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REVIEW ARTICLE

Growing Role of Regorafenib in the Treatment of Patients with Sarcoma

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Abstract
Sarcomas encompass a group of rare solid tumors responsible for approximately 1% of all cancer-related deaths in the United States each year. Subtypes include, but are not limited to, soft tissue sarcomas (STS) such as leiomyosarcoma, liposarcoma, pleomorphic sarcoma, and gastrointestinal stromal tumor (GIST). Treatment options for patients with STS vary depending on, among other factors, histological subtype. Data from a mix of phase 2 and phase 3 trials have suggested that the orally available multikinase inhibitor regorafenib may have efficacy in patients with STS who have progressed on previous lines of systemic therapy. Some clinical benefit of regorafenib has been shown in patients with leiomyosarcoma, synovial sarcoma, GIST, Ewing's sarcoma, and other sarcoma subtypes, suggesting a broad spectrum of potential activity in this population. Studies have also shown that the safety profile of regorafenib is acceptable in these patients, with adverse events that can be managed through dose reductions and/or interruptions as well as other supportive measures.

Key Points

Data from phase 2 studies suggest that regorafenib has promising efficacy in patients with non-adipocytic soft tissue sarcomas and Ewing's sarcoma

The phase 3, randomized, placebo-controlled GRID study demonstrated significant improvements in progression-free survival for patients with gastrointestinal stromal tumors who had prior treatment with imatinib and sunitinib

1 Introduction

Approximately 12,390 patients were expected to be diagnosed with soft tissue sarcomas (STS) in 2017, accounting for about 1% of all cancer diagnoses in the United States [1]. Of these patients, approximately 4990 were expected to die, making up 1% of all cancer-related deaths. Many different histological subtypes of sarcoma have been identified, with gastrointestinal stromal tumor (GIST), liposarcoma, leiomyosarcoma, pleomorphic sarcoma, and synovial sarcoma among the most prevalent [2]. GIST is the most common mesenchymal tumor of the gastrointestinal tract, accounting for approximately 2.2% of gastric, 13.9% of small bowel, and 0.1% of colorectal cancers, with an age-adjusted yearly incidence of 6.8 per million people in the United States [3]. Sarcomas can also occur in the bone (i.e., Ewing's sarcoma) [1].

STS can have a variety of presentations depending on the location of the tumor [4]. Once a diagnosis is made, it is recommended that patients with STS be treated by a multidisciplinary team from an experienced center due to the relative rarity of STS subtypes. Surgery is the mainstay of curative-intent treatment for patients with STS, with radiation sometimes used as an adjunct to treatment. In the advanced setting, systemic therapies are the backbone of treatment for patients with STS, with surgery and radiation used as palliative measures. Currently, the recommended systemic treatments for patients with advanced STS include doxorubicin, ifosfamide, and pazopanib (for patients who progressed on anthracycline treatment) as single agents as well as anthracycline-based combination regimens and doxorubicin + olaratumab (for anthracycline-naïve patients) [4]. Gemcitabine + docetaxel, temozolomide, PEGylated liposomal doxorubicin, vinorelbine, trabectedin (specifically for patients with liposarcoma and leiomyosarcoma), and eribulin (specifically for patients with liposarcoma) are also recommended [4]. The CDK4 inhibitor palbociclib may also be used in a select group of

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patients with liposarcoma [5]. Lastly, the PD-1 receptor blocker pembrolizumab has been approved for the treatment of patients with any type of tumor, including sarcomas, that have an increase in microsatellite instability due to a deficient mismatch repair system. Recent data now also suggest the multikinase inhibitor regorafenib may be beneficial for patients with STS [6, 7].

For patients with metastatic or unresectable GIST, oral targeted treatments are preferred as no other systemic agents have demonstrated clinical efficacy in this population [4]. The tyrosine kinase inhibitor imatinib was the first agent to improve overall survival (OS) relative to historical controls in patients with advanced GIST in phase 3 trials [8, 9]. Sunitinib, a multikinase inhibitor, has been shown to prolong survival in patients who have progressed on or were intolerant to imatinib [10]. Regorafenib has demonstrated improvements in progression-free survival (PFS) in patients who have failed both imatinib and sunitinib [11].

2 Overview of Regorafenib

Regorafenib is an oral multikinase inhibitor that is similar to sorafenib in structure with the addition of a fluorine atom to the central phenyl ring [12]. This relatively small structural change gives regorafenib a distinct targeting profile, including oncogenic kinases implicated in STS and GIST [12]. In preclinical experiments, regorafenib was found to inhibit the activity of KIT and PDGFRα, key oncogenic drivers in GIST. Regorafenib also inhibits VEGFR1, VEGFR2, and VEGFR3, which have been implicated as a therapeutic target in patients with STS [13]. In addition to these targets, regorafenib inhibits other cell signaling molecules implicated in oncogenesis (TIE2, RET, RAF), support from the tumor microenvironment (FGFR1, PDGFRβ), and tumor immunity (CSFR-1).

Regorafenib has been investigated in multiple tumor types [14]. It has met its primary endpoints in phase 3 trials of patients with metastatic colorectal cancer who have received fluoropyrimidines, oxaliplatin, irinotecan, an anti-VEGF agent, and (if *RAS* wild-type) an anti-EGFR agent [15, 16]; locally advanced, unresectable, or metastatic GIST who have been previously treated with imatinib and sunitinib [11]; and hepatocellular carcinoma who have been previously treated with sorafenib [17].

3 Regorafenib for Patients with STS and Bone Sarcoma

REGOSARC was a double-blind, randomized, placebo-controlled phase 2 study to assess safety and activity of regorafenib in patients with STS [7]. Enrollment took place in France and Austria. Enrolled patients were diagnosed with liposarcoma, leiomyosarcoma, synovial sarcoma, or other sarcomas, and these independent cohorts were each analyzed separately. In addition, an amendment to the original study protocol allowed for inclusion of patients with non-adipocytic sarcoma who had already received pazopanib.

All patients had progressed or were intolerant to doxorubicin or another anthracycline-based chemotherapy. No more than three prior lines of therapy for STS were permitted. The majority of patients in REGOSARC did not receive prior pazopanib, which has since become a key component of the standard of care for patients with STS. Patients with GIST, neuroectodermal tumor, alveolar or embryonal rhabdomyosarcoma, or primary bone sarcoma were excluded. All patients in REGOSARC were required to have Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1.

One hundred eighty-two patients were randomly assigned in a 1:1 ratio to receive regorafenib or placebo, including 44 with liposarcoma, 55 with leiomyosarcoma, 27 with synovial sarcoma, and 65 with others sarcomas [7]. Within these cohorts, multiple different histological subtypes were represented. Across cohorts, 60 patients (33%) had retroperitoneal sarcomas and 22 (12%) had uterine sarcomas. The most common diagnoses in the other sarcoma cohort were undifferentiated pleomorphic sarcoma ($n = 26$), malignant solitary fibrous tumors ($n = 7$), angiosarcoma ($n = 6$), and fibrosarcoma ($n = 5$).

Regorafenib was started at 160 mg/d (3 weeks on, 1 week off) but dose adjustments and/or interruptions were allowed for patients with adverse events (AEs). All patients also received best supportive care that included any measure to preserve the comfort of the patient but excluded anti-cancer treatments. At disease progression, patients on placebo could crossover to open-label regorafenib. The primary endpoint in REGOSARC was PFS per RECIST 1.1 according to central review [7]. Secondary endpoints included disease control rate, time to progression, ratio of time to progression on regorafenib to time to progression on previous treatment, tumor response, duration of response, OS, and AEs.

Results showed significant improvements in PFS with regorafenib relative to placebo in the leiomyosarcoma, synovial sarcoma, and other sarcoma groups (Table 1) [7]. PFS did not differ significantly between regorafenib and placebo in the liposarcoma cohort. Secondary endpoints generally favored regorafenib in the leiomyosarcoma, synovial sarcoma, and other sarcoma cohorts, although there were no significant differences in OS between treatment arms. When patients from multiple cohorts with non-adipocytic sarcomas were pooled together in an unplanned analysis, median PFS was 4.0 (IQR 1.8–9.0) months in the regorafenib arm and 1.0 (IQR 0.9–2.8) month in the placebo arm (HR 0.36 [95% CI 0.25–0.53], $P < .0001$).

Safety data were pooled across all four cohorts in REGOSARC [7]. Ten patients (11%) in the regorafenib arm

Table 1 The table shows an overview of the results from the REGOSARC study of patients with STS. There were 182 patients randomized to regorafenib 160 mg/d or placebo with a primary endpoint of PFS per central review using RECIST 1.1 [7]

		Liposarcoma	Leiomyosarcoma	Synovial sarcoma	Other sarcoma
Number of patients	Regorafenib	20	28	13	27[a]
	Placebo	23	28	14	27
Median (IQR) follow up, months		18.6 (17.6–20.9)	16.3 (14.6–19.4)	14.8 (11.8–21.7)	18.7 (15.1–19.8)
Median (IQR) duration of treatment, months	Regorafenib	1.6 (0.7–2.4)	3.9 (2.0–8.7)	3.4 (0.7–6.7)	3.5 (0.6–10.2)
	Placebo	1.9 (1.6–4.8)	2.3 (1.6–4.6)	1.4 (0.7–2.0)	2.8 (1.1–5.1)
Median (95% CI) PFS, months	Regorafenib	1.1 (0.9–2.3)	3.7 (2.5–5.0)	5.6 (1.4–11.6)	2.9 (1.0–7.8)
	Placebo	1.7 (0.9–1.8)	1.8 (1.0–2.8)	1.0 (0.8–1.4)	1.0 (0.9–1.9)
		HR 0.89 (95% CI 0.48–1.64), $P = .70$	HR 0.46 (95% CI 0.26–0.80), $P = .0045$	HR 0.10 (95% CI 0.03–0.35), $P < .0001$	HR 0.46 (95% CI 0.25–0.82), $P = .0061$
Median (95% CI) OS, months	Regorafenib	4.7 (2.9–10.1)	21.0 (7.2-NR)	13.4 (5.3-NR)	12.1 (6.9–16.6)
	Placebo	8.8 (7.0–13.8)	9.1 (7.7–13.4)	6.7 (2.2-NR)	9.5 (4.7–16.6)
		HR 1.57 (95% CI 0.77–3.20), $P = .21$	HR 0.50 (95% CI 0.24–1.03), $P = .056$	HR 0.87 (95% CI 0.32–2.35), $P = .79$	HR 0.75 (95% CI 0.41–1.40), $P = .37$
Disease control rate, %[b]	Regorafenib	45	86	85	78
	Placebo	57	58	22	34

IQR, interquartile range; OS, overall survival; PFS, progression-free survival

[a] 28 patients were randomized to regorafenib but 1 refused treatment

[b] Partial response + stable disease per RECIST 1.1

and two patients (2%) in the placebo arm permanently discontinued treatment due to AEs. The AEs that led to discontinuation in the regorafenib arm most often were hand-foot skin reaction (HFSR, 13%), other skin reactions (8%), elevated transaminases (3%), and infection (3%). Temporary interruptions in therapy were reported in 32 patients (36%) in the regorafenib group and five patients (5%) in the placebo group. Dose reductions due to AEs occurred in 40 regorafenib-treated patients (45%), most often due to HFSR (21%), elevated transaminases (7%), asthenia (5%), or diarrhea (5%). Thirty patients (34%) had 120 mg/d as their lowest regorafenib dose after one dose reduction while 15 patients (17%) had 80 mg/d as their lowest dose after two dose reductions. One death due to hepatitis-induced liver failure was noted in the regorafenib arm.

Overall, the results of REGOSARC suggested promising safety and efficacy of regorafenib in the treatment of patients with non-adipocytic STS. PFS was significantly improved relative to placebo; no differences in OS were observed, but it is important to note that crossover from placebo to regorafenib at progression may have masked the effect of active treatment on survival. Response rates were relatively low with regorafenib, but this could have been expected given that regorafenib is a multikinase inhibitor and not a cytotoxic drug. Toxicities were generally consistent with the known profile of regorafenib and could be managed through dose reductions/interruptions and other supportive measures for most patients.

An additional phase 2 study, SARC024, examined the efficacy and safety of regorafenib in patients with selected sarcoma types (liposarcoma, osteogenic sarcoma, Ewing's sarcoma, or rhabdomyosarcoma) [18]. Preliminary data from a cohort of 30 patients with Ewing's sarcoma from 14 participating centers in the United States who had progressed after at least one line of prior therapy has been reported [6]. The median number of prior treatments among patients in this cohort was 5 (range 1–10), although importantly no prior treatment with kinase inhibitors was allowed. PFS at 8 weeks, the primary endpoint, was 73% (95% CI 57%–89%), with a median PFS of 3.6 (95% CI 2.8–3.8) months. Per RECIST 1.1 criteria, three patients had partial responses, 18 had stable disease, and seven had progressive disease. Median duration of response was 5.5 (95% CI 2.9–8.0) months. AEs were generally similar to what was reported in other trials, with 13 patients requiring at least one dose reduction and two patients discontinuing regorafenib due to toxicities. No grade 4 AEs or regorafenib-related deaths were reported.

Between REGOSARC and SARC024, regorafenib has shown promising efficacy in patients with several different histological subtypes of sarcoma, although these findings could be considered fairly preliminary in some sarcoma types and larger confirmatory trials are needed. The findings indicate that patients with sarcoma could be considered for treatment with regorafenib in the appropriate line of therapy; however, it has not been approved in the United States in this setting. Furthermore, the potential benefits of regorafenib in patients who have already been treated with pazopanib, which is approved for patients with STS, remain to be defined. Understanding of the optimal sequencing of multiple tyrosine kinase inhibitors and the impact this has on patient's disease status remains uncertain.

4 Regorafenib in GIST

Approximately 85% of GIST are caused by mutations in *KIT* [19], and consequently this tyrosine kinase receptor has been a key therapeutic target for many years. Mutations in *PDGFRA* are also relatively common in GIST, accounting for about 8% of all tumors [19]. The inclusion of these targets in the kinase selectivity profile of regorafenib, as well as preclinical studies using models of human GIST, suggested that this agent could have efficacy in the treatment of this patient population [12].

The potential efficacy of regorafenib in GIST was first assessed in an investigator-initiated phase 2 study [20]. The study enrolled 34 patients with metastatic and/or unresectable GIST who had progressed on or were intolerant to imatinib and who had progressed on sunitinib, all of whom were treated with regorafenib starting at the 160 mg/d dose [20]. Long-term follow-up from this study showed a median PFS of 13.2 months with an OS of 25 months [21]. After a median follow-up of 10.9 months, 16 patients (48.5%) were still on regorafenib and progression free [20]. Toxicities, including HFSR, fatigue, and hypertension, were primarily Grade 1 or 2, and; therefore, the decision was made to enroll patients in a larger, placebo-controlled, phase 3 study [20].

The eventual approval of regorafenib for the treatment of patients with metastatic or unresectable GIST was supported by the multinational, randomized, placebo-controlled phase 3 GRID study where PFS was the primary endpoint [11]. One hundred ninety-nine patients with GIST who had progressed or were intolerant to imatinib and who progressed on sunitinib were enrolled. Of these, 133 were treated with regorafenib and 66 were treated with placebo.

Median treatment duration was 22.9 (IQR 9.3–28.6) weeks in the regorafenib arm and 7.0 (IQR 5.1–11.3) weeks in the placebo arm [11]. Median PFS, the primary endpoint, was significantly improved with regorafenib treatment relative to placebo (4.8 [IQR 1.4–9.2] vs 0.9 [IQR 0.9–1.8] months, HR 0.27 [95% CI 0.19–0.39], $P < .0001$). As with REGOSARC, OS was not significantly different between treatment groups at the time of publication, although crossover from placebo to regorafenib at progression was again allowed. Subsequent analyses of OS found median OS of 17.4 months in both arms although correction for crossover to active treatment from placebo found treatment effects favored regorafenib [22].

The safety profile of regorafenib during this trial was similar to what was reported in the phase 2 study as well as REGOSARC [11]. AEs were primarily Grade 1 or 2 and the most common drug-related events were HFSR, hypertension, diarrhea, and fatigue. Twenty-nine percent of patients in the regorafenib arm and 21% of patients in the placebo arm reported serious AEs. A higher percentage of patients in the regorafenib arm had dose reductions relative to the placebo arm (72 vs 26%) but the rate of discontinuation due to AEs was similar between groups. Based on these data, regorafenib was approved for the treatment of patients with GIST who have had prior treatment with imatinib and sunitinib. It is also now the recommended option for patients in this setting according to NCCN Guidelines [4].

Following the completion of the GRID study, a single-center retrospective review of patients with GIST was conducted to assess real-world treatment patterns in a sample of 28 regorafenib-treated patients in the United States [23]. Within this sample, 22 patients (79%) were started on a continuous 120 mg/d dosing schedule while six patients (21%) initiated treatment at the approved dose of 160 mg/d (3 weeks on/1 week off). At a median follow-up of 26.8 months, median PFS and OS were 8.7 and 18.3 months, respectively, with a disease control rate of 71.4% in the total study population. These results were largely comparable to what was found in GRID although the continuous 120 mg/d dosing schedule appeared to have a more favorable toxicity profile relative to the intermittent 160 mg/d schedule used in the phase 3 study, with 43% of patients experiencing grade 3 or 4 toxicities (vs 61%) and 61% having dose reductions (vs 72%). Patients on the continuous dosing schedule also had a longer treatment duration (7.3 months vs 22.9 weeks). These findings suggest that alternative dosing schedules to manage toxicity should be

Table 2 The table shows an overview ongoing clinical trials targeting patients with various sarcoma subtypes [18]

Registration number	Title	Sarcoma type(s) included	Primary outcome	Location
NCT02048722	Daily oral regorafenib for chemotherapy-refractory, metastatic and locally advanced angiosarcoma	Angiosarcoma	PFS at 4 months	United States
NCT02048371	SARC024: a blanket protocol to study oral regorafenib in patients with selected sarcoma subtypes	Liposarcoma, osteogenic sarcoma, Ewing's sarcoma, rhabdomyosarcoma	PFS	United States
NCT02389244	A phase II study evaluating efficacy and safety of regorafenib in patients with metastatic bone sarcomas (REGOBONE)	Ewing's sarcoma, chondrosarcoma, osteosarcoma, chondroma	PFS	France

PFS, progression-free survival

considered when treating patients with GIST using regorafenib.

An additional study was conducted to assess the efficacy and safety of regorafenib in Korean patients with GIST who had previous treatment with imatinib and sunitinib [24]. For this study, 57 patients from three different treatment centers were treated with regorafenib through a management access program. Efficacy results largely supported the findings from GRID, with median PFS and OS of 4.5 and 12.9 months, respectively, and 44% of patients with SD lasting ≥12 weeks. Patients underwent a median of five treatment cycles and 53% experienced a grade 3 AE (most often HFSR, hypertension, or skin rash). Dose reductions were needed for 44 patients (77%). Overall, this study supported the use of regorafenib in Korean patients with GIST who have had prior treatment with imatinib and sunitinib.

5 Future Directions in Treatment of Patients with Sarcoma

These data indicate a potential role for regorafenib in the treatment of patients with sarcomas, including GIST. Continued research is needed to determine how to sequence treatments in this setting as only six patients in REGOSARC had received prior treatment with pazopanib [7]. Further analysis of patient subtypes based on histology and/or genetics as well as results from ongoing studies (Table 2) may also help define the patient groups who will derive the most benefit from regorafenib.

The treatment landscape for patients with STS continues to evolve. For example, the selective KIT and PDGFRα inhibitor BLU-285 recently showed promising preliminary results in patients with GIST who had mutations in *PDGFRA D842V* in a phase 1 study, including a 41% ORR [25]. DCC-2618, a switch control inhibitor for KIT and PDGFR, also demonstrated promising phase 1 findings, including a high response rate, in patients with GIST [26].

The role of immunotherapy has also been further defined as the results of the SARC028 study showed an ORR of 18% with 55% of patients progression-free at 12 weeks in patients with undifferentiated pleomorphic sarcoma, dedifferentiated liposarcoma, synovial sarcoma, or leiomyosarcoma who were treated with pembrolizumab [27]. Similar findings were seen in patients with osteosarcoma or Ewing's sarcoma [27]. Expansion cohorts from this study will further investigate pembrolizumab for patients with undifferentiated pleomorphic sarcoma and liposarcoma. Similarly positive preliminary results were seen in a phase 2 study nivolumab ± ipilimumab in patients with metastatic sarcoma [28]. The 6-month PFS rate of the combination was 36%, compared with 16% for nivolumab alone [28].

New research focusing on personalized treatments and combinations of existing agents should further improve the options for these patients. Continued efforts to enroll patients in international clinical trials will expand the development of new agents for this diverse population. Additional research in larger trials of promising agents such as olaratumab is also needed to broaden the therapeutic options for this patient population.

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Compliance with Ethical Standards

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