NCCN Guidelines® Insights

Gastrointestinal Stromal Tumors, Version 2.2014

Featured Updates to the NCCN Guidelines

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Abstract

Gastrointestinal stromal tumors (GIST) are the most common soft tissue sarcoma of the gastrointestinal tract, resulting most commonly from *KIT* or platelet-derived growth factor receptor α (*PDGFRα*)–activating mutations. These NCCN Guideline Insights highlight the important updates to the NCCN Guidelines for Soft Tissue Sarcoma specific to the management of patients with GIST experiencing disease progression while on imatinib and/or sunitinib. (*J Natl Compr Canc Netw* 2014;12:853–862)

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Learning Objectives:

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

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

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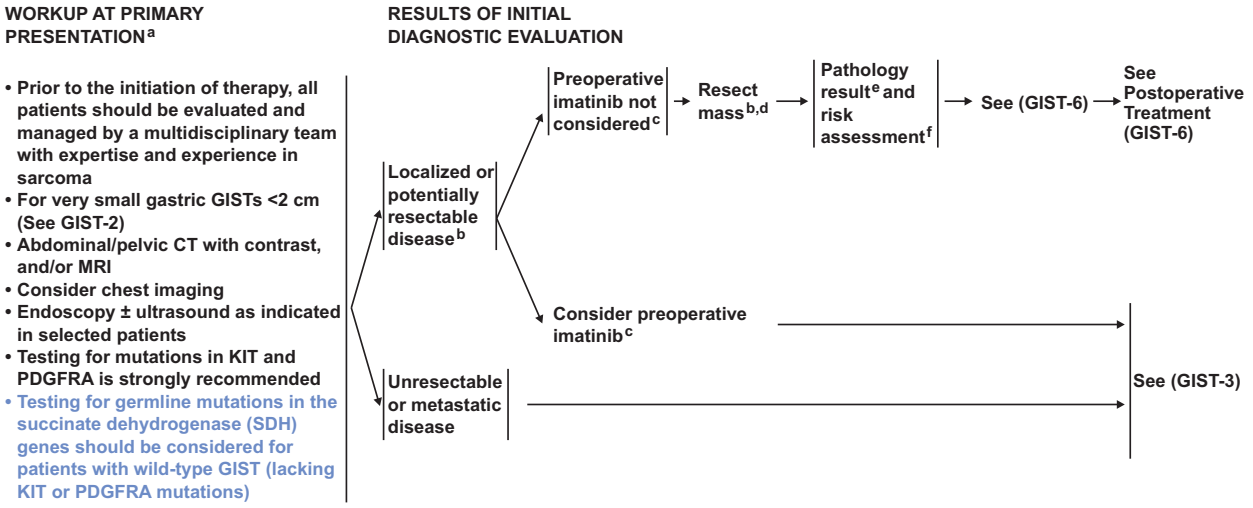


[a]See American Joint Committee on Cancer (AJCC) Staging, 7th Edition (ST-3/GIST).
[b]Surgery should induce minimal surgical morbidity; consider preoperative imatinib if surgery would induce significant morbidity.
[c]Preoperative imatinib may prohibit accurate assessment of recurrence risk. Consider preoperative imatinib only if surgical morbidity could be reduced by downstaging the tumor preoperatively.
[d]See Principles of Surgery for GIST (GIST-C).
[e]Pathology report should include anatomic location, size, and an accurate assessment of the mitotic rate measured in the most proliferative area of the tumor. Mutational analysis may predict response to therapy with tyrosine kinase inhibitors. (See Principles of Pathologic Assessment For GIST [GIST-B]).
[f]See RETSARC-1, if the pathology results indicate sarcomas of GI origin other than GIST.

GIST-1

NCCN Categories of Evidence and Consensus

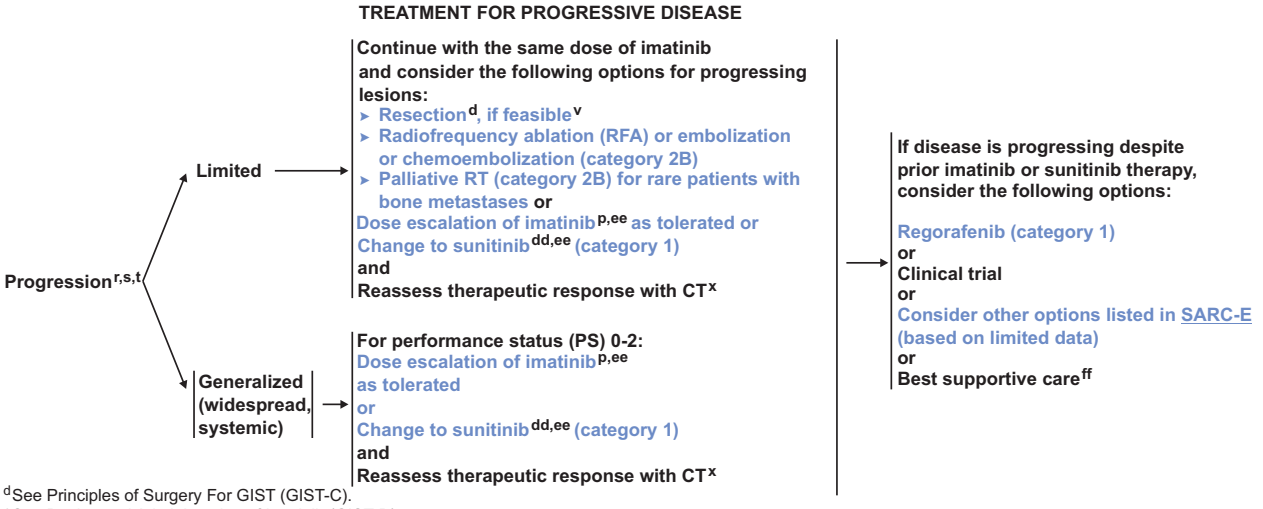
Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that 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 for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Soft tissue sarcomas (STS) are a heterogeneous group of rare solid tumors with distinct clinical and pathologic features. In 2014, an estimated 12,020 people will be diagnosed with STS in the United States, and approximately 4740 will die of the disease.[1] Gastrointestinal stromal tumors (GIST) are the most common STS of the gastrointestinal tract, resulting most commonly from *KIT* or platelet-derived growth factor receptor α (*PDGFRα*)–activating mutations.[2] Loss-of-function mutations in the succinate dehydrogenase (*SDH*) gene subunits or loss of SDH subunit B (SDHB) protein expression by immunohistochemistry have been identified in wild-type GIST lacking *KIT* and *PDGFRα* mutations; these findings have led to the use of the term *SDH-deficient GIST*, which is preferred over the older term, *wild-type GIST*, for this subset of GIST.[3–7] *SDH* gene mutational analysis for the identification of germline mutations in the *SDH* gene subunits should be considered for patients



[d] See Principles of Surgery For GIST (GIST-C).
[p] See Dosing and Administration of Imatinib (GIST-D).
[r] Rarely, increase in tumor size may not indicate lack of drug efficacy; all clinical and radiographic data should be taken into account, including lesion density on CT.
[s] Progression may be determined by CT or MRI with clinical interpretation; PET scan may be used to clarify if CT or MRI are ambiguous.
[t] Suggest referral to a sarcoma specialty center.
[v] Imatinib can be stopped right before surgery and restarted as soon as the patient is able to tolerate oral medications. If other TKIs, such as sunitinib or regorafenib, are being used, therapy should be stopped at least one week prior to surgery and can be restarted based on clinical judgement or recovery from surgery.
[x] Consider PET only if CT results are ambiguous.
[dd] See Dosing and Administration of Sunitinib (GIST-E).
[ee] Clinical experience suggests that discontinuing tyrosine kinase inhibitor (TKI) therapy, even in the setting of progressive disease, may accelerate the pace of disease progression and worsen symptoms.
[ff] In patients with GIST progressing despite prior imatinib, sunitinib, and regorafenib consider other options listed in SARC-E (based on limited data) or reintroduction of a previously tolerated and effective TKI for palliation of symptoms. Consider continuation of TKI therapy life-long for palliation of symptoms as part of best supportive care.

GIST-7

with GIST lacking *KIT* or *PDGFRα* mutations (see GIST-1 and GIST-B, pages 855 and 857).

The introduction of KIT and PDGFRα inhibitors such as imatinib and sunitinib has significantly improved the outcomes in patients with unresectable or metastatic GIST. Regorafenib, another multikinase inhibitor, was recently approved for the treatment of patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib.

These NCCN Guidelines Insights discuss the management of patients with GIST experiencing disease progression while on imatinib and/or sunitinib.

GIST: Management of Progressive Disease

Resistance to Imatinib and Sunitinib

Imatinib is the standard first-line therapy for patients with unresectable or metastatic GIST. In phase II and III studies, imatinib has resulted in high overall response rates and exceptionally good progression-free survival (PFS) in patients with unresectable and/or metastatic GIST, inducing objective responses in more than 50%.[8–12] The presence and type of *KIT* or *PDGFRα* mutation status has been identified as the predictor of response to imatinib. In randomized clinical trials, the presence of a *KIT* exon 11 mutation was associated with better response rates, PFS, and overall survival (OS) than *KIT* exon 9 mutations or wild-type GISTs.[13–16]

The EORTC 62005 study group identified the presence of *KIT* exon 9 mutation as the strongest adverse prognostic factor for risk of progression and death.[14] A meta-analysis of the EORTC 62005 and SWOG S0033/CALGB 150105 phase III trials that randomized 1640 patients with advanced GIST to standard-dose (400 mg/d) or high-dose imatinib (800 mg/d) showed a PFS benefit for patients with *KIT* exon 9 mutations treated with 800 mg of ima-

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PRINCIPLES OF PATHOLOGIC ASSESSMENT FOR GIST

- **Pathologic assessment should follow the guidelines outlined in SARC-A.**
- **Morphologic diagnosis based on microscopic examination of histologic sections is the standard for GIST diagnosis. Several ancillary techniques are useful in support of GIST diagnosis, including immunohistochemistry (95% express CD117 and 80% express CD34, DOG1) and molecular genetic testing (for mutations in *KIT* or *PDGFRA*). DOG1 immunostaining may be useful for cases that cannot be categorized as GIST based on CD117 immunostaining. Referral to centers with expertise in sarcoma diagnosis is recommended for cases with complex or unusual histopathologic features.**
- **Tumors lacking KIT or PDGFRA mutations should be considered for further evaluations such as staining for SDHB by immunohistochemistry, BRAF mutation analysis and SDH gene mutation analysis.**
- **Tumor size and mitotic rate are used as guides to predict the malignant potential of GISTs, although it is notoriously difficult to predict the biologic potential of individual cases. The mitotic rate should be measured in the most proliferative area of the tumor, and reported as the number of mitoses per 5 mm^2 of tissue.**
- **Approximately 80% of GISTs have a mutation in the gene encoding the *KIT* receptor tyrosine kinase; another 5%-10% of GISTs have a mutation in the gene encoding the related *PDGFRA* receptor tyrosine kinase. Since about 10%-15% of GISTs have no detectable *KIT* or *PDGFRA* mutation, the absence of a mutation does not exclude the diagnosis of GIST. The presence and type of *KIT* and *PDGFRA* mutations are not strongly correlated with prognosis.**
- **The mutations in *KIT* and *PDGFRA* in GIST result in expression of mutant proteins with constitutive tyrosine kinase activity. If tyrosine kinase inhibitors are considered as part of the treatment plan, genetic analysis of the tumor should be considered since the presence of mutations (or absence of mutations) in specific regions of the *KIT* and *PDGFRA* genes are correlated with response (or lack of a response) to specific tyrosine kinase inhibitors. However, the type of mutation cannot be accurately predicted based on the anatomic site of origin or histopathologic features.**
- **In patients with advanced GISTs, approximately 90% of patients benefit from imatinib when their tumors have a *KIT* exon 11 mutation; approximately 50% of patients benefit from imatinib when their tumors harbor a *KIT* exon 9 mutation, and the likelihood of response improves with the use of 800 mg imatinib rather than the standard 400 mg dose. Most mutations in the *PDGFRA* gene are associated with a response to imatinib, with the notable exception of D842V. In the absence of *KIT* and *PDGFRA* mutations, only a subset of patients with advanced GISTs benefit from imatinib. Metastatic disease with acquired drug resistance is usually the result of secondary, imatinib-resistant mutations in *KIT* or *PDGFRA*. Sunitinib treatment is indicated for patients with imatinib-resistant tumors, or imatinib intolerance. Regorafenib is indicated for patients with disease progression on imatinib and sunitnib.**

GIST-B

tinib.[17] In a recent international survey that reported the outcome of patients with GIST with *PDGFRα* mutations, none of the 31 evaluable patients with D842V mutation experienced a response, whereas 21 (68%) experienced disease progression.[18] Median PFS was 2.8 months for patients with D842V substitution and 28.5 months for patients with other *PDGFRα* mutations. With 46 months of follow-up, median OS was 14.7 months for patients with D842V substitutions and was not reached for those with other *PDGFRα* mutations.

Although imatinib benefits most patients with advanced GIST, some develop resistance to the drug. Primary resistance is defined as the evidence of clinical progression developing during the first 6 months of imatinib therapy, and is most commonly seen in patients with *KIT* exon 9 mutations treated with imatinib at 400 mg/d or patients with *PDGFRα* exon 18 D842V mutations, or those with tumors that lack identifiable activating mutations in *KIT* or *PDGFRα*, most of which are SDH-deficient GIST.[13,14,16,19] Secondary resistance is seen in patients who have been on imatinib for more than 6 months with an initial response or disease stabilization followed by progression, most commonly because of the outgrowth of tumor clones with secondary mutations in *KIT*.[20–23] Dose escalation to 800 mg/d or switching to sunitinib is a reasonable option for patients experiencing disease progression on imatinib at 400 mg/d.[10,24,25]

Sunitinib is a multikinase inhibitor active against a variety of tyrosine kinases, including KIT, PDGFR, and vascular endothelial growth factor receptor (VEGFR). In randomized clinical studies, sunitinib has resulted in a significant improvement in median time to progression and a significantly greater estimated OS in patients with imatinib-resistant GIST compared with placebo.[24,25] Heinrich et al[19] reported that sunitinib induced higher response rates in patients with primary *KIT* exon 9 mutations than those with

SYSTEMIC THERAPY AGENTS AND REGIMENS WITH ACTIVITY IN GASTROINTESTINAL STROMAL TUMORS (GIST)[a]

GIST[b]
- **Imatinib[1,2]**
- **Sunitinib[3]**
- **Regorafenib[4]**

Disease progression after imatinib, sunitinib, and regorafenib
- **Sorafenib[5-7]**
- **Nilotinib[8,9]**
- **Dasatinib[10] (for patients with D842V mutation)**

[a]Prior to the initiation of therapy, all patients should be evaluated and managed by a multidisciplinary team with expertise and experience in sarcoma.
[b]Imatinib, sunitinib, and regorafenib are the three agents that are FDA approved for the treatment of GIST.

[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(9440):1127-1134.
[3]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.
[4] 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.
[5] 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.
[6]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.
[7]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.
[8]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.
[9]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.
[10]Trent JC, Wathen K, von Mehren M, et al. A phase II study of dasatinib for patients with imatinib-resistant gastrointestinal stromal tumor (GIST). J Clin Oncol 2011;29:Abstract 10006.

SARC-E

KIT exon 11 mutations (58% vs 34%, respectively). PFS and OS were significantly longer for patients with *KIT* exon 9 mutations or wild-type GIST compared with those with *KIT* exon 11 mutations. Only 4 patients had *PDGFRα* mutations; of these, 2 had a primary and 1 a secondary D842V mutation and did not experience response to treatment. In patients with *KIT* exon 11 mutations, PFS and OS were longer for those with secondary exon 13 or 14 mutations compared with those with exon 17 or 18 mutations. Additional studies are needed to confirm these findings.

Comprehensive molecular studies investigating the mechanisms of resistance to sunitinib are limited because of the small number of patients who are surgical candidates after failure of 2 tyrosine kinase inhibitor (TKI) therapies. Nevertheless, available evidence (both clinical and preclinical) indicates that although sunitinib is very sensitive to ATP-binding pocket mutations that confer resistance to imatinib, it has little activity against other imatinib-resistant mutations in the KIT activation loop.[26–28]

Management of Resistance to Imatinib and Sunitinib

Regorafenib, a multikinase inhibitor with activity against KIT, PDGFR, and VEGFR, was recently approved by the FDA for the treatment of patients with locally advanced, unresectable, or metastatic GIST previously treated with imatinib and sunitinib. A phase III study randomized 199 patients with metastatic and/or unresectable GIST experiencing disease progression on prior therapy with imatinib and sunitinib to either regorafenib (n=133) or placebo (n=66).[29] The median PFS (4.8 vs 0.9 months; $P<.0001$) and disease control rate (53% vs 9%) were significantly higher for regorafenib compared with 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

hazard ratio for OS was 0.77, with 85% of patients in the placebo arm crossing over to regorafenib because of disease progression. The most common treatment-related adverse events (≥ grade 3) were hypertension (23%), hand-foot skin reaction (20%), and diarrhea (5%).

Sorafenib,[30–33] nilotinib,[34–38] dasatinib,[39,40] and pazopanib[41] have also shown activity in patients with GIST resistant to imatinib and sunitinib. Much of the data on these TKIs are from phase II studies and retrospective analyses involving small numbers of patients.

In a prospective multicenter phase II study of 38 patients with unresectable KIT$^+$ GIST that had progressed on imatinib and sunitinib, sorafenib resulted in a disease control rate of 68% (55% of patients had stable disease and 13% had a partial response).[30] Median PFS and OS were 5.2 and 11.6 months, respectively; 1- and 2-year survival rates were 50% and 29%, respectively. In a retrospective analysis of 124 patients with metastatic GIST resistant to imatinib and sunitinib, sorafenib also demonstrated activity, resulting in a median PFS and OS of 6.4 and 13.5 months, respectively.[32] Notably, patients included in this study had not been treated with regorafenib, and the efficacy of sorafenib following regorafenib therapy in patients with metastatic GIST resistant to imatinib and sunitinib has not been studied.

In a retrospective analysis of 52 patients with advanced GIST resistant to imatinib and sunitinib, nilotinib resulted in response and disease control rates of 10% and 37%, respectively.[35] Median PFS and OS were 12 and 34 weeks, respectively. In a randomized phase III study of nilotinib as third-line therapy and best supportive care (with or without a TKI) in patients who were resistant or intolerant to imatinib and sunitinib (248 patients), the PFS associated with nilotinib was not found to be superior to best supportive care (109 vs 111 days; P=.56). In a post hoc subset analysis, patients experiencing progression on both imatinib and sunitinib who had not received any other therapy had an improved OS (>4 months) with nilotinib compared with best supportive care (405 vs 280 days; P=.02). The clinical benefit associated with nilotinib may be specific to subsets of patients with *KIT* exon 17 mutations, previously treated with imatinib and sunitinib.[38]

Dasatinib has demonstrated activity against the *PDGFRα* D842V mutation that confers the highest resistance to imatinib, and it could be an effective treatment option for this group of patients with imatinib-resistant GIST.[39] In the phase II study of 50 patients with advanced GIST resistant to imatinib, dasatinib was associated with a median PFS and OS of 2 and 19 months, respectively, with response assessment based on Choi criteria.[40] Median PFS for patients with wild-type GIST was 8.4 months.

Pazopanib has also shown marginal activity in heavily pretreated patients with advanced GIST. In a multicenter phase II study of patients with advanced GIST following failure of at least imatinib and sunitinib (n=25), pazopanib was well tolerated, resulting in stable disease in 48% of patients, with a 24-week nonprogression (complete response + partial response + stable disease) rate of 17%.[41] The median PFS and OS were 1.9 and 10.7 months, respectively.

NCCN Recommendations

Dose escalation of imatinib up to 800 mg/d (given as 400 mg twice daily) as tolerated or switching to sunitinib (category 1) are included as options for patients experiencing progressive disease (limited disease or widespread systemic disease in patients with good performance status) on standard-dose imatinib (see GIST-7, page 856).[10,24,25] All clinical and radiologic data, including lesion density on CT and patient compliance to treatment with standard-dose imatinib, should be assessed before dose escalation of imatinib or switching to sunitinib.

For patients with limited progressive disease on standard-dose imatinib, second-line therapy with sunitinib should be initiated only if most of the disease is no longer controlled by imatinib; consideration of other therapeutic interventions for progressing lesions is warranted. Surgical resection should be considered in carefully selected patients with limited progressive disease that is potentially easily resectable.[42–44] However, incomplete resections are frequent, with high complication rates. The guidelines have included, only for patients with limited progressive disease, continuation of imatinib at the same initial dose and treatment of progressing lesions with resection or radiofrequency ablation or chemoembolization or palliative RT (for rare patients with bone metastases) as an option.[45]

Regorafenib (category 1) is recommended for patients experiencing disease progression on imatinib and sunitinib.[29] Based on the limited data,[30–40]

the NCCN Guidelines have also included sorafenib, dasatinib, and nilotinib as additional options for patients who are no longer receiving clinical benefit from imatinib, sunitinib, or regorafenib (see SARC-E, page 858), although all data regarding the potential benefit of these agents are from the pre-regorafenib era.

In patients with progressive disease no longer receiving benefit from current TKI therapy, reintroduction of previously tolerated and effective TKI therapy for palliation of symptoms can be considered (see GIST-7, page 856).[46,47] The results of a recent randomized study showed that imatinib rechallenge significantly improved PFS and disease control rate in patients with advanced GIST after failure of at least imatinib and sunitinib.[47] However, the duration of survival benefit was brief because of continued progression of TKI-resistant clones.

Any patient who experiences disease progression despite prior therapy or who has a recurrence, regardless of presentation, should be considered a candidate for enrollment in a clinical trial, if an appropriate trial is available.

Continuation of TKI Therapy

The optimal duration of TKI therapy in patients with responding or stable disease is not known. The results of a prospective, multicenter, randomized phase III study (BFR14) showed a significant increase in the rate of disease progression when imatinib was interrupted in patients with advanced disease who were stable or responding to imatinib.[48,49] A recent report from this study confirmed that patients with rapid disease progression after interruption of imatinib had a poorer prognosis.[50] More importantly, the quality of response on reintroduction of imatinib did not reach the tumor status observed at randomization.

The panel strongly recommends that TKI therapy at the prescribed daily dose should be continued as long as patients are experiencing clinical benefit (response or stable disease). The panel also feels that continuation of TKI therapy lifelong for palliation of symptoms should be an essential component of best supportive care (see GIST-7, page 856). However, short interruptions of 1 to 2 weeks, when medically necessary, have not been shown to impact negatively on disease control or other outcomes.

Summary

GIST is the most common STS of the gastrointestinal tract, resulting most commonly from *KIT*- or *PDGFRα*-activating mutations. TKI therapy with imatinib, sunitinib, and regorafenib has emerged as an effective treatment option for patients with unresectable or metastatic GIST. Dose escalation of imatinib up to 800 mg/d as tolerated or switching to sunitinib are included as options for patients with progressive disease on standard-dose imatinib. Regorafenib is recommended for patients experiencing disease progression while on imatinib and sunitinib. TKI therapy at the prescribed daily dose should be continued as long as patients are receiving clinical benefit (response or stable disease).

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA Cancer J Clin 2014;64:9–29.
2. 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.
3. 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 U S A 2011;108:314–318.
4. Italiano A, Chen CL, Sung YS, et al. SDHA loss of function mutations in a subset of young adult wild-type gastrointestinal stromal tumors. BMC Cancer 2012;12:408.
5. Oudijk L, Gaal J, Korpershoek E, et al. SDHA mutations in adult and pediatric wild-type gastrointestinal stromal tumors. Mod Pathol 2013;26:456–463.
6. Pantaleo MA, Astolfi A, Urbini M, et al. Analysis of all subunits, SDHA, SDHB, SDHC, SDHD, of the succinate dehydrogenase complex in KIT/PDGFRA wild-type GIST. Eur J Hum Genet 2014;22:32–39.
7. Doyle LA, Nelson D, Heinrich MC, et al. Loss of succinate dehydrogenase subunit B (SDHB) expression is limited to a distinctive subset of gastric wild-type gastrointestinal stromal tumours: a comprehensive genotype-phenotype correlation study. Histopathology 2012;61:801–809.
8. 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.
9. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomised trial. Lancet 2004;364:1127–1134.
10. 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.
11. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic

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gastrointestinal stromal tumors expressing KIT. J Clin Oncol 2008;26:620–625.

12. Blanke CD, Rankin C, Demetri GD, et al. Phase III randomized, intergroup trial assessing imatinib mesylate at two dose levels in patients with unresectable or metastatic gastrointestinal stromal tumors expressing the kit receptor tyrosine kinase: S0033. J Clin Oncol 2008;26:626–632.
13. 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.
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. 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.
16. 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.
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. 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.
19. 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.
20. 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.
21. Heinrich MC, Corless CL, Blanke CD, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24:4764–4774.
22. 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.
23. 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.
24. 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.
25. 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.
26. 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 U S A 2009;106:1542–1547.
27. 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.
28. 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.
29. 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.
30. 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(15 Suppl):Abstract 10009.
31. 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.
32. 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.
33. 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.
34. 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.
35. 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.
36. 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.
37. 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.
38. 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.
39. 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.
40. 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(15 Suppl):Abstract 10006.

41. 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.

42. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol 2006;24:2325–2331.

43. Sym SJ, Ryu MH, Lee JL, et al. Surgical intervention following imatinib treatment in patients with advanced gastrointestinal stromal tumors (GISTs). J Surg Oncol 2008;98:27–33.

44. Raut CP, Wang Q, Manola J, et al. Cytoreductive surgery in patients with metastatic gastrointestinal stromal tumor treated with sunitinib malate. Ann Surg Oncol 2010;17:407–415.

45. Demetri GD, von Mehren M, Antonescu CR, et al. NCCN Task Force report: update on the management of patients with gastrointestinal stromal tumors. J Natl Compr Canc Netw 2010;8(Suppl 2):S1–41.

46. Fumagalli E, Coco P, Morosi C, et al. Rechallenge with imatinib in GIST patients resistant to second or third line therapy [abstract]. Presented at the Connective Tissue Oncology Society (CTOS) 15th Annual Meeting; November 5–7, 2009; Miami, Florida. Abstract 39404.

47. Kang YK, Ryu MH, Yoo C, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2013;14:1175–1182.

48. Blay JY, Le Cesne A, Ray-Coquard I, et al. Prospective multicentric randomized phase III study of imatinib in patients with advanced gastrointestinal stromal tumors comparing interruption versus continuation of treatment beyond 1 year: the French Sarcoma Group. J Clin Oncol 2007;25:1107–1113.

49. Le Cesne A, Ray-Coquard I, Bui BN, et al. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. Lancet Oncol 2010;11:942–949.

50. Patrikidou A, Chabaud S, Ray-Coquard I, et al. Influence of imatinib interruption and rechallenge on the residual disease in patients with advanced GIST: results of the BFR14 prospective French Sarcoma Group randomised, phase III trial. Ann Oncol 2013;24:1087–1093.

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Posttest Questions

1. Which of the following are included as treatment options in the NCCN Guidelines for patients with GIST progressing on standard-dose imatinib?
   a. Dose escalation of imatinib up to 800 mg/d as tolerated
   b. Switching to sunitinib
   c. Continuation of imatinib at the same initial dose and treatment of progressing lesions with other therapeutic interventions
   d. All of the above
2. Regorafenib is recommended for patients with GIST experiencing disease progression while on imatinib and sunitinib.
   a. True
   b. False
3. Which of the following mutations is associated with better clinical outcomes in patients with unresectable or metastatic GIST treated with standard-dose imatinib?
   a. *KIT* exon 9
   b. *KIT* exon 11
   c. *PDGFR*α D842V
   d. All of the above