Ripretinib in gastrointestinal stromal tumor: the long-awaited step forward

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Abstract: Gastrointestinal stromal tumor (GIST) represents a paradigm for clinically effective targeted inhibition of oncogenic driver mutations in cancer. Five drugs are currently positioned as the standard of care for the treatment of advanced or metastatic GIST patients. This is the result of continuous, deep understanding of KIT and PDGFRA GIST oncogenic drivers as well as the resistance mechanisms associated to tumor progression. However, the complexity of GIST molecular heterogeneity is an evolving field, and critical questions remain open. Specifically, the clinical benefit of approved and/or investigated targeted agents is strikingly modest at advanced stages of the disease when compared with the activity of first-line imatinib. Ripretinib is a novel switch-pocket inhibitor with broad activity against KIT and PDGFRA oncoproteins and has recently demonstrated antitumoral activity across phase I to phase III clinical trials. Therefore, ripretinib has emerged as a new standard of care for advanced, multi-resistant GIST patients. Based on this data, the Food and Drug Administration has granted in 2020 the approval of ripretinib for GIST patients after progression to imatinib, sunitinib and regorafenib. This, in turn, constitutes a major breakthrough in sarcoma drug development, as there have not been new treatment approvals in GIST for nearly a decade. Herein, we provide a critical review on the preclinical and clinical development of ripretinib in GIST. Furthermore, we seek to assess the biological and clinical impact of this new standard of care on the course of the disease, aiming to provide an insight on future treatments strategies for the next coming years.

Keywords: avapritinib, ctDNA, DCC-2618, gastrointestinal stromal tumor, GIST, imatinib, KIT, PDGFRA, ripretinib, sarcoma, targeted therapy, tyrosine kinase inhibitor

Introduction

Gastrointestinal stromal tumor (GIST) is the most frequent cancer from mesenchymal origin, with a reported incidence of 10–15 cases per million per year.1,2 GIST originates in the interstitial cells of Cajal (ICCs), which are located in the smooth muscle across the gastrointestinal tract. Importantly, ICCs features high basal expression of KIT, a receptor tyrosine kinase (RTK) essential for their physiological development and function. Likewise, the expression of KIT (CD117) in GIST cells is present in up to 95% of the cases and its immunohistochemistry assessment is routinely performed to identify such neoplasms.3,4 The discovery of the GIST oncogenic drivers, KIT and PDGFRA gain-of-function mutations, at the turn of the century, shook the biological understanding of this neoplasm and its therapeutic development.5,6 Nowadays, GIST is regarded as a compelling clinical and biological model for the rational development of molecularly targeted agents. The switch-pocket inhibitor ripretinib constitutes the latest success in a list of standard-of-care treatments that includes tyrosine kinase inhibitors (TKIs) imatinib, sunitinib and regorafenib.

Clinical and biological background

KIT and PDGFRA mutations are central to GIST biology

GIST initiation, growth and progression are governed by mutually exclusive oncogenic activation of KIT or PDGFRA RTKs. KIT and PDGFRA...
are transmembrane receptors that belong to the type III RTK family, and their constitutive activation through gain-of-function mutations constitutes the primary event in GIST oncogenesis. KIT mutations are more frequently observed in GIST—approximately 80%—while 10–15% emerge in PDGFRA. Importantly, these mutations are not random and emerge in well-known hotspot regions across both genes. Overall, the most common alterations occur in KIT exon 11 (67%), which codifies the juxtamembrane intracellular domain of the RTK. The loss of this region’s autoinhibitory role results in constitutive kinase activation. Additional KIT primary mutations are also seen in the extracellular ligand-binding domain (10%), codified by KIT exon 9, and more rarely in the kinase domains (<2%), codified by exons 13 and 17. PDGFRA mutations are shown in homologous regions from the kinase domains encoded by exons 12, 14, and mainly, the exon 18 (5%).

So-called wild-type (WT) GISTs are not driven by KIT nor by PDGFRA mutations and account for approximately 5–10% of all cases. Under this label, there is a wide range of heterogeneous molecular drivers. The first group includes those WT GISTs that are driven by events leading to the constitutive activation of the RAS/MAPK pathway, such as oncogenic mutations in RAS or BRAF, loss-of-function mutations in NF1, and genetic rearrangements involving NTRK. The second broad group encompasses around 5% of GISTs driven by the accumulation of the oncometabolite succinate (SDH) complex at the mitochondria. Finally, there is still a small subset of KIT/PDGFRA WT GISTs not harboring any of the previous alterations.

Together, the critical relevance of KIT and PDGFRA oncogenic signaling throughout the course of the disease in most GISTs was translated into therapeutics early after their discovery. Indeed, the oncogenic addiction to these kinases constitutes a therapeutic vulnerability that has been historically exploited through the development of small molecules inhibitors aiming to target the diversity of KIT and PDGFRA oncoproteins.

First-line treatment with imatinib for advanced or metastatic GIST

This exquisite addiction to oncogenic KIT/PDGFRA signaling explains the profound effect of targeted inhibition of these RTKs with small molecules such as first-line imatinib in GIST cell viability and growth. Imatinib was in 2002 the first therapy granted with Food and Drug Administration (FDA) approval for the treatment of KIT-positive metastatic and/or unresectable GISTs following the demonstration of sustained activity in a landmark phase II trial (B2222 study) (Figure 1). A median overall survival (mOS) of 57 months underscored the clinical benefit provided by effective KIT/PDGFRA inhibition in a disease formerly deemed resistant to all known treatments. Remarkably, a subset of GIST patients (7–9%) demonstrates substantial sensitivity to KIT-targeted inhibition with imatinib, remaining progression free for more than 10 years.
Importantly, KIT and PDGFRA genotypes in GIST predict the response to imatinib. Hence, there is some level of variation between the different regions of KIT, and KIT primary mutations emerging in exon 11 show longer and deeper responses than those encoded by exon 9—which, however, benefits more from higher doses of imatinib than KIT exon 11 mutants.9,10 Unlike previous mutations, the D842V substitution emerging in PDGFRA as the primary driver in 5% of GIST is intrinsically resistant to imatinib and to all known TKIs until now.11 Remarkably, avapritinib, a novel type-I TKI specifically designed against this mutation, obtained FDA approval in 2020 for the treatment of this GIST subtype after showing high activity and safety in the phase I NAVIGATOR study (16) (Figure 1).12

**Imatinib-resistant GIST**

The vast majority of patients with metastatic GIST eventually progress to first-line imatinib after a median time of approximately 20–24 months.7,13 Resistance to imatinib most commonly entails KIT or PDGFRA reactivation through the polyclonal emergence of heterogeneous subpopulations harboring secondary mutations. Imatinib-resistant mutations are not random, and cluster in hotspot regions across the KIT kinase domains: the ATP-binding pocket (encoded by exons 13 and 14) and the activation loop (encoded by exons 17 and 18), which constitute the only mechanism of resistance to imatinib in up to 85–90% of GIST patients (Figure 2).14–16 Accordingly, PDGFRA secondary mutations in homologous regions were recently found as the main mechanism of resistance to avapritinib in D842V-mutant GIST patients.17 Together, this evidence collectively supports the continuous critical role of KIT and PDGFRA oncogenic signaling after resistance to front-line targeted treatments.

Multi-kinase inhibitors sunitinib and regorafenib are the standard second and third lines, respectively, approved in GIST.18,19 Both agents display broad activity against KIT primary and secondary oncoproteins, in addition to a wealth of several other kinases. However, their benefit is modest compared with imatinib, exhibiting an overall response rate (ORR) lower than 10% and median progression-free survival (mPFS) of 4–6 months (18,19) (Figure 1). Single-agent activity is alike in other non-approved TKIs studied across various phase I to phase III clinical trials.20 This is largely explained by the combined facts of (1) heterogeneity of KIT secondary mutations after imatinib failure; and (2) the inhibitory profile of all TKIs against a specific subset of the KIT secondary mutational spectrum, which leads to the growth of cross-resistant subpopulations, eventually leading to clinical progression.15,16 For instance, we have shown how sunitinib is highly active against KIT exon 13 V654A secondary mutation—the most common secondary mutation emerging at the onset of imatinib failure—while regorafenib is preferentially effective against most secondary mutations emerging in the activation loop.16

After the approval of regorafenib back in 2012, the various attempts of achieving regulatory approvals for novel anti-GIST therapies have failed despite the sustained efforts of the sarcoma community. The leitmotiv throughout has been the quest for novel therapeutic mechanisms capable of overcoming the inter- and intra-tumor heterogeneity of subclones harboring different KIT secondary mutations.

**Ripretinib: a novel tyrosine kinase inhibitor for the treatment of GIST**

In the past two decades, there has been a deeper understanding of the molecular heterogeneity behind KIT and PDGFRA mutations in GIST, not only as primary drivers of the disease, but also as the result of tumor dynamics once imatinib resistance is established. In this context, ripretinib, an orally available switch-pocket kinase inhibitor with broad activity against KIT primary and secondary mutations, has been recently granted FDA approval for the treatment of TKI-refractory GIST.

**Preclinical development of ripretinib**

The three agents currently holding worldwide regulatory approval for the treatment of GIST (imatinib, sunitinib and regorafenib) bind to the inactive conformation of KIT and PDGFRA, and therefore are categorized as type II inhibitors. Although KIT primary exon 11 mutations disrupt the autoinhibitory properties of the juxtamembrane domain, the shift induced toward an active state of the kinase must be minor, based on the profound activity of such inhibitors in patients with GIST. However, whereas secondary mutations emerging in the ATP-binding pocket (KIT exon 13 V654A) or in the gatekeeper residues (KIT exon 14, T670I) hinder drug–protein
interactions, secondary mutations in the activation loop induce a more prominent equilibrium shift toward the active confirmation, which seriously hampers the binding of type II inhibitors. Ripretinib (formerly known as DCC-2618) is therefore the logical consequence in drug development to solve the following two premises in GIST progression: heterogeneity of KIT secondary mutations and kinase stabilization in the active state.

In this scenario, the concept of conformational control inhibition brought by ripretinib irrupts as an innovative approach to target both the activated form of the kinases and the wide range of kinase mutants. Ripretinib was designed to inhibit both switches by antagonizing the active state conformation and stabilizing switch elements in the inactive state, thus rendering the kinase in its inactive conformation. Therefore, this unique dual mechanism provides the basis for the strong inhibition of the full spectrum of primary and secondary drug-resistant mutants of KIT and PDGFR kinases.

Ripretinib has been studied preclinically across a broad range of models, including transfected CHO or Ba/F3 cells expressing KIT or PDGFRA mutants, primary human GIST cell lines and sublines, GIST xenografts and patient-derived xenografts (PDX). Overall, ripretinib and

![Figure 2. Sensitivity profile of ripretinib in KIT-mutant GIST across known secondary mutations, and in PDGFRA-mutant GIST across known primary genotypes. Comparisons have been established with current approved agents. Green color in stars indicate sensitivity and red color resistance.](image-url)
ripretinib active metabolite DP-5439 showed significant anti-tumor effects regardless the type of primary or secondary KIT mutation, as assessed mainly by viability, proliferation and phosphorylation inhibition assays. In addition, ripretinib showed preliminary proof-of-concept activity in two TKI-refractory KIT-mutant metastatic GIST patients harboring secondary mutations in the circulating tumor (ct)DNA across exons 13, 17 and 18, further confirming the encouraging preclinical activity observed in the laboratory (Figure 2). Ripretinib also appeared to be effective against the multi-resistant PDGFRA D842V in transfected mutant models, although no primary human cell lines or PDX exist for this specific subset of GIST patients.

In summary, approved small molecule KIT-inhibitor monotherapies have a drug-specific activity profile only against a subset of the KIT secondary mutational spectrum, which constitutes the molecular basis for the modest clinical benefit observed with successive lines of treatment in imatinib-resistant GIST. Therefore, the relevance of ripretinib in the GIST field lies in its broad range of activity against resistance mutations, considering that the polyclonal expansion of KIT secondary mutations is the main driver of tumor progression in imatinib-resistant GIST.

Early clinical development of ripretinib
Ripretinib first entered into clinical investigation in 2015. A phase I, open-label, first-in-human, clinical trial studied the safety, recommended phase II dose (RP2D), pharmacokinetics (PK), pharmacodynamics (PD) and preliminary anti-tumor activity in 258 patients with cancer, including 184 GIST.23 GIST patients had experienced progression or intolerance to at least one line of systemic therapy. Patients in the dose-escalation part of the trial (n=68) received ripretinib 20–200 mg twice a day or 100–250 mg once daily in repeated 28-day cycles. A pharmacologically guided 3+3 design was used to determine the maximum tolerated dose (MTD) of ripretinib administered once or twice daily. However, the MTD could not be determined. Three dose-limiting toxicities were reported in the dose-escalation phase, and occurred at 100 mg twice daily (asymptomatic grade 3 lipase elevation), 200 mg twice daily (asymptomatic grade 3 lipase elevation), and at 150 mg once daily (asymptomatic grade 4 creatine phosphokinase increase). The combined assessment of the safety, PK/PD and early activity resulted in determination of an RP2D of ripretinib 150 mg once daily.

Efficacy and safety at the RP2D were evaluated in a total of 142 patients with advanced GIST recruited across the dose escalation (n=12) and the expansion (n=130) phases.

Ripretinib was generally well tolerated in patients with advanced GIST receiving 150 mg once daily, with only eight of 142 (5.6%) patients discontinuing the study secondary to a drug-related adverse event. Treatment was overall well tolerated and toxicities were manageable, most being grades 1 and 2 (Table 1). Only 5.6% patients with GIST discontinued the study treatment due to drug-related adverse events. Ripretinib exhibited a toxicity profile resembling prior specific KIT/PDGFRα inhibitors such as imatinib, with the exception of alopecia and hand-foot skin reaction (HFSR) that will be commented on in more detail below.

Ripretinib showed encouraging anti-tumoral activity in GIST patients at the recommended dose of 150 mg QD. ORR and mPFS were explored according to the line of treatment, and ripretinib showed more activity in earlier lines. ORR, mPFS and number of patients according to the line of treatment were, respectively, as follows: second line (19.4%, 10.7 months, n=31); third line (14.3%, 8.3 months, n=28); and fourth line and beyond (7.2%, 5.5 months, n=83) (Table 2). These efficacy results were critical to support further development of ripretinib in GIST patients not only in the fourth line, where no treatment is available (INVICTUS trial), but also in the second line in comparison with sunitinib, the current standard of care (INTRIGUE trial).

Phase III clinical trial of ripretinib in advanced, TKI-refractory GIST
The INVICTUS study examined the efficacy of ripretinib in advanced or metastatic GIST patients that were refractory or intolerant to at least all three TKIs approved for the treatment of GIST.24 This was an international, multicenter, double-blind, phase III trial that randomized 2:1 129 metastatic GIST patients to either ripretinib (n=85) or placebo (n=44). Crossover was allowed after unblinding, and patients progressing to ripretinib were offered an increase in the dose to ripretinib 150 mg BID. At least 60% of the patients received ripretinib as a true
fourth-line therapy, while approximately 40% had received 4–7 lines before.

The INVICTUS trial met its primary endpoint, as ripretinib significantly improved the mPFS compared with placebo from 1.0 (95% CI 0.9–1.7) to 6.3 months (95% CI 4.6–6.9), with a hazard ratio of 0.15 (95% CI 0.09–0.25, \( p < 0.0001 \)) by blinded independent central review. This mPFS result is in the same line with the data

|                      | Phase I Grade 1/2 (%) | Grade 3/4 (%) | Total % | Phase III Grade 1/2 (%) | Grade 3/4 (%) | Total % |
|----------------------|-----------------------|---------------|---------|-------------------------|---------------|---------|
| Alopecia             | 62.0                  | –             | 62.0    | 49.0                    | –             | 49.0    |
| Fatigue              | 52.1                  | 2.8           | 54.9    | 24.0                    | 2.0           | 26.0    |
| Myalgia              | 48.6                  | 0             | 48.6    | 27.0                    | 1.0           | 28.0    |
| Nausea               | 44.4                  | 1.4           | 45.8    | 25.1                    | 1.0           | 26.0    |
| PPES                 | 43.0                  | 0.7           | 43.7    | 21.0                    | 0             | 21.0    |
| Constipation         | 39.4                  | 0             | 39.4    | 15.0                    | 0             | 15.0    |
| Hyporexia            | 32.4                  | 1.4           | 33.8    | 14.0                    | 1.0           | 15.0    |
| Diarrhea             | 31.0                  | 2.1           | 33.1    | 20.0                    | 1.0           | 21.0    |
| Abdominal pain       | 20.4                  | 9.2           | 29.6    | –                      | –             | –       |
| Muscle spasms        | 29.6                  | 0             | 29.6    | 12.0                    | 0             | 12.0    |
| Lipase increased     | 9.9                   | 17.6          | 27.5    | 5.0                     | 5.0           | 10.0    |
| Weight loss          | 27.5                  | 0             | 27.5    | 15.0                    | 0             | 15.0    |
| Vomiting             | 26.1                  | 0.7           | 26.8    | –                      | –             | –       |
| Headache             | 25.4                  | 0.7           | 26.1    | –                      | –             | –       |
| Arthralgia           | 22.5                  | 0             | 22.5    | 12.0                    | 0             | 12.0    |
| Dry skin             | 22.5                  | 0             | 22.5    | –                      | –             | –       |
| Hypertension         | 16.9                  | 5.6           | 22.5    | 5.0                     | 4.0           | 9.0     |
| Anemia               | 13.4                  | 7.0           | 20.4    | 2.0                     | 1.0           | 3.0     |
| Back pain            | 19.0                  | 1.4           | 20.4    | –                      | –             | –       |
| Dyspnea              | 17.6                  | 2.1           | 19.7    | –                      | –             | –       |
| Cough                | 17.6                  | 0             | 17.6    | –                      | –             | –       |
| Dizziness            | 17.6                  | 0             | 17.6    | –                      | –             | –       |
| Hypophosphatemia     | 12.0                  | 4.9           | 16.9    | 4.0                     | 2.0           | 6.0     |
| Rash                 | 16.2                  | 0             | 16.2    | –                      | –             | –       |
| Seborrheic keratosis | 16.2                  | 0             | 16.2    | –                      | –             | –       |
| Actinic keratosis    | 15.5                  | 0             | 15.5    | –                      | –             | –       |

PPES, Palmar-plantar erythrodysesthesia syndrome.
obtained during the phase I clinical trial (Table 2). Most of ripretinib activity was achieved through disease stabilization, with 66% and 47% of the patients remaining stable at 6 and 12 weeks, respectively. Some 19% of the patients had progressed to ripretinib in the first computed tomography (CT) scan evaluation. Eight (9.5%) out of 85 evaluable patients on ripretinib had a confirmed objective response, all of whom were partial responses, while no responses were seen in the placebo group. These responses are apparently lengthy. Indeed, the median duration of response was 18.4 months in the phase I clinical trial regardless of the line of treatment, which suggests that specific molecular subtypes of resistance benefit particularly well from ripretinib-mediated inhibition. Finally, it is worth to mention the positive impact of ripretinib treatment on overall survival. GIST patients receiving ripretinib achieved a mOS of 15.1 months, which was superior to the 6.6 months from the placebo group, despite some of these patients also received ripretinib after the crossover. Although, due to hierarchal testing, mOS could not be formally tested for statistical significance, ripretinib is the first agent in imatinib-resistant disease showing such benefit. This, in turn, underscores the benefit from continuous KIT/PDGFRA suppression in the highly aggressive setting of TKI-refractory GIST.

The safety profile of ripretinib in the phase III trial was consistent with previous evaluations (Table 1), and was overall favorable, with most side effects being low grade and manageable. Common treatment-related adverse events occurring in more than 20% of the patients were alopecia (49–63% in women), myalgia (28%), fatigue (26%), HFSR (21%) and diarrhea (20%). It is worth noticing a single episode of each cardiac failure and upper gastrointestinal hemorrhage were among the eight treatment-related serious adverse events. Five (6%) patients on ripretinib required dose reduction and only four patients (5%) had treatment-related adverse events that led to definitive study drug discontinuation. Together, the ripretinib safety profile seems to be similar to, if not better than, previous TKIs approved after failure to imatinib. In particular, alopecia and HFSR are noteworthy for a KIT/ PDGFRA-specific targeted agent. In fact, the ripretinib kinase profile shows that several other kinases besides KIT and PDGFRA are inhibited with an IC50 below 100nM: BRAF, DDR2, CSF1R, EPHB2, LCK, PDGFRB, RAF1, TAOK2, TIE2, TRKA and ZAK. Thus the impact, although likely mild, in other kinases related to the MAPK pathway and angiogenesis can explain these two side effects. However, unlike sunitinib and, especially, regorafenib, ripretinib-induced HFSR always fell in the low range of the toxicity profile.

Based on this data, the US FDA approved ripretinib on 15 May 2020, for adult patients with GIST who have prior treatment with three or more kinase inhibitors, including imatinib. Further steps are being taken to obtain a worldwide regulatory approval.
Future perspectives

The introduction of ripretinib as a novel standard of care in the fourth line constitutes an enormous step forward in the ever-challenging field of drug development in rare diseases, such as GIST. The results from the INVICTUS trial have highlighted the relevance of continuous suppression of KIT/PDGFRA oncogenic signaling in TKI-refractory GIST, while leaving open questions concerning tumor dynamics and future drug development.

Ripretinib versus sunitinib in second-line treatment

The first future direction that will be solved concerns whether ripretinib will advance as an earlier line of treatment in GIST therapeutics. Phase I and phase III studies demonstrated that ripretinib is a very well-tolerated drug, also showing higher activity in the second line compared with the historical sunitinib data. These results triggered the ongoing phase III INTRIGUE trial, which is currently comparing ripretinib with sunitinib in patients with advanced GIST after front-line imatinib failure (NCT03673501). Although the rationale behind this trial seemingly favors the ripretinib arm, there are several nuances that mean we await the results with bated breath: first, although ripretinib is a pan-KIT inhibitor, sunitinib is very potent against the KIT exon 13 V654A mutation, the most common secondary mutation emerging after imatinib failure; second, the multikinase inhibitory nature of sunitinib, compared with ripretinib, may account as an extra aid by inhibiting several other kinases that can be somewhat relevant for GIST cell survival; and third, current GIST disease extension and volume after imatinib failure is less bulky than it was back in 2006 when sunitinib was first tested—meaning that current sunitinib mPFS may be higher than that described in the original trial.

The phase III INTRIGUE trial has mPFS as the primary endpoint. Key secondary objectives include objective response rate, overall survival and quality of life. If this trial provides positive results, we will certainly welcome a new therapy following imatinib failure that will maintain disease control for a longer time and potentially with fewer side effects. However, we will need to understand the optimal sequence of sunitinib and regorafenib after the failure of a pan-KIT inhibitor such as ripretinib. ctDNA studies have taught us that there seems to be a predominance of KIT secondary mutations in the activation loop after sunitinib progression, which is maintained in later stages of the disease. Thus, how tumor dynamics evolve after ripretinib failure and how this would impact on the activity of subsequent approved treatments (sunitinib and regorafenib) would need to be solved shortly.

Remaining open questions after the phase I and phase III clinical trials

Several insights into ripretinib activity are still needed, and the data collected throughout the phase I and III studies will certainly shed light in these areas of uncertainty.

Clinical activity of ripretinib against specific Kit and PDGFRA mutations. KIT and PDGFRA primary and secondary genotypes have consistently predicted the activity of the different TKIs investigated in GIST. The innovative dual mechanism of action of ripretinib allows the effective inhibition of a broad range of KIT and PDGFRA mutations through promoting the shift toward the inactive conformation of the kinases. Although ripretinib has shown to be effective against all KIT and PDGFRA mutants tested in a wide range of cellular models, it is necessary to see if this holds true in correlative studies from the two clinical trials. Basically, there is a very simple observation: patients with KIT/PDGFRA mutation keep progressing to a pan-KIT inhibitor after initial response or disease stabilization. Additionally, ripretinib is still a type II TKI that does not bind irreversibly to the kinase. Potentially, KIT-independent mechanisms may arise as the main driver of resistance—something that can be addressed thanks to the tumor biopsies and plasma samples for ctDNA analysis collected across the trials. However, it would seem biologically unlikely that there is an “explosion” of such mechanisms in the majority of patients. Therefore, it is more reasonable to think that some specific secondary KIT mutations will be insufficiently suppressed in a long-lasting manner, or that some parallel mechanisms will attenuate the effect of ripretinib, or a blend of both. Ripretinib specifically targets the switch pockets located in the juxtamembrane (exon 11) and the activation loop (exons 17 and 18) domains. Although these two are the triggers of the conformational switch, ripretinib could potentially provide a less efficient and durable inhibition if mutations arise in different regions, such as KIT primary mutations in the...
extracellular domain (exon 9) or secondary mutations in the ATP-binding pocket (exon 13). Alternatively, novel KIT mutations could emerge in other regions of the kinase.

In addition, although ripretinib seems to be preclinically active against the multi-resistant PDGFRα exon 18 D842V mutation, IC50 values were three-fold higher compared with other secondary mutants.25 In recent preclinical work, a novel human GIST cell line with a knocked-in D842V mutation was highly resistant to ripretinib, thus arguing against ripretinib activity in these patients.17 This data points in the same direction regarding its homologous KIT exon 18 D816V mutation. Finally, although ripretinib was granted for the treatment of all GIST molecular subtypes, only seven GIST WT patients were randomized to ripretinib, and therefore ripretinib activity in this setting remains unknown.

Open questions from the clinical side. Patients with advanced GIST progressing to the standard dose of ripretinib (150 mg QD) in the INVICTUS trial were offered to double it to 150 mg BID. If there is some benefit derived from this intervention, this is something that will need to be formally analyzed in the near future, but this is certainly interesting at first glance. Ripretinib MTD was not reached and can initially be pushed safely up to 150 mg BID. Based on prior reasoning regarding ripretinib potential liabilities, it is conceivable that this dose increase could inhibit more efficiently determined KIT and PDGFRα mutants—thus paralleling imatinib 400 mg QD and BID in the first line.9

Ripretinib appears to be well tolerated across the phase I and III trials. Nonetheless, as is usual with recently approved agents, prolonged follow-up is required to assess how side effects evolve in the long term as well as to detect previously unknown or infrequent adverse events, especially serious adverse events. For instance, two patients in the INVICTUS trial had, each one, cardiac failure and upper gastrointestinal hemorrhage that were deemed related to ripretinib. Likewise, although dermatologic examinations have been present across the phase I and III trials, no keratoacanthomas/squamous cell carcinomas have been reported so far.23,24

Finally, it will be intriguing to better understand the clinical and molecular features from those TKI-refractory GIST patients achieving durable responses with ripretinib, something completely unexpected in this population before the arrival of ripretinib.

Next steps in clinical drug development in GIST

The introduction of ripretinib as a new standard of care for the treatment of TKI-refractory GIST will reformulate some aspects of future therapeutic development. Ripretinib is active in patients with GIST at an advanced stage of disease, showing a slightly superior mPFS and ORR than sunitinib and regorafenib at later lines of treatment. However, these numbers still fall in the range of 4–6 months of mPFS and <10% ORR seen across several TKIs tested in imatinib-resistant GIST.20 While prior TKIs had anti-tumor activity against specific subset of KIT secondary mutations, ripretinib is a pan-KIT inhibitor. This makes us speculate that ripretinib, although an agent with broad activity against KIT mutations, might not be inducing enough cell death, as imatinib does in the first line,29 and hence the differences in ORR and mPFS. Indeed, it is likely that KIT oncogenic signaling is not completely shut down in imatinib-resistant disease, as has been shown, for instance, with regorafenib.30 Thus, future strategies for drug development in GIST will need to enhance apoptosis induction and/or target the heterogeneity of resistance mutations using different approaches.

Combination trials. In the past, therapeutic strategies were focused on the combined inhibition of KIT/PDGFRα and other targets in order to either enhance apoptosis (RAS/MAPK and PI3K/mTOR pathways inhibition) or prevent treatment adaptation [i.e. fibroblast growth factor receptor (FGFR) inhibition].31–33 The backbone for such combinations was imatinib. However, the use of imatinib in imatinib-resistant disease likely did not yield the expected clinical results. There is no question that the preclinical rationale behind such combinations is sound, and that ripretinib, with its pan-KIT inhibitory activity, will be the poster child for a new generation of clinical trials in imatinib-resistant disease aiming to maximize responses and induce more durable responses.

Other therapeutic strategies. Future drug development in GIST will maintain the focus on novel therapeutic strategies aiming to overcome the heterogeneity of KIT secondary mutations, as this remains the main driver of disease progression. To do so, several strategies are on the horizon. GIST is possibly one of the best cancer models for the clinical implementation of ctDNA,
which can be used for ctDNA-guided TKI rotation strategies by assessing specific resistance mutations and matching them with effective therapies. Further clinical validations are nonetheless warranted.

A different perspective to approach KIT oncogenic signal inhibition irrespective of KIT secondary mutations leads to identifying and targeting critical biological mechanisms involved in KIT oncoprotein stabilization. Several heat-shock protein 90 (HSP90) inhibitors have successfully demonstrated preclinical activity. However, its translation into the clinic remains challenging. Nonetheless, any strategy aiming to target KIT protein degradation could be a window of opportunity to develop novel treatments.

Finally, there are already some ongoing trials targeting KIT-independent mechanisms that likely funnel KIT oncogenic signaling, such as selinexor, a selective inhibitor of the nuclear exportin XPO1 (NCT04138381), or DS-6157a, a GPR20 inhibitor (NCT04276415).

Rethinking the design of future phase III trials. GIST trials leading to drug approvals have consistently used placebo-controlled randomized designs, considering that there was no efficient standard of care for such resistant populations. Interestingly, the INVICTUS trial has highlighted first, that a significant proportion of TKI-refractory GIST patients has a very rapid clinical progression in the absence of any TKI, and second, that KIT suppression at this late stage of disease is beneficial. Therefore, for future phase III clinical trials in advanced, multi-resistant GIST patients we should encourage the incorporation of a non-placebo option. For instance, there are several reports supporting the survival benefit of maintaining TKI treatment after progression. Imatinib re-challenge could be an option as well. Other considerations could be: include shorter washing times from prior treatments (i.e. 1 week maximum); use a more intensive schedule of CT scans, particularly at the beginning of treatment; and always allow crossover. These and other measures would need to be discussed ideally between clinical investigators and patient advocacy groups.

In conclusion, two decades of dynamic clinical and translational research have led to the discovery and understanding of crucial biological mechanisms that drive GIST survival and proliferation. Ripretinib is the result of these investigations aiming to overcome the heterogeneity of KIT secondary mutations in imatinib-resistant disease. The innovative mechanism based on switch-pocket inhibition for conformational control ensures a broad activity against a wide range of KIT and PDGFRA mutations. A better understanding of some aspects concerning preclinical and clinical ripretinib activity is still needed, and will be addressed in the near future. Finally, new lines of drug development will be triggered rooted in ripretinib approval, with drug combinations having the potential to maximize treatment response.

**Conflict of interest statement**

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