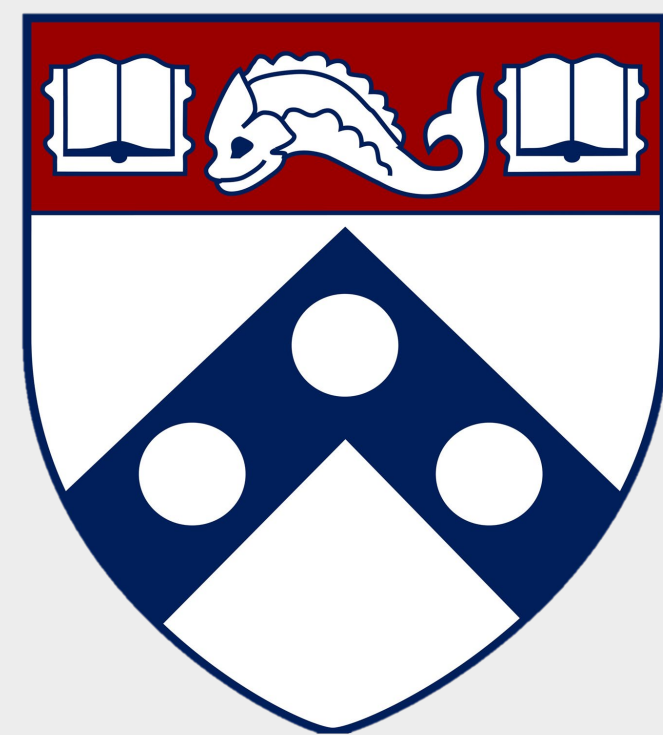




Effect of telotristat ethyl on growth of small bowel neuroendocrine hepatic metastases

Joshua K. Cho¹; David C. Metz²; Michael C. Soulen³

Hospital of the University of Pennsylvania: ¹Department of Radiology; ²Division of Gastroenterology; ³Division of Interventional Radiology

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INTRODUCTION

The novel agent telotristat ethyl (telotristat), an inhibitor of tryptophan hydroxylase (the rate limiting enzyme of serotonin synthesis) is indicated for patients with metastatic small bowel neuroendocrine tumors (NETs) who have intractable carcinoid syndrome despite somatostatin analog (SSA) therapy. It is unknown whether telotristat affects tumor growth. This single-center study analyzed the difference in hepatic metastatic growth rates before and after telotristat therapy was initiated.

METHODS

This IRB-approved retrospective cohort review studied all consecutive patients prescribed telotristat (n=35) since 2015. Index hepatic metastases were measured on all cross-sectional imaging studies performed within 12 months of telotristat initiation. Largest orthogonal dimensions were measured to calculate axial cross-sectional areas. For available computed tomography (CT) studies, the arterial phase was utilized for measurements. Whereas, for MRI studies, the sequence with clearest margins was utilized. Pre- and post-telotristat slopes of the best-fit lines were calculated in all patients with at least 2 pre- and 2 post-telotristat studies. For each patient, the pre- and post-telotristat slopes were compared utilizing the Wilcoxon sign ranked test, with statistical significance set to 0.05.

RESULTS

Nine patients with metastatic small bowel NETs were included. All were also receiving SSA therapy (octreotide or lanreotide) prior to initiation of telotristat. On average, hepatic metastases were 130% of baseline index cross-sectional area at the time of telotristat initiation and 121% of index cross-sectional area by the latest available time point after telotristat initiation. Comparing the pre- and post-telotristat area slopes (Table 1), a Wilcoxon W of 21 was calculated (p>0.20).

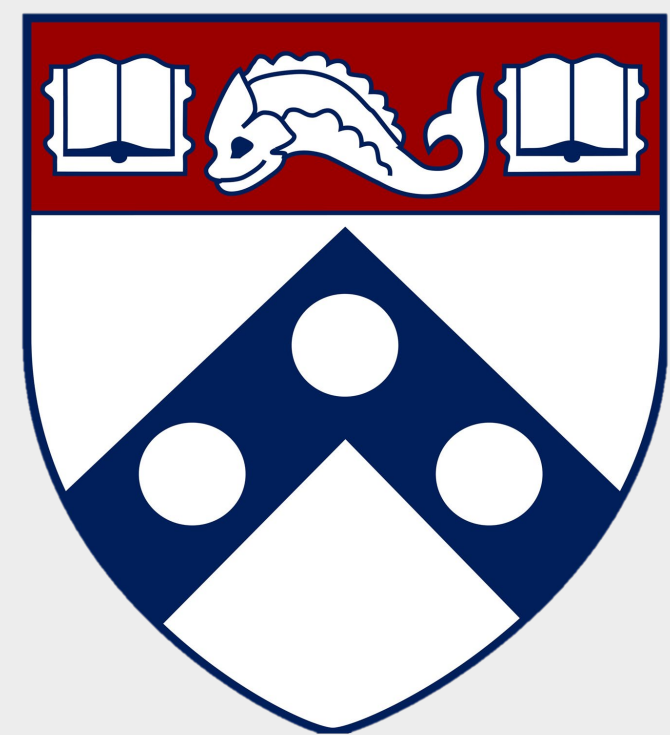
CONCLUSION

Preliminary results show that the distributions of slopes, pre- and post-telotristat initiation, are not statistically different. Notably, the study is not adequately powered for a small effect size. Whether tryptophan hydroxylase inhibition leads to downstream effects on regulatory mechanisms involved in tumor growth, is unknown.

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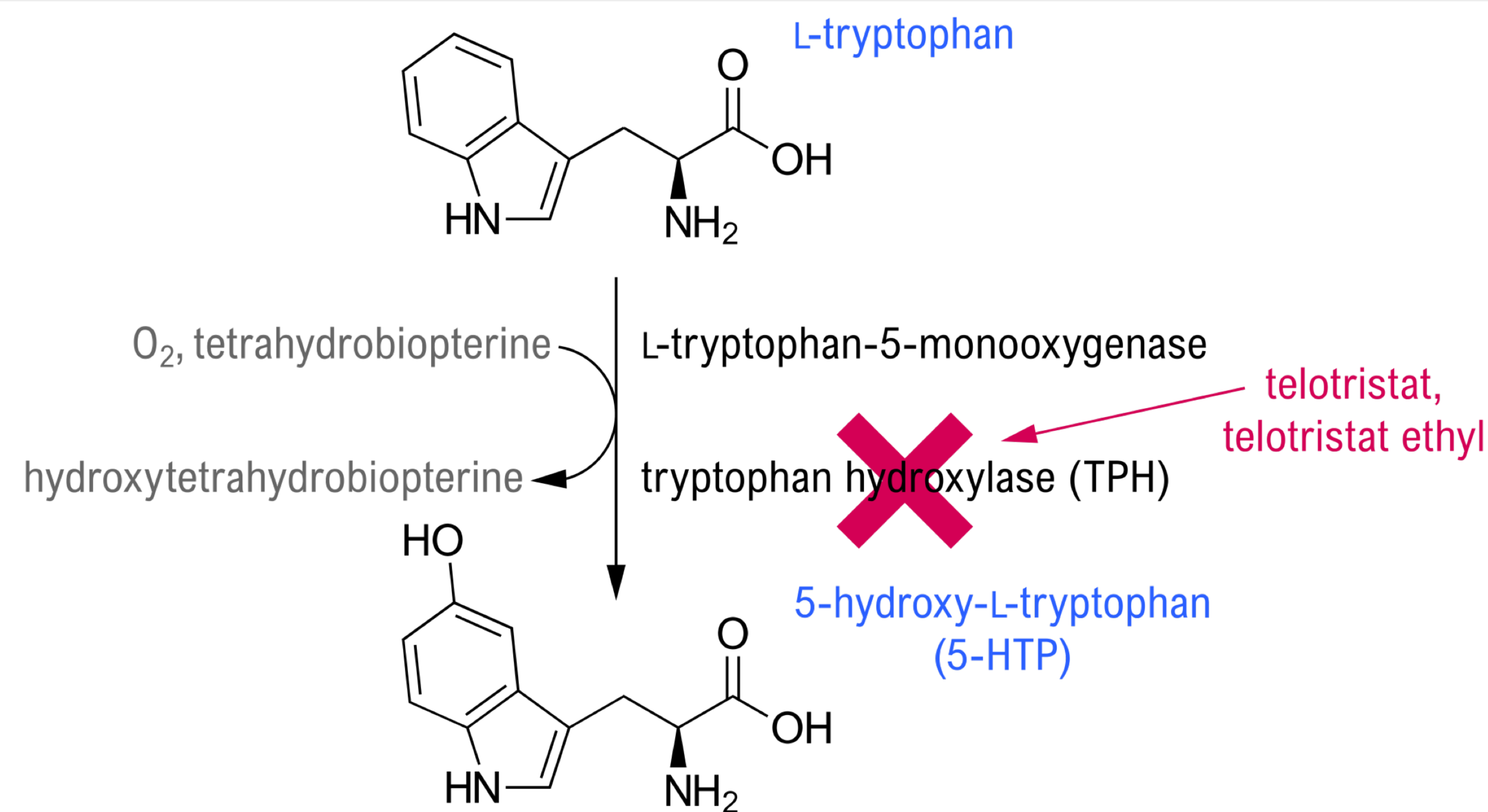
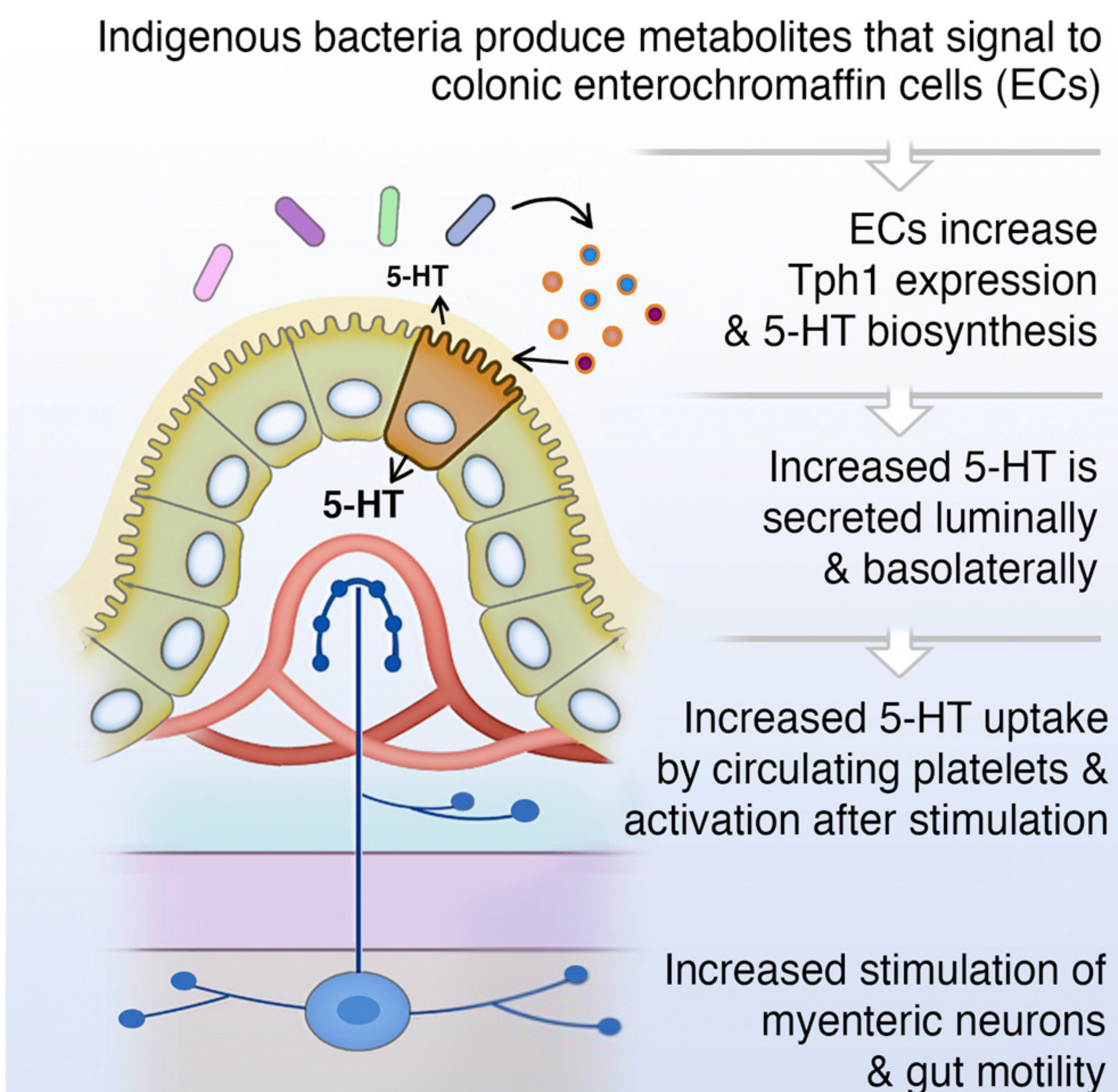
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Telotristat received FDA approval February 2017.
Well tolerated by patients in phase III clinical trials.
Side effects include nausea, deranged LFTs, and depression.

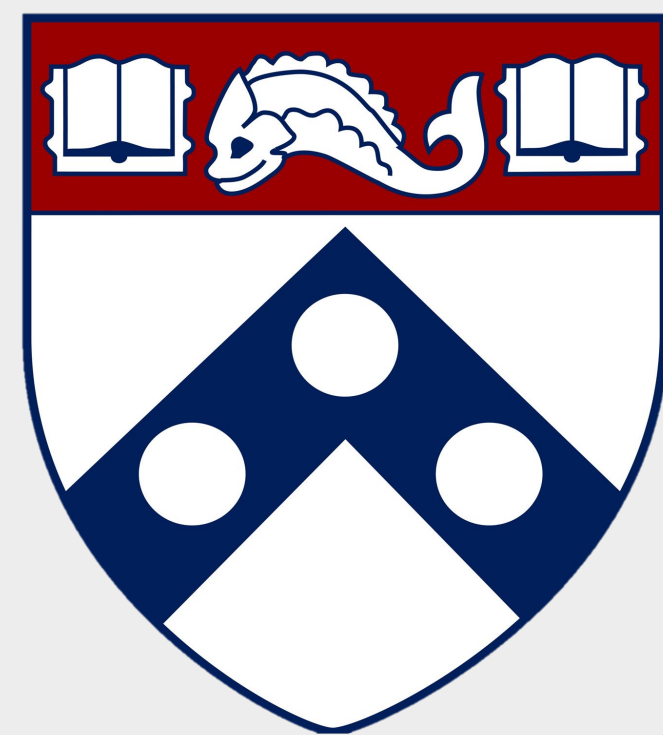
Questions:

- 1) Does inhibition of peripheral serotonin synthesis affect tumor growth?
- 2) Can we measure the change in tumor growth before and after therapy?

1) Yano et al. <https://doi.org/10.1016/j.cell.2015.02.047>

2) <https://commons.wikimedia.org/w/index.php?curid=56720695>

Image References



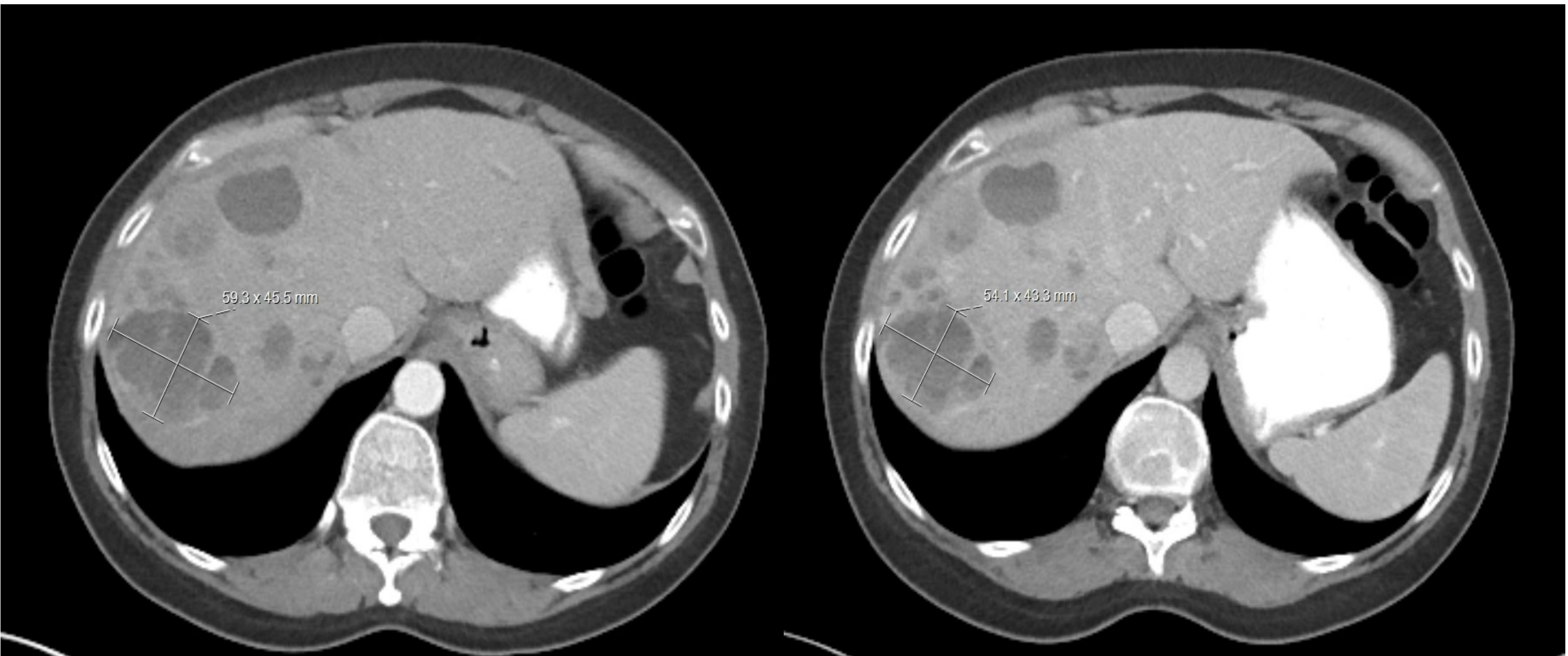
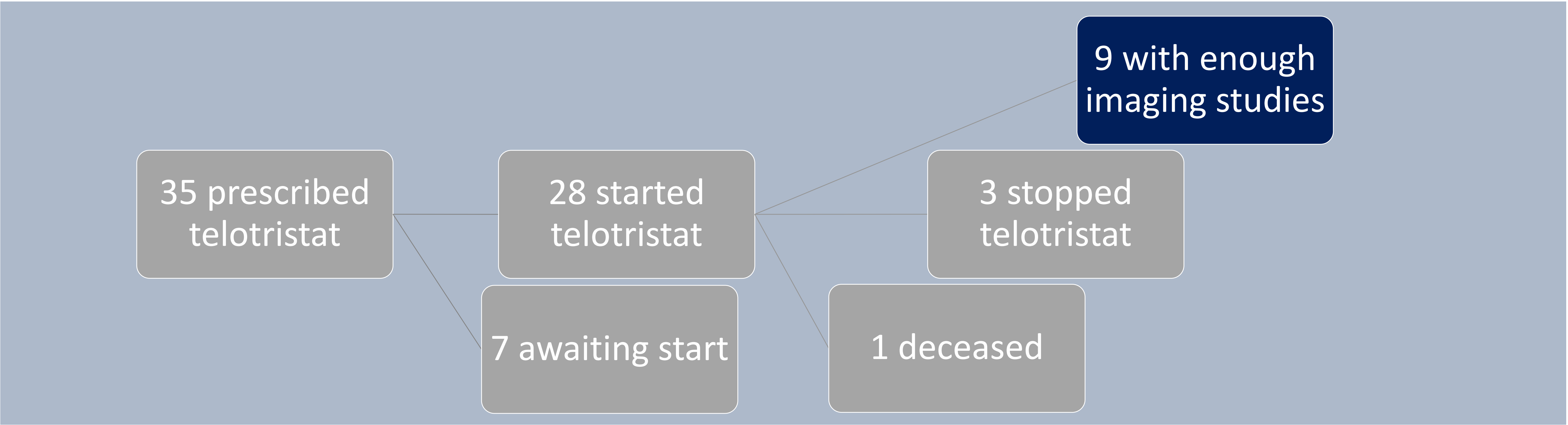
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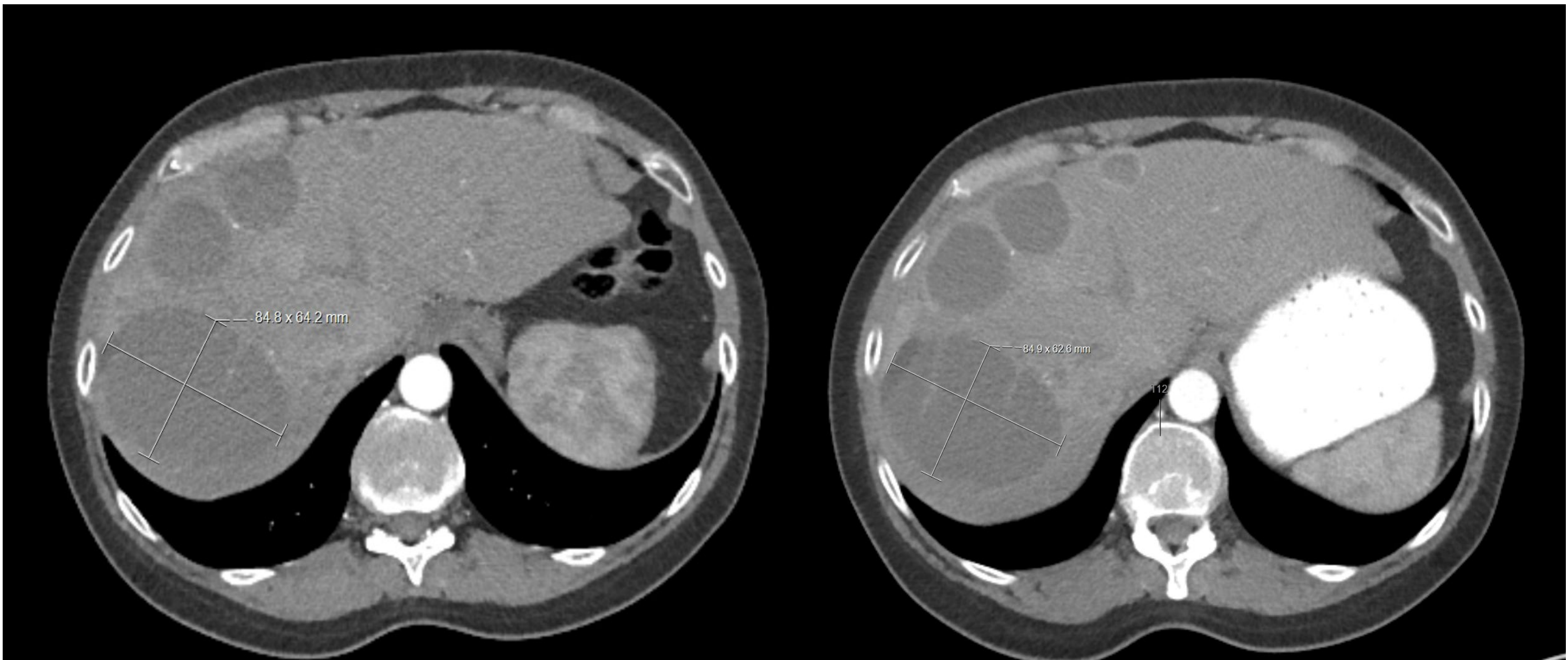
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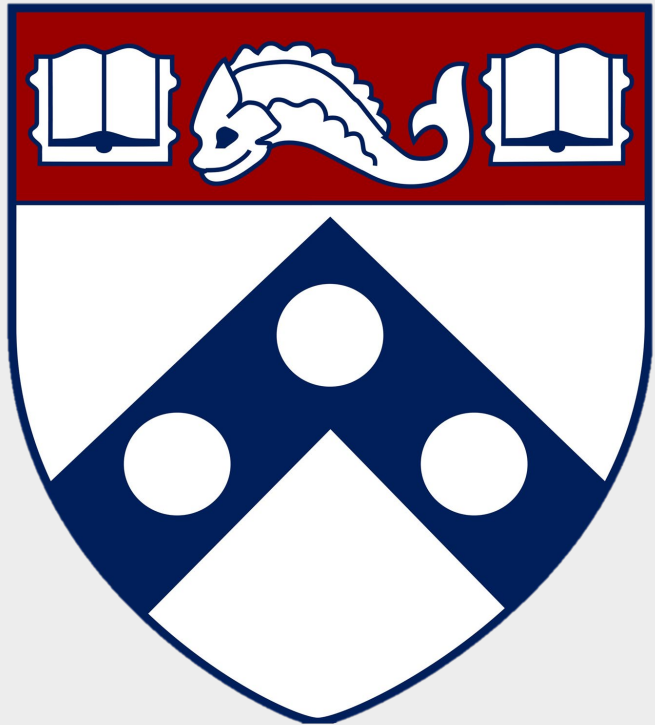
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Pre-telotristat: CTs from 12 and 9 months prior to initiation



Post-telotristat: CTs from 6 and 9 months after initiation



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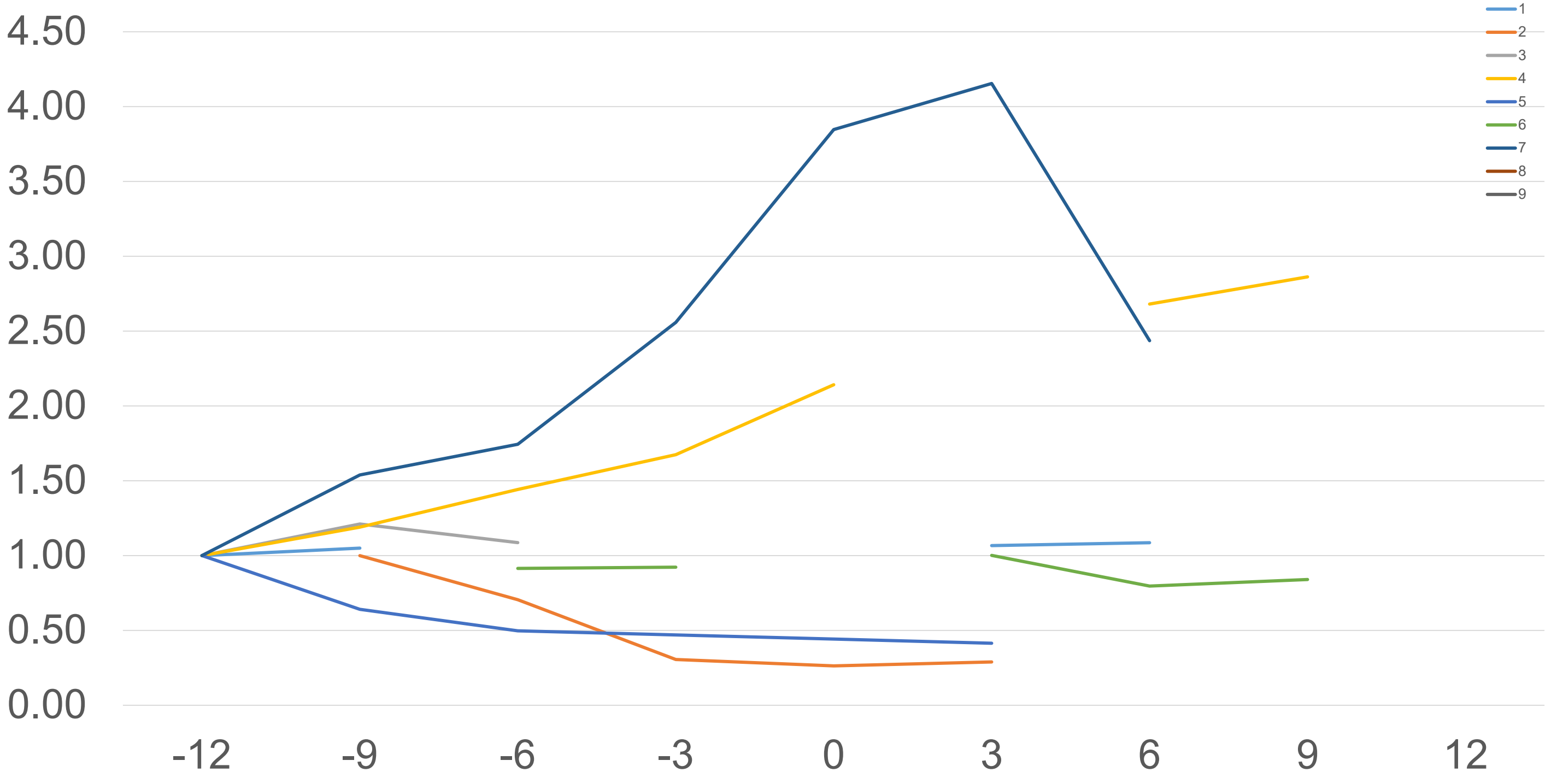
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Figure 1

Size Ratio (compared to index) versus Time (months)



Pre- and Post-Telotristat Slopes

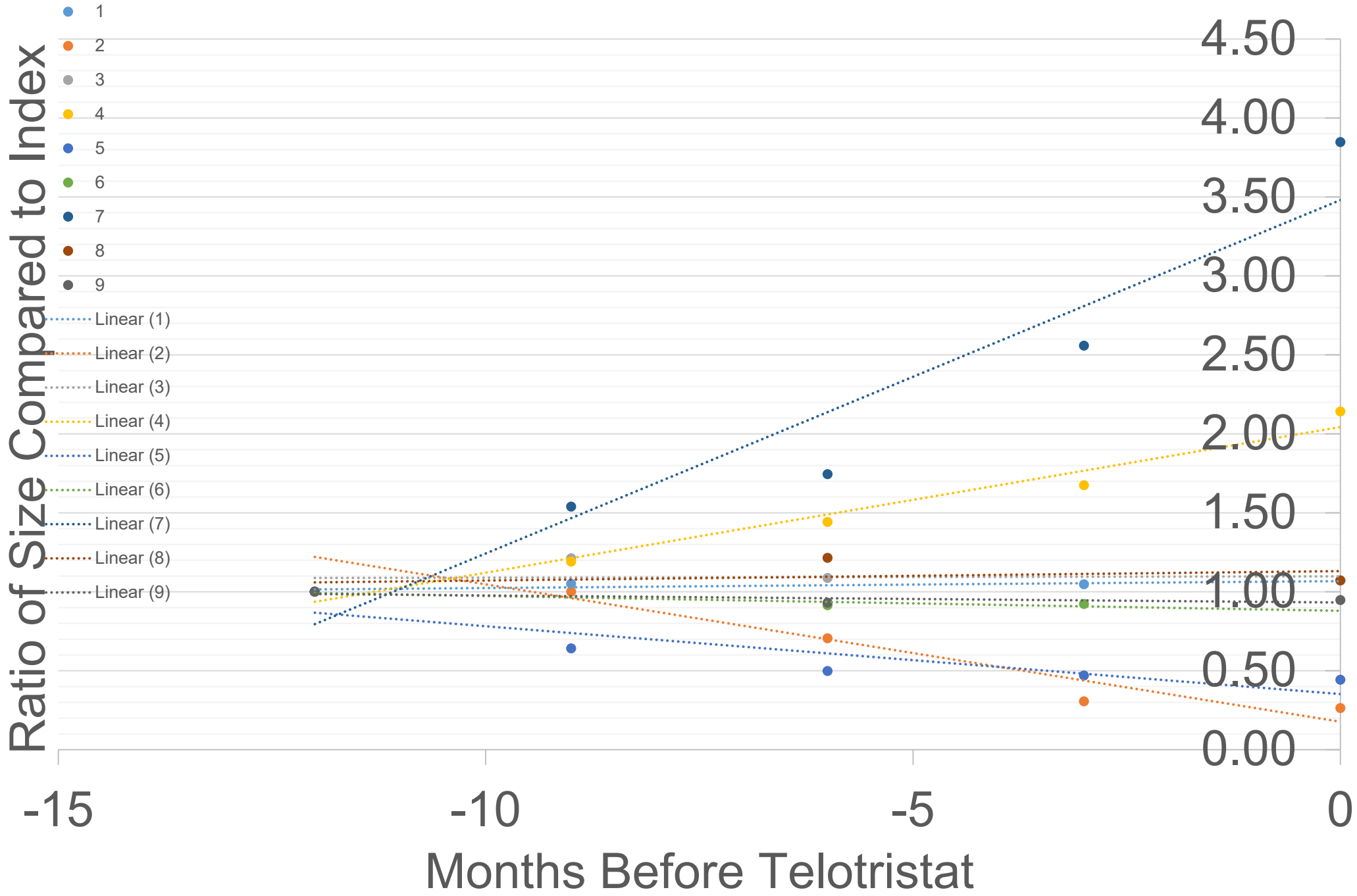
Table 1

1	0.0044	-0.0106
2	-0.0870	0.0088
3	0.0008	-0.0008
4	0.0923	0.0815
5	-0.0429	-0.0141
6	-0.0094	-0.0269
7	0.2238	-0.2351
8	0.0060	0.0238
9	-0.0044	-0.0097

Wilcoxon W = 21
p value > 0.20

Figure 2

Tumor Growth Slopes Pre-Telotristat



Tumor Growth Slopes Post-Telotristat

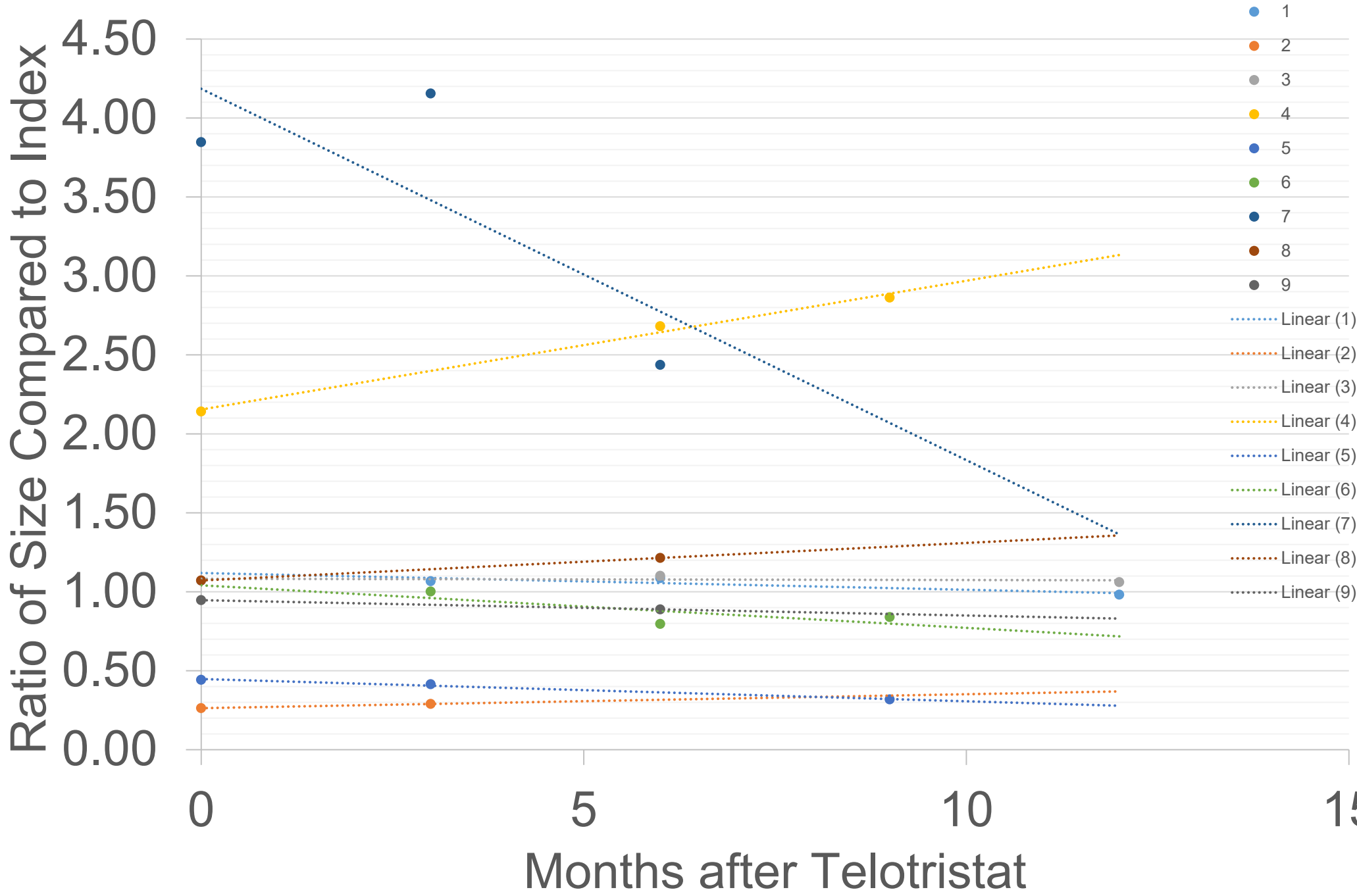
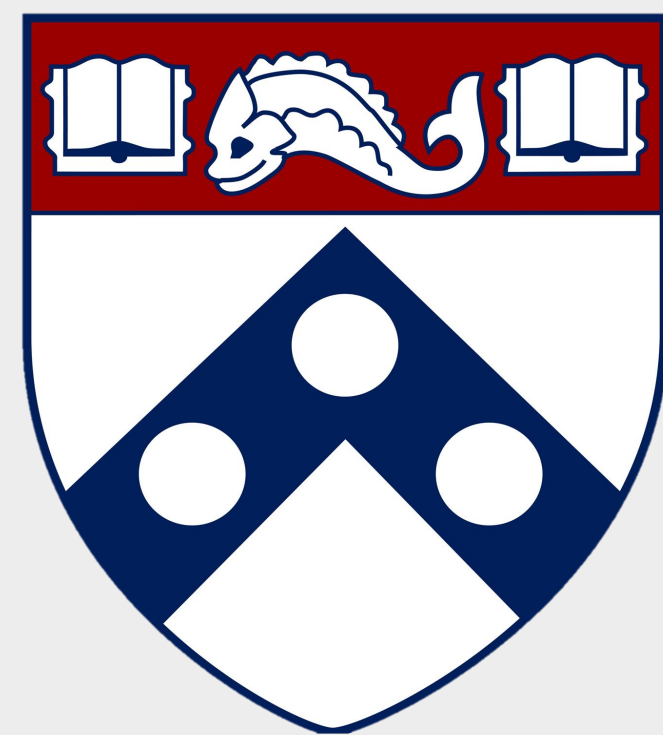


Figure 3



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Preliminary results: **Pre- and post-telotristat slopes were NOT statistically different**

Future directions:

- 1) Study was inadequately powered for small treatment effects
- 2) Chart review in 6 months to continue enrolling patients who have obtained imaging in the interim
- 3) Continue refining a working hypothesis for telotristat's potential effects on neuroendocrine physiology

Conclusion: **Whether tryptophan hydroxylase inhibition affects tumor growth is yet unknown**

References:

- 1) Kulke, M.H., et al., *Telotristat etiprate, a novel serotonin synthesis inhibitor, in patients with carcinoid syndrome and diarrhea not adequately controlled by octreotide*. Endocr Relat Cancer, 2014. **21**(5): p. 705-14.
- 2) Pavel, M., et al., *Telotristat etiprate for carcinoid syndrome: a single-arm, multicenter trial*. J Clin Endocrinol Metab, 2015. **100**(4): p. 1511-9.
- 3) Pavel, M., et al., *Telotristat ethyl in carcinoid syndrome: safety and efficacy in the TELECAST phase 3 trial*. Endocr Relat Cancer, 2018. **25**(3): p. 309-322.
- 4) Kulke, M.H., et al., *Telotristat Ethyl, a Tryptophan Hydroxylase Inhibitor for the Treatment of Carcinoid Syndrome*. J Clin Oncol, 2017. **35**(1): p. 14-23.
- 5) Molina-Cerrillo, J., et al., *Inhibition of Peripheral Synthesis of Serotonin as a New Target in Neuroendocrine Tumors*. Oncologist, 2016. **21**(6): p. 701-7.