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Beyond Standard Therapy: Drugs Under Investigation for The Treatment of Gastrointestinal Stromal Tumor

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Abstract

Introduction—Gastrointestinal stromal tumor (GIST) is the most common non-epithelial malignancy of the GI tract. With the discovery of KIT and later PDGFRA gain-of-function mutations as factors in the pathogenesis of the disease, GIST was the quintessential model for targeted therapy. Despite the successful clinical use of imatinib mesylate, a selective receptor tyrosine kinase (RTK) inhibitor that targets KIT, PDGFRA and BCR-ABL, we still do not have treatment for the long-term control of advanced GIST.

Areas covered—This review summarizes the drugs that are under investigation or have been assessed in trials for GIST treatment. The article focuses on their mechanisms of actions, the preclinical evidence of efficacy, and the clinical trials concerning safety and efficacy in humans.

Expert opinion—It is known that KIT and PDGFRA mutations in GIST patients influence the response to treatment. This observation should be taken into consideration when investigating new drugs. RECIST was developed to help uniformly report efficacy trials in oncology. Despite the usefulness of this system, many questions are being addressed about its validity in evaluating the true efficacy of drugs knowing that new targeted therapies do not affect the tumor size as much as they halt progression and prolong survival.

1. Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms that arise from the interstitial cells of Cajal (ICC), or their precursor stem cells [1]. GIST was initially a purely descriptive term coined in 1983 by Mazur and Clark to define intra-abdominal tumors that were definitely not carcinomas [2, 3]. GISTs account for about 80% of gastrointestinal sarcomas, with a mean annual incidence of 10-15 per million [4, 5]. Nearly 50-70% of the clinically apparent tumors arise in the stomach, 20-30% arise in the small intestine, 5-15% in the large intestine, and less than 5% in other locations [6]. Activating mutations in the c-

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KIT (the normal cellular homologue of the Hardy Zuckerman 4 feline sarcoma viral oncogene homologue, NCBI gene ID: 3815) or the *platelet-derived growth factor α* (*PDGFRA*) proto-oncogenes exist in about 85% of GISTs and are important factors in the pathogenesis of these tumors [7, 8]. The other 10-15% of tumors were originally defined as *KIT/PDGFRA* “wild-type” and also encompass the vast majority of pediatric GIST, which constitutes ~2% of all GIST cases [9-11]. GIST in the pediatric population has an indolent course and shows a predilection for females (~85%), occurs almost exclusively in the stomach, and frequently presents as a multi-focal growth with lymph node involvement [12]. The hallmarks of pediatric GIST suggest an association with the multi-tumor syndrome known as Carney triad [11]. Carney triad, originally described as an association of GIST along with paraganglioma and/or pulmonary chondroma, now also encompasses cases of esophageal leiomyomas and adrenal cortical adenomas [13, 14]. Carney triad is a rare non-familial syndrome affecting mainly females under the age of 30; the GIST component predominantly arises in the stomach, lacks detectable *KIT* and *PDGFRA* mutations, and the disease displays a chronic yet indolent course. We were the first to report that most adult wild-type GISTs express insulin-like growth factor 1 receptor (IGF-1R) mRNA and protein at much higher levels in comparison to adult mutant GISTs [15], a phenomenon described also for pediatric GIST [9, 12, 15-18]. It has now been demonstrated that succinate dehydrogenase (SDH) complex deficiency, characteristic of most pediatric and syndromic GISTs, also occurs in a subset of sporadic, kinase-wild type adult GISTs [18-22]. Hence, *KIT/PDGFRA* wild-type GISTs can further be classified into two main groups according to the status of succinate dehydrogenase subunit B (SDHB) immunohistochemical staining (IHC): SDHB positive (SDHB^{IHC+}) and SDHB negative (SDHB^{IHC-}). The SDHB positive (SDHB^{IHC+}) group includes *NF1*-mutated GIST and some sporadic *KIT/PDGFRA* wild-type GIST. The second group of *KIT/PDGFRA* wild-type GIST is characterized by a lack of *SDHB* protein expression (SDHB^{IHC-}) and significant overexpression of IGF-1R [18, 23]. These SDH deficient tumors are often more indolent and many are associated with mutations or epigenetic silencing in one of 4 subunits of the SDH complex, a component of the Krebs cycle [18, 24]. Recently, activating mutations in the serine-threonine kinase BRAF and, more rarely, in RAS and *NF1* have been identified in a small number of GISTs [23, 25-27]. This group of tumors has recently been referred to as “quadruple wild-type” GIST, because they lack mutations in *KIT*, *PDGFRA*, *SDHA*, *B*, *C*, and *D*, and the RAS pathway (BRAF, *NF1*, and RAS) [28].

Surgical resection remains the mainstay approach in treating patients with localized, nonmetastatic GIST. However, about half of these patients experience disease recurrence after surgery [29]. Conventional chemotherapy was found to be only effective in a small subset of patients, with the majority experiencing a median survival of less than 2 years [29, 30]. The medical management of GIST was revolutionized by the discovery of the gain-of-function mutation in *KIT* in 1998 by Hirota and colleagues, which led to the use of tyrosine kinase inhibitors (TKI) [31]. Imatinib mesylate (IM, also known as Gleevec or STI-571) is an oral 2-phenylaminopyrimidine derivative that acts as a selective inhibitor against receptor tyrosine kinases [32]. IM was first approved by the FDA in May 2001 for the advanced stages of CML (chronic myelogenous leukemia) [33]. In 2002, imatinib also received approval for the treatment of patients with *KIT*-positive unresectable and/or metastatic GIST

[34] and is, currently, the front-line therapy for most GIST patients [35]. It targets the ATP-binding site of the tyrosinekinase region of KIT, PDGFR, and ABL. This in turn inhibits the phosphorylation and interrupts cell signaling leading to cell death [36-38].

The clinical success of imatinib mesylate (IM) and other TKIs was tempered by the realization that patients frequently develop resistance to these agents [39]. More than 15% of patients display primary resistance to IM and more than 50% eventually develop secondary resistance [29, 40]. Secondary mutations in *KIT* and *PDGFRA* are thought to be involved in the development of the resistance observed in patients on IM [41]. Through our gene expression studies in GIST, we have found several new mechanisms associated with IM resistance [39, 42, 43]. Randomized clinical trials showed increased rates of recurrence in patients when IM is discontinued. This led to the belief that IM has a “cytostatic” activity [44]. Therefore, patients will have to remain on IM therapy for long periods of time to delay recurrence. However, the adverse effects of long-term IM therapy can limit its use in some patients. For example, more than 30% of patients treated for over 3 years with IM developed grade 3 or higher toxicities leading to discontinuation of the medication in some cases [45]. The observed limitation of IM in some patients led to the FDA approval of sunitinib (Sutent[®], Pfizer Inc) in 2006. Sunitinib is an oral, small-molecule inhibitor of KIT, PDGFRA and other receptor tyrosine kinases and is used for the treatment of advanced GIST patients who are either resistant or intolerant to IM [46, 47]. Unfortunately, many GIST patients fail to receive clinical benefit from sunitinib. This resulted in the recent approval of regorafenib by the FDA as a third-line agent for the treatment of patients with GIST refractory to IM and sunitinib [48]. Regorafenib is a broad inhibitor of receptor tyrosine kinases that targets KIT, PDGFRA/B, RET, RAF1, BRAF, vascular endothelial growth factor receptor (VEGFR) and fibroblast growth factor receptor [49].

The inability to effectively control GIST continues to mandate the search for alternative therapies. In this review, we will present and discuss therapies that have been tested in clinical trials or are currently under development for patients with GIST. Drugs discussed in this article are summarized in Table 1.

2. KIT and PDGFRA Inhibitors

As mentioned above, approximately 85% of GISTs contain either a *KIT* or a *PDGFRA* gain-of-function mutation [7]. The *KIT* and *PDGFRA* genes belong to the class III Receptor Protein Tyrosine Kinases (RTKs) family, which also includes the colony-stimulating factor I receptor, PDGFRB, and FMS-related tyrosine kinase [50-53]. *KIT* and *PDGFRA* are both located on chromosome 4q12 and have structural similarities with the other *PDGFR* family members [54, 55]. Mutations in these genes play a central role in the pathogenesis of GIST [7, 56].

2.1 Nilotinib (AMN107, Novartis Pharma AG)

Nilotinib is a very selective and potent inhibitor of the BCR-ABL oncoprotein's tyrosine kinase activity, as well as an inhibitor of KIT and PDGFRA, with a comparable *in vitro* affinity to that of IM [57]. In a preclinical study, nilotinib was found to have a considerable antitumor activity against IM-resistant cell lines [58]. The study; however, could not assess

the efficacy of nilotinib in IM-resistant tumors *in vivo* due to the difficulty of establishing an IM-resistant xenograft model. A phase I clinical study, conducted in 53 patients with advanced IM-resistant GIST, showed that nilotinib was generally well tolerated, and it demonstrated an antitumor activity, both, as a single agent and when combined with IM [59]. In a phase II clinical trial, Sawaki and colleagues enrolled 35 patients with advanced GIST who failed both IM and sunitinib treatment [60]. The primary endpoint was disease control rate, which was defined as the percentage of patients lasting 24 weeks or longer with complete response (CR), partial response (PR), or stable disease (SD). Patients were given 400 mg of oral nilotinib twice daily, which was generally well tolerated. Twenty-nine percent of study participants achieved the primary endpoint at 24 weeks. The median progression free survival (PFS) was 113 days, and the median overall survival (OS) was 310 days. Sixty-six percent of patients achieved SD 6 weeks. They concluded that nilotinib has an encouraging antitumor activity for patients who failed to benefit from IM and sunitinib.

2.2 Amuvatinib (MP470)

Amuvatinib is an orally administered small molecule drug that targets c-KIT, PDGFRA, and RAD51 [61]. A 'kinase switch' from KIT-dependent to AXL-dependent receptor tyrosine kinase activity was observed in GIST cell lines when the cells acquired IM resistance [62]. Molecular modeling of the mutant c-KIT and AXL failed to show IM binding but displayed efficient binding to amuvatinib. In the first-in-human phase I trial of amuvatinib in 22 patients with solid malignancies, the initial formulation did not show consistent pharmacokinetic properties [63]. The plasma levels of the drug were generally low and highly variable. This limitation led to the development of a new lipid-suspension capsule formula that was tested in healthy volunteers in another phase I clinical trial [64] and showed better bioavailability compared to the dry powder capsule formula. Both formulas were well tolerated and showed a good safety profile. In another phase I dose-escalation study of amuvatinib, it was noted that 2 of 4 refractory GIST patients showed SD despite the low and variable plasma levels of amuvatinib, suggesting further investigation of this drug as a single agent in refractory GIST [65]. An additional phase I trial demonstrated that amuvatinib has an antitumor activity in neuroendocrine, non-small cell and small cell lung cancers when combined with either paclitaxel/carboplatin or carboplatin/etoposide [61]. There was no report of increased frequency of the adverse effects commonly seen in the abovementioned chemotherapeutic agent.

2.3 Masitinib (AB1010, AB Science)

Masitinib is an oral tyrosine kinase inhibitor that acts on KIT, PDGFR (A + B), and LYN [66, 67]. It has been found to be superior to IM in antitumor activity and selectivity against those tumors lacking a kinase mutation or those with a *KIT* exon 11 mutation [68]. Masitinib showed an encouraging tumor control rate in a phase I clinical trial assessing the maximum tolerated dose (MTD) and antitumor activity [69]. One GIST patient displayed PR, and about 29% of patients with IM-resistant GIST displayed SD. The drug was generally tolerable, with most AEs being grade 1 or 2. As a first-line therapy, masitinib was shown to have safety and efficacy comparable to those of IM in patients with advanced GIST [70].

In a randomized, open-label, and phase II trial, masitinib and sunitinib were assessed in patients with advanced GIST who failed IM [71]. Patients receiving masitinib alone reached their pre-specified PFS, with less toxicity compared to the sunitinib arm. Overall survival (OS) in patients receiving sunitinib after progression on masitinib was significantly higher than patients receiving sunitinib alone. A phase III clinical trial is currently accruing patients to assess the safety and efficacy of masitinib in comparison to sunitinib in the setting of IM resistance (clinicaltrials.gov, NCT01694277).

2.4 Ponatinib (ARIAD Pharmaceuticals)

Ponatinib is a potent third-generation inhibitor of multiple tyrosine kinases such as BCR-ABL1, KIT, PDGFRA, and FGFR1 [72]. It was shown to significantly inhibit tumor growth in *in vitro* and *in vivo* models of glioblastoma multiforme [73] and acute myeloid leukemia [74]. To elucidate the *in vitro* and *in vivo* efficacy of ponatinib, Garner and colleagues assessed the drug across a panel of GIST cell lines derived from patients with varying mutational statuses [75]. They demonstrated that ponatinib was highly active in lines containing *KIT* exon 11 mutation and an array of secondary mutations, including activation loop and T670I gatekeeper mutations, but not V654A secondary mutation. Although IM, sunitinib and regorafenib were active in the patient-derived GIST xenograft mouse model, ponatinib was the only agent to induce complete regression of tumor growth over a period of 4 weeks. In addition, the complete regression was maintained for 6 weeks after ponatinib treatment was discontinued. An ongoing phase II trial for ponatinib in patients with refractory GIST is currently ongoing (clinicaltrials.gov, NCT01874665), and an initial report of the trial showed that ponatinib has activity in this patient population [76].

2.5 Sorafenib (Bayer and ONYX Pharmaceuticals)

Sorafenib is a bi-aryl urea that is known to inhibit RAF-1. Sorafenib has also been noted for its inhibitory activity against a range of tyrosine kinases including c-KIT, PDGFRB, VEGFR-2, and VEGFR-3 [77]. Furthermore, it demonstrated an antitumor activity against a patient-derived GIST xenograft model [78] and multiple other xenograft models of human malignancies, including lung, colon, breast and pancreatic cancers [79]. Sorafenib was tested in a phase I clinical study as a single agent and was found to have an acceptable safety profile [80]. In a retrospective analysis, Montemurro *et al.* evaluated the efficacy of sorafenib in a cohort of 124 GIST patients who failed multiple TKIs [81]. Twelve patients showed response to sorafenib, and 70 showed SD. The tolerability to the drug was moderate and the dose was lowered in about a third of the patients. It was concluded that sorafenib is active in patients with GIST refractory to IM, sunitinib and nilotinib. In a phase II clinical trial, a Korean group studied the efficacy of sorafenib in patients with metastatic GIST who failed prior TKIs [82]. Out of 32 patients, 4 patients showed PR and 16 patients showed SD. About one-third of the patients maintained disease control for more than 24 weeks.

3. Vascular Endothelial Growth Factor Inhibitors

When tumors exceed the size of 1-2 mm, diffusion becomes insufficient to maintain tumor growth, and angiogenesis can occur to help prevent necrosis [83]. Vascular Endothelial

Growth Factor (VEGF) is essential in tumor angiogenesis and progression [84]. It has been shown that VEGF plays an important role in GIST growth and metastasis [85].

3.1 Cediranib (RECENTIN; AZD2171)

Cediranib is a potent oral inhibitor of vascular endothelial growth factor (VEGF) signaling via targeting its receptors [86]. It has also shown to possess an antagonist activity against KIT [87]. Wedge and colleagues reported significant activity of cediranib *in vivo* when evaluated against a wide array of solid tumors (>90% growth inhibition) [87]. In 2007, a phase I clinical trial was conducted by Drevs and colleagues [88]. In the phase IA portion of the trial, 36 patients with solid malignancies and liver metastasis that were refractory to other conventional therapies were evaluated. The dose was escalated (from 0.5 to 60 mg) until MTD was reached. In the phase IB portion, they compared patients with liver metastasis (n=36) to patients without liver metastasis (n=11). Patients were randomly assigned to receive oral doses of cediranib (20, 30, or 45 mg) daily. Cediranib was well tolerated in most patients with the most frequently reported AEs being diarrhea, dysphonia and hypertension (most common dose-limiting toxicity). Their study showed 2 confirmed PR cases and 22 patients with SD. A phase II clinical trial was conducted to assess the activity of cediranib in patients with metastatic GIST or soft-tissue sarcoma who were resistant or intolerant to IM [89]. Changes in 2[18F]fluoro-2-deoxy-D-glucose positron emission tomography (¹⁸FDG-PET) were used to determine the antitumor activity of cediranib using maximum standardized uptake values (SUV_{max}). Only 40% of patients showed SD of >16 weeks with a median PFS of 2 months. The study failed to manifest any direct correlation between ¹⁸FDG-PET uptake and disease stabilization. No further clinical trials were recommended by the authors.

4. Cyclin-Dependant Kinase (CDK) Inhibitors

Although the majority of GIST cells harbor either *KIT* or *PDGFRA* mutations, other DNA aberrancies have been linked to GIST growth and metastasis [90]. El-Rifai and colleagues showed that the loss of chromosome arm 9p is common to most *KIT* mutant malignant and metastatic GIST [91]. The locus 9p21 contains *CDKN2A* that encodes for P16, a CDK inhibitor, which suppresses tumor growth by arresting the cell cycle at G₁ phase via reducing the activity of CDK4 and CDK6. Subsequently, the retinoblastoma tumor suppressor protein (RB) remains in the active unphosphorylated state, which causes the blockade of the E2F transcription factor 1 (E2F1). Therefore, the loss of 9p21 locus leads to a constitutive phosphorylation of RB and E2F1 leading to the transition of the cell cycle from G₁ to S phase, and thus promoting DNA synthesis and tumor growth [90, 92].

4.1 Palbociclib (PD-0332991; IBRANCE, Pfizer, Inc.)

Palbociclib is a selective inhibitor of CDK4 and CDK6 and has shown a strong antitumor activity against a wide array of human solid tumor xenograft models [93]. Palbociclib was shown to exert its activity through an RB-dependent manner in breast, brain, blood and pancreatic cancer cells. It was also shown to cause G₁ arrest in the cell cycle of colorectal carcinoma cells and inhibit their growth [94]. Schwartz *et al.* assessed the MTD of palbociclib in a phase I study of 33 patients with retinoblastoma protein-positive solid

tumors or non-Hodgkin lymphoma that were refractory to conventional therapy [95]. Six patients experienced DLTs (dose-limiting toxicities) that were solely myelosuppression related, and MTD was defined as 200 mg QD. Hematological toxicities of grade 3 or 4 were frequent with lymphopenia being the most common. Fatigue (33%), nausea (30%), and diarrhea (18%) were also reported. Out of the 31 patients who completed a post-treatment tumor evaluation, 1 patient with non-seminomatous germ cell testicular cancer showed PR, and 9 patients achieved SD for 2 treatment cycles or more. It was noted that one patient with liposarcoma received 23 cycles while demonstrating SD. The study team concluded that a phase II clinical trial is recommended with MTD of 200 mg QD. Flaherty *et al.* conducted another phase I, open-label clinical trial with a similar primary goal and patient inclusion criteria [96]. Although efficacy was not the end point of this study, patients showed a significant tumor control. The study concluded that the safety profile of palbociclib is acceptable and a phase II clinical trial was recommended. A phase II clinical trial (clinicaltrials.gov, NCT01907607) carried out by Institut Bergonié in France to assess the efficacy of palbociclib is currently accruing patients with advanced GIST who failed to benefit from IM and sunitinib therapies.

5. Phosphoinositide 3-kinase (PI3K) Inhibitors

PI3K/AKT/mTOR is a key signaling pathway that has been shown to be significantly involved in the growth and proliferation of tumor cells [97]. PI3K is also known to be a downstream mediator of KIT signaling and therefore linked to GIST pathophysiology [43, 98]. Tarn and colleagues found that PI3K has a significant role in the glucose uptake in GIST cells. They also found that the inhibition of PI3K mediates the effects of KIT inhibition by IM [37].

5.1 Buparlisib, BEZ235 and BYL719

Van Looy and colleagues assessed the *in vivo* efficacy of three PI3K inhibitors, buparlisib, BEZ235 and BYL719 (Novartis Pharmaceuticals), in combination with IM in a panel of patient-derived xenograft GIST models [99]. Mice treated with a PI3K inhibitor alone showed a significant reduction in tumor size. The combination therapy; however, showed a response superior to either drug alone.

5.2 GDC-0941

The same group above evaluated the *in vivo* efficacy of GDC-0941, an oral pan PI3K inhibitor, in 5 GIST xenograft models alone and when combined with IM [100]. In this study, GDC-0941 treatment alone stabilized tumor growth in 3 of 5 xenografts. Combining both drugs led to a significant reduction in tumor volume in an additive manner when compared to IM alone. After 28 days of treatment cessation, the antitumor effect of the combination treatment was still present (tumor size was at 73% of the pre-treatment baseline), whereas the IM-treated tumors regrew rapidly. It is noteworthy that the antitumor activity of GDC-0941 combined with IM showed a positive correlation with the loss of *PTEN* [100], which is a tumor suppressor gene that buffers PI3K's activity [101]. A multicenter, open-label, and phase I clinical trial on IM and BYL719 combination as a third-

line therapy for GIST patients who failed prior IM and sunitinib therapy is now accruing participants (clinicaltrials.gov, NCT01735968).

6. Histone Deacetylases Inhibitors

Epigenetic abnormalities are known to be involved in the pathophysiology of cancer [102]. The major epigenetic modifications are DNA methylation and histone modification [103]. Histone deacetylases (HDACs) are epigenetic regulators of genes involved in cell proliferation and differentiation during normal and cancerous cell development [104]. Acetylation of the lysine residues leads to the relaxation of the chromatin, subsequently leading to gene transcription. Whereas, deacetylation causes gene silencing via condensing the chromatin [105].

6.1 Panobinostat (LBH589, Novartis Pharmaceuticals)

Panobinostat is a pan inhibitor of HDACs that acts on several neoplastic pathways. It reverses cancer-related epigenetic aberrancies and it also acts on HSP90 proteins as part of its non-histone antitumor activity [106]. Panobinostat has shown a preclinical evidence of antitumor activity in several hematological malignancies [107]. Floris *et al.* evaluated the anti-GIST properties of panobinostat, alone and in combination with IM, using three xenograft lines in nude mice [108]. The three lines were different in regard to their *KIT* mutation status (exon 9, exon 11, and exon 13 mutations). Panobinostat and IM alone caused a 25% and 62% reduction in tumor size, respectively, compared to baseline. The combination treatment of both drugs led to an enhanced reduction in tumor size by 73% compared to controls. It is worth mentioning that the additive effect of combining both drugs was only statistically significant in xenografts harboring *KIT* exon 13 mutations. In a phase I trial, Bauer and colleagues enrolled 12 GIST patients who failed IM and sunitinib to determine the MTD and DLT of panobinostat in combination with IM [109]. Patients underwent a 7-day run-in cycle of a daily 400 mg of IM followed by an escalating dose of panobinostat (3 times a week for 3 weeks). All patients experienced at least 1 AE, and most of them were considered to be mild. The most common AEs were thrombocytopenia (92%) and fatigue (67%). Panobinostat at 30 mg was associated with severe reversible thrombocytopenia and was regarded as DLT. In regard to activity, none of the patients showed response as assessed by RECIST criteria. After the imatinib run-in and 3 weeks of panobinostat treatment, 7 of 11 evaluable patients showed metabolic disease stability, and 1 patient showed a metabolic partial response (mPR) as per EORTC-PET Study Group criteria using ¹⁸FDG-PET-CT scans.

7. HSP90 Inhibitors

Heat Shock Proteins (HSPs) are overexpressed when mammalian cells are exposed to heat or physical stress. In normal cells, these proteins have essential roles in protein assembly, folding, trafficking and degradation [110, 111]. In the cancerous cell; however, HSPs are implicated in the growth of tumors and their invasion into the surrounding tissue, and the overexpression of HSPs is thought to be an indicator of poor prognosis. These observations led to the idea that targeting HSPs might be an effective therapeutic approach in cancer therapy [112]. The *KIT* oncoprotein is stabilized by HSP90, and inhibiting HSP90 showed

some antitumor activity in multiple IM-sensitive and IM-resistant GIST cell lines [113]. AT13387, BIIB021, AUY922, and ganetespib are HSP90 inhibitors under investigation for the treatment of GIST.

7.1 BIIB021

BIIB021 is an oral synthetic compound that inhibits HSP90 by binding to its ATP-binding pocket [114]. It was shown to have antitumor activities in xenograft models and was the first synthetic HSP90 inhibitor to undergo clinical assessment due to its superior pharmacological properties compared to early HSP90 inhibitors [115]. A phase I trial defined MTD as 600 mg twice weekly in continuous dosing [116]. It also showed that the drug was tolerated, and the most commonly reported AEs were gastrointestinal complaints, hot flashes and dizziness. A phase II, open-label, and non-randomized trial assessed the efficacy of BIIB021 as a single agent in 23 participants with refractory GIST [117]. The primary endpoint of the study was metabolic partial response (mPR) determined by ¹⁸FDG-PET. Twenty-two percent of patients achieved the abovementioned endpoint with a range of 25-138 days. The drug was generally tolerated with most AEs being no greater than grade 2. The authors recommended further investigation of BIIB021 in GIST treatment.

7.2 AT13387 (Astex Pharmaceuticals Inc)

AT13387 is a small molecule inhibitor of HSP90 [118] that has shown *in vitro* and *in vivo* antitumor activities [119]. In regard to GIST, a preclinical study demonstrated that AT13387 has *in vitro* and *in vivo* antitumor activity against IM-sensitive and IM-resistant lines alone and in combination with IM; with the combination treatment being significantly more effective than either drug alone [120]. The study also showed that AT13387 depletes KIT, AKT and their phosphorylated forms in GIST cell lines regardless of the *KIT* mutation status. A phase I, open-label trial evaluated AT13387 in 62 patients with refractory solid tumors (7 of who had GIST) [121]. The drug was given through an i.v. infusion over 1 hour. The drug was well tolerated, and the most frequent AEs were diarrhea (73%), visual disturbances (45%), injection site reactions (29%), and systemic infusion reactions (27%). Out of the 62 patients, 1 patient with GIST showed PR, and 3 of the remaining 6 GIST patients displayed an evidence of SD. These findings led to a phase II trial (clinicaltrials.gov, NCT01294202) currently in progress aiming to assess the efficacy of AT13387 in combination with IM in GIST patients.

7.3 AUY922 (Novartis)

AUY922 is a synthetic second-generation HSP90 inhibitor with a potent antitumor activity in several malignancies [122, 123]. In a dose-escalation and phase I trial, AUY922 was evaluated in patients with advanced solid tumors to determine the safety, PK, and PD [124]. AUY922 was given through an i.v. infusion once weekly, and it showed an acceptable safety profile with only 8 out of 101 patients discontinuing the drug due to DLT. No antitumor activity was noted based on RECIST 1.0 system. However, authors recommended moving forwards to phase II trial. Our literature search showed two phase II clinical trials assessing AUY922 currently accruing GIST patients (clinicaltrials.gov, NCT01404650 and NCT01389583).

7.4 Ganetespib (STA9090, Synta Pharmaceuticals Corp)

Ganetespib is a second-generation synthetic HSP90 inhibitor that binds competitively to HSP90 and interrupts the chaperone cycle. Like other new generation HSP90 inhibitors, ganetespib has an improved safety profile and is well tolerated [125]. Preclinical studies showed that ganetespib has a better safety profile and a more potent activity against a broad array of human xenograft models when compared to other HSP90 inhibitors [126]. In a phase I clinical trial, 53 patients with advanced solid neoplasms were given ganetespib as an i.v. infusion once weekly for 3 weeks followed by 1 week off-treatment until disease progression or DLT were observed [127]. The aim was to assess the PK, safety profile, and clinical activity of ganetespib. Disease control rate, which was defined as objective response and stable disease at 16 weeks, was 24.4%. Ganetespib showed an acceptable tolerability and was recommended for a phase II trial. In a recent phase II clinical trial; however, ganetespib had limited activity as a single agent in heavily pretreated GIST patients [128].

8. Insulin-like Growth Factor-1 Receptor (IGF-1R) Kinase Inhibitor

The IGF-1R is abnormal in various cancers and plays an essential role in tumor growth [129]. IGF-1R acts on IGF-1, IGF-2 and insulin leading to autophosphorylation that activates PI3K/mTOR signaling pathway, which suppresses apoptosis and stimulates cell proliferation [130]. The inhibition of IGF-1R has been shown to reduce tumor growth in human cancer xenograft models [131].

With respect to GIST, our group was the first to report that a subset of these tumors that lack mutations in *KIT/PDGFR*A, including pediatric cases, express high levels of IGF-1R [15, 18]. Tarn and colleagues also demonstrated that the small-molecule tyrosine kinase inhibitor, NVP-AEW541 (Novartis), which has activity against IGF-1R can lead to cytotoxicity in mutant GIST cell lines, via AKT and MAPK signaling that is independent from KIT signaling [17]. Similar findings were observed when IGF-1R levels were impaired using targeted siRNAs. We observed additive effects by combining NVP-AEW541 and IM, suggesting a potential therapeutic benefit in targeting IGF-1R in GISTs that are unresponsive to IM, as well as pediatric GISTs, which overexpress IGF-1R [15]. These studies supported the first clinical trial of an IGF-1R inhibitor in RTK mutation negative GISTs.

8.1 Linsitinib (OSI-906)

Linsitinib is a highly selective small-molecule inhibitor of IGF-1R and insulin receptor (IR) kinase that has shown antitumor activity in IGF-1R-driven fibrosarcoma xenograft models [132]. In a phase I clinical study, Puzanov and colleagues evaluated the safety, PK/PD, and activity of linsitinib in patients with advanced solid tumors [133]. Out of 85 patients, who received at least one dose of linsitinib, 31 showed SD and 1 patient with melanoma showed a radiographic PR. The drug was well tolerated and a phase II trial was recommended based on the observed antitumor activity. As a result of our and others' preclinical studies, a CTEP sponsored multi-institutional trial of linsitinib in wild-type GIST patients was completed through the Sarcoma Alliance for Research through Collaboration. This study accrued 20

patients from 4 institutions between November 2012 and May 2013. The outcomes of the study are pending (clinicaltrials.gov, NCT01560260).

9. Drug Repurposing

Rare diseases, such as GIST, individually affect small groups of patients but collectively are estimated to affect 30 million people in the U.S. alone (www.globalgenes.org). Given the costs of discovery, development and registration of new drugs, orphan diseases such as GIST are often not pursued by mainstream pharmaceutical companies [134]. As a result, “drug repurposing” or “repositioning” strategies of approved and abandoned drugs have emerged as an alternative. These strategies represent an opportunity to rapidly advance and deliver new drug therapies to GIST patients by capitalizing on data readily available. Based on the recent recognition of drug repurposing by Dr. Francis Collins, NIH Director, as a key strategy to accelerate translational research for orphan diseases [134, 135], we and others initiated studies using a dual drug repurposing and rediscovery strategy to provide additional therapeutic options for GIST patients which are proceeding to the clinic [136-138]. In a drug-repurposing screen, we evaluated a library of 796 FDA-approved drugs to determine any potential activity against GIST cell lines [137]. We identified fludarabine phosphate (F-AMP) and auranofin (Ridaura®) to have an effective and selective antitumor activity against IM-sensitive and resistant GIST cell lines. Auranofin is a gold-containing compound that was FDA-approved in 1985 for the treatment of rheumatoid arthritis. It was found to inhibit the activity of thioredoxin reductase (TrxR) and increase the levels of reactive oxygen species (ROS) leading to the death of GIST cells regardless of the IM resistance status. A subsequent study by our group showed that fludarabine phosphate (F-AMP) exhibits synergy with and/or decreases resistance to IM in IM-resistant GIST cell lines [136]. To confirm the combination's efficacy, an *in vivo* study was carried out and showed enhanced antitumor activity of the combination compared to IM alone, which makes F-AMP a promising repurposed drug.

10. Conclusion

Gastrointestinal stromal tumor (GIST) is the most common non-epithelial tumor of the gastrointestinal tract. Despite the dramatic progress in GIST treatment brought by imatinib, the development of primary and secondary resistance is a substantial obstacle that mandates exploring other therapy alternatives. A wide range of drug classes is currently under the investigation for efficacy in GIST. The mechanism of action of these drugs vary from KIT and PDGFRA signaling inhibitors, to epigenetic modulators, IGF-1R inhibitors, HSP90 inhibitors, to CDK inhibitors and most recently to repurposed drugs. To date, very few therapies have had the impact of IM for GIST patients. A number of new therapies hold a modicum of promise in treating IM-refractory disease and are being considered for phase III trials. Time will tell if any drug, alone or in combination, will help lead to a cure.

11. Expert opinion

11.1 Genotype and Response

From the experience with IM, the type of *KIT* or *PDGFRA* mutations greatly influenced how the patients responded to therapy [139]. Mutations in exon 11, the most common, have the highest IM response rates and prolonged disease control in clinical trials [40]. In addition, a minority of GISTs has mutations in exon 13 (sensitive to IM) or exon 17 (variable sensitivity to IM). Nonetheless, for exon 9 mutant tumors (second most common), progression free survival using standard dose IM (400 mg daily) is still poor and maximum disease control requires the use of higher doses of IM (400 mg twice daily). Furthermore, about 5% of GISTs have mutations in *PDGFRA* and not *KIT*. *PDGFRA* exon 12 mutations are typically sensitive to IM, while D842V in exon 18 is associated with imatinib-resistance. Unfortunately, trials of *PDGFRA* targeted therapies have not demonstrated significant response to date. Sunitinib was also shown to have a variable response depending on the genotype. Rutkowski and colleagues studied 89 samples from patients with advanced GIST on sunitinib therapy [140]. They found that tumors harboring *KIT* exon 9 mutation as well as *KIT*/*PDGFRA* wild-type GIST had a better response compared to tumors with *KIT* exon 11 mutation. Tumors carrying a *PDGFRA* mutation showed no significant response to sunitinib [140]. Differences in the tumor genotype have also been noted in drugs other than TKIs. A study of IM with panobinostat (LBH589) achieved a significant reduction in tumor size in a mouse model harboring *KIT* exon 13 mutant tumors, but not with other *KIT* mutations [108]. The established correlation between genotype and response in IM might also exist in some of the drugs mentioned in this review, which might explain the observed variability in outcome among study participants. However, genotyping of GIST is still not mandated. In addition, management of advanced disease in succinate dehydrogenase deficient GIST is challenging due to lack of response to known therapies. Although not required, GIST patients should undergo genotyping as well as clinical testing for SDHB and IGF-1R by standard immunohistochemical approaches. This might help identify those patients with *KIT* exon 9 mutations to determine IM dosing, and identify those who are either quadruple wild-type GIST or SDH deficient since they will likely gain only modest, if any, benefit from front-line IM.

11.2 RECIST and its validity

The Response Evaluation Criteria in Solid Tumors (RECIST) were developed in the year 2000 to be used as a simple guide to uniformly report efficacy trials. The criteria were designed for cytotoxic drugs and focuses heavily on tumor size changes [141]. Much of the criticism against RECIST revolves around its inability to assess response parameters other than tumor size [142], which might result in masking potential clinical benefits of some drugs under investigation. This is supported by the conclusion of the GIST consensus conference, held by the European Society for Medical Oncology (ESMO) in 2004, that RECIST is not the best tool to evaluate the response to tyrosine kinase inhibitors [67]. It should also be taken into account that targeted therapies are not highly likely to produce dramatic changes in tumor size, but they are more likely to arrest disease progression [143]. This raises questions about RECIST's ability to assess the true potential of new targeted therapies. Positron Emission Tomography (PET), using fluorine-18-fluorodeoxyglucose

(^{18}F FDG), has shown to be more sensitive in predicting tumor response to therapy in multiple malignancies [144]. In regard to GIST, ^{18}F FDG-PET has proved to be highly sensitive in detecting early response to IM treatment and to predict long-term response [145]. In a clinical study, our group showed that metabolic response detected by ^{18}F FDG-PET was identified earlier and with a higher magnitude compared to RECIST [146]. Wahl *et al.* proposed to integrate ^{18}F FDG-PET into RECIST to reach a better assessment validity [147]. However, high cost and availability issues limit the use of this technology. In addition, not all GIST cases show a significant uptake of glucose, which further challenges the use of ^{18}F FDG-PET scans [39, 148]. Choi *et al.* proposed new criteria to measure response on the basis of tumor density and size on Computed Tomography (CT) scans, in which they claim to have a better prognostic value than RECIST [145]. The questions about the validity of RECIST in determining the true potential of investigational drugs are rational and should be addressed before labeling a drug “ineffective”.

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Table 1
Summary of drugs under investigation for GISTs

Drug Class	Mechanism of Action	Drugs	Most Recent Level of Evidence
VEGFR inhibitors	VEGF is crucial for the growth and metastasis of GIST. Blocking its receptors potentially leads to growth inhibition of tumors. Some of the drugs in this class also act on KIT and PDGFR α .	Cediranib (AZD2171)	Phase II trial
CDK Inhibitors	Antagonizing CDK leads to inhibition of growth by arresting the cell cycle at G ₁ phase	Palbociclib (PD-0332991)	Phase I trial
KIT and PDGFRα Inhibitors	Interrupting KIT and PDGFR α signaling leads to cell death. About 90% of GISTs harbor <i>KIT</i> and <i>PDGFRα</i> mutations	Nilotinib (AMN107)	Phase II trial
		Amuvatinib (MP470)	Phase I trial
		Masitinib (AB1010)	Phase II trial
		Ponatinib	Phase II trial
		Sorafenib	Phase II trial
PI3K Inhibitors	Inhibits PI3K, which downstream of KIT and involved in tumor cell growth	Buparlisib BEZ235 BYL719 GDC-0941	All <i>in vivo</i>
HDACs inhibitors	Inhibition of deacetylation of histone leads to the transcription of genes that controls cell growth	Panobinostat (LBH589)	Phase I trial
Hsp90 inhibitors	Heat shock proteins are involved in tumor growth and invasion of adjacent tissues	BIIB021	Phase II trial
		AT13387	Phase I trial
		AUY922	Phase I trial
		Ganetespib	Phase II trial
IGF-1R kinase inhibitors	Abnormal IGF-1R function activates PI3K/mTOR pathway leading to cell growth	Linsitinib (OSI-906)	Phase I/II trial
		NVP-AEW541	<i>In vitro</i>
Purine analog	Acts on ribonucleotide reductase and DNA polymerase leading to DNA synthesis inhibition	Fludarabine phosphate	<i>In vivo</i>
Gold compounds	Thioredoxin reductase (TrxR) inhibition	Auranofin	<i>In vitro</i>

VEGFR: Vascular endothelial growth factor receptor; CDK: Cyclin-dependant kinase; PDGFR α : platelet-derived growth factor α ; PI3K: phosphatidylinositol 3-kinases; HDACs: Histone deacetylases; Hsp90: Heat shock protein 90; IGF-1R: Insulin-like growth factor-1 receptor