REVIEW ARTICLE

TKI Treatment Sequencing in Advanced Gastrointestinal Stromal Tumors

Homma M. Khosroyani[1] · Lillian R. Klug[1] · Michael C. Heinrich[1]

Abstract

Prior to the early 2000s, patients with advanced gastrointestinal stromal tumors (GIST) had very poor prognoses owing to a lack of effective therapies. The development of tyrosine kinase inhibitors at the turn of the century significantly improved the overall survival for patients with GIST. The resounding success of imatinib in the first clinical trial of a tyrosine kinase inhibitor to treat GIST led to its approval for first-line therapy for advanced GIST; this study was open to all comers and not restricted to any GIST subtype(s). The trials that led to the approvals of second-, third-, and fourth-line therapy for advanced GIST were also open to all patients with advanced/metastatic GIST. Only in retrospect do we realize the role that the molecular subtypes played in the results observed in these studies. In this review, we discuss the studies that led to the US Food and Drug Administration approval of imatinib (first line), sunitinib (second line), regorafenib (third line), and ripretinib (fourth line) for advanced KIT-mutant GIST. In addition, we review how information about GIST molecular subtypes has been used to accelerate the approval of other targeted therapies for non-KIT mutant GIST, leading to the approval of five additional drugs indicated for the treatment of specific GIST molecular subtypes. We also discuss how our understanding of the molecular subtypes will play a role in the next generation of therapeutic approaches for treating advanced GIST.

1 Introduction

Gastrointestinal stromal tumors (GIST), the most common soft-tissue sarcoma, are driven by a variety of oncogenic drivers. The understanding of GIST molecular drivers has resulted in the clinical testing and eventual approval of multiple targeted therapies, specifically tyrosine kinase inhibitors (TKIs), which have revolutionized the treatment of the majority of patients with GIST [1]. Since the implementation of effective targeted therapies, the overall survival (OS) of patients with advanced GIST has improved to the current estimated range of 6–8 years, compared with historical results of approximately 1.5 years when treated with chemotherapy or radiation (neither of which is effective in GIST), or < 15 months with surgery alone [1–5]. This improvement in survival is mostly confined to the population of patients with GIST with driver mutations in the receptor tyrosine kinase (RTK) KIT, which can be effectively targeted with KIT TKIs. The KIT TKIs imatinib (first line), sunitinib (second line), regorafenib (third line), and ripretinib (fourth line) were approved by health authorities, such as the US Food and Drug Administration, based on studies in which eligibility required only a diagnosis of advanced GIST and no requirements of any particular molecular driver [4, 6–8]. For the purposes of classification, we have labeled these registrational studies as examples of a *mutation-agnostic/histology-specific study design*. This approach was successful for the clinical development of KIT TKIs because the vast majority (70%) of patients with GIST have KIT mutations (Fig. 1A) that can be effectively targeted by these agents [9]. However, we believe that this approach is not viable for the development of future therapies. It has become apparent that mutation-agnostic clinical studies using KIT TKIs to treat patients of other molecular subtypes outside of KIT-mutant GIST do not provide the same degree of clinical benefit, therefore leaving these patients with advanced GIST with few to no options for effective therapy [10–15].

Recently, rational drug design and biological approaches focused on these less common GIST molecular subtypes (remaining 30% of cases) have resulted in successful clinical

✉ Michael C. Heinrich
heinrich@ohsu.edu

[1] Portland VA Health Care System and Knight Cancer Institute, Oregon Health & Science University, R&D-19, 3710 SW US Veterans Hospital Road, Portland, OR 97239, USA

Extended author information available on the last page of the article

Key Points

The discovery and use of tyrosine kinase inhibitors significantly improved the overall survival of patients with advanced/metastatic gastrointestinal stromal tumors (GIST), as surgery alone and traditional chemotherapy/radiation therapies provide little clinical benefit.

The studies that led to the approval of first-, second-, third-, and fourth-line therapies included all patients with advanced/metastatic GIST, regardless of mutational driver status, and only provided clinical benefit to a subset of patients.

Our understanding of the molecular mechanisms of various GIST subtypes has informed precision medicine-focused studies, and led to the development and approval of more successful targeted therapies for those patients with rarer GIST subtypes.

We propose that future drug development should focus on mutation-specific subsets of GIST, rather than simply selecting patients based only on the number of specific types of prior therapy.

studies testing novel therapeutics. These drugs include: avapritinib (a novel type I platelet-derived growth factor receptor alpha [PDGFRA]/KIT TKI), larotrectinib and entrectinib (potent NTRK TKIs for targeting NTRK fusions in GIST) [16–19], and the combination of a BRAF inhibitor (dabrafenib) and a MEK inhibitor (trametinib) for BRAF V600E-mutant GIST [20–22]. The recent approvals of these five treatments, each for a specific molecular subtype, were enabled by clinical studies with fundamentally different approaches for selecting eligible patients for participation than those used for the early KIT TKI trials. The inclusion criteria of avapritinib, larotrectinib or entrectinib, and the combination of dabrafenib and trametinib, phase I–II studies required the presence of a PDGFRA D842V mutation [23, 24], a NTRK family fusion, or a BRAF V600E mutation [16–19, 22], respectively. In this review, we refer to these studies as having a *precision medicine study design* (i.e., mutation-specific patient eligibility). This type of study design can be histology specific (e.g., GIST avapritinib approval) or histology agnostic (e.g., BRAF V600E-mutant solid tumors and approval of dabrafenib and trametinib combination [22]). We posit that precision medicine approaches, facilitated by diagnostic molecular testing and pre-clinical research, will be the most successful strategy for developing new GIST treatment strategies, especially for those less common, non-KIT mutant GIST subtypes.

2 GIST Drivers and Molecular Subtypes

Over the past 20 years, analysis of tens of thousands of cases of primary GIST have led to the identification of molecular drivers in almost all cases. Mutations in homologous RTKs, KIT and PDGFRA, account for 70 and 15% of cases, respectively (Fig. 1A) [1, 11, 25–28]. As is well known, most (RTKs), including mutant forms of KIT or PDGFRA, signal through the canonical JAK/STAT, PI3K/AKT/mTORC, and RAS/RAF/MEK/ERK pathways (Fig. 1B) [29–34]. Along this line, a minority of GIST cases have other RTKs in addition to KIT/PDGFRA as molecular drivers, including more recent descriptions of activating translocations of FGFR1, FGFR2, NTRK1, NTRK3, and ALK (Fig. 1A, B) [28, 35–38]. In addition, there are cases of GIST that arise because of activating mutations of PIK3CA, BRAF, or RAS family members (Fig. 1A, B) [39–42]. More recently, BRAF translocations have been reported as a molecular driver in GIST [43]. In addition, homozygous/hemizygous loss of neurofibromatosis (type 1) [NF1] is a well-established cause of some cases of GIST, likely due to dysregulation of the RAS/RAF/MEK/ERK pathway. Neurofibromatosis (type 1) loss giving rise to GIST can occur sporadically owing to a somatic mutation or in the setting of NF1 with a heterozygous germline NF1 mutation [44–48]. In total, cases of RTK translocation-mutant GIST or those with mutations of downstream signaling pathways account for approximately 5% of all cases of GIST (Fig. 1A) [9].

In addition to mutations that activate RTK downstream signaling pathways, a biologically and clinically distinct subtype of GIST is driven by succinate dehydrogenase (SDH) deficiency [49–51]. Gastrointestinal stromal tumors of this subtype result from inactivating hemizygous or compound heterozygous mutations of one the four SDH subunits (SDHA, SDHB, SDHC, or SDHD) or epimutation of the SDHC promoter (Fig. 1C) [49, 52–56]. In total, 9% of GIST are SDH deficient, comprising the third largest molecular subtype after KIT- and PDGFRA-mutant GIST. In contrast to GIST driven by activating mutations in RTKs or within the classical RTK-signaling pathways, these cases arise as a consequence of SDH loss of function. Succinate dehydrogenase loss of function results in increased intracellular succinate that inhibits a certain class of enzymes leading to activation of the VHL pathway (pseudohypoxia), as well as inhibition of ten-eleven translocation and KDM family enzymes with resultant genome-wide epigenetic reprogramming (Fig. 1C) [51, 53, 57, 58].
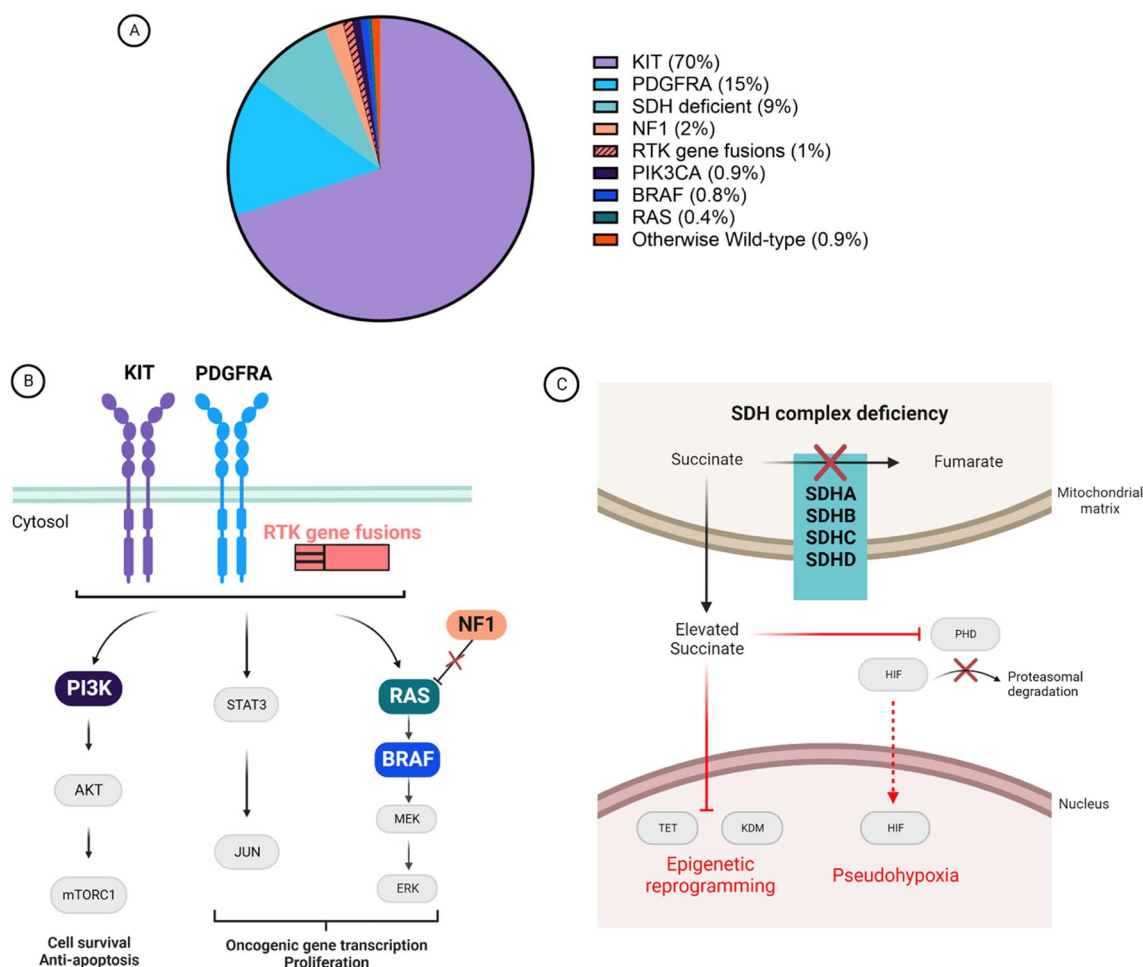
Fig. 1 Molecular drivers of gastrointestinal stromal tumors (GIST) and their corresponding oncogenic signaling mechanisms. **A** Proportion of GIST cases based on oncogenic driver subtype. **B** The majority of genetic aberrations that drive GIST development result in the activation of downstream signaling pathways. The downstream pathways (JAK/STAT, PI3K/AKT/mTORC1, and RAS/RAF/MEK/ERK) activated are similar for GIST driven by KIT, platelet-derived growth factor receptor alpha (PDGFRA), or receptor tyrosine kinase (RTK) gene fusions (e.g., FGFR1, FGFR2, NTRK1, NTRK3, and ALK). Gastrointestinal stromal tumors driven by neurofibromatosis (type 1) (NF1) loss, RAS, BRAF, or PI3K activation also utilize similar pathways for oncogenesis. The colors for these genetic aberrations correspond to the pie chart in panel **A**. **C** A subset of GIST is driven by succinate dehydrogenase (SDH) complex deficiency. This deficiency results from an inactivating mutation of any one of the four SDH subunit genes (SDHA, SDHB, SDHC, or SDHD) or epimutation of the SDHC promoter leading to gene silencing. The SDH complex converts succinate to fumarate, but in SDH-deficient GIST the inactive complex results in the accumulation of succinate. This accumulated succinate leads to the inhibition of prolyl hydroxylase (PHD), which is involved in the proteasomal degradation of hypoxia-inducible factor (HIF). Elevated succinate levels also have an effect on epigenetic reprogramming, by inhibiting ten-eleven translocation methylcytosine dioxygenase (TET) and lysine-specific histone demethylase (KDM) family proteins. Image created using BioRender.com

3 Traditional TKI Treatment Paradigm for Advanced GIST

Slightly more than two decades ago, the first clinical trial of a targeted therapy in GIST began [8, 59]. There are now nine targeted therapies approved for GIST, and while we now know that each drug is most effective for specific subtypes of GIST, four of these agents are still approved for the treatment of all forms of GIST because their registrational studies included all patients with advanced GIST (Table 1). The current treatment sequencing for KIT-mutant GIST remains in the order of original drug development and US Food and Drug Administration (FDA) approval: imatinib (first line), sunitinib (second line), regorafenib (third line), and ripretinib (fourth line). The trials that led to the approvals of imatinib, sunitinib, regorafenib, and ripretinib were open to all patients with advanced/metastatic GIST and only later was it fully appreciated the role molecular subtypes played in the results reported from those studies [4, 7, 8, 10–13, 60–65]. Figure 2 highlights the results from these studies and showcases that the traditional treatment paradigm was mostly successful for patients with KIT-mutant and certain

non-exon 18 PDGFRA-mutant GIST and minimally effective for patients with other subtypes. In the following sections, we focus on the preclinical and clinical studies that led to the approval of imatinib, sunitinib, regorafenib, and ripretinib.

3.1 Imatinib

Imatinib, a novel agent originally designed to inhibit the aberrant enzymatic function of the oncogenic driver in chronic myelogenous leukemia, BCR::ABL1, was found to be similarly effective in inhibiting the enzymatic function of KIT, the main driver in the majority of GIST cases (Fig. 1) [66–68]. Despite being designed for targeted cancer therapy, the phase I, II, and III studies of imatinib that led to its approval for advanced GIST included patients of all GIST subtypes, the only criteria being "metastatic or advanced CD117+ GIST" (Table 1) [8, 59, 69, 70]. The response rate to imatinib in the initial studies was 50–80% [8, 11, 14, 70–73]. At that time, molecular analysis of GIST was in its infancy, thus the vast majority of patients were enrolled without any molecular testing results, but it was subsequently determined that almost all of the responders in this trial had driver mutations that were sensitive to imatinib (e.g., KIT exons 9, 11, or 13; PDGFRA exon 12) [Fig. 2] [13, 14, 70, 73]. Those with the third most common subtype, SDH-deficient GIST, had a < 5% objective response rate (ORR) to imatinib [51, 74]. With the appreciation of the molecular underpinnings of the success of imatinib as a targeted therapy in GIST, the search for additional targetable drivers accelerated. For example, analysis of a patient with a partial response to imatinib whose tumor lacked a KIT mutation led to investigations that identified an imatinib-sensitive PDGFRA mutation [11, 14]. Likewise, investigation of patients with "wild-type" KIT (meaning no KIT mutation) GIST who had rapid progression during imatinib therapy led to the identification of the imatinib-resistant primary PDGFRA D842V mutation [25, 75]. It is known that TKIs that target wild-type KIT also inhibit wild-type PDGFRA and the converse is true as well [66, 76–78]. Therefore, at the time, the treatment of PDGFRA mutant-GIST followed the same clinical development paradigm as the treatment of KIT-mutant GIST with the exception of patients with imatinib-resistant PDGFRA D842V, which we discuss in a later section.

After several years, the first reports about patients with GIST with delayed resistance to imatinib began to appear because of acquired secondary intra-allelic KIT mutations that disrupted drug binding [79–83]. We now appreciate that intra-allelic secondary kinase mutations are the most common mechanism of acquired resistance to imatinib in GIST [1, 9, 84–87]. This mechanism of resistance demonstrated the continued dependence of GIST on the enzymatic activity of the initial driver, and led to the development of additional targeted TKIs to overcome specific secondary KIT mutations in imatinib-resistant patients.

3.2 Sunitinib

The "next-generation" GIST TKIs arose from the rapid development of various small-molecule kinase inhibitors in the early 2000s. In most cases, KIT was not the primary target of the drug development program, but drugs designed to inhibit vascular endothelial growth factors and/or PDGFRs commonly had similar, or even greater, potency against KIT. Sunitinib, a type II multi-kinase inhibitor, entered phase I–II studies and then proceeded to be tested in a phase III clinical study in patients with imatinib-refractory GIST in 2003 [7, 88]. Again, these trials were conducted with a mutation-agnostic approach. "Imatinib-refractory" patients that enrolled in the registrational sunitinib phase study included both those with primary resistance (progression in < 6 months, e.g., PDGFRA D842V) and those with secondary resistance, meaning they initially responded to imatinib, but then their tumors progressed after months or even years of clinical response. No molecular testing was required for study eligibility (Table 1). Pre-clinically, sunitinib was shown to inhibit some imatinib-resistant KIT secondary mutations, including the most common imatinib-resistance mutation, V654A, and other secondary KIT mutations in exons 13 and 14, which encode the ATP binding pocket (ABP) [Fig. 3] [10, 12]. However, as sunitinib is a type II TKI like imatinib, it does not inhibit activation loop mutations that confer primary resistance (PDGFRA D842V and cases lacking a KIT/PDGFRA driver mutation [historically classified as "wild-type" cases]) nor those with secondary KIT activation loop (exons 17–18) mutations of the kinase domain [12, 89–94]. Notably, these studies were predictive of the results of the sunitinib clinical studies, specifically the greatly reduced response rate compared with the initial imatinib trials (6.8 vs ~ 51.4%, respectively), largely owing to the presence of heterogeneous tumor clones, some with sunitinib-sensitive mutations and others with resistant mutations [10, 12, 86, 87, 95]. It was also thought that a minority of SDH-deficient GIST cases may respond to sunitinib or regorafenib (discussed below), likely due to vascular endothelial growth factor receptor inhibitory activity against these agents [51, 62, 96, 97]. However, at that time, after progression on imatinib, patients had no other options, therefore the criteria for approval were low. Sunitinib was approved for second-line treatment of patients with GIST after progression on imatinib, although it is now clear that it mainly benefits only a select subset patients with the KIT mutation (those with secondary ABP or primary KIT exon 9 mutations) [98, 99]. Potentially, the results of these trials could have had a higher response rate if the eligibility

Table 1 List of US FDA-approved therapies for the treatment of advanced/metastatic GIST with summary details on FDA-approved prescribing indication, study design leading to drug approval for this indication, and reported major clinical outcomes of interest

Agent	Year of approval	Approval	Studies leading to approval	Inclusion criteria	ORR	PFS	OS	References
Imatinib (Gleevec)	2002	Patients with KIT (CD117) positive unresectable and/or metastatic malignant GIST	Phase I/II	Adults with a histologically confirmed, unresectable or metastatic GIST that expressed CD117 (a marker of KIT-receptor tyrosine kinase)				Demetri [8]
			Phase III	Patients with metastatic or unresectable GIST	400 mg: 51%, 800 mg: 54%	400 mg: 18.9 months; 800 mg: 23.2 months	400 mg: 49.0 months, 800 mg: 48.7 months	Verweij [69]
Sunitinib (Sutent)	2006	GIST after disease progression on or intolerance to imatinib mesylate	Phase I/II	Patients with imatinib-resistant/intolerant GIST	7%	7.8 months	19.0 months	Demetri [95]
			Phase II (assess morning vs evening dosing)	Patients with imatinib-resistant/intolerant GIST		34 weeks (7.8 months)	107 weeks (24.6 months)	George [88]
			Phase III (NCT00075218)	Patients with unresectable GIST and progression following imatinib	6.80%	5.6 months		Demetri [7]
Regorafenib (Stivarga)	2012	Locally advanced, unresectable or metastatic GIST who have been previously treated with imatinib mesylate and sunitinib malate	Phase II (NCT01068769)	Patients with advanced GIST after failure of at least imatinib and sunitinib	18%	13.2 months	25.0 months	George [6] Ben-Ami [101]
			Phase III (NCT01271712)	Patients with metastatic and/or unresectable GIST progressing after failure of at least imatinib and sunitinib	4.50%	4.8 months	NR	Demetri [61]
Ripretinib (Qinlock)	2020	Indicated for the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more kinase inhibitors, including imatinib	Phase I (NCT02571036)	Patients with advanced GIST, intolerant to or experienced progression on 1st line of systemic therapy, and other advanced malignancies	11.3% (> fourth line: 7.2%, second line: 19.4%)	5.5 months (> fourth line), 10.7 months (second line)	NR	Janku [102]
			Phase III (NCT03353753: INVICTUS)	Patients with previously treated, advanced GIST	9.40%	6.3 months	15.1 months	Blay [4]

Table 1 (continued)

Agent	Year of approval	Approval	Studies leading to approval	Inclusion criteria	ORR	PFS	OS	References
			Phase III (NCT03673501: INTRIGUE)	Patients with advanced GIST after front-line imatinib failure vs sunitinib	NR	NR	NR	Heinrich [23] Jones [24]
Avapritinib (Ayvakit)	2020	Inhibitor indicated for the treatment of adults with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including PDGFRA D842V mutations	Phase I (NCT02508532)	Dose escalation: patients with unresectable GIST and progression following imatinib and > 1 other TKI or PDGFRA D842V mutation Dose expansion: patients with unresectable GIST	Patients with PDGFRA D842V: 89%, patients with other PDGFRA ex 18 mutations: 84%	29.5 months	NR	
Larotrectinib (Vitrakvi)	2018	Indicated for the treatment of adult and pediatric patients with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, are metastatic or where surgical resection is likely to result in severe morbidity, and have no satisfactory alternative treatments or that have progressed following treatment	Phase I/II (NCT02122913) Phase I/II (NCT02637687) Phase I/II (NCT02576431)	Pediatric and adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion	75% (patients with GIST [n = 3]: 100%)	NR specifically for GIST	NR specifically for GIST	Drilon [17]
Entrectinib (Rozlytrek)	2019	Indicated for the treatment of adult and pediatric patients 12 years of age and older with solid tumors that have a NTRK gene fusion without a known acquired resistance mutation, whose disease is metastatic or where surgical resection is likely to result in severe morbidity, and who have progressed following treatment or have no satisfactory alternative therapy	Phase I (NCT02097810) Phase II (NCT02568267)	Adult patients with unresectable or metastatic solid tumors with an NTRK fusion	NR specifically for GIST [n = 1]	NR specifically for GIST	NR specifically for GIST	Doebele [126]

Table 1 (continued)

Agent	Year of approval	Approval	Studies leading to approval	Inclusion criteria	ORR	PFS	OS	References
Dabrafenib (Tafinlar) given with Trametinib (Mekinist)	2022	Trametinib is indicated, in combination with dabrafenib, for the treatment of adult and pediatric patients 6 years of age and older with unresectable or metastatic solid tumors with a BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options This indication is approved under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s)	Phase II (NCT02034110) NCT MATCH (NCT02465060)	Adult patients with unresectable or metasttic solid tumors with a BRAF V600E mutation, excluding patients with melanoma, thyroid cancer, or colorectal cancer	0% GIST [n = 1]	NR specifically for GIST	NR specifically for GIST	See prescribing information [20]

FDA Food and Drug Administration, *GIST* gastrointestinal stromal tumors, *NR* not reported, *NTRK* neurotrophic tyrosine receptor kinase, *ORR* objective response rate, *OS* median overall survival, *PDGFRA* platelet-derived growth factor receptor alpha, *PFS* progression-free survival, *REF* primary study publication(s)
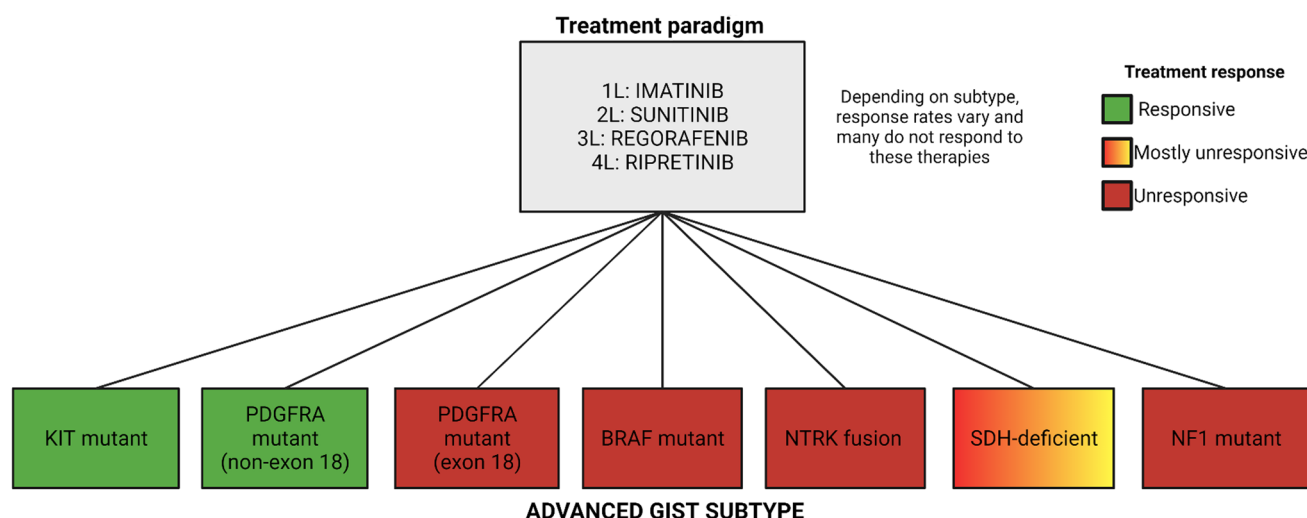
Fig. 2 Traditional treatment paradigm for advanced gastrointestinal stromal tumors. The gray box shows the list of US Food and Drug Administration-approved drugs in the traditional treatment paradigm, and 1L, 2L, 3L, and 4L correspond to first-, second-, third-, and fourth-line therapy, respectively. The advanced gastrointestinal stromal tumor subtypes are listed in the colored boxes, and those colors correspond to patient treatment response to 1L, 2L, 3L, and 4L therapy. It was later discovered after clinical trials that based on the advanced gastrointestinal stromal tumor subtype, response rates vary amongst patients depending on the mutational status. *NF1* neurofibromatosis (type 1), *NTRK* neurotrophic tyrosine receptor kinase, *PDGFRA* platelet-derived growth factor receptor alpha, *SDH* succinate dehydrogenase. Image created using BioRender.com

criteria were limited to those with ABP mutations; however, there would still remain the issue of how to treat patients with heterogeneous tumor clones after progression on imatinib.

3.3 Regorafenib

Regorafenib, a more promiscuous type II TKI, entered clinical testing for all patients with GIST who had not responded to both imatinib and sunitinib (first- and second-line therapy) [100]. Pre-clinical testing indicated improved potency against activation loop mutations in exons 17 or 18 [100]. Unfortunately, potency against these mutations came at the expense of potency against secondary resistance mutations in KIT exons 13 and 14 (Fig. 3) [86]. Promising results were seen in a phase II study, with a partial response rate of 18% and a median progression-free survival (PFS) of 13 months (Table 1) [6, 61, 101]. This study led to a randomized, double-blind, placebo-controlled phase III study (NCT01271712) of regorafenib in patients with progression or intolerance to prior imatinib and sunitinib. This study was open to all mutational subgroups and in fact did not require any testing in order to be eligible for enrollment (mutation agnostic). In this study, the ORR was slightly lower than that seen in the phase III, second-line sunitinib study (4.5%) [61]. Despite this low response rate, regorafenib offered a statistically significant benefit in PFS compared with placebo and was FDA approved as a third-line GIST therapy in 2012 [6, 61, 101].

3.4 Ripretinib

A program to rationally design a TKI that could overcome secondary resistance mutations specifically led to the development of ripretinib (originally known as DCC-2618), a TKI that binds KIT in the "switch pocket" rather than the classical ABP, thereby preventing conformational change of the kinase to the active form [76]. Pre-clinical studies showed improved potency against many of the KIT secondary mutations when compared with approved KIT TKIs (Fig. 3) [76]. In the first in-human phase I trial (NCT02571036), promising results were seen in terms of ORR and PFS from patients treated with different numbers of prior lines of therapy (Table 1). Notably, the PFS for patients treated in the second, third, or fourth line or later was 10.7, 8.3, and 5.5 months, respectively [102]. Based on these results, a randomized, placebo-controlled, double-blind phase III trial (INVICTUS, NCT03353753) was conducted to study the efficacy of ripretinib in patients who had progressed on prior treatment with imatinib, sunitinib, and regorafenib or those who have documented intolerance to any of these treatments [102, 103]. The eligibility criteria specified prior lines of therapy but did not require molecular testing or exclude any molecular subtypes (similar to a mutation-agnostic study design). In this registrational study, treatment with ripretinib significantly improved PFS compared with placebo (6 months vs 1 month, hazard ratio = 0.15, $p < 0.0001$). These results led to FDA approval of ripretinib for treatment of patients
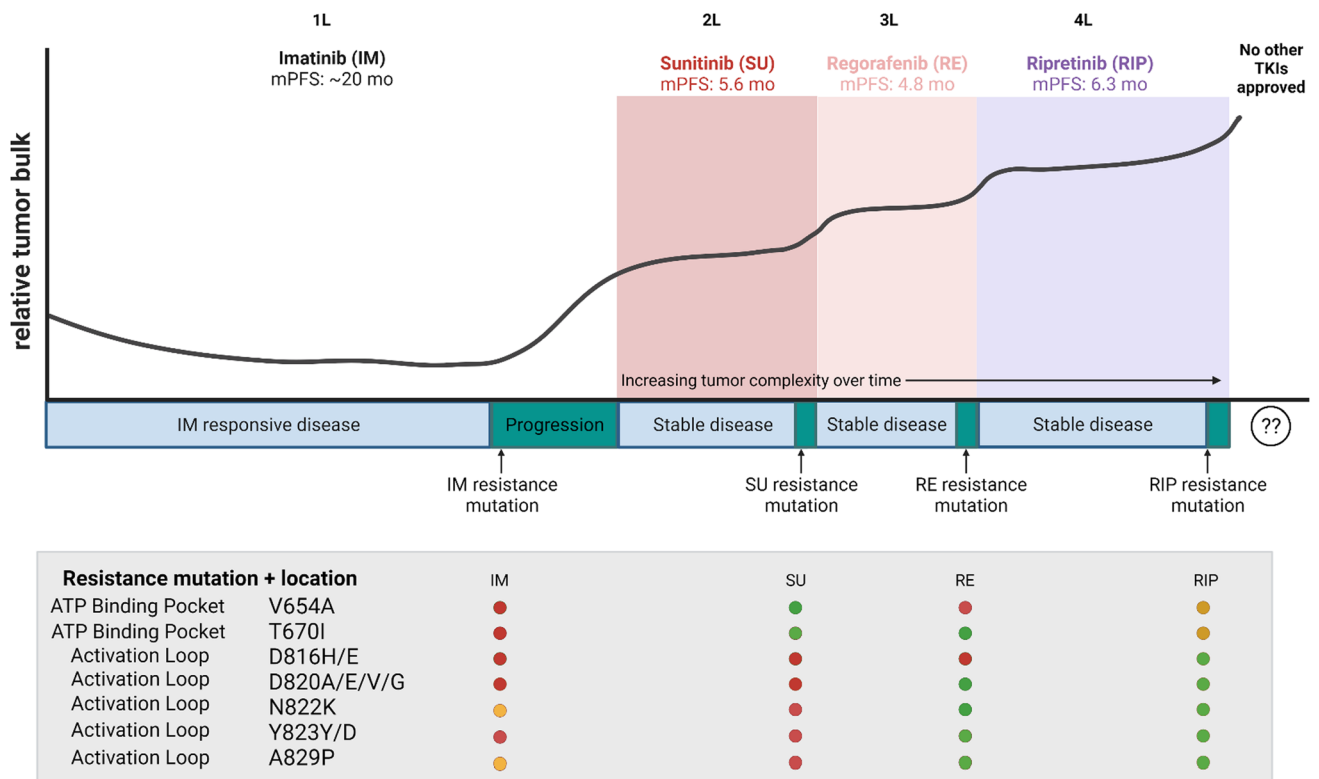
Fig. 3 Representation of tyrosine kinase inhibitor (TKI) therapy and the emergence of secondary resistance in patient with hypothetical KIT-exon 11-mutant gastrointestinal stromal tumors. Initially KIT-exon 11-mutant gastrointestinal stromal tumor cells typically respond to first-line (1L) imatinib therapy, and correspond to a decrease in relative tumor bulk and lead to sustained stable disease. However, over time, residual tumor cells acquire imatinib-resistant mutations and lead to tumor progression. The table shows the various areas in which resistance mutations occur, either in the ATP binding pocket or activation loop of KIT. As tumor cells no longer respond to imatinib therapy, relative tumor bulk increases and a new therapy is required.

Sunitinib, used as second-line (2L) therapy, can target only some of the most common imatinib-resistant mutations. As a patient progresses through various therapies, tumor cell heterogeneity increases over time as additional mutations arise to ongoing therapy. Third- and fourth-line (3L and 4L, respectively) therapies can target previously acquired mutations, but not all of these are sensitive to a given drug. This is indicated in the graph as an overall increase in tumor bulk with intermittent stable disease. After ripretinib (4L), there are no other US Food and Drug Administration-approved therapies to target ripretinib-resistant tumor cells. *mo* months, *mPFS* median progression-free survival. Image created using BioRender.com

with GIST who had not responded to at least imatinib, sunitinib, and regorafenib [4, 102]. Even though this study incorporated a cross-over from placebo to ripretinib at the time of progression, OS was improved for patients initially assigned to ripretinib treatment (15.1 months vs 6.6 months, hazard ratio = 0.36, no statistical testing because of the hierarchical study design). In addition, the ORR for ripretinib was numerically superior to that seen in the second-line sunitinib, or third/fourth-line regorafenib studies. These results suggest an improved ability of ripretinib to control complex heterogeneous TKI-resistant disease compared with sunitinib or regorafenib [104]. However, given that the PFS with ripretinib was only 6 months, the results also indicate that either ripretinib cannot durably control all secondary KIT resistance mutations and/or KIT-independent resistance mutations that arise in heavily pre-treated KIT-mutant GIST [105, 106]. In addition to the issue of KIT secondary resistance mutations, the study

also enrolled patients lacking KIT or PDGFRA mutations (approximately 8%) or with tumors that had not been genotyped (approximately 15%), likely diluting some of the benefit from this therapy [4, 104].

These clinical results suggested that ripretinib might be able to control disease if used earlier in the treatment sequence, rather than as fourth-line or later therapy. A phase III clinical trial (INTRIGUE, NCT03673501) was conducted to compare the activity of ripretinib versus sunitinib for the treatment of patients with failure of prior imatinib therapy (progression or documented intolerance but no other TKI therapy). In a departure from previous studies, in order to be eligible for this study, a molecular pathology report was required, although no specific patients with subtypes of GIST were excluded. However, patients were stratified based on mutational status as well as a history of imatinib intolerance. The primary endpoint of the study was PFS, per the statistical design plan, this endpoint was analyzed first in the

KIT exon 11 intention-to-treat patient population and then in the all-patient intention-to-treat population. Therefore, the overall study design was mutation agnostic, but the initial endpoint analyzed was for a *mutation-specific* patient population [103]. Despite the expectation that ripretinib would yield superior PFS results compared with sunitinib, the study failed to meet the endpoint of superior PFS with ripretinib compared with sunitinib. Specifically, the median PFS in the KIT exon 11 intention-to-treat population for ripretinib versus sunitinib was 8.3 and 7.0 months, respectively (hazard ratio 0.88, $p = 0.36$) [107, 108].

3.5 Disease Heterogeneity and Tumor Burden Increases with Successive Lines of Therapy in KIT-Mutant GIST

Figure 3 summarizes the overall tumor burden in a hypothetical KIT-exon 11-mutant patient with metastatic disease from initial imatinib therapy through the end of ripretinib treatment. With each line of therapy, there is a progressive increase in tumor burden, suggesting that it will not be possible to indefinitely add on sequential salvage therapies (e.g., fifth-, sixth-,…-, and nth-line) unless new therapies cause significant tumor regression. Eventually the increasing tumor burden will not be compatible with survival to the next line of therapy. This was suggested in the INVICTUS study, where the OS of patients initially randomized to placebo was inferior to patients initially assigned to ripretinib, despite the presence of a cross-over in the study design [4]. This is likely due to these placebo-assigned patients experiencing such clinical deterioration in which they were either too ill to cross-over or the tumor burden became so large that ripretinib could no longer provide sufficient clinical benefit and improve survival. Although the registrational studies for sunitinib, regorafenib, and ripretinib all included a blinded placebo arm, the results from INVICTUS suggest that further placebo-controlled studies in advanced GIST might violate the concept of equipoise [4, 7, 61, 109]. Notably, the PFS of placebo patients was very similar in all of these studies, averaging 4–6 weeks, suggesting that perhaps this duration could be used to conduct future single-arm studies of new agents in the fifth line or later.

As predicted by in vitro profiling, each of the approved KIT inhibitors has different liabilities against secondary resistance mutations, likely explaining the limited overall duration of PFS for agents used after imatinib (Fig. 3) [4, 7, 61, 62, 110, 111]. For example, sunitinib has minimal activity against secondary KIT activation loop mutations (e.g., D816H), but potently inhibits the common secondary ABP mutations such as V654A and T670I (Fig. 3) [10, 86]. Regorafenib has better activity than sunitinib against some but not all activation loop mutations, with inferior activity against V654A. Of the approved agents, ripretinib has the best activity across the entire spectrum of activation loop mutations, but may lack sufficient clinical activity against the ABP mutations [105, 106]. However, the mechanisms leading to ripretinib resistance are just beginning to be elucidated and may include both KIT-dependent (secondary mutations) and KIT-independent mechanisms that activate downstream signaling pathways (e.g., RAS mutations or NF1 loss [Fig. 1]) [85, 112]. Despite the data suggesting differential activity of sunitinib, regorafenib, and ripretinib against different secondary mutations, currently, treatment is prescribed based on the line of therapy, rather than any individualized biomarkers such as sequencing of tumor biopsy and/or circulating tumor DNA (ctDNA) samples. As we continue to understand resistance mechanisms and the molecular drivers of GIST, and with the development of new technologies and approaches, we posit that the use of precision medicine study designs may be more useful in creating new targeted therapies, especially for specific GIST subtypes.

4 Precision Medicine Approaches Accelerated FDA Approvals for Non-KIT Mutant GIST Therapies

While the mutation-agnostic approach to clinical drug development in GIST has undeniably benefited the majority of patients with GIST, increasing the median OS for patients with KIT-mutant/imatinib-sensitive GIST to the range of 6–8 years, there remained unmet clinical needs [1]. Outside of KIT-mutant GIST and certain patients with PDGFRA mutations outside of exon 18, the traditional mutation-agnostic approach and treatment paradigm provides limited benefit to other patients with GIST, leaving these patients subject to physical and financial toxicity (Fig. 2). Most notably was the challenge of primary TKI resistance associated with PDGFRA D842V-mutant GIST and the many historically designated patients with KIT/PDGFRA "wild-type" GIST. The traditional treatment paradigm highlighted above was unsuitable for addressing these rare, but not insignificant populations and therefore called for a different approach to clinical study designs. A shift to a mutation-focused treatment approach was facilitated by an increased understanding of the molecular subtypes of GIST and improved availability of molecular testing. This precision medicine study approach has demonstrated great success for patients with rare GIST subtypes that were not addressed in the original KIT TKI mutation-agnostic trials.

4.1 Avapritinib for PDGFRA-Exon 18-Mutant GIST

The most common PDGFRA driver mutation seen in GIST, exon 18 D842V (in the kinase activation loop), displays primary resistance to imatinib and other type II TKIs (e.g.,

sunitinib) [10, 25, 26, 73, 113]. It is now appreciated that certain PDGFRA activation loop mutations, such as PDG-FRA D842V, lock the kinase in the active confirmation, which interferes with type II TKI binding [114]. Therefore, rational drug design was used to specifically develop a type I TKI to target activation loop mutation PDGFRA D842V, and the homologous mutation KIT D816V (seen in mastocytosis). Preclinical in vitro studies demonstrated that avapritinib (formally BLU-285) had potent biochemical activity against these KIT and PDGFRA activation loop mutations, which was further explored in clinical trials [115].

In 2015, the phase I NAVIGATOR (NCT02508532) study, a two-part, open-label, non-randomized trial, was initiated [23, 24]. NAVIGATOR represents a prototypical example of a precision medicine approach, which describes a mutation-specific, histology-specific study design. Patients with PDGFRA-D842V mutant GIST were a pre-specified subgroup within the overall safety population (20/46 in the dose-escalation phase and 36/204 for the dose-expansion phase). The other patients enrolled were those without PDGFRA D842V mutations treated with imatinib and one or more other TKIs (Table 1). At the time of data cut-off, the ORR for patients with PDGFRA D842V was 88%, with seven complete responses and 44 partial responses [24]. In contrast, the ORR for all other patients was 22% [23]. This highlights the importance of molecular testing and tailoring treatments based on mutational status, as avapritinib was initially developed to target PDGFRA activation loop mutations, and those patients without these mutations did not respond as well [116]. The success of avapritinib specifically in PDGFRA-D842V patients fast tracked its FDA approval in February 2020 for the treatment of all exon 18 PDGFRA-mutant GIST (Fig. 4) [117].

Despite a much lower response rate in non-PDGFRA D842V patients, clinical trials (specifically VOYAGER, NCT03465722) continued with avapritinib, primarily to compare its efficacy to regorafenib for third-line treatment in patients with GIST previously treated with imatinib and one or two other TKIs. This phase III study failed to show a significant improvement in median PFS (4.2 and 5.6 months for avapritinib and regorafenib, respectively) [116]. Based on this disappointing result, avapritinib is no longer being developed for the treatment of KIT-mutant GIST, although it is now FDA approved for the treatment of advanced systemic mastocytosis, another neoplasm driven by activating KIT mutations (most typically KIT D816V) [118]. These results highlight the contrast in success rates between mutation-specific (PDGFRA D842V) and mutation-agnostic (GIST treated with one to two other TKIs) studies for the same drug. In the case of avapritinib, this rationally designed drug did not fare well in a mutation-agnostic study with previously treated GIST, as mutational load increases in complexity as disease progresses and avapritinib could not overcome tumor heterogeneity any better than regorafenib.

4.2 Larotrectinib and Entrectinib for NTRK-Fused GIST

Gastrointestinal stromal tumors with unidentified drivers have been a continued area of ongoing research. Originally referred to as "wild type" because sequencing of the tumors failed to detect any of the known driver mutations, the proportion of these GIST cases has consistently shrunk as drivers have been identified [119–121]. The most recently identified and exceptionally rare drivers in GIST are RTK gene fusions (1% of GIST cases, Fig. 1A), including those involving NTRK family members [122, 123]. NTRK fusions as oncogenes had previously been discovered in other cancers, and as a result, NRTK TKIs were developed and clinically tested in these select populations [17, 19, 124]. The first NTRK-fusion genes were identified in GIST over 5 years ago, just when NTRK TKIs were entering clinical study. Shi et al. identified a fusion between *NTRK3* and *ETV6* in a patient with GIST who then was able to enter the phase I trial of larotrectinib (LOXO-101, NCT02122913) and responded well despite rapid progressive disease when previously treated with the KIT/PDGFRA TKIs imatinib (3 months), sunitinib (2 months), and sorafenib (2 months) [17, 19]. Since then, a handful of patients with GIST with NTRK fusions have been identified and successfully treated with larotrectinib. In a pooled analysis of three phase I/II trials, three patients with GIST were treated and all achieved complete responses (Table 1) [17, 19]. Because these studies defined eligibility using a molecular rather than a histological diagnosis, FDA approval was granted for this mutation-selected/histology-agnostic population, both for larotrectinib and subsequently for another NTRK TKI, entrectinib (Fig. 4) [16]. Because of the rarity of this type of GIST, four patients in total were included in the larotrectinib ($n = 3$, response rate 100%) and entrectinib ($n = 1$, response not reported) registrational studies (Table 1) [17–19, 124–126]. Therefore, it remains important that additional cases of response/non-response to these agents in patients with GIST be reported, thereby strengthening the rationale for physicians to identify and treat patients with NTRK-translocated GIST with these drugs.

4.3 Dabrafenib and Trametinib for BRAF-V600E Mutant GIST

BRAF V600E-mutant GIST accounts for approximately 0.8% of all cases of GIST (Fig. 1A). Because of the rarity, there are few reports describing this subtype, but one case report demonstrates the successful use of dabrafenib monotherapy in BRAF V600E-mutant GIST [127]. In June 2022, the FDA granted accelerated approval to the
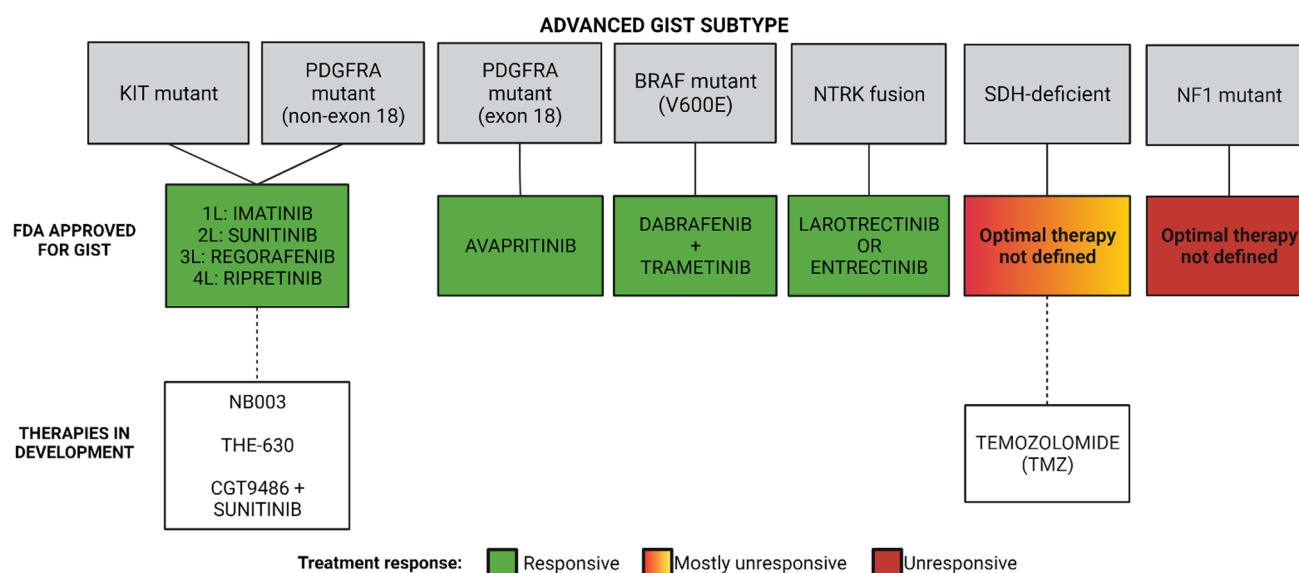
Fig. 4 Using precision oncology approaches to treat advanced gastrointestinal stromal tumors (GIST) significantly improves patient outcomes and treatment options by improving the likelihood of clinical response and minimizing the treatment of patients who are unlikely to respond to a given therapy. Colors correspond to patient outcomes; white boxes indicate therapies that are in development. *FDA* Food and Drug Administration, *NF1* neurofibromatosis (type 1), *NTRK* neurotrophic tyrosine receptor kinase, *PDGFRA* platelet-derived growth factor receptor alpha, *SDH* succinate dehydrogenase. Image created using BioRender.com

combination of dabrafenib and trametinib for the treatment of adult and pediatric BRAF V600E-mutant solid tumors after progression on prior treatment and for whom no satisfactory treatment options were available [21]. Previously, this combination had been approved for the treatment of BRAF-mutant melanoma (adjuvant and advanced disease), metastatic non-small cell lung cancer, and anaplastic thyroid cancer based on mutation-specific/histology-agnostic clinical studies, MFR1117019 (NCT02034110) and NCI-MATCH (NCT02465060) [20]. Between these two studies, only a single patient with GIST was treated, and this patient did not have an objective response endpoint reported. Despite this, the combination of dabrafenib and trametinib was still approved for BRAF V600E-mutant solid tumors, which would then include BRAF V600E-mutant GIST (Fig. 4). As noted above for the case of larotrectinib and entrectinib, post-marketing reporting of additional cases of treated patients with GIST will be helpful to understand the efficacy of this combination.

5 Future Directions in GIST Drug Development

5.1 Next Generation of KIT (and PDGFRA) Inhibitors

Currently, a number of new KIT inhibitors are entering phase I studies, including NB003 (formerly AZD3229, NCT04936178) and THE-630 (NCT05160168) [105, 106, 128]. Both of these agents have potency against a broader range of KIT TKI-resistant mutations, including both ABP and activation loop mutations, offering the possibility of controlling a broader range of TKI-resistant residual tumor cells and providing clinical activity even in late-line therapy. An alternative approach is being tested in the case of CGT-9486 (previously PLX-9486), where combination therapy using CGT-9486 (active against activation loop mutations) plus sunitinib (active against ABP mutations) is being tested in sunitinib-naïve patient to see if the combination is superior to standard single-agent sunitinib (NCT02401815) [129, 130].

Although registrational studies of these new agents could continue the historical practice of enrolling all patients with advanced GIST, we suggest that limiting enrollment to patients with KIT-mutant GIST as well a subset of PDG-FRA-mutant GIST would result in superior ORRs and improved PFS compared with testing these agents against all patients with advanced GIST selected only based on the number and type of previous lines of therapy (Fig. 4). This type of design would be crucial to any attempt at regulatory approval based on a single-arm study in last-line therapy, where a sufficiently high ORR and duration of response would be required [131]. Eliminating GIST cases lacking KIT mutations from the denominator would improve the odds of success of such a study. Following approval as an "nth-line therapy", future studies could test these new therapies against approved agents in a phase III study for earlier lines of therapy, but again the use of eligibility

requirements that include a molecular definition for patient eligibility would be predicted to improve the odds of success. A limitation to this approach would be determining how patients with advanced heterogeneous disease (e.g., two or more resistance mutations) should be enrolled in these types of clinical studies. In order to change the current drug sequencing for KIT-mutant GIST, future studies could use ctDNA to select or exclude patients for studies that compare two approved agents [104, 132]. For example, despite the failure of ripretinib to be proven superior to sunitinib in a second-line phase III study [108], it remains possible that biomarker selection of patients might have yielded a different outcome. The ctDNA selection of patients could either enrich for patients expected to have a superior response to ripretinib versus sunitinib or exclude patients who would be predicted to have a better response to sunitinib versus ripretinib [133]. Currently, there are no published data that would allow an estimation of the likelihood of success of such a study design, but hopefully such data will be available in the future. One practical issue for the use of ctDNA for study eligibility is the observation that patients with GIST on average shed less tumor DNA than other types of solid tumors (e.g., lung cancer or melanoma), with 20–25% of patients with advanced GIST having undetectable levels of ctDNA [134–136]. In addition, the use of ctDNA as an eligibility criterion would require the development, validation, and regulatory approval of a companion diagnostic [137].

5.2 Targeting SDH-Deficient GIST

As mentioned previously, SDH-deficient GIST cases have a dismal ORR to imatinib (< 5%) and, at most, 20–30% of cases have a partial response to sunitinib or regorafenib [49, 51, 96, 101]. During the conduct of the mutation-agnostic registrational studies for these agents, these studies were open to patients who met eligibility criteria based on the number of lines of prior therapy and the drugs used for prior therapy. However, current treatment strategies are now focused on targeting unique characteristics in SDH-deficient GIST. Notably, compared with KIT and PDGFRA-mutant GIST, SDH-deficient GIST show global hyper-methylation [53, 138]. Succinate dehydrogenase deficiency in GIST leads to succinate accumulation and inhibition of histone lysine demethylases (KDM) and ten-eleven translocation enzymes, which leads to DNA and histone hyper-methylation (Fig. 1C) [139, 140]. A study by Ricci et al. reported that the epigenetic inactivation (i.e., methylation) of O^6-methylguanine DNA methyl-transferase is higher in SDH-deficient GIST than compared with SDH-proficient GIST [141]. It has been reported that the inactivation of O^6-methylguanine DNA methyl-transferase leads to an increased effectiveness of alkylating agents in several other cancers, such as gliomas, colorectal cancer, and large B-cell lymphoma [141, 142].

These results led to the hypothesis that DNA methylation could affect O^6-methylguanine DNA methyl-transferase in SDH-deficient GIST, therefore inducing a favorable response to alkylating agents. This hypothesis was experimentally supported using patient-derived tumor models that were very sensitive to temozolomide (TMZ) treatment [143]. Notably, TMZ is an alkylating agent that is currently approved by the FDA for the treatment of glioblastoma multiforme and refractory anaplastic astrocytomas [144]. A 2014 study showed that in 15 patients with SDHB-mutant paraganglioma/pheochromocytoma, 50% had a partial response to TMZ [145]. These studies suggest that SDH deficiency could be a biomarker for TMZ sensitivity [74]. Another case study conducted by De Silva et al. shows the efficacy of using TMZ in one patient with SDH-deficient GIST, indicated by a durable partial response, ongoing through 18 cycles [146]. Based on these preliminary data, a two-arm phase II study of TMZ in patients with SDH-deficient GIST (NCT03556384) began in 2018 to determine the overall response rate of 6 months of TMZ therapy (Fig. 4). In an initial report, 2/5 patients had a partial response [143]. The primary results from this study are expected to be updated in the fall of 2022.

5.3 Other Potential Targetable Mutations

Other GIST subtypes that could be potentially treated with approved or emerging agents include ALK-translocated and FGFR-translocated GIST. To date, there have been very limited reports of where patients with GIST were treated with specific inhibitors of these molecular drivers, but presumably these GIST subtypes would respond to kinase inhibitors specifically targeting the underlying molecular driver [127]. In addition, NF1 mutant GIST remains without a known FDA-approved optimal therapy, and future studies should focus on new treatment strategies for these patients.

6 Conclusions

Although the historical pathway to GIST treatment approval has used a mutation-agnostic design, a precision medicine approach informed by the molecular underpinnings of GIST subtypes has shown incredible success for rare GIST subtypes. Advances in technology have facilitated the utility of this approach, both in GIST-specific studies (e.g., avapritinib) as well as in histology-agnostic (but mutation-specific) studies (e.g., larotrectinib and entrectinib). Using up-front molecular testing and precision oncology treatment of GIST results in superior clinical outcomes and minimizes the number of patients treated with biologically inactive therapies (Fig. 4). The use of a precision medicine approach

necessitates the widespread use of comprehensive molecular profiling of all cases of advanced GIST requiring medical therapy. However, in certain countries including the USA, such molecular profiling occurs in less than 50% of patients, at least in certain countries including the USA [147, 148]. The push for molecular testing and profiling will definitely be needed for the less common forms of GIST for which there is no effective FDA-approved therapy (e.g., NF1-deficient or SDH-deficient GIST). We believe that future registration studies of KIT/PDGFRA inhibitors should also utilize a precision oncology approach and enroll only those patients with KIT/PDGFRA mutations that would be predicted to respond to these novel agents (Fig. 4).

A limitation to these precision medicine-driven clinical studies includes determining the criteria for those patients previously treated with other TKIs and who have highly heterogeneous disease. These patients differ from TKI-naïve patients, as their disease may not be effectively targeted by a single drug, as previously shown in Fig. 3. With the emergence of new technologies and models, we should focus on how to combat heterogeneous disease, and the optimal selection of patients for testing new targeted therapies. In recent years, mutation-agnostic studies that included all patients with advanced disease were successful for patients with a specific subtype of GIST. While precision medicine approaches narrow the inclusion criteria for a study, subjecting patients to new therapies in which they may not receive a clinical benefit unnecessarily exposes them to potential toxicities. To address this issue, correlative studies that compare tumor biopsy with ctDNA mutation profiling should be integrated into future studies, not only to identify those patients most likely to benefit from a new therapy, but also to identify mechanisms of acquired resistance to novel agents. Continuing to understand the mechanisms of acquired resistance and the molecular underpinnings of each subtype of GIST will aid in the development of the next generation of targeted therapies.

Declarations

Conflict of interest Homma M. Khosroyani and Lillian R. Klug have no conflicts of interest that are directly relevant to the content of this article. Michael C. Heinrich has the following conflicts of interest: honoraria: Novartis; consulting or advisory role: Novartis, Blueprint Medicines, Deciphera, Theseus Pharmaceuticals; and patents, royalties, other intellectual property: patent on treatment of GIST licensed to Novartis (Inst).

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Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

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