Medical Therapy of Gastrointestinal Stromal Tumors

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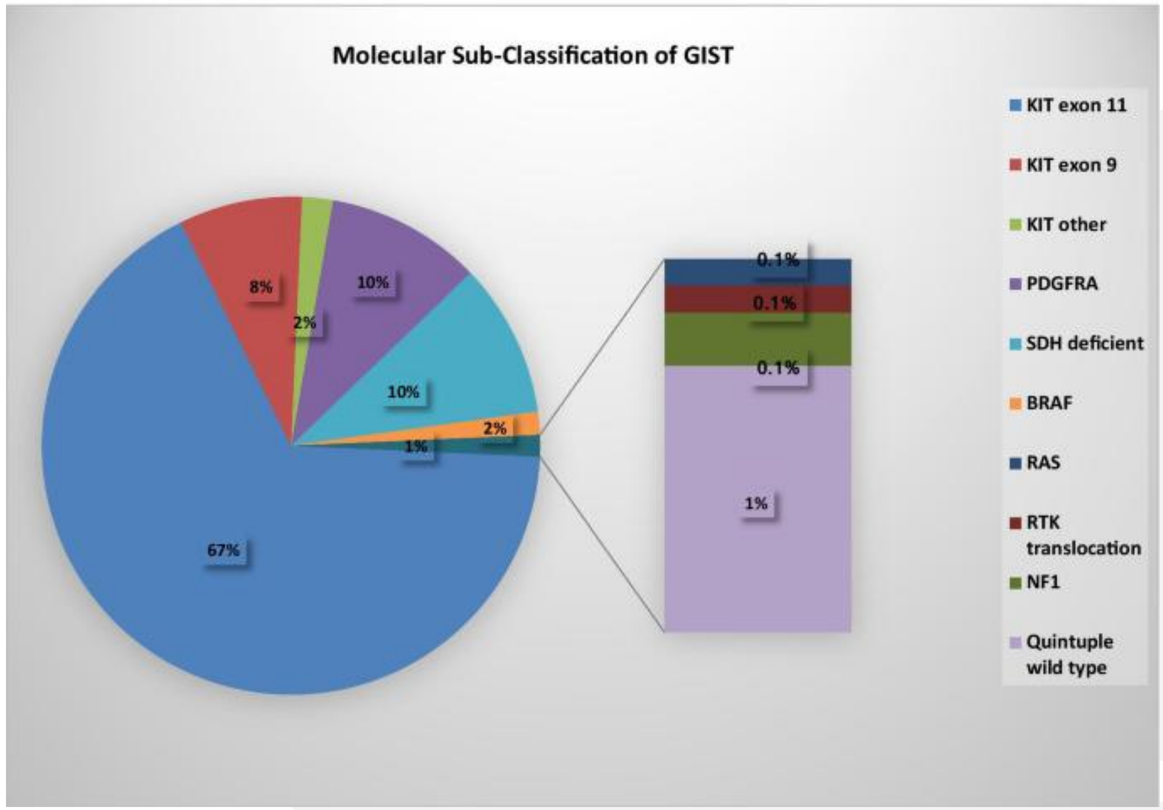
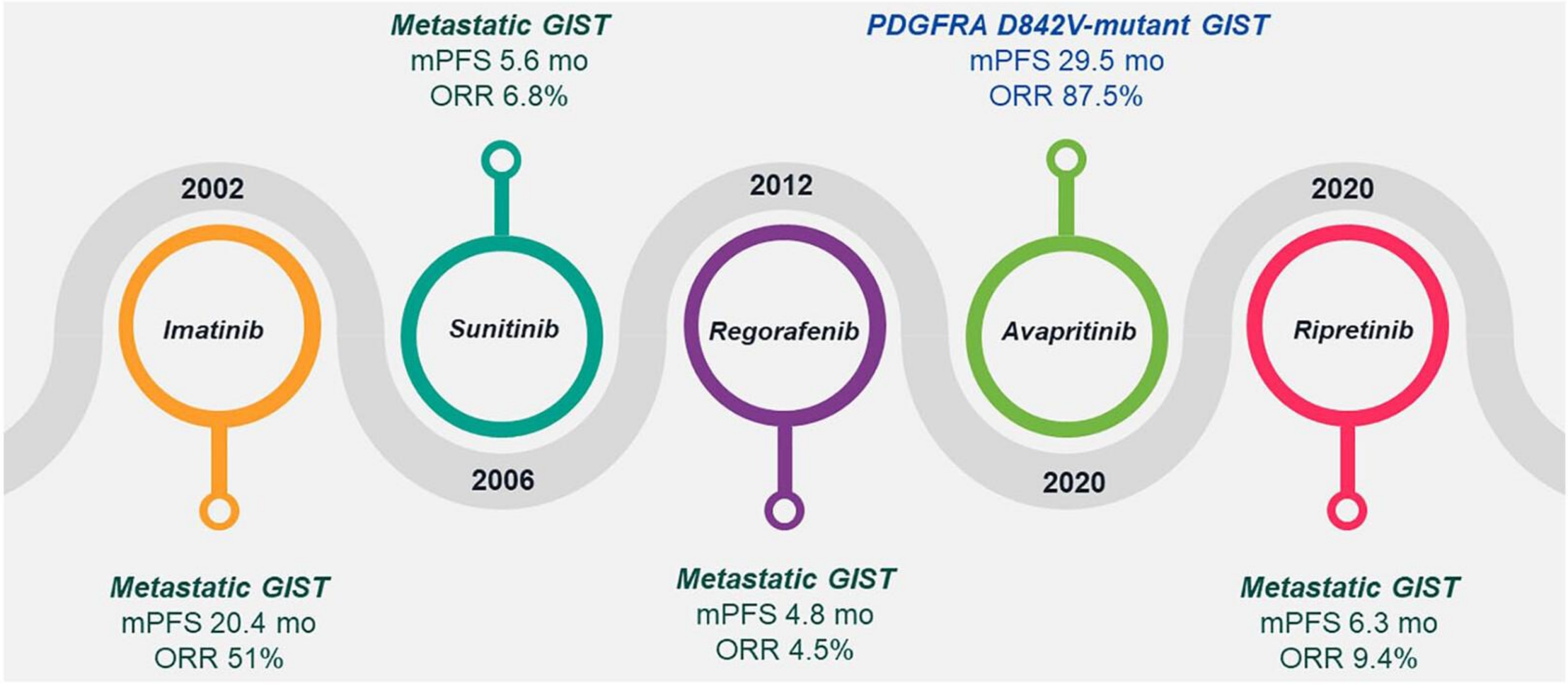
Gastrointestinal Stromal Tumors

- Most common sarcoma subtype
- Any part of the GI tract
  - Stomach 56%
- Majority positive for KIT (CD117) and DOG1
- 75% harbor gain of function KIT mutations
  - Exon 11 in ~2/3
  - Exon 9 in 8-10%, most commonly in small/large intestines
- PDGFRA mutations in ~10%
  - Usually stomach
  - Exon 18 D842V ~70% of PDGFRA mutations



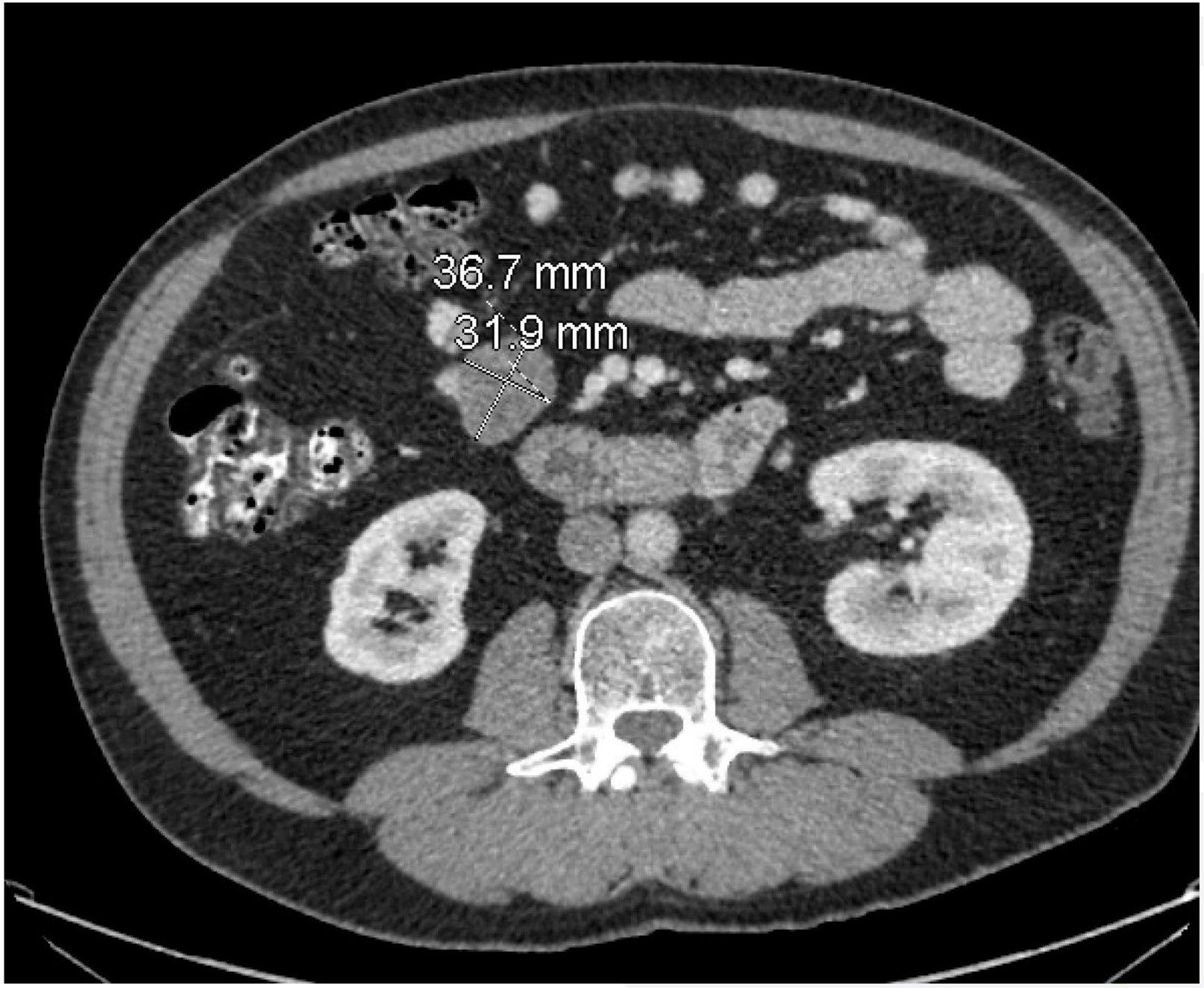
Kelly CM, et al. *J Hematol Oncol*. 2021;14(1):2.

FDA-Approved TKIs in GIST



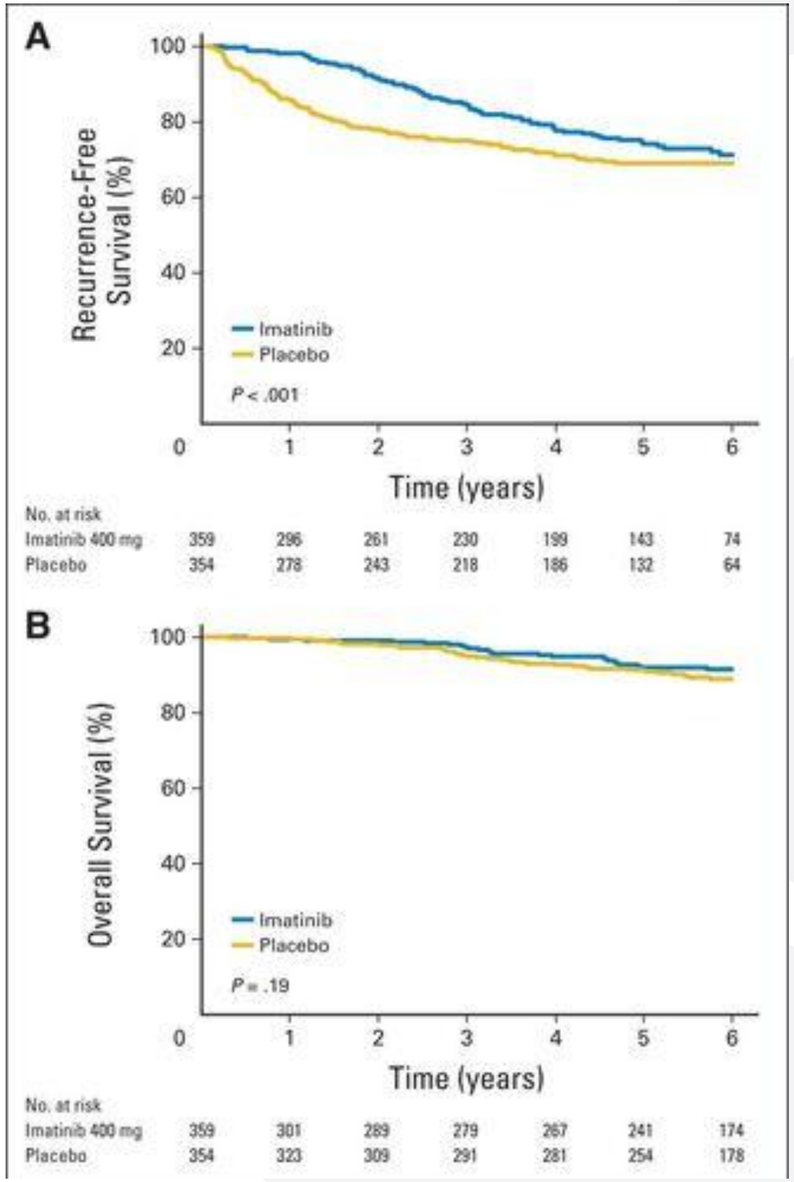
Lostes-Bardaji MJ et al. *Ther Adv Med Oncol*. 2021;13:1758835920986498.

Treatment of localized GIST



ACOSOG Z9001

- Primary GIST at least 3 cm
- Expressed KIT (CD117) by IHC
  - mutation testing not performed
- Double blind RCT of 1 year of adjuvant imatinib 400 mg daily vs. placebo.
- Crossover allowed upon progression
  - Also allowed to increase to 800 mg/day
- RFS at 1 year: 98% vs. 83% (HR 0.35; p<0.0001). No difference in OS.



Dematteo RP et al. *Lancet*. 2009; 373(9669):1097-104.
Corless CL et al. *J Clin Oncol.* 2014; 32(15):1563-70.

SSG XIII/AIO

- High risk by NIH consensus criteria
  - >10 cm, mitotic count > 10 mitoses/50 hpf, or >5 cm and mitotic index >5, or tumor rupture
- Imatinib 400 mg daily for 1 or 3 years
  - randomized, open label
- 10-year RFS 71.4% vs. 53.0%
- 10-year OS 79% vs. 65.3%

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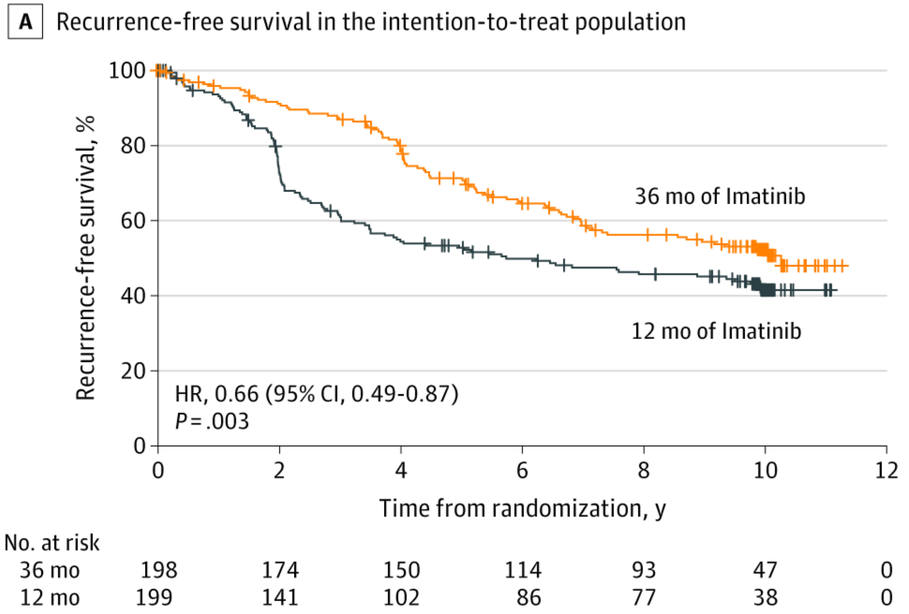
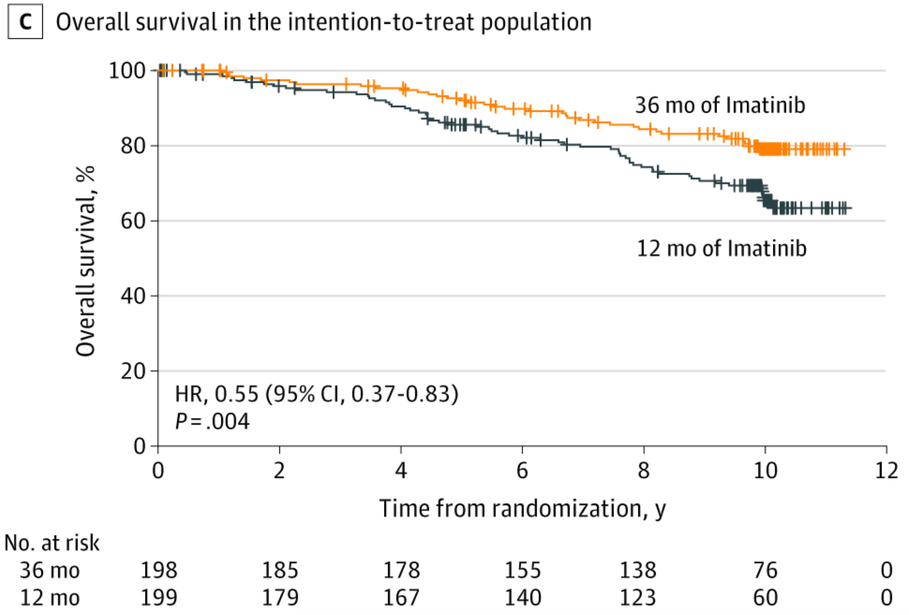
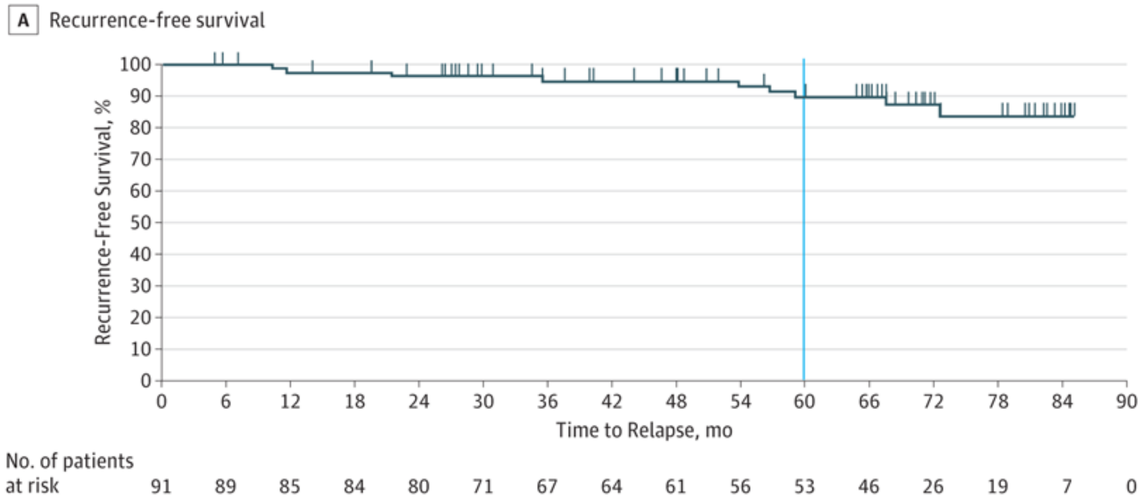




Joensuu H et al. *JAMA*. 2012;307(12):1265–1272.
Joensuu H et al. *JAMA Oncol*. 2020;6(8):1241–1246.

PERSIST-5



- Phase 2 study of 91 patients with resected GIST at intermediate or high risk of recurrence
- Imatinib 400 mg daily for 5 years
- 5-year RFS 90%
- 5-year OS 95%
- Only 1 patient recurred while on imatinib
  - PGDFRA D842V mutation
- 45 (49%) of patients stopped treatment early

Raut CP et al. *JAMA Oncol.* 2018;4(12):e184060.

Neoadjuvant therapy in GIST

- Locally advanced, unresectable/borderline resectable
- High-morbidity surgery/multivisceral resection
- Rupture or bleeding risk
- Sensitive genotype



Efficacy of neoadjvuant imatinib

Meta-analysis

- Meta-analysis of 36 studies
- R0 resection rate 89%
- Response rate 67%
- Mean duration 8.41 ± 0.367 months
- KIT exon 9 mutation associated with poorer 5-yr DFS

	1-year	3-year	5-year
DFS	99%	89%	79%
OS	100%	89%	79%

Lam TJR et al. World J Surg, 2024; 48: 1681-1691.

Metastatic GIST



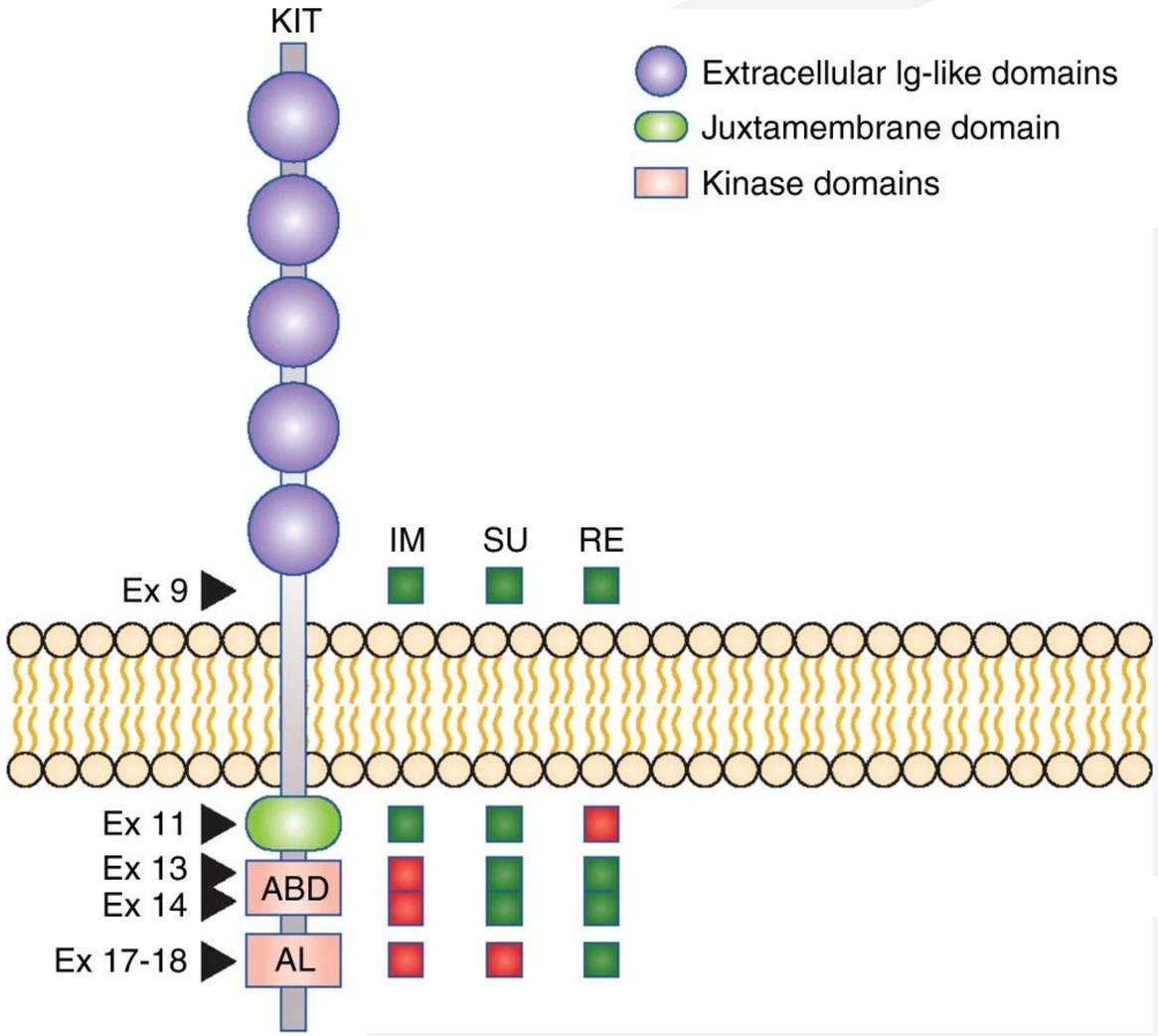
Treatment Options in Metastatic GIST

	Imatinib	Sunitinib	Regorafenib	Ripretinib	Avapritinib
Year Approved	2002	2006	2013	2020	2020
Indication	1st line	2nd line	3rd line	4th line	PDGFRA exon 18 mutation including D842V
Efficacy	ORR 53.7% mPFS 24.0 months 10-yr OS 23%	ORR 6.8% mPFS 5.6 months	ORR 4.5% mPFS 4.8 months	ORR 9.4% mPFS 6.3 mOS 15.1 months	ORR 91% mPFS 34 months
Major Toxicities	Edema, nausea, diarrhea	Fatigue, diarrhea, skin discoloration, nausea	Hypertension, HFS, diarrhea	Alopecia, fatigue, nausea, abdominal pain	Nausea, fatigue, edema, anemia diarrhea, cognitive impairment

1. Demetri GD et al. *N Engl J Med.* 2002 Aug 15;347(7):472-80.
2. Heinrich MC et al. *JAMA Oncol.* 2017;3(7):944–952.
3. Demetri GD et al. *Lancet*. 2006;368(9544):1329-38.
4. Demetri GD et al. *Lancet*. 2013;381(9863):295-302.
5. Blay JY, et al. *Lancet Oncol.* 2020;21(7):923-934.
6. Jones RL et al. *Eur J Cancer.* 2021;145:132-142.
7. Schaefer IM et al. *Am Soc Clin Oncol Educ Book*. 2022;42:1-15.

Do Secondary Mutations Matter?

- Sunitinib is active against secondary mutations in KIT exons 13/14 (ATP-binding pocket) but less active against exons 17/18 (activation loop)
- Ripretinib was designed to be active against a wide variety of KIT and PDGFRA mutations

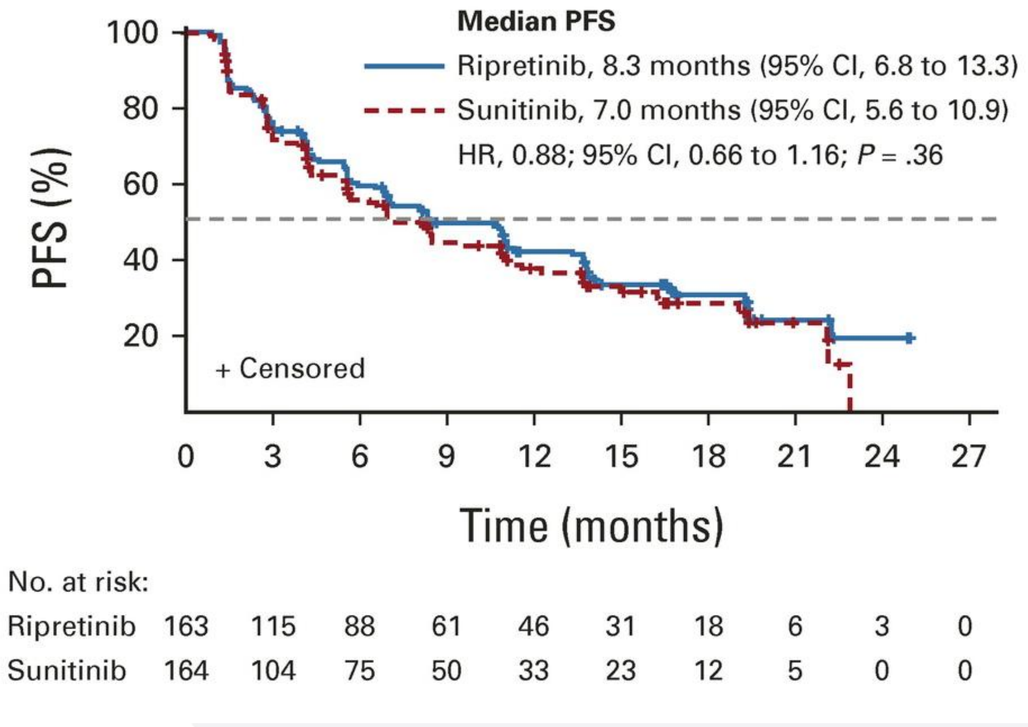


Bauer S et al. *J Clin Oncol*. 2022;40(34):3918-3928.
Smith BD et al. *Cancer Cell. 2019;* 35:738-751.
Napolitano, A., Vincenzi, B. *Br J Cancer. 2019;* 120: 577–578.

Intrigue

Ripretinib vs. Sunitinib in 2nd line GIST

- Open-label randomized phase III study of patients with metastatic GIST with imatinib resistance/intolerance
- No significant difference in PFS
- Ripretinib associated with fewer AEs and better PRO scores of tolerability

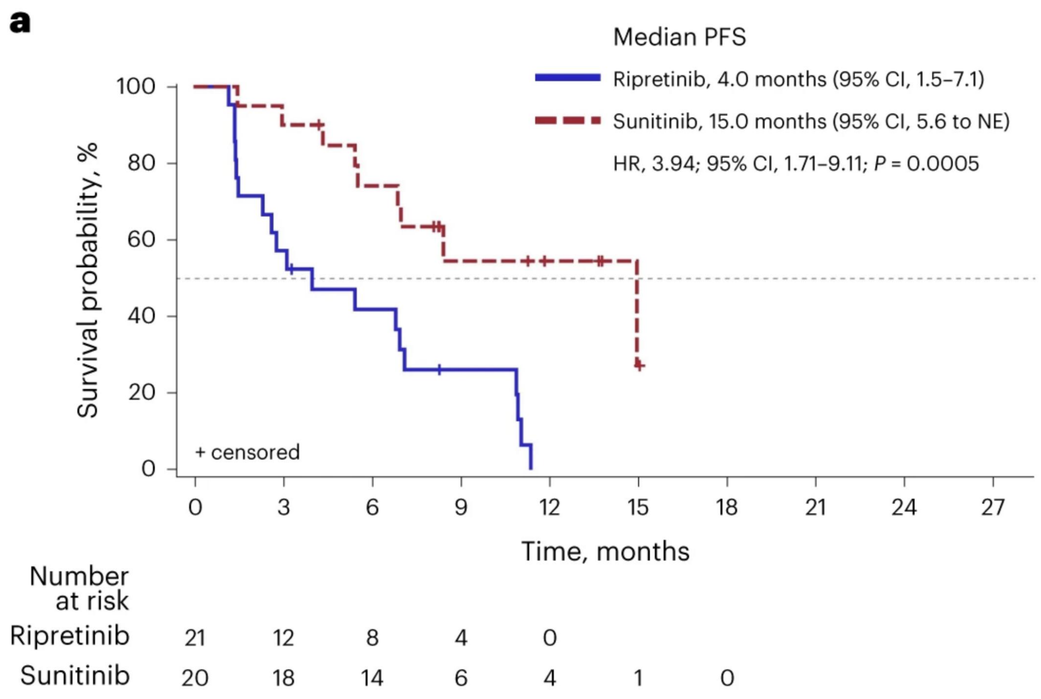


Bauer S et al. *J Clin Oncol*. 2022;40(34):3918-3928.

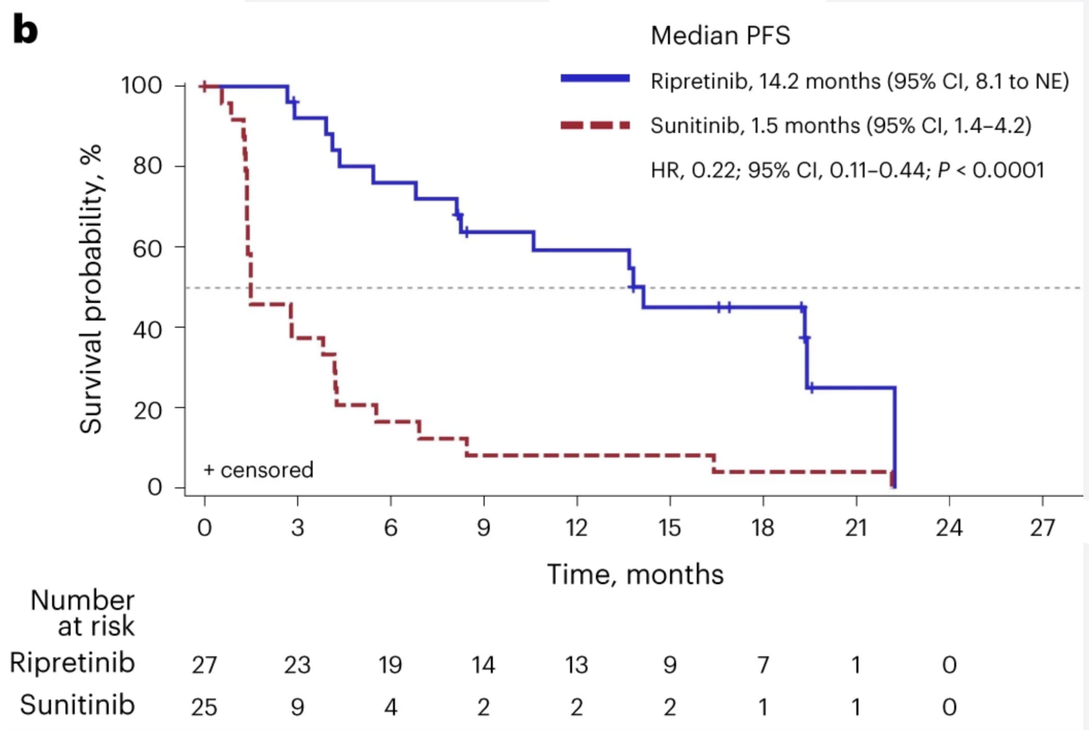
Impact of Secondary Mutations on TKI Response

ctDNA Biomarker Analysis of INTRIGUE

KIT Exon 11 + 13/14



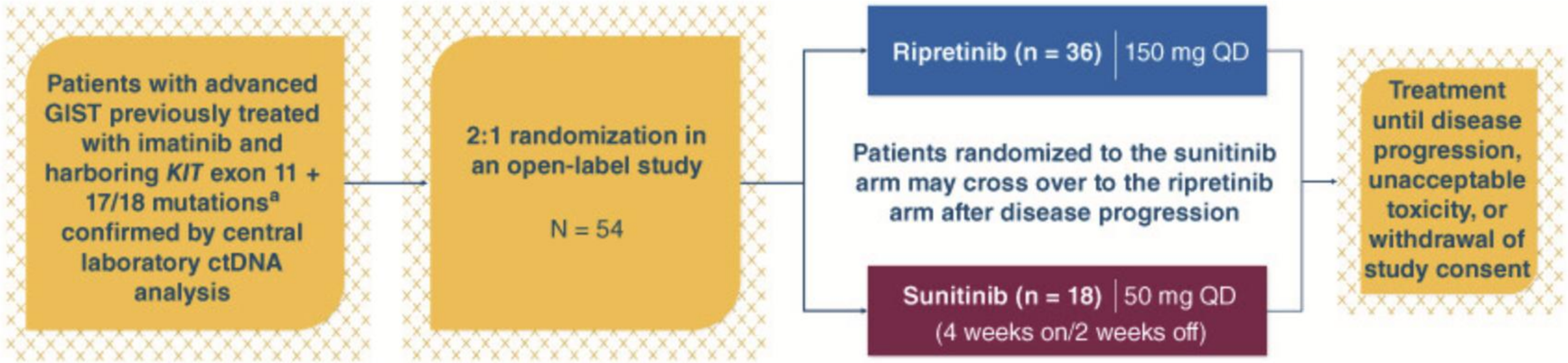
KIT Exon 11 + 17/18



Heinrich MC et al. *Nat Med.* 2024 Feb;30(2):498-506.

INSIGHT

- Prospectively study of patients with GIST exon 11 and secondary exon 17/18 mutations 2:1 randomized to ripretinib and sunitinib
- Shows importance of molecular profiling of GIST after progression
  - However, yield of ctDNA in GIST is relatively low



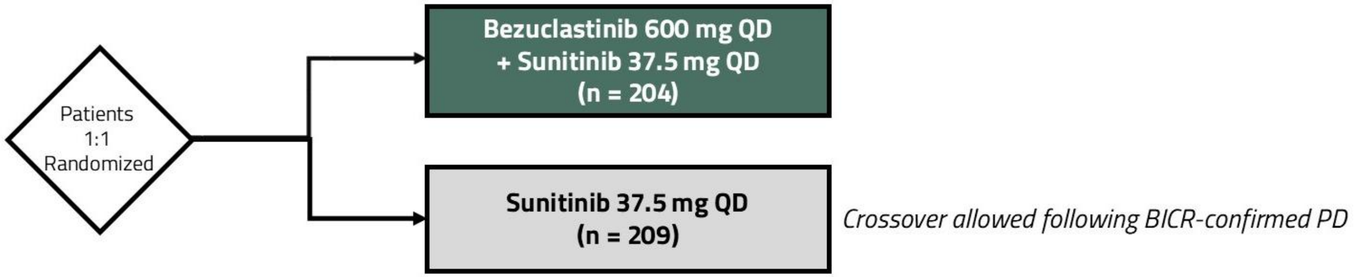
George, S. et al. *Future Oncology*, 20(27), 1973–1982.

Emerging Treatments

Bezuclastinib

- Active against KIT primary KIT mutations(exons 9 and 11) and activating loop mutations (exons 17 and 18)
- Highly selective, lacking activity against VEGFR2 and PDGFR.
  - Can be combined with TKIs with that have activity against ATP-binding pocket mutations (exons 13 and 14)

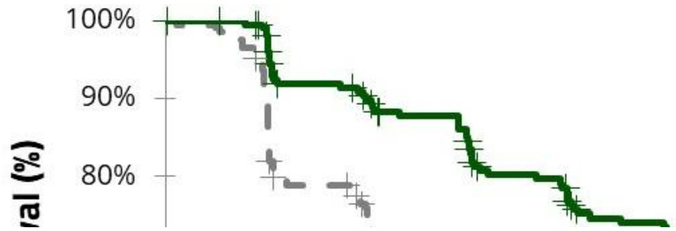
PEAK Trial



- Randomized open label phase 3 trial
- 2nd line after progression on imatinib

Wagner AJ et al. J Clin Oncol 44, 2026 (suppl 16; abstr 11500)

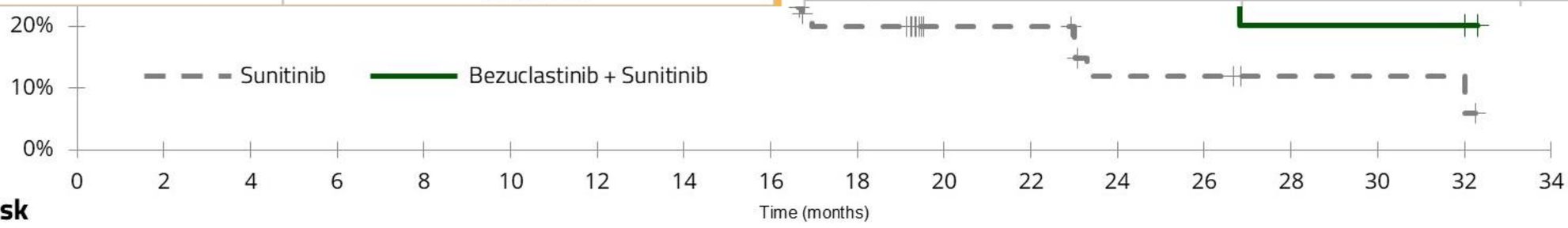
Bezuclastinib plus sunitinib



Median PFS	
Bezuclastinib + Sunitinib	**16.5 months** *95% CI (13.8 to 19.2)*
	9.2 months

Objective Response	Bezuclastinib + Sunitinib (n=204)	Sunitinib (n=209)
Objective response, % (95% CI)	**45.6** (38.6-52.7)	**25.8** (20.0-32.3)
P value[a]	**<0.0001**	

Additional End Points	Bezuclastinib + Sunitinib (n=204)	Sunitinib (n=209)
Disease control rate,%[b] (95% CI)	**86.8** (81.3-91.1)	**76.1** (69.7-81.7)
Median duration of response,[c] mos (95% CI)	**15.7** (12.2-NE)	**12.0** (7.6-14.9)



Patients at Risk

Bezuclastinib + Sunitinib	204	180	166	146	130	119	102	76	72	51	24	23	8	6	2	2	2	0
Sunitinib	209	161	137	113	97	85	64	39	35	19	9	9	4	4	2	2	2	0

Wagner AJ et al. J Clin Oncol 44, 2026 (suppl 16; abstr 11500)

PEAK: Toxicities

- TEAEs reported at a higher frequency in the combination arm:
  - ALT/AST increase
  - Taste disorder
  - Hair color change

All grade TEAEs ≥ 20% in either treatment arm

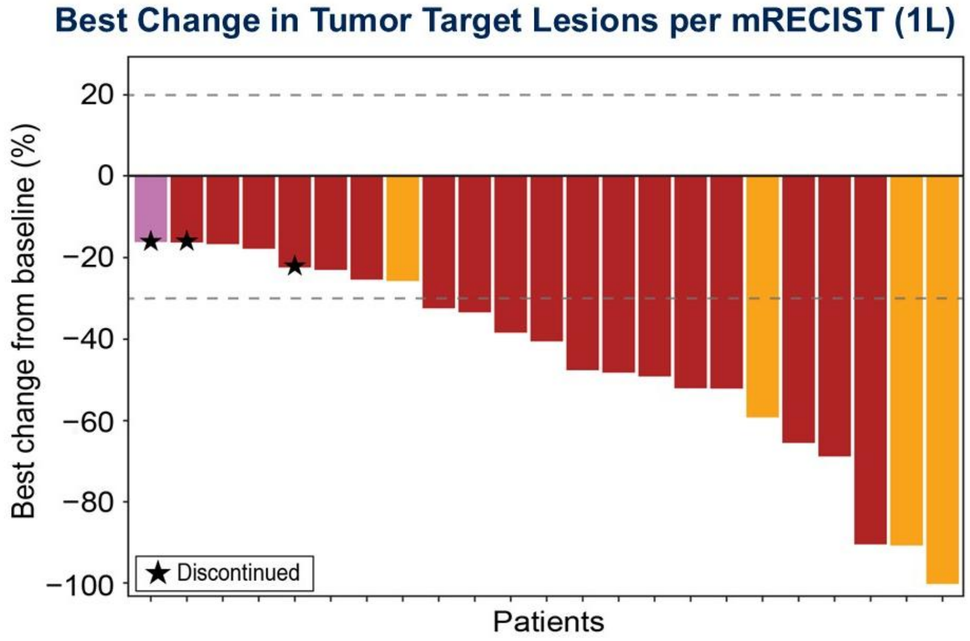
	Bezuclastinib + Sunitinib (n=204)		Sunitinib (n=208)[a]	
Preferred term, n (%)	**All Grade**	**Grade 3+**	**All Grade**	**Grade 3+**
Diarrhea	159 (77.9)	16 (7.8)	138 (66.3)	15 (7.2)
ALT/AST increased[b]	115 (56.4)	22 (10.8)	35 (16.8)	3 (1.4)
Hypertension	106 (52.0)	60 (29.4)	108 (51.9)	57 (27.4)
Taste disorder[b]	97 (47.5)	0	52 (25.0)	0
Nausea	81 (39.7)	1 (0.5)	56 (26.9)	2 (1.0)
Hair color changes	79 (38.7)	0	37 (17.8)	0
Fatigue	72 (35.3)	9 (4.4)	70 (33.7)	5 (2.4)
Neutropenia[b]	71 (34.8)	31 (15.2)	70 (33.7)	32 (15.4)
PPE	59 (28.9)	6 (2.9)	95 (45.7)	5 (2.4)
Vomiting	56 (27.5)	2 (1.0)	45 (21.6)	4 (1.9)
Decreased appetite	55 (27.0)	6 (2.9)	46 (22.1)	0
Anemia	54 (26.5)	19 (9.3)	42 (20.2)	10 (4.8)
Abdominal pain	51 (25.0)	6 (2.9)	52 (25.0)	4 (1.9)
Stomatitis	46 (22.5)	6 (2.9)	68 (32.7)	10 (4.8)
GERD	45 (22.1)	0	30 (14.4)	0
Dyspepsia	43 (21.1)	5 (2.5)	29 (13.9)	0
Thrombocytopenia[b]	39 (19.1)	2 (1.0)	55 (26.4)	9 (4.3)

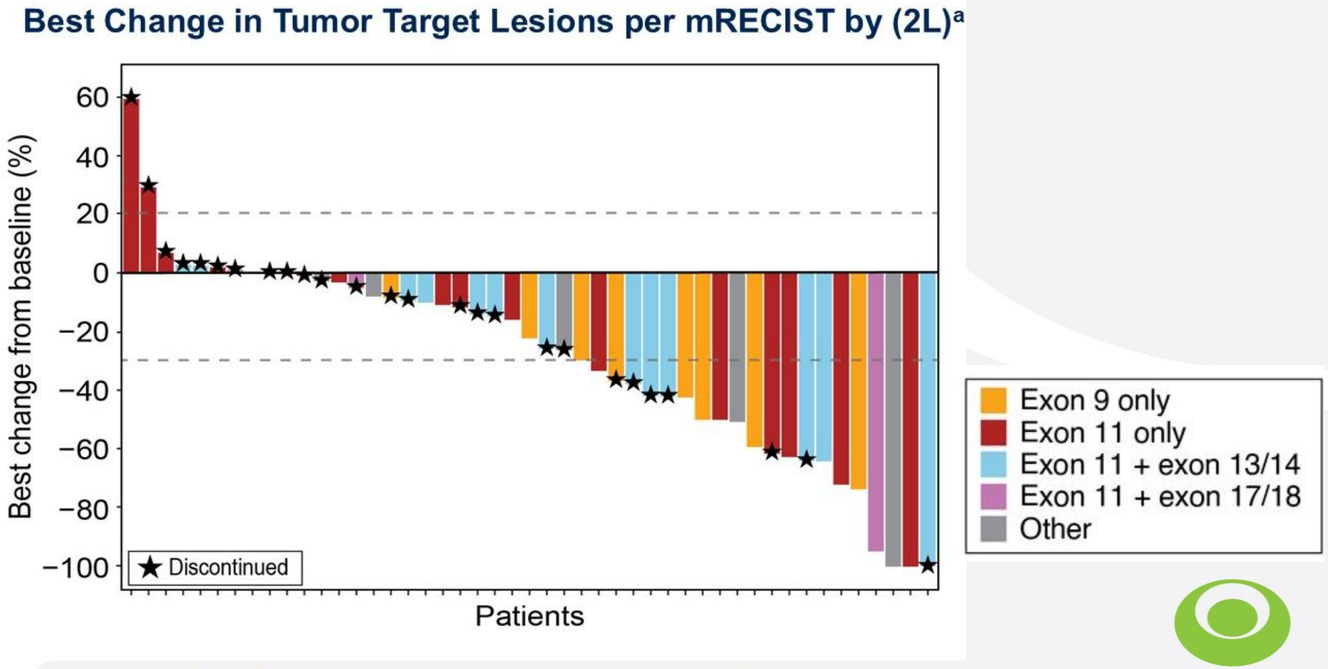
Wagner AJ et al. J Clin Oncol 44, 2026 (suppl 16; abstr 11500)

Velzatinib

StrateGIST-1

- Highly selective KIT inhibitor targeting a broad spectrum of KIT mutations
- Activity against exons 9 and 11 as well as secondary mutations in exons 13, 17, and 18
- 1st line: unconfirmed ORR 65%
- 2nd line: unconfirmed ORR 40%, mPFS 13.7 months
- Most common AEs: diarrhea, nausea, dysgeusia, neutropenia





Jones RL et al. J Clin Oncol 44, 2026 (suppl 16; abstr 11501)

TKI Sensitivity by Mutation Status

KIT mutation	Imatinib	Sunitinib	Regorafenib	Ripretinib	Avapritinib	Bezuclastinib	Bezu + sunitinib	Velzatinib
Primary								
Exon 11	High	High	High	High	Mod	High	High	High
Exon 9	Mod	High	Mod	High	Mod	Mod	High	High
Secondary: ATP pocket								
Exon 13 V654A	Low	High	Mod	Mod	Low	Low	High	High
Exon 14 T670I	Low	High	Mod	Mod	Low	Low	High	High
Secondary: activation loop								
Exon 17 D816/N822/Y823	Low	Low	Mod	High	High	High	High	High
Exon 18 A829P	Low	Low	Low	High	Mod	Mod	High	High

High sensitivity Moderate / partial Low / resistant Limited data or inferred

Summary

- Systemic management of GIST is guided by molecular classification in both the localized and metastatic setting.
- In the adjuvant setting, 3 years of imatinib is recommended, but extended duration of imatinib can be considered.
- In the neoadjuvant setting, multidisciplinary discussion should determine the duration of therapy
- Following the typical sequence of TKIs in the metastatic setting appears to no longer be the best way forward
- Identification of secondary mutations may influence treatment options