



Regorafenib as second-line therapy for intermediate or advanced hepatocellular carcinoma: Multicentre, open-label, phase II safety study [☆]

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KEYWORDS

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Abstract Purpose: We assessed the safety of the multikinase inhibitor regorafenib in patients with hepatocellular carcinoma (HCC) that had progressed following first-line sorafenib.

Patients and methods: Thirty-six patients with Barcelona Clinic Liver Cancer stage B or C HCC and preserved to mildly impaired liver function (Child–Pugh class A) received regorafenib 160 mg once daily in cycles of 3 weeks on/1 week off treatment until disease progression, unacceptable toxicity, death or patient/physician decision to discontinue. The primary end-point was safety; secondary end-points included efficacy (including time to progression and overall survival).

Results: The median treatment duration was 19.5 weeks (range 2–103). At data cutoff, three patients remained on treatment. Reasons for discontinuation were adverse events ($n = 20$),

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disease progression ($n = 10$), consent withdrawal ($n = 2$) and death ($n = 1$). Seventeen patients required dose reductions (mostly for adverse events [$n = 15$]); 35 patients had treatment interruption (mostly for adverse events [$n = 32$] or patient error [$n = 11$]). The most frequent treatment-related adverse events were hand–foot skin reaction (any grade $n = 19$; grade ≥ 3 $n = 5$), diarrhoea ($n = 19$; $n = 2$), fatigue ($n = 19$; $n = 6$), hypothyroidism ($n = 15$; $n = 0$), anorexia ($n = 13$; $n = 0$), hypertension ($n = 13$; $n = 1$), nausea ($n = 12$; $n = 0$) and voice changes ($n = 10$; $n = 0$). Disease control was achieved in 26 patients (partial response $n = 1$; stable disease $n = 25$). Median time to progression was 4.3 months. Median overall survival was 13.8 months.

Conclusion: Regorafenib had acceptable tolerability and evidence of antitumour activity in patients with intermediate or advanced HCC that progressed following first-line sorafenib.

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1. Introduction

Improved understanding of the molecular pathogenesis of hepatocellular carcinoma (HCC) has highlighted the role of several angiogenic and oncogenic signalling pathways, which offer promising targets for therapy.^{1,2} In clinical trials, the tyrosine kinase inhibitor (TKI) sorafenib, which targets vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and Raf, was associated with significantly longer time to progression and improved overall survival compared with placebo.^{3,4} As a result, sorafenib has become the standard of care as first-line systemic therapy for patients with advanced HCC.^{5,6}

Unfortunately, the benefits of sorafenib may not be sustained (median time to radiological progression 2.8–5.5 months in the phase III clinical trials^{3,4}), although patients with good liver function could well benefit from further therapy.⁷ To date, no available agents have shown clinical benefit as second-line treatment following sorafenib, and the results of clinical trials of several targeted therapies have been disappointing. A phase III study of linifanib was halted early for failing to meet the primary end-point,⁸ and brivanib has failed in phase III trials in the first-line⁹ and second-line¹⁰ settings (versus sorafenib and placebo, respectively). Similarly, a non-inferiority phase III trial comparing first-line sunitinib with sorafenib failed,¹¹ and concerns were raised about potential liver toxicities.^{6,12} There is thus a pressing need for effective and tolerable options to allow patients with advanced HCC to continue treatment after their disease progresses on sorafenib.

We report here data from an uncontrolled, open-label, phase II study of regorafenib as second-line therapy in patients with HCC. Regorafenib is a novel multikinase inhibitor that targets kinases involved in angiogenesis (e.g. VEGFR1–3 and TIE2), oncogenesis (e.g. c-kit, Ret and wild-type and V600-mutated BRAF) and the tumour microenvironment (e.g. PDGFR and fibroblast growth factor receptor).¹³ In preclinical *in vivo* models, regorafenib showed a broad spectrum of antitumour activity,¹³ and it has been evaluated as

monotherapy in clinical phase I^{14,15} to phase III trials in patients with solid tumours, including colorectal cancer, renal cell cancer and HCC.^{16,17} A phase I study identified a regorafenib dosing schedule of 160 mg once daily in repeating cycles of 3 weeks on treatment followed by 1 week off treatment as the recommended regimen for further clinical investigation.¹⁴ We therefore undertook the present study to assess the safety, efficacy and pharmacokinetics of regorafenib in the recommended regimen in patients with HCC that had progressed following sorafenib treatment.

2. Patients and methods

The trial was conducted at 13 centres in Europe and Asia. Each centre's institutional review board or independent ethics committee approved the protocol and all patients provided written informed consent before participation. The trial was conducted under the principles of the Declaration of Helsinki and its amendments, in line with Good Clinical Practice and local laws and regulations.

2.1. Patients

The study involved patients with Barcelona Clinic Liver Cancer stage B or C⁵ HCC that would not benefit from treatments of established efficacy, such as resection, liver transplantation, local ablation, chemoembolisation or sorafenib therapy. Eligibility criteria included radiological progression following previous sorafenib therapy with evidence of at least one new lesion; age 18 years or older; life expectancy of at least 3 months; Eastern Cooperative Oncology Group performance status 0 or 1; preserved to mildly impaired liver function (non-cirrhotic or Child–Pugh class A); adequate bone-marrow and renal function.

Exclusion criteria included the following: previous systemic treatment with molecular targeted agents other than sorafenib (including regorafenib); discontinuation of previous sorafenib due to drug toxicity; bleeding risk (e.g. major surgery, traumatic injury or clinically significant bleeding in the past month, thromboembolic event

in the past 6 months, oesophageal varices or non-healing wound or ulcer); a history of cardiac disease or congestive heart failure; uncontrolled hypertension; and other primary cancers or central nervous system metastases.

2.2. Study medication

Participants received regorafenib 160 mg orally once daily for the first 3 weeks of each 4-week cycle, followed by 1 week off treatment. Prespecified dose reductions (to 120 or 80 mg) and delay of the following cycle (up to 28 days) were allowed to manage adverse events. The dose could be re-escalated to 160 mg at the investigator's discretion if the toxicity had resolved to baseline level. If the patient required more than two dose reductions or a delay of more than 28 days between cycles, regorafenib treatment had to be stopped. Other reasons for treatment discontinuation included clinical progression, intolerable toxicity, withdrawal of consent and investigator decision that stopping treatment would be in the patient's best interest.

2.3. Assessments

The primary end-point of the study was to assess the safety of regorafenib in patients with HCC that had progressed on treatment with sorafenib. Secondary end-points included efficacy and pharmacokinetics.

All patients who received at least one dose of regorafenib and had one safety assessment after the start of study medication were included in the safety analysis. Safety variables included adverse events, laboratory changes (haematology, clinical chemistry and urine analysis), changes in vital signs (blood pressure, heart rate, respiratory rate and temperature) and changes in Child–Pugh class and electrocardiography. Patients were assessed within 7 days before study start (within 14 days for physical examination and blood pressure measurements), on days 1 and 15 of each cycle and within 14 days after the end of treatment.

All treated patients were included in the efficacy analysis. Efficacy variables were time to progression (evaluated using the modified version of the Response Evaluation Criteria In Solid Tumors 1.0 [mRECIST] proposed by Llovet et al. for use in HCC clinical trials^{18,19}), objective tumour response rate (complete + partial response), disease control rate (complete + partial response + stable disease) and overall survival. Tumour measurements were conducted using computed tomography or magnetic resonance imaging every 6 weeks (± 7 days) for the first six cycles and then every three cycles (± 14 days).

Blood samples for pharmacokinetic assessment were collected after at least 14 days of uninterrupted stable dosing of regorafenib in cycle 1 (or later cycle if required) and at the start of the next treatment cycle. Concentrations of regorafenib and its active metabolites M2 (*N*-oxide metabolite; BAY 75-7495) and M5

(*N*-oxide/*N*-desmethyl metabolite; BAY 81-8752) were determined using a validated bioanalytical analysis.

2.4. Sample size calculation and statistical analysis

To achieve the primary objective (safety), a sample size of approximately 31–38 patients (25–30 from Europe and 6–8 from Asia) was considered sufficient. This was a single-arm, non-comparative study and data are presented as descriptive summaries. Adverse events and laboratory abnormalities are summarised by category and grade using the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. For efficacy data, frequency counts and percentages are provided for response and disease control rates; for analyses of time to progression and overall survival, the median time to event and 95% confidence intervals (CIs) are calculated using the Kaplan–Meier method. Peak and trough concentrations of regorafenib and its metabolites are reported as geometric means with coefficient of variance (CV).

3. Results

Fifty-six patients signed the informed consent form; however, 20 patients did not receive any study medication (screening failure $n = 17$, adverse event $n = 1$, death $n = 1$ and consent withdrawal $n = 1$). Thus, from September 2009, 36 patients received at least one dose of regorafenib and were included in the safety analysis. Baseline characteristics of these 36 patients (median age 61 years, range 40–76) are shown in Table 1. The median duration of previous sorafenib treatment was 4.5 months (range 0.5–32.6).

3.1. Treatment duration

The median duration of regorafenib treatment was 19.5 weeks (range 2–103). At the data cutoff (1st March 2012), three patients were still on treatment. In the remaining 33 patients, the reasons for treatment discontinuation were adverse events ($n = 20$, 56%), disease progression ($n = 10$, 28%), withdrawal of consent ($n = 2$, 6%) and death ($n = 1$, 3%).

Thirty-five patients (97%) required dose modifications during the study: 17 patients (47%) required regorafenib dose reduction, mostly to manage adverse events ($n = 15$); 35 patients (97%) had at least one dose interruption during daily treatment or delay to the start of the next cycle, mostly for adverse events ($n = 32$) or patient error ($n = 11$); patients may have had dose modifications for more than one reason.

3.2. Safety and tolerability

All 36 patients experienced at least one treatment-emergent adverse event, and 35 of the 36 patients

Table 1
Baseline patient and tumour characteristics.

		Regorafenib 160 mg (<i>n</i> = 36)
		<i>n</i> (%)
Sex	Male	32 (89)
	Female	4 (11)
Ethnicity	Caucasian	26 (72)
	Asian	10 (28)
Eastern Cooperative Oncology Group performance status	0	28 (78)
	1	8 (22)
Barcelona Clinic Liver Cancer stage	B (intermediate)	4 (11)
	C (advanced)	32 (89)
Overall Child–Pugh score	5	27 (75)
	6	9 (25)
Hepatitis infection	B	14 (39)
	C	13 (36)
Alcohol use	Abstinent	28 (78)
	Light	6 (17)
	Moderate	2 (6)
Ascites	Absent	35 (97)
	Slight	1 (3)
Liver cirrhosis	No	12 (33)
	Yes	24 (67)
Number of target lesions	1	6 (17)
	2	5 (14)
	3	6 (17)
	4	4 (11)
	5	6 (17)
	6	5 (14)
	9	2 (6)
	10	2 (6)
Tumour stage	II	1 (3)
	IIIA	6 (17)
	IIIB	1 (3)
	IIIC	1 (3)
	IV	26 (72)
	Unknown	1 (3)
Number of previous lines of chemotherapy (any intention) ^a	1	30 (83)
	2	4 (11)
	3	1 (3)
	4	1 (3)

^a Previous chemotherapy agents included sorafenib (*n* = 36; one patient received concomitant S-1; one patient received two lines of sorafenib [first- and third-line treatment]), capecitabine monotherapy (*n* = 1), capecitabine + cisplatin (*n* = 1), capecitabine + thalidomide (*n* = 1), doxorubicin monotherapy (*n* = 1), doxorubicin + cisplatin (*n* = 1), gemcitabine + cisplatin (*n* = 1), mitoxantrone (*n* = 1), not specified (*n* = 1).

(97%) had at least one drug-related adverse event. Twenty-one patients (58%) had a grade 3 or higher drug-related adverse event. The most frequent drug-related, treatment-emergent adverse events are shown in Table 2.

Five patients (14%) experienced serious adverse events that were deemed to be related to the study medication: these events were grade 2 fever (*n* = 1; regorafenib treatment interrupted), grade 3 diarrhoea (*n* = 1; regorafenib treatment permanently stopped), grade 3 supraventricular arrhythmia/atrial fibrillation (*n* = 1;

regorafenib treatment permanently stopped), grade 4 fatigue (*n* = 1; regorafenib treatment interrupted) and grade 5 haematoma in the right thigh following a fall (*n* = 1; patient died 44 days after starting regorafenib treatment). Seven other patients died as a result of adverse events during the study or survival follow up; none of these deaths was deemed to be related to study medication. Details of these deaths are as follows. Two patients died from liver failure: one patient had previously experienced rapid progression of HCC from stage II to stage IV in 9 months despite sorafenib treatment,

and had evidence of disease progression after 1 month on regorafenib, stopped treatment 2 weeks later and died 16 days after the last dose; the other patient had evidence of grade 3 aspartate aminotransferase and grade 2 alanine aminotransferase at baseline and died from hepatic encephalopathy 23 days after stopping regorafenib treatment, which he had received for 9 weeks. Two patients experienced central nervous system haemorrhage 2 and 5 months, respectively, after starting regorafenib treatment: one patient, with mild coagulopathy and thrombocytopenia at baseline, suffered a high-impact accidental head injury with a basal skull fracture, subdural haematoma and high intracranial pressures—the patient did not recover and died postoperatively; the other had progression of HCC at multiple sites and normal coagulation parameters, but experienced bleeding into a new cerebral metastasis and died several months after treatment discontinuation. One patient died from an unspecified metabolic or laboratory disorder 10 months after starting regorafenib. Two patients had other adverse events deemed to be due to disease progression, both of which occurred during survival follow up (at 6.6 and 13.8 months after starting regorafenib treatment) and were reported without details of the specific adverse event or relationship to treatment.

Among the 18 patients (50%) who stopped study medication as a result of adverse events, the reason was deemed to be related to study medication in seven patients (19%), including fatigue in four patients (in

association with dysphagia and hand–foot skin reaction in one patient and with an unspecified dermatological condition, anorexia and proteinuria in another) and three patients with the serious adverse events described above: haematoma, supraventricular arrhythmia/atrial fibrillation and diarrhoea.

All 36 patients had abnormal laboratory results during the study. The most frequent laboratory abnormalities were raised aspartate aminotransferase ($n = 33$, 92%), anaemia ($n = 31$, 86%), raised alkaline phosphatase ($n = 30$, 83%) and raised gamma glutamyltransferase ($n = 30$, 83%). The most frequent grade 3 laboratory abnormalities were raised gamma glutamyltransferase ($n = 13$, 36%), hypophosphataemia ($n = 10$, 28%), hyponatraemia ($n = 9$, 25%), lymphopenia ($n = 6$, 17%), hyperbilirubinaemia ($n = 5$, 14%) and raised aspartate aminotransferase ($n = 4$, 11%). For most patients, there was no change from baseline in worst grade of haematological and biochemical toxicities.

Laboratory test abnormalities were reported as adverse events in any of the following situations: they caused the patient to withdraw from the study, they required treatment, they caused apparent clinical manifestations, or they were judged to be clinically relevant by an investigator. Drug-related biochemistry laboratory adverse events of any grade were reported in 14 regorafenib-treated patients (39%), and were usually mild in severity, with grade 3 laboratory adverse events reported in four patients (11%). The most frequent regorafenib-related laboratory adverse events were proteinuria ($n = 4$, 11%), acidosis ($n = 3$, 8%), bilirubin ($n = 3$, 8%), creatinine ($n = 2$, 6%), hypoalbuminaemia ($n = 2$, 8%) and hypophosphataemia ($n = 2$, 6%).

Table 2

Drug-related, treatment-emergent adverse events affecting at least 10% of patients at any grade, or at least 5% of patients at grade 3 or higher.

	Any grade	Grade ≥ 3
	<i>n</i> (%)	<i>n</i> (%)
Any adverse event	35 (97)	21 (58)
Diarrhoea	19 (53)	2 (6)
Fatigue	19 (53)	6 (17)
Hand–foot skin reaction	19 (53)	5 (14)
Hypothyroidism	15 (42)	0
Anorexia	13 (36)	0
Hypertension	13 (36)	1 (3)
Nausea	12 (33)	0
Voice changes	10 (28)	0
Constipation	9 (25)	0
Headache	7 (19)	0
Weight loss	7 (19)	0
Proteinuria	6 (17)	1 (3)
Oral mucositis	5 (14)	1 (3)
Vomiting	5 (14)	0
Abdominal pain	4 (11)	1 (3)
Anaemia	4 (11)	1 (3)
Fever	4 (11)	0
Hyperbilirubinaemia	4 (11)	2 (6)
Hyperthyroidism	4 (11)	1 (3)
Mood alteration, depression	4 (11)	0
Hypophosphataemia	2 (6)	2 (6)

3.3. Efficacy

The median time to progression was 4.3 months (95% CI 2.9–13.1; Fig. 1). The progression-free rate was 65% (95% CI 45–79%) at 3 months and 44% (95% CI 26–60%) at 6 months. Median overall survival was 13.8 months (95% CI 9.3–18.3; Fig. 2). The overall survival rate was 88% (95% CI 72–95%) at 3 months and 79% (95% CI 61–89%) at 6 months.

Fig. 3 shows the best change in target lesion from baseline in 31 evaluable patients. The best response, based on mRECIST, was partial response in one patient (3%), stable disease in 25 patients (69%) and progressive disease in five patients (14%). Response was not assessable in five patients (14%). As a result, the overall response rate (complete + partial response) for regorafenib was 3% and the disease control rate (complete + partial response + stable disease) was 72%. In the patient with partial response, the time to response was 1.3 months, the duration of response was

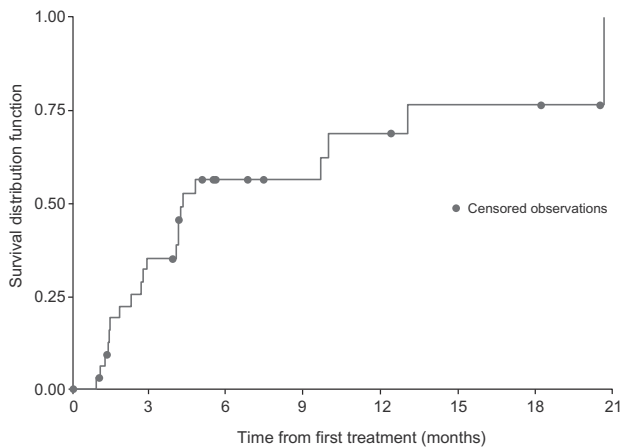


Fig. 1. Time from start of treatment to disease progression, measured using modified Response Evaluation Criteria In Solid Tumors 1.0.^{19,20} Median time to progression was 4.3 months (95% confidence interval 2.9–13.1).

5.5 months and the maximum reduction in tumour size was 33%.

3.4. Pharmacokinetics

The mean maximum plasma concentration of regorafenib in Caucasian patients was 1772.1 $\mu\text{g/l}$ (CV 94.86; $n = 20$) at steady state on day 15; the mean trough concentration was 50.9 $\mu\text{g/l}$ (CV 260.19; $n = 14$) on day 1 of the following cycle after 7 days off treatment. The equivalent mean concentrations for the M2 and M5 metabolites were 1112.3 $\mu\text{g/l}$ (CV 155.93) and 858.8 $\mu\text{g/l}$ (CV 144.66), respectively, at steady state on day 15 and 25.7 $\mu\text{g/l}$ (CV 393.46) and 277.2 $\mu\text{g/l}$ (CV 447.44), respectively, after 7 days off treatment. For Asian patients ($n = 8$), the mean maximum concentrations of regorafenib, M2 and M5 on day 15 of cycle 1 were 2509.3 $\mu\text{g/l}$ (CV 40.96), 862.2 $\mu\text{g/l}$ (CV 76.17) and 336.2 $\mu\text{g/l}$ (CV 150.43), respectively. Additional pharmacokinetic data from Asian patients are provided online as [Supplementary Material](#).

4. Discussion

The present study is the first to investigate the safety and antitumour activity of regorafenib in patients with HCC progressing after first-line sorafenib treatment, using a dose schedule of 160 mg once daily in repeating 4-week cycles of 3 weeks on, 1 week off treatment. Although all patients experienced at least one adverse event during treatment, these could typically be managed with supportive measures and dose reductions or treatment interruption, and relatively few patients needed to stop treatment permanently because of drug-related adverse events ($n = 7$, 19%). Drug-related laboratory adverse events occurred in 14 patients (39%), and were mostly mild in severity. Only five

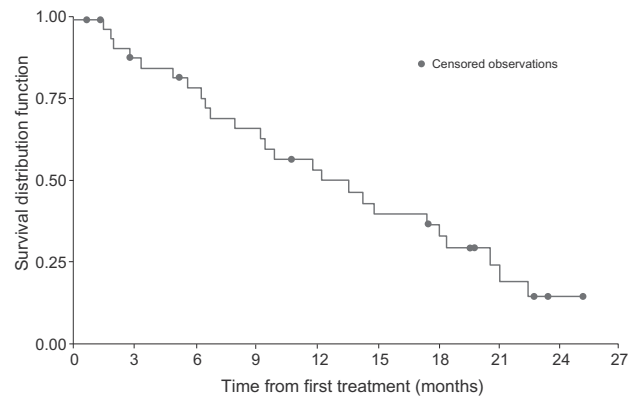


Fig. 2. Kaplan–Meier estimate of overall survival from start of treatment to data cutoff date of 1st March 2012. Median overall survival was 13.8 months (95% confidence interval 9.3–18.3).

patients (14%) experienced drug-related serious adverse events, and only one death during the study was deemed to be related to study medication (haematoma in the right thigh following a fall).

It is noteworthy that our patients had tolerated prior treatment with sorafenib. The toxicity profiles of these two kinase inhibitor agents are somewhat similar, with diarrhoea, fatigue and hand–foot skin reaction being the most frequently reported adverse events in the SHARP and Asia-Pacific trials of sorafenib, as well as in our trial and other studies of regorafenib in patients with different tumour types.^{3,4,14–17,20,21}

In patients with HCC, liver failure is a major concern and severe drug-related liver toxicities have been reported in trials of other TKIs in HCC (e.g. sunitinib^{6,12}). In our study, two patients died from liver dysfunction, but neither case was deemed to be related to study medication. Furthermore, liver function tests showed no sudden significant increases in liver transaminases that might indicate acute liver damage leading to progressive liver failure. In fact, more than half of the patients maintained Child–Pugh status A throughout the study (data not shown), and most patients had no change from baseline in grade of biochemical and haematological toxicities.

Efficacy data from this study indicate promising anti-tumour activity of regorafenib in patients with progressive HCC following sorafenib treatment. Over a median treatment duration of 19.5 weeks, nearly three-quarters of patients ($n = 26$, 72%) achieved disease control, with a median time to progression of 4.3 months and median overall survival of 13.8 months. We chose time to progression as an end-point, rather than progression-free survival, to avoid the risk of counting death from underlying liver disease as progression.¹⁸ Furthermore, progression-free survival has been criticised as an end-point in HCC phase III clinical trials because there is no evidence that it translates into meaningful benefit for patients in terms of overall survival or quality of

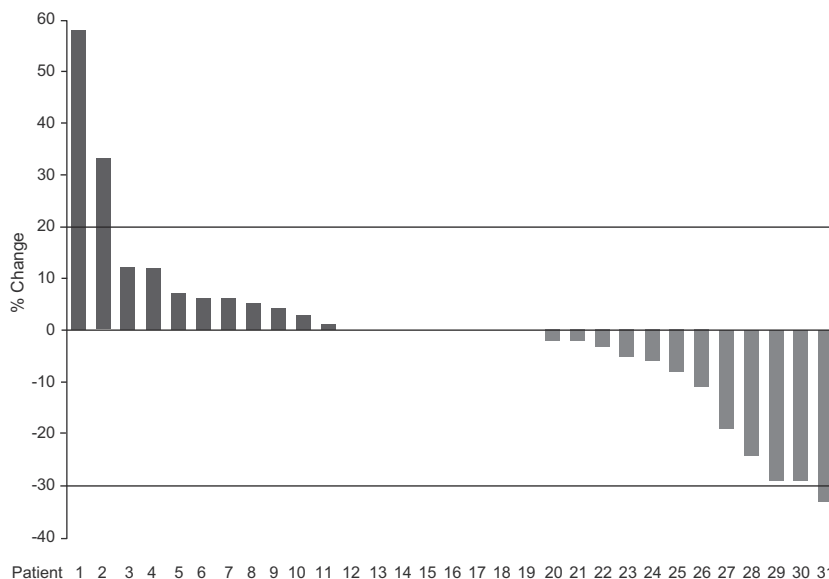


Fig. 3. Best change from baseline in target lesion, measured using modified Response Evaluation Criteria In Solid Tumors 1.0,^{19,20} following treatment with regorafenib in 31 evaluable patients. Best response was partial response in one patient (3%), stable disease in 25 patients (69%) and progressive disease in five patients (14%).

life.^{5,22,23} Time to progression is also preferred as an end-point over tumour response because targeted therapy typically has a cytostatic rather than a cytotoxic effect, and may therefore not have a visible effect on tumour size.¹⁸ Indeed, sorafenib had no significant impact on tumour response in the pivotal SHARP trial, although survival end-points were clearly improved versus placebo.³ While time to progression still needs to be validated as a meaningful and relevant surrogate marker of overall survival, an international panel of experts has recommended that it should be included as a primary efficacy end-point in all future phase II trials of treatments for advanced HCC.¹⁸

We believe that our study shows promise for regorafenib in the second-line treatment of patients with progressive HCC, in terms of a manageable adverse event profile and evidence of antitumour activity, which warrant further investigation in a phase III trial (recently opened to recruitment, ClinicalTrials.gov identifier NCT01774344). Nonetheless, we acknowledge that our study has limitations: robust data to allow baseline assumptions for time to progression in second-line therapy are not available and second-line trials may have a risk of selection bias, as participants are likely to have underlying liver disease. However, the treated natural history of HCC has been changing since the pivotal sorafenib trials, and patients are often started on first-line sorafenib at an earlier disease stage than in the phase III studies; this is having an impact on overall survival in both first- and, potentially, second-line settings. Further studies are needed to explore how the impact of first-line treatment on survival is likely to affect outcomes in second-line therapy.

The present study suggests that, in patients with advanced HCC that has progressed following first-line treatment with sorafenib, regorafenib can be beneficial. The mechanism by which regorafenib may overcome resistance to sorafenib remains to be investigated in future studies.

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Conflict of interest statement

Jordi Bruix: consulting for Sumitomo, Pharmexa, Eisai, Lilly, Biocompatibles, ArQule, BioAlliance, Novartis, ImClone, Schering-Plough, MedImmune, Roche, Abbott, BMS, Jennerex, OSI, Sanofi, GSK, AngioDynamics and Kowa.

Won-Young Tak: advisory board member for Bayer, BMS, MSD and Roche.

Antonio Gasbarrini: advisory board member for MSD, Bayer, Angelini and Sanofi.

Armando Santoro: advisory board member.

Massimo Colombo: grants and research support from Merck, Roche, BMS and Gilead Sciences; advisory board member for Merck, Roche, Novartis, Bayer, BMS, Gilead Sciences, Tibotec, Vertex, Janssen-Cilag

and Achillion; speaking and teaching for Tibotec, Roche, Novartis, Bayer, BMS, Gilead Sciences and Vertex.

Ho-Yeong Lim: no conflict of interest.

Vincenzo Mazzaferro: advisory board member for Bayer; speaker bureau for Bayer and Nordion.

Reiner Wiest: no conflict of interest.

María Reig: consulting for Bayer.

Andrea Wagner: employee of Bayer.

Luigi Bolondi: speaker bureau for Bayer, Roche, Bracco, Esaote and Sirtex; on advisory boards for Bayer and BMS.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.ejca.2013.05.028>.

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