Review Article

New molecularly targeted drugs for gist after imatinib, sunitinib and regorafenib: a narrative review

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Background and Objective: Targeting KIT and PDGFRA with traditional tyrosine kinase inhibitors (TKIs) such as imatinib, sunitinib and regorafenib has revolutionized the treatment and the prognosis of patients diagnosed with locally advanced and metastatic gastrointestinal stromal tumors (GISTs) but resistance to those therapies represents a major challenge in the management of patients with progression disease after the third line. In this review we shed light on the latest updates about management options in GIST, discussing novel molecular compound, combination therapy and future prospects with further personalisation of treatment.

Methods: A narrative review of the literature was performed to evaluate new systemic treatment options for patients with metastatic GIST. Randomized controlled trials, single-arm phase I–III trials and retrospective analyses were included by a PubMed research and were included studied published from 2008 to 2021.

Key Content and Findings: Ninety-seven relevant articles were considered eligible and analyzed. As results, this review shows as the armamentarium of GIST therapy has been enriched of some new drugs. The INVICTUS trial, investigating fourth line Ripretinib achieved its primary endpoint, as in the double-blind period median progression-free survival (mPFS) of patients taking the experimental drug was 6.3 months [95% confidence interval (CI): 4.6–6.9 months] compared with 1.0 months of those receiving placebo (95% CI: 0.9–1.7 months) with a hazard ratio of 0.15 (95% CI: 0.09–0.25 months, P<0.0001). The VOYAGER study failed to demonstrate an advantage of avapritinib versus regorafenib as third-line treatment, but it showed activity of the drugs in patients harbouring *PDGFRA* D842V mutation.

Conclusions: After the approval of regorafenib in 2013, several efforts have been made to find novel therapies capable of targeting the wide range of *KIT* and/or *PDGFRA* secondary mutations arising in individual patients and latterly new molecularly targeted drugs have shown encouraging results in patients whose GIST is resistant to the conventional treatment options. The occurrence of secondary resistance mutations is a main challenge in the management of GIST. Advances in our understanding of GIST biology have facilitated the development of various novel therapeutic options with the aim to overcome this issue. Several clinical trials testing new promising compounds have been designed and should be supported in order to improve patients' outcomes.

Keywords: Gastrointestinal stromal tumors (GISTs); avapritinib; ripretinib; target therapy; INVICTUS

Received: 08 April 2021; Accepted: 22 March 2022; Published: 30 May 2022.

doi: 10.21037/gist-21-6

View this article at: https://dx.doi.org/10.21037/gist-21-6

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Introduction

Gastrointestinal stromal tumors (GISTs) are mesenchymal neoplasms that arise from the gastrointestinal tract (1).

GISTs are thought to originate from the Cajal interstitial cells (2), which are pacemaker cells responsible for intestinal peristaltic contractions and are found in the myenteric plexus of the gastrointestinal tract. These tumors can occur anywhere along the gastrointestinal tract.

GIST are most usually seen in the stomach (50–60%) and the small bowel (30–35%), with the colon and rectum (5%) and esophagus (1%), being the least prevalent (3).

They account for roughly 20% of soft tissue sarcomas with an annual incidence of approximately 10 per million people.

They can anyone of any age, but more than 80% of those affected are over 50 years old (with a median age of 60–65 years) (4).

GIST is generally linked with a syndrome (Carney's triad, Carney-Stratakis syndrome, and type 1 neurofibromatosis) in patients younger than 20 years (approximately 0.4 percent) (5-7).

Biological background

There are three histological patterns, morphologically different from each other, recognized in GIST: spindle cell, epithelioid and mixed (8).

GISTs have two particularly sensitive and specific histological markers: KIT (also known as CD117; present 95%) and Anoctamin1 (ANO1, also known as DOG1; present in 98%) (9,10).

Only 5% GISTs are negative for KIT, but the expression of ANO1 is present in many of these cases. This molecular expression is important because it will allow the response to KIT-targeted treatment even in the KIT-negative GIST subset (11).

Activating mutations in *KIT* and *PDGFRA* (which encode KIT and platelet-derived growth factor receptor tyrosine kinases, respectively) are currently thought to be the principal oncogenic drivers of GIST (2). Micro-GISTs (less than 1 cm) have similar mutations to clinical GISTs, implying that more genetic abnormalities are necessary for tumor growth.

KIT mutations are found in 75–80% of GISTs. Exon 11 encodes the juxtamembrane domain, which is most affected by these alterations (90%). Deletions, frame insertions, missense mutations, and combinations are all examples of molecular changes. *KIT*'s extracellular domains (typically exon 9; prevalence about 8%) and kinase domains I and II (exons 13 and 17; prevalence about 2%) are also mutated, but in a smaller percentage of instances (12).

PDGFRA mutations account for 10–20% of GIST mutations, particularly in exons 12, 14, and 18 (the *KIT* and *PDGFRA* mutations are mutually exclusive) (13). KIT and PDGFRA kinase domains are generally activated by ligand binding (stem-cell factor or platelet-derived growth factor), resulting in receptor dimerization (14). These kinases' juxtamembrane regions control dimerization, and mutations in these domains affect this function (15). Changes in the kinase II domains of KIT and PDGFRA, on the other hand, change the activation loop that controls the ATP-binding pocket conformation of each kinase. *KIT* and *PDGFRA* mutations increase oncogenic signaling via the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) pathways through these and perhaps other mechanisms (16). About 5–10% of GISTs, referred to as wild-type, lack either a *KIT* mutation or a *PDGFRA* mutation. Despite the name, neurofibromatosis 1 (*NF1* gene mutation), Carney-Stratakis syndrome (rare), Carney triad (rare), *BRAF* mutation (rare), succinate dehydrogenase (SDH) subunit mutations (*SDHA*, *SDHB*, *SDHC*, *SDHD*), and RAS-family mutations (*HRAS*, *NRAS*, *KRAS*) are now known to be present in this subtype of GIST (17,18). For the optimal treatment of GISTs, the mutational analysis of KIT and PDGFRA is mandatory. Approximately 8% of GISTs have a *PDGFRA* D842V mutation, which provides primary resistance to imatinib and other approved tyrosine kinase inhibitors (TKIs) (19); however, most of them can respond to avapritinib (20).

Treatment for metastatic GIST: imatinib, sunitinib and regorafenib

Before the advent of TKIs, chemotherapy was the first line of therapy for metastatic GISTs, with unsatisfactory responses and a median survival of approximately 1 year (21). In the first phase I study, imatinib was tested at various doses, ranging from 400 mg per day to 500 mg twice a day; the 400 mg twice daily dose was established as the maximum tolerated dose (MTD) (22). In phase I and II studies where imatinib was administered at a daily dose of 400–600 mg, response rates [complete (CR) and partial (PR)] were between 40% and 74%, values similar to those obtained with the dosage of 800 mg per day (between 45%

and 52%) but with a lower toxicity (22,23).

The efficacy of imatinib at 400 and 800 mg per day was compared in the pivotal phase III studies 6200550.51 and S003352. Both studies found that using imatinib 400 mg once a day had a significant therapeutic benefit. CR rates were between 3% and 6%, PR rates were between 45% and 48%, and disease stability rates (SD) were between 26% and 32%. Because there was no difference in overall survival (OS) between the two dosages, the 400 mg once day dose was designated as the standard dose. OS was 47 to 55 months, which was a significant improvement over chemotherapy. The imatinib 800 mg daily arm had a better progression-free survival (PFS) in a joint analysis of trials S0033 and the European Organization for Research and Treatment of Cancer 62005 (24). *KIT* exon 9 mutant tumors treated at the greatest dose showed improvement (25). Patients with exon 9 mutations should get imatinib 800 mg daily if tolerated, in light of this. The adverse effects of therapy at larger dosages are reduced when imatinib is started at 400 mg once day and gradually increased to the goal dose of 800 mg daily (26).

In advanced GISTs with a progression disease during therapy with imatinib 400 mg per day, imatinib dose escalation at 600 or 800 mg per day may lead to disease stability in approximately one third of patients and a response in 2% of patients. After dose escalation, over two-thirds of patients who respond or have stable illness with imatinib 800 mg stay progression-free for more than 2 years (27).

Sunitinib is a multitargeted TKI that inhibits KIT, PDGFR, vascular endothelial growth factor receptor (VEGFR), and FLT-1/KDR. MTD was determined in phase I investigations to be 50 mg per day for 28 days with 14 days of rest (28). This medicine is used as a second-line treatment following imatinib progression or as a first-line treatment in individuals who are unable to take imatinib. In 312 patients, a phase III research compared the use of placebo *vs.* sunitinib (50 mg per day, orally, in 6-week cycles with 4 weeks of activation and 2 weeks of interruption). The median duration to disease progression was 6.3 months with sunitinib and 1.5 months with placebo in this research [hazard ratio (HR) 0.33, 95% confidence interval (CI): 0.23–0.47; P=0.001]. Fatigue, diarrhea, skin discolouration, and nausea were the most common adverse effects (29). Patients with a *KIT* exon 9 mutation or wild type (WT) genotype showed a better PFS and survival rate than those with a *KIT* exon 11 mutation (30).

Regorafenib is a VEGFR1–3, TEK, KIT, RET, RAF1, BRAF, PDGFR, and FGFR multitarget TKI. This medicine is licensed for the treatment of GIST patients who have previously received imatinib or sunitinib (31). Regorafenib is given at a dose of 160 mg per day for 21 days, followed by a 7-day break, and repeated every 28 days. The GIST-Regorafenib in Progressive Disease (GRID) study, was a phase III, randomized, placebo-controlled trial in which patients were switched to regorafenib when their disease progressed with placebo. Regorafenib patients had a median PFS (mPFS) of 4.8 months compared to 0.9 months for placebo patients (HR 0.27, 95% CI: 0.18–0.39; P=0.001) (32).

Secondary resistance

Despite the great majority of patients with metastatic GIST showing a durable benefit from imatinib and the recent identification of long-term survivors with sustained responses (<2 years) (33), most of them develop imatinib resistance and progress within 2 years of treatment. Between 46% and 67% of patients develop secondary drug-resistance mutations due to TKI exposure (34,35). Increasing evidence suggests that each TKI has its own resistance profile. The most frequent mechanism of acquired resistance to imatinib is the occurrence of subclones harboring secondary *KIT* point mutations. These mutations usually involve exons 13 and 14, encoding for KIT ATP-binding domain, and/or exons 17 and 18, encoding for the activation loop and resulting in the stabilization of KIT in the active conformation, so preventing imatinib binding (36) (*Figure 1*). Several mutations can coexist in the same disease, reflecting inter- and intra-lesional heterogeneity of molecular drug resistance mechanisms in progressing GIST (35). After the onset of imatinib resistance, *KIT* secondary mutations can be detected through the analysis of circulating tumor DNA (ctDNA), which can be considered a useful and non-invasive method for the selection of targeted agents and predictions of antitumor effects (37). Despite most resistant tumors remaining addicted to the initial driver oncogene, alternative mechanisms for drug failure have been proposed, particularly in GIST lacking *KIT* mutations (WT). These resistance mechanisms include MAPK pathway activation, IGFR1 or AXL amplification, upregulation of focal adhesion kinase (FAK) and AKT or intratumoral VEGF expression (38,39). Several novel therapeutic strategies are being developed. Currently

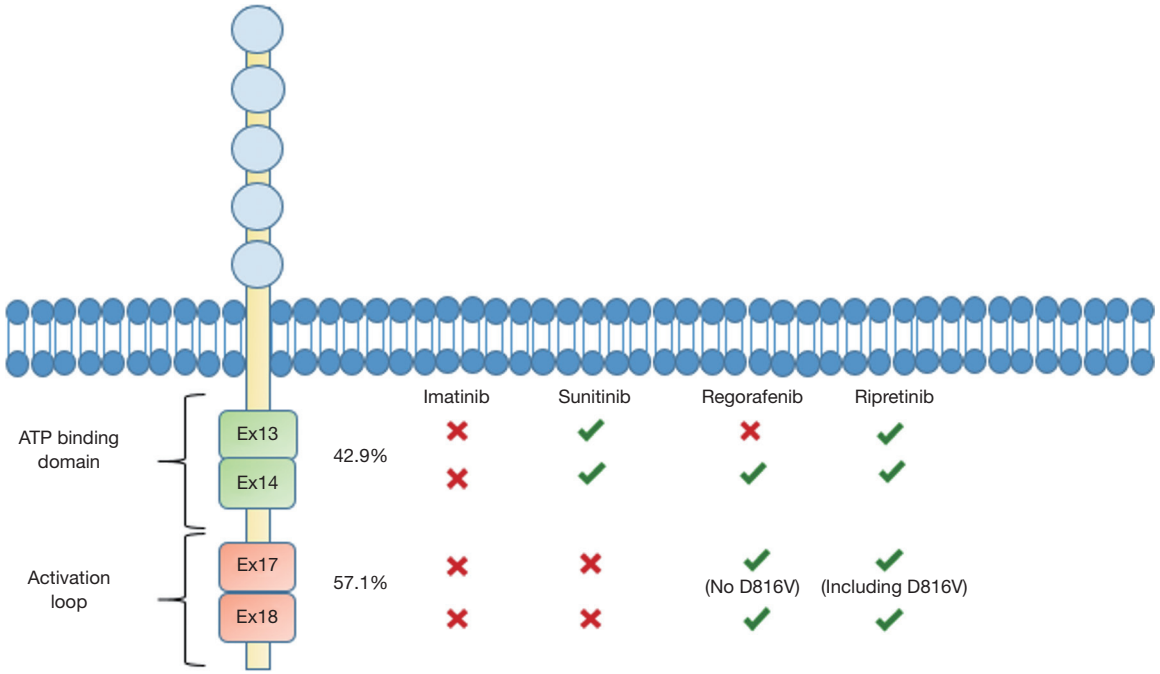

Figure 1 *KIT* secondary resistance mutations and main TKI sensitivity profile. TKI, tyrosine kinase inhibitor.

under investigation there are new next-generation selective tyrosine kinases, inhibiting a broader spectrum of secondary mutations or with a target-specific secondary *KIT* mutation.

Methods

An analytical and comparative PubMed research for novel therapeutic strategies in GIST treatment was conducted. All types of articles with a focus on prospective randomized trials and large meta-analysis were included. The search period has been from the year 2008 till 2021 to guarantee more recent studies on this topic. We used the following keywords: "GIST", "Avapritinib", "Ripretinib", "target therapy", "kinase inhibitors" and "combination". A total of 637 items were identified. After removing duplicates and screening titles and abstract, 376 full text papers were evaluated. In total, 279 papers were further eliminated thus 97 relevant articles were considered eligible (*Table 1*).

Novel drugs

Traditional TKIs (imatinib, sunitinib and regorafenib) have revolutionized GIST treatment but the development of secondary resistance has become one of the major challenges in the management of locally advanced and metastatic GISTs.

After the approval of regorafenib in 2013 as a third-line therapy, several efforts have been made to find novel therapies capable of targeting the broad range of *KIT* and/or *PDGFRA* secondary mutations arising in individual patients (40) and latterly new molecularly targeted drugs have shown encouraging results in patients whose GIST is resistant to the conventional treatment options (41) (*Table 2*).

The main objective of this review is to provide an overview of the newest drugs developed for the management of metastatic GIST and to discuss new candidate targets on the horizon that can cover conventional TKIs secondary resistance mutations and expand the treatment landscapes of GISTs.

This review has few limitations. First, there were only a few randomized studies included. Some of the articles are retrospective in nature, which may have led to selection and reporting bias. Therefore, heterogeneity may exist among the selected randomized clinical trials due to the study protocols, patient baseline characteristics, and response evaluation bias. We present the following article in accordance with the Narrative Review reporting checklist (available at https://gist.amegroups.com/article/view/10.21037/gist-21-6/rc).

Table 1 Search Items

Items	Specification
Date of search (specified to date, month and year)	10/Feb/2021–30/Jun/2021
Databases and other sources searched	PubMed
Search terms used	"GIST", "Avapritinib", "Ripretinib", "target therapy", "kinase inhibitors" and "combination"
Timeframe	2008–2021
Inclusion and exclusion criteria	Randomized trials and large meta-analysis, English language
Selection process	All authors, removed duplicates, screening titles and abstract

GIST, gastrointestinal stromal tumor.

Table 2 Efficacy of novel target therapies

Drug	Line	Phase	N	Comparator	RR	PFS	OS	AE
Ripretinib	4th	III	129	Placebo	9.4%	6.3 months	15.1 months	Alopecia, fatigue, nausea, myalgia
Avapritinib, *PDGFRA* D842V	Any	I	56	Single arm	88%	N/A	N/A	Memory impairment, hyperbilirubinemia, hypertension
Sorafenib	3rd	II	38	Single arm	PR 13%, SD 55%	5.2 months	11.6 months	Hand and foot syndrome, hypertension, diarrhea
Pazopanib	3rd	II	81	BSC	SD 84%	3.4 months	17,4 months	Hypertension, pulmonary embolism
Nilotinib	3rd	III	248	BSC	CBR 52.7%	3.6 months	13.3 months	Nausea, abdominal pain, fatigue
Cabozantinib	3rd	II	50	Single arm	PR 14%, SD 68%	5.5 months	18.2 months	Diarrhea, palmoplantar erythrodysesthesia, fatigue
Dovitinib	2nd	II	39	Single arm	PR 2.6%, SD 50%	4.6 months	Not reached	Hypertension, fatigue, vomiting
Masitinib	2nd	II	44	Sunitinib	20%	3.7 months	29.8 months	Rash, neutropenia
Ponatinib	2nd or 4th	II	39	Single arm	CBR 35%	2.8 months	N/A	Pain, hypertension, γ-GT or lipase increasing
Dasatinib	3rd	II	47	Single arm	PR 32%, SD 24%	2 months, 8.4 months WT GIST	19 months	Constitutional pain, myelosuppression
Vatalanib	2nd	II	45	Single arm	PR 4.4%, SD 35.6%	4.5 months	N/A	Hypertension, nausea, dizziness, proteinuria
Linsitinib, wild type GIST	Any	II	20	Single arm	CBR 40%, PMR 12%	52% at 9 months	80% at 9 months	Nausea, fatigue, elevated liver function test

AE, adverse events; BSC, best supportive care; CBR, clinical benefit rate; GIST, gastrointestinal stromal tumor; N, number of patients; N/A, not available; OS, overall survival; PFS, progression-free survival; PMR, partial metabolic response; PR, partial response; RR, response rate; SD, stable disease; WT, wild type; γ-GT, γ-glutamyl transpeptidase.

Ripretinib

Ripretinib (also known as DCC-2618) is a type II tyrosine switch control kinase inhibitor that has been shown to inhibit KIT and PDGFRA kinase signaling through a novel double mechanism of action: it binds precisely and strongly to both the activation loop and the switch pocket to seal and stabilize the kinase in the inactive or off state, arresting downstream signaling and cell proliferation (42).

Ripretinib *in vitro* showed powerful antineoplastic effects thanks to its ability to bind with high affinity to KIT receptors with mutations in exons 9,11,13,14,17,18 and PDGFRA receptors with 12,14 and 18 mutated exons (43). Ripretinib also demonstrated to inhibit other receptors such as platelet-derived growth factor receptor beta (PDGFRB), VEGFR2, BRAF and TIE2 (angiopoietin-1 receptor) (44).

In 2015 a phase I study (45) evaluated dose-limiting toxicities (DLTs), MTD, safety and antitumor activity in 258 patients, including 184 patients with advanced GIST, with intolerance to or experiencing progression after one or more line of treatment and 74 patients with other neoplasms with amplification and/or mutations determining sensitivity to ripretinib.

In the dose-escalation section of the study patients (n=68) were given ripretinib 20–200 mg twice daily or 100–250 mg once daily in consecutive 28-day cycles until disease progression, study discontinuation or intolerable toxicity.

No MTD was reached as <33% of patients experienced a DLT at every dose level.

The study led to the recommended phase II dose (RP2D) of 150 mg once daily taken orally, which was related with an agreeable tolerability and safety profile.

Ripretinib was generally well tolerated and only 5.6% of patients dropped out because of treatment-emergent adverse event (TEAE).

One of the most common TEAE was grade 1 alopecia (62%) whose pathogenesis is still undefined, but perhaps due to inhibition of several other kinases besides KIT and PDGFRA.

Other toxicities were mostly manageable, like palmar-plantar erythrodysesthesia (43.7%), reported with grade 3 in only one patient (0.7%), fatigue (54.9%), myalgia (48.6%), nausea (45.8%), decreased appetite (33.8%) and diarrhea (33.1%).

Grade 3 or 4 lipase elevation was described in 17.6% of patients but was generally asymptomatic and not clinically relevant, while in two patients pancreatitis was diagnosed but with improvement after a dosing interruption and no recurrence after restarting treatment.

Early antitumor activity results in patients with GIST taking ripretinib showed encouraging efficacy among all line of therapy: objective response rate (ORR) and median progression free survival were respectively 19.4% and 10.7 months in 31 patients in second line, 14.3% and 8.3 months in 28 patients in third line and 7.2% and 5.5 months in 83 patients in fourth line or beyond.

Preliminary results of this study contributed to the design of INVICTUS (NCT03353753) (38), a double-blind, randomized, placebo-controlled phase III trial of ripretinib in previously treated patients with advanced GIST.

A total of 129 patients were randomized in a 2:1 ratio to receive either oral ripretinib 150 mg once daily (n=85) or placebo (n=44), allowing cross over to ripretinib in case of disease progression.

The trial achieved its primary endpoint, as in the double-blind period mPFS of patients taking ripretinib was 6.3 months (95% CI: 4.6–6.9 months) compared with 1.0 months of those receiving placebo (95% CI: 0.9–1.7 months) with a HR of 0.15 (95% CI: 0.09–0.25, P<0.0001).

Since the ORR was not statistically significant, due to hierarchical testing median OS was not formally tested, but in the experimental arm mOS was 15.1 months (95% CI: 12.3–15.1 months) and 6.6 months (95% CI: 4.1–11.6 months) in the control arm (HR 0.36, 95% CI: 0.21–0.62), including both the double-blind and the open-label periods, with patients underwent cross over.

Safety of ripretinib was in harmony with prior knowledge: the most common grade 1–2 drug-related adverse events (AEs) were alopecia (49%), myalgia (28%), nausea (26%), fatigue (26%), palmar-plantar erythrodysesthesia (21%) and diarrhea (20%).

Most usual grade 3–4 AEs in the experimental arm were instead lipase increase (5%), hypertension (4%), hypophosphatemia (2%) and fatigue (2%).

Among the most severe drug-related AEs it is worth noticing a single event of cardiac failure and upper gastrointestinal hemorrhage. Six percent of patients receiving ripretinib had to reduce dosage and only 5% had to definitively discontinue the drug for treatment-related AEs.

After INVICTUS, INTRIGUE (NCT03673501) (46,47), a randomized, open-label, phase III trial is enrolling patients to investigate the efficacy of ripretinib compared to sunitinib as second-line therapy following imatinib in patients with advanced GIST. About 358 patients will be randomly assigned in a 1:1 ratio to receive either ripretinib 150 mg daily continuous on 42-day cycles or sunitinib 50 mg daily for 4 weeks with 2-week pause on 42-day cycles.

The primary endpoint of INTRIGUE is PFS as assessed by blinded independent central review (BICR), while

secondary endpoints are OS and ORR (assessed by BICR).

In China an open-label, multicentre, phase II trial (NCT04282980) is recruiting patients to evaluate safety, efficacy and pharmacokinetics of ripretinib in approximately 35 patients with advanced GIST whit progressive disease after previous treatments. The primary endpoint is PFS based on independent imaging review and secondary endpoints are ORR and OS.

In USA on 15 May 2020 ripretinib was approved by the Food and Drug Administration (FDA) for adult patients with advanced GIST who were treated with ≥3 kinase inhibitors, including imatinib (48).

In Europe a Marketing Authorisation Application for Ripretinib has been submitted to the European Medicines Agency (EMA) and an Expanded Access Program (EAP) is still available for the supply of ripretinib for patients receiving the drug (49).

Avapritinib

Avapritinib (formerly known as BLU-285) is a novel, strong and selective type I inhibitor with activity against *KIT* and *PDGFRA* activation loop mutations, including *PDGFRA* exon 18 (D842V) and *KIT* exon 11, exons 11/17 and exon 17 (D816V).

Both *in vitro* and *in vivo* preclinical studies avapritinib revealed a robust activity in GISTs harboring different *KIT* and *PDGFRA* mutations with dissimilar sensitivity to traditional TKIs, resulting in reduction of tumor volume, suppression of proliferation, amplifying apoptosis and sometimes in conspicuous histologic responses (50,51).

Regarding *PDGFRA*, some mutations are proved to be sensitive to imatinib, for example V561D or deletion DIMH842-845, whereas other alterations, like *PDGFRA* D842V, *PDGFRA* D842Y, or *PDGFRA* DI842-843IM, are related with treatment refractory *in vitro*.

The most typical *PDGFRA* mutation is the D842V which arises in the exon 18 that codifies for the activation loop, causing resistance to other type 2 TKIs that usually bind to the inactive conformation (50,52).

In fact, before avapritinib approval, patients with advanced gastrointestinal stromal tumours carrying the D842V mutation had a prognosis comparable to those in pre-imatinib era (53).

NAVIGATOR (NCT02508532) (54) was the first prospective trial testing the use of avapritinib in D842V mutated gastrointestinal stromal tumours, evaluating ORR, safety and duration of response (DOR) as crucial endpoints.

It was a multicenter, open-label, phase I trial with two phases: a dose-escalation phase for patients with unresectable GIST and a subsequent dose expansion phase for patients with unresectable *PDGFRA* D842V-mutant GIST despite previous therapy or GIST with other mutations and progressive disease after treatment with imatinib or more TKIs.

At the time of the data cut-off, 46 patients were enrolled in the dose-escalation phase, 20 of them had a *PDGFRA* D842V-mutant GIST; following that, 36 patients with a *PDGFRA* D842V-mutant GIST were included in the dose-expansion phase.

The maximum tolerable dose was 400 mg, with a 300 mg oral dose advised for phase II.

Avapritinib had excellent anticancer activity, with an ORR of 88% (95% CI: 76–95%) in the *PDGFRA* exon 18 mutant group, with 9% full response and 79% PR. At 12 months, the response duration was 70% (95% CI: 54–87%), and PFS was 81% (95% CI: 69–93%).

The trial also revealed that the drug had a tolerable safety profile: the majority of treatment-related AEs were grade 1–2, with the 400-mg cohort having a greater incidence of commonly reported AEs than the 300-mg group. The most common side effects with the 300 mg dose were nausea (69%), diarrhea (41%), hyporexia (38%), and exhaustion (38%), while the most common side effects with the 400 mg dose were nausea (71%), vomiting (47%), and periorbital edema (38%). Anemia was the most common grade 3–4 drug-related side event (17%).

Conversely, toxicities associated with other anti-angiogenic TKI like hypertension and hand-foot skin reactions were infrequent.

Among AEs it is worth to mention intracranial bleeding (2%) and cognitive effects such as memory impairment (30%), cognitive disorder (10%), confusional state (9%) and encephalopathy (2%): those effects were generally grade 1, more frequent at 400 mg and showed improvement after discontinuation or dose reduction, although the most common reasons for treatment suspension were disease progression (32%). No treatment-related deaths were registered.

VOYAGER (NCT03465722) (55,56) is an open-label phase III study randomizing patients previously treated with imatinib or 1 or 2 other TKIs with locally advanced

unresectable or metastatic GIST to receive either oral avapritinib (n=240) at 300 mg daily or oral regorafenib (n=236) at 160 mg daily on a 3-week-on/1-week-off schedule.

The study has missed the primary end point with avapritinib showing a mPFS of 4.2 months compared to 5.6 months for regorafenib, with a non-stat significant difference between groups.

Secondary endpoints were ORR, OS, and quality of life. The overall response rate was 17% for the experimental arm and 7% for the control group.

However, avapritinib was basically well-tolerated with most AEs described as grade 1 or 2, in line with previously reported data.

The results of the VOYAGER study are currently being analyzed.

The FDA approved avapritinib (AYVAKITTM, Blueprint Medicines Corporation) for adults with unresectable or metastatic GIST with a *PDGFRA* exon 18 mutation, such as the D842V mutation, on January 9, 2020, and the EMA approved it on September 24, 2020 (57,58).

In the United States, the TKI is being evaluated as a 4th-line treatment for GIST, while in the EU, it is being evaluated for the treatment of *PDGFRA* D842V GIST, regardless of previous therapy (59).

Other investigational drugs

Sorafenib

Sorafenib is an oral multikinase inhibitor that blocks RAF kinase and VEGFR2 and 3, as well as PDGFRB, KIT, FLT-3 and RET, resulting in antiproliferative and antiangiogenic properties. In a prospective, multicenter, phase II trial, sorafenib demonstrated activity in unresectable, *KIT* mutated, imatinib and sunitinib resistant GIST. In this trial were reported a PFS of 5.2 months and a disease control rate (DCR) of 68%, with 13% of patients obtaining a PR and 55% a SD (60). Other multicenter studies confirm the efficacy of sorafenib to achieve long-term tumor control. In a retrospective analysis conducted on 124 patients who progressed on imatinib and sunitinib, sorafenib demonstrated a DCR of 67% and a mPFS of 6.4 months (61). Similarly, a Korean study on 31 patients progressing after imatinib and sunitinib treatment showed a mPFS of 4.9 months. All these data were obtained in the pre-regorafenib era and, to the best of our knowledge, no further clinical trials were conducted endorsing the use of sorafenib in GIST pre-treated patients. Despite the encouraging results described, neither FDA or EMA approved the use of sorafenib in GIST patients, even if it may be prescribed off-label for this indication.

Nilotinib

Nilotinib is a selective TKI targeting BCR-ABL, PDGFRA, PDGFRB, KIT, ABL1, DDR-1 and DDR-2. This drug was investigated as third-line therapy in a phase III study in 248 patients who were resistant or intolerant to imatinib or sunitinib. mPFS, which was the primary endpoint of the trial, was not superior in the investigational arm if compared to best supportive care (BSC) (111 *vs.* 109 days, HR 0.90, P=0.56). Anyway, a *post-hoc* subset analysis revealed that, in patients who received only one prior therapy, OS was longer in favor of nilotinib (405 *vs.* 280 days) (62). Efficacy of nilotinib was investigated also in the first-line setting in a phase III trial (ENESTg1), compared with imatinib. Although the tolerability profile of nilotinib was similar to imatinib, the study did not meet its primary endpoint, with a 2-year PFS higher in the imatinib arm (59.2% *vs.* 51.6%) (63). As for sorafenib, nilotinib is mentioned in the National Comprehensive Cancer Network (NCCN) GIST treatment guidelines for possible off-label use in patients with imatinib and sunitinib resistant disease.

Pazopanib

Pazopanib is a multitargeted TKI which inhibits KIT, PDGFR, and is particularly active against VEGFR. Pazopanib has been studied in 25 patients after failure of imatinib and sunitinib, in a phase II multicenter trial. The 24-week non-progression (CR + PR + SD), was 17% with SD observed in 48% of patients. The study included one patient with SDH-deficient GIST, who exhibited prolonged disease control after 17 months (64). In 2016 were published on *Lancet* the results of the PAZOGIST, a phase II trial comparing pazopanib plus BSC *vs.* BSC alone in patients with imatinib and sunitinib resistant GIST. mPFS was longer in the investigational arm (3.4 *vs.* 2.3 months; 95% CI: 0.37–0.96, P=0.03). It should be noted that study patients did not receive regorafenib, that is the approved third-line therapy in refractory GIST. Despite the modest improvement in PFS, this study contributed to adding another useful agent to the existing TKI arsenal. Anyway, FDA or EMA have still not approved pazopanib for treatment of GIST (65). These results were confirmed by the recent PAGIST trial, a phase II multicenter trial

evaluating safety and efficacy of pazopanib in 72 patients with locally advanced or progressive metastatic GIST. The mPFS was 19.6 weeks (95% CI: 12.6–23.4 weeks), similar to the results observed in the GRID trial with regorafenib (66).

Cabozantinib

Cabozantinib is a novel compound targeting MET, RET, KIT, VEGFR, AXL. This small molecule has proven to be effective in both imatinib-sensitive and resistant models. This effect is believed to be related to the dual KIT and MET inhibition: in fact, the upregulation of MET signaling seems to be the result of imatinib inhibition of the KIT pathway (67). The European Organization for Treatment of Cancer (EORTC) conducted the CaboGIST trial, a multicenter, open-label, phase II study, assessing the activity and safety of cabozantinib after progression with imatinib and sunitinib, including a total of 50 patients. This trial met its primary endpoint with 60% of patients (30/50) being progression-free at 12 weeks. mPFS was 5.5 months (95% CI: 3.6–6.0 months) and median OS was 18.2 months (95% CI: 14.3–22.3 months). Clinical benefit (CR, PR and SD) was observed in patients with different mutational status, including *KIT* exons 11, 9, 13, 14 and 17 and also in *NF1*- and *RBPMS-NTRK3* driven GIST (68).

FGFR inhibitors

Recently, FGF activation signaling has been identified as an alternative mechanism promoting imatinib resistance in *KIT/PDGFRA* mutant GIST (69). Some authors described the existence of a crosstalk between FGFR and KIT illustrating how *FGF2* silencing restores imatinib response in resistant GIST cells line (70). Moreover, the combination of imatinib with BGJ398, a selective FGFR inhibitor, resulted in an impressive effect on tumor growth *in vivo* (71), despite the following phase Ib study was early interrupted due to unacceptable toxicity (72). Therefore, FGF/FGFR events, as receptor gene mutation or fusion and ligand overexpression have been described as possible oncogenic mechanisms in SDH-deficient and quadruple WT GIST (69). These observations led to clinical investigation of multi-target compounds, active against FGF/FGFR signaling, beside Regorafenib, which has known FGFR inhibiting activity.

Dovitinib

Dovitinib, a multikinase inhibitor targeting FGFR1/2/3 has been investigated in the multicenter, prospective, phase II DOVIGIST study as second line therapy in GIST patients after imatinib failure. Among 39 patients enrolled, the ORR (CR + PR) and the DCR (CR + PR + SD), were 5.6% and 60.5% respectively at the end of the study, while mPFS was 4.6 months (90% CI: 2.8–7.4 months). Despite the study included patients with different *KIT* and *PDGFRA* baseline mutations, the small sample size precluded the efficacy of dovitinib according to GIST mutational status (73).

Masitinib

Masitinib was tested in both first- and second-line settings. A phase II clinical trial of masitinib was conducted in 30 imatinib naïve patients. At 2 months, response rate was 20% according to RECIST 1.1 criteria and 86% according to FDG-PET response criteria. The estimated PFS was 41.3 months (74). As mentioned, masitinib was also investigated in a multicenter, prospective, randomized phase II trial *vs.* sunitinib, after imatinib failure. Forty-four patients were randomized to receive masitinib or sunitinib (1:1). The masitinib group had a mPFS of 3.7 months after 14 months, while the control group had a mPFS of 1.9 months. The median OS in the masitinib group was not reached (expected to be 21.2 months), but it was 15.2 months in the sunitinib group. Researchers did a follow-up analysis at 26 months to see if the OS improvement had been sustained over time. Results showed median OS was 29.8 months in the investigational arm and 17.4 months in the sunitinib arm. Moreover, masitinib showed a better safety profile than sunitinib (75).

Ponatinib

Ponatinib, another multi-TKI inhibitor, with activity against a broad spectrum of mutant isoforms of KIT, including secondary exon 17 resistance mutants. The phase II multicenter POETIG trial evaluated safety and efficacy of lower dose of ponatinib in pretreated patients with *KIT* mutant GIST. mPFS was 86 days with single patients experiencing long lasting responses (75% quartile 210 days, maximum 420 days) (76). Despite the well0known inhibitory activity against *KIT* mutations, some studies highlighted the ponatinib effect also in *FGFR* amplified or *FGFR* mutated cancer cell lines (77).

Lenvatinib

Lenvatinib is a multikinase inhibitor active against FGFR, KIT, PDGFRA, RET and VEGFR. Efficacy and safety of lenvatinib in patients with GIST after failure

of imatinib and sunitinib, is still under evaluation in the multicenter, randomized, placebo-controlled phase II trial LENVAGIST. Recruitment started in January 2020 and its completion is expected for March 2023 (78).

A number of other multitarget TKI have been investigated in the setting of patients with pretreated metastatic GIST, showing promising results in small phase II trials. Beyond the compounds previously mentioned, other drugs examined include dasatinib, vatalanib, and linsitinib (79-81).

PDGFRA D842V mutant GIST

Crenolanib

Crenolanib is a selective inhibitor of FTL3 and PDGFRA, and the first TKI with encouraging activity against *PDGFRA* D842V mutant GIST. Its efficacy in GIST patients was tested in a phase II trial (82) and is currently being assessed in 120 patients with D842V mutant GIST in the CrenoGIST trial, a randomized, double blind, placebo-controlled phase III study (83).

Target therapies beyond KIT and PDGFRA and combination treatments

Secondary resistance emerging from TKI exposure is one of the most critical problems in the treatment of GIST, with each TKI having its own resistance profile. The discovery of novel chemical agents targeting dysregulated downstream signaling pathways beyond the recognized oncogenic driver has resulted from breakthroughs in understanding the molecular basis of GIST.

PI3K/AKT/mTOR pathway

KIT and *PDGFRA* mutations have an impact on the activation of the PI3K/AKT/mTOR signaling which has a critical effect on cell proliferation, apoptosis, differentiation and metabolism. Some clinical trials explored this pathway as a promising target therapy strategy for GIST treatment (84).

A phase II study explored efficacy and safety of imatinib, given at 600 mg daily, combined with 2.5 mg/day everolimus. Seventy-five patients were enrolled and stratified in two groups, according to progression after imatinib only or imatinib and sunitinib/other TKI. mPFS was 1.9 months in the first group and 3.5 months in the second one. Median OS was 14.9 and 10.7 months, respectively. The combination treatment was well tolerated in the treated population (85).

Other PI3K/mTOR inhibitors have been studied, showing promising effects against both imatinib resistant and sensitive xenograft models, but further investigations are needed (86).

ETS variant transcription factor 1 (ETV1)

The ETV1 has been shown to be involved in growth and survival of interstitial cells of Cajal and GIST and represents a key downstream effector of KIT. In GIST, the constitutive activation of KIT and its downstream MAPK, prolongs ETV1 protein stability, promoting tumorigenesis. Some studies demonstrated that the concomitant inhibition of KIT and MAPK destabilizes ETV1, resulting in cytotoxic effects (87). The combination of imatinib (400 mg daily) and the MAPK inhibitor binimetinib (30 mg twice daily) was evaluated in a single arm phase II trial which enrolled 39 patients with untreated advanced GIST. The study met its primary endpoint showing an overall response rate of 68.4% and a resectability conversion rate (RCR) of 88.9%. The combination treatment showed a manageable toxicity and considering the promising results, further investigation in comparison with imatinib as frontline treatment is needed (88).

Heat shock protein 90 (HSP90)

HSP90 regulates conformation, function and activation of a number of client proteins including KIT. Inhibition of HSP90 has been explored as a novel strategy for treatment of GIST. A phase II Japanese trial investigated the efficacy of pimitespib (also known as TAS-116), an orally selective HSP90 inhibitor in 41 patients with advanced GIST after failure of imatinib, sunitinib and regorafenib. mPFS and OS were 4.4 and 11.5 months respectively, with 85% of patients achieving SD for more than 6 weeks (89).

Histone deacetylase

Histone acetylation and deacetylation are critical epigenetic mechanisms regulating gene expression and transcription. Histone deacetylase also targets multiple nonhistone substrates involved in cell proliferation, metastasis and

invasion, such as α-tubulin, cortactin or HSP90. A phase I trial evaluated the activity of panobinostat, a histone deacetylase inhibitor, in combination with imatinib in extensively pretreated GIST patients. One of the 11 patients recruited had metabolic PR, seven had metabolic stability for more than 3 weeks, and three had advanced. Treatment lasted a total of 17 weeks, with a median of 6 weeks (90).

Insulin-like growth factor 1

Insulin-like growth factor 1 receptor is overexpressed in KIT/PDGFR WT GIST, particularly in those with SDH-deficiency, contributing to an increased growth signaling. A phase II study investigated the efficacy of linsitinib, a IGFR1 inhibitor in patients with WT GIST. While no objective responses were observed, metabolic PR and SD were seen in 12% and 65% of patients respectively. Clinical benefit rate (CR, PR and SD ≥9 months) at 9 months was 40%, while PFS and OS estimates at 9 months were 52% and 80% respectively (81).

Neurotrophic tropomyosin receptor kinase (NTRK)

NTRK chromosomal aberrations are observed in several tumor types, resulting in constitutive activation and aberrant expression of tropomyosin receptor kinase (TRK) kinases. *NTRK* gene fusions are uncommon in GIST and should be checked in patients with quadruple WT GIST (lacking *KIT*, *PDGFRA*, *BRA*F, *SDH* mutations). The oral TRK inhibitor larotrectinib was found to be effective in 17 different tumor types. In the larotrectinib data set, 71 tumors treated (47%) were sarcomas, with 4 of them (6%), being GIST. In adult and pediatric patients with sarcoma harboring an *NTRK* fusion, the ORR with larotrectinib was 74% and 94%, respectively. The median length of response, PFS, and OS at 15.6, 13.0, and 14.1 months, respectively, were not estimable, 28.3, and 44.4 months. A minor number of sarcoma patients (n=13), including GIST, were included in the overall entrectinib clinical trial dataset. The ORR was 46% in the sarcoma subset, while median DOR, PFS and OS were 10.3, 11.0 and 16.8 months, respectively. Larotrectinib is approved by FDA and EMA, while entrectinib only by FDA, for treatment of adults and pediatric patients with advanced solid tumors harboring *NTRK* gene fusions (91,92).

Immunotherapy

In the last few years, several investigations explored the role of GIST immune microenvironment. Some researchers shown how tumor-infiltrating immune cells play an important role in tumor surveillance and are linked to disease outcome, as well as enhancing imatinib's anticancer activity. In patients with advanced GIST who had had at least imatinib, a phase II trial looked at the efficacy of nivolumab with or without ipilimumab. In the nivolumab arm, SD was the best response in 7 of the 15 patients. In the combo arm, 1 out of every 12 patients had PR and 2 out of every 12 had SD. The nivolumab alone arm had a mPFS of 12.1 weeks and the doublet checkpoint inhibition arm had a mPFS of 8.3 weeks (93). Currently, several clinical trials are ongoing with the aim to explore the activity of immune checkpoint inhibitors alone or in combination with similar agents or with TKI.

Conclusions

GIST treatment and prognosis have been revolutionized in 2001 by the advent of imatinib, which is still the first line treatment of choice for the majority of patients with advanced disease. Since then, other two TKI, have been approved for GIST treatment, with tangible improvement in patient outcome in a disease previously deemed as resistant to systemic therapy. Despite this substantial survival benefit, secondary resistance mutations to current drugs and their heterogeneity, remains a major challenge in GIST management. Advances in our understanding of GIST biology have facilitated the development of various novel therapeutic options with the aim to overcome this issue. Recently the armamentarium for treatment of GIST has been enriched by ripretinib, active against multiple resistance mutations, and avapritinib effective in *PDGFRA* D842V GIST. Several clinical trials testing other promising compounds have been designed and should be supported in order to improve patients' outcomes. Future arduous challenges will be to personalize GIST treatment through the identification of predictive factors of response to target drugs, the systematic characterization of resistance mechanism (with liquid biopsy potentially representing an ideal ally) and to better understand the optimal way to sequence and combine treatments. The ability to tailor GIST treatment to the characteristics of each patient will

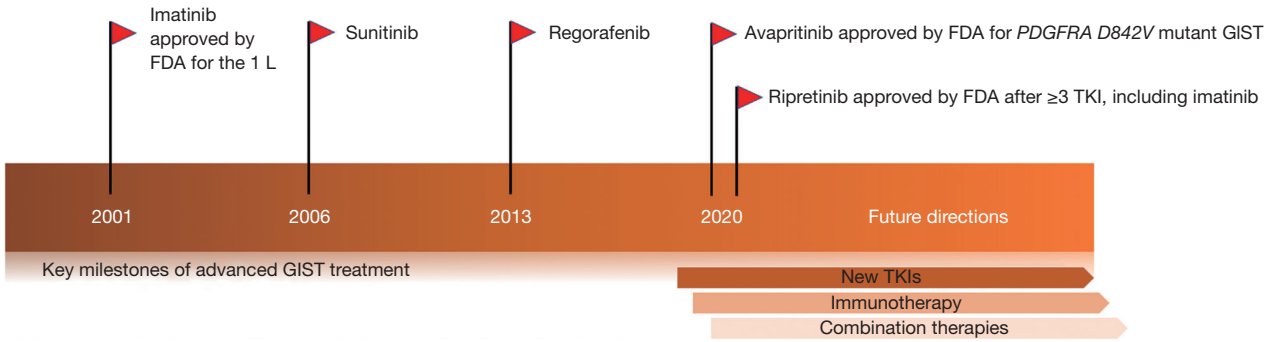

Figure 2 Timeline of GIST approved therapies. FDA, Food and Drug Administration; GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor; 1L, 1st line.

help to maximize the benefits of these targeted therapies, with the aim to improve patient prognosis *Figure 2*.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Bernd Kasper and Eva Wardelmann) for the series "Gastrointestinal Stromal Tumors" published in *Gastrointestinal Stromal Tumor*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://gist.amegroups.com/article/view/10.21037/gist-21-6/rc

Peer Review File: Available at https://gist.amegroups.com/article/view/10.21037/gist-21-6/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gist.amegroups.com/article/view/10.21037/gist-21-6/coif). The series "Gastrointestinal Stromal Tumors" was commissioned by the editorial office without any funding or sponsorship. AM reports grants from Deciphera, Eli Lilli, Pharmamar and Molteni. FP reports grants from Pharmamar and Molteni, outside the submitted work. AN reports grants from Eli Lilli, Pharmamar and Molteni, and personal fees from Eli Lilli, outside the submitted work. MS reports personal fees from Eisai and Bayer, outside the submitted work. BV reports personal fees from Eisai, Eli Lilli, Pharmamar, Abbott, Novartis, outside the submitted work. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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doi: 10.21037/gist-21-6

Cite this article as: Mazzocca A, Minelli A, Paternostro F, Silletta M, Napolitano A, Vincenzi B. New molecularly targeted drugs for gist after imatinib, sunitinib and regorafenib: a narrative review. Gastrointest Stromal Tumor 2022;5:4.