An updated review of the treatment landscape for advanced gastrointestinal stromal tumors

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Before the introduction of tyrosine kinase inhibitors (TKIs), the overall survival of patients with advanced or metastatic gastrointestinal stromal tumors (GISTs) was 10 to 20 months because of the lack of approved therapies. In the last 20 years, a treatment algorithm for patients with advanced GISTs, which includes imatinib, sunitinib, and regorafenib as first-, second-, and third-line therapies, respectively, has been established. Recently, 2 new TKIs have been approved: ripretinib for fourth-line therapy and avapritinib as first-line therapy in patients harboring platelet-derived growth factor receptor alpha (PDGFRA) exon 18 D842V mutations. Additionally, there are several experimental therapies under investigation that could advance individualized patient care. All of these therapies have varying efficacies and safety profiles that warrant an updated treatment landscape review. This review article summarizes the efficacy and safety data currently available for conventional TKIs along with recently approved and experimental therapies.

The first line of treatment for patients with localized GISTs is surgical resection, but patients may experience recurrent disease even with complete resection. The risk of recurrence is based on several factors, including location, size, and mitotic activity. Systemic intravenous chemotherapy is ineffective against GISTs with response rates < 10%. Before the introduction of targeted inhibitors, the median overall survival (mOS) for patients with advanced or metastatic GISTs was 10 to 20 months. For these reasons, tyrosine kinase inhibitors (TKIs) became the standard of care for patients with advanced GISTs, which includes imatinib, sunitinib, and regorafenib as first-, second-, and third-line therapies, respectively. These inhibitors, however, differ in their efficacies against certain mutations and often become ineffective because of the development of secondary resistance mutations. Traditional TKIs—imatinib, sunitinib, and regorafenib—also have varying safety profiles. The recent approval of 2 new TKIs with unique mechanisms of action and favorable safety profiles will likely alter the current treatment algorithm and provide more treatment choices (Fig. 1). Therefore, an update on the current treatment landscape is warranted. In this review, we discuss the safety and efficacy of approved therapies and detail the newer approved therapies (ripretinib and avapritinib) and experimental therapies.
EARLY APPROVED TARGETED THERAPIES

**Imatinib, First-Line Therapy**

Imatinib mesylate was approved for the treatment of Philadelphia chromosome–positive chronic myelogenous leukemia because of its effective targeting of the Bcr-Abl tyrosine kinase.\textsuperscript{15} This compound also inhibits KIT and PDGFRA activity by binding to the adenosine triphosphate–binding pocket and preventing substrate phosphorylation and downstream signaling.\textsuperscript{16-18} After 1 month of treatment with 400 mg of imatinib once daily, 1 patient with an advanced GIST demonstrated histologic and radiologic evidence of anticancer activity (decreased tumor cell density and tumor volume).\textsuperscript{19} In the initial phase 1 study, lower doses (400 mg once daily, 300 mg twice daily, and 400 mg twice daily) were well tolerated, but 500 mg twice daily resulted in dose-limiting toxicities (DLTs), including dyspnea, edema, and severe nausea.\textsuperscript{20} In the randomized phase 2 trial, 53.7% of patients treated with 400 or 600 mg once daily achieved partial responses (PR), and 27.9% had stable disease (SD) after 9 months of treatment.\textsuperscript{21} However, 13.6% of patients developed early resistance to imatinib therapy. Follow-up revealed an mOS of 57 months, regardless of the treatment regimen.\textsuperscript{22} In the
phase 3 trial that compared 400 mg once daily and 400 mg twice daily, patients had mOS times of 55 and 51 months, respectively; the overall response rate was 45% for either dosing strategy (Table 1). Of the 117 patients who progressed on low-dose imatinib (400 mg once daily) and crossed over to a high dose (400 mg twice daily), 31% achieved an objective response or SD. At the 10-year follow-up, the overall survival rate was 19.4% for patients receiving 400 mg once daily and 21.5% for patients receiving 400 mg twice daily. Data from the 10-year follow-up also indicated that age (<60 years), the size of the largest lesion (smaller), and KIT mutations (exon 11) were associated with a better prognosis. In a large meta-analysis, patients with a KIT exon 9 mutation demonstrated an increased progression-free survival benefit from 400 mg twice daily versus 400 mg once daily (P = .017).

In dose-comparison studies, high-dose imatinib was more likely to result in dose reductions and discontinuations. In the phase 3 study, 43% of patients in the low-dose arm and 63% in the high-dose arm experienced grade 3 to 5 toxicities. These severe toxicities included anemia, cardiac toxicity, gastrointestinal toxicity, and hemorrhage. There were 2 and 9 deaths in the low-dose and high-dose arms, respectively, that were possibly related to treatment, with a contribution from the tumor far more likely. Specifically, 4 patients in the high-dose arm died because of gastrointestinal hemorrhage.

Patients who respond well to imatinib therapy are often reevaluated for surgical intervention. If progression is focal, local treatment of the progressing lesion (ie, surgery or liver-directed ablation) and continuation of the same TKI dose are an option. If diffuse progression occurs, patients may opt to cross over to 400 mg of imatinib twice daily. Although crossing over to the higher dose can be beneficial for patients with GISTs harboring a KIT exon 9 mutation, the potential increase in adverse events (AEs) often leads to the need for a dose reduction. Patients may stop responding to imatinib because of the development of secondary mutations acquired during treatment. Approximately 12% of GISTs harbor primary resistance to imatinib, and approximately 40% of patients develop secondary resistance. In these cases, the next option is to switch to the approved second-line therapy, sunitinib.

### Sunitinib, Second-Line Therapy

Sunitinib was approved in 2006 for patients with advanced GISTs after progression on imatinib. Sunitinib inhibits multiple receptor tyrosine kinases, including PDGFRα and KIT. Like imatinib, sunitinib binds to the kinase adenosine triphosphate–binding pocket and locks it in the inactive conformation. In an early trial, sunitinib provided a clinical benefit to 36% of patients who progressed on imatinib (PR, 7%; SD for ≥6 months, 29%). The maximum tolerated dose was established at 50 mg once daily with a recommended schedule of 4 weeks on treatment followed by 2 weeks off after patients on higher doses experienced DLTs of fatigue, nausea, and vomiting. In a separate study, the median time to tumor progression in patients resistant or intolerant to imatinib was 27.3 weeks for patients receiving sunitinib and 6.4 weeks for patients receiving a placebo. The overall objective response rates in the sunitinib and placebo groups were 7% (all PRs) and 0%, respectively (Table 1). Similarly, a clinical benefit was observed in 53% of patients receiving sunitinib with a median progression-free survival (mPFS) of 34 weeks. Of patients receiving sunitinib, 20% reported serious AEs, whereas 5% of patients receiving a placebo did. Common AEs (grade 3 or higher) were fatigue, diarrhea, palmar-plantar erythrodysesthesia syndrome (PPES), hypertension, neutropenia,
and lymphopenia; 4% of patients taking sunitinib developed hypothyroidism.24

In another study, sunitinib treatment on alternative dosing schedules (continuous dosing at 37.5 mg once daily or other modifications) provided longer survival than the recommended dosing schedule (50 mg once daily, 4 weeks on, 2 weeks off).41 Continuous dosing modifications of sunitinib included reductions to 25 or 12.5 mg once daily or an escalation to 50 mg once daily.40 The mOS was 23.5 months for patients on an alternative dosing schedule and 11.1 months for patients on the recommended dosing schedule.41 The investigators theorized that dose adjustments allowed for patients to avoid toxicities and continue treatment for longer; this emphasizes the need for dose maintenance and supportive care. The proportion of patients who discontinued sunitinib because of AEs was higher with the recommended schedule versus alternative schedules (34% vs 26%). Similarly to previous studies, the most common treatment-related AEs were diarrhea, fatigue, and PPES.41

Patients can also develop resistance to sunitinib therapy. Some patients develop mutations in the activation loop of the KIT gene and become resistant to further treatment42; such mutations can shift the ratio of inactive KIT to active KIT and render sunitinib ineffective.38 In the event of resistance to sunitinib, patients can begin the approved third-line therapy, regorafenib.

**Regorafenib, Third-Line Therapy**

Regorafenib is an oral, multitargeted TKI that acts against KIT and PDGFRA, among others.43 In a phase 1 study in patients with solid tumors, the optimal dosing schedule for regorafenib was determined to be 160 mg once daily on a schedule of 3 weeks on treatment and 1 week off.44 When administered in patients with advanced GISTs after the failure of imatinib and sunitinib, regorafenib demonstrated a clinical benefit in 75% of patients with an mPFS of 10 months.45 In a phase 3 study, the mPFS was 4.8 months for patients receiving regorafenib and 0.9 months for patients receiving a placebo (P < .0001); patients who crossed over from the placebo to regorafenib had an mPFS of 5 months.25 The overall response rate was 4.5% in the regorafenib group and 1.5% in the placebo group; all were PRs (Table 1). A best possible response of a PR or SD was observed in 76% of patients receiving regorafenib and in 35% of placebo patients.25 Similarly, in a retrospective analysis of 50 patients with GISTs previously treated with at least 2 therapies, the mPFS was 7.7 months.46 In a study that evaluated continuous regorafenib dosing (120 mg once daily), the mPFS was 8.7 months.47

In the phase 2 study, the most common AEs of any grade were PPES, fatigue, hypertension, and diarrhea.45 The most common grade 3 AEs were hypertension, PPES, and hypophosphatemia, and grade 4 AEs included hyperuricemia and thrombotic events. Six patients died during the study: 5 deaths were attributed to disease progression, and 1 was attributed to an unrelated illness. In the phase 3 study, all patients receiving regorafenib experienced an AE of any grade; 98.5% of these were determined to be related to the study drug.25 Of these related AEs, 61% were grade 3 or higher and included hypertension, PPES, and diarrhea. Serious AEs were reported in 29% of patients receiving regorafenib and in 21% of patients receiving a placebo, and permanent discontinuations were similar between the 2 groups (regorafenib, 6.1%; placebo, 7.6%). There were 2 grade 5 AEs of cardiac arrest and hepatic failure related to regorafenib treatment. In a retrospective analysis, 46% of patients experienced grade 3 or 4 AEs of PPES, fatigue, hypertension, hepatotoxicity, diarrhea, and arthralgia.46 Patients on the continuous schedule (120 mg once daily) demonstrated similar grade 3 or 4 AEs of PPES and fatigue, and 59% required dose reductions.47

In the retrospective analysis, 20% discontinued regorafenib therapy because of AEs, but none of these patients had a prior dose reduction; this indicated a failure to effectively manage associated toxicities.46 Research shows that supportive care and dose maintenance can extend the use of regorafenib in patients experiencing AEs.48 Until recently, there were no approved treatment options for patients who progressed on regorafenib treatment after the failure of imatinib and sunitinib. In May 2020, the Food and Drug Administration approved the novel TKI ripretinib for use as a fourth-line therapy in patients with advanced GISTs.49

**NOVEL APPROVED TARGETED THERAPIES**

**Ripretinib, Fourth-Line Therapy**

Ripretinib is a switch-control TKI that broadly inhibits a spectrum of KIT and PDGFRA mutations through a dual mechanism of action.50 Different from conventional TKIs, ripretinib specifically binds to both the switch pocket and the activation loop to lock the kinase in an inactive state and prevent downstream signaling and cell proliferation. The dual mechanism of action provides broad inhibition of KIT and PDGFRA kinase activity, including wild type and multiple primary and secondary mutations. Targeting
both the switch pocket (KIT exons 13 and 14) and the activation loop (KIT exons 17 and 18) allows ripretinib to be effective against a variety of treatment-resistant GISTs, as conventional inhibitors generally do not perform well against both types of mutations.\textsuperscript{50,51}

Ripretinib demonstrated promising efficacy in a phase 1 study in patients receiving 150 mg of ripretinib once daily as second-line therapy (mPFS, 10.7 months), third-line therapy (mPFS, 8.3 months), or fourth-line therapy (mPFS, 5.5 months).\textsuperscript{52} Additionally, a dose escalation to 150 mg twice daily provided additional clinical benefit for second-line (mPFS, 5.6 months) and third-/fourth-line patients (mPFS, 3.7 months).\textsuperscript{55} In the pivotal INVICTUS phase 3 trial, ripretinib at 150 mg once daily was evaluated in patients for whom treatment with at least imatinib, sunitinib, and regorafenib had failed. The mPFS and mOS for fourth-line or higher patients receiving ripretinib were 6.3 and 15.1 months, respectively, whereas they were 1.0 and 6.6 months, respectively, for patients receiving a placebo.\textsuperscript{26} The overall response rate was 9.4% for the ripretinib group (all PRs) and 0% for the placebo group (Table 1).\textsuperscript{26}

In addition to promising efficacy, ripretinib has a well-tolerated safety profile. In the phase 1 study, most AEs were minor, and common events included alopecia, myalgia, nausea, fatigue, PPES, and muscle spasms. The safety profile was similar during the period of 150 mg once daily and the period of dose escalation (150 mg twice daily); this demonstrated that ripretinib was similarly well tolerated.\textsuperscript{53} The most common AEs (grades 1 and 2) reported by ripretinib patients in the phase 3 study were alopecia, myalgia, nausea, fatigue, and PPES.\textsuperscript{26} The majority of AEs were categorized as mild (grades 1 and 2), and the most common grade 3 or 4 event was increased lipase, which was observed in 4 patients. Only 6% experienced AEs that were categorized as mild (grades 1 and 2), and the most common events included nausea, diarrhea, decreased appetite, and fatigue. At the once daily dose of 300 mg, the most common grade 3 AE was anemia. The appearance of cognitive difficulties was of special interest in these patients. In the safety population, 40% developed a cognitive difficulty (memory impairment, cognitive disorder, confused state, or encephalopathy). Additionally, 2 patients had intracranial bleeding considered possibly related to the study drug. In the safety population, 54% of patients discontinued
# Selected Investigational Therapeutic Strategies for Advanced GISTs

| Therapeutic Agent | Indication | Efficacy | Safety |
|-------------------|------------|----------|--------|
| **Targeted therapies** | | | |
| Cabozantinib[^61] | KI used in thyroid cancer, renal cell carcinoma, and hepatocellular carcinoma; tested in third-line GIST | PFS at 12 wk, 60%; mPFS, 6.0 mo; 80% of patients achieved a PR or SD | The most common treatment-related AEs ≥ grade 3 were diarrhea, PPES, fatigue, and hypertension. Treatment-related AEs were reported in 72% of patients; none of the patients discontinued. |
| Sorafenib[^62] | KI used in kidney, liver, and thyroid cancer; tested in ≥ third-line GIST | PR or SD achieved in 40% of patients; mPFS, 7.2 mo | First line: The study’s rates of discontinuation due to AEs were 8.0% with nilotinib and 5.3% with imatinib; frequently reported AEs in the nilotinib arm were rash, nausea, and abdominal pain. |
| Nilotinib[^63,^64] | KI used to treat Philadelphia chromosome CML; tested in ≥ first-line GIST | First line: PFS at 24 mo with nilotinib, 51.6%; with imatinib, 59.2% | Second/third line: The most common AEs were fatigue, anemia, and anorexia; 1 patient experienced grade 4 anemia. |
| Dasatinib[^65] | KI used to treat CML and ALL; tested in second-line GIST | mPFS, 2.9 mo; PR reported in 25% of patients | Serious AEs occurred in 24% of patients and included pleural effusion, nausea/vomiting, and muscle weakness. |
| Pazopanib[^66] | KI used in advanced renal cell cancer and metastatic soft tissue sarcoma; tested in third-line GIST | mPFS with pazopanib, 3.4 mo; mPFS with supportive care only, 2.3 mo | Grade 3 or higher AEs were reported in 72% of pazopanib-treated patients; the most common was hypertension. |
| Ponatinib[^67] | KI used to treat CML and ALL; tested in ≥ third-line GIST | CBR at ≥ 16 wk for patients with a primary KIT exon 11 mutation, 55%; without a primary KIT exon 11 mutation, 22% | Seventeen of 35 patients discontinued treatment; the most common AEs were rash, fatigue, myalgia, and dry skin. |
| **Immunotherapy** | | | |
| Pembrolizumab[^68] | Anti–PD-1 antibody used to treat multiple forms of cancer | 6-mo nonprogression rate, 11.1% | AEs were mild and included fatigue, diarrhea, and anemia. |
| Nivolumab + ipilimumab[^69] | Anti–PD-1 antibody used to treat multiple forms of cancer; tested in ≥ second-line GIST | mPFS with nivolumab only, 8 wk; with nivolumab + ipilimumab, 8.43 wk | Grade 3 fatigue (1 patient in the nivolumab-only arm) and diarrhea (1 patient in the nivolumab + ipilimumab arm). |
| **Combination therapy** | | | |
| Imatinib + peginterferon α-2b[^70] | Interferon given to promote antitumor activity; used to treat hepatitis C and melanoma; tested in ≥ third-line GIST | All 7 patients had a CR or PR; OS at 3.6-y follow-up, 100% | All patients experienced temporary low-grade fever and flu-like symptoms; grade 3 neutropenia (3 patients) and skin rash (2 patients). |
| Imatinib + buparlisib[^71] | Phosphoinositide 3-kinase inhibitor used experimentally to treat breast cancer; tested in third-line GIST | No PR or CR; mPFS, 3.5 mo | Treatment-related AEs were reported in 98.3% of patients; 45% of these patients had grade 3–4 AEs; the most common were nausea and fatigue. |
| Imatinib + binimetinib[^72] | MAPK inhibitor used to treat metastatic melanoma; tested in first-line GIST | Of 38 patients, 26 had a PR; best objective response rate, 68.4% | Grade 3–4 toxicities included CPK elevations, neutrophil decreases, rash, and anemia. |
| **Cycling therapies** | | | |
| Imatinib/regorafenib (ALT-GIST)[^73] | Imatinib for 21–25 d, 3- to 7-d washout, regorafenib for 21 d, 7-d washout; tested in first-line GIST | Responses to imatinib only and the alternating therapy were similar; 1 patient on alternating therapy had a CR, 23 had a PR, and 15 had SD; PFS at 1 y, 86% | Seven patients on alternating therapy discontinued because of toxicity; 8% of patients on alternating therapy had serious AEs. |
| Sunitinib/regorafenib[^74] | Sunitinib for 3 d, regorafenib for 4 d, no washout; tested in fourth-line GIST | SD was achieved in 4 patients; mPFS, 1.9 mo; mOS, 10.8 mo | All patients experienced treatment-related AEs, but the majority were mild (grades 1 and 2); 4 patients experienced grade 3 AEs of hypertension or PPES. |
| Imatinib rechallenge (RIGHT)[^75] | Imatinib rechallenge for patients who progressed on imatinib and sunitinib; tested in third-line GIST | mPFS with imatinib, 1.8 mo; with placebo, 0.9 mo | Grade 3 or higher toxicities included anemia, fatigue, and hyperbilirubinemia. |

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Abbreviations: AE, adverse event; ALL, acute lymphocytic leukemia; ALT-GIST, alternating-regimen gastrointestinal stromal tumor; CBR, clinical benefit rate; CML, chronic myeloid leukemia; CPK, creatinine phosphokinase; CR, complete response; GIST, gastrointestinal stromal tumor; KI, kinase inhibitor; MAPK, mitogen-activated protein kinase; mOS, median overall survival; mPFS, median progression-free survival; OS, overall survival; PD-1, programmed cell death protein 1; PFS, progression-free survival; PPES, palmar-plantar erythrodysesthesia syndrome; PR, partial response; SD, stable disease.
treatment, but the proportion of patients who discontinued was lower in the PDGFRA exon 18 D842V mutation group (34%).

INVESTIGATIONAL THERAPIES
Several alternative strategies were investigated in patients with advanced GISTs because, until the recent approval of ripretinib, there were no further treatment options for patients for whom the first 3 lines of treatment failed. These strategies include kinase inhibitors approved for other forms of cancer, immunotherapies, combination therapies, and alternating or cycling therapies; examples of these therapeutic strategies are provided in Table 2.

Other kinase inhibitors used in different types of cancers and tested in patients with advanced GISTs include cabozantinib, sorafenib, nilotinib, dasatinib, pazopanib, and ponatinib (Table 2). With the approval of ripretinib, it is unclear whether the use of these types of inhibitors will continue. However, promising preliminary results with cabozantinib may provide patients with an additional treatment option (Table 2). The combination of imatinib and interferon showed promising efficacy in a small number of patients, whereas the combination of imatinib and phosphoinositide 3-kinase inhibitor paralisib had no effect as a third-line therapy (Table 2). Cycling therapies such as rapid alternation between imatinib and regorafenib or between sunitinib and regorafenib have demonstrated only modest benefits, but they may be options for individualized patient care.

Imatinib rechallenge as a third-line therapy extended patients’ progression-free survival but was not as effective as regorafenib as a third-line option (Table 2). A comprehensive list of recent or ongoing clinical trials evaluating various therapeutic agents and/or strategies for the treatment of advanced GISTs can be found at ClinicalTrials.gov.

CONCLUSIONS
The traditional treatment algorithm for advanced GISTs has been imatinib as first-line therapy, sunitinib as second-line therapy, and regorafenib as third-line therapy. Now, however, the GIST treatment landscape is evolving, and patients with PDGFRA exon 18 D842V mutations have the option of receiving avapritinib as first-line therapy. Additionally, patients who progress on imatinib, sunitinib, and regorafenib now have the option of receiving ripretinib as fourth-line therapy (Fig. 1). With ripretinib’s broad efficacy and favorable safety profile, this therapy has the potential to alter the current treatment algorithm, as it is being investigated as a second-line therapy versus sunitinib in a randomized study (Fig. 1). Although these are the currently approved therapies, there are several alternative strategies being investigated that could further advance individualized care of patients with advanced GISTs. With all therapies, however, the effective management of AEs and supportive care are crucial to ensuring the longevity of treatment and the maximum clinical benefit. With evolving treatment options and effective toxicity management, patients with advanced GISTs are living longer than ever before.

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