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The GIST of Advances in Treatment of Advanced Gastrointestinal Stromal Tumor

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overview

Gastrointestinal stromal tumor (GIST) is the most common malignant neoplasm of mesenchymal origin and a compelling clinical and biologic model for the rational development of molecularly targeted agents. This is because the majority of GISTs are driven by gain-of-function mutations in KIT or PDGFRA receptor tyrosine kinases. Specific GIST mutations circumscribe well-defined molecular subgroups that must be determined during the diagnostic work-up to guide clinical management, including therapeutic decisions. Surgery is the cornerstone treatment in localized disease and can also be clinically relevant in the metastatic setting. The correct combination and sequence of targeted agents and surgical procedures improves outcomes for patients with GIST and should be discussed individually within multidisciplinary expert teams. All currently approved agents for the treatment of GIST are based on orally available tyrosine kinase inhibitors targeting KIT and PDGFRA oncogenic activation. Although first-line imatinib achieves remarkable prolonged disease control, the benefit of subsequent lines of treatment is more modest. Novel therapeutic strategies focus on overcoming the heterogeneity of KIT or PDGFRA secondary mutations and providing more potent inhibition of specific challenging mutations. This article reviews the current understanding and treatment of GIST, with an emphasis on recent advances.

In this review, we first address the state-of-the-art diagnostic work-up of gastrointestinal stromal tumor (GIST), with a special focus on ancillary immunohistochemical and molecular genetic testing that enables subclassification into genomic subtypes and informed treatment decisions. We then provide an update on shifting indications for surgery in the management of locally advanced and metastatic GIST. Finally, we explore in detail the role of newer-generation tyrosine kinase inhibitors (TKIs), such as avapritinib and ripretinib, for the management of locally advanced and metastatic GIST.

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UPDATE ON THE ROLE OF ANCILLARY PATHOLOGIC TECHNIQUES IN OPTIMIZING TARGETED THERAPY FOR GASTROINTESTINAL STROMAL TUMOR

Gastrointestinal Stromal Tumor Origin, Epidemiology, and Clinical Presentation

Gastrointestinal stromal tumor is the most common neoplasm of mesenchymal origin,[1] with an annual incidence of approximately 6,000 cases in the United States. Most cases are driven by oncogenic *KIT*[2] or *PDGFRA*[3] tyrosine kinase gain-of-function mutations; a subset of cases is driven by alternate mechanisms, which include inactivation of *NF1*[4] or genes encoding succinate dehydrogenase (SDH) subunits[5] (Fig. 1).[6] Although most GISTs occur sporadically among middle-aged adults with a median age of 60 to 65,[1] a minority can be found among children and young adults, where they may arise as part of the nonhereditary Carney triad[7] (including paraganglioma and pulmonary chondroma) or autosomal-dominant Carney-Stratakis syndrome (together with paragongliomas) with predisposing germline *SDH* subunit mutations.[8,9] Despite propensity for multifocality and lymphatic spread, SDH-deficient GISTs usually follow a more indolent clinical course compared to *KIT/PDGFRA*-mutant GIST.[10]

Since their recognition as a distinct type of "gastrointestinal stromal tumor"[11] and the discovery of their origin from the interstitial cell of Cajal lineage[12] in the 1990s, advances have been made that have substantially shaped the diagnostic work-up, refined subclassification and risk assessment, and improved clinical management. A morphology-based diagnosis with immunohistochemical testing in conjunction with genetic evaluation of molecular markers is now considered the gold standard for the diagnostic work-up of GIST. Here, we provide an overview of the histopathologic diagnosis of GIST and key biomarkers that aid in the distinction of GIST genomic subtypes with crucial implications for prognosis and therapy.

Histopathologic Diagnosis of Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumors usually present as a sharply demarcated submucosal or subserosal mass in the stomach (60%) and small intestine (25%), and they less commonly arise in the colon, rectum, esophagus, mesentery, and omentum.[13] They show either spindled (70%), epithelioid (20%), or mixed (10%) cytomorphology.[14] Neurofibromatosis type 1–associated GISTs have a predilection for intestinal location, spindled morphology, and multifocality,[4] whereas SDH-deficient GISTs are nearly always located in the stomach, display a unique multilobular or plexiform architecture, and show either epithelioid or mixed morphology but virtually never pure spindle-cell morphology.[15]

The Role of Immunohistochemistry

KIT is expressed in 95% of GISTs, DOG-1 in 98%, PDGFRA in 80%, and CD34 in 70% to 80%, and expression of SDHA and SDHB is generally retained, with the exception of SDH-deficient GISTs[14,16] (Fig. 2). The latter are characterized by loss-of-function mutations of *SDHA, SDHB, SDHC*, or *SDHD* (accounting for approximately 80% of cases) or *SDHC* promoter methylation (SDHC "epimutated," accounting for approximately 20% of cases),

all leading to the inactivation of the SDH complex. Loss of function of any of these SDH subunits leads to loss of SDHB expression by immunohistochemistry,[17] which is a useful marker for SDH-deficient GIST in the routine diagnostic setting (Fig. 2). Additional loss of SDHA expression by immunohistochemistry is observed in the subset of GISTs with *SDHA*-inactivating mutations.[15] Although the mechanism is unknown, SDH-deficient GISTs express activated KIT[17] (Fig. 2).

Risk Stratification of Localized Primary Gastrointestinal Stromal Tumor

Approximately 30% of GISTs develop metastases. Thus, accurate prediction of the metastatic potential based on histopathologic evaluation of resection specimens is crucial to identifying the subset of patients with localized GISTs who have a high risk of relapse, as they ultimately would benefit from adjuvant TKI imatinib. The first stratification system was introduced in 2002 by Fletcher et al[18] and relies on tumor size and mitotic rate to classify GISTs into very low–, low-, intermediate-, and high-risk categories.

In 2006, Miettinen and Lasota[19] introduced a modified risk stratification scheme that includes anatomic site as a third independent factor and has led to the Armed Forces Institute of Pathology criteria and the National Comprehensive Cancer Network risk criteria,[20] reliably predicting risk of progression in GIST (Tables 1 and 2). However, these conventional risk stratification approaches do not apply to the distinct subtype of SDH-deficient GISTs, where they have been shown to fail to predict disease progression.[10] Specifically, 60% to 80% of patients with SDH-deficient GISTs developed distant metastases, regardless of risk category, and stratification systems that more accurately predict risk of progression and survival for patients with SDH-deficient GIST remain to be developed.[10]

Recurrent Molecular Alterations In Gastrointestinal Stromal Tumor and Ancillary Genetic Testing

Approximately 85% of GISTs harbor mutually exclusive gain-of-function mutations of the *KIT* or *PDGFRA* genes located on 4q12 encoding type III receptor tyrosine kinases, which lead to constitutive activation of the PI3K/AKT/mTOR and RAS/MAPK kinase signaling pathways. Primary activating *KIT* mutations most frequently involve the intracellular juxtamembrane domain (exon 11) or the extracellular dimerization domain (exon 9), with only rare cases involving the adenosine triphosphate binding domain (exon 13) or activation loop (exon 17).[2] Primary *PDGFRA* mutations are most common in the activation loop (exon 18), particularly codon 842, and less frequently involve the juxtamembrane domain (exon 12) or the adenosine triphosphate binding domain (exon 14). It has been shown that the specific type of mutation (particularly, *KIT* exon 9 vs. 11; and *KIT* exon 11 point mutation vs. deletion) predicts sensitivity to therapeutic KIT inhibition with imatinib,[21,22] as will be further discussed in detail. Certain kinase mutations, such as *PDGFRA* D842V, are imatinib-resistant but may respond to newer-generation TKIs such as avapritinib.[23] Alternate drivers in *KIT/PDGFRA* wild-type GISTs include mutations of *NF1, PIK3CA, BRAF*, or *RAS* or fusions affecting NTRK3, which constitutively activate the same downstream signaling pathways that are usually activated by KIT or PDGFRA.[24] Based on these insights, identification of the underlying type of mutation can be crucial for making the

appropriate treatment decisions for patients with localized primary GISTs with a high (or intermediate) risk of progression. As per the National Comprehensive Cancer Network[25] guidelines, genotyping should be performed when medical treatment is being considered. Molecular genetic testing in GIST is now typically performed using targeted next-generation sequencing approaches, which can identify activating *KIT* or *PDGFRA* tyrosine kinase mutations but also alternate drivers (Fig. 3) in the subset of GISTs that are wild type for *KIT* and *PDGFRA*, which may require different therapeutic strategies.

Disease progression during TKI therapy generally results from the emergence of secondary *KIT* or *PDGFRA* mutations. Such secondary mutations typically localize to the *KIT* adenosine triphosphate binding pocket (exons 13 to 14) or activation loop (exons 17 to 18) domains[26] or to the *PDGFRA* adenosine triphosphate binding pocket (exons 13, 14, and 15).[24]

Although single cases of putative GISTs have been reported to harbor *NTRK* gene rearrangements,[27,28] such cases seem to be exceptionally rare. A recent detailed clinicopathological, immunophenotypic, and molecular analysis of eight *NTRK*-rearranged mesenchymal tumors of the gastrointestinal tract suggests that these tumors are clinically and morphologically heterogeneous, and few, if any, appear related to GIST.[29] Moreover, false-positive staining with pan-TRK immunohistochemical antibodies can occur in non–*NTRK*-fused tumors, specifically those with neural and smooth muscle differentiation such as GISTs,[30] suggesting that routine screening of GISTs for NTRK abnormalities does not seem indicated. Therefore, it would be appropriate to use massive parallel sequencing panels to identify NTRK fusions in GIST wild type for KIT and PDGFRA, and SDHB immunohistochemical stain–conserved.[31]

In addition to the initiating KIT or PDGFRA driver mutations, which are detectable in subcentimeter forms of GISTs (so-called “microscopic [or micro-] GISTs”), stepwise GIST progression to clinically relevant tumors is driven by a sequence of additional aberrations that include chromosomal deletion of 14q inactivating the *MAX* tumor suppressor leading to p16 transcriptional inactivation,[32] 22q deletion inactivating the mTORC1 repressor *DEPDC5*,[33] 1p deletion,[34] cell cycle regulator mutations,[35] 15q deletion,[34] and inactivation of *DMD* on the X chromosome encoding dystrophin and fostering metastatic spread.[36]

Succinate dehydrogenase–deficient GISTs generally lack large-scale genomic aberrations, but they may show occasional 1q deletion, which can apparently target *SDHC*.[7,9] Although identification of these GIST-typical chromosomal aberrations by molecular genetic or cytogenetics methods is of no immediate therapeutic relevance, it may help confirm the diagnosis and provide additional insights for a refined assessment of the risk of progression.[34,37]

SHIFTING INDICATIONS FOR SURGERY IN THE MANAGEMENT OF LOCALLY ADVANCED AND METASTATIC GASTROINTESTINAL STROMAL TUMOR

The role of surgery in primary and metastatic GIST has evolved considerably over the past 20 years. Here, we highlight the management principles and the results of surgery that we have previously reviewed in detail elsewhere.[38,39] Multidisciplinary evaluation that includes surgical oncologists, medical oncologists, pathologists, and radiologists is necessary for most patients, as the type, sequence, and duration of therapies are critical to optimizing outcome. Although there is no doubt that imatinib has had a considerable impact in the adjuvant and metastatic settings in GIST clinical trials, the benefit was also recently demonstrated in a large, retrospective single-institution experience.[40]

Surgery for Primary Gastrointestinal Stromal Tumor

Establishing the diagnosis of GIST can be challenging with some patients, particularly those with small tumors. Computed tomography with oral and intravenous contrast of the abdomen and pelvis typically reveals a well-circumscribed, vascular mass that is often exophytic to the site of origin. MRI is particularly helpful in rectal GISTs but is less sensitive in demonstrating peritoneal metastasis. ^{18}F-fluorodeoxyglucose PET scans are essentially never required and should be reserved for research studies. Histologic confirmation is recommended but occasionally cannot be achieved. Endoscopic ultrasound-guided biopsy may not provide sufficient tissue to confirm the diagnosis of GIST, in which case clinical suspicion guides the decision to perform surgery. Percutaneous biopsy is no longer commonly used and carries the risk of bleeding and tumor dissemination. Mutation analysis on biopsy specimens is not performed routinely at most centers, often because there is an insufficient amount of tissue.

The treatment algorithm for primary GIST without metastasis is shown in Fig. 4. Gastric tumors less than 2 cm may be observed. Certain GISTs up to 8 cm in size can be removed laparoscopically.[41] Some GISTs originate in technically challenging areas, such as the gastroesophageal junction, duodenum,[42] or rectum.[43] Neoadjuvant therapy is often indicated for such tumors positioned in difficult locations, those that are very large (> 10 cm), or those that require an extensive amount of normal tissue to be removed. If neoadjuvant imatinib is initiated, our practice has been to repeat a contrast CT at 3 weeks to evaluate reductions in tumor enhancement and density, which would indicate a response. If the tumor has responded, we generally obtain the next imaging at 4 months and usually operate between 6 and 9 months, after which there is generally little additional tumor shrinkage. If the tumor has not responded, then the tumor may be imatinib-insensitive because it contains a *PDGFRA* D842V mutation or lacks a *KIT* or *PDGFRA* mutation altogether. Although there have been a few trials showing the safety of neoadjuvant therapy,[44,45] an improvement in the rate of RO resection or overall survival has not been proven. Nevertheless, the decreased vascularity and size of the tumor facilitates resection and allows for preservation of normal tissue.

Before the advent of TKIs, we reported that the overall survival of patients with primary GIST after surgical resection was 54% at 5 years.[46] However, we now know that 70% of patients with a GIST of 3 cm or greater will be cured by surgery alone, based on the placebo arm of the phase III American College of Surgeons Oncology Group (ACOSOG) Z9001 trial.[47] This trial established that 1 year of adjuvant imatinib increases recurrence-free survival, and led to approval of adjuvant imatinib by the U.S. Food and Drug Administration and the European Medicines Agency.[47,48] Importantly, the rate of tumor recurrence increased substantially after imatinib was stopped following the first year of therapy. Strikingly, the placebo and imatinib recurrence-free survival curves came together after prolonged patient follow-up, indicating that adjuvant imatinib is not curative in the presence of residual, microscopic disease. The phase III Scandinavian SSG XVIII trial showed that recurrence-free survival was greater after 3 years of adjuvant imatinib than after just 1 year,[49] and overall survival was also increased.[50,51] The phase II PERSIST-5 trial (Postresection Evaluation of Recurrence-free Survival for Gastrointestinal Stromal Tumors With 5 Years of Adjuvant Imatinib) demonstrated that no patient with an imatinib-sensitive mutation developed tumor recurrence while taking the drug.[52] Of note, however, therapy was discontinued for half of patients, mostly owing to patient preference.

Prognosis after resection of a primary, localized GIST is a function of tumor size, location, and mitotic rate. A variety of prognostic tools exist. Miettinen and Lasota[19] incorporated tumor mitotic rate, size, and location (the stomach is more favorable than the small intestine or rectum) and is the basis for the American Joint Commission on Cancer staging system.[53] Subsequently, we created an online nomogram to estimate 2- and 5-year recurrence-free survival after resection (https://www.mskcc.org/nomograms/gastrointestinal),[54] which has been validated by others.[55,56] Tumor mutation status is another important variable, as patients with a *KIT* exon 11 deletion, particularly involving amino acids 557 and 558, fare worse in the absence of imatinib.[57,58] The current recommendation is 3 years of adjuvant imatinib therapy for patients at moderate to high risk of recurrence, although chronic therapy (> 5 years) may be indicated for certain patients, such as those with a high mitotic rate or tumor rupture before or during operation. When neoadjuvant imatinib is used, imatinib is generally continued postoperatively, especially since the pretreatment mitotic rate may not be known. Adjuvant trials using other TKIs have not yet been performed.

Surgery for Metastatic Gastrointestinal Stromal Tumor

The most frequent sites of recurrence in GIST are the liver and peritoneum. Some patients have disease confined to one of these locations. Bone metastases are uncommon and lung metastases are rare. Surgery is seldom the first line of therapy for metastatic GIST. Uncontrollable bleeding, severe pain, and intestinal obstruction occur rarely but are indications for surgery. All other patients are treated initially with a TKI if their tumor has a KIT or PDGFRA mutation.

Multiple studies have shown that surgery for metastatic GIST is safe.[59,60] However, the efficacy of surgery in prolonging overall survival is unproven. There have been multiple attempts to conduct a randomized clinical trial of surgery for patients with imatinib-responsive, metastatic GIST. Endeavors in the United States, Europe, and China have failed.

The rationale for surgery is that imatinib has a complete response rate of less than 3% and a median progression-free survival (PFS) of less than 2 years.[61] In addition, cytoreduction may reduce the number of preexisting resistant clones, thereby delaying tumor progression. For patients with limited disease burden, there is even curative potential as long as TKI therapy is continued after surgery. All of these points should be covered in helping a patient to decide whether to undergo resection of metastatic GIST.

Analogous to our approach to neoadjuvant therapy for patients with primary GIST, we assess early imatinib response in metastatic GIST with a contrast CT scan at 3 weeks and generally operate at 6 to 9 months of treatment, after which the operation is unlikely to be altered. Surgery is considered if there is a possibility of treating all disease that is identifiable by radiologic evaluation. In terms of liver metastases, this may include a combination of resection and ablation. Unlike in the liver, it is common to discover additional tumors in the peritoneal cavity at operation, and the patient should be advised of this preoperatively. Peritoneal tumors usually are situated on top of structures such as the intestine, omentum or other fat, or undersurface of the abdominal wall and can often be removed with minimal sacrifice of normal tissue.

The combined results of surgical resection in metastatic GIST at two institutions are shown in Fig. 5. As expected, patients who had stable disease or disease that was still responding to TKI therapy had the longest PFS (median 30–36 months).[62] However, there is considerable lead time bias in this analysis of the different patient groups, which precludes definitive conclusions. What is clear, though, is that surgery for multifocal resistance is of uncertain value. Some patients with metastatic GIST will have disease progression initially limited to one tumor (i.e., unifocal progression). In the past, surgery was often considered for unifocal progression, but now there are multiple TKIs available. Nonetheless, patients who had surgery for unifocal disease achieved a median PFS of 11 months, whereas those who received second-line agent sunitinib had a median PFS of 6.8 months.[63] Interestingly, the mitotic rate of the resected metastases correlates with subsequent survival, emphasizing that mitotic rate also signifies tumor biology in the metastatic setting after therapy.[62]

After surgical resection of metastatic GIST, a TKI is continued because progression is highly likely, given that recurrence almost always occurred after the resection of metastatic disease before the advent of TKIs[64] and we know that adjuvant imatinib is not even curative. For patients who were not experiencing tumor progression, the TKI that was used preoperatively is usually continued. For those with a TKI-resistant GIST, there are no clear guidelines to choose the postoperative TKI. In this situation, mutation analysis is often performed but usually only one tumor is profiled. It has been shown that individual metastases may develop different secondary mutations[65] and the same likely applies to residual foci of microscopic metastatic disease.

Overall, surgery plays a vital role in primary GIST because it leads to cure for more than two-thirds of patients. Resection likely improves outcomes for selected patients with metastatic GIST, particularly those whose tumors are responsive to TKI therapy. Additional approaches are needed to increase the rate of cure after surgical resection of primary GIST and prolong PFS after cytoreduction in metastatic GIST.

NOVEL TYROSINE KINASE INHIBITORS FOR THE MANAGEMENT OF LOCALLY ADVANCED AND METASTATIC GASTROINTESTINAL STROMAL TUMOR

Five therapies have received regulatory approval for the treatment of unresectable and/or metastatic GIST, which represents a remarkable achievement for a rare neoplasm. This is possible because of the exquisite reliance of GIST cells on KIT or PDGFRA oncogenic signaling. Accordingly, clinical drug development in GIST during the past decades has successfully exploited kinase inhibition with specific small molecule inhibitors.

Treatment-Naive, Locally Advanced, or Metastatic Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumor has a typical pattern of metastatic spread that commonly involves the liver and the peritoneum, whereas other locations are rarely involved. Newly diagnosed locally advanced or metastatic GISTs are treated with 400 mg daily of first-line imatinib, a TKI with activity against mutant KIT and PDGFRA receptor tyrosine kinases.[66] This treatment decision will be considered if surgery is postponed or rejected by a multidisciplinary sarcoma board, and molecular genetic testing confirms the presence of an imatinib-sensitive mutation. With the exception of some specific molecular subtypes (*KIT/PDGFRA* wild type and *PDGFRA* D842V mutant), most GISTs will respond to imatinib treatment, with an average benefit between 20 and 24 months of median PFS, although it is likely that this figure is even higher with the contemporary treatment of these patients.[63,66–69]

KIT/PDGFRA genotyping also provides valuable information for the treatment of these patients in the metastatic setting. Patients whose tumor has a primary *KIT* exon 11 mutation are notably more likely to achieve a complete or a partial response and longer PFS than patients with a *KIT* exon 9 mutation or no kinase mutations detected.[21] Likewise, the subset of patients with GIST with a primary *KIT* exon 9 mutation particularly benefit from a double dose of imatinib (400 mg of imatinib twice daily).[70] Remarkably, and unlike other tumor types with similar biologic patterns, there is a meaningful subgroup of patients with metastatic GIST exhibiting exceptional long-term response to imatinib, with one-third reaching disease control for 5 years or more and 7% to 9% with disease control of 10 years or more.[71,72]

Challenges in the Treatment of Imatinib-Resistant Gastrointestinal Stromal Tumor

The main mechanism of imatinib failure involves the emergence of resistant subpopulations harboring heterogeneous secondary mutations in *KIT*, which occurs for up to 90% of patients with GIST[26,73] (Fig. 6). These mutations are not random and cluster in two hotspot regions of the KIT kinase domain: the adenosine triphosphate binding pocket (encoded by exons 13 and 14) and the activation loop (encoded by exons 17 and 18). Hence, drug development during the past decades was focused on multikinase inhibitors, aiming to broader the spectrum of KIT kinase mutations effectively inhibited. As a result, sunitinib in 2006 and regorafenib in 2013 received regulatory approval for the treatment of patients with metastatic GIST in the second and third line, respectively.[63,67] This benefit, however,

is modest compared with imatinib, with median PFS of approximately 5 months and an overall response rate of less than 10% (Table 3). These outcomes are largely paralleled by several other active TKIs investigated mostly in single-arm phase II studies (Table 4).[74] We and others have demonstrated that all TKIs approved or studied clinically in GIST are active against only a subset of the *KIT* secondary mutational spectrum, which in the context of intratumoral heterogeneity constitutes the main determinant for treatment failure in imatinib-resistant GIST.[75–77]

The predominance of KIT reactivation as a result of secondary resistance mutations in *KIT* after imatinib failure firmly supports the prominent role of KIT or PDGFRA as the critical drivers throughout the course of the disease. Therefore, novel therapeutic strategies will focus on targeting KIT and PDGFRA receptors but will also address the heterogeneity of resistant mutations and specific multiresistant mutants.

Ripretinib, a Switch-Control Tyrosine Kinase Inhibitor for the Treatment of Imatinib-Resistant Gastrointestinal Stromal Tumor

Ripretinib was specifically designed to inhibit the two switch-control regions that tightly regulate the transition between the inactive and the active conformation of the kinase: the inhibitory pocket at the juxtamembrane domain (encoded by *KIT* exon 11 or *PDGFRA* exon 12) and the activating switch in the activation loop (*KIT* exons 17 and 18, and *PDGFRA* exons 18 and 19). Thus, the antagonization of the active state of the kinase and its stabilization into its inactive conformation allows ripretinib to target more broadly the heterogeneity of primary and secondary mutations in *KIT* and *PDGFRA*.[94]

After a rapid early clinical development, ripretinib was eventually studied in an international, multicenter, double-blind, phase III trial that randomly assigned 129 patients with metastatic GIST 2:1 to either ripretinib (85 patients) or placebo (44 patients) after disease progression to at least the three approved therapies (imatinib, sunitinib, and regorafenib).[68] The trial met its primary endpoint, as ripretinib significantly improved the median PFS compared with placebo from 1.0 to 6.3 months (HR, 0.15; 95% CI, 0.09–0.25; $p < .0001$). Ripretinib activity was largely achieved through disease stabilization, with 47% of the patients remaining stable at 12 weeks, and eight (9.5%) of the 85 evaluable patients receiving ripretinib obtaining partial response. Nineteen percent of patients demonstrated disease progression in the first radiologic assessment (Table 3). Ripretinib was well tolerated overall, with side effects that were commonly low-grade and manageable. The safety profile was consistent with a TKI with KIT/PDGFRA inhibitory activity; the most common treatment-related or treatment-emergent adverse events (≥ 20%) were alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia, and diarrhea. Five patients (6%) receiving ripretinib required a dose reduction and only four patients (5%) had treatment-related adverse events that led to definitive study drug discontinuation. Together, the ripretinib safety profile appears to be more favorable than that from previous TKIs approved after a lack of response to imatinib. Based on these data, the U.S. Food and Drug Administration and the European Medicines Agency approved 150 mg of ripretinib daily for the treatment of patients with GIST who have received prior treatment with three or more kinase inhibitors, including imatinib.

How does GIST disease progress in patients treated with a broad KIT/PDGFRA inhibitor such as ripretinib? It is critical to answer this question to advance novel therapeutic strategies in the near future. It is conceivable that broader kinase inhibition can lead to KIT-independent mechanisms of progression.[95,96] However, preliminary data from recent studies may argue against this and suggest that particular KIT or PDGFRA substitutions can be challenging to fully inhibit, such as the multiresistant GIST *PDGFRA* D842V (and its homologous *KIT* D816V) (Fig. 6).[24] Likewise, although ripretinib benefits all *KIT*-mutant GISTs, the PFS curve with patients with GIST harboring any *KIT* exon 17 mutation appears to be more favorable than mutations emerging in the exon 13.[97] Finally, ripretinib-induced cell death is seemingly insufficient,[98] as the response rate achieved is below the 10% bar and thus not different from other TKIs after imatinib failure.

Finally, it is also worth noting that this trial uncovered a highly aggressive nature of GIST at this stage of the disease, which should have clinical implications: the median overall survival was 15.1 months for patients treated in the ripretinib arm and 11.6 months for patients with placebo with crossover (29 patients).[68] However, the median overall survival for the 15 patients who did not cross over was 1.8 months. These findings should alert clinicians to minimize as much as possible the time without TKI treatment in this patient population.

Avapritinib for the Treatment of Patients With *PDGFRA* D842V–Mutant Gastrointestinal Stromal Tumor

Most primary *PDGFRA* gain-of-function mutations involve the substitution of aspartic acid for valine at codon 842 in exon 18 of *PDGFRA* (D842V). Importantly, the *PDGFRA* D842V mutation (approximately 5% of all GISTs) together with its homologous substitution in *KIT* (D816V)—an uncommon secondary mutation—are intrinsically resistant to all known therapies.[99,100] This occurs because all TKIs targeting KIT and PDGFRA are type II inhibitors and are therefore uncapable of binding to the active conformation strongly induced by this specific mutation. By contrast, avapritinib was specifically designed as a potent and highly selective type I inhibitor, exhibiting high affinitive and inhibitory activity against *PDGFRA* D842V and *KIT* D816V as well as other mutants across the activation loop.[101]

Avapritinib was investigated in a large first-in-human phase I trial that recruited a total of 250 patients with advanced or metastatic GIST, including 56 with *PDGFRA* D842V–mutant GIST (20 from the dose-escalation group and 36 at the recommended phase II dose).[23] Avapritinib proved to be a milestone in cancer treatment, with a disease control rate of 100% at all doses, achieving an overall response rate of 91% (13% complete response, 79% partial response) and a median PFS of 34 months—an exceptional activity for this subset of patients with formerly multiresistant disease (Table 3 and Table 4). The toxicity profile of avapritinib includes data from 250 patients, including 167 patients treated with the recommended phase II dose of 300 mg daily. Overall, adverse events were consistent with on-target inhibition of KIT and PDGFRA, thus overlapping with the side effects seen with other TKIs targeting these receptors (≥ 20%): nausea, anemia, diarrhea, fatigue, decreased appetite, periorbital edema, face edema, memory impairment, peripheral edema, blood bilirubin increased, neutropenia, hair color changes, and dysgeusia. Dose interruptions

and dose reductions in the safety population due to all-cause adverse events were required, respectively, for 67.6% and 32.4% of patients, respectively. Drug discontinuation owing to treatment-related adverse events occurred for 9.6% of the patients at the recommended phase II dose.[102] Although cognitive effects and intracranial bleeding are reported with other antitumoral agents, they were more noticeable in this clinical trial, particularly the former. Thus, it is advised to monitor cognitive effects carefully to interrupt the treatment in a timely fashion, particularly during the first months of treatment for older patients.

Based on these data, the U.S. Food and Drug Administration approved avapritinib for the treatment of unresectable or metastatic GIST harboring any *PDGFRA* exon 18 mutation, whereas the European Medicines Agency approval is restricted only to *PDGFRA* D842V mutants. However, no approval has been granted for the treatment of patients with *KIT*-mutant GIST, despite showing activity in the phase I trial and in a randomized phase III trial in comparison with regorafenib in the third line.[103] Given the high antitumoral activity in the subset of patients with GIST with the *PDGFRA* D842V substitution, it would be recommended to treat these patients with avapritinib in the first line. Resistance will eventually occur as a result of polyclonal expansion of resistant clones with secondary mutations in the adenosine triphosphate binding pocket, thus paralleling resistance in *KIT*-mutant GIST.[24] Although multikinase inhibitors such as sunitinib and regorafenib might have some activity, there is a lack of truly effective treatments after avapritinib progression. In the absence of any treatment alternative, it could be considered to maintain avapritinib, as it seems to improve overall survival despite progression.[24]

CONCLUSION

The determination of specific molecular subtypes is the cornerstone for the clinical management of GIST from localized to metastatic disease, given their relevance to predicting the clinical behavior and the response to molecularly targeted agents. Although GIST is broadly known, it is still a rare disease; therefore, treatment decisions should be made within multidisciplinary teams with expertise in sarcoma to recommend the correct combinations of systemic agents and local treatments. In this sense, we encourage clinicians to treat these patients in clinical trials and thus pave the way for novel therapeutic opportunities to further improve the outcomes in GIST.

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AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/EDBK_351231.

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PRACTICAL APPLICATIONS

- Morphology-based diagnosis with immunohistochemical testing and ancillary molecular genetic testing is recommended for the diagnostic work-up of gastrointestinal stromal tumor (GIST).
- Neoadjuvant therapy is used for a primary GIST that is very large or in a difficult anatomic location to facilitate surgical resection and minimize sacrifice of normal tissue.
- Surgery is performed for selected patients with metastatic GIST after treatment with a tyrosine kinase inhibitor and may prolong progression-free survival.
- Two new drugs have been approved recently for the treatment of GIST: ripretinib for patients with unresectable and/or metastatic GIST after progression to imatinib, sunitinib, and regorafenib; and avapritinib, the first-ever therapeutic agent effective among patients with GIST harboring the primary *PDGFRA* D842V mutation, a subset with formerly multiresistant disease.
- Determining GIST molecular subtypes to tailor treatment and foster personalized medicine remains critical in this disease.

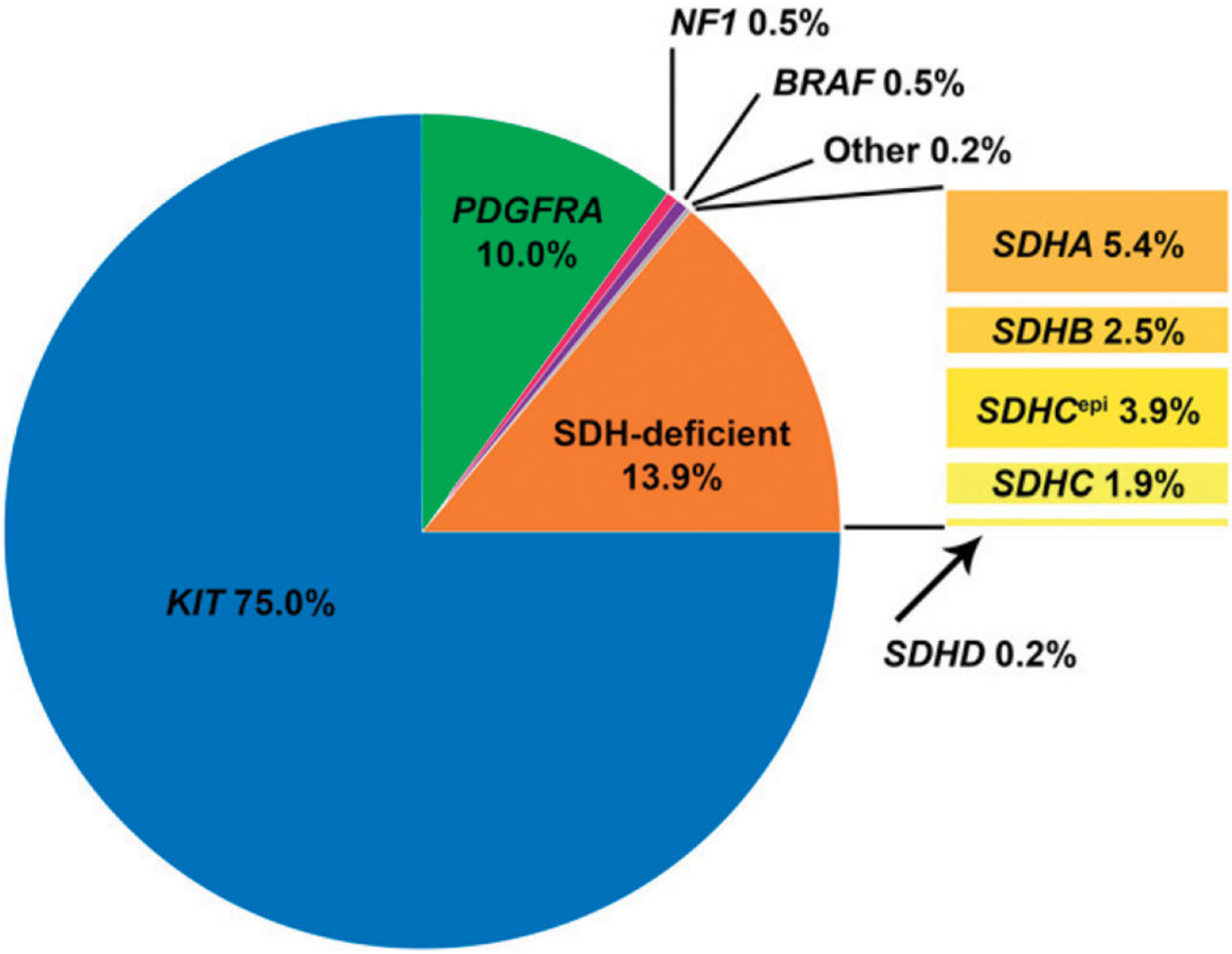

FIGURE 1. Frequency of Gastrointestinal Stromal Tumor Molecular Subtypes
Abbreviation: SDH, succinate dehydrogenase.
Adapted from Schaefer et al.[6]

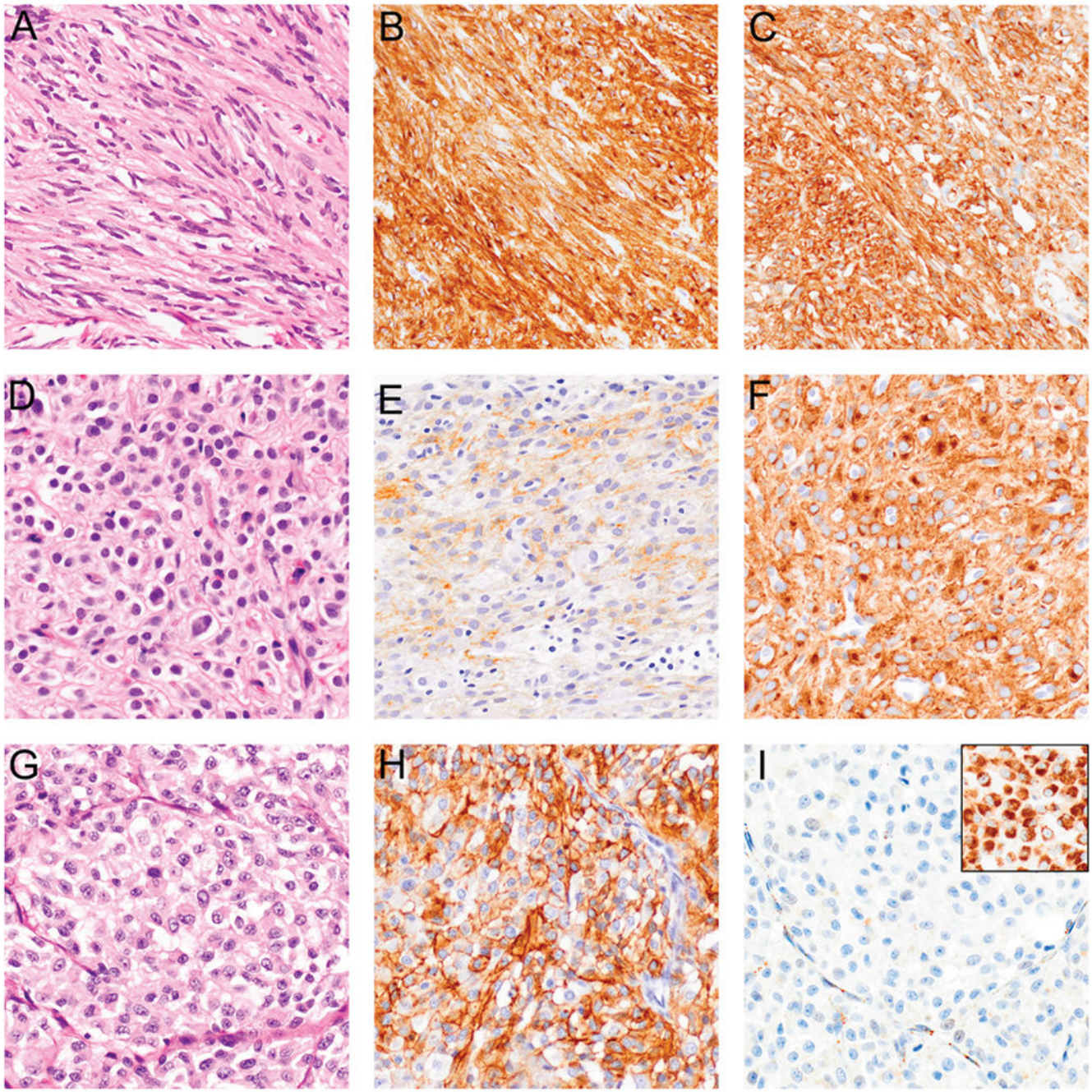

FIGURE 2. Immunohistochemical Markers in the Diagnostic Work-Up of Gastrointestinal Stromal Tumor

(A–C) Example of a *KIT*-mutant GIST with typical spindle-cell morphology (A) and strong and diffuse expression of KIT (B) and DOG-1 (C). (D–F) In contrast, a *PDGFRA*-mutant GIST displays epithelioid morphology (D) and weak expression of KIT (E), but strong and diffuse staining for PDGFRA (F). (G–I) Example of an SDH-deficient GIST characterized by epithelioid morphology (G), strong expression of KIT (H), and loss of SDHB expression in tumor cells (I), whereas SDHA expression is retained (I, inset), suggestive of an underlying mutation inactivating *SDHB*, *SDHC*, or *SDHD*.

Abbreviations: GIST, gastrointestinal stromal tumor; SDH, succinate dehydrogenase.

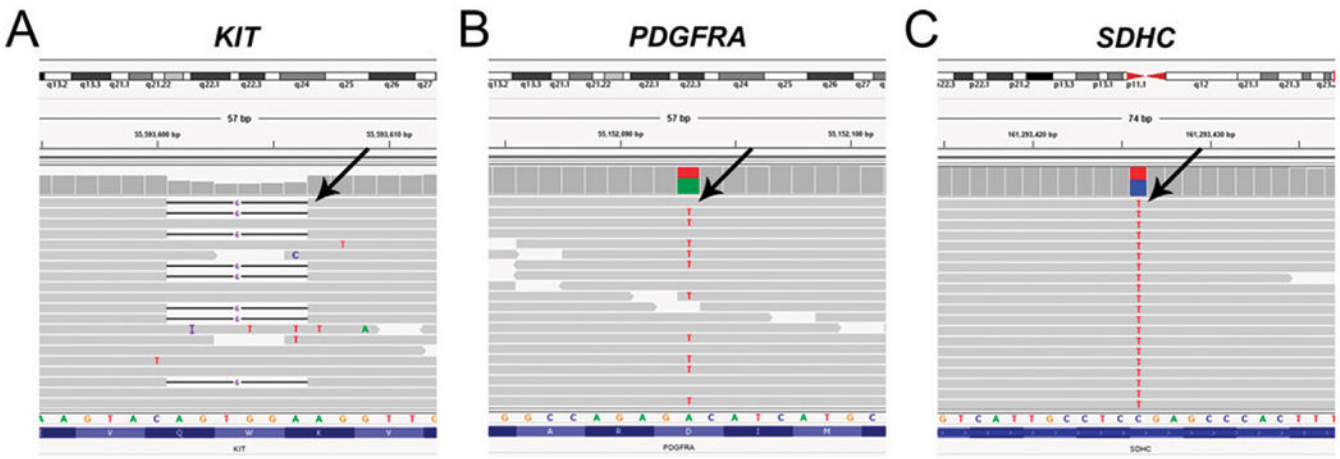

FIGURE 3. Targeted Next-Generation Sequencing in Clinical Cases of Gastrointestinal Stromal Tumor

(A) An exon 11 *KIT* mutation (c.1667_1672delAGTGGA; p.W557_K558del; allele fraction 0.29) (arrow) is detected in a low-risk gastric GIST. (B) Atypical *PDGFRA* exon 18 mutation (c.2525A> T; p.D842; allele fraction 0.4) (arrow) is found in a low-risk gastric GIST. (C) An inactivating *SDHC* mutation (c.43C> T; p.R15*; allele fraction; 0.44; additional copy loss of the remaining allele) (arrow) is identified for a young patient with gastric GIST.

Abbreviations: GIST, gastrointestinal stromal tumor; SDH, succinate dehydrogenase.

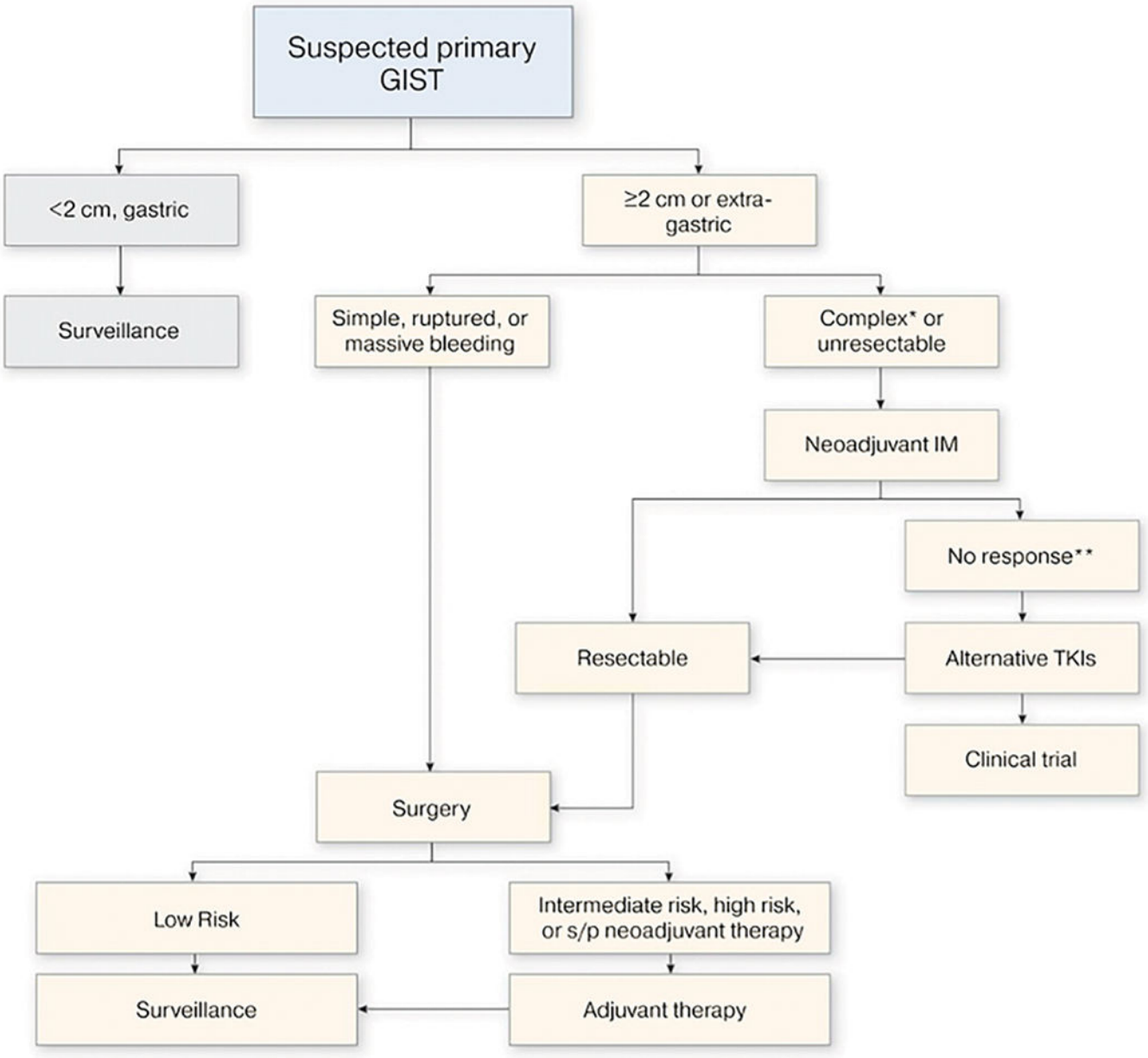

FIGURE 4. Treatment Algorithm to Guide the Management of Primary Gastrointestinal Stromal Tumor

Abbreviations: GIST, gastrointestinal stromal tumor; IM, imatinib mesylate; SDH, succinate dehydrogenase; TKI, tyrosine kinase inhibitor.

*Complex-extensive tumor or multivisceral resection is required. **Complex but resectable tumors that are unresponsive to neoadjuvant IM can also be treated directly with surgery. Adapted from Etherington and DeMatteo[38] and Joensuu and DeMatteo[39] with permission.

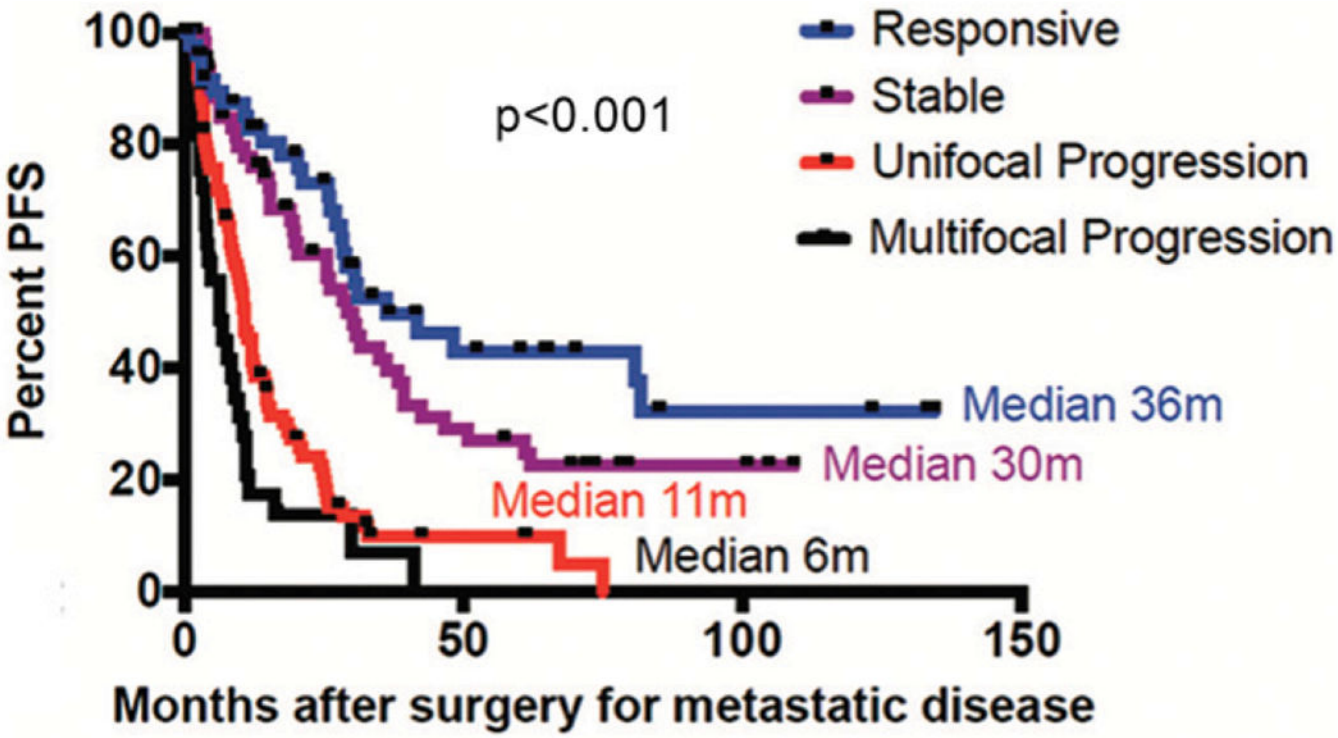

FIGURE 5. Impact of Surgical Resection in Metastatic Gastrointestinal Stromal Tumor
Abbreviation: PFS, progression-free survival.
Based on Etherington and DeMatteo[38] and Joensuu and DeMatteo.[39]

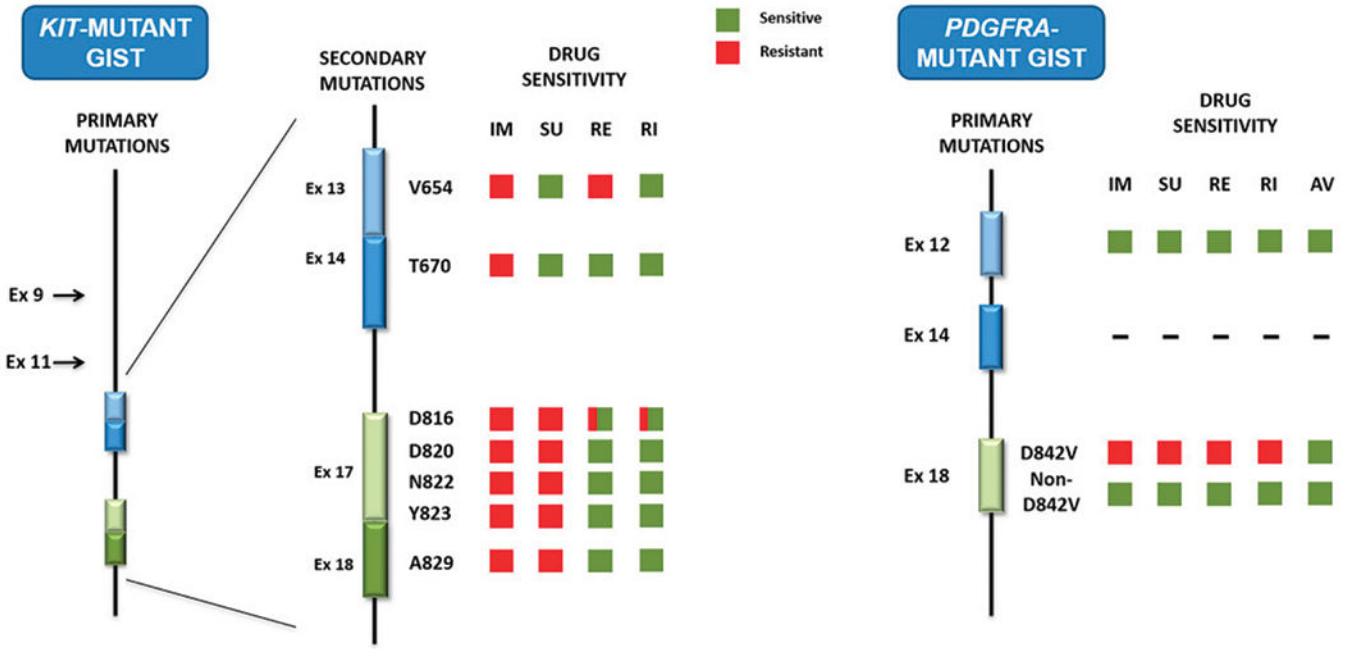

FIGURE 6. Sensitivity Profile of the Five Drugs With Regulatory Approval for Gastrointestinal Stromal Tumor

Green indicates sensitivity and red indicates resistance. The red and green boxes in D816 indicate the differences in sensitivities depending on the amino acid change (these drugs are resistant to the D816V substitution). These profiles have been established based on literature research from in vitro and in vivo studies and clinical data if available. Future research with patients' correlative studies will further confirm or redefine laboratory findings.

Abbreviations: AV, avapritinib; Ex, exon; GIST, gastrointestinal stromal tumor; IM, imatinib mesylate; RE, regorafenib; RI, ripretinib; SU, sunitinib.

TABLE 1.

Overview of the Armed Forces Institute of Pathology[19] Criteria for Risk Assessment in Gastrointestinal Stromal Tumor

			Risk of Progressive Disease (%)*			
Tumor Group	**Tumor Size (cm)**	**Tumor Mitotic Rate (per 50 HPFs)**	**Gastric GISTs**	**Jejunal and Ileal GISTs**	**Duodenal GISTs**	**Rectal GISTs**
1	≤ 2	≤ 5	0 (none)	0 (none)	0 (none)	0 (none)
2	> 2 to ≤ 5	≤ 5	1.9 (very low)	4.3 (low)	8.3 (low)	8.5 (low)
3a	> 5 to ≤ 10	≤ 5	3.6 (low)	25 (moderate)	34 (high**)	57† (high**)
3b	> 10	≤ 5	12 (moderate)	52 (high)		
4	≤ 2	> 5	0†	50†	‡	54 (high)
5	> 2 to ≤ 5	> 5	16 (moderate)	73 (high)	50 (high)	52 (high)
6a	> 5 to ≤ 10	> 5	55 (high)	85 (high)	86 (high**)	71 (high**)
6b	>10	> 5	86 (high)	90 (high)		

Abbreviations: HPF, high-power field; GIST, gastrointestinal stromal tumor.

*GIST data are presented for patients with progressive disease during long-term follow-up and characterization of risk for metastasis.

**Combined groups because of the small number of cases.

†Small number of cases.

‡No tumors of such category included.

TABLE 2.

Overview of the National Comprehensive Cancer Network[20] Criteria for Risk Assessment in Gastrointestinal Stromal Tumor

	Tumor Parameter		Risk of Progressive Disease (%)		
Mitotic Index (per 50 HPFs)	**Size (cm)**	**Gastric (%)**	**Duodenum**	**Jejunum/Ileum**	**Rectum**
≤ 5	≤ 2	0 (none)	0 (none)	0 (none)	0 (none)
≤ 5	> 2 to ≤ 5	1.9 (very low)	4.3 (low)	8.3 (low)	8.5 (low)
≤ 5	> 5 to ≤ 10	3.6 (low)	24 (moderate)	Insufficient data	Insufficient data
≤ 5	> 10	10 (moderate)	52 (high)	34 (high)	57 (high)
> 5	≤ 2	None *	High *	Insufficient data	54 (high)
> 5	> 2 to ≤ 5	16 (moderate)	73 (high)	50 (high)	52 (high)
> 5	> 5 to ≤ 10	55 (high)	85 (high)	Insufficient data	Insufficient data
> 5	> 10	86 (high)	90 (high)	86 (high)	71 (high)

Abbreviation: HPF, high-power field.

* Small numbers of cases.

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TABLE 3.

Clinical Activity Shown in Pivotal Clinical Trials by the Five Tyrosine Kinase Inhibitors With Regulatory Approval for the Treatment of Unresectable or Metastatic Gastrointestinal Stromal Tumor

	***KIT/PDGFRA*-Mutant GIST**				***PDGFRA* D842V**
Parameter	**Imatinib**	**Sunitinib**	**Regorafenib**	**Ripretinib**	**Avapritinib**
Reference	Demetri et al[66]	Demetri et al[63]	Demetri et al[67]	Blay et al[68]	Heinrich et al[23]
Treatment line	First	Second	Third	Fourth or more	Any
ORR (%)	68.1	6.8	4.5	9.4	91.0
Stable disease at 12 weeks (%)	15.6	53.0	53.0	47.0	98.0
mPFS (mo)	24.0	5.6	4.8	6.3	34.0*

Abbreviations: GIST, gastrointestinal stromal tumor; ORR, overall response rate; mPFS, median progression-free survival.

*Updated mPFS from Jones et al.[69]

TABLE 4.

Tyrosine Kinase Inhibitors With KIT/PDGFRA Inhibitory Activity Tested in Advanced and Metastatic Gastrointestinal Stromal Tumor, But Without Regulatory Approval for This Indication

Drug	Clinical Trial	Setting Treatment Line	ORR (%)	mPFS (mo)	Phase
Avapritinib	Kang (2021)[78]	Third/fourth	17	4.2	III-R
Cabozantinib	Schöffski (2020)[79]	Third	14	5.5	II
Dasatinib	Schuetze (2018)[80]	Second or more	4	2.9	II
Dovitinib	Kang (2013)[81]	Third or more	3	3.6	II
	Joensuu (2017)[82]	Third or more	5	4.6	II
Masitinib	Adenis (2014)[83]	Second	NA	3.7	II
Nilotinib	Montemurro (2009)[84]	Third or more	10	2.8	II
	Sawaki (2011)[85]	Third	3	3.7	II
	Cauchi (2012)[86]	Third or more	0	2.0	II
	Reichardt (2012)[87]	Third	< 1	3.6	III-R
Pazopanib	Ganjoo (2014)[88]	Second or more	0	1.9	II
	Mir (2016)[89]	Second or more	0	3.4	II-R
	Eriksson (2021)[90]	Third/fourth	3	4.5	II
Ponatinib *	George (2022)[91]	Second or more	8	4.3	II
Sorafenib	Kindler (2011)[92]	Second or more	13	5.2	II
	Park (2012)[93]	Third or more	13	4.9	II

Abbreviations: ORR, overall response rate (complete and partial responses) determined by RECIST criteria; mPFS, median progression-free survival; NA, not available.

*Data from patients with *KIT* exon 11 mutant gastrointestinal stromal tumor.

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