and the anti-KIT action of regorafenib might also contribute to the activity observed—these questions are important for future research. Since this academic trial was designed to explore the activity and safety of regorafenib and was funded only for these clinical outcome trial elements, practical limitations restricted our ability to do correlative science analyses. Although to study biological correlates and perform mechanistic studies that might clarify the specific molecular target(s) of regorafenib responsible for the activity noted was beyond the scope of our trial, we hope that our results will stimulate more fundamental research in this area.

As reported by Omer and colleagues[32] in their recent systematic review of past experience in phase 2 trials in recurrent osteosarcoma, we agree that there is a need to develop international randomised phase 2 trials across all age ranges in metastatic and advanced osteosarcoma with a standardised primary endpoint. The results of the ongoing randomised, placebo-controlled trial by the SARC group (NCT02048371), also exploring the activity and safety of regorafenib versus placebo in patients with metastatic osteosarcoma, will also be interesting in light of the encouraging results from our trial. Our results might also provide a basis for future trials in adults with osteosarcoma, such as in patients with earlier stage disease or those with suboptimal histological responses to first-line chemotherapy who are at high risk of relapse. Although the complex biology of osteosarcoma makes targeted agents unlikely to succeed as monotherapy, very few combination treatments have been tested so far. Future studies of combined therapies targeting different and potentially synergistic pathways are warranted, especially given the new biology showing common DNA damage and repair aberrancies in osteosarcomas. Sequencing tyrosine kinase inhibitor therapy with other conventional therapies is also a new concept for osteosarcoma that deserves to be an area for future research.

Contributors

SC and FD contributed to the trial concept and design. All authors contributed to data collection. SC and CS did the statistical analysis. SC, CS, and FD did the data analysis and the interpretation. FD, JD, and SC supervised the study. All the authors reviewed the report for intellectual content, provided comments, and approved the manuscript for publication.

Declaration of interests

FD reports personal fees from Lilly, Pharmamar, and Bayer outside the submitted work. OM reports personal fees from Amgen, Bayer, Blueprint Medicines, BMS, Lilly, Ipsen, Lundbeck, MSD, Pfizer, Roche, Servier, and Vifor Pharma, outside the submitted work. J-YB reports personal fees from BMS, Roche, and Novartis, outside the submitted work. All other authors declare no competing interests.

Data sharing

This statement is intended to clarify UNICANCER'S position on data sharing with regard to applicable regulatory frameworks. European regulatory framework: De-identified study data are considered as personal data within the meaning of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016, known as GDPR. As a result, their transfer places further processors in the scope of GDPR (Art. 2 and 3) and is notably subject to: precise information of study subjects (Art. 14); prior identification of further processors and signature of a transfer agreement (Chapter V); and data protection impact assessment (Art. 35). French regulatory framework: In addition to GDPR, the transfer of this data by UNICANCER is a processing in itself that is subject to Chapter IX and XII of the updated Law no. 78–17 of Jan 6, 1978. Within the framework of this law, the data processing is permitted by UNICANCER's conformity to the MR-001 Code of conduct (Délibération no. 2018-153 du 3 mai 2018 portant homologation d'une méthodologie de référence relative aux traitements de données à caractère personnel mis en œuvre dans le cadre des recherches dans le domaine de la santé avec recueil du consentement de la personne concernée). In its last update from May 2018, MR-001 was updated to allow transfer to reviewers within certain conditions (Article 2.4). These conditions can be summarised as follows: The access to study data by an independent mandated reviewer can only be granted through an interface chosen by the data processor (ie, UNICANCER, in this context) for the purpose of re-analysis, or for any

other purpose supported by a strong rational and a project synopsis describing why access to the REGOBONE study data is necessary. The data processor shall ensure: that the chosen sharing platform cannot allow extraction of the data; to grant specific personal and differentiated authorisations to access the data; that the users be reliably identified; that state of the art cryptography and security measures are used; that an audit trail of accesses is used; when data are transferred outside of the EU, that applicable transfer contracts are established; that study subjects are informed on the data recipients; that the data are used for the sole purpose of reproducing published results; and that the data is cleaned from any directly identifying data and that the principle of data minimisation is applied (ie, limiting the transfer to data used in the publication). As a result, for the REGOBONE trial, UNICANCER can share individual participant data that underlie the results reported in the article, or other data as stipulated above, under the following conditions: limitation to the data processing to the purpose of independent review of the published results or for a new intended project; prior minimisation of the data (ie, restriction to data strictly adequate, relevant and limited to the purpose of the independent review of results or for the intended new project); prior identification of the reviewer and authorisation from UNICANCER for a personal access; and following the signature of a transfer agreement with UNICANCER, in conformity with the European Commission's Standard Contractual Clauses. Access to study data will be assessed, upon written detailed request sent to the regobone@unicancer.fr email address, from 6 months until 5 years following article publication.

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