

EXPERT OPINION

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Regorafenib for treatment of advanced gastrointestinal stromal tumors

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Introduction: Gastrointestinal stromal tumors (GISTs) are abdominal sarcomas which are extremely refractory to chemotherapy treatment. The treatment of GISTs has been revolutionized by use of KIT/platelet-derived growth factor receptor- α (PDGFRA) kinase inhibitors. Unfortunately, most tumors develop resistance to front-line (imatinib) or second-line (sunitinib) therapy. Regorafenib, a KIT/PDGFRA/vascular endothelial growth factor receptor (VEGFR) oral kinase inhibitor, has been shown to improve progression-free survival in the third- or fourth-line setting.

Areas covered: This review covers the preclinical and clinical studies of regorafenib for treatment of GIST. A literature search on regorafenib was carried out using the PubMed database up to October 2013.

Expert opinion: Currently, imatinib and sunitinib represent the only proven first- and second-line therapies, respectively, for advanced GISTs. Based on the results of a Phase III study, regorafenib is now established as the only proven third-line therapy. Regorafenib activity in this setting is believed to be due to its activity against oncogenic forms of KIT/PDGFRA. Although side effects are common with this agent, they can be effectively managed with a combination of supportive care, dose interruptions/reductions. The toxicity profile is similar to other oral kinase inhibitors with anti-VEGFR activity. Regorafenib is mainly metabolized by CYP3A4, and concomitant use of strong inducers/inhibitors of this enzyme should be avoided.

Keywords: gastrointestinal stromal tumor, kinase inhibitors, KIT, platelet-derived growth factor receptor α , sarcoma, vascular endothelial growth factor receptor

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1. Introduction

1.1 Advanced gastrointestinal stromal tumor

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors (sarcomas) that arise from the gastrointestinal (GI) tract [1]. While GISTs most frequently develop in the stomach or small bowel, they can originate anywhere along the GI tract [1,2]. GIST is the most common non-epithelial cancer of the GI tract, but represents only 1% of all GI malignancies [3]. While the true incidence is difficult to establish, it is estimated that there are 3000 – 6000 new cases of GISTs diagnosed annually in the United States [4,5]. Historically, GISTs were misclassified as leiomyosarcoma; however, in 1998, the development of immunohistochemistry for the KIT protein (CD117) led to the reclassification of these tumors as a distinct clinicopathological entity. At the same time, it was discovered that many GISTs express mutant forms of KIT with constitutive kinase activity [6-8]. Prior to this discovery, many attempts had been made to identify effective cytotoxic chemotherapy treatment for advanced GISTs, but none proved successful [9,10].

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Box 1. Drug summary.

Drug name	Regorafenib
Phase	I, II and III
Indication (specific to discussion)	Gastrointestinal stromal tumor, advanced
Pharmacology	Multi-tyrosine kinase inhibitor
Route of administration	Oral
Chemical structure	4-[4-((4-Chloro-3-(trifluoromethyl)phenyl)carbamoyl)amino]-3-fluorophenoxy]-N-methylpyridine-2-carboxamide hydrate (Figure 1)
Pivotal trial(s)	GRID [55]

Following the discovery of *KIT* mutations, the concept of targeted therapy was clinically explored. In 2001, it was established that imatinib, a potent inhibitor of the kinase activity of KIT and platelet-derived growth factor receptors (PDGFRs), was efficacious for treatment of GIST [11,12]. Overall, about 85% of GISTs harbor a gain-of-function mutation of *KIT* [13]. Alternatively, about 8% of GISTs have an activating mutation of the homologous receptor tyrosine kinase PDGFR- α (*PDGFRA*) [13-15]. The remainder of GIST tumors are classified as 'wild-type', although many of these harbor mutations in alternative genes, including *NFI*, *BRAF* and members of the succinate dehydrogenase family (e.g., *SDHA*) [14]. Surgery remains the only established curative treatment for primary GIST, however about 10 – 20% of patients present with metastatic disease and another 40% of patients will develop recurrent/metastatic disease after surgery [16-18].

Imatinib was the first medical therapy to demonstrate efficacy for treatment of GIST tumors [12,19]. Overall, progression-free survival (PFS) in two Phase III studies was in the range of 20 – 22 months, with a median overall survival (OS) of ~ 5 years. With front-line imatinib treatment, the majority of GIST patients obtain clinical benefit; however 15% of patients have primary resistance to imatinib [20-23] and over time, at least 80% of patients will experience disease progression due to the development of tumor-associated secondary kinase mutations [23-27]. In the setting of imatinib-resistance or intolerance, sunitinib has proven clinical activity for second-line GIST treatment [28]. Compared to imatinib, sunitinib has greater potency against wild-type KIT as well as some mutant isoforms. Additionally, sunitinib also inhibits multiple other tyrosine kinase pathways, including vascular endothelial growth factor receptors (VEGFR1/2), Fms-like tyrosine kinase-3, and RET [29-31]. Overall, sunitinib showed sufficient activity against imatinib-resistant GISTs to receive FDA approval. Sunitinib is approved for treatment of patients with imatinib-resistant disease or imatinib intolerance. Sunitinib is thought to overcome some cases of imatinib-resistance due to its smaller size and ability to enter the ATP-binding site despite

ATP-pocket mutations that prevent the entrance of the larger imatinib molecule [32]. However, sunitinib has limited activity against activation loop mutations of KIT. As most patients with imatinib-resistant GIST have multiple lesions with heterogeneous secondary resistance mutations, it is not surprising that mixed responses to this agent are commonly seen. Unfortunately, the majority of sunitinib-treated patients develop progressive disease with a median progression time of between 6 and 7 months [28].

1.2 Competitor compounds

Multiple other tyrosine kinase inhibitors have been evaluated for treatment of advanced GISTs. However, prior to the approval of regorafenib, the only FDA-approved treatments were imatinib (front-line) and sunitinib (second-line). Currently, regorafenib stands alone as the only medication approved for treatment of GIST after failure of prior imatinib and sunitinib therapies. However, multiple other tyrosine kinase inhibitors are being evaluated as potential treatment options for drug-resistant metastatic GIST. Kang *et al.* presented data in 2013 at ASCO from a small Phase III study that compared imatinib rechallenge to placebo after failure of both imatinib and sunitinib treatments [33]. PFS for patients rechallenged with imatinib was 1.9 months compared to 0.9 months in the placebo group ($p = 0.002$, hazard ratio [HR] of 0.45 [95% CI: 0.27 – 0.76]). OS data was not different between the groups, but this is difficult to interpret given that 93% of patients in the placebo group crossed over to imatinib at the time of progression. Whereas most agents for treatment of GIST in the third-line or later have only been tested in Phase II studies, nilotinib was also evaluated in a Phase III trial published in 2012 [34]. This study compared nilotinib to best-supportive care for patients that had failed both imatinib and sunitinib; notably, there was no difference in PFS for patients treated with nilotinib. *Post-hoc* analysis looking only at patients that received nilotinib as true third-line therapy did show an improvement in OS with a hazard ratio of 0.67. Multiple other agents have been examined in Phase II studies of GIST patients undergoing third-line or subsequent treatment, including dasatinib, motesanib, vatalanib and sorafenib to name a few [35-39]. Small studies of combination therapies such as imatinib and everolimus have suggested potential efficacy for imatinib-resistant GIST, but the relative efficacy of these therapies compared with sunitinib or regorafenib is unknown [40]. Multiple clinical trials are currently underway to evaluate the efficacy of other kinase inhibitors, including cediranib, pazopanib, crenolanib, ponatinib and masitinib [41]. Overall, regorafenib is currently well established as the only proven third-line treatment for metastatic GIST. Alternative therapeutic approaches would include rechallenge with imatinib, off-label use of another approved KIT/PDGFR inhibitor, or participation in a clinical study.

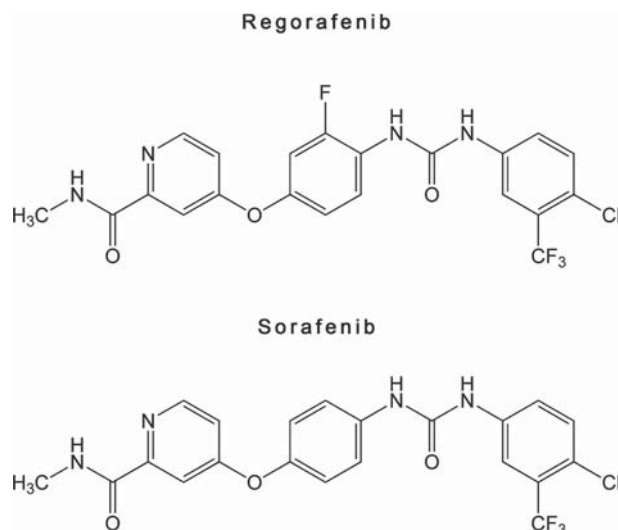


Figure 1. The chemical structures of regorafenib (top) and sorafenib (bottom) only differ by the substitution of fluorine for hydrogen on the central carbon ring.

2. Introduction of the compound

Regorafenib, 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide hydrate is a novel biaryl urea compound with multikinase inhibitory activity as an oral agent (Figure 1 and Box 1 for compound summary) [42]. Regorafenib is closely related to another FDA-approved agent, sorafenib, differing only by the addition of a fluorine atom to the center phenyl ring (Figure 1). The two agents have similar, but distinct biochemical profiles [43-45]. In a tumor microenvironment, tyrosine kinase activation plays important direct (tumor growth) and indirect roles (regulation of stroma, angiogenesis). Notably, multiple receptor tyrosine kinases (RTKs) help regulate tumor angiogenesis; these include VEGFRs, fibroblast growth factor receptors (FGFRs) and PDGFRs [42]. These pathways work in conjunction to modulate tumor growth, suggesting that blockade of multiple receptors might be an effective anticancer strategy [46]. Currently, there are several approved multi-targeted kinase inhibitors. Representative examples include sorafenib (approved for renal cell carcinoma [RCC] and hepatocellular carcinoma) as well as sunitinib (RCC, pancreatic neuroendocrine tumors and GIST) [28,47-50].

3. Chemistry

In vitro studies of regorafenib by Wilhelm *et al.* [42] demonstrated a broad spectrum of biochemical kinase inhibition. These targets included tumor, vascular and stromal cell RTKs, including VEGFR1 – 3, TIE2, FGFR1 and PDGFR- β , oncogenic forms of KIT and RET as well as the

intracellular signaling kinases c-RAF/RAF-1 and B-RAF and its V600E mutant isoform. No *in vitro* inhibition was seen for kinases in the epidermal growth factor receptor family, protein kinase C family, cyclin-dependent kinases, insulin and insulin growth factor receptor kinase, MET, MEK, ERK1/2 or AKT. In addition, *in vivo* assessment was done utilizing xenograft models and dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). In tumor-bearing rats, regorafenib decreased tumor perfusion with effects persisting up to 2 days after a single dose. Inhibition of tumor angiogenesis was also confirmed by assessing tumor vasculature in rat xenograft models. Endothelial markers such as CD-31 were significantly reduced in rats treated with regorafenib and this reduction was accompanied by tumor necrosis. Of note, these rat tumor studies included lung, melanoma, pancreatic and ovarian cancer cell models [42]. Thus, both *in vitro* and *in vivo* studies of regorafenib confirmed the inhibition of multiple angiogenesis pathways including VEGFR2 and TIE2. With specific regard to GISTs, regorafenib showed potent *in vitro* inhibition of KIT, including cell lines with compound KIT exon 11-primary and imatinib-resistant secondary mutations of the ATP-binding pocket or the activation loop [44].

4. Pharmacodynamics

Regorafenib pharmacodynamics were evaluated in a conventional Phase I study as well as Phase I study restricted to colorectal cancer patients [51,52]. In the conventional Phase I study, assessments were done by evaluating plasma concentrations of VEGF and sVEGFR2 pre-dose, 8 h post-dose on the first and twenty-first days of the first three cycles, as well as pre-dose on day 1 of all subsequent cycles. sVEGFR2 plasma concentrations varied in a dose-dependent manner. Measured VEGF concentration steadily increased over the 21 days of dose administration and returned to baseline during the 7-day treatment break [51].

Both studies evaluated tumor perfusion by DCE-MRI [51,52]. MRIs were performed at the start of treatment and day 21 in both studies; there was some variation in MRI frequency in the conventional Phase I study with the first dose cohort. In both studies, there was about a 40% decrease in the perfusion measurement at 21 days compared to baseline. This reduction was seen for doses 120 mg and higher in the conventional Phase I study; unfortunately, the colorectal Phase I study did not comment on the dose relationship to perfusion.

5. Pharmacokinetics and metabolism

Pharmacokinetics (PK) and metabolism can be evaluated by measuring plasma concentrations of regorafenib as well as two pharmacologically active/major metabolites, N-oxide metabolite (M-2) and N-oxide/N-desmethyl metabolite (M-5), utilizing liquid chromatography with tandem mass

Table 1. Summary of Pharmacokinetic data.

	160 mg/day conventional Phase I [51]			160 mg/day colorectal Phase I [52]		
	AUC ₀₋₂₄ $\mu\text{g}\cdot\text{h}/\text{ml}$	C _{max} $\mu\text{g}/\text{ml}$	t _{1/2} h	AUC ₀₋₂₄ $\mu\text{g}\cdot\text{h}/\text{ml}$	C _{max} $\mu\text{g}/\text{ml}$	t _{1/2} h
Regorafenib	58.3	3.9	22.2	50.3	3.4	28.4
M2	53.7	3.3	21	48.1	3.2	25
M5	48.7	2.9	NR	64.6	4	50.9

NR: Not reported.

spectrometric detection. In the conventional Phase I study, both a liquid formulation and a coprecipitate tablet were utilized and the bioavailability was compared between the two formulations utilizing inpatient crossover [51]. With the liquid formulation, there was a dose-dependent increase in plasma concentrations for doses up to 60 mg; however, no further increase was seen using a 120 mg dose. All doses > 120 mg were given in the coprecipitate form. There was no proportional increase in the area under the curve using coprecipitate doses from 120 to 220 mg. The half-life varied between 20 and 40 h for regorafenib and M-2 and 40 and 60 h for M-5 resulting in an accumulation of regorafenib and its metabolites after multiple doses. This increase was predictable based on a time-linear PK. Given this half-life, these data support daily dosing as currently recommended. With the regorafenib metabolites, M2 and M5, there was more than a proportional increase at lower doses, but proportional increases of serum levels at higher doses [51]. Summary of the PK data is available in Table 1.

6. Clinical efficacy

6.1 Phase I studies

Clinical studies of regorafenib began in 2005 with a Phase I open-label, nonrandomized, dose-escalation study to evaluate safety, maximum-tolerated dose (MTD) and PK [51]. No GIST patients were enrolled in this study, although four patients had other types of soft tissue sarcoma. Overall, 53 patients with a median age 60 (22 – 70) were enrolled. These patients had been treated with median of three prior therapies (range 0 – 9). Doses up to 220 mg were evaluated; however, 160 mg was determined to be the MTD. Dose-limiting toxicities (DLTs) at 220 mg included hand-foot skin reaction, skin rash, asthma and abdominal pain. The median duration of regorafenib treatment was 78 days (range 3 – 1239). Notably, the dosing that was predominantly evaluated was for 21 days out of a 28-day cycle; however, initial test dosing included 1 day of drug with 6 days off and then 7 days of drug with 14 days off. At the time of study closure, only two patients remained on treatment. The disease control rate (defined as either stable disease or partial response) was 66%; however, only three patients had a documented partial response (one patient each with a diagnosis of RCC,

osteosarcoma and colorectal cancer). To date, the median PFS and OS for patients in this study have not been reported (Table 2).

An additional Phase I study restricted to patients with colorectal cancer was also performed [52]. Doses studied included 60 – 220 mg all given 21 out of 28 days. Only one patient (out of 38) had a partial response (4%); however, 70% of patients had stable disease as their best clinical response (Table 2). The median PFS was 107 days (3.5 months). To date, no OS data has been reported for this study.

6.2 Phase II study

Based on preclinical data suggesting target inhibition of multiple kinases thought to be important in GIST biology (KIT, PDGFRs, VEGFRs), a Phase II trial was performed to evaluate regorafenib in patients with metastatic GIST who experienced disease progression during prior imatinib and sunitinib treatments. Any number of treatments in addition to imatinib or sunitinib were allowed; however, prior exposure to sorafenib was not permitted [53]. The primary objective of this study was to assess the clinical benefit rate, which was defined as a composite of complete response, partial response and stable disease rates. Secondary end points included PFS and safety/tolerability in the GIST population. A total of 34 patients were enrolled with all but one of these patients receiving at least one dose of regorafenib. At median follow up of 10.9 months, 21 of the 33 patients continued on treatment. Of the 12 patients that discontinued drug, the majority did so for disease progression (either by RECIST- or investigator-defined disease progression). Overall, 75% of patients experienced clinical benefit with four patients achieving a partial response and the remaining 22 patients experiencing stable disease. The median PFS was 10 months and median OS had not been achieved at the time of study publication (Table 2). An update with a median follow up of 20 months was presented at the 2013 ASCO annual meeting. At that time, 81% of patients demonstrated clinical benefit, with four patients remaining on trial at a median follow up of 20 months. For the entire cohort, the median PFS was 13 months with an OS of 27 months [54].

A secondary objective of this study was to explore the relationship between primary tumor genotype and response to therapy. There was no significant difference in clinical

Table 2. Summary of efficacy data across all regorafenib trials.

	Study	Disease control (%)	Stable disease (%)	Partial response (%)	Progression-free survival (months)	Overall survival (months)
All solid tumor	Phase I [51]	66	60	6	NR	NR
Gastrointestinal stromal tumor	Phase II [53]	78	67	12	13*	27*
	Phase III: Regorafenib [55]	52.6	48.1	4.5	4.8	NR
	Phase III: Placebo [55]	9.1	7.6	1.5	0.9	NR
Colorectal cancer	Phase I [52]	74	70	4	3.5	NR
	Phase III: Regorafenib [60]	41	40	1	1.9	6.4
	Phase III: Placebo [60]	15	14.6	0.4	1.7	5

NR: Not reported

*: PFS and OS are updated to reflect updated results from the ASCO annual meeting [54].

benefit among patients with different tumor genotypes, although the comparative subsets were small. After pairwise comparisons, patients with tumors with a primary exon 11 *KIT* mutation had a significantly longer PFS compared with patients with tumors with primary exon 9 *KIT* mutations ($p = 0.01$), although it should be noted that there were only three patients with *KIT* exon 9-mutant tumors. There was no significant difference in PFS when comparing patients with wild-type GIST with patients with either exon 9 or 11 *KIT*-mutant tumors. Of note, one patient with a *BRAF* exon 15 mutation had rapid disease progression [53]. The ASCO 2013 update also reported on the correlation of response to tumor genotype. Patients with primary mutations in *KIT* exon-11 had a PFS of 13 months compared with only 6 months in patients with *KIT* exon-9 mutations; however, this difference was no longer statistically significant. Notably, there were six patients with succinate dehydrogenase subunit B (SDHB)-deficient GIST, as assessed by immunohistochemistry, and two of these demonstrated a partial response to regorafenib, suggesting SDHB deficiency as a potential biomarker for regorafenib response. Correlation of secondary *KIT* mutations and regorafenib response was also evaluated. Patients with secondary *KIT* exon 17 mutations had a PFS of 18 months [54].

6.3 Phase III studies

Following completion of the Phase I studies that showed safety and tolerability and the Phase II study that showed activity of regorafenib in multidrug-resistant GIST, a Phase III trial for treatment of advanced GIST was initiated (GRID study: GIST- Regorafenib in Progressive Disease). The GRID study was a randomized, placebo-controlled, double-blind study with a 2:1 randomization between regorafenib and placebo. This study was designed to evaluate the efficacy of regorafenib in GIST patients who had failed prior imatinib or sunitinib [55]. Patients who had received any prior VEGFR inhibitor therapy were excluded. The study

was conducted across 17 countries and 57 hospital sites. The starting dose of regorafenib was 160 mg/day (based on the MTD from the Phase I studies) for the first 21 days of a 28-day cycle. This study allowed patients originally assigned to placebo to crossover at the time of progression. The primary end point of the study was PFS based on RESIST 1.1 criteria using blinded central radiology review, with secondary end points of OS, time to progression, objective response rate and disease control rate (total of complete response, partial response and stable disease rates), as well as safety/tolerability. A total of 199 patients were randomized and the overall pretreatment characteristics were well balanced. However, compared with the placebo arm, more patients assigned to regorafenib had been treated with imatinib for > 18 months. As of the original data cutoff in 2012, 50% of the patients in the regorafenib group remained on treatment, whereas only 5% of patients in the placebo group remained on their originally assigned treatment. Roughly 85% of patients in the placebo group crossed over to open-label regorafenib with 50% of these patients remaining on regorafenib treatment at the data cutoff time. Median regorafenib treatment duration was 22.9 versus 7 weeks for placebo. Correlating with the longer duration of treatment, patients on regorafenib had a median PFS of 4.8 months compared to 0.9 months for placebo-treated patients ($p < 0.0001$, HR = 0.27 [CI: 0.19 – 0.39]) (Table 2). For patients who crossed over to regorafenib from placebo, the median PFS was 5 months, which is very similar to the PFS for patients originally assigned to regorafenib treatment. No difference was noted in OS; however, at the time of analysis, only around 25% of patients had died. In addition, the high crossover rate of 85% from placebo to regorafenib would be expected to obscure differences in OS benefit between these treatments. Clinical benefit from regorafenib treatment was noted in patients with both *KIT* exon 9- and exon 11-mutant tumors. Similar to the Phase I and Phase II studies, there were no complete responses seen and

Table 3. Summary of toxicity from all regorafenib trials.

	All solid tumor		Gastrointestinal stromal tumor				Colorectal cancer			
	Phase I [51]		Phase II [53]		Phase III [55]		Phase I [52]		Phase III [60]	
	Any grade (%)	Grade 3/4 (%)	Any grade (%)	Grade 3/4 (%)	Any grade (%)	Grade 3/4 (%)	Any grade (%)	Grade 3/4 (%)	Any grade (%)	Grade 3/4 (%)
Any event	83	49	NR	NR	98	60	84	58	93	54
Hand-foot	40	19	85	24	56	20	61	32	47	17
Mucositis	36	2	38	0	38	2	18	0	27	3
Hypertension	30	11	67	36	49	24	18	11	28	7
Diarrhea	32	8	60	6	40	5	24	3	34	7
Fatigue	28	4	79	6	39	2	50	11	47	9
Voice changes	55	2	47	0	22	0	34	3	29	< 1

NR: Not reported.

partial responses were uncommon; only 4.5% of patients in the regorafenib arm had a partial response. In regard to disease control, 52.6% of patients in the regorafenib arm had disease control compared with only 9.1% of the placebo-treated patients.

Unlike GIST, where biochemical inhibition of KIT/PDGFR is known to be the therapeutic target, the target in colon cancer is hypothesized to be inhibition of VEGFR based on the efficacy of other VEGFR inhibitors such as bevacizumab and aflibercept [56-59]. There is no compelling evidence to suggest that KIT or PDGFR kinases are important targets in colorectal cancer biology. In addition to the Phase III trial in GIST, regorafenib was also studied in a Phase III study of patients with metastatic colorectal cancer (CORRECT study) [60]. Eligible patients included those who had received all locally and currently approved standard therapies with disease progression. Given that this study was done across 16 countries, available standard therapies varied but included fluoropyrimidine, oxaliplatin, irinotecan and bevacizumab in addition to cetuximab and/or panitumumab for patients with *KRAS* wild-type tumors. Unlike the GRID study, the CORRECT study did not allow crossover. Using a similar 2:1 treatment allocation design, 760 patients were randomized to regorafenib versus placebo. The primary end point of this study was OS: regorafenib-treated patients experienced a 1.4 months improvement in OS (6.4 months compared to 5 months, $p = 0.0052$, HR = 0.77 [95% CI: 0.64 - 0.94]). Notably, there was no improvement in median PFS; with a median PFS of 1.9 months with regorafenib treatment versus 1.7 months in the placebo group (Table 2). However, it is important to note that the HR for PFS was 0.49 (95% CI: 0.42 - 0.58, $p < 0.0001$). Compared with the GRID study, the median duration of treatment in the CORRECT study was shorter, with regorafenib-treated patients receiving a median of 2.8 months of treatment. None of the patients achieved a complete response. Partial responses were noted in only 1% of patients. The overall disease control rate was

41% in this study, similar to the rate in the GIST study. In subset analyses, there was no particular group that had differential benefit from regorafenib treatment. These studies included correlation with *KRAS* mutation status and the use of previous VEGF or EGFR inhibitors.

6.4 Post-marketing surveillance

At this time, post-marketing surveillance for regorafenib is being conducted for patients with colorectal cancers and this study is actively recruiting. Patient recruitment began in September 2013 (NCT01843400).

7. Safety and tolerability

The safety and tolerability of regorafenib was assessed in each of the trials conducted to date with regorafenib. The Phase I studies in solid tumors and colorectal cancer had safety/tolerability as a primary outcome measures. The spectrum and frequency of regorafenib side effects have been fairly consistent across disease types and different phases of clinical development (Table 3) [24,51-53,55,60]. In the Phase I studies, toxicity from regorafenib was dose-dependent, 42% of patients (5 of 12) experienced DLTs with the 220 mg dose, whereas only 17% (2 of 12) of patients on the 160 mg dose had DLTs. As noted previously, based on this data, the MTD was determined to be 160 mg/day for 3 weeks with a 1-week washout period. Overall, over 80% of the patients experienced at least one treatment-related adverse event (AE). The most frequently documented AEs included voice changes, hand-foot syndrome, hypertension, diarrhea and rash. Serious adverse events (SAEs) were documented in 30% of the patients; the most frequently observed SAE was hypertension [51].

A similar spectrum and frequency of side effects was seen in the Phase II GIST study, with the most commonly observed toxicities being hand-foot skin reaction, fatigue, hypertension and diarrhea (Table 3). The only grade 4 events were

hyperuricemia and a thrombotic event. Only one patient discontinued treatment as a result of toxicity [53].

In the Phase III GIST trial, a similar spectrum and frequency of AEs were noted. Almost all patients (98%) reported at least one drug-related AE, while on regorafenib. Similar to the previous trials, hand-foot reaction was the most frequent side effect, followed by hypertension, diarrhea and fatigue (Table 3). About 61% of patients experienced at least one grade 3 or higher AE, the most common being hypertension. Seven patients (5%) died while on treatment in the regorafenib arm, compared to three (5%) in the placebo group during treatment. Notably, two of the seven deaths on the regorafenib treatment arm were felt to be drug-related (one case each of cardiac arrest and hepatic failure). One of the five deaths in the placebo arm was attributed to treatment toxicity (attribution was made prior to treatment unblinding). Overall, dose modifications related to AEs were common in the regorafenib group with 72% of patients requiring dose adjustment. However, only 6% of the regorafenib-treated patients required permanent discontinuation; interestingly, 8% of patients in the placebo group required permanent discontinuation for presumed drug toxicity.

The CORRECT colorectal study reported similar toxicity results, with 76% of patients requiring dose modification (Table 3) [60]. The most common AEs were fatigue followed by hand-foot skin reaction, diarrhea and anorexia. Over 50% of patients experienced grade 3 or 4 treatment-related events. Of note, one episode of fatal drug-induced liver injury felt to be related to regorafenib was noted; most liver-related events were grade 1 or grade 2. In the CORRECT study, quality of life assessments were also performed which showed no difference in the deterioration in patient's perceived quality of life and health status between the study arms [60].

8. Regulatory affairs

Regorafenib was initially FDA-approved in the fall of 2012 for colorectal cancer and subsequently approved for GIST in February 2013. For colorectal cancer, the specific FDA indication for regorafenib is for patients who have previously received fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, an anti-VEGF therapy and, if *KRAS* wild-type, an anti-EGFR therapy. Regorafenib is FDA-approved for treatment of GISTs that cannot be surgically removed and that no longer respond to other FDA-approved treatments for this disease (this includes imatinib and sunitinib). In May 2013, the FDA issued additional guidance regarding drug interactions related to strong CYP3A4 inducers (e.g., rifampin) and inhibitors (e.g., ketoconazole). The FDA recommends avoidance of concomitant use of regorafenib with strong inducers or inhibitors of CYP3A4 [61]. There is also a black box warning noting severe and sometimes fatal hepatotoxicity with guidance to monitor hepatic function before and during treatment. More recently, the European Medicines Agency (EMA) approved regorafenib for treatment of

colorectal cancer patients on 30 August 2013 with similar indications as endorsed by the FDA. The manufacturer of regorafenib has submitted a request for EMA approval for treatment of advanced GISTs.

9. Conclusion

Overall, as noted above, clinical development of regorafenib has spanned Phase I to Phase III, including Phase II and Phase III studies for GIST. At this time, only the Phase III study in colorectal cancer has reported data indicating an improvement in OS data with use of this agent [60]. A consistent finding across all five studies reviewed above is that regorafenib treatment is commonly associated with stable disease, with only a small proportion of patients achieving a partial response [51-53,55,60]. In the Phase III study of regorafenib in GIST patients (GRID), there was almost a 4-month improvement in PFS with over 50% of the patients experiencing disease control [55]. Based on this Phase III data, regorafenib received FDA approval in February 2013.

10. Expert opinion

The use of KIT/PDGFR kinase inhibitors has transformed the treatment of advanced GISTs. These tumors respond poorly or not at all to cytotoxic chemotherapy but have a high response rate to front-line imatinib. Imatinib treatment is associated with prolonged PFS (median 20 months in Phase III studies) and OS (~ 5 years in several studies). These clinical results are likely a consequence of the dependence (so-called oncogene addiction) of most GISTs to mutated oncogenic kinases (KIT 80%, PDGFRA 5 – 10%). Both primary and secondary resistance to imatinib is determined by the intrinsic imatinib sensitivity of the target kinase in any given tumor. Acquired (secondary) mutations limit the overall duration of response to imatinib [14].

Sunitinib, a multi-targeted kinase inhibitor of KIT/PDGFR as well as VEGFR family members, has activity against imatinib-resistant GIST. This clinical activity is likely a consequence of the sensitivity of some, but not all, secondary mutations to this agent. Despite its potent anti-VEGFR activity, there is no convincing evidence that this activity is required or even contributes to the clinical activity of sunitinib against imatinib-resistant GIST. Numerous studies have detailed the heterogeneity of imatinib-resistance mutations between different metastatic sites. Overall, only about 50% of imatinib-resistant lesions have *in vitro* sensitivity to sunitinib (ATP pocket mutations being sunitinib-sensitive, activation loop mutations being resistant). These data likely explain the mixed imaging responses commonly observed during sunitinib treatment of imatinib-resistant GIST and the relatively short PFS with sunitinib compared with front-line treatment [14]. Regorafenib is a structurally distinct multi-targeted kinase inhibitor with demonstrated activity in the third-line metastatic GIST treatment setting [53,55]. As with sunitinib, the efficacy of

regorafenib is likely to be substantially determined by its spectrum of activity against drug-resistant KIT mutations rather than by its anti-angiogenic effects. To date, limited data indicate that regorafenib has superior potency to imatinib or sunitinib for some common secondary activation loop mutations. Unlike imatinib, both regorafenib and sunitinib inhibit the *KIT* gatekeeper mutation (T670I). However, regorafenib appears markedly inferior to sunitinib for treatment of the common *KIT* V654A secondary imatinib-resistance mutation [54]. As discussed above for sunitinib, the incomplete spectrum of kinase inhibitory activity for regorafenib limits the duration of response as drug-resistant lesions will progress at the same time that drug-sensitive lesions regress or remain stable. Given its spectrum of activity, it is possible that regorafenib could outperform sunitinib in the second-line setting. In addition, it is also possible that regorafenib could improve on the results of front-line imatinib. However, given the superior tolerability of imatinib compared with regorafenib and the prolonged PFS observed with front-line imatinib, it is questionable whether such a large comparative study will ever be performed. To date, there has been no initiative to study regorafenib in earlier lines of therapy of advanced GIST.

For the conceivable future, it seems likely that regorafenib will remain as the standard third-line therapy for metastatic GIST. Future studies may explore novel combination

treatments using regorafenib as a backbone. As additional KIT inhibitors demonstrate activity in the third-line or later setting, these agents may be tested against regorafenib in the third-line setting.

The toxicities associated with regorafenib are similar to other kinase inhibitors that include activity against VEGFR family members. Close attention to severity of side effects and individualization of supportive care are necessary for optimal use of this agent. Despite the modest improvement in median PFS observed in the Phase III GRID study, in our experience, many patients obtain meaningful palliation of their GIST-associated symptoms from this agent. In addition, a minority of patients may experience prolonged disease control.

Declaration of interest

M Heinrich: Consultant – Ariad, Molecular MD, Novartis, Pfizer. Speaker's honorarium – Onyx, Novartis. Equity interest – Molecular MD. Intellectual property – patent on treatment of GIST with imatinib – assigned to my institution and licensed to Novartis. L Overton has no conflicts of interest. This paper has been supported by a VA Merit Review Grant, GIST Cancer Research Fund, Life Raft Group.

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