Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial

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Summary

Background Until now, only imatinib and sunitinib have proven clinical benefit in patients with gastrointestinal stromal tumours (GIST), but almost all metastatic GIST eventually develop resistance to these agents, resulting in fatal disease progression. We aimed to assess efficacy and safety of regorafenib in patients with metastatic or unresectable GIST progressing after failure of at least imatinib and sunitinib.

Methods We did this phase 3 trial at 57 hospitals in 17 countries. Patients with histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib and sunitinib were randomised in a 2:1 ratio (by computer-generated randomisation list and interactive voice response system; preallocated block design (block size 12); stratified by treatment line and geographical region) to receive either oral regorafenib 160 mg daily or placebo, plus best supportive care in both groups, for the first 3 weeks of each 4 week cycle. The study sponsor, participants, and investigators were masked to treatment assignment. The primary endpoint was progression-free survival (PFS). At disease progression, patients assigned placebo could crossover to open-label regorafenib. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01271712.

Results From Jan 4, to Aug 18, 2011, 240 patients were screened and 199 were randomised to receive regorafenib (n=133) or matching placebo (n=66). Data cutoff was Jan 26, 2012. Median PFS per independent blinded central review was 4·8 months (IQR 1·4–9·2) for regorafenib and 0·9 months (0·9–1·8) for placebo (hazard ratio [HR] 0·27, 95% CI 0·19–0·39; p<0·0001). After progression, 56 patients (85%) assigned placebo crossed over to regorafenib. Drug-related adverse events were reported in 130 (98%) patients assigned regorafenib and 45 (68%) patients assigned placebo. The most common regorafenib-related adverse events of grade 3 or higher were hypertension (31 of 132, 23%), hand-foot skin reaction (26 of 132, 20%), and diarrhoea (seven of 132, 5%).

Interpretation The results of this study show that oral regorafenib can provide a significant improvement in progression-free survival compared with placebo in patients with metastatic GIST after progression on standard treatments. As far as we are aware, this is the first clinical trial to show benefit from a kinase inhibitor in this highly refractory population of patients.

Funding Bayer HealthCare Pharmaceuticals.

Introduction

Gastrointestinal stromal tumours (GIST) are the most common sarcomas arising in the gastrointestinal tract. Worldwide, the annual incidence of GIST is about 10 cases per million people,[1] corresponding to at least 8000 new cases per year in Europe. Early-stage disease can be surgically resected, but more than 40% of cases recur and metastasise.[2]

Cytotoxic chemotherapy, although active in other subtypes of sarcomas, is ineffective in metastatic GIST.[3,4] Elucidation of GIST molecular pathophysiology as a mutation-driven cancer has facilitated the development of targeted kinase-inhibitor therapies that have revolutionised treatment options and clinical outcomes for this malignancy.[5] About 85% of GIST are caused by gain-of-function mutations in the proto-oncogene *KIT*,[6] which encodes a tyrosine-kinase receptor. These mutations result in constitutive ligand-independent activation of KIT intracellular signalling.[1,7,8] Roughly 8% of metastatic GIST are associated with gain-of-function mutations in the structurally similar tyrosine-kinase receptor gene *PDGFRA*, encoding the platelet-derived growth factor receptor α.[6,8,9] Other rare subtypes of GIST exist that harbour no mutations in *KIT* or *PDGFRA*, but are probably driven by other mutations in genes such as *BRAF*, *NF1*, or those encoding subunits of the succinate dehydrogenase (SDH) complex.[9]

Lancet 2013; 381: 295–302

Published Online November 22, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61857-1

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See Online for appendix

Imatinib mesylate, a selective tyrosine-kinase inhibitor of KIT, PDGFRA, and ABL, significantly improves clinical outcomes in GIST both as therapy for advanced metastatic disease and in the postsurgical adjuvant setting.[10–13] However, imatinib therapy is limited by primary resistance to the drug in about 15% of patients,[5,14–16] and more than 80% of patients eventually develop disease progression driven by secondary resistance mutations located in *KIT* exons.[16–20]

The first drug shown definitively to provide clinical benefit in GIST after resistance to imatinib was sunitinib malate, which has more potent activity against the wild-type KIT kinase than the first-line treatment, imatinib, and also inhibits several other signalling pathways related to tyrosine-kinase receptors, including the vascular endothelial growth factor receptors (VEGFR1 [also known as FLT1], VEGFR2 [KDR], and VEGFR3 [FLT4]), Fms-like tyrosine kinase-3 (FLT3), and the receptor encoded by the proto-oncogene *RET*.[21–25] A randomised, placebo-controlled phase 3 trial assessing sunitinib in imatinib-resistant patients showed a significant improvement in median time to tumour progression for sunitinib compared with placebo (all patients also received best supportive care).[26] However, clinical progression and drug resistance to sunitinib subsequently evolve, generally within 1 year of treatment, and up to now, no other effective therapy has been developed for tyrosine-kinase inhibitor-resistant GIST. Structural biology studies have explained that the smaller sunitinib molecule shows activity in patients who are imatinib-resistant because sunitinib is able to avoid steric hindrance by gatekeeper mutations that block entrance of the larger imatinib molecule to the ATP-binding pocket of the KIT protein.[27]

Regorafenib is a novel, oral multikinase inhibitor that blocks the activity of several protein kinases, including those involved in the regulation of tumour angiogenesis (VEGFR1–3 and TEK), oncogenesis (KIT, RET, RAF1, BRAF, and $BRAF^{V600E}$), and the tumour microenvironment (PDGFR and FGFR).[28] In preclinical studies, regorafenib showed antitumour activity against human GIST and other tumour models.[28]

After the phase 1 study that defined the safety, tolerability, and recommended dose of regorafenib in unselected patients with solid tumours,[29] a phase 2 multicentre trial was designed and done under independent academic sponsorship to assess regorafenib in patients with GIST with metastatic disease, after failure of at least previous imatinib and sunitinib.[30] In that phase 2 study, regorafenib showed activity against tyrosine-kinase inhibitor-resistant GIST, including some partial responses, a high occurrence of durable stable disease, and median progression-free survival (PFS) of 10 months, along with the expected incidence of grade 3 toxic effects of hypertension and hand-foot skin reaction.[30] On the basis of these data and the preclinical rationale of targeting the pathogenic mutant kinases with a structurally distinct small-molecule inhibitor, we did this phase 3 trial (GIST—regorafenib in progressive disease [GRID]) to assess efficacy and safety of regorafenib in patients with metastatic or unresectable GIST, progressing after failure of at least previous imatinib and sunitinib. We report the efficacy and safety results of this trial; quality-of-life data were collected and will be reported separately and a final analysis of overall survival will be done when approximately 136 events have been recorded.

Methods

Study design and participants

We did this randomised, placebo-controlled, multicentre, phase 3 trial at 57 hospital sites in 17 countries (Austria, Belgium, Canada, China, Finland, France, Germany, Israel, Italy, Japan, Netherlands, Poland, Singapore, South Korea, Spain, UK, and USA).

Eligibility criteria included histologically confirmed, metastatic or unresectable GIST, with failure of at least previous imatinib (defined as either disease progression or intolerance) and previous sunitinib (defined solely as progression to decrease heterogeneity, since the definition of intolerance is more variable with this agent than with imatinib). Patients could have received other systemic therapies, including investigational agents, except any VEGFR inhibitors other than sunitinib. Additional inclusion criteria included: at least one measurable lesion with CT or MRI; resolution of all toxic effects of previous therapy to grade 1 or lower; adequate haematological, hepatic, cardiac, and renal function; and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The appendix provides additional details of inclusion and exclusion criteria.

The study protocol was approved by the institutional review board of each participating institution and complied with the Declaration of Helsinki, existing good clinical practice guidelines, and local laws and regulations. An independent data monitoring committee, of three oncologists and a statistician, ensured the overall integrity of the trial and safety of participants. All participants provided written informed consent before enrolment.

Randomisation and masking

Patients were randomly assigned in a 2:1 ratio to regorafenib or placebo with a computer-generated randomisation list prepared by the study sponsor (pre-allocated block design, block size 12). Investigators received the randomisation number for each participant through an interactive voice response system, which was also used to manage study drug supply. Randomisation was stratified by treatment line (failure of previous imatinib and sunitinib [true third-line] *vs* failure of previous imatinib, sunitinib, and other GIST therapies) and geographical region (Asia *vs* rest of world).

Randomisation was masked so that neither the patient, nor the investigator, nor the sponsor knew which agent was being administered. To maintain

concealment, study medication was labelled with a unique drug pack number preprinted on each bottle, which was assigned to the patient through the interactive voice response system. Unmasking for individual patients could occur via the voice response system for emergencies; serious adverse events did not necessarily precipitate immediate unmasking.

Procedures

Enrolled patients received either oral regorafenib 160 mg once daily or matching placebo, for the first 3 weeks of each 4 week cycle. All patients also received best supportive care (defined as any method to preserve the comfort and dignity of the patient, excluding disease-specific antineoplastic therapy, such as tyrosine-kinase therapy other than study drug, chemotherapy, radiation therapy, or surgical intervention). Masked study drug administration was continued until disease progression, occurrence of unacceptable toxic effects, or withdrawal of the patient from the study.

In the event of centrally assessed tumour progression, treatment assignment could be unmasked. Patients originally assigned to the placebo group were offered the option to crossover to receive open-label regorafenib, and patients originally assigned to the regorafenib group could continue to receive open-label regorafenib, both at the discretion of the investigator. Throughout both the masked and open-label phases of the trial, the dose of study drug could be delayed or reduced according to a prespecified schedule in the case of unacceptable toxic effects (appendix).

Tumour assessments were made at baseline, then every 4 weeks for the first 3 months, every 6 weeks for the next 3 months, and subsequently every 8 weeks until the end of study drug administration. Intervening tumour assessments could be made more frequently when clinically indicated. In addition to central review, an investigator assessment was also made at each evaluation. During the open-label period, only investigator assessments were made.

We assessed safety and tolerability by analysis of adverse events, physical examinations, vital signs, ECOG performance status, and laboratory assessments, on days 1 and 15 of each treatment cycle for the first six cycles. Cardiac function was assessed with 12-lead electrocardiogram at screening, day 1 of the first two treatment cycles (and subsequent cycles at the discretion of the investigator), and at treatment end. Investigators rated severity of adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0).

The primary endpoint was PFS per modified Response Evaluation Criteria In Solid Tumors (RECIST) 1.1, assessed by central radiology reviewers who were masked to assignment and data from patients. The prospectively defined RECIST modifications, which were unique to this study and developed to apply specifically to GIST, were the following criteria: no lymph nodes were chosen as target lesions—enlarged lymph nodes were followed up as non-target lesions; no bone lesions were chosen as target lesions; and PET was not acceptable for radiological assessment. Additionally a progressively growing new tumour nodule within a pre-existing tumour mass had to meet the following criteria to be regarded as unequivocal evidence of progression according to our modification to RECIST 1.1: the lesion was at least 2 cm in size and definitely a new active GIST lesion (eg, enhanced with contrast or other criteria to rule out artifact); or the lesion had to be expanding on at least two sequential imaging studies. The masked central radiology review was done according to a prospectively agreed central imaging charter and undertaken by an external imaging contract research organisation. Two readers reviewed the images. Adjudication by another radiology reviewer was used when only one reader assessed a progression or when the date of progression was discordant between the two independent readers.

Secondary endpoints included overall survival, time to progression, objective response rate, and disease control rate (defined as rate of complete response or partial response plus stable disease lasting for at least 12 weeks), safety, and tolerability. Exploratory endpoints (not reported here) were health-related quality of life, pharmacokinetics, secondary PFS during open label treatment, and biomarker assessment, including tumour genotype for mutational status of target oncogene.

Statistical analysis

With 199 patients randomised, assuming a target treatment effect of 100% improvement in PFS, a randomisation ratio of 2:1 (regorafenib to placebo), a one-sided alpha of 0·01, and a power of 0·94, 144 events were needed for the final PFS analysis. A preplanned interim analysis of overall survival was done at the time of the final PFS analysis.

We did statistical analyses with SAS (version 9.1 or higher). Efficacy analyses were by intention to treat. Safety analyses included all patients who received at least one dose of study drug. We calculated PFS and overall survival estimates with the Kaplan-Meier method. We derived hazard ratios (HRs) and 95% CIs from a Cox proportional hazard model and p values with the stratified log-rank test. Overall response rate and disease control rate were analysed with the Cochran-Mantel-Haenszel test. This trial is registered with ClinicalTrials.gov, number NCT01271712.

Role of the funding source

The study sponsor provided regorafenib and matching placebo, and collaborated with the principal investigator (GDD) and an international steering committee of academic investigators on protocol design, data collection and interpretation, and preparation of this report. All logistical study operations were managed by the sponsor. Data were

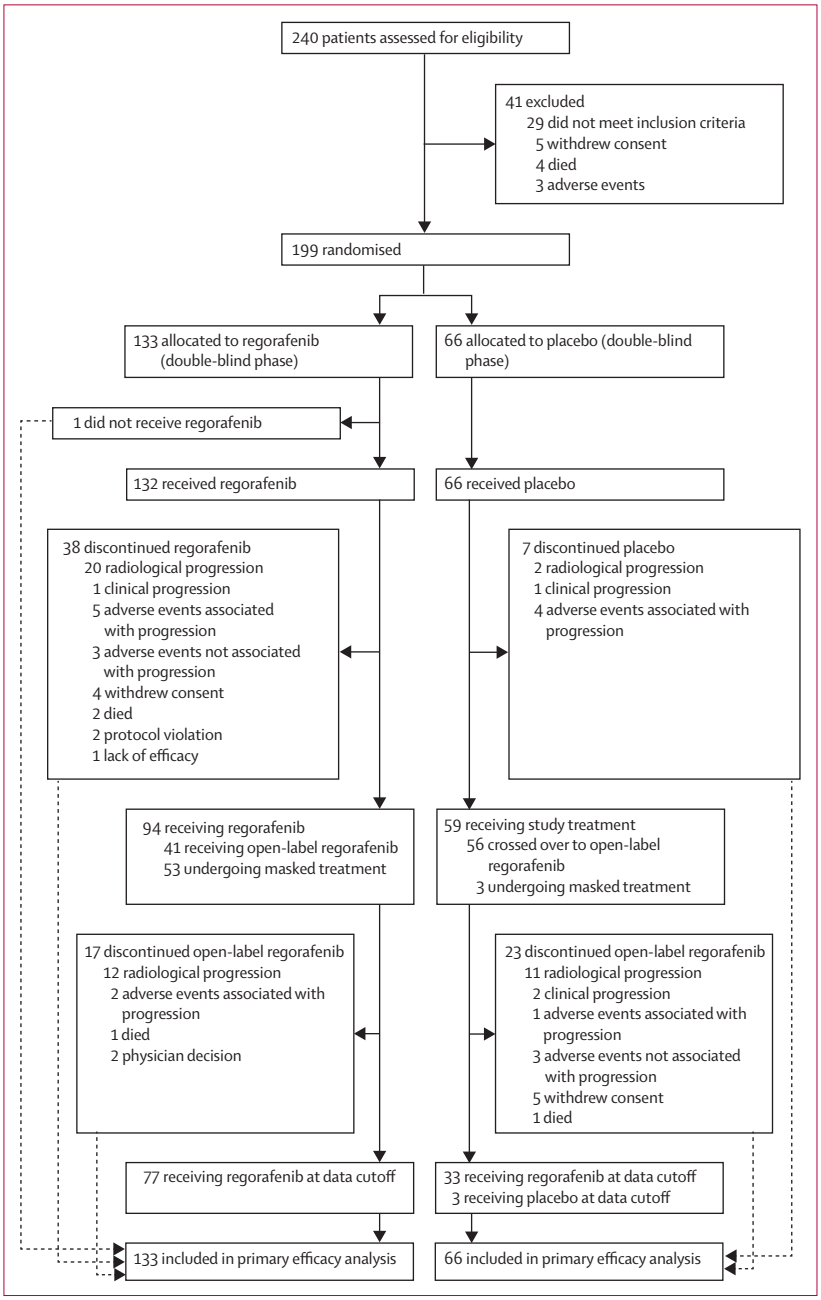

Figure 1: **Trial profile**

	Regorafenib (N=133)	Placebo (N=66)
Median age	60 (51–67)	61 (48–66)
Sex		
Men	85 (64%)	42 (64%)
Women	48 (36%)	24 (36%)
Ethnic group		
White	90 (68%)	45 (68%)
Black or African American	0	1 (2%)
Asian	34 (26%)	16 (24%)
Not reported or missing	9 (7%)	4 (6%)
ECOG performance status		
0	73 (55%)	37 (56%)
1	60 (45%)	29 (44%)
Previous systemic anticancer therapy		
2 lines	74 (56%)	39 (59%)
>2 lines	59 (44%)	27 (41%)
Duration of previous imatinib therapy		
≤6 months	18 (14%)	4 (6%)
6–18 months	26 (20%)	7 (11%)
>18 months	89 (67%)	55 (83%)

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group.

Table 1: **Baseline patient characteristics**

collected by the sponsor and analysed by the principal investigator, steering committee, and sponsor. All authors had full access to all data and vouch for the accuracy and completeness of the data presentation and analysis. The authors had final responsibility to submit for publication.

Results

Between Jan 04, and Aug 18, 2011, 240 patients were screened and 199 patients were randomised to receive regorafenib (n=133) or placebo (n=66; figure 1). One patient randomised to the regorafenib group died before receiving study treatment. Baseline characteristics and previous treatments were much the same between the two groups, although by chance a higher proportion of patients in the placebo group had received imatinib therapy for more than 18 months than in the regorafenib group (table 1); 193 patients (97%) had previous disease progression while on both imatinib and sunitinib, with only six patients (3%) entered with a history of intolerance to imatinib. Notably, 86 patients (43%) had received three or more previous lines of anticancer therapy for GIST.

Analysis was done when the predetermined criteria of 144 PFS events was reached: 81 events among the 133 patients (61%) in the regorafenib group and 63 events among the 66 patients (95%) in the placebo group. During the double-blind period, 38 patients (29%) in the regorafenib group and seven (11%) patients in the placebo group discontinued study treatment (appendix). The most common reason for termination of study treatment was radiologically confirmed disease progression.

At the data cutoff (Jan 26, 2012), 53 (40%) of the 133 patients in the regorafenib group and three (5%) of the 66 patients in the placebo group were still receiving double-blind treatment (figure 1). A further 41 patients (31%) in the regorafenib group continued to receive open-label regorafenib after disease progression, and 24 (18%) of the 41 patients were still receiving regorafenib at the time of analysis. In the placebo group, 56 patients (85%) crossed over to receive open-label regorafenib after progression, and 33 (50%) were still receiving treatment at data cutoff (figure 1, appendix). The appendix includes a summary of post-study treatments.

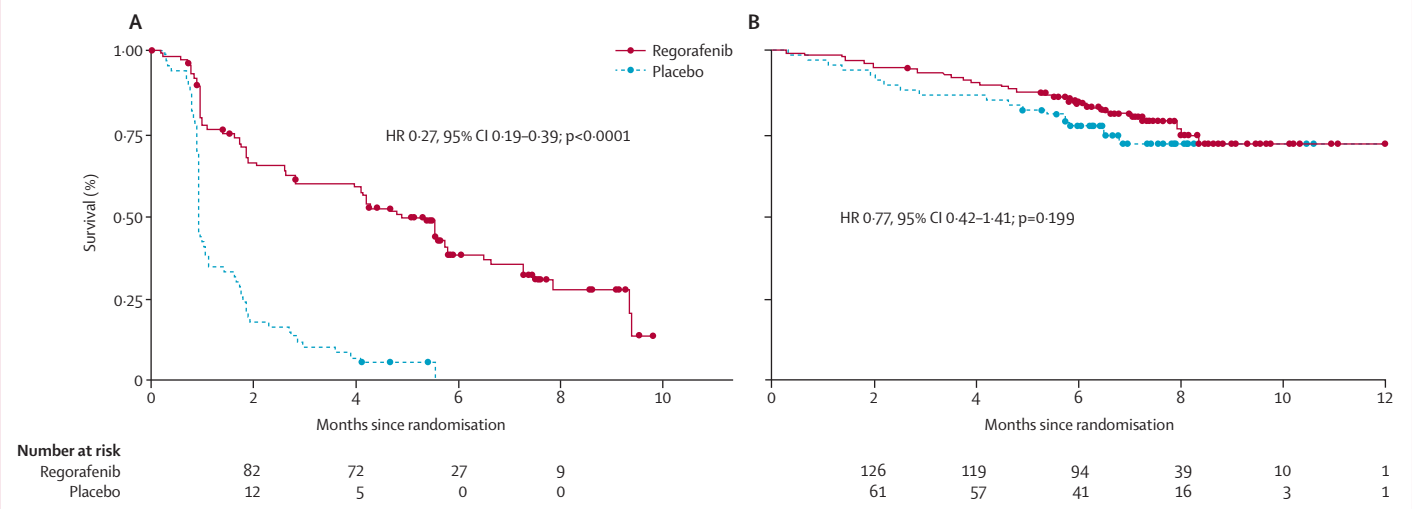

Figure 2: **Kaplan-Meier survival analysis after treatment with regorafenib or placebo**
(A) Progression-free survival, per central review (primary endpoint, final analysis). (B) Overall survival (interim analysis). HR=hazard ratio.

During the double-blind period, patients who were assigned to receive regorafenib had a median treatment duration of 22·9 weeks (IQR 9·3–28·6), with a mean of 20·2 weeks (SD 11·6), and patients who were assigned to receive placebo had a median treatment duration of 7·0 weeks (IQR 5·1–11·3), with a mean of 9·1 weeks (SD 5·9). The median daily dose during the double-blind treatment period was 146·8 mg (IQR 125·1–160·0) for regorafenib-treated patients (mean 139·8 mg, SD 22·9) and 160 mg (IQR 160·0–160·0) for placebo recipients (mean 159·5 mg, SD 3·0). In the regorafenib group, patients received 78·0% of the planned dose; in the placebo group, patients received 83·8% of the planned dose.

Median PFS was 4·8 months (IQR 1·4–9·2) in the regorafenib group and 0·9 months (0·9–1·8) in the placebo group, according to blinded central review (HR 0·27, 95% CI 0·19–0·39; p<0·0001; figure 2A), meeting the primary endpoint of the study. PFS at 3 and 6 months was 60% (95% CI 51–68) and 38% (29–48), respectively, for regorafenib, and 11% (3–18) and 0% (0–0), respectively, for placebo. Investigator assessment showed a median PFS of 7·4 months (IQR 2·7–not calculable) in the regorafenib group and 1·7 months (0·9–2·7) in the placebo group (HR 0·22, 95% CI 0·14–0·35; p<0·0001; appendix). Median PFS for the 56 patients in the placebo group who crossed over to open-label regorafenib after progression was 5·0 months (IQR 3·1–8·7) per investigator assessment). We noted no significant difference in overall survival between the regorafenib and placebo groups (29 [22%] events in the regorafenib group *vs* 17 [26%] events in the placebo group; HR 0·77, 95% CI 0·42–1·41; p=0·199; figure 2B).

We analysed the effect of baseline factors on treatment effect with a Cox proportional hazard model (figure 3). The benefits of regorafenib on centrally assessed PFS were identified across all subgroups, except for the small subset of patients with duration of imatinib treatment of less than 6 months. We identified much the same benefits of regorafenib in patients whose tumours harboured the two most common primary *KIT* mutations (exon 11 mutation, n=51, HR 0·212, 95% CI 0·098–0·458; exon 9 mutation, n=15, 0·239, 0·065–0·876).

No patients in either group had a complete response, whereas six of the 133 patients in the regorafenib group and one of the 66 patients in the placebo group had a partial response, giving overall response rates of 4·5% for regorafenib and 1·5% for placebo. The occurrence of stable disease as best response (occurring at any time and for any duration) was 71·4% (95 of 133 patients) in the regorafenib group and 33·3% (22 of 66 patients) in the placebo group. The more clinically meaningful disease control rate was 52·6% (70 of 133 patients) for regorafenib and 9·1% (six of 66 patients) for placebo (95% CI –54·72 to –32·49; p<0·0001).

During the double-blind period, all 132 assessable patients in the regorafenib group and 61 (92%) of the 66 patients in the placebo group had adverse events. Drug-related adverse events were reported in 130 (98%) patients in the regorafenib group and 45 (68%) patients in the placebo group (table 2). The most common adverse event of any grade was hand-foot skin reaction, which occurred in 74 (56%) patients in the regorafenib group and nine (14%) patients in the placebo group. Drug-related adverse events of grade 3 or higher were reported in 81 (61%) patients assigned regorafenib and nine (14%) patients assigned placebo. The most common regorafenib-related adverse events of grade 3 or higher were hypertension (31 of 132 patients, 23%), hand-foot skin reaction (26 of 132, 20%), and diarrhoea (seven of 132, 5%). Grade 5 adverse events were reported in seven (5%) patients in the regorafenib group and three (5%) patients in the placebo group. In three patients, the

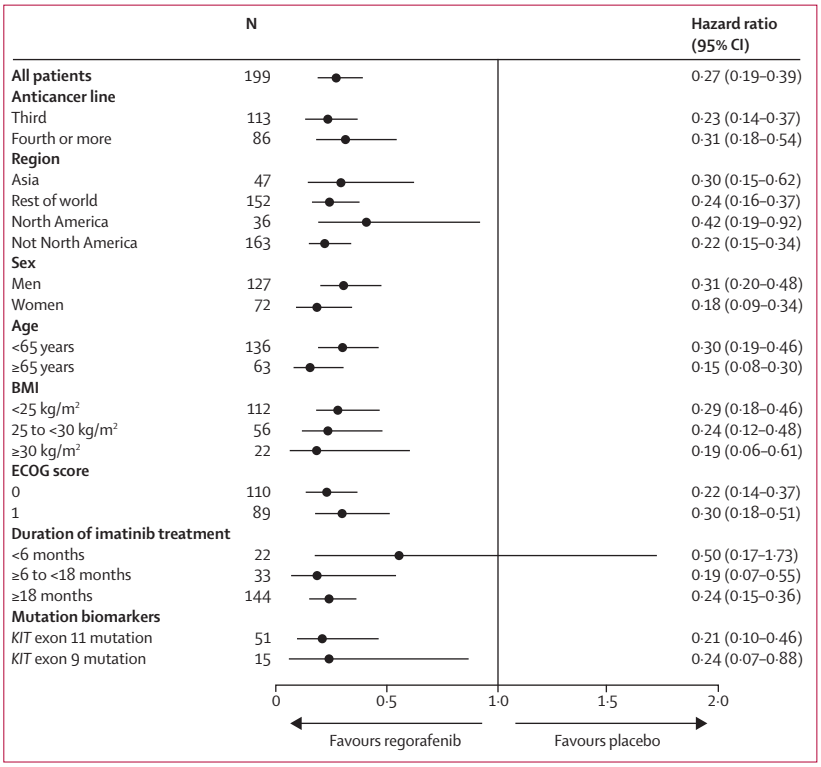

***Figure 3*: Progression-free survival by subgroup**
BMI=body-mass index. ECOG=Eastern Cooperative Oncology Group.

	Regorafenib (N=132*)			Placebo (N=66)		
	Any grade	Grade 3	Grade 4	Any grade	Grade 3	Grade 4
Any event	130 (98%)	77 (58%)	2 (2%)	45 (68%)	5 (8%)	1 (2%)
Hand-foot skin reaction	74 (56%)	26 (20%)	0	9 (14%)	0	0
Hypertension	64 (49%)	30 (23%)	1 (1%)	11 (17%)	2 (3%)	0
Diarrhoea	53 (40%)	7 (5%)	0	3 (5%)	0	0
Fatigue	51 (39%)	3 (2%)	0	18 (27%)	0	0
Oral mucositis	50 (38%)	2 (2%)	0	5 (8%)	1 (2%)	0
Alopecia	31 (24%)	2 (2%)	0	1 (2%)	0	0
Hoarseness	29 (22%)	0	0	3 (5%)	0	0
Anorexia	27 (21%)	0	0	5 (8%)	0	0
Rash, maculopapular	24 (18%)	3 (2%)	0	2 (3%)	0	0
Nausea	21 (16%)	1 (1%)	0	6 (9%)	1 (2%)	0
Constipation	20 (15%)	1 (1%)	0	4 (6%)	0	0
Myalgia	18 (14%)	1 (1%)	0	6 (9%)	0	0
Voice alteration	14 (11%)	0	0	2 (3%)	0	0

Data are n (%). *Excluding one patient who did not receive study treatment.

***Table 2*: Drug-related adverse events in ≥10% of patients during double-blind treatment period**

grade 5 adverse events were deemed by the investigator to be drug-related: two (2%) in the regorafenib group (cardiac arrest and hepatic failure) and one (2%) in the placebo group (fatigue).

Serious adverse events were reported in 38 (29%) of 132 patients in the regorafenib group and 14 (21%) of 66 patients in the placebo group during the double-blind phase. The most common serious adverse events in patients in the regorafenib group were abdominal pain (five [4%] patients), fever (three [2%] patients), and dehydration (three [2%] patients). In the placebo group the most common serious events were fatigue (two [3%] patients) and pain (two [3%] patients). Although dose modifications (appendix) were more frequent in the regorafenib group (72% [95 patients] *vs* 26% [17 patients] in the placebo group), the occurrence of adverse events that led to permanent discontinuation of treatment was much the same between the groups (6% [eight patients] in the regorafenib group *vs* 8% [five patients] in the placebo group), showing that adverse events were manageable by dose modification without the need to discontinue treatment in most cases.

Discussion

When added to best supportive care, regorafenib significantly improves PFS in a population of patients with GIST with progressive disease after failure of all approved previous therapies, compared with matching placebo. Median PFS with regorafenib was more than five times that with placebo, reducing the risk of progression or death by 73%. Although the regorafenib group might have included patients with more indolent disease, we believe that the robust results argue against any such confounding effect of disease-specific variables and instead are evidence of regorafenib activity to arrest disease progression. 56 (85%) of the 66 patients assigned placebo accessed regorafenib after disease progression, which could have confounded any potential difference in overall survival between groups.

GIST is the most common sarcoma subtype.[31] Elucidation of GIST molecular pathogenesis has allowed rational translation of basic science into clinical therapies targeting the root cause of the disease, usually *KIT* or *PDGFRA* mutations. Inhibition of these driver mutations has improved disease control, leading to increased survival of patients with GIST.[10,11,26] Despite these advances, only two tyrosine-kinase inhibitors, imatinib and sunitinib, have been shown to be clinically beneficial to patients with GIST, and resistance to these agents eventually leads to disease progression and death in most patients with advanced GIST. Several other structurally distinct inhibitors of KIT and PDGFRA kinases have been developed, but, despite promise in control of tyrosine-kinase inhibitor-resistant disease in early phase trials, until now, none has shown benefit in prospective phase 3 trials (panel).[32,33]

As with other effective kinase inhibitors in tyrosine-kinase inhibitor-resistant disease, in the present study regorafenib did not induce high rates of objective tumour response per modified RECIST.[26] However, disease control rate was higher in patients in the regorafenib group than in those in the placebo group, suggesting that regorafenib was associated with clinically

meaningful tumour control in patients with advanced GIST after failure of all other approved tyrosine-kinase inhibitor therapies.

Efficacy analysis in prespecified subgroups showed robustness in the benefit of regorafenib compared with placebo in nearly all subgroups. In particular, regorafenib had much the same benefit compared with placebo for patients receiving treatment either as third-line therapy or as fourth or later line of therapy. This result suggests that regorafenib can achieve therapeutic benefit independent of previous treatment regimens. A possible explanation is that regorafenib targets several pathways contributing to GIST pathogenesis, which might block resistance mechanisms.[28]

The safety profile of regorafenib in this study was much the same as that identified in previous clinical trials.[29,30] Regorafenib dosing was reasonably well tolerated within the predefined rules for dose modification (dose delays or reductions, with an option to dose escalate again on the basis of tolerability; appendix). Adverse events leading to permanent treatment discontinuation were much the same in the two study groups. The most common drug-related adverse events in the regorafenib group were hypertension, hand-foot skin reaction, and diarrhoea. Drug-related grade 3 or higher hypertension was reported in 31 (23%) of 132 patients assigned regorafenib and, similarly to other therapies targeting the VEGF/VEGFR pathway,[26,32] is probably related to antiangiogenic effects. This adverse event could be managed with dose modification and appropriate antihypertensive intervention. Drug-related hand-foot skin reaction is also commonly associated with other multitargeted kinase inhibitors.[26,32] In GRID, this adverse event was generally manageable with dose modifications and proper care of the affected skin area.

This rigorously conducted large-scale international collaboration provides robust evidence that regorafenib can control progressive GIST after failure of other approved kinase inhibitors, and this benefit is much the same across many characteristics of patients, including ethnic group, age, performance status, and commonly mutated forms of the oncogenic *KIT* driver mutations. Further work is underway to understand more fully the activity of regorafenib among rare mutational subtypes of GIST besides these common *KIT* mutant subtypes.

Future studies of regorafenib in GIST will investigate further the molecular mechanisms by which the treatment can induce disease control after failure of both imatinib and sunitinib. Specifically, tumour genotypes will be studied as predictive tumour biomarkers in an effort to correlate molecular subtypes of the disease with regorafenib activity. Increased understanding of the key pathways involved in successful treatment of GIST refractory to both imatinib and sunitinib could provide new insight into mechanisms of resistance to molecularly targeted therapies.

Panel: Research in context

Systematic review

We searched PubMed articles added since 2010 (last search Aug 15, 2012), the abstracts of relevant oncology congresses (American Society of Clinical Oncology [ASCO] annual meeting, ASCO Gastrointestinal Cancer Symposium, Connective Tissue Oncology Society conference, European Multidisciplinary Cancer Congress, European Society for Medical Oncology conference, Molecular Markers in Cancer, Molecular Targets and Cancer Therapeutics, Targeted Anticancer Therapies, and the World Congress on Gastrointestinal Cancers), and ClinicalTrials.gov. For the scientific literature and congress searches, we used MeSH and full-text search terms for metastatic or unresectable gastrointestinal stromal tumours (GISTs). For PubMed, we used the search terms ("secondary" OR "metastatic" OR "unresectable") AND ("gastrointestinal stromal tumors" OR ("gastrointestinal" AND "stromal" AND ("tumor" OR "tumour")) AND ("2010/01/01" : "2012/12/31"). For conference searches we used the terms "gastrointestinal stromal tumor" or "gastrointestinal stromal tumour", with results restricted to metastatic or unresectable disease (by the conference search engine if possible or manually otherwise). We restricted the ClinicalTrials.gov search to agents identified in the scientific literature and congress searches, including inhibitors of KIT, PDGFRA, HSP90, MTOR, RAF, VEGF, and ABLkinases. We placed no date or language restrictions on the search. However, two agents failed to show clinical activity in phase 3 trials (nilotinib [Novartis Oncology, Basel, Switzerland] and retaspimycin [Infinity Pharmaceuticals, Cambridge, MA, USA]), and others have not entered phase 3 trials in this specific indication (eg, everolimus, masitinib, motesanib, sorafenib, vatalanib [Novartis Oncology in partnership with Bayer Pharmaceuticals, Berlin, Germany], dasatinib [Bristol-Myers Squibb Oncology, New York, NY, USA], ganetespib [Synta Pharmaceuticals, Lexington, MA, USA], and pazopanib).

Interpretation

Our work is a translation of the evolving scientific understanding of aberrant intracellular signalling in GIST. Since 1998, researchers have recognised that most GIST lesions have constitutively activated signalling through either the KIT or PDGRFA kinase pathways. The existing treatment options for patients with metastatic GIST are limited to only two kinase-inhibiting drugs, imatinib and sunitinib. Once a patient has disease progressing despite therapy with these two agents, no therapeutic options have shown efficacy. Our translational science has previously suggested that structurally distinct kinase-inhibiting agents with novel activities could overcome resistance to imatinib and sunitinib, and thereby offer clinical benefits to patients with this life-threatening disease. After promising clinical phase 2 evidence of antitumour activity of regorafenib in pretreated patients, this international, randomised, placebo-controlled phase 3 trial shows that oral regorafenib can indeed provide a significant progression-free survival benefit compared with placebo in patients with pretreated, progressive metastatic GIST. The study confirms that drug-resistant GIST remains an oncogene-addicted disease that can be therapeutically targeted by new structural inhibitory attacks on the pathogenic mutated kinase. As far as we are aware, this is the first clinical trial to show benefit from a kinase inhibitor after objective resistance to two previous kinase-inhibiting therapies in a disease driven by an oncogenic kinase mechanism.

Contributors

GDD, IK, DL, HJ, PRe, J-YB, PC, Y-KK, and CK contributed to trial conception and design. All authors contributed to data collection. GDD, PC, PRe, PRu, Y-KK, J-YB, HJ, CK, IK, DL, JC, and RGM contributed to data analysis and interpretation. All authors reviewed the report and agreed on submission for publication.

Conflicts of interest

GDD has served as scientific adviser or consultant to Novartis, Pfizer, Lilly, Infinity, GlaxoSmithKline, Plexxikon, Kolltan, and Blueprint Medicines. PRe sits on advisory boards for and has received honoraria from Novartis, Pfizer, and Bayer. J-YB received compensation from Bayer to serve as a member of the GRID steering committee. PRu has received honoraria and travel grants from Novartis and Pfizer and has served as an

advisory board member for Novartis. MvM has served as a scientific adviser to Novartis and Pfizer. ALC has received honoraria from Novartis, Pfizer, and Pharmamar. PS has been a member of speaker bureaus and received grants for translational and clinical research for Novartis, Pfizer, and Bayer. RGM has provided consultancy for Bayer. SB has received honoraria from Novartis and Pfizer and research support from Novartis. TN has received research funding from Novartis, sits on an advisory board for Novartis, and has received honoraria for speaking from Novartis and Pfizer. CK, JC, DL, and IK are employees of Bayer, and CK owns shares in Bayer. All other authors declare that they have no conflicts of interest.

Acknowledgments

We thank the participating patients and staff at each of the study centres. The trial was supported by Bayer HealthCare Pharmaceuticals. Administrative and minor editorial assistance in the preparation of this report was provided by Succinct Healthcare Communications, with financial support from Bayer HealthCare Pharmaceuticals; the authors retained complete editorial control over the content. Additional support for this work has been provided to GDD from the following sources: The Virginia and Daniel K Ludwig Trust for Cancer Research, Team Russo, Paul's Posse and the Pan Mass Challenge, and Gastrointestinal Cancer SPORE Grant 1P50CA127003-05 from the US National Cancer Institute.

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