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Gastrointestinal Stromal Tumors, Version 2.2022:

Featured Updates to the NCCN Guidelines

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Abstract

Gastrointestinal stromal tumors (GIST) are the most common type of soft tissue sarcoma that occur throughout the gastrointestinal tract. Most of these tumors are caused by oncogenic activating mutations in the *KIT* or *PDGFRA* genes. The NCCN Guidelines for GIST provide recommendations for the diagnosis, evaluation, treatment, and follow-up of patients with these tumors. These NCCN Guidelines Insights summarize the panel discussion behind recent important updates to the guidelines, including revised systemic therapy options for unresectable, progressive, or metastatic GIST based on mutational status, and updated recommendations for the management of GIST that develop resistance to specific tyrosine kinase inhibitors.

Overview

Gastrointestinal stromal tumors (GIST) are the most common soft tissue sarcoma (STS) of the gastrointestinal tract, resulting primarily from *KIT* or *PDGFRA* activating mutations.[1] The annual incidence of GIST in the United States is estimated to be between 0.68 to 0.78 per 100,000.[2–5] GIST can arise anywhere along the gastrointestinal tract, but stomach (60%) and small intestine (30%) are the most common primary sites.[6] Duodenum (4%–5%) and rectum (4%) are less common primary sites, and only a small number of cases have been reported in the esophagus (<1%) and colon and appendix (1%–2%).[6] In rare instances, GIST can occur in extraintestinal sites. Patients with a suspected GIST may present with a variety of symptoms, which may include early satiety, abdominal discomfort due to pain or swelling, intraperitoneal hemorrhage, gastrointestinal bleeding, or fatigue related to anemia. Some patients may present with an acute abdomen (as a result of tumor rupture, gastrointestinal obstruction, or peritonitis-like pain), which requires immediate medical attention. Liver and/or the peritoneal surfaces are the most common sites of metastases, whereas lymph node metastases are extremely rare, except in select GIST subtypes. Metastases in the lungs, bone, and other extraabdominal locations are observed only in advanced cases.

These NCCN Guidelines Insights summarize the panel discussion behind recent important updates to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for GIST, including revised systemic therapy options for unresectable, progressive, or metastatic GIST based on mutational status, and updated management strategies for resistance to tyrosine kinase inhibitors (TKIs).

Impact of Mutational Status on Tumor Response to First-Line TKIs in Patients With Advanced or Metastatic GIST

GIST are generally more resistant to traditional systemic chemotherapeutic agents and radiation therapy (RT) than other STS subtypes; therefore, treatment options for patients with advanced or metastatic GIST were historically limited.[7] The discovery that many GIST are driven by constitutively activated KIT or PDGFRA receptor tyrosine kinases was a significant breakthrough, enabling GIST to be managed with targeted therapies. TKIs have now emerged as the standard-of-care treatment for patients with advanced or metastatic GIST (see GIST-4 and GIST-D 1 of 2, above and page 1208, respectively). Imatinib, the first TKI approved for the treatment of patients with GIST, is clinically active against many GIST

in the first-line setting.[8,9] However, not all GIST are responsive to imatinib, given that tumor response is primarily dependent on tumor mutational status.

GIST With *KIT* or *PDGFRA* Mutations

Imatinib-Sensitive Mutations—Up to approximately 80% of GIST have a *KIT* mutation, whereas 5% to 10% have a *PDGFRA* mutation.[10–13] The presence and type of *KIT* or *PDGFRA* mutations are not strongly correlated with prognosis. However, the presence (or absence) of mutations in specific regions of *KIT* and *PDGFRA* genes are associated with a response to specific TKIs.

In randomized trials evaluating imatinib in the advanced disease setting, the presence of a *KIT* exon 11 mutation was associated with better response rates, median progression-free survival (PFS), and median overall survival (OS) than *KIT* exon 9 mutations or nonmutated *KIT* or *PDGFRA*.[8,13–16] Long-term follow-up (median 73 months) from the randomized phase III BFR14 trial by the French Sarcoma Group identified *KIT* exon 11 mutations as an independent prognostic factor for longer PFS and OS in patients treated with standard-dose imatinib when compared with *KIT* exon 9 mutations or nonmutated *KIT*.[16] In the USFinland B2222 phase II study, imatinib was associated with better outcomes for patients with *KIT* exon 11 mutations than for those with *KIT* exon 9 mutations or who had no detectable kinase mutations.[8] The partial response (PR) rates for patients with *KIT* exon 11 mutations, *KIT* exon 9 mutations, or no detectable kinase mutations were 83.5%, 47.8%, and 0%, respectively. The presence of *KIT* exon 11 mutations was the strongest prognostic factor reducing the risk of death by >95%.

GIST with *KIT* exon 9 mutations treated with imatinib generally have a lower response rate and PFS than those with *KIT* exon 11 tumors at a dose of 400 mg daily, but imatinib at 400 mg twice daily may lead to a better response and PFS. In the randomized EORTC 62005 study, the presence of *KIT* exon 9 mutations was the strongest adverse prognostic factor for risk of progression and death.[13] High-dose imatinib (400 mg twice daily) resulted in a significantly superior PFS with a 61% (P=.0013) reduction in relative risk among patients whose tumors expressed a *KIT* exon 9 mutation compared with the standard 400 mg/d imatinib dose.[13] Additionally, the response rate after crossover from imatinib at 400 mg once daily to 400 mg twice daily was higher in patients with *KIT* exon 9 mutations (57%) than in those with *KIT* exon 11 mutations (7%). Similarly, results from the phase III SWOG S0033/ CALGB 150105 trial showed that imatinib at 400 mg twice daily resulted in a higher response rate in patients with a *KIT* exon 9 mutation than imatinib at 400 mg once daily (67% vs 17%, respectively).[15] A meta-analysis of EORTC 62005 and SWOG S0033/ CALGB 150105 trials that randomized 1,640 patients with advanced GIST to standard-dose imatinib(400mg once daily) or high-dose imatinib (400mg twice daily) showed a benefit in PFS for patients with *KIT* exon 9 mutations treated with high-dose imatinib.[17]

Although most GIST with *PDGFRA* mutations are associated with a response to imatinib, those with certain mutations, such as D842V, generally do not respond.[11,18] In a survey of patients with confirmed *PDGFRA* mutations, none of 31 evaluable patients with a D842V mutation experienced a response to imatinib, and 21 of 31 (68%) experienced disease progression.[19] The median PFS was 2.8 months for patients with D842V compared with

28.5 months for those with other *PDGFRA* mutations (eg, indels in exon 18). With 46 months of follow-up, the median OS was 14.7 months for patients with D842V and not reached for patients with other *PDGFRA* mutations.

Imatinib is included in the guidelines as a category 1 preferred first-line treatment option for patients with advanced or metastatic GIST with imatinib-sensitive mutations; however, it is not recommended for the treatment of GIST with *PDGFRA* exon 18 mutations that are in sensitive to imatinib, especially D842V (see GIST-4 and GIST-D 1 of 2, page 1206 and above , respectively).

In the adjuvant setting, a longer duration of imatinib treatment may be beneficial for patients with GIST that have certain *KIT* mutations. Follow-up analysis of a randomized phase III study from the Scandinavian Sarcoma Group (SSG XVIII/AIO) revealed that patients with GIST harboring a *KIT* exon 11 deletion appear to benefit most from longer-duration imatinib, showing higher recurrence-free survival when allocated to the 3-year versus 1-year imatinib group.[20] A similar pattern related to duration of treatment was not observed for GIST harboring other mutations.

Imatinib-Insensitive Mutations—GIST with imatinib-insensitive mutations such as *PDGFRA* D842V are managed differently from most GIST. Avapritinib is a TKI approved for the treatment of patients with unresectable or metastatic GIST with a *PDGFRA* exon 18 mutation, including D842V mutations.[21,22] The approval of avapritinib for GIST was based on results from the open-label, single-arm, phase I NAVIGATOR trial that evaluated the safety and antitumor activity of avapritinib in 56 patients with *PDGFRA* D842V–containing GIST that were unresectable and/or metastatic.[23,24] In the long-term analysis of the trial, at data cutoff (median follow-up of 27.5 months), the overall response rate with avapritinib was 91%, with a median duration of response of 27.6 months.[24]

Given these data, the panel recommends avapritinib as the preferred first-line treatment option for patients with unresectable, progressive, or metastatic GIST with imatinib-resistant *PDGFRA* D842V mutations or other *PDGFRA* exon 18 mutations that are known to be imatinib-insensitive (see GIST-4 and GIST-D 1 of 2, pages 1206 and 1208, respectively).

GIST *Without* KIT *or* PDGFRA *Mutations*

Approximately 10% to 15% of GIST lack a mutation in either *KIT* or *PDGFRA*.[10,25] Most of these have functional inactivation of the succinate dehydrogenase (SDH) complex (either from mutations or epigenetic silencing leading to a lack of SDH protein expression),[25] which has been shown to be a cause of tumorigenesis. GIST with SDH deficiency generally lack the gain-of-function tyrosine kinase mutations found in most GIST[26]; therefore, certain TKIs (specifically imatinib) have limited efficacy in this setting.[27]

However, TKIs with activity against VEGFR can be considered as potential options for SDH-deficient GIST. Data from 2 small retrospective studies suggested that sunitinib may be active in SDH-deficient GIST.[28,29] Although sunitinib targets KIT and PDGFRA, it is also active against other kinases, including VEGFR.[30] Regorafenib is another TKI with activity against VEGFR, and was reported to be clinically active against SDH-deficient

GIST in a small number of patients.[31,32] In a phase II study, prolonged disease control was achieved in one patient with SDH-deficient GIST treated with pazopanib, another TKI that targets VEGFR.[33,34] Based on these limited data, the NCCN Guidelines recommend consideration of sunitinib, regorafenib, and pazopanib as options for unresectable SDH-deficient GIST (see GIST-D 1 of 2 and GIST-D 2 of 2, page 1208 and above, respectively). There are other potential treatments on the horizon for patients with SDH-deficient GIST; for example, temozolomide has shown promise in this setting based on preclinical data,[35] and is currently undergoing clinical testing (NCT03556384).

GIST with *NTRK* fusions in the absence of *KIT*/*PDGFRA* mutations may occur.[36–38] *NTRK* fusion is an actionable alteration, and both larotrectinib and entrectinib were granted accelerated approval by the FDA for the treatment of solid tumors with *NTRK* gene fusions.[39,40] In a combined analysis of 3 studies, larotrectinib resulted in an overall response rate of 75% (based on independent review) in children and adults with locally advanced or metastatic *NTRK* fusion–positive solid tumors, including GIST.[41] An integrated analysis of 3 trials found that entrectinib led to an objective response in 57% of adults with locally advanced or metastatic *NTRK* fusion–positive solid tumors.[42] The NCCN Guidelines recommend larotrectinib and entrectinib as preferred first-line treatment options for patients with unresectable, progressive, or metastatic GIST that are *NTRK* fusion–positive (see GIST-D 1 of 2, page 1208).

Other genomic events, such as alterations in *BRAF, NF1*, and *FGFR*, may also occur in GIST.[38,43–48] The NCCN Guidelines do not recommend specific therapies for GIST with these alterations; however, the presence of these genomic events could be used to identify potential targeted therapy options. For example, combination therapy with dabrafenib and trametinib was recently approved by the FDA for the treatment of patients with advanced solid tumors with *BRAF* V600E mutations.[49]

Management of Resistance to TKIs

Resistance to Imatinib—Although imatinib improves outcomes for patients with advanced or metastatic GIST, many will develop resistance to the drug. Primary imatinib resistance is defined as the evidence of clinical progression developing during the first 6 months of imatinib therapy; this is most commonly seen in patients with *KIT* exon 9 mutations treated with imatinib at 400 mg daily, patients with *PDGFRA* D842V mutations, or those with tumors that lack identifiable activating mutations in *KIT* or *PDGFRA*, most of which are SDH-deficient GIST, thus underscoring the importance of genotyping GIST.[8,14,15,50] Secondary resistance is seen in patients who have been taking imatinib for >6 months who experienced an initial response or disease stabilization followed by progression, most commonly due to the outgrowth of tumor clones with secondary mutations in *KIT*.[51–54]

For GIST with limited progression following the standard imatinib dose regimen, several options are available (see GIST-5, page 1207). The same dose of imatinib can be continued, while also considering resection (if feasible), ablation procedures/embolization/chemoembolization, or palliative RT (category 2B) for symptomatic lesions. The TKI can also be switched to sunitinib (category 1); alternatively, dose escalation of imatinib to

800 mg/d (400 mg twice daily) is another option.[55–57] Data have suggested that certain patients with GIST, particularly those with *KIT* exon 9 mutations, may derive benefit from imatinib dose escalation.[17,58] For patients with performance status (PS) of 0 to 2 and generalized disease progression following treatment with imatinib at 400 mg/d, the guidelines recommend switching to an alternate TKI or escalating the dose of imatinib, as tolerated (see GIST-5 and GIST-D 1 of 2, pages 1207and 1208,respectively).

The approval of sunitinib for the treatment of patients with imatinib-refractory or imatinib-intolerant GIST was primarily based on a phase III randomized controlled study in 312 patients with advanced GIST that were resistant or intolerant to prior imatinib treatment.[56,59] The median time to tumor progression was 27.3 weeks in the sunitinib group versus 6.4 weeks in the placebo group (hazard ratio[HR], 0.33; $P<.0001$).

The clinical activity of sunitinib in imatinib-resistant GIST can vary depending on the presence of primary and secondary *KIT* mutations. One study found that second-line sunitinib induced higher clinical benefit (PR or stable disease for ≥6 months) in patients with imatinib-resistant/intolerant GIST with primary *KIT* exon 9 mutations than in patients with *KIT* exon 11 mutations (58% vs 34%, respectively).[50] Median PFS and OS were significantly longer for patients with *KIT* exon 9 mutations or nonmutated *KIT* than in patients with *KIT* exon 11 mutations. In patients with *KIT* exon 11 mutations, median PFS and OS were longer for those with secondary exon 13 or 14 mutations compared with those with exon 17 or 18 mutations. Although sunitinib appears to have activity against tumors with *KIT* ATP-binding pocket mutations (exons 13 and 14) that confer resistance to imatinib, it has little activity against tumors with imatinib-resistant mutations in the *KIT* activation loop (exons 17and 18).[60–62]

Based on these data, sunitinib has a category 1 recommendation as a preferred second-line option for patients with unresectable, progressive, or metastatic GIST previously treated with imatinib (see GIST-D 1 of 2, page 1208).

For patients with a *PDGFRA* D842V mutation or other *PDGFRA* exon 18 mutations that are insensitive to imatinib, the guidelines recommend dasatinib as a second-line option. The clinical evidence supporting use of dasatinib as a second-line therapy is described in more detail in the “Resistance to Avapritinib” section on opposite page.

Resistance to Imatinib and Sunitinib

Regorafenib, a multikinase inhibitor with activity against KIT, PDGFR, VEGFR,and others,can be considered for patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib.[31] The FDA approval of regorafenib in this setting was based on results from the phase III randomized GRID trial, in which regorafenib versus placebo was evaluated in 199 patients with metastatic and/or unresectable GIST that progressed on prior therapy with imatinib and sunitinib.[63] The median PFS (4.8 vs 0.9 months; $P<.0001$) and the disease control rate (DCR; 53% vs 9%)were significantly higher for regorafenib than placebo. The PFS rates at 3 and 6 months were 60% and 38%, respectively, for regorafenib compared with 11% and 0%, respectively, for placebo. The HR for OS was 0.77, with 85% of patients in the placebo arm crossing over to regorafenib due

to disease progression. Long-term follow-up (median, 41 months) from a phase II study in unresectable or metastatic GIST (n533) suggested that patients with *KIT* exon 11 mutations or SDH-deficient GIST may derive a greater PFS benefit from regorafenib than patients with *KIT*/*PDGFRA* wild-type, non–SDH-deficient tumors.[32] Given these data, regorafenib (category 1) is included in the guidelines on GIST-D 1 of 2 as a preferred third-line option following imatinib and sunitinib (page 1208).

Resistance to Imatinib, Sunitinib, and Regorafenib

Ripretinib, a TKI that inhibits KIT and PDGFRA kinases, is approved by the FDA for adults with advanced GIST who have received prior treatment with ≥3 kinase inhibitors, including imatinib.[64] In the phase III INVICTUS trial, ripretinib at 150 mg daily was evaluated against placebo in patients with advanced GIST who were previously treated with imatinib, sunitinib, and regorafenib.[65] The median PFS of the ripretinib group was 6.3 months, compared with 1.0 months in the placebo group ($P<.0001$). Ripretinib (category 1) is recommended in the guidelines as a preferred fourth-line option for patients with unresectable, progressive, or metastatic GIST after treatment with imatinib, sunitinib, and regorafenib (see GIST-D 1 of 2, page 1208).

In a follow-up analysis of INVICTUS, dose escalation of ripretinib to 150 mg twice daily was evaluated in 43 patients who experienced disease progression while on ripretinib at 150 mg daily.[66] The median OS was 18.4 months for patients who switched to ripretinib at 150 mg twice daily, compared with 14.2 months for patients from INVICTUS who experienced disease progression but did not undergo dose escalation. The median PFS after receiving the first dose of 150 mg twice daily was 3.7 months. The guidelines include dose escalation of ripretinib to 150 mg twice dailyas an option for patients who experience disease progression while on ripretinib at 150 mg daily (see GIST-D 1 of 2, page 1208).

Resistance to Imatinib, Sunitinib, Regorafenib, and Ripretinib

Other TKIs are recommended in the guidelines as off-label options after disease progression on approved therapies (see GIST-D 1 of 2, page 1208). Much of the data on these TKIs are derived from phase II studies and retrospective analyses involving a small number of patients. Additionally, many of these studies only included patients previously treated with imatinib and sunitinib, but not regorafenib and/or ripretinib.

A few studies have evaluated sorafenib as an option for some patients with advanced or metastatic GIST.[67–70] In a prospective, multicenter, phase II study of 38 patients with unresectable, *KIT*-positive GIST that had progressed on imatinib and sunitinib, sorafenib resulted in a DCR of 68% (55% of patients had stable disease and 13% had PR).[67] Median PFS and OS were 5.2 and 11.6 months, respectively. In a retrospective analysis of 124 patients with metastatic GIST resistant to imatinib and sunitinib, the median PFS and OS of patients who received sorafenib was 6.4 and 13.5 months, respectively.[69]

Another TKI that can be considered is nilotinib.[71–75] In a retrospective analysis of 52 patients with advanced imatinib- and sunitinib-resistant GIST, nilotinib resulted in a 10% response rate and 37% DCR.[72] Median PFS and OS were 12 and 34 weeks, respectively. In a randomized phase III study of nilotinib as third-line therapy in patients with GIST

resistant or intolerant to imatinib and sunitinib (n=248), PFS with nilotinib was not superior to best supportive care (109 vs 111 days; *P*=.56).[74] In a post hoc analysis, nilotinib led to an improved OS (>4 months) compared with best supportive care (405 vs 280 days; *P*=.02) in patients whose disease progressed on both imatinib and sunitinib. This clinical benefit may be specific to patients with secondary *KIT* exon 17 mutations.[75] In a phase III trial that evaluated nilotinib versus imatinib in the first-line setting, none of the patients with *KIT* exon 9 mutations treated with nilotinib achieved an objective response. Additionally, nilotinib resulted in a shorter PFS than imatinib in those with *KIT* exon 9 mutations, suggesting that nilotinib is not effectiveforthismutationtype.[76]

Pazopanib also has modest activity in unselected, heavily pretreated patients with advanced GIST.[33,77] In a randomized phase II trial comparing pazopanib versus best supportive care in imatinib- and sunitinib-resistant GIST (n=81), median PFS was 3.4 versus 2.3 months, respectively (HR, 0.59; 95% CI, 0.37–0.96; *P*=.03).[77]

Cabozantinib is another TKI that may be considered for patients whose disease has progressed on approved therapies.[78] Everolimus in combination with a TKI (ie, imatinib, sunitinib, regorafenib) may also be active in imatinib-resistant GIST.[79]

For a complete list of additional options for GIST that have progressed on approved therapies, see GIST-D 1 of 2, page 1208.

Resistance to Avapritinib

For GIST that become avapritinib-resistant, several options are recommended (see GIST-5, page 1207). For limited disease progression, avapritinib treatment can be continued while also considering additional options, such as resection (if feasible), ablation procedures, embolization, chemoembolization, or palliative RT (category 2B) for symptomatic lesions. For patients with generalized disease progression following first-line avapritinib who also have PS of 0 to 2, the NCCN Guidelines recommend switching to an alternate TKI. Several studies have suggested that dasatinib can be considered as another option for GIST with *PDGFRA* D842V.[80–82] Dasatinib has been shown to be a potent inhibitor of cells expressing the *PDGFRA* D842V mutation in vitro.[80] Additionally, a single-arm, open-label study evaluated the antitumor activity of dasatinib in 50 patients with advanced imatinib-refractory GIST.[82] The primary endpoint (>30% 6-month PFS) was not met, as the 6-month PFS was 29%. However, the study provided evidence that dasatinib may have some clinical activity in this population, given that a partial tumor response was observed in 25% of patients, including one with an imatinib-resistant *PDGFRA* exon 18 (D842V) mutation. Therefore, the guidelines recommend dasatinib as a preferred second-line therapy option for patients with *PDGFRA* exon 18 mutations (including D842V) whose disease has become resistant to either avapritinib or imatinib (see GIST-D 1 of 2, page 1208).

Ripretinib is another TKI that exhibits broad activity against both *KIT* and *PDGFRA* (including D842V) in the preclinical setting[83]; however, additional clinical trials are needed to confirm the efficacy of ripretinib against GIST with *PDGFRA* D842V mutations. The guidelines recommend ripretinib at 150 mg daily as an option that may be useful in certain

circumstances for GIST that progress following avapritinib and dasatinib (see GIST-D 1 of 2, page 1208). Dose escalation of ripretinib to 150 mg twice daily can alsobe considered.

Other Options for Progressive Disease—In addition to the systemic therapies described, other options are recommended for progressive disease (see GIST-5, page 1207). Resection (if feasible), ablation procedures, embolization, or chemoembolization are options for patients with limited disease progression; palliative RT is another alternative for those with symptomatic lesions. If the disease continues to progress despite prior therapies, a repeat tumor biopsy can be considered to potentially identify uncommon mutations that may have a corresponding targeted therapy.[84,85] Clinical trials and best supportive care are also recommended. Reintroduction of a previously tolerated and effective TKI can be considered for palliation of symptoms. Continuation of lifelong TKI therapy can be considered for palliation of symptoms as part of best supportive care.

Summary

Recent updates to the NCCN Guidelines for GIST include revised guidance for the management of unresectable, progressive, or metastatic disease. Recommendations for first-line systemic therapy agents are now stratified based on mutation status and other alterations. Management strategies for GIST that develop resistance to first-line and subsequent TKIs have also been updated to include emerging therapeutic options based on clinical evidence.

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NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.

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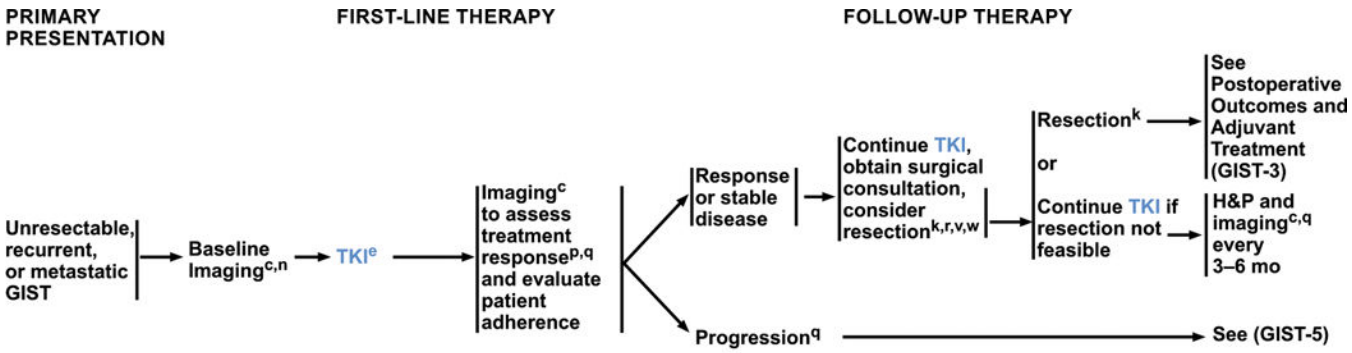


GIST-4.

[c] See Principles of Imaging (GIST-E).

[e] Mutational analysis may predict response to therapy with TKIs (See GIST-B).

[k] See General Principles of Surgery for GIST (GIST-C).

[n] Consider baseline PET/CT, if using PET/CT during follow-up. PET/CT is not a substitute for CT.

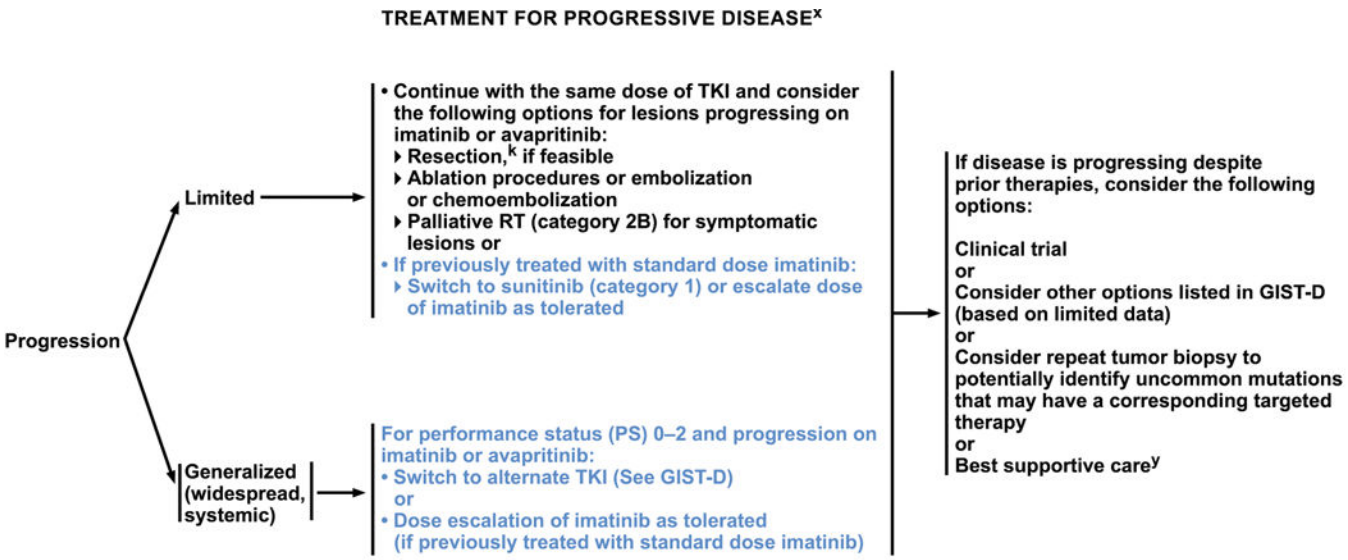
[p] PET/CT may give indication of imatinib efficacy after 2–4 weeks of therapy when rapid readout of activity is necessary. Diagnostic abdominal/pelvic CT or MRI with contrast is indicated every 8–12 weeks; routine long-term PET/CT follow-up is rarely indicated. Frequency of response assessment imaging may be decreased if patient is responding to treatment.

[q] Progression may be determined by abdominal/pelvic CT or MRI with contrast with clinical interpretation; increase in tumor size in the presence of decrease in tumor density is consistent with drug efficacy or benefit. PET/CT scan may be used to clarify if CT or MRI are ambiguous.

[r] Collaboration between medical oncologist and surgeon is necessary to determine the appropriateness and timing of surgery, following major response or sustained stable disease. Maximal response may require treatment for 6 months or more to achieve.

[v] Consider resection or ablation/liver-directed therapy for hepatic metastatic disease.

[w] Resection of metastatic disease, especially if complete resection can be achieved, and may be beneficial in patients on imatinib or sunitinib who have evidence of radiographic response, or limited disease progression.



GIST-5.

[k] See General Principles of Surgery for GIST (GIST-C).

[x] Clinical experience suggests that discontinuing TKI therapy, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.

[y] Reintroduction of a previously tolerated and effective TKI can be considered for palliation of symptoms. Consider continuation of TKI therapy life-long for palliation of symptoms as part of best supportive care.

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR GISTs

Neoadjuvant Therapy for Resectable Disease with Significant Morbidity	Adjuvant Therapy for Resectable Disease
Preferred Regimens • Imatinib for GISTs with imatinib-sensitive mutations[a] • Avapritinib for GISTs with *PDGFRA* exon 18 mutations that are insensitive to imatinib (including the D842V mutation)	Preferred Reaimen • Adjuvant imatinib[b] for patients with significant risk of recurrence, intermediate or high risk (category 1 following complete resection with no preoperative imatinib; category 2A following complete resection after preoperative imatinib) See GIST-3

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR UNRESECTABLE,[c] PROGRESSIVE OR METASTATIC DISEASE

First-line therapy	Second-line therapy	Third-line therapy	Fourth-line therapy	Additional options after progression on approved therapies[d,e]
Preferred Regimen • Imatinib[f,1,2] (category 1) for sensitive mutations or for ***PDGFRA*** exon 18 mutations (excluding the D842V mutation)	Preferred Regimen • Sunitinib[f,6] (category 1) • Dasatinib[7] for patients with PDGFRA exon 18 mutations that are insensitive to imatinib (including the PDGFRA D842V mutation)	Preferred Reaimen • Regorafenib[f,8] (category 1)	Preferred Reaimen • Ripretinib 150 mg daily[f,9](category 1)	Useful in Certain Circumstances • Avapritinib[f,3] • Cabozantinib[10] • Everolimus + TKI[g,11] • Nilotinib[12,13] • Pazopanib[14] • Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)[f,h,15] • Sorafenib[16–18]
Preferred Regimen • Avapritinib[f,3] for GIST with *PDGFRA* exon 18 mutations that are insensitive to imatinib (including the PDGFRA D842V mutation)	• Dasatinib			Useful in Certain Circumstances • Ripretinib 150 mg daily • Ripretinib dose escalation to 150 mg BID (if previously treated with ripretinib 150 mg daily)[f,h,15]
Useful in Certain Circumstances • *NTRK* gene-fusion positive GISTs only - Larotrectinib[4] - Entrectinib[5]				

See footnotes and references, on GIST-D (2 of 2)

SYSTEMIC THERAPY AGENTS AND REGIMENS FOR GISTs FOOTNOTES

[a] Although mutational analysis is recommended (other than rare circumstances, family history, etc.), it is appropriate to start neoadjuvant imatinib pending confirmation of the mutational analysis.

[b] Data do not support routine use in GIST without mutation in KIT or with an imatinib-resistant mutation in PDGFRA.

[c] For unresectable disease, sunitinib, regorafenib, and pazopanib are special considerations for SDH-deficient GIST.

[d] Therapies based on identification of driver mutations

[e] Regimens are ordered alphabetically and not according to order of preference.

[f] FDA-approved TKIs for the treatment of GIST.

[g] TKIs to be considered for use in combination with everolimus include imatinib, sunitinib, or regorafenib.

[h] Ripretinib 150 mg daily is indicated for fourth-line therapy. An additional clinical benefit may be obtained with the use of ripretinib 150 mg BID upon progression on ripretinib 150 mg daily.

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