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SARCOMAS (SR PATEL, SECTION EDITOR)

New Tyrosine Kinase Inhibitors for the Treatment of Gastrointestinal Stromal Tumors

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Abstract

Purpose of Review This article critically revisits novel data on tyrosine kinase inhibitors that have shown clinical activity in the treatment of gastrointestinal stromal tumor (GIST).

Recent Findings GIST therapeutic development exploits the oncogene addiction to KIT or PDGFRA receptor tyrosine kinases. Based on this principle, two new drugs were approved in 2020: ripretinib in GIST patients after progression to all standard treatments and avapritinib, the first agent ever active in the multiresistant PDGFRA D842V-mutant GIST. Additionally, cabozantinib has also shown encouraging activity in imatinib-resistant GIST patients. Finally, novel agents targeting NTRK-driven GIST have emerged as a breakthrough for the treatment of a subset of KIT/PDGFRA wild-type GIST patients.

Summary GIST is a paradigmatic tumor model for the rational and successful development of molecularly targeted agents directed against driver mutations in cancer.

Keywords Avapritinib · Cabozantinib · GIST · Imatinib · NTRK · Ripretinib

Introduction

It was not until 1998 that gastrointestinal stromal tumors (GISTs) could be recognized as a distinctive entity due to the discovery of gain-of-function mutations in the KIT receptor tyrosine kinase (RTK) [1], which were present in a subset of malignant mesenchymal neoplasms originated in the gastrointestinal tract. The identification shortly thereafter of similar activation mechanisms in the homologous PDGFRA RTK [2] completed the molecular landscape of nearly 90% of GIST patients [3]. This high reliance of GIST cells on KIT or PDGFRA oncogenic signaling traces its roots back to the interstitial cells of Cajal (ICC), the postulated cells of origin for GIST [4]. Physiological KIT signaling is already essential for ICC survival and function, thus turning GIST into a very particular case of oncogene addiction. Indeed, GISTs exhibit continuous dependence upon a well-preserved KIT/PDGFRA-driven program throughout all stages of the disease [5]. This exquisite dependency on KIT/PDGFRA oncogenic signaling explains the profound antitumor effect of targeted inhibition of these RTKs with small molecules—the basis of therapeutic development in GIST [3].

At the turn of the century, the approval of imatinib for the treatment of advanced or metastatic GIST patients constituted a major breakthrough in cancer therapeutics. GIST was one of the first tumor types demonstrating the positive impact of effective targeted inhibition of cancer drivers on patients' outcomes: up to 90% of GIST patients experienced clinical benefit after treatment with imatinib, showing a median progression-free survival (mPFS) of 20–24 months [6, 7]. These results were certainly remarkable in a disease

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formerly deemed to be resistant to all known treatments. Updates from the original trials evidenced that a significant proportion of metastatic GIST patients achieved long-term control of the disease: approximately 30% of the patients remained progression-free after 5 years of continuous imatinib and 7 to 9% after 10 years [8, 9]. Together, these figures make GIST a paradigmatic model of oncogenic addiction among solid neoplasms.

Even though imatinib is highly effective in the first line, the great majority of patients will develop resistance. It entails reactivation of KIT/PDGFRA receptor and downstream pathways in the presence of imatinib due to positive selection and expansion of clones with acquired secondary mutations in KIT or PDGFRA, which constitutes the main mechanism of failure to imatinib in 70 to 90% of GIST patients [10, 11, 12•]. This highlights the relevance of KIT/PDGFRA oncogenic signaling throughout the entire course of the disease. Secondary mutations cluster in two regions of the KIT kinase domain: the ATP-binding pocket (codified by exons 13 and 14) and the activation loop (codified by exons 17 and 18) [3]. Secondary mutations in homologous regions of PDGFRA have been described as well [13••].

Treatment strategies after imatinib failure exploit KIT/PDGFRA dependency, and sunitinib and regorafenib, two tyrosine kinase inhibitors (TKIs) with broad KIT inhibitory activity, have worldwide regulatory approval for, respectively, the second and the third lines [14, 15]. Additional TKIs have also shown clinical benefit after imatinib failure [16]. However, we and others have shown that the structural heterogeneity of different KIT-resistant oncoproteins hinders the design of drugs that could effectively bind to and specifically inhibit all mutants [10, 11, 12•]. Thus, KIT secondary subclones cannot be completely suppressed by any given KIT inhibitor, ultimately leading to clinical progression in 4–6 months regardless of the TKI used (Table 1). Therefore, there is an unmet clinical need to overcome both tumor heterogeneity and the short-lived responses occurring after imatinib failure.

Ripretinib (DCC-2618) Treatment in Imatinib-Resistant GIST

The polyclonal emergence of KIT secondary mutations is the main driver of tumor progression in imatinib-resistant GIST, and therefore, therapeutic strategies based on KIT inhibition remain useful in this setting. Small-molecule KIT inhibitor monotherapies have a drug-specific activity profile against a subset of the KIT secondary mutational spectrum. Additionally, these agents are only capable of binding to the inactive conformation of KIT and PDGFRA, being classified as type II kinase inhibitors. In this scenario, ripretinib was specifically designed to target both the activated form of the kinases and the wide range of kinase mutants.

Preclinical Development of Ripretinib

The conformational shift from the inactive to the active state of KIT and PDGFRA kinases is regulated by two switch pockets present in the juxtamembrane domain (encoded by *KIT* exon 11 or *PDGFRA* exon 12) and in the activation loop (*KIT* exons 17 and 18, and *PDGFRA* exons 18 and 19) [17]. Ripretinib innovative mechanism of action is based on the dual antagonization of both switch regions, thus forcing the kinases toward the inactive conformational state regardless of the type of primary and secondary mutations. Therefore, this unique dual mechanism provides the basis for the strong and selective inhibition at low nanomolar concentrations demonstrated preclinically against a broad range of primary and secondary KIT and PDGFRA oncoproteins [18•].

Clinical Development of Ripretinib in GIST

Ripretinib underwent a rapid and successful development in a first-in-human phase I clinical trial [19]. The maximum tolerated dose (MTD) was not reached, and the recommended phase II dose (RP2D) of 150 mg taken orally once daily was based upon the combined assessment of safety, PK/PD, and early activity. Remarkably, ripretinib showed encouraging antitumor activity in GIST patients at the RP2D after imatinib failure. Specifically, overall response rate (ORR)

Table 1 Activity of approved agents in advanced/metastatic GIST

	KIT/PDGFRA-mutant GIST				PDGFRA D842V
	Imatinib [8]	Sunitinib [14]	Regorafenib [15]	Ripretinib [20••]	Avapritinib [31••]
Treatment line	1st	2nd	3rd	≥4th	Any
ORR (%)	68.1	6.8	4.5	9.4	91.0
$SD_{12\ weeks}$ (%)	15.6	53.0	48.1	47.0	9.0
mPFS (mo)	24.0	5.6	4.8	6.3	34.0

ORR, overall response rate; *SD*, stable disease; *mPFS*, median progression-free survival; *mo*, months

and mPFS according to the line of treatment were, respectively: 19.4% and 10.7 months (second line, $n=31$); 14.3% and 8.3 months (third line, $n=28$); 7.2% and 5.5 months ($\geq$ fourth line, $n=83$). These early efficacy results were instrumental to trigger further ripretinib investigation in subsequent phase III pivotal trials, first in the fourth line, with no approved treatments available (INVICTUS trial), and currently in the second line in comparison with sunitinib (INTRIGUE trial).

The INVICTUS study was an international, multicenter, double-blind, phase III trial that randomized 2:1 129 metastatic GIST patients to either ripretinib ($n=85$) or placebo ($n=44$) [20••]. GIST patients were refractory or intolerant to at least all three TKIs approved for the treatment of GIST (imatinib, sunitinib, and regorafenib). Cross-over was allowed after unblinding and patients progressing on ripretinib were offered an intrapatient dose escalation (IPDE) to ripretinib 150 mg BID. The trial met the primary end point, 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, $p<0.0001$). Ripretinib ORR $\leq$ 10% was in line with that from prior TKIs, and most of its clinical benefit was derived from disease stabilization, 47% at 12 weeks (Table 1). Finally, ripretinib showed a notable mOS of 15.1 months which was compared favorably to the 6.6 months in the placebo group representing a nominal p value of 0.0004. Due to hierarchal testing procedures of the end points, the OS end point could not be formally tested because the ORR was not statistically significant. To this end, the rapid clinical decline in patients who received placebo highlighted the risk and potential limitation of placebo controls in randomized trials of heavily pretreated GIST, as a third of patients had not been able to cross-over to the ripretinib arm.

The overall safety profile of ripretinib was favorable, with most side effects being low grade and manageable. Accordingly, five (6%) patients on ripretinib required dose reduction and only four patients (5%) had treatment-related adverse events leading to definitive study drug discontinuation. Common treatment-related adverse events occurring in more than 20% of the patients were alopecia (49–63% in women), myalgia (28%), nausea (26%), fatigue (26%), hand-foot skin reaction (HFSR) (21%), and diarrhea (20%). Thus, ripretinib safety profile has typical drug class effects, although it appears to be comparatively more favorable than other multikinase inhibitors given after imatinib failure [14, 15]. Only alopecia and HFSR are noteworthy for a KIT/PDGFRA-specific targeted agent, although other kinases in the MAPK pathway are inhibited as well [18•]. Collectively, the positive results from the INVICTUS trial led in 2020 to the US FDA approval of ripretinib as a new standard of care for the treatment of advanced or metastatic GIST who have received prior treatment with three or more kinase inhibitors, including imatinib. Further steps are being taken to obtain a worldwide regulatory approval.

Additional Insights into Ripretinib Activity

Ripretinib mechanism of action predicts suppression of oncogenic signaling in virtually all KIT/PDGFRA oncoproteins. Tissue- and plasma-based correlative science studies were presented recently at the Connectivity Tissue and Oncology Society (CTOS) 2020 Annual Meeting [21, 22] and further confirmed a broad activity of ripretinib against common KIT primary (exons 9 and 11) mutations. Ripretinib was also superior to placebo regardless of the detection of secondary imatinib resistance mutations in KIT (exons 13, 17, and 18) as detected in tumor biopsies and/or plasma at baseline, suggesting clinical activity against most known KIT resistance mutations. This strongly suggests broader activity than what is known for sunitinib (exon 13/14) and regorafenib (exon 17), which have rather complementary activity against secondary mutants [12•]. The mechanism of ripretinib is yet not fully understood. Preclinical studies show higher IC_{50} values for KIT exon 13 and 14 mutations, which are nonetheless in a low nanomolar range [18•]. It is not clear if this difference is clinically relevant or if resistance occurs independently of KIT secondary resistance mutations. With more potent KIT inhibition, we expect to observe mutations in KIT-dependent signaling pathways to become more prevalent in patients failing ripretinib [23, 24]. However, it is likely that some specific resistance mutations can demonstrate high sensitivity to ripretinib suppression, as the few patients that responded to ripretinib (9.5%) were apparently durable, 18.4 months in the phase I clinical trial regardless of the line of treatment. Nonetheless, although some clinical correlates may be challenging to obtain, further clinical data on ripretinib activity against the multiresistant PDGFRA D842V mutation is warranted, as recent preclinical studies predict little activity [13••].

Further open questions will be answered surely during the next months. For instance, whether double dose of ripretinib (150 mg BID) extends the effect of this drug, as it occurs with imatinib in the first line [25]. An early report from the phase I trial showed additional PFS clinical benefit across all treatment lines upon ripretinib dose escalation to 150 mg BID after progression to the standard dose [26]. Also, the results of the INTRIGUE trial (NCT03673501) comparing head-to-head sunitinib and ripretinib in the second line are highly awaited. Finally, there is still the clinical need to maximize the effects of currently available KIT inhibitors. Based on ORR and mPFS, ripretinib seems to achieve a similar level of activity compared with other TKIs after imatinib failure, which indicates insufficient KIT suppression to induce cell death. However, ripretinib will be the preferential

backbone for future strategies based on therapeutic combinations, based on the broad range of KIT oncoproteins effectively blocked combined with, in historical comparison, a favorable toxicity profile.

Avapritinib (BLU-285) Activity in PDGFRA- and KIT-Mutant GIST

Between 10 and 15% of GIST are driven by primary mutations in PDGFRA, more than a half of whom occur in the activation loop involving the substitution of the aspartic acid for a valine at codon 842 (D842V) [27]. Likewise, a homologous although much less frequent mutation can be found in KIT (D816V), which emerges subclonally as a mechanism of resistance to KIT inhibitors in GIST [10, 11, 12•]. Notably, neither of them is efficiently targeted by any available therapy [28]. Avapritinib was developed as a potent inhibitor of PDGFRA exon 18 and KIT pan-exon 17 inhibitor.

Preclinical Development of Avapritinib

All agents currently approved for the treatment of GIST are type II kinase inhibitors and therefore bind to KIT and PDGFRA in their inactive conformational state. Although all oncogenic mutations shift the kinase conformation toward the active state to a greater or lesser extent, activation loop mutants induce more steadily the active conformation and therefore remain a challenge in drug development [29]. Avapritinib was specifically designed as a potent and highly selective type I inhibitor. Accordingly, preclinical studies demonstrated that avapritinib binds to the active conformation, leading to substantial activity at subnanomolar concentrations for all activation loop mutants, which are encoded by exon 17 in *KIT* and exon 18 in *PDGFRA*. Notably, the biochemical and in vitro activity of avapritinib against PDGFRA D842V and KIT D816V mutations also fell within the subnanomolar range, thus underscoring the potential of avapritinib for the treatment of these mutations [30•].

Avapritinib in PDGFRA D842V-Mutant GIST

Avapritinib was initially investigated in the NAVIGATOR study [31••], a first-in-human phase I clinical trial consisting of a dose escalation cohort that followed a classical 3 + 3 design and a dose expansion part at the RP2D that included the following 3 groups of metastatic GIST patients: non-D842V mutant treated with imatinib and one or more TKIs (group 1); PDGFRA D842V mutant (group 2); and non-D842V mutant treated in the second line after imatinib (group 3). The final report of the NAVIGATOR study included 82 patients in the safety analysis (dose escalation, 46 patients; and group 2, 36 patients) and 56 PDGFRA D842V-mutant GIST in the efficacy analysis (20 from the dose escalation and 36 from group 2).

The MTD was found at 400 mg. However, the RP2D was finally established at 300 mg orally once daily based on safety, PK/PD, clinical activity data, and a higher incidence of grade 3 cognitive adverse events requiring dose reduction during the early expansion at 400 mg. The NAVIGATOR trial demonstrated that avapritinib is the first-ever therapeutic agent effective in GIST patients harboring the primary PDGFRA D842V mutation. All 56 patients achieved clinical benefit irrespective of avapritinib dose. From the 56 patients included, 51 achieved complete or partial response ($n = 7$, 13%, and $n = 44$, 79%, respectively). Furthermore, responses were durable, with a median duration of response (mDOR) of 27.6 months (95% CI: 17.6–not reached [NR]) and a mPFS of 34 months (95% CI: 22.9–NR) (Table 1). This durable clinical benefit was translated in increased overall survival: although not reached yet after 27.5 months of follow-up, OS at 12, 24, and 36 months was 93%, 75%, and 61%, respectively [32].

A specific post hoc analysis of safety and tolerability was recently reported and included 250 GIST patients treated with avapritinib in the safety population [33]. The most common treatment-related adverse events were nausea (59.2%), fatigue (50.0%), periorbital edema (42.0%), anemia (39.2%), diarrhea (36.0%), vomiting (33.2%), and increased lacrimation (30.8%). Although most of them were grades 1 and 2 and manageable, treatment-related adverse events leading to dose reduction and discontinuation occurred, respectively, in 32.4% and 11.2% of the patients. Two toxicities were particularly relevant: cognitive effects and intracranial bleeding (ICB). Cognitive effects were reported in up to 40% of the GIST patients at the dose of 300 mg. Most patients (70%) experiencing a cognitive effect consisted of memory impairment and did not affect activities of daily living (grade 1), whereas the remaining patients had grade 2 (22.4%) or grade 3 (7.5%) events. The only factor associated with a higher risk of cognitive adverse events was age (≥ 65 years, 58.5%). Dose interruption with or without dose reduction resulted in improvement of this toxicity within 1 to 3 weeks. ICB occurred in 4/167 (2.4%) patients who started on 300 mg avapritinib. Although not all ICBs were considered treatment related, such events could be related to KIT or PDGFRA inhibition, as subdural hematomas have been reported in patients treated with imatinib. No patient died due to ICB, although it is advised to permanently discontinue the treatment in patients developing ICB.

Based on this data, the FDA granted avapritinib approval for the treatment of advanced or metastatic PDGFRA mutant (exon 18) GIST. This was followed by an approval by the EMA which was restricted to the D842V substitution mutation only. Given the lack of any alternative treatment, avapritinib should be considered as first-line therapy for these

patients. For patients with non-D842V, PDGFRA exon 18 mutant GIST, imatinib may have profound activity which is the treatment of choice. Resistance to imatinib may also cause cross-resistance to avapritinib [13••].

Avapritinib in KIT-Mutant GIST

A separated analysis of the phase NAVIGATOR study reported outcomes from 103 GIST patients with KIT or non-D842V PDGFRA mutations treated with avapritinib following ≥ 3 prior therapies [34•]. Although avapritinib is mainly active against activation loop mutants, we have observed the enrichment of these mutations in the circulating tumor (ct)DNA after several lines of treatment [35, 36]. Thus, avapritinib demonstrated to be active in this population, with an ORR of 17% and a mDOR of 10.2 months. Additionally, 22 patients had disease stabilization ≥ 4 months. This encouraging data led to the phase III trial VOYAGER (NCT03465722) that randomized metastatic GIST patients to either avapritinib ($n = 240$) or placebo ($n = 236$) in the third or fourth line. Although the results of this trial have not been communicated yet, a press release from Blueprint Medicines on April 28, 2020, reported that the trial did not meet the primary end point, mPFS: avapritinib showed a mPFS of 4.2 months compared to 5.6 months for regorafenib, a difference that was not statistically significant. Thus, although avapritinib is an active agent in heavily pretreated GIST patients, the results from the VOYAGER trial prevent a regulatory approval for that indication.

Additional Tyrosine Kinase Inhibitors for the Treatment of Metastatic GIST

The clinical success of sunitinib and regorafenib boosted the development of a wide range of TKIs in imatinib-resistant disease. All these orally available small-molecule inhibitors were mainly investigated in single-arm, phase II trials [37–46]. Overall, their clinical activity was similar irrespective of the agent used, with an ORR < 10% and PFS < 6 months (Table 2). This is consistent with an activity profile based on the inhibition of a subset of secondary mutations in a context of polyclonal outgrowth of resistant subpopulations. However, it is conceivable that the inhibition of multiple other kinases would aid in the observed antitumoral effects as well as contributed to increase drug-related adverse events. Cabozantinib was the most recent TKI studied in a single-arm, phase II study that recruited 50 advanced or metastatic GIST patients that previously had received only imatinib and sunitinib [47]. A total of 7 patients achieved a partial response (14%), and the mPFS was 5.5 months. The trial met the primary end point, with 24 out of 41 evaluable patients (58.5%) remaining progression-free at week 12. Together, these agents are unquestionably active in imatinib-resistant GIST, although have never been formally investigated in randomized phase III trials. However, their clinical impact after the approvals of regorafenib and, specially, ripretinib is unknown. Thus, the inclusion of these patients in clinical trials would be a priority.

Table 2 TKIs with KIT inhibitory activity tested in advanced/metastatic GIST patients after progression to imatinib

Drug	Clinical trial	Setting	ORR (%)	mPFS (months)	Phase
Cabozantinib	Schöffski, 2020	3rd line	14	5.5	II
Dasatinib	Schuetze, 2018	≥ 2nd line	4	2.9	II
Dovitinib	Kang, 2013	≥ 3rd line	3	3.6	II
	Joensuu, 2017	≥ 3rd line	5.3	4.6	II
Masitinib	Adenis, 2014	2nd line	N.A	3.7	II
Nilotinib	Sawaki, 2011	3rd line	3	3.7	II
	Cauchi, 2012	≥ 3rd line	0	2.0	II
	Reichardt, 2012	3rd line	< 1	3.6	III
Pazopanib	Ganjoo, 2014	≥ 2nd line	0	1.9	II
	Mir, 2016	≥ 2nd line	0	3.4	II
Sorafenib	Park, 2012	≥ 3rd line	13	4.9	II

ORR, overall response rate (complete and partial responses) determined by RECIST criteria; *mPFS*, median progression-free survival; *N.A.*, not available

Several strategies, based on therapeutic combinations, aimed to either overcome the heterogeneity of mechanisms of resistance or to maximize the effects of TKIs. In the first group, the complementary pattern of anti-KIT activity of sunitinib and regorafenib led to a phase I trial investigating the rapid alternation of these two drugs in heavily pretreated GIST patients [35]. This innovative concept aimed to treat patients with effective doses while minimizing the toxicity. Although feasible, tolerable, and somewhat active, PK/PD data predicted higher chances of success for this approach if using drugs that reach more quickly steady-state levels. Another phase I trial simultaneously combined sunitinib with PLX9486, also investigating two agents with complementary activity profile patterns. Results were promising, with 3 out of 18 heavily pretreated GIST patients achieving response and an estimated mPFS of 12 months [48].

The second group of therapeutic combinations encompasses those trials that aimed to maximize the therapeutic response to KIT/PDGFRA inhibition [3]. In broad strokes,

imatinib was either combined with kinase inhibitors targeting KIT downstream pathways (RAS/MAPK or PI3K/mTOR) [49, 50] or mechanisms of therapeutic adaptation (i.e., fibroblast growth factor receptor) [51]. Despite their sound rationale, these trials failed to increase tumor responses and extend the clinical benefit. This is probably due to insufficient suppression of KIT or PDGFRA oncogenic signaling with imatinib in the context of imatinib-resistant disease. However, the recent approval of ripretinib, a TKI with a broad activity against KIT and PDGFRA mutations, emerges as a major opportunity for future therapeutic combinations in GIST patients after imatinib failure. In this sense, recently, preclinical work predicts major cell death induction of ripretinib in combination with MEK inhibitors in GIST cell and mouse models with different KIT secondary mutations [52]. Therefore, this new generation of clinical trials is highly awaited.

Targeting NTRK in KIT/PDGFRA Wild-Type GIST Driven by NTRK Fusions

GIST wild-type (WT) for KIT and PDGFRA mutations encompasses a varied group of GIST with heterogeneous molecular drivers, accounting for 10 to 15% of all GIST [3]. The recent clinical development of targeted inhibitors against NTRK fusions triggered a quest for such rare cases. In the pooled analysis of three phase I/II larotrectinib trials, sarcoma was the most common tumor type (47%) among the 17 included. Of the 71 patients with sarcoma, 4 had GIST, all of them wild-type for KIT and PDGFRA [53]. The benefit of NTRK inhibitors in this subset of patients is comparable to that from any molecularly targeted agent against any given tyrosine kinase [54, 55]. Therefore, NTRK fusions should be actively determined in WT GIST patients [56]. However, special attention should be given to the diagnoses, as a recent series has emphasized the rarity of GIST diagnosis among mesenchymal tumors of the gastrointestinal tract harboring NTRK rearrangements [57].

Broadly speaking, WT GIST can be subdivided between those driven by deficiency in the succinate dehydrogenase (SDH) and a heterogeneous subgroup with a wide range of events leading to RAS/MAPK pathway overactivation [58]. More active investigation in this field is urgently needed, as it suffers from a chronic paucity in therapeutic development. SDH-deficient GISTs continue being treated with TKIs with antiangiogenic activity, given the relevant role of HIF1a in the biology of these tumors [59, 60]. Interestingly, it has been recently found that the accumulation of succinate is the root of a central epigenetic dysregulation that converges in the functional activation of KIT and FGF, leading to a highly expressed MAPK signature [61]. On the other hand, GISTs driven initially by MAPK pathway activation (NF1, RAS, BRAF) are resistant to TKIs with KIT inhibitory therapy and, essentially, to any given multikinase inhibitor [62]. Moreover, we have shown that these molecular events can emerge during tumor evolution in KIT/PDGFRA-driven GIST [13••, 23, 24]. Interestingly, there is a biological trend to activate conjointly—through simultaneous but independent oncogenic events—RAS/MAPK and PI3K/mTOR KIT downstream pathways, resulting in highly aggressive neoplasms that bypass KIT or PDGFRA as the critical driver event. It is conceivable that these mechanisms can be enriched after successive lines of treatment [35], although this is not known yet. Likewise, MEK inhibitors can potentially be active in this subset of patients, but this is something that is yet to be determined in the clinical setting.

Conclusions

Two decades ago, GIST emerged as one of the first solid neoplasms successfully treated with a molecularly targeted agent. Throughout, GIST has confirmed its prominent role as a paradigmatic tumor model for understanding the mechanisms of drug sensitivity and drug resistance, and for the rational development of therapies inhibiting tyrosine kinases. These efforts have led to the regulatory approval of 5 different TKIs that have consistently exploited GIST reliance on KIT and PDGFRA oncogenic signaling. While both the sarcoma research community and GIST patients can feel proud of these achievements, future preclinical and clinical investigations must be focused on maximizing the clinical benefit of current treatments in early lines and finding innovative approaches against tumor heterogeneity. Additionally, all this research needs to put a special emphasis on long-term tolerability, given the enormous impact that these treatments have already obtained in GIST patients survival.

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