LIFEFEST2026

Nashville

The Grand Ole Update: Latest from the GIST Stage

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LIFE FEST 2026• PATIENT & CAREGIVER MEETING

The Grand Ole Update: *Latest from the* GIST stage

A QUICK REFRESHER

Why does GIST treatment get harder over time?

GIST tumors are driven by mutations in a gene called KIT. Imatinib (the usual first treatment) works well against the **original** mutation — but over time, tumors often develop **new, additional** mutations that let them escape the drug.

1

Primary mutation

Drives the original tumor. Imatinib usually controls this well.

→

2

Resistance mutations emerge

~60% of patients within 2 years. Different patients develop different ones.

→

?

One drug isn't enough

Each later medicine only blocks *some* of the new mutations.

Newer studies today try to close that gap — either by matching therapy to the known alteration, or broader coverage of resistance mechanisms by combination strategies

PART 1

The PEAK Study: Global, Randomized, Open-Label Phase 3 Study Evaluating the Efficacy and Safety of Bezuclastinib + Sunitinib versus Sunitinib as 2nd line treatment Post- Imatinib (NCT05208047)

Bezuclastinib + sunitinib vs. sunitinib alone — results just presented at ASCO 2026

PEAK STUDY — RATIONALE

Sequential monotherapies only cover a subset of mutations

Primary	**Exon 9 — ~10% of patients**	**Exon 11 — ~67% of patients**
Secondary (resistance)	**Exons 13 / 14** — ATP-binding pocket	**Exons 17 / 18** — activation loop

~60%

of patients develop resistance within 2 years of starting imatinib

Resistance mutations vary **patient to patient — even lesion to lesion** , so each later-line monotherapy (sunitinib, regorafenib, ripretinib) only blocks part of the spectrum, and combining approved KIT inhibitors has been limited by overlapping toxicity

Inhibition coverage by exon

	Current monotherapy*				Combination
Exon	Imatinib	Sunitinib	Regorafenib	Ripretinib	Bezuclastinib + sunitinib
9	Moderate	Strong	Strong	Moderate	Strong
11	Strong	Strong	Strong	Strong	Strong
13	None	Strong	None	Moderate	Strong
14	None	Strong	Strong	None	Strong
17	None	None	Moderate	Strong	Strong
18	None	None	Strong	Strong	Strong

Inhibition: None | Moderate | Strong

PEAK STUDY

What was studied?

PEAK is a large, global phase 3 trial for people whose GIST progressed on imatinib (second-line treatment). It compared:

- **Bezuclastinib + sunitinib** (combination, n=204) — bezuclastinib is an investigational medicine, not yet approved outside clinical trials

- **Sunitinib alone** (standard second-line treatment, n=209)

BY THE NUMBERS

413
patients worldwide

1:1
randomly assigned to each group

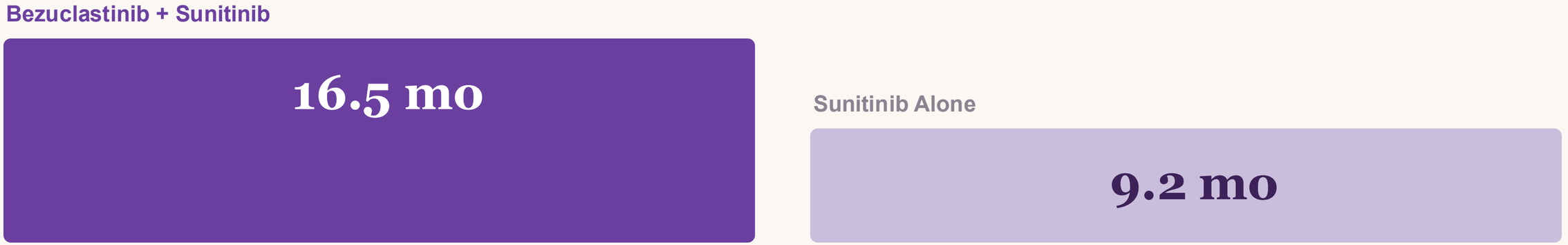
Main question
Does the combination keep the disease under control longer?

Population was representative of patients with second line GIST and balanced on both arms

- ~90% had documented KIT mutations on each arm
- 64% male
- Average age 63yrs

PEAK STUDY — HEADLINE RESULT

The combination kept disease under control significantly longer



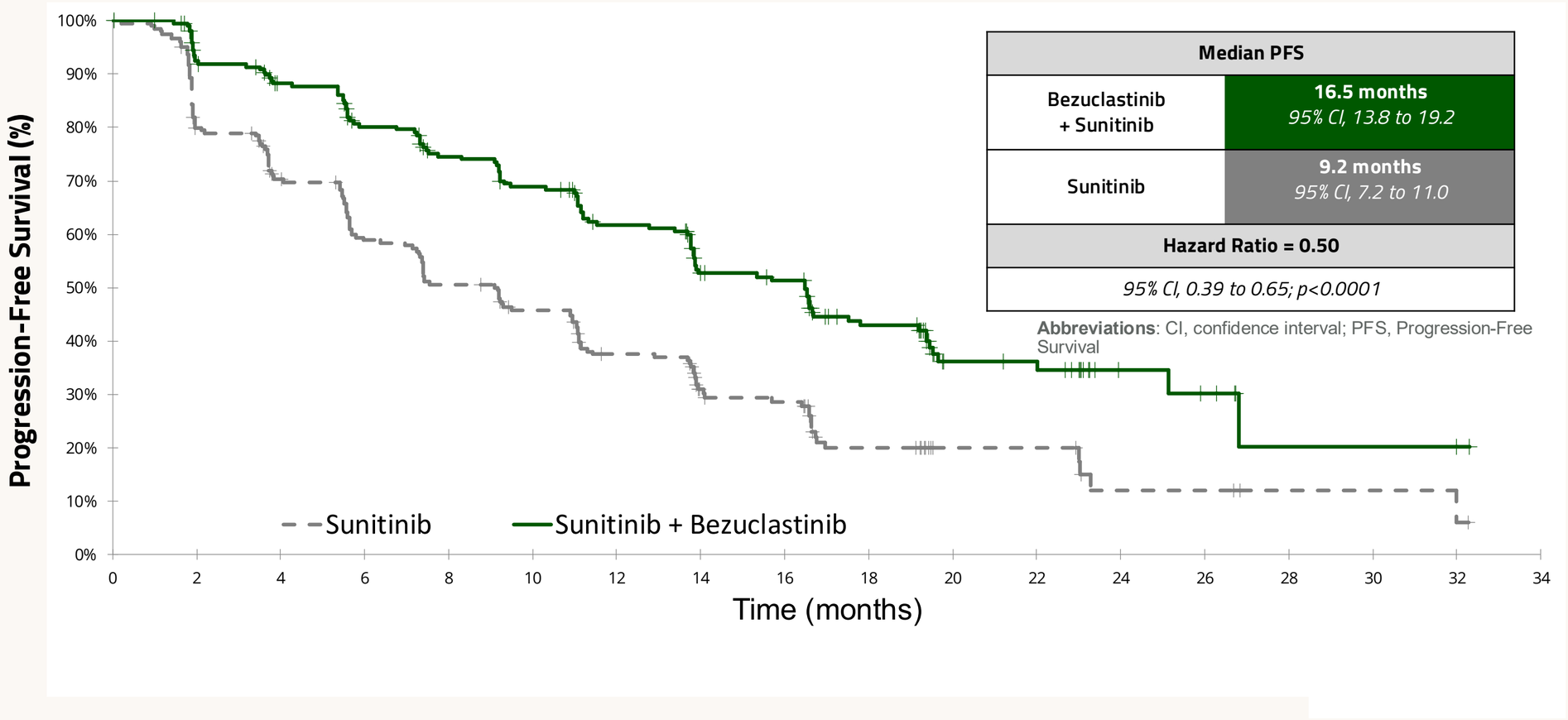
Median progression-free survival — how long, on average, before the disease worsened

50% lower risk of the disease progressing or death with the combination, compared to sunitinib alone **(statistically significant, p<0.0001)**

Data cutoff: Sept 30, 2025

PEAK STUDY

Curves Showing How Many Patients Remain Progression Free as Time Progresses on Each Arm



Median PFS	
Bezuclastinib + Sunitinib	**16.5 months** *95% CI, 13.8 to 19.2*
Sunitinib	**9.2 months** *95% CI, 7.2 to 11.0*
Hazard Ratio = 0.50	
95% CI, 0.39 to 0.65; p<0.0001	

Abbreviations: CI, confidence interval; PFS, Progression-Free Survival

PEAK STUDY — TUMOR RESPONSE

More patients saw their tumors shrink on combination

Tumor shrinkage (objective response)

Disease control (shrinkage or stable)

A small number of patients (6.4% combination vs 1.9% sunitinib) had a complete response — no detectable tumor on scans.

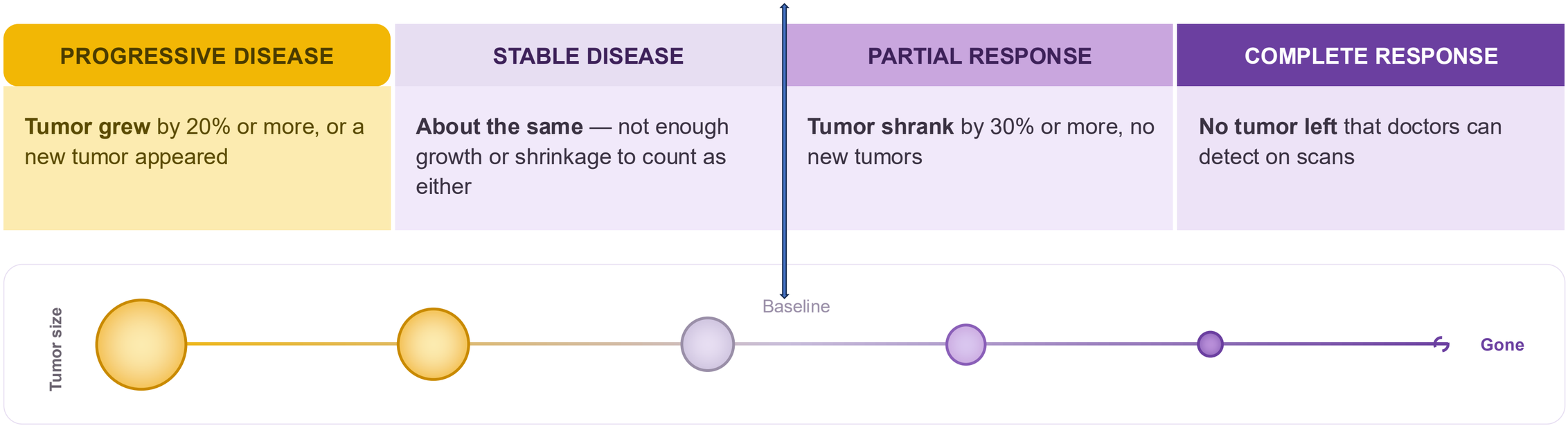
Data cutoff: Sept 30, 2025

RESPONSE RATE on TRIALS — A QUICK DEFINITION

What does "response" mean on a scan?

Every few months, patients get a scan. Doctors compare the tumor size to the last scan and sort the result into one of four categories:

PROGRESSIVE DISEASE	STABLE DISEASE	PARTIAL RESPONSE	COMPLETE RESPONSE
Tumor grew by 20% or more, or a new tumor appeared	**About the same** — not enough growth or shrinkage to count as either	**Tumor shrank** by 30% or more, no new tumors	**No tumor left** that doctors can detect on scans



PEAK STUDY — SAFETY

Generally well tolerated, no new safety concerns

Most common side effects reported

- Diarrhea
- Elevated liver enzymes*
- High blood pressure
- Taste changes
- Nausea
- Hair color changes
- Fatigue

*Liver enzyme elevations were mostly mild, without symptoms, and went away — very few patients had to stop treatment because of them.

Patients on the combination had **lower** rates of some sunitinib side effects, including hand-foot skin reactions, mouth sores, and low platelet counts.

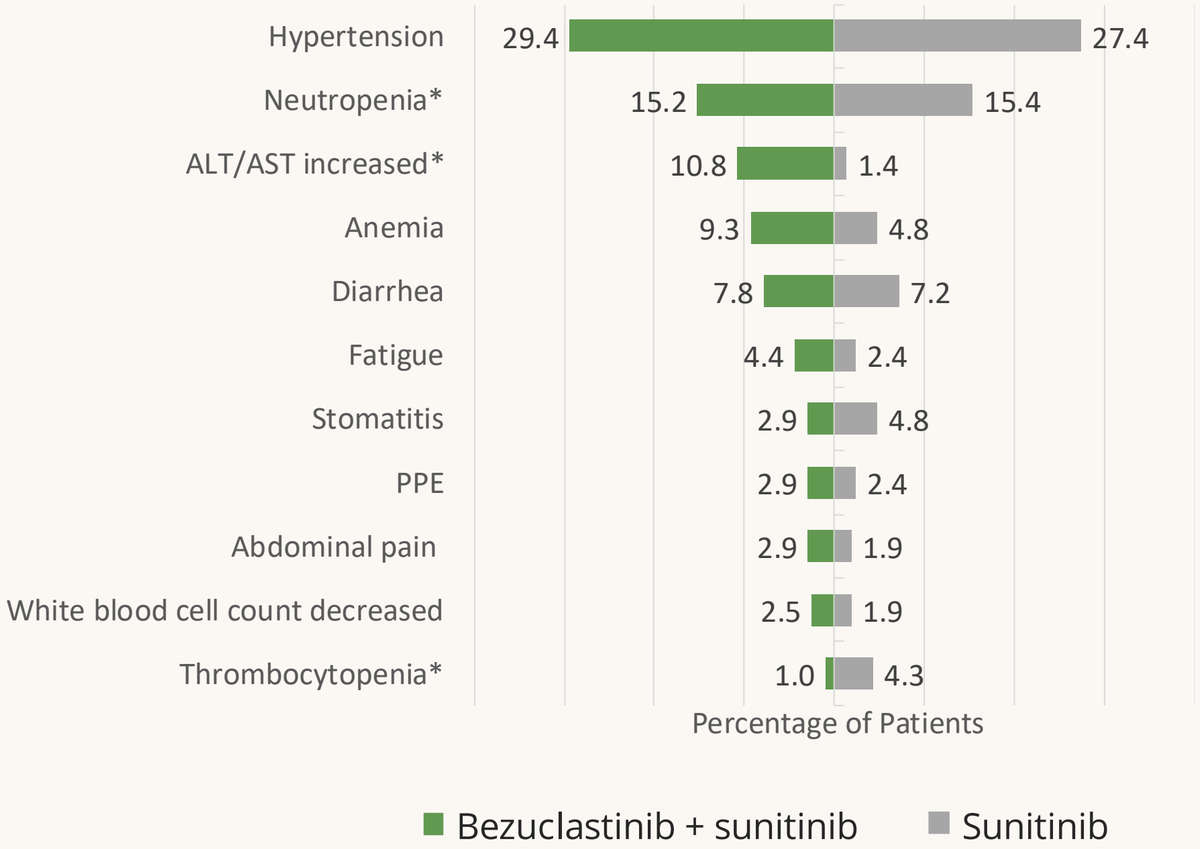
0
treatment-related deaths on the combination

Similar
overall rates of side effects between both groups

No new risks
identified with the combination

PEAK STUDY — SAFETY

Incidence of Higher-Grade Safety Events (≥grade 3) Balanced



Key Safety Findings

ALT/AST increase and anemia reported at higher incidence in the combination arm

No increase in frequency of severe events observed in combination arm for some key risks seen with sunitinib (hypertension, neutropenia and diarrhea)

PEAK STUDY — TAKEAWAY

What this means, in plain terms

✓ The combination controlled disease roughly **7 months longer** than sunitinib alone, on average

✓ Nearly **twice as many** patients had tumor shrinkage

✓ Side effects were **manageable**, with no new safety concerns

✓ Mutational heterogeneity of GIST resistance more effectively treated with the combination of two kinase inhibitors, bezuclastinib + sunitinib

✓ Currently access to the combination for any line therapy is available via an **Expanded Access Protocol**

ⓘ Bezuclastinib is still investigational — it is not yet FDA-approved for routine use outside of clinical trials or expanded access

PART 2

The INSIGHT Study

Ripretinib vs. sunitinib in a specific KIT mutation group (exon 11 +17/18) — enrollment complete, results expected November 2026

INSIGHT STUDY

Why this study? A clue from earlier research

EARLIER TRIAL (INTRIGUE)

Compared ripretinib to sunitinib broadly. Overall, ripretinib was **not** superior to sunitinib for most patients.

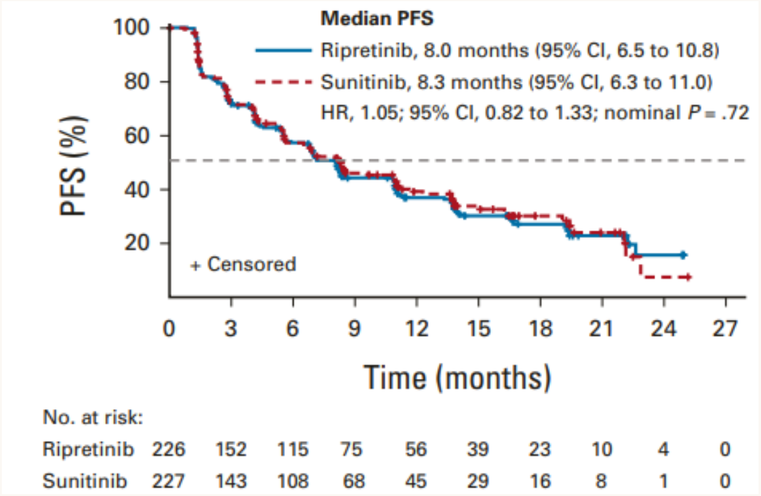
→

BUT LOOKING CLOSER...

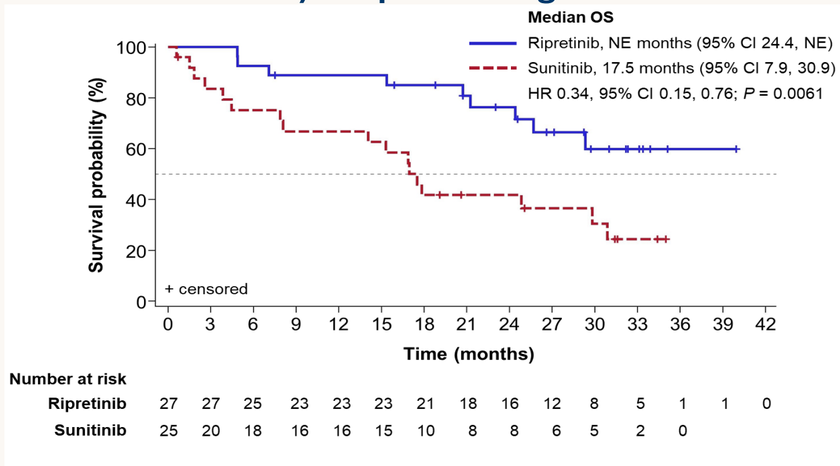
Patients whose tumors carried **both** a KIT exon 11 mutation **and** an exon 17/18 mutation seemed to do notably better on ripretinib than on sunitinib.

INSIGHT was designed to test this idea directly: does ripretinib work better than sunitinib specifically for patients with this exon 11 + 17/18 mutation pattern?

Progression- Free-Survival of Ripretinib vs Sunitinib Arms



Exploratory Analysis: KIT exon 11 + 17/18 population on Ripretinib vs Sunitinib (excludes KIT exons 9/13/14) : Superior Progression Free and Overall Survival



INSIGHT STUDY

Who was studied, and how

Who could join

- GIST that progressed after 1 prior imatinib treatment
- Confirmed KIT exon 11 + 17 and/or 18 mutation (via a blood test)
- Exon 9, 13, or 14 mutations excluded

How the study was run

- 54 patients, randomized **2:1** to ripretinib or sunitinib
- Patients on sunitinib could cross over to ripretinib after progression
- Main question: which controls the disease longer (PFS)?

Ripretinib is FDA-approved today as a later-line (4th-line+) GIST treatment. INSIGHT is testing if using it earlier is advantageous.

INSIGHT STUDY — WHERE THINGS STAND

Enrollment is complete — results expected soon

Enrollment complete
All 54 patients enrolled

You are here — today
July 2026

Results expected
Around November 2026

LOOKING AHEAD

If both studies read out positively, how might 2nd line treatment sequencing change?

Pending regulatory review.

TODAY'S TYPICAL SEQUENCE

1ST LINE	2ND LINE	3RD LINE	4TH LINE
Imatinib	Sunitinib alone	Regorafenib	Ripretinib

LIKELY FUTURE SEQUENCE

1st line: Imatinib	2nd line: Bezuclastinib + sunitinib — likely new standard	3rd line: Regorafenib ??	4th line: Ripretinib ??

IF BOTH PEAK AND INSIGHT ARE POSITIVE —

1st line: Imatinib	KIT exon 11 + 17/18 confirmed:	combination or ripretinib alone — patient or physician preference
	All other mutations:	combination remains the 2nd-line standard

Some patients may stay on sunitinib alone

If someone is already stable and tolerating sunitinib well, continuing it rather than switching may still make sense — a decision made with their care team.

Some may prefer ripretinib alone, earlier

If a patient's resistance mutation is known to match the exon 11 + 17/18 pattern INSIGHT studies, ripretinib monotherapy could become a preferred earlier option — pending INSIGHT's results.

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