Drug Design, Development and Therapy

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REVIEW

# Targeted Therapy for Advanced Gastrointestinal Stromal Tumors: Evolution and Future Directions

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**Abstract:** Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract, with its pathogenesis primarily linked to activating mutations in the *KIT* or platelet derived growth factor receptor alpha (*PDGFRA*) genes. Surgical resection remains the standard curative treatment for localized GIST; however, ~50% of patients eventually develop recurrence or metastasis. Since the introduction of imatinib in the early 21st century, the management of metastatic GIST has shifted from solely surgical intervention to a systemic, chronic disease management model centered on tyrosine kinase inhibitors (TKIs). However, during the course of treatment, most patients develop drug resistance. Despite the transformative impact of TKIs, some critical clinical challenges remain unresolved. Intratumoral heterogeneity, in particular, poses a significant obstacle, as tumors often comprise diverse populations of cells with varying genetic and molecular profiles. This diversity means that while some subclones may initially respond well to TKI therapy, others harboring inherent or acquired resistance mutations can continue to proliferate, ultimately leading to treatment failure. Additionally, the limited durability of TKIs responses, even in tumors initially sensitive to treatment, remains a pressing concern. Moreover, the lack of curative systemic options for advanced GIST, along with adverse drug reactions, underscores the unmet needs within this patient population. These challenges underscore the necessity of this review, which discusses current standard drug treatment strategies for advanced GIST, including sequential TKIs therapy and investigations into mechanisms of drug resistance. Finally, the review explores precise and actionable future directions for GIST drug development and clinical management, including mutation-stratified therapeutic sequencing, rational TKI-based combination regimens, and circulating tumor DNA (ctDNA)-guided real-time treatment monitoring and resistance surveillance.

**Plain Language Summary:** For patients with advanced GIST, targeted drug therapy is the mainstay of treatment, guided by the specific genetic changes in each patient's tumor. While current standard treatments can control the disease for many patients, drug resistance remains the biggest challenge, most often caused by new genetic mutations in the tumor that make the drugs stop working. In this review, we explain how current treatments work, why resistance develops, and what new treatment approaches are being studied to help patients live longer and better lives with this disease.

**Keywords:** drug resistance, combination therapy, epigenetic modification, tumor microenvironment

## Introduction

Gastrointestinal stromal tumor (GIST) is the most common subtype of soft tissue sarcoma. The incidence of GIST ranges from 10 to 15 cases per million people worldwide.[1,2] GISTs do not originate from the epithelial cells of the gastrointestinal mucosa but rather arise from a specialized type of cell in the gastrointestinal wall known as the interstitial cells of Cajal, or from primitive mesenchymal stem cells with the potential to differentiate into Cajal cells. The origin of GISTs is closely linked to their unique molecular characteristics, immunohistochemical labeling demonstrates that tumor cells typically express CD117 and DOG-1, which are critical targets for diagnosis and treatment. Before GISTs were

https://doi.org/10.2147/DDDT.S594043
Received: 6 January 2026
Accepted: 14 March 2026
Published: 31 March 2026

accurately identified, they were often misdiagnosed as leiomyoma, leiomyosarcoma, or other soft tissue sarcomas. Although most GISTs can be cured by surgical resection during initial treatment, some patients present with metastasis at diagnosis or experience recurrence and metastasis after surgery. These tumors typically respond poorly to traditional radiotherapy and chemotherapy, resulting in a poor prognosis.[3–6] It was not until 1983 that GISTs were truly recognized as a distinct entity.[7] In 1998, Japanese researchers discovered that GIST cells generally express high levels of the KIT protein (CD117). Subsequently, American scientists confirmed that the vast majority of GISTs harbor mutations in the *KIT* gene. This discovery revealed the "cancer engine" driving GIST and identified an ideal drug target.[8–10] In 2001, imatinib was approved, ushering in a new era of targeted oncological therapy, which significantly improved median overall survival (OS) for patients with advanced GIST from 20 to 57 months.[11–13] Although imatinib represents a significant breakthrough in the treatment of GISTs, ~50% of patients develop drug resistance after 2–3 years of therapy.[14–16] Current clinical management of advanced GIST still faces several critical challenges. Firstly, the emergence of primary and secondary resistance to tyrosine kinase inhibitors (TKIs) remains a major hurdle. Secondly, the sequential TKIs strategy, which involves switching to second-line or third-line agents upon disease progression, has shown only modest efficacy. These subsequent TKIs often have limited response rates and are associated with significant toxicities, compromising patients' quality of life. Additionally, there is a lack of reliable biomarkers to predict treatment response and resistance, making it difficult to tailor therapy for individual patients. Furthermore, for patients with refractory disease after multiple TKIs failures, there are currently no standard-of-care treatments, highlighting an unmet medical need. With an in-depth understanding of the molecular mechanisms underlying GIST and the development of TKIs, the treatment strategy for advanced GIST has evolved from relying solely on surgery to a comprehensive approach centered on targeted therapy. In this review, we first outline the genetic landscape of GIST, which serve as the molecular basis for targeted therapy selection and resistance development. Next, we will discuss the current standard therapeutic approaches, with a particular focus on the application of TKIs and their clinical efficacy. Following that, we will delve into the intricate mechanisms underlying drug resistance, including primary resistance related to specific genetic alterations and secondary resistance involving bypass signaling pathways. Finally, we will synthesize ongoing new treatment strategies, such as novel TKIs, combination therapies, and immunotherapeutic approaches, aiming to provide a structured and valuable reference for clinical practice.

## Types of Gene Mutations in Gist

GIST can occur in any part of the digestive tract. GIST in the stomach (60–70%) and small intestine (25–30%) are the most common, while those in rectum, colon, esophagus, and other sites are rare.[13,17–21] The pathogenesis of GIST primarily arises from activating mutations in receptor tyrosine kinases (RTKs), which result in the continuous activation of downstream signaling pathways, such as PI3K/AKT/mTOR (mammalian target of rapamycin) and RAS/MAPK.[22–25] This persistent signaling promotes tumor cell proliferation and survival. The main driver mutations occur in the *KIT* and *PDGFRA* genes.[21,26–28] These genetic alterations directly determine the response to TKIs, the cornerstone of advanced GIST treatment, as discussed in subsequent sections.

*KIT* gene mutation (approximately 80% of cases) is the most common cause. The *KIT* gene encodes a transmembrane receptor protein, also known as CD117. KIT is a transmembrane RTK whose ligand is stem cell factor, mutations in *KIT* gene lead to its dimerization and activation independent of ligand binding. Exon 11 of *KIT* gene, which encodes the juxtamembrane domain, is the most commonly mutated region (65–70%), with mutations including deletions, point mutations, insertions or duplications. Notably, most GISTs harboring exon 11 mutations are highly sensitive to first-line imatinib, with a significantly higher objective response rate (ORR) and longer progression-free survival (PFS) than other mutation subtypes; this sensitivity also supports imatinib as the preferred first-line therapy for this subgroup. For patients with acquired resistance to imatinib in this subtype, second-line sunitinib and third-line regorafenib have shown moderate efficacy, while fourth-line ripretinib can cover most secondary resistance mutations in exon 11.[29–32] Exon 9, encoding the extracellular dimerization domain, accounts for 10–15% of mutations, predominantly involving the A502_Y503 duplication. In contrast to exon 11 mutations, GISTs with *KIT* exon 9 mutations exhibit relative resistance to standard-dose imatinib.[19,31,33] Mutations in exon 13 (ATP-binding pocket) and exon 17 (activation loop) are primarily secondary mutations associated with drug resistance and are typically observed in advanced patients following imatinib treatment;

these mutations often confer cross-resistance to second-line sunitinib, making third-line broad-spectrum TKIs (eg, ripretinib) the preferred therapeutic option.[34–36]

Mutations in *PDGFRA* (5–10% of cases) have a mechanism similar to that of *KIT* mutations, resulting in continuous activation of downstream signaling pathways.[37–39] GISTs harboring mutations in *PDGFRA* exhibit structural characteristics and mutation mechanisms analogous to those observed in *KIT*. Exon 18, encoding the activation loop, is the most frequently mutated region in *PDGFRA*, with the D842V mutation being the most common. Critically, *PDGFRA* exon 18 D842V mutations are associated with primary resistance to both imatinib and sunitinib.[36,40,41] Mutations in exon 12 (juxtamembrane domain) and exon 14 (ATP-binding pocket) of *PDGFRA* are relatively rare.[42–44]

Additionally, 10–15% of GISTs lack mutations in *KIT* or *PDGFRA* and are classified as wild-type GISTs, which encompass multiple molecular subtypes. Their origin may be associated with other genes, such as succinate dehydrogenase (SDH), BRAF, neurofibromatosis 1(NF1), KRAS or neurotrophic receptor tyrosine kinase 3 (NTRK3).[26,45–49] Among these, succinate dehydrogenase-deficient (SDH-deficient) GISTs represent a distinct subgroup, accounting for a significant proportion of wild-type GISTs, particularly in younger patients and those with gastric localization. SDH is a mitochondrial enzyme complex composed of four subunits (SDHA, SDHB, SDHC, SDHD), and mutations in any of these subunits can lead to loss of SDH function, resulting in the accumulation of succinate and subsequent epigenetic dysregulation.[50] Clinically, SDH-deficient GISTs often exhibit unique features such as multifocality, lymph node metastases, and a predilection for children and young adults, and they typically lack KIT and PDGFRA expression.[50,51] Notably, SDH-deficient GISTs exhibit poor responses to all currently available TKIs, including imatinib, sunitinib, and regorafenib. There are no standardized systemic treatment guidelines or approved targeted therapies for this patient population. These tumors also have a high rate of lymph node metastasis and multifocality, which contribute to poor surgical resectability, and clinical trials have reported a low ORR. All of these factors present a major therapeutic challenges.[50–53] These diverse genetic alterations in GISTs not only drive their pathogenesis but also have significant implications for diagnosis, prognosis, and treatment strategies (Figure 1).

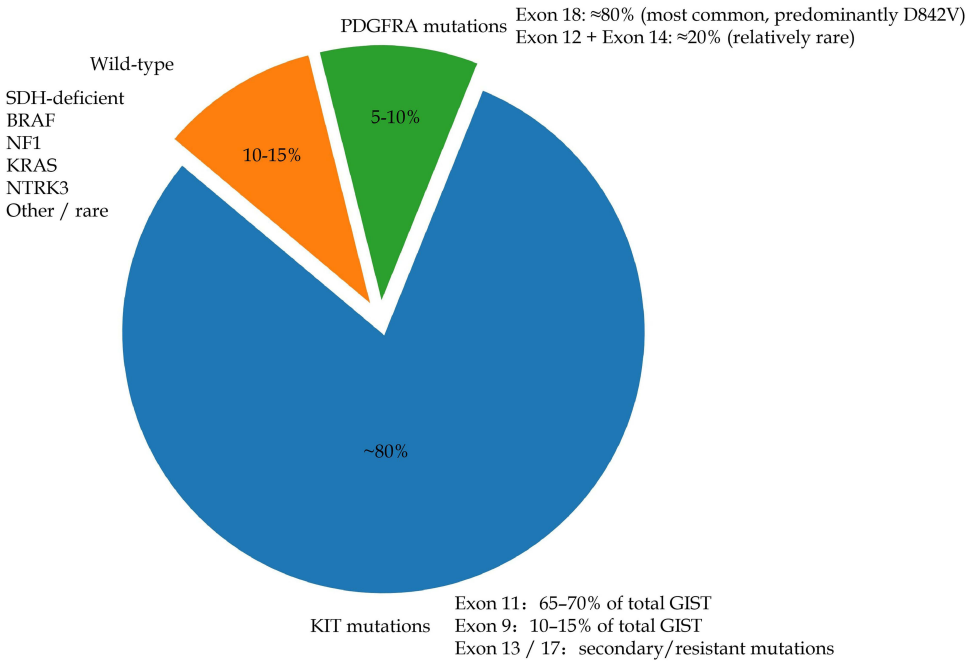


**Figure 1** Distribution of driver gene mutation types in GIST. KIT mutations account for approximately 80% of GIST cases, PDGFRA mutations for 5–10%, and wild-type GIST for 10–15%. Among KIT-mutant GISTs, exon 11 mutations are the most frequent (approximately 65–70%), followed by exon 9 mutations (10–15%). Exon 13 and exon 17 mutations are less common and are primarily associated with secondary resistance to tyrosine kinase inhibitors. Exon 18 is the most frequently mutated region in PDGFRA-mutant GIST, accounting for approximately 80% of cases, while mutations in exons 12 and 14 are relatively rare. The D842V mutation in exon 18 is linked to primary resistance to imatinib. Wild-type GIST lacks KIT and PDGFRA mutations and includes multiple molecular subgroups, such as SDH-deficient GIST, BRAF-mutant, NF1-mutant, KRAS-mutant, and NTRK3-rearranged subtypes. Among these, SDH-deficient GIST represents a distinct clinicopathological entity associated with primary resistance to currently available tyrosine kinase inhibitors. These genetic alterations determine the response to tyrosine kinase inhibitor therapy.


https://doi.org/10.2147/DDDT.S594043

## Current Standard Target Treatment: Sequential Treatment Mode of TKIs

The current standard target treatment for GISTs is based on a sequential TKIs approach, which is primarily guided by the type of gene mutation. TKIs, such as imatinib mesylate (Gleevec), have demonstrated remarkable efficacy in treating GIST. As a result, GIST has become a model for targeted therapy in solid tumors during the era of precision medicine. Accurate and standardized pathological diagnosis is crucial for guiding clinical treatment and predicting prognosis in GIST patients. Although some studies have demonstrated that surgical treatment can be beneficial for late-stage GIST, drug therapy remains the primary approach for advanced GIST at present.[54,55]

Imatinib is widely used as the first-line treatment for metastatic and recurrent/unresectable GIST, primarily targeting KIT and PDGFRA. Imatinib is effective against most *KIT* and *PDGFRA* gene mutations, including GIST with *KIT* exon 11 mutations and those with *PDGFRA* exon 18 mutations, except for the D842V mutation. The generally recommended initial dose is 400 mg/day. If imatinib is effective, treatment should continue until disease progression or intolerable toxicity occurs. For patients who do not respond to imatinib, alternative drug therapies are recommended according to subsequent treatment guidelines.[56] For patients with *KIT* exon 9 mutations, the optimal treatment remains controversial and presents a significant challenge in managing GIST with *KIT* gene mutations. The exon 9 mutation is located in the extracellular dimerization domain of the KIT protein. This mutation causes receptor dimerization and continuous activation; however, its sensitivity to imatinib is lower than that of the exon 11 mutation. Clinical studies have demonstrated that the PFS and OS of patients with exon 9 mutation GIST treated with the standard dose of imatinib (400 mg/day) are significantly worse than those of patients with exon 11 mutations.[57,58] To investigate whether increasing the drug dose may improve the prognosis of patients with exon 9-mutant GIST, some studies recommend an initial dose of 600 mg/day or 800 mg/day.[20,21,59–62] However, Judson et al showed that patients with mutations in exon 9 of *KIT* should be considered for treatment with imatinib 800 mg daily, but their data do not indicate whether there is a survival advantage for immediate treatment at 800 mg. Doubling the dose from 400 mg to 800 mg also significantly increased the incidence and severity of adverse drug reactions.[63] For GIST with *KIT* exon 9 mutations, the appropriate dosage remains controversial, and further clinical research is needed to establish optimal treatment guidelines.

Avapritinib is currently the first-line treatment for patients with *PDGFRA* exon 18 D842V mutations. Avapritinib is a type I TKIs that primarily targets the activation loops of KIT and PDGFRA, demonstrating particularly strong inhibitory effects against the PDGFRA D842V mutation. In a Phase 1 study, avapritinib was used to treat metastatic GIST with the PDGFRA D842V mutation, achieving an ORR of 84% and a tumor control rate >90%.[56,64–67] For GISTs harboring NTRK gene fusions, NTRK inhibitors larotrectinib and entrectinib have demonstrated good efficacy and safety and are recommended as first-line treatments for NTRK fusion-positive GIST.[68–71] Currently, there are no approved targeted drugs that can directly reverse SDH deficiency. However, olverembatinib, a third-generation BCR-ABL inhibitor with potent activity against various kinase targets, appears to exert its anti-tumor effects through mechanisms that circumvent the metabolic dependencies created by SDH loss. The preclinical data suggest that this compound may target alternative signaling nodes that become essential for survival in SDH-deficient cells, potentially exploiting the metabolic vulnerabilities associated with succinate accumulation and pseudohypoxia[72] This finding represents a significant breakthrough in addressing one of the most challenging subtypes of GIST, as SDH-deficient tumors have historically been refractory to conventional tyrosine kinase inhibitors. These results have prompted further investigation into the precise molecular mechanisms underlying olverembatinib's efficacy in this context, with particular interest in whether its effects are mediated through direct kinase inhibition or through modulation of the altered metabolic state characteristic of SDH-deficient GIST.

Sunitinib is widely accepted as a second-line treatment for advanced GIST. Regarding sunitinib treatment, both continuous administration at 37.5 mg/day and 50 mg/day (4 weeks on, 2 weeks off) are options.[73] The 37.5 mg continuous daily dosing schedule may be a more suitable regimen for Chinese patients with advanced GIST following imatinib failure. For instance, recent research by Zhang et al showed that the sunitinib 375 mg continuous daily dosing schedule was associated with improved adherence and prognosis compared to the 50 mg 4/2 schedule. This study included 107 patients and found that those receiving a continuous daily dosage of 37.5 mg had significantly longer PFS and OS compared to patients on the "50 mg off" schedule (50 mg 4/2 schedule) ($P$ = 0.044 and 0.016, respectively). Additionally, 64.1% of patients on the 50 mg 4/2 schedule experienced severe treatment toxicity of Grade 2/3; a significantly higher rate than that

observed in patients receiving the 37.5 mg continuous daily dosage schedule.[73] Notably, the sunitinib dosing data in Zhang's study were obtained from Chinese patient cohorts, and clearly state that these findings may not be generalizable to other populations. Further research aims to expand the range of conditions for which sunitinib is adaptable A Phase 1/2 clinical study demonstrated that, among imatinib-resistant patients, those with primary KIT exon 9 mutations or wild-type GIST exhibited longer PFS compared to patients with primary KIT exon 11 mutations.[74]

Regorafenib is recommended as a third-line treatment for advanced GISTs. In 2013, the FDA approved regorafenib for use in the management of patients with advanced GIST refractory to imatinib and sunitinib. The recommended dose is 160 mg/day, administered for 3 weeks followed by a 1-week break.[65,75–77] The results of a multicenter Phase 2 clinical study indicate that the clinical benefit rate of regorafenib treatment may reach 79% following the failure of first- and second-line therapies. Among the 34 participants, four achieved partial remission, and 22 patients maintained stable tumors for > 16 weeks. The average PFS was 10.0 months, with a high safety profile observed concurrently.[75] A Phase 3 clinical study involving 240 participants randomized 199 to receive regorafenib (n = 133) or a matched placebo (n = 66). Median PFS was 4.8 months in the regorafenib group and 0.9 months in the control group ($P < 0.0001$).[65] Regorafenib is a multi-target TKIs with a broader range of targets than the previous two drugs. Its primary targets include KIT and PDGFRA, which directly inhibit the key driver genes of GIST, as well as vascular endothelial growth factor receptor 1/2/3 (VEGFR 1/2/3), strongly inhibit angiogenesis. Additionally, it targets other kinases such as fibroblast growth factor receptor (FGFR) and BRAF.[78] This multitarget mechanism, particularly its potent anti-angiogenic effect, helps overcome multiple drug resistance pathways that arise from first- and second-line TKIs treatments.

Ripretinib is recommended as a fourth-line treatment for advanced GISTs. The approval of ripretinib is based on INVICTUS, a global, randomized, double-blind, placebo-controlled Phase 3 clinical trial.[66] Traditional TKIs, such as imatinib and sunitinib, primarily target the ATP-binding pocket of KIT and PDGFRA receptors, blocking signal transduction by competitively inhibiting ATP binding. However, tumor cells can develop secondary mutations – most commonly in the ATP-binding pockets (exons 13 and 14) and activation loops (exons 17 and 18) – which alter the conformation of drug-binding sites and lead to drug resistance. Ripretinib is a broad-spectrum KIT and PDGFRA inhibitor with a unique structure that allows it to bind simultaneously to both the ATP-binding pocket and the switching pocket of the kinase. This dual binding mechanism enables ripretinib to effectively inhibit various common primary and secondary KIT/PDGFRA mutations (including exons 9, 11, 13, 14, 17, and 18), as well as PDGFRA D842V mutations.[79,80] Recently, some studies suggested that repritinib could be used as a second-line treatment for GIST. All 453 patients included in this Phase 3 clinical trial (INTRIGUE, ClinicalTrials.gov identifier: NCT03673501) were imatinib-resistant and were divided into ripretinib and sunitinib treatment groups. The overall PFS was 8.0 months in the ripretinib group and 8.3 months in the sunitinib group ($P = 0.72$). For patients with KIT exon 11 mutations, PFS was 8.3 months in the ripretinib group and 7.0 months in the sunitinib group ($P = 0.36$). Although there was little difference in OS, patients in the ripretinib group experienced fewer grade 3/4 treatment-emergent adverse events (41.3% vs. 65.6%, nominal $P < 0.0001$) and demonstrated a better ORR in the KIT exon 11 mutation subgroup (23.9% vs. 14.6%, nominal $P = 0.03$).[81] Ripretinib demonstrates a higher ORR and may provide an opportunity for reoperation following tumor shrinkage in the second-line treatment of GIST. However, the indication of ripretinib as a second-line treatment has not yet been approved, and further research and clinical data are still needed for support.

This sequential use of TKIs, tailored to the patient's mutation profile and treatment history, aims to maximize disease control and quality of life by targeting the evolving molecular landscape of GISTs during treatment. However, the molecular heterogeneity of GISTs presents significant challenges (Figure 2 and Table 1).

## Exploration of Imatinib Resistance Mechanisms in GIST

GISTs are notorious for their variable biological behavior, which complicates the assessment of malignant potential and the prevention of drug resistance. Recent studies on circulating tumor DNA (ctDNA) have demonstrated that secondary mutations in the KIT gene are the primary drivers of drug resistance in GIST patients following imatinib treatment.[82–84] However, most of this knowledge has been derived from tumor samples collected after imatinib treatment failure, and the evolutionary dynamics of this heterogeneity remain unclear. In this context, it is crucial to further investigate the mechanisms underlying GIST drug resistance and to identify new therapeutic targets to halt disease progression.

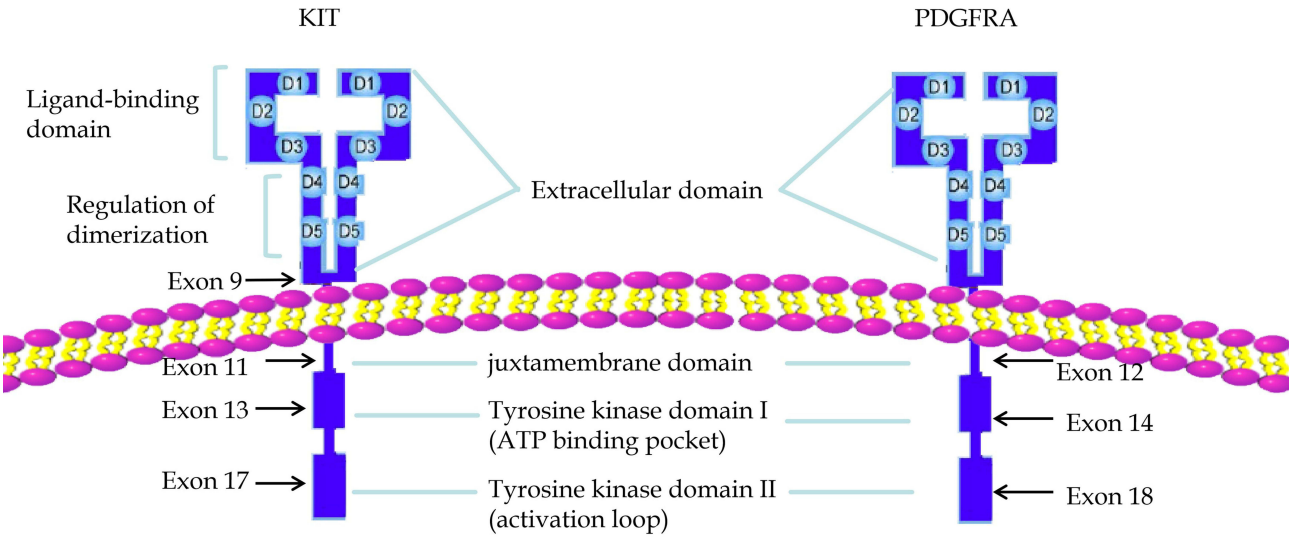


**Figure 2** Schematic representation of KIT and PDGFRA receptor structures and their functional domains in GIST. KIT and PDGFRA are receptor tyrosine kinases with similar domain architectures, including an extracellular domain, a juxtamembrane domain, and an intracellular tyrosine kinase domain containing the ATP-binding pocket and activation loop. In GIST, the most common mutations occur in KIT exon 11 (juxtamembrane domain), KIT exon 9 (extracellular domain), KIT exon 13 (ATP-binding pocket), and KIT exon 17 (activation loop). For PDGFRA, the majority of mutations occur in exon 18 (activation loop, e.g, D842V), which confers primary resistance to imatinib. These mutation sites determine sensitivity to different tyrosine kinase inhibitors (imatinib, sunitinib, regorafenib, avapritinib, ripretinib) and guide the sequential targeted therapy of GIST.

## Primary Imatinib Resistance

Primary imatinib resistance refers to disease progression or lack of response at the start of therapy, and is driven by genetic or biological features present before drug exposure. This form of resistance is typically associated with specific gene mutations in GIST. These include KIT exon 9 mutations, *PDGFRA* D842V mutations, KIT exon 17 mutations, and wild-type GISTs, all of which may contribute to primary, intrinsic resistance to imatinib.[36,85,86] These mutations can cause intrinsic resistance of cells

**Table 1** Summary of Sequential Treatment with TKIs for GIST Targeted Therapy

| Treatment Line | Drug Name | Primary Target/ Mechanism of Action | Key Indications/Mutation Types | Mechanism of Action |
|---|---|---|---|---|
| First-Line | Imatinib | Targets KIT and PDGFRA | KIT exon 11 mutation<br>KIT exon 9 mutation (lower sensitivity)<br>PDGFRA exon 18 mutation (non-D842V) | Competes for the ATP-binding pocket, inhibiting KIT/PDGFRA phosphorylation and downstream signaling |
| First-Line *(Special Mutation)* | Avapritinib | Targets the KIT/PDGFRA activation loop | PDGFRA exon 18 D842V mutation | Specifically binds to the activation loop |
| First-Line *(Rare Fusion)* | LarotrectinibgEntrectinib | NTRK inhibitors | NTRK gene fusion-positive GIST | Inhibits NTRK fusion-mediated downstream signaling |
| Second-Line | Sunitinib | A multi-targeted TKI (targets KIT, PDGFRA, VEGFR, etc.) | Secondary mutation in KIT/PDGFRA exon 13, exon 14 | Inhibits KIT/PDGFRA kinase activity and exerts anti-angiogenic effects by blocking VEGFR |
| Third-Line | Regorafenib | Multi-kinase Inhibitor (targets KIT, PDGFRA, VEGFR1/2/3, FGFR, BRAF, etc.) | Secondary mutation in KIT/PDGFRA exon 17, exon 18 | Multi-target kinase inhibition with potent anti-angiogenic activity; blocks resistance bypass pathways. |
| Fourth-Line | Ripretinib | Broad-spectrum KIT /PDGFRA Inhibitor. | Primary and secondary KIT/ PDGFRA mutations (exon 9, 11, 13, 14, 17, 18) and PDGFRA D842V. | Simultaneously binds to both the ATP-binding pocket and the switch pocket. |

**Abbreviations**: PDGFRA, platelet-derived growth factor receptor-α; TKI, tyrosine kinase inhibitor; NTRK, neurotrophic receptor tyrosine kinase; VEGFR, vascular endothelial growth factor receptor; FGFR, fibroblast growth factor receptor.


https://doi.org/10.2147/DDDT.S594043

or tumors to imatinib and most TKIs due to structural changes in the activation loop, which prevent the drug from effectively binding to the ATP binding pocket of the receptor.[74,87,88] As an intrinsic resistance mechanism, the imatinib resistance mechanism in wild-type GIST primarily involves the absence of drug targets within the mutations themselves, as well as the influence of other mutant genes.[89–92] For SDH-deficient GIST, SDH inactivation leads to the accumulation of succinate, which activates pathways including hypoxia-inducible factor (HIF) and angiogenesis.[93–97] In addition to these well-characterized intrinsic genetic alterations, emerging studies have suggested that the presence of rare or compound mutations may also contribute to primary imatinib resistance. For instance, some GIST cases harbor concurrent mutations in KIT exons 9 and 11, which can lead to a more intrinsic complex resistance phenotype compared to single exon mutations.[98] The interaction between these mutations may alter the receptor's conformation in a way that further reduces imatinib binding affinity or enhances downstream signaling activation, thereby diminishing the therapeutic response. Another mechanism that contributes specifically to primary resistance is intratumoral genetic heterogeneity. In this scenario, distinct subclones with different mutations exist before treatment initiation, leading to inherently imatinib-resistant subpopulations from the outset. These resistant subclones may then proliferate preferentially under imatinib treatment, leading to early treatment failure.[99] Additional primary, non-genetic mechanisms have also been identified. There is evidence that certain polymorphisms in drug transporters or metabolizing enzymes could influence the pharmacokinetics of imatinib, affecting its intracellular concentration and thus contributing to intrinsic resistance. For example, variations in the ATP binding cassette subfamily B member 1 gene, which encodes the P-glycoprotein (P-gp) efflux pump, might result in increased drug efflux, reducing the amount of imatinib available to interact with its target in tumor cells.[100]

Overexpression of KIT or PDGFRA has been recognized as another crucial mechanism contributing to primary imatinib resistance. In such cases, even in the absence of activating mutations within the kinase domain, the elevated protein levels of these receptors can overwhelm the inhibitory capacity of standard imatinib doses. The increased abundance of KIT/PDGFRA molecules leads to a higher baseline level of receptor dimerization and autophosphorylation. Debiec-Rychter et al investigated 26 cases of KIT/PDGFRA-mutated drug-resistant GIST The results suggested that, in some treatment-naïve, resistant samples, genomic amplification of *KIT*/*PDGFRA* serves as an intrinsic mechanism of resistance to imatinib.[101] In this study, two patients with imatinib resistance were found to have KIT or *KIT*/*PDGFRA* gene amplification. These patients experienced rapid tumor progression just 5 weeks after starting oral imatinib. Therefore, this amplification likely existed in the tumor cells prior to imatinib treatment. This results in a residual pool of active receptors that continue to transduce mitogenic signals, rendering the tumor cells less responsive or completely unresponsive to imatinib-mediated growth suppression. Studies have demonstrated that GIST cell lines and clinical specimens with KIT overexpression, independent of mutation status, exhibit significantly higher IC50 values for imatinib compared to those with normal receptor levels. Immunohistochemical analysis of primary GIST tumors has revealed a positive correlation between high KIT expression levels and poorer initial responses to imatinib therapy, highlighting the clinical relevance of this primary resistance mechanism. The underlying causes of KIT/PDGFRA overexpression in GIST without kinase domain mutations can be multifactorial, including gene amplification events, transcriptional upregulation driven by aberrant transcription factors, or enhanced protein stability due to altered ubiquitination and degradation pathways.[102,103] Furthermore, the level of mutant allele burden has been proposed as a potential contributing factor. Higher mutant allele frequencies might result in a greater number of active kinase molecules, overwhelming the inhibitory capacity of standard imatinib doses and leading to insufficient target suppression.[104] Although the exact mechanisms by which these factors contribute to primary resistance are still being elucidated, their identification highlights the complexity of primary imatinib resistance in GIST and underscores the need for comprehensive genetic profiling and consideration of multiple biological factors when evaluating treatment response in patients with GIST (Figure 3A).

## Secondary Mutations in the KIT/PDGFRA Gene Lead to Drug Resistance in GIST

In contrast to primary resistance, secondary (acquired) resistance develops during therapy, driven by clonal evolution under the selective pressure of imatinib treatment. Secondary mutations is currently considered the most significant cause of acquired imatinib resistance in GISTs. Among patients with metastatic GIST treated with imatinib, up to 80% achieve partial remission or stable disease.[56] However, imatinib rarely results in a cure, and tumors initially sensitive to the drug

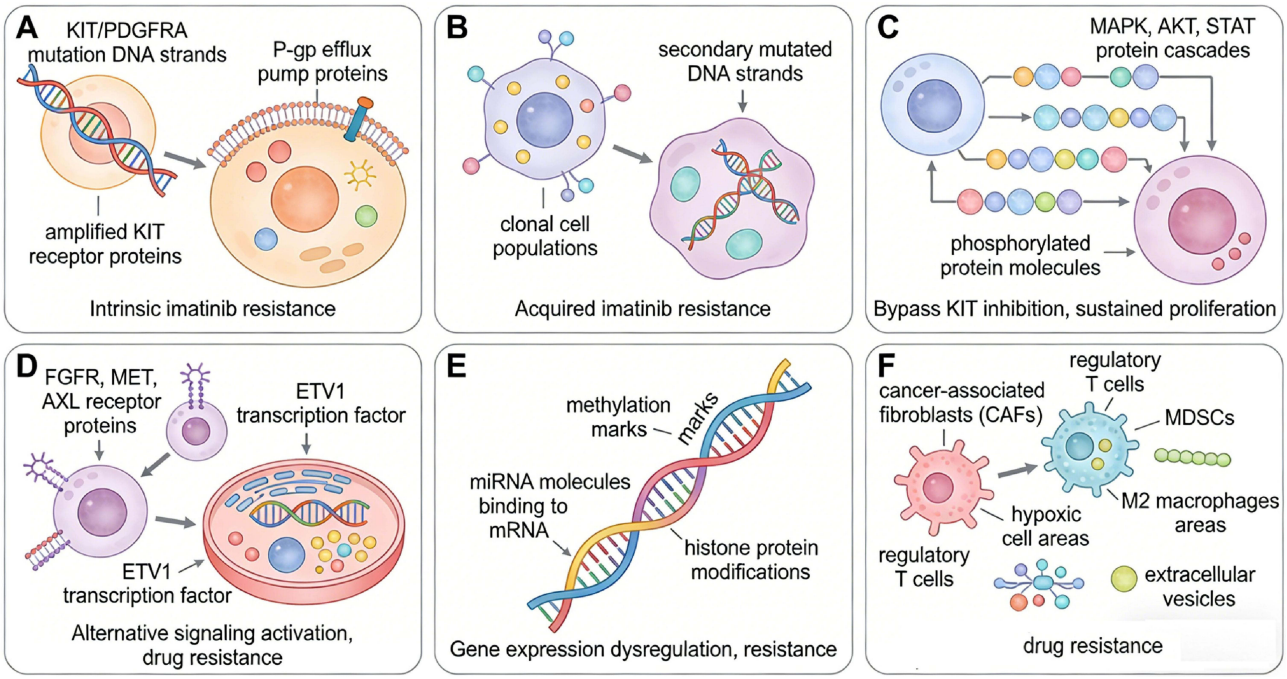


**Figure 3** Exploration of drug resistance mechanisms in GIST. (**A**) Primary imatinib resistance is driven by primary *KIT*/*PDGFRA* mutations, wild-type mutations, intratumor heterogeneity, drug efflux, and receptor overexpression. (**B**) Secondary mutations in *KIT*/*PDGFRA* contribute to drug resistance in GIST. (**C**) Sustained activation of KIT/PDGFRA downstream signaling pathways represents a major mechanism of drug resistance in GIST. (**D**) Bypass pathway activation enables GIST cells to evade KIT/PDGFRA inhibition through alternative receptor tyrosine kinases and signaling axes. (**E**) Epigenetic dysregulation, including DNA methylation, non-coding RNA networks, and histone modifications, remodels gene expression profiles to facilitate resistance. (**F**) The tumor microenvironment, comprising cancer-associated fibroblasts, immune cells, hypoxic conditions, and extracellular vesicles, creates a supportive niche that promotes imatinib resistance via paracrine signaling and intercellular communication.

typically develop acquired resistance within 2 years.[105,106] Approximately half of all cases of acquired resistance to imatinib are due to secondary mutations in the *KIT*/*PDGFRA* gene.[107] Such secondary mutations are typically located in the following regions: the ATP binding pocket (exons 13/14) or the activation loop (exons 17/18) of the KIT gene, or the ATP binding pocket (exons 13–15) of the *PDGFRA* gene.[108,109] These mutations arise during treatment and directly mediate acquired resistance. They lead to structural changes in the KIT/PDGFRA proteins, which can directly interfere with the binding of imatinib to its target. For instance, mutations in the ATP binding pocket may alter the conformation of the binding site, reducing the affinity of imatinib for the kinase domain.[110] Similarly, activation loop mutations can stabilize the active conformation of the kinase, rendering imatinib ineffective as it preferentially binds to the inactive conformation.[111] The specific location and type of secondary mutation often correlate with the degree of resistance and may influence the response to subsequent TKIs. For example, KIT exon 17 mutations generally confer high-level resistance to imatinib, whereas some exon 13 mutations may still respond to increased doses of imatinib or alternative TKIs.[112,113] Notably, the emergence of these secondary mutations is a direct consequence of clonal evolution under therapeutic pressure. Resistant subclones expand and dominate the tumor population during imatinib treatment.[88] This clonal heterogeneity poses a significant challenge for the management of acquired resistance, as different subclones may require distinct therapeutic approaches (Figure 3B).

## Continuous Activation of the Downstream Signaling Pathways of KIT and PDGFRA

GISTs are characterized by a set of homologous transcription factors, reflecting the continuous reliance of the tumor on a highly conserved regulatory program driven by KIT/PDGFRA throughout all stages of the disease.[114] Substantial evidence indicates that the RAS/MAPK and PI3K/mTOR pathways are the primary mediators of the KIT/PDGFRA oncogenic program. However, the specific biological roles of these pathways within the GIST cellular environment require further investigation. The KIT-activated RAS/MAPK signaling pathway is essential for the oncogenic function of the ETS family transcription factor ETV1.[115] Similarly, the KIT-dependent PI3K/mTOR signaling pathway is critical for

 https://doi.org/10.2147/DDDT.S594043 

GIST initiation and early tumor development, and it also plays a significant role in regulating tumor cell proliferation and evasion of apoptosis.[116,117] Wild-type GISTs with SDH deficiency exhibit core epigenetic dysregulation, leading to functional activation of KIT and FGF signaling, which results in pronounced MAPK pathway activation.[49] Early studies have demonstrated that by detecting protein activation through Western blotting and combining this with cell proliferation and apoptosis assays in various GIST cell lines, the biological effects resulting from the biochemical inhibition of KIT, PI3K, PLC, MAPK/ERK kinase/MAPK (MEK/MAPK), mammalian target of rapamycin (mTOR), and JAK were characterized.[116,118] These findings underscore the dependence of GIST tumor cells on KIT and its downstream signaling pathways.

MAPK activation is largely KIT dependent in GISTs and the MAPK pathway is the most prominent target for common inhibition of PDGFRA and KIT oncogenic signaling.[118–120] Raf kinase inhibitor protein (RKIP), a suppressor of the MAPK signaling pathway, may potentially inhibit metastasis and, consequently, improve prognosis in GIST.[121] Extracellular signal-regulated kinase (ERK)1/2, a member of the MAPK family, is a key component of this signaling pathway. The expression levels of RKIP, phosphorylated ERK (p-ERK), and phosphorylated MEK (p-MEK) proteins in GIST can serve as risk factors for predicting patient prognosis and may play a crucial role in drug resistance in GIST.[122] PLX9486, a new broad-spectrum TKIs may target both primary KIT exon 9 and 11 mutations as well as secondary exon 17 and 18 mutations in GIST. Its mechanism of action may involve modulating the activity of specific proteins in the MAPK pathway rather than affecting the phosphorylation of KIT at tyrosine residues Y703 and Y719.[123] Some research has also shown that the activation of the FGF/FGFR pathway, which in turn reactivates the MAPK pathway, is one of the possible reasons for imatinib resistance in GISTs.[124,125]

In addition to the MAPK pathway, the PI3K/Akt/mTOR signaling cascade also plays a vital role in mediating primary imatinib resistance in GIST. The inhibition of PI3K induced significant apoptosis in imatinib-resistant GIST.[126,127] Daniels et al suggested that in wild-type GIST, mutations in BRAF and excessive activation of the PI3K pathway were closely associated with drug resistance in GISTs.[128] The phosphorylation of PI3K and the activation of its downstream pathways play crucial roles in various aspects of tumor cell behavior, including proliferation, apoptosis, and autophagy.[129–132]

Studies have demonstrated that activation of this pathway can occur independently of KIT in some GIST cases, leading to the survival and proliferation of tumor cells even in the presence of imatinib. For instance, loss of phosphatase and tensin homolog (PTEN), a negative regulator of PI3K, has been observed in a subset of GISTs, resulting in constitutive activation of Akt and downstream mTOR signaling. This activation promotes cell growth, inhibits apoptosis, and reduces the sensitivity of GIST cells to imatinib-induced cytotoxicity.[132,133] Preclinical studies using dual inhibitors targeting both KIT and mTOR have shown promising results in overcoming this form of resistance, as they can simultaneously block the primary oncogenic driver and the alternative survival pathway, leading to enhanced tumor cell death compared to imatinib alone.[129,134]

The JAK/STAT pathways play an important role in the proliferation and survival of GIST cells.[116,135] The continuous activation of the JAK/STAT pathways is associated with drug resistance in GIST. Targeting JAK2/STAT3 reduces cell proliferation, induces apoptosis, decreases cell migration and invasion, and demonstrates antitumor effects in vivo and in vitro.[135–137] The secondary KIT V654A mutation is associated with imatinib resistance in GIST, and activation of the KIT-related JAK/STAT pathway may also contribute to drug resistance.[138] These findings highlight the complex interplay between different signaling pathways in GIST and emphasize the need for combinatorial therapeutic strategies to effectively combat primary imatinib resistance (Figure 3C).

## Activation of Bypass Metabolic Pathways

Bypass pathway activation is an evolutionary escape mechanism in which GIST, under the selective pressure of targeted drug therapy, activate alternative receptor tyrosine kinases. This process bypasses the inhibited primary KIT pathway and reactivates downstream core signaling pathways, leading to drug resistance. Activation of the FGF/FGFR and FGF/VEGFR pathways may be involved in the resistance of GIST to imatinib. Studies have shown that in imatinib-resistant GIST cell lines and clinical specimens, the expression levels of FGF ligands (such as FGF2, FGF7) and their corresponding receptors (FGFR1, FGFR2, VEGFR2) are significantly upregulated compared to sensitive counterparts.

For example, activation of FGFR1 can phosphorylate and activate MEK and Akt, resulting in increased cell cycle progression from G1 to S phase and inhibition of apoptosis through upregulating anti-apoptotic proteins like Bcl-2. Additionally, the cross-talk between FGF/FGFR and FGF/VEGFR pathways further amplifies these pro-tumorigenic signals. VEGFR2, upon activation by FGF, not only enhances angiogenesis to provide sufficient nutrients for tumor growth but also directly interacts with KIT to modulate its phosphorylation status, potentially reducing the sensitivity of KIT to imatinib. These findings suggest that the FGF/FGFR and FGF/VEGFR pathways play crucial roles in mediating imatinib resistance in GIST by activating alternative signaling axes.[124,139–141] Furthermore, overexpression of insulin-like growth factor 1 receptor (IGF-1R) can form heterodimers with KIT or activate downstream signaling molecules such as PI3K directly, bypassing the inhibited KIT kinase domain and thus contributing to resistance.[142,143]

Research has found that in some GISTs resistant to imatinib, there is amplification of the MET gene or overexpression of the protein. This overexpression or amplification can lead to the activation of MET signaling pathways independently of KIT, thereby promoting cell proliferation and survival. For example, activation of MET can phosphorylate downstream molecules like AKT and ERK, which are crucial for cell growth and anti-apoptotic processes, thus bypassing the inhibited KIT signaling and contributing to imatinib resistance in GISTs.[142] Additionally, some studies have indicated that there may be crosstalk between MET and other receptor tyrosine kinases, further complicating the resistance mechanism by providing alternative routes for signal transduction.[144,145] In imatinib-resistant GIST models, ETV1 expression is often sustained or even upregulated, which can partially offset the growth inhibitory effects of imatinib despite KIT pathway inhibition. ETV1 acts as a critical transcriptional regulator that maintains the survival and proliferation of GIST cells by controlling the expression of genes involved in cell cycle progression, anti-apoptosis, and stemness. Mechanistically, ETV1 may transcriptionally activate alternative pro-survival genes, such as those encoding for certain cyclins (eg, cyclin D1) and anti-apoptotic proteins, thereby promoting cell cycle entry and inhibiting programmed cell death. Additionally, ETV1 might interact with other signaling pathways activated in resistant GIST, such as the FGF/FGFR or IGF-1R pathways, to amplify their downstream oncogenic signals. For instance, ETV1 could potentially bind to the promoters of FGFR1 or IGF-1R and enhance their expression, creating a feed-forward loop that further strengthens bypass pathway activation. This sustained or increased ETV1 activity thus represents another layer of adaptive resistance, allowing GIST cells to maintain their malignant phenotype even when the primary KIT/PDGFRA pathway is effectively blocked by imatinib. In GIST cells, MAPK downstream of KIT activates a positive feedback loop that stabilizes the ETV1 protein, while ETV1, in turn, positively regulates KIT expression.[146] In addition to the above, activation of AXL not only promotes proliferation through pathways such as MAPK but, more importantly, induces epithelial–mesenchymal transition. AXL is a member of the TYRO3/AXL/MER receptor family, and its overexpression is associated with increased drug resistance and invasiveness in various cancers. This process renders the tumor both drug-resistant and more aggressive.[144,147,148] Gasparotto et al found that the Hedgehog and WNT/β-catenin signaling pathways were activated in GISTs[149] Iruzubieta et al have also suggested that the activation of Hedgehog signaling is closely related to the homeostasis of the tumor microenvironment in GIST and the survival of tumor cells[150] Collectively, the activation of these diverse bypass metabolic pathways highlights the complex and multifactorial nature of drug resistance in GIST, underscoring the need for combinatorial therapeutic strategies that target both the primary KIT pathway and these alternative signaling axes to overcome resistance. Mastering the mechanisms of bypass activation in GISTs is crucial for understanding the disease progression of GIST and developing future treatment strategies (Figure 3D).

## Epigenetic Modification Changes Lead to Drug Resistance in GIST

Epigenetic modifications, which involve heritable changes in gene expression without altering the DNA sequence itself, have emerged as critical regulators of imatinib resistance in GIST. The key molecular mechanisms of DNA and chromatin epigenetic modifications can be classified into four major categories: DNA and RNA methylation, regulation of noncoding RNA (ncRNA), covalent post-translational modifications of histones, and noncovalent interaction mechanisms. Among these, DNA methylation, histone modifications, and non-coding RNA (ncRNA)-mediated gene silencing or activation play pivotal roles in rewiring the tumor cell's signaling landscape to evade the inhibitory effects of imatinib.

DNA methylation, the most extensively studied epigenetic modification, often occurs at CpG dinucleotides in gene promoter regions, typically leading to transcriptional repression. In GIST, aberrant hypermethylation of tumor suppressor genes or genes encoding negative regulators of oncogenic pathways has been linked to imatinib resistance. For instance, hypermethylation of the *PTEN* gene promoter results in decreased PTEN expression.[151] This loss of PTEN function leads to unchecked activation of the PI3K/AKT/mTOR cascade, which may independently drive cell proliferation and survival even when KIT is inhibited by imatinib. A genome-wide DNA methylation analysis also revealed that hypermethylation of REC8, p16, PAX3, SDH is closely associated with the poor prognosis of GIST.[152,153] Similarly, methylation-dependent silencing of genes involved in drug influx (eg, organic cation transporters) or efflux (eg, ATP-binding cassette transporters) can alter imatinib's intracellular concentration, reducing its efficacy. Conversely, hypomethylation of proto-oncogenes or genes encoding positive regulators of alternative signaling pathways can lead to their upregulation, further contributing to resistance. Furthermore, post-transcriptional modifications also play a significant role in drug resistance mechanisms. For example, N6-methyladenosine (m6A) is a frequently occurring mRNA modification, which regulates mRNA stability, splicing, and translation. Methyltransferase METTL3 can enhance the expression of MRP1 by facilitating the m6A modification of the 5' untranslated region of MRP1 mRNA, thereby further promoting drug resistance in GIST.[154] While these preclinical observations suggest that DNA and RNA methylation could be potential targets for overcoming imatinib resistance, their clinical applicability remains to be fully validated, and these findings should be interpreted as observational hypotheses rather than clinically actionable strategies at this stage.

Non-coding RNAs (ncRNAs), particularly microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), have emerged as key epigenetic modulators in GIST imatinib resistance. These molecules form a complex regulatory network that influences drug response by modulating gene expression at the post-transcriptional and epigenetic levels. MiRNAs are small (~22 nucleotide) ncRNAs that post-transcriptionally regulate gene expression by binding to the 3'-untranslated region (3'UTR) of target mRNAs, leading to mRNA degradation or translational repression. In GIST cells, miR-409-5p may promote imatinib resistance by targeting the expression of lysine-specific demethylase 4D (KDM4D).[155] Overexpression of miR-218 can reduce the resistance of GIST cells to imatinib.[156] MiR-125a-5p can promote drug resistance in GISTs by regulating the phosphorylation of focal adhesion kinase.[157] Conversely, downregulation of tumor-suppressive miRNAs (eg, miR-34a, miR-143/145 clusters) can result in the overexpression of their oncogenic targets.[158–160] LncRNAs, which are longer than 200 nucleotides, exert their regulatory functions through diverse mechanisms, including acting as sponges for miRNAs (competing endogenous RNAs), guiding chromatin-modifying complexes to specific genomic loci, or interacting with proteins to modulate their activity. For example, the lncRNA OIP5-AS1 modulates SOX9 expression through miR-145, influencing drug resistance in GIST.[161] LncRNA HOTAIR and lncRNA MSC-AS1 also confer imatinib resistance in GIST.[162,163] Additionally, Recent studies on circular RNAs (circRNA) have also demonstrated dysregulated circRNAs, such as circRNA_06551, circRNA_14668, circRNA_04497, circRNA_08683, circRNA_09923, circRNA_23636, and circRNA_15734, exhibit differences in drug-resistant GIST cells; however, their functions require further investigation.[164] A study showed that circ-CCS promotes autophagy-related drug resistance in GIST.[165] Collectively, ncRNAs form a delicate and adaptable regulatory network that precisely controls the core mutation pathway and numerous bypass pathways at post-transcriptional and epigenetic levels, collectively determining the ultimate fate of tumor cells. NcRNAs have opened a novel and promising research frontier for understanding and ultimately overcoming drug resistance in GIST. It is important to emphasize that these findings are primarily preclinical, and distinguishing between these observational hypotheses and clinically actionable strategies remains critical. Currently, no ncRNA - based therapies for GIST drug resistance have been validated for routine clinical use (Table 2).

Histone modifications, including acetylation, methylation, phosphorylation, and ubiquitination, dynamically regulate chromatin structure and accessibility, thereby influencing gene transcription. In imatinib-resistant GIST cells, alterations in the activity of histone-modifying enzymes, such as histone deacetylases (HDACs) and histone methyltransferases (HMTs), have been observed. Increased HDAC activity, for example, leads to deacetylation of histone tails, resulting in a condensed chromatin structure that restricts the access of transcriptional machinery to tumor suppressor gene promoters. This can silence genes that are crucial for inducing apoptosis or cell cycle arrest in response to imatinib.[166,167] On the other hand, specific histone methylation marks, such as trimethylation of histone H3 at lysine 4 (H3K4me3, associated with active transcription) or lysine 27 (H3K27me3, associated with transcriptional repression),

**Table 2** Summary of ncRNAs Involved in Imatinib Resistance in GIST

| ncRNA Type | ncRNA Name | Expression in Resistant Cells | Proposed Mechanism/Target | Reference |
|---|---|---|---|---|
| **miRNA** | miR-409-5p | Upregulated | Targets KDM4D | [153] |
| | miR-218 | Downregulated | Regulates PI3K/AKT pathway | [154] |
| | miR-125a-5p | Upregulated | Regulates FAK phosphorylation | [155] |
| | miR-34a | Downregulated | Loss of tumor-suppressive function | [156] |
| | miR-143/145 cluster | Downregulated | Targets peroxiredoxin 5 | [157,158] |
| **lncRNA** | OIP5-AS1 | Upregulated | Sponges miR-145 to modulate SOX9 | [159] |
| | HOTAIR | Upregulated | Regulates miR-130a/ATG2B pathway (autophagy) | [160] |
| | MSC-AS1 | Upregulated | Activates FNDC1/ANLN-mediated PI3K/AKT pathway | [161] |
| **circRNA** | Multiple circRNAs* | Dysregulated | Functions require further investigation | [162] |
| | circ-CCS | Upregulated | Regulates miR-197-3p/ATG10 axis (autophagy) | [163] |

**Abbreviations**: ncRNA, non-coding RNA; miRNA, microRNA; lncRNA, long non-coding RNA; KDM4D, lysine-specific demethylase 4D; circRNA, circular RNA; SOX9, SRY-box transcription factor 9; ATG2B, autophagy-related protein 2 homolog B; FNDC1, fibronectin type III domain containing 1; ANLN, anillin; ATG10, autophagy-related 10.

can be dysregulated. For instance, upregulation of certain HMTs might lead to increased H3K4me3 at the promoters of genes involved in bypass pathways like the MAPK/ERK or JAK/STAT pathways, enhancing their expression and promoting resistance.[168] KDM4D, as a histone demethylase, is overexpressed in GIST and promotes the progression of GIST via HIF1-β/VEGFA signaling.[169] In GIST, EZH2 may be overexpressed, resulting in excess addition of H3K27me3 inhibitory marks to differentiation genes. This locks cells in a differentiated state and promotes imatinib resistance.[170,171] BET family proteins act as readers of acetylated lysine residues by noncovalently binding to acetylated histones through their bromodomains, subsequently recruiting transcriptional machinery to robustly drive gene transcription.[172] While HDAC inhibitors, BET inhibitors, and other epigenetic-targeting agents have shown promise in preclinical GIST models, their efficacy and safety in clinical settings for treating imatinib-resistant GIST remain under investigation, and these agents should not be considered clinically actionable strategies until further clinical validation is completed.

Furthermore, the interplay between epigenetic modifications and genetic mutations in GIST is increasingly recognized. For example, primary KIT mutations themselves may influence the epigenetic landscape of the tumor cell. Mutant KIT can interact with and activate epigenetic modifiers, leading to changes in DNA methylation or histone modification patterns that favor resistance. Additionally, epigenetic modifications can create a permissive environment for the acquisition of secondary mutations in KIT or other genes, accelerating the development of resistance.[173]

Collectively, these epigenetic modifications contribute to imatinib resistance in GIST by altering the expression of a broad spectrum of genes involved in cell survival, proliferation, drug metabolism, and alternative signaling pathway activation. Understanding the specific epigenetic changes and their functional consequences in resistant GIST not only enhances our comprehension of the molecular basis of resistance in preclinical systems but also highlights potential therapeutic targets that merit further clinical investigation to bridge this translational gap (Figure 3E).

## Tumor Microenvironment Contribute to Imatinib Resistance

The heterogeneous nature of tumors poses a significant challenge in overcoming imatinib resistance in advanced GIST. Within the complex tumor microenvironment (TME) of GIST, various cellular and non-cellular components interact dynamically to foster a niche that promotes imatinib resistance. Cancer-associated fibroblasts (CAFs), a prominent stromal cell type, play a crucial role. They can secrete a plethora of growth factors, such as hepatocyte growth factor (HGF), FGF, and PDGF, which bind to their respective receptors on GIST cells.[174,175] Yoon et al indicates that CAFs highly express PDGFC, which can promote the progression of GIST by activating the PDGFC/PDGFRA signaling pathway[176] CAFs may secrete transforming growth factor-β2, activate the PI3K/AKT signaling pathway, and thereby promote drug resistance in GIST cells.[177] This ligand-receptor interaction activates downstream signaling cascades, most notably the PI3K/AKT/mTOR and RAS/RAF/MEK/ERK pathways, which are known to drive cell survival and proliferation independently of KIT or PDGFRA, thereby bypassing the inhibitory effect of imatinib.[176] For instance,

HGF binding to MET receptor tyrosine kinase on GIST cells leads to the activation of PI3K, resulting in AKT phosphorylation and subsequent inhibition of apoptotic pathways, allowing the tumor cells to survive even in the presence of imatinib.[178] Additionally, CAFs can remodel the extracellular matrix by producing excessive collagen and matrix metalloproteinases.[179] This remodeling not only provides structural support for tumor growth but also creates a physical barrier that may limit the penetration of imatinib into the core of the tumor, reducing its effective concentration at the target site.

Immune cells within the TME also contribute to imatinib resistance. Immune infiltration in patients with GIST is associated with tumor-stem-cell-like characteristics, and this relationship depends on tumor purity.[180] Single-cell analysis revealed a substantial presence of immune cells in the GIST microenvironment, including T cells, macrophages, tumor cells, and natural killer cells.[181] Liu et al revealed the single-cell characteristics within the tumor microenvironment of imatinib-resistant GISTs through single-cell analysis Their findings suggest that imatinib resistance in GISTs is closely associated with regulatory T cells, which may influence tumor imatinib resistance via the TIGIT/NECTIN2 axis. Myeloid-derived suppressor cells (MDSCs) and tumor-associated macrophages, often of the M2 polarization phenotype, can exert immunosuppressive effects, preventing an effective anti-tumor immune response. Xiao et al explored the function of macrophages GIST cells can regulate the differentiation of macrophages into M2-type macrophages through the MIF/CXCR4 axis, thereby facilitating immune escape.[182] However, beyond immune suppression, these cells can also directly influence therapeutic resistance. MDSCs, for example, have been shown to release reactive oxygen species and nitric oxide, which can induce oxidative stress in GIST cells. This stress may lead to the upregulation of drug efflux transporters, such as P-gp, which actively pump imatinib out of the cells, decreasing intracellular drug accumulation.[183,184] Additionally, IDO-positive dendritic cells are highly expressed in the microenvironment of imatinib-resistant GISTs, although their mechanisms of action require further investigation.[185]

The hypoxic microenvironment, a common feature of solid tumors including GIST due to rapid growth outpacing angiogenesis, is another key contributor. Hypoxia-inducible factor-1 alpha (HIF-1α), a master regulator of the cellular response to hypoxia, is stabilized under low oxygen conditions. HIF-1α can transcriptionally activate the expression of various genes involved in angiogenesis (eg, VEGF), glycolysis (eg, glucose transporter 1, GLUT1; hexokinase 2, HK2), and cell survival.[186–188] The shift towards glycolytic metabolism, known as the Warburg effect, allows GIST cells to generate ATP even in hypoxic conditions, ensuring their energy supply for proliferation and survival. Furthermore, the extracellular vesicles (EVs) released by both tumor cells and stromal cells in the TME have emerged as important mediators of intercellular communication and drug resistance. These EVs can carry bioactive molecules such as proteins, lipids, and nucleic acids (including miRNAs and mRNAs) that can be transferred to recipient GIST cells.[189,190] EVs from imatinib-resistant GIST cells can transfer resistance-related proteins or miRNAs to sensitive cells, thereby propagating the resistant phenotype.[191,192] This horizontal transfer of resistance mechanisms within the TME exacerbates the problem of heterogeneity and makes the development of effective therapies more challenging. Notably, these TME components may function as an integrated network to collectively drive imatinib resistance in GISTs. CAFs initiate resistance by activating bypass signaling and remodeling the extracellular matrix. Transforming growth factor beta 1 (TGFβ1), secreted by CAFs, amplifies the cellular communication network factor 2 (CCN2) signaling axis, which subsequently activates the PI3K/AKT pathway, ultimately driving metabolic reprogramming in tumor cells. Conversely, CCN2 secreted by GIST cells promotes TGFβ1 production in CAFs, thereby further enhancing the drug resistance-promoting effect.[174,176,193] Immune cells such as MDSCs and regulatory T cells reinforce resistance by inducing oxidative stress and suppressing anti-tumor immunity, while EVs serve as a universal mediator to transfer resistance traits between all TME components, propagating resistance across the tumor.[194–197] This synergistic crosstalk creates a self-sustaining, resistance-promoting niche that amplifies the individual effects of each component, making the TME a robust driver of imatinib insensitivity. Collectively, the intricate interplay between GIST cells and their microenvironment creates multiple layers of bypass signaling activation, significantly contributing to the development and maintenance of imatinib resistance. Expanding the research perspective on GIST drug resistance from focusing solely on tumor cells to encompassing the entire tumor microenvironment offers a broader range of promising therapeutic targets and combination strategies to overcome this clinical challenge (Figure 3F).

## Ongoing New Treatment Strategy

To address imatinib resistance in GIST and improve outcomes for advanced patients, numerous emerging therapeutic strategies are under development. These strategies aim to overcome resistance mechanisms through diverse approaches, including novel tyrosine kinase inhibitors (TKIs) with broader specificity or ability to target mutant kinases, combination therapies that simultaneously inhibit multiple signaling pathways, and targeted delivery systems to enhance drug efficacy and reduce off-target effects. Furthermore, preclinical studies are investigating the potential of epigenetic modulators, which can reverse aberrant gene expression patterns associated with drug resistance, as well as proteolysis-targeting chimeras (PROTACs) that selectively degrade oncogenic proteins, offering a novel mechanism to overcome resistance.

### Next-Generation TKIs and Downstream Pathway Inhibitors

The development of next-generation TKIs targeting KIT and PDGFRA remains the most clinically validated strategy for overcoming imatinib resistance, as these agents address core resistance mechanisms including secondary KIT mutations and primary PDGFRA alterations. Currently, clinical trials are underway to develop new TKIs or inhibitors targeting downstream signaling pathways. By 2024, a total of 57 targets had been involved in drug clinical trials for GIST.[198] The top six targets with the highest frequency of occurrence are KIT, PDGFRA, KDR (VEGFR2), FMS-like tyrosine kinase (FLT)3, FLT1 (VEGFR1), and FLT4 (VEGFR3).[198] Drug development involves not only multipathway inhibitors such as crenolanib (a TKI targeted to PDGFR-β, PDGFRA and FLT3, more selective for PDGFR),[199,200] famitinib [a TKI targeted to KDR (VEGFR2), FLT4 (VEGFR3), KIT and FLT3], and nilotinib (a TKI targeting the BCR activator of RhoGEF and GTPase, ABL1, KIT and PDGFRA),[201–203] but also some non-TKIs, such as pimitespib (heat shock protein 90 inhibitor).[204,205] TKIs and downstream pathway inhibitors, such as the MEK inhibitor binimetinib, can enhance the induction of apoptosis in GIST cells.[206]

### Combination Therapy Strategies

Rationally designed combination therapies, targeting multiple resistance pathways simultaneously, represent another high-priority approach with strong emerging clinical evidence. A key strategy involves combining TKIs with inhibitors of downstream signaling pathways to block bypass mechanisms. For example, a Phase 2 clinical study investigated the role of imatinib combined with binimetinib in primary progressive stromal tumors. The results indicate that the best ORR was 69.0%, and the median PFS was 29.9 months.[207] In addition to the favorable efficacy of imatinib combined with bimethimib in treating primary progressive tumors observed in the aforementioned Phase II clinical study, basic research has demonstrated that MEK, a key kinase in the RAS-RAF-MEK-ERK signaling pathway, plays a significant role in the pathogenesis of certain GISTs through its aberrant activation.[208] This is particularly evident in GISTs with wild-type KIT/PDGFRA or secondary drug-resistant mutations, where this pathway may serve as a critical driver. The combined use of MEK inhibitors can effectively block this alternative activation pathway, thereby enhancing the cytotoxic effect of imatinib on tumor cells and delaying the development of drug resistance. Furthermore, strategies involving inhibitors targeting other signaling pathways are actively under investigation. Multiple preclinical studies have shown that PI3K inhibitors can synergistically enhance the antitumor effects of imatinib by inhibiting various aspects of tumor cell proliferation, survival, and angiogenesis.[117]

### Immunotherapy

Immunotherapy, though historically challenging in GIST due to its low mutational burden and immunosuppressive microenvironment, is gaining attention with the development of novel agents. Seifert et al demonstrated that PD-1/PD-L1 blockade alone had no therapeutic effect on stromal tumors However, when combined with imatinib, it can enhance the function of effector T cells and improve the therapeutic efficacy of imatinib.[209,210] Similarly, comparable conclusions were drawn in the relevant clinical trials of CTLA-4.[211,212] Furthermore, adoptive cell therapy, including chimeric antigen receptor (CAR)-T cells engineered to target GIST-specific antigens like KIT or PDGFRA, is in the early stages of development. Preclinical models have shown that CAR-T cells targeting KIT can specifically recognize and eliminate

GIST cells, with some studies reporting tumor regression in xenograft models.[210,213] Immunotherapy has emerged as a transformative approach in multiple solid tumors, but it is critical to explicitly acknowledge that results to date in GIST have been largely disappointing. These findings highlight the significant challenges in applying conventional immunotherapeutic strategies to GIST and underscore the need for more refined approaches that address the unique immunological features of this disease.

## Other Emerging Approaches (Limited Clinical Evidence)

Antibody-drug conjugates (ADCs) represent a promising approach, which can specifically deliver cytotoxic payloads to GIST cells by targeting antigens highly expressed on the tumor surface. For example, preclinical studies have evaluated ADCs targeting KIT, a key driver in GIST, showing potent antitumor activity in imatinib-resistant models by effectively internalizing and releasing cytotoxic agents within the tumor cells.[214,215]

Epigenetic modifiers, such as HDAC inhibitors, DNA methyltransferase inhibitors, and miRNA mimics or antagomiRs, are therefore being explored as promising agents to reverse epigenetic silencing of tumor suppressors or to downregulate oncogenic pathways, potentially resensitizing resistant GIST cells to imatinib.[216] The combination of exosomes, nanomaterials, and targeted therapy for treating GIST may represent a future trend in cancer treatment. Exosomes are natural nanomedicine carriers, loaded with TKIs like imatinib and sunitinib, or with siRNA/ncRNA targeting drug resistance genes, may be used to treat drug-resistant progressive GISTs. A few studies have confirmed that exosomes are associated with prognosis of GIST. As early as 2014, Atay et al proposed that GIST could affect the function of surrounding muscle cells through KIT proteins in exosomes, thereby promoting tumor metastasis[190] Subsequent studies have also demonstrated that GIST exhibits a distinct secretome signature, exosome transmission between tumor cells may be a mechanism contributing to drug resistance.[217,218] It was also mentioned in the previous text that the enriched exosomal lncRNA OIP5-AS1 mediates imatinib resistance in GIST by regulating miR-145 and SOX9.[161] Nanotechnology-based drug delivery systems have significantly improved the therapeutic efficacy and specificity of targeted drugs in cancer treatment. It is often used to facilitate the combined administration of other anticancer drugs that face significant challenges in cancer treatment.[219] At present, although many challenges remain, such as large-scale isolation, purification, and drug loading of exosomes, technical difficulties persist, and batch-to-batch variability is hard to control. Efficient and stable drug loading, as well as achieving specific and controllable release at tumor sites, still require optimization. Nevertheless, the potential demonstrated by exosomes will undoubtedly secure their important role in the future treatment of GIST and the broader field of oncology. The development of such epigenetic-based combinatorial therapies holds significant promise for improving outcomes in patients with imatinib-resistant GIST. These ongoing efforts in drug development, combination strategies, and novel therapeutic modalities hold great promise for improving the outcomes of GIST patients, especially those with advanced or refractory disease.

Another area of focus is personalized medicine based on molecular profiling. With the advancement of next-generation sequencing, it is now possible to identify rare or unique genetic alterations in individual GIST patients, which can guide the selection of tailored therapies. For instance, patients harboring *PDGFRA* D842V mutations, which are highly resistant to imatinib, may benefit from specific inhibitors like avapritinib. Moreover, liquid biopsies, such as ctDNA analysis, are being utilized to monitor treatment response and detect early resistance mechanisms, allowing for timely adjustment of therapeutic regimens.[220,221] The integration of liquid biopsy technologies into clinical practice holds great promise for real-time monitoring of clonal evolution and early detection of emerging resistance mutations, enabling timely adjustments to treatment regimens. Collaborative efforts between basic researchers, clinicians, and pharmaceutical companies are crucial to accelerate the translation of preclinical discoveries into novel therapeutic agents and optimize combination strategies. Additionally, addressing the challenges of intratumoral heterogeneity and ensuring equitable access to these advanced treatments across diverse patient populations will be essential to fully realize the potential of precision oncology in metastatic GIST.

# Conclusion

In summary, drug resistance in GIST is a complex, multifactorial phenomenon driven by diverse molecular mechanisms, including secondary mutations in KIT and PDGFRA, aberrant epigenetic modifications, dysregulation of the TME, and

activation of bypass signaling pathways. This review synthesizes the current understanding of these resistance mechanisms while prioritizing evidence-based emerging treatment strategies—most notably next-generation tyrosine kinase inhibitors (TKIs) and rationally designed combination therapies—that hold the greatest potential for improving clinical outcomes in patients with advanced GIST. It is important to explicitly acknowledge the inherent limitations of this review. As a narrative review, it relies on a non-systematic selection of literature, which may introduce potential selection bias. The evidence discussed encompasses heterogeneous study designs, including preclinical models and clinical trials of varying phases with differing levels of methodological rigor. This consideration should be taken into account when interpreting the collective findings. Given the rapidly evolving therapeutic landscape of GIST, some of the emerging strategies highlighted herein may be updated or refined as new clinical and preclinical data emerge. Despite these limitations, this review provides a comprehensive overview of the current state of knowledge regarding imatinib resistance mechanisms and ongoing treatment strategies in GIST. Future research should focus on bridging the translational gap between preclinical findings and clinical application, optimizing combination therapies to target multiple resistance pathways, and addressing the challenges posed by intratumoral heterogeneity. Additionally, continued advancements in molecular profiling and liquid biopsy technologies will facilitate the development of more personalized therapeutic approaches, ultimately improving the prognosis of patients with advanced or refractory GIST.

## Abbreviations

GIST, Gastrointestinal stromal tumors; PDGFRA, platelet-derived growth factor receptor-α; TKI, tyrosine kinase inhibitor; OS, overall survival; RTKs, receptor tyrosine kinases; SDH, succinate dehydrogenase; NF1, neurofibromatosis 1; NTRK3, neurotrophic receptor tyrosine kinase 3; ORR, objective response rate; PFS, progression-free survival; PTEN, phosphatase and tensin homolog; FGFR, fibroblast growth factor receptor; VEGFR, vascular endothelial growth factor receptor; mTOR, mammalian target of rapamycin; IGF-1R, insulin-like growth factor 1 receptor; ncRNA, non-coding RNA; miRNA, microRNA; lncRNA, long non-coding RNA; KDM4D, lysine-specific demethylase 4D; circRNA, circular RNA; HDAC, histone deacetylases; TME, tumor microenvironment; CAFs, cancer-associated fibroblasts; HGF, hepatocyte growth factor; HIF-1α, hypoxia-inducible factor-1 alpha; EV, extracellular vesicle; FLT, FMS-like tyrosine kinase; MDSC, Myeloid-derived suppressor cells; ADC, Antibody-drug conjugate; ctDNA, circulating DNA.

## Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China Programs [grant number 82001695]; Beijing Xisike Clinical Oncology Research Foundation [grant number Y-zai2021/ms-0133].

## Disclosure

The Authors declare that there are no conflicts of interest in this work.

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