Review

Therapeutic Role of Ripretinib in Gastrointestinal Stromal Tumor: A Next-Generation Tyrosine Kinase Inhibitor Addressing Resistance and Mutation Diversity

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Abstract: This review evaluates the efficacy of ripretinib in the management of gastrointestinal stromal tumors (GISTs), rare mesenchymal neoplasms. These tumors are primarily caused by mutations in the KIT proto-oncogene (CD117) or platelet-derived growth factor receptor alpha (PDGFRA) gene. The introduction of tyrosine kinase inhibitors (TKIs) such as imatinib has improved the treatment of GIST. However, the resistance to these TKIs has become a major impediment to its clinical management, particularly due to the occurrence of secondary resistance mutations in the KIT gene. Ripretinib, a novel switch-control inhibitor, represents a new-generation TKI designed to overcome this challenge. By targeting the switch pocket and activation loop, it has been reported to inhibit various KIT mutations, including secondary resistance mutations, as well as PDGFRA mutations. Clinical trials have demonstrated that ripretinib significantly prolongs progression-free and overall survival in patients who have failed third-line or later treatments. It also improves objective response rate and durability of response, with manageable adverse effects such as alopecia and fatigue. Emerging data further suggest mutation-specific efficacy, particularly in exon 11 and exon 17/18 combinations, highlighting the potential for personalized therapy. This review highlights the development, mechanism of action, and key clinical outcomes of ripretinib, with an emphasis on its potential to overcome resistance and its role in personalized GIST therapy.

Keywords: gastrointestinal stromal tumor; KIT; tyrosine kinase inhibitor; ripretinib

1. Introduction

Gastrointestinal stromal tumor (GIST) is a rare tumor that occurs in the gastrointestinal tract, primarily caused by mutations in the KIT gene. It is often difficult to diagnose early due to their asymptomatic nature. The majority of GIST patients carry KIT gene mutations, while some exhibit platelet-derived growth factor receptor alpha (PDGFRA) gene mutations [1].

The treatment of GIST has significantly advanced with the introduction of tyrosine kinase inhibitors (TKIs). TKIs, such as imatinib, sunitinib, and regorafenib, have been used in GIST treatment and have substantially improved patient outcomes; however, resistance to these drugs has emerged as a major issue, and most patients ultimately experience disease progression despite sequential therapy. In particular, the occurrence of secondary resistance mutations in the KIT gene often limits the effectiveness of existing therapies [2,3]. Considering this background, there is an urgent need to develop new therapies with more effective mechanisms of action. Although avapritinib has also been approved, its use is restricted to patients with PDGFRA D842V mutations, highlighting the need for broader-spectrum options such as ripretinib.

Ripretinib, a recently designed new-generation TKI, can effectively inhibit various KIT and PDGFRA mutations. Known as a 'switch control inhibitor', ripretinib has a unique mechanism of action that simultaneously targets the switch pocket and activation loop of KIT and PDGFRA. Due to these characteristics, ripretinib is expected to provide a new treatment option for GIST patients who show resistance to existing therapies [4].

This review discusses the significance of ripretinib in GIST treatment and proposes future research directions based on its development background, mechanism of action, and key clinical research findings. Additionally, the safety profile and clinical applications of ripretinib are discussed, emphasizing the importance of personalized treatment strategies in providing optimal treatment options for GIST patients.

2. KIT

KIT, also known as CD117, is a type of protein tyrosine kinase. It is a receptor tyrosine kinase that spans the cell membrane and is activated by binding to its ligand, stem cell factor. When KIT binds to its ligand, it activates signaling pathways related to cell proliferation and survival, such as Janus kinase (JAK)/Signal transducer and activator of transcription (STAT), RAS/mitogen-activated protein kinase (MAPK), and phosphatidylinositol 3-kinase (PI3K)/Akt pathways (Figure 1) [5]. KIT is characteristically expressed in hematopoietic stem cells, melanocytes, and interstitial cells of Cajal [6].

The c-kit gene, which encodes KIT, is a proto-oncogene. Mutations in c-kit can lead to excessive activation or ligand-independent activation of KIT, potentially causing tumors. Diseases caused by c-kit mutations include GISTs, acute myeloid leukaemia (AML), and melanoma. In particular, GIST is closely associated with KIT mutations, with the majority of GIST patients expressing KIT mutations, which is used as a diagnostic marker [5].

KIT mutations primarily occur in exon 11, a region known as the juxtamembrane (JM) segment, which regulates the KIT signaling pathway through phosphorylation. Deletions or missense mutations in this region alter the protein structure, resulting in the loss of the JM segment's inhibitory function on KIT signaling. Other significant KIT mutations include those in exon 9, which affects the extracellular domain where the ligand binds, and exon 17, which involves the activation segment [7,8].

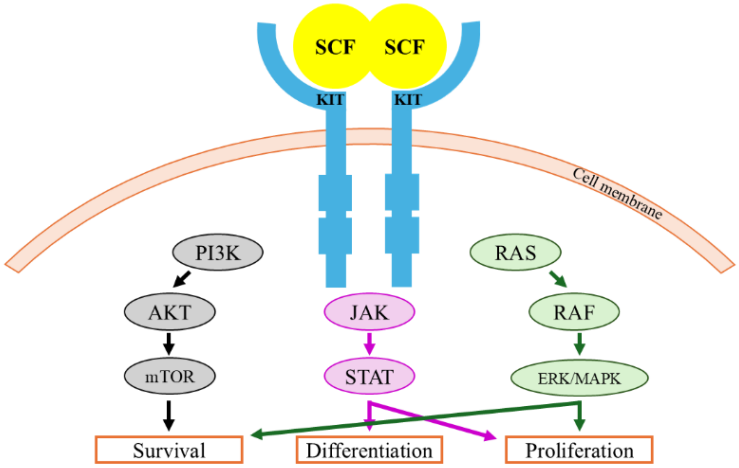

Figure 1. Major signaling pathway of KIT. The binding of stem cell factor (SCF) to the KIT receptor induces receptor dimerization and activates various signaling pathways, including JAK/STAT, RAS/MAPK, and PI3K/AKT. These are associated with cell survival, differentiation, and proliferation. JAK, Janus kinase; STAT, signal transducer and activator of transcription; RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; ERK, extracellular signal–regulated kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mechanistic target of rapamycin.

3. GIST

GIST is a rare cancer that occurs in the gastrointestinal tract, accounting for approximately 1–3% of all gastrointestinal tumors. It primarily originates from the interstitial cells of Cajal in the gastrointestinal tract, mainly occurring in the stomach (60%) and small intestine (30%), but can be found throughout the gastrointestinal system. When the tumor is small, symptoms may not appear. As it grows, non-specific symptoms, such as abdominal pain, fatigue, indigestion, and fever, may develop. Lymph node metastasis is rare, and when metastasis occurs, it primarily spreads to the liver. In the early stages, it's difficult to recognize the disease due to its asymptomatic nature [1].

GIST is often discovered during health screenings, primarily through endoscopy, and subsequently diagnosed through imaging tests and biopsies. About 75–80% of GIST patients have KIT gene mutations, followed by SDH-deficient GIST (about 13.9%) and PDGFRA mutations (about 10%). Therefore, KIT expression is the first marker checked during diagnosis [1]. Although less frequent, PDGFRA encodes a receptor tyrosine kinase closely related to KIT and represents another key oncogenic driver in GIST. If KIT is negative, other diseases can be ruled out, or a diagnosis can be made through testing with the Discovered On GIST 1(DOG-1) antibody, which is sensitive to GIST [2,9]; in addition, molecular analysis of PDGFRA mutations can support the diagnosis, particularly in KIT/DOG-1–negative cases [10,11].

Most GIST patients are classified into KIT mutation subtypes, with KIT mutations primarily occurring in exons 11, 9, 13, and 17. Exon 11 mutations are mainly deletion or missense mutations, with deletion mutations

accounting for 60–70% and missense mutations for 20–30%. Generally, deletion mutations have a poorer prognosis than missense mutations. Exon 9 mutations tend to be resistant to imatinib, the first-line treatment, and show an aggressive prognosis. Exon 13 mutations don't have a poor prognosis, but may develop resistance to imatinib. Exon 17 mutations have a poor prognosis and a high risk of recurrence due to resistance mutations to treatment. Exon 11 and 9 mutations are primarily first-line mutations related to initial tumor formation, while exon 13 and 17 mutations are mainly secondary mutations associated with resistance during treatment [12,13].

Since most GISTs are caused by KIT mutations, treatments primarily use drugs that inhibit KIT. TKIs are classified as therapeutic agents that inhibit tyrosine kinases, targeting BCR-ABL, KIT, PDGFR, and others. Imatinib is typically used for GIST treatment, with sunitinib and regorafenib also used depending on the situation [2].

The primary treatment for resectable GIST is surgery, aiming for complete resection. Resection is strongly recommended for tumors larger than 2 cm or growing. The main goal of surgery is to resect the tumor without rupture. Small tumors have a low malignancy potential but cannot be ruled out for malignant transformation, so caution is needed. When a small GIST is suspected, resection should be performed instead of endoscopic removal. Laparoscopic or lymph node metastasis resection can be performed as needed [2].

When resection is deemed impossible or advanced GIST is diagnosed, drug treatment with TKIs is initiated. Both domestic and international guidelines recommend an initial imatinib dose of 400 mg orally once daily for GIST treatment. However, for patients with KIT exon 9 mutations, who may be resistant, increasing the dose to 800 mg is recommended. If the disease progresses during imatinib treatment, increasing the imatinib dose or switching to another TKI like sunitinib is considered. In cases where no improvement is observed following sunitinib treatment, regorafenib is considered a third-line treatment [2].

The first-line GIST treatment, imatinib, has a progression-free survival of about 1.7–2 years, after which secondary resistance mutations can lead to progressive GIST. Second- and third-line treatments, sunitinib and regorafenib, have progression-free survival periods of 5.6 and 4.8 months, respectively, indicating incomplete inhibition of secondary resistance mutations (Figure 2) [3]. Particularly, when secondary resistance mutations occur, they often appear in exon 17, which frequently shows resistance to existing treatments like imatinib, sunitinib, and regorafenib. Therefore, current TKIs are not adequate for GIST treatment, which calls for the need for new therapeutic agents.

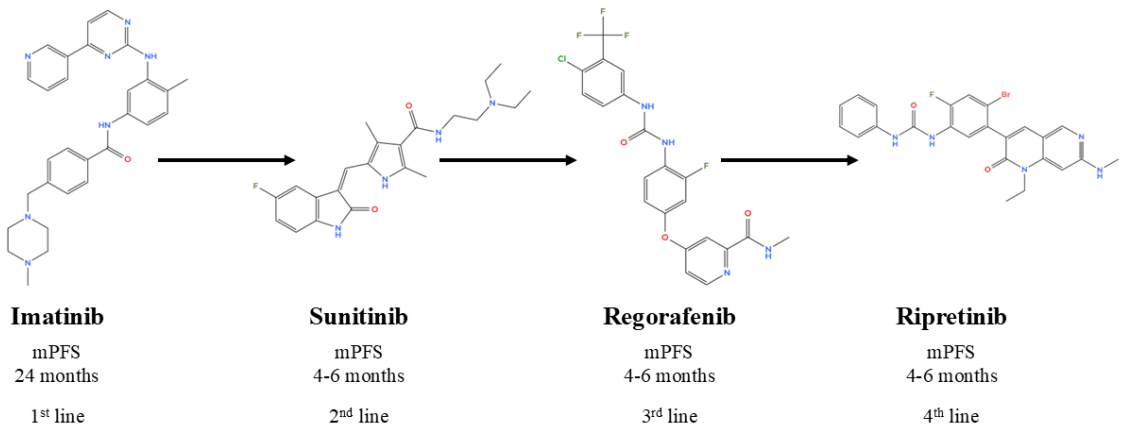

Figure 2. The structures and stages of four GIST treatment drugs. Structures were generated using *MolView.org v2.4.* mPFS, median progression-free survival.

4. Ripretinib

Ripretinib is an oral targeted anticancer drug developed for GIST treatment. Developed by Deciphera Pharmaceuticals, this drug is a multi-tyrosine kinase inhibitor that effectively inhibits various tyrosine kinases, including KIT and PDGFRA mutations. Ripretinib was specifically designed for GIST patients showing resistance to three or more TKI treatments and has a unique mechanism that effectively acts on tumor cells resistant to existing TKI treatments [13]. In clinical trials, ripretinib significantly improved progression-free survival (PFS) and overall survival (OS), while showing a relatively manageable side effect profile [14,15]. Based on these results, it received FDA approval in 2020 and EMA approval in 2021 and is now used clinically under the brand name Qinlock. Therefore, ripretinib is considered a new treatment modality for GIST patients who are unresponsive to existing therapies.

4.1. Structure and Mechanism of Action of Ripretinib

Ripretinib is also classified as a switch control tyrosine kinase inhibitor as it inhibits KIT and PDGFRA by regulating the Switch pocket of tyrosine kinase. KIT is a dual-switch kinase with two switches: the ATP-binding site in the exon 13/14 region and the activation loop in the exon 17/18 region. The key structures of ripretinib include the terminal phenyl, bromine, and pyridone ring. The terminal phenyl portion of ripretinib binds to exon 11, inhibiting the JM segment and the adjacent ATP binding site, while the bromine substituent and pyridone ring bind to exon 17, inhibiting the activation loop [4]. Unlike existing TKIs used in GIST treatment that only bind to the ATP binding site to inhibit KIT, ripretinib also binds to exon 17, inhibiting the activation loop, thus overcoming exon 17 secondary resistance mutations. This allows ripretinib to effectively act on various KIT mutations [4].

In recombinant KIT in vitro inhibition experiments, imatinib, sunitinib, regorafenib, and ripretinib were all effective against wild-type KIT. However, imatinib showed resistance to all KIT exon 13, 14, and 17 mutants used in the experiment, while sunitinib and regorafenib showed resistance to exon 17 (Table 1) [4]. Experiments using GIST cell lines showed similar trends. All four types of TKIs showed activity against exon 11 mutant GIST, but imatinib was resistant to mutations, including exon 13 and exon 17. Sunitinib also showed resistance to mutations, including exon 17. Regorafenib and ripretinib demonstrated activity against mutations, including exon 17 (Table 2) [4]. These in vitro experiments demonstrate that ripretinib can effectively inhibit various KIT mutations. Notably, it shows efficacy even in GIST cell lines resistant to existing treatments, including various drug-resistant mutations.

Table 1. In vitro inhibition of recombinant KIT kinase by TKIs. The table summarises the responsiveness of representative KIT statuses/mutations to four TKIs (imatinib, sunitinib, regorafenib, and ripretinib) [4].

	Recombinant KIT Statuses/Mutations				
	JMD Phosphorylated WT KIT	**KIT V654A Exon 13**	**KIT T670I Exon 14**	**KIT D816H Exon 17**	**KIT D816V Exon 17**
Tyrosine Kinase Inhibitor	**IC_{50} (nM)**				
Imatinib	66 ± 10	>3300	>3300	>3300	>3300
Sunitinib	2.9 ± 0.5	8.1 ± 1.0	1.3 ± 0.6	>3300	2800 ± 900
Regorafenib	4.4 ± 0.5	17 ± 8	2.6 ± 0.7	1450 ± 140	>3300
Ripretinib	3.0 ± 0.5	11 ± 6	9.2 ± 1.1	18 ± 4	25 ± 9

Table 2. Suppression of KIT phosphorylation in GIST cell lines. The table summarizes the responsiveness of various GIST cell lines to four TKIs (imatinib, sunitinib, regorafenib, and ripretinib) [4].

	Types Of GIST Cell Lines			
	GIST T1 Exon 11 (△JMD)	**GIST 430 Exon 13 (△JMD/V654A)**	**GIST 48 Exon 11/17 (V560D/D820A)**	**GIST 882 Exon 13 (K642E)**
Tyrosine Kinase Inhibitor	**IC_{50} (nM)**			
Imatinib	12	>3000	>3000	12
Sunitinib	3	37	>3000	>3000
Regorafenib	2	9	41	137
Ripretinib	3.0 ± 0.9	7.9 ± 2.1	53 ± 29	21 ± 10

4.2. Ripretinib Clinical Trials

4.2.1. Preclinical Studies

To verify ripretinib's antitumor activity, efficacy experiments used a GIST T1 xenograft mouse model with exon 11 mutations and a GIST patient-derived xenograft (PDX) mouse model with exon 11 and 17 mutations. In the T1 xenograft model, ripretinib treatment achieved an approximately five-fold reduction in the tumor burden compared to the control group. In the PDX model, the tumor burden was also significantly reduced in a dose-dependent manner, showing a two-fold decrease at the lower dose and a five-fold decrease at the higher dose. Importantly, survival rates were markedly improved in both models: in the T1 model, survival increased from 25% in the control group to 100%

with treatment; in the PDX model, survival rose from 10% in the control group to 90–100% in the treated groups, depending on dose. Analysis of the phosphorylation level of proteins associated with the KIT signaling pathway after ripretinib administration in GIST PDX mice showed significantly decreased phosphorylation of KIT, STAT5, AKT, and extracellular signal-regulated kinase1/2 compared to the control group [4].

4.2.2. Phase 1 and 2 Trials

A total of 258 patients participated in trials evaluating the safety and efficacy of ripretinib. The Phase 1 dose-escalation phase included 68 patients with advanced GIST and other advanced malignancies, while the Phase 2 expansion phase included 184 patients with advanced GIST. In Phase 1, the initial oral dose of 20 mg was escalated, ultimately determining 150 mg once daily as the recommended Phase 2 dose (RP2D), which was used in the expansion phase.

All 142 advanced GIST patients treated with ripretinib 150 mg once daily experienced treatment-emergent adverse events, with drug-related events occurring in 99.3% of patients. Despite the high incidence, most adverse events were manageable, and the rate of treatment discontinuation remained relatively low (14.1%) [14]. The median PFS (mPFS) with ripretinib was 10.7 months for second-line treatment, 8.3 months for third-line, and 5.5 months for fourth-line or beyond. Given the limited efficacy of sunitinib and regorafenib, ripretinib was evaluated as a well-tolerated and effective treatment. Based on this research, the INVICTUS phase 3 trial for fourth-line or beyond treatment with ripretinib was initiated [14].

4.2.3. Phase 3 Trial (INVICTUS)

The Phase 3 INVICTUS trial involved patients with advanced GIST who had progressed on imatinib, sunitinib, and regorafenib. Patients were randomly assigned to receive either ripretinib 150 mg once daily or placebo. A total of 129 patients participated. The primary endpoints were PFS and the objective response rate (ORR), and overall survival (OS) was a secondary endpoint.

Results showed that the ripretinib group had a significantly longer median PFS of 6.3 months compared to 1.0 months in the placebo group (HR 0.15, 95% CI 0.09–0.25, $p < 0.0001$). Although OS could not be formally tested for statistical significance due to the hierarchical testing structure—since the ORR was only 9.4%—patients receiving ripretinib demonstrated a markedly improved OS compared to placebo (median OS: 15.1 vs. 6.6 months; HR 0.36, 95% CI 0.21–0.62). Ripretinib demonstrated a favorable safety profile, with the main side effects being alopecia and palmar-plantar erythrodysesthesia, most of which were mild.

The study used EORTC-QLQ-C30 and EQ-VAS to measure patients' quality of life. By Cycle 2, ripretinib-treated patients showed significantly better preservation of role and physical functioning compared to placebo, with between-group differences of +20.6 (95% CI: 8.6–32.6) and +10.5 (3.4–17.6), respectively. Although within-group improvement in EQ-VAS was not statistically significant in the ripretinib group (mean change +3.7, 95% CI: −1.1 to 8.6), the placebo group experienced a significant decline (−8.9, −15.9 to −1.9), indicating a relative benefit in perceived overall health [15].

4.3. Efficacy of Ripretinib

Ripretinib's clinical efficacy has been demonstrated through clinical trial results. In Phase 1 and 3 clinical trials, the ORR for GIST patients who had received fourth-line or later treatment was 7.2% and 9.0% respectively, which are notable results in a patient population with extensive prior treatment experience. Objective response is defined as a partial or complete reduction in tumor size. The mPFS was observed to be 5.5 months in Phase 1 and 6.3 months in Phase 3, showing significant improvement compared to the placebo group's mPFS of 1 month in the Phase 3 clinical trial. The 6-month progression-free survival rate for the ripretinib group was 51%, showing a large difference compared to 3.2% for the placebo group, and the median OS was also significantly longer at 15.1 months compared to 6.6 months for the placebo. Ripretinib also exhibited good response in terms of response durability; in the Phase 3 clinical trial, 7 out of 8 patients who showed an objective response had not progressed by the data cutoff point, with only one patient progressing after about 3 months. The median duration of response had not yet been reached, and the median time to best response was 1.9 months (IQR 1.0–2.7), indicating that responses tended to occur early and were generally sustained. This suggests that ripretinib can maintain continuous antitumor effects in most responders. These results indicate that ripretinib may be effective even in GIST patients who show resistance to existing treatments, and that the effect is likely to be sustained with long-term use [14,15].

Another study evaluating the clinical efficacy of ripretinib was conducted in the UK on GIST patients resistant to existing treatments. This study was conducted from January 2020 to October 2021 in the UK and included a total of 45 patients. The mPFS for patients taking ripretinib 150 mg once daily was 7.9 months, and for

patients who increased the dose to 150 mg twice daily after tumor progression, the mPFS was 5.4 months. Overall, patients taking ripretinib had an mPFS of 9.7 months and an OS of 14.0 months. The ORR was 16.7% for 150 mg once daily dosing and 10.0% for twice daily dosing. This study concluded that ripretinib provides clinically significant survival extension effects for GIST patients, and no new safety issues were identified [16]. These results indicate that ripretinib shows efficacy and safety consistent with previous clinical trial results.

4.4. Adverse Reactions of Ripretinib

The INVICTUS study, a Phase 3 clinical trial evaluating the efficacy and safety of ripretinib, compared patients taking ripretinib 150 mg once daily with those taking a placebo. Among the ripretinib group, the most common grade 3 or higher treatment-related adverse reactions were increased lipase (5%), hypertension (4%), fatigue (2%), and hypophosphatemia (2%), while in the placebo group, anaemia (7%) and fatigue (2%) were reported. The most frequently observed adverse reactions included alopecia (52%), fatigue (42%), nausea (35%), and abdominal pain (33%), most of which were manageable. Treatment-related serious adverse reactions occurred in 9% of patients in the ripretinib group and 7% in the placebo group. This study demonstrated that ripretinib provides clinically significant survival extension effects for GIST patients and has a favorable safety profile [14,15].

The INTRIGUE study, which compared sunitinib and ripretinib, showed that ripretinib had a safer adverse reaction profile than sunitinib. Notably, the incidence of grade 3/4 treatment-related adverse reactions was lower for ripretinib at 41.3% compared to 65.6% for sunitinib. The frequency of grade 3 or higher palmar-plantar erythrodysesthesia syndrome was 10.0% for sunitinib but only 1.3% for ripretinib, and the incidence of hypertension was also lower for ripretinib at 8.5% compared to 26.7% for sunitinib. Although alopecia was more frequently reported in the ripretinib group at 64.1% compared to 8.1% in the sunitinib group, the severity did not exceed grade 2 [17]. Based on these results, the U.S. NCCN guidelines recommend considering ripretinib as a second-line treatment for GIST patients who cannot tolerate sunitinib.

Studies on ripretinib's adverse reactions include research from China and the UK. In the Chinese study, 20.5% of patients using ripretinib as fourth-line or later treatment experienced grade 3 or higher treatment-related adverse reactions. The most common adverse reactions reported were alopecia, fatigue, and nausea [18]. The UK study involved 45 GIST patients and reported major adverse reactions, including alopecia, fatigue, and nausea. Grade 3 or higher treatment-related adverse reactions included palmar-plantar erythrodysesthesia syndrome, constipation, myalgia, and diarrhoea. Interestingly, the 150 mg twice-daily regimen showed a lower frequency of grade 3 or higher treatment-related adverse reactions compared to the once-daily regimen [16]. These two studies demonstrate various adverse reactions that can occur with the use of ripretinib, in addition to those reported in the INVICTUS clinical trial. They suggest that most adverse reactions are manageable.

4.5. Pharmacokinetics of Ripretinib

Ripretinib is well absorbed when administered orally, and its absorption is not significantly affected when taken with gastric acid suppressants. After administration, the drug reaches peak plasma concentration at approximately 4 h, and it exhibits a large mean volume of distribution of about 307 L, indicating extensive tissue penetration. The elimination half-life is around 14.8 h, supporting sustained systemic exposure [19]. Ripretinib distributes widely throughout the body, showing high binding affinity to KIT and PDGFRA mutation-inducing cells, making it effective for GIST treatment. It is primarily metabolised in the liver by CYP3A4/5 enzymes. When ripretinib and its metabolite (DP-5439) are taken with strong CYP3A inhibitors (e.g., itraconazole), their Cmax and AUC increase: ripretinib by 36% and 99%, respectively, and DP-5439 by 6% and 99%. In contrast, co-administration with CYP3A inducers (e.g., rifampicin) decreases their Cmax and AUC: ripretinib by 18% and 61%, respectively, and DP-5439 by 63% and 57%. Therefore, to prevent adverse effects due to drug interactions, co-administration with CYP3A inhibitors and inducers should be avoided [20].

Ripretinib and its metabolites are mainly excreted through bile, allowing its use in patients with impaired renal function without special dose adjustments. This indicates that patients with kidney dysfunction can also be treated with ripretinib. While dose adjustment is not necessary for patients with mild hepatic impairment, those with moderate to severe hepatic impairment may require dose adjustments as AUC tends to increase by 100% and 160% respectively [20].

Based on these pharmacokinetic characteristics, guidelines for the safe and effective administration of ripretinib can be established. Personalized dosing considering the individual patient's condition, especially liver function and concomitant medications, is important. This approach can help achieve optimal therapeutic effects while minimising side effects.

4.6. Follow-Up Studies for Ripretinib

One of the significant follow-up studies related to ripretinib is the INTRIGUE study, which compares sunitinib and ripretinib. The INTRIGUE study can be seen as an attempt to expand ripretinib's indications by demonstrating its efficacy in comparison with sunitinib, which is used as a second-line treatment for GIST. The study results showed that ripretinib did not have an efficacy advantage over sunitinib (ORR 21.7% vs. 17.6%; p = 0.27), but it suggested the possibility of a favorable adverse reaction profile and therapeutic benefits for exon 11 mutations (ORR 23.9% vs. 14.6%; p = 0.03) [17]. Based on this, ripretinib can now be considered as a second-line treatment for patients who have difficulty tolerating sunitinib.

To confirm the benefit for specific exon mutations, which was one of the findings from the INTRIGUE study, the INSIGHT study was initiated. The INSIGHT study aims to compare the efficacy and safety of sunitinib and ripretinib in patients with KIT exon 11 + 17/18 mutations and without exon 9, 13, and 14 mutations [21]. While the study is still ongoing, its results are expected to contribute to expanding ripretinib's indications and providing optimal treatment options for patients.

In addition, early-phase trials are investigating ripretinib in combination with novel agents such as the ULK1/2 inhibitor DCC-3116 (NCT05957367), which aims to block autophagy as a resistance mechanism [22]. These combination approaches may provide new avenues to enhance ripretinib efficacy in advanced GIST.

5. Discussion

The introduction of TKIs has improved the treatment of GIST, however, drug resistance is still a major problem. In particular, secondary resistance mutations in KIT and PDGFRA genes reduce the effectiveness of existing treatments. Therefore, ripretinib appears to open a new chapter in GIST treatment. However, despite broad target coverage, its clinical benefit in later treatment lines remains modest, and no validated predictive biomarkers exist, warranting a critical comparison with other TKIs and a focus on future solutions. Compared with sunitinib and regorafenib, ripretinib demonstrates broader inhibition across KIT mutations, especially in exon 17, yet its efficacy advantage was not established in the INTRIGUE trial, suggesting that its primary role may lie in patients intolerant to sunitinib rather than as a replacement in the second-line setting.

Ripretinib is a 'switch control inhibitor' with a unique mechanism of action different from existing TKIs, simultaneously targeting the switch pocket and activation loop of KIT and PDGFRA. This dual inhibition mechanism provides a theoretical basis for effectively acting on various KIT and PDGFRA mutations. Indeed, in vitro experiments have shown that ripretinib exhibits superior inhibitory effects on various KIT mutations resistant to existing TKIs [4]. The potential benefit in exon 11 + 17/18 double mutations may be explained by this dual inhibition, providing biological plausibility for the ongoing INSIGHT trial.

Clinical trial results, including the INVICTUS study, showed that ripretinib significantly prolongs PFS versus placebo and is associated with longer OS, especially in patients who failed third-line or later treatments. Although the objective responses are infrequent in the fourth-line or later setting (ORR ~7–9%), clinical benefit is supported by PFS/OS gains versus placebo, and the durability of response is notable. Quality-of-life analyses also favored ripretinib [14,15]. Even with these gains, efficacy in late lines remains modest. Robust biomarker-based stratification is lacking, and on-treatment resistance persists.

Ripretinib demonstrated a generally favorable safety profile, with alopecia, fatigue, and nausea being the most commonly reported adverse reactions, but most were manageable. Particularly in the INTRIGUE study, grade 3/4 adverse reactions were less frequent with ripretinib than with sunitinib, with lower rates of palmar–plantar erythrodysesthesia and hypertension, although alopecia was more common and largely low-grade [17]. NCCN guidelines recommend ripretinib as the standard 4th-line therapy and as a second-line option for patients intolerant to sunitinib. Real-world data from the UK and China further support its low toxicity and consistent efficacy, though alopecia may affect patient perception of quality of life [16,18]. Furthermore, therapeutic benefits for specific exon mutations (exon 11 + 17/18) have been suggested, opening up possibilities for personalised treatment [21].

There are several important challenges that need to be addressed in future research. First, the INSIGHT study should clarify the effects of ripretinib across specific gene mutations [21]. Second, finding the optimal combination strategies with other targeted therapies or immunotherapies may provide synergistic benefit [22]. Third, resistance continues to arise under therapy. This underscores the need for longitudinal ctDNA monitoring to track resistant clones and guide adaptive treatment approaches [23]. Meanwhile, the lack of sufficient long-term safety data for ripretinib is noted as a major limitation. Accordingly, there is a need to more clearly establish the safety profile through long-term follow-up studies. Furthermore, additional cost-effectiveness analyses of ripretinib treatment should be conducted; in the U.S. study, ripretinib is not cost-effective as a fourth-line therapy at current prices [24].

Through these multifaceted studies, the clinical value of ripretinib can be more accurately evaluated. This will help establish optimal usage strategies.

In conclusion, ripretinib demonstrates good clinical effectiveness in the fourth-line or later setting. However, in the second line, its efficacy is not superior to that of sunitinib, but it has a comparable safety profile. It presents an alternative option for treating patients who show resistance to existing treatments and may be used to facilitate mutation-guided personalized therapy. It is expected that future studies centered on ripretinib will contribute to improving the survival rate and quality of life of GIST patients.

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Abbreviations

GIST, gastrointestinal stromal tumor; TKI, tyrosine kinase inhibitor; PDGFRA, platelet-derived growth factor receptor alpha; SCF, stem cell factor; JAK, Janus kinase; STAT, signal transducer and activator of transcription; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; AML, acute myeloid leukemia; JM, juxtamembrane; CDS, coding sequence; ECD, extracellular domain; TMD, transmembrane domain; CTD, cytoplasmic domain; DOG-1, Discovered On GIST 1; PFS, progression-free survival; OS, overall survival; PDX, patient-derived xenograft; ERK1/2, extracellular signal-regulated kinase1/2; RP2D, Phase 2 dose; mPFS, median PFS

References

1. Schaefer, I.M.; DeMatteo, R.P.; Serrano, C. The GIST of Advances in Treatment of Advanced Gastrointestinal Stromal Tumor. *Am. Soc. Clin. Oncol. Educ. Book* **2022**, *42*, 1–15.
2. Kang, Y.K.; Kang, H.J.; Kim, K.M.; Sohn, T.; Choi, D.; Ryu, M.H.; Kim, W.H.; Yang, H.K.; Korean, G.S.G. Clinical practice guideline for accurate diagnosis and effective treatment of gastrointestinal stromal tumor in Korea. *Cancer Res. Treat.* **2012**, *44*, 85–96.
3. Di Vito, A.; Ravegnini, G.; Gorini, F.; Aasen, T.; Serrano, C.; Benuzzi, E.; Coschina, E.; Monesmith, S.; Morroni, F.; Angelini, S.; et al. The multifaceted landscape behind imatinib resistance in gastrointestinal stromal tumors (GISTs): A lesson from ripretinib. *Pharmacol. Ther.* **2023**, *248*, 108475.
4. Smith, B.D.; Kaufman, M.D.; Lu, W.P.; Gupta, A.; Leary, C.B.; Wise, S.C.; Rutkoski, T.J.; Ahn, Y.M.; Al-Ani, G.; Bulfer, S.L.; et al. Ripretinib (DCC-2618) Is a Switch Control Kinase Inhibitor of a Broad Spectrum of Oncogenic and Drug-Resistant KIT and PDGFRA Variants. *Cancer Cell* **2019**, *35*, 738–751.
5. Foster, B.M.; Zaidi, D.; Young, T.R.; Mobley, M.E.; Kerr, B.A. CD117/c-kit in Cancer Stem Cell-Mediated Progression and Therapeutic Resistance. *Biomedicines* **2018**, *6*, 31.
6. Wang, L.; Felix, J.C.; Lee, J.L.; Tan, P.Y.; Tourgeman, D.E.; O'Meara, A.T.; Amezcua, C.A. The proto-oncogene c-kit is expressed in leiomyosarcomas of the uterus. *Gynecol. Oncol.* **2003**, *90*, 402–406.
7. Roskoski, R., Jr. The role of small molecule Kit protein-tyrosine kinase inhibitors in the treatment of neoplastic disorders. *Pharmacol. Res.* **2018**, *133*, 35–52.
8. Liu, P.; Tan, F.; Liu, H.; Li, B.; Lei, T.; Zhao, X. The Use of Molecular Subtypes for Precision Therapy of Recurrent and Metastatic Gastrointestinal Stromal Tumor. *Onco Targets Ther.* **2020**, *13*, 2433–2447.
9. Hwang, D.G.; Qian, X.; Hornick, J.L. DOG1 antibody is a highly sensitive and specific marker for gastrointestinal stromal tumors in cytology cell blocks. *Am. J. Clin. Pathol.* **2011**, *135*, 448–453.
10. Wu, C.E.; Tzen, C.Y.; Wang, S.Y.; Yeh, C.N. Clinical Diagnosis of Gastrointestinal Stromal Tumor (GIST): From the Molecular Genetic Point of View. *Cancers* **2019**, *11*, 679.
11. Rahman, J.; Rahmanuddin, S.; Sham, S.; Sonawane, S. Extensive Degenerative Change Masquerading Histomorphology

in a Giant Cystic Gastrointestinal Stromal Tumor With Rare PDGFRA Mutation. *Cureus* **2020**, *12*, e10772.

12. Sanlorenzo, M.; Vujic, I.; Posch, C.; Ma, J.; Lin, K.; Lai, K.; Lee, D.; Vujic, M.; Oses-Prieto, J.A.; Chand, S.; et al. Oncogenic KIT mutations in different exons lead to specific changes in melanocyte phospho-proteome. *J. Proteom.* **2016**, *144*, 140–147.
13. Calderillo-Ruiz, G.; Perez-Yepez, E.A.; Garcia-Gamez, M.A.; Millan-Catalan, O.; Diaz-Romero, C.; Ugalde-Silva, P.; Salas-Benavides, R.; Perez-Plasencia, C.; Carbajal-Lopez, B. Genomic profiling in GIST: Implications in clinical outcome and future challenges. *Neoplasia* **2024**, *48*, 100959.
14. Janku, F.; Abdul Razak, A.R.; Chi, P.; Heinrich, M.C.; von Mehren, M.; Jones, R.L.; Ganjoo, K.; Trent, J.; Gelderblom, H.; Somaiah, N.; et al. Switch Control Inhibition of KIT and PDGFRA in Patients with Advanced Gastrointestinal Stromal Tumor: A Phase I Study of Ripretinib. *J. Clin. Oncol.* **2020**, *38*, 3294–3303.
15. Blay, J.Y.; Serrano, C.; Heinrich, M.C.; Zalcberg, J.; Bauer, S.; Gelderblom, H.; Schoffski, P.; Jones, R.L.; Attia, S.; D'Amato, G.; et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): A double-blind, randomised, placebo-controlled, phase 3 trial. *Lancet Oncol.* **2020**, *21*, 923–934.
16. Lim, S.Y.; Ferro-Lopez, L.; Barquin, E.; Lindsay, D.; Thway, K.; Smith, M.J.; Benson, C.; Jones, R.L.; Napolitano, A. Efficacy and Safety of Ripretinib in Advanced Gastrointestinal Stromal Tumors within an Expanded Access Program: A Cohort Study. *Cancers* **2024**, *16*, 985.
17. Bauer, S.; Jones, R.L.; Blay, J.Y.; Gelderblom, H.; George, S.; Schoffski, P.; von Mehren, M.; Zalcberg, J.R.; Kang, Y.K.; Razak, A.A.; et al. Ripretinib Versus Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumor After Treatment With Imatinib (INTRIGUE): A Randomized, Open-Label, Phase III Trial. *J. Clin. Oncol.* **2022**, *40*, 3918–3928.
18. Li, J.; Cai, S.; Zhou, Y.; Zhang, J.; Zhou, Y.; Cao, H.; Wu, X.; Deng, Y.; Huang, Z.; Dong, J.; et al. Efficacy and Safety of Ripretinib in Chinese Patients with Advanced Gastrointestinal Stromal Tumors as a Fourth- or Later-Line Therapy: A Multicenter, Single-Arm, Open-Label Phase II Study. *Clin. Cancer Res.* **2022**, *28*, 3425–3432.
19. Kumar, S.S.; Philip, A.; Pavithran, K. Ripretinib. *CancerRes.Stat. Treat.* **2021**, *4*, 93–98.
20. Li, X.; Shelton, M.J.; Wang, J.; Meade, J.; Ruiz-Soto, R. Effects of CYP3A Inhibition, CYP3A Induction, and Gastric Acid Reduction on the Pharmacokinetics of Ripretinib, a Switch Control KIT Tyrosine Kinase Inhibitor. *Clin. Pharmacol. Drug Dev.* **2022**, *11*, 1165–1176.
21. George, S.; Blay, J.-Y.; Chi, P.; Jones, R.L.; Serrano, C.; Somaiah, N.; Reichmann, W.; Sprott, K.; Achour, H.; Sherman, M.L.; et al. INSIGHT: A phase 3, randomized, multicenter, open-label study of ripretinib vs. sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib harboring KIT exon 11 + 17 and/or 18 mutations. *J. Clin. Oncol.* **2023**, *41*, TPS11582.
22. Chandana, S.R.; Shepard, D.R.; Mehnert, J.M.; Chi, P.; Trent, J.C.; Psoinos, C.M.; Zhou, B.; Black, V.; Viswanathan, L.; Gozo, M.; et al. DCC-3116 in combination with ripretinib for patients with advanced gastrointestinal stromal tumor: A phase 1/2 study. *J. Clin. Oncol.* **2024**, *42*, TPS11587.
23. Heinrich, M.C.; Jones, R.L.; George, S.; Gelderblom, H.; Schoffski, P.; von Mehren, M.; Zalcberg, J.R.; Kang, Y.K.; Razak, A.A.; Trent, J.; et al. Ripretinib versus sunitinib in gastrointestinal stromal tumor: ctDNA biomarker analysis of the phase 3 INTRIGUE trial. *Nat. Med.* **2024**, *30*, 498–506.
24. Liao, W.; Xu, H.; Hutton, D.; Wu, Q.; Zhou, K.; Luo, H.; Lei, W.; Feng, M.; Yang, Y.; Wen, F.; et al. Cost-Effectiveness Analysis of Fourth- or Further-Line Ripretinib in Advanced Gastrointestinal Stromal Tumors. *Front. Oncol.* **2021**, *11*, 692005.