Outcomes in patients with advanced gastrointestinal stromal tumor who did not have baseline ctDNA detected in the INTRIGUE study

Abstract: 11536

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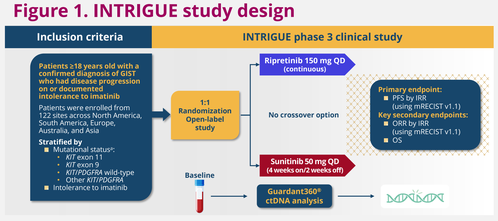
Introduction

- Ripretinib is a switch-control KIT/PDGFRA tyrosine kinase inhibitor (TKI) approved for patients with gastrointestinal stromal tumor (GIST) who received prior treatment with 3 or more kinase inhibitors, including imatinib[1]
- Sunitinib is the approved second-line therapy for patients with advanced GIST following progression on or intolerance to imatinib[2]
- INTRIGUE (NCT03673501) is a randomized, open-label, global, multicenter phase 3 study comparing ripretinib vs sunitinib in patients with advanced GIST who had disease progression on or were intolerant to imatinib[3]
  - Ripretinib and sunitinib were comparable in terms of progression-free survival (PFS) in the *KIT* exon 11 intention-to-treat (ITT) and all-patient ITT populations ; meaningful clinical activity, fewer grade 3/4 treatment-emergent adverse events (TEAEs), and improved tolerability were observed with ripretinib[3]
  - 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 intolerant to sunitinib[4]
  - Exploratory baseline circulating tumor DNA (ctDNA) next-generation sequencing (NGS) analysis from INTRIGUE showed that patients harboring primary *KIT* exon 11 mutations and secondary resistance mutations exclusively in *KIT* exons 17/18 (KIT activation loop) derived greater clinical benefit from ripretinib vs sunitinib[5]; these results support further investigation in the phase 3 INSIGHT trial (NCT05734105)
  - Patients harboring primary *KIT* exon 11 mutations and secondary resistance mutations exclusively in *KIT* exons 13/14 (KIT ATP-binding pocket) derived greater clinical benefit from sunitinib vs ripretinib
- Outcomes in patients with advanced GIST who had no detectable ctDNA (ctDNA-ND) at baseline have not been thoroughly evaluated previously
  - In the VOYAGER trial, 14% of patients had ctDNA-ND in third-line GIST; however, outcomes were not explored for these patients[6]
- Here, we present exploratory data from patients in the phase 3 INTRIGUE trial[3] who had ctDNA-ND vs ctDNA detected (ctDNA-D) at baseline

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; **Figure 1**)[3]
- 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[7]
- DNA extraction was performed by Guardant Health, and samples were analyzed using Guardant360®, a 74-gene ctDNA NGS-based assay[4]
- ctDNA-D = sample successfully analyzed with ≥1 somatic alteration detected (single nucleotide variant [SNV] or insertion and deletion [INDEL])
- Data cutoff was September 1, 2021, for all data except overall survival (OS), which had a data cutoff of September 1, 2022

Figure 1. INTRIGUE study design

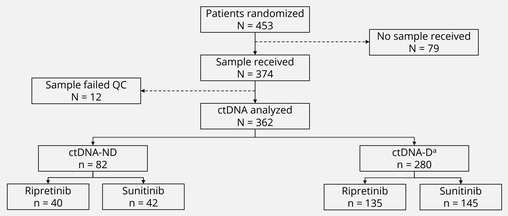


[a]As determined by local pathology report at randomization.
Data cutoff: September 1, 2021, for all data except OS (data cutoff: September 1, 2022).
ctDNA, circulating tumor DNA; GIST, gastrointestinal stromal tumor; IRR, independent radiologic review; mRECIST v1.1, modified response evaluation criteria in solid tumors version 1.1; ORR, objective response rate; OS, overall survival; PDGFRA, platelet-derived growth factor receptor α; PFS, progression-free survival; QD, once daily.

Results

- ctDNA was analyzed from 362/453 randomized patients (**Figure 2**)
- ctDNA was detected for 280/362 (77.3%) patients, whereas 82/362 (22.7%) patients did not have detectable ctDNA
  - Among patients with ctDNA-ND, 40 received ripretinib, while 42 received sunitinib
  - Among patients with ctDNA-D, 135 received ripretinib and 145 received sunitinib

Figure 2. ctDNA analysis and detection



[a]ctDNA-D only for SNV or INDEL; 2 patients had CNV-only mutations and were categorized as ctDNA-ND.
ctDNA-D is defined as sample successfully analyzed with at least 1 somatic alteration detected (SNV or INDEL).
CNV, copy number variant; ctDNA, circulating tumor DNA; ctDNA-D, ctDNA detected; ctDNA-ND, ctDNA not detected; INDEL, insertion and deletion; QC, quality control; SNV, single nucleotide variant.

- Patients with ctDNA-ND (82/362, 22.7%) were younger (median: 55.5 vs 62.0 years) and had smaller sums of longest diameters of target lesions (median [range]: 57.6 [11–459] vs 108.8 [15–418] mm) vs patients with ctDNA-D (280/362, 77.3%; **Table 1**)

Table 1. Patient demographics and baseline clinical characteristics

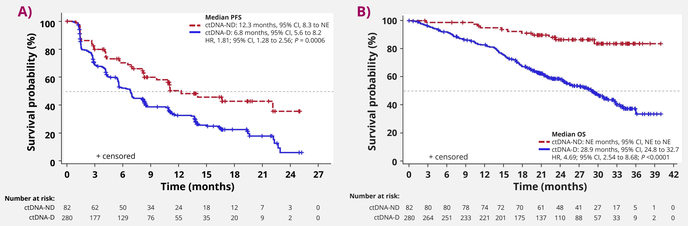
	ctDNA-ND			ctDNA-D		
	Ripretinib (n = 40)	Sunitinib (n = 42)	Total (N = 82)	Ripretinib (n = 135)	Sunitinib (n = 145)	Total (N = 280)
Sex, n (%)						
Female	13 (32.5)	18 (42.9)	31 (37.8)	49 (36.3)	53 (36.6)	102 (36.4)
Male	27 (67.5)	24 (57.1)	51 (62.2)	86 (63.7)	92 (63.4)	178 (63.6)
Age, years, median, (min, max)	52.5 (18, 80)	57.5 (39, 77)	55.5 (18, 80)	62.0 (25, 86)	63.0 (28, 88)	62.0 (25, 88)
Race, n (%)						
White	28 (70.0)	31 (73.8)	59 (72.0)	96 (71.1)	103 (71.0)	199 (71.1)
Asian	6 (15.0)	6 (14.3)	12 (14.6)	10 (7.4)	8 (5.5)	18 (6.4)
Black or African American	1 (2.5)	0	1 (1.2)	11 (8.1)	11 (7.6)	22 (7.9)
Native Hawaiian or Other Pacific Islander	0	0	0	2 (1.5)	1 (0.7)	3 (1.1)
American Indian or Alaska Native	0	0	0	0	1 (0.7)	1 (0.4)
Not reported/Other	5 (12.5)	5 (11.9)	10 (12.2)	16 (11.9)	21 (14.5)	37 (13.2)
Region, n (%)						
North America	17 (42.5)	11 (26.2)	28 (34.1)	63 (46.7)	56 (38.6)	119 (42.5)
Europe	16 (40.0)	22 (52.4)	38 (46.3)	60 (44.4)	73 (50.3)	133 (47.5)
Asia-Pacific	5 (12.5)	5 (11.9)	10 (12.2)	7 (5.2)	10 (6.9)	17 (6.1)
South America	2 (5.0)	4 (9.5)	6 (7.3)	5 (3.7)	6 (4.1)	11 (3.9)
ECOG PS at screening, n (%)						
0	25 (62.5)	33 (78.6)	58 (70.7)	84 (62.2)	74 (51.0)	158 (56.4)
1	14 (35.0)	9 (21.4)	23 (28.0)	50 (37.0)	70 (48.3)	120 (42.9)
2	1 (2.5)	0	1 (1.2)	1 (0.7)	1 (0.7)	2 (0.7)
Mutation type[a], n (%)						
KIT exon 9	6 (15.0)	5 (11.9)	11 (13.4)	20 (14.8)	19 (13.1)	39 (13.9)
KIT exon 11	26 (65.0)	31 (73.8)	57 (69.5)	98 (72.6)	104 (71.7)	202 (72.1)
KIT/*PDGFRA* WT	6 (15.0)	3 (7.1)	9 (11.0)	6 (4.4)	10 (6.9)	16 (5.7)
Other *KIT*[b]/*PDGFRA*	2 (5.0)	3 (7.1)	5 (6.1)	11 (8.1)	12 (8.3)	23 (8.2)
Sum of longest diameters of target lesions at baseline based on IRR						
Median, mm, (min, max)	73.2 (11, 459)	50.2 (15, 209)	57.6 (11, 459)	111.2 (15, 392)	106.0 (15, 418)	108.8 (15, 418)

Results are from the ctDNA analysis of all patients in the ITT population.
[a]As determined by local pathology report at randomization.
[b]Other *KIT* indicates a mutation in a *KIT* exon other than exon 9 or 11.
ctDNA, circulating tumor DNA; ctDNA-D, ctDNA detected; ctDNA-ND, ctDNA not detected; ECOG PS, Eastern Cooperative Oncology Group performance status; IRR, independent radiologic review; ITT, intention-to-treat; PDGFRA, platelet-derived growth factor receptor α; WT, wild-type.

Efficacy

- PFS and OS were longer in patients with ctDNA-ND vs ctDNA-D (**Figure 3**)

Figure 3. Kaplan-Meier analysis of PFS (A) and OS (B) for patients with ctDNA-ND vs ctDNA-D



PFS analysis was performed based on IRR using mRECIST v1.1 in the ITT population.
ctDNA-D is defined as sample successfully analyzed with at least 1 somatic alteration detected (SNV or INDEL).
Data cutoff for PFS: September 1, 2021. Data cutoff for OS: September 1, 2022.
CI, confidence interval; ctDNA, circulating tumor DNA; ctDNA-D, ctDNA detected; ctDNA-ND, ctDNA not detected; HR, hazard ratio; INDEL, insertion and deletion; IRR, independent radiologic review; ITT, intention-to-treat; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; NE, not estimable; OS, overall survival; PFS, progression-free survival; SNV, single nucleotide variant.

- Objective response rate was higher in patients with ctDNA-ND vs ctDNA-D (**Table 2**)

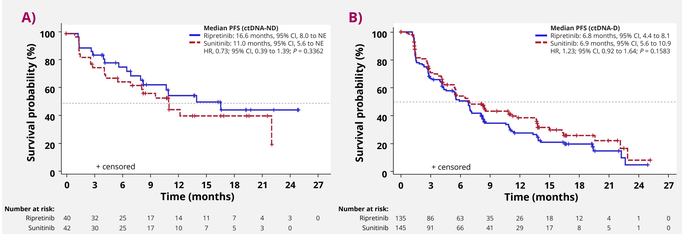
Table 2. ORR in patients with ctDNA-ND vs ctDNA-D

	ctDNA-ND (n = 82)	ctDNA-D (n = 280)	ctDNA-ND		ctDNA-D	
			Ripretinib (n = 40)	Sunitinib (n = 42)	Ripretinib (n = 135)	Sunitinib (n = 145)
ORR, n (%)	21 (25.6)	49 (17.5)	10 (25.0)	11 (26.2)	26 (19.3)	23 (15.9)
95% CI	(16.6 to 36.4)	(13.2 to 22.5)	(12.7 to 41.2)	(13.9 to 42.0)	(13.0 to 26.9)	(10.3 to 22.8)
Response difference, % (95% CI)		−8.1 (−19.2 to 1.4)		−1.2 (−19.6 to 17.5)		3.4 (−5.5 to 12.4)

Results are from the ctDNA analysis of all patients in the ITT population.
ctDNA-D is defined as sample successfully analyzed with at least 1 somatic alteration detected (SNV or INDEL).
Data cutoff: September 1, 2021.
CI, confidence interval; ctDNA, circulating tumor DNA; ctDNA-D, ctDNA detected; ctDNA-ND, ctDNA not detected; INDEL, insertion and deletion; ITT, intention-to-treat; ORR, objective response rate; SNV, single nucleotide variant.

- Median PFS was not different between treatment arms in patients with ctDNA-ND (**Figure 4**)
- OS was similar with ripretinib vs sunitinib in the ctDNA-ND group (not estimable for both ripretinib and sunitinib; HR 0.84; 95% CI, 0.25 to 2.75; nominal $P = 0.7674$) and in the ctDNA-D group (median 27.7 vs 29.5 months; HR 1.05; 95% CI, 0.75 to 1.47; nominal $P = 0.7609$; data not shown)

Figure 4. Kaplan-Meier analysis of PFS for patients treated with ripretinib or sunitinib in the ctDNA-ND (A) and ctDNA-D (B) populations

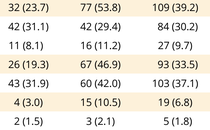


PFS analysis was performed based on IRR using mRECIST v1.1 in the ITT population.
ctDNA-D is defined as sample successfully analyzed with at least 1 somatic alteration detected (SNV or INDEL).
Data cutoff: September 1, 2021.
CI, confidence interval; ctDNA, circulating tumor DNA; ctDNA-D, ctDNA detected; ctDNA-ND, ctDNA not detected; HR, hazard ratio; INDEL, insertion and deletion; IRR, independent radiologic review; ITT, intention-to-treat; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; NE, not estimable; PFS, progression-free survival; SNV, single nucleotide variant.

- Patients in the ctDNA-ND group with a *KIT* exon 11 mutation, other *KIT*/*PDGFRA* mutation, or no *KIT*/*PDGFRA* mutation (*KIT*/*PDGFRA* wild-type) based on local pathology report at randomization, had numerically longer PFS with ripretinib vs sunitinib, whereas patients with a *KIT* exon 9 mutation had numerically longer PFS with sunitinib vs ripretinib in both the ctDNA-ND and ctDNA-D groups (**Figure 4**)

Figure 5. Forest plot of PFS by *KIT* mutational status as determined by local pathology report at randomization

	Ripretinib n (E)	Sunitinib n (E)	Median ripretinib (months)	Median sunitinib (months)	HR (95% CI)
ctDNA-ND	40 (17)	42 (22)	16.6	11.0	0.73 (0.39, 1.39)
KIT exon 11, other *KIT*/*PDGFRA*, *KIT*/*PDGFRA* WT[a]	34 (13)	37 (21)	NE	11.0	0.56 (0.28, 1.12)
KIT exon 9[a]	6 (4)	5 (1)	4.0	NE	4.34 (0.47, 40.09)
ctDNA-D	135 (101)	145 (87)	6.8	6.9	1.23 (0.92, 1.64)
KIT exon 11, other *KIT*/*PDGFRA*, *KIT*/*PDGFRA* WT[a]	115 (82)	126 (77)	6.8	6.3	1.06 (0.77, 1.44)
KIT exon 9[a]	20 (19)	19 (10)	5.5	13.8	2.96 (1.37, 6.41)



ctDNA-D is defined as sample successfully analyzed with at least 1 somatic alteration detected (SNV or INDEL).
[a]As determined by local pathology report at randomization.
CI, confidence interval; ctDNA, circulating tumor DNA; ctDNA-D, ctDNA detected; E, number of events; HR, hazard ratio; INDEL, insertion and deletion; IRT, interactive response technology; NE, not estimable; PDGFRA, platelet-derived growth factor receptor α; PFS, progression-free survival; SNV, single nucleotide variant; WT, wild-type.

Safety

- Safety was similar between ctDNA groups and consistent with the primary analysis (**Table 3**)
- Fewer patients had grade 3/4 TEAEs with ripretinib vs sunitinib in both groups (ctDNA-ND, 14 [35.0%] vs 29 [69.0%]; ctDNA-D, 56 [41.5%] vs 94 [65.7%]; **Table 3**)
- In general, dose interruptions, dose reductions, and treatment discontinuations due to TEAEs were lower with ripretinib vs sunitinib; however, there were more treatment discontinuations due to TEAEs with ripretinib vs sunitinib in the ctDNA-ND group (**Table 3**)

Table 3. TEAE summary for patients with ctDNA-ND and ctDNA-D

	ctDNA-ND			ctDNA-D		
	Ripretinib (n = 40)	Sunitinib (n = 42)	Total (N = 82)	Ripretinib (n = 135)	Sunitinib (n = 143)	Total (N = 278)
Number of patients, n (%)						
Any TEAE	40 (100.0)	41 (97.6)	81 (98.8)	134 (99.3)	143 (100.0)	277 (99.6)
Any grade 3/4 TEAE	14 (35.0)	29 (69.0)	43 (52.4)	56 (41.5)	94 (65.7)	150 (54.0)
Any drug-related TEAE	39 (97.5)	40 (95.2)	79 (96.3)	126 (93.3)	141 (98.6)	267 (96.0)
Any grade 3/4 drug-related TEAE	10 (25.0)	25 (59.5)	35 (42.7)	32 (23.7)	77 (53.8)	109 (39.2)
Any treatment-emergent SAE	6 (15.0)	6 (14.3)	12 (14.6)	42 (31.1)	42 (29.4)	84 (30.2)
Any drug-related treatment-emergent SAE	3 (7.5)	2 (4.8)	5 (6.1)	11 (8.1)	16 (11.2)	27 (9.7)
Any TEAE leading to dose reduction	9 (22.5)	20 (47.6)	29 (35.4)	26 (19.3)	67 (46.9)	93 (33.5)
Any TEAE leading to dose interruption	10 (25.0)	20 (47.6)	30 (36.6)	43 (31.9)	60 (42.0)	103 (37.1)
Any TEAE leading to treatment discontinuation	3 (7.5)	2 (4.8)	5 (6.1)	4 (3.0)	15 (10.5)	19 (6.8)
Any TEAE leading to death	1 (2.5)	0	1 (1.2)	2 (1.5)	3 (2.1)	5 (1.8)
Any drug-related TEAE leading to death	0	0	0	0	1 (0.7)	1 (0.4)

The analysis was performed on the safety population.
ctDNA-D is defined as sample successfully analyzed with at least 1 somatic alteration detected (SNV or INDEL).
Data cutoff: September 1, 2021.
ctDNA, circulating tumor DNA; ctDNA-D, ctDNA detected; ctDNA-ND, ctDNA not detected; INDEL, insertion and deletion; SAE, serious adverse event; SNV, single nucleotide variant; TEAE, treatment-emergent adverse event.

CONCLUSIONS

- Patients with ctDNA-ND in both treatment arms had better efficacy outcomes vs patients with ctDNA-D
- Patients with ctDNA-ND were younger and had smaller sums of longest diameters of target lesions vs patients with ctDNA-D
- Median PFS was not different between treatment arms in patients with ctDNA-ND, suggesting ctDNA-ND was not a predictor of response for either ripretinib or sunitinib
- Although little is known about the biology determining the shedding of ctDNA in GIST, these data warrant further investigation of ctDNA-ND as both a predictive and prognostic marker

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

Study sponsor

This study is sponsored by Deciphera Pharmaceuticals, LLC, Waltham, MA, USA.

Acknowledgments

The authors thank the patients and their families and caregivers, the investigators, and the investigational site staff of the INTRIGUE study. Medical writing support was provided by Marita Chakhtoura, MS, PhD, of AlphaBioCom, a Red Nucleus company, and was funded by Deciphera Pharmaceuticals, LLC.

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