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Future Oncology

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/ifon20

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To cite this article: Suzanne George, Jean-Yves Blay, Ping Chi, Robin L Jones, César Serrano, Neeta Somaiah, Hans Gelderblom, John R Zalcberg, William Reichmann, Kam Sprott, Paulina Cox, Matthew L Sherman, Rodrigo Ruiz-Soto, Michael C Heinrich & Sebastian Bauer (2024) The INSIGHT study: a randomized, Phase III study of ripretinib versus sunitinib for advanced gastrointestinal stromal tumor with *KIT* exon 11 + 17/18 mutations, Future Oncology, 20:27, 1973-1982, DOI: 10.1080/14796694.2024.2376521

To link to this article: https://doi.org/10.1080/14796694.2024.2376521

FUTURE ONCOLOGY
2024, VOL. 20, NO. 27, 1973–1982
https://doi.org/10.1080/14796694.2024.2376521

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The INSIGHT study: a randomized, Phase III study of ripretinib versus sunitinib for advanced gastrointestinal stromal tumor with *KIT* exon 11 + 17/18 mutations

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ABSTRACT

Somatic *KIT* activating mutations drive most gastrointestinal stromal tumors (GISTs). Disease progression eventually develops with first-line imatinib, commonly due to *KIT* secondary mutations, and different kinase inhibitors have various levels of treatment efficacy dependent on specific acquired resistance mutations. Ripretinib is a broad-spectrum switch-control KIT/PDGFRA tyrosine kinase inhibitor for patients with advanced GIST who received prior treatment with three or more kinase inhibitors, including imatinib. Exploratory baseline circulating tumor DNA analysis from the second-line INTRIGUE trial determined that patients with advanced GIST previously treated with imatinib harboring primary *KIT* exon 11 mutations and secondary resistance mutations restricted to *KIT* exons 17/18 had greater clinical benefit with ripretinib versus sunitinib. We describe the rationale and design of INSIGHT (NCT05734105), an ongoing Phase III open-label study of ripretinib versus sunitinib in patients with advanced GIST previously treated with imatinib exclusively harboring *KIT* exon 11 + 17/18 mutations detected by circulating tumor DNA.

Clinical Trial Registration: NCT05734105 (ClinicalTrials.gov)

PLAIN LANGUAGE SUMMARY

Gastrointestinal stromal tumor (GIST) is rare, but it is the most common mesenchymal tumor (a type of tumor that develops from cells which give rise to soft tissues) of the gastrointestinal tract. The primary treatment for advanced GIST is medication that targets the abnormal mechanisms in cancer cells in order to block tumor growth and spread. Ripretinib is an inhibitor of a protein known as KIT, which is a member of the tyrosine kinase protein family and is involved in the growth of GIST. In a Phase III clinical trial called INTRIGUE, the effects of ripretinib and another receptor tyrosine kinase inhibitor, sunitinib, were compared in patients with advanced GIST previously treated with the drug imatinib. An exploratory analysis from the INTRIGUE trial that characterized baseline circulating tumor DNA in the blood showed a greater clinical benefit with ripretinib versus sunitinib in patients with gene mutations solely occurring in *KIT* exon 11 + 17 and/or 18 (exon 11 + 17/18). This article describes the rationale and design for a Phase III clinical trial called INSIGHT that will evaluate the benefit of ripretinib compared with sunitinib in patients with advanced GIST whose tumors have mutations in *KIT* exon 11 and *KIT* exon 17 and/or 18. Patients will receive ripretinib or sunitinib in 6-week cycles, and investigators will assess survival without cancer progression as the primary outcome, and overall survival, and response of the tumor to these two drugs as secondary outcomes.

TWEETABLE ABSTRACT

This article describes the rationale and design for the INSIGHT Phase III trial evaluating patients with second-line advanced GIST who harbor primary *KIT* exon 11 mutations and secondary resistance mutations restricted to the activation loop (*KIT* exons 17/18).

ARTICLE HISTORY

Received 20 February 2024
Accepted 2 July 2024

KEYWORDS

ctDNA mutational analysis; gastrointestinal stromal tumor; INSIGHT; *KIT* mutations; Phase III trial; predictive marker; ripretinib; sunitinib; targeted therapy; tyrosine kinase inhibitor

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This article has been corrected with minor changes. These changes do not impact the academic content of the article.

Supplemental data for this article can be accessed at https://doi.org/10.1080/14796694.2024.2376521

1. Disease overview & management

Gastrointestinal stromal tumor (GIST) is a rare gastrointestinal (GI) neoplasm [1], but it is the most common GI sarcoma, with approximately 80% of cases driven by activating mutations in *KIT* and 5–10% by *PDGFRA* mutations [2–4]. GIST can originate in different locations along the GI tract; however, the most common primary sites are the stomach (60%) and the jejunum and ileum (30%), followed by the duodenum (4–5%), and rectum (4%) [5]. The symptoms associated with GIST may include early satiety, abdominal discomfort, intraperitoneal hemorrhage, GI bleeding, fatigue due to anemia or acute abdomen requiring medical attention [2]. GIST has an approximate incidence of 10–15 cases per million per year worldwide [1], with a median age of 60–65 years at diagnosis [6]. GIST originates from the interstitial cells of Cajal and is characterized by varying degrees of malignancy [7,8]. The primary treatment approach for patients with localized, resectable GIST is surgery; systemic targeted therapy has become the primary therapeutic approach for advanced unresectable and/or metastatic GIST and is used as adjuvant therapy in localized high-risk disease [2].

The tyrosine kinase inhibitor (TKI) imatinib is approved as a first-line therapy for advanced GIST [9]. In the long-term follow-up from a Phase II study, an objective response was seen in almost 70% of patients and prolonged stable disease was observed in 15.6% of patients receiving imatinib, the majority of these for longer than a year, while primary progression occurred in 11.6% of patients [10]. The most common primary *KIT* mutations in GIST occur in either exon 11 or exon 9 [11], both of which have shown varying sensitivity to imatinib [11–13]. Primary *KIT* exon 11 mutations are sensitive to imatinib at the standard dose, while *KIT* exon 9 mutations respond better to a high-dose imatinib regimen [11–13]. The vast majority of patients treated with imatinib eventually experience disease progression due to the development of secondary mutations in the KIT adenosine triphosphate (ATP)-binding pocket (encoded by exons 13 and 14) or the KIT activation loop (encoded by exons 17 and 18; Figure 1) [13,14].

Sunitinib is a multitargeted TKI approved as a second-line therapy for advanced GIST after disease progression on or intolerance to imatinib [15]. In the registrational Phase III trial, median progression-free survival (PFS) was 5.5 months in patients treated with sunitinib compared with 1.4 months for placebo [16].

Ripretinib, a broad-spectrum switch-control KIT/PDGFRA TKI, is approved for adult patients with advanced GIST who received prior treatment with three or more kinase inhibitors, including imatinib, based on the results of the Phase III randomized, placebo-controlled INVICTUS trial [17,18]. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for GIST (version 1.2024) list ripretinib as a preferred fourth-line regimen for certain patients with advanced GIST [2]. Ripretinib utilizes a dual mechanism of action to bind both the switch pocket region and the activation loop, securing the target kinase (i.e., KIT and PDGFRA) in an inactive conformation (Figure 2) [19]. In the INTRIGUE Phase III trial, the primary end point of superior PFS with ripretinib versus sunitinib was not met when administered as a second-line therapy; however, ripretinib demonstrated comparable efficacy and a more favorable safety profile and patient-reported outcomes compared with sunitinib [20]. Long-term overall survival (OS) analysis from the INTRIGUE trial further confirmed comparable efficacy between arms in both the overall intention-to-treat (ITT) and *KIT* exon 11 ITT populations [21]. Based on the results from INTRIGUE, NCCN Guidelines® for GIST (version 1.2024) include ripretinib as an option for patients with advanced GIST who are intolerant of second-line sunitinib [2,20].

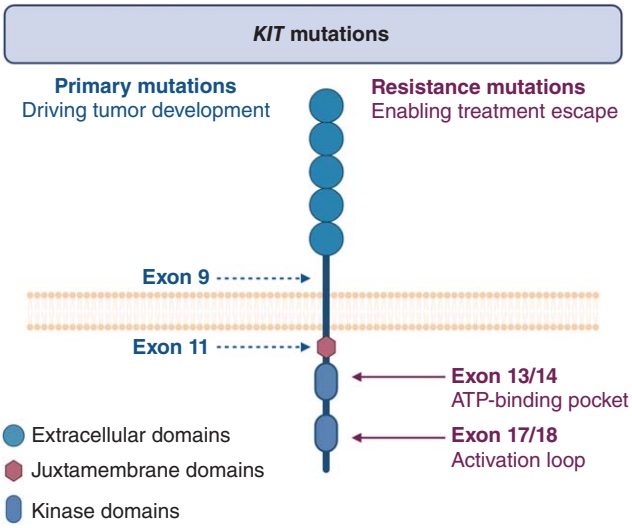

Figure 1. *KIT* mutations in gastrointestinal stromal tumor.
Figure created with BioRender.com.
ATP: Adenosine triphosphate.

2. Differential activity of ripretinib & sunitinib against secondary *KIT* mutations

Ripretinib and sunitinib demonstrate differential activity based on the location of *KIT* secondary resistance mutations. Preclinically, sunitinib was potent against secondary mutations in the KIT ATP-binding pocket (exons 13 and 14), particularly V654A mutants. However, it was inactive against all secondary mutations in the KIT activation loop (exons 17 and 18) [19]. In preclinical studies, ripretinib was more potent against secondary

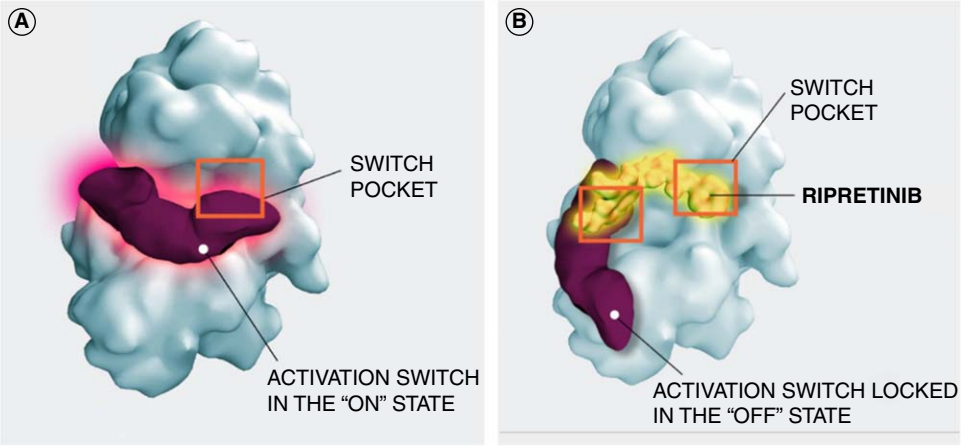

Figure 2. Dual mechanism of ripretinib as a tyrosine kinase inhibitor. **(A)** Activated tyrosine kinase. **(B)** Ripretinib bound to the switch pocket and activation loop locking the kinase in an inactive conformation.
Figure adapted from Bauer S, et al. 2021 [22].

mutations in the KIT activation loop compared with those in the KIT ATP-binding pocket, regardless of the primary mutation (*KIT* exon 9 or 11) [19].

When evaluating tumor specimens from a Phase I/II study of sunitinib in advanced GIST, the median PFS for sunitinib was 7.8 months in patients with mutations in the KIT ATP-binding pocket compared with 2.3 months for activation loop mutations [23]. In later-line settings, such as the fourth line, patients with GIST demonstrate significant mutational heterogeneity in *KIT* resistance mutations; therefore, broad activity is needed [24]. In the INVICTUS Phase III trial in ≥fourth-line advanced GIST, ripretinib showed a PFS benefit versus placebo in all assessed mutational subgroups (any *KIT* exon 9, 11, 13 and 17), as determined by tumor tissue and liquid (plasma circulating tumor DNA [ctDNA]) biopsies at baseline, suggesting broad activity in this later-line setting [24]. In an earlier setting where less heterogeneity might exist, the impact of differential activity and focus on subdomain-restricted secondary mutations may be more important [24].

Mutational analysis of tumor tissue comes with risks and challenges, namely the invasive biopsy procedure and sampling bias from only the biopsied lesion, especially in the setting of extensive tumor heterogeneity that is characteristic of advanced imatinib-resistant GIST. Analysis using ctDNA can theoretically overcome these challenges with easy access to blood and the potential for the sample to reflect the full mutational burden across lesions [25–27]. However, mutational analysis of ctDNA also comes with challenges, such as the sensitivity to detect alterations in tumors with varying shedding rates [24], which may prevent a complete understanding of the allelic context of primary and subsequent mutations.

It was hypothesized that mutational analysis of baseline ctDNA from patients in the INTRIGUE trial could provide more insight into the primary efficacy results [13,19,23,28]. In the overall ITT population, ctDNA was analyzed from 362/453 (80%) patients, with ctDNA detected in 280/362 (77%) samples [29]. *KIT* mutations were detected in 213/362 (59%) samples, with common secondary mutations found in *KIT* exons 13 and/or 14 (ATP-binding pocket; 81/213 [38%]) and exons 17 and/or 18 (activation loop; 89/213 [42%]) [29]. Among patients with detected *KIT* mutations, 41/213 (19%) had primary mutations in *KIT* exon 11 with secondary mutations exclusively in *KIT* exons 13 and/or 14 (excluding mutations in *KIT* exons 9, 17 or 18; hereafter referred to as *KIT* exon 11 + 13/14) [29]. Similarly, 52/213 (24%) had primary mutations in *KIT* exon 11 with secondary mutations exclusively in *KIT* exons 17 and/or 18 (excluding mutations in *KIT* exons 9, 13, or 14; hereafter referred to as *KIT* exon 11 + 17/18) [29].

Baseline ctDNA analysis from INTRIGUE determined that patients with *KIT* exon 11 + 13/14 mutations had a median PFS of 15.0 months with sunitinib versus 4.0 months with ripretinib (nominal $p = 0.0005$) and an objective response rate (ORR) of 15.0% with sunitinib versus 9.5% with ripretinib (nominal $p = 0.5922$) [29]. Median OS was not reached for patients receiving sunitinib in the *KIT* exon 11 + 13/14 population, while the median OS for patients receiving ripretinib was 24.5 months (nominal $p = 0.2085$) [29]. Patients with *KIT* exon 11 + 17/18 mutations had a median PFS of 14.2 months with ripretinib versus 1.5 months with sunitinib (nominal $p < 0.0001$) [29,30]. Additionally, these patients had an ORR of 44.4% with ripretinib versus 0% with sunitinib (nominal $p = 0.0001$). Median OS was not estimable with ripretinib, whereas it was

17.5 months with sunitinib (nominal $p = 0.0061$) [29]. The safety profile across these two mutational subgroups was consistent with the primary analysis, and fewer grade 3/4 drug-related treatment-emergent adverse events were observed with ripretinib compared with sunitinib [20,29].

These findings provided the framework for the INSIGHT Phase III study to investigate the efficacy of ripretinib versus sunitinib in patients with advanced GIST previously treated with imatinib who harbor *KIT* exon 11 + 17/18 mutations.

3. The INSIGHT study

This article describes the design and rationale of INSIGHT (NCT05734105, registered 17 February 2023), an ongoing Phase III open-label study of ripretinib versus sunitinib in patients with advanced GIST previously treated with imatinib and exclusively harboring *KIT* exon 11 + 17/18 mutations as identified by ctDNA analysis [31], for which ripretinib was granted Breakthrough Therapy designation by the FDA. This study is sponsored by Deciphera Pharmaceuticals, LLC, MA, USA. The INSIGHT study is still enrolling as of July 2024.

4. Design

4.1. INSIGHT study design

INSIGHT is an international, Phase III, randomized, multicenter, open-label study evaluating the efficacy of ripretinib versus sunitinib in patients with advanced GIST previously treated with imatinib and who have detectable *KIT* exon 11 mutations and co-occurring mutations exclusively in *KIT* exons 17/18 as identified by ctDNA analysis [30,31]. INSIGHT is being conducted globally in the USA, Canada, Europe, Taiwan, Brazil, Chile, Korea and Australia (trial sites can be found on clinicaltrials.gov).

Approximately 54 patients (ripretinib, n = ~36; sunitinib, n = ~18) with advanced GIST previously treated with imatinib and harboring *KIT* exon 11 + 17/18 mutations will be randomized 2:1 by interactive response technology to receive ripretinib 150 mg once daily (QD; continuous) or sunitinib 50 mg QD (4 weeks on/2 weeks off) in 6-week cycles (Figure 3) [30]. The sample size was chosen with sufficient power to detect a difference between treatment arms for the primary and key secondary end points.

Patients will receive the study drug until disease progression as determined by independent radiologic review (IRR) using modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1), unacceptable toxicity or withdrawal of consent. The independent imaging vendor must remain blinded to the local assessment from the investigator. Upon disease progression, patients in the sunitinib arm may cross over to receive ripretinib [30]. For sunitinib, dose modifications per the prescribing information or institutional guidelines will be allowed. For ripretinib, the first dose reduction level is 100 mg QD and the second is 50 mg QD. If any patient requires a dose of ripretinib lower than 50 mg QD or experiences disease progression on a reduced dose, as assessed by IRR, the patient must be discontinued from ripretinib.

4.2. Key eligibility criteria

Males or females aged 18 years or older with a histologic diagnosis of GIST and co-occurring *KIT* exon 11 + 17/18 mutations confirmed by central laboratory ctDNA analysis at prescreening are eligible for inclusion in the trial. Eligible patients must have advanced GIST and radiologic progression on imatinib treatment. Key inclusion criteria also include the presence of at least 1 measurable lesion according to mRECIST v1.1 within 21 days prior to the first dose of the study drug, and an Eastern Cooperative Oncology Group performance status $\leq$2 at screening.

Key exclusion criteria include a history of *KIT* exon 9 mutation or detection of *KIT* exon 9, 13 or 14 mutations by central laboratory ctDNA analysis at prescreening, and the use of strong or moderate inhibitors or inducers of CYP3A. Any major surgeries within 4 weeks of the first dose of the study drug as well as known active metastasis of the central nervous system, are not allowed. The list of key eligibility criteria is shown in Table 1.

4.3. Outcome measures

The primary outcome measure is PFS based on blinded IRR using mRECIST v1.1 [30]. Key secondary outcome measures are ORR as determined by blinded IRR using mRECIST v1.1 and OS (Table 2) [30].

4.4. Safety monitoring

Safety analyses are performed on all patients who receive any dose of study medication based on the actual therapy received. The safety and tolerability of the study drug is determined by reported adverse events, physical examinations, laboratory tests and electrocardiograms. All patients are assessed regularly for potential occurrence of adverse events from the time that treatment starts until 30 days after the last dose of study drug or the day before the start of subsequent new anticancer drug therapy, whichever occurs first.

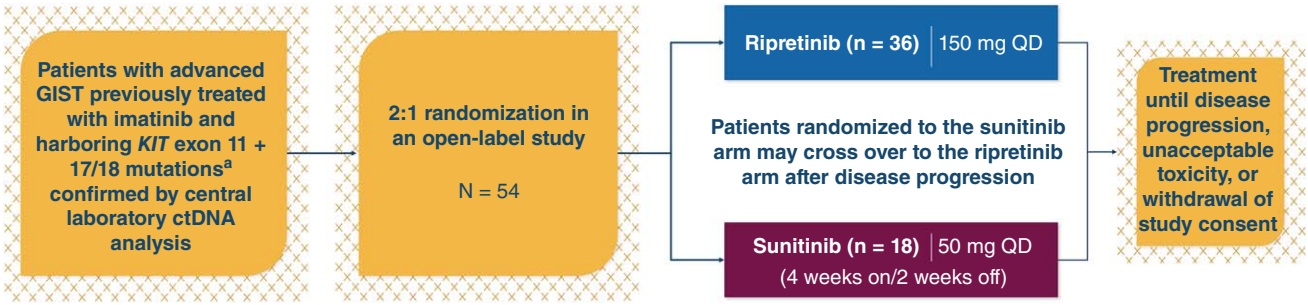

Figure 3. INSIGHT study design.
[a]Excludes additional *KIT* primary and secondary mutations in exons 9, 13 or 14.
ctDNA: Circulating tumor DNA; GIST: Gastrointestinal stromal tumor; QD: Once daily.

Table 1. INSIGHT key eligibility criteria.

Key inclusion criteria
Patients must meet all of the following criteria to be eligible to enroll in the trial: • Male or female ≥18 years of age • Histologic diagnosis of GIST with co-occurring *KIT* exon 11 + 17/18 mutations confirmed by ctDNA sample analyzed by the central laboratory at prescreening • Patients must have advanced GIST and radiologic progression on imatinib treatment • ECOG PS ≤2 at screening • Female patients of childbearing potential must have a negative serum β-HCG pregnancy test at screening and a negative pregnancy test at cycle 1 day 1 prior to the first dose of the study drug • Patients of reproductive potential must agree to follow contraception requirements • Patients must have at least 1 measurable lesion according to mRECIST v1.1 within 21 days prior to the first dose of the study drug • Adequate organ function and bone marrow reserve as indicated by central laboratory assessments performed at screening • Resolution of all toxicities from prior therapy to grade ≤1 (or patient baseline) within 1 week prior to the first dose of the study drug
Key exclusion criteria
Patients meeting any of the following criteria will be excluded from the trial: • History of *KIT* exon 9 mutation or detection of *KIT* exon 9, 13 or 14 mutations in a ctDNA sample by the central laboratory at prescreening • Known active central nervous system metastases • New York Heart Association Class II–IV heart disease, myocardial infarction within 6 months of cycle 1 day 1, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure • Use of strong or moderate inhibitors or inducers of CYP3A prior to the first dose of the study drug and consumption of grapefruit or grapefruit juice within 14 days prior to the first dose of the study drug • Major surgeries (e.g., abdominal laparotomy) within 4 weeks of the first dose of the study drug • Known HIV or hepatitis C infection only if the patient is taking medications that are excluded per protocol, acute or chronic hepatitis B infection or acute or chronic hepatitis C infection • Gastrointestinal abnormalities including, but not limited to a. Inability to take oral medication b. Malabsorption syndromes c. Requirement for intravenous alimentation • Any active bleeding, excluding hemorrhoidal or gum bleeding

ctDNA: Circulating tumor DNA; ECOG PS: Eastern Cooperative Oncology Group performance status; GIST: Gastrointestinal stromal tumor; HIV: Human immunodeficiency virus; mRECIST v1.1: Modified Response Evaluation Criteria in Solid Tumors version 1.1.

4.5. Statistical analyses

The primary outcome measure, PFS (reported in months), is defined as the time from randomization until documented disease progression based on blinded IRR using mRECIST v1.1 or death due to any cause, whichever occurs first. PFS curves will be computed using the Kaplan-Meier method, and the unstratified Cox proportional hazards regression model will be used to estimate the hazard ratio and its 95% CI. The primary analysis will be performed when the planned number of PFS events are observed.

ORR is defined as the proportion of patients with confirmed complete or partial response as determined by blinded IRR using mRECIST v1.1. The ORR, response difference, and their associated 95% CIs will be calculated.

OS is defined as the time from randomization until death due to any cause. OS curves will be computed using the Kaplan-Meier method, and the unstratified Cox proportional hazards regression model will be used to estimate the hazard ratio and its 95% CI. Primary analysis of OS will coincide with that of PFS. An additional long-term follow-up analysis of OS may also be conducted at least 1 year after the final PFS analysis.

Table 2. INSIGHT trial outcome measures.

Primary outcome measure
• PFS based on blinded IRR using mRECIST v1.1
Key secondary outcome measures
• ORR based on blinded IRR using mRECIST v1.1 • OS
Other secondary outcome measures
• Safety (frequency and severity of TEAEs) • PROs as measured by the EORTC QLQ-C30, parts of the NCI PRO-CTCAE, and the 5-level EQ-5D • Disease control rate based on blinded IRR using mRECIST v1.1 • TTP based on blinded IRR using mRECIST v1.1 • DOR based on blinded IRR using mRECIST v1.1 • TTR based on blinded IRR using mRECIST v1.1

DOR: Duration of response; EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (30-item); IRR: Independent radiologic review; mRECIST v1.1: Modified Response Evaluation Criteria in Solid Tumors version 1.1; NCI: National Cancer Institute; ORR: Objective response rate; OS: Overall survival; PFS: Progression-free survival; PRO: Patient-reported outcome; PRO-CTCAE: PROs version of the Common Terminology Criteria for Adverse Events; TEAE: Treatment-emergent adverse event; TTP: Time to progression; TTR: Time to response.

4.6. Data monitoring committee

An independent data monitoring committee will periodically monitor the safety data from this study to ensure the ongoing safety of study participants. The data monitoring committee will consist of an experienced biostatistician and two qualified clinicians, who are not Deciphera employees, with combined scientific expertise in general oncology and GIST and practical experience conducting clinical studies and monitoring safety of clinical studies.

5. Conclusion

The INSIGHT study is the first Phase III trial in advanced GIST to compare 2 active agents in patients enrolled based on their ctDNA profiles at baseline. This study aims to evaluate ripretinib versus sunitinib in patients with advanced GIST previously treated with imatinib and exclusively harboring *KIT* exon 11 + 17/18 mutations as identified by ctDNA analysis.

This study will compare the PFS between patients treated with ripretinib versus sunitinib to prospectively confirm the efficacy observed with ripretinib in patients with KIT activation loop mutations in the INTRIGUE study. Based on the exploratory baseline ctDNA analysis from INTRIGUE, approximately 15% of analyzed samples from all patients with advanced GIST are expected to harbor mutations exclusively in *KIT* exon 11 + 17/18 [29]. By further evaluating ripretinib versus sunitinib in adults with advanced GIST who were previously treated with imatinib and harbor *KIT* exon 11 + 17/18 mutations, the INSIGHT study may demonstrate the efficient use of ctDNA mutational analysis as a predictive biomarker to determine single-drug treatment approaches and predict response to second-line therapies in advanced GIST. As such, INSIGHT is one of the first prospective trials where patient eligibility, tumor genomic composition and treatment determination for a subset of patients with advanced GIST may be possible using ctDNA mutational analysis requiring only a blood sample.

Executive summary

Disease overview & management

- Gastrointestinal stromal tumor (GIST) is the most common gastrointestinal sarcoma, with approximately 80% of cases driven by activating mutations in *KIT*.
- Sunitinib is a multitargeted tyrosine kinase inhibitor (TKI) approved as a second-line therapy for advanced GIST after disease progression on or intolerance to imatinib.
- Ripretinib is a broad-spectrum switch-control KIT/PDGFRA TKI approved as a fourth-line therapy for advanced GIST.

Differential activity of ripretinib & sunitinib against secondary *KIT* mutations

- Exploratory baseline circulating tumor DNA (ctDNA) analysis from INTRIGUE determined that patients with *KIT* exon 11 + 13/14 mutations had improved progression-free survival (PFS) and objective response rate (ORR) with sunitinib versus ripretinib, while those with *KIT* exon 11 + 17/18 mutations had improved PFS, ORR and overall survival (OS) and a better safety profile with ripretinib versus sunitinib.

Design

- INSIGHT is an international, Phase III, randomized, multicenter, open-label study evaluating the efficacy of ripretinib versus sunitinib in patients with advanced GIST previously treated with imatinib and who have *KIT* exon 11 mutations and co-occurring mutations exclusively in *KIT* exons 17/18, as identified by ctDNA.
- Approximately 54 patients will be randomized 2:1 to receive ripretinib 150 mg once daily (QD; continuous) or sunitinib 50 mg QD (4 weeks on/2 weeks off) in 6-week cycles.
- Eligible patients must have a histologic diagnosis of advanced GIST and co-occurring *KIT* exon 11 + 17/18 mutations confirmed by central laboratory ctDNA analysis, as well as radiologic progression on imatinib.
- The primary outcome measure is PFS based on blinded independent radiologic review (IRR) using modified Response Evaluation Criteria in Solid Tumors version 1.1 (mRECIST v1.1), while key secondary outcome measures are ORR based on blinded IRR using mRECIST v1.1 and OS.

Acknowledgments

The authors thank the patients and their families and caregivers, the investigators and the investigational site staff for their participation in the INSIGHT study.

Author contributions

S George, MC Heinrich, S Bauer, ML Sherman, R Ruiz-Soto, W Reichmann, K Sprott and P Cox conceived the study. All authors contributed to the implementation of the study and to the refinement of the study protocol. All authors contributed to the drafting and critical review of this manuscript. All authors have given their final approval of the submitted version.

Financial disclosure

This study is sponsored by Deciphera Pharmaceuticals, LLC. Protocol number: DCC-2618-03-003 (An international, Phase III, randomized, multicenter, open-label study of ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor [GIST] with KIT exon 11 and co-occurring KIT exons 17 and/or 18 mutations who were previously treated with imatinib [INSIGHT]). For inquiries about this trial, please contact Deciphera Pharmaceuticals, LLC (781-209-6400 or clinicaltrials@deciphera.com). The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

S George reports stock/other ownership interests from Abbott Laboratories and Pfizer; honoraria from CStone Pharmaceuticals; consulting or advisory roles for Blueprint Medicines, Daiichi Sankyo, Immunicum, Kayothera, Lilly, MORE Health, Research To Practice, UpToDate, and Deciphera Pharmaceuticals, LLC; research funding from BioAtla (Inst), Blueprint Medicines (Inst), Daiichi Sankyo (Inst), Eisai (Inst), IDRX (Inst), Merck (Inst), NewBay (Inst), SpringWorks Therapeutics (Inst), Theseus Pharmaceuticals (Inst), TRACON Pharmaceuticals (Inst), and Deciphera Pharmaceuticals, LLC (Inst); patents/royalties/other intellectual property from UpToDate; and other relationships with WCG. 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H Gelderblom reports institutional research funding from Abbisko, AmMax Bio, Bayer, Blueprint Medicines, Daiichi Sankyo, Ipsen, Novartis, Pfizer, and Deciphera Pharmaceuticals, LLC. 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Writing disclosure

Medical writing and editorial support were provided by M Chakhtoura of AlphaBioCom, a Red Nucleus company, and were funded by Deciphera Pharmaceuticals, LLC.

Ethical conduct of research

This study is being performed in accordance with the Declaration of Helsinki and is consistent with International Conference on Harmonization and Good Clinical Practice guidelines. Applicable local regulatory requirements are being followed, and the investigators ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research. The study is approved by a central institutional review board (WIRB-Copernicus Group). The investigators ensure that each study participant is fully informed about the nature and objectives of the study and possible risks associated with participation and obtain written informed consent from each participant before any study-specific activity is performed.

Data availability statement

Not applicable.

Previous presentation

A trial-in-progress abstract and poster for the INSIGHT trial were originally presented at the 2023 American Society of Clinical Oncology (ASCO) meeting, 2–6 June 2023 in Chicago, IL, USA. Abstract number: TPS11582 [30].

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