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Systemic Therapy for Advanced Gastrointestinal Stromal Tumors: Beyond Imatinib

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Progression on first-line therapy with imatinib in gastrointestinal stromal tumors (GIST) is caused by either initial resistance or more often a secondary mutation in tyrosine kinases KIT or PDGFR. Therapies in development for imatinib-resistant GIST include agents that target KIT/PDGFR with greater potency or possess broader kinase inhibition profiles including VEGFR. To circumvent secondary mutations in KIT/PDGFR, inhibition of the downstream signaling in PI3K/Akt/mTOR pathway and enhanced degradation of KIT/PDGFR are also under investigation. *J. Surg. Oncol. 2011;104:901–906.* © 2011 Wiley Periodicals, Inc.

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INTRODUCTION

Overview of Systemic Therapy for Advanced GIST

The story of systemic therapy for advanced gastrointestinal stromal tumors (GIST) as of now can be divided into three chapters. The first chapter describes an interval before the turn of the 21st century when there were no known effective systemic therapies for this disease. Gastrointestinal tract sarcomas, mainly GIST, demonstrated a high rate of primary resistance to chemotherapy, low response rates, and overall poor prognosis. Complicating matters was a lack of uniformity in what was recognized as a GIST. The second chapter began with the pivotal identification of over-expression of the membrane receptor tyrosine kinase KIT (CD117) as a unifying feature diagnostic for a majority of GISTs. Subsequently, GIST tumors were found to have gain-of-function mutations in KIT [1] which fundamentally changed the therapeutic approach to one targeting this specific kinase. Imatinib mesylate, a selective inhibitor of KIT and PDGFR (in addition to Bcr-Abl) was shown to lead to high rates of response and disease control [45% response rate and 25% stable disease (SD)] with resultant improvements in median overall survival to approximately 50 months [2]. Since its FDA approval in 2002, imatinib has remained the standard first-line systemic therapy for GIST. However, over the past decade, it has become apparent that the tale of imatinib's success is tempered by the observation that patients treated with imatinib are not cured nor controlled indefinitely, with median progression free survivals of <2 years reported in initial phase III trials [2,3]. Progression is primarily attributed to the development of secondary mutations that confer resistance to imatinib [4]. Thus, we enter the third chapter of the GIST story in which the next generation of novel therapies is under development for treatment of imatinib-resistant disease. This review will focus on those therapies central to this most recent chapter of systemic treatment for advanced GIST.

KIT and PDGFR Mutations

Prior to introducing the next generation of therapies, it is necessary to first review in greater detail the biology of GIST pathogenesis and in particular the relationship between specific kinase mutations and corresponding response or resistance to imatinib. Activating mutations in the tyrosine kinases KIT (90%) and PDGFR (5%) are responsible for development of most GISTs. The remaining small fraction of GISTs that lack mutations in both KIT and PDGFR are referred to as wild-type GIST. Activation of KIT or PDGFR leads to downstream signaling in the PI3K, Ras, and Jak/Stat pathways resulting in increased cell proliferation and inhibition of apoptosis. The most common mutations in KIT are found in exon 11, the regulatory juxtamembrane (JM) domain (~70%), or in exon 9, the extracellular (EC) regulatory domain (~15%). Rarely, primary mutations in KIT occur in the kinase domains encoded by exons 13/14 for the ATP binding domain (TK1) and exon 17 for the kinase activation loop (TK2). In contrast, the most common primary mutations found in PDGFR are in the kinase activation loop (TK2) encoded by exon 18, specifically the D842V point mutation [5]. Imatinib binds to the inactive conformation of TK1 and prevents binding of ATP. GIST tumors with exon 11 mutations are responsive to imatinib, with an objective response rate of 72% which compares favorably to the response rate with exon 9 mutations (44%) and wild-type GIST (45%) [6]. Exon 11 mutations also confer favorable time to disease progression (25 months) as compared to exon 9 mutations (17 months) and wild-type GIST (13 months). A higher dose (800 mg) of imatinib may benefit patients with exon 9 mutations with a longer progression-free survival but this does not translate to improved overall survival [7]. Primary mutations in either TK1 or TK2 of KIT are rare but do appear to still confer some sensitivity to imatinib [7,8]. In contrast, the D842V mutation in TK2 of PDGFR appears to be inherently resistant to imatinib. Notably, mutations in TK1 and TK2 are frequently found in GIST that has progressed on imatinib and are thought to play a dominant role in this development of *secondary* resistance to imatinib [4]. Interestingly, it has been shown that multiple distinct mutations can develop independently within different sites of progressing disease within a single patient [9]. Understanding the variety, frequency, and biological significance of these mutations is critical to identifying novel agents that can overcome resultant imatinib resistance.

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Sunitinib

Sunitinib (SU11248) is an oral small molecule inhibitor of multiple receptor tyrosine kinases including KIT, PDGFR ($\alpha + \beta$), VEGFR (1,2,3), FLT3, CSF-1R, and RET. Sunitinib, like imatinib, binds to the inactive conformation of target tyrosine kinases and inhibits binding of ATP. Despite this similarity, sunitinib has potential for activity in imatinib-resistant disease presumably through unique binding characteristics and broader spectrum of kinase inhibition including the tumor-associated angiogenic VEGFR family of tyrosine kinases. Among the next generation of agents for imatinib-resistant GIST, sunitinib has been the most extensively studied. Sunitinib was tested in a double-blinded phase III trial of 312 patients with advanced GIST intolerant or resistant to imatinib who were randomized 2:1 to receive either sunitinib ($n = 207$) or placebo ($n = 105$) [10]. Sunitinib was given at a dose of 50 mg daily for 4 weeks followed by 2 weeks of treatment. The primary endpoint of median time to tumor progression was significantly longer with sunitinib compared with placebo (6.8 vs. 1.6 months, HR 0.33, $P = < 0.0001$). Clinical benefit was obtained by 65% of patients with 7% achieving partial response (PR) and 58% SD. After a planned interim analysis of the first 149 patients revealed benefit with sunitinib in time to tumor progression, the study was unblinded and crossover was allowed for patients progressing on placebo. In spite of this crossover to active therapy, there was still a detectable improvement in overall survival in patients receiving initial sunitinib treatment (HR 0.49, $P = 0.007$). Sunitinib was relatively well tolerated with no significant difference in discontinuation of treatment due to toxicity between sunitinib (9%) and placebo (8%). The most common treatment-associated non-hematologic adverse events were fatigue, diarrhea, hand–foot syndrome, and hypertension. There was also a significant difference in hematologic toxicity with greater leukopenia and thrombocytopenia with sunitinib. Based on the observed efficacy and tolerability, sunitinib was approved by the FDA in 2006 for patients with GIST and progressive disease on, or intolerant to, imatinib.

Unfortunately, not all patients with imatinib-resistant GIST benefit from sunitinib. Similar to the differential sensitivity to imatinib, sunitinib has also been shown to have variable efficacy depending on the specific mutation(s) present. Sunitinib appears to have preferential activity against mutations involving exons 13/14 of KIT (TK1), and less activity against mutations in the kinase activating loop (TK2) encoded by exon 17 in KIT and exon 18 in PDGFR (D842V) [11,12]. While sunitinib is the current standard of care for second line therapy of imatinib-resistant disease, there is an obvious need for additional therapeutic options to treat patients whose disease is not controlled with sunitinib or imatinib.

NEW TKI'S THAT INHIBIT KIT AND PDGFR

In this section, we describe three of the next generation agents which are similar to imatinib in that that they target KIT and PDGFR, but do not target VEGFR like sunitinib.

Nilotinib

Nilotinib (AMN107) is an orally delivered small molecule inhibitor of KIT, PDGFRα, and Bcr-Abl, similar to imatinib and sunitinib in that it also binds the inactive conformation of target tyrosine kinases. Despite a similar target kinase inhibition profile to imatinib, nilotinib exhibits enhanced cellular uptake which results in a sevenfold to tenfold higher intracellular concentration than imatinib [13]. A phase I study demonstrated clinical activity of nilotinib in patients with imatinib-resistant GIST with 14 out of 18 patients achieving either PR (1) or SD (13) and a median progression-free survival of 5.5 months [14]. A retrospective analysis was performed on 52 consecutive patients who failed both imatinib and sunitinib and were then treated with nilotinib given 400 mg twice daily [15]. Five patients (10%) benefitted from nilotinib with objective response (1 CR, 4 PR) and an additional 19 patients (37%) achieved stability of disease for a 47% clinical benefit rate. Median progression-free survival was 3 months with a median overall survival of 8.5 months. A phase II trial further confirmed activity of nilotinib in the third-line setting with 35 patients enrolled and 24 patients (69%) demonstrating benefit (1PR and 23 SD) with a median progression-free survival of 4 months and median overall survival of 11 months [16]. A phase III trial was conducted in 248 patients who had failed both imatinib and sunitinib randomized 2:1 to either nilotinib or best supportive care [17]. There was no statistical difference in the intent-to-treat population for progression-free survival or overall survival. However, one potential confounding factor in the results of this study was allowance of patients on the best supportive care arm to continue to receive imatinib or sunitinib as the majority did (93%). An exploratory analysis of 197 patients (79%) receiving treatment as true third line (excluded patients who received more than two prior regimens) demonstrated a longer survival with nilotinib (14.5 vs. 10 months, $P = 0.02$). Overall, nilotinib appeared to be well tolerated in the studies above with no difference in adverse events between the two arms of the phase III trial. Treatment-related adverse events were noted to most commonly include anorexia, nausea and vomiting, and diarrhea. In an attempt to assess whether nilotinib might have more activity in untreated patients, nilotinib was tested in a phase II study of 19 treatment-naïve patients with advanced metastatic disease. Preliminary analysis of 14 patients who completed 6 months of therapy revealed benefit in 12 patients with either PR (43%) or SD (43%) [18].

The preliminary results of these studies do not include comprehensive analysis of mutation status at time of treatment with nilotinib and therefore it is difficult to hypothesize incorporation of a risk-adaptive strategy for nilotinib. Nevertheless, the range of benefit achieved in the third line setting suggests nilotinib may provide benefit to some portion of patients despite secondary mutations that confer resistance to imatinib and sunitinib.

Masitinib

Masitinib (AB1010) is an orally administered small molecule inhibitor of KIT, PDGFR ($\alpha + \beta$), and Lyn [19]. Preclinical evaluation of masitinib demonstrated inhibition of mutations in exon 11 (JM) and wild-type KIT but not the D816V mutation in exon 17 (TK2). A phase 1 study of masitinib for patients with solid tumors included 19 patients with imatinib resistant or intolerant GIST and clinical benefit was achieved in seven of those patients (1 PR and 6 SD) [20]. Based on pharmacokinetic data from this phase I study, a weight adjusted dosing was tested in a phase II study of masitinib in the first-line treatment of 30 patients with advanced GIST. Twenty-nine patients (96.7%) achieved disease control with 1 CR, 15 PR, and 13 SD [21]. A promising median progression-free survival of 41.3 months yielded a 3-year survival rate of 89.9%. Notable toxicities included asthenia, diarrhea, nausea and vomiting, muscle spasms, rash, and abdominal pain. A majority of patients also experienced treatment-related edema. Rates of hematologic events were low (13% anemia and 17% neutropenia) compared to imatinib. Furthermore, masitinib's selective inhibition of KIT and PDGFR but not Abl kinase was hypothesized to cause less cardiotoxicity than imatinib and, at least in this small study, there were no reports of cardiotoxicity with masitinib. Based on the high rate of response and sustained benefit in this phase II trial of untreated advanced GIST, masitinib is a potential candidate to compare with imatinib in future first-line therapy trials. Efficacy of masitinib in patients previously treated with imatinib or other agents has not been studied other than the phase I study described above.

Dasatinib

Dasatinib (BMS-3548245) is an oral small molecule which potently not only inhibits Bcr-Abl and the Src family of kinases but also inhibits KIT and PDGFR. Unlike the previously described tyrosine kinase inhibitors which bind the inactive conformation, dasatinib binds to the active conformation [22]. This unique characteristic is thought to explain the ability of dasitinib to inhibit the PDGFR mutation D842V found in the kinase activation loop (TK2) which stabilizes the kinase in the active conformation [23,24]. A phase II trial in the United States investigating dasatinib in sarcomas including GIST is ongoing. Additionally, a phase II study in Switzerland is investigating efficacy of dasatinib as first-line treatment for GIST. Analysis of the results of these trials will hopefully detail, specific efficacy in patients with PDGFR D842V mutation for whom other kinase inhibitors have been ineffective.

TKI'S THAT INHIBIT KIT/PDGFR AND VEGFR

Whereas the three previously described kinase inhibitors (nilotinib, masitinib, and dasatinib) are similar to imatinib in that they target KIT and PDGFR, they are unlike sunitinib in that they do not target VEGF(R). We will next describe a series of novel therapies which are similar to sunitinib and target VEGF in addition to KIT and PDGFR. GIST tumors are highly vascular and angiogenesis has been suggested to play a significant role in tumor progression. Increased VEGF expression and high micro-vessel density have been shown to correlate with prognosis [25,26]. Targeting angiogenesis in combination with KIT or PDGFR inhibition is thus hypothesized to improve on efficacy achieved with inhibition of KIT/PDGFR only.

Sorafenib

Sorafenib (BAY 43-9006) is a small molecule given orally that inhibits the serine/threonine Raf kinases but also has activity against the tyrosine kinases KIT, PDGFRβ, VEGFR(2,3), Flt3, and Ret. Sorafenib was shown in preclinical testing to inhibit wild-type KIT and PDGFR as well as mutation T670I found in exon 14 of KIT (TK1) [27]. It appeared to have less activity against an imatinib-resistant mutation found in the kinase activation loop (TK2). Preliminary results of a phase II trial in 26 patients in whom disease progressed on both imatinib and sunitinib revealed a clinical benefit rate of 71% with 3 PR (13%) and 14 SD (58%) [28]. Median progression-free survival was 5.3 months with a 13-month median survival. Sorafenib appeared to be well tolerated with the most frequent grade 3 toxicities being hand–foot syndrome and hypertension. A retrospective study of sorafenib given to 32 patients in the fourth line setting after progression on imatinib, sunitinib and nilotinib also demonstrated activity in heavily pre-treated patients [29]. Clinical benefit rate was 63% with 19% PR and 44% SD with a median progression-free survival of 5 months and median overall survival of 10.5 months. Mutational analysis has not yet been reported in this advanced setting but the results are nevertheless encouraging based on efficacy despite a presumption of mutations conferring resistance to prior therapies.

Motesanib

Motesanib (AMG 706) is another small molecule given orally that potently inhibits VEGFR (1,2,3) and KIT and to a lesser degree inhibits RET and PDGFR [30]. Motesanib binds the inactive conformation of the ATP-binding domain (JM) similar to imatinib. However, preclinical evaluation demonstrated motesanib has greater potency than imatinib in inhibiting the common primary KIT mutations found in exons 11 (JM) and 9 (EC) [31]. In addition, motesanib appears to have activity against wild-type KIT, secondary mutations in the ATP-binding domain (TK1), and even a mutation found in the kinase activation loop (TK2) Y823D. It does not appear, however, to inhibit the D816V kinase activation loop (TK2) mutation. Like the other multi-kinase inhibitors in this group that also target VEGFR, motesanib has the potential to augment the clinical benefit of inhibiting KIT or PDGFR by also inhibiting angiogenesis. The anti-angiogenic properties of motesanib were shown to contribute to reduction in tumor growth in a preclinical xenograft model of breast cancer through decrease in neovascularization [32]. Based on this preclinical data and a phase I study in solid malignancies establishing a daily dose of 125 mg of motesanib, a phase II study in the second line setting was completed for patients with advanced GIST who had failed imatinib [33]. Clinical benefit was achieved in 62% of 102 evaluable patients with 3% achieving PR and 59% SD (14% durable SD $>$ 6 months). Median progression-free survival was a modest 4 months. Patients not uncommonly discontinued treatment (27%) as a result of an adverse event, with the most common grade 3 toxicities noted as hypertension, fatigue, and diarrhea. No mutational analysis has been reported and it is possible that motesanib may have utility in GIST with specific mutations such as the Y823D mutation (TK2).

Vatalanib

Vatalanib (PTK787/ZK222584) is a small molecule multi-kinase inhibitor given orally, which like motesanib, potently inhibits VEGFR (1,2,3) and to a lesser degree KIT and PDGFRβ [34]. Nevertheless, given its potential dual activity against both KIT/PDGFR and VEGFR, like the other agents in this group, it has been studied for potential efficacy in GIST. A small phase II study evaluated vatalanib in the second line setting, treating 15 patients with imatinib-resistant advanced GIST [35]. Vatalanib appeared to have moderate activity with two patients achieving a PR and eight patients maintaining SD for over 3 months for a clinical benefit rate of 67% and a median time to progression of 8.5 months. Vatalanib was dosed once daily at 1250 mg and was reportedly well tolerated with no treatment related grade 3 or 4 toxicities. A larger phase II study of vatalanib in the third line setting for patients with GIST refractory to both imatinib and sunitinib is currently in progress. At this time, there is no information available about any potential selective inhibition of specific mutations in KIT and PDGFR.

Bevacizumab

Bevacizumab is a monoclonal antibody which affects angiogenesis by binding circulating VEGF with subsequent inhibition of VEGF signaling. Unlike the other agents in this section, it does not directly target tyrosine kinases. Based on the same theoretical rationale as described for the multi-kinase inhibitors, bevacizumab was proposed for use in combination with imatinib to augment the clinical benefit achieved with KIT/PDGFR inhibition by also targeting angiogenesis. A phase III trial was initiated randomizing patients with advanced GIST to imatinib with or without bevacizumab. Accrual to this trial has been slow and no results have been reported to date.

INDIRECT INHIBITORS

All of the above agents except bevacizumab share a common feature in that they are direct tyrosine kinase inhibitors which target KIT and PDGFR. Some of the more promiscuous agents also target other pathways such as angiogenesis through inhibition of VEGFRs, as well as other kinases like Src and Raf. It is reasonable to hypothesize that the previously described novel agents have different binding characteristics and inhibition of other pathways may have resulted in the variable efficacy in treating resistance to imatinib by circumventing primary and secondary mutations in KIT and PDGFR. An alternative approach under active investigation is an attempt to

nullify sensitivity of specific mutations to inhibition by targeting the kinase indirectly either through enhanced degradation of the kinase or targeting downstream pathways activated by KIT/PDGFR.

Hsp-90 Inhibition

Hsp90 functions as a chaperone protein which protects client proteins from ubiquitination and degradation. Both KIT and PDGFR have been shown to depend on Hsp90 for stabilization [36,37]. This dependence has been demonstrated in preclinical evaluation to be a target that can be exploited for inhibition of KIT and PDGFR despite mutations in TK1 and TK2 [24,38]. The documented inhibition of KIT and PDGFR with mutations in TK2, KIT D816V, and PDGFR D842V, are particularly notable as these mutations confer resistance to all the above kinase inhibitors with the exception of dasatanib. Thus, based on preclinical data, inhibition of Hsp90 appears to have potential broad utility in imatinib-resistant GIST.

IPI-504. The novel Hsp90 inhibitor IPI-504 has been tested in a phase I study of 38 patients with metastatic GIST resistant to imatinib and sunitinib (95%) as well as additional prior agents (38%) [39]. An encouraging 78% of 37 evaluable patients achieved a best response of SD, although there were no partial or complete responses. Treatment was reportedly well tolerated in this phase I study with a defined MTD of 400 mg/m^2 given IV twice weekly for 2 weeks followed by 1 week of rest. Mutational analysis of KIT and PDGFR in patients treated with IPI-504 in this study has not been reported. This type of analysis is needed to confirm the hypothesized benefit of this strategy for patients with disease driven by mutations otherwise refractory to direct tyrosine kinase inhibitors.

PI3K/AKT/mTOR Pathway Inhibition

Growth factor activation of the PI3K/AKT/mTOR pathway has been shown to play a physiologic role in cell proliferation. Dysregulation of this pathway in cancer leads to proliferation of cancer cells and has therefore been targeted in multiple malignancies. The PI3K/AKT/mTOR pathway is downstream of the receptor tyrosine kinases KIT and PDGFR which are constitutively activated in GIST. It has been hypothesized that targeting a downstream effector pathway of KIT and PDGFR could augment efficacy in treatment of GIST. Preclinical results from combining imatinib with inhibitors of the PI3K/AKT/mTOR pathway suggested a potential synergy in promoting apoptosis in imatinib-resistant GIST [40]. This result led to the trials below combining imatinib with either inhibitors of Akt or mTOR.

Perifosine. Perifosine (KRX0401) is an oral alkylphospholipid that inhibits Akt phosphorylation by preventing its translocation to the cell membrane [41]. A phase II study investigated the activity of perifosine in combination with imatinib in 40 patients with imatinib-refractory disease [42]. Patients were randomly assigned to two different dosing schedules of perifosine, either 100 mg daily or 900 mg dose given weekly. Of the 36 patients evaluable for response, 44% achieved SD but no patient achieved a defined partial or complete response. This result translated to a median progression-free survival of only 2.2 months although overall survival was 18.3 months. Notably, four out of five patients with wild-type KIT achieved SD suggesting potential benefit of targeting the PI3K/AKT/mTOR pathway in wild-type GIST. Interestingly, it was recently reported that insulin-like growth factor 1 receptor (IGF-1R) which signals through the PI3K/AKT pathway is over-expressed in GIST tumors with wild-type KIT and PDGFR [43]. This provides a mechanistic explanation for the potential specific efficacy of Akt inhibition with perifosine in wild-type GIST. The combination of perifosine and imatinib did incur moderate toxicity, but only three (8%) patients were removed from the study for toxicity, with the most common grade 3 event fatigue occurring in 20%. These preliminary results suggest potential activity of combining Akt inhibition with imatinib to overcome resistance, particularly in wild-type GIST. However, the short median progression-free survival suggests less clinical benefit from combining perifosine with imatinib in imatinib-resistant disease than one may have thought based on the preclinical data. In order to better assess whether Akt inhibition can synergize with KIT/PDGFR inhibition to overcome imatinib resistance, it may be necessary to study perifosine in combination with one of the next generation tyrosine kinase inhibitors.

Everolimus. Downstream of PI3K and Akt is the intracellular kinase, mammalian target of rapamycin (mTOR) which helps regulate response to growth factors as well as signals of cellular stress. Everolimus (RAD001) is an oral mTOR inhibitor which has been studied in combination with imatinib for patients with GIST. A phase II study tested this combination in two groups of patients, 28 patients who progressed on imatinib only (second line) and 47 patients who progressed on imatinib and either sunitinib or another tyrosine kinase inhibitor (third line) [44]. In patients treated in the second line setting, 36% achieved a best response of SD yielding a disappointing 1.9-month progression-free survival but a median overall survival of 14.9 months. For patients treated in the third line setting, 2% had a PR and 43% had SD resulting in 3.5-month median progression-free survival and median overall survival of 10.7 months. Grades 3 and 4 adverse events were experienced by 67% of treated patients with the most common noted to be hypokalemia, anemia, vomiting, and fatigue. A second phase II study investigated this same combination of everolimus and imatinib in 27 patients in the second line setting after progression on imatinib [45]. Results of this study were similar to the prior study with 33% achieving SD as a best response and no objective responses. These results demonstrate a modest benefit of adding mTOR inhibition to imatinib in imatinib-refractory disease. The mutational status of KIT and PDGFR was not reported in the above studies with everolimus

TABLE I. Systemic Therapy for Gastrointestinal Stromal Tumors

Category	Agent	Molecular target	Comments
Inhibits KIT/PDGFR	Imatinib	KIT, PDGFRα + β, Bcr-Abl	Used first line in advanced disease Effective as adjuvant treatment
	Nilotinib	KIT, PDGFRα, Bcr-Abl	Second generation imatinib Increased intracellular concentration
	Masitinib	KIT, PDGFRα + β, Lyn	High specificity for KIT and PDGFR
	Dasatinib	KIT, PDGFR, Bcr-Abl, Src	Binds active conformation KIT/PDGFR unlike other TKI's
Inhibits KIT/PDGFR and angiogenesis	Sunitinib	KIT, PDGFR, VEGFR (1,2,3), FLT3, CSF-1R, RET	FDA approved for second line therapy May be preferred first line for exon 9 KIT mutations
	Sorafenib	KIT, PDGFRβ, VEGFR(2,3), Flt3, Ret	Broad kinase inhibition profile
	Motesanib	KIT, PDGFR, VEGFR(1,2,3), Ret	Potent VEGFR inhibitor
	Vatalanib	KIT, PDGFRβ, VEGFR(1,2,3)	Less active against KIT/PDGFR
Indirect inhibitors	IPI-504	Hsp90	Promotes degradation of KIT/PDGFR Independent of specific kinase primary and secondary mutations
	Perifosine	Akt	Inhibits downstream of KIT/PDGFR
	Everolimus	mTOR	Inhibits downstream of KIT/PDGFR

and thus it remains unknown whether there may be any mutational dependence or selectivity for response to the addition of mTOR inhibition.

CONCLUSION

At the present time, imatinib and sunitinib remain the standard first and second line therapies for patients with advanced GIST. This review highlights multiple new tyrosine kinase inhibitors with potential utility when standard options have failed (Table I). As more experience and information is obtained for each of the described next generation agents, it is necessary to develop better understanding of the sensitivity of specific mutations to specific agents. Obtaining a complete profile of mutations in GIST tumors treated in clinical trials with novel agents is critical. This information is required to begin to consider applying genotyping to a risk-adaptive strategy with assignment of specific therapeutic options based on an individual patient's tumor mutation profile to ultimately provide personally tailored targeted therapy. One might hypothesize newer agents that potentially circumvent-specific mutations (e.g., inhibition of Hsp90) may play a critical role in salvaging patients who are refractory to direct tyrosine kinase inhibition. One can also imagine that combining these types of agents in an earlier line of therapy may lead to a more meaningful response of longer duration by eliminating selective pressure for development of secondary mutations. We are still very early in this third chapter of the story of systemic therapy for GIST. Preliminary efforts and trial results provide promise and encouragement for how this chapter of the story will ultimately unfold for patients with advanced GIST.

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