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Regorafenib for treatment of imatinib- and sunitinib-resistant metastatic gastrointestinal stromal tumors

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1. Introduction

1.1. Advanced gastrointestinal stromal tumor (GIST)

GISTs are a type of abdominal sarcoma and most frequently develop in the stomach or small bowel. However, GIST can originate anywhere along the length of the gastrointestinal (GI) tract, and even, in rare cases, from the omentum or peritoneum. GIST is the most common soft tissue sarcoma (STS) arising in the abdominal cavity, but represents only 1% of all GI malignancies. While the true incidence is difficult to establish, it is estimated that the annual incidence of GIST in the United States is approximately 3000–6000. [4] Historically, GIST was misdiagnosed as leiomyosarcoma; however, in 1998, the development of immunohistochemistry for the KIT protein (CD117) led to the categorization of GIST as a distinct diagnostic entity. Simultaneously with the reports of KIT expression by GIST, it was also discovered that most GISTs express mutant isoforms of KIT with constitutive tyrosine kinase activity. [1,5–8] Prior to this discovery, numerous studies had attempted to identify effective cytotoxic chemotherapy treatment for advanced GIST. But, with most agents producing partial responses rates in the range of 0–5%, it was hard to consider these therapies as effective options. [9,10]

Following the discovery of KIT mutations, the concept of therapy to clinically target the constitutive kinase activity was proposed and validated in vitro. [11] 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 the treatment of GIST. [12,13] Overall, about 85% of GISTs harbor a gain-of-function mutation of KIT. Alternatively, about 8% of GISTs have an activating mutation of the homologous receptor tyrosine kinase platelet-derived growth factor receptor alpha (PDGFRα). The remainder of GIST tumors are classified as ‘wild-type’, although many of these harbor mutations in alternative genes including NF1, BRAF, and members of the succinate dehydrogenase family (e.g. SDHA). [1,14–16]

Surgery remains the only established curative treatment for localized GIST, however, about 10–20% of patients present with metastatic disease and another 40–50% of patients will develop recurrent/metastatic disease after surgery. [17–20]

Imatinib was the first medical therapy with proven efficacy for the treatment of advanced or metastatic GIST. [13,21–23] Overall, progression-free survival (PFS) in two randomized phase III studies comparing imatinib 400 versus 800 mg daily was in the range of 20–22 months, with a median overall survival (OS) of approximately 5 years. [21,23] With front-line imatinib treatment, the majority of GIST patients obtain clinical benefit; however, 15% of patients have primary resistance to imatinib, [24,25] and over time the vast majority of patients will experience disease progression due to the development of tumor-associated secondary kinase mutations. [25–29]

Following its demonstrated activity in advanced GIST, imatinib
was subsequently shown to improved relapse-free and OS in the adjuvant setting.\[30\]

In the setting of imatinib-resistant GIST or imatinib intolerance, sunitinib has been proven to have substantial activity as a second-line agent.\[31,32\] Notably, sunitinib has greater potency against wild-type KIT, as well as some KIT mutant isoforms (e.g. KIT exon 9 mutant isoforms) compared to imatinib.\[31\] In addition, sunitinib inhibits a broader array of receptor tyrosine kinases, including vascular endothelial growth factor receptors (VEGFR1/2), Fms-like tyrosine kinase-3 (FLT3), and RET.\[33,34\] Overall, sunitinib showed sufficient activity against imatinib-resistant GIST to receive approval of US Food and Drug Administration (FDA) and European Medicines Agency (EMA). Currently, sunitinib is approved for the treatment of patients with imatinib-resistant disease or with intolerance to imatinib. Sunitinib is thought to overcome some cases of imatinib-resistance by its ability to bind to the KIT/PDGFRA ATP-binding pocket site despite mutations of this region (e.g. KIT V654A or T670I) that hinder the binding of the larger imatinib molecule.\[31,35\] Unfortunately, sunitinib has limited activity against activation loop mutations of KIT (mutations in KIT exons 17 or 18) (Figure 1). As most patients with imatinib-resistant GIST have multiple lesions with heterogeneous secondary resistance mutations both intra- and inter-lesionally, it is not surprising that mixed responses to this agent are commonly seen.\[28,31,32\] Therefore, most patients with imatinib-resistant GIST would be expected to harbor clones with intrinsic sunitinib resistance. As a consequence of these pre-existing sunitinib-resistant clones, the majority of sunitinib-treated patients develop progressive disease with a median time to progression between 6 and 7 months.\[32,36\] As will be discussed extensively in the following, regorafenib has now emerged as the standard third-line treatment for patients with metastatic (Box 1).

### Box 1. Drug summary

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Regorafenib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase</td>
<td>I, II, and III</td>
</tr>
<tr>
<td>Indication (specific to discussion)</td>
<td>Gastrointestinal stromal tumor, advanced</td>
</tr>
<tr>
<td>Pharmacology</td>
<td>Multi-tyrosine kinase inhibitor</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Oral, days 1–21, 7-day rest period constitute a 28-day cycle</td>
</tr>
<tr>
<td>Chemical structure</td>
<td>4-[(4-chloro-3-(trifluoromethyl)phenyl)carbamoyl]amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide hydrate</td>
</tr>
<tr>
<td>Pivotal trial</td>
<td>Phase 3 GRID [62]</td>
</tr>
</tbody>
</table>

1.2. Competitor compounds

Based on the success of imatinib, a number of KIT/PDGFRa TKIs have been evaluated for the treatment of advanced/metastatic GIST. However, prior to the FDA approval of regorafenib in February of 2013, the only FDA-approved treatments were imatinib (front-line therapy, approved in February 2002) and sunitinib (second-line therapy, approved in January 2006). As of the end of 2015, regorafenib remains as the only medication approved for treatment of GIST after failure of prior imatinib and sunitinib therapy. Based on the approval of these three agents, multiple TKIs have been evaluated as potential treatment options for drug-resistant metastatic GIST, usually in

![Figure 1](image-url) The primary protein structure and location and frequency of primary activating KIT mutations are shown in the left stick figure. The kinase domain of the KIT protein has been magnified to highlight exon structure and amino acid substitutions associated with TKI resistance (e.g. V654A). The activity of imatinib (IM), sunitinib (SU), and regorafenib (REG) against the various drug resistance mutations is indicated by a colored box (red for mutations that confer resistance to a given drug [e.g. V654A is resistant to inhibition by imatinib], green for mutations that are sensitive to a given drug [e.g. V654A can be potently inhibited by sunitinib]).\[37\]
the third-line or later setting. Kang et al. [38] have published a small phase III study that compared imatinib re-challenge to placebo after failure of both imatinib and sunitinib treatment. [33] PFS for patients re-challenged with imatinib was 1.8 months compared to 0.9 months in the placebo group \( (p = 0.005, \text{ hazard ratio (HR) of } 0.46 \text{ [95% confidence interval (CI), 0.27–0.78]}) \). Overall survival 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 after progression. [38]

Whereas most agents for treatment of GIST in the third-line or later have only been tested in phase II studies, nilotinib was evaluated in a phase III trial published in 2012. This study compared nilotinib to best-supportive care for patients who had progression with prior imatinib and sunitinib therapy; notably, there was no difference in PFS for patients treated with nilotinib. A post hoc analysis suggested that patients who received nilotinib as true third-line therapy did show an improvement in OS with a hazard ratio of 0.67. [39] 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. [2] Small studies of combination therapies, such as imatinib and everolimus have suggested potential efficacy of this combination to treat imatinib-resistant GIST, but the relative efficacy of this therapy compared with sunitinib or regorafenib is unknown. [40]

Multiple clinical trials are currently underway to evaluate the efficacy of other kinase inhibitors including pazopanib, BLU-285, MEK162, ponatinib, and masitinib (complete details available at clinicaltrials.gov). Currently, regorafenib is the only proven third-line treatment for metastatic GIST. Alternative therapeutic approaches in the third-line setting would include re-challenge with imatinib, off-label use of another approved KIT/PDGFRα inhibitor, or participation in a clinical study.

2. Introduction of the compound

Regorafenib, known by the chemical name 4-[4-[[4-chloro-3 (trifluoromethyl)phenyl] carbamoyl]amino]-3-fluorophenoxo]-N-methylpyridine-2-carboxamide hydrate, is a novel multikinase inhibitor. It shares a similar molecular structure with sorafenib (Figure 2) but, as many preclinical and clinical studies have shown, has a unique biochemical and pharmacological profile. [40, 41] In vitro, regorafenib potently inhibits the angiogenic and stromal receptor tyrosine kinases (RTKs), VEGFR1–2, PDGFR, fibroblast growth factor receptor (FGFR), and tyrosine kinase immunoglobulin, and epidermal growth factor homology domain 2 (TIE2), as well as the oncogenic RTKs, KIT, and RET. Regorafenib also inhibits intracellular signaling kinases c-RAF/RAF-1, B-Raf, and its V600E mutant isoform, as well. [41] An extensive study of the inhibitory properties of regorafenib against primary and secondary KIT mutant isoforms was recently reported by Garner et al. [37] (Figure 1).

Tumor growth and angiogenesis result from the activation of multiple signaling pathways, many of which are regulated by RTKs including VEGFRs, PDGFR, FGFR, and TIE2. It has long been theorized that inhibiting the activation of these receptors and their associated signaling pathways would suppress angiogenesis and thereby inhibit cancer cell growth. [42, 43] In addition, in some cases, the cancer cells may have a partial or substantial dependence upon activation of drugable RTKs (e.g. KIT and GIST). An anti-tumor effect has been observed in clinical studies of a number of other multikinase inhibitors with activity against angiogenesis associated RTKs – such as sorafenib (approved for renal cell carcinoma, differentiated thyroid cancer, and hepatocellular carcinoma) and sunitinib (approved for renal cell carcinoma, pancreatic neuroendocrine tumors, and imatinib-resistant GIST). [32, 44–48] The successful development of these multi-targeted RTKs paved the way for preclinical studies of regorafenib.

In vivo preclinical studies of regorafenib demonstrated that it significantly decreased tumor perfusion, through utilization of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and immunohistochemical staining with endothelial cell marker CD-31 to measure tumor microvessel area. It significantly limited tumor growth in a wide variety of murine xenografts derived from human colon, renal, lung, melanoma, pancreatic, and ovarian cancer cell lines. [41, 49, 50] This parallel result was found in a recently published preclinical study in which regorafenib was shown to be an effective inhibitor of tumor growth in patient-derived murine xenograft models of gastric cancer. [51]

3. Chemistry

As noted above, Regorafenib is known by the chemical name 4-[4-[[4-chloro-3 (trifluoromethyl)phenyl] carbamoyl]amino]-3-fluorophenoxo]-N-methylpyridine-2-carboxamide hydrate. Regorafenib was developed out of a chemistry program that originally identified biaryl ureas as potent inhibitors of p38 MAPK and c-Raf. [52] The synthesis of regorafenib and related salts is described in US Patent 8637553 B2. [53] To briefly summarize, regorafenib can be synthesized starting with 3-fluoro-4-nitrophenol to generate 4-amino-3-fluorophenol. This intermediary reagent can be further converted to 4-(4-amino-3-fluorophenoxo)pyridine-2-carboxylic acid methylamide, which then can be reacted with 4-chloro-3-(trifluoromethyl)phenyl isocyanate to yield regorafenib. [53]
In addition, this patent also details methods for preparing mesylate and phenylsulfonate salt forms of the compound. [53]

The in vitro kinase inhibitor properties of regorafenib were originally described by Wilhelm et al. [41] In vitro, regorafenib potently inhibited the angiogenic and stromal RTKs, VEGFR1-2, PDGFR, FGFR, and TIE2, as well as the oncogenic RTKs, KIT and RET. Regorafenib also inhibited intracellular signaling kinases c-RAF/RAF-1, B-RAF and its V600E mutant isoform, as well. In contrast, it did not inhibit 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, however.[41] In terms of treating GIST, the efficacy of regorafenib is likely related to its ability to inhibit secondary KIT kinase mutations. The reported potency of regorafenib against various secondary KIT mutations found in drug resistant GIST is depicted in Figure 1.[37]

4. Pharmacodynamics

Regorafenib’s pharmacodynamics were evaluated in a conventional phase I study as well as a second phase I study whose enrollment was restricted to metastatic colorectal cancer patients (mCRC).[54,55] In conventional phase I study, assessments were done by evaluating plasma concentrations of VEGF and sVEGFR-2 at screening, pre-dose, and 8 h post-dose on the 1st and 21st days of the first cycle, pre-dose on 1st and 21st days of the second cycle, and pre-dose on the 1st day of all subsequent cycles. sVEGFR-2 plasma concentrations varied based in 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.[54] The rise in VEGF ligand is consistent with the pharmacodynamic effects of other VEGFR kinase inhibitors.[56]

Both phase 1 studies evaluated tumor perfusion by DCE-MRI.[54,55] MRIs were performed at the start of treatment and on 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 after 21 days of treatment when compared to baseline values. This reduction was seen for doses 120 mg and higher in the conventional phase I study. However, the mCRC phase 1 study did not comment on the dose relationship to perfusion.

A more recent biomarker study by Wong et al. performed immunohistochemical analyses of pre- and post-treatment tumor biopsies in patients with mCRC. They found that the majority of patients had downregulation of phosphorylated-VEGFR2, podoplanin, phosphorylated-AKT, Ki-67, and upregulation of the MEK-ERK axis, phosphorylated-C-MET, phosphorylated-SRC, phosphorylated-STAT3, and phosphorylated-JUN. Notably, proteomic analysis of fine needle tumor aspirates showed downregulation of PI3K was associated with longer PFS. These studies confirmed for the first time that regorafenib inhibited in vivo VEGFR activation in tumor cells and/or endothelial cells in patients with mCRC.[57]

All of the above biomarkers evaluated the activity of regorafenib to inhibit VEGFR1/2, but do not evaluate its ability to inhibit the most important target in GIST, the KIT RTK. In a small series of GIST tumor biopsies obtained before and during treatment, regorafenib was shown to have in vivo inhibitory effects on KIT activation in GIST tumors that were resistant to multiple prior lines of TKI therapy.[58]

5. Pharmacokinetics and metabolism

Regorafenib is metabolized by CYP3A4 and UGT1A9 into its active metabolites: M-2 (N-oxide-regorafenib) and M-5 (N-oxide and N-desmethyl-regorafenib).[54,59] In vitro studies have shown that regorafenib, M2, and M5 all competitively inhibit several cytochrome P450 enzymes (most notably CYP2C9, CYP2C8, CYP3A4) and uridine diphosphate glucuronosyltransferases (most notably UGT1A9 and UGT1A1) to some extent. Per the package insert, concomitant use of strong inducers/inhibitors of CYP3A4 during regorafenib treatment should be avoided.[60] Dose adjustment for mild-to-moderate hepatic impairment and mild, moderate, and severe renal impairment is not required. Use in patients with severe renal and hepatic impairment is not advised, as it has not been adequately studied (regorafenib package insert).[60]

In the two phase 1 clinical studies, the half-life varied between 20 and 40 h for regorafenib and M-2 and 40–60 h for M-5 resulting in an accumulation of regorafenib and its metabolites after multiple doses.[54,55] This increase was predictable based on a time-linear pharmacokinetics. Given this half-life, the rationale for daily dosing as currently recommended is well supported. With the regorafenib metabolites, M2, and M5, there was a more than a proportional increase at lower doses, but proportional increases of serum levels at higher doses.[55] Summary of the pharmacokinetic data from the phase 1 studies is available in Table 1.

6. Clinical efficacy

6.1. Phase I studies

In 2005, a ‘first in man’ clinical trial of regorafenib began enrolling patients for a phase I open-label, nonrandomized, dose-escalation study to evaluate safety, tolerability, and pharmacokinetics.[54] Fifty-three adults with advanced solid tumors, refractory to standard therapies, were enrolled to receive regorafenib in escalating doses, ranging 10–220 mg daily, using ‘3 weeks on/1 week off’ repeating cycles. Overall, 83% of patients experienced at least one treatment-related adverse effect (AE), the most common of which were voice

<table>
<thead>
<tr>
<th>Table 1. Summary of regorafenib pharmacokinetic data.</th>
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</thead>
<tbody>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Regorafenib</td>
</tr>
<tr>
<td>M2</td>
</tr>
<tr>
<td>M5</td>
</tr>
</tbody>
</table>

NR: not reported.
changes, hand-foot skin reaction (HFSR), oral mucositis, diarrhea and hypertension (HTN). The incidence of AEs increased in a dose-dependent manner. Ultimately, 160 mg daily was determined to be the maximum tolerated dose (MTD). The observed half-life of regorafenib was 20–40 h, validating treatment with once daily dosing and a 1-week washout period.[54]

The investigators examined efficacy as a secondary endpoint. Sixty-six percent of patients experienced disease control, defined as the summation of partial responses (PR) and stable disease (SD) per RECIST criteria. Three patients had PRs (one with RCC, one with osteosarcoma, and one with colorectal cancer), but median PFS and OS were not reported (Table 2).[54]

Following these results, Strumberg et al. conducted a phase I trial in 38 patients with treatment refractory mCRC.[55] Escalating doses from 60 to 220 mg daily were administered using the same ‘3 weeks on/1 week off’ schedule. Of the 27 patients evaluable for response, 74% had disease control, comprised of one partial response (4%), and SD in 19 patients (70%). Median PFS was 107 days. OS was not reported (Table 2).[55]

6.2. Phase II and III studies: GIST

Following the phase I trials that defined the safety profile and established MTD, a single-arm phase II study of regorafenib was conducted in 33 patients with advanced GIST who experienced disease progression during prior first-line imatinib and second-line sunitinib treatment.[58,61] Patients were treated with regorafenib 160 mg daily using a ‘3 weeks on/1 week off’ schedule. The primary endpoint was disease control rate (DCR) – defined as objective responses (complete response, partial response, or SD) sustained for ≥16 weeks per RECIST 1.1 criteria. The secondary endpoint was PFS, but OS and subgroup analysis of response based on primary tumor genotype were also reported. Eighty-one percent patients demonstrated clinical benefit. For the entire cohort, median PFS was 13 months, and OS was 27 months (Table 2). There was no statistically significant difference in DCR among patients with different tumor genotypes, but the analyzed subgroups were small. Patients with primary exon 11 KIT mutations and SDH-deficient GIST had a longer PFS compared to patients with primary exon 9 KIT mutations (13 months and 12 months vs. 6 months, respectively; no statistical testing of these results reported).[58,61] These findings suggest a more favorable response rate to regorafenib in patients with certain pathogenic mutations, and warrant further investigation. Currently, there is an ongoing trial of regorafenib in patients with advanced GIST and KIT exon 17 mutations (NCT02606097).

Based on data from phase I/II trials and the preclinical rationale of targeting mutant kinases (including KIT) with a structurally unique multi-kinase inhibitor, a randomized, placebo-controlled phase III trial (GRID: GIST – regorafenib in progressive disease) was conducted to more definitively determine the efficacy of regorafenib in advanced GIST disease.[62]

### Table 2. Summary of reported regorafenib efficacy outcomes.

<table>
<thead>
<tr>
<th>Study</th>
<th>Cancer</th>
<th>Phase</th>
<th>Evaluable patients (n)</th>
<th>Duration of treatment</th>
<th>DCR (%)</th>
<th>SD (%)</th>
<th>PR (%)</th>
<th>PFS (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mross et al. [54]</td>
<td>Solid tumors I</td>
<td>Efficacy: 47</td>
<td>Median: 78 days</td>
<td>66</td>
<td>60</td>
<td>6</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Strumberg et al. [55]</td>
<td>mCRC I</td>
<td>Efficacy: 27</td>
<td>Median: 53 days</td>
<td>74</td>
<td>70</td>
<td>4</td>
<td>107 days</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>George et al. [58,61]</td>
<td>GIST II</td>
<td>Efficacy: 33</td>
<td>Median: 8 cycle</td>
<td>81</td>
<td>72</td>
<td>9</td>
<td>13</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>Demetri et al. [62]</td>
<td>GIST III</td>
<td>Efficacy: 199</td>
<td>Median: 23 week</td>
<td>53</td>
<td>71</td>
<td>5</td>
<td>5</td>
<td>HR = 0.27</td>
<td></td>
</tr>
<tr>
<td>Kollár et al. [63]</td>
<td>GIST MAP</td>
<td>Efficacy: 18</td>
<td>Median: 9 months</td>
<td>100</td>
<td>11</td>
<td>9.4</td>
<td>12.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Komatsu et al. [64]</td>
<td>GIST III</td>
<td>Efficacy: 17</td>
<td>Median: 23 week</td>
<td>58</td>
<td>92</td>
<td>0</td>
<td>7.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grothey et al. [65]</td>
<td>mCRC III</td>
<td>Efficacy: 760</td>
<td>Median: 7 week</td>
<td>41</td>
<td>40</td>
<td>1.0 (p = 0.19)</td>
<td>1.9 (HR = 0.49)</td>
<td>6.4 (HR = 0.77)</td>
<td></td>
</tr>
<tr>
<td>Li et al. [66]</td>
<td>mCRC III</td>
<td>Efficacy: 204</td>
<td>Median: 2 months</td>
<td>51</td>
<td>NR</td>
<td>4 (p = 0.05)</td>
<td>3.2 (HR = 0.31)</td>
<td>8.8 (HR = 0.55)</td>
<td></td>
</tr>
<tr>
<td>Eisen et al. [67]</td>
<td>RCC II</td>
<td>Efficacy: 48</td>
<td>Median: 7 months</td>
<td>63</td>
<td>60</td>
<td>42</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mir et al. [68]</td>
<td>LMS</td>
<td>Efficacy: 55</td>
<td>Median: 8 cycle</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>4.0 (HR = 0.49)</td>
<td>87% 6-month survival (HR = 0.25)</td>
<td></td>
</tr>
<tr>
<td>Mir et al. [68]</td>
<td>Non-LMS STS</td>
<td>Efficacy: 55</td>
<td>Median: 8 cycle</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>4.6 (HR = 0.38)</td>
<td>79% 6-month survival (HR = 0.64; p = 0.4)</td>
<td></td>
</tr>
</tbody>
</table>

DCR: disease control rate; SD: stable disease; PR: partial response; PFS: progression-free survival; OS: overall survival; NR: not reported; MAP: managed access program; IQR: interquartile range; HR: hazard ratio; mCRC: metastatic colorectal cancer; GIST: gastrointestinal stromal tumor; RCC: renal cell carcinoma; LMS: leiomyosarcoma; STS: soft tissue sarcoma.

*DCR defined as PR + CR + SD lasting for ≥12 weeks.

*SD defined as best response (occurring at any time for any duration).

*p-value <0.05.

*Includes both LMS and Non-LMS STS patients (not specified in abstract publication).
In the GRID study, 199 patients with metastatic or unresectable GIST refractory to imatinib and sunitinib were randomized in 2:1 fashion to receive either regorafenib (n = 133) or placebo (n = 66) until disease progression, occurrence of unacceptable side effects, or withdrawal of the patient from the study. The primary endpoint of interest was PFS, and secondary endpoints included OS and DCR – defined as SD lasting for ≥12 weeks plus complete responses (CR) and partial responses (PR). Patients randomized to regorafenib had a median PFS of 4.8 months, compared with 0.9 months for placebo-treated patients (p < 0.0001, HR 0.27 [CI: 0.19–0.39]) (Table 2). There was no difference in OS between the two groups, but cross-over to open-label regorafenib was allowed at disease progression and may have obscured any potential difference in OS between groups.[62] As with phase I/II studies, there were no complete responses, and the partial response rate was low. Disease control was observed in 52.6% of patients in regorafenib group compared to 9.1% of patients in the placebo group (p < 0.0001) (Table 2).[62] In February of 2013, as a result of the GRID study, the FDA approved regorafenib for the treatment of inoperable GIST refractory to imatinib and sunitinib.[69]

Komatsu et al. performed a subgroup analysis of Japanese patients treated in GRID to determine if similar clinical benefit and safety profile were observed in this population when compared with non-Japanese patients. Of the 17 Japanese patients in the GRID study, 12 were randomized to regorafenib and 5 were randomized to placebo. PFS was significantly longer with regorafenib than placebo, 7.1 months versus 0.9 months, respectively (HR: 0.08, 95% CI: 0.02–0.45, one-sided p = 0.0002). A partial response was observed in one patient in the placebo group. SD was observed in 11 patients (92%) in regorafenib group, and zero patients in the placebo group (Table 2).[64] These results were similar to those observed in the overall GRID study population.

In the United Kingdom, a managed access program including 20 patients with metastatic GIST refractory to imatinib and/or sunitinib was conducted.[63] Using the standard dosing and treatment schedule of George et al. [58], patients received the study drug for a median duration of 9.3 months. At median follow up of 12.6 months, 18 of 20 patients were evaluable for response, and all achieved a best response of at least SD. Notably, 11% had PR (n = 2) per RECIST, and 39% had PR (n = 7) per Choi criteria. Median PFS was 9.4 months and median OS was 12.2 months (Table 2).[63]

### 6.3. Phase II and III studies: metastatic colorectal cancer

Unlike GIST, where the known therapeutic targets are oncogenic KIT or PDGFRA, the efficacy of regorafenib in mCRC is hypothesized to be due to tumor angiogenesis inhibition via the VEGFR pathway. This hypothesis is based in part on the known efficacy of other VEGFR inhibitors, such as bevacizumab, in the treatment of mCRC.[70–75] The clinical benefit of regorafenib in mCRC was demonstrated for the first time in the CORRECT trial, an international phase III study in which 760 patients with refractory mCRC were randomized (2:1) to receive best supportive care plus regorafenib 160 mg daily or placebo daily for the first 3 weeks of each 4 week cycle. The primary endpoint of OS was significantly improved in the regorafenib group compared to the placebo arm with a median OS of 6.4 versus 5.0 months, respectively (HR: 0.77; 95% CI: 0.64–0.94; p = 0.0052). There was a small but statistically significant increase in PFS, 1.9 months versus 1.7 months (HR: 0.49; p < 0.0001). Regarding radiological response, similar to GRID, there were no CRs and a low rate of patients with PRs. However, DCR was substantially higher in the treatment versus placebo group, 41% versus 15%, respectively (p < 0.0001) (Table 2).[65] Quality of life (QoL) measures were also assessed in this study. Interestingly, there was no difference in patients’ perceived QoL between study arms, suggesting a tolerable side effect profile. Following this landmark trial, in September of 2012, regorafenib became the first small-molecule multi-kinase inhibitor to be FDA approved for the treatment of mCRC refractory to standard therapies.[76]

After the CORRECT trial, Li et al. conducted CONCUR – a randomized, placebo-controlled phase III trial aimed to evaluate the efficacy and safety of regorafenib in Asian patients with previously treated mCRC.[66] Two-hundred four patients with previously treated mCRC were randomized 2:1 to regorafenib 160 mg daily versus placebo for the first 3 weeks of each 4 week cycle until disease progression, development of intolerable side effects or consent withdrawal. The study met its primary endpoint of improved OS, with a median OS in the regorafenib group of 8.8 months versus 6.3 months with placebo (HR: 0.55; 95% CI: 0.40–0.77). Secondary study endpoints also indicated regorafenib efficacy in this population: (1) PFS increased from 3.2 months to 1.7 months with regorafenib versus placebo treatment, respectively (HR: 0.31; 95% CI: 0.22–0.44) and (2) DCR was 51% versus 7% (p < 0.0001) in regorafenib and placebo groups (Table 2).[66] There is an ongoing open label, phase IIb trial of regorafenib in patients with mCRC refractory to standard treatment but whose disease has not been previously treated with anti-angiogenic therapies (NCT02465502).

### 6.4. Phase II studies: renal cell carcinoma

The activity of regorafenib in metastatic renal cell carcinoma (mRCC) was evaluated in a single arm phase II study of 49 patients with previously untreated mRCC, with the primary objective of overall response rate (per RECIST 1.0) and secondary endpoints of clinical benefit rate (CRB – defined as complete response, partial response, and/or SD), PFS, and OS.[67] Nineteen patients (40%) had an objective overall response, all of which were PRs. The CRB from treatment (PR + SD) was 81% (n = 39). Median PFS was 11.0 months in this study. Median OS could not be assessed due to censored data (Table 2).[67] This study suggests that the anti-VEGF and anti-PDGFR activity of regorafenib have efficacy in the treatment of mRCC, similar to the results of treatment with other multi-targeted TKIs in this setting.[77,78]

### 6.5. Phase II: non-GIST STSs

The anti-angiogenic activity of regorafenib has therapeutic potential in many types of non-GIST sarcoma, but this possibility has gone untested until recently. Currently, there is an
ongoing international trial consisting of four parallel randomized, placebo-controlled phase II trials designed to study the efficacy of regorafenib for advanced non-GIST STS.[79]

Each of the treatment arms is restricted to a specific type of STS: liposarcoma, leiomyosarcoma (LMS), synovial sarcoma, and other sarcoma (OTS). Patients in each group are randomized (1:1) to receive regorafenib 160 mg daily for ‘3 weeks on/1 week off’ or placebo. The primary endpoint of this study is PFS. Preliminary results of the LMS and OTS cohorts were reported at the ASCO 2015 conference.[78] Median PFS in the LMS group was 4.0 versus 1.9 months for regorafenib versus placebo, a clinically but not statistically significant difference (HR = 0.49; 95% CI = 0.27–0.89; p = 0.017). Median PFS of OTS group was 4.6 and 1.0 months for regorafenib compared to placebo, respectively (HR = 0.38, 95% CI = 0.20–0.74; p = 0.002). The 6-month OS of LMS patients was significantly higher in the treatment arm 87.0% versus 75.9% (HR = 0.25; 95% CI = 0.08–0.81; p = 0.013). This difference was not significant in the OTS cohort (79.0% vs. 62.0%; HR = 0.64, 95% CI = 0.23–1.74; p = 0.4) (Table 2).[80] Another phase II trial is underway to examine the efficacy of regorafenib in patients with refractory liposarcoma, osteosarcoma, and Ewing/Ewing-like sarcomas (NCT02048371). The primary endpoint is PFS. No clinical results have been reported.

7. Safety and tolerability

The frequency and severity of regorafenib-emergent toxicities were assessed in each of the aforementioned trials, and were found to be consistent across different cancer types, ethnic groups, and phases of clinical development (Table 3). In the phase I studies, drug-related adverse events (AEs) occurred in >80% of patients, and serious AEs (grade ≥3 per v3.0 of the NCI CTC-AE criteria) were documented in approximately 50%.[54,55] The most frequently observed toxicities were voice changes, HFSR, diarrhea, HTN, rash/desquamation, and oral mucositis. Treatment-related AEs occurred in a dose-dependent manner. The incidence of treatment-related dose-limiting adverse events occurring in cycle 1 leading to dose reduction, interruption or permanent discontinuation was around 17% and 42% of patients receiving 160 and 220 mg regorafenib, respectively.[54,55] Comparison of dose-limiting toxicities was performed to determine the MTD of 160 mg/day for 3 weeks with a 1-week washout period.

Drug-related adverse effects occurred in the majority of patients in phase II/III trials, most often manifesting as HFSR, HTN, fatigue, and diarrhea.[58,62–68] In the GRID study, up to 99% of patients receiving regorafenib experienced one or more drug-related AE.[62] In this study, 68% of patients receiving placebo reported symptoms of ‘drug-related’ AEs. Dose modification was more common in the regorafenib group versus placebo (72% vs. 26%, respectively). Interestingly, treatment-related AEs that led to permanent discontinuation of treatment was similar between the two groups (6% in regorafenib group and 8% in placebo), suggesting that adverse events were manageable in most cases (Table 3).[62] In the Japanese patient subgroup analysis of GRID, while the type of adverse events were similar, the incidence of HFSR and maculopapular rash were higher in Japanese subgroup compared to the general GRID population, 92% versus 56%, and 50% versus 18%, respectively.[64] Consequently, there were more frequent dose modifications, but, interestingly, the rate of permanent discontinuation was low. Anticipating the need for dose modifications in this population may be indicated in clinical practice. Additional studies are required to better define if there are any racial/ethnic differences in the incidence and/or severity of regorafenib toxicity.

Table 3. Summary of reported regorafenib drug-related toxicities.

<table>
<thead>
<tr>
<th>Adverse event (%)</th>
<th>Grade</th>
<th>Mross et al. [54]</th>
<th>Strumberg et al. [55]</th>
<th>George et al. [58]</th>
<th>Kollar et al. [63]</th>
<th>Demetri et al. [62]</th>
<th>Komatsu et al. [64]</th>
<th>Grothey et al. [65]</th>
<th>Li et al. [66]</th>
<th>Eisen et al. [67]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Solid tumors</td>
<td>mCRC</td>
<td>GIST</td>
<td>GIST</td>
<td>GIST</td>
<td>GIST</td>
<td>mCRC</td>
<td>mCRC</td>
<td>RCC</td>
</tr>
<tr>
<td>Total events</td>
<td>grade ≥3</td>
<td>83</td>
<td>84</td>
<td>NR</td>
<td>NR</td>
<td>98</td>
<td>100</td>
<td>93</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>Voice changesa</td>
<td>grade ≥3</td>
<td>55</td>
<td>58</td>
<td>45</td>
<td>40</td>
<td>22</td>
<td>50</td>
<td>29</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>HFSR</td>
<td>grade ≥3</td>
<td>40</td>
<td>61</td>
<td>85</td>
<td>55</td>
<td>56</td>
<td>92</td>
<td>47</td>
<td>74</td>
<td>71</td>
</tr>
<tr>
<td>Oral mucositis</td>
<td>grade ≥3</td>
<td>36</td>
<td>18</td>
<td>38</td>
<td>40</td>
<td>38</td>
<td>58</td>
<td>27</td>
<td>NR</td>
<td>43</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>grade 3</td>
<td>32</td>
<td>24</td>
<td>61</td>
<td>50</td>
<td>40</td>
<td>50</td>
<td>34</td>
<td>18</td>
<td>45</td>
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<tr>
<td>HTN</td>
<td>grade ≥3</td>
<td>8</td>
<td>3</td>
<td>6</td>
<td>0</td>
<td>5</td>
<td>8</td>
<td>7</td>
<td>NR</td>
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<tr>
<td>Fatigue</td>
<td>grade ≥3</td>
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<td>11</td>
<td>36</td>
<td>15</td>
<td>23</td>
<td>25</td>
<td>7</td>
<td>NR</td>
<td>6</td>
</tr>
<tr>
<td>Rash</td>
<td>grade ≥3</td>
<td>28</td>
<td>50</td>
<td>79</td>
<td>80</td>
<td>39</td>
<td>42</td>
<td>47</td>
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<td>53</td>
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<tr>
<td>Alopecia</td>
<td>grade ≥3</td>
<td>4</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>0</td>
<td>10</td>
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<tr>
<td>Thrombocytopenia</td>
<td>grade ≥3</td>
<td>23</td>
<td>29</td>
<td>NR</td>
<td>30</td>
<td>18</td>
<td>50</td>
<td>26</td>
<td>9</td>
<td>39</td>
</tr>
</tbody>
</table>

mCRC: metastatic colorectal cancer; GIST: gastrointestinal stromal tumor; RCC: renal cell carcinoma; STS: soft tissue sarcoma; NR: not reported; HFSR: hand foot skin reaction; HTN: hypertension.

Grade ≥3 based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE).

aIncludes ‘hoarseness’ as mentioned in Kollar and Komatsu.

Specifically maculopapular rash.
In the CORRECT trial, similar toxicity profiles were seen: 93% of patients in regorafenib group had treatment-related AEs compared to 61% in placebo (Table 3). The high rate for AEs in the placebo population indicates the high symptom burden in patients with advanced mCRC, due to disease and/or prior treatments. It was noted that the majority of AEs occurred during the first two cycles of treatment (cycles 1–2) and were readily manageable with dose reduction and/or treatment interruption.[65]

Serious adverse events (SAEs) and treatment-related deaths were rare but did occur. In GRID, treatment-related grade 5 AEs occurred in three patients: two patients (1.5%) in the regorafenib group (cardiac arrest and hepatic failure, respectively) and one patient (1.5%) in the placebo group (fatigue).[62] In CORRECT, there was one death (0.2%) from hepatic failure that investigators deemed drug-related study.[65] In CONCUR, SAEs were reported in 32% of regorafenib group versus 26% of placebo group. Two deaths (1%) in the regorafenib group were felt to be due to toxicity: one woman died from cardiac arrest after an episode of hematemesis, and one man died from cardiac arrest of unknown cause; autopsy was not performed.[66] In the RCC study, two deaths related to regorafenib were reported: one from pulmonary embolism, one from hemoptysis.[67] However, in the latter case, post-mortem analysis revealed severe pulmonary metastases and pneumonia, so metastatic RCC was considered an alternate explanation. In a phase I open label study of 53 patients with advanced cancer, regorafenib was not demonstrated to have any significant effect on QT/QTc or left ventricular ejection fraction.[81] No cardiac events were reported in this study which was conducted to better define the cardiovascular safety profile of regorafenib.

Overall, dose modification rates in regorafenib treated patients in these studies were high, occurring between 55% and 92% of the time.[58,62–67] Protocol-driven dose modifications in these studies included dose holds and/or dose reductions, but these protocols also allowed re-escalation when tolerated. For example, In the phase II study GIST study, 27 of 33 patients (82%) in the treatment arm required dose reduction due to dose-limiting toxicity.[57] However, 85% of patients tolerated dose re-escalation to between 120 and 160 mg daily.[57] The overall rate of permanent discontinuation due to AEs was low, <20% in most studies, suggesting that most toxicities were manageable with dose modification.[58,62–67] A randomized trial to evaluate the impact of healthcare provider education on treatment discontinuation rates in the absence of disease progression in patients with metastatic colorectal cancer treated with regorafenib is currently underway (NCT02287025).

9. Conclusion

Overall, as discussed above, a consistent finding in the phase II and III GIST studies was that regorafenib treatment was commonly associated with SD, with only a small proportion of patients achieving a partial response. In the phase III study of regorafenib in GIST patients (GRID), there was almost a 4-month improvement in PFS compared with placebo treatment, with over half the patients experiencing disease control. No improvement in OS was reported with regorafenib treatment in the pivotal phase III study, possibly due to the very high rate of cross-over from placebo to regorafenib. Regorafenib was approved by the FDA in February 2013 and by the EMA in August 2014 for treatment of patients with advanced GIST who had disease progression or drug intolerance during prior imatinib and sunitinib therapy. Currently, there are no clinical studies of competitor agents for third-line therapy of GIST, suggesting that regorafenib will remain the standard third line agent for advanced GIST for the foreseeable future.

10. Expert opinion

The use of KIT/PDGFRA kinase inhibitors has transformed the treatment of advanced GIST. Notably, GIST tumors have an extremely low response rate to all tested cytotoxic chemotherapy agents but have a high response rate to front-line imatinib. Imatinib treatment is associated with prolonged PFS (median 20 months in several phase III studies) and OS (approximately 5 years in these studies). These impressive results are likely a consequence of the exquisite dependence (so-called ‘oncogene addiction’) of most GISTs to mutated oncogenic kinases (KIT 80%, PDGFRA 5–10%).[83] Both primary and secondary resistance to imatinib is related to the intrinsic sensitivity of the target kinase in any given tumor to imatinib. Despite the impressive results achieved with imatinib, acquired (secondary) mutations limit the overall duration of response to front-line therapy (Figure 1).

Sunitinib, a multi-targeted kinase inhibitor of KIT/PDGFRA as well as VEGFR family members, has proven activity against imatinib-resistant GIST and has been approved by the FDA and EMA for treatment of patients with imatinib resistant GIST and/or imatinib intolerance. The clinical activity of sunitinib in this setting is likely a consequence of the sensitivity of some, but not all, secondary mutations to this agent (Figure 1). 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, Figure 1). These data likely explain the mixed clinical responses commonly observed during sunitinib treatment of imatinib-resistant GIST and the relatively short PFS with sunitinib compared with front-line treatment.

Regorafenib is a structurally distinct multi-targeted kinase inhibitor (KIT/PDGFR/VEGFR1-2) with proven activity in the third-line metastatic GIST treatment setting. As with sunitinib, the efficacy of regorafenib is likely to be strongly determined by its spectrum of activity against drug-resistant KIT mutations. To date, in vitro 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 (Figure 1). 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 unclear whether regorafenib would outperform sunitinib in the second-line setting. It is possible that regorafenib could improve upon 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 unclear whether it would be desirable to use regorafenib as a front-line agent. Recently, the Australasian Gastro-Intestinal Trials Group has activated an open label, randomized phase 3 study comparing PFS at 24 months with front-line imatinib for patients with advanced GIST (standard therapy arm, imatinib 400 mg daily) versus alternating regorafenib (160 mg 21–25 days, 3–7-day washout). This trial is currently enrolling in Australia and Singapore and will also be activated by the Scandinavian Sarcoma Group and the European Organisation for Research and Treatment of Cancer. The planned enrollment for this study is 240 patients with a planned study primary completion date (final data collection for primary outcome measure) of December of 2019 (NCT02365441).

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. More likely, such agents will be initially developed as fourth-line agents, as there are no approved drugs for this line of therapy thus enabling an easier pathway to regulatory approval. A number of novel agents continue to be tested in the fourth line setting, based on the continued dependence of drug-resistant KIT-mutant GIST on KIT kinase activity (e.g. BLU-285, NCT02508532).

The toxicities associated with regorafenib are similar to other kinase inhibitors that include activity against VEGFR family members. Given the large number of currently approved drugs with VEGFR inhibitory activity, the recognition and management of such symptoms will be familiar to most oncologists. Close attention to severity of side effects and individualization of supportive care are necessary for optimal use of this agent. In addition, we have noted that many patients cannot tolerate the recommend starting dose of 160 mg per day. However, we have also noted responses in patients treated with doses as low as 40–80 mg per day. In fit patients, we usually start with the standard 160 mg dosing, but will decrease the dose as needed to improve tolerability. In less fit patients, we will sometimes start at doses of 80–120 mg per day and dose escalate (minimal side effects) or de-escalate (severe side effects despite optimal supportive care) as appropriate for tolerance and clinical efficacy. It is also clear from previous studies that many patients can be safely re-escalated to higher doses that were previously poorly tolerated. We will often consider this in cases where disease progress is noted on less than maximal doses of regorafenib.

Despite the modest improvement in median PFS observed in the phase III GRID study, we strongly believe that many patients obtain meaningful palliation of their GIST-associated symptoms and clinically significant disease stabilization or improvement during regorafenib treatment. In addition, a minority of patients may experience prolonged disease control that significantly exceeds the median duration reported in the phase III study.

Declaration of interest
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• Results from the Phase II study of imatinib that lead to FDA approval for treatment of advanced GIST.
• Results from the Phase II study of imatinib that lead to FDA approval for treatment of advanced GIST.
• Phase III study demonstrating activity of sunitinib for imatinib-resistant GIST.
Phase III study of regorafenib for advanced GIST. The results of this study lead to FDA-approval of regorafenib for the treatment of advanced GIST after prior treatment with imatinib and sunitinib.


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