Abstract: 11524

Overall survival and long-term safety in patients with advanced gastrointestinal stromal tumor previously treated with imatinib: Updated analyses from INTRIGUE

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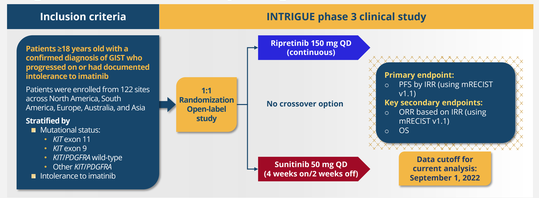
Introduction

- INTRIGUE (NCT03673501) is a randomized, open-label, global, multicenter phase 3 study comparing ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor (GIST) who had disease progression on or were intolerant to first-line treatment with imatinib[1]
- Ripretinib is a switch-control KIT/PDGFRA tyrosine kinase inhibitor (TKI) approved for patients with GIST who received prior treatment with 3 or more kinase inhibitors, including imatinib[2,3]
- Sunitinib is the approved second-line therapy for patients with advanced GIST following progression on or intolerance to imatinib[4]
- At the time of primary analysis of progression-free survival (PFS) in the INTRIGUE trial, the first interim analysis (IA) for overall survival (OS) was conducted
  - OS data were immature, with overall OS event rates of 21.1% and 22.3% in the *KIT* exon 11 intention-to-treat (ITT) and all-patient (AP) ITT populations, respectively; median OS was not reached in either arm for either population[1]
  - Ripretinib demonstrated similar PFS to sunitinib in both the *KIT* exon 11 ITT (median PFS, 8.3 vs 7.0 months; HR, 0.88; 95% CI, 0.66 to 1.16; $P = 0.36$) and overall ITT populations (median PFS, 8.0 vs 8.3 months; HR, 1.05; 95% CI, 0.82 to 1.33; nominal $P = 0.72$)[1]; no update in PFS analysis will be reported, as there was no change observed
- Ripretinib had a more favorable safety profile with fewer grade 3/4 treatment-emergent adverse events (TEAEs) than sunitinib[1]
  - Ripretinib was included in the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology for GIST (version 1.2023) as a preferred second-line regimen for patients who are intolerant to sunitinib[5]
- Here, we present updated OS, PFS on next line of therapy, and safety based on the second IA of OS from INTRIGUE, with data cutoff date of September 1, 2022

Methods

- In INTRIGUE, 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) and were stratified by *KIT* mutational status and imatinib intolerance (**Figure 1**)[1]
- OS was a key secondary endpoint in INTRIGUE,[1] and there were three prespecified OS analyses
  - The first IA for OS was planned and conducted at the time of the primary analysis of PFS (data cutoff: September 1, 2021)[1]
  - The second IA for OS was planned and conducted 1 year after the first IA for OS (data cutoff: September 1, 2022)
  - The final analysis for OS is planned for when ≥200 OS events are observed with ≥145 of those events coming from the *KIT* exon 11 population

Figure 1. INTRIGUE study design



Mutational status used for randomization was based on local pathology reports at the time of randomization.
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; PDGFRA, platelet-derived growth factor receptor α; PFS, progression-free survival; QD, once daily.

Results

Patient disposition

- A total of 453 patients were randomized, and 444 received treatment (**Table 1**)
- Overall, 51 of the 444 treated patients (11.5%; AP ITT population) remain on treatment; 33/223 (14.8%) on ripretinib and 18/221 (8.1%) on sunitinib (**Table 1**)
- The most common reasons for treatment discontinuation in the AP ITT population were progressive disease (PD) as determined by independent radiologic review (IRR; 55.4%), PD assessed by investigator (10.6%), clinical PD (5.9%), withdrawal of consent (5.4%), and adverse events (AEs; 4.5%; **Table 1**)
  - Fewer patients discontinued treatment due to an AE for ripretinib vs sunitinib (2.7% vs 6.3%)
  - Similar results were observed in the *KIT* exon 11 ITT population (**Table 1**)

Table 1. Patient disposition at the cutoff date

	AP ITT population			*KIT* exon 11 ITT population		
Number of patients, n (%)	**Ripretinib (n = 226)**	**Sunitinib (n = 227)**	**Total (N = 453)**	**Ripretinib (n = 163)**	**Sunitinib (n = 164)**	**Total (N = 327)**
Not treated[a]	3 (1.3)	6 (2.6)	9 (2.0)	1 (0.6)	5 (3.0)	6 (1.8)
Treated[a]	223 (98.7)	221 (97.4)	444 (98.0)	162 (99.4)	159 (97.0)	321 (98.2)
Ongoing treatment[b]	33 (14.8)	18 (8.1)	51 (11.5)	28 (17.3)	14 (8.8)	42 (13.1)
Discontinued treatment[b]	190 (85.2)	203 (91.9)	393 (88.5)	134 (82.7)	145 (91.2)	279 (86.9)
Primary reason for treatment discontinuation						
PD by IRR	134 (60.1)	112 (50.7)	246 (55.4)	92 (56.8)	87 (54.7)	179 (55.8)
PD by investigator assessment	18 (8.1)	29 (13.1)	47 (10.6)	14 (8.6)	19 (11.9)	33 (10.3)
Clinical progression	11 (4.9)	15 (6.8)	26 (5.9)	10 (6.2)	5 (3.1)	15 (4.7)
Withdrawal of consent	11 (4.9)	13 (5.9)	24 (5.4)	7 (4.3)	10 (6.3)	17 (5.3)
AE	6 (2.7)	14 (6.3)	20 (4.5)	5 (3.1)	9 (5.7)	14 (4.4)
Death	4 (1.8)	5 (2.3)	9 (2.0)	3 (1.9)	4 (2.5)	7 (2.2)
Physician decision	3 (1.3)	6 (2.7)	9 (2.0)	2 (1.2)	6 (3.8)	8 (2.5)
Noncompliance with study drug	1 (0.4)	0	1 (0.2)	1 (0.6)	0	1 (0.3)
Other	2 (0.9)	9 (4.1)	11 (2.5)	0	5 (3.1)	5 (1.6)
Ongoing in study[a]	116 (51.3)	106 (46.7)	222 (49.0)	81 (49.7)	80 (48.8)	161 (49.2)

Data cutoff: September 1, 2022.
[a]Percentage is based on the number of patients in the ITT population.
[b]Percentage is based on the number of treated patients.
AE, adverse event; AP, all-patient; IRR, independent radiologic review; ITT, intention-to-treat; PD, progressive disease.

- Following study treatment discontinuation, 58 patients (25.6%) from the sunitinib arm received ripretinib, and 139 patients (61.5%) from the ripretinib arm later received sunitinib (**Table 2**)

Table 2. Follow-up anticancer therapies

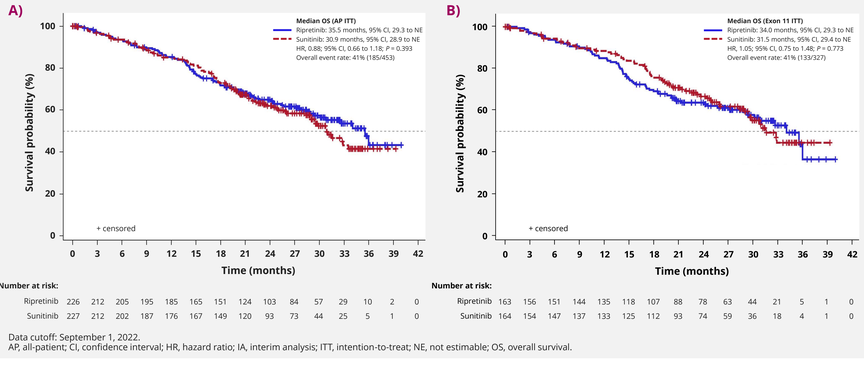
	AP ITT population			*KIT* exon 11 ITT population		
Number of patients, n (%)	**Ripretinib (n = 226)**	**Sunitinib (n = 227)**	**Total (N = 453)**	**Ripretinib (n = 163)**	**Sunitinib (n = 164)**	**Total (N = 327)**
Follow-up anticancer therapy[a]	156 (69.0)	139 (61.2)	295 (65.1)	111 (68.1)	102 (62.2)	213 (65.1)
Sunitinib	139 (61.5)	4 (1.8)	143 (31.6)	101 (62.0)	3 (1.8)	104 (31.8)
Regorafenib	54 (23.9)	106 (46.7)	160 (35.3)	38 (23.3)	78 (47.6)	116 (35.5)
Ripretinib	2 (0.9)	58 (25.6)	60 (13.2)	1 (0.6)	45 (27.4)	46 (14.1)
Imatinib	23 (10.2)	26 (11.5)	49 (10.8)	14 (8.6)	22 (13.4)	36 (11.0)
Avapritinib	7 (3.1)	5 (2.2)	12 (2.6)	3 (1.8)	2 (1.2)	5 (1.5)
Follow-up therapy by line						
Third-line therapy	156 (69.0)	139 (61.2)	295 (65.1)	111 (68.1)	102 (62.2)	213 (65.1)
Sunitinib	133 (58.8)	0	133 (29.4)	97 (59.5)	0	97 (29.7)
Regorafenib	7 (3.1)	96 (42.3)	103 (22.7)	6 (3.7)	70 (42.7)	76 (23.2)
Ripretinib	0	20 (8.8)	20 (4.4)	0	16 (9.8)	16 (4.9)
Imatinib	10 (4.4)	10 (4.4)	20 (4.4)	6 (3.7)	8 (4.9)	14 (4.3)
Avapritinib	4 (1.8)	3 (1.3)	7 (1.5)	1 (0.6)	2 (1.2)	3 (0.9)
Other	2 (0.9)	10 (4.4)	12 (2.6)	1 (0.6)	6 (3.7)	7 (2.1)
Fourth-line therapy	60 (26.5)	63 (27.8)	123 (27.2)	43 (26.4)	48 (29.3)	91 (27.8)
Sunitinib	6 (2.7)	1 (0.4)	7 (1.5)	4 (2.5)	1 (0.6)	5 (1.5)
Regorafenib	43 (19.0)	9 (4.0)	52 (11.5)	31 (19.0)	8 (4.9)	39 (11.9)
Ripretinib	2 (0.9)	32 (14.1)	34 (7.5)	1 (0.6)	24 (14.6)	25 (7.6)
Imatinib	4 (1.8)	6 (2.6)	10 (2.2)	2 (1.2)	5 (3.0)	7 (2.1)
Avapritinib	1 (0.4)	1 (0.4)	2 (0.4)	1 (0.6)	0	1 (0.3)
Other	4 (1.8)	14 (6.2)	18 (4.0)	4 (2.5)	10 (6.1)	14 (4.3)

[a]Patients may receive multiple lines of follow-up anticancer therapies. Several patients received >fourth-line therapies (AP ITT: fifth-line, n = 49; sixth-line, n = 18; seventh-line, n = 4. *KIT* exon 11 ITT: fifth-line, n = 33; sixth-line, n = 8; seventh-line, n = 2).
AP, all-patient; ITT, intention-to-treat.

Efficacy

- OS was more mature after additional follow-up (**Figure 2**)
  - There were 185 OS events (40.8%) in the AP ITT population; median duration of follow-up was 28.7 and 28.5 months for ripretinib and sunitinib, respectively
- OS was similar with ripretinib vs sunitinib in the AP ITT (median 35.5 vs 30.9 months; hazard ratio [HR] 0.88; 95% confidence interval [CI], 0.66 to 1.18; nominal $P = 0.39$) and *KIT* exon 11 ITT populations (median 34.0 vs 31.5 months; HR 1.05; 95% CI, 0.75 to 1.48; nominal $P = 0.77$; **Figure 2**)

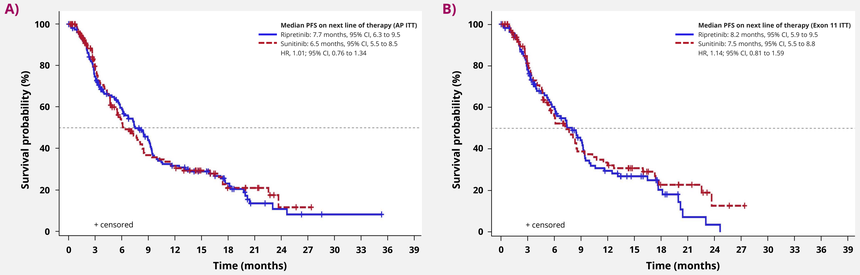
Figure 2. Kaplan-Meier analysis of OS for patients treated with ripretinib or sunitinib in the AP ITT (A) and *KIT* exon 11 ITT (B) populations



Data cutoff: September 1, 2022.
AP, all-patient; CI, confidence interval; HR, hazard ratio; IA, interim analysis; ITT, intention-to-treat; NE, not estimable; OS, overall survival.

- PFS on next line of therapy in the second IA by randomized treatment assignment was similar with ripretinib vs sunitinib in the AP ITT (median 7.7 vs 6.5 months; HR 1.01; 95% CI, 0.76 to 1.34) and *KIT* exon 11 ITT populations (median 8.2 vs 7.5 months; HR 1.14; 95% CI, 0.81 to 1.59; **Figure 3**)

Figure 3. Kaplan-Meier analysis of PFS on next line of therapy by randomized treatment assignment (ripretinib or sunitinib) in the AP ITT (A) and *KIT* exon 11 ITT (B) populations



PFS on next line therapy is defined as the time interval between the date of first nonprotocol follow-up drug therapy and disease progression on this drug therapy based on the local assessment or death due to any cause, whichever comes first.
Kaplan-Meier curves are presented by randomized treatment assignment.
Data cutoff: September 1, 2022.
AP, all-patient; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Safety

- The updated safety profile was consistent with the primary analysis (**Table 3**)
  - Fewer patients had grade 3/4 TEAEs with ripretinib vs sunitinib (95 [42.6%] vs 149 [67.4%])
  - Dose interruptions and reductions, and treatment discontinuations due to TEAEs were lower with ripretinib vs sunitinib
- The most common TEAEs of any grade in the ripretinib arm were alopecia, fatigue, and myalgia, whereas the most common TEAEs of any grade in patients treated with sunitinib were palmar-plantar erythrodysesthesia syndrome, diarrhea, and hypertension (**Table 4**)
- The median (range) treatment duration was 7.9 (0.2–38.2) months for ripretinib and 6.5 (0.2–38.3) months for sunitinib

Table 3. TEAE summary in the safety population

TEAE summary, n (%)	**Ripretinib (n = 223)**	**Sunitinib (n = 221)**
Any TEAE	221 (99.1)	219 (99.1)
Any grade 3/4 TEAE	95 (42.6)	149 (67.4)
Any drug-related TEAE	211 (94.6)	214 (96.8)
Any grade 3/4 drug-related TEAE	60 (26.9)	128 (57.9)
Any treatment-emergent SAE	64 (28.7)	61 (27.6)
Any drug-related treatment-emergent SAE	19 (8.5)	22 (10.0)
Any TEAE leading to dose reduction	45 (20.2)	107 (48.4)
Any TEAE leading to dose interruption	70 (31.4)	95 (43.0)
Any TEAE leading to treatment discontinuation	11 (4.9)	20 (9.0)
Any TEAE leading to death	6 (2.7)	8 (3.6)
Any drug-related TEAE leading to death	0	1 (0.5)

SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 4. TEAEs in ≥20% of patients in the safety population

Preferred term, n (%)	**Ripretinib (n = 223)**	**Sunitinib (n = 221)**
Any TEAE	221 (99.1)	219 (99.1)
Palmar-plantar erythrodysesthesia syndrome	61 (27.4)	116 (52.5)
Fatigue	84 (37.7)	91 (41.2)
Hypertension	60 (26.9)	106 (48.0)
Alopecia	144 (64.6)	18 (8.1)
Diarrhea	47 (21.1)	107 (48.4)
Constipation	79 (35.4)	49 (22.2)
Decreased appetite	60 (26.9)	54 (24.4)
Nausea	54 (24.2)	57 (25.8)
Myalgia	81 (36.3)	25 (11.3)
Abdominal pain	61 (27.4)	39 (17.6)
Stomatitis	18 (8.1)	81 (36.7)

TEAE, treatment-emergent adverse event.

CONCLUSIONS

- In the second IA for OS from the phase 3 INTRIGUE trial, OS was more mature and similar between the treatment arms
- PFS on next line of therapy was also similar between the treatment arms
- The safety profile remained consistent with additional data; the results demonstrated favorable safety with ripretinib in patients with advanced GIST previously treated with imatinib

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Study sponsor

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