Drug Evaluation

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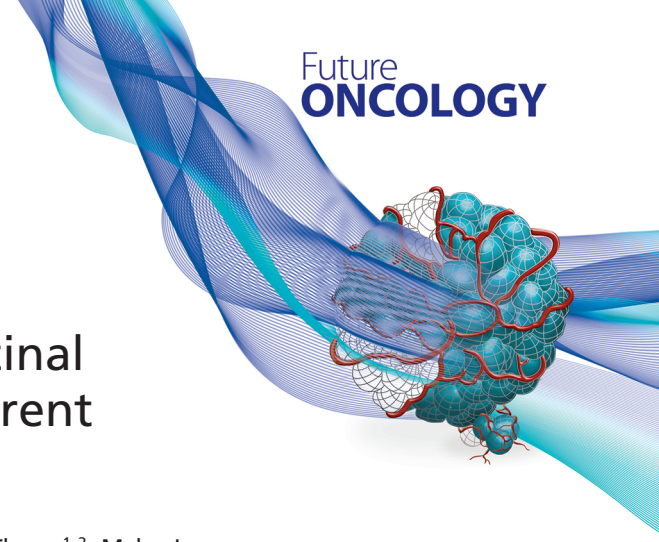

Ripretinib in advanced gastrointestinal stromal tumors: an overview of current evidence and drug approval

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Over the past 20 years, the management of gastrointestinal stromal tumors has acted as an important model in the advancement of molecularly targeted therapies for solid tumors. The success of imatinib has established it as a lasting therapy in the management of early-stage and advanced disease in the first-line setting. Imatinib resistance inevitably develops, resulting in the need for further lines of therapy. Ripretinib is an orally administered switch-control tyrosine kinase inhibitor, specifically developed to target both primary and secondary KIT and PDGFRα resistance mutations. Herein, the authors discuss the molecular rationale, the preclinical evidence and the clinical use of ripretinib in the treatment of gastrointestinal stromal tumors in the advanced stages of disease.

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Gastrointestinal stromal tumors (GISTs) are connective tissue tumors derived from the interstitial cells of Cajal, the pacemaker cells of the digestive tract responsible for peristalsis [1]. Although GISTs are the most common mesenchymal tumor of the GI tract, they account for less than 5% of all gastrointestinal malignancies. Incidence in the UK is estimated at approximately 900 new diagnoses per year, or 1.5/100,000/year [2]. GIST most commonly arise in the stomach (60–65%), followed by the small bowel (25–30%), rectum (3%) and colon (<3%) [3,4]. Less common origins in the GI tract include the esophagus and appendix [5]. Extragastrointestinal GISTs have also been reported [6,7].

From a genetic perspective, GISTs are characterized by the presence, in most cases, of activating mutations in proto-oncogenic receptor tyrosine kinases. This results in an intrinsic resistance to the standard cytotoxic chemotherapy used in other soft tissue sarcomas while conferring sensitivity to different tyrosine kinase inhibitors (TKIs), depending on the tumor's underlying mutational status [8]. For this reason, mutational analysis is part of the standard of care and it should be performed prior to the initiation of systemic therapy [9]. Mutually exclusive mutations occurring in KIT (encoded by the *KIT* gene) and PDGFRα account for up to 85% of all primary mutations in GISTs [10], respectively, encompassing 75–80% and 5–10% of all GIST cases [11–13]. Rarer forms of GISTs known as *KIT*/*PDGFRA* wild-type tumors account for approximately 15% of all cases and may harbor alterations in the genes encoding for the subunits of the SDH complex, *BRAF*, *NF1*, *NTRK* or *FGFR1* [14,15].

The most recent international guidelines recommend surgical resection for patients with primary resectable GISTs [9,16]. As anticipated, patients with unresectable GISTs are treated with TKIs, whose efficacy is associated with the tumor's mutational status. In first-line treatment, imatinib represents the standard of care for most patients with *KIT* and *PDGFRA* mutations [17–19], whereas avapritinib should be preferred in the presence of the imatinib-resistant *PDGFRA* D842V mutation [20]. Neoadjuvant and adjuvant treatment with imatinib, respectively, are also recommended for patients with imatinib-sensitive mutations and localized disease only resectable with significant morbidity [21,22] and resected disease with high risk of relapse, based on anatomic location, size and mitotic rate [23,24].

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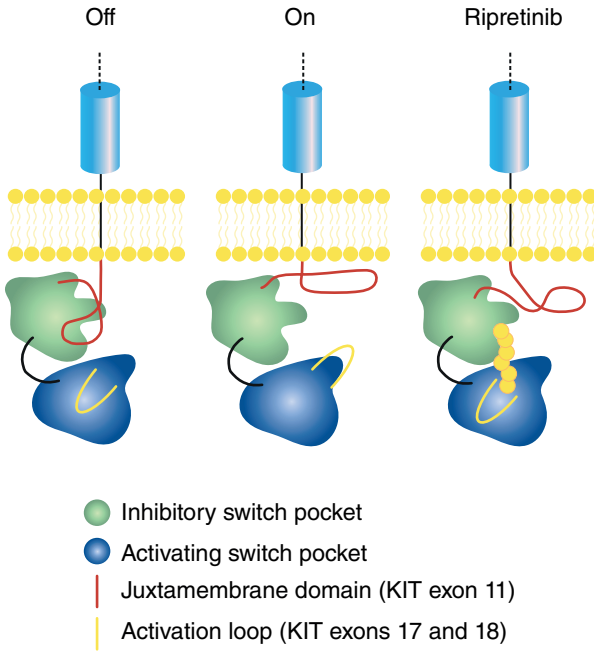

Figure 1. Mechanism of action of ripretinib: ripretinib stabilizes the inactive KIT conformation. In its inactive state (off), the inhibitory switch pocket of KIT is occupied by its juxtamembrane domain and the activation loop does not contact the activating switch pocket. In its active state (on), the inhibitory switch pocket of KIT is no longer occupied by its juxtamembrane domain and the activation loop contacts the activating switch pocket. Ripretinib stabilizes the inactive KIT conformation, occupying the inhibitory switch pocket normally occupied by the juxtamembrane domain and stabilizing the activating switch pocket in its inactive state.

In most advanced GIST cases, prolonged exposure to multiple lines of treatment with different TKIs ultimately results in the accumulation of secondary mutations associated with treatment resistance. In this review, the authors summarize the most common mechanisms of resistance to imatinib and other TKIs, as well as the preclinical and clinical evidence supporting the use of ripretinib, a recently approved TKI with a unique mechanism of action, in advanced GIST patients.

Mechanism of resistance to imatinib & other TKIs

Primary resistance

Response to imatinib correlates with underlying mutational status, with subgroups of patients showing primary resistance to imatinib. The largest group of patients with primary resistance to imatinib are those harboring *KIT*/*PDGFRA* wild-type GISTs [14,15]. In these patients, imatinib is not usually recommended and alternative therapeutic strategies are being investigated. Among patients with *KIT*/*PDGFRA* mutations, approximately 5% show primary resistance within the first 3–6 months of treatment with imatinib [25].

Mutations in *KIT* mainly affect exons 9, 11, 13 and 17 [26]. Primary driver mutations occur most frequently in *KIT* exon 11 and include deletions, deletion-insertions, insertions and missense mutations [12]. *KIT* exon 11 encodes for the juxtamembrane domain, which stabilizes the inactive conformation of *KIT* via binding of an inhibitory pocket of the kinase domain (Figure 1) [27]. Mutations in exon 11 are largely imatinib-sensitive, as this is the area where imatinib binds [28]. The second most common primary *KIT* mutation is represented by a duplication in exon 9 (encoding for an extracellular KIT domain), which occur in 7–15% of GISTs, more frequently of small bowel origin [14]. Recent evidence suggests that *KIT* exon 9 and exon 11 GISTs might be more different than previously appreciated [29,30]. Superior treatment outcomes with standard-dose imatinib (400 mg daily) have been observed in patients with *KIT* exon 11 mutations in comparison with patients with exon 9 mutations or wild-type GISTs [17–19]. *KIT* exon 9 mutation is of relevance due to the evidence that its relative primary resistance to standard-dose imatinib can be partially reverted with the administration of a higher dose (800 mg daily) in the advanced setting [31]. In the adjuvant setting, however, retrospective data comparing this higher dose with standard-dose imatinib did not show superior results in terms of survival outcomes for patients with exon 9 mutations treated with 800 mg daily [32].

Finally, the *PDGFRA* D824V mutation is also associated with primary resistance to imatinib [33,34]. One study has shown that none of 31 evaluable patients with D842V mutation obtained response to imatinib, whereas other *PDGFRA* mutations appeared to be imatinib sensitive [35].

Secondary resistance

Since the advent of imatinib and the approval of its use in metastatic GISTs in 2001, many long-term survivors have been reported, with reports of patients with metastatic disease living longer than 20 years [36]. Median progression-free survival on imatinib, however, is approximately 2 years [36], with acquired resistance to imatinib developing over time [37,38]. This is often due to the emergence of secondary resistance mutations in the *KIT* and *PDGFRA* genes. These secondary mutations usually occur in either the kinase ATP-binding pocket, which is encoded by *KIT* exons 13 and 14 and *PDGFRA* exons 14 and 15, or in the activation loop switch, a critical loop responsible for the final kinase activation, which is encoded by *KIT* exons 17 and 18 and *PDGFRA* exon 18 [39–41]. Individual tumor heterogeneity within the same patient can also occur for secondary resistant mutations.

Several other mechanisms of resistance can occur with multiple potential pathways converging and reactivating the MAPK pathway in the setting of *KIT*/*PDGFRA* inhibition, resulting in treatment adaptation and drug resistance. This led to the addition of TKIs with a broader spectrum of kinase inhibition to the treatment paradigm of unresectable and metastatic, imatinib-resistant GISTs.

Sunitinib, a KIT, PDGRFA and VEGFR inhibitor, was approved as second-line therapy in imatinib-resistant GISTs in 2006. In a worldwide phase III study, compared with placebo, sunitinib demonstrated a median progression-free survival of approximately 5.6 months versus 1.4 months (6 weeks) for the placebo. Overall response rate was 6.8% per Response Evaluation Criteria in Solid Tumors. Although the VEGFR inhibition by sunitinib introduced a different profile of adverse events such as hypertension and cardiac toxicity, therapy was reasonably tolerated and introduced as second-line standard of care [42]. As with imatinib, the underlying mutational status also relates to sunitinib responses: patients with primary *KIT* exon 9 mutations or *KIT*/*PDGFRA* wild-type tumors show a higher benefit than other subgroups. Moreover, patients with secondary *KIT* mutations involving the ATP-binding pocket (exons 13 and 14) are more sensitive to sunitinib than those involving the activation loop domain.

The multikinase inhibitor regorafenib followed 7 years later and has remained the standard third-line therapy in metastatic GIST since 2013. In a phase III study, the median progression-free survival of patients receiving regorafenib was 4.8 months compared with 0.9 months for placebo, with an overall response rate of 4.5% for regorafenib [43]. Dose-limiting toxicities are frequently seen with this agent, with real-world data suggesting a longer duration of treatment and response with rigorous toxicity management [44]. Importantly, regorafenib appeared to be effective independently of the mutational status and in the presence of most mutations in the activation loop (exons 17 and 18), although it is known to weakly inhibit *KIT* exon 17 D816V mutants [45]. Nevertheless, even with newer drugs such as regorafenib, resistance develops over time and limited options have existed for patients who have progressed on sunitinib or regorafenib or were intolerant to the drug-related side effects.

From a biochemical perspective, KIT and PDGFRα oscillate between an inactive (type II) and an active (type I) conformation. Imatinib, sunitinib and regorafenib are all considered type II kinase inhibitors, as they bind KIT and PDGFRα in their inactive conformation. Secondary mutations, especially in the activation loop, tend to stabilize the receptors in their active conformation, therefore limiting the accessibility of these TKIs to their binding domains [40,46].

Other drugs have therefore been designed to overcome primary or secondary imatinib resistance, including the type I inhibitor avapritinib [47]; the multi-TKIs cabozantinib [48], famitinib [49] and dasatinib [50]; and temozolomide in wild-type GIST [51]. Novel treatment approaches assessing the activity of checkpoint inhibition in GISTs are also under way with studies combining TKIs with checkpoint inhibition, such as axitinib and avelumab [52], as well as combinations of checkpoint inhibition [53]. The results of a phase I study combining dasatinib with ipilimumab in both GIST and soft tissue sarcoma patients have shown that the combination can be safely administered; however, limited clinical efficacy was observed [54].

Ripretinib: preclinical development

Switch kinase inhibitors are a novel and innovative class of drugs. Ripretinib is a type II switch-control TKI with a complex mechanism of action: certain elements of the inhibitor structure antagonize the activation loop switch occupancy of the KIT type I active conformation, and other elements of the inhibitor stabilize the activation loop switch in the type II inactive conformation. In addition, ripretinib occupies the inhibitory pocket occupied by the juxtamembrane domain, in the absence of exon 11 mutations (Figure 1) [39].

Initially known as DCC-2618 and now branded as Qinlock®, ripretinib was developed by Deciphera Pharmaceuticals to inhibit primary and drug-resistant secondary *KIT* and *PDGFRA* mutations. Ripretinib is active

Table 1. Summary of pharmacokinetic and pharmacodynamic characteristics of ripretinib.

Pharmaceutical property	Ripretinib/active metabolite DP-5439
Mechanism of action/drug class	Switch-control tyrosine kinase inhibitor/small molecule
Drug targets	*KIT*, *PDGFRA*, *PDGFRB*, *VEGFR2*, *TIE2*, *BRAF*
Route of administration	Oral
Time to steady state	14 days
Mean elimination half-life	14.8 h
Dosing and administration in gastrointestinal stromal tumors	Starting dose 150 mg once a day Increase to 150 mg twice a day at progression
Drug interactions	CYP3A: strong inhibitors – administer with caution; monitor patients treated with CYP3A inhibitors more frequently for adverse reactions CYP3A: strong inducers – avoid concomitant use
Safety in renal impairment	No dose adjustment needed
Safety in hepatic impairment	No dose adjustment in mild impairment Recommended dose not established in moderate/severe hepatic impairment

against wild-type *KIT* and *PDGFRA* and a broad spectrum of *KIT* and *PDGFRA* mutations, including primary and resistance mutations in *KIT* exons 9, 11, 13, 14, 17 and 18, including the regorafenib-resistant D816V mutation, outperforming competitor type I and II inhibitors [39]. In *in vitro* and cell-based studies, significant inhibitory activity has also been shown against the proto-oncogenic kinase receptors PDGFRB, TIE2, VEGFR2 and BRAF [39]. The broad activity of ripretinib was further confirmed in murine models, including an exon 17 drug-resistant, gastrointestinal stromal tumor patient-derived xenograft model, supporting its clinical development [39].

Ripretinib: clinical studies

Phase I

Following the promising preclinical evidence of ripretinib activity in GISTs, the first-in-human study (NCT02571036) began in 2015 [55]. This was a multicenter, phase I, dose-escalation study of ripretinib in patients with GISTs that had progressive disease on at least one line of therapy. This open-label trial investigated the safety, recommended phase II dose, pharmacokinetics, pharmacodynamics and preliminary anticancer activity of ripretinib. In the dose-escalation phase, the tested doses included 20 mg (n = 4), 30 mg (n = 4), 50 mg (n = 11), 100 mg (n = 12), 150 mg (n = 6) and 200 mg (n = 7) twice a day and 100 mg (n = 6), 150 mg (n = 12) and 250 mg (n = 6) once daily [55]. The pharmacokinetics and pharmacodynamics data obtained from this trial are summarized in Table 1. The established recommended phase II dose for ripretinib was 150 mg once daily. Three dose-limiting toxicities were identified, including elevation of lipase (n = 2) and creatinine phosphokinase (n = 1). The maximum tolerated dose was not reached. In the expansion phase, patients who experienced progression on 150 mg once daily and continued to receive clinical benefit were allowed to stay on treatment with the option of dose escalation to 150 mg twice a day. Intrapatient dose escalation provided benefit across all lines of therapy with a safety profile similar to that observed with the once-a-day regimen [56].

In this phase I study, patients with advanced GISTs received ripretinib 150 mg once daily in either the second-line, third-line, fourth-line or greater treatment setting. Unsurprisingly, ripretinib showed more activity in earlier lines of therapy. The overall response rate (ORR) observed was 11.3%, ranging from 7.2% (fourth-line or greater; n = 83) to 14.3% (third-line; n = 28) to 19.4% (second-line; n = 31). The progression-free survival (mPFS) varied from 5.5 months in fourth-line treatment to 10.7 months in second-line treatment [55]. Data on overall survival (OS) have not been published to date. These results supported the ongoing development and evaluation of ripretinib in both the fourth-line treatment (INVICTUS trial) and the second-line setting (INTRIGUE trial).

In current practice, ripretinib is taken once daily for 28-day cycles. The initial starting dose is 150 mg orally once daily with a first dose reduction to 100 mg once daily, and the second to the lowest dose on 50 mg once daily. A summary of the key pharmacological and pharmaceutical properties of ripretinib appears in Table 1.

Phase III INVICTUS: fourth-line setting & beyond

INVICTUS (NCT0335373) was the first phase III trial of ripretinib in the advanced GIST setting. This was a double-blind, randomized, placebo-controlled trial enrolling patients with advanced/metastatic GISTs who had progression of disease on at least imatinib, sunitinib and regorafenib (fourth-line treatment and beyond). Following

Table 2. Overview of the efficacy of trials with ripretinib in advanced gastrointestinal stromal tumors.

Trial	Phase	Study design	Study population	n	Comparator arm	Median PFS (months)	Median OS (months)	ORR	Ref.
NCT02571036	I	First-in-human, dose-escalation/expansion	≥Second-line GISTs	258 (184 GISTs)	Single arm	10.7 (second-line) 8.3 (third-line) 5.5 (fourth-line)	–	11.3%	[55]
INVICTUS (NCT0335373)	III	Randomized, controlled trial	≥Fourth-line GISTs	129	Placebo	6.3	18.2	11.8%	[57]
INTRIGUE (NCT03673501)	III	Randomized, controlled trial	Second-line GISTs	453	Sunitinib	8.0	–	21.7%	[59]

GIST: Gastrointestinal stromal tumor; ORR: Overall response rate; OS: Overall survival; PFS: Progression-free survival.

publication of the study results, ripretinib is now considered the standard of care in fourth-line management of advanced GISTs [57].

Study participants were randomized 2:1 and stratified according to prior lines of treatment (3 vs ≥4) and Eastern Cooperative Oncology Group performance status of 0 versus 1 or 2. Eligibility criteria initially excluded patients with wild-type GISTs, with expansion of the eligibility criteria after study commencement to include patients with *KIT* and *PDGFRA* wild-type GISTs (8% of the final study population). Study participants who received the placebo were permitted crossover at the time of progression. The primary end point of mPFS was significantly improved with ripretinib relative to placebo (6.3 vs 1.0 month) [57]. The most recent update of the study was presented at the European Society for Medical Oncology 2021 conference, and a median overall survival of 18.2 months was reported with ripretinib versus 6.3 months with placebo, with a median overall survival of 10.0 months in placebo patients who crossed over to ripretinib. ORR in the ripretinib arm was 11.8 versus 0% in the placebo arm (Table 2) [58]. A critique of the study is the placebo-controlled design, and thus the outcome in the placebo arm was inferior.

As part of the phase III INVICTUS trial, patients who received ripretinib 150 mg once daily, with evidence of progressive disease by blinded, independent central review, were permitted to dose-increase to 150 mg twice daily if they tolerated treatment well [57]. The efficacy and safety of ripretinib intrapatient dose escalation to 150 mg twice daily after progressive disease was again associated with a safety profile similar to that of once-daily dosing, with no increase in grade 3 or 4 adverse events. Dose escalation also appeared to lead to response and further control of disease, adding an additional mPFS of 3.7 months after intrapatient dose escalation [56,60].

A subgroup analysis has also been published evaluating efficacy across *KIT* and *PDGFRA* mutation subgroups by combined tumor and liquid biopsy. One hundred twenty-nine of the INVICTUS study participants enrolled in this substudy. Interestingly, patients receiving ripretinib showed PFS benefit versus placebo regardless of mutation status and in all assessed subgroups (exon 11, $p < 0.0001$; exon 9, $p = 0.0023$; exon 13, $p < 0.0001$; exon 17, $p < 0.0001$). Activity of ripretinib in patients with *KIT*/*PDGFRA* wild-type GISTs could not be concluded from the analysis, highlighting the need for further study with more patients in this setting [61].

Phase III INTRIGUE: second-line setting

INTRIGUE (NCT03673501) is an open-label, randomized, phase III study comparing ripretinib with sunitinib after imatinib, as a second-line treatment option in advanced GISTs. It is a large, multinational study conducted in 22 countries and 122 investigational sites. The study end point is PFS as assessed by blinded, independent central review. Secondary end points include ORR as determined by blinded, independent central review using modified Response Evaluation Criteria in Solid Tumors and OS [59]. Study participants were stratified by mutational status in prespecified subgroups, including patients with a *KIT* exon 11 primary mutation, and an all-patient intention-to-treat population. Patients who received any other line of therapy in addition to imatinib were excluded. In the trial, 453 patients were randomized to ripretinib 150 mg once daily or sunitinib 50 mg once daily for 4 weeks of a 6-week cycle. Of note, dose escalation of ripretinib to twice-daily dosing was not permitted in the INTRIGUE study and may have impacted study results. Escalation to twice-daily dosing is expected to become standard practice for patients who progress on once-daily dosing and have good drug tolerance.

In November 2021, Deciphera revealed that the study had not met its primary end point of PFS compared with standard of care sunitinib in metastatic GISTs [62]. The INTRIGUE study results were presented by abstract and oral presentation at the January 2022 American Society of Clinical Oncology Plenary Series [63]. Two hundred twenty-six

patients were randomized to the ripretinib arm (163 with exon 11), and 227 were randomized to sunitinib (164 with exon 11). In patients with an exon 11 mutation, ripretinib demonstrated an mPFS of 8.3 months compared with 7.0 months in the sunitinib arm (hazard ratio: 0.88; p = 0.360) [62]. While not formally tested due to the rules of the hierarchical testing sequence, in the all-patient population, ripretinib demonstrated an mPFS of 8.0 months compared with 8.3 months in the sunitinib arm (hazard ratio: 1.05; nominal p = 0.715). The ORR for ripretinib was 21.7% compared with 17.6% in the sunitinib arm. In patients with a *KIT* exon 11 primary mutation, the ORR for ripretinib was 23.9% compared with 14.6% for sunitinib. The final OS data were immature at the time of the presentation and are yet to be reported.

Updated patient-reported outcome data presented at the 2022 American Society of Clinical Oncology annual meeting showed that patients receiving ripretinib versus sunitinib experienced fewer severe or life-threatening (grade $\geq$3) treatment-related adverse events prior to progression (24 vs 51%, respectively). Patients in the ripretinib arm reported significantly ($p < 0.05$) less decline compared to their pre-ripretinib baseline in patient-reported functional assessment, as well as less increase, or improvement, in symptoms of fatigue, appetite loss, diarrhea, nausea/vomiting and pain versus patients in the sunitinib arm [64].

Additional studies

An ongoing phase II, open-label, multicenter study (NCT04282980) in China is assessing the pharmacokinetics, safety and efficacy of ripretinib in Asian patients with advanced GISTs whose disease progressed on previous therapy. The primary end points include PFS, and the secondary end points include ORR and OS [65]. A comparative study randomizing to ripretinib and sunitinib in second-line therapy in the Asian population is also currently recruiting (NCT04633122).

Given the acceptable and well-tolerated toxicity profile of ripretinib in heavily pre-treated patient populations, an open-label, phase Ib/II study of ripretinib in combination with binimetinib, a MEK inhibitor, in patients with unresectable or metastatic GISTs had been planned in second-line therapy post-imatinib or further (NCT05080621) [66]. The study has recently been withdrawn by the sponsor due to corporate restructuring and reprioritization of development programs. No patients had enrolled in the study prior to its withdrawal [66]. This had been a promising study scientifically, due to synergistic effects seen with this drug combination in preclinical models, leading to induction of apoptosis in GIST cell lines [67].

Safety & tolerability

Ripretinib has been shown to be a well-tolerated drug with an acceptable safety profile in the earlier phase I study and more recent phase III trials. In all studies, most adverse events (AEs) were grade 1/2 in severity [55,57,63].

The most common drug-related AEs of any grade observed in the phase I study and ripretinib arm of the INVICTUS trial included alopecia, myalgia, nausea, fatigue, palmar-plantar erythrodysesthesia syndrome and diarrhea. In INVICTUS, the most common treatment-related grade 3/4 events were lipase increase (5%), hypertension (4%), fatigue (2%) and hypophosphatemia (2%). Eight (9%) patients in the ripretinib arm experienced treatment-related serious AEs compared with 7% of patients in the placebo arm. Serious AEs in the ripretinib group included anemia, cardiac failure, death of unknown cause, dyspnea, fecaloma, gastroesophageal reflux, hyperkalemia, hypophosphatemia, nausea and upper gastrointestinal hemorrhage. Six percent of patients receiving ripretinib had dose reductions because of treatment-related AEs, and 5% of patients discontinued therapy related to AEs. One treatment-related death was recorded in each group [57].

INTRIGUE results presented at the American Society of Clinical Oncology plenary session reported that ripretinib was generally well tolerated. Fewer patients in the ripretinib arm experienced grade 3/4 AEs compared with sunitinib (41.3 vs 65.6%). Sunitinib was three-times more likely to cause grade 3 hypertension compared with ripretinib (26.7 vs 8.5%) and more likely to cause grade 3 hand–foot syndrome compared with ripretinib (10 vs 1.3%). Patients receiving ripretinib also experienced less deterioration in their ability to engage in either work or leisure activities during treatment [63].

Ripretinib was shown to have certain AEs, such as alopecia and new primary cutaneous malignancies, that have not been commonly observed in other TKIs used in this setting. A longitudinal analysis of alopecia in the INVICTUS trial found that it did not worsen over time. In terms of new primary cutaneous malignancies, in INVICTUS, cutaneous squamous cell carcinoma (cuSCC) occurred in 4.7% of the 85 patients treated with ripretinib with a median time to event of 4.6 months (range: 3.8–6 months). In the pooled safety population, cuSCC and keratoacanthoma occurred in 7 and 1.9% of 351 patients, respectively. In INVICTUS, melanoma

Table 3. Summary of safety outcomes in ripretinib clinical trials.

Adverse event	Phase I reference (ripretinib n = 142)		INVICTUS reference (ripretinib n = 85)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Alopecia	62%	0	49%	0
Fatigue	52.1%	2.8%	24%	2%
Myalgia	48.6%	0	27%	1%
Nausea	44.4%	1.4%	25%	1%
Palmar-plantar erythrodysesthesia	43%	0.7%	18%	0
Diarrhea	31%	2.1%	20%	1%
Constipation	39.4%	0	15%	0
Decreased appetite	32.4%	1.4%	14%	1%
Weight loss	27.5%	0	15%	0
Bilirubin elevation	–	–	14%	0
Arthralgia	22.5%	0	12%	0
Muscle spasm	29.6%	0	12%	0
Hypertension	16.9%	5.6%	5%	4%
Lipase increase	9.9%	17.6%	5%	5%
Hypophosphatemia	12%	4.9%	4%	2%
New cutaneous malignancy (squamous cell carcinoma)	–	–	4.7%	–
Cardiac failure	–	–	0	1%

Data taken from [55,57].

occurred in 2.4% of the 85 patients who received ripretinib. In the pooled safety population, melanoma occurred in 0.9% of 351 patients. This highlights the need to perform dermatologic evaluations when initiating treatment and routinely during treatment with ripretinib. Suspicious skin lesions should be managed promptly with dermatologic assessment and excision where possible [57]. The results of a centralized dermatopathologic review of reported cuSCC events in patients treated with ripretinib demonstrated that the patients were elderly (mean age: 72 years), with lesions located in sun-exposed areas. The cuSCC lesions did not show aggressive histopathologic features and were analogous to their lowest-risk, ultraviolet-induced counterparts. Thus, the cuSCC lesions in patients treated with ripretinib can generally be managed using local interventions, without the need for dosing modifications or interruptions [68].

As with other TKIs, dose modification is recommended for any clinically meaningful AEs, with an initial reduction to 100 mg once daily. Specific dosage modifications are recommended in the package labeling for grade $\geq$2 palmar-plantar erythrodysesthesia syndrome, arthralgia or myalgia and for left ventricular systolic dysfunction, grade $\geq$3 hypertension and other AEs. Similar to the management guidance for sunitinib and regorafenib, ripretinib should not be initiated in patients with uncontrolled hypertension. Blood pressure should be monitored as clinically indicated, with withholding of ripretinib based on severity and resuming at the same or reduced dosing or permanent discontinuation of the drug, should hypertension remain uncontrolled, with appropriate medical management. Cardiac dysfunction was infrequently observed in patients who received ripretinib. Prescribing guidelines recommend the assessment of ejection fraction by echocardiogram or multiple-gated acquisition scan prior to commencing ripretinib and during treatment, as clinically indicated. Ripretinib should be permanently discontinued in the event of grade 3 or 4 left ventricular systolic dysfunction. A summary of ripretinib safety outcomes is shown in Table 3.

Regulatory affairs

Uniform consensus on the benefit of ripretinib from phase III INVICTUS resulted in the first regulatory approval for ripretinib in the fourth-line setting of metastatic GISTs in May 2020 by the US FDA (Figure 2) [69]. The EMA's Committee for Medicinal Products for Human Use recommended the granting of a marketing authorization for ripretinib in the same treatment setting in September 2021 [70], with subsequent approval granted by the European Commission in the EU for this indication in November 2021. The European Commission decision is

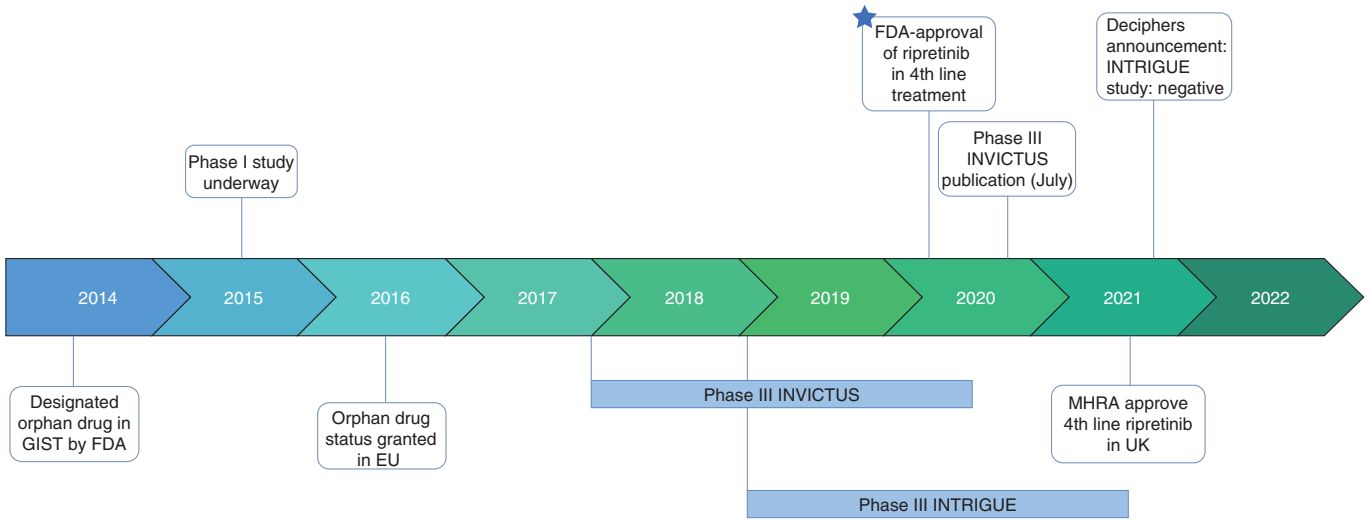

Figure 2. Time line of key milestones of phase III trials and regulatory approval of ripretinib for advanced gastrointestinal stromal tumors.
GIST: Gastrointestinal stromal tumor; MHRA: Medicines and Healthcare products Regulatory Agency.

applicable to all 27 EU member states plus Iceland, Norway and Liechtenstein. Most recently, the UK Medicines and Healthcare products Regulatory Agency granted marketing authorization for ripretinib in the UK in December 2021 [71]. Following further regulatory submissions, it has now also been approved in Canada, Australia, Hong Kong, Taiwan, China and Switzerland.

Recommendations for use of the drug in the fourth-line setting have also been incorporated into the European Society for Medical Oncology–European Reference Network for Rare Adult Solid Cancers–European Reference Network for Genetic Tumour Risk Syndromes clinical guidelines and the National Comprehensive Cancer Network recommendations in the management algorithm of advanced/metastatic GISTs as a fourth-line treatment for patients progressing or intolerant of imatinib, sunitinib and regorafenib [9,16]. In addition, a recent update to the National Comprehensive Cancer Network gastrointestinal stromal tumor guidelines includes the recommendation of ripretinib dose escalation to 150 mg twice daily (if previously treated with ripretinib 150 mg daily) [16].

Conclusion

Understanding the molecular landscape of GISTs has resulted in improvements in treatment options and the power to provide a personalized medicine approach. The efficacy of approved drugs in advanced, treatment-refractory GISTs is relatively modest, however, in comparison with first-line imatinib. For many years, current standard-of-care treatments included imatinib, sunitinib and regorafenib. The inevitable resistance to TKIs remains a challenge for patients with metastatic disease. Ripretinib was developed to address the multiple potential secondary mutations associated with drug resistance in GISTs, via a novel mechanism of action.

The practice-changing INVICTUS trial has led to approval of this drug in the fourth-line setting, which was the first drug approval for GIST in almost 10 years. The results demonstrated that ripretinib given as fourth-line treatment, or further, for the treatment of advanced GISTs was associated with significantly improved progression-free and overall survival compared with placebo.

The approval of ripretinib in the second-line setting is unlikely, as the INTRIGUE study did not meet its primary end points; however, the overall response rate and tolerability of ripretinib were superior to those of sunitinib. Subgroup analyses based on the mutational status will tell whether specific subgroups of patients benefit more from either drug. Of note, in the INTRIGUE trial the outcomes in the sunitinib arm were better than expected and described in its original phase III GIST registration study. This may be explained by a lower disease burden following imatinib failure in this group in comparison with that in the original trials when sunitinib was first used in advanced GISTs in 2006. The future analysis of overall survival data in the INTRIGUE trial might provide some information on the efficacy of subsequent treatments.

Finally, the progress of the treatment of GISTs has shown dramatic improvement in recent years, from multivisceral resection with rapid recurrence and chemotherapy resistance to long-term responses demonstrated, with over 20-year survival in some patients. Following disease progression on three lines of treatment, ripretinib offers an additional therapeutic option with low-level toxicity. Ripretinib has been firmly added to the treatment armamentarium of GISTs, which continues to expand.

Executive summary

Background

- Secondary mutations are a major cause of drug resistance in gastrointestinal stromal tumors (GISTs).
- Ripretinib is a type II switch-control tyrosine kinase inhibitor designed to overcome acquired *KIT*/*PDGFRA* resistance mutations.

Ripretinib clinical evidence

- Ripretinib showed clinically meaningful progression-free and overall survival benefit versus placebo in the INVICTUS phase III study in the fourth-line setting.
- No meaningful difference in progression-free survival was seen between ripretinib and sunitinib in the second-line treatment of advanced/unresectable GISTs (phase III INTRIGUE).

Safety & tolerability

- Ripretinib is a safe and well-tolerated drug, with a favorable side-effect profile in comparison with sunitinib and regorafenib.

Approval

- Ripretinib is approved in the fourth-line setting for advanced GISTs and is the only approved agent in this setting.

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In addition to the peer-review process, with the author's consent, the manufacturer of the product discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made by the author at their discretion and based on scientific or editorial merit only. The author maintained full control over the manuscript, including content, wording and conclusions.

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RL Jones is a member of the Future Oncology Editorial Board. They were not involved in any editorial decisions related to the publication of this article, and all author details were blinded to the article's peer reviewers as per the journal's double-blind peer review policy.

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