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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Abstract: TPS11582

Gastrointestinal stromal tumor

- Gastrointestinal stromal tumor (GIST) is the most common gastrointestinal sarcoma, with ~80% of cases driven by KIT mutations.
- Imatinib, a tyrosine kinase inhibitor (TKI), is approved as first-line therapy for advanced GIST and leads to objective response in ~50% of patients.
- 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).
- Sunitinib is a multitargeted TKI approved as second-line therapy for advanced GIST after imatinib failure.
- Ripretinib is a broad-spectrum switch-control KIT/PDGFRα TKI approved for patients with advanced GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib.

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.
- 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).
- 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 9%; 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.

Study Design

Figure 2. INSIGHT study design

- Patients with advanced GIST previously treated with imatinib harboring KIT exon 11 + 17/18 mutations confirmed by central laboratory ctDNA analysis (N = 94).
- 2:1 Randomization of patients to ripretinib (150 mg QD) or sunitinib (50 mg QD).
- Treatment until disease progression, unacceptable toxicity, or withdrawal of consent.

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-SD.
- Disease control rate.
- Time-to-progression as determined by blinded IRR.
- Duration of response.
- Time-to-resistance.

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.
- Improving/minimally stable disease remaining on imatinib.
- Known active metastasis of the central nervous system.

Gastrointestinal stromal tumor (GIST)

- ATP, adenosine triphosphate; GIST, gastrointestinal stromal tumor.

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