# Randomized Clinical Trials in Gastrointestinal Stromal Tumors

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**KEYWORDS**

• Gastrointestinal stromal tumors • Imatinib • Tyrosine kinase inhibitors

**KEY POINTS**

- In limited stage disease, complete surgical resection remains the standard of care.
- There is a role for surgical resection in metastatic disease in the setting of limited disease progression, and for tumors that have experienced significant clinical response to neoadjuvant imatinib.
- The current standard of care in the adjuvant setting is 3 years of adjuvant imatinib therapy in patients with features putting them at high risk of disease recurrence; the benefit and tolerability of 5 years of adjuvant imatinib is currently being investigated.
- In patients with metastatic disease, imatinib is continued indefinitely until disease progression or side-effect intolerance. Rechallenge with imatinib after progression off of therapy or after progression on imatinib and sunitinib has been associated with clinical response.
- Both regorafenib and nilotinib are novel tyrosine kinase inhibitors that have been investigated in the management of advanced metastatic gastrointestinal stromal tumors, with regorafenib receiving US Food and Drug Administration approval in 2013; masitinib is a potentially promising tyrosine kinase inhibitor that is being investigated in metastatic gastrointestinal stromal tumors.

Gastrointestinal stromal tumors (GISTs) are mesenchymal or stromal tumors involving the gastrointestinal tract, originating most commonly in the stomach and the small intestine. They are rare tumors and make up approximately 1% of all of gastrointestinal cancers. The true incidence of GIST is unknown, with studies

Disclosure: Dr Y. Liu has no relationships to disclose. Dr M. von Mehren served as an investigator for the GRID trial and the nilotinib randomized trial in the advanced disease setting. She has served as a paid consultant to Bayer and Novartis in the past.

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Surg Oncol Clin N Am ■ (2017) ■–■
http://dx.doi.org/10.1016/j.soc.2017.05.004 surgonc.theclinics.com

suggesting approximately 4000 to 6000 new cases each year. Although most cases are sporadic, some are associated with familial autosomal dominant syndromes, including neurofibromatosis 1, primary familial GIST syndrome, and Carney-Stratakis syndrome. GISTs are primarily characterized by activating mutations in *KIT* (85%) or platelet-derived growth factor-$\alpha$ *(PDGFRA*; 5%), whereas a small percentage are wild-type in both genes and require further characterization. Mutations in *KIT* lead to constitutive activation of the KIT receptor tyrosine kinase; 75% of *KIT* mutations involve exon 11, which encodes the intracellular juxtamembrane domain resulting in spontaneous ligand-independent dimerization and activation. Mutations in exon 11 generally confer response to imatinib mesylate, a tyrosine kinase inhibitor (TKI) that inhibits activation induced by *KIT* and *PDGFRA* mutations; imatinib has been the backbone of therapy in both the adjuvant and metastatic setting for most GIST tumors.

This review focuses on therapeutic advances in the management of GIST, with an emphasis on randomized clinical trials (RCTS) performed between 2010 to 2016 related to medical management; there are no recent RCTs in the literature that have changed the surgical approach to this disease. The consensus among the surgical community is to pursue complete surgical resection with histologically negative margins, with careful attention to maintain the integrity of the tumor pseudocapsule because of its friable nature to avoid tumor spillage. Per the National Comprehensive Cancer Network guidelines, resection of adjacent lymph nodes is not indicated because of the low rate of metastases. Furthermore, re-resection is generally not indicated for microscopic positive margins on final pathology. In general, there is a limited role for surgical resection in metastatic disease, unless there is disease progression in a limited area and for tumors that have experienced significant clinical benefit from imatinib or other TKIs.[1]

Between 2010 and 2016, several key RCTs were published that changed the management of patients with GIST. These studies evaluated the optimal duration of adjuvant imatinib after R0 or R1 resections in high-risk disease, made further explorations into the optimal duration of imatinib treatment in metastatic disease, and explored the efficacy and safety of novel TKIs in the metastatic setting.

## THE ROLE OF IMATINIB IN ADJUVANT THERAPY

Before 2010, the American College of Surgical Oncology Z9001 study established imatinib as standard adjuvant treatment after resected GIST. In a large phase III study, 713 patients with localized primary GIST who had received complete gross resection were randomly assigned to receive either imatinib, 400 mg daily, or placebo for 1 year after surgical resection. The study found that at a median follow-up of 19.7 months, imatinib significantly improved recurrence-free survival at 1 year compared with placebo (98%; 95% confidence interval [CI], 96–100 vs 83%; 95% CI, 78–88; hazard ratio [HR], 0.35; $P<.0001$). This study established adjuvant imatinib as a safe, tolerable, and effective therapy after resection. However, further follow-up found an increase in disease recurrence around 18 months after surgery, raising questions regarding the optimal duration of imatinib therapy.[2] Factors associated with lower rates of recurrence-free survival included large tumor size, small bowel location, and high mitotic rate.

The SSG XVIII trial from the Scandinavian Sarcoma Group established 3 years of adjuvant imatinib as the standard of care in resected GIST with a high risk of recurrence.[3]