Updated overall survival with ripretinib vs sunitinib in patients with second-line advanced gastrointestinal stromal tumor and *KIT* exon 11+17/18 mutations: circulating tumor DNA analysis from INTRIGUE

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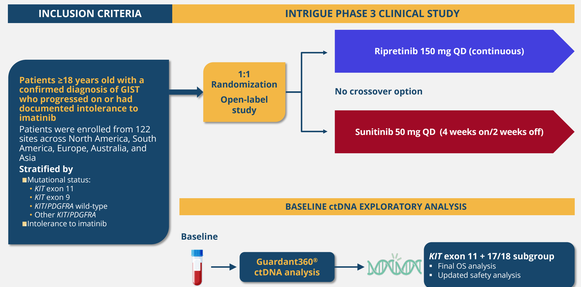
Introduction

- Gastrointestinal stromal tumor (GIST) is the most common sarcoma of the GI tract[1]
- Most GIST cases have activating mutations in *KIT* (~80%) or *PDGFRA* (5%–10%)[2]
- The standard treatment regimen for patients with advanced GIST is sequential tyrosine kinase inhibitor (TKI) therapy, including first-line imatinib and second-line sunitinib[3]
- Ripretinib is a switch-control TKI approved for adult patients with advanced GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib[4,5]
- Patients with advanced GIST often progress on imatinib due to the emergence of heterogeneous secondary mutations in the KIT ATP-binding pocket (exons 13/14) and/or the activation loop (exons 17/18)[6]
- In an exploratory analysis of baseline circulating tumor DNA (ctDNA) from the INTRIGUE trial (NCT03673501), patients with primary mutations in *KIT* exon 11 and secondary mutations exclusively in *KIT* exons 17 and/or 18 (*KIT* exon 11 + 17/18) received clinical benefit from ripretinib but not sunitinib[7]
- Here, we present the final overall survival (OS) and updated safety from an exploratory analysis in patients with *KIT* exon 11 + 17/18 mutations from INTRIGUE

Methods

- In the INTRIGUE phase 3 trial, adult patients with advanced GIST who had disease progression on or intolerance to imatinib were randomized 1:1 to receive ripretinib 150 mg once daily (QD) or sunitinib 50 mg QD (4 weeks on/2 weeks off; **Figure 1**)[8]
- For this exploratory analysis, baseline (cycle 1, day 1) peripheral whole blood was collected in 10-mL Streck cell-free DNA blood collection tubes and shipped to central laboratories for plasma isolation
- DNA extraction was performed by Guardant Health, and samples were analyzed using Guardant360®, a 74-gene ctDNA next-generation sequencing–based assay
- Data cutoff was March 15, 2023

Figure 1. INTRIGUE study design and exploratory analysis



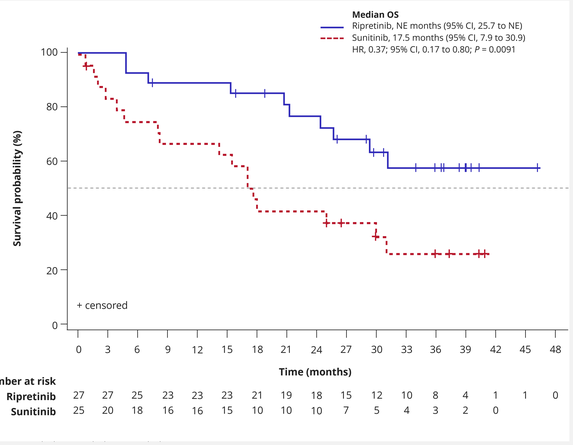
Mutational status used for randomization was based on local pathology reports at the time of randomization.
ctDNA; circulating tumor DNA; GIST, gastrointestinal stromal tumor; OS, overall survival; *PDGFRA*, platelet-derived growth factor receptor α; QD, once daily.

Results

Efficacy

- ctDNA was detected in 77% (280/362) of patients with samples analyzed; *KIT* mutations were detected in 59% (213/362) of samples analyzed[7]
- The most common primary *KIT* mutations were in exon 11 (157/213); of patients with primary *KIT* exon 11 mutations, 52 had secondary mutations exclusively in exons 17/18[7]
- In this long-term update, patients with *KIT* exon 11 + 17/18 mutations had better OS with ripretinib vs sunitinib (median, not reached vs 17.5 months; hazard ratio, 0.37; 95% confidence interval, 0.17 to 0.80; nominal *P* = 0.0091; **Figure 2**)

Figure 2. Final OS in the *KIT* exon 11 + 17/18 population



Safety

- In the *KIT* exon 11 + 17/18 population, fewer patients had grade 3/4 drug-related treatment-emergent adverse events (TEAEs) and drug-related serious adverse events with ripretinib vs sunitinib (33% vs 50% and 4% vs 13%, respectively; **Table 1**)
- Patients in the ripretinib arm experienced more TEAEs leading to dose reduction or interruption than patients in the sunitinib arm (37% vs 29% and 63% vs 42%, respectively; **Table 1**)
  - These numbers reflect the longer median treatment duration in the ripretinib arm (15.6 months [range, 2.6 to 40.3]) vs the sunitinib arm (3.0 months [range, 0.5 to 22.3])
- The most common TEAEs were alopecia (78%) in the ripretinib arm and hypertension (50%) in the sunitinib arm (**Table 2**)

Table 1. TEAE summary in the *KIT* exon 11 + 17/18 safety population

Category, n (%)	Ripretinib n = 27	Sunitinib n = 24[a]
Any TEAE	27 (100)	24 (100)
Any grade 3/4 TEAE	15 (56)	14 (58)
Any drug-related TEAE	27 (100)	24 (100)
Any drug-related grade 3/4 TEAE	9 (33)	12 (50)
Any treatment-emergent SAE	11 (41)	9 (38)
Any drug-related treatment-emergent SAE	1 (4)	3 (13)
Any TEAE leading to dose reduction	10 (37)	7 (29)
Any TEAE leading to dose interruption	17 (63)	10 (42)
Any TEAE leading to study treatment discontinuation	1 (4)	1 (4)

Data cutoff: March 15, 2023.
There were no drug-related TEAEs leading to death.
[a]One patient randomized to sunitinib did not receive treatment.
SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 2. TEAEs in ≥20% of patients in either arm in the *KIT* exon 11 + 17/18 safety population

Preferred term, n (%)	Ripretinib n = 27	Sunitinib n = 24[a]
Alopecia	21 (78)	2 (8)
Constipation	14 (52)	8 (33)
Fatigue	14 (52)	9 (38)
Myalgia	12 (44)	3 (13)
Palmer-plantar erythrodysesthesia syndrome	11 (41)	10 (42)
Hypertension	9 (33)	12 (50)
Muscle spasms	9 (33)	2 (8)
Abdominal pain	8 (30)	8 (33)
Decreased appetite	7 (26)	8 (33)
Diarrhea	7 (26)	9 (38)
Nausea	7 (26)	7 (29)
Headache	7 (26)	3 (13)
Pruritus	7 (26)	4 (17)
Asthenia	6 (22)	2 (8)
Cough	6 (22)	0
Seborrheic keratosis	6 (22)	0
Weight decreased	5 (19)	5 (21)
Arthralgia	4 (15)	5 (21)
Anemia	3 (11)	5 (21)
Vomiting	1 (4)	7 (29)

Data cutoff: March 15, 2023.
[a]One patient randomized to sunitinib did not receive treatment.
TEAE, treatment-emergent adverse event.

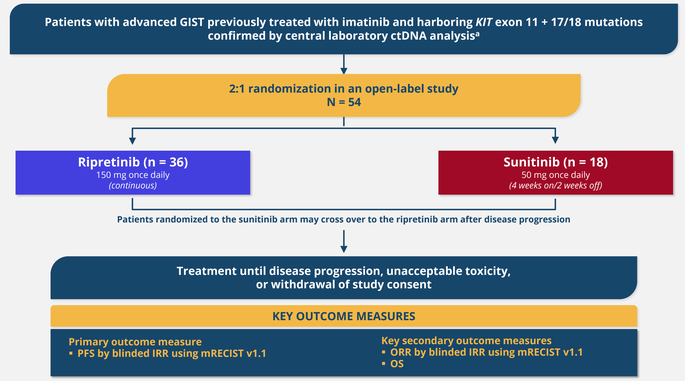
CONCLUSIONS

- In this final update from the exploratory INTRIGUE mutational analysis, ripretinib continued to show long-term OS benefit vs sunitinib for patients with *KIT* exon 11 + 17/18 mutations identified by baseline ctDNA
- The safety profile was favorable for patients with *KIT* exon 11 + 17/18 mutations in the ripretinib arm; even with a longer treatment duration, there were fewer grade 3/4 drug-related TEAEs with ripretinib
- These data support the basis of the INSIGHT phase 3 trial

INSIGHT Trial

- The INSIGHT phase 3 trial (NCT05734105) is designed to evaluate ripretinib as a second-line therapy for patients with advanced GIST and *KIT* exon 11 + 17/18 mutations (**Figure 3, Table 3**)

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; IRR, independent radiologic review; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Table 3. Key eligibility criteria for the INSIGHT trial

INCLUSION
Male or female ≥18 years of age with a histologic diagnosis of GIST with co-occurring *KIT* exon 11 + 17/18 mutations confirmed by central laboratory ctDNA analysis at prescreening
Advanced GIST with ≥1 measurable lesion according to mRECIST v1.1 and radiologic progression on imatinib treatment
EXCLUSION
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

ctDNA, circulating tumor DNA; GIST, gastrointestinal stromal tumor; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1.

- INSIGHT is currently enrolling patients, with new countries and sites being added and current active sites located in Australia, Brazil, Canada, Chile, France, Germany, Italy, Netherlands, Norway, Poland, Spain, South Korea, Taiwan, the United Kingdom, and the United States
- To learn more about enrolling your patient, please contact medicalinformation@Deciphera.com; recruiting locations can be found at clinicaltrials.gov by scanning the QR code

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REFERENCES
1. Rubin S, et al. *Lancet*. 2007;369:1731-41.
2. Debiec-Rychter M, et al. *Eur J Cancer*. 2006;42:1093-103.
3. Kelly CM, et al. *J Hematol Oncol*. 2021;14:2.
4. Blay JY, et al. *Lancet Oncol*. 2020;21(7):923-34.
5. QINLOCK. Prescribing Information. Deciphera Pharmaceuticals, LLC; 2023.
6. Liegl B, et al. *J Pathol*. 2008;216:64-74.
7. Heinrich MC, et al. *Nat Med*. 2024;30:498-506.
8. Bauer S, et al. *J Clin Oncol*. 2022;40:3918-28.