Gastrointestinal Stromal Tumor: Challenges and Opportunities for a New Decade

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ABSTRACT

Gastrointestinal stromal tumor (GIST) provides a paradigm to evaluate new molecularly targeted therapies and to identify structural and functional mechanisms for drug response and resistance. Drug development in GIST has successfully exploited the high reliance on KIT/PDGFRA oncogenic signaling as a therapeutic vulnerability. The recent arrival of avapritinib and ripretinib to the GIST arena has aimed to further improve on precision kinase inhibition and address tumor heterogeneity in imatinib-resistant GIST. The two main clinical challenges for the forthcoming years entail tumor eradication in patients with early-stage GIST, and maximization of tumor response in late-stage disease. To succeed, we will need to better understand the mechanisms behind adaptation to KIT inhibition and apoptosis evasion, tumor evolution after successive lines of treatment, and to explore clinically novel creative therapeutic strategies, with the overarching goal to tackle the intrinsic oncogenic complexity while minimizing adverse events.

Introduction

Only a subset of patients with cancer currently benefits from personalized treatment approaches. Gastrointestinal stromal tumor (GIST), the most common malignant mesenchymal neoplasm, was one of the first cancer types leading to the approval of a molecularly targeted therapy—imatinib—nearly two decades ago. Since then, GIST has proven to be a paradigmatic model to study oncogene addiction, and to identify structural and functional mechanisms for drug resistance and response. Remarkably, the GIST field has been shaken once more: in 2020, ripretinib and avapritinib come into play by continuing to exploit GIST oncogenic dependencies to KIT and PDGFRA receptor tyrosine kinases (RTK).

Leveraging critical insights in GIST biology, this review will address how the current landscape of treatment in GIST is reshaping the field, and how it will impact on GIST preclinical and clinical research in the short-to-medium term.

Biological Principles of GIST Therapeutics

KIT/PDGFRA activation is the central tumorigenic event in GIST

GIST was first recognized as a distinctive entity in 1998 after the discovery that gain-of-function mutations in KIT or PDGFRA RTKs govern GIST growth and survival from tumor initiation to clinically symptomatic disease (1, 2). The high cell-context dependency on KIT signaling can be traced back to the putative cells of origin of GIST, the interstitial cells of Cajal (ICC), where KIT physiologic activity is indispensable for normal ICC function (3, 4).

Oncogenic KIT mutations are found in approximately 80% of GISTs. Gain-of-function mutations, deletions, or indels in the intracellular juxtamembrane domain—encoded by *KIT* exon 11—are the most common mutations in KIT (67%) and disrupt its normal autoinhibitory state of KIT resulting in constitutive activation. The remaining KIT-mutant GISTs have activating mutations in the extracellular ligand–binding domain, encoded by exon 9 (10%), and, to a lesser extent (<2%), in the kinase domains (exons 13 and 17; ref. 5). Approximately, 15% of GIST are driven by PDGFRA activation, showing oncogenic mutations in homologous regions to KIT receptor (exons 12, 14, and 18; ref. 6). KIT and PDGFRA mutations are mutually exclusive because they are initiating clonal events. So-called wild-type (WT) GIST account for 5% to 10% of GIST and do not harbor KIT or PDGFRA mutations (**Table 1**).

GIST exhibits a homogeneous repertoire of transcription factors that stems from GIST continual dependence upon a well-preserved KIT/PDGFRA-driven program throughout all stages of disease (7). A wealth of evidence supports RAS/MAPK and PI3K/mTOR as the two main pathways transducing KIT/PDGFRA oncogenic program, thus playing an instrumental role in GIST proliferation and survival. Although other pathways might have some oncogenic function (i.e., STAT3, AXL, Src), their biological role in a specific GIST-cell context remains poorly understood. KIT-activated RAS/MAPK signaling is essential for the oncogenic function of the ETS-family transcription factor ETV1, a lineage-specific master regulator in GIST critical for maintenance and development of ICCs and for KIT-mediated oncogenesis (3). Furthermore, genomic events leading to MAPK pathway hyperactivation, such as RAS and BRAF mutations, and NF1 loss-of-function mutations, are oncogenic drivers in WT GIST (**Table 1**; refs. 5, 8). Similarly, KIT-dependent PI3K/mTOR signaling is indispensable for GIST initiation and early tumor development, also exerting critical regulation of proliferation and apoptosis evasion (9, 10). Interestingly, WT GIST deficient in the succinate dehydrogenase (SDH) harbor a central epigenetic dysregulation that converges in the functional activation of KIT and FGF, leading to a highly expressed MAPK signature (11). Together, this evidence emphasizes the restrictive context of oncogene addiction to KIT and KIT-downstream signaling.

KIT mutations alone are insufficient to induce malignant behavior, and additional genetic events are necessary to transform micro-GISTs (<1 cm tumors present in one third of the population) into tumors with increasingly malignant potential. Indeed, clinical and biological

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Table 1. Oncogenic initiating mutations in localized GIST and relative frequency based on literature review (5, 66–68).

Genetic alteration	Relative frequency (%)
KIT mutation	75%–80%
Exon 9	10%
Exon 11	67%
Exon 13	1%
Exon 17	<1%
PDGFRA mutation	10%–15%
Exon 12	1%
Exon 14	<1%
Exon 18 D842V	8%
Exon 18 non-D842V	3%
KIT/PDGFRA wild-type	10%
SDH-deficient	8%
RAS mutant	<1%
BRAF mutant	1%
NF1 mutant	<1%
NTRK-translocated	<1%
Unknown	<1%

Abbreviation: SDH, succinate dehydrogenase.

progression of GIST represents a continuum that spans from micro-GISTs to clinically aggressive and metastasizing GIST and requires a well-established multistep cytogenetic progression involving typical chromosomic regions targeting genes such as *MAX, DEPDC5, CDKN2A*, and *DMD* (**Fig. 1**; refs. 12–15).

Clinical and biological consequences of therapeutic inhibition of KIT oncogenic activity

Drug development in GIST has been oriented to exploit the high reliance on KIT/PDGFRA oncogenic signaling as a therapeutic vulnerability. The regulatory approval of imatinib as first-line treatment in patients with advanced/metastatic GIST triggered a new era of targeted therapies. Approximately, two thirds of the patients had objective radiographic response, the median progression-free survival (mPFS) was 20 months, and median overall survival (mOS) 57 months (**Fig. 2**; ref. 16). OS in the preimatinib era was 10–20 months, which underscores the striking clinical impact of KIT inhibition in GIST. Between 7% and 9% of the patients shows exquisite sensitivity to KIT/PDGFRA inhibition and remain progression-free after 10 years on continuous imatinib (17). However, the disease is not deemed cured, as complete remissions are rare and imatinib interruption leads to tumor relapse in virtually all patients (18). Several hints of evidence point out that GIST cells not undergoing imatinib-induced apoptosis enter in quiescence through various mechanisms involving cell-cycle regulation, autophagy, and other adaptation mechanisms (19–21). This might explain as well that the OS benefit observed with 3 years of adjuvant imatinib (22) is most likely due to a delay in the relapse, rather than an actual tumor eradication.

Importantly, KIT and PDGFRA genotype predict imatinib activity, which results in a very valuable clinical information. Genetic alterations involving *KIT* exon 11 predict for deeper and prolonged responses. Patients with GIST harboring mutations in *KIT* exon 9 also benefit from imatinib. However, compared with *KIT* exon 11 mutants, exon 9 mutant is less sensitive to standard doses of imatinib (400 mg once daily), and appears to benefit from dose increase of imatinib to 400 mg twice daily. Conversely, primary mutations in *PDGFRA* exon 18 D842V are intrinsically insensitive to imatinib (6, 23, 24).

The selective pressure exerted by imatinib most commonly trigger the positive selection and expansion of clones with acquired secondary mutations in KIT, which constitutes the main mechanism of failure to imatinib in approximately 90% of patients with GIST (25). Secondary mutations cluster in two regions of the KIT kinase domain: the ATP-binding pocket and the activation loop. Resistance in imatinib-sensitive PDGFRA-driven tumors is not well known, although it is conceivable that homologous domains to KIT receptor will be affected. It is also yet to be understood whether resistance mutations are preexistent, emerge through selective pressure, or both mechanisms are involved. In addition, imatinib failure may not result from biological progression, but from a reduction in drug exposure, particularly after prolonged treatments and/or major gastrectomy (26, 27). However, the high interpatient and intrapatient variability has limited the widespread use of plasma imatinib concentrations to drive treatment decisions (26).

At the onset of imatinib failure, two treatment strategies are equally valid, although never compared formally: imatinib dose doubling (400 mg twice daily), and sunitinib. A PFS advantage without OS benefit is observed among *KIT* exon 9 mutant patients with high-dose imatinib (23). However, the question remains unanswered: what is the best choice? An interesting evolutionary phenomenon involves a shift from heterozygosity to homozygosity in the KIT-mutant locus through loss-of-heterozygosity and/or duplication of the KIT mutant allele in chromosome 4 (28, 29). This increase in "KIT-mutant dosage" might lead to a pattern of resistance characterized by the regrowth of preexistent lesions, and an increase in imatinib dose could be potentially beneficious. However, the emergence of new metastases, and specially the nodule-within-a-mass pattern, most likely herald the presence of resistant subclones against which imatinib cannot bind, and therefore starting sunitinib would seem a better choice. Nonetheless, this is still an area of clinical and biological uncertainty and both options are considered reasonable (30, 31).

Strategies aiming to target KIT after imatinib failure remain useful in GIST. Tyrosine kinase inhibitors (TKI) sunitinib and regorafenib are the standard second and third line of treatment, respectively (**Fig. 2**; refs. 32, 33). Several other TKIs with KIT inhibitory activity have been clinically investigated in imatinib-resistant GIST (34). However, the overall clinical benefit of these agents is modest irrespective of the line of treatment, achieving 4–6 months mPFS and <10% responses. We recently demonstrated that KIT-directed TKIs have drug-specific activity against only a subset of the KIT secondary mutational spectrum, which in the context of intratumoral heterogeneity constitutes the molecular basis for treatment failure in imatinib-resistant GIST (35). In addition, and unlike imatinib, sunitinib, and regorafenib appear to only partially inhibit KIT kinase activity of imatinib-resistant subclones within their respective inhibitory profiles (36). This observed effect is probably due to increased KIT kinase activity resulting from the secondary mutations, and likely leads to little apoptotic induction and lower response rate. Together, novel treatment strategies in GIST will need to overcome tumor heterogeneity and insufficient kinase inhibition.

New TKIs in GIST

Ripretinib

Ripretinib (DCC-2618) is an orally available type II switch-control TKI designed to inhibit the full spectrum of KIT and PDGFRA mutations, and therefore emerges as an innovative therapeutic approach against the heterogeneity of mechanisms of resistance. The encouraging signs of ripretinib activity in patients with advanced GIST

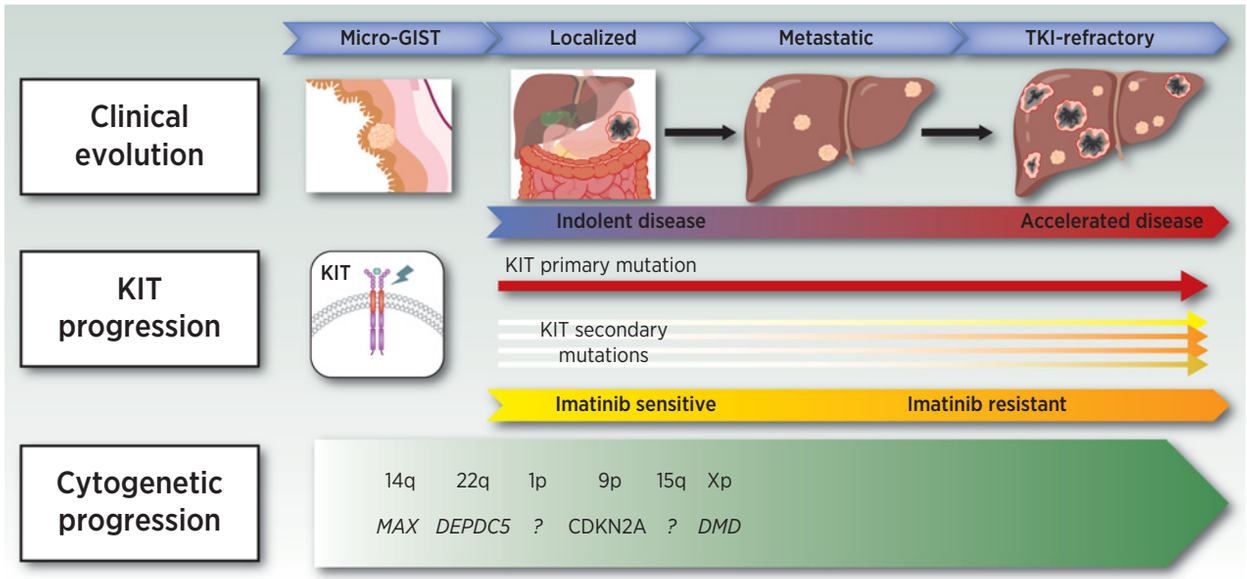

Figure 1.
Clinical and molecular progression of GIST from the putative cell of origin, ICCs, to metastatic, TKI-refractory GIST.

observed in an early phase I trial (37) were recently confirmed in the phase III INVICTUS trial, which led to the FDA approval of ripretinib in the fourth line and beyond, a population previously without any approved treatment options (38). The trial met its primary endpoint as ripretinib significantly improved mPFS compared with placebo (6.3 months vs. 1 month, respectively; **Fig. 2**). Although the response rate of nearly 10% was more in line with previous TKIs in the postimatinib setting, the remarkable benefit in mOS over placebo underscores the rapid decline of patients with heavily pretreated GIST while emphasizes how critical remains therapeutic KIT/PDGFRA inhibition even at this advanced stage of disease. Ripretinib safety profile was favorable and side effects were mostly low-grade and manageable. Alopecia was observed in half of the patients, noticeably higher than with other TKIs.

Ripretinib binds reversibly to both the switch pocket and the activation loop, locking KIT and PDGFRA in the inactive state and achieving broad inhibition of multiple primary and secondary mutations associated with drug resistance (39). However, as patients keep progressing, clinical trial correlative studies are needed to confirm this proposed pan-KIT inhibitory activity. Ripretinib mechanism of action might have ATP binding–pocket resistance mutations as a potential, or at least partial liability. Likewise, IC_{50} values for multiresistant KIT D816V and its homologous PDGFRA D842V are 2-to-3-fold higher compared with other secondary mutants. Finally, the response rate within the same range from prior TKIs (<10%) predicts low apoptosis induction and suggests that additional resistance mechanisms may be relevant.

Avapritinib

The path of development of avapritinib (BLU-285) was the opposite of ripretinib, but also successful. Type II kinase inhibitors (imatinib, sunitinib, and regorafenib) bind to KIT/PDGFRA in their inactive conformational state. However, mutations in the activation loop induce more steadily the active conformation of the kinase and remain a challenge. Avapritinib was designed as a potent and highly selective type I inhibitor able to bind to the active conformation and inhibit all activation loop mutants (40). The phase I NAVIGATOR proved that avapritinib is the first-ever therapeutic agent effective in patients with GIST harboring the primary *PDGFRA* D842V mutation. The activity of avapritinib in this formerly multiresistant subset of patients (∼6% of all GISTs) is remarkable: from the 56 patients included in the phase I trial, 49 achieved complete or partial response (8.9% and 78.6%, respectively). Responses were lengthy, with a median duration of response (mDOR) of 27.6 months and a 12-month PFS of 81% (**Fig. 2**; ref. 41). Avapritinib also showed antitumor activity as ≥fourth-line therapy in 103 KIT-mutant patients with GIST: overall response rate was 17%, mDOR 10.2 months, and mPFS 3.7 months (42). This high mDOR clearly reflects a subset of KIT-mutant patients likely harboring a molecular profile with unique sensitivity to avapritinib, and therefore achieving the greatest benefit. However, a recent press release noted that phase III VOYAGER trial (NCT03465722), which compared avapritinib with regorafenib in the third line, did not meet the PFS endpoint.

On the basis of the data above, avapritinib has become the first drug approved in PDGFRA D842V-mutant metastatic GIST. Overall toxicity is manageable, but the main challenge is the cognitive side effects. Although activity is still present at lower doses, a tweak in the drug design impeding drug delivery across the blood–brain barrier would be ideal. An exciting area of interest will involve the characterization of resistance to avapritinib in D842V-mutant patients. On the basis of the high selectivity of avapritinib against the activation loop and the progression model of KIT-mutant GIST, the most plausible hypothesis is the polyclonal emergence of secondary mutations in other regions of the kinase (i.e., ATP binding–pocket, gatekeeper mutations).

Novel Insights in GIST Biology Oriented Toward Therapeutic Development

The two main clinical challenges for the forthcoming years entail tumor eradication in patients with early-stage GIST, and maximize

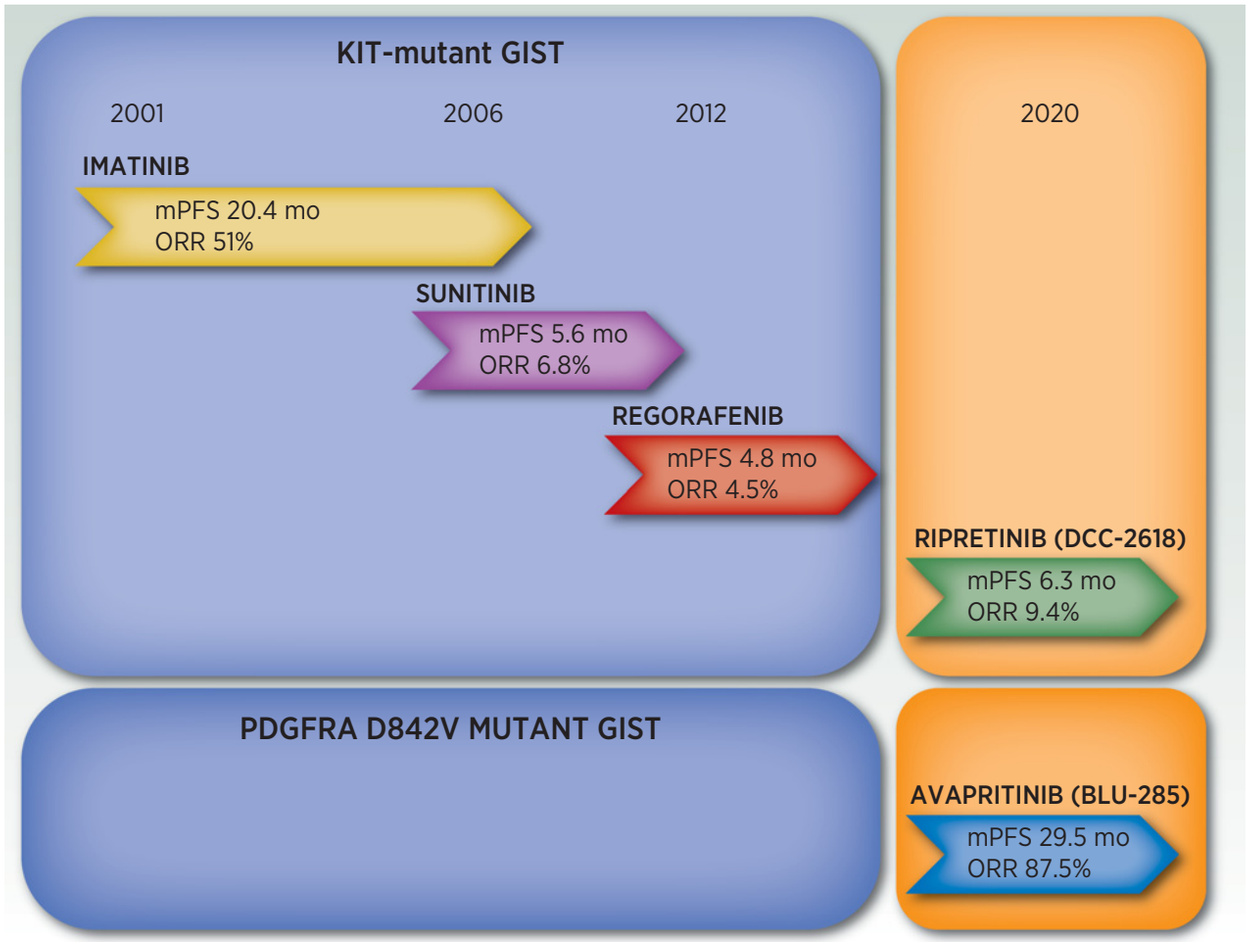

Figure 2.
Clinical activity of the current standard-of-care—imatinib, sunitinib, and regorafenib—for the treatment of patient with advanced or metastatic GIST; and efficacy data from the novel agents ripretinib and avapritinib in their respective FDA-approved indications. mPFS, median progression-free survival; mo, months; ORR, overall response rate.

tumor response in late-stage disease. Conceptually speaking, there are three broad and interwoven molecular mechanisms that merit our next-future preclinical and clinical research (**Fig. 3**):

1. Tumor adaptation to KIT/PDGFRA inhibition leads to apoptosis evasion and GIST survival most probably through two interlaced events: a stress response first induces a quiescence state involving cell-cycle regulators, autophagy, and likely other unknown mechanisms (19–21). This antiapoptotic response is sustained over time by FGFR- and c-MET–mediated MAPK pathway reactivation (43, 44). It is plausible that GIST follows the same principles of chronic myeloid leukemia, where growth factor receptors are inhibited by a MEK-dependent negative feedback that is released upon BCR-ABL TKI inhibition (45).
2. The heterogeneity of KIT secondary mutations leads to mixed responses and modest clinical benefit (25, 35). However, most of this knowledge was generated with tumor samples at the onset of imatinib failure, and it is yet unknown how this heterogeneity evolves. Recent circulating tumor DNA (ctDNA) studies showed that KIT secondary mutations remain the principal mediator of resistance in patients with heavily pretreated GIST without a substantial increase in KIT heterogeneity (46–49). These results will need to be confirmed in tumor tissue.
3. Alternatively, tumor evolution may challenge KIT dependence after several lines of treatment. Ripretinib activity in heavily pretreated GIST confirmed maintained KIT dependence in this population. However, the fine print underscores that a subset of patients randomized to placebo had rapid disease progression leading to death. Notably, this is the first trial in advanced GIST with OS benefit in the presence of crossover (38). Together, there is a clinical transition from a KIT-dependent state to an accelerated phase with attenuation in KIT/PDGFRA oncogenic dependence (**Fig. 1**). The identification of the mediators of this GIST "accelerated phase" will be critical for further therapeutic development. In addition, KIT-driver supplantation has been observed in infrequent cases with conjoined hyperactivation of KIT-downstream RAS/MAPK and PI3K/mTOR pathways—a clear example of convergent phenotype (50, 51). Less explored remains the KIT-low, stem-like pattern emerging after imatinib treatment (52).

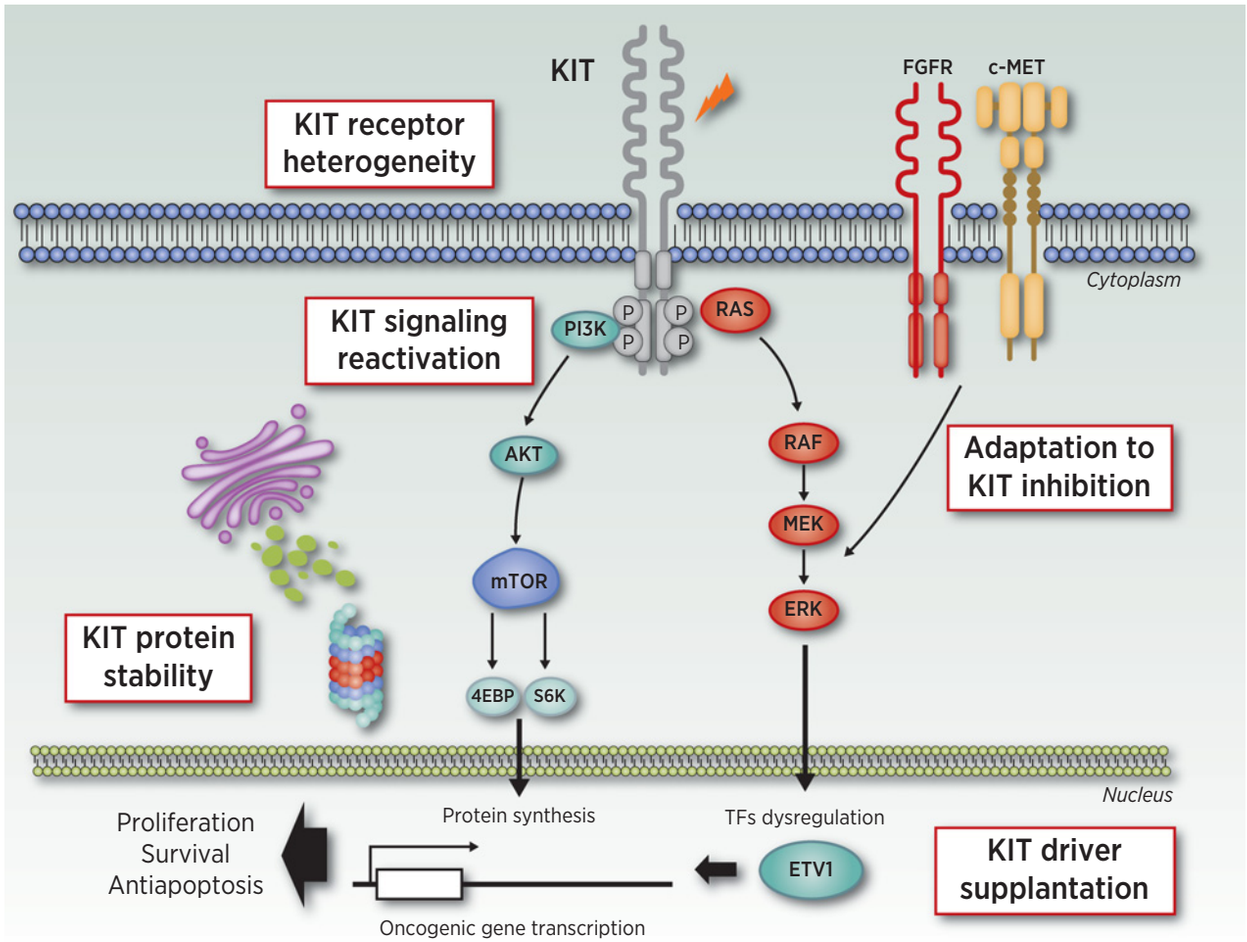

Figure 3.
KIT signaling pathway and main treatment strategies. FGFR, fibroblast growth factor receptor; TF, transcription factor.

Areas of preclinical and clinical research in GIST

The GIST field will be reshaped in the short-to-medium term thanks to the invested effort across the following areas of preclinical and clinical research (**Table 2**).

Milestone clinical trials

Ripretinib is currently being compared head-to-head in the second line with sunitinib (NCT03673501) and, if positive, will reshape the current treatment algorithm. Crenolanib, another TKI with preliminary activity against PDGFRA D842V, is currently being investigated in a phase III trial (NCT02847429); if positive, this previously multiresistant subset of patients would have two effective therapies and understanding the relative benefit of each and sequence will be a new challenge.

Imatinib remains the standard first-line therapy because of its high efficacy and safety profile. However, investigating ripretinib in the first line is tantalizing, a step successfully taken in other RTK-driven neoplasms when new-generation TKIs entered into play (53, 54).

Maximizing treatment response

The complexity of the oncogenic machinery makes ablation of a single target unlikely to induce sustained growth inhibition (55). Past efforts focused on the combined inhibition of KIT/PDGFRA with imatinib and other critical targets to enhance apoptosis (RAS/MAPK and PI3K/mTOR pathways) or prevent treatment adaptation (i.e., FGFR). However, such trials failed to meet the expectations despite the preclinical rationale (34). The most plausible explanation is that these studies were developed in imatinib-resistant disease, a setting in which imatinib is unlikely to bind to KIT-secondary mutants and exert its KIT-inhibitory effect within the combinations. However, we must take advantage of these previous efforts and the current exciting therapeutic landscape in GIST to design novel trials. Creative forms of combination, such as intermittent or drug-rotation schemes (48), must be explored aiming to reach effective doses while minimizing overlapping toxicities. Although these strategies will be preferably explored in imatinib-resistant disease, short-term combined treatments could be a window of opportunity as upfront therapy in imatinib-naïve disease to increase the chances of tumor eradication.

Targeting heterogeneity

GIST is by all odds one of the best cancer models to implement ctDNA-guided treatment given the overwhelming presence of KIT secondary mutations in imatinib-resistant disease and the TKI predictable activity against such mutants. We and others have validated

Table 2. Future areas of preclinical and clinical research in GIST.

Ongoing potentially paradigm-shifting clinical trials
INTRIGUE: second line ripretinib vs. sunitinib
CRENOGIST: crenolanib vs. placebo (PDGFRA D842V)
Maximizing treatment response
Upfront investigation of new-generation TKIs
Enhancing apoptosis induction
TKI + inhibition of KIT-downstream pathways
TKI + inhibition of apoptosis inducers
TKI + inhibition of KIT-independent mechanisms
TKI + immunotherapy
Preventing adaptation to KIT inhibition
TKI + inhibition of other growth factor receptors
TKI + MAPK pathway inhibition
Targeting heterogeneity
ctDNA-guided treatments—prospective clinical trials
Combination of TKIs with complementary activity
Combined inhibition of KIT-downstream pathways
Targeting KIT/PDGFRA protein degradation
Laboratory research
Discovery of novel lineage-specific KIT/PDGFRA mediators
High-throughput synthetic lethality screenings
Central role of KIT/PDGFRA in metabolism and immune response
Clinical validation of ctDNA technologies specifically in GIST
Integration of clinical-genomic data
Generation of robust preclinical models
Expand the knowledge in KIT/PDGFRA WT GIST

Abbreviations: CRENOGIST trial (NCT03465722); ctDNA, circulating tumor DNA; GIST, gastrointestinal stromal tumor; INTRIGUE trial (NCT03673501); VOYAGER trial (NCT03673501); WT, wild-type.

next-generation sequencing and droplet digital PCR in GIST showing that: (i) ctDNA shedding in GIST appears to be low and poses a challenge to a widespread application at this time; (ii) ctDNA detection is more successful in advanced, imatinib-resistant patients; (iii) when positive, ctDNA monitoring reflects the course of the disease and the expected sensitivity pattern to TKIs (46–49, 56). Nonetheless, prospective clinical trials, with increasingly sensitive and specific technology, should be pursued for its possible clinical implementation. Alternatively, a different approach could be the combination of highly selective TKIs with complementary activity against KIT secondary mutations (i.e., avapritinib with a hypothetical V654A inhibitor). Finally, targeting KIT protein degradation has been of interest in GIST (i.e., HSP90 inhibition), and cutting-edge PROTAC technology could be explored (57, 58).

Laboratory research

The quest for novel therapeutic vulnerabilities in GIST will rely necessarily on deciphering lineage-specific KIT dependencies. For instance, the discovery of ETV1 transcription factor opened the interest in the RAS/MAPK pathway and had translational implications (59, 60). A parallel effort should also be invested in high-throughput synthetic lethality screenings (i.e., ORFs, CRISPRs), following in the footsteps of previous successful initiatives (61). The narrow context of oncogene addiction to KIT/PGFRA must be exploited in novel directions because other similar models support a holistic role of oncogenic drivers in processes such as antitumor immune response or cancer metabolism (62, 63). Finally, integration of clinical-genomic data and generation of robust preclinical models will be the last pillars for a successful future in GIST research.

KIT/PDGFRA WT GIST

WT GIST includes GIST with unique clinical and molecular subtypes, such as SDH deficiency, RAS/MAPK pathway activation, NTRK fusions, and other with unknown biology. The recognition of these entities is clinically crucial due to the decreased response to imatinib and the need for therapeutic alternatives. While TKIs with antiangiogenic activity such as sunitinib and regorafenib are effective in SDH-deficient GIST (36, 64), approved KIT/PDGFRA inhibitors are ineffective against the remaining subtypes. NTRK inhibitors certainly offers a treatment option in non-SDH–deficient WT GIST if an NTRK fusion is identified (65), whereas the potential effectivity of MAPK pathway inhibitors in GIST harboring RAS/MAPK hyperactivation is anecdotal or absent. Therefore, translational and clinical efforts must be made in WT GIST to inform future clinical trials.

In conclusion, two decades of active translational and clinical research have demonstrated the uniqueness of GIST as a paradigm to successfully exploit KIT-dependent vulnerabilities with therapeutic strategies. Preclinical and clinical evidence support the exploration of novel treatment modalities aiming to simultaneously block various resistance or adaptation mechanisms, with the overarching goal of tumor eradication in early disease, and maximize tumor response in patients with late-stage GIST.

Disclosure of Potential Conflicts of Interest

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