Recent advances in the treatment of gastrointestinal stromal tumors

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***Abstract*:** Constitutively activating mutations in the KIT and platelet-derived growth factor receptor α (PDGFRA) RTKs play a crucial role in the biology of gastrointestinal stromal tumors (GISTs), and this disease has served as an effective model for targeting gain-of-function kinase mutations in cancer. Imatinib has entered the clinical arena in the last decade and substantially improved the outcome in these formerly untreatable cancers. However, most advanced GISTs responding to imatinib progress within 2–3 years due to heterogeneous subclones harboring a range of imatinib-resistant secondary KIT mutations. Sunitinib, and more recently, regorafenib, have obtained US Food and Drug Administration approval for the treatment of GISTs after imatinib failure, and thus expanded the treatment options in resistant disease. Within this framework, we present an evaluation of current GIST management, emphasizing the most recent advances in the field together with a discussion on future steps to be taken in refractory disease.

Keywords: c-KIT, gastrointestinal stromal tumors, imatinib, masitinib, nilotinib, regorafenib, sorafenib, sunitinib

Introduction

Novel insights into the biology of gastrointestinal stromal tumors (GISTs) have revolutionized the therapeutic options for management of both localized and advanced GISTs. It was not until 1998 that Hirota and colleagues identified gain-of-function mutations of the receptor tyrosine kinase (RTK) KIT in the majority of GISTs as the primary oncogenic driver of the disease [Hirota *et al.* 1998]. Platelet-derived growth factor receptor α (PDGFRA)-activating mutations were also reported shortly thereafter and found mutually exclusive with KIT mutations [Heinrich *et al.* 2003b]. GISTs have therefore emerged as a solid paradigm of RTK-driven tumors in which strategies that inhibit the oncogenic kinase lead to significant disease control.

This review provides an overview of the current treatment strategies in GISTs and emphasizes the major therapeutic breakthroughs that have been achieved in recent years.

Imatinib, sunitinib and regorafenib are standards of care in advanced and metastatic GISTs

Molecular biology of GISTs

GISTs are the most common primary mesenchymal tumors of the gastrointestinal tract [Fletcher *et al.* 2002; Joensuu *et al.* 2002] and are characterized by expression of KIT (CD117) in approximately 95% of cases. Constitutive activation of KIT occurs in approximately 80–85% of GIST cases through activating mutations in the *KIT* gene and constitutes one of the earliest transforming events in GISTs [Corless *et al.* 2002]. Activating mutations of the *KIT* gene in GISTs occur most frequently in *KIT* exon 11 (juxtamembrane domain), followed by *KIT* exon 9 (extracellular domain) (Figure 1). Less frequently, primary mutations in the adenosine triphosphate (ATP)-binding pocket (exon 13) or activation loop (exon 17) are found [Corless *et al.* 2011]. Primary PDGFRA mutations in the juxtamembrane domain (exon 12), the first tyrosine kinase

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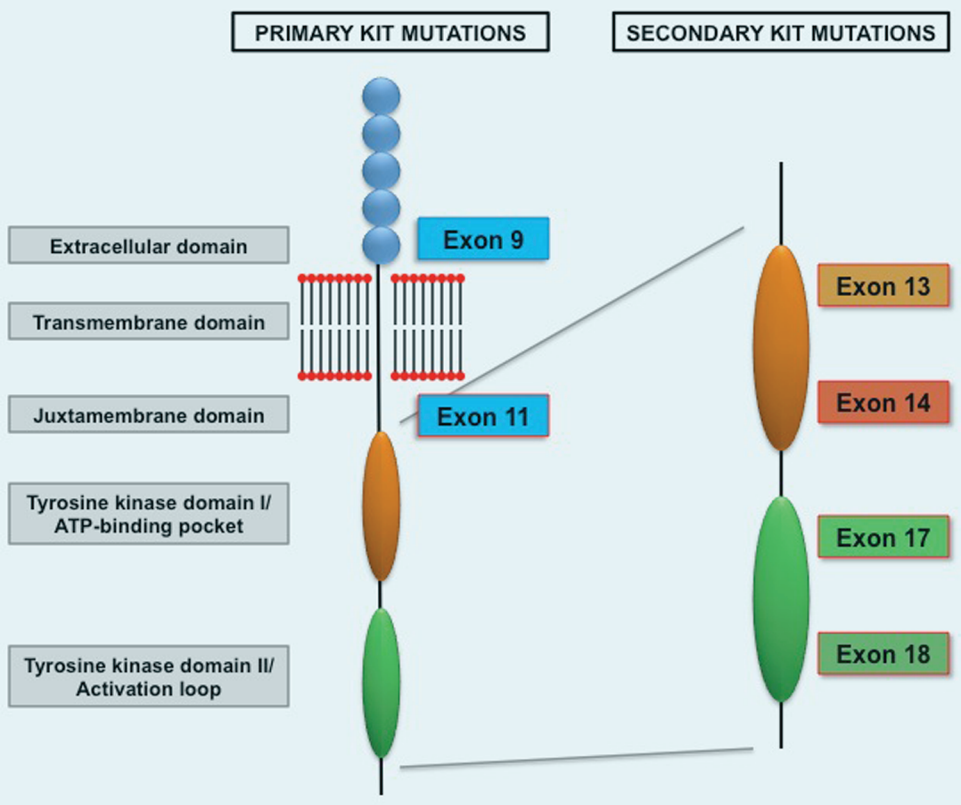

Figure 1. KIT activation in gastrointestinal stromal tumors. ATP, adenosine triphosphatase.

domain (exon 14), and the activation loop (exon 18) are also associated with the pathogenesis of GISTs in approximately 5–7% of cases [Cassier *et al.* 2012; Corless *et al.* 2005].

Downstream PI3K/AKT and RAS/RAF/mitogen-activated protein kinase (MAPK) pathways are constitutively active in GIST models and cell lines in a KIT-dependent manner through direct interaction with signal intermediates PI3K and GRB2 [Duensing *et al.* 2004; Zhu *et al.* 2007]. *In vitro* pharmacological studies have corroborated the importance of these two signaling cascades in both imatinib-sensitive and imatinib-resistant GISTs [Bauer *et al.* 2007]. Particularly, KIT activation of the MAPK pathway is crucial to stabilize ETS translocation variant 1 (ETV1), a lineage survival transcription factor indispensable for oncogenic KIT-mediated transformation [Chi *et al.* 2010].

Imatinib: first-line treatment in advanced/metastatic GISTs

Imatinib (Gleevec in USA, Glivec elsewhere; Novartis Oncology, Basel), a small molecule tyrosine kinase inhibitor (TKI) with activity against KIT, PDGFR and ABL kinase, was the first TKI approved by the US Food and Drug Administration (FDA) for the treatment of metastatic or unresectable GISTs following the demonstration of sustained response to imatinib 400 mg daily in an open-label, randomized, multicenter phase II trial [Demetri *et al.* 2002]. After follow up of 71 months, approximately two-thirds of the patients had objective radiographic response to imatinib, and an additional 15% of patients experienced prolonged stable disease [Blanke *et al.* 2008a; Demetri *et al.* 2002] (Table 1). Patients with stable disease had similar long-term benefit and favorable survival outcomes as those with objective responses [Blanke *et al.* 2008a]. The median time to progression (mTTP) was 24 months, and median overall survival (mOS) for all patients studied was 57 months, superior to that achieved in the pre-imatinib era, typically around 10–20 months [Joensuu *et al.* 2002]. Patients with *KIT* exon 11 mutation had a substantially greater likelihood of a partial response and longer time to treatment failure compared with patients with either an exon 9 mutation or

Table 1. Comparative activity of imatinib, sunitinib, regorafenib and imatinib rechallenge in patients with advanced or metastatic gastrointestinal stromal tumor.

	Imatinib (*n* = 147) [Blanke *et al*. 2008a]	Sunitinib (*n* = 207) [Demetri *et al*. 2012]	Regorafenib (*n* = 133) [Demetri *et al*. 2013]	Imatinib rechallenge (*n* = 41) [Kang *et al*. 2013]
ORR (%)	68.1	7	4.5	0
$SD_{12\ weeks}$ (%)	15.6	53	48.1	32
TTP/PFS (months)	24	6.1	4.8	1.8

ORR includes complete response and partial response.
ORR, overall response rate; PFS, progression-free survival; SD, stable disease; TTP, time to treatment progression.

no detectable mutation in either KIT or PDGFRA [Heinrich *et al.* 2003a].

Two phase III trials further confirmed the benefit of imatinib in GIST and also studied the efficacy of higher imatinib doses (800 *versus* 400 mg daily) [Blanke *et al.* 2008b; Verweij *et al.* 2004]. Overall, a small but statistically significant progression-free survival (PFS) advantage was seen with the higher dose, with no difference in overall survival between the two arms. Notably, the presence of *KIT* exon 9 mutation was the only significant predictive factor for benefit from higher doses [MetaGIST 2010], whereas patients with tumors which harbor KIT exon 11 mutation, did not benefit from higher-dose imatinib. Therapy was well tolerated, with mild diarrhea, edema and fatigue being the most common treatment-related toxicities. Patients on higher-dose therapy reported more side effects.

Unless significant toxicities occur, continuous therapy until disease progression is recommended, since interruption of imatinib results in disease progression within 12 months in most patients [Patrikidou *et al.* 2013]. Remarkably, a subset of patients with GIST have demonstrated 10 years of disease control, as shown in a preliminary report from the initial phase II trial, in which 18% of the patients survived long term on first-line imatinib since study entry, at a median follow up of 9.4 years [von Mehren *et al.* 2011]. The only prognostic factor predictive of longer TTP was low volume of disease at baseline.

Nonetheless, the vast majority of patients with advanced GISTs who benefit from imatinib have persistent measurable disease and eventually progressive disease, typically within 2–3 years. The most common mechanism of resistance to TKIs in patients with GIST entails expansion of tumor clones harboring a range of secondary mutations in KIT or PDGFRA which are resistant to imatinib. KIT TKI-resistant mutations in GISTs cluster in two regions of the KIT kinase domain: the ATP-binding pocket (encoded by exons 13 and 14), and the activation loop (encoded by exons 17 and 18), and these mutations occur almost exclusively in the same gene and allele as the primary oncogenic driver mutation [Antonescu *et al.* 2005; biec-Rychter *et al.* 2005; Chen *et al.* 2004; Heinrich *et al.* 2006] (Figure 1). Moreover, there is substantial heterogeneity of secondary resistant mutations between and within metastases from individual patients, which underscores the complexity of the TKI-resistant population and emerges as the main treatment challenge in patients with GIST after frontline imatinib treatment [Liegl *et al.* 2008; Wardelmann *et al.* 2005].

Sunitinib: second-line treatment in patients with GIST after failure of or intolerance to imatinib

Following failure of imatinib, sunitinib (Sutent; Pfizer Inc., New York, USA), a multitargeted small-molecule TKI with potent activity against KIT and PDGFRA, among several other kinases, has been shown to be an effective second-line therapy and is currently approved worldwide for metastatic GISTs in patients with imatinib resistance or intolerance. In a pivotal randomized, double-blind, placebo-controlled phase III trial in patients with imatinib-refractory or -intolerant GISTs, 312 patients were enrolled and randomized to receive sunitinib or placebo. Sunitinib dose was 50 mg daily, 4 weeks on, 2 weeks off. Despite a low objective response rate in the sunitinib group (7% response rate), TTP, the primary endpoint, was fourfold higher in the sunitinib arm compared with placebo, 27 weeks *versus* 6 weeks respectively (Table 1) [Demetri *et al.* 2006, 2012].

Continuous daily dosing of sunitinib 37.5 mg has also shown activity in an open-label phase II

clinical trial in 61 patients with GIST resistant or intolerant to imatinib, with a clinical benefit rate of 53% (13% response rate), and mPFS of 34 weeks [George *et al.* 2009].

Due to the wider spectrum of target inhibition, the range of side effects of sunitinib is greater than those for imatinib, although the majority are mild to moderate in severity and manageable through dose modification or interruption. The most commonly reported treatment-related adverse events were fatigue, diarrhea, skin discoloration, and nausea [Demetri *et al.* 2006; George *et al.* 2009].

As with imatinib, resistance to sunitinib develops, likely secondary to resistant KIT mutations. GIST kinase genotype after imatinib failure correlates with sunitinib activity. First, clinical benefit, mPFS and mOS were significantly higher for those with a primary *KIT* exon 9 or wild-type KIT/PDGFRA mutation. Second, there was also correlation between secondary KIT mutations and response to sunitinib: while KIT ATP-binding pocket mutations are exquisitely sensitive to sunitinib, the activation loop mutations are cross resistant [Heinrich *et al.* 2008].

Regorafenib: a recent standard of care for GISTs

Regorafenib (Stirvarga, Bayer HealthCare Pharmaceuticals Inc., Montville, NJ, USA) is an orally active multikinase inhibitor with activity against a variety of kinases, including those involved in oncogenesis (KIT, RET, RAF1, BRAF and BRAF V600E), regulation of tumor angiogenesis (VEGFR1-3 and TEK), and the tumor microenvironment (PDGFR and fibroblast growth factor receptor). Regorafenib has shown potent antitumor activity in a variety of preclinical models, including inhibition of growth of GIST cell lines, and inhibition of tumor growth as well as antimetastatic activity in several mouse xenografts, including some GIST xenograft models [Wilhelm *et al.* 2011].

Regorafenib, as a single agent, has been evaluated in renal cell carcinoma, colorectal cancer and GIST. The recommended dose is 160 mg taken orally once daily for the first 21 days of each 28-day cycle. Cycles are typically continued until disease progression or unacceptable toxicity. Regorafenib was first evaluated in an academic-initiated phase II clinical trial in patients with TKI-refractory GIST [George *et al.* 2012]. Clinical benefit rate, as defined by the composite of complete response (CR), partial response (PR) and stable disease (SD) lasting at least 16 weeks, was the primary endpoint of the study and resulted in four PRs and 22 SDs (26 of 33 evaluable patients). mPFS for the entire cohort was 10.0 months.

Based on these promising results, an international, randomized (2:1), placebo-controlled, multicenter, phase III trial (GRID trial) was performed. In this trial a total of 199 patients with advanced GIST previously treated with at least imatinib and sunitinib were randomized: 133 GISTs were randomized to regorafenib as a single agent, and 66 to placebo [Demetri *et al.* 2013]. The primary endpoint of the study was PFS. At the time of disease progression, patients were unblinded, and if on placebo, allowed to crossover to regorafenib at the investigator's discretion. A statistically significant improvement in PFS was demonstrated among patients treated with regorafenib compared with placebo at 3 months. PFS at 3 months was 60% for regorafenib and 11% for placebo; and at 6 months, 38% *versus* 0%. Median PFS was also statistically significantly longer for patients treated with regorafenib: 4.8 months compared with 0.9 months in the placebo group [hazard ratio (HR) 0·27, 95% confidence interval (CI) 0·19–0·39; $p < 0·0001$). No difference was observed in mOS between the groups due to the crossover design. Benefit of regorafenib on centrally assessed PFS was identified across all subgroups, except for the small subset of patients with duration of imatinib treatment of less than 6 months. As observed with sunitinib, overall response rate was low, 4.5%, with primary benefit seen as SD which was seen as best response at any time in, 71.4% of study participants randomized to regorafenib compared with 33.3% of patients in the placebo arm. Disease control rate, defined as CR, PR or SD at 12 weeks was 52.6% for patients treated with regorafenib (Table 1) and 9.1% of those treated with placebo (95% CI −54·72 to −32·49; $p < 0·0001$).

The toxicity profile of regorafenib was consistent with that of other kinase inhibitors with similar target spectrum. The most common adverse events were hand–foot skin reaction, hypertension, diarrhea, fatigue, and oral mucositis.

Adverse events grade 3 or higher were reported in 61% of patients receiving regorafenib, and the most common were hypertension and hand–foot

skin reaction. Overall, dose interruptions and dose reductions for adverse events were required in 58% and 50% of patients receiving regorafenib, but the rate of treatment discontinuation was low (2.3%).

Based on these results, regorafenib obtained FDA approval in February 2013 for the treatment of metastatic or unresectable GIST after failure or intolerance to imatinib and sunitinib.

Imatinib rechallenge as an alternative therapeutic strategy after failure of imatinib and sunitinib

Despite the remarkable advances in therapeutic options for advanced GIST, disease progression occurs in the majority of patients following use of imatinib, sunitinib and regorafenib. Resumption of imatinib with palliative purposes has been a common practice in spite of prior failure, mainly based on the evidence of rapid progression and symptom worsening after TKI discontinuation. The randomized, double-blind, placebo-controlled, phase III RIGHT trial formally addressed this question in patients with imatinib-refractory GIST who had progressed to receiving at least imatinib and sunitinib, but had achieved prior benefit with imatinib in the first-line setting [Kang *et al.* 2013].

A total of 81 patients were randomized 1:1 to receive imatinib 400 mg daily or placebo after failure of at least imatinib and sunitinib. Imatinib was well tolerated, and PFS was found to be significantly longer in the imatinib arm compared with placebo, 1.8 months *versus* 0.9 months, together with a disease control rate at 12 weeks of 32% (Table 1). There were no significant improvements in objective response and overall survival.

Therefore, it is hypothesized that the benefit observed with the rechallenge of imatinib in TKI-refractory GIST is due to continuous kinase inhibition of the bulk of disease clones that have not acquired secondary resistant mutations, although resistant clones continue to grow, as observed from the short PFS.

Newer therapies in TKI-refractory GISTs are an unmet clinical need, and we encourage treating these patients in clinical trials. Rechallenge of imatinib may serve as a useful therapeutic approach to palliate and minimize symptom worsening in GISTs when additional options are no longer available, although no data on quality of life were presented in the RIGHT trial.

Other targeted agents in GISTs

Despite the demonstrated success of imatinib, sunitinib and regorafenib, virtually all patients with metastatic GIST will become resistant to these therapies. Furthermore, the polyclonal evolution of resistant clones after progression to imatinib leads to a drop in the efficacy of subsequent lines, such as sunitinib and regorafenib. Several other TKIs have been tested in this setting (Table 2), but in some cases the studies have found only limited activity, and in other cases, there are limited data to support widespread use in the clinic.

Sorafenib (Nexavar, Bayer Healthcare Pharmaceuticals and ONYX Pharmaceuticals, San Francisco, CA, USA) is a by-aryl urea multikinase inhibitor closely related to regorafenib, with activity against KIT and PDGFRA among several other kinases. Two single-arm phase II clinical trials have demonstrated activity in patients with GIST after progression to at least imatinib and sunitinib, with an overall response rate of approximately 10% and disease control rate at 24 weeks of 36%. mPFS in both trials was around 5 months [Park *et al.* 2012; Kindler *et al.* 2013]. Similarly to sunitinib, the activity of sorafenib in GIST is due to inhibition of KIT activity in both KIT primary and secondary mutations, as assessed *in vitro* in transfected KIT constructs and GIST cell lines [Heinrich *et al.* 2012a].

Nilotinib (Tasigna; Novartis Pharma AG, Basel) is a second-generation KIT and PDGFRA inhibitor derived from imatinib. *In vitro* activity of nilotinib is greater than imatinib against BRC-ABL, but comparable regarding KIT/PDGFRA inhibition [Weisberg *et al.* 2005], although nilotinib passive intracellular transport results in a 7- to 10-fold higher intracellular concentration in imatinib-sensitive and -resistant cell lines [Prenen *et al.* 2006].

Results from a phase I study, two phase II studies and a compassionate use program [Cauchi *et al.* 2012; Demetri *et al.* 2009; Montemurro *et al.* 2009; Sawaki *et al.* 2011] provided preliminary evidence of clinical benefit in TKI-refractory GIST. However, two later randomized phase III studies have failed to demonstrate significant

Table 2. Tyrosine kinase inhibitors with KIT inhibitory activity tested in clinical trials in patients with gastrointestinal stromal tumor.

	Study	Setting	Phase	N	ORR (%)	PFS (months)
Sorafenib	Park *et al*. [2012]	≥Third line	II	31	13	4.9
	Kindler *et al*. [2011]	≥Second line	II	38	13	5.2
Nilotinib	Cauchi *et al*. [2012]	Third line	II	13	0	6
	Sawaki *et al*. [2011]	Third line	II	35	3	3.7
	Reichardt *et al*. [2012]	Third line	III	165	<1	3.6
	Blay *et al*. [2013]	First line	III	324	NA	25.9
Masitinib	Le Cesne *et al*. [2010]	First line	II	30	41.3	41.3

N, number of patients treated with the corresponding drug; NA, not available; ORR, overall response rate; PFS, progression-free survival.

activity in either the first- or third-line setting [Reichardt *et al.* 2012; Blay *et al.* 2013].

Dasatinib (Sprycel; Bristol-Myers Squibb, New York, USA) was developed as a dual SRC/ABL inhibitor with activity against other kinases including KIT, with the particularity that dasatinib is able to bind to KIT regardless of the conformation of the KIT activation loop [Bantscheff *et al.* 2007]. Dasatinib has been investigated in TKI-naïve GIST in a single-arm phase II clinical trial, but the trial was terminated earlier due to slow accrual. Activity reported from 43 eligible patients showed 67% of FDG-PET response rate at 4 weeks, and a mPFS of 11 months [Montemurro *et al.* 2012].

Masitinib mesylate (AB1010; AB Sciences, Paris, France) is an orally available TKI with greater activity and selectivity than imatinib against KIT exon 11 mutant and wild-type KIT receptor [Soria *et al.* 2009]. Masitinib showed encouraging activity in a subset of patients with GIST in a phase I clinical trial [Soria *et al.* 2009], and particularly later in a pilot phase II study in 30 patients with metastatic imatinib-naïve GIST [Le Cesne *et al.* 2010]. In this study, masitinib obtained comparable results to imatinib in terms of responses and tolerability: 29 out of 30 patients achieved disease control, and mPFS was 41.3 months. Masitinib is currently being compared in the first-line setting with imatinib in a randomized phase III clinical trial [ClinicalTrials.gov identifier: NCT00812240] [Montemurro *et al.* 2012].

Adjuvant and neoadjuvant imatinib

The success of imatinib in advanced disease prompted interest in its perioperative use, which includes both preoperative therapy for patients with unresectable or borderline resectable tumors, and postoperative treatment for patients at high risk of recurrence after complete resection of a primary GIST tumor.

Adjuvant treatment of GISTs

Complete resection is possible in most localized GISTs and constitutes the current standard of care. Although a significant proportion of patients will be cured with surgery alone, approximately 40% will eventually have relapsing disease, the great majority within the first 5 years. There are several criteria specifically created to better define the subset of patients with GIST with the highest likelihood of relapse and that could obtain more benefit from adjuvant treatment with imatinib. Among these risk-stratification schemes available for operable GIST, the most widely used are the National Institutes of Health (NIH) consensus classification [Fletcher *et al.* 2002], the Armed Forces Institute of Pathology classification [Miettinen *et al.* 2001, 2005, 2006], and the modified NIH classification [Joensuu 2008]. Tumor size, mitotic count, and tumor site are well established risk factors for recurrence, and tumor rupture has later been associated independently with higher risk of recurrence. These three classifications were recently found to have roughly similar prognostic accuracy in a series of 2560 patients with completely resected GIST, none of whom received adjuvant imatinib [Joensuu *et al.* 2012b]. Notably, regardless of the classification scheme used, patients identified as intermediate risk had a clinical course that was similar to the low-risk group, suggesting that only the high-risk group follows a more aggressive course and would be the target population to consider for adjuvant treatments.

Three randomized phase III clinical trials have evaluated the role of imatinib 400 mg daily in the adjuvant setting for 1, 2 and 3 years [DeMatteo *et al.* 2009; Joensuu *et al.* 2012a; Casali *et al.* 2013], and all of them have demonstrated that adjuvant imatinib prolongs recurrence-free survival (RFS) compared with placebo. Additionally, the results provided by the SSG XVIII study demonstrate that 3 years of imatinib significantly improves RFS and overall survival compared with 1 year of therapy. However, benefit on RFS appears to be more evident during imatinib treatment and shortly thereafter, whereas the curves tend to overlap with longer follow up, as disease recurrence increases within 6–12 months after discontinuing adjuvant imatinib, regardless of the length of the treatment. This finding therefore raises the question of mechanism of action of adjuvant imatinib in GIST, as it is not known whether recurrences are truly being prevented or just delayed. Together, current evidence supports at least 3 years of adjuvant imatinib as a new standard for patients with resected, high-risk GIST, although the optimal duration of therapy remains unknown.

Future studies should focus on clarifying this and other areas of uncertainty. For instance, preliminary data from the EORTC62024 trial reported no difference in the imatinib failure-free survival endpoint with 2 years of adjuvant imatinib compared with placebo. Finally, whether doses greater than 400 mg should be used in the adjuvant setting, or whether only high-risk patients derive benefit from adjuvant imatinib, will require prospective study.

Neoadjuvant imatinib in GISTs

Based on the high rate of responses observed with imatinib in patients with metastatic GIST, preoperative use of imatinib aims to reduce tumor bulk to facilitate complete surgical resection or increase the likelihood of organ preservation of initially unresectable or borderline resectable disease.

There are no randomized trials evaluating the benefit of neoadjuvant imatinib, but data from retrospective series and a few prospective phase II trials [Eisenberg *et al.* 2009; McAuliffe *et al.* 2009; Hohenberger *et al.* 2009] suggest that preoperative imatinib can reduce tumor size and permit later surgery in patients with locally advanced GIST. Long-term outcome appears to be comparable to a standard population of patients with GIST [Rutkowski *et al.* 2013].

Currently, National Comprehensive Cancer Network guidelines recommend initial (preoperative) treatment with imatinib in patients with marginally resectable tumors and in those with potentially resectable disease but with the risk of significant morbidity. Thus, those GISTs arising in anatomically compromised locations would be a preferred target population, and particularly rectal GISTs, that usually have responsive *KIT* exon 11 mutations and involve challenging surgeries [Jakob *et al.* 2013; Tielen *et al.* 2013].

Future directions

KIT/PDGFR-mutant GISTs

The past decade has led to discovery and understanding of crucial biological mechanisms that drive GIST survival and proliferation. This has led to the approval of three drugs (imatinib, sunitinib and regorafenib) for the treatment of advanced GIST, which have significantly improved survival in a disease formerly deemed resistant to all systemic therapies.

Drug treatment with imatinib causes substantial KIT inhibition and symptom palliation, together with a low rate of secondary effects. However, the great majority of patients develop resistance to first-line treatment due to secondary KIT mutations that lead to reactivation of KIT receptor and KIT downstream pathways in the presence of imatinib. One strategy could consist of maximizing the effect of imatinib and delay the appearance of resistant clones. Therefore, drug development of next-generation TKIs for KIT inhibition through irreversible binding (such as afatinib in *epidermal growth factor receptor* mutant non-small cell lung cancer) [Li *et al.* 2008] or conformational control inhibition (such as DCC-2036 in BCR-ABL chronic myeloid leukemia) [Chan *et al.* 2011] would constitute a major therapeutic advance with potential impact in both adjuvant and metastatic settings.

Imatinib-resistant GISTs are still dependent upon KIT signaling for survival and proliferation, as evidenced in GIST cell lines with KIT secondary mutations by decreased proliferation and increased apoptosis following inhibition of KIT activation by either RNA interference knockdown [Heinrich *et al.*

Table 3. New drugs currently being tested in clinical trials in gastrointestinal stromal tumor.

Drugs	Phase	ClinicalTrials.gov identifier
Tyrosine kinase inhibitors		
Pazopanib	II	NCT01323400
Ponatinib	II	NCT01874665
XL820	II	NCT00570635
HSP90 inhibitors		
STA-9090	II	NCT01039519
Imatinib + AT13387	II	NCT01294202
AUY922	II	NCT01404650
Combination treatments		
Imatinib + BYL719	I	NCT01735968
Imatinib + BKM120	I	NCT01468688
Imatinib + perifosine	II	NCT00455559

HSP90, heat shock protein 90.

2006], alternative KIT kinase inhibitors such as sunitinib [Heinrich *et al.* 2008] or heat shock protein 90 (HSP90) inhibitors [Bauer *et al.* 2006]. Novel strategies in imatinib-resistant GISTs have to address the inevitable intratumor heterogeneity by inhibiting KIT activation regardless of KIT genotype. In this sense, targeting HSP90 [Bauer *et al.* 2006] or the more selective HSP90 cofactor CDC37 [Marino-Enriquez *et al.* 2013] constitute two attractive approaches. Three HSP90 inhibitors (STA-9090, AT-13387 and AUY922) are currently being tested in patients with GIST [ClinicalTrials.gov identifier: NCT01039519, NCT01294202, NCT01404650]. Other approaches include the wide range of TKIs with KIT inhibitory activity (see section Other targeted agents in GISTs). Among them, ponatinib, a next-generation TKI recently approved in imatinib-resistant BCR-ABL leukemia [Cortes *et al.* 2012] is currently being studied in a phase II clinical trial in patients with GIST [ClinicalTrials.gov identifier: NCT01874665] given its promising preclinical activity against KIT [Lierman *et al.* 2012]. Additionally, KIT downstream PI3K/AKT and RAS/RAF/MEK pathways emerge as two crucial targets regardless of KIT genotype. Indeed, recent *in vitro* and *in vivo* data [Bauer *et al.* 2007; Floris *et al.* 2013] suggest potent synergy of dual KIT and PI3K inhibition, and two ongoing clinical trials are investigating this combination in metastatic GIST [ClinicalTrials.gov identifier: NCT01735968, NCT01468688].

Current approved TKIs in GIST target both KIT and PDGFRA mutations, and the majority of PDGFRA-driven GISTs appear to benefit from these treatments, A notable exception, however, is the substitutions involving codon D842 in exon 18 of PDGFRA which is universally resistant to current approved KIT/PDGFRA inhibitors [Corless *et al.* 2005; Cassier *et al.* 2012]. Crenolanib is a potent inhibitor of imatinib-resistant PDGFRA mutants in GISTs [Heinrich *et al.* 2012b], and a phase II clinical trial is ongoing to address the efficacy of this drug in this selected GIST subpopulation [ClinicalTrials.gov identifier: NCT01243346].

Finally, the efficacy of a monoclonal antibody against KIT has recently been demonstrated for the first time *in vitro* and *in vivo* [Edris *et al.* 2013]. Monoclonal antibody SR1 decreases proliferation, induces KIT downregulation and enhances cell-mediated tumor clearance, resulting in a novel approach for possible exploration in the treatment of GIST.

Non-KIT/PDGFR-mutant GISTs ('wild-type' GISTs)

It has long been recognized that a subset of GISTs do not harbor an activating mutation in either KIT or PDGFRA. These tumors have historically been classified as 'wild type' GISTs. Recently, it has become apparent that a wild-type GIST is composed of several subtypes of GIST, including GISTs associated with type I neurofibromatosis, and importantly, GISTs associated with Succinate dehydrogenase (SDH) deficiency (SDH-deficient GISTs) [Janeway *et al.* 2011; Killian *et al.* 2013]. Extensive discussion of these

subtypes is beyond the scope of this review, however the recognition of these unique clinical and biologic subtypes of GIST is important due to the somewhat more indolent natural history of these tumors, predilection of younger age at presentation, high rate of metastasis, and decreased bidimensional response to imatinib. Additional studies to further define these subtypes and unique therapeutic strategies are ongoing. At this time, however, standard treatment with approved TKIs is recommended.

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