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Release date: November 10, 2022; Expiration date: November 10, 2023

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Gastrointestinal Stromal Tumors
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Gastrointestinal Stromal Tumors

Disclosure of Relevant Financial Relationships

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To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/guidelines/guidelines-panels-and-disclosure/disclosure-panels

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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.

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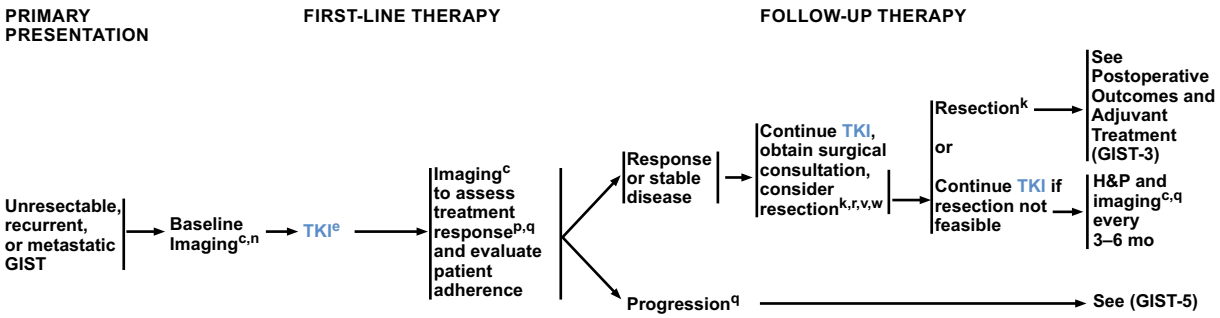


[c] See Principles of Imaging (GIST-E).
[e] Mutational analysis may predict response to therapy with TKIs (See GIST-B).
[k] See General Principles of Surgery for GIST (GIST-C).
[n] Consider baseline PET/CT, if using PET/CT during follow-up. PET/CT is not a substitute for CT.
[p] PET/CT may give indication 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-4

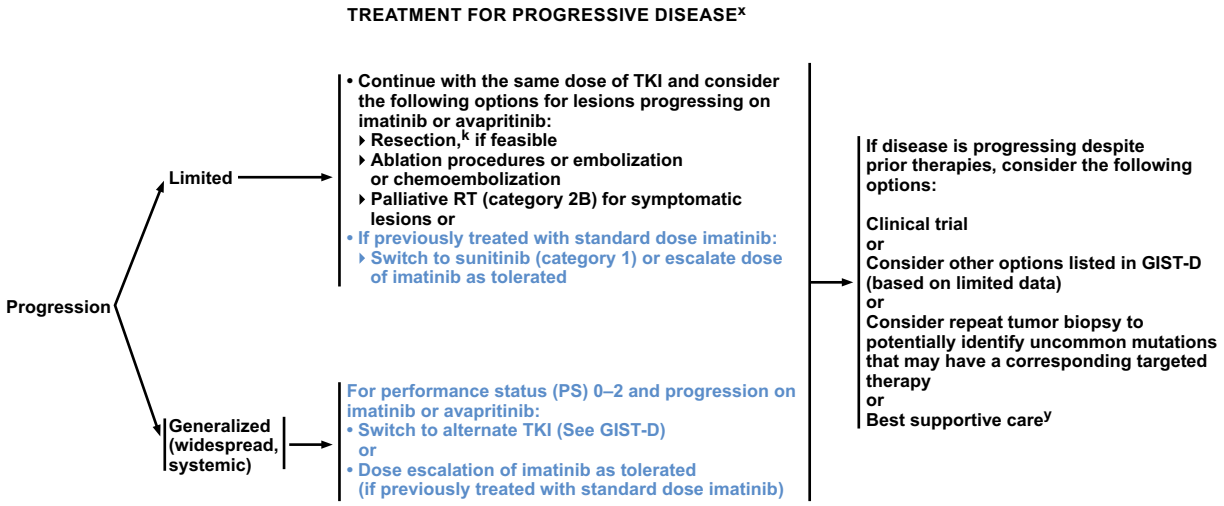
Overview

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 extra-abdominal 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]



[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.

GIST-5

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 US-Finland 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

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 Regimen** • 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 Regimen** • Regorafenib[f,8] (category 1)	**Preferred Regimen** • 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)

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 (400 mg once daily) or high-dose imatinib (400 mg 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 insensitive 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

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.

REFERENCES

1 Demetri GD, von Mehren M, Blanke CD, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. N Engl J Med 2002;347:472-480.
2 Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomized trial. Lancet 2004;364:1127-1134.
3 Heinrich M, Jones RL, von Mehren M, et al. Clinical response to avapritinib by RECIST and Choi Criteria in ≥4th line and PDGFRA exon 18 gastrointestinal stromal tumors (GIST). Connective Tissue Oncology Society Annual Meeting, Tokyo, Japan, November 15, 2019.
4 Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adult and children. N Engl J Med 2018;378:731-739.
5 Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271-282.
6 Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329-1338.
7 Schuetze SM, Bolejack V, Thomas DG, et al. Association of dasatinib with progression-free survival among patients with advanced gastrointestinal stromal tumors resistant to imatinib. JAMA Oncol 2018;4:814-820.
8 Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295-302.
9 Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:923-934.
10 Schöffski P, Mir O, Kasper B, et al. Activity and safety of the multi-target tyrosine kinase inhibitor cabozantinib in patients with metastatic gastrointestinal stromal tumour after treatment with imatinib and sunitinib: European Organisation for Research and Treatment of Cancer phase II trial 1317 'CaboGIST' Eur J Cancer 2020;134:62-74.
11 Schöffski P, Reichardt P, Blay JY, et al. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Ann Oncol 2010;21:1990-1998.
12 Montemurro M, Schoffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer 2009;45:2293-2297.
13 Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer 2011;117:4633-4641.
14 Ganjoo KN, Villalobos VM, Kamaya A., et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol 2014;25:236-40.
15 Zalcberg JR, Heinrich MC, George S, et al. Clinical benefit of ripretinib dose escalation after disease progression in advanced gastrointestinal stromal tumor: an analysis of the INVICTUS study. Oncologist 2021;26:e2053-e2060.
16 Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: A retrospective analysis. Eur J Cancer 2013;49:1027-1031.
17 Kindler HL, Campbell NP, Wroblewski K, et al. Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES) gastrointestinal stromal tumors (GIST): Final results of a University of Chicago Phase II Consortium trial. J Clin Oncol 2011;29:Abstract 10009.
18 Park SH, Ryu MH, Ryoo BY, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs 2012;30:2377-2383.

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 1207 and 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 17 and 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 (n=33) 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 daily as 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 effective for this mutation type.[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 also be 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.

References

1. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577–580.
2. Ma GL, Murphy JD, Martinez ME, et al. Epidemiology of gastrointestinal stromal tumors in the era of histology codes: results of a population-based study. Cancer Epidemiol Biomarkers Prev 2015;24:298–302.
3. Tran T, Davila JA, El-Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1,458 cases from 1992 to 2000. Am J Gastroenterol 2005;100:162–168.
4. Perez EA, Livingstone AS, Franceschi D, et al. Current incidence and outcomes of gastrointestinal mesenchymal tumors including gastrointestinal stromal tumors. J Am Coll Surg 2006;202:623–629.
5. Patel N, Benipal B. Incidence of gastrointestinal stromal tumors in the United States from 2001-2015: a United States cancer statistics analysis of 50 States. Cureus 2019;11:e4120.
6. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006;23:70–83.
7. Dematteo RP, Heinrich MC, El-Rifai WM, et al. Clinical management of gastrointestinal stromal tumors: before and after STI-571. Hum Pathol 2002;33:466–477.
8. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol 2003;21:4342–4349.
9. Casali PG, Zalcberg J, Le Cesne A, et al. Ten-year progression-free and overall survival in patients with unresectable or metastatic GI stromal tumors: long-term analysis of the European Organisation for Research and Treatment of Cancer, Italian Sarcoma Group, and Australasian Gastrointestinal Trials Group intergroup phase III randomized trial on imatinib at two dose levels. J Clin Oncol 2017;35:1713–1720.
10. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol 2004;22:3813–3825.
11. Corless CL, Schroeder A, Griffith D, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357–5364.
12. Martin-Broto J, Martinez-Marín V, Serrano C, et al. Gastrointestinal stromal tumors (GISTs): SEAP-SEOM consensus on pathologic and molecular diagnosis. Clin Transl Oncol 2017;19:536–545.
13. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006;42:1093–1103.
14. Debiec-Rychter M, Dumez H, Judson I, et al. Use of c-KIT/PDGFRA mutational analysis to predict the clinical response to imatinib in patients with advanced gastrointestinal stromal tumours entered on phase I and II studies of the EORTC Soft Tissue and Bone Sarcoma Group. Eur J Cancer 2004;40:689–695.
15. Heinrich MC, Owzar K, Corless CL, et al. Correlation of kinase genotype and clinical outcome in the North American Intergroup phase III trial of imatinib mesylate for treatment of advanced gastrointestinal stromal tumor: CALGB 150105 study by Cancer and Leukemia Group B and Southwest Oncology Group. J Clin Oncol 2008;26:5360–5367.
16. Patrikidou A, Domont J, Chabaud S, et al. Long-term outcome of molecular subgroups of GIST patients treated with standard-dose imatinib in the BFR14 trial of the French Sarcoma Group. Eur J Cancer 2016;52:173–180.
17. Gastrointestinal Stromal Tumor Meta-Analysis Group (MetaGIST). Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. J Clin Oncol 2010;28:1247–1253.
18. Hirota S, Ohashi A, Nishida T, et al. Gain-of-function mutations of platelet-derived growth factor receptor alpha gene in gastrointestinal stromal tumors. Gastroenterology 2003;125:660–667.
19. Cassier PA, Fumagalli E, Rutkowski P, et al. Outcome of patients with platelet-derived growth factor receptor alpha-mutated gastrointestinal

stromal tumors in the tyrosine kinase inhibitor era. Clin Cancer Res 2012; 18:4458–4464.
20. Joensuu H, Wardelmann E, Sihto H, et al. Effect of KIT and PDGFRA mutations on survival in patients with gastrointestinal stromal tumors treated with adjuvant imatinib: an exploratory analysis of a randomized clinical trial. JAMA Oncol 2017;3:602–609.
21. U.S. Food & Drug Administration. FDA approves avapritinib for gastrointestinal stromal tumor with a rare mutation. Accessed August 16, 2022. Available at: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-avapritinib-gastrointestinal-stromal-tumor-rare-mutation
22. Ayvakit (avapritinib) tablets, for oral use [prescribing information]. Cambridge, MA: Blueprint Medicines Corporation; 2020.
23. Heinrich MC, Jones RL, von Mehren M, et al. Avapritinib in advanced PDGFRA D842V-mutant gastrointestinal stromal tumour (NAVIGATOR): a multicentre, open-label, phase 1 trial. Lancet Oncol 2020;21:935–946.
24. Jones RL, Serrano C, von Mehren M, et al. Avapritinib in unresectable or metastatic PDGFRA D842V-mutant gastrointestinal stromal tumours: long-term efficacy and safety data from the NAVIGATOR phase I trial. Eur J Cancer 2021;145:132–142.
25. Janeway KA, Kim SY, Lodish M, et al. Defects in succinate dehydrogenase in gastrointestinal stromal tumors lacking KIT and PDGFRA mutations. Proc Natl Acad Sci USA 2011;108:314–318.
26. Miettinen M, Wang ZF, Sarlomo-Rikala M, et al. Succinate dehydrogenase-deficient GISTs: a clinicopathologic, immunohistochemical, and molecular genetic study of 66 gastric GISTs with predilection to young age. Am J Surg Pathol 2011;35:1712–1721.
27. Heinrich MC, Rankin C, Blanke CD, et al. Correlation of long-term results of imatinib in advanced gastrointestinal stromal tumors with next-generation sequencing results: analysis of phase 3 SWOG intergroup trial S0033. JAMA Oncol 2017;3:944–952.
28. Boikos SA, Pappo AS, Killian JK, et al. Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors: a report from the National Institutes of Health Gastrointestinal Stromal Tumor Clinic. JAMA Oncol 2016;2:922–928.
29. Liu W, Zeng X, Wu X, et al. Clinicopathologic study of succinate-dehydrogenase-deficient gastrointestinal stromal tumors: a single-institutional experience in China. Medicine (Baltimore) 2017;96:e7668.
30. Sutent (sunitinib malate) capsules, for oral use [prescribing information]. New York, NY: Pfizer Labs; 2021.
31. Stivarga (regorafenib) tablets, for oral use [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals Inc.; 2020.
32. Ben-Ami E, Barysauskas CM, von Mehren M, et al. Long-term follow-up results of the multicenter phase II trial of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of standard tyrosine kinase inhibitor therapy. Ann Oncol 2016;27:1794–1799.
33. Ganjoo KN, Villalobos VM, Kamaya A, et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol 2014;25:236–240.
34. Votrient (pazopanib) tablets, for oral use [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2021.
35. Yebra M, Bhargava S, Kumar A, et al. Establishment of patient-derived succinate dehydrogenase-deficient gastrointestinal stromal tumor models for predicting therapeutic response. Clin Cancer Res 2022;28:187–200.
36. Lee JH, Shin SJ, Choe EA, et al. Tropomyosin-related kinase fusions in gastrointestinal stromal tumors. Cancers (Basel) 2022;14:2659.
37. Brenca M, Rossi S, Polano M, et al. Transcriptome sequencing identifies ETV6-NTRK3 as a gene fusion involved in GIST. J Pathol 2016;238: 543–549.
38. Shi E, Chmielecki J, Tang CM, et al. FGFR1 and NTRK3 actionable alterations in "wild-type" gastrointestinal stromal tumors. J Transl Med 2016;14:339.
39. Vitrakvi (larotrectinib) capsules, for oral use [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc.; 2022.
40. Rozlytrek (entrectinib) capsules, for oral use [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2021.
41. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. N Engl J Med 2018;378: 731–739.
42. Doebele RC, Drilon A, Paz-Ares L, et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol 2020;21:271–282.
43. Agaram NP, Wong GC, Guo T, et al. Novel V600E BRAF mutations in imatinib-naive and imatinib-resistant gastrointestinal stromal tumors. Genes Chromosomes Cancer 2008;47:853–859.
44. Hostein I, Faur N, Primois C, et al. BRAF mutation status in gastrointestinal stromal tumors. Am J Clin Pathol 2010;133:141–148.
45. Maertens O, Prenen H, Debiec-Rychter M, et al. Molecular pathogenesis of multiple gastrointestinal stromal tumors in NF1 patients. Hum Mol Genet 2006;15:1015–1023.
46. Belinsky MG, Rink L, Cai KQ, et al. Somatic loss of function mutations in neurofibromin 1 and MYC associated factor X genes identified by exome-wide sequencing in a wild-type GIST case. BMC Cancer 2015;15:887.
47. Burgoyne AM, De Siena M, Alkhuziem M, et al. Duodenal-jejunal flexure GI stromal tumor frequently heralds somatic NF1 and Notch pathway mutations. JCO Precis Oncol 2017;1:1–12.
48. Charo LM, Burgoyne AM, Fanta PT, et al. A novel PRKAR1B-BRAF fusion in gastrointestinal stromal tumor guides adjuvant treatment decision-making during pregnancy. J Natl Compr Canc Netw 2018;16:238–242.
49. NCI Staff. Dabrafenib-trametinib combination approved for solid tumors with BRAF mutations. Accessed August 16, 2022. Available at: https://www.cancer.gov/news-events/cancer-currents-blog/2022/fda-dabrafenib-trametinib-braf-solid-tumors
50. Heinrich MC, Maki RG, Corless CL, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26: 5352–5359.
51. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res 2005;11:4182–4190.
52. Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24: 4764–4774.
53. Wardelmann E, Merkelbach-Bruse S, Pauls K, et al. Polyclonal evolution of multiple secondary KIT mutations in gastrointestinal stromal tumors under treatment with imatinib mesylate. Clin Cancer Res 2006;12:1743–1749.
54. Desai J, Shankar S, Heinrich MC, et al. Clonal evolution of resistance to imatinib in patients with metastatic gastrointestinal stromal tumors. Clin Cancer Res 2007;13:5398–5405.
55. Zalcberg JR, Verweij J, Casali PG, et al. Outcome of patients with advanced gastro-intestinal stromal tumours crossing over to a daily imatinib dose of 800 mg after progression on 400 mg. Eur J Cancer 2005;41: 1751–1757.
56. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. Lancet 2006;368:1329–1338.
57. George S, Blay JY, Casali PG, et al. Clinical evaluation of continuous daily dosing of sunitinib malate in patients with advanced gastrointestinal stromal tumour after imatinib failure. Eur J Cancer 2009;45:1959–1968.
58. Patel S, Zalcberg JR. Optimizing the dose of imatinib for treatment of gastrointestinal stromal tumours: lessons from the phase 3 trials. Eur J Cancer 2008;44:501–509.
59. Goodman VL, Rock EP, Dagher R, et al. Approval summary: sunitinib for the treatment of imatinib refractory or intolerant gastrointestinal stromal tumors and advanced renal cell carcinoma. Clin Cancer Res 2007;13: 1367–1373.
60. Gajiwala KS, Wu JC, Christensen J, et al. KIT kinase mutants show unique mechanisms of drug resistance to imatinib and sunitinib in gastrointestinal stromal tumor patients. Proc Natl Acad Sci USA 2009;106:1542–1547.
61. Guo T, Hajdu M, Agaram NP, et al. Mechanisms of sunitinib resistance in gastrointestinal stromal tumors harboring KITAY502-3ins mutation: an in vitro mutagenesis screen for drug resistance. Clin Cancer Res 2009;15:6862–6870.
62. Nishida T, Takahashi T, Nishitani A, et al. Sunitinib-resistant gastrointestinal stromal tumors harbor cis-mutations in the activation loop of the KIT gene. Int J Clin Oncol 2009;14:143–149.
63. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295–302.
64. Qinlock (ripretinib) tablets, for oral use [prescription information]. Waltham, MA: Deciphera, LLC; 2021.
65. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:923–934.
66. Zalcberg JR, Heinrich MC, George S, et al. Clinical benefit of ripretinib dose escalation after disease progression in advanced gastrointestinal stromal tumor: an analysis of the INVICTUS study. Oncologist 2021;26: e2053–2060.
67. Kindler HL, Campbell NP, Wroblewski K, et al. Sorafenib (SOR) in patients (pts) with imatinib (IM) and sunitinib (SU)-resistant (RES)

gastrointestinal stromal tumors (GIST): final results of a University of Chicago phase II consortium trial [abstract]. J Clin Oncol 2011; 29(Suppl):Abstract 10009.
68. Park SH, Ryu MH, Ryoo BY, et al. Sorafenib in patients with metastatic gastrointestinal stromal tumors who failed two or more prior tyrosine kinase inhibitors: a phase II study of Korean gastrointestinal stromal tumors study group. Invest New Drugs 2012;30:2377–2383.
69. Montemurro M, Gelderblom H, Bitz U, et al. Sorafenib as third- or fourth-line treatment of advanced gastrointestinal stromal tumour and pretreatment including both imatinib and sunitinib, and nilotinib: a retrospective analysis. Eur J Cancer 2013;49:1027–1031.
70. Kefeli U, Benekli M, Sevinc A, et al. Efficacy of sorafenib in patients with gastrointestinal stromal tumors in the third- or fourth-line treatment: a retrospective multicenter experience. Oncol Lett 2013;6:605–611.
71. Demetri GD, Casali PG, Blay JY, et al. A phase I study of single-agent nilotinib or in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Clin Cancer Res 2009;15: 5910–5916.
72. Montemurro M, Schöffski P, Reichardt P, et al. Nilotinib in the treatment of advanced gastrointestinal stromal tumours resistant to both imatinib and sunitinib. Eur J Cancer 2009;45:2293–2297.
73. Sawaki A, Nishida T, Doi T, et al. Phase 2 study of nilotinib as third-line therapy for patients with gastrointestinal stromal tumor. Cancer 2011; 117:4633–4641.
74. Reichardt P, Blay JY, Gelderblom H, et al. Phase III study of nilotinib versus best supportive care with or without a TKI in patients with gastrointestinal stromal tumors resistant to or intolerant of imatinib and sunitinib. Ann Oncol 2012;23:1680–1687.
75. Cauchi C, Somaiah N, Engstrom PF, et al. Evaluation of nilotinib in advanced GIST previously treated with imatinib and sunitinib. Cancer Chemother Pharmacol 2012;69:977–982.
76. Blay JY, Shen L, Kang YK, et al. Nilotinib versus imatinib as first-line therapy for patients with unresectable or metastatic gastrointestinal stromal tumours (ENESTg1): a randomised phase 3 trial. Lancet Oncol 2015;16: 550–560.
77. Mir O, Cropet C, Toulmonde M, et al. Pazopanib plus best supportive care versus best supportive care alone in advanced gastrointestinal stromal tumours resistant to imatinib and sunitinib (PAZOGIST): a randomised, multicentre, open-label phase 2 trial. Lancet Oncol 2016;17:632–641.
78. Schöffski P, Mir O, Kasper B, et al. Activity and safety of the multi-target tyrosine kinase inhibitor cabozantinib in patients with metastatic gastrointestinal stromal tumour after treatment with imatinib and sunitinib: European Organisation for Research and Treatment of Cancer phase II trial 1317 'CaboGIST'. Eur J Cancer 2020;134:62–74.
79. Schöffski P, Reichardt P, Blay JY, et al. A phase I-II study of everolimus (RAD001) in combination with imatinib in patients with imatinib-resistant gastrointestinal stromal tumors. Ann Oncol 2010;21:1990–1998.
80. Dewaele B, Wasag B, Cools J, et al. Activity of dasatinib, a dual SRC/ABL kinase inhibitor, and IPI-504, a heat shock protein 90 inhibitor, against gastrointestinal stromal tumor-associated PDGFRAD842V mutation. Clin Cancer Res 2008;14:5749–5758.
81. Trent JC, Wathen K, von Mehren M, et al. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST) [abstract]. J Clin Oncol 2011;29(Suppl):Abstract 10006.
82. Schuetze SM, Bolejack V, Thomas DG, et al. Association of dasatinib with progression-free survival among patients with advanced gastrointestinal stromal tumors resistant to imatinib. JAMA Oncol 2018;4: 814–820.
83. Smith BD, Kaufman MD, Lu WP, et al. Ripretinib (DCC-2618) is a switch control kinase inhibitor of a broad spectrum of oncogenic and drug-resistant KIT and PDGFRA variants. Cancer Cell 2019;35:738–751.e9.
84. Alkhuziem M, Burgoyne AM, Fanta PT, et al. The call of "the wild"-type GIST: it's time for domestication. J Natl Compr Canc Netw 2017;15:551–554.
85. Kato S, Adashek JJ, Shaya J, et al. Concomitant MEK and cyclin gene alterations: implications for response to targeted therapeutics. Clin Cancer Res 2021;27:2792–2797.