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New Therapeutic Approaches for Advanced Gastrointestinal Stromal Tumors (GISTs)

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Synopsis

The management of advanced GIST is increasingly complex due to imatinib refractory disease. Primary resistance to imatinib is uncommon, and most patients progress after development of additional genetic changes. This article reviews management strategies including surgical approaches, local modalities for progressive liver metastases, as well as novel therapeutic agents.

Keywords

GIST; nilotinib; sorafenib; HSP-90 inhibitors; IGF-1R; tyrosine kinase inhibitors

Gastrointestinal stromal tumors (GISTs) are the most common type of GI mesenchymal tumors, which as a group are relatively uncommon and constitute less than 1% of all GI tumors. They develop from connective tissue precursors in the gastrointestinal tract, the Interstitial cells of Cajal or its stem cell precursor.[1,2] Management of GISTs has changed dramatically since the discovery that GIST cells express KIT, a receptor tyrosine kinase (RTK) growth factor receptor. CD117 is an antigen on the KIT RTK, the product of the *KIT* proto-oncogene. Staining for CD117 has greatly improved the diagnosis of GIST as it is expressed on 90–95% of tumors.[3]

KIT is not only expressed, but is mutated in 85% of cases leading to constitutive activation of the receptor. Mutations are most commonly seen in exon 11, followed in frequency by exons 9, 13, and 17.[4,5] A subset of non-mutated *KIT* tumors have activating mutations in *platelet derived growth factor alpha* (*PDGFRA*), a related RTK. In *PDGFRA*, mutations are found primarily in exons 12 and 18. Approximately 10% of GISTs do not contain mutations in either *KIT* or *PDGFRA*, the so-called wild-type (WT) GIST. The expression of KIT and the understanding that KIT or *PDGFRA* are constitutively activated has led to the development of effective targeted therapies using small molecules like imatinib and sunitinib that are tyrosine kinase inhibitors (TKI).

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The therapeutic use of imatinib has revolutionized the treatment in GIST, however resistance does occur and is a major challenge now. Sensitivity to TKIs such as imatinib and sunitinib depends on the site of mutation(s) in *KIT* and *PDGFRA* (Table 1).[6–8] In patients who respond upfront, unfortunately secondary mutations occur over time leading to resistance. Studies have established the preferred starting dose for imatinib to be 400 mg once daily, with higher dose of 400 mg twice daily recommended as initial therapy only for tumors with exon 9 mutations.[9,10,11,12] Dose escalating from low dose over a 4–8 week period to the higher dose therapy may lead to fewer severe side effects, which is a significant issue when starting at 400 mg twice daily.[13] Treatment should be continued till progression or intolerance to therapy given the evidence that disease progression occurs rapidly off of therapy.[14] Here we discuss the approach to advanced GIST, focusing on the different strategies beyond imatinib therapy.

Sunitinib

For patients who progress on imatinib or are intolerant to imatinib, sunitinib is available as a second-line therapy. Sunitinib is an oral multi-targeted receptor tyrosine kinase inhibitor; though it binds within the ATP-binding domain of KIT and PDGFRs like imatinib, it is from a different chemical class with presumably different binding affinities. In addition it also inhibits signaling by all the vascular endothelial growth factor receptor isoforms (VEGF-R1, -R2, -R3), important in tumor angiogenesis, the Fms-like tyrosine kinase-3 receptor (FLT3) and the receptor coded by the ret proto-oncogene (RET). This agent was initially tested using a once daily 50mg starting dose on a 4-weeks-on followed by 2-weeks-off schedule. After encouraging clinical activity from a phase1/2 study in patients with imatinib resistant disease, a phase 3 placebo controlled trial was conducted by Demetri and colleagues testing the efficacy and safety of sunitinib after failure of imatinib.[15] Three hundred and twelve patients were randomized in a 2:1 ratio to sunitinib or placebo and cross over was allowed at the time of progression. The trial was unblinded early when a planned interim analysis revealed a statistically significant longer time to progression (TTP) of 27.3 weeks (95% CI 16–32) with sunitinib vs. 6.4 weeks (95% CI 4.4–10) with placebo. Progression free survival (PFS) and overall survival (OS) were also significantly improved in patients who received sunitinib rather than placebo. Overall objective response rate was similar to previous reports with 7% showing partial response and 58% with stable disease in the sunitinib group, compared to 0% and 48% respectively in the placebo group. Toxicities with this agent are notable for fatigue, hand-foot syndrome, diarrhea, hypertension, mucositis, hypothyroidism and some serious cytopenias. There have been reports of cardiac toxicity secondary to decrease in ejection fraction as well necessitating monitoring of cardiac function when using this agent.

The schedule of sunitinib has recently been re-evaluated to test the efficacy and safety of continuous dosing. The rationale for testing a continuous dosing schedule was to avoid the resurgence of metabolic activity in tumors during the 2-week break from sunitinib, as demonstrated by PET scan imaging. This phase 2 study of daily sunitinib at a starting dose of 37.5 mg, showed it was tolerable and with comparable efficacy to the 50 mg starting dose on the conventional schedule.[16] Sixty patients received continuous dosing and the last reported PFS was 27 weeks (95% CI 24–41), with 11% patients experiencing partial response (PR). This schedule is now being tested in a large phase 3 trial compared to high-dose imatinib for patients who have progressed on low-dose imatinib.

Similar to imatinib, there does appear to be selected genotypes that benefit from sunitinib therapy (Table 1). *In vitro*, the agent is effective against exon 11 mutations. However, the majority of patients treated with sunitinib are patients with tumors containing exon 11 mutations that have progressed after a period of benefit from imatinib. Their tumors

typically contain secondary mutations. Sunitinib has activity against those with exon 13 and 14 secondary mutations, with no significant activity against secondary mutations in exon 17. In addition, similar to imatinib it has minimal activity against primary tumors with *KIT* exon 17 and *PDGFR* exon 18 mutations.[17]

It is not known if the inhibition of angiogenesis by sunitinib contributes to its efficacy over imatinib as it blocks VEGFR in addition to KIT and PDGFR. An ongoing phase 3 trial of imatinib plus bevacizumab compared to imatinib alone in metastatic GIST patients, might shed some light on the added benefit of targeting VEGFR for the treatment of advanced GIST.

Therapies with these TKIs have provided substantial benefits but are not curative in the advanced setting. The role of surgery and other localized therapies have been studied in the metastatic setting, particularly for those patients with focal progression. However for patients with diffuse progression at multiple sites, other options for the imatinib resistant tumors are needed. We will review the role of local therapies as well as discuss additional systemic therapies currently being investigated, including alternative TKI therapies as well as agents with novel therapeutic targets.

Surgery and other local therapies

Surgery is the mainstay of curative therapy in primary GIST and has traditionally played a palliative role in the advanced disease setting. In the era of targeted therapy, the role for surgery as a part of multimodality management of advanced GISTs has been looked at in small patient series and retrospective studies. One of the rationales for resecting metastases is to eliminate tumors from which drug-resistant clones might develop. The Radiation Therapy Oncology Group (RTOG) studied the role of pre-op imatinib followed by surgery in a phase 2 study in patients with primary locally advanced disease or with recurrent/metastatic disease.[18] Patients with locally advanced disease received 2 years of post-op imatinib and those with metastatic disease were continued on imatinib till progression. At 2 yrs patients with locally advanced disease and metastatic disease had a PFS of 82% (95% CI 68–97) and 73% (95% CI 54–91), respectively, which are encouraging results, suggesting a benefit to surgical debulking in advanced disease.

Studies published from several institutions have demonstrated, that surgical debulking might benefit patients with responsive disease or limited progression on kinase inhibitor therapy, but is not beneficial for multifocal progression.[19,20,21,22] The largest of these is the retrospective study by Raut and colleagues that evaluated 69 patients who underwent surgery while on kinase inhibitors.[20] The patients were categorized as stable disease, limited progression or generalized progression, based on their pre-op status. Almost all patients were continued on systemic therapy post surgery. There was a significant association between the pre-op disease status and the extent of residual disease post surgery as well as the 12-month PFS after surgery. The 12-month PFS was 80%, 33% and 0% for patients with stable disease, limited progression and generalized progression, respectively. The complexity of imatinib- and sunitinib-resistance has been demonstrated by molecular studies showing different secondary mutations in several areas within one resected lesion. We now need randomized trials to better evaluate the role of surgery in the metastatic setting and currently studies are being developed to test this in patients who have had disease stabilization on TKI therapy.

Hepatic artery chemoembolization (HACE), and bland embolization has been used for GISTs metastatic to the liver.[23,24] A retrospective series spanning the pre- and post-imatinib era showed HACE induced a radiographic durable tumor response and disease stabilization of the liver metastases in 88% of the 85 evaluable patients. The number of

embolization treatments, presence of extrahepatic disease, extent of hepatic disease and use of imatinib were found to have prognostic influence on PFS and OS. Postembolization syndrome with abdominal pain, fever, nausea and vomiting is a common complication with embolization procedures, and therefore may limit the utility of this therapy.

Radio-frequency ablation (RFA) can also be used to treat metastatic lesions within the liver that have focal progression on TKI therapy. Dileo and associates reported the outcome with percutaneous CT-guided RFA in nine GIST patients with a single or limited site(s) of progression while on imatinib. [25] Eight of nine patients were treated for progression in the liver, and most of them had a new nodule develop within a pre existing responding lesion. The procedure was safe and all patients underwent successful ablation of the targeted lesion. Three patients remained stable post RFA after a median follow up of 13.6 months on imatinib, while 6 progressed systemically after a median of 4.7 months and were increased to 800mg/day of imatinib, resulting in control for additional 2–6 months (median 3.5 months).

Alternate Tyrosine Kinase Inhibitors

Tyrosine kinase inhibitors other than imatinib and sunitinib are being tested for the management of advanced GIST refractory to standard therapy (Table 2).

Nilotinib is a second-generation TKI, designed from the crystal structures of imatinib and the ABL-kinase complex and initially developed as a more potent Bcr-Abl inhibitor to override imatinib resistance in chronic myelogenous leukemia.[26] The agent also selectively inhibits phosphorylation of KIT and PDGFR *in vitro*, and showed promising activity against cell lines expressing exon 13 and 17 double mutants, resistant to imatinib. [27] Nilotinib is believed to have enhanced penetration into cells. In addition, encouraging phase 1 data demonstrated stable disease as well as response for this drug in patients with imatinib-resistant GIST, when used as a single agent or in combination with imatinib.[28] The recommended doses were nilotinib 400 mg twice daily alone or in combination with imatinib 400 mg daily. Stable disease was noted in 13 out of 18 patients (72%) in the nilotinib alone arm and 9 of 16 patients (56%) in the combination arm. One patient in each arm experienced a PR, although it should be noted that there were some patients with imatinib intolerant disease in the nilotinib alone cohort. Combination therapy was associated with longer duration of therapy and PFS. Grade3/4 toxicities were seen in 50% of the nilotinib alone arm and 44% of the combination arm, with the most common adverse effect being grade 3 GI disorders. Dose-limiting toxicities noted were hyperbilirubinemia and rash. This study has completed accrual. A phase 3 randomized trial comparing nilotinib versus best supportive care, including continued therapy on imatinib or sunitinib has completed accrual. Patients on the best supportive care arm are allowed to cross over to nilotinib at the time of progression. Should the results of this study demonstrate an improved progression free survival with nilotinib therapy, this may lead to approval of a third line agent in advanced GIST.

Masitinib mesylate targets c-KIT, PDGFR, and fibroblast growth factor receptor 3 (FGFR3). *In vitro*, masitinib has demonstrated superior activity to imatinib against WT-*KIT* and *KIT* containing a juxtamembrane region mutation. A phase 1 study of masitinib demonstrated safety and activity, including a complete response in an imatinib-intolerant patient. A multicenter nonrandomized phase 2 trial reported data on 21 imatinib naïve patients with masitinib at 7.5 mg/kg/day.[29] With a median follow up of 9 months, 16 of 21 patients have been on study for greater than 8 weeks. Eleven patients have had a PR (52%), with an additional 8 patients achieving SD (38%), and 2 patients demonstrating progressive disease at 8 weeks (10%). One patient with stable disease has subsequently progressed. There were

two skin-related grade 3 toxicities and the most frequent side effects were GI-related with nausea, vomiting, abdominal pain and diarrhea. These results suggest activity for this agent in GIST. Masitinib will be compared with imatinib in a phase 3 non-inferiority trial assessing PFS as the primary study endpoint.

Sorafenib is a raf kinase inhibitor that also has activity against KIT, PDGFR, and VEGFR 2 and 3. *In vitro* it has demonstrated activity against the imatinib-resistant *PDGFRB* mutation T681 and against cell lines transfected with imatinib-resistant *KIT* mutations, particularly those involving exon 14 T670I and D820Y.[27,30] Single-agent activity of oral sorafenib 400mg twice daily has been recently reported in patients with imatinib- and sunitinib-resistant GIST.[31] In this phase 2 study, of the 24 patients evaluable for response, there were 3 patients with partial responses and 14 with stable disease (disease control rate 71%). The PFS was 23 weeks, similar to that seen in the randomized phase 3 trial of sunitinib, which had a PFS of 27 weeks. Grade 3 toxicities commonly reported include hand-foot syndrome, hypertension, rash and diarrhea. The role of this agent for refractory disease is of interest and likely will be evaluated further.

PKC412, another broad spectrum kinase inhibitor, has demonstrated preclinical activity against certain *KIT* mutants resistant to imatinib, and the *PDGFRA*-D842V mutation on exon 18 that is relatively insensitive to imatinib and sunitinib.[32,33,34] Based on *in vitro* data suggesting synergism with imatinib, PKC412 was evaluated in a phase 1/2 trial in combination with imatinib in patients who developed resistance to imatinib.[35] Unfortunately strong drug-drug interactions occurred causing a near doubling of PKC steady state levels and significant decrease in imatinib levels with unusual toxicities and poor efficacy results. After dose modifications to adjust for the interactions some stabilization of disease was noted in 2 out of 5 patients. Increasing TSH levels were noted in 4 of 7 patients, with one showing clinical hyperthyroidism. The significant pharmacokinetic interactions have limited its tolerability to date, and it is not clear if this agent will be developed further in GIST. Of note, a case report documented disease stabilization with the addition of sirolimus an mTOR inhibitor to PKC412, after the patient had progressed on imatinib alone and PKC412 alone. This suggests that inhibition of two components of the KIT/PDGFR signaling pathway may be more effective therapeutically (see discussion of the mTOR inhibitor RAD001 below). [36]

Vatalanib (PTK787/ZK222584), a multitargeted TKI, with activity against KIT, PDGFR, and VEGFR-1 and 2, was evaluated in a phase 2 trial in patients with imatinib-resistant GIST. [37] Once daily oral dosing of 1250 mg produced objective responses as well as stable disease. Of 15 patients enrolled, most of whom had progressed on 800mg of imatinib daily, 2 achieved PR with an additional 8 having stable disease for 3 or more months, for a clinical benefit rate of 67%. The median TTP was 8.5 months in this small study, which is longer than that reported for sunitinib. The PR's lasted for 9.7 and 20.2+ months and the median duration for SD was 10.1 months. Three patients had ongoing favorable responses at the time of analysis. Mutation analysis was available only from two patients, one patient who progressed by week 8 was WT and another with prolonged PR had *KIT* exon 11 deletion. The safety profile was favorable with only two grade 4 events (hypercalcemia and pain), suggesting it may have some advantages over sunitinib. Vatalanib has a short half-life, raising the possibility of better efficacy with twice daily dosing.

Dasatinib is a kinase inhibitor against BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EphA2, and PDGFRB. It is been approved for treatment of imatinib resistant or intolerant Chronic Myeloid Leukemia and Philadelphia chromosome positive Acute Lymphoblastic Leukemia. Preclinical data by Heinrich and colleagues show that dasatinib potently inhibits the kinase activity of WT KIT and juxtamembrane domain mutant KIT

isoforms [38], which are commonly associated with human GISTs. *In vitro* screening has shown that dasatinib might provide greater benefit than imatinib in certain *KIT* mutants and WT GIST.[27,39] There are ongoing Phase 2 studies with dasatinib in front line advanced GIST as well as in imatinib-resistant GISTs.

There are other kinase inhibitors currently being tested in phase 1 or 2 studies, such as XL820, AZD2171, BMS-354825, MP-470 and OSI930. Some of them have shown activity against secondary mutations resistant to imatinib and sunitinib *in vitro*. Their role in the management of advanced GIST awaits results from these clinical trials.

Novel therapeutic targets

Other therapeutic strategies being explored in the management of GIST include targeting intracellular components of the KIT/PDGFR signaling pathways, molecules that help maintain the growth factor receptors on the cell surface, or targeting alternative oncogenic pathways (Table 3).

m-TOR /PI3K/Akt

mTOR is a protein kinase and part of the PI3K/Akt pathway that plays a pivotal role in cell growth and development. Phase 1 and 2 studies have evaluated RAD001, a mammalian target of rapamycin (mTOR) inhibitor, in combination with imatinib.[40] mTOR is downstream of AKT and is important for cell growth and survival. Two cohorts of patients were treated in this study: imatinib-refractory patients and those who had progressed following imatinib and another therapy, usually sunitinib. Patients received imatinib 600 mg and RAD001 2.5 mg per day. PFS was 17.4% and 37.1% in the 2 cohorts, respectively. Although some activity has been noted, randomized studies will be required to determine RAD001's role compared with other therapeutic strategies available.

In vitro data utilizing cell lines with secondary *KIT* mutations in GIST have demonstrated KIT hyperactivation and imatinib resistance. Therefore targeting critical downstream signaling proteins, such as PI3-K, might be a promising therapeutic strategy in imatinib-resistant GISTs.[41] Current clinical development of MEK and AKT inhibitors is underway and may be useful in combination with TKI therapies. There are currently a few studies testing PI3K inhibitors as single agents. A phase 2 trial is also testing the value of perifosine, a novel AKT inhibitor in combination with imatinib in advanced resistant GIST.

HSP90

HSP-90 is a novel target in cancer therapeutics. It functions as a molecular chaperone required for the stability and function of several proteins involved not only in normal homeostasis but also in maintaining malignant cell pathways.[42] In particular, it stabilizes oncogenes and receptors, which become more dependent on HSP-90 as they become increasingly mutated. Although directed toward a specific target, HSP-90 inhibitors are capable of inhibiting multiple signaling pathways. This unique feature of inhibiting multiple overlapping survival pathways used by cancer cells, give them the potential to circumvent the genetic plasticity that allow these cells to eventually evade the cytotoxic effects of targeted agents.

KIT activation has been shown to be dependent on protein stabilization by HSP-90 and its inhibition causing degradation of WT KIT and an imatinib resistant mutant *in vitro*. [43] In GISTs, it is thought that HSP-90 inhibition would result in the loss of the growth signal that emanates from the mutated receptor and, therefore, inhibition of cell growth. Preclinical data have demonstrated activity of HSP-90 inhibitors in cell lines that express either imatinib-sensitive or imatinib-resistant mutations.[44,45] IPI-504 is a water-soluble HSP-90 inhibitor

that has undergone testing in the phase 1 setting in patients progressing on imatinib and sunitinib.[46] Therapy was administered IV at test doses of 90 mg/m² to 500 mg/m² twice weekly for 2 weeks followed by 1 week off. The dose-limiting toxicities were grade 3 headache and myalgias at the highest dose level, with 400 mg/m² selected for further study. In a group of 36 patients with advanced GIST, there was 1 PR and an additional 24 patients with stable disease. The median TTP was 12 weeks, assessing all dose levels. There was evidence of increased tumor shrinkage in patients receiving higher doses, with one documented partial response. This agent will be entering phase 3 testing in the fall of 2008, comparing it with best supportive care in patients who have progressed following standard therapies. There are additional trials open testing new HSP-90 inhibitors. One of them is CNF2024 in a phase 2 trial in metastatic GIST. Others being tested in solid tumors including GIST are IPI-493, SNX-5422 and AUY-922.

HDAC

Epigenetic alterations such as histone acetylation, have been shown to play a role in the initiation and progression of neoplasm.[47] Histone acetyltransferases (HATs) and histone deacetylases (HDACs) are two opposing classes of enzymes, which tightly control the equilibrium of histone acetylation. This balance plays an important role in the modulation of chromatin structure, chromatin function and in the regulation of gene expression. An imbalance between these enzyme classes has been associated with carcinogenesis and cancer progression. HDAC inhibitors lead to an accumulation of acetylated histone proteins both in tumor cells and in normal tissues and are able to activate differentiation, to arrest the cell cycle in G1 and/or G2, and to induce apoptosis in transformed cells. The potential therapeutic value of HDAC inhibitors in treating cancer has been evaluated in clinical trials with a promising outcome.

FR901228 is a new molecule that belongs to this class of therapy and is currently in phase 2 testing for metastatic sarcoma patients including GIST. HDAC inhibitors are also being evaluated in combination with differentiation-inducing agents and cytotoxic drugs for enhanced anti-tumor activity. Vorinostat (suberoylanilide hydroxamic acid, SAHA) an HDAC inhibitor resulted in a prolonged PR for one patient with sarcoma when used along with bortezomib.[48] A similar combination utilizing doxorubicin and flavopiridol is under study in an ongoing phase 1 study for advanced sarcomas including GIST. Results from these will determine if they hold promise for advanced GIST and should be tested further.

IGF-1R

Several reports recently have identified the insulin-like growth factor type I receptor (IGF-1R) pathway as a potential pathway in the oncogenesis of GIST. A subset of GISTs lack *KIT* and *PDGFRA* mutations, and these WT-GISTs tend to be less responsive to imatinib-based therapies. Tarn and colleagues [49] reported a higher frequency of aberrant amplification of IGF-1R in WT GISTs and one pediatric WT GIST. In addition, cell lines treated *in vitro* with an IGF-1R inhibitor (NVP-AEW541), or siRNA silencing of IGF-1R led to cell death and induced apoptosis. The combination of NVP-AEW541 with imatinib induced strong cytotoxicity. A second report highlighted this pathway in pediatric GIST, which usually presents in young girls and commonly are WT.[39] A third report suggested that the presence of ligands for IGF-1R may predict tumor outcome.[50] These reports are exciting and serve as the preclinical data for several upcoming studies testing antibody-based therapies alone or in combination with targeted agents in the treatment of GIST.

Conclusion

Prior to the advent of targeted therapy with imatinib, GIST patients who could not be surgically cured had a grim prognosis, since these tumors are resistant to conventional chemotherapy. Apart from its use in first-line treatment of metastatic GIST, imatinib is also being used in the adjuvant setting, where it has shown to prolong recurrence-free survival. Sunitinib is the only approved agent for second-line therapy. Primary and secondary resistance to these agents has been correlated to certain *KIT* and *PDGFRA* mutations. *KIT* and *PDGFRA* mutation testing is being incorporated in some big centers to guide therapy; escalating to high dose imatinib sooner for exon 9 mutations and opting for closer follow up for mutations unlikely to respond. The challenge for clinicians now is the approach to the patients with disease that is refractory to standard therapies. Several newer TKIs are currently under study and may have a role in the treatment of GIST. Among other agents being studied, the role of HSP-90 inhibitors is intriguing given that it utilizes a unique therapeutic mechanism. Also, clinical data for IGF-1R inhibitors is eagerly awaited given their potential role in patients with WT tumors. In the future treatment algorithms for GIST patients will change with the identification of tumor subtypes that respond better to one therapy than another.

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Table 1

Potential for Disease Control with TKI Therapy based on Site of Mutation.

TKI	Primary mutations				Secondary mutations		
	<i>KIT</i> exon9	<i>KIT</i> exon11	<i>KIT</i> exon17	<i>PDGFR</i> exon18	<i>KIT</i> exon13	<i>KIT</i> exon14	
Imatinib	↓*	↑	↓	↓	↓	↓	
Sunitinib following Imatinib	↑	ND	↓	↓	↑	↑	

↓: Low potential. ↑: High potential. ND: No data.

^{*} Less likely to respond to low dose therapy

Table 2

Other TKI's for Advanced GIST

Agent	Target in GIST	Phase of Study
Nilotinib	KIT and PDGFR	3
Masitinib	KIT, PDGFR, and FGFR3	3
Sorafenib	Raf kinase, KIT, PDGFR, VEGFR-R2 and R3	2
PKC412	Protein kinase C, KIT, PDGFR, FLT3 and VEGF-R2	1
Vatalanib	KIT, PDGFR, VEGFR-1R and 2R	2
Dasatinib	KIT, PDGFR and SRC family	2
OSI930	KIT and VEGF-R2	1
XL820	KIT, VEGF-R2, and PDGFR	2
AZD2171	KIT, VEGF-R1, R2, R3 and PDGFR	2
MP-470	KIT, PDGFR, c-Met, c-RET and AXL	1
BMS-354825	KIT, SRC, and PDGFR	2

Table 3

Agents with novel targets being tested in GIST.

Agent	Target	Phase of trial
RAD001	mTOR inhibitor	2
Perifosine	AKT inhibitor	2
IPI-504 CNF2024	HSP-90 inhibitor	3 2
NVP-AEW541	IGF-1R inhibitor	preclinical
FR901228 Flavopiridol	HDAC inhibitor	2 1