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Ripretinib for the treatment of adult patients with advanced gastrointestinal stromal tumors

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ABSTRACT

Introduction: Gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the gastrointestinal tract. Imatinib mesylate revolutionized the management of advanced/metastatic GIST, and remains the standard first-line therapy in this setting. Upon development of secondary resistance, sunitinib and regorafenib are used as subsequent treatments, although clinical benefit is often non-durable. Ripretinib is a type II kinase inhibitor targeting *KIT* and *PDGFRA* mutations and resistance through switching active I and inactive II forms.

Areas covered: This drug profile article provides an overview of the current state of the art treatment algorithm for advanced/metastatic GIST, focusing on the role of ripretinib in the fourth-line setting as defined by currently available clinical trials evidence. The mechanism of action, the safety profile, efficacy, and clinical application of ripretinib are presented. In addition, the Phase I study (NCT02571036) through which the optimal dose was established and the Phase III trials that assessed the efficacy and safety of ripretinib as fourth- (INVICTUS) and second-line treatment (INTRIGUE) are presented.

Expert opinion: Ripretinib is a safe and an effective therapy for the fourth-line setting in advanced/metastatic GIST. Future studies should evaluate combination schedules and the identification of markers predictive of benefit from ripretinib.

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KEYWORDS
Gastrointestinal stromal tumor; kinase inhibitor; KIT; mutations; resistance; ripretinib; systemic treatment

1. Background

Gastrointestinal stromal tumors (GIST) represent the most common soft tissue sarcoma subtype of the gastrointestinal tract, yet they are rare, comprising less than 1% of all gastrointestinal tumors [1,2]. The reported incidence of the disease varies across countries, with the most recent data suggesting an incidence range from 0.4 to 2 cases per 100 000 per year [3]. Most GISTs occurring in adults harbor activating mutations in the *KIT* or *PDGFRA* genes which are not only crucial events for tumorigenesis but also serve as drug targets (actionable mutations) [1,3]. Considering the fundamental role of the KIT tyrosine kinase activity in the pathogenesis of GISTs, it is obvious why its kinase domains have become the most meaningful therapeutic target [4]. The treatment outcome for locally advanced and metastatic GIST patients changed significantly after the introduction of imatinib, a tyrosine kinase inhibitor (TKI) that targets *BCR-ABL*, *KIT*, and *PDGFRA* [1]. It remains the first-line therapy for advanced and metastatic GIST patients, with a clear clinical benefit and a median overall survival of approximately 50 months [5]. Multitargeted receptor tyrosine kinase inhibitors sunitinib and regorafenib are approved as second- and third-line treatment options, yet with limited clinical benefit and less tolerability [6–8]. Hence, there is a major need to develop new therapeutic approaches. Ripretinib is a novel type II switch-controlled TKI, approved for the management of advanced/metastatic GIST patients as a fourth-line treatment with proven clinical benefit and acceptable toxicity profile [9,10].

1.1. Overview of the market

Since the majority of GISTs harbor *KIT* or *PDGFRA* activating mutations, targeted treatment with TKIs is currently the mainstay of treatment. According to NCCN and ESMO guidelines, for imatinib-sensitive molecular subtypes, imatinib is the treatment of choice in intermediate and high-risk GIST patients in the adjuvant and neoadjuvant setting for resectable disease and the first-line treatment for unresectable/advanced or metastatic disease. For *PDGFRA* exon 18 mutations, avapritinib is the treatment of choice, as cases carrying this mutation are resistant to imatinib [11,12]. Second-line therapy for advanced/metastatic disease is sunitinib. Following progression, regorafenib is recommended for the third-line setting after sunitinib [2,13]. Other therapeutic options can be used for specific mutations if detected, such as larotrectinib and entrectinib for *NTRK* gene fusion positive GISTs or BRAF inhibitors, such as dabrafenib (including BRAF/MEK inhibitor combinations) for *BRAF* mutated GISTs [14,15].

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Article highlights

- Ripretinib is a novel type II switch-controlled TKI, approved for the management of advanced/metastatic GIST patients as fourth-line treatment, with proven clinical benefit and acceptable toxicity profile.
- In the phase III INVICTUS trial, ripretinib was compared to placebo, in the fourth-line setting, and it demonstrated substantial improvement in median (m) PFS in comparison to placebo (mPFS 6.3 months vs 1.0 months, HR 0.15, 95% CI 0.09–0.25; p<0·0001).
- In the phase III INTRIGUE trial, ripretinib was compared to the standard second-line therapy, showing no improvement in mPFS in comparison to sunitinib, and statistical significance was not reached (mPFS 8.0 months vs 8.3 months HR, 1.05;95% CI, 0.82-1.33; nominal P-value = 0.72).
- Combination schedules should be evaluated in future trials to fully unravel the potential role ripretinib in the management of GIST.

1.2. Currently available therapeutic approaches and unmet needs

Despite the impressive clinical improvement achieved by imatinib, not all patients benefit from this drug. Between 10 and 20% of GIST patients will exhibit primary resistance to imatinib and up to 80% will develop secondary resistance, 50% of which will become resistant in the first 2 years of treatment [16].

Some genotypes (*D842V* in exon 18 of the *PDGFRA, KIT*, and *PDGFRA* wild type) are associated with primary resistance to imatinib at any dose, while others (*KIT* mutation in exon 9) are more sensitive to high-dose imatinib (800 mg) [17]. Although imatinib is the first-choice treatment for locally advanced and metastatic imatinib-sensitive GIST patients, there are no available standard/effective therapeutic alternatives for patients without *KIT* and *PDGFRA* (wild type) mutations [18].

In the imatinib-insensitive subtype *PDGFRA* exon 18 *D842V* mutant GIST, avapritinib is recommended by the NCCN and ESMO [11,19,20]. There is a subset of GIST patients lacking defining mutations of the *KIT* and *PDGFRA* oncogenes, instead having another mutation causing loss of expression of succinate dehydrogenase *(SDH)* either by gene mutation or by transcriptional silencing. In this subset of patients with SDH-deficient expression, imatinib is not effective; NCCN and ESMO recommend consideration of sunitinib and regorafenib based on available evidence [2,13,21]. A phase II study of temozolomide showed very modest benefit and limited activity in patients with SDH-deficient GIST subtype [22,23].

In imatinib-sensitive subtypes the use of imatinib achieves 75–80% disease control rate for metastatic GIST with median PFS of 21 months (95% CI, 18 to 25) and median OS of about 55 months (95% CI, 47 to 62 months), with acceptable toxicity profile [19,24]. However, a large subset of patients experience disease progression after 2–3 years of imatinib treatment; thus, there is a need for new therapeutic options. Sunitinib and regorafenib are approved as second- and third-line treatment options, respectively, based on improvement in PFS compared to placebo but modest clinical benefit, probably due to multiple drug-resistant mutations arising in individual tumors [25]. Secondary resistance mutations in *KIT* typically occur in exons 13, 14, 17, and 18 [26]. They can alter the activation loop, switching it to a conformationally active state or change conformation in a way the drugs cannot bind to the region. With the use of second- and further-line treatments, there is an accumulation of activation loop mutations, which are less likely to be controlled by available drugs currently on the market [18,27]. Regorafenib is approved in the third-line setting with a modest benefit of lengthening PFS by 4.8 months [8]. Even in the more recent comparison with avapritinib in a phase III trial, no significant difference in median PFS was noted [28]. In the fourth-line setting, after prior treatment with imatinib, sunitinib, and regorafenib, no other alternative options were approved prior to ripretinib. The available second- and third-line therapies are usually not very well-tolerated and are accompanied by adverse effects impacting the quality of life and often leading to dose reductions, interruptions, or discontinuations [29].

2. Introduction of the drug

2.1. Chemistry

Ripretinib (DCC-2618; QINLOCK, Deciphera Pharmaceuticals, USA) is a novel, KIT/PDGFRA kinase inhibitor, presented as white to off-white tablets for oral administration. The chemical name of ripretinib is 1-(4-bromo-5-[1-ethyl-7-(methylamino)-2oxo-1,2-dihydro-1,6-naphthyridin-3-yl]-2-fluorophenyl)-3-phenylurea. The molecular formula is $C_{24}H_{21}BrFN_5O_2$, and the molecular weight is 510.36 g/mol [30].

2.2. Pharmacodynamics

Ripretinib is a type II kinase inhibitor which inhibits wild type, primary, and secondary mutations of KIT proto-oncogene receptor tyrosine kinase and PDGFRA kinase. In vitro, it also inhibits other kinases, such as *PDGFRB, TIE2, VEGFR2*, and *BRAF* [31]. KIT and PDGFR are dual-switch kinases, containing an inhibitory switch in the intracellular juxtamembrane domain encoded by *KIT* exon 11 or *PDGFRA* exon 12, and a main activation loop (AL) switch within the kinase domain encoded by *KIT* exons 17 and 18 or *PDGFRA* exon 18 and 19 [32,33]. Ripretinib is a switch-control kinase inhibitor that alters the activation loop into an inactive conformation. This allows to control the conformational equilibrium toward active I and inactive II forms. Ripretinib acts as an antagonist of switching to type I active state and as an agonist of stabilizing switch toward type II inactive state. It targets all relevant known resistance mutations, including activation loop mutations, previously thought to be on the target of only type I kinase inhibitors [33]. Since various secondary mutations can occur simultaneously in pre-treated, TKI-resistant GIST, targeting a wide range of mutations, as well as *de novo* KIT resistance through newly occurring mutations is a major advantage of the drug.

Ripretinib induces apoptosis in treatment-resistant GIST cell lines, as well as other cancers with *KIT* or *PDFRA* mutations [33,34]. In preclinical models, it was shown that ripretinib in combination with MEK inhibitors trametinib and binimetinib in imatinib-sensitive, as well as in imatinib-resistant GIST and mastocytosis cell lines, has a synergistic effect in inducing

apoptosis. In xenograft models, the effect of the combination was seen even after the drug was removed [35].

2.3. Pharmacokinetics and drug metabolism

The assessment of the pharmacokinetics of ripretinib along with DP-5439 (its active metabolite) was performed subsequent to the administration of the single dose to healthy participants and compared to the multiple-dose intake by subjects with advanced malignancies. Following a single-dose of 150 mg of ripretinib, it took 4 h for ripretinib to reach Cmax and 15.6 h for DP-5439, and the steady-state apparent volume of distribution was 307 L and 507 L respectively. For both, the steady state occurred after 14 days. Ripretinib and its active metabolite are highly (>99%) plasma protein attached to human serum albumin and orosomucoid [36]. Elimination half-life of ripretinib is 14.8 h, and 17.8 h for DP-5439. CYP3A4 is the main enzyme responsible for the metabolism of ripretinib and DP-5439. Hence, coadministration of the drug with CYP3A enzyme inhibitors can increase the exposure and potency of the drugs, while with enzyme inducers may decrease the therapeutic efficacy [32].

3. Clinical efficacy, safety, and tolerability

3.1. Phase I and phase II studies

The first-in-human, Phase I study (ClinicalTrials.gov identifier: NCT02571036) of DCC-2618 (ripretinib) was conducted to evaluate optimal dose, safety, tolerability, and preliminary antitumor activity (expansion phase) of the drug. The majority (>90%) of patients in this trial receiving ripretinib 150 mg once daily achieved desirable exposure of ripretinib and its active metabolite (DP-5439) – sufficient for >90% KIT inhibition; therefore in the dose-escalation phase, the recommended dose was determined as 150 mg once daily for the further part of phase I and the phase III trials [36]. Although preliminary, the overall response rate (ORR) with ripretinib in second- and third-line cohorts exceeded the values reported for sunitinib in second-line patients (7%) and regorafenib in third-line patients (5%) in their registration trials (central review) [37]. The preliminary data indicated the efficacy of ripretinib for all doses above ≥100 mg per day with reduced *KIT* mutant allele frequency in plasma circulating tumor DNA [38]. There is an ongoing Phase II study conducted in China (ClinicalTrials.gov Identifier: NCT04282980) for further evaluating the safety, clinical efficacy, and tolerability of ripretinib, with the primary objective of PFS in advanced, pre-treated GIST patients (ClinicalTrials.gov identifier: NCT04282980) [39].

The efficacy and safety of ripretinib in the Phase 1 trial supported further evaluation in advanced GIST.

3.2. Phase III studies

3.2.1. INVICTUS trial

INVICTUS (ClinicalTrials.gov identifier: NCT03353753) is a 2-arm, randomized, double-blind, placebo-controlled, multicentre study comparing the efficacy of ripretinib to placebo in patients who had previously received at least three lines of treatment including imatinib, sunitinib, regorafenib with disease progression, or had documented intolerance to any of the drugs mentioned (table 1). From 154 screened patients 129 were randomized with 2:1 ratio to receive either ripretinib 150 mg once daily, or placebo, with the possibility to cross over to ripretinib at the time of disease progression on placebo. Upon disease progression for patients in the ripretinib arm, the dose could be escalated to 150 mg twice daily, continued at 150 mg once daily if still beneficial or discontinued. Randomization was stratified based on the number of prior therapies (three vs four or more) and Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1 or 2). The primary endpoint was PFS assessed by blinded independent central review (BICR). At data cutoff (31 May 2019), the median follow-up time in the double-blind period was 6.3 months (IQR 3 · 2–8 · 2) for the ripretinib group and 1.6 months (1.1–2.7) for the placebo group. Fifty-one (60%) of 85 patients receiving ripretinib and 37 (84%) of 44 patients receiving placebo had progression or died [40]. In the ripretinib arm there was a statistically significant improvement in median PFS compared to placebo – 6.3 months (95% confidence interval (CI) 4.6, 6.9) versus 1.0 months (95% CI 0.9, 1.7), indicating 85% reduction in the risk of the disease progression or death (hazard ratio 0.15, 95% CI 0.09–0.25; $p < 0.0001$) [41]. PFS at 6 months was estimated to be 51% and 3.2% for ripretinib and placebo respectively. Median OS for the ripretinib group was 15.1 months (95% CI 12.3–15.1) and for the placebo – 6.6 months (95% CI 4.1–11.6) for both double-blind and open-label periods (HR 0.36, 95% CI 0.21–0.62) [40]. The estimated 12-month OS rates were 65.4% (ripretinib) and 25.9% (lower case placebo) respectively. Subsequent extended follow-up results showed the median OS for the ripretinib group was 18.2 months (95% CI, 13.1–30.7) and for the placebo 6.3 months (95% CI, 4.1–10.0) for both double-blind and open-label periods (HR 0.41, 95% CI 0.26–0.65) [42].

Ripretinib was well-tolerated in patients with advanced GIST according to the trial results. The most common (>20%) treatment-related any-grade adverse reactions were alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia, and diarrhea. The most common (>2%) treatment-related grade 3/4 emergent events were lipase increase (5%), hypertension (4%), fatigue (2%), and hypophosphatemia (2%). Treatment-related serious adverse events were documented in 8/85 patients in the ripretinib group, and 3/43 in the placebo group. One treatment-related death was reported in each of the arms [40,43]. Of note, both in the INVICTUS trial and in the phase I trial, patients with disease progression on 150 mg daily that were subsequently treated with ripretinib 150 mg twice per day were noted to derive continued clinical benefit. Importantly, the twice-daily dosing schedule had a similar safety profile to the once-daily dosing. In INVICTUS 16% of the 43 patients on ripretinib 150 mg twice-daily regimen discontinued the medication. However, given the clinical benefit of intra-patient dose escalation, ripretinib 150 mg twice daily might be a treatment option for those with disease progression on ripretinib 150 mg daily [44,45].

Also interesting is the characterization of the GIST cases of the INVICTUS trial by mutational status and the evaluation of

Table 1. Summary of phase III trials INVICTUS and INTRIGUE.

TRIAL	Phase	Line of the treatment	Intervention	Number of participants	Median PFS	ORR	median OS
INVICTUS	3	4th	Ripretinib	85	6.3 months	9.4%	15.1 months
			Placebo	44	1.0 months (HR 0.15, 95% CI 0.09–0.25; p < 0 · 0001)	0%	6.6 months (HR 0.36; 95% CI 0.21–0.62)
INTRIGUE	3	2nd	Ripretinib	226	8.0 months	21.7%	Not Reported
			Sunitinib	227	8.3 months (HR, 1.05;95% CI, 0.82–1.33; nominal P value = .72).	17.6% (nominal P = 0.27)	

ripretinib efficacy across KIT/PDGFRA mutation subgroups. Ripretinib was shown to have clinically meaningful benefit compared to placebo (HR, 0.16) in all subgroups of patients including those with mutations in KIT exon 11 (P < 0.0001), exon 9 (P = 0.0023), exon 13 (P < 0.0001), and exon 17 (P < 0.0001). The poor response of exon 9 mutation-driven GIST was noted, and based on the knowledge of the heterogeneity of metastatic GIST, the cause behind the poor effect of GIST with KIT exon 9 mutations would need to be further evaluated. On one hand, these results suggest a wide clinical activity of ripretinib; on the other hand, the range of potency against different resistance mutations in patients previously treated with three or more lines of treatment remains undefined [46].

In relation to quality of life (QoL), this was assessed using the EuroQol-5D (EQ-5D-5 L) and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire\EORTC QLQ-C30. Patients receiving ripretinib performed better compared to placebo on all questionnaires, including EQ-5D-5 L VAS, physical and role functioning on the EORTC QLQ-C30 (P = 0.004, P = 0.004, P = 0.001) [47].

3.2.2. *INTRIGUE trial*

The randomized, open-label, multicentre, phase III trial, INTRIGUE (ClinicalTrials.gov identifier: NCT03673501), was performed to evaluate the efficacy and safety of ripretinib versus sunitinib as a second-line treatment for patients with advanced GIST previously treated with imatinib (Table 1). Overall, 453 patients were randomized 1:1 to receive ripretinib 150 mg once daily (QD) or sunitinib 50 mg QD (4 weeks on/2 weeks off) [48]. Overall ripretinib was better tolerated than sunitinib, and grade 3 or 4 treatment-emergent adverse effects (TEAEs) were observed less frequently in the ripretinib group (41.3%) compared to the sunitinib group (65.6%).

Although ripretinib had a numerical advantage over sunitinib in the subgroup of patients with a *KIT* exon 11 mutation in both PFS (8.3 vs 7.0 months HR, 0.88; 95% CI, 0.66–1.16; p = 0.36) and ORR (23.9% vs 14.6%, nominal p = 0.03), no significant difference was observed in the entire study population. A hierarchical testing sequence was performed for primary and secondary endpoints, statistical testing of patients with KIT exon 11 primary mutation preceded the all-patient (AP) population. The median PFS for ripretinib was 8.0 months compared to 8.3 months in the sunitinib arm (HR, 1.05; 95% CI, 0.82–1.33; nominal P value = 0.72) [9]. Notably, in patients with KIT exon 9 mutation, the PFS in the ripretinib group was inferior to that of sunitinib (5.5 months vs 13.8 months HR, 2.85; 95% CI, 1.48–5.48).

Patient-reported outcomes (PRO) in the INTRIGUE clinical trial were measured using EORTC QLQ-C30 and Dermatology Life Quality Index (DLQI). The number of days and severity of symptoms associated with the most common TRAEs was lower in the ripretinib arm compared to sunitinib (P < 0.05) – except constipation. A percentage of 6.6% of patients in the ripretinib arm and 14.8% in the sunitinib arm had moderate or severe skin toxicity assessed by DLQI (P = 0.015%) [49].

While a number of clinical trials involving ripretinib are currently ongoing (Table 2), its role in the fourth-line setting of advanced GIST is secured. Combinations with other targeted agents have been explored including the NCT05080621 (clinicaltrials.gov). NCT05080621 a Phase I and Phase II non-randomized, open-label trial, now discontinued due to restructuring of the company, had been planned to assess the safety, tolerability, efficacy, and pharmacokinetics of ripretinib in combination with binimetinib in patients with advanced GIST, who either progressed on imatinib or developed resistance. NCT04530981 a Phase I, open-label, multicentre study aimed at assessing the effect of ripretinib on the pharmacokinetics of a CYP2C8 Probe Substrate (repaglinide) in individuals with advanced GIST. Participants are administered repaglinide 0.5 mg combined with ripretinib 150 mg once daily.

4. Post-marketing surveillance

According to the data from the INTRIGUE and INVICTUS trials, ripretinib is a well-tolerated drug. Most of the side effects in the INVICTUS study were grade 1/2, with a predominance of alopecia, myalgia, nausea, fatigue, hand-foot syndrome, diarrhea, and less common grade 3/4 treatment-related emergent adverse events – such as hypertension, lipase increase, fatigue, and hypophosphatemia [4].

In the INTRIGUE trial, only 38.1% of patients receiving ripretinib required dose adjustments, whereas in the sunitinib arm this percentage was 63.3%. Another indicator of better tolerability was the reports of discontinuation of the drugs, reported in 3.6% and 7.7% of patients on ripretinib and sunitinib, respectively. There was a statistically significant difference (nominal p < 0.0001) in documented grade 3 and 4 adverse events in the advantage of ripretinib (41.3%) vs sunitinib (65.6%). Though the direct comparison of ripretinib and

Table 2. Treatment-related adverse events of TKIs approved for the treatment of GIST in pivotal phase III trials.

Adverse effects	Ripretinib n = 85 [39]	Regorafenib n = 132 [29]	Sunitinib n = 202 [7]	Imatinib n = 73 [51]
Any grade adverse events (%)				
Alopecia	49%	24%	-	-
Abdominal pain	-	-	-	26%
Hand-foot syndrome	21%	56%	13%	-
Nausea	26%	16%	24%	51%
Fatigue	26%	39%	34%	30%
Diarrhea	21%	40%	29%	40%
Hypertension	9%	49%	11%	-
Myalgia	28%	14%	-	37%
Grade 3–4 Adverse events (%)				
Anemia	1%	-	4%	1%
Abdominal pain	-	-	-	1%
Nausea	1%	1%	1%	1%
Hypertension	4%	24%	3%	-
Hand-foot skin reaction	-	20%	4%	-
Any grade adverse events leading to dose modification and/or discontinuation				
Treatment discontinuation	5%	-	9%	-
Dose reduction	6%	-	11%	-
Treatment interruption	14%	-	28%	-

Table 3. Currently ongoing clinical trials on ripretinib according to clinicaltrials.gov.

Study title	Status	Phase	Intervention	Location
Ripretinib Used for Resectable Metastatic GIST After Failure of Imatinib Therapy (NCT05132738)	Recruiting	-	Ripretinib 150 mg BID qd	Shanghai, China
Ripretinib Combined With Surgery in Advanced GIST That Have Failed Imatinib Therapy: A Multicenter,Observational Study (NCT05354388)	Recruiting	-	Ripretinib 150 mg BID qd, followed by resection for those with PR, CR	Chengdu, Sichuan, China
A Drug-Drug Interaction Study to Evaluate the Effect of Ripretinib on the Pharmacokinetics of a CYP2C8 Probe Substrate in Patients With Advanced GIST (NCT04530981)	Recruiting	I	Repaglinide 0.5 mg + Ripretinib 150 mg QD	USA
A Study of DCC-2618 (Ripretinib) In Patients With With Advanced Gastrointestinal Stromal Tumors (GIST) (NCT04282980)	Completed	II	Ripretinib 150 mg qD	Shanghai, China
A Study to Assess the Efficacy and Safety of DCC-2618 and Sunitinib in Patients With Advanced Gastrointestinal Stromal Tumors After Treatment With Imatinib (NCT04633122)	Completed	II	Ripretinib 150 mg BID qd vs Sunitinib 50 mg QD	Beijing, China
Phase 3 Study of DCC-2618 vs Placebo in Advanced GIST Patients Who Have Been Treated With Prior Anticancer Therapies (INVICTUS) (NCT03353753)	Active, not recruiting	III	DCC-2618 150 mg QD vs Placebo	USA
A Study of DCC-2618 vs Sunitinib in Advanced GIST Patients After Treatment With Imatinib (INTRIGUE) (NCT03673501)	Active, not recruiting	III	DCC-2618 150 mg QD vs Sunitinib 50 mg qd	USA
A Safety, Tolerability and PK Study of DCC-2618 in Patients With Advanced Malignancies (NCT02571036)	Active, not recruiting	I	DCC-2618 dose-escalation phase, and an expansion phase	USA
A Study of THE-630 in Patients With Advanced Gastrointestinal Stromal Tumors (GIST) (NCT05160168)	Completed	I/II	THE-630 administered once daily in a continuous regimen	Beijing, China

regorafenib was not evaluated in a trial, according to the available data for both sunitinib and regorafenib, these were widely associated with grade ≥3 adverse events including hypertension, diarrhea, and hand-foot skin reaction, while with the ripretinib, grade 3 hypertension was seen 3 times less often (compared to sunitinib) and grade 3 hand-foot syndrome was seen 7 times less frequent than with sunitinib. This suggests better tolerability, safety, and less impact on quality of life with ripretinib [48,50,51]. A summary of treatment-related adverse events of TKIs approved for the treatment of GIST in pivotal phase III trials is presented in Table 3.

5. Regulatory affairs

Based on the results of the INVICTUS trial, on 15 May 2020, the US Food and Drug Administration (FDA) approved ripretinib (QINLOCK, Deciphera Pharmaceuticals, LLC.) for the treatment of adult patients with advanced GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib [52]. The EMA granted marketing approval for ripretinib (Qinlock) in November 2021 [31]. QINLOCK is also approved for the treatment of fourth-line GIST in Australia, Canada, China, Hong Kong, Switzerland, and Taiwan [53–59].

6. Conclusion

Although GISTs are rare cancers, they are the most common sarcoma subtype of the gastrointestinal track, with a global incidence of up to 2 cases per 100,000 per year. These tumors are not responsive to conventional chemotherapy. The very poor outcome of advanced GIST changed dramatically after the introduction of tyrosine kinase inhibitors, specifically imatinib. Despite revolutionizing outcomes, primary and secondary resistance is a critical issue with the use of TKIs, driving the need to develop newer drugs. After imatinib failure, sunitinib and regorafenib are approved for second- and third-line settings and novel broad-spectrum KIT tyrosine kinase inhibitor ripretinib for the fourth-line setting. Targeting the broad spectrum of *KIT* and *PDGFRA* mutations and showing clinical

activity against GIST-resistant to previous lines of therapies make ripretinib a meaningful option for further management of advanced/metastatic GIST. Following the results of the preclinical studies, ripretinib was further evaluated in phase III clinical trials, showing significant improvement compared to placebo in the fourth-line setting (INVICTUS trial) (mPFS 6.3 months vs 1.0 months, HR 0.15, 95% CI 0.09–0.25; p < 0 · 0001), but not demonstrating superiority compared to sunitinib in the second-line setting (INTRIGUE trial) for the entire population (8.0 months vs 8.3 months HR, 1.05;95% CI, 0.82–1.33; nominal P-value = 0.72). With some potential advantages in distinct molecular subtypes, and an acceptable safety profile, ripretinib is worth to be further evaluated in combination trials as well as for the identification of predictive markers of benefit.

7. Expert opinion

The management of advanced/metastatic GIST is evolving with the introduction of novel therapies in clinical practice. Although imatinib remains the standard of care for first-line treatment, secondary resistance is inevitable in the majority of cases, necessitating efficacious therapies in the second-line setting and beyond. Sunitinib and regorafenib are currently recommended for the second- and third-line settings; however, their clinical benefit is modest, and they may often be associated with intolerable toxicity, requiring dose reductions or interruptions. By targeting the broad spectrum of KIT and PDGFRA mutations through switching active I and inactive II forms, and by showing clinical activity against GIST-resistant to previous lines of therapies, ripretinib provides a valid fourth-line option for the management of advanced/metastatic GIST over placebo (INVICTUS trial). Based on the results of the INVICTUS trial, showing PFS at 6.3 months (95% CI, 4.6–6.9) with ripretinib vs 1.0 month (95% CI, 0.9–1.7) with placebo (HR, 0.15; 95% CI, 0.09–0.25; P < 0.0001), ripretinib was approved by FDA in May 2020. By reducing the risk of disease progression or death by 85% in comparison to placebo and having a favorable toxicity profile, ripretinib was included in the Version 1.2022 NCCN guidelines as a category 1 fourth-line treatment option in advanced GIST. Further analysis of the expanded access program is underway and will provide insight into the utilization of this agent in daily clinical practice.

Upon comparison with sunitinib in the second-line setting, although ripretinib showed a clearly better toxicity profile, there was no improvement in PFS (INTRIGUE trial).

Given the prolonged overall survival, the wide efficacy profile across different mutational subtypes but mainly its favorable toxicity outlook, ripretinib should be tested in combination schedules with other targeted agents, both conventional and newer TKIs, to fully unravel its potential role in advanced GIST. The role of intrapatient dose escalation upon progression on 150 mg qd may also be of value, and relevant evidence has already been provided through an INVICTUS subgroup analysis.

The upcoming few years will see results of several ongoing clinical trials testing the exact role of newer agents in the therapeutic algorithm of advanced GIST. Key to the development of this algorithm is tailoring of therapy depending on either the primary or the secondary resistance-related mutations in GIST. Successful examples of this approach are already incorporated in the management of advanced GIST, namely the introduction of avapritinib in the first-line setting in patients with tumors harboring a D842V mutation in PDGFRA exon 18, which have primary resistance to imatinib. Or the consideration of larotrectinib and entrectinib for NTRK gene fusion positive GISTs or BRAF inhibitors (such as dabrafenib) for BRAF mutated GISTs. Most critical is the lack of appropriate therapies for cases with secondary mutations found in imatinib-resistant GISTs in the second- and third-line settings.

What is undoubtable is that the number of available newer agents for the management of advanced/metastatic GIST has increased, with ripretinib being the first TKI after years of stagnation to change the outlook of the disease. The management of advanced GIST is expected to further evolve in the next five years, ultimately further improving patients' outcomes.

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Scientific accuracy review

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Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

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• **Randomized, open-label, multicentre, phase III trial, performed to evaluate the efficacy and safety of ripretinib versus sunitinib as a second-line treatment for patients with advanced GIST previously treated with imatinib. Ripretinib was not superior to sunitinib in terms of PFS. However, meaningful clinical activity, fewer grade 3/4 treatment-emergent adverse events, and improved tolerability were observed with ripretinib.**

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