Gastrointestinal Stromal Tumors

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ABSTRACT

GI stromal tumors (GISTs) are neoplasms with a varying malignancy potential ranging from virtually indolent tumors to rapidly progressing cancers. GISTs occur throughout the intestinal tract, and most harbor an activating mutation in either *KIT* or platelet-derived growth factor A (*PDGFRA*). Diagnosis is made using immunohistochemistry, but molecular testing with mutation analysis is paramount for selection of appropriate therapy. Most small GISTs are cured with surgery. Tyrosine kinase inhibitor (TKI) therapy has led to substantial improvements in survival, both for patients with localized GIST and those with advanced disease. Adjuvant therapy with imatinib benefits patients with a high risk of recurrence, with studies suggesting most benefit with at least 3 years of therapy. Neoadjuvant imatinib therapy should be considered for patients requiring extensive surgery, aiming at shrinking the tumor to allow organ preservation and less extensive surgery. The following three TKIs have been approved for the management of advanced disease: imatinib, sunitinib, and regorafenib; imatinib is usually the best tolerated of the three and the standard first-line treatment. TKIs benefit the majority of patients with advanced GIST but have no or limited efficacy in patients with the *PDGFRA* D842V mutation or patients with GIST lacking *KIT* and *PDGFRA* mutations. Surgery, the mainstay of primary tumor management, also plays a role in the advanced disease setting for selected patients, as do some other approaches such as palliative radiation therapy. Research continues to identify novel therapies, in particular effective agents to treat TKI-refractory disease.

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INTRODUCTION

GI stromal tumors (GIST) compose approximately 20% of soft tissue sarcomas with an annual incidence of approximately 10 per million population.^{1,2} In addition, small (< 1 cm) gastric micro-GISTs are common (10% to 35%) in the middle-aged and elderly populations.^{3,4} Micro-GISTs have low or no mitotic activity and have little clinical significance.

GISTs occur throughout the GI tract, most commonly in the stomach or small intestine. GISTs rarely (< 5%) arise within the abdominal cavity without an apparent connection to the GI tract. Such GISTs are known as extra-GI GISTs.

PATIENT PRESENTATION

GISTs occur at any age, with a median age at detection of 65 years, but they rarely occur (< 0.5%) in individuals younger than age 20 years.⁵ GIST occurs with similar frequency in males and females. The median tumor size at diagnosis is approximately 6 cm, but it may be > 20 cm.

GISTs are often vascular tumors that bulge from the GI tract into spaces between the abdominal organs (Fig 1). Tumor bleeding into the abdominal cavity or bowel is a common presentation. Bleeding may be slow, resulting in anemia, or sudden, causing tachycardia, fainting, stomach pain, melena, or hematemesis. GISTs may cause other symptoms depending on size and location, such as abdominal pain, fullness or pressure, or bowel obstruction. Asymptomatic GISTs may be detected by palpation, during imaging, or at surgery for other conditions.

Up to 20% of patients have overt metastases at diagnosis.⁶ Metastases typically occur in the abdominal cavity or the liver, whereas metastases in the lungs, bones, or brain are rare. Lymph node metastases are found in 20% to 60% of pediatric GISTs, pediatric-type GISTs in young adults, and syndromic GISTs.^{7,8} An abdominal tumor with lung metastases is likely not GIST.

SYNDROMIC GIST

Most GISTs (97%) are sporadic.⁹ No risk factors have been recognized apart from rare tumor

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Fig 1. A 15-cm gastric GI stromal tumor (GIST; star) in a 64-year-old man. The GIST harbored a *KIT* exon 11 deletion mutation of codons 557 and 558. The arrow points at the stomach.

syndromes, including neurofibromatosis type 1, Carney-Stratakis syndrome, and Carney triad. Neurofibromatosis type 1 presents with multiple intestinal GISTs that harbor mutated *NF1*. The Carney-Stratakis syndrome is a rare heritable condition with a germline mutation in the succinate dehydrogenase (SDH) complex genes, *SDHA* (C. Stratakis, personal communication, June 2017), *SDHB*, *SDHC*, or *SDHD*.⁹ Patients have a high risk for gastric GIST at a young age and paraganglioma. The Carney triad is a rare non-heritable condition. The triad consists of multiple gastric GISTs in young females, paraganglioma, and pulmonary chondroma, but may present without all three components or with adrenal cortical adenoma or esophageal leiomyoma. The molecular pathogenesis depends on epigenetic SDHC inactivation through *SDHC* hypermethylation.¹⁰ Collectively, tumors with *SDH* gene mutations or hypermethylation are referred to as SDH-deficient GISTs. Rarely, GIST can be familial, with a germline mutation in either *KIT* or platelet-derived growth factor receptor A (*PDGFRA*).⁹

STAGING

Standard imaging consists of computed tomography of the abdomen and pelvis. Imaging of the chest may be considered to exclude rare metastases above the diaphragm. Magnetic resonance imaging may provide additional information, particularly for GIST of the rectum or duodenum. Other examinations, such as computed tomography–positron emission tomography or ultrasound of the liver, may also be considered.

BIOPSY

Histopathologic evaluation of the excised tumor allows best estimation of the risk of recurrence when considering adjuvant therapy. A core needle biopsy can be taken safely endoscopically.

Mitotic counts from a needle biopsy may underestimate the risk of recurrence. The safety of a transabdominal wall biopsy is controversial as a result of concern for tumor cell seeding to the abdominal cavity when GIST is necrotic. One study found that performing a diagnostic transabdominal wall biopsy does not adversely influence prognosis in patients who received adjuvant imatinib after surgery.¹¹ Some data suggest that small tumor capsule lesions have little adverse impact on patient outcome, unlike large tumor ruptures.¹²

TISSUE DIAGNOSIS AND MOLECULAR BIOLOGY

GIST morphology is variable, and immunohistochemical staining usually establishes the diagnosis. Most GISTs stain for KIT (95%)¹³ and anoctamin-1 (DOG-1; 98%),¹⁴ whereas most do not stain with smooth muscle biomarkers such as desmin.

Activating mutations in *KIT* and *PDGFRA* (encoding KIT and platelet-derived growth factor receptor tyrosine kinases, respectively) are considered the main oncogenic drivers of GIST.¹⁵ Similar mutations occurring in clinical GISTs are found in micro-GISTs,^{4,16} suggesting that further genetic aberrations are required for tumor progression. Mutations occur occasionally in several other genes in GISTs, including *SETD2*, *SDH*, *BRAF*, *TP53*, *MEN1*, *MAX*, and *Rb1*, and translocations involving *FGFR* and *NTRK*.^{17–21}

Most GISTs (75%) harbor a mutation in *KIT*,²² occurring in exon 11 (90%) or exon 9 (8%) and, less often, in exon 13 (1%) or exon 17 (1%).²³ *PDGFRA* mutations occur in 10% to 20% of GISTs, most commonly in exons 12, 14, and 18. GISTs that do not harbor a *KIT* or *PDGFRA* mutation (5% to 10% of GISTs) were called wild-type GISTs in the past, but such GISTs are now known to have other mutations, frequently in *NF1* or genes of the SDH complex.⁹ GISTs in children typically have *SDH* mutations or epigenetic silencing of the *SDHC* promoter.²⁴

Mutation analysis of *KIT* and *PDGFRA* is mandatory for optimal care of GIST. GISTs harboring the *PDGFRA* mutation D842V (approximately 8% of GISTs)^{6,23} do not respond to imatinib or other approved tyrosine kinase inhibitors (TKIs),²⁵ but most may respond to BLU-285.²⁶ GISTs that do not contain *KIT* or *PDGFRA* mutations are unlikely to benefit from imatinib treatment (Table 1). Tumor immunostaining for SDHB is recommended when no *KIT* or *PDGFRA* mutation is present, as absence of SDHB staining indicates SDH deficiency and potentially an *SDH* mutation,¹¹ in which case genetic counseling is appropriate.

RISK STRATIFICATION

The malignant potential of GISTs varies greatly from virtually benign tumors to rapidly progressing cancers. The estimation of the risk of recurrence is particularly important for localized tumors when considering adjuvant treatment.

Several validated stratification schemes to estimate the risk of recurrence after macroscopically complete surgery are available (Table 2).^{2,6,27–30} These methods are largely equivalent,³¹ although factors included and the cutoff values vary between methods. It may be best to consult another scheme when either the tumor diameter or the mitotic count is close to the cutoff value or to use

Table 1. Clinical Interpretation of Molecular Analysis Findings

Analysis Result	Prognostic Implication	Predictive Implication
<i>PDGFRA</i> mutation (various types, most commonly in exon 12 or 18)	Usually gastric; low mitotic count; favorable prognosis	Many imatinib sensitive; <i>PDGFRA</i> D842V is unresponsive to imatinib and other standard TKIs
<i>KIT</i> exon 11 deletion mutation (various types)	Variable	Response to imatinib likely
<i>KIT</i> exon 11 deletion of codons 557/558	Often a high mitotic count; a high risk of recurrence	Response to imatinib likely
<i>KIT</i> exon 11 duplication	Often favorable prognosis	Response to imatinib likely
<i>KIT</i> exon 9 (98% are Ala502_Tyr503dup)	Usually intestinal location; often unfavorable prognosis	Imatinib sensitive, but a high dose required (400 mg twice daily)
<i>SDH</i> deficient	Female predominance; multiple gastric GISTs; lymph node involvement common; often indolent clinical course; may be associated with paraganglioma and germline mutations; genetic counseling recommended	No documented benefit from imatinib; limited benefit reported for sunitinib or regorafenib
<i>NF1</i> mutation	Intestinal; often multiple; may sometimes harbor also <i>KIT</i> mutation	Little or no benefit from TKIs

Abbreviations: GIST, GI stromal tumor; TKI, tyrosine kinase inhibitor.

a method where size and mitotic count are expressed as continuous variables,^{5,30} because the true risk of recurrence does not change abruptly at any variable cutoff. Some novel prognostic approaches, such as multigene panels and circulating tumor DNA, seem promising.

TREATMENT OF LOCALIZED GIST

Surgery

Approximately 60% of patients with localized GIST are cured with surgery.⁵ The aim is to completely excise GIST macroscopically and microscopically, without rupturing the tumor capsule. This can be done at open surgery or, for smaller tumors, by laparoscopic surgery.^{32,33} A 1- to 2-cm macroscopic margin may be sufficient to achieve microscopically negative margins.² Lymph node dissection is usually not indicated in adults.

Preoperative Imatinib

Preoperative imatinib, an inhibitor of KIT and *PDGFRA*, should be considered to shrink the tumor and allow organ sparing when up-front surgery might lead to extensive organ resections.³⁴ Indications for preoperative imatinib include rectal GISTs in an attempt to avoid abdominoperineal resection, some duodenal and esophageal GISTs, and large gastric GISTs that might require total gastrectomy. A tissue diagnosis using a core needle biopsy should

be taken before starting imatinib to confirm the diagnosis, and a mutation analysis should be obtained whenever feasible. The optimal duration of preoperative imatinib is unknown, but it is often administered for 6 to 12 months to allow maximal tumor shrinkage. Response to treatment should be monitored because some GISTs do not respond and a few may develop imatinib resistance. Imatinib is continued until surgery and should be resumed after surgery to complete 3 years of treatment when the risk of recurrence is substantial.

A limitation of preoperative imatinib is that tumor mitotic activity often cannot be estimated reliably from the diagnostic biopsy or from the residual resected GIST after imatinib therapy. Because standard risk estimation often cannot be done, the benefits of adjuvant imatinib may become challenging to assess, particularly when the tumor diameter is < 10 cm.

Adjuvant Imatinib

Imatinib is the only TKI that has been studied as adjuvant treatment of operable GIST, at a dose of 400 mg/d (Table 3).³⁵⁻⁴² In two of three randomized trials with results, adjuvant imatinib administered for 1 year³⁵ or 2 years³⁶ improved recurrence-free survival compared with placebo or observation; overall survival (OS) benefit was not observed in either study. In the third trial, patients with GIST with a high risk for recurrence received adjuvant imatinib for 1 or 3 years after surgery. With a median follow-up of 7.5 years, patients who received 3 years of imatinib

Table 2. Selected Methods for Estimation of the Risk of GIST Recurrence After Macroscopically Complete Surgery

Method	GIST Feature				Prognostic Risk Groups
	Diameter (cm)	Mitotic Count	Sites	Rupture	
Modified NIH ^{2,28}	≤ 2.0, 2.1-5.0, 5.1-10.0, or > 10.0	≤ 5, 6-10, or > 10 per 50 HPFs	Gastric or nongastric	Rupture or no rupture	Four groups (very low, low, intermediate, or high risk)
AFIP ²⁹	≤ 2.0, 2.1-5.0, 5.1-10.0, or > 10.0	≤ 5 or > 5 per 50 HPFs	Criteria available for gastric, duodenal, jejunal, ileal, and rectal GISTs	Not considered	Eight groups (1, 2, 3a, 3b, 4, 5, 6a, 6b)
Nomogram ³⁰	Continuous	≤ 5 or > 5 per 50 HPFs	Stomach/other, colon/rectum, or small intestine	Not considered	Risk of recurrence 2 and 5 years after surgery
Prognostic contour map ⁵	Continuous	Continuous	Gastric, nongastric, or extra-GI GIST	Rupture or no rupture	Risk of recurrence within 15 years of surgery

Abbreviations: AFIP, Armed Forces Institute of Pathology; GIST, GI stromal tumor; HPF, high-power field; NIH, National Institutes of Health.

Table 3. Trials Evaluating Adjuvant Imatinib

ClinicalTrials.gov Identifier	Phase	Design	Key Eligibility Criteria	Primary End Point	Main Results
ACOSOG Z9001 ³⁵ (NCT00041197)	III	Randomized; imatinib 400 mg/d for 1 year v placebo for 1 year	Size $\geq$ 3 cm	RFS	HR, 0.6; 95% CI, 0.43 to 0.75 ($P < .001$). No difference in OS ($P < .19$)
EORTC 62024 ³⁶ (NCT00103168)	III	Randomized; imatinib 400 mg/d for 2 years v observation	Intermediate or high risk according to NIH consensus classification ²⁹	IFFS	5-year IFFS, 87% v 84%; HR, 0.79; 98.5% CI, 0.50 to 1.25 ($P = .21$). No difference in OS
SSG XVIII/German ³⁷ (NCT00116935)	III	Randomized; imatinib 400 mg/d 1 v 3 years	High risk using modified NIH criteria ³⁰ (size $\geq$ 10 cm, rupture, mitotic count > 10 per 50 HPFs, or size > 5 cm and mitotic rate > 5 per 50 HPFs)	RFS	5-year RFS, 71% v 52%; HR, 0.60; 95% CI, 0.44 to 0.81 ($P < .001$). 5-year OS, 92% v 85%; HR, 0.60; 95% CI, 0.37 to 0.97 ($P = .036$).
SSG XXII (NCT02413736)	III	Randomized; imatinib 400 mg/d for 3 v 5 years	Gastric GIST with > 10 mitoses per 50 HPFs, nongastric with > 5 mitoses per 50 HPFs, or rupture	RFS	Accrual ongoing
ImadGist (NCT02260505)	III	Randomized; imatinib 400 mg/d for 3 v 6 years	Estimated risk of recurrence $\geq 35\%$	DFS	Accrual ongoing
ACOSOG Z9000 ³⁸ (NCT00025246)	II	Single cohort; Imatinib 400 mg/d for 1 year	Size > 10 cm, rupture, up to 4 peritoneal implants	OS	5-year OS, 83%
Japanese study ³⁹ (NCT00171977)	II	Single cohort; Imatinib 400 mg/d for 1 year	High risk according to NIH consensus classification ²⁹	RFS	3-year RFS, 43%
Korean study ⁴⁰ (NCT00278876)	II	Single cohort; Imatinib 400 mg/d for 2 years	Size ≥ 10 cm, mitotic count ≥ 10 per 50 HPFs, or size 5-10 cm and mitotic count 5-10 per 50 HPFs	RFS	5-year RFS, 46%
PERSIST-5 ⁴¹ (NCT00867113)	II	Single cohort; Imatinib 400 mg/d for 5 years	Size ≥ 2 cm and mitotic count ≥ 5 per 50 HPFs, or nongastric GIST ≥ 5 cm	RFS	5-year RFS, 90%

Abbreviations: ACOSOG, American College of Surgeons Oncology Group; DFS, disease-free survival; EORTC, European Organisation for Research and Treatment of Cancer; GIST, GI stromal tumor; HPF, high-power field; HR, hazard ratio; IFFS, imatinib failure-free survival (calculated from the date of random assignment to the date of the start of a new systemic treatment or death); NIH, National Institutes of Health; OS, overall survival; RFS, recurrence-free survival; SSG, Scandinavian Sarcoma Group.

had longer recurrence-free survival and OS times compared with those who were on imatinib for 1 year.³⁷ In these studies, patients with *KIT* exon 11 deletion mutations benefitted most from imatinib.^{35,42}

Imatinib is relatively well tolerated. However, 26% of patients receiving 3 years of adjuvant imatinib discontinued treatment for reasons other than GIST recurrence,⁴² and 49% of patients in the PERSIST trial discontinued imatinib before 5 years.⁴¹ Supportive measures (Table 4) can alleviate adverse effects and help in maintaining compliance.

Patients who have a substantial risk for recurrence should be treated with at least 3 years of imatinib.^{43,44} The optimal duration remains unknown. Two randomized trials are comparing 5 or 6 years to 3 years of adjuvant imatinib (Table 3). GISTs with *PDGFRA* D842V mutation or lacking a mutation in *KIT* or *PDGFRA* are unlikely to benefit from adjuvant imatinib. Patients with *KIT* exon 9 mutation are usually treated with higher imatinib doses (up to 800 mg/d, if tolerated) based on data from patients with advanced GIST,⁴⁵ without prospective data in the adjuvant setting.

Follow-Up

The optimal patient follow-up strategies after surgery or during and after adjuvant imatinib are unknown. Periodic imaging of the abdomen is likely beneficial because detecting GIST recurrences when tumors are small may result in a longer time to imatinib resistance compared with bulky recurrences. A reasonable strategy may be to image the abdomen at 6- to 12-month intervals for the first 10 years after surgery. More frequent imaging at 3- or 4-month intervals may be considered

for 2 years after stopping adjuvant imatinib because many GISTs recur during this time period.⁴⁴

ADVANCED GIST

TKIs

Before the availability of TKIs, chemotherapy was the primary treatment modality for advanced GIST, but responses were few and the median survival was only approximately 1 year.^{46,47} In phase I evaluation of imatinib administered at 400 mg daily to 500 mg twice daily, a dose of 400 mg twice daily was established as the maximum-tolerated dose (MTD).⁴⁸ The complete and partial response rates in the phase I and II studies with the 400-mg daily dose ranged from 40% to 74%, which was similar to the rates of 45% to 52% with the MTD but with less toxicity.^{48,49} The pivotal phase III European Organisation for Research and Treatment of Cancer 62005^{50,51} and S0033 trials⁵² compared imatinib 400 mg once daily with 400 mg twice daily (Table 5). Both trials confirmed the meaningful clinical benefit of imatinib 400 mg once daily, first reported in the B2222 study,^{49,55} with complete response rates of 3% to 6%, partial response rates of 45% to 48%, and stable disease (SD) rates of 26% to 32%. No difference was noted in OS between the 400-mg and 800-mg doses, establishing 400 mg once daily as the standard dose. OS ranged from 47 to 55 months, a substantial improvement compared with chemotherapy.

In the joint analysis of the S0033 and European Organisation for Research and Treatment of Cancer 62005 trials, progression-free survival (PFS) was longer in the imatinib 400 mg twice daily arm.⁵⁶ The improvement was a result of *KIT* exon 9 mutated

Table 4. Common Adverse Effects of the Tyrosine Kinase Inhibitors Approved for the Treatment of GIST and Their Management

Adverse Event and TKI (imatinib, sunitinib, or regorafenib)	Management
Fatigue Imatinib Sunitinib and regorafenib	Assess anemia Assess anemia and thyroid function; consider assessing cardiac function
Nausea and vomiting Imatinib Sunitinib and regorafenib	Take with low-fat food; antiemetics; consider administration twice daily Antiemetics
Diarrhea: seen with all three TKIs	Antidiarrheals; consider dose reduction if not manageable with medications
Skin toxicities Rash: Imatinib Hand-foot syndrome: sunitinib and regorafenib	Benadryl for itching, topical corticosteroids; often resolves without treatment Before treatment: minimize callouses On treatment: apply moisturizing cream; if severe, apply a cream with urea; minimize friction to hands and feet; consider dose reduction if not manageable with medications Stop treatment
Steven-Johnson syndrome: rare, described with all three agents Edema, periorbital and extremity: common with imatinib, rare with sunitinib or regorafenib	Monitor weight with starting therapy; avoid excessive salt intake; diuretics; consider dose reduction if not manageable with medications
Muscle cramps: seen with all three agents; common with imatinib	Check electrolytes: potassium, magnesium, phosphate; ensure good hydration, warm clothing
Hypertension: sunitinib and regorafenib.	Monitor blood pressure; initiate or increase antihypertensive therapy for increased blood pressure; consider dose reduction if not manageable with medications
Decreased WBC count: seen with all three agents	Monitor CBC; assess potential drug interactions; consider dose reduction if there is significant neutropenia
Anemia: seen with all three agents	Macrocytic anemia secondary to TKIs; check blood vitamin B ₁₂ , folate, and iron panel for reversible causes
Decreased platelet count: seen with all three agents, uncommon with imatinib	Monitor CBC; assess for potential interactions; consider dose reduction if there is significant neutropenia
Abnormal aminotransferases: seen with all three agents	Monitor liver function tests; consider a course of corticosteroids for imatinib-induced hepatitis
Hypothyroidism: seen with all three agents, less common with imatinib unless already on thyroid replacement therapy	Monitor thyroid functions tests and institute or increase dosage of replacement therapy

Abbreviations: GIST, GI stromal tumor; TKI, tyrosine kinase inhibitor.

tumors treated at the higher dose.⁴⁵ Therefore, patients with exon 9 mutations should receive imatinib 400 mg twice daily if tolerated.⁵⁷ Starting imatinib at 400 mg once daily and increasing the dose up to 400 mg twice daily decreases adverse effects of higher-dose therapy.⁵⁷

The impact of stopping therapy after 1, 3, or 5 years in patients whose tumors had responded or stabilized on imatinib was tested in the BFR14 trial.^{58,59} Patients randomly assigned to stop therapy had shorter PFS compared with those who remained on treatment, with a suggestion that the time to progression increases with longer time on imatinib before discontinuation. Fortunately, the majority of patients achieved disease control again after restarting imatinib, and OS was no different between the groups. These data support uninterrupted treatment with imatinib.

Sunitinib is a multitargeted TKI with activity against KIT, PDGFR, VEGFR, and FLT-1/KDR. Phase I studies identified 50 mg daily for 28 days with 14 days of rest as the MTD.⁵³ Response data in an early trial⁵³ and the phase III placebo-controlled trial⁶⁰ demonstrated no complete responses and partial response rates of 7% to 13%. In the phase III trial, both the median PFS and OS were longer in the sunitinib group than in the placebo group despite the study crossover design⁶⁰ (Table 5). Disease symptoms and metabolic activity by positron emission tomography may return on the 2-week treatment break.⁵³ To avoid recurrent tumor symptoms during the 2-week break and to manage adverse effects, a phase II trial of continuous daily dosing starting at 37.5 mg was conducted.⁶¹ Given that the safety, tolerability, and response rates were similar to those with the 4 weeks on/2 weeks off regimen, continuous administration is a valid option.

In a study of imatinib-resistant or -intolerant GIST, response to sunitinib was obtained in seven (37%) of 19 patients with *KIT* exon 9 mutations and in two (5%) of 44 patients with exon 11 mutation.⁶² One of the 10 patients with *KIT* exon 11 mutation and a second mutation in exon 13 or 14 responded, and six patients had SD for ≥ 6 months, whereas none of the 10 patients with a second mutation in *KIT* exon 17 benefitted, consistent with in vitro findings. Treatment with sunitinib in five pediatric patients with *KIT/PDGFR* mutant-negative tumors resulted in one patient with partial response and four patients with SD.⁶³

Regorafenib, a multitargeted TKI targeting VEGFR1-3, TEK, KIT, RET, RAF1, BRAF, PDGFR, and FGFR, was approved for treatment of patients with GIST previously treated with imatinib and sunitinib.^{54,64} Regorafenib is dosed at 160 mg daily for 21 days with 7 days off, repeated every 28 days. The phase III GIST-Regorafenib in Progressive Disease (GRID) trial was a randomized placebo-controlled study with crossover to regorafenib at the time of disease progression on placebo (Table 5).⁶⁴ The median PFS was 4 months longer with regorafenib, but no difference in OS was observed, probably because 85% of the patients on placebo crossed over to active therapy. The response rates were low (4.5% for regorafenib and 1.5% for placebo). As with sunitinib, regorafenib benefited patients with primary tumor *KIT* exon 11 or exon 9 mutations, with in vitro data showing activity for some secondary mutations in exon 17; two patients with SDH-deficient GIST demonstrated partial response, with four others achieving SD.⁵⁴

Table 5. Randomized Trials That Led to US Food and Drug Administration Approval of an Agent for Advanced GI Stromal Tumors

Study	Agent and Line of Treatment	Allocation Groups	Main Results	
			Median PFS	Median OS
B2222 ^{48,52}	Imatinib, first line	Imatinib 400 v 600 mg	20 v 26 months ($P = .371$)	57 v 57 months; HR, 0.87 ($P = .551$).
S0033 ⁵¹	Imatinib, first line	Imatinib 400 mg daily v 400 mg twice daily	18 v 20 months ($P = .13$)	55 v 51 months; HR, 0.98; 95% CI, 0.79 to 1.21 ($P = .83$).
EORTC ^{49,50}	Imatinib, first line	Imatinib 400 mg daily v 400 mg twice daily	1.7 v 2.0 years; HR, 0.91; 95% CI, 0.79 to 1.04 ($P = .18$)	3.9 years in both arms; HR, 0.93; 95% CI, 0.80 to 1.07 ($P = .31$)
NCT00075218 ⁵³	Sunitinib, second line	Sunitinib 50 mg daily for 4 weeks on, 2 weeks off v placebo	27.3 v 6.4 weeks ($P < .001$)	HR, 0.49; 95% CI, 0.29 to 0.83 ($P = .007$).
GRID ⁵⁴ (NCT01271712)	Regorafenib, third line	Regorafenib 160 mg daily for 3 weeks on, 1 week off v placebo	4.8 v 0.9 months; HR, 0.27; 95% CI, 0.19 to 0.39 ($P < .001$)	HR, 0.77; 95% CI, 0.42 to 1.41 ($P = .199$, crossover design)

Abbreviations: EORTC, European Organisation for Research and Treatment of Cancer; GRID, GI Stromal Tumor–Regorafenib in Progressive Disease; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.

Mutational Testing in Advanced Disease

Tumor tissue mutation analysis is indicated when it is not available from the primary tumor. In refractory disease, a single biopsy under-represents the potential tumor heterogeneity. Circulating plasma DNA may be more representative of the spectrum of clones with variable secondary mutations, but to date, it is rarely available for routine management of advanced disease.

Surgical Management

The role of metastasectomy in patients whose disease is controlled with imatinib is controversial.⁶⁵ The extent of tumor bulk was identified as a factor impacting PFS on imatinib.⁶⁶ This raises the possibility that debulking of metastatic disease after an initial stabilization or response to imatinib may help in prolonging disease control by preventing emergence of resistant clones. Prospective randomized trials studying the benefit of debulking surgery unfortunately failed to accrue enough patients, but the results of one small randomized study suggest that resection of the residual disease on imatinib treatment improves OS.⁶⁷ A retrospective report demonstrated longer OS with debulking that achieved R0 or R1 sections compared with those where surgery left gross tumor behind.⁶⁸ Resection of a focal progressing lesion may allow the use of imatinib to be prolonged, whereas surgery for diffuse progression does not.⁶⁵

The role of metastasis surgery in patients on sunitinib or regorafenib is unclear, except for patients who require emergency surgery.⁶⁶ These agents target VEGFR and require a longer period off-therapy to undergo surgery safely and achieve wound closure; this contrasts with imatinib, which may be taken the day before surgery and resumed when a patient is able to eat. Patients with progressive disease on sunitinib and regorafenib also likely have multiple resistant clones and greater tumor bulk, and therefore, the potential benefits versus risks of surgery need to be carefully considered.

Other Palliative Approaches

Although not used in the primary management of GIST, radiotherapy plays a role in palliation and may stabilize single

progressing liver or intra-abdominal lesions for several months.⁶⁹ In addition, local interventional modalities, such as embolization or radiofrequency ablation, are considerations for liver metastases. For patients with progressive GIST after all standard therapies, discontinuing TKI therapy is not recommended given the rapid rate of progression documented after discontinuation.^{60,64} Restarting imatinib after progression on at least prior imatinib and sunitinib increased PFS slightly from 0.9 to 1.8 months compared with best supportive care ($P = .005$).⁷⁰ In a small randomized trial of patients whose GIST was resistant to imatinib and sunitinib, pazopanib plus best supportive care improved PFS compared with best supportive care alone (median, 3.4 v 2.3 months, respectively; $P = .03$).⁷¹

In conclusion, the management of GIST changed radically with the understanding of its molecular drivers. Although first described as having oncogenic mutations in *KIT*, we now know that *PDGFRA* mutations and *SDH* deficiency by mutation and methylation each account for a subset of GISTs, with additional drivers. TKI therapy has greatly impacted survival in patients with GIST, increasing the life expectancy from about 1 year to 5 years in the advanced setting; adjuvant imatinib for 3 years also improves survival. These advances underscore the need for molecular testing of GIST, recognizing that some patients (eg, those with *PDGFRA* D842V mutation) do not respond to the present standard therapies. Patients with *SDH* mutation or hypermethylation require specialized surgical considerations but may benefit from VEGFR-targeted agents.

Patients with advanced disease that has progressed on standard therapies often are clinically well and candidates for additional therapy. Trials continue testing novel TKIs and combination therapies that exploit resistance pathways. The role of immunotherapy is yet to be defined in GIST but includes use of antibodies targeting tumor or immune pathways and use of chimeric antigen receptor T cells. Finally, the role of serum surveillance is developing and will potentially better define disease progression with molecular information to target emerging resistance clones.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Gastrointestinal Stromal Tumors

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