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Efficacy and safety of regorafenib in patients with metastatic or locally-advanced chondrosarcoma: results of a non-comparative, randomised, double-blind, placebo controlled, multicentre phase II study

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Highlights:

Progression-free rate at 12 weeks was 54% on regorafenib and 31% on placebo

Median PFS was 19.9 weeks on regorafenib, and 8.0 weeks on placebo

PFS rate at 24 weeks was 43% for patients on regorafenib, and 25% on placebo

The safety of regorafenib was as expected despite one fatal case of hepatic toxicity

These results suggest modest activity of regorafenib in metastatic chondrosarcoma

Abstract:

Background: This multi-cohort trial explored the efficacy and safety of regorafenib for patients with advanced sarcomas of bone origin; this report details the cohort of patients with metastatic or locally-advanced chondrosarcoma (CS), progressing after prior chemotherapy.

Patients and Methods: Patients with CS, progressing despite prior standard therapy, were randomised (2:1) to receive regorafenib or placebo. Patients on placebo could cross-over to receive regorafenib after centrally-confirmed progressive disease. The primary-end point was progression-free rate (PFR) at 12 weeks. With 1-sided α of 0.05, and 80% power, at least 16/24 progression-free patients at 12 weeks were needed for success ($P_0=50\%$, $P_1=75\%$).

Results: From September 2014 to February 2019, 46 patients were included in the CS cohort. 40 patients were evaluable for efficacy: 16 on placebo, and 24 on regorafenib. Thirteen patients (54.2% ; 95% CI [35.8%-]) were non-progressive at 12 weeks on regorafenib vs. 5 (31.3%; 95% CI [13.2%-]) on placebo. Median PFS was 19.9 weeks on regorafenib, and 8.0 on placebo. Fourteen placebo patients crossed over to regorafenib after progression. The most common Grade ≥ 3 treatment-related adverse events on regorafenib included hypertension (12%), asthenia (8%), thrombocytopenia (8%), and diarrhea (8%). One episode of fatal liver dysfunction occurred on regorafenib.

Conclusion: Although the primary-endpoint was not met statistically in this small randomized cohort, there is modest evidence to suggest that regorafenib might slow disease progression in patients with metastatic CS after failure of prior chemotherapy.

Clinical Trial Registration: The trial is registered at ClinicalTrials.gov (NCT02389244)

Key words: metastatic chondrosarcoma, progression after standard chemotherapy, regorafenib

Introduction:

Chondrosarcomas are a heterogeneous group of mesenchymal tumors representing the second most common primary bone tumor in adults, and accounting for 20% of new primary bone cancer cases. In the past three decades, there has been no significant improvement in the survival of patients with metastatic chondrosarcoma, which has no standard systemic therapy of any proven efficacy; nothing beyond surgical resection has proven benefit, (1,2) with only anecdotal activity reported with a variety of sarcoma-focused cytotoxic regimens (2-5). Consequently, there is a clear need for more effective systemic treatment for patients with metastatic and/or unresectable advanced chondrosarcoma.

Early clinical data suggest activity of VEGFR kinase inhibitors such as sorafenib and sunitinib in patients with bone sarcomas (6,7). Regorafenib demonstrated antitumour activity in pretreated metastatic non-adipocytic soft tissue sarcoma (8), a population for which pazopanib has also

demonstrated activity in prolonging PFS (9). Furthermore, compared with placebo, regorafenib also improved PFS in chemotherapy-refractory metastatic osteosarcoma (10) (4.0 versus 1.0 months) in the REGOBONE osteosarcoma cohort. The objective of the present study, was to explore the antitumour activity of regorafenib in patients with progressive metastatic and/or recurrent chondrosarcoma after failure of conventional chemotherapy.

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 histopathologic subtypes. Parallel cohorts assessed the activity and safety of regorafenib or placebo, using a randomised, non-comparative, double-blind, placebo-controlled phase 2 trial design. We present now the results of the chondrosarcoma cohort.

The study was approved by an ethical and regulatory committee (French Ethical Committee, Comité de Protection des Personnes Sud Méditerranée 1, approved on March 26, 2014). All patients provided written informed consent before enrolment, and one study amendment (protocol V6, June 29, 2016) expanded enrollment to include paediatric patients aged > 10 years (although ultimately no children were enrolled). The trial is registered in the European Clinical Trials Register database (EudraCT N°: 2013-003910-42) and at ClinicalTrials.gov (NCT02389244). Eligible patients were required to have histological diagnosis of chondrosarcoma, and objective disease progression within 6 months prior to 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 1-2 previous lines of chemotherapy for locally-advanced or metastatic disease. The complete list of other eligibility criteria, along with the protocol are described in the **Appendix A1** are 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 crossover 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, 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, three 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 anti-neoplastic agents. Dose interruptions and/or dose reductions recommendations have been previously described (10).

The primary endpoint was the progression-free rate (PFR) at 12 weeks, defined as the proportion of patients without disease progression at 12 weeks, after confirmation by central radiological review according to RECIST1.1. Secondary endpoints included: progression-free survival (PFS) per modified RECISTv1.1, objective response rate (ORR), overall survival (OS), duration of overall response (DoR), 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 chondrosarcoma following failure of standard treatments. The literature reported the median of PFS with an inactive drug was about 12 weeks for metastatic chondrosarcoma (5, 12), and that an active drug should at least double this median to be considered of interest. At the same time, a large retrospective study (4) that analysed the benefit of first-line chemotherapy in 180 metastatic chondrosarcoma patients reported a median PFS for the overall group of 4.7 months [95% confidence interval (CI) 3–6.5]. Therefore, we chose progression-free rate at 12 weeks as the primary endpoint. We calculated the sample size by A'Hern single stage design for phase 2 trials similar to a Fleming phase II design but assuming an exact binomial distribution (13). These hypotheses on median PFS translated into a 75% progression-free rate at 12 weeks, defined as the expected efficacy in the experimental arm. A limit of 50% or less would mean that the regorafenib did not warrant further investigation. A sample size of 23 patients provided 80% power to reject the null hypothesis with a one-sided, type 1 error of 5%, with 16 successful patients being the lower cutoff point of decision making. To account for a possible non-assessable patient rate of 5%, an additional patient was required in the experimental arm (total 24 patients). A sample size of 12 evaluable 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 CS patients who received at least one dose of the intended treatment. The severity of the adverse events was graded according to the NCI-CTCv4.0. The percentage of progression-free patients at 12 weeks was calculated in each arm with their respective 95% confidence interval. PFS and OS were estimated using the Kaplan-Meier method. We used SAS (version 9.4) for all analyses.

Results

From September 24, 2014 to February 04, 2019, forty-six adult patients were accrued and randomised in this CS cohort, representing the population for safety analysis (**Figure 1**). Five patients were excluded from safety and efficacy analyses, all in the regorafenib arm, because the CS diagnosis was not histologically confirmed by central review (2 patients with diagnosis changed to osteosarcoma were included in the REGOBONE osteosarcoma cohort (29), 1 patient with chordoma, and 2 patients with soft tissue sarcomas). One CS was excluded from the efficacy analysis, in the regorafenib arm, due to lack of confirmed progressive disease at study entry. In total, 40 patients with histologically confirmed advanced chondrosarcoma with confirmed disease progression constitute the population for efficacy analysis: 24 patients randomised to regorafenib, and 16 initially on placebo. Two patients remain on therapy at the time of analysis, 1 on blinded treatment, and 1 on regorafenib after cross-over.

As described precisely in **Table 1**, the baseline characteristics of 40 patients were well balanced between the two arms except for a small imbalance in age, ECOG Performance Status, and in histological subtype. Histological subtypes other than conventional CS were slightly more frequent in the regorafenib arm (21%), than on placebo (13%). Seventy-two percent of patients received only one previous chemotherapy regimen for metastatic/recurrent disease prior to study entry. All patients had metastatic disease except two with locally advanced disease in the placebo arm. The majority of patients had previously received doxorubicin, cisplatin and ifosfamide.

At the time of the analysis, the median follow-up of surviving patients was 35.9 months (IQR 29-46.8). Efficacy endpoints are reported in **Table 2**. Thirteen patients (54% one-sided 95% CI [35.8%-]) were non progressive at 12 weeks in the regorafenib group while 5 (31% one-sided 95% CI [13.2%-]) were progression-free on placebo. Two durable partial responses were observed in the regorafenib arm of 6.6 and 16.6 months respectively. At the time of the analysis, 18 of 24 patients (75%) progressed

after randomisation to the regorafenib arm, *versus* 15 of 16 patients (94%) initially randomised to placebo; 18 deaths in 24 patients (75%) were reported in the regorafenib arm versus 11/16 (69%) deaths on placebo. All causes of death except one were disease progression.

Median PFS was 19.9 weeks (95%CI 11.4-34.9) in the regorafenib arm, and 8.0 weeks (95%CI 4.3-23.4) on placebo. PFS rate at 12 weeks was 61% (95%CI 39-78), and 43% (95%CI 23-62) at 24 weeks, for patients on regorafenib, versus 31% (95%CI 11-54) and 25% (95%CI 8-47) on placebo, respectively. Following centralised confirmation of progressive disease, 15 of 16 patients randomised to placebo crossed over to regorafenib. One placebo patient did not crossover due to major decline of performance status.

Figure 2 shows the PFS curves per blinded central review. **Figure 3** shows the Overall Survival (OS) curves, including 15 of 16 (94%) of placebo patients who crossed over to open-label regorafenib.

The median OS is 11.7 months (95% CI 7.2-18.8) for patients randomised to regorafenib and 19.9 months (95% CI 6.2-40) for those randomised to placebo. The swimmer plots on **Figure 4** show the initial PFS and PFS after cross over for the 15 patients initially randomised to placebo who subsequently received open-label regorafenib. The waterfall plots on **Figures 5** show the tumour responses obtained on blinded treatment, and on open-label regorafenib.

The median treatment duration was 3.4 months (95%CI 1.6-8.3) on regorafenib, 1.7 months (95%CI 1.6-1.7) on placebo. Transient discontinuation, occurred in 11 (46%) of 24 patients in the regorafenib arm, and in 7 (44%) of 16 patients on placebo. Dose reductions were reported in 15 (63%) of 24 patients in the regorafenib arm *versus* 1 (6%) of 16 patients on placebo. Regorafenib was reduced to 120mg/ day for 10 patients (41.7%) and to 80 mg/ day for 5 patients (20.8%), placebo was reduced to 80 mg/day for one patient (6.3%).

Dose reductions for toxicity were reported in 12 (50%) of 24 patients in the regorafenib arm *versus* 0 (0%) of 16 patients on placebo, and were due to haematological toxicity in 1 patient (thrombocytopenia), and to non-haematological toxicities in 12 patients, mainly hand-foot syndrome (N=4), asthenia (N=3), diarrhea (N=3), weight loss (N=2) and arthralgia (N=2). Four treatment-related serious adverse events occurred (16%) in 25 patients in the regorafenib arm vs 0 (0%) of 16 patients on placebo. All were at least grade 2, including arrhythmia (N=1), ulcerative keratitis (N=1), hepatocellular injury/liver cytolysis (N=1), and headache (N=1). Safety data are shown in **Table 3** for the two groups until optional crossover. The most common grade ≥ 3 treatment-related AEs during the double-blind period in the regorafenib arm included pain (20%), hypertension (12%), asthenia (12%), thrombocytopenia (8%), diarrhoea (8%), and hypokaliemia (8%). There was one toxic death reported on regorafenib linked to Grade V hepatic toxicity.

Discussion

Prior data from the osteosarcoma cohort of this multi-cohort trial indicated activity of regorafenib in delaying progression of that form of bone sarcomas. However, the data from this cohort study did not meet the primary endpoint to be considered a success. According to the study design criteria for success, 16/24 non progressive patients at 12 weeks in the regorafenib arm would have been necessary for a positive criterion. This number is not reached with only 13 successes (54.2%). However, considering placebo results: with only 5/16 (31.3%) non progressive patients at 12 weeks, widely below P0 hypothesis, and with a median PFS of 19.9 weeks with regorafenib, versus of 8 weeks on placebo, or 12.0 weeks in the placebo patients who crossed-over to open-label regorafenib, our study suggest that regorafenib might nonetheless have modest activity in this setting. It might slow disease progression in patients with progressive metastatic CS after failure of prior chemotherapy

Furthermore, our study showed a meaningful result with 47% of these metastatic patients remaining progression-free at 6 months on regorafenib, while only 25% on placebo remained with stable disease. Surprisingly in our regorafenib arm, our results may appear inconsistent with those reported with pazopanib (14) in a single-arm phase 2 study, with a median PFS of 19.9 weeks (less than 5 months) with regorafenib versus 7.9 months with pazopanib, and with PFR at 12 weeks of 54.2% with regorafenib versus a DCR (disease control rate) at 16 weeks (primary endpoint) of 43% with pazopanib. However, the 6-month PFS rates with kinase inhibitors are quite similar with a 6-months (24-weeks) PFS rates of 47% with regorafenib, 47% with dasatinib (15), and 55% with pazopanib (14) respectively.

Although the median OS is 11.7 months (95% CI 7.2-18.8) for patients randomised to regorafenib and 19.9 months (95% CI 6.2-40) for those on placebo, the confidence intervals are overlapping in this small study and, virtually all the placebo-treated patients crossed over to receive open-label regorafenib.

This study also confirms that metastatic chondrosarcoma is a very aggressive disease, with median PFS of 8 weeks on placebo, worse than our null hypothesis of 12 weeks in the study design. Our null hypothesis was probably overestimated. The possible inappropriate choice of our H0 hypothesis might have contributed to the fact that our primary objective was not achieved statistically.

We note that regorafenib may not be tolerable when initiated at full dose (160 mg per day) in a large fraction of patients, and our data suggest that patient-specific dose modifications to deliver a dose tailored to individual patient tolerance may nonetheless represent a clinically beneficial dosing strategy. The overall safety profile of regorafenib was as previously published and generally amenable to dose modifications, although we did note one episode of fatal hepatic toxicity.

The present study has other limitations, since it was statistically non-comparative, done in only one country, and included a relatively small number of patients.

Although this trial did not meet the statistical plan to be judged positive, this exploratory randomized trial confirms the aggressive behavior of metastatic CS overall. The data from this cohort will help investigators design other trials to study novel strategies which might eventually improve outcomes for patients with advanced chondrosarcomas. For example, although activity from single agent immune checkpoint inhibitor therapy has been only rarely noted in chondrosarcomas (16-18), regorafenib in combination with anti-PD1 therapy has recently demonstrated very encouraging antitumour activity in patients with advanced gastrointestinal cancers (19). Future studies should extrapolate from the carcinomas to determine if these two therapies (immune activation and targeted therapy) can be combined in a synergistic way to improve chondrosarcoma outcomes.

Additionally, new insights might evolve as to whether molecularly distinct subsets of chondrosarcomas (e.g. CS with IDH1 or IDH2 mutations, or CS with aberrant DNA damage/repair genes) might have different responses to multi-kinase inhibition with regorafenib or other agents. Future trials of new agents will need to take validated targets and explore them for clinical effect in patients with chondrosarcomas in order to make progress against this mesenchymal malignancy.

Funding

Bayer Healthcare SAS (Loos, France) supplied regorafenib and placebo tablets and provided funding to UNICANCER. 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. This study was not funded by NIH.

Author contributions

FD and SC designed and supervised the trial and wrote the article ; FD, SC, and CS, analysed the data and contributed to the trial design. All other authors supervised clinical patient management, reviewed and approved the article.

Conflict of interest statement

FD received travel grants from Pharmamar, and Leo Pharma, attended advisory boards for Bayer, Lilly. CC attended advisory boards for Leo Pharma, OM attended advisory boards and chaired meetings with Amgen, Astra Zeneca, Bayer, Blueprint, Eli Lilly, Roche, Servier, PBR received travel

grants from Pfizer, Takeda, JYB receives research support and honoraria from Eisai, Eli Lilly, MSD, BMS, GSK, Ignyta, Novartis, Pharmamar and Roche unrelated to this work, and AI, CP, NP, OC, LC, CD, MC, LM, MR, EB, SC, FB, CS, SPN, CB, VV, AH, ESB, have declared no conflicts of interest.

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Figure 1: Consort diagram - study population

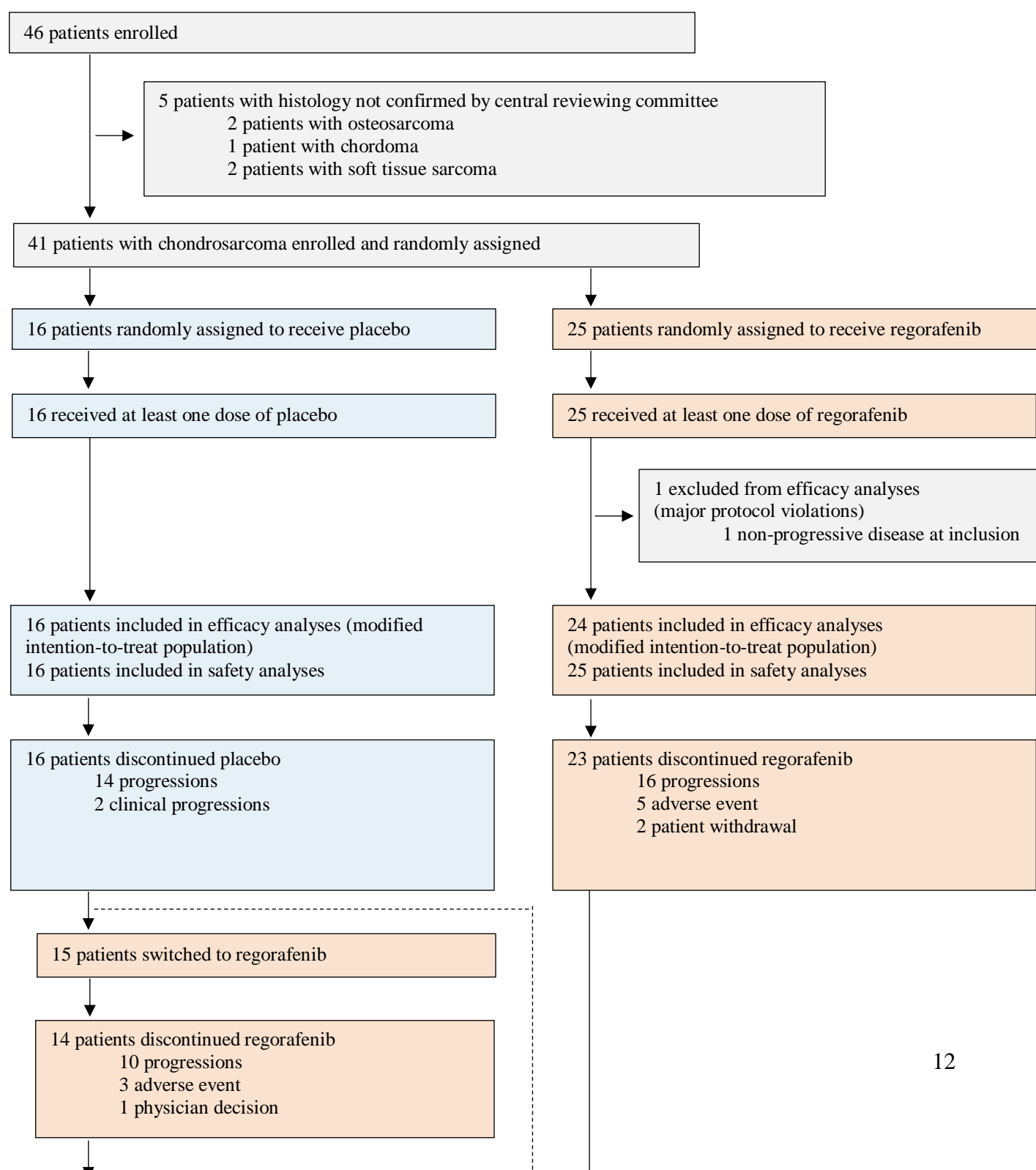


Figure 2: Progression free survival (primary endpoint per blinded central review)

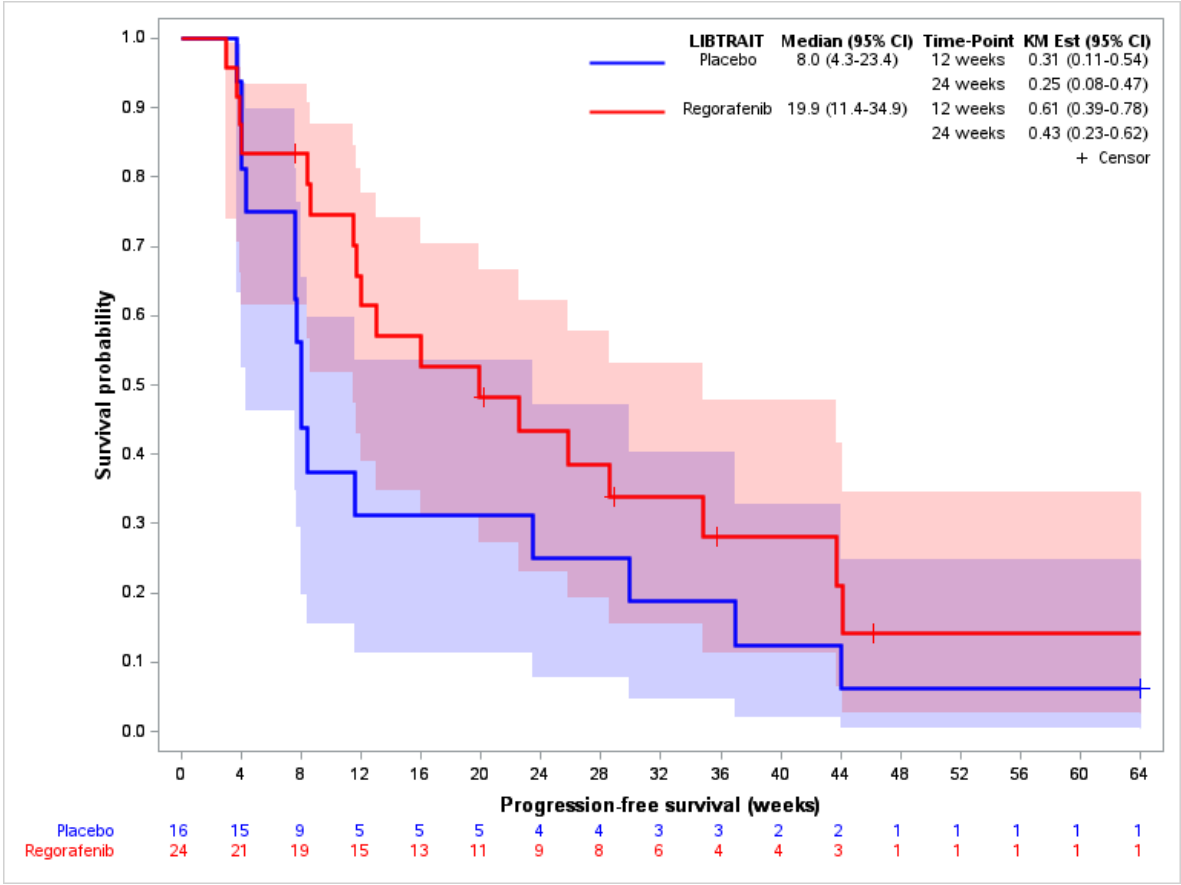


Figure 3: Overall survival including crossed over of 83% of placebo patients

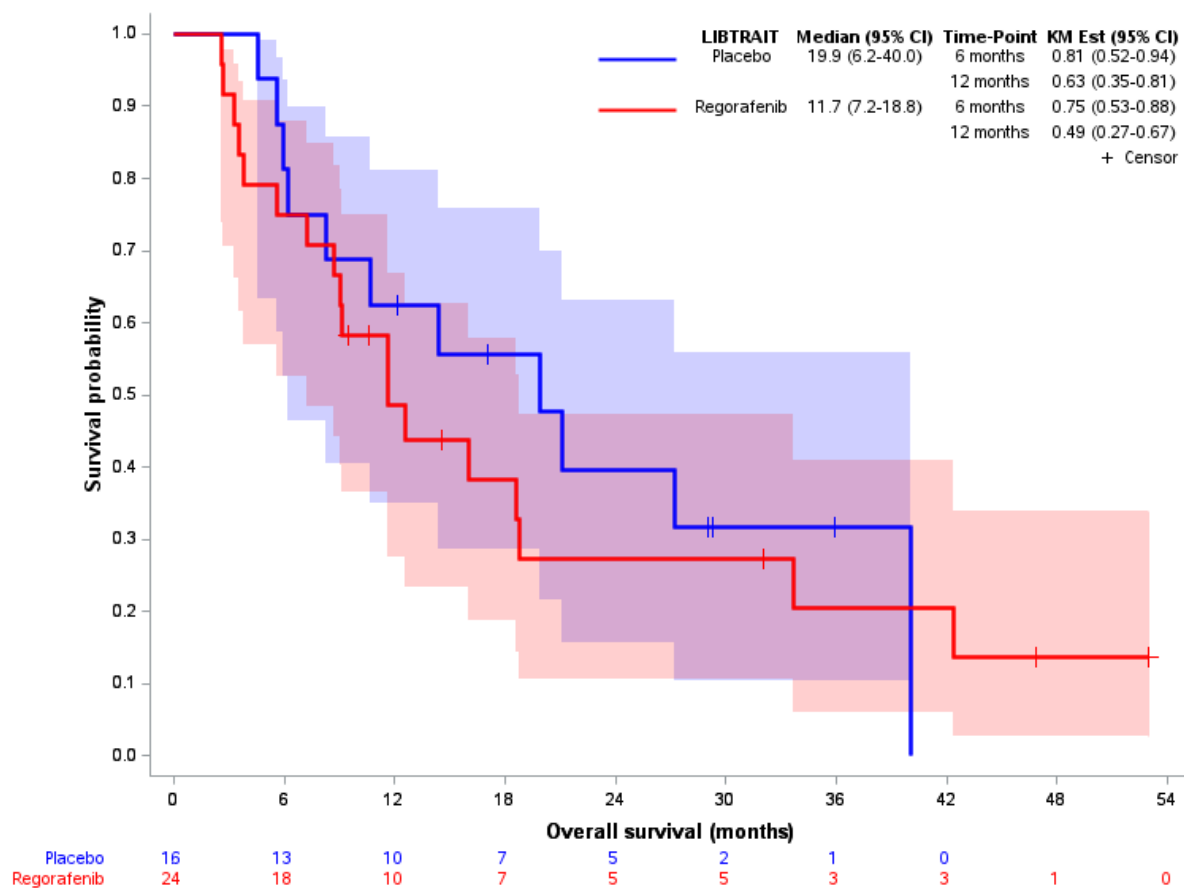


Figure 4: Swimmer plots (in supplementary material)

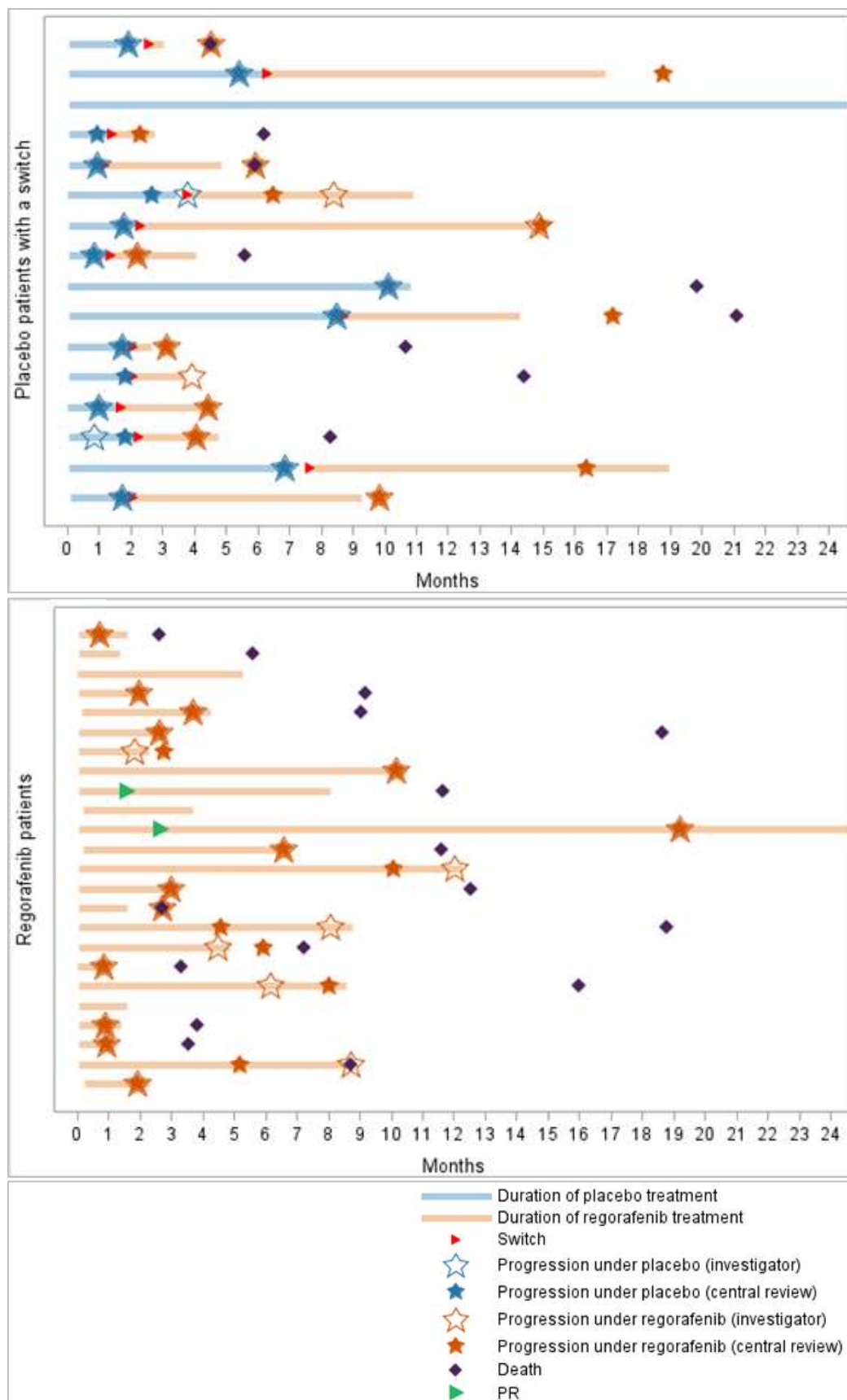


Figure 5: Waterfall plots of best responses (regorafenib arm and placebo arm)

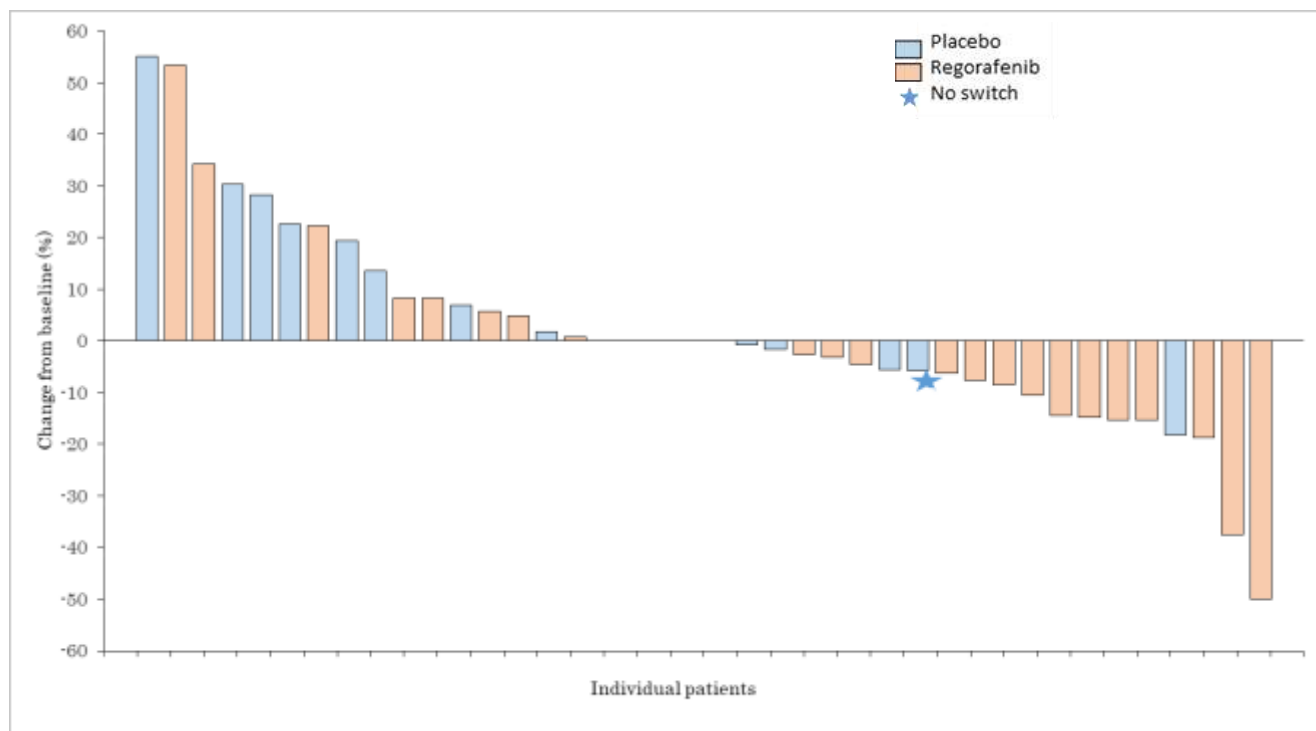


Table 1 : Baseline patient characteristics

		Regorafenib (N=24)	Placebo (N=16)	Excluded from Efficacy analysis (N=1)
Age (median, IQR)		64 (37.5-67.5)	53 (45-67)	60
Sex (n,%)	Male	15 (62)	10 (62)	0 (0)
	Female	9 (38)	6 (38)	1 (100)
ECOG PS (n,%)	0	8 (33)	7 (44)	0 (0)
	1	16 (67)	9 (56)	1 (100)
Histological subtype	Conventional/ other	19 (79) / 5 +(21)	14 (87) / 2++ (13)	1 (100) / 0
Presence of metastases (n,%)	No*	0	2 (12)	0 (0)
	Yes	24 (100)	14 (88)	1 (100)
Sites of metastases (n, %)	Lung	20 (83)	12 (75)	0 (0)
	Bone	3 (12.5)	1 (6.3)	1 (100)
	Lymph node	3 (12.5)	2 (12.5)	0 (0)
Prior lines of chemo for met dis	1	17 (71)	12 (75)	3 (60)
	2	7 (29)	4 (25)	2 (40)
Previous therapy at entry	Doxorubicine	22 (92)	13 (81)	1 (100)
	Ifosfamide	7 (29)	3 (19)	0
	Cisplatin	10 (41)	6 (37)	0
	Oral Cyclo**	5 (21)	3 (19)	0

Data are number of patients (%) or median (range). ECOG= Eastern Cooperative Oncology Group. Patients could have more than one metastasis. No*: locally advanced disease, Oral cyclo**: oral cyclophosphamide
+:2 mesenchymal CS, 2 dedifferennciated CS, and 1 clear cell CS; ++ 1 mesenchymal CS, 1 dedifferenciati CS

Table 2 : Efficacy end-points

		Regorafenib (n=24)	Placebo (n=16)
Non progressive rate at 12 weeks (%)		13 (54)	5 (31)
One-sided Confidence Interval (CI95%)		[35.8 - [[13.2% - [
Response at 12 weeks (%)	PR	2 (8.3)	0
	SD	11 (45.8)	5 (31.3)
	PD	10 (41.7)	11 (68.8)
Median PFS (CI95%), weeks		19.9 (11.4-34.9)	8 (4.3-23.4)
PFS rate at 12 weeks (CI95%)		61 (39-78)	31 (11-54)
PFS rate at 24 weeks (CI95%)		43 (23-62)	25 (8-47)

Table 3: Adverse events in $\geq 10\%$ of patients per treatment group before crossover

	Regorafenib		Placebo	
	N=25		N=16	
	Any grade	>= 3	Any grade	>=3
BLOOD AND LYMPHATIC SYSTEM DISORDERS				
ANAEMIA	4 (12.0%)	1 (4.0%)	1 (6.3%)	0 (0.0%)
THROMBOCYTOPENIA	4 (16.0%)	2 (8.0%)	1 (6.3%)	0 (0.0%)
LYMPHOPENIA	3 (12.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)
GASTROINTESTINAL DISORDERS				
DIARRHOEA	13 (52.0%)	2 (8.0%)	5 (31.3%)	0 (0.0%)
NAUSEA	11 (44.0%)	1 (4.0%)	5 (31.3%)	0 (0.0%)
CONSTIPATION	8 (32.0%)	0 (0.0%)	2 (12.5%)	0 (0.0%)
STOMATITIS	8 (32.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
VOMITING	6 (24.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)
DRY MOUTH	6 (24.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
ABDOMINAL PAIN	3 (12.0%)	0 (0.0%)	2 (12.5%)	0 (0.0%)
HAEMORRHOIDS	4 (16.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS				
PAIN	20 (80.0%)	5* (20.0%)	11 (68.7%)	1 (6.3%)
ASTHENIA/FATIGUE	18 (72.0%)	3 (12.0%)	6 (37.5%)	0 (0.0%)
MUCOSITIS	8 (32.0%)	1 (4.0%)	1 (6.3%)	0 (0.0%)
FEVER	3 (12.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
INFECTION	4 (16.0%)	1 (4.0%)	3 (18.7%)	1 (6.3%)
EYE DISORDERS				
ULCERATIVE KERATITIS	0 (0.0%)	1* (4.0%)	0 (0.0%)	0 (0.0%)
INVESTIGATIONS				
WEIGHT DECREASED	12 (48.0%)	1 (4.0%)	1 (6.3%)	0 (0.0%)
HEPATOCELLULAR INJURY	0 (0.0%)	1* (4.0%)	0 (0.0%)	0 (0.0%)
WEIGHT INCREASED	0 (0.0%)	0 (0.0%)	2 (12.5%)	0 (0.0%)
METABOLISM AND NUTRITION DISORDERS				
ANOREXIA	11 (44.0%)	1 (4.0%)	2 (12.5%)	0 (0.0%)
HYPOALBUMINAEMIA	3 (12.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
NERVOUS SYSTEM DISORDERS				
DYSGEUSIA	5 (20.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)
NEURALGIA	4 (16.0%)	2 (8.0%)	1 (6.3%)	0 (0.0%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS				
DYSPHONIA	10 (40.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)
DYSPNOEA	4 (16.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)
COUGH	4 (16.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS				
OTHER SKIN TOXICITY	15 (60.0%)	1 (4.0%)	1 (6.3%)	1 (6.3%)
HAND AND FOOT SKIN REACTION	12 (48.0%)	1 (4.0%)	3 (18.8%)	0 (0.0%)
PRURITUS	3 (12.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)

CARDIAC/VASCULAR DISORDERS					
ARRHYTHMIA	1* (4.0%)	0 (0.0%)	1 (6.3%)	0 (0.0%)	
HYPERTENSION	9 (36.0%)	3 (12.0%)	4 (33%)	2 (12.5%)	

*** related serious adverse event**