Abstract: TPS11582

INSIGHT: A phase 3, 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

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Introduction

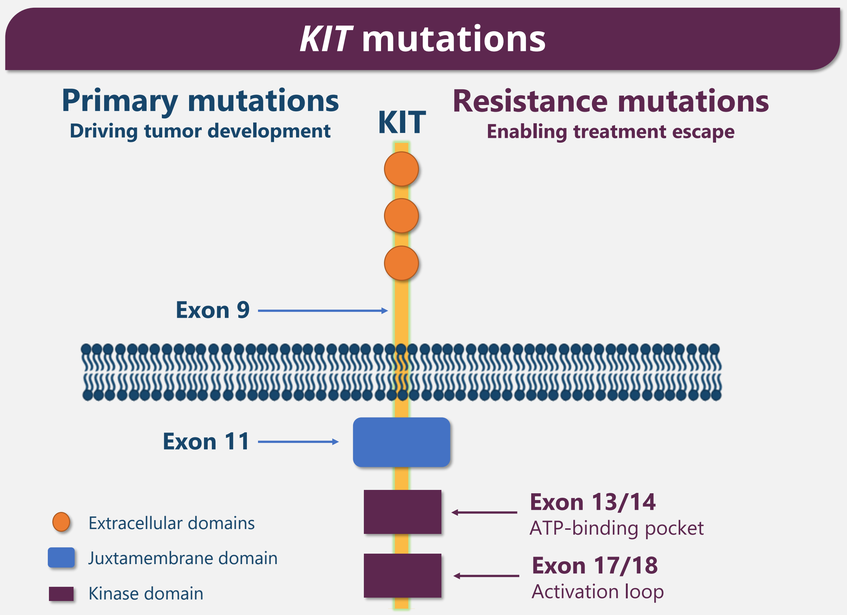
Gastrointestinal stromal tumor

- Gastrointestinal stromal tumor (GIST) is the most common gastrointestinal sarcoma, with ~80% of cases driven by KIT mutations[1]
- Imatinib, a tyrosine kinase inhibitor (TKI), is approved as first-line therapy for advanced GIST and leads to objective response in ~50% of patients[2]
  - Many patients treated with imatinib eventually experience tumor progression due to development of secondary mutations in the KIT ATP-binding pocket (encoded by exons 13/14) or activation loop (encoded by exons 17/18; **Figure 1**)[3,4]
- Sunitinib is a multitargeted TKI approved as second-line therapy for advanced GIST after imatinib failure[5]
- Ripretinib is a broad-spectrum switch-control KIT/PDGFRA TKI approved for patients with advanced GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib[6,7]

Ripretinib vs sunitinib for KIT mutations

- In the phase 3 INTRIGUE trial, ripretinib demonstrated comparable efficacy to sunitinib as second-line therapy for patients with advanced GIST[8]
  - Ripretinib showed more favorable safety and patient-reported outcomes vs sunitinib
- An exploratory analysis from INTRIGUE using baseline circulating tumor DNA (ctDNA) demonstrated meaningful clinical benefit with ripretinib vs sunitinib in patients with co-occurring *KIT* exon 11 + 17/18 mutations, excluding mutations in exons 9, 13, and/or 14 (median progression-free survival [PFS], 14.2 vs 1.5 months; hazard ratio [HR], 0.22; 95% confidence interval [CI], 0.11 to 0.44; nominal *P* <0.0001)[9]
  - Objective response rate (ORR) and overall survival (OS) favored ripretinib vs sunitinib in patients with *KIT* exon 11 + 17/18 mutations (ORR, 44.4% vs 0%; response difference, 44.4%; 95% CI, 23.0 to 62.7; nominal *P* = 0.0001; median OS, not estimable vs 17.5 months; HR, 0.34; 95% CI, 0.15 to 0.76; nominal *P* = 0.0061)
- Here we describe INSIGHT (NCT05734105), a planned phase 3 study for patients with advanced GIST previously treated with imatinib exclusively harboring *KIT* exon 11 + 17 and/or 18 mutations, which was granted Breakthrough Therapy designation by the US FDA

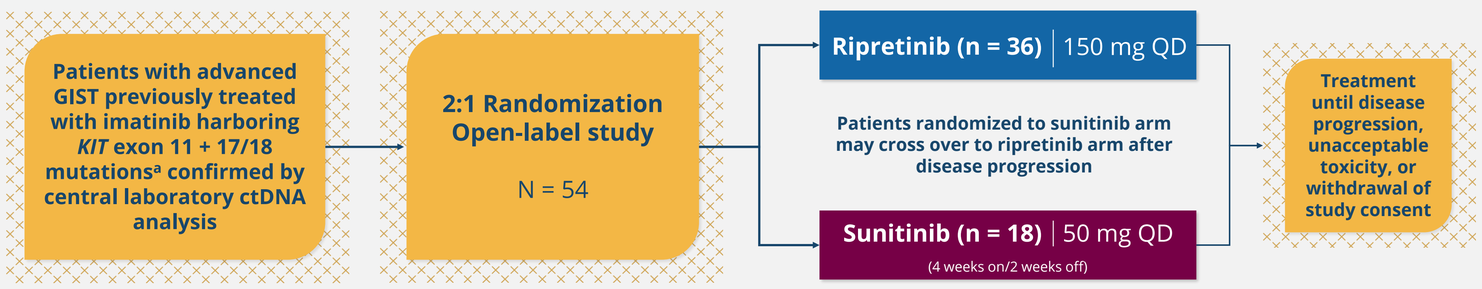
Figure 1. *KIT* mutations in GIST



ATP, adenosine triphosphate; GIST, gastrointestinal stromal tumor.

Study Design

Figure 2. 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.

- INSIGHT is an international, phase 3, randomized, multicenter, open-label study to evaluate the efficacy of ripretinib vs sunitinib in patients with advanced GIST previously treated with imatinib and who have *KIT* exon 11 mutations and co-occurring mutations exclusively in *KIT* exon 17 and/or 18 (**Figure 2**)
- Participants will receive ripretinib 150 mg once daily (QD; continuous) or sunitinib 50 mg QD (4 weeks on/2 weeks off) in 6-week cycles
- Patients will receive the study drug until disease progression 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
- Upon disease progression as determined by blinded IRR, patients in the sunitinib arm may cross over to receive ripretinib

Outcome Measures

Primary outcome measure

- The primary outcome measure is PFS based on blinded IRR
  - PFS will be analyzed using a 2-sided, unstratified, log-rank test; PFS curves will be computed using the Kaplan-Meier method and the unstratified Cox proportional hazards regression model will be used to estimate the HR and 95% CIs

Secondary outcome measures

- ORR as determined by blinded IRR using mRECIST v1.1
- OS
- Safety (frequency and severity of treatment-emergent adverse events)
- Patient-reported quality of life
  - Patient-reported outcomes as measured by the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (30-item), parts of the National Cancer Institute Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events, and the 5-level EQ-5D
- Disease control rate
- Time-to-progression as determined by blinded IRR
- Duration of response
- Time-to-response

Key Eligibility Criteria

INCLUSION
Male or female ≥18 years of age
Histologic diagnosis of GIST with co-occurring *KIT* exon 11 + 17 and/or 18 mutations confirmed by central laboratory ctDNA analysis at pre-screening
Advanced GIST and radiologic progression on imatinib treatment, which was discontinued ≥10 days prior to receiving first dose of study drug
Must have at least 1 measurable lesion according to mRECIST v1.1 within 21 days prior to the first dose of study drug
ECOG PS ≤2 at screening

EXCLUSION
Co-occurring *KIT* exon 11 + 17 and/or 18 mutations that cannot be confirmed by central laboratory ctDNA analysis
History of *KIT* exon 9 mutation or detection of *KIT* exon 9, 13, or 14 mutations by central laboratory ctDNA analysis
Treatment with any other line of therapy in addition to imatinib for advanced GIST (imatinib-containing combination therapy in the first-line setting is not allowed)
Any prior or concurrent malignancy whose treatment may interfere with safety or efficacy assessment of this study
Known active metastasis of the central nervous system

ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; GIST, gastrointestinal stromal tumor; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1.

Presented at the 2023 ASCO Annual Meeting, June 2–6, 2023; Chicago, IL, USA

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Acknowledgments
This study is sponsored by Deciphera Pharmaceuticals, LLC. Medical writing and editorial support were provided by Steven Walker, PhD, of AlphaBioCom, a Red Nucleus company, and were funded by Deciphera Pharmaceuticals, LLC.

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