Mutational heterogeneity of imatinib resistance and efficacy of ripretinib vs sunitinib in patients with gastrointestinal stromal tumor: ctDNA analysis from INTRIGUE

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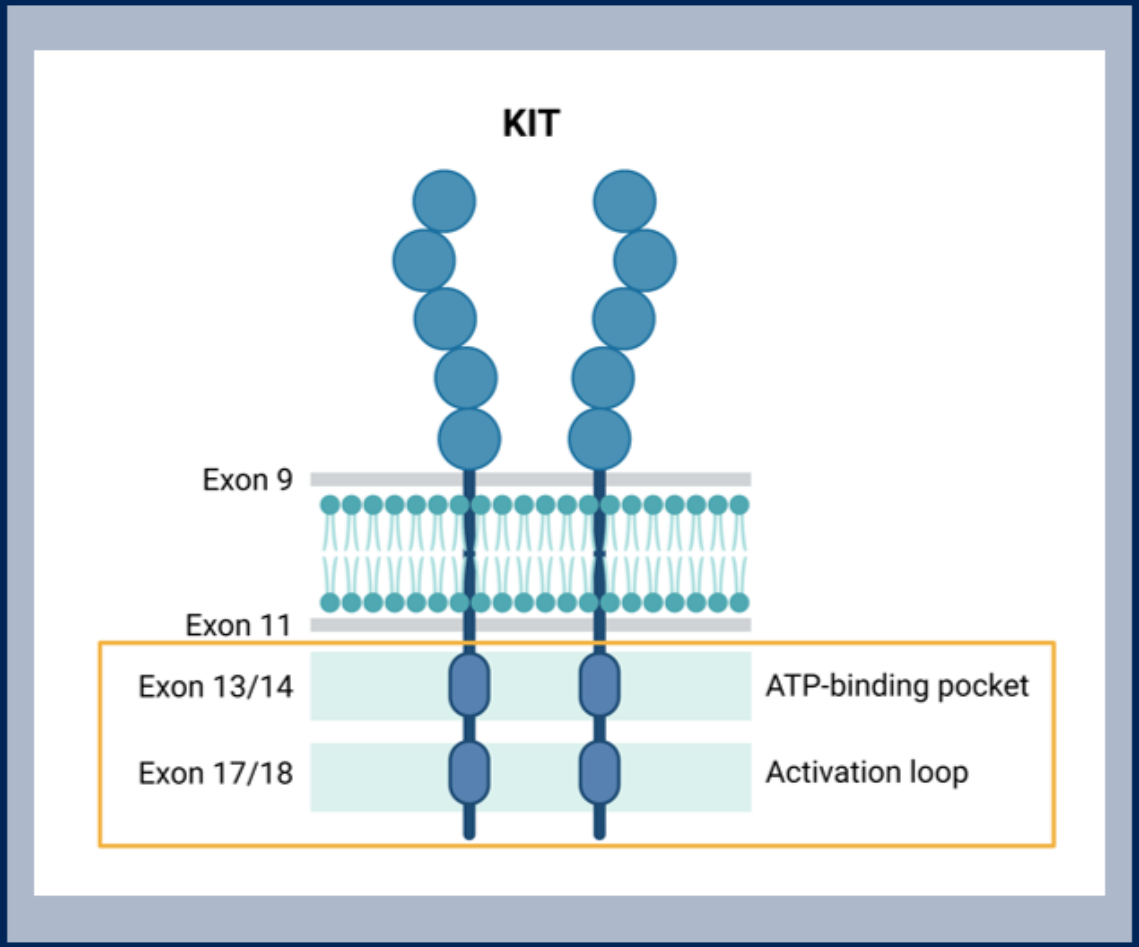
January Program
January 24, 2023

Reference: Bauer S, et al. Mutational heterogeneity of imatinib resistance and efficacy of Ripretinib vs sunitinib in patients with gastrointestinal stromal tumor: ctDNA analysis from INTRIGUE. *J Clin Oncol* 41, 2023 (suppl 36; abstr 397784)

Background

- 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]
- Imatinib, a KIT/PDGFRA TKI, induces objective responses or stable disease in most cases of advanced GIST[3]
- Most imatinib-treated patients will experience tumor progression due to development of secondary resistance mutations in KIT or PDGFRA[4–7]
- The main mechanism of imatinib resistance is the emergence of heterogeneous *KIT* secondary mutations in the kinase domain (~90% of patients)[8]
  - ATP-binding pocket (exons 13/14)
  - Activation loop (exons 17/18)



1) Rubin S, et al. *Lancet*. 2007;369:1731–41. 2) NCCN Guidelines v2.2022. 3) Blanke CD, et al. *J Clin Oncol*. 2008;26:626–32. 4) Antonescu CR, et al. *Clin Cancer Res*. 2005;11:4182–90. 5) Heinrich MC, et al. *J Clin Oncol*. 2008;26:5352–59. 6) Kelly CM, et al. *J Hematol Oncol*. 2021;14:2–12. 7) Grunewald S, et al. *Cancer Discov*. 2021;11:108–25. 8) Schaefer I-M, et al. *ASCO Ed Book*. 2022;42:885–99.
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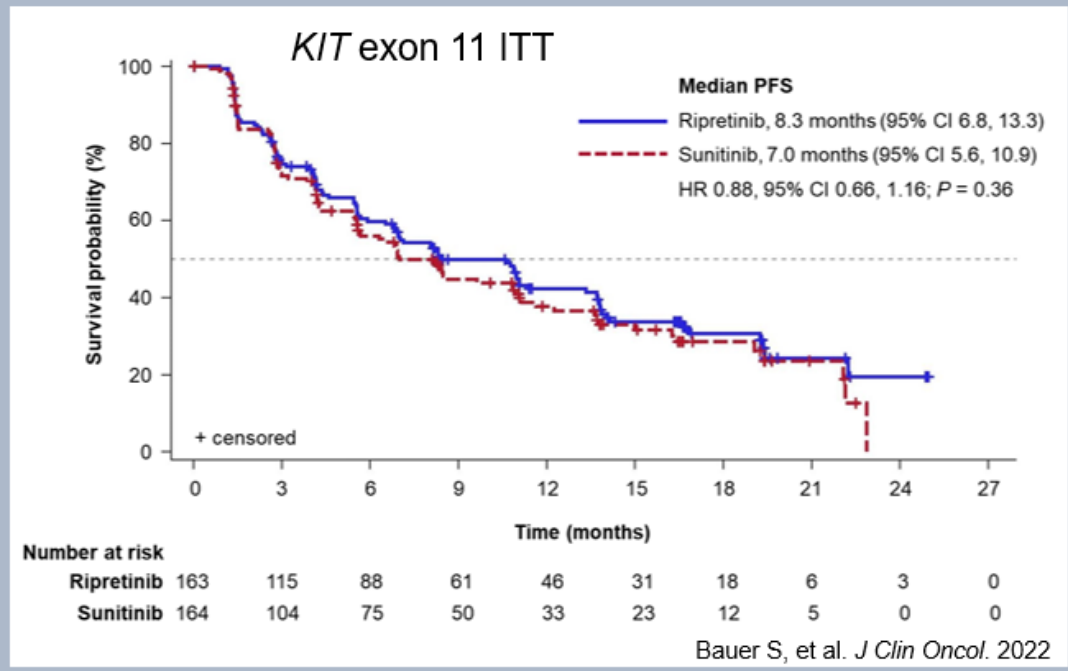
ATP, adenosine triphosphate; GI, gastrointestinal; GIST, GI stromal tumor; PDGFRA, platelet-derived growth factor receptor alpha; TKI, tyrosine kinase inhibitor.

Background

- Ripretinib is a switch-control TKI approved for adult patients with advanced GIST who received prior treatment with 3 or more TKIs, including imatinib[1]
- Sunitinib is approved for advanced GIST after disease progression or intolerance to imatinib[2]
- In the primary analysis from the INTRIGUE study in second-line GIST, ripretinib was not superior to sunitinib in terms of PFS in the *KIT* exon 11 ITT population or in the overall ITT population[3]
- Mutational ctDNA analysis can provide more insight into imatinib resistance mutations
  - *KIT* exon 17 mutations account for as many as 50% of the cases of acquired resistance to imatinib[4]
  - Ripretinib and sunitinib have highly differential activity against *KIT* exon 17 activation loop mutations[5,6]



Bauer S, et al. *J Clin Oncol*. 2022

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CI, confidence interval; ctDNA, circulating tumor DNA; GIST, gastrointestinal stromal tumor; HR, hazard ratio; ITT, intent-to-treat; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

INTRIGUE trial design

INCLUSION CRITERIA

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* wild type
  - Other *KIT*/*PDGFRA*
- Intolerance to imatinib

INTRIGUE PHASE 3 CLINICAL STUDY

1:1 Randomization
Open-label study

Ripretinib 150 mg QD
(continuous)

No crossover option

Sunitinib 50 mg QD
(4 weeks on, 2 weeks off)

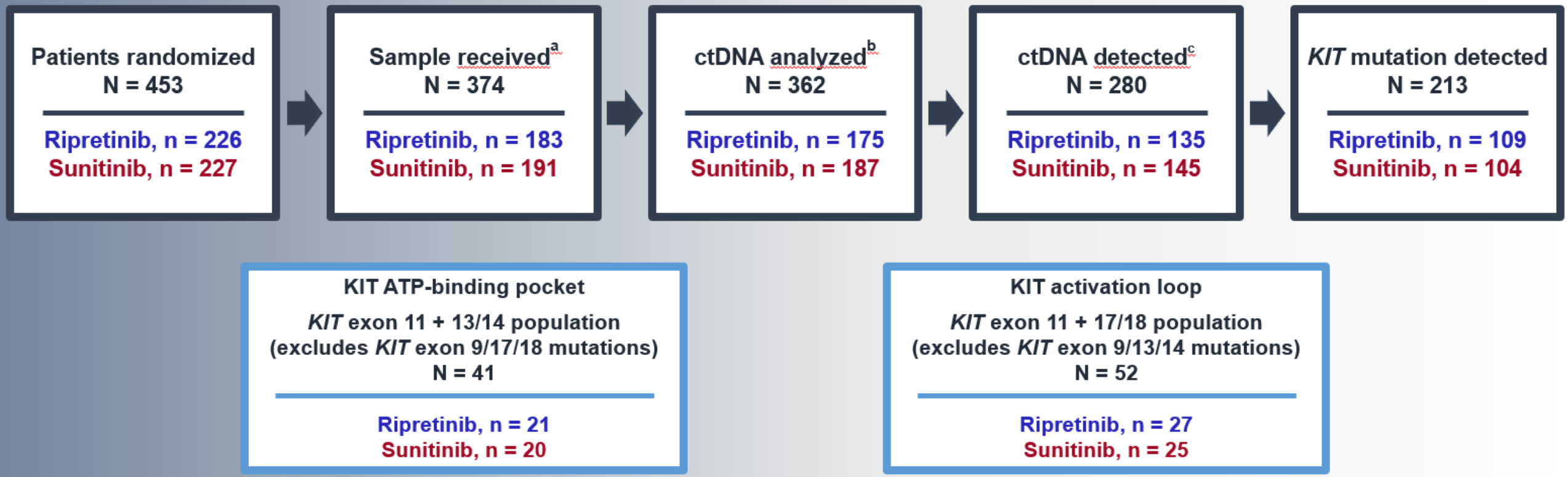
Primary endpoint:
- PFS by IRR (using mRECIST v1.1)

Baseline

Guardant360® ctDNA analysis

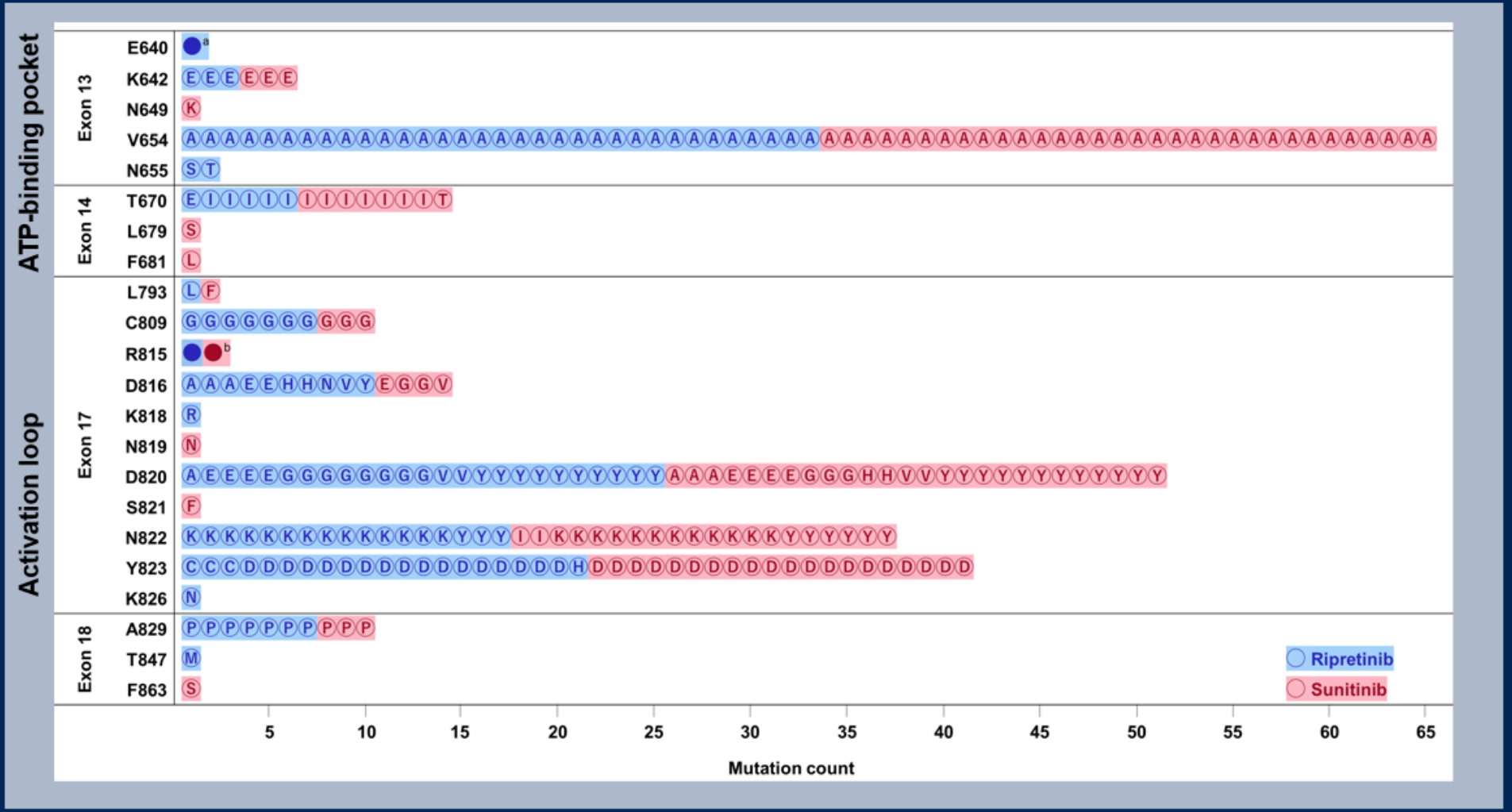
Data cutoff (except OS): September 1, 2021; OS data cutoff: September 1, 2022.
ctDNA, circulating tumor DNA; GIST, gastrointestinal stromal tumor; IRR, independent radiologic review; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1; OS, overall survival; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival; QD, once daily.

ctDNA analysis and detection



Plasma originated from one 10 mL tube.
[a]No sample received, N = 79.
[b]Sample failed quality control, N = 12.
[c]ctDNA not detected, N = 82. ctDNA detected includes only single nucleotide variants and insertions/deletions. Copy number variations were observed in 2 patients categorized as ctDNA not detected.
ctDNA, circulating tumor DNA.

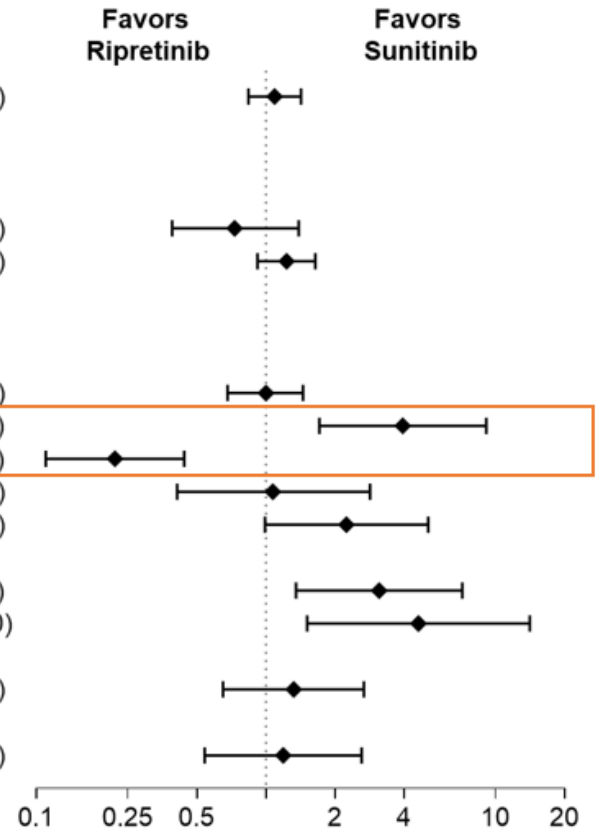
Heterogeneity of mutations in the KIT kinase domain



Patients were included in multiple groups if they had mutations in more than one exon; analysis of the total population (N = 213).
[a]_L641delinsD; [b]Ripretinib: _D816delinsN, Sunitinib: _D816delinsK.

PFS by IRR in mutational subgroups by ctDNA analysis

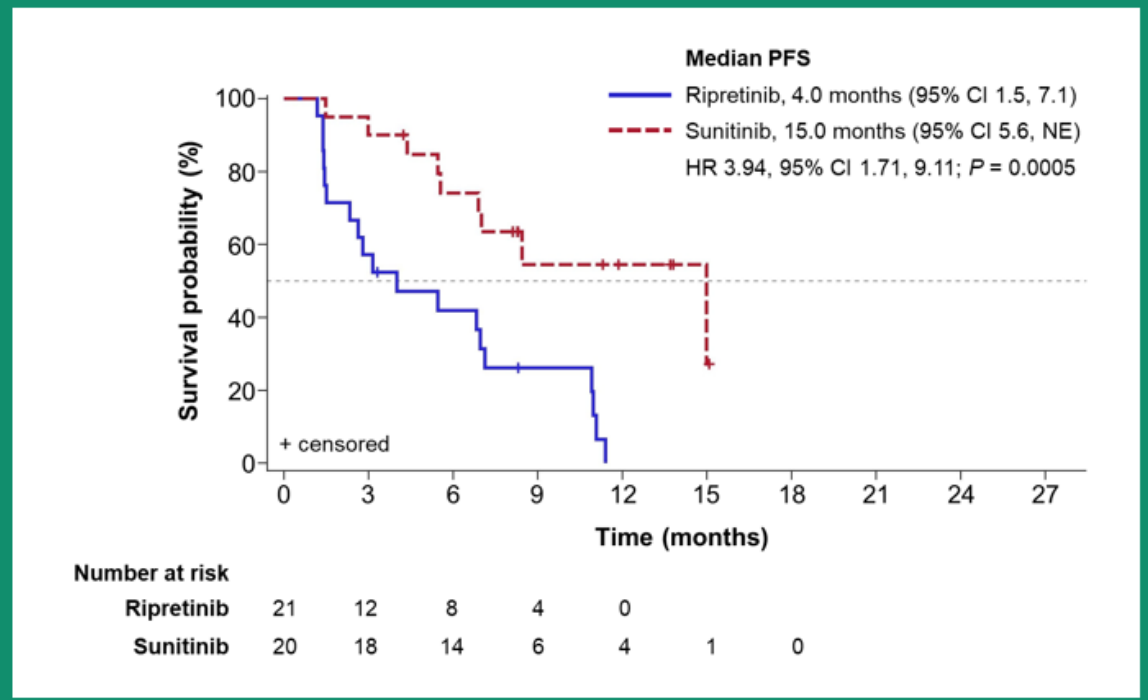
	Ripretinib n (E)	Sunitinib n (E)	mPFS Ripretinib (months)	mPFS Sunitinib (months)	Hazard ratio (95% CI)
All samples analyzed	175 (118)	187 (109)	7.0	8.3	1.09 (0.84, 1.42)
ctDNA					
Not detected	40 (17)	42 (22)	16.6	11.0	0.73 (0.39, 1.39)
Detected	135 (101)	145 (87)	6.8	6.9	1.23 (0.92, 1.64)
Mutations					
Any *KIT* exon 11	81 (60)	76 (52)	7.0	6.3	1.00 (0.68, 1.45)
Exon 11 + 13/14	21 (19)	20 (9)	4.0	15.0	3.94 (1.71, 9.11)
Exon 11 + 17/18	27 (16)	25 (24)	14.2	1.5	0.22 (0.11, 0.44)
Exon 11 + 13/14 + 17/18	11 (8)	11 (9)	8.1	10.9	1.07 (0.41, 2.84)
Exon 11 only	21 (16)	20 (10)	2.2	16.3	2.24 (0.99, 5.09)
Any *KIT* exon 9	21 (20)	15 (8)	4.3	13.8	3.11 (1.35, 7.17)
Exon 9 only	17 (16)	10 (4)	5.3	19.6	4.61 (1.51, 14.10)
KIT/*PDGFRA* not detected	24 (15)	35 (16)	8.3	11.6	1.32 (0.65, 2.67)
Other *KIT*/*PDGFRA*	15 (12)	22 (13)	2.9	4.2	1.19 (0.54, 2.61)

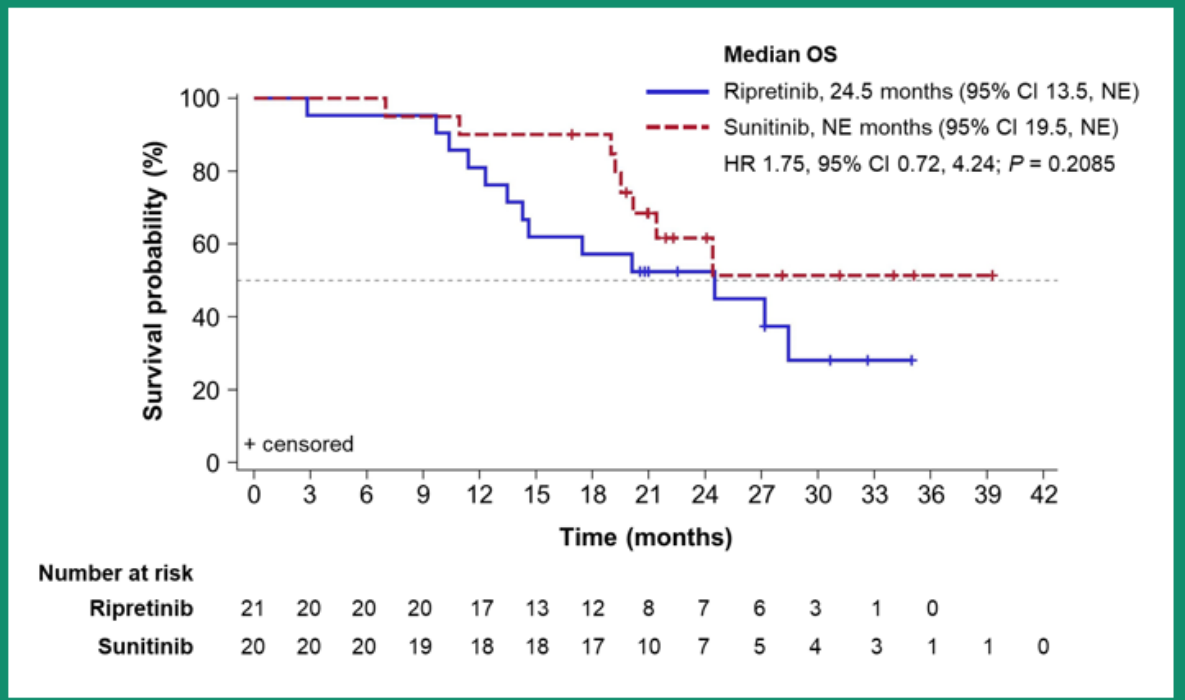


Data cutoff: September 1, 2021.
CI, confidence interval; ctDNA, circulating tumor DNA; E, events; IRR, independent radiologic review; m, median; PDGFRA, platelet-derived growth factor receptor alpha; PFS, progression-free survival.

Efficacy in *KIT* exon 11 + 13/14 population

ATP-binding pocket

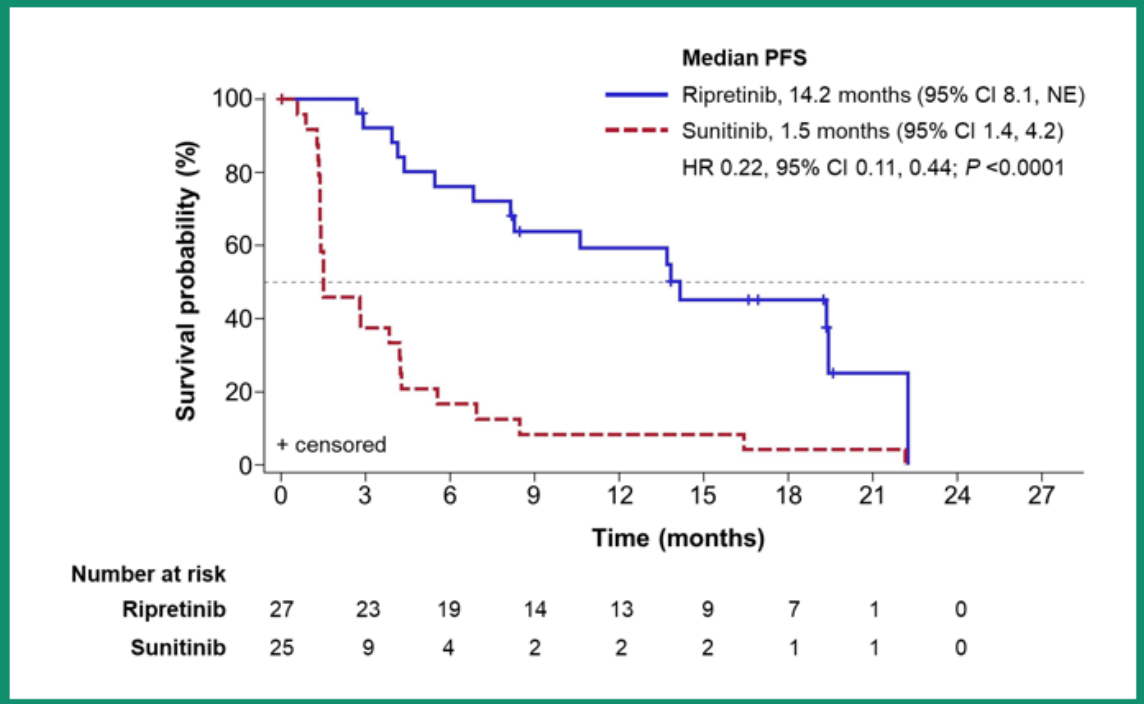


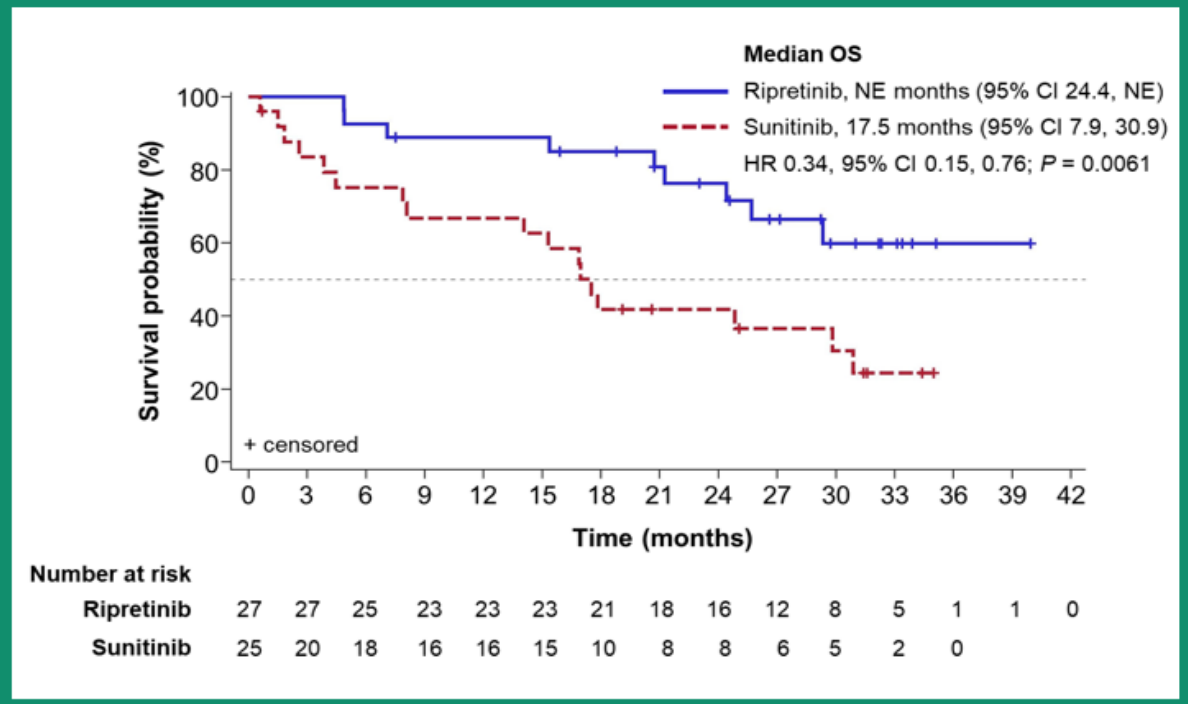


PFS data cutoff: September 1, 2021; OS data cutoff: September 1, 2022. Excludes *KIT* exons 9/17/18. *P*-values are nominal.
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Efficacy in *KIT* exon 11 + 17/18 population

Activation loop

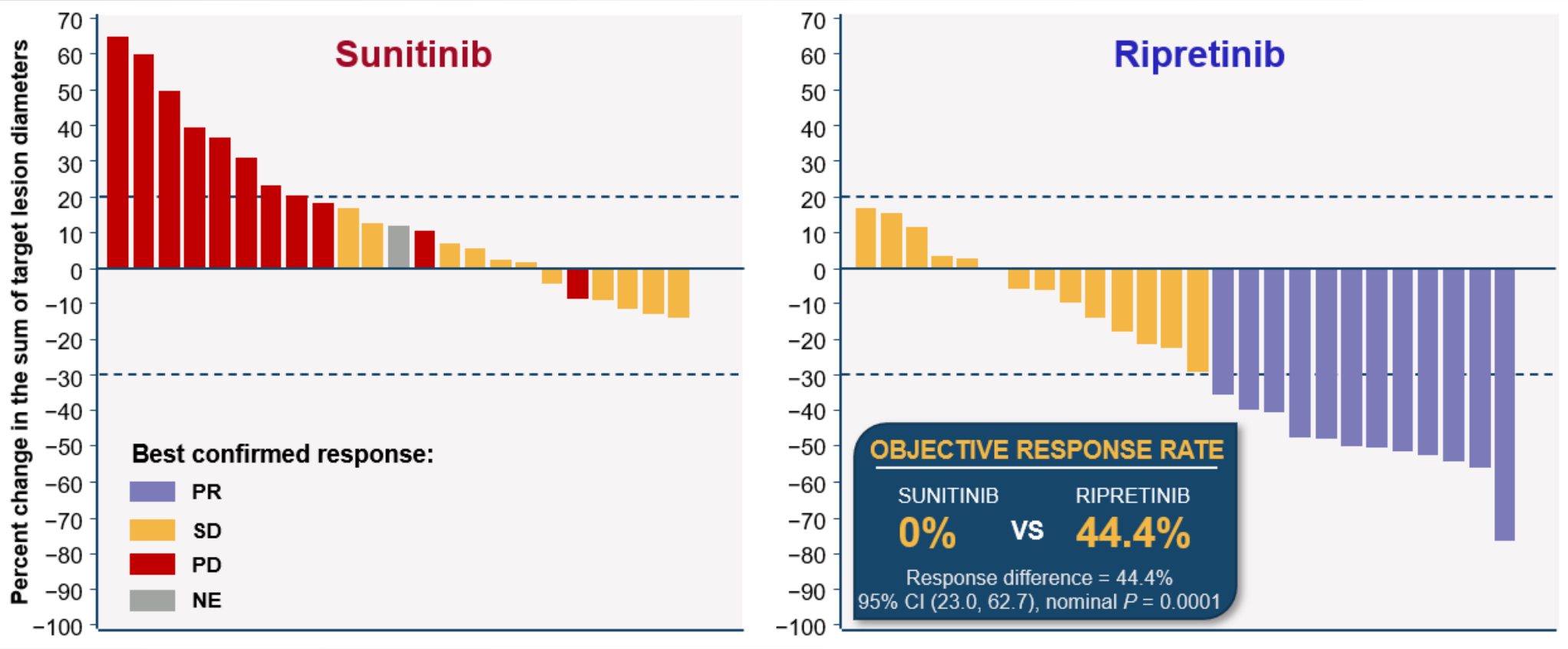




PFS data cutoff: September 1, 2021; OS data cutoff: September 1, 2022. Excludes *KIT* exons 9/13/14. *P*-values are nominal.
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Efficacy in *KIT* exon 11 + 17/18 population

Activation loop



Data cutoff: September 1, 2021. Excludes *KIT* exons 9/13/14. No postbaseline disease assessment was available for 2 patients in the sunitinib arm and 1 patient in the ripretinib arm.
Objective response rate was confirmed with follow-up imaging and determined using modified Response Evaluation Criteria in Solid Tumors version 1.1 criteria.
The median (95% CI) duration of response for patients receiving ripretinib was 16.7 (9.7–not estimable) months.
CI, confidence interval; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

Outcomes by ctDNA analysis in *KIT* exon 11 + secondary resistance mutation subpopulations

	Activation loop (*KIT* exon 11 + 17/18)[a]		ATP-binding pocket (*KIT* exon 11 + 13/14)[b]		Activation loop/ATP-binding pocket co-mutants (*KIT* exon 11 + 13/14 + 17/18)[c]	
	Ripretinib n = 27	**Sunitinib n = 25**	**Ripretinib n = 21**	**Sunitinib n = 20**	**Ripretinib n = 11**	**Sunitinib n = 11**
mPFS, months	14.2	1.5	4.0	15.0	8.1	10.9
HR (95% CI)	0.22 (0.11, 0.44)		3.94 (1.71, 9.11)		1.07 (0.41, 2.84)	
ORR, %	44.4	0	9.5	15.0	27.3	9.1
mOS, months	Not estimable	17.5	24.5	Not estimable	14.7	20.3
HR (95% CI)	0.34 (0.15, 0.76)		1.75 (0.72, 4.24)		2.61 (0.95, 7.19)	

PFS and ORR data cutoff: September 1, 2021; OS data cutoff: September 1, 2022.
[a]Excludes *KIT* exons 9/13/14; [b]Excludes *KIT* exons 9/17/18; [c]Excludes *KIT* exon 9.
ATP, adenosine triphosphate; CI, confidence interval; ctDNA, circulating tumor DNA; HR, hazard ratio; m, median; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Follow-up anticancer therapies in *KIT* exon 11 + 17/18 population

Activation loop

Category, n (%)	Ripretinib n = 27	Sunitinib n = 25	Total N = 52
Patients with follow-up anticancer therapy	20 (74)	16 (64)	36 (69)
Sunitinib	18 (67)	1 (4.0)	19 (37)
Regorafenib	7 (26)	12 (48)	19 (37)
Ripretinib	0	10 (40)	10 (19)
Imatinib	1 (3.7)	1 (4.0)	2 (3.8)
Other	3 (11)	0	3 (5.8)

Data cutoff: September 1, 2022. Excludes *KIT* exons 9/13/14.
4 patients initiated fifth-line therapy (3 in the ripretinib arm and 1 in the sunitinib arm); 3 patients initiated sixth-line therapy (2 in ripretinib arm and 1 in the sunitinib arm).

TEAEs ≥20% in the *KIT* exon 11 + 17/18 population

Activation loop

Category, n (%)	Ripretinib n = 27	Sunitinib n = 24	Total N = 51
Any grade 3/4 drug-related TEAE	9 (33)	12 (50)	21 (41)
Any drug-related treatment-emergent SAE	1 (3.7)	3 (13)	4 (7.8)
All grades TEAEs, preferred term			
Alopecia	21 (78)	2 (8.3)	23 (45)
Constipation	14 (52)	8 (33)	22 (43)
Fatigue	13 (48)	9 (38)	22 (43)
Hypertension	9 (33)	12 (50)	21 (41)
PPES	10 (37)	10 (42)	20 (39)
Myalgia	12 (44)	3 (13)	15 (29)
Abdominal pain	7 (26)	8 (33)	15 (29)
Decreased appetite	7 (26)	8 (33)	15 (29)
Diarrhea	6 (22)	9 (38)	15 (29)
Nausea	7 (26)	7 (29)	14 (27)
Pruritus	7 (26)	4 (17)	11 (22)
Muscle spasms	8 (30)	2 (8.3)	10 (20)

Data cutoff: September 1, 2021. Excludes *KIT* exons 9/13/14. Safety population.
PPES, palmar-plantar erythrodysesthesia syndrome; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Conclusions

- This is the largest global phase 3 trial in second-line imatinib-resistant advanced GIST that demonstrates the significance of ctDNA NGS-based analysis of the complex landscape of *KIT* mutations and correlates mutational status with treatment response
- Patients with *KIT* exon 11 + 13/14 (ATP-binding pocket) mutations derived clinical benefit from sunitinib but not ripretinib
- Patients with *KIT* exon 11 + 17/18 (activation loop) mutations derived clinical benefit from ripretinib but not sunitinib
- INSIGHT: Planned phase 3, randomized, multicenter, open-label study evaluating ripretinib vs sunitinib in patients with advanced GIST previously treated with imatinib harboring *KIT* exon 11 + 17 and/or 18 mutations

ATP, adenosine triphosphate; ctDNA, circulating tumor DNA; GIST, gastrointestinal stromal tumor; NGS, next generation sequencing.

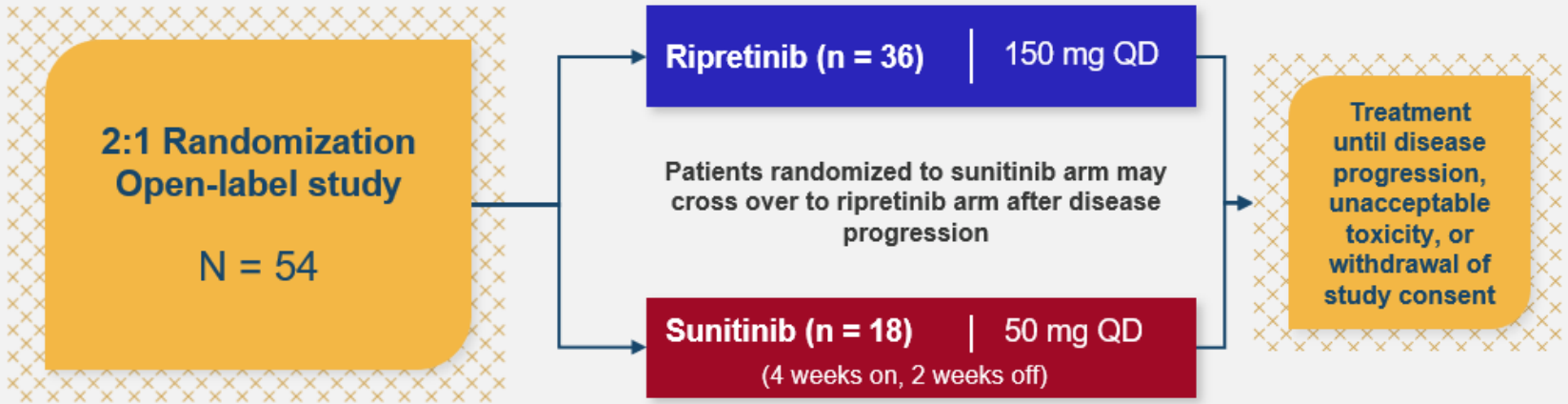
INSIGHT trial design

INCLUSION CRITERIA

Patients with GIST previously treated with imatinib

- 1 prior line of imatinib
- *KIT* exon 11 + 17 and/or 18 via ctDNA during screening
  - *KIT* exon 9, 13, and/or 14 excluded
  - Other co-mutations are allowed
- Measurable disease per mRECIST
- ECOG performance status ≤2

PLANNED PHASE 3, RANDOMIZED, MULTICENTER, OPEN-LABEL STUDY



Primary endpoint
- PFS by IRR using mRECIST

Key secondary endpoints
- ORR by IRR using mRECIST
- OS

ctDNA, circulating tumor DNA; ECOG, Eastern Cooperative Oncology Group; GIST, gastrointestinal stromal tumor; IRR, independent radiologic review; mRECIST, modified Response Evaluation Criteria in Solid Tumors; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QD, once daily.

Acknowledgments

- We thank the patients and their families and caregivers, the investigators, and the investigational site staff of the INTRIGUE study
- The INTRIGUE study was funded by Deciphera Pharmaceuticals, LLC
- We thank Meena Kusi, MS, PhD (Deciphera Pharmaceuticals, LLC) for contributing to this analysis
- Medical writing support was provided by Lauren Hanlon, PhD, CMPP, of AlphaBioCom, LLC, King of Prussia, PA, USA, and was funded by Deciphera Pharmaceuticals, LLC