ASCO Plenary Series

INTRIGUE: A phase III, randomized, open-label study to evaluate the efficacy and safety of ripretinib vs sunitinib in patients with advanced gastrointestinal stromal tumor previously treated with imatinib

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January Program
Tuesday, January 25, 2022

Background

- GIST is the most common sarcoma of the gastrointestinal tract[1]
- The majority of GIST cases have activating mutations in *KIT* (70%–85%) or *PDGFRA* (5%–10%) that drive tumor growth[2,3]
- Imatinib, a KIT/PDGFRA TKI, induces objective responses or stable disease in most cases of advanced GIST with a median PFS of 18–20 months[4]
- However, over time, most imatinib-treated patients will experience tumor progression due to development of secondary kinase domain mutations[5–7]

ATP, adenosine triphosphate; GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

1) Rubin S, et al. *Lancet*. 2007;369:1731–41. 2) Szucs Z, et al. *Future Oncol*. 2017;13:93–107. 3) Corless CL et al. *J Clin Oncol*. 2004;22:3813–25. 4) Blanke CD, et al. *J Clin Oncol*. 2008;26:626–32. 5) Antonescu CR, et al. *Clin Cancer Res*. 2005;11:4182–90. 6) Heinrich MC, et al. *J Clin Oncol*. 2008;26:5352–59. 7) Kelly CM, et al. *J Hematol Oncol*. 2021;14:2–12.

Background

- Sunitinib is a multitargeted TKI that inhibits KIT, PDGFRA, and VEGFRs and is approved for advanced GIST after the failure of imatinib (median PFS 5.6 months)[1,2]
- Ripretinib, a broad-spectrum KIT and PDGFRA switch-control TKI, has superior in vitro activity to sunitinib against imatinib-resistant secondary *KIT* mutations[3]
- Ripretinib is indicated for the treatment of adult patients with advanced GIST who have received prior treatment with 3 or more TKIs, including imatinib[4]
- In a phase I study, the median PFS for ripretinib as a second-line therapy was 10.7 months[5]
- We hypothesized that ripretinib would be superior to sunitinib for the treatment of patients with advanced GIST who were previously treated with imatinib

GIST, gastrointestinal stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

1) Demetri GD, et al. *Lancet*. 2006;368:1329–38. 2) Pfizer Laboratories. Sutent Prescribing Information. https://labeling.pfizer.com/ShowLabeling.aspx?id=607. Last Revised: August 2021. 3) Smith BD, et al. *Cancer Cell*. 2019;35:738–51. 4) Deciphera Pharmaceuticals. Qinlock Prescribing Information. https://www.qinlockhcp.com/Content/files/qinlock-prescribing-information.pdf. Last Revised: June 2021. 5) Janku F, et al. *J Clin Oncol*. 2020;38:3294–303.

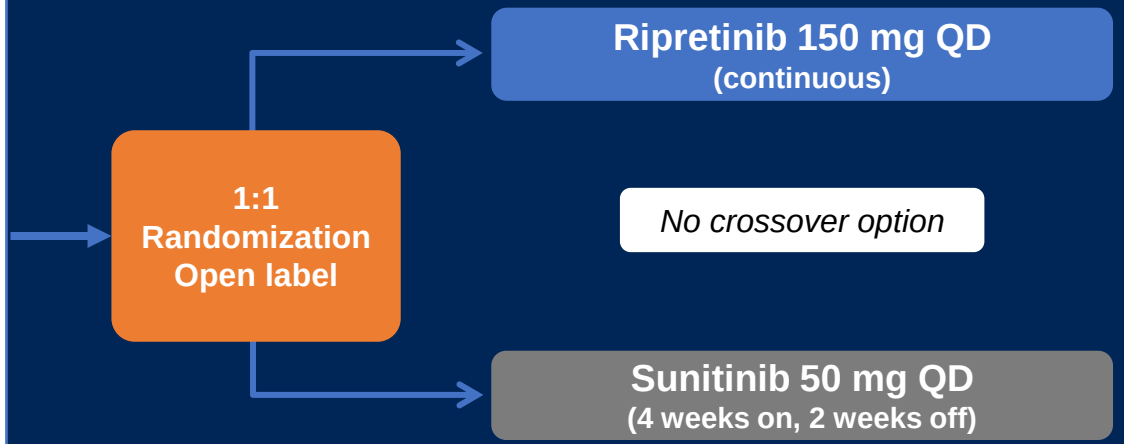
Methods

Patients ≥18 years old with a confirmed diagnosis of GIST who progressed on or had documented intolerance to imatinib

Patients were enrolled from 122 sites across North America, South America, Europe, Australia, and Asia

Stratified by

- Mutational status:
  - *KIT* exon 11
  - *KIT* exon 9
  - *KIT*/*PDGFRA* WT
  - Other *KIT*/*PDGFRA*
- Intolerance to imatinib



Primary endpoint:
PFS by IRR (using mRECIST v 1.1) in the *KIT* exon 11 ITT and AP ITT populations

Key secondary endpoints:
ORR by IRR and OS in the *KIT* exon 11 ITT and AP ITT populations

Other secondary endpoints:
TTR, QoL (EORTC QLQ-C30 and DLQI), DCR, safety

Data cutoff: September 1, 2021

- A hierarchical testing sequence was performed for primary and key secondary endpoints; statistical testing of patients with a *KIT* exon 11 primary mutation preceded the AP population
- The estimated 426-patient sample size was based on the assumption that the median PFS would be 9 months for ripretinib and 6 months for sunitinib according to previous studies[1,2]

AP, all-patient; DCR, disease control rate; DLQI, Dermatology Life Quality Index; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of life questionnaire for cancer-30 item; GIST, gastrointestinal stromal tumor; IRR, independent radiologic review; ITT, intention-to-treat; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; QD, once daily; QoL, quality of life; TTR, time to response; WT, wild-type.

1) Demetri GD, et al. *Lancet*. 2006;368:1329–38. 2) Janku F, et al. *J Clin Oncol*. 2020;38:3294–303.

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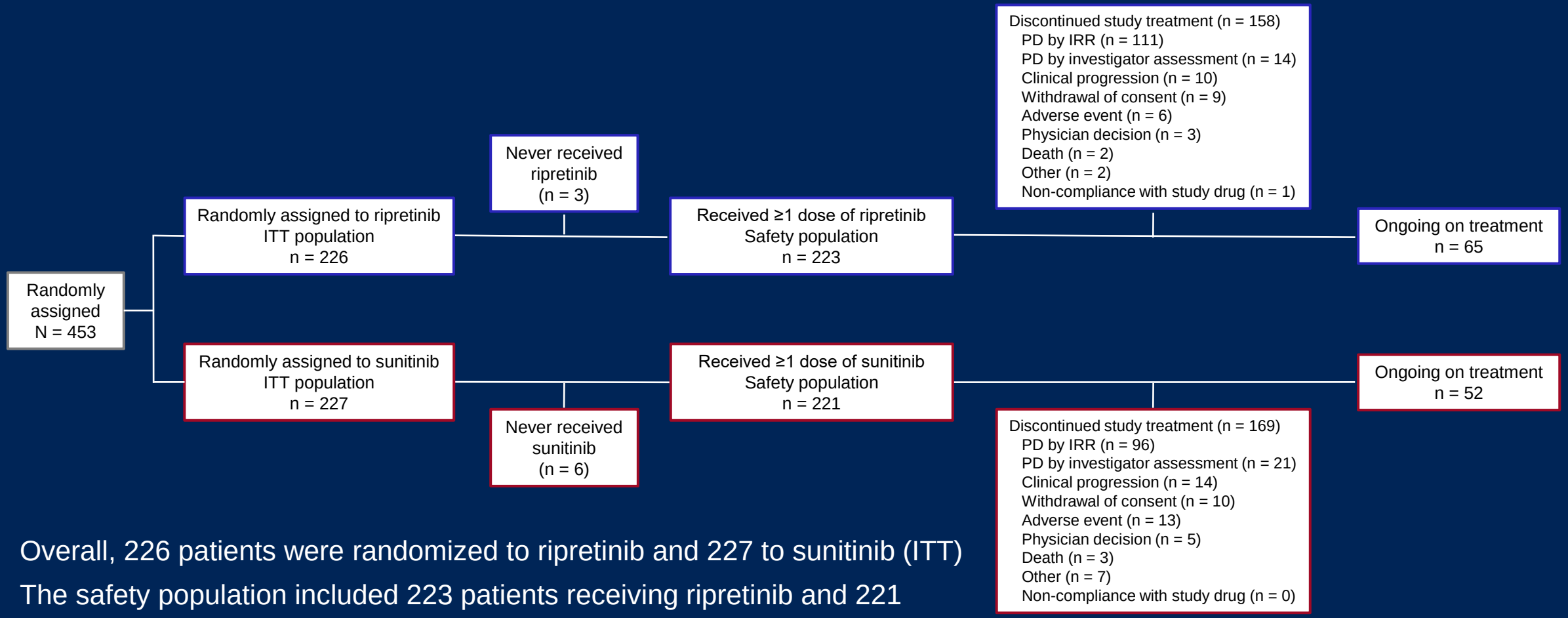
Patient disposition



- Overall, 226 patients were randomized to ripretinib and 227 to sunitinib (ITT)
- The safety population included 223 patients receiving ripretinib and 221 patients receiving sunitinib

IRR, independent radiologic review; ITT, intention-to-treat; PD, progressive disease.

Patient demographics and clinical characteristics

	Ripretinib (n = 226)	Sunitinib (n = 227)	Total (N = 453)
Age, median (min, max)	59.5 (18, 86)	60 (26, 88)	60 (18, 88)
Sex, male, n (%)	139 (61.5)	142 (62.6)	281 (62.0)
Race, white, n (%)	148 (65.5)	152 (67.0)	300 (66.2)
Region, n (%)			
North America	87 (38.5)	76 (33.5)	163 (36.0)
South America	7 (3.1)	11 (4.8)	18 (4.0)
Europe	102 (45.1)	110 (48.5)	212 (46.8)
Asia-Pacific	30 (13.3)	30 (13.2)	60 (13.2)
ECOG, n (%)			
ECOG PS 0	131 (58.0)	128 (56.4)	259 (57.2)
ECOG PS 1	92 (40.7)	98 (43.2)	190 (41.9)
ECOG PS 2	3 (1.3)	1 (0.4)	4 (0.9)
Mutation, n (%)			
KIT Exon 11	163 (72.1)	164 (72.2)	327 (72.2)
KIT Exon 9	31 (13.7)	29 (12.8)	60 (13.2)
KIT/*PDGFRA* WT	15 (6.6)	18 (7.9)	33 (7.3)
Other *KIT*/*PDGFRA*[a]	17 (7.5)	16 (7.0)	33 (7.3)
Imatinib intolerance, n (%)	22 (9.7)	23 (10.1)	45 (9.9)
Sum of longest diameters of target lesions (mm), median (min, max)	93.1 (11, 459)	84.1 (15, 418)	90.5 (11, 459)

- There were 163 patients in the ripretinib arm and 164 in the sunitinib arm with a primary *KIT* exon 11 mutation (*KIT* exon 11 ITT population)
- Demographics and characteristics were well balanced between arms

[a]Other *KIT* included any patient with a *KIT* mutation other than exon 9 or exon 11.
ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; PDGFRA, platelet-derived growth factor receptor alpha; PS, performance score; WT, wild-type.

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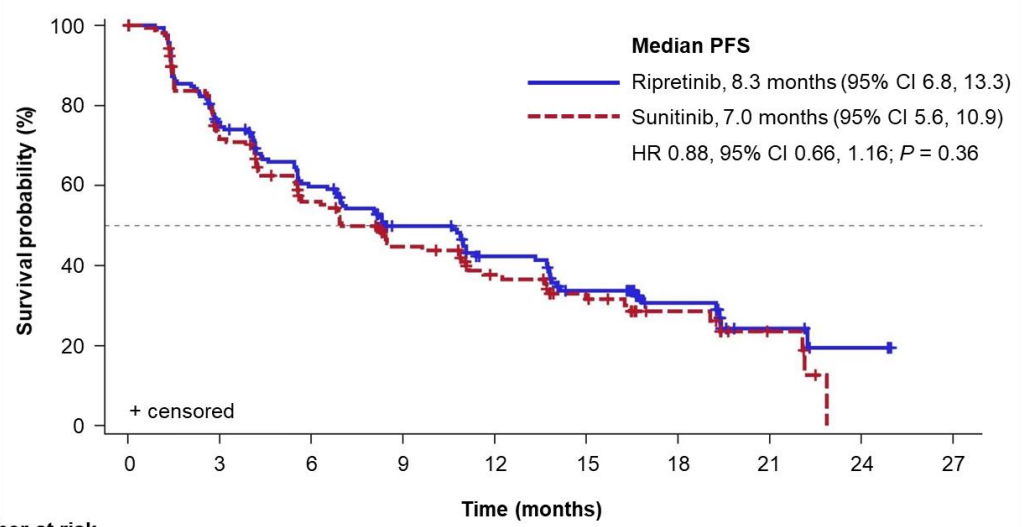
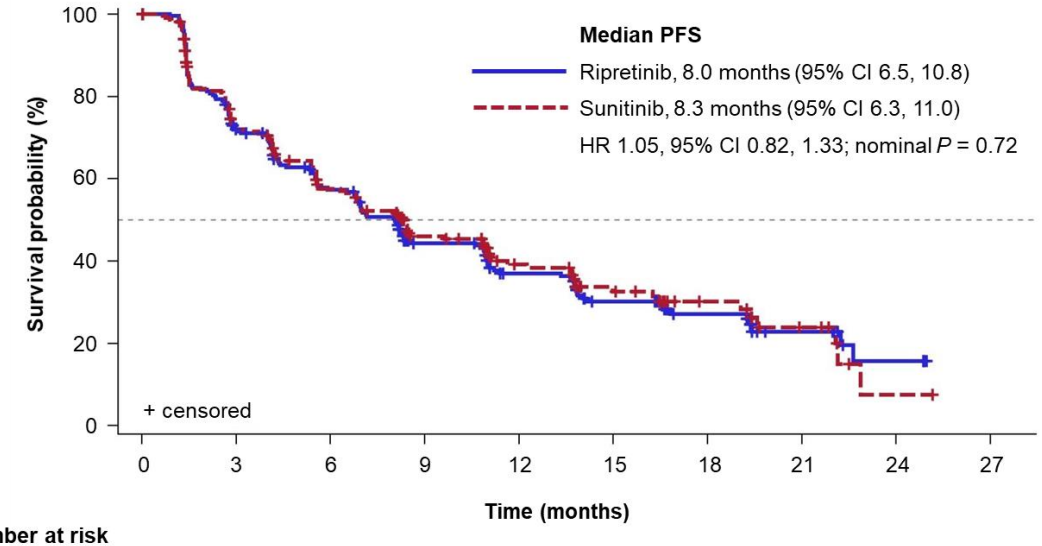
Kaplan-Meier analysis of PFS by IRR

KIT exon 11 ITT



Number at risk										
Ripretinib	163	115	88	61	46	31	18	6	3	0
Sunitinib	164	104	75	50	33	23	12	5	0	0

AP ITT



Number at risk										
Ripretinib	226	152	115	75	56	39	23	10	4	0
Sunitinib	227	143	108	68	45	29	16	8	1	0

- Ripretinib did not meet the primary endpoint of superiority in PFS over sunitinib
- However, the median PFS observed with ripretinib was comparable to the median PFS observed with sunitinib in the exon 11 ITT population (8.3 months vs 7.0 months) and AP ITT population (8.0 months vs 8.3 months)

AP, all patients; CI, confidence interval; HR, hazard ratio; IRR, independent radiologic review; ITT, intention-to-treat; PFS, progression-free survival.

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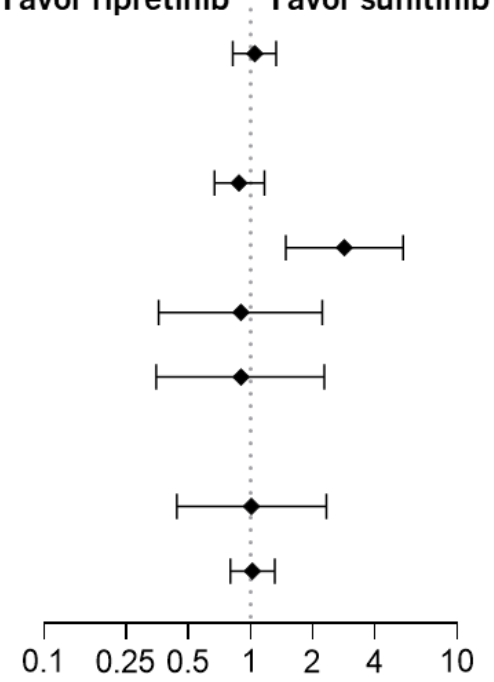
PFS by IRR according to stratification subgroups

	Ripretinib n (events)	Sunitinib n (events)	Median ripretinib (months)	Median sunitinib (months)	Hazard ratio (95% CI)
Overall	226 (146)	227 (130)	8.0	8.3	1.05 (0.82, 1.33)
Mutation type					
KIT exon 11	163 (100)	164 (98)	8.3	7.0	0.88 (0.67, 1.17)
KIT exon 9	31 (27)	29 (14)	5.5	13.8	2.85 (1.48, 5.48)
KIT/PDGFRA WT	15 (9)	18 (10)	7.0	4.1	0.90 (0.36, 2.23)
Other *KIT/PDGFRA*	17 (10)	16 (8)	6.8	8.4	0.90 (0.35, 2.28)
Imatinib intolerance					
Yes	22 (14)	23 (10)	13.7	10.9	1.01 (0.44, 2.33)
No	204 (132)	204 (120)	7.1	8.1	1.02 (0.80, 1.31)



- Subgroup analyses of PFS based on stratification factors (*KIT/PDGFRA* mutation type and imatinib intolerance) revealed that PFS benefit for patients with primary *KIT* exon 9 mutations favored treatment with sunitinib vs ripretinib

CI, confidence interval; IRR, independent radiologic review; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; WT, wild-type.

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ORR and duration of response by IRR

	KIT exon 11 ITT population		AP ITT population	
	Ripretinib (n = 163)	**Sunitinib (n = 164)**	**Ripretinib (n = 226)**	**Sunitinib (n = 227)**
Objective response rate, n (%) [95% CI]	39 (23.9) [17.6, 31.2]	24 (14.6) [9.6, 21.0]	49 (21.7) [16.5, 27.6]	40 (17.6) [12.9, 23.2]
Complete response,[a] n (%)	0	2 (1.2)	1 (0.4)	3 (1.3)
Partial response,[a] n (%)	39 (23.9)	22 (13.4)	48 (21.2)	37 (16.3)
Difference in objective response rate, % [95% CI]	9.3 [0.7, 17.8]		4.2 [−3.2, 11.5]	
***P*-value,[b] n (%)**	**0.03**		0.27	
Duration of response, median, months [95% CI]	16.7 [12.5, NE]	20.1 [11.0, NE]	16.7 [12.5, NE]	20.1 [12.3, NE]

- The ORR in the *KIT* exon 11 ITT population was higher with ripretinib vs sunitinib (nominal *P* = 0.03)
- The ORR in the all-patient ITT population was similar between treatment arms (nominal *P* = 0.27)
- Median duration of response for both populations was 16.7 months for patients randomized to ripretinib and 20.1 months for patients randomized to sunitinib

[a]Confirmed complete and partial responses.
[b]*P*-values reported are nominal and no statistical significance can be claimed.
AP, all patients; CI, confidence interval; IRR, independent radiologic review; ITT, intention-to-treat; NE, not estimable; ORR, objective response rate.

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Dose modifications

	Ripretinib (n = 223)	Sunitinib (n = 221)
Treatment duration, months		
Mean (SD)	9.1 (6.65)	8.1 (6.28)
Median (range)	7.9 (0.20, 26.45)	6.5 (0.20, 26.32)
Any dose modification, n (%)	85 (38.1)	140 (63.3)
Any dose reduction	44 (19.7)	111 (50.2)
Any dose interruption	62 (27.8)	84 (38.0)
Sunitinib dose regimen modification,[a] n (%)		
No	N/A	174 (78.7)
Yes	N/A	47 (21.3)
Continuous dosing	N/A	33 (14.9)
Other	N/A	19 (8.6)

- Fewer patients who received ripretinib underwent any dose modification compared with those who received sunitinib

[a]Modification from the standard 4 weeks on/2 weeks off schedule.
N/A, not applicable; SD, standard deviation.

TEAE summary

TEAE summary, n (%)	Ripretinib (n = 223)	Sunitinib (n = 221)
Any TEAE	221 (99.1)	219 (99.1)
Any Grade 3/4 TEAE	92 (41.3)	145 (65.6)
Any drug-related TEAE	211 (94.6)	214 (96.8)
Any Grade 3/4 drug-related TEAE	59 (26.5)	122 (55.2)
Any treatment-emergent SAE	57 (25.6)	57 (25.8)
Any drug-related treatment-emergent SAE	17 (7.6)	20 (9.0)
Any TEAE leading to dose reduction	45 (20.2)	106 (48.0)
Any TEAE leading to dose interruption	65 (29.1)	92 (41.6)
Any TEAE leading to study treatment discontinuation	8 (3.6)	17 (7.7)
Any TEAE leading to death	4 (1.8)	5 (2.3)
Any drug-related TEAE leading to death	0	1 (0.5)

- There were fewer Grade 3/4 TEAEs in the ripretinib arm compared with the sunitinib arm (nominal *P* <0.0001)
- Similarly, there were fewer Grade 3/4 drug-related TEAEs with ripretinib compared with sunitinib
- Rates of dose interruptions, dose reductions, and treatment discontinuations due to TEAEs were all lower with ripretinib vs sunitinib
- The incidence of treatment-emergent SAEs was similar between arms

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

TEAEs of ≥20% in either treatment arm

Preferred term, n (%)	Ripretinib (n = 223) All Grades	Ripretinib (n = 223) Grade 3/4	Sunitinib (n = 221) All Grades	Sunitinib (n = 221) Grade 3/4
Alopecia	143 (64.1)	N/A	18 (8.1)	N/A
Fatigue	84 (37.7)	7 (3.1)	91 (41.2)	4 (1.8)
Myalgia	81 (36.3)	4 (1.8)	24 (10.9)	0
Constipation	78 (35.0)	1 (0.4)	48 (21.7)	0
Decreased appetite	60 (26.9)	2 (0.9)	54 (24.4)	2 (0.9)
Hypertension	59 (26.5)	19 (8.5)	104 (47.1)	59 (26.7)
Palmar-plantar erythrodysesthesia	59 (26.5)	3 (1.3)	113 (51.1)	22 (10.0)
Abdominal pain	58 (26.0)	6 (2.7)	38 (17.2)	6 (2.7)
Muscle spasms	55 (24.7)	1 (0.4)	12 (5.4)	0
Nausea	53 (23.8)	2 (0.9)	56 (25.3)	1 (0.5)
Pruritus	48 (21.5)	1 (0.4)	16 (7.2)	0
Diarrhea	42 (18.8)	2 (0.9)	106 (48.0)	6 (2.7)
Stomatitis	15 (6.7)	0	80 (36.2)	6 (2.7)

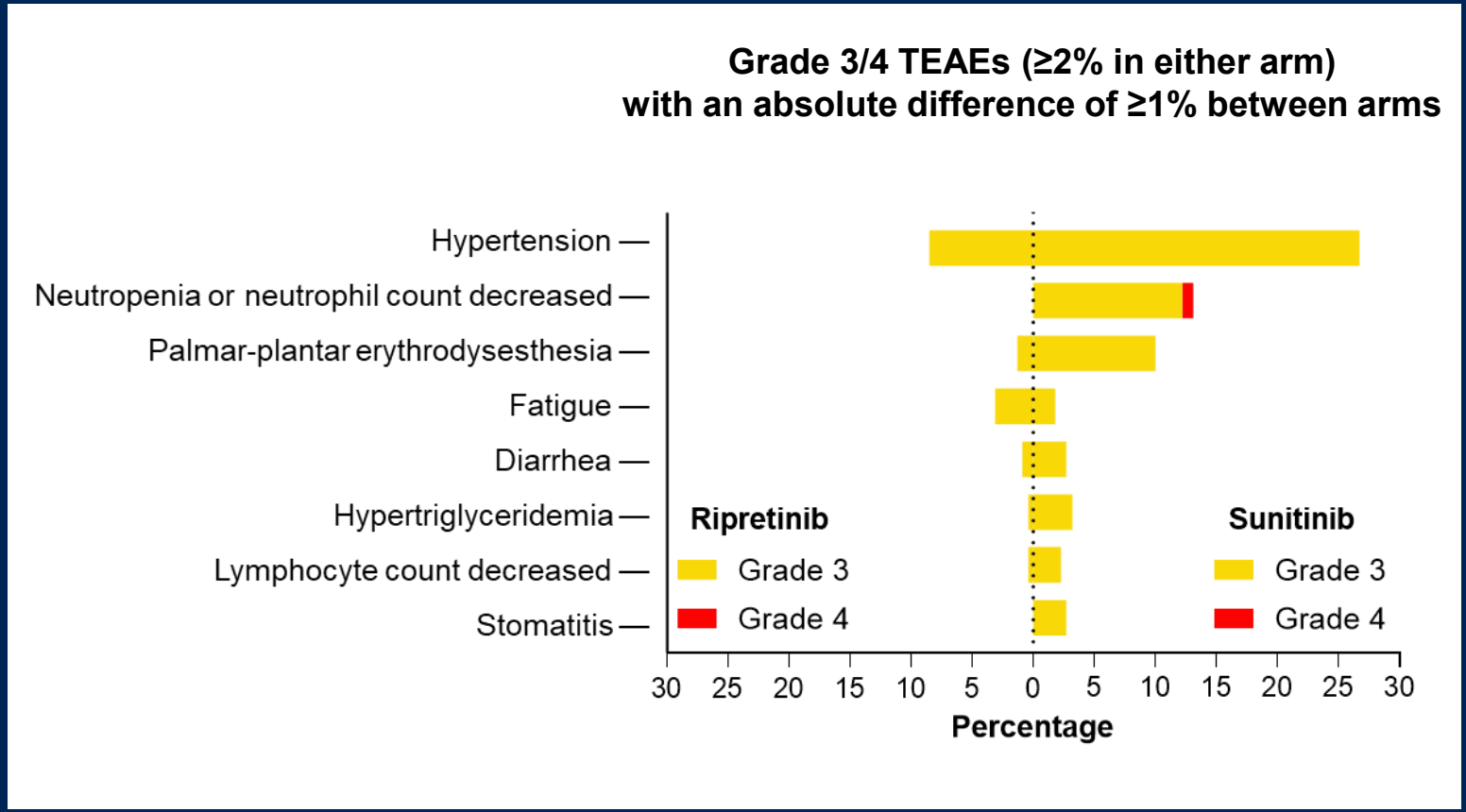
- Ripretinib was generally well tolerated and its safety profile was consistent with its existing prescribing information[1]
- The most common TEAE of any grade in patients treated with ripretinib was alopecia; the most common TEAE of any grade in patients treated with sunitinib was palmar-plantar erythrodysesthesia syndrome

N/A, not applicable; TEAE, treatment-emergent adverse event.

1) Deciphera Pharmaceuticals, LLC. QINLOCK™ (ripretinib) tablets: US prescribing information. 2021.

Grade 3/4 TEAEs for ripretinib vs sunitinib

- Grade 3/4 TEAEs (≥2% in either arm) with an absolute difference ≥1% were nearly all lower with ripretinib vs sunitinib
- Patients receiving sunitinib were 3 times more likely to experience Grade 3 hypertension compared with patients receiving ripretinib
- Patients receiving sunitinib were 7 times more likely to develop Grade 3 PPES vs patients receiving ripretinib



TEAE, treatment-emergent adverse event.

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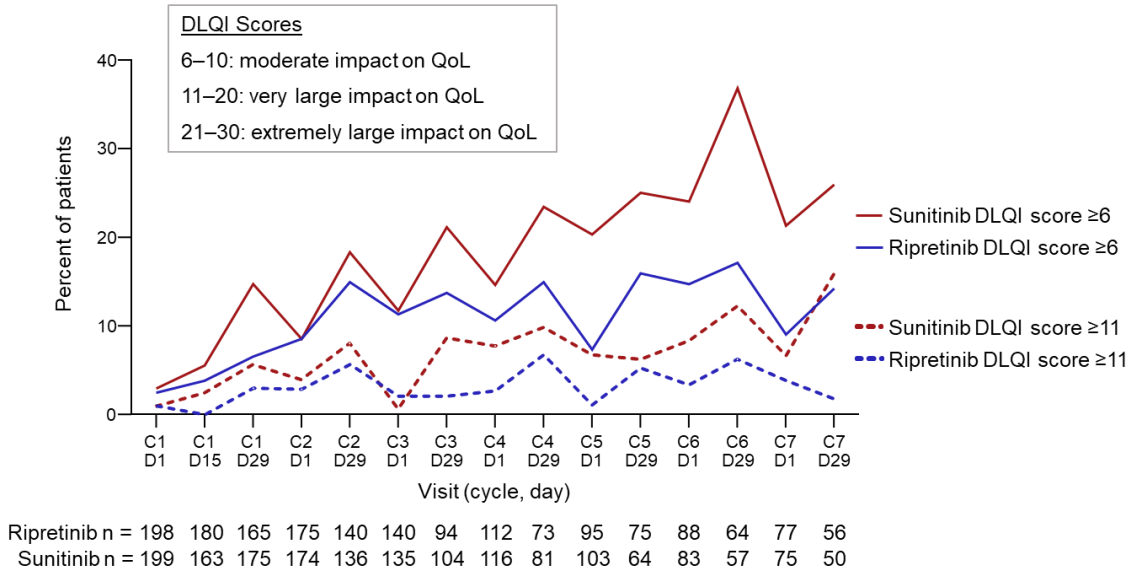
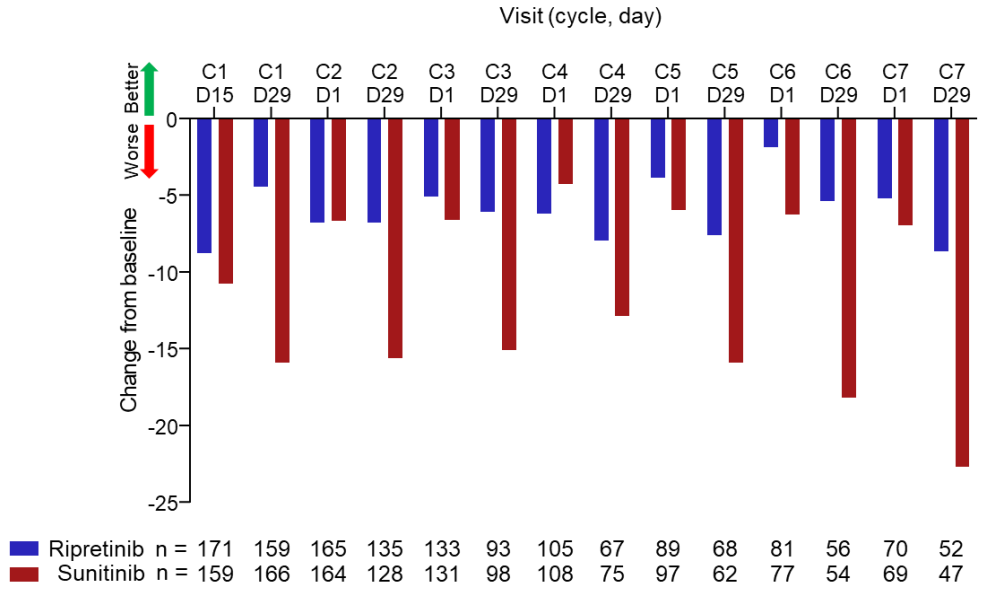
Patient-reported measures of tolerability

Patients reporting impact due to skin toxicity (DLQI)



Ripretinib n =	198	180	165	175	140	140	94	112	73	95	75	88	64	77	56
Sunitinib n =	199	163	175	174	136	135	104	116	81	103	64	83	57	75	50

EORTC QLQ-C30 role functioning



Ripretinib n =	171	159	165	135	133	93	105	67	89	68	81	56	70	52
Sunitinib n =	159	166	164	128	131	98	108	75	97	62	77	54	69	47

- The impact of skin toxicity on patient QoL was measured by the DLQI; fewer patients receiving ripretinib experienced moderate to extremely large impact on their lives due to skin toxicity across treatment cycles vs sunitinib
- Patients receiving ripretinib experienced less deterioration in EORTC QLQ-C30 role functioning (the ability to engage in either work or leisure activities) during treatment vs patients receiving sunitinib
- Patients receiving sunitinib reported less impact of skin toxicity/role function deterioration on D1 of each cycle immediately following the 2-week off period compared with D29

C, cycle; D, day; DLQI, Dermatology Life Quality Index; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of life questionnaire for cancer-30; QoL, quality of life.

Conclusions

- Ripretinib did not meet the primary endpoint of superiority in PFS over sunitinib
  - However, the median PFS observed with ripretinib was comparable to the median PFS observed with sunitinib
  - The ORR was higher for patients receiving ripretinib in the *KIT* exon 11 ITT population compared with sunitinib
- Ripretinib had a more favorable safety profile compared with sunitinib
  - Patients receiving ripretinib were less likely to experience Grade 3/4 TEAEs including hypertension, palmar-plantar erythrodysesthesia, diarrhea, and stomatitis compared with patients receiving sunitinib
  - Patients receiving ripretinib were less likely to need dose modification compared with patients receiving sunitinib
  - Patients receiving ripretinib reported better tolerability than patients receiving sunitinib
- Ripretinib may provide meaningful clinical benefit to patients with advanced GIST previously treated with imatinib

GIST, gastrointestinal stromal tumor; ITT, intention-to-treat; ORR, objective response rate; PFS, progression-free survival; TEAE, treatment-emergent adverse event.

Acknowledgments

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Q & A

There will be a panel question-and-answer session following the discussant for each abstract presented.

Type your question in the chat to participate in the Q&A.

See a question you like? Select  **to increase its visibility**