Published in final edited form as:

Hematol Oncol Clin North Am. 2013 October ; 27(5): 905–920. doi:10.1016/j.hoc.2013.07.007.

Gastrointestinal Stromal Tumors: Management of metastatic disease and emerging therapies

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Synopsis

Gastrointestinal stromal tumors (GIST) are the most common mesenchymal tumors of the gastrointestinal tract. Prior to the advent of tyrosine kinase inhibitors like imatinib, there were few treatment options available to patients with metastatic GIST. Surgery was the mainstay of treatment and the prognosis for patients with metastatic GIST was dismal. With the advent of imatinib the prognosis of metastatic GIST has improved dramatically. Second line tyrosine kinase inhibitors (TKI) such as sunitinib and regorafenib have further bettered prognosis, however there is still a need for therapies for patients with disease refractory to TKI therapy. Newer agents such as the Hsp90 inhibitors, PI3K-AKT-mTOR inhibitors and IGF1-R inhibitors are currently under investigation and may have promise. This review discusses the current standard of care in terms of pharmacotherapy, both standard and investigational (summarized in Box 1), in the management of metastatic GIST.

Keywords

GIST; tyrosine kinase inhibitors; SDH deficient GIST; KIT; PDGFRA; IGF-1R; HSP90

Tyrosine Kinase Inhibitors (TKI)

Activating mutations in the KIT and platelet derived growth factor alpha (PDGFRA) genes have been implicated in the pathogenesis of GIST. The majority of GIST have an activating mutation in the KIT gene most commonly in exon 11 followed by exons 9, 13 and 17, that constitutively activates the gene product, a cell surface protein kinase receptor, [1] Activating mutations in the PDGFRA gene occur in one third GIST tumors which lack KIT mutations. [2] TKI target mutated KIT and PDGFRA. Currently imatinib is the agent of choice in the first line setting followed by sunitinib in patients who are imatinib intolerant or resistant. Reports of GIST with alternate kinase mutations in B-RAF and RAS have been described [3]. GIST without kinase mutations, classically called wild type, represent a family of tumors associated with loss of succinate dehydrogenase B protein expression with or without mutations in the SDH family of genes, occur in patients with Neurofibromatosis,

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Disclosures:

JV- None

or may have a novel mechanism not yet identified [4, 5]. The mechanism of action of currently approved and investigational TKI are summarized in Table 1.

FDA Approved Agents for GIST

Imatinib

Imatinib (Gleevec) is a small molecule tyrosine kinase inhibitor (TKI) that exhibits inhibitory activity against ABL kinase, as well as KIT and PDGFRA receptor. Imatinib was first tested in a proof of principle trial in a patient with KIT exon 11 mutated metastatic GIST; the patient experienced a dramatic and durable response to therapy.[6] Subsequent phase I-III studies demonstrated significant objective responses summarized in Table 2 [7–10]. Phase I studies determined the maximum tolerated dose (MTD) for imatinib to be 800 mg daily, with edema, including periorbital edema, diarrhea, nausea, vomiting, and myelosuppression being the main adverse events. The studies evaluated a range of doses: 400 mg daily, 600 mg daily and 400 mg twice daily, with all studies demonstrating a high rate of objective responses. Two phase III studies compared 400 mg daily to 400 mg twice daily in advanced disease with similar ORR, CR, PR, and SD rates between the two arms. [11, 12] Patients were allowed to crossover from the 400 mg daily dose to 400mg twice daily for progression; in one study 3% of patients who crossed over to the high dose imatinib arm at the time of progression achieved a partial response and 28% achieved disease stabilization, albeit for a median PFS of 5 months. [12] A meta analysis of the phase III studies evaluated dosage of imatinib and showed that there was a PFS advantage for patients treated at the higher dose with a hazard ratio hazard ratio (HR) of 0.89 (95% CI; 0.79–1.00, $p=.04$), however there was no difference seen in overall survival between the two arms. On subset analysis it was found that patients with KIT exon 9 mutations had a better ORR (47% vs. 21%, $p=.0037$) and a significantly better PFS with an adjusted HR of 0.58 (95% CI; 0.38–0.91), again without a difference in overall survival between the two dose levels.[13] The PFS benefit seen at the higher dose level in the Meta analysis was attributed to the benefit in patients with exon 9 tumors.

Based on the above data the current standard of care for advanced GIST is initiation of imatinib at a dose of 400mg daily for all patients except for those with an exon 9 mutation and those who progressed on the lower dose of imatinib; these patients do better at a dose of 800mg daily.

Approximately 14% of GIST tumors have primary resistance to imatinib, progressing within six months of initiating therapy. [9] These tumors most commonly are those with mutations in PDGFRA in exon 18, D842V, or those lacking mutations in either KIT or PDGFRA. Secondary resistance occurs in patients on long term imatinib, greater than six months. The majority of this resistance occurs due to clonal evolution. These clones express the primary mutation along with additional mutations that render them resistant to imatinib, leading to treatment failure and relapse; the secondary mutations occur within the same gene. The most common secondary mutations seen are in exons 13, 14 and 17 of the KIT gene and the D842V mutation in exon 18 of PDGFRA.[14–16] The median time to progression on imatinib is approximately 2 years, however some patients remain free of progression for greater than 10 years. Factors associated with long term disease stability are good performance status and low base line neutrophil count. Factors that are associated with better overall survival include younger age, female sex, low neutrophil count, normal albumin and good performance status. [12] In addition, smaller tumor volume has also been associated with longer progression free survival [17].

Sunitinib

Sunitinib (Sutent) is a small molecule tyrosine kinase inhibitor that inhibits VEGFR-1,2,3, PDGFRA, PDGFRB, KIT, Flt3, RET and CSF1R.[18] In an early phase I study that looked at the use of sunitinib in patients with advanced malignancies, 6 of 22 evaluable patients had an objective response including one patient with imatinib resistant GIST.[19] A subsequent Phase I/II study tested sunitinib in 97 patients who were intolerant to, or had progressed on imatinib. A clinical benefit rate (CBR) defined as PR or SD lasting for more than six months was seen in 58%, 34% and 56% of KIT exon 9, 11 and KIT/ PDGFRA wild type mutations respectively. Interestingly, the chances of achieving a PR with sunitinib was greater in tumors with an exon 9 KIT mutation compared to exon 11 KIT mutations (37% vs. 5%). The median PFS was better for patients with exon 9 mutant and KIT/PDGFR wild type tumors when compared to those with exon 11 mutations (19.4, 19.0 and 5.1 months respectively). Median OS was also longer for patients with exon 9 mutants and KIT/ PDGFRA wild type tumors compared to the exon 11 mutants (26.9, 30.5, 12.3 months respectively) indicating that imatinib insensitive mutations were more responsive to sunitinib in the second line setting. While those with KIT exon 11 mutations had less benefit, these patients represent a different population than those with imatinib naïve disease; rather, they represented those patients with clonal evolution and imatinib insensitive secondary mutations. When secondary mutations were considered, the PFS for mutant KIT exon 11 patients with secondary KIT exon 13 or 14 mutation was 7.8 months with a median overall survival of 13.0 months and a CBR of 61% compared to a PFS of 2.3 months and a median OS of 4.0 months with a CBR of 15% for those with a KIT exon 17 or 18 mutation. [20–22]

The pivotal phase III trial of sunitinib was a double blind placebo controlled study that enrolled patients with advanced GIST that had failed therapy with imatinib or who were intolerant to imatinib. Patients were treated with sunitinib at a dose of 50mg daily for 4 weeks followed by a 2 week break in 6 week cycles. The primary endpoint of the study was time to tumor progression (TTP); secondary endpoints included PFS, OS, confirmed ORR, time to tumor response, duration of response and duration of performance status maintenance. The results were impressive with the TTP for the sunitinib arm being 27.3 weeks, vs. 6.4 weeks in the placebo arm with a HR 0.33(95% CI 0.23–0.47; $p<0.0001$). The study was unblinded at the first interim analysis and all patients on placebo were allowed to cross over to sunitinib. Even with crossover there was an OS advantage in the sunitinib arm with a HR of 0.49 (95% CI 0.29–0.83; $p=0.007$). The main toxicities were hematological including anemia, thrombocytopenia and leucopenia, fatigue, diarrhea, nausea, vomiting, anorexia, stomatitis, and hand foot syndrome.[23]

The phase III trial of sunitinib administered sunitinib for 4 week followed by 2 week off drug. A schedule with intermittent breaks is less flexible and convenient for patients than a continuous dosing schedule. In addition, some patients experienced symptomatic progression and/or metabolic progression by FDG-PET scans during the time off drug. A phase II single arm study looked at the feasibility of daily dosing of sunitinib at a dose of 37.5mg daily given continuously. The study demonstrated a CBR of 53%, including 13% PR and 40% SD. The median PFS was 34 weeks and the median overall survival was 107 weeks. The toxicity profile was similar to the Phase III study.[24] Based on these studies sunitinib is now the standard of care in patients with GIST who have failed imatinib, and is commonly given in a daily fashion.

Regorafenib

Regorafenib (Stivarga, BAY 73–4506) is a small molecule TKI that inhibits VEGFR1,2,3, PDGFRB, FGFR1, KIT, RET and BRAF among others.[25] In a phase II trial of

regorafenib, 33 patients with GIST tumors resistant to imatinib and sunitinib, but sorafenib naïve, showed a clinical benefit rate of 75% (4 PR+ 22SD); the median PFS was 10 months and the median OS was not achieved at the time of reporting. Patients with a primary exon 11 mutation had a better PFS than patients with exon 9 mutations however there was no difference when they were compared to patients with wild type GIST. The major toxicities that were reported were hypertension, hand foot syndrome, hypophosphatemia, rash, fatigue and diarrhea.[26] In the recently reported phase III randomized controlled double blind placebo controlled GRID trial of regorafenib in patients with GIST tumors resistant to both imatinib and sunitinib, the median PFS of patients on the regorafenib arm was 4.8 months and 0.9 months for those on placebo with a HR 0.27 (95% CI, 0.18–0.39), $p < 0.0001$. [27] Both these studies show promising results and regorafenib was approved in February 2013 as the third line drug of choice.

Other Therapies evaluated for therapy in GIST

VEGFR targeted TKIs

Sorafenib—Sorafenib (Nexavar) is a small molecule TKI that inhibits Raf-1, VEGFR-1, 2, 3, Flt3 KIT and PDGFRB among others.[28] Structurally, this agent is very similar to regorafenib. Preclinical studies of sorafenib in imatinib resistant cell lines showed that it was similar in potency to sunitinib in cell lines harboring KIT mutations affecting the ATP binding domain, but importantly, more potent than sunitinib in cell lines harboring KIT mutations affecting the ATP binding domain, exons 13 and 14.[29] A retrospective study of 32 patients treated with sorafenib in the fourth line setting after failing imatinib, sunitinib and nilotinib showed a 63% benefit (19% PR and 44% SD). The median PFS was 20 weeks and the median OS was 42 weeks.[30] A subsequent Phase II trial of sorafenib in resistant GIST enrolled 38 patients (6 were imatinib resistant and 32 were imatinib and sunitinib resistant) showed a disease control rate of 68% (13% PR+ 55%SD). The main toxicities seen were hand foot syndrome, hypertension, diarrhea, hypophosphatemia, GI bleeding and perforation, thrombosis and intracranial hemorrhage.[31] Based on these studies sorafenib is a reasonable drug for the third and fourth line setting; however, it is not known if patients that have received regorafenib prior to sorafenib will derive benefit.

Vatalanib—Vatalanib (PTK787/ZK 222584) is a small molecule tyrosine kinase inhibitor that inhibits VEGFR1, 2,3, KIT, c-Fms and PDGFR- .[32] In a Phase II study of the agent in 45 patients with imatinib resistant metastatic GIST, 18 (40%) had a clinical benefit with 2 (4.4%) achieving PR and 16 (35.6%) achieving SD. The clinical benefit and median time to progression was higher in those who received only imatinib in the past (46.2% and 5.8 months) when compared to those who received both imatinib and sunitinib (31.6% and 3.2 months). The drug was relatively well tolerated with the common side effects being hypertension, nausea, dizziness, proteinuria, abdominal pain and diarrhea.[33]

Dovitinib—Dovitinib (TKI258, CHR-258) is a small molecule tyrosine kinase inhibitor of KIT, PDGFRA, PDGFRB, FGFR, VEGFR1,2,3 among others.[34] A Phase I study of this agent in patients with advanced solid tumors showed that this drug was safe. A patient with refractory GIST in this study achieved stable disease that lasted for eight months.[35] Dovitinib is currently in Phase II clinical trials in patients who are refractory or intolerant to imatinib (NCT01478373) and in patients who are refractory to both imatinib and sunitinib (NCT01440959).

Pazopanib—Pazopanib (Votrient, GW786034) is an oral multi-kinase inhibitor and inhibits VEGFR1,2,3, PDGFRA, PDGFRB, KIT, and FGFR among others.[36] The drug is currently approved in the United States for patients with renal cell carcinoma and advanced

soft tissue sarcoma. Currently Pazopanib is being evaluated in Phase II studies in the imatinib resistant setting (NCT01391611) and in the third line setting after failure of imatinib and sunitinib (NCT01524848, NCT01323400).

Cedarinib—Cedarinib (AZD2171) is an oral tyrosine kinase inhibitor of VEGFR 2.[37] A phase II clinical trial looking at the activity of cedarinib in patients with imatinib resistant GIST and soft tissue sarcoma has been completed and results are awaited (NCT00385203).

Non-VEGFR targeted TKIs

Nilotinib—Nilotinib (Tasigna) is a small molecule TKI that was designed specifically to inhibit bcr-abl for the treatment of chronic myelogenous leukemia (CML). However it has additional biologic targets including ARG, KIT, PDGFRA, and PDGFRB. [38] In a Phase I study that evaluated the combination of nilotinib with imatinib as well as nilotinib alone in patients with imatinib resistant GIST, the drug was found to be safe with evidence of benefit. The primary therapeutic benefit was SD (72%) with PR seen in (4%).[39] In phase II and retrospective studies, summarized in table 3, responses ranged from PR 10–12%, with SD of 37–59%. [40–42] Interestingly, two of the studies demonstrated response and prolonged stable disease in patients with KIT exon 11 mutations with secondary exon 17 mutations (D820G, N822K, and Y823D). The phase III study of nilotinib versus best supportive care (BSC) did not demonstrate an improvement in PFS on central review with a median of 109 days in the nilotinib arm versus 111 days in the control arm; it should be noted that in this study patients could have received other investigational TKI's or therapies prior to study entry and that best supportive care included the use of imatinib or sunitinib in the control arm. Of the patients in the control arm, 93% continued to receive imatinib or sunitinib as part of best supportive care. A post hoc analysis of patients who were receiving nilotinib in the true third line setting, i.e. after failure of imatinib and sunitinib, demonstrated an OS advantage with a median OS of 405 days vs. 280 days, HR = 0.67; p=0.02 difference. This difference was not seen in the intent to treat population where the median OS was 361days vs. 300 days (HR = 0.84, p = 0.28).[43]

Masitinib—Masitinib mesylate (AB1010) is a small molecule tyrosine kinase inhibitor that inhibits KIT(wild type and activated with juxtamembrane mutations), PDGFRA, PDGFRB, Lyn kinase, FGFR3 and FAK pathway.[44] In a phase I study of patients with advanced malignancies, including 19 with GIST, the drug was found to have an acceptable tolerability profile. Masitinib showed a clinical benefit in both the imatinib naïve and the imatinib resistant cohort of patients. One of two imatinib intolerant patients achieved a PR and the other SD. In the imatinib resistant group (n=17), five patients achieved stable disease. [44] In a Phase II study of the agent in 30 imatinib naïve patients with locally advanced or metastatic GIST, 96.7% of the patients had a clinical benefit (3.3% CR+ 50% PR+ 43.3% SD); four year follow up results of the study showed that the median PFS was 41 months and median OS was not reached. The mutation status of the patients were known in 53% (16) of the patients; the majority had a mutation in exon 11 (56%), followed by wild type KIT/PDGFRB (19%), exon 11 and exon 13 (13%) and PDGFRA (6%).[45, 46] Masitinib has also been studied in the second line setting in imatinib resistant GIST in a phase II randomized trial between masitinib and sunitinib in patients with imatinib resistant GIST. Masitinib was better tolerated than sunitinib with a lower rate of severe adverse events (17% vs. 52%). The median PFS was 3. 9 months for the masitinib arm vs. 3.8 months for the sunitinib arm with a median OS of 15 months for the sunitinib while that for masitinib was not reached. At 24 months the OS was 53% and 0% respectively in the masitinib and sunitinib arms respectively. [47] It should be noted that this study was not powered to determine a statistical difference in outcome and further data are needed to assess the benefit of masitinib in this setting. It is likely that patients on the masitinib treatment arm received

sunitinib at the time of progression. Additional phase III studies are underway comparing masitinib to imatinib in the frontline setting (NCT00812240) and to sunitinib in the imatinib resistant setting (NCT01694277).

Non-TKI Targeted Therapies

Hsp90 inhibitors

Heat shock protein 90 (Hsp90) belongs to a family of proteins that function as molecular chaperons and bind other proteins denoted as client proteins. They play an important role in the folding, transport and degradation of client proteins. There are many client proteins for Hsp90, including KIT and PDGFRA. Inhibition of Hsp90 in vitro leads to cell death in GIST cell lines that express KIT, including cell lines with secondary KIT mutations resistant to imatinib [48]. Therefore, targeting Hsp90 may be an effective strategy in GIST. One challenge with this class of agents is that most agents have intravenous formulations, which is change for patients who have been taking an oral agent for therapy.

IPI-504—The first agent of this class to be tested was IPI-504, a water-soluble HSP-90 inhibitor. [49, 50] Phase I testing revealed dose-limiting toxicities of headache and myalgias. In a group of 36 patients with advanced GIST, there was 1 partial response and an additional 24 patients with stable disease. A phase III placebo controlled double blind study was initiated using 400 mg/m² IV twice weekly for 2 out of every 3 weeks. The study was terminated prior to meeting its accrual goals due to increased mortality in the patients receiving IPI-504 [50].

BIIB021—BIIB021 is an oral synthetic inhibitor of Hsp90 and binds to the ATP binding pocket of Hsp90.[51] BIIB021 was studied in a phase II trial in patients with imatinib and sunitinib resistant GIST. Ten patients out of 23 (43%) achieved stable disease by RECIST criteria. One patient had a metabolic partial response (>25% reduction in mean SUVmax) and six patients achieved SD by this criteria. The agent was well tolerated and had minimal toxicities with dizziness and syncope being dose limiting toxicities.[52]

AT13387—Is a synthetic Hsp90 inhibitor and has been shown to be active in imatinib sensitive and resistant GIST cell lines and xenograft models.[53] A phase II open labeled randomized study is looking at intravenous AT13387 as monotherapy or in combination with imatinib in patients with advanced GIST who have progressed on a maximum of three tyrosine kinase inhibitors (NCT01294202).

AUY922—Is also a synthetic Hsp90 inhibitor and has shown activity in preclinical studies in GIST.[54] The agent has been found to be safe in phase I clinical trials. [55] AUY922 is now being studied in a Phase II clinical trial in patients with imatinib and sunitinib resistant GIST (NCT01404650).

Ganestespib—Ganestespib (STA-9090) is also a synthetic Hsp90 inhibitor. Preclinical studies have shown that Ganestespib has activity in imatinib sensitive and resistant cell lines.[56] A phase II study looking at Ganestespib in patients who are refractory to both imatinib and sunitinib has shown some benefits but has not been reported yet.[57]

PI3K–AKT–mTOR inhibitors

The PI3K–AKT– mTOR pathway is downstream of KIT and plays an important role in cell signaling and survival in imatinib resistant GIST.[58] Animal models have shown that inhibition of this pathway inhibits cell proliferation.[59]

Perifosine

Perifosine is an oral alkylphospholipid and inhibits the phosphorylation of AKT.[60] It has been studied in a Phase II trial along with imatinib in patients with imatinib resistant GIST. Perifosine did not show significant clinical activity with no partial or complete responses the majority of the benefit was in the form of SD.[61 [ENREF 55](#)]

mTOR Inhibitors

Everolimus (RAD001; Afinitor) is an oral mTOR inhibitor preclinical studies of everolimus in combination with imatinib have shown some benefit.[62, 63] A phase I/II study looking at the use of everolimus in combination with imatinib in patients who had progressed on imatinib and both imatinib and sunitinib or another TKI. Up to 37% of patients achieved stable disease for 4 months or greater. The PFS for patients in the second line setting was 1.9 months and 3.5 months in those who had progressed after sunitinib or another TKI. [62] Another Phase II study looked at the combination of imatinib and everolimus in imatinib resistant GIST; none of 27 patients in the study achieved SD. [63] Both studies have shown an acceptable toxicity profile with modest clinical benefit. Currently a Phase II/III trial is ongoing that is looking at the combination of everolimus and imatinib in imatinib resistant GIST (NCT00510354).

Sirolimus is an mTOR inhibitor and has also shown benefit when combined with other tyrosine kinase inhibitors such as imatinib or PKC412 (a multi targeted TKI that inhibits KIT among other targets) in patients with the PDGFRA- D842V mutations.[64, 65]

Temsirolimus is yet another mTOR inhibitor that is approved for the management of metastatic renal cell cancer. A phase II study looking at Temsirolimus in GIST and other soft tissue sarcomas has been completed and results are awaited (NCT00087074).

Agents for Special GIST Populations

Crenolanib

Crenolanib (CP-868,596) is an oral TKI with potent activity against PDGFR and . Preclinical studies have shown that crenolanib is significantly more potent than imatinib in inhibiting imatinib resistant mutant PDGFR kinases including the D842V mutants.[66] Phase I studies of the agent had shown that this agent is safe with gastrointestinal side effects being the major adverse effects observed.[67] Based on the in vitro data in PDGFRA D842V, a phase II Phase II trial is currently evaluating its efficacy in patients with advanced PDGFRA D842 related mutations and deletions GIST tumors (NCT01243346).

Olaratumab

Olaratumab (IMC-3G3) is a fully human IgG1 monoclonal antibody that, in vitro, binds to PDGFRA and blocks its activation. It can also mediate immune mediated cell destruction by means of antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). A phase II study of IMC3G3 has been completed in patients with GIST who progressed on imatinib and sunitinib; results are awaited (NCT01316263).

Insulin-like growth factor 1 receptor inhibitors

Approximately 10% of GIST tumors do not have mutations of KIT or PDGFRA and are termed wild type GIST. In addition to these adult patients, GIST that arise in the pediatric population are also usually without mutations in these two genes. These tumors have been shown to have mutations in succinate dehydrogenase (SDH) genes and to have high expression of IGF-1R, albeit without any mutations [4, 68–75] Mutations in SDH genes (A, B, C, and D), result in loss of the formation of a complex made by the 4 protein products.

This can be identified by loss of SDHB expression by Immunohistochemistry, which has lead these tumors to be called SDH deficient GIST [76]. Loss of the SDH complex leads to activation of HIF transcriptional programs promoting angiogenesis, glycolysis, and cell proliferation [77]. This is the likely mechanism for the over expression of IGF-1R in SDH-deficient GIST.

IGF-1R is a receptor tyrosine kinase and binds to its ligand IGF1 and IGF2 and mediates intracellular signaling through the Ras-Raf-ERK-MAPK and PI3K-AKT-mTOR pathways. The IGF-1R mediated signaling is implicated in many cancers and is important in its development and progression. [78] In preclinical studies it has been shown that inhibition of IGF-1R in GIST cell lines induced apoptosis.[75] Linsitinib (OSI-906) an oral IGF-1R inhibitor is being investigated in a Phase II clinical trial in patients with pediatric GIST and adult wild type GIST (NCT01560260).

Conclusions

Over a decade has elapsed since the routine use of TKI therapies for the management of advanced GIST. This has lead to increased survival for many patients in a disease which was universally lethal within one year if disease was unresectable. Today, there are three approved agents for the treatment of GIST, as well as several other agents in which data supports its use. Tumors that are refractory to TKI's remain a challenge and novel combination therapies being tested in the phase I setting will likely lead to new therapeutic options; in particular agents targeting downstream pathways which have been shown to remain active in spite of KIT/PDGFRα targeting, such as AKT, are of great interest. In addition, we have come to appreciate that GIST represents a family of tumors with similar histological features but different molecular drivers. As agents targeting specific mutations or mechanisms are developed it will become increasingly important to genotype patients so as to prescribe appropriate therapies.

Acknowledgments

MvM- served as a scientific advisor to Novartis and Pfizer; MvM supported in part by R21, CA150381 and R01 CA106588

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Box 1: Currently approved and investigational agents for the management of GIST

Tyrosine Kinase Inhibitors

Imatinib *

Sunitinib *

Regorafenib *

Nilotinib *

Sorafenib *

Masitinib

Vatalanib

Dovitinib

Pazopanib *

Cedarinib

Crenolanib

Hsp90 Inhibitors

BIIB021

AT13387

AUY922

Ganestespib (STA-9090)

PI3K–AKT–mTOR inhibitors

Perifosine

Everolimus *

Sirolimus *

Temsirolimus *

Monoclonal Antibodies

Olaratumab

Insulin-like growth factor 1 receptor inhibitors.

OSI-906 (Linsitinib)

* Commercially available

Key Points

- The routine use of TKI therapies for the management of advanced GIST has led to increased survival for many patients.
- There are three approved agents for the treatment of GIST, as well as several other agents in which data supports its use.
- Tumors that are refractory to TKI's remain a challenge and novel combination therapies being tested in the phase I setting will likely lead to new therapeutic options.
- GIST represents a family of tumors with similar histological features but different molecular drivers.

Table 1

GIST Targets of currently approved and investigational TKI's.

	KIT	PDGFR ,	VEGFR 1,2,3	RET	FGFR 1,3
Imatinib	+	+			
Sunitinib	+	+	+		
Regorafenib	+	+	+	+	+
Nilotinib	+	+			
Sorafenib	+	+	+		
Masitinib	+	+			
Vatalanib	+	+	+		
Dovitinib	+	+	+		+
Papzopanib	+	+	+		+
Cedarinib			+		
Crenolanib		+			

Table 2

Clinical trials of imatinib in metastatic GIST

Study	Study Type	Dosages studied	Number of patients	Results
van Oosterom, A.T., et al	Phase I	400mg q.d., 300mg b.i.d., 400mg b.i.d., 500mg b.i.d	40	54% PR 37% SD
Demetri, G.D., et al.	Phase II	400mg q.d vs. 600mg q.d	147	No statistically significant differences in toxicity or response between the two doses. Response rate in the 400mg q.d arm 49.3% PR, 31.5%SD, and 16.4 % PD. Response rate in the 600mg q.d arm 58.1%PR, 24.3%SD, and 10.8% PD.
Verweij, J., et al.	Phase II	400mg b.i.d	27	4% CR, 67% PR, 19% SD, 11% PD 73% free from disease at 1 year
Verweij, J., et al.	Phase III	400mg q.d vs. 400mg b.i.d	946	Response rate in the 400mg q.d arm 4% CR, 45% PR, 32% SD, 13% PD. Response rate in the 400mg b.i.d arm 6% CR, 48% PR, 32% SD, 9% PD. After a median follow-up of 760 days, 263 (56%) of 473 patients in the once a day arm had progressed compared with 235 (50%) of 473 in the twice a day arm hazard ratio 0.82 [95% CI 0.69–0.98]; p=0.026. OS was 85% at 1 year and 69% at 2 years in patients treated once a day, and 86% at 1 year and 74% at 2 years in those treated twice a day. Increased dose reductions (77 [16%] vs 282 [60%]) and interruptions (189 [40%] vs 302 [64%]) in the twice a day arm.
Blanke, C.D., et al	Phase III	400mg q.d vs. 400mg b.i.d	694	Response rate in the 400mg q.d arm 5% CR, 40% PR, 25% SD, 12% PD. Response rate in the 400mg b.i.d arm 3% CR, 42% PR, 22% SD, 10% PD Median PFS was 18 and 20 months in the once daily and twice daily arms respectively. Median OS was 55 and 51 months, in the once daily and twice daily arms respectively. No statistically significant differences in objective response rates, PFS or OS.

Data from Refs 7–12.

Table 3

Phase II and retrospective studies of Nilotinib in metastatic / recurrent GIST.

Study	Study Type	Number of patients	Results
Cauchi, C., et,br/>al	Phase II	13	Majority of the responses were stable disease, 7.7% (1) PR by Choi criteria. 61% (8) PD by RECIST and 38.5 % (5) PD by Choi criteria.
Sawaki, A., et al.	Phase II	35	3% PR, 66% SD. Median PFS of 113 days and OS of 310 days.
Montemurro, M., et al.	Retrospective analysis	52	47 evaluable patients. 10% had SD, 2% CR, 8.5% PR. Median PFS 12 weeks Median OS 34 weeks. Median survival from the first diagnosis of GIST was 72 months.

Data from Refs ^{40–42}.