

First-in-Human Administration of the Mitochondria-Targeted Hsp90 Inhibitor Gamitrinib: A Case Report in a Patient with Advanced Gastrointestinal Stromal Tumor (NCT04827810)

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Background

Gastrointestinal stromal tumors (GIST):

- Resistant to traditional chemotherapy and radiation therapies;
- Limited effective options in *KIT*/*PDGFRA* tyrosine kinase resistant disease
- Secondary *KIT*/*PDGFRA* resistance mutations are polyclonal and heterogeneous, limiting the durability of sequential TKI therapy.

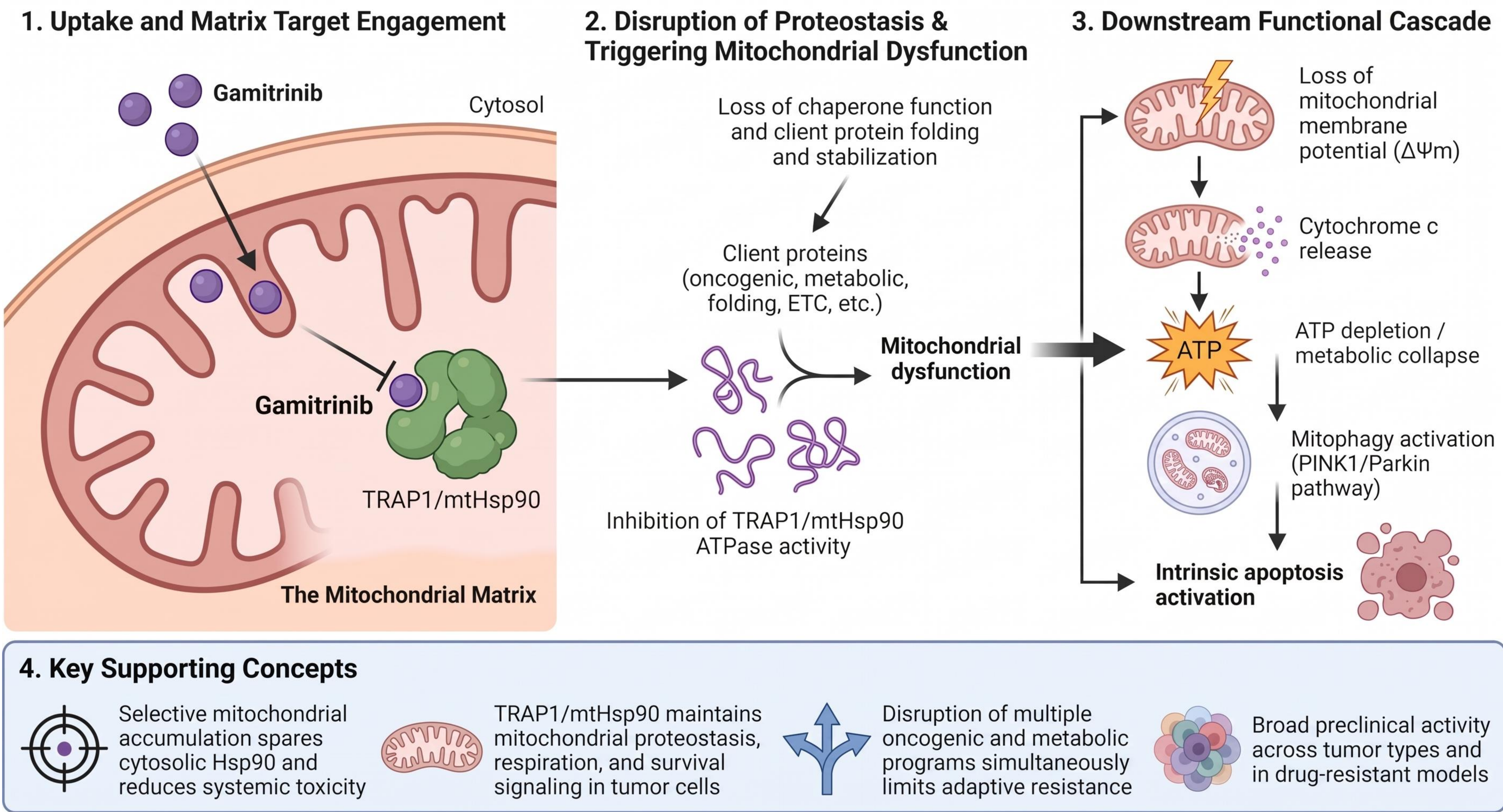
Unique therapeutic opportunity:

- Tumor cells depend on mitochondrial proteostasis and oxidative metabolism for survival under stress.
- Hsp90 chaperones stabilize oncogenic client proteins, including *KIT*; a mitochondrial Hsp90/TRAP1 pool supports tumor cell survival and is not targeted by cytosolic Hsp90 inhibitors.
- Gamitrinib is a first-in-class mitochondria-targeted Hsp90 inhibitor.

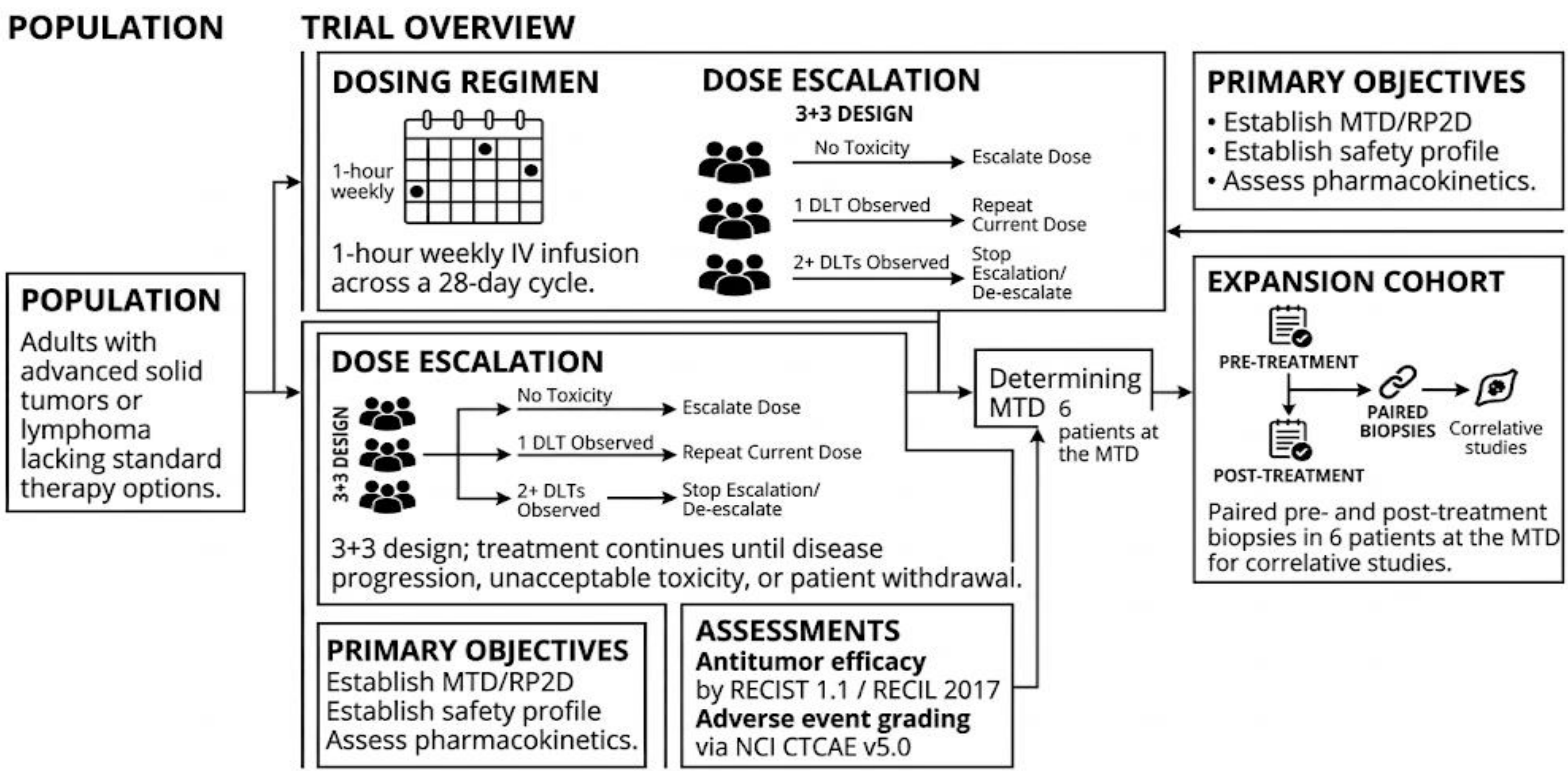
Preclinical studies:

- Antiproliferative activity across tumor cell lines (IC₅₀ 0.16-29 μ M).
- No treatment-related findings (chemistry, hematology, or histopathology) at doses up to 5 times (in rats) and 12 times (in dogs) the therapeutic dose used in mice.

Mechanism of Action



Study Design



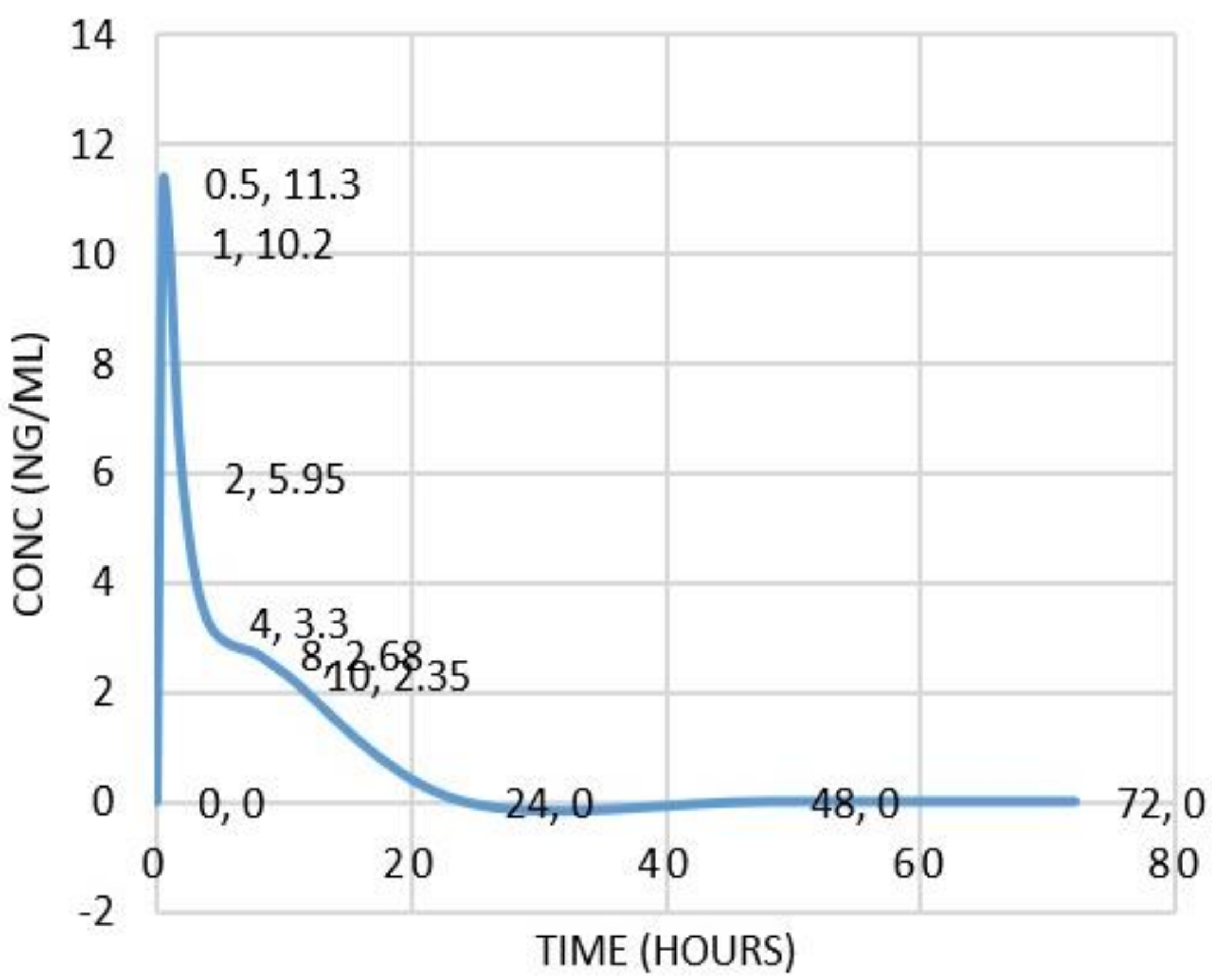
Results

Patient Profile

- 1 patient with Advanced GIST
- Enrolled at 35 mg dose level
- Rapid tumor progression through Imatinib, Sutent, Temozolomide, Regorafenib, and Repritinib
- Mutated SDHA, key subunit in complex II of the mitochondrial electron transport chain that requires mt Hsp90/TRAP1 for proper folding and activity

Clinical Trial Status

- As of June 2025, 13 patients received Gamitrinib across five dose levels (10–85 mg) with no dose-limiting toxicities (NCI CTCAE v5.0); 336 plasma samples for PK analysis collected.
- Dose-escalation continues
- No dose-limiting toxicity to date
- Twice-weekly dosing cohort added



PK Analysis | Cycle 1

C_{max} 11.3 ng/mL T_{max} 0.5h

Best Overall Response

- Safety: No DLTs
- Stable disease for ~196 days
- Disease Progression observed at cycle 7

Conclusion

Weekly intravenous gamitrinib was tolerated without DLTs. A single patient cannot establish safety or antitumor activity in this population. A dose-escalation study in advanced GIST is planned to characterize safety, pharmacokinetics, and preliminary antitumor activity.

References

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*Graphics created with AI, BioRender, Adobe Express and image modification

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