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Clinical Activity of Ripretinib in Patients with Advanced Gastrointestinal Stromal Tumor Harboring Heterogeneous *KIT/PDGFRA* Mutations in the Phase III INVICTUS Study

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ABSTRACT

Purpose: Most patients with gastrointestinal stromal tumor (GIST) have activating mutations in *KIT/PDGFRA* and are initially responsive to tyrosine kinase inhibitors (TKI). The acquisition of secondary mutations leads to refractory/relapsed disease. This study reports the results of an analysis from the phase III INVICTUS study (NCT03353753) characterizing the genomic heterogeneity of tumors from patients with advanced GIST and evaluating ripretinib efficacy across *KIT/PDGFRA* mutation subgroups.

Patients and Methods: Tumor tissue and liquid biopsy samples that captured circulating tumor DNA were collected prior to study enrollment and sequenced using next-generation sequencing. Subgroups were determined by *KIT/PDGFRA* mutations and correlation of clinical outcomes and *KIT/PDGFRA* mutational status was assessed.

Results: Overall, 129 patients enrolled (ripretinib 150 mg once daily, $n = 85$; placebo, $n = 44$). The most common primary mutation subgroup detected by combined tissue and liquid biopsies were in *KIT* exon 11 (ripretinib, 61.2%; placebo, 77.3%) and *KIT* exon 9 (ripretinib, 18.8%; placebo, 15.9%). Patients receiving ripretinib demonstrated progression-free survival (PFS) benefit versus placebo regardless of mutation status (HR 0.16) and in all assessed subgroups in Kaplan–Meier PFS analysis (exon 11, $P < 0.0001$; exon 9, $P = 0.0023$; exon 13, $P < 0.0001$; exon 17, $P < 0.0001$). Among patients with wild-type *KIT/PDGFRA* by tumor tissue, PFS ranged from 2 to 23 months for ripretinib versus 0.9 to 10.1 months for placebo.

Conclusions: Ripretinib provided clinically meaningful activity across mutation subgroups in patients with advanced GIST, demonstrating that ripretinib inhibits a broad range of *KIT/PDGFRA* mutations in patients with advanced GIST who were previously treated with three or more TKIs.

Introduction

Gastrointestinal stromal tumors (GIST) are the most common sarcomas of the digestive tract (annual incidence 10–15 per million individuals) and typically occur in the stomach and small intestine, but can arise anywhere in the gastrointestinal tract (1–3). Most GISTs have activating mutations either in receptor tyrosine kinase: KIT (approximately 69%–83% of all GISTs) or platelet-derived growth factor receptor α (PDGFRA; approximately 5%–10% of all GISTs; refs. 4–6). Approximately 15% of GISTs lack a *KIT* or *PDGFRA* mutation and are historically classified as *KIT/PDGFRA* wild-type (WT; ref. 6); these tumors are also referred to as non-*KIT*/non–*PDGFRA*-mutant GIST, as they usually harbor other known oncogenic mutations [proto-oncogene B-Raf (BRAF), neurofibromatosis type-1 (NF1), succinate dehydrogenase deficiency (SDHX); refs. 7, 8]. KIT/PDGFRA are dual switch-containing kinases (9, 10). These switch mechanisms regulate cellular KIT/PDGFRA conformations and catalytic activities (9). Primary mutations in the *KIT* gene are most commonly found in the juxtamembrane domain inhibitory switch (exon 11, approximately 70%) or the extracellular domain (exon 9, approximately 10%; ref. 11). Mutations in the KIT switch pocket adjacent to the ATP-binding pocket (exon 13, approximately 1%) and the KIT activation switch

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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Translational Relevance

KIT/PDGFRA mutations are early oncogenic events in gastrointestinal stromal tumors (GIST) and are key oncogenic metastatic drivers. Clonal evolution of mutations within multiple exons that encode the functional domains of tyrosine kinase receptors have been observed leading to both intra- and intertumor mutational heterogeneity, representing a major mechanism of resistance to existing tyrosine kinase inhibitors (TKI). Here we describe the genomic landscape of KIT-related resistance based on an exploratory analysis from INVICTUS. This study investigated *KIT/PDGFRA* mutations using both tumor tissue and liquid biopsies in patients with advanced GIST who were previously treated with at least imatinib, sunitinib, and regorafenib. This is the largest study to reflect the spectrum and extent of mutational heterogeneity in pretreated GIST, underscoring the broad inhibitory activity of ripretinib in this treatment line.

(exon 17, approximately 1%) are less frequent (11). The most common *PDGFRA* primary mutations occur in the activation switch (exon 18, approximately 6%; ref. 11). These mutations in the conformation-controlling switch mechanism, regardless of location, disrupt the autoinhibited forms of KIT and PDGFRA kinases and cause constitutive, ligand-independent kinase activity and signaling, ultimately leading to tumor growth and metastasis (12–14).

The current treatment algorithm for patients with advanced, inoperable GIST includes the sequential use of tyrosine kinase inhibitors (TKI) such as imatinib, sunitinib, and regorafenib, which are approved first-, second-, and third-line treatments, respectively (15, 16). These established treatments target the "switch-off" inactive conformation of the kinase by competitively binding to the ATP-binding site (17–19). In particular, some specific *PDGFRA* mutations, mostly the exon 18 D842V substitution mutation, are highly resistant to imatinib treatment. Patients with these mutations may receive the recently approved TKI avapritinib as first-line treatment, as it is approved for patients with unresectable or metastatic GIST that have a *PDGFRA* exon 18 mutation (4, 20, 21).

Secondary mutations typically arise during treatment and can confer resistance to the therapeutic agent. Specifically, secondary *KIT* mutations involving the switch pocket adjacent to the ATP-binding site (exons 13 and 14) or the activation switch (exons 17 and 18) can directly hinder binding of imatinib or stabilize KIT oncoprotein in the active conformation (22). These resistance mutations develop within switch domains, driving *KIT/PDGFRA* to an active state. Sunitinib and regorafenib inhibit some resistance mutations, but neither cover the full spectrum of mutations (23–25). Moreover, patients frequently develop separate resistance clones that harbor different resistance mutations, leading to relatively short disease control in second- and third-line treatments for GIST (23–27).

Ripretinib was approved by the FDA in May 2020 for the treatment of adult patients with advanced GIST who received prior treatment with three or more kinase inhibitors, including imatinib (28). In contrast to the mechanism of action of the first three lines of therapy, ripretinib is a switch-control TKI that broadly inhibits KIT and PDGFRA kinase signaling through a dual mechanism of action (9, 29). Designed to bind to both the switch pocket and the activation switch to lock the kinase in the inactive state, ripretinib prevents downstream signaling and cell proliferation and provides broad inhibition of KIT and PDGFRA kinase activity brought on by both primary mutations and secondary mutations that lead to drug-resistant GIST (29). In the phase III INVICTUS study (NCT03353753), patients receiving ripretinib had a statistically significantly longer median progression-free survival (mPFS; 6.3 months) compared with patients receiving placebo (1.0 month; ref. 29).

Tumor tissue biopsy is the traditional gold standard of genotyping in patients with GIST. However, due to the invasive procedures that carry the risk of complications and the time-consuming nature of acquiring tumor tissue biopsies, liquid biopsy that captures circulating tumor DNA (ctDNA) has been used in research in recent years and has demonstrated feasibility and accuracy in detecting *KIT/PDGFRA* mutations in patients with GIST (30–32).

The objectives of this study were to demonstrate the utility of tissue and liquid biopsy in detecting *KIT/PDGFRA* mutations in patients with advanced GIST, characterize the genomic heterogeneity of tumors from patients with advanced GIST enrolled in the INVICTUS trial, and correlate the clinical benefit of ripretinib with baseline mutations.

Patients and Methods

Patient population

The study enrolled patients aged 18 years or older with diagnosed GIST and at least one measurable lesion according to modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST 1.1). Patients who had progressive disease on or documented intolerance to at least imatinib, sunitinib, and regorafenib and an Eastern Cooperative Oncology Group (ECOG) score of 0 to 2 were included. Patients were excluded from the study if they underwent any anticancer therapy within 14 days of starting the study, had uncontrolled hypertension, or had a left ventricular ejection fraction less than 50% at screening. Full inclusion and exclusion criteria can be found in the Supplementary data and have been previously described (29).

Study design and treatment

INVICTUS is an international, multicenter, randomized, double-blind, placebo-controlled phase III trial in 129 patients who received at least three prior anticancer therapies for advanced GIST. Patients were randomized 2:1 to receive ripretinib 150 mg once daily or placebo until disease progression, as determined by blinded independent central review using mRECIST criteria. Randomization was stratified by number of prior anticancer therapies (3 or ≥4) and ECOG score (0 vs. 1 or 2), but not by *KIT/PDGFRA* mutation status. The study design and patient disposition for this trial has been published previously (29). This study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonization Guidelines for Good Clinical Practice. All patients were capable of understanding and complying with the protocol and provided informed written consent to participate in the study. The protocol, protocol amendments, and informed consent documents were approved by the institutional review board or ethics committee at each site before beginning the study.

Outcomes

The primary efficacy outcome for the INVICTUS trial was progression-free survival (PFS). Characterization of mutational status and retrospective correlation between baseline mutation subgroups and efficacy were exploratory outcomes. PFS was assessed for each baseline

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mutational subgroup, detected by combining results from the tissue and liquid biopsies.

Sample collection and sequencing analytics

Fresh tumor tissue samples were collected during screening prior to beginning the study drug (baseline). Archival tumor tissue samples could be used as long as no anticancer therapy was administered after the sample was collected. Additional tumor tissue samples may have been collected during the course of the trial (while on study drug) to be used for further molecular testing. However, the data presented here reflect only biopsy samples collected prior to ripretinib treatment. Tumor tissue specimens were analyzed using a next-generation sequencing (NGS), FDA-approved 324-gene assay, FoundationOne (Foundation Medicine, Inc.). Mutations reported in this manuscript are categorized as known or likely cancer-driving alterations and genomic signatures by the assay (33).

Liquid biopsy samples (plasma ctDNA) were collected at cycle 1 day 1 prior to the first dose of study drug (baseline), at the start of every other 28-day cycle, and at the end of treatment. Samples were analyzed via an NGS 73-gene FDA-approved liquid biopsy assay, Guardant360 (Guardant Health, Inc.). This assay reports mutations in a panel of genes that are frequently mutated in cancer and align with the mutations reported by the FoundationOne assay (34). All variants reported by the assay are ≥0.02% mutant allele frequency.

Data analysis

Analysis was conducted for the entire intent-to-treat population ($N = 129$) until data cutoff (March 9, 2020). Continuous variables were summarized using descriptive statistics while categorical variables were summarized using frequencies and proportions. Time-to-event data were summarized via Kaplan–Meier methodology with associated two-sided 95% confidence intervals (CI). A two-sided stratified log–rank test (0.05 significance level) was used to evaluate treatment difference. HRs were obtained using a Cox regression analysis adjusted for covariates and the 95% CIs were obtained using the Wald method. PFS was analyzed only during the double-blind treatment period.

Primary mutation subgroups are presented as detected in tissue, liquid, and combined biopsies. *KIT* exon 9, *KIT* exon 11, or *PDGFRA* mutations were deemed as primary mutations. Any *KIT* mutations detected in addition to primary *KIT* exon 9 or *KIT* exon 11 in a patient were considered secondary mutations. In the absence of a *KIT* exon 9/exon 11 mutation, patients were categorized as "other" *KIT* primary subgroup.

Results

Primary mutation subgroups detected in baseline tissue, liquid, and combined biopsies

A total of 129 patients were randomized to either the ripretinib group ($n = 85$) or the placebo arm ($n = 44$). Patient demographics and clinical characteristics were published previously (29). Overall, 128 tumor samples were collected (**Fig. 1**): 119 during the screening period and 9 prior to study screening. Optional posttreatment tumor tissue samples were collected in only 2 patients and were not analyzed for this manuscript. Most tissue samples were obtained from metastatic lesions. Tissue biopsy detected a single *KIT* mutation in 34 patients, 2 *KIT* mutations in 49 patients, and ≥3 *KIT* mutations in 16 patients. The most common primary mutation subgroup in either treatment arm detected in tissue biopsy was in *KIT* exon 11 (ripretinib, 55.3% of tumors, $n = 47$; placebo, 63.6%, $n = 28$) followed by *KIT* exon 9 (ripretinib, 16.5%, $n = 14$; placebo, 13.6%, $n = 6$; **Table 1**). Only 3 patients (2.34%), all in the ripretinib arm, had a single *PDGFRA* mutation (all exon 18, non-D842V); 10 patients (7.75%; 7 in the ripretinib arm and 3 in the placebo arm) were *KIT/PDGFRA* WT (**Table 1**). A total of 16 tissue biopsy samples failed sequencing, mostly due to low tumor content (**Fig. 1**).

Liquid biopsy detected a single *KIT* mutation in 25 patients, while 28 patients had 2 *KIT* mutations and 37 patients had ≥3 *KIT* mutations. Similar to tissue biopsy, *KIT* exon 11 mutations were the most

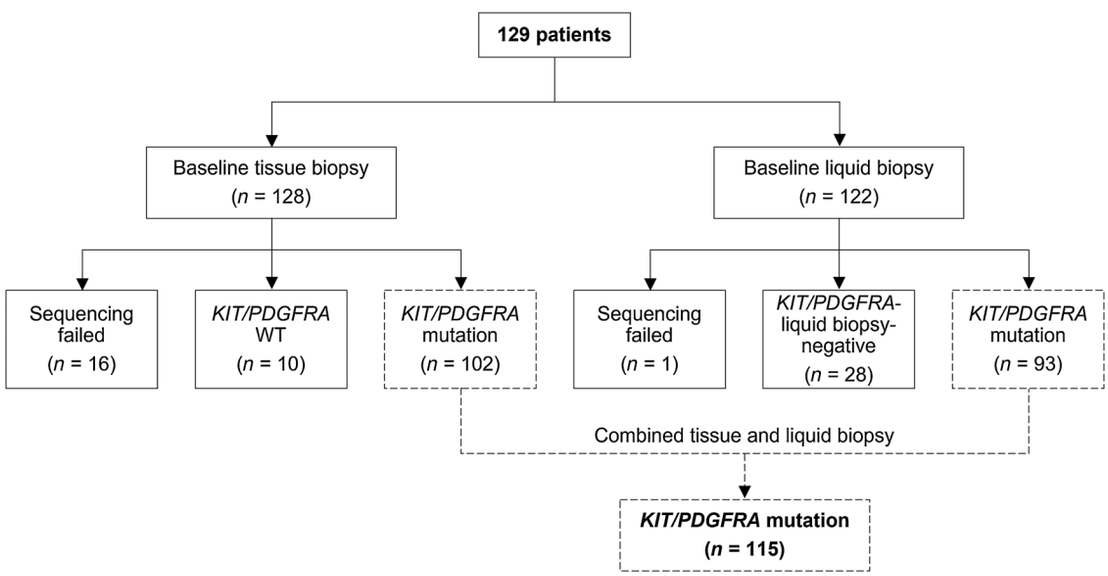

Figure 1.

Flow chart of patient biopsies and mutational status. On average, 1.85 *KIT/PDGFRA* mutations were detected in each tissue biopsy, while 2.61 *KIT/PDGFRA* mutations were detected in each liquid biopsy. PDGFRA, platelet-derived growth factor alpha; WT, wild-type.

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Table 1. Primary mutation subgroups detected in baseline tissue, liquid, and combined biopsies.

	Ripretinib ($n = 85$)	Placebo ($n = 44$)	Total ($N = 129$)
Baseline tissue biopsy			
Detected mutation, *n* (%)			
KIT exon 11	47 (55.3)	28 (63.6)	75 (58.1)
KIT exon 9	14 (16.5)	6 (13.6)	20 (15.5)
Not available/not done[a]	12 (14.1)	5 (11.4)	17 (13.2)
Other	12 (14.1)	5 (11.4)	17 (13.2)
KIT/PDGFRA WT	7 (8.24)	3 (6.81)	10 (7.75)
PDGFRA[b]	3 (3.53)	0	3 (2.34)
KIT other exon[c]	2 (2.35)	2 (4.55)	4 (3.10)
Baseline liquid biopsy			
Detected mutation, *n* (%)			
KIT exon 11[d]	38 (44.7)	28 (63.6)	66 (51.2)
KIT exon 9[d]	12 (14.1)	7 (15.9)	19 (14.7)
Not available/not done[a]	6 (7.06)	2 (4.55)	8 (6.20)
Other	29 (34.1)	8 (18.2)	37 (28.7)
KIT/PDGFRA, liquid biopsy negative	22 (25.9)	6 (13.6)	28 (21.7)
PDGFRA[b]	3 (3.53)	0	3 (2.33)
KIT other exon[c]	4 (4.71)	2 (4.55)	6 (4.65)
Baseline combined biopsies			
Detected mutation, *n* (%)			
KIT exon 11[d]	52 (61.2)	34 (77.3)	86 (66.7)
KIT exon 9[d]	16 (18.8)	7 (15.9)	23 (17.8)
Not available/not done[a]	5 (5.88)	0	5 (3.88)
Other	12 (14.1)	4 (9.09)	16 (12.4)
KIT/PDGFRA, liquid biopsy negative	6 (7.06)	3 (6.82)	9 (6.98)
PDGFRA[b]	3 (3.53)	0	3 (2.33)
KIT other exon[c]	3 (3.53)	1 (2.27)	4 (3.10)

[a]Includes patients who failed sequencing due to low tumor content and patients with no specimen.
[b]All patients with *PDGFRA* mutations had exon 18 non-D842V mutations.
[c]*KIT* other exon includes any mutation in a *KIT* exon that is not 9 or 11.
[d]*KIT* exon 9 + 11 mutation was detected via liquid biopsy in 1 patient receiving placebo and was counted in both groups.

common mutations detected in liquid biopsy (ripretinib, 44.7%, $n = 38$; placebo, 63.6%, $n = 28$) followed by *KIT* exon 9 (ripretinib, 14.1%, $n = 12$; placebo, 15.9%, $n = 7$; **Table 1**). Liquid biopsy detected the same 3 patients in the ripretinib arm with *PDGFRA* mutations (**Table 1**). Liquid biopsy detected primary *KIT/PDGFRA* mutations in 94 patients, while 28 patients were *KIT/PDGFRA* liquid biopsy negative (22 in the ripretinib arm and 6 in the placebo arm; **Table 1**). Only 1 liquid biopsy sample failed sequencing (**Fig. 1**). Among the patients ($n = 80$) with detectable *KIT/PDGFRA* mutations in both tissue and liquid biopsies, the concordance rate of primary mutation was 93.75% ($n = 75$). Consequently, the combination of both technologies (tissue and liquid biopsies) allowed for greater detection of mutations (27 patients had 1 *KIT* mutation, 36 patients had 2 *KIT* mutations, and 49 patients had ≥3 *KIT* mutations) and there were fewer samples deemed as not evaluable or not done (tissue biopsy, $n = 17$; liquid biopsy, $n = 8$; combined biopsy, $n = 5$; **Table 1**).

Baseline *KIT* mutations detected outside exons 9 or 11

KIT mutations were detected in both tissue and liquid biopsy outside of exons 9 and 11 in the switch pocket adjacent to the ATP-binding pocket (exons 13 and 14) and the activation switch (exons 17 and 18). Exon 17 and exon 13 mutation commonly coexist with exon 9 or exon 11 mutations (**Fig. 2**). Five different mutations were found in exons 13/14 via tissue biopsy compared with 12 different mutations with liquid biopsy. Fifteen different mutations were found in exons 17/18 via tissue biopsy compared with 26 different mutations with liquid biopsy. When the data were merged, liquid biopsy detected most of the mutations found in tissue biopsy in addition to several unique mutations. Tissue biopsy only detected four mutations that were not detected in liquid biopsy: two K642Q substitutions in exon 13 and two D820E substitutions in exon 17 (**Fig. 2**). The most common mutations detected by both technologies were V654A substitutions in exon 13 ($n = 23$), N822K substitutions in exon 17 ($n = 14$), and Y823D substitutions in exon 17 ($n = 12$; **Fig. 2**).

Efficacy using baseline combined tumor and liquid biopsy data

Efficacy results in the INVICTUS trial were explored by mutation subgroup using combined tissue and liquid biopsy data. Patients were grouped into 4 subsets based on results of both technologies: any *KIT* exon 9, any *KIT* exon 11, any *KIT* exon 13, and any *KIT* exon 17. Patients were included in multiple groups if they had mutations in more than one exon (i.e., a patient that has a tumor with *KIT* exon 11 and exon 17 mutations would fall into both the "any *KIT* exon 11 group" and the "any *KIT* exon 17 group"). Patients receiving ripretinib showed PFS benefit over placebo regardless of mutation status (HR 0.16, 95% CI, 0.10–0.27) and in all assessed subgroups in Kaplan–Meier PFS analysis (exon 11, $P < 0.0001$; exon 9, $P = 0.0023$; exon 13, $P < 0.0001$; exon 17, $P < 0.0001$; **Fig. 3**). Moreover, the calculated HRs for each subgroup favored ripretinib treatment over placebo (any *KIT* exon 11: HR 0.13, 95% CI, 0.06–0.24; any *KIT* exon 9: HR 0.16, 95% CI, 0.05–0.51; any *KIT* exon 13: HR 0.14, 95% CI, 0.06–0.34; any *KIT* exon 17: HR 0.14, 95% CI, 0.07–0.29; **Fig. 4**).

Common secondary mutations detected in patients with a *KIT* exon 11 primary mutation were in exon 13, exon 17, or both exons 13 and 17.

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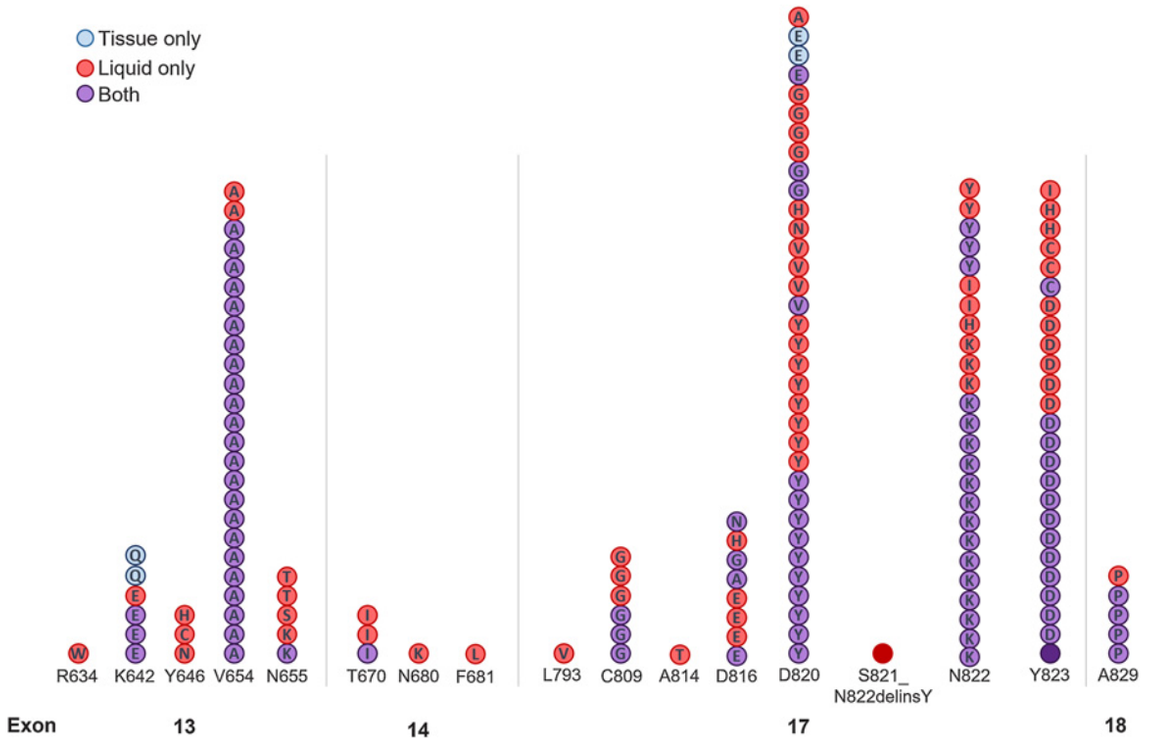

Figure 2.

KIT mutations detected outside of exons 9/11. Each circle represents 1 patient and the letter within each circle represents the amino-acid mutation location. Lettered circle indicates the protein change that occurred; nonlettered circle indicates an in-frame deletion. There were 3 patients with exon 13–only mutations, 1 patient with an exon 17–only mutation, 1 patient with exon 13 and exon 17 mutations, and 1 patient with exon 13, exon 14, and exon 17 mutations detected in liquid biopsies.

The most common secondary mutation detected in patients with a *KIT* exon 9 primary mutation was in exon 17. The calculated HRs across all of the assessed secondary subgroups within the *KIT* exon 11 or 9 subgroups favored ripretinib versus placebo (**Fig. 5**). Patients were categorized as *KIT/PDGFRA* WT if they had no detectable *KIT* or *PDGFRA* mutation in tissue biopsy, while patients with no *KIT* or *PDGFRA* mutations detected with liquid biopsy were categorized as *KIT/PDGFRA* liquid biopsy negative. Patients with *KIT/PDGFRA* WT receiving ripretinib ($n = 7$) had varying genetic alterations detected in tumor tissue, including *SDHA* and *SDHC*, *NF1*, and *KRAS* mutations, and other pathogenic alterations, such as myeloid cell leukemia 1 (*MCL1*) amplification. Two of the 7 patients had no alterations identified. Patients with *KIT/PDGFRA* WT on the ripretinib arm had PFS measurements that ranged from 2 to 23 months (Supplementary Table S1). Among the 10 patients with *KIT/PDGFRA* WT, 8 were also *KIT/PDGFRA* liquid biopsy negative. Of the 2 remaining patients that were considered *KIT/PDGFRA* WT but not *KIT/PDGFRA* liquid biopsy negative, liquid biopsy genotyping failed in 1 patient and an exon 13 mutation was detected in the other patient.

Discussion

The current study is the first genomic characterization of baseline mutations using tissue and liquid biopsy in patients with advanced GIST with disease progression following imatinib, sunitinib, and regorafenib treatment. This study provides a comprehensive genomic landscape of resistance mutations in a ≥ fourth-line treatment setting in metastatic GIST. In this exploratory analysis, ripretinib demonstrated clinically meaningful activity against a broad spectrum of mutations in patients with ≥ fourth-line advanced GIST, with a heterogeneous genetic mutation profile as shown by the PFS benefit of ripretinib compared with placebo independent of mutation status. Patients receiving ripretinib who had tumors with any *KIT* exon 9, 11, 13, or 17 mutations showed significant PFS benefit compared with patients with these mutations receiving placebo.

In this analysis, we observed a complex and heterogeneous mutational landscape, which highlights the need for therapies that are effective against a broad spectrum of mutations. The earlier lines of approved therapy for patients with GIST inhibit certain mutations in *KIT* and *PDGFRA*, but do not inhibit all secondary mutations (23–27). Imatinib demonstrated efficacy against different primary mutations including some of the most common mutations, such as *KIT* exon 11 and *KIT* exon 9, and showed variable efficacy with *PDGFRA* exon 18 mutations (non-D842V; refs. 11, 35, 36). Imatinib shows reduced efficacy against some primary and many acquired mutations, with secondary mutations in *KIT* exon 17 and exon 13 being more frequently associated with treatment resistance and *KIT* exon 9 mutations requiring higher doses of imatinib to achieve optimal PFS (24, 26, 37). In patients receiving sunitinib, mPFS was significantly longer in patients with *KIT* exon 9 mutations compared with *KIT* exon 11 mutations (38). Additionally, patients with secondary mutations in *KIT* exon 13/14 had better outcomes on sunitinib compared with patients with mutations in *KIT* exon 17/18 (24). In contrast, third-line treatment with regorafenib demonstrated clinical benefit in patients with secondary *KIT* exon 17 mutated tumors (39). This clinical observation has been recapitulated using a mutagenesis-screen that showed complementary activity of

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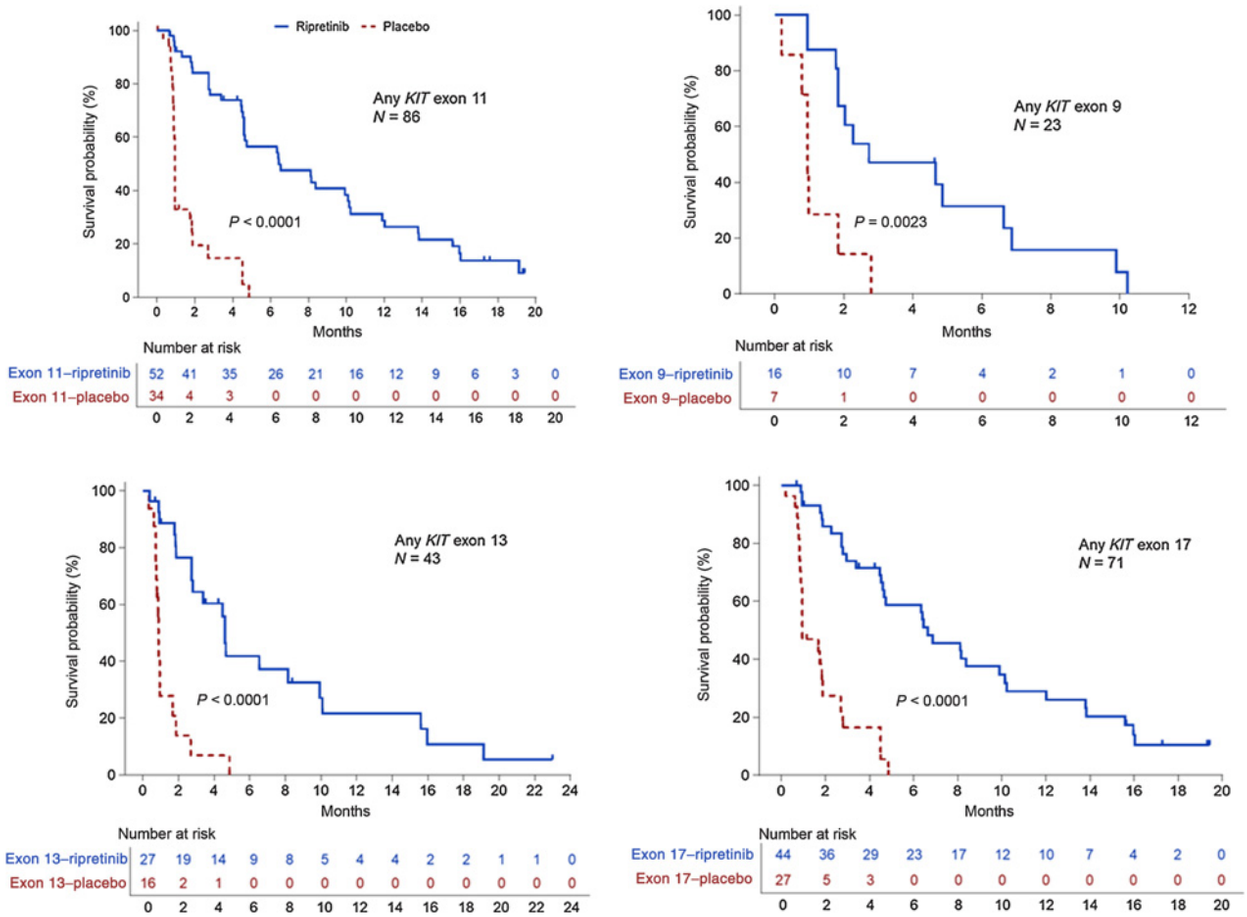

Figure 3.

Kaplan–Meier curves of PFS by any exon 9, 11, 13, or 17. Patients may be included in multiple subgroups if they had multiple mutations. Due to low numbers, patients with any *KIT* exon 14 ($n = 6$), any *KIT* exon 18 ($n = 6$), or *PDGFRA* ($n = 3$) mutations were not analyzed.

sunitinib and regorafenib, with neither of them inhibiting mutations affecting *KIT* exon 17/18 codon D816 (23).

In the current study, when compared with placebo, ripretinib demonstrated improved efficacy in heavily pretreated patients with tumors harboring *KIT* exon 9 and exon 11 mutations. While the numbers were small, ripretinib was also more effective than placebo in patients in whom mutations in *KIT* exon 13 or *KIT* exon 17 were found. This finding is highly suggestive of the broad clinical activity of ripretinib, based on its different binding mode and activity against both activation loop and switch pocket mutations, which are associated with variable efficacy for other TKIs (24). It is important to emphasize, however, that treatment efficacy cannot be predicted solely on the presence of secondary mutations and it is not clear that ripretinib is equally potent against every resistance mutation. Both the number and allelic frequencies of different resistance mutations in liquid biopsies may not be representative of the actual distribution in all tumor cells. In addition, various genetic alterations in patients with *KIT/PDGFRA* WT were detected, including *SDHA*, *SDHC*, *NF-1*, *KRAS*, and *MCL1*. In particular, some cases of *SDH*-mutant GIST exhibit a slower, indolent growth (8). Disease stabilization as measured by mRECIST may represent the natural course of the disease in patients with *KIT/PDGFRA* WT and thus explain the PFS of 10 months in a patient in the placebo arm with genetic alterations in *SDHA/TP53*. Consequently, activity of ripretinib in patients with *KIT/PDGFRA* WT cannot be concluded from our series and will require further study with more patients. Nonetheless, our findings using state-of-the-art NGS plasma sequencing in fourth-line GIST demonstrated no evidence of secondary resistance *KIT* mutations that would preclude clinical benefit with ripretinib treatment.

This study utilized two different technologies in order to characterize mutational status: genetic analysis based on traditional tumor tissue biopsy and liquid plasma ctDNA biopsy. The combination of these two technologies revealed a greater range of *KIT* mutations in tumors of heavily pretreated patients with GIST. There are, however, pros and cons to both tissue and liquid-biopsy methodology. Tissue biopsy is still considered the traditional gold standard methodology in clinical practice, while liquid biopsy is most commonly utilized for research purposes in sarcomas including GIST (30, 40). Archival tumor tissue is not always available and can be time consuming to retrieve. Not all tumors can be easily and safely biopsied. Moreover, although tissue biopsy is associated with high sensitivity and specificity, sampled tissue collected may not always reflect the overall frequency and spectrum of intra- and interlesional resistance mutations (40).

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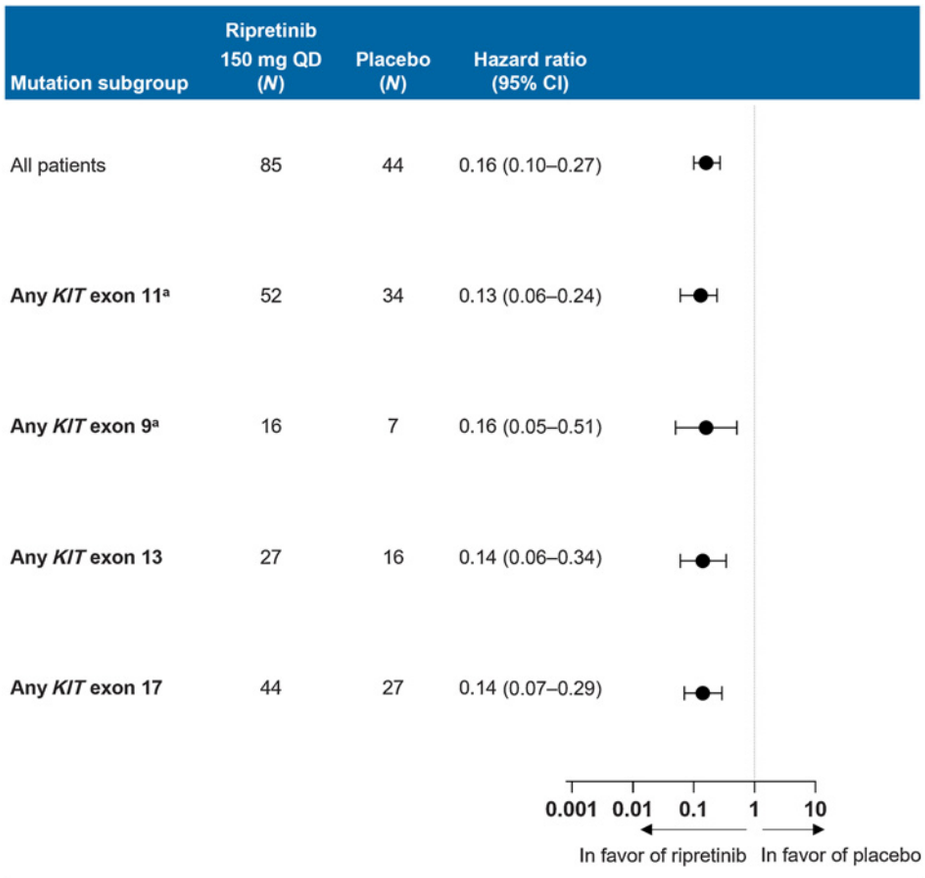

Figure 4.
Forest plot of HRs of PFS by any *KIT* exon 9, 11, 13, or 17. Patients may be included in multiple subgroups if they had multiple mutations. Due to low numbers, patients with any *KIT* exon 14 ($n = 6$), any *KIT* exon 18 ($n = 6$), or *PDGFRA* ($n = 3$) mutations were excluded from this analysis. [a]1 patient had both *KIT* exon 11 and *KIT* exon 9 mutations detected in liquid biopsy. QD, once daily.

Liquid biopsy is noninvasive and represents minimal burden to the patient. While tissue biopsy may be limited to easily accessible tumor tissue, and potential low tumor content due to necrosis, liquid biopsy has the potential to detect ctDNA from all tumors that shed into the circulation, potentially providing more information regarding tumor heterogeneity. However, low tumor shedding can result in a high false-negative rate in this type of biopsy (30, 40). Conversely, there may be a risk of false-positive findings when combining the two biopsy methods. In the context of resistance mutations in GIST, however, only a few hotspots are relevant in KIT.

In addition, it is unclear how observed mutation allele frequency relates to the underlying clone size in the patient and whether the most frequent resistance mutations found by liquid biopsy reflect the most common mutation in terms of tumor mass. In the NAVIGATOR trial, ctDNA detection correlated with the sum of the target lesions (41). In this study, however, we did not attempt to correlate ctDNA detection with tumor burden because tumor measurement per mRECIST is not equivalent to total tumor burden. Consequently, the use of both traditional tumor biopsy and liquid biopsy demonstrated the heterogeneity of *KIT* mutations in individual patients, which may not always be captured when using only one modality of tumor genomic analysis.

Additional limitations of this exploratory analysis include that patients were not randomized according to the mutational status of *KIT/PDGFRA* genes, and the small sample sizes did not allow for full efficacy evaluations of *KIT* exon 14 mutations, *KIT* exon 18 mutations, *KIT/PDGFRA* WT, or *PDGFRA* mutations (particularly the exon 18 D842V substitution mutation). However, the rationale for this study design was to provide patients with ≥ fourth-line advanced GIST effective treatment, since the median PFS for patients with untreated GIST after failing several TKIs is approximately 1 month (42, 43). While the grouping for the efficacy analysis (*KIT* exons 9, 11, 13, and 17) was driven by sample size, these are common primary and secondary mutations in GIST, and efficacy against these mutations support ripretinib's broad mechanism of action (24, 26). Longitudinal liquid biopsy analysis is ongoing and will add valuable information to the complexity of mutational status while patients are on treatment. In addition, previous studies have also identified *KIT*- and *PDGFRA*-independent mechanisms of resistance, such as mutations in PI3K, TSC1, MAPK, RAF, and RAS (7, 44). These may represent escape mechanisms that could also potentiate mechanisms of resistance to ripretinib, regardless of effective *KIT/PDGFRA* inhibition.

In conclusion, patients from the INVICTUS study exhibited complex and heterogeneous mutational backgrounds as determined by both tissue and liquid biopsy. Despite some limitations with liquid biopsy results, this screening technique provides a novel and noninvasive investigational tool with potential high clinical utility to determine patients' genotype. This analysis demonstrates that ripretinib provided clinically meaningful benefit across mutation subgroups when compared with placebo. These results support the use of ripretinib as a fourth-line therapy in patients with advanced GIST harboring a broad spectrum of mutations.

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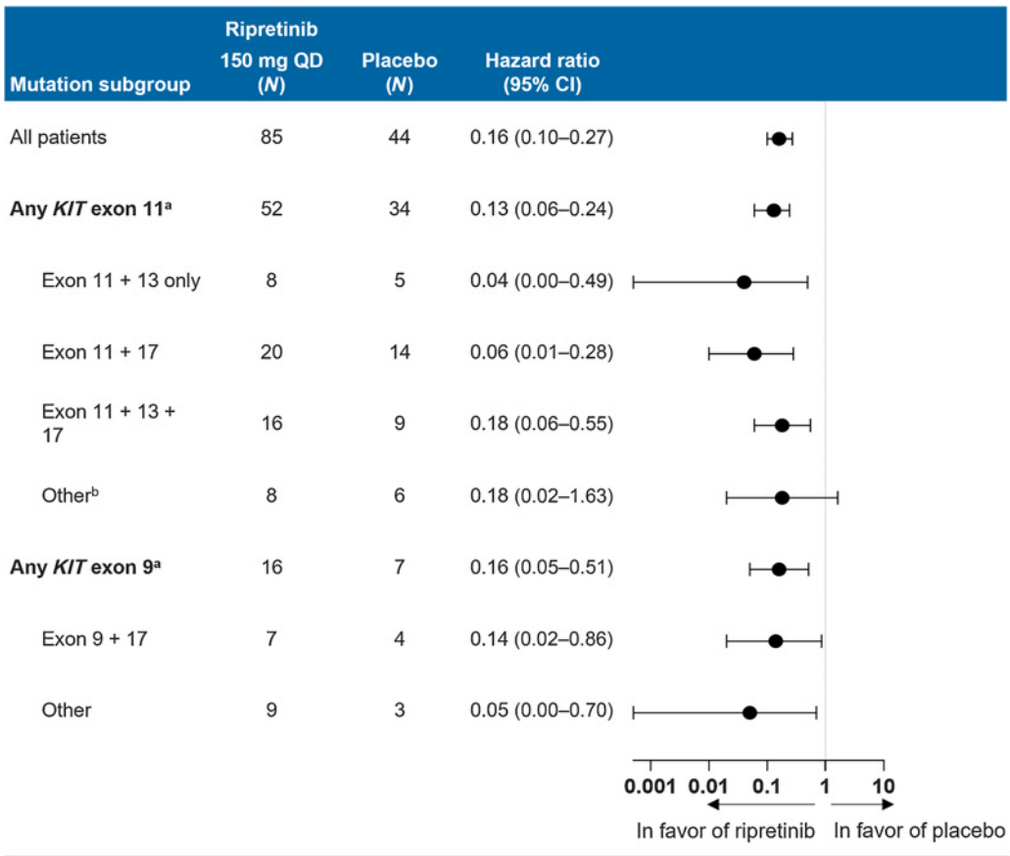

Figure 5.

Forest plot of hazard ratios of PFS within any *KIT* exons 9 or 11. [a]One patient had both a *KIT* exon 11 mutation and a *KIT* exon 9 mutation detected in liquid biopsy. [b]Includes exon 11–only mutations ($n = 13$) and exon 11 + 18 mutations ($n = 1$).

Authors' Disclosures

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References

1. Patel N, Benipal B. Incidence of gastrointestinal stromal tumors in the United States from 2001–2015: a United States cancer statistics analysis of 50 states. Cureus 2019;11:e4120.
2. Rubin BP, Heinrich MC, Corless CL. Gastrointestinal stromal tumour. Lancet 2007;369:1731–41.
3. Soreide K, Sandvik OM, Soreide JA, Giljaca V, Jureckova A, Bulusu VR. Global epidemiology of gastrointestinal stromal tumours (GIST): a systematic review of population-based cohort studies. Cancer Epidemiol 2016;40:39–46.
4. Corless CL, Schroeder A, Griffith D, Town A, McGreevey L, Harrell P, et al. PDGFRA mutations in gastrointestinal stromal tumors: frequency, spectrum and in vitro sensitivity to imatinib. J Clin Oncol 2005;23:5357–64.
5. Martin-Broto J, Martinez-Marin V, Serrano C, Hindi N, Lopez-Guerrero JA, Bisculoa M, et al. Gastrointestinal stromal tumors (GISTs): SEAP-SEOM consensus on pathologic and molecular diagnosis. Clin Transl Oncol 2017;19:536–45.
6. Szucs Z, Thway K, Fisher C, Bulusu R, Constantinidou A, Benson C, et al. Molecular subtypes of gastrointestinal stromal tumors and their prognostic and therapeutic implications. Future Oncol 2017;13:93–107.
7. Mühlenberg T, Ketzer J, Heinrich MC, Grunewald S, Marino-Enriquez A, Trautmann M, et al. KIT-dependent and KIT-independent genomic heterogeneity of resistance in gastrointestinal stromal tumors - TORC1/2 inhibition as salvage strategy. Mol Cancer Ther 2019;18:1985–96.
8. Boikos SA, Pappo AS, Killian JK, LaQuaglia MP, Weldon CB, George S, et al. Molecular subtypes of KIT/PDGFRA wild-type gastrointestinal stromal tumors: a report from the National Institutes of Health gastrointestinal stromal tumor clinic. JAMA Oncol 2016;2:922–8.
9. Smith BD, Kaufman MD, Lu WP, Gupta A, Leary CB, Wise SC, 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; 35:738–51e9.
10. Mol CD, Dougan DR, Schneider TR, Skene RJ, Kraus ML, Scheibe DN, et al. Structural basis for the autoinhibition and STI-571 inhibition of c-Kit tyrosine kinase. J Biol Chem 2004;279:31655–63.
11. Corless CL, Fletcher JA, Heinrich MC. Biology of gastrointestinal stromal tumors. J Clin Oncol 2004;22:3813–25.
12. Hirota S, Isozaki K, Moriyama Y, Hashimoto K, Nishida T, Ishiguro S, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science 1998;279:577–80.
13. Rubin BP, Singer S, Tsao C, Duensing A, Lux ML, Ruiz R, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res 2001;61: 8118–21.
14. Heinrich MC, Corless CL, Duensing A, McGreevey L, Chen CJ, Joseph N, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science 2003; 299:708–10.
15. Dematteo RP, Heinrich MC, El-Rifai WM, Demetri G. Clinical management of gastrointestinal stromal tumors: before and after STI-571. Hum Pathol 2002;33: 466–77.
16. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology (NCCN guidelines) soft tissue sarcoma 2020; Version 1.2021.
17. Iqbal N, Iqbal N. Imatinib: a breakthrough of targeted therapy in cancer. Chemother Res Pract 2014;2014:357027.
18. Christensen JG. A preclinical review of sunitinib, a multitargeted receptor tyrosine kinase inhibitor with anti-angiogenic and antitumour activities. Ann Oncol 2007;18 Suppl 10:x3–10.
19. Wilhelm SM, Dumas J, Adnane L, Lynch M, Carter CA, Schutz G, et al. Regorafenib (BAY 73–4506): a new oral multikinase inhibitor of angiogenic, stromal and oncogenic receptor tyrosine kinases with potent preclinical antitumor activity. Int J Cancer 2011;129:245–55.
20. Blueprint Medicines. Ayvakit. Prescribing information. Cambridge (MA): Blueprint Medicines Corporation; 2020. Reference ID: 4544122. Available from: https://www.blueprintmedicines.com/uspi/AYVAKIT.pdf.
21. Gebreyohannes YK, Wozniak A, Zhai ME, Wellens J, Cornillie J, Vanleeuw U, et al. Robust activity of avapritinib, potent and highly selective inhibitor of mutated KIT, in patient-derived xenograft models of gastrointestinal stromal tumors. Clin Cancer Res 2019;25:609–18.
22. Li K, Cheng H, Li Z, Pang Y, Jia X, Xie F, et al. Genetic progression in gastrointestinal stromal tumors: mechanisms and molecular interventions. Oncotarget 2017;8:60589–604.
23. Garner AP, Gozgit JM, Anjum R, Vodala S, Schrock A, Zhou T, et al. Ponatinib inhibits polyclonal drug-resistant KIT oncoproteins and shows therapeutic potential in heavily pretreated gastrointestinal stromal tumor (GIST) patients. Clin Cancer Res 2014;20:5745–55.
24. Heinrich MC, Maki RG, Corless CL, Antonescu CR, Harlow A, Griffith D, et al. Primary and secondary kinase genotypes correlate with the biological and clinical activity of sunitinib in imatinib-resistant gastrointestinal stromal tumor. J Clin Oncol 2008;26:5352–9.
25. Serrano C, Marino-Enriquez A, Tao DL, Ketzer J, Eilers G, Zhu M, et al. Complementary activity of tyrosine kinase inhibitors against secondary kit mutations in imatinib-resistant gastrointestinal stromal tumours. Br J Cancer 2019;120:612–20.
26. Antonescu CR, Besmer P, Guo T, Arkun K, Hom G, Koryotowski B, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. Clin Cancer Res 2005;11:4182–90.
27. Wardelmann E, Thomas N, Merkelbach-Bruse S, Pauls K, Speidel N, Büttner R, et al. Acquired resistance to imatinib in gastrointestinal stromal tumours caused by multiple KIT mutations. Lancet Oncol 2005;6:249–51.
28. Qinlock. Prescribing information. Waltham (MA): Deciphera Pharmaceuticals, LLC; 2020. [updated 2020 May]. Available from: https://qinlockhcp.com/Content/files/qinlock-prescribing-information.pdf.
29. Blay JY, Serrano C, Heinrich MC, Zalcberg J, Bauer S, Gelderblom H, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2020;21:923–34.

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30. Nannini M, Astolfi A, Urbini M, Biasco G, Pantaleo MA. Liquid biopsy in gastrointestinal stromal tumors: a novel approach. J Transl Med 2014;12:210.
31. Ravegnini G, Sammarini G, Serrano C, Nannini M, Pantaleo MA, Hrelia P, et al. Clinical relevance of circulating molecules in cancer: focus on gastrointestinal stromal tumors. Ther Adv Med Oncol 2019;11:1758835919831902.
32. Gómez-Peregrina D, García-Valverde A, Pilco-Janeta D, Serrano C. Liquid biopsy in gastrointestinal stromal tumors: ready for prime time? Curr Treat Options Oncol 2021;22:32.
33. FoundationOne CDx Technical Information. Cambridge, MA: Foundation Medicine, Inc.; 2020. Reference ID: RAL-0003–10. Available from: https://info.foundationmedicine.com/hubfs/FMI%20Labels/FoundationOne_CDx_Label_Technical_Info.pdf.
34. Guardant360 CDx Technical Information. Redwood City (CA): Guardant Health, Inc.; 2020. Reference ID: D-000352 R1. Available from: https://guardant360cdx.com/wp-content/uploads/2021/06/D-001590-Guardant360-CDx-Technical-Information-Document-R1.pdf.
35. Chen P, Zong L, Zhao W, Shi L. Efficacy evaluation of imatinib treatment in patients with gastrointestinal stromal tumors: a meta-analysis. World J Gastroenterol 2010;16:4227–32.
36. Heinrich MC, Corless CL, Blanke CD, Demetri GD, Joensuu H, Roberts PJ, et al. Molecular correlates of imatinib resistance in gastrointestinal stromal tumors. J Clin Oncol 2006;24:4764–74.
37. Debiec-Rychter M, Sciot R, Le Cesne A, Schlemmer M, Hohenberger P, van Oosterom AT, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. Eur J Cancer 2006;42:1093–103.
38. Reichardt P, Demetri GD, Gelderblom H, Rutkowski P, Im SA, Gupta S, et al. Correlation of KIT and PDGFRA mutational status with clinical benefit in patients with gastrointestinal stromal tumor treated with sunitinib in a worldwide treatment-use trial. BMC Cancer 2016;16:22.
39. Yeh CN, Chen MH, Chen YY, Yang CY, Yen CC, Tzen CY, et al. A phase II trial of regorafenib in patients with metastatic and/or a unresectable gastrointestinal stromal tumor harboring secondary mutations of exon 17. Oncotarget 2017;8:44121–30.
40. Diaz LA Jr., Bardelli A. Liquid biopsies: genotyping circulating tumor DNA. J Clin Oncol 2014;32:579–86.
41. Grunewald S, Klug LR, Muhlenberg T, Lategahn J, Falkenhorst J, Town A, et al. Resistance to avapritinib in PDGFRA-Driven GIST is caused by secondary mutations in the PDGFRA kinase domain. Cancer Discov 2021;11:108–25.
42. Demetri GD, Reichardt P, Kang YK, Blay JY, Rutkowski P, Gelderblom H, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:295–302.
43. Kang YK, Ryu MH, Yoo C, Ryoo BY, Kim HJ, Lee JJ, et al. Resumption of imatinib to control metastatic or unresectable gastrointestinal stromal tumours after failure of imatinib and sunitinib (RIGHT): a randomised, placebo-controlled, phase 3 trial. Lancet Oncol 2013;14:1175–82.
44. Serrano C, Wang Y, Mariño-Enríquez A, Lee JC, Ravegnini G, Morgan JA, et al. KRAS and KIT gatekeeper mutations confer polyclonal primary imatinib resistance in GI stromal tumors: relevance of concomitant phosphatidylinositol 3-kinase/AKT dysregulation. J Clin Oncol 2015;33:e93–6.

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Clinical Activity of Ripretinib in Patients with Advanced Gastrointestinal Stromal Tumor Harboring Heterogeneous *KIT/PDGFRA* Mutations in the Phase III INVICTUS Study

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