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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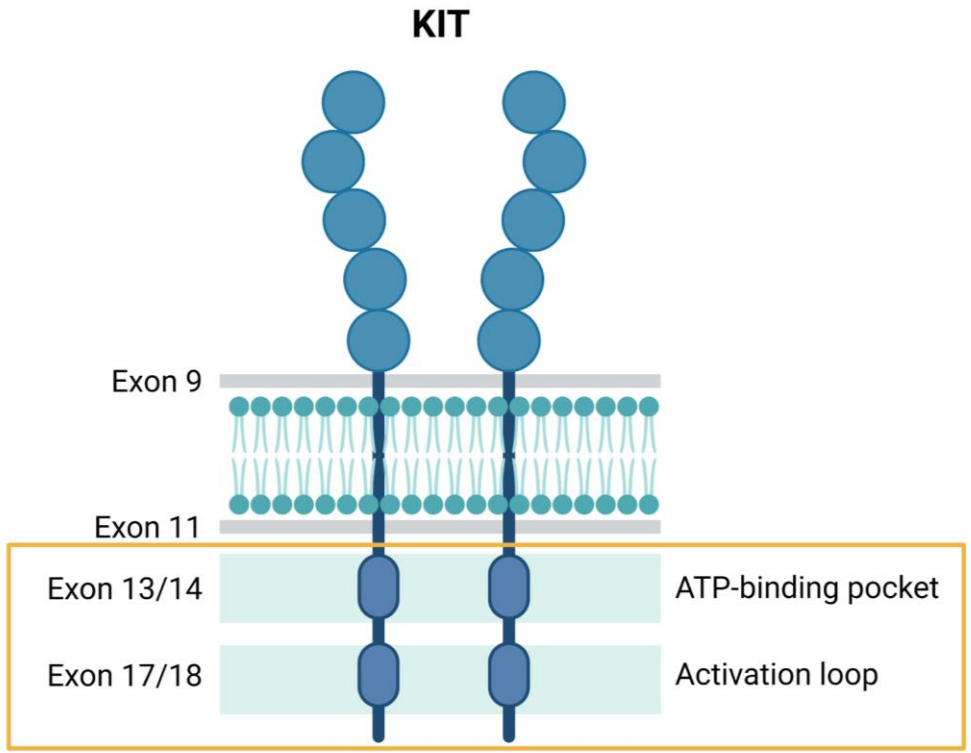
Background

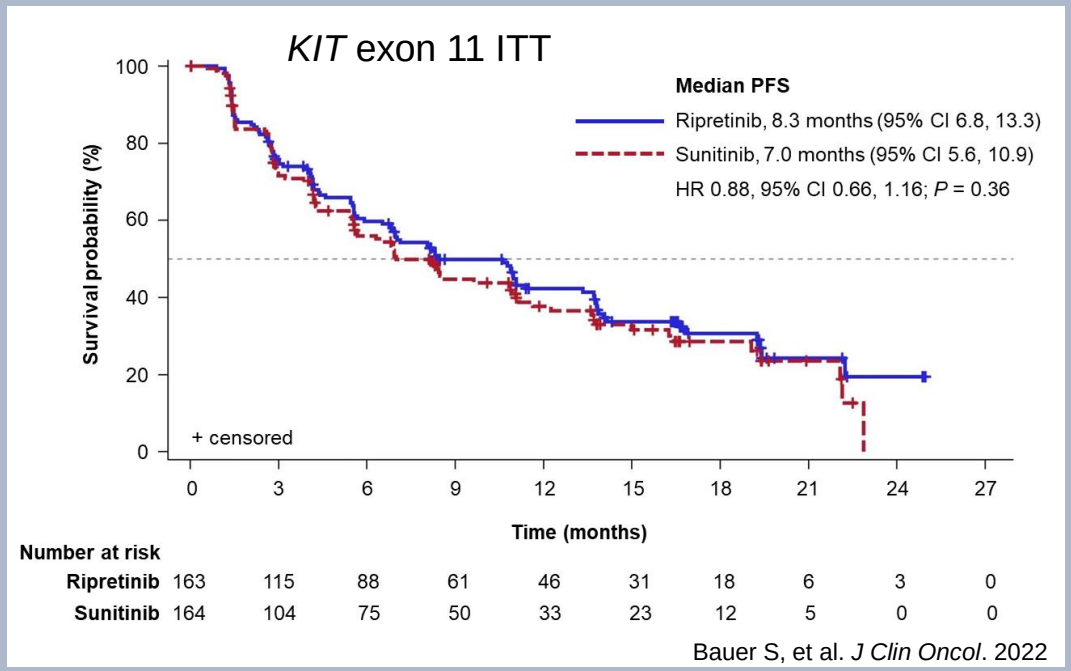
- GIST is the most common sarcoma of the GI tract,[1] with most patients harboring activating mutations in *KIT* (~80%) or *PDGFRA* (5%–10%)[2]
- Imatinib, a KIT/PDGFRA TKI, induces objective responses or stable disease in most patients with advanced GIST[3]
- Most imatinib-treated patients will experience tumor progression, mainly due to the emergence of heterogeneous *KIT* secondary mutations in the kinase domain in ~90% of patients[4]
  - 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) Schaefer I-M, et al. *ASCO Ed Book. 2022*;42:885–99.
Figure created with biorender.com.
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 kinase inhibitors, including imatinib[1]
- Sunitinib is approved for advanced GIST after disease progression on 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 or overall ITT population[3]
- Mutational ctDNA analysis can provide additional insight into imatinib resistance mutations



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

1) Deciphera Pharmaceuticals. Qinlock Prescribing Information. https://www.qinlockhcp.com/Content/files/qinlock-prescribing-information.pdf. Last Revised: December 2022. 2) Pfizer Laboratories. Sutent Prescribing Information. https://labeling.pfizer.com/ShowLabeling.aspx?id=607. Last Revised: August 2021. 3) Bauer S, et al. *J Clin Oncol*. 2022;40:3918–28.
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)

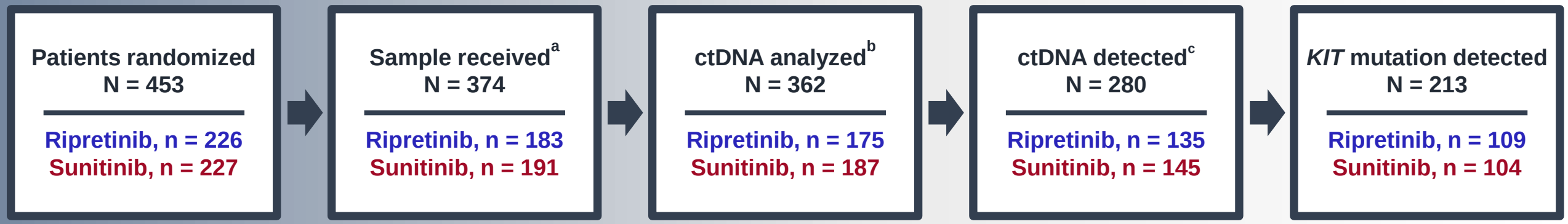
Primary endpoint:
- PFS by IRR (using mRECIST v1.1)

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.

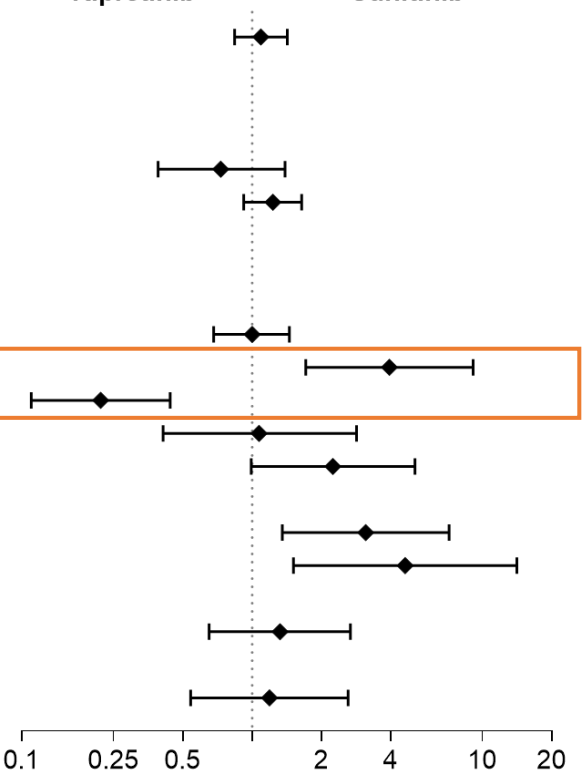
ctDNA analysis and detection



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.

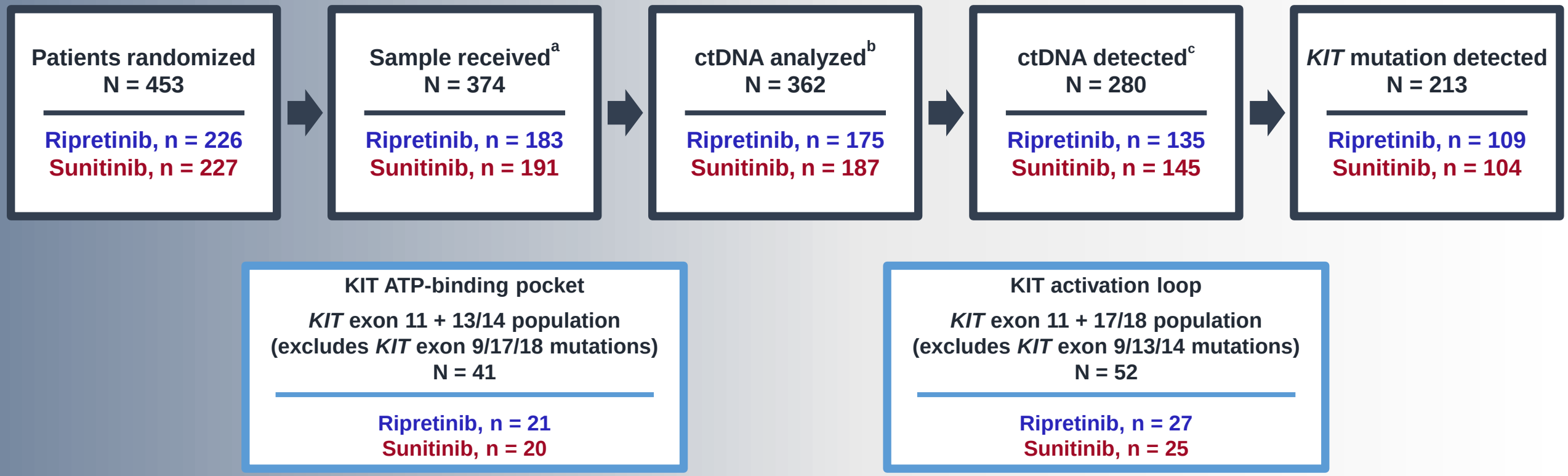
PFS by IRR in mutational subgroups by ctDNA analysis

	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.

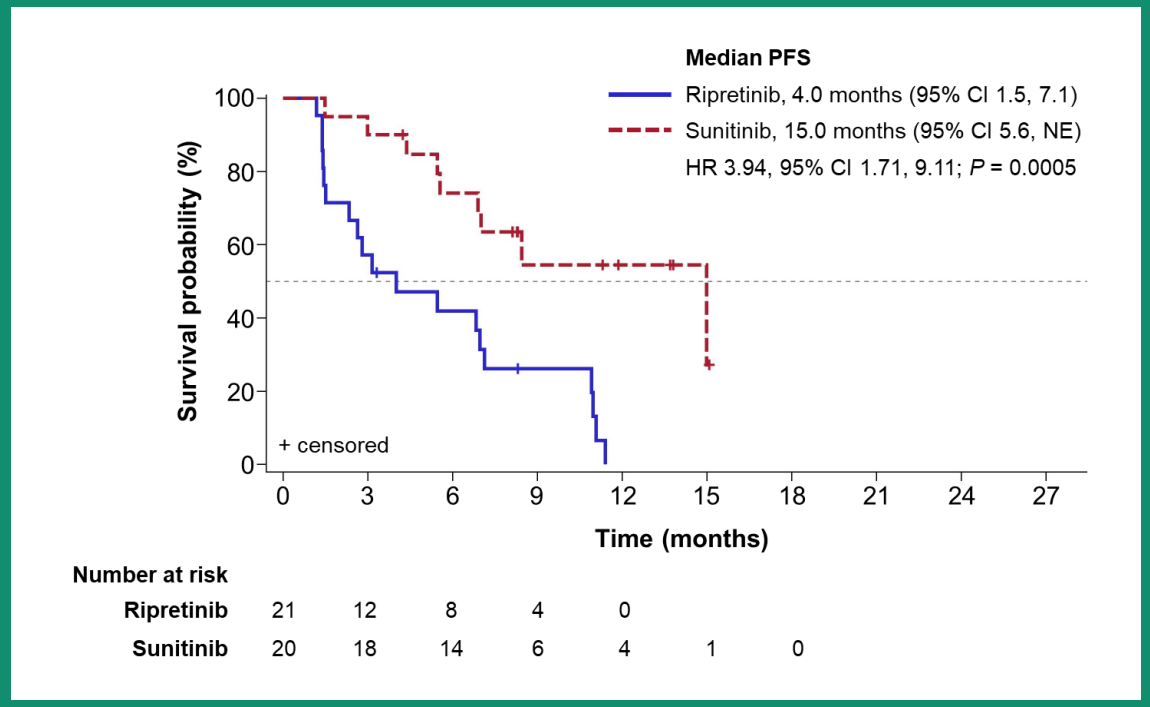
ctDNA analysis and detection

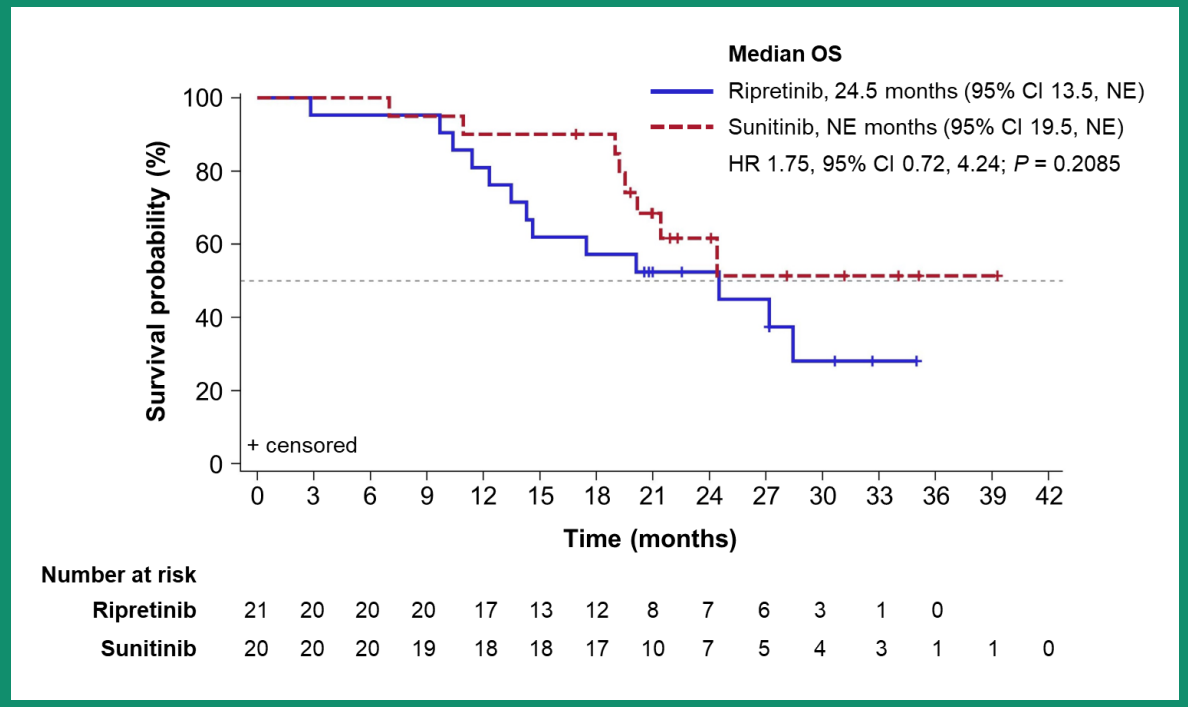


Plasma originated from one 10 mL tube.
[a]No sample received, N = 79.
[b]Sample failed quality control, N = 12.
[c]ctDNA not detected, N = 82. ctDNA detected includes only single nucleotide variants and insertions/deletions. Copy number variations were observed in 2 patients categorized as ctDNA not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

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

ATP-binding pocket

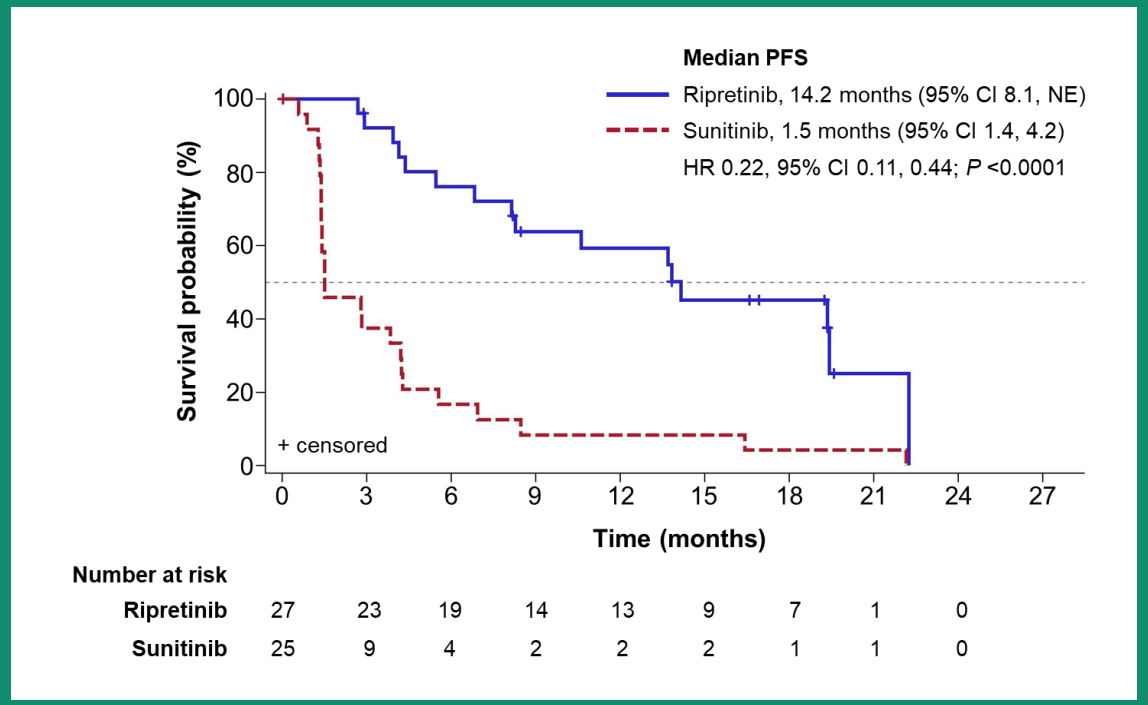


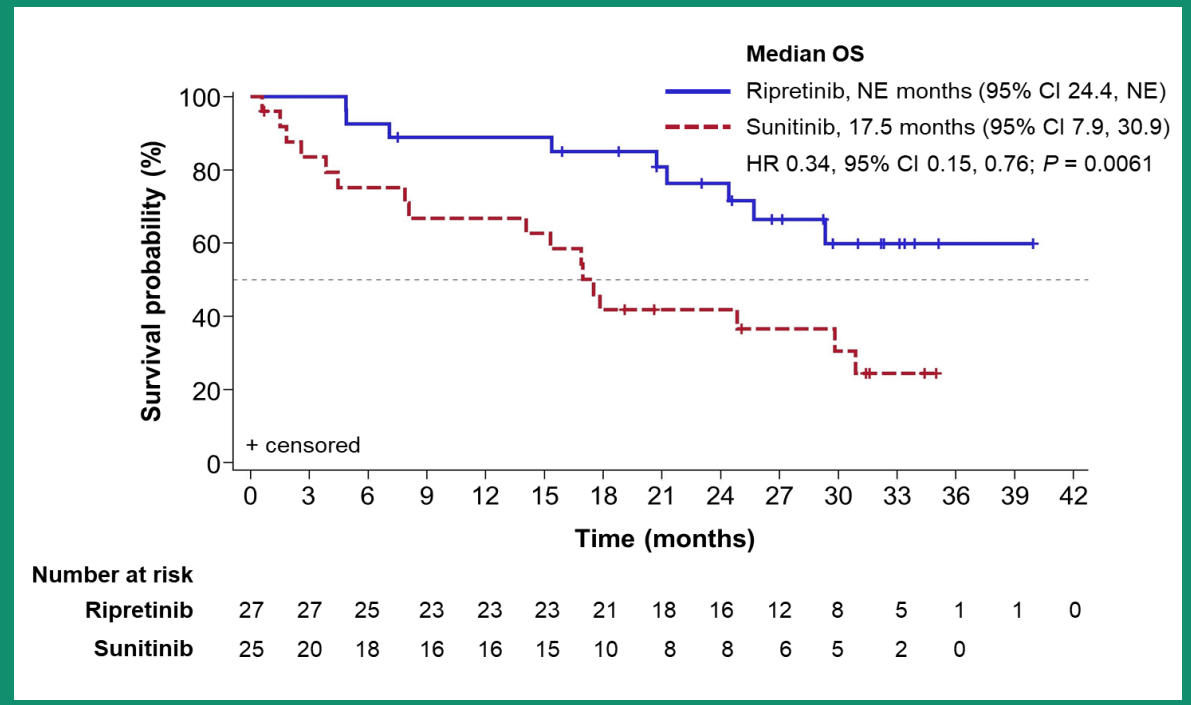


PFS data cutoff: September 1, 2021; OS data cutoff: September 1, 2022. Excludes *KIT* exons 9/17/18. *P*-values are nominal.
CI, confidence interval; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.

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

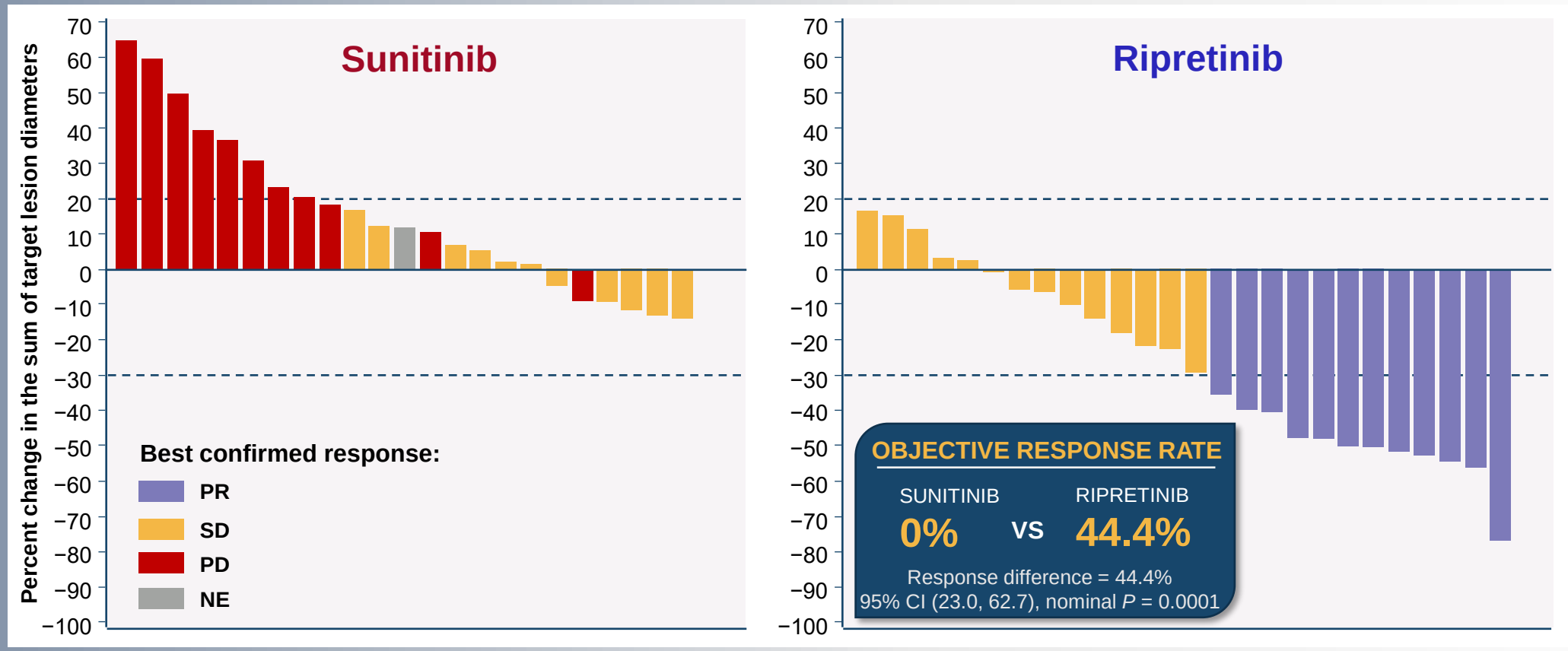
Activation loop





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.

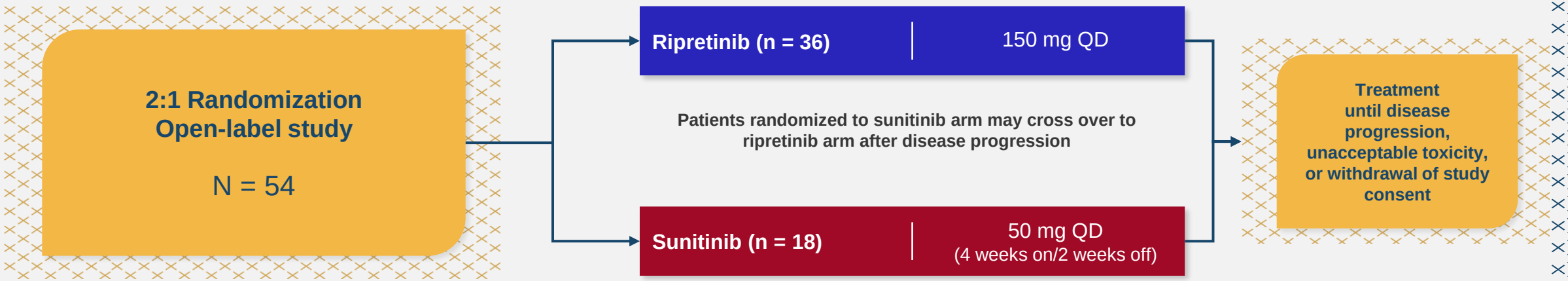
Efficacy in *KIT* exon 11 + 17/18 population
Activation loop



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.

INSIGHT trial design

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



Primary endpoint
- PFS by IRR using mRECIST

Key secondary endpoints
- ORR by IRR using mRECIST
- OS

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.

Key eligibility criteria

Inclusion
Male or female ≥18 years of age
Confirmed histologic diagnosis of GIST with co-occurring *KIT* exon 11 + 17 and/or 18 mutations by ctDNA analysis at prescreening
Advanced GIST and radiologic progression on imatinib treatment
Must have at least 1 measurable lesion per mRECIST v1.1 within 21 days prior to the first dose of study drug
ECOG PS ≤2 at screening

Exclusion
Co-occurring *KIT* exon 11 + 17 and/or 18 mutations that cannot be confirmed by ctDNA analysis
History of *KIT* exon 9 mutation or detection of *KIT* exon 9, 13, or 14 mutations by ctDNA analysis
Treatment with any other line of therapy in addition to imatinib for advanced GIST
Any prior or concurrent malignancy whose treatment may interfere with safety or efficacy assessment in this study
Known active metastasis of the central nervous system

ctDNA, circulating tumor DNA; ECOG PS, Eastern Cooperative Oncology Group performance status; GIST, gastrointestinal stromal tumor; mRECIST v1.1, modified Response Evaluation Criteria in Solid Tumors version 1.1.

Conclusions

- INTRIGUE 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 greater clinical benefit from sunitinib vs ripretinib
- Patients with *KIT* exon 11 + 17/18 (activation loop) mutations derived greater clinical benefit from ripretinib vs sunitinib
- INSIGHT (NCT05734105): 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.

Acknowledgments

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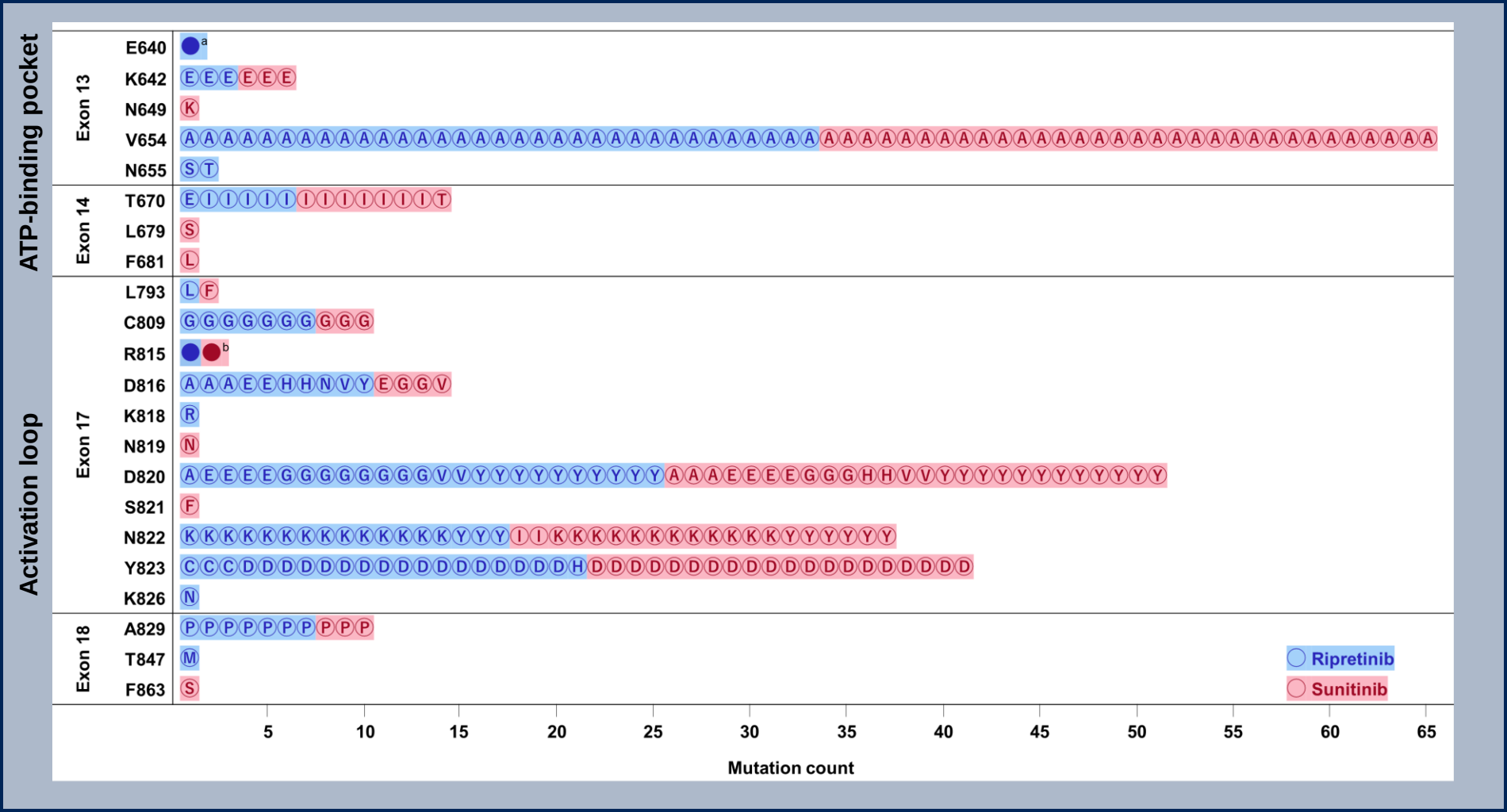
- We thank Meena Kusi, MS, PhD (Deciphera Pharmaceuticals, LLC) for contributing to this analysis
- Medical writing support was provided by Lauren Hanlon, PhD, CMPP, of AlphaBioCom, a Red Nucleus company, and was funded by Deciphera Pharmaceuticals, LLC

Heterogeneity of mutations in the KIT kinase domain



[a]E640_L641delinsD. [b]Ripretinib: R815_D816delinsN; sunitinib: R815_D816delinsK.
This plot illustrates the number of mutations; each patient could have multiple mutations. The letters in the bubbles and in front of each listed codon represent amino acids.
A, alanine; ATP, adenosine triphosphate; C, cysteine; D, aspartic acid; E, glutamic acid; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; R, arginine; S, serine; T, threonine; V, valine; Y, tyrosine.

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.