Tumor Growth Rate (TGR) in Intestinal/Pancreatic Neuroendocrine Tumors: Post Hoc Exploratory Analysis of Data from the CLARINET Study

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Background: The phase III CLARINET study showed significantly improved progression-free survival (PFS) with lanreotide autogel/depot (LAN) vs. placebo (PBO) in intestinal and pancreatic neuroendocrine tumors (NETs). This exploratory analysis evaluated TGR, a novel measure of tumor response, in NET patients from CLARINET.

Methods: Patients with metastatic intestinal/pancreatic NETs received LAN 120 mg or PBO every 4 weeks for 96 weeks. Target lesions were assessed by central radiologic review based on RECIST v1.0. TGR (% variation of tumor volume per month) was calculated from sum-of-longest-diameters (SLD) of original target lesions (excluding new ones) on two CT scans during defined periods: 12–24 weeks prior to randomization vs. baseline (pretreatment); and baseline vs. each visit or between consecutive visits. TGR pre- and post-treatment were compared between treatment groups.

Results: Almost all patients were classified as stable on RECIST after 12 weeks of treatment (LAN, 90/96; PBO, 94/98), whereas a large proportion exhibited TGR changes. An early reduction in mean TGR was observed after only 12 weeks treatment with LAN but not with PBO, resulting in a significant difference in TGR between treatments which was maintained at subsequent study visits. (Table 1). ROC analysis showed that pretreatment TGR≤/>4% was the best cut-off value for predicting risk of progression, independently of treatment; TGR>4% resulted in a 4-fold higher risk of progression than TGR≤4% (HR 4.1; [95%CI 2.5, 6.5]; $p<0.001$). Regardless of pretreatment TGR, LAN was more effective than PBO in delaying progression.

Conclusion: These results suggest TGR may provide an early and more precise characterization of treatment activity than RECIST criteria in NET patients. The potential clinical utility of TGR requires validation in prospective studies as a pre-specified outcome measure.

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Table 1: TGR values at each study visit with LAN vs. PBO

Treatment period, weeks (patients)	LAN, mean [95% CI]	PBO, mean [95% CI]	Difference, mean [95% CI] (p-value)
Pretreatment (n=200)	4.1 [2.6, 5.6]	3.3 [1.7, 4.8]	0.8 [−1.4, 3.0] (0.46)
0–12 (n=196)	1.2 [-0.4, 2.7]	4.1 [2.6, 5.6]	−2.9 [−5.1, −0.8] (0.008)
12–24 (n=174)	2.0 [0.5, 3.5]	3.2 [1.7, 4.6]	−1.2 [−3.3, 0.9] (0.28)
24–36 (n=154)	1.8 [0.4, 3.2]	4.0 [2.6, 5.4]	−2.2 [−4.2, −0.3] (0.03)
36–48 (n=132)	−0.3 [−1.7, 1.3]	3.1 [1.5, 4.7]	−3.4 [−5.6, −1.1] (0.003)
48–72 (n=108)	1.3 [0.4, 2.1]	3.0 [2.0, 4.0]	−1.7 [−3.0, −0.4] (0.009)
72–96 (n=90)	0.6 [−0.5, 1.7]	3.1 [1.7, 4.6]	−2.6 [−4.4, −0.7] (0.007)