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

Abstract: #748

John R. Zalcberg[1], Robin L. Jones[2], Jean-Yves Blay[3], Suzanne George[4], Hans Gelderblom[5], Patrick Schöffski[6], Margaret von Mehren[7], Yoon-Koo Kang[8], Albiruni Abdul Razak[9], Jonathan Trent[10], Steven Attia[11], Axel Le Cesne[12], Erika Davis[13], Haroun Achour[13], Matthew L. Sherman[13], Rodrigo Ruiz-Soto[13], Sebastian Bauer[14,15], Michael C. Heinrich[16,17] on behalf of the INTRIGUE study investigators

[1]Monash University School of Public Health and Preventive Medicine and Department of Medical Oncology, Alfred Health, Melbourne, Victoria, Australia; [2]Sarcoma Unit, The Royal Marsden NHS Foundation Trust and Institute of Cancer Research, London, UK; [3]Centre Léon Bérard, Lyon, France; [4]Dana-Farber Cancer Institute, Boston, MA, USA; [5]Leiden University Medical Center, Leiden, Netherlands; [6]University Hospitals Leuven, Department of General Medical Oncology, Leuven Cancer Institute, KU Leuven, Leuven, Belgium; [7]Fox Chase Cancer Center, Philadelphia, PA, USA; [8]Asan Medical Center, University of Ulsan, Seoul, Korea; [9]Toronto Sarcoma Program, Princess Margaret Cancer Center, Toronto, ON, Canada; [10]Sylvester Comprehensive Cancer Center, University of Miami Health System, Miami, FL, USA; [11]Mayo Clinic, Jacksonville, FL, USA; [12]Gustave Roussy, Villejuif, France; [13]Deciphera Pharmaceuticals, LLC, Waltham, MA, USA; [14]Department of Medical Oncology and Sarcoma Center/West German Cancer Center, University Hospital Essen, University Duisburg-Essen, Essen, Germany; [15]German Cancer Consortium (DKTK), Partner Site University Hospital Essen, Essen, Germany; [16]Portland VA Health Care System, Portland, OR, USA; [17]OHSU Knight Cancer Institute, Portland, OR, USA

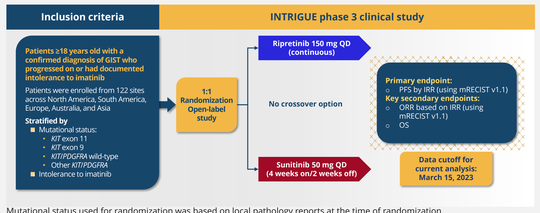
Introduction

- 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 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]
- In the INTRIGUE trial, the primary endpoint of superior progression-free survival (PFS) with ripretinib over sunitinib was not met[1]
  - In the *KIT* exon 11 intention-to-treat (ITT) population (n = 327), ripretinib demonstrated a median PFS of 8.3 months compared with 7.0 months for sunitinib (hazard ratio [HR], 0.88; *P* = 0.36)
  - In the all-patient (AP) ITT population (N = 453), the median PFS with ripretinib was 8.0 months compared with 8.3 months for sunitinib (HR, 1.05; nominal *P* = 0.72)
- At the time of primary analysis of PFS in the INTRIGUE trial, the first interim analysis (IA) for overall survival (OS) was conducted
  - The OS event rates for both the AP ITT and *KIT* exon 11 ITT populations were immature (22.3% and 21.1%, respectively), and the median OS was not reached in either arm for either population[1]
- In the second IA of OS, the event rate was 41% in both ITT populations, with no significant differences in OS between treatment arms[5]
- 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[6]
- Here, we present the final OS analysis and updated safety profile, as well as exploratory PFS on next line of therapy from the INTRIGUE trial

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]; the final OS analysis was prespecified to occur when ≥200 OS events were observed with ≥145 of those events coming from the *KIT* exon 11 population
- Evaluation of PFS on next line of therapy (third-line therapy) was an exploratory objective and was analyzed based on local investigator assessment
- The data cutoff for these analyses was March 15, 2023

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

- Of the 453 patients who were randomized, 444 received treatment (**Table 1**)
- Overall, 40 of 444 treated patients (9.0%; AP ITT population) remained on treatment at the time of data cutoff: 28/223 (12.6%) on ripretinib and 12/221 (5.4%) on sunitinib
- The most common reasons for treatment discontinuation in the AP ITT population were progressive disease (PD) as determined by independent radiologic review (IRR; 56.1%), PD assessed by investigator (10.8%), clinical PD (6.1%), withdrawal of consent (5.6%), and adverse events (AEs; 4.7%)
  - Fewer patients discontinued treatment due to an AE for ripretinib vs sunitinib (3.1% vs 6.3%)

Table 1. Patient disposition

AP ITT population Number of patients, n (%)	Ripretinib n = 226	Sunitinib n = 227	Total N = 453
Not treated[a]	3 (1.3)	6 (2.6)	9 (2.0)
Treated[a]	223 (98.7)	221 (97.4)	444 (98.0)
Ongoing treatment[b]	28 (12.6)	12 (5.4)	40 (9.0)
Discontinued treatment[b]	195 (87.4)	209 (94.6)	404 (91.0)
Primary reason for treatment discontinuation[b]			
PD by IRR	136 (61.0)	113 (51.1)	249 (56.1)
PD by investigator assessment	18 (8.1)	30 (13.6)	48 (10.8)
Clinical progression	12 (5.4)	15 (6.8)	27 (6.1)
Withdrawal of consent	11 (4.9)	14 (6.3)	25 (5.6)
AE	7 (3.1)	14 (6.3)	21 (4.7)
Death	4 (1.8)	5 (2.3)	9 (2.0)
Other[c]	7 (3.1)	18 (8.1)	25 (5.6)
Ongoing treatment study[a]	99 (43.8)	90 (39.6)	189 (41.7)

Data cutoff: March 15, 2023.
[a]Percentage is based on the number of patients in the ITT population.
[b]Percentage is based on the number of treated patients.
[c]Other reasons for treatment discontinuation included lost to follow-up, noncompliance with study drug, physician decision, and other not specified.
AE, adverse event; AP, all patient; IRR, independent radiologic review; ITT, intention-to-treat; PD, progressive disease.

- Following study treatment discontinuation, the most common third-line therapy was sunitinib for patients in the ripretinib arm (n = 135, 59.7%) and regorafenib for patients in the sunitinib arm (n = 97, 42.7%; **Table 2**)

Table 2. Third-line therapies for patients in the AP ITT population

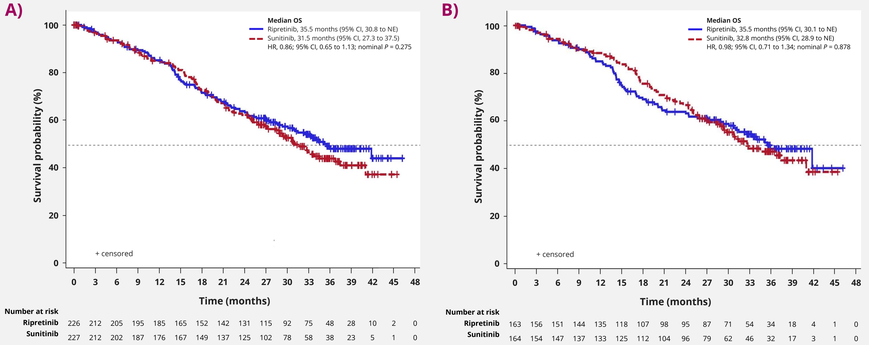
Therapy	Ripretinib n = 226	Sunitinib n = 227
Patients who received third-line therapy, n (%)	158 (69.9)	142 (62.6)
Sunitinib	135 (59.7)	0
Imatinib	9 (4.0)	10 (4.4)
Regorafenib	7 (3.1)	97 (42.7)
Avapritinib	4 (1.8)	3 (1.3)
Imatinib mesylate	1 (0.4)	0
Imatinib + selinexor	1 (0.4)	0
Selumetinib	1 (0.4)	0
Ripretinib	0	20 (8.8)
Investigational drugs[a]	0	3 (1.3)
Avelumab + regorafenib	0	2 (0.9)
Lenvatinib	0	2 (0.9)
Regorafenib + sirolimus	0	1 (0.4)
Repaglinide + ripretinib	0	1 (0.4)
Sorafenib	0	1 (0.4)
Temozolomide	0	1 (0.4)
Trametinib	0	1 (0.4)

[a]Includes investigational drugs alone, investigational drugs + unknown, and investigational antineoplastic drugs.
AP, all patient; ITT, intention-to-treat.

Efficacy

- There were 211 OS events (46.6%) in the AP ITT population; median duration of follow-up in the ripretinib and sunitinib arms were 35.1 (95% confidence interval [CI], 33.3 to 36.5) and 34.1 months (95% CI, 32.1 to 35.6), respectively
- OS was similar with ripretinib vs sunitinib in the AP ITT (median, 35.5 vs 31.5 months; HR, 0.86; 95% CI, 0.65 to 1.13; nominal *P* = 0.275; **Figure 2A**) and *KIT* exon 11 ITT populations (median, 35.5 vs 32.8 months; HR, 0.98; 95% CI, 0.71 to 1.34; nominal *P* = 0.878; **Figure 2B**)

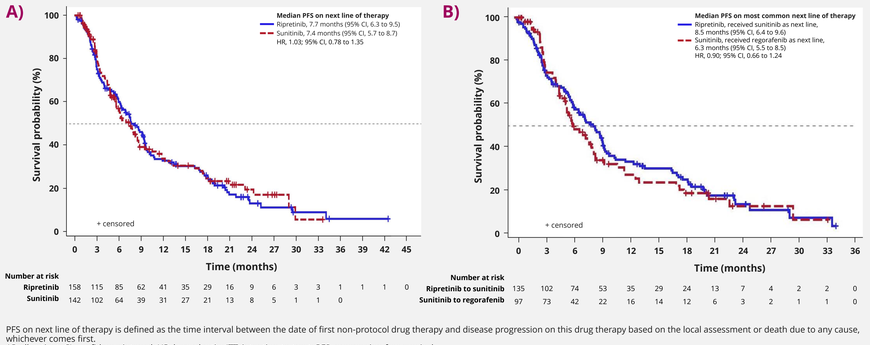
Figure 2. Final OS in the (A) AP ITT and (B) *KIT* exon 11 ITT populations



AP, all patient; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; NE, not estimable; OS, overall survival.

- PFS on next line of therapy by randomized treatment assignment was similar for ripretinib vs sunitinib in the AP ITT population (median, 7.7 vs 7.4 months; HR, 1.03; 95% CI, 0.78 to 1.35; **Figure 3A**)
- Patients in the ripretinib arm who received third-line sunitinib (59.7%) had a median PFS on next line of therapy of 8.5 months compared with 6.3 months for patients in the sunitinib arm who received third-line regorafenib (42.7%; HR, 0.90; 95% CI, 0.66 to 1.24; **Figure 3B**)

Figure 3. PFS on next line of therapy by randomized treatment assignment for patients in the AP ITT population who received (A) any third-line treatment and (B) the most common third-line treatment



PFS on next line of therapy is defined as the time interval between the date of first non-protocol drug therapy and disease progression on this drug therapy based on the local assessment or death due to any cause, whichever comes first.
AP, all patient; CI, confidence interval; HR, hazard ratio; ITT, intention-to-treat; PFS, progression-free survival.

Safety

- The long-term safety profile was consistent with the primary analysis (**Table 3**)
  - Fewer patients had grade 3/4 TEAEs with ripretinib vs sunitinib (96 [43.0%] vs 149 [67.4%])
  - Dose interruptions and reductions as well as treatment discontinuations due to TEAEs were lower with ripretinib vs sunitinib
- The most common TEAEs in the ripretinib arm were alopecia, fatigue, and myalgia
  - The most common TEAEs in patients treated with sunitinib were palmar-plantar erythrodysesthesia syndrome, diarrhea, and hypertension (**Table 4**)
- The median (range) treatment duration was 7.9 (0.2–43.3) months for ripretinib and 6.5 (0.2–44.7) months for sunitinib

Table 3. TEAE summary in the safety population

Patients with	Ripretinib n = 223	Sunitinib n = 221	Total N = 444
Any TEAE[a]	221 (99.1)	219 (99.1)	440 (99.1)
Any grade 3/4 TEAE	96 (43.0)	149 (67.4)	245 (55.2)
Any drug-related TEAE[b]	211 (94.6)	214 (96.8)	425 (95.7)
Any grade 3/4 drug-related TEAE	61 (27.4)	128 (57.9)	189 (42.6)
Any treatment-emergent SAE	64 (28.7)	61 (27.6)	125 (28.2)
Any drug-related treatment-emergent SAE	19 (8.5)	22 (10.0)	41 (9.2)
Any TEAE leading to dose reduction	45 (20.2)	107 (48.4)	152 (34.2)
Any TEAE leading to dose interruption	70 (31.4)	95 (43.0)	165 (37.2)
Any TEAE leading to study treatment discontinuation	11 (4.9)	20 (9.0)	31 (7.0)
Any TEAE leading to death	6 (2.7)	8 (3.6)	14 (3.2)
Any drug-related TEAE leading to death	0	1 (0.5)	1 (0.2)

Data are shown as n (%).
[a]TEAEs are defined as any AE that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug or the day before the start of subsequent new anticancer drug therapy, whichever occurs first. Drug-related AEs reported ≥30 days after the last dose of study drug are also considered TEAEs.
[b]Drug-related TEAEs are defined as those related or possibly related to study drug as assessed by the investigator. Any AE with missing relationship to study drug will be counted as related to study drug.
AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE.

Table 4. TEAEs occurring in ≥20% of patients in either arm

Preferred term, n (%)	Ripretinib n = 223		Sunitinib n = 221	
	All grade	Grade 3/4	All grade	Grade 3/4
Alopecia	144 (64.6)	0	18 (8.1)	0
Fatigue	85 (38.1)	7 (3.1)	91 (41.2)	4 (1.8)
Myalgia	81 (36.3)	4 (1.8)	26 (11.8)	1 (0.5)
Constipation	80 (35.9)	1 (0.4)	50 (22.6)	0
Abdominal pain	62 (27.8)	8 (3.6)	40 (18.1)	7 (3.2)
Palmar-plantar erythrodysesthesia syndrome	62 (27.8)	3 (1.3)	116 (52.5)	22 (10.0)
Hypertension	61 (27.4)	20 (9.0)	106 (48.0)	59 (26.7)
Decreased appetite	60 (26.9)	2 (0.9)	54 (24.4)	2 (0.9)
Muscle spasms	60 (26.9)	1 (0.4)	15 (6.8)	0
Nausea	54 (24.2)	3 (1.3)	57 (25.8)	1 (0.5)
Pruritus	49 (22.0)	1 (0.4)	16 (7.2)	0
Diarrhea	47 (21.1)	3 (1.3)	107 (48.4)	8 (3.6)
Stomatitis	19 (8.5)	0	82 (37.1)	6 (2.7)

AEs are coded using MedDRA version 24.0.
TEAEs are defined as any AE that occurs after administration of the first dose of study drug and through 30 days after the last dose of study drug or the day before the start of subsequent new anticancer drug therapy, whichever occurs first. Drug-related AEs reported ≥30 days after the last dose of study drug are also considered TEAEs.
Patients are counted once for each preferred term.
AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent AE.

CONCLUSIONS

- With 18 months of additional follow-up from the primary analysis, OS was similar between treatment arms in both the AP ITT and *KIT* exon 11 ITT populations
- PFS on next line of therapy was comparable between treatment arms, suggesting that third-line treatment efficacy was not adversely affected by receiving ripretinib in the second-line setting
- Safety remained consistent with the primary analysis; ripretinib demonstrated a favorable safety profile compared with sunitinib for patients with advanced GIST previously treated with imatinib

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Study Sponsor

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