



Universiteit  
Leiden  
The Netherlands

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

George, S.; Blay, J.Y.; Chi, P.; Jones, R.L.; Serrano, C.; Somaiah, N.; ... ; Bauer, S.

**Citation**

George, S., Blay, J. Y., Chi, P., Jones, R. L., Serrano, C., Somaiah, N., ... Bauer, S. (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

Version: Publisher's Version

License: [Creative Commons CC BY-NC-ND 4.0 license](#)

Downloaded from: <https://hdl.handle.net/1887/4195712>

**Note:** To cite this publication please use the final published version (if applicable).



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

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

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](https://doi.org/10.1080/14796694.2024.2376521)

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



© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group



[View supplementary material](#)



Published online: 04 Sep 2024.



[Submit your article to this journal](#)



Article views: 1708



[View related articles](#)


















[View Crossmark data](#)



Citing articles: 2 [View citing articles](#)

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

Suzanne George<sup>a</sup> , Jean-Yves Blay<sup>b</sup> , Ping Chi<sup>c,d</sup> , Robin L Jones<sup>e</sup> , César Serrano<sup>f</sup> , Neeta Somaiah<sup>g</sup> , Hans Gelderblom<sup>h</sup> , John R Zalcberg<sup>i</sup> , William Reichmann<sup>j</sup> , Kam Sprott<sup>j</sup> , Paulina Cox<sup>j</sup> , Matthew L Sherman<sup>j</sup> , Rodrigo Ruiz-Soto<sup>j</sup> , Michael C Heinrich<sup>k,l</sup>  and Sebastian Bauer<sup>\*,m,n</sup> 

<sup>a</sup>Dana-Farber Cancer Institute, Boston, MA 02215, USA; <sup>b</sup>Centre Léon Bérard, Lyon, 69008, France; <sup>c</sup>Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA; <sup>d</sup>Weill Cornell Medicine, New York, NY 10065, USA; <sup>e</sup>Sarcoma Unit, The Royal Marsden NHS Foundation Trust & Institute of Cancer Research, London, SW3 6JJ, UK; <sup>f</sup>Vall d'Hebron Institute of Oncology, Barcelona, 08035, Spain; <sup>g</sup>The University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA; <sup>h</sup>Leiden University Medical Center, Leiden, 2333 ZA, Netherlands; <sup>i</sup>Monash University School of Public Health & Preventive Medicine & Department of Medical Oncology, Alfred Health, Melbourne, Victoria, 3004, Australia; <sup>j</sup>Deciphera Pharmaceuticals, LLC, Waltham, MA 02451, USA; <sup>k</sup>Portland VA Health Care System, Portland, OR 97239, USA; <sup>l</sup>OHSU Knight Cancer Institute, Portland, OR 97239, USA; <sup>m</sup>Department of Medical Oncology, Sarcoma Center, West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, 45147, Germany; <sup>n</sup>German Cancer Consortium (DKTK), Partner Site University Hospital Essen, Essen, 45147, Germany

### 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 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

**CONTACT** Sebastian Bauer Tel.: +49 0 201 723 2112;  [Sebastian.Bauer@uk-essen.de](mailto:Sebastian.Bauer@uk-essen.de)

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>

© 2024 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

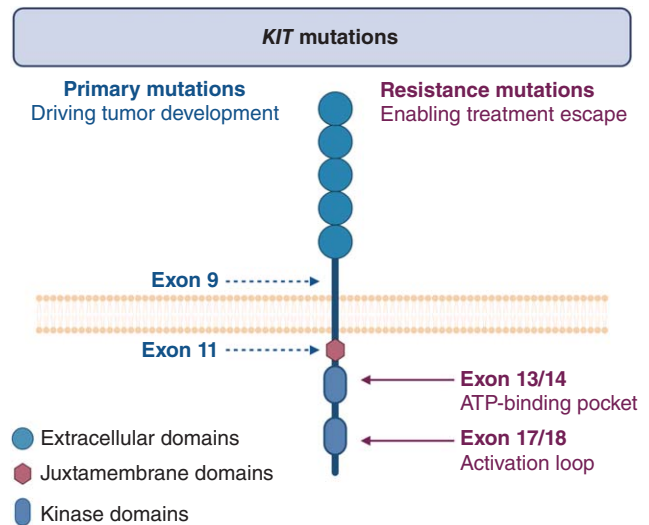
## 1. Disease overview & management

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



**Figure 1.** *KIT* mutations in gastrointestinal stromal tumor.

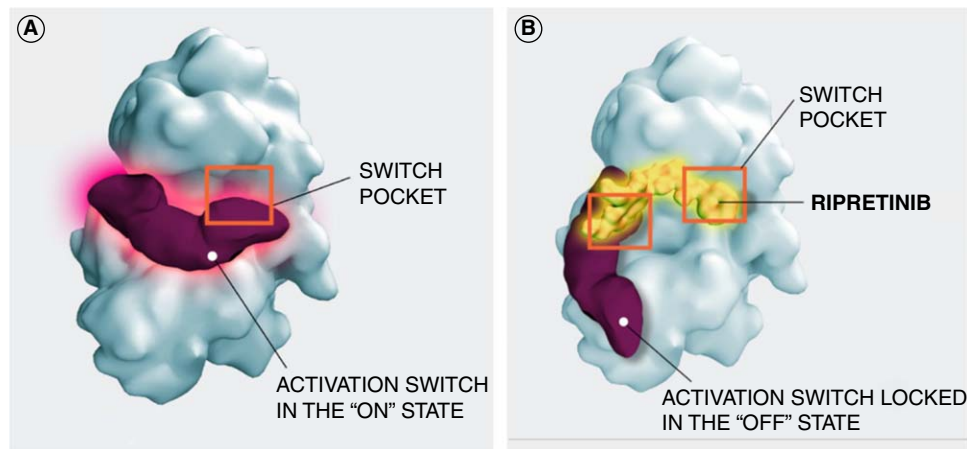
Figure created with BioRender.com.

ATP: Adenosine triphosphate.

results of the Phase III randomized, placebo-controlled INVICTUS trial [17,18]. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines<sup>®</sup>) 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<sup>®</sup> for GIST (version 1.2024) include ripretinib as an option for patients with advanced GIST who are intolerant of second-line sunitinib [2,20].

## 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  $\geq$ 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](https://clinicaltrials.gov)).

Approximately 54 patients (ripretinib,  $n = \sim 36$ ; sunitinib,  $n = \sim 18$ ) 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.

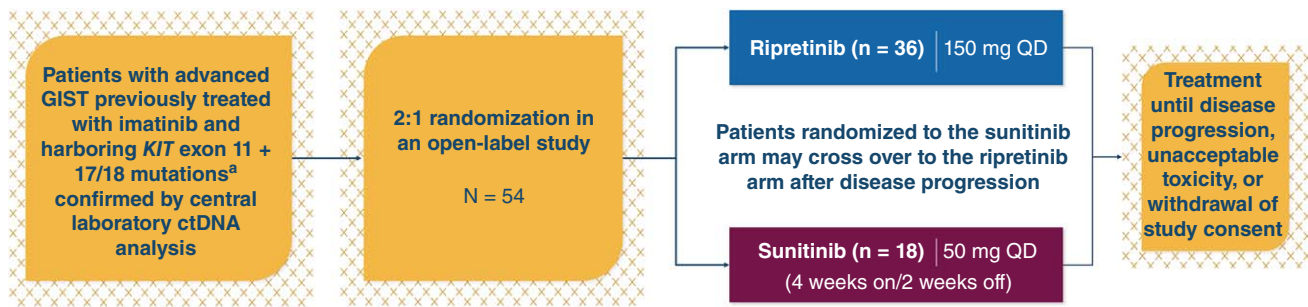
Key exclusion criteria include a history of *KIT* exon 9 mutation or detection of *KIT* exon 9, 13 or 14 mutations by central laboratory ctDNA analysis at prescreening, and the use of strong or moderate inhibitors or inducers of CYP3A. Any major surgeries within 4 weeks of the first dose of the study 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.

<sup>a</sup>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  $\geq 18$  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  $\leq 2$  at screening
- Female patients of childbearing potential must have a negative serum  $\beta$ -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  $\leq 1$  (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.

<b>Primary outcome measure</b>
• PFS based on blinded IRR using mRECIST v1.1
<b>Key secondary outcome measures</b>
• ORR based on blinded IRR using mRECIST v1.1
• OS
<b>Other secondary outcome measures</b>
• 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. J-Y Blay reports a leadership role with Innate Pharma; honoraria from AstraZeneca, Bayer, Bristol Myers Squibb, Ignyta, Merck Sharp & Dohme, PharmaMar, Roche, and Deciphera Pharmaceuticals, LLC; consulting/advisory roles with Bayer, Blueprint Medicines, Karyopharm Therapeutics, PharmaMar, Roche, and Deciphera Pharmaceuticals, LLC; research funding from AstraZeneca (Inst), Bayer (Inst), Bristol Myers Squibb (Inst), GlaxoSmithKline (Inst), Merck Sharp & Dohme (Inst), Novartis (Inst), OSE Immunotherapeutics (Inst), PharmaMar (Inst), Roche (Inst), and Deciphera Pharmaceuticals, LLC (Inst); and funding for travel/accommodations/expenses from Roche. P Chi reports consulting/advisory roles for NewBay Pharma, Zai Lab, and Deciphera Pharmaceuticals, LLC; patents/royalties/other intellectual property from ORIC Pharmaceuticals (immediate family member); stock/other ownership interests in ORIC Pharmaceuticals (immediate family member); and research funding from NewBay Pharma (Inst),

Pfizer (Inst), and Deciphera Pharmaceuticals, LLC (Inst). RL Jones reports consulting/advisory roles for Adaptimmune Therapeutics, Athenex, Bayer, Blueprint Medicines, Boehringer Ingelheim, Clinigen Group, Daiichi Sankyo, Eisai, Epizyme, Immodulon Therapeutics, Immune Design, Karma Oncology, Lilly, Merck, Morphotek, Mundipharma, PharmaMar, Immunicum, SpringWorks Therapeutics, SynOx, TRACON Pharmaceuticals, UpToDate, and Deciphera Pharmaceuticals, LLC; funding for travel/accommodations/expenses from PharmaMar; and research funding from GlaxoSmithKline (Inst). C Serrano reports consulting/advisory roles for Blueprint Medicines, Cogent Biosciences, IDRX, Immunicum, NewBay, and Deciphera, Pharmaceuticals, LLC; funding for travel/accommodations/expenses from Bayer, Gilead Sciences, Inc., Pfizer, and PharmaMar; honoraria from PharmaMar, Roche, and Deciphera Pharmaceuticals, LLC; and research funding from IDRX (Inst) and Karyopharm Therapeutics (Inst). N Somaiah reports consulting/advisory roles for AADI Bioscience, Bayer, Blueprint Medicines, Boehringer Ingelheim, Epizyme, and Deciphera Pharmaceuticals, LLC; stock/other ownership interests (immediate family member) in Johnson & Johnson, Natera, and Pfizer; and research funding from Ascentage Pharma, GlaxoSmithKline, Karyopharm Therapeutics, Daiichi Sankyo/Lilly, AstraZeneca/MedImmune (Inst), and Deciphera Pharmaceuticals, LLC. H Gelderblom reports institutional research funding from Abbisko, AmMax Bio, Bayer, Blueprint Medicines, Daiichi Sankyo, Ipsen, Novartis, Pfizer, and Deciphera Pharmaceuticals, LLC. JR Zalberg reports a leadership role with ICON Group; stock/other ownership interests in Amarin Corporation, BioMarin, Concert Pharmaceuticals, Frequency Therapeutics, Gilead Sciences, Madrigal Pharmaceuticals, Moderna Therapeutics, Novavax, Opthea, Orphazyme, Twist Bioscience, UniQure, and Zogenix; honoraria from Gilead Sciences, Halozyme, Merck Serono, Specialised Therapeutics, Targovax, and Deciphera Pharmaceuticals, LLC; consulting/advisory roles with 1Globe Health Institute, Center for Emerging & Neglected Diseases (CEND), FivePHusion, Genor BioPharma, Halozyme, Lipotek, Merck Serono, Merck Sharp & Dohme, Novotech, REVOLUTION MEDICINE, Specialised Therapeutics, Targovax, and Deciphera Pharmaceuticals, LLC; research funding from AstraZeneca (Inst), Bristol Myers Squibb (Inst), Eisai (Inst), Ipsen (Inst), IQVIA (Inst), Medtronic (Inst), Merck Serono (Inst), MSD Oncology (Inst), Mylan (Inst), and Pfizer (Inst); and funding for travel/accommodations/expenses from AstraZeneca, Merck Serono, Merck Sharp & Dohme, Sanofi, and Deciphera Pharmaceuticals, LLC. W Reichmann reports employment with Deciphera Pharmaceuticals, LLC, and stock and other ownership interests in Deciphera Pharmaceuticals, LLC. K Sprott reports employment with Deciphera Pharmaceuticals, LLC (self), and Stablix (immediate family member); and stock and other ownership interests in Deciphera Pharmaceuticals, LLC (self), and Stablix (immediate family member). P Cox reports employment with Deciphera Pharmaceuticals, LLC (self), and stock and other ownership interests in Deciphera Pharmaceuticals, LLC. ML Sherman reports employment with Deciphera Pharmaceuticals, LLC; an independent board of directors position with Pieris Pharmaceuticals; leadership roles with Deciphera Pharmaceuticals, LLC, and Pieris Pharmaceuticals; stock/other ownership interests in Deciphera Pharmaceuticals, LLC, and Pieris Pharmaceuticals; and patents/royalties/other

intellectual property from Acceleron Pharma. R Ruiz-Soto reports employment with Deciphera Pharmaceuticals, LLC; stock/other ownership interests in ImmunoGen and Deciphera Pharmaceuticals, LLC; and patents/royalties/other intellectual property from Deciphera Pharmaceuticals, LLC (inventor in pending patents at Deciphera Pharmaceuticals, LLC, transferred the rights to Deciphera Pharmaceuticals, LLC, has not received [and will not receive] any royalties), and ImmunoGen (inventor in 3 patents with ImmunoGen, transferred the rights to ImmunoGen, has not received [and will not receive] any royalties). MC Heinrich reports honorarium from Novartis; consulting/advisory roles for Blueprint Medicines, Novartis, Theseus Pharmaceuticals, and Deciphera Pharmaceuticals, LLC; patents/royalties/other intellectual property licensed to Novartis (institutional; treatment of GIST); and partial salary from a research grant from the Jonathan David Foundation, a VA Merit Review grant (I01BX005358), and an NCI R21 grant (R21CA263400). S Bauer reports honoraria from Bayer, GlaxoSmithKline, Novartis, Pfizer, PharmaMar, and Deciphera Pharmaceuticals, LLC; consulting/advisory roles with ADC Therapeutics, Adcendo, Bayer, Blueprint Medicines, Boehringer Ingelheim, Daiichi Sankyo, Exelixis, GlaxoSmithKline, Janssen-Cilag, Lilly, Mundipharma, Nanobiotix, and Deciphera Pharmaceuticals, LLC; research funding from Blueprint Medicines, Incyte (Inst), and Novartis; and funding for travel/accommodations/expenses from PharmaMar. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

### 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].

### ORCID

Suzanne George  <https://orcid.org/0000-0002-1284-8493>  
 Jean-Yves Blay  <https://orcid.org/0000-0001-7190-120X>  
 Ping Chi  <https://orcid.org/0000-0002-0159-5531>  
 Robin L Jones  <https://orcid.org/0000-0003-4173-3844>  
 César Serrano  <https://orcid.org/0000-0003-1416-8739>  
 Neeta Somaiah  <https://orcid.org/0000-0002-0146-7732>  
 Hans Gelderblom  <https://orcid.org/0000-0001-9270-8636>  
 John R Zalberg  <https://orcid.org/0000-0002-6624-0782>  
 William Reichmann  <https://orcid.org/0009-0006-9954-2740>  
 Kam Sprott  <https://orcid.org/0009-0006-3712-8114>  
 Paulina Cox  <https://orcid.org/0009-0001-2565-3169>  
 Matthew L Sherman  <https://orcid.org/0009-0009-4646-5819>  
 Rodrigo Ruiz-Soto  <https://orcid.org/0000-0003-3057-7735>  
 Michael C Heinrich  <https://orcid.org/0000-0003-3790-0478>  
 Sebastian Bauer  <https://orcid.org/0000-0001-5949-8120>

### References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

1. Søreide 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. doi:10.1016/j.canep.2015.10.031
2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Gastrointestinal Stromal Tumors V. 1.2024©. National Comprehensive Cancer Network, Inc. 2024. All rights reserved. Accessed [March 10, 2024]. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way.
  - Discusses clinical practice guidelines for gastrointestinal stromal tumors (GIST) developed by the National Comprehensive Cancer Network®.
3. Szucs Z, Thway K, Fisher C, et al. Molecular subtypes of gastrointestinal stromal tumors and their prognostic and therapeutic implications. *Future Oncol.* 2017;13(1):93–107. doi:10.2217/fon-2016-0192
4. Debiec-Rychter M, Sciot R, Le Cesne A, et al. KIT mutations and dose selection for imatinib in patients with advanced gastrointestinal stromal tumours. *Eur J Cancer.* 2006;42(8):1093–1103. doi:10.1016/j.ejca.2006.01.030
5. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. *Semin Diagn Pathol.* 2006;23(2):70–83. doi:10.1053/j.semdp.2006.09.001
6. Casali PG, Blay JY, Abecassis N, et al. Gastrointestinal stromal tumours: ESMO-EURACAN-GENTURIS Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2022;33(1):20–33. doi:10.1016/j.annonc.2021.09.005
7. Coe TM, Fero KE, Fanta PT, et al. Population-based epidemiology and mortality of small malignant gastrointestinal stromal tumors in the USA. *J Gastrointest Surg.* 2016;20(6):1132–1140. doi:10.1007/s11605-016-3134-y
8. Zhu H, Yang G, Ma Y, Huo Q, Wan D, Yang Q. Update of epidemiology, survival and initial treatment in patients

- with gastrointestinal stromal tumour in the USA: a retrospective study based on SEER database. *BMJ Open*. 2023;13(7):e072945. doi:10.1136/bmjopen-2023-072945
9. Novartis Pharmaceuticals Corporation. GLEEVEC® (imatinib mesylate) tablets, for oral use. Prescribing information. 2022. [https://www.novartis.com/us-en/sites/novartis\\_us/files/gleevec\\_tabs.pdf](https://www.novartis.com/us-en/sites/novartis_us/files/gleevec_tabs.pdf)
  10. Blanke CD, Demetri GD, von Mehren M, et al. Long-term results from a randomized Phase II trial of standard- versus higher-dose imatinib mesylate for patients with unresectable or metastatic gastrointestinal stromal tumors expressing KIT. *J Clin Oncol*. 2008;26(4):620–625. doi:10.1200/JCO.2007.13.4403
  11. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. *J Clin Oncol*. 2003;21(23):4342–4349. doi:10.1200/JCO.2003.04.190
  12. Gastrointestinal Stromal Tumor Meta-Analysis G. Comparison of two doses of imatinib for the treatment of unresectable or metastatic gastrointestinal stromal tumors: a meta-analysis of 1,640 patients. *J Clin Oncol*. 2010;28(7):1247–1253. doi:10.1200/JCO.2009.24.2099
  13. Kelly CM, Gutierrez Sainz L, Chi P. The management of metastatic GIST: current standard and investigational therapeutics. *J Hematol Oncol*. 2021;14(1):2. doi:10.1186/s13045-020-01026-6
  14. Antonescu CR, Besmer P, Guo T, et al. Acquired resistance to imatinib in gastrointestinal stromal tumor occurs through secondary gene mutation. *Clin Cancer Res*. 2005;11(11):4182–4190. doi:10.1158/1078-0432.CCR-04-2245
  15. Pfizer Laboratories. SUTENT® (sunitinib malate) capsules, for oral use. Prescribing Information. 2021. <https://labeling.pfizer.com/showlabeling.aspx?id=607>
  16. Demetri GD, van Oosterom AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomised controlled trial. *Lancet*. 2006;368(9544):1329–1338. doi:10.1016/S0140-6736(06)69446-4
  17. Blay JY, Serrano C, Heinrich MC, et al. Ripretinib in patients with advanced gastrointestinal stromal tumours (INVICTUS): a double-blind, randomised, placebo-controlled, Phase III trial. *Lancet Oncol*. 2020;21(7):923–934. doi:10.1016/S1470-2045(20)30168-6
  - **Publication of the primary safety and efficacy results from the INVICTUS Phase III trial for ripretinib as a ≥fourth-line therapy versus placebo in advanced GIST.**
  18. Deciphera Pharmaceuticals, LLC. QINLOCK® (ripertinib) tablets, for oral use. Prescribing Information. 2023. <https://www.qinlockhcp.com/content/files/qinlock-prescribing-information.pdf>
  19. Smith BD, Kaufman MD, Lu WP, 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(5):738–751e739. doi:10.1016/j.ccell.2019.04.006
  20. Bauer S, Jones RL, Blay JY, et al. Ripretinib versus sunitinib in patients with advanced gastrointestinal stromal tumor after treatment with imatinib (INTRIGUE): a randomized, open-label, Phase III trial. *J Clin Oncol*. 2022;40(34):3918–3928.
  - **Publication of the primary safety and efficacy results from the INTRIGUE Phase III trial for ripretinib versus sunitinib as a second-line therapy in advanced GIST.**
  21. Zalcberg J, Jones RL, Blay JY, et al. Overall survival and long-term safety with ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib: final analyses from INTRIGUE. *J Clin Oncol*. 2024;42(3):748. doi:10.1200/JCO.2024.42.3\_suppl.748
  22. Bauer S, George S, von Mehren M, Heinrich MC. Early and next-generation KIT/PDGFR kinase inhibitors and the future of treatment for advanced gastrointestinal stromal tumor. *Front Oncol*. 2021;11:672500. doi:10.3389/fonc.2021.672500
  23. Heinrich MC, Maki RG, Corless CL, 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(33):5352–5359. doi:10.1200/JCO.2007.15.7461
  - **Provides an analysis of molecular markers of imatinib resistance in patients enrolled in a Phase II study of sunitinib.**
  24. Bauer S, Heinrich MC, George S, et al. Clinical activity of ripretinib in patients with advanced gastrointestinal stromal tumor harboring heterogeneous KIT/PDGFR mutations in the Phase III INVICTUS study. *Clin Cancer Res*. 2021;27(23):6333–6342. doi:10.1158/1078-0432.CCR-21-1864
  - **Provides results of the mutational analysis and characterization of genomic heterogeneity of tumors in patients with advanced GIST from the INVICTUS trial.**
  25. Elazezy M, Joosse SA. Techniques of using circulating tumor DNA as a liquid biopsy component in cancer management. *Comput Struct Biotechnol J*. 2018;16:370–378. doi:10.1016/j.csbj.2018.10.002
  26. Lim M, Kim CJ, Sunkara V, Kim MH, Cho YK. Liquid biopsy in lung cancer: clinical applications of circulating biomarkers (CTCs and ctDNA). *Micromachines (Basel)*. 2018;9(3):100. doi:10.3390/mi9030100
  27. Merker JD, Oxnard GR, Compton C, et al. Circulating tumor DNA analysis in patients with cancer: American Society of Clinical Oncology and College of American Pathologists Joint Review. *J Clin Oncol*. 2018;36(16):1631–1641. doi:10.1200/JCO.2017.76.8671
  28. Chen M, Zhao H. Next-generation sequencing in liquid biopsy: cancer screening and early detection. *Hum Genomics*. 2019;13(1):34. doi:10.1186/s40246-019-0220-8
  - **Discusses the application, advantages and disadvantages of circulating tumor DNA (ctDNA) analysis in the detection and diagnosis of cancer.**
  29. Heinrich MC, Jones RL, George S, et al. Ripretinib versus sunitinib in gastrointestinal stromal tumor: ctDNA biomarker analysis of the Phase III INTRIGUE trial. *Nat Med*. 2024;30(2):498–506. doi:10.1038/s41591-023-02734-5
  - **Provides results of exploratory baseline ctDNA mutational analysis and characterization of genomic heterogeneity of tumors in patients with advanced GIST from the INTRIGUE trial, which provided the rationale for the INSIGHT trial.**

30. George S, Blay JY, Chi P, et al. INSIGHT: a Phase III, randomized, multicenter, open-label study of ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib harboring *KIT* exon 11 + 17 and/or 18 mutations. *J Clin Oncol*. 2023;41(Suppl. TPS11582). doi:10.1200/JCO.2023.41.16\_suppl.TPS11582
31. U.S. National Library of Medicine. A study of ripretinib vs sunitinib in patients with advanced GIST with specific *KIT* exon mutations who were previously treated with imatinib (INSIGHT). 2023. <https://classic.clinicaltrials.gov/ct2/show/NCT05734105>