Targeted Therapy for Gastrointestinal Stromal Tumor
Emerging concepts in oncogenetics and therapy sequencing

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Key Words

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Gastrointestinal stromal tumor (GIST) is a relatively new tumor entity with the term first used 1983. GISTs were rarely diagnosed until after 2000 when Hiroto described the gain-of-function mutation in the c-kit proto-oncogene that was present in almost all GISTs. This discovery represented a major breakthrough in the classification, approach and treatment of these tumors. Shortly after this discovery, imatinib, a tyrosine kinase inhibitor initially developed as an agent for chronic mylogenous leukemia was found to inhibit KIT. The drug was demonstrated to be effective against metastatic GIST in a single patient with metastatic disease, and efficacy was confirmed in multiple subsequent phase II and phase III trials in the United States and Europe. Further understanding of tumor biology and oncogenetics, along with the application of targeted therapy, has revolutionized the treatment options and sequencing for patients with advanced GISTs. Available data suggest that mutational status has important implications for prognosis, recurrence, response to therapy and tyrosine kinase inhibitor resistance. A through understanding of mutational status in GIST is critical for appropriate selection of therapy, as well as understanding emerging areas for investigation.
INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract, with an incidence of at least 10 new occurrences per million[1]. These tumors represent a relatively new clinic-pathologic entity with the term first used in 1983 to describe non-epithelial tumors arising in the gastrointestinal tract that lacked immune-histochemical features of Schwann cells, and did not have the ultra-structural features of smooth muscle cells[2]. GISTs were rarely diagnosed until after 2000 when Hiroto et al described the gain-of-function mutation in the c-kit proto-oncogene that was present in nearly all GIST[3]. The ability to detect KIT over-expression by immunohistochemistry represented a major breakthrough in the classification, approach and treatment of these tumors. Shortly after this discovery, imatinib, a tyrosine kinase inhibitor initially developed as an agent for chronic mylogenous leukemia, was found to inhibit KIT[4, 5]. The drug was demonstrated to be effective against GIST in a single patient with metastatic disease[6], and efficacy was confirmed in multiple subsequent phase II and phase III trials in the United States and Europe. Since these initial reports, the genotypic characteristics of GISTs have been further described and these features have been shown to have important implications for the application of targeted therapy.
**DIAGNOSIS AND ONCOGENETICS**

The *KIT* proto-oncogene encodes a type III trans-membrane receptor tyrosine kinase (KIT)[7], the ligand of which is SCF (stem cell factor)[8] (Figure 1). SCF binds to KIT inducing KIT dimerization, activation of the tyrosine kinase activity, and resultant phosphorylation of a variety of substrates. This action is essential for the development of melanocytes, erythrocytes, germ cells mast cells and interstitial cells of Cajal[9]. In its mutated state, the KIT isoform demonstrates constitutive kinase activity allowing for ligand-independent receptor dimerization, uncontrolled cell proliferation, and stimulation of downstream signaling pathways, including those involving phosphatidylinositol 3-kinase and mitogen-activated protein kinases. In a 1998 landmark report, Hirota *et al* first described the over-expression of KIT in mesenchymal tumors of the GI tract. In this study, 46 of 49 (82%) GISTs stained positive for KIT (Figure 2). Follow up studies have confirmed that approximately 95% of GISTs exhibit unequivocal staining for KIT[10-12]. Some GISTs with known mutations of *KIT* or *PDGRFA* have been noted to have low expression by immunohistochemistry, and a new antibody DOG-1 (discovered on GIST), has further improved the diagnostic accuracy in GISTs[13]. The use of KIT and DOG-1 as immunohistochemical stains has improved uniformity in the diagnosis which has important implications for both clinical and research applications.

In the landmark report, Hirota *et al* further documented that mutations in *KIT* predominantly occur in the juxtamembrane domain (exon 11)[3] (Figure 1). In five of six (80%) tumors examined, the *KIT* mutation was located at exon 11 with four in-frame deletions and one point mutation, and these mutant isoforms demonstrated activity in vitro in the absence of SCF. The overall frequency of exon 11 mutations vary from 20-92% in GISTs, with higher yields reported in studies based on c-DNA from frozen tumor specimens versus tumors embedded in
paraffin[14-17] (Table 1). Before the use of targeted therapy, exon 11 mutations were associated with a worse prognosis, with fewer than 30% of patients surviving more than 3 years, compared with over 65% survival for patients whose tumors did not bear the mutation[16]. In the setting of imatinib therapy, however, exon 11 mutations are associated with improved response rates and progression free survival as compared to patients with non-exon 11 mutations[18].

Lux et al were the first to describe a mutation in the extracellular domain of KIT (exon 9)[19]. Other groups have confirmed that this mutation results in constitutive activation of KIT, reporting frequencies of mutations between 10-18%[20-22]. These mutations appear to be more commonly associated with tumors of small intestinal origin (95% or greater), and among malignant or high risk GISTs. Mutations of exon 13 (the kinase I domain), exon 17 (the activation loop) and exon 8 have been described, but are rare. The frequency of the exon 13 mutation ranges from 1-4%, whereas exon 17 and 8 mutations are presents in less than 1% of tumors[14]. The clinical implications for these mutations regarding prognosis and response to treatment are unknown, but exon 8 mutations have been linked to extra-gastric GISTs[23].

Although most GISTs have activating KIT mutations, a subset are KIT wild type (KIT-WT). Up to 35% of KIT-WT and 5-7% of all GISTs have a mutation in platelet derived growth factor-alpha (PDGFRA)(Figure 1)[24]. PDGFRA is a receptor tyrosine kinase that shares extensive similarities with KIT, but the kinases remain distinct in that they do not respond to the same ligands. PDGFRA and KIT mutations also appear to be mutually exclusive with no PDGFRA mutations detected in KIT mutated GISTs[17, 24]. In tumors with PDGRFA mutations, signal transduction is indistinguishable from KIT-mutated tumors, suggesting that PDGRFA can substitute for KIT in GIST oncogenesis[24]. GIST tumors with PDGFRA mutations tend to display weak or no CD117 staining and are usually localized to the stomach.
As many as 60% of PDGFRA mutations occur in the activation loop (exon 18) and the remainder of the mutations occur in the juxtamembrane domain (exon 12). Approximately half of the exon 18 mutations are due to PDGFRA missense mutations, leading to substitution of valine for the highly conserved aspartic acid at codon 842 (PDGRFA D842V). The D842V substitution in exon 18 is highly resistant to imatinib.

Several subtypes of GIST frequently do not have mutations of KIT or PDGRFA such as pediatric GISTs[25] and GISTs associated with neurofibromatosis[26]. Pediatric GISTs tend to be associated with germline mutations in a gene that encodes for a subunit of the succinate dehydrogenase (SDH) enzyme, and all have loss of function[27]. Other possible mechanism of oncogenesis in wild type tumors include mutations of IGF1R or BRAF, inactivation of KIT-inhibitor phosphatases, up-regulation of the KIT ligand, and KIT heterodimerization with other activated receptor-tyrosine kinase proteins[28]. KIT appears to be activated in many of these tumors despite lack of a detectable KIT mutation[29]. These tumors have a less indolent course than KIT or PDGRFA mutant tumors, but are generally less sensitive to tyrosine kinase inhibition[17, 30-32]. A subset of GISTs lack mutations in KIT, PDGRFA and RAS pathways while maintaining an intact SDH complex has recently been described. These tumors are designated as quadruple wild-type GIST and appear to have unique molecular expressions as compared to KIT/PDGFRA and SDH mutated tumors[29, 33].

TARGETED THERAPY FOR UNRESECTABLE/METASTATIC GIST

Systemic chemotherapy and radiation are notoriously inactive against GISTs and prior to 2001, there was no effective therapy for advanced, metastatic disease[34, 35]. Since tyrosine kinase constitutive activation occurs in the majority of GISTs, tyrosine kinase inhibition has
emerged as the primary therapeutic modality for locally advanced, metastatic or recurrent GISTs. Imatinib and other agents have demonstrated activity against GISTs, and emerging data has provided guidance regarding treatment sequencing (neoadjuvant and adjuvant), as well therapy for imatinib-resistance GIST.

Imatinib is an oral agent that is a selective molecular inhibitor of the KIT tyrosine kinase. In 2001, imatinib was reported to be effective against metastatic GISTs in a single patient[6]. A 50-year old woman presented with rapidly progressive, diffuse metastatic GIST with an exon 11 KIT mutation, refractory to doxorubicin, ifosfamide and dacarbazine. She was treated with imatinib 400mg twice daily and demonstrated a complete metabolic response by PET and a 52% decrease in tumor volume by MRI with minimal observed toxicity. This favorable response supported the concept that therapy targeted to aberrant tyrosine kinase activity could prove clinically useful in advanced GISTs.

The efficacy of imatinib was later confirmed in multiple subsequent phase II and phase III trials. The US Finnish B222 trial randomized 147 adult patients with unresectable or metastatic GISTs that expressed CD117 to either 400 mg (n=73) or 600 mg (n=74) daily of imatinib[36, 37]. Patients on the lower dose experiencing progression were allowed to crossover to 600 mg daily and ultimately 400mg twice daily. The overall response rates after 63 months of follow-up was 68.1% (95% confidence interval, 59.8-75.5%) with a progression free survival of 20 and 26 months respectively (no statistical difference between dosing regimens, p=0.3). Of note, nearly 25% of patients required over 5 months to demonstrate a response by imaging, and overall survival was identical for patients achieving either a partial or complete response. Archived pathology specimens were available for 127 patients and genotyping confirmed that 112 had KIT mutations (85 mutations in exon 11 and 23 in exon 9), 6 had PDGFRA mutations,
and 9 were *KIT* and *PDGFRA-WT*[17]. Median overall survival was 63 months in patients with *KIT* exon 11 mutations and was 44 months for patients with *KIT* exon 9 mutations, and exon 11 mutation was independently associated with improved survival (HR=0.148, p<0.001) over the first 30 months of therapy (Table 2). Significantly shorter median overall survival was noted (26 months) in patients with other *KIT* mutations and *KIT-WT* tumors (p=0.005).

The European Organization for Research and Treatment of Cancer (EORTC) phase II trial examined the response rate and time to progression for patients with metastatic GISTs and other soft tissue sarcomas[38]. A total of 51 patients (27 GISTs and 24 other soft tissue sarcomas) were treated with imatinib 400 mg twice daily. Of the patients with GISTs, 71% (n=19) experienced either a partial or complete (n=1) response, with 73% of patients remaining free of progression at 1 year. This trial also confirmed that other soft tissue sarcomas did not respond to imatinib, with no objective responses and a median time to progression of 58 days in this group. The drug was well tolerated and no patient discontinued treatment due to adverse events.

These small safety and efficacy trials were followed by two large phase III trials: the first was conducted jointly in Europe and Australia by the EORTC, the Italian Sarcoma Group (ISG) and the Australasian Gastrointestinal Trials Group (AGITG) (EU-AUS trial), and the second was conducted by SWOG, Cancer and Leukemia Group B (CALGB), National Cancer Institute of Canada and the Eastern Cooperative Oncology (ECOG) group (US-CDN). The EU-AUS study randomized 946 patients to either low dose (400 mg daily) or high dose (400 mg twice daily) imatinib therapy with a primary end point of progression free survival[39]. With a median follow-up of 25 months, progression free survival was longer in patients receiving higher dose imatinib, but this difference was no longer significant after 40 months of follow-up. *KIT* exon 9
mutational status had prognostic and predictive value, with exon 9 patients responding to high
dose imatinib after progression. In this trial, patients on the low dose regimen were allowed to
cross over to the higher dose regimen and these patients achieved an objective response rate and
stable disease[40].

The US-CDN randomized 746 patients with unresectable or metastatic GISTs to either
400 mg daily (standard dose) or 400 mg twice daily (high dose) with overall survival as the
primary endpoint. At a median follow-up of 4.5 years there was no difference in dose response,
progression free survival or overall survival between dosing regimens[32]. After progression on
standard dose, 33% of patients who crossed over to high-dose imatinib achieved either a partial
response or stabilization of disease. Tumor samples were obtained from 447 patients of whom
368 expressed CD117. KIT mutations were noted in 308 tumors (269 in exon 11 and 31 in exon
9) while 4 tumors had mutations in PDGFRA and 56 were KIT-WT/PDGFRA-WT. Mutation
status was again confirmed to be both predictive of response to imatinib therapy and prognostic,
with exon 11 mutation corresponding to a higher response rate (71.7%, 44.4% and 44.6% respectively) and median overall survival (60 months, 38.4 months and 49 months). Treatment
with high dose imatinib improved response rates in patients with exon 9 mutations, without a
meaningful correlation in improved progression free or overall survival.

Given the similarities in study design, a meta-analysis of 1,640 patients from the EU-
AUS and US-CDN trials was conducted to further explore progression free and overall survival
in patients with metastatic GIST treated with standard and high dose imatinib. [41] At a median
follow-up of 45 months, this analysis demonstrated a small but significant improvement in
progression free survival for patients in the high dose arm. In patients analyzed for mutations,
patients with KIT-WT, patients with KIT exon 9 mutations and patients with other mutations had
a worse prognosis than patients with $KIT$ exon 11 mutations. Patients who had $KIT$ exon 9 mutations benefited most from high-dose therapy in terms of progression free survival as opposed to other genomic subpopulations.

Debiec-Rychter et al further described the association of tumor genotype with clinical response[42]. In an analysis of 377 patients from the EU-AUS trial, this report expanded on observations related to dose-response relationships and tumor genotype. Patients with exon 11 $KIT$ mutants treated with imatinib had higher response rates, a substantially lower likelihood of progression, and a longer median survival than other genotypes. In patients with exon 9 or $KIT$-WT type tumors, the cumulative incidence of response after two years of treatment was 34% and 25% respectively, as compared to 69% in exon 11-mutated tumors.

**Neoadjuvant Therapy**

Operative resection remains the treatment of choice for small, localized GIST, but many patients present with advanced disease and are not resectable at presentation, or present with tumors in which complete resection would be associated with considerable morbidity[43]. Given that both non-radical resection with a positive margin (R1) and tumor rupture are associated with adverse outcomes[44], selected patients may benefit from neoadjuvant imatinib therapy.

The Radiation Therapy Oncology Group/American College of Radiology Imaging Network (RTOG 0132/ACRIN 6665) trial was the first to evaluate the efficacy of neoadjuvant imatinib in a nonrandomized phase II trial[40, 45]. In this trial, 63 patients with advanced primary (>5cm) (n=30) or potentially operable metastatic or recurrent disease (>2cm) (n=22) were treated with imatinib 600 mg daily for 8 to 12 weeks (median duration of 65 days). Following resection, all patients received at least 24 months of adjuvant imatinib 600 mg daily. Partial response rates of 7% and 5% (primary and metastatic/recurrent disease, respectively) and
stable disease rates of 83 and 91% were observed with preoperative imatinib of 600 mg daily. The estimated 2-year progression free survival rate was 83% for those patients with primary disease and 77% for those with recurrent or metastatic disease. The preoperative therapy was well tolerated with most patients continuing imatinib to a median of 2 days preoperative, and the rate and nature of complications being consistent with other surgical series involving patients with extensive and re-operative abdominal surgery. This trial confirmed the safety of neoadjuvant imatinib, and provides rationale for its use in patients where a responsive tumor might be downsized to allow for less morbid surgery. This trial did not test or report on specific mutational tumor status, so it is unclear if mutational status may influence the response to neoadjuvant imatinib, and if some patients should not be offered neoadjuvant therapy due to intrinsic imatinib resistance.

There currently is no consensus as to the indications for neoadjuvant imatinib, with some limiting treatment to those with high risk tumors or tumors in anatomic locations resulting in a potentially morbid resection. Neoadjuvant imatinib should be considered for patients with marginally resectable GISTs (Figure 2), and in those with tumors in anatomic locations where resection presents significant morbidity (esophagus, esophagogastric junction, duodenum and distal rectum). The most commonly recommended treatment regimen is 3 to 12 months of 400 mg daily of imatinib, with the duration of time dependent on ongoing radiographic response. Maximal response (defined as no further improvement between 2 successive CT scans) typically occurs between 4 to 6 months. Before initiating therapy, genotyping is recommended if feasible, and patients with exon 9 mutations should be treated with 800 mg of imatinib daily, and those with mutations typically resistant to imatinib (PDGFRA exon 18 D842V) should proceed directly
to resection. Rarely patients may require emergent surgery related to tumor necrosis and or bleeding from neoadjuvant imatinib therapy[47].

**ADJUVANT THERAPY**

While surgery is considered the optimal treatment option for localized GISTs, it does not routinely produce a durable cure. Despite complete gross tumor resection as many as 50% of patients eventually die from recurrent disease with a median time to recurrence of approximately 2 years[48]. Given the activity of imatinib and the high recurrence rates after GIST resection, there is substantial rational for adjuvant imatinib in high risk patients.

The American College of Surgeons Oncology Group (ACOSOG) conducted a phase II trial to evaluate the safety and efficacy of adjuvant imatinib (400 mg daily) for one year following a complete resection[49]. A total of 106 patients who had undergone complete gross tumor resection for localized, primary disease but were deemed at high risk for recurrence were enrolled. High risk was defined at a tumor >10 cm, intra-peritoneal tumor rupture, or up to 4 peritoneal implants. Mutational analysis was available in 78 patients demonstrating a *KIT* exon 11 mutation in 58%, exon 9 mutation in 13% and *PDGRFA* mutation in 13%. With a median follow up of 7.7 years, 54% of patients developed a recurrence and 26% (n=28) died. The type of mutation was important with recurrence free survival lowest (median 19 months) in patients with a *KIT* exon 9 mutation as compared to patients with a *KIT* exon 11 mutation (42 months). Notably, exon 9 mutation patients received standard dose imatinib. Patients with *PDGFRA* or *KIT-WT* tumors fared better, but overall numbers too small to draw meaningful conclusions. Both relapse free survival and overall survival were improved compared to historical controls with patients considered to have a high risk of recurrence.
These results were confirmed in a subsequent phase III trial (ACOSOG Z9001) which demonstrated improved relapse free survival after one year of adjuvant imatinib in a randomized, double-blind, placebo-controlled, multicenter trial of 713 patients[50]. Patients who underwent a complete gross resection (R0 or R1) of a primary GIST 3cm or larger and KIT positive by immunohistochemistry were eligible. Accrual was stopped early based on interim analysis showing that imatinib significantly improved recurrence free survival compared to placebo (98% v 83% at 1 year). There was no difference in overall survival, but this may have been due to the short duration of follow up, and the high degree of efficacy of imatinib in relapsed disease. Additionally, there were a limited number of relapses, possibly due to the inclusion of patients with low-risk tumors. After the study was unblinded, patients were allowed to crossover to active treatment, thus obscuring potential difference in overall survival. Further analysis of the pathologic and molecular features correlating with outcomes after adjuvant imatinib, demonstrated that large tumor size, small bowel location and a high mitotic rate. Relapse free survival for patients with a \textit{KIT} exon-11 mutation was longer in the imatinib group than in the placebo group (p<0.001), but differences in relapse free survival in patients with \textit{KIT} exon 9 and wild-type tumors did not seem to be associated with treatment[51].

The Scandinavian Sarcoma Group (SSG) XVIII trial further compared 36 versus 12 months of adjuvant imatinib in 400 patients with high risk GISTs[52]. This study included patients with resected primary KIT-positive GIST with a high estimated recurrence risk defined by a tumor greater than 10cm, or a mitotic rate greater than 10/50 HPF, or a tumor greater than 5cm and a mitotic rate greater than 5/50 HPF. At a median follow-up of 54 months, prolonged treatment was associated with a significant improved in relapse free survival as well as overall survival. Prolonged treatment was associated with more treatment related adverse events, but
these were generally mild (grade 1 or 2). In further analysis, exon 11 mutations were a significant predictor of prolonged relapse free survival for the 3-year cohort versus the 1-year cohort while there was no improvement in a longer duration of therapy for patients with exon 9, wild type or PDGFRA mutations.

While these data provide rationale for 36 months of adjuvant imatinib in patients with high-risk GISTs, questions remain as to whether or not an even longer duration of therapy would be beneficial. Two keys trials investigating the role of imatinib including the optimal duration of therapy in the adjuvant setting have completed enrollment and are awaiting data maturation--(1) EORTC 62024, a phase III trial randomizing 750 patients to either imatinib 400 mg daily for 2 years versus observation with a primary endpoint of overall survival, and (2) a PERSIST5 phase II trial treating 85 postsurgical patients with imatinib 400 mg daily for 5 years with a primary outcome of time to progression. Patients enrolled in EORTC have resected (R0 or R1) primary KIT-positive GIST and are further defined as either intermediate or high risk. High-risk patients had a tumor greater than 10 cm, or a mitotic rate greater than 10/50 HPF, or a tumor greater than 5 cm and a mitotic rate greater than 5/50 HPF while intermediate-risk patients have a tumor size less than 5 cm and a mitotic rate 6-10/50 HPF, or a tumor size 5-10 cm and a mitotic rate <5/50 HPF. Patients enrolled in the PERSIST-5 trial were patients with resected (R0) primary KIT-positive GIST at high risk for recurrence defined as a tumor size greater than 2 cm and a mitotic rate greater than 5/50 HPF or a non-gastric primary GIST greater than 5 cm (Table 1).
**Resistant Disease**

Up to 20% of GIST patients will not respond to imatinib therapy, and most patients who initially respond to will ultimately acquire resistance and demonstrate disease progression. Median time to progression is typically two to three years. Primary resistance is defined as evidence of clinical progression in the first 6 months of imatinib therapy and is most commonly seen in patients with KIT exon 9, PDGFRα exon 18 or those with KIT-WT GISTs. Patients with an exon 9 KIT mutation have been noted to have improved response to high dose imatinib and should be offered dose escalation. Treatment of PDGFRα-mutant GIST with currently available tyrosine kinase inhibitors has yielded mixed results. In vitro, some PDGFRα-mutant kinases (V561D) are extremely sensitive to imatinib, and patients with these underlying mutations appear to have similar outcomes as patients with exon 11 mutations[17, 30, 53]. In contrast, the most common PDGFRα mutation D842V is strongly resistant to imatinib and sunitinib. Crenolanib is an oral, selective and potent inhibitor of PDGFRα that has been shown to have preclinical activity against imatinib-resistant PDGFRα kinases and clinical trials are underway[54]. Patients with unresectable or metastatic D842V mutated GISTs should be considered for enrollment in a clinical trial.

Secondary resistance typically presents with progression at 18-24 months, and is often due to a secondary mutation in KIT or PDGFRα that interfere with imatinib binding to the kinase[42, 55-57]. Other mechanisms such as activation of other receptor tyrosine kinases, downstream mutations within the MAPK pathway (such as BRAF)[58], or mutations in other cell signaling pathways may also play a role[42]. Once clinical progression occurs, the imatinib dose can be escalated from 400 mg daily to 400 mg twice daily. Approximately 5% of patients
who progress on standard dose imatinib will have a partial response to dose escalation, with another 30% achieving disease stabilization.

For patients who progress despite imatinib dose escalation, sunitinib is the current standard for patients who have failed or are intolerant to imatinib. Sunitinib targets multiple tyrosine kinases and has demonstrated efficacy in imatinib-refractory or intolerant patients[59]. In a randomized phase III placebo-controlled trial, sunitinib was associated with an improved time to progression (27.3 vs. 6.4 weeks) and greater estimated overall survival. In a subsequent open label, multicenter, randomized placebo controlled phase II study, patients with advanced GISTs and imatinib failure where randomized to either sunitinib or placebo. The overall clinical benefit rate was 53%, with median progression free and overall survival of 34 and 107 weeks respectively. The clinical activity of sunitinib in imatinib-resistant patients is also significantly influenced by mutation type. Sunitinib induced higher response rates in patients with primary KIT exon 9 mutations as compared to exon 11 mutations (58% vs. 34%). Progression free and overall survival were also longer for patients with the exon 9 mutation, while patients with the PDGFRA demonstrated no clinical benefit.

Other agents for resistant disease have been developed and evaluated. Regorafenib, an oral multikinase inhibitor, has shown activity in phase II and phase III trials in patients progressing on both imatinib and sunitinib[60, 61]. This agent blocks vascular endothelial growth factor receptor 2-3 (VEGFR2-3), c-kit, TIE2, PDGFRB, fibroblast growth factor receptor 1, RET, RAF and p38 mitogen activated protein kinase. In the phase III trial comparing regorafenib (n=133) and placebo (n=66), median progression free survival was 4.8 months for patients treated with regorafenib and 0.9 months for placebo (HR 0.27, 95% CI 0.19-0.39, p<0.001) and the benefit appeared to be similar between exon 11 and exon 9 patients.
Masitinib, a newer tyrosine kinase inhibitor has been compared with sunitinib in patients with imatinib-resistant GIST[62]. In a randomized trial comparing masitinib to imatinib in 44 patients with inoperable, advanced imatinib-resistant GIST, masitinib attained a median progression-free survival of 3.7 months and median overall survival was significantly longer for patients receiving masitinib followed by post-progression sunitinib when compared to patients treated directly with sunitinib (HR=0.27, 95% CI 0.09-0.85, p=0.02). Masitinib was also associated with less adverse events and a more tolerable toxicity profile than sunitinib. Mutational status was tested and the distribution was similar between groups, but given the small numbers no meaningful conclusion could be drawn regarding the relationship to therapy response. Masitinib has also been evaluated for use as a first line agent. In a phase II trial, imatinib-naïve patients with advanced GIST were treated with masitinib with 16 of 30 patients demonstrating a complete (n=1) or partial (n=15) partial response with an estimated median progression free survival of 41.3 months[63].

For patients exhibiting resistance in oligometastatic disease, metastatecomy may be useful in a highly selected population. The nodule-within-a-tumor is a radiologic sign of progression and signifies the emergence of a resistance clone[64]. Surgical resection of resistant clones has yielded positive results in some cases allowing imatinib or other tyrosine kinase inhibitors to be used to maintain control of sensitive clones[65]. In these cases, repeat tumor sampling may be useful in helping to detect potential mechanisms for resistance (new mutations) and guide ongoing therapy. In addition to resection, other local therapies such as radiofrequency ablation and external beam radiation may be considered[66, 67].

**Conclusion**
Systemic chemotherapy and radiation are notoriously inactive against GISTs and prior to 2001, there was no effective therapy for advanced, metastatic disease. Since tyrosine kinase inhibitors the overall survival of patients with metastatic GIST has improved. Tumor genotyping for KIT and PDGFRA mutations is critical in identifying patients who are unlikely to respond to imatinib therapy (PDGFRA D842V mutations) or require a higher dose (exon 9 mutations). For these non-exon 11 mutant tumors, alternative therapies or enrollment in a clinical trial should be considered. For patients with resistant disease, dose escalation, or alternative therapy with sunitib or other tyrosine kinase inhibitors should be pursued. Future studies should focus on the role of mutational status in outcome, and tailor the study design and/or therapies to known response relationships. Other questions that remain unanswered include the role of non-imatinib/sunitinib therapy for PDGFRA mutant tumors, optimal dose and therapy sequencing for exon 9 mutant tumors, and the role of combination therapy for resistant disease. These and other relationships with tumor oncogenetics should guide future investigations aimed at improving overall survival for patients with advanced GIST.
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Figure 1. Schematic of KIT and PDGFRA Mutations in GIST. Simplified structure of the receptor of tyrosine kinases KIT and PDGFRA with the location of the exons commonly mutated in GISTs.
FIGURE 2. EXAMPLE OF RADIOGRAPHIC RESPONSE WITH NEOADJUVANT IMATINIB THERAPY.

Computed tomography (CT) scan of a patient with a locally advanced GIST before (Day 0) and after (12 months and preop) neoadjuvant imatinib therapy demonstrating significant radiographic response.
**Table 1.** Common mutations in GIST and their reported frequency.

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>KIT exon 11</td>
<td>20-92%[14-17]</td>
</tr>
<tr>
<td>KIT exon 9</td>
<td>10-18%[20-22]</td>
</tr>
<tr>
<td>PDGFRA</td>
<td>5-7%[24]</td>
</tr>
</tbody>
</table>

**Table 2.** Imatinib trials in GIST and genotype dependent response

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>US Finnish B222[37]</td>
<td>Phase II, metastatic or unresectable GIST</td>
<td><em>KIT</em> exon 11 mutation associated with improved survival</td>
</tr>
<tr>
<td>EU-AUS Trial[30]</td>
<td>Phase III, metastatic or unresectable GIST</td>
<td><em>KIT</em> exon 9 responded to high dose imatinib after progression</td>
</tr>
<tr>
<td>US-CDN[31, 32]</td>
<td>Phase III, metastatic or unresectable GIST</td>
<td>Mutation status predictive and prognostic with exon 11 patients having improved response rate and longer median overall survival</td>
</tr>
<tr>
<td>GIST Meta-analysis[41]</td>
<td>Meta-analysis of EU-AUS and US-CDN</td>
<td><em>KIT</em> exon 11 mutation associated with improved response and survival; exon 9 mutation patients benefited from high dose therapy</td>
</tr>
<tr>
<td>ACOSOG[49]</td>
<td>Phase II, adjuvant therapy</td>
<td><em>KIT</em> 11 mutation patients with improved recurrence free survival</td>
</tr>
<tr>
<td>ACOSOG Z9001[50]</td>
<td>Phase III, adjuvant therapy (all patients with tumor 3cm or greater irrespective of recurrence risk)</td>
<td>Improved recurrence free survival in exon 11 patients treated with adjuvant imatinib</td>
</tr>
<tr>
<td>SSG XVIII[52]</td>
<td>Phase III, adjuvant therapy (intermediate and high risk tumors only)</td>
<td><em>KIT</em> exon 11 mutation patients had improved recurrence free survival with prolonged therapy</td>
</tr>
</tbody>
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