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Tumor Growth and Regression Rate Constants from the CLARINET Study as Surrogate Endpoints for Progression-Free Survival: A Novel Assessment Approach in Cancer Therapy

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BACKGROUND: Tumor size following cancer-related therapy is the result of regression of the treatment-sensitive fraction and growth of the treatment-resistant fraction (f), occurring simultaneously at constant rates. Exponential rate constants for tumor regression/decay (d) and growth (g) can be calculated using the equation, $f = e^{(g.t)}+e^{(-d.t)}-1$. Previous studies established that g is associated with overall survival, increases after treatment cessation, and can assess treatment effectiveness in small patient cohorts by benchmarking to reference data sets from large trials. Using this approach, we analyzed data from the CLARINET study that evaluated lanreotide autogel/depot (LAN) 120mg/4 weeks in patients with neuroendocrine tumors (NETs).

METHODS: Available computed tomography (CT) imaging data from n=97 LAN and n=101 placebo (PBO) patients from CLARINET were analyzed to estimate exponential rate constants for g and d.

RESULTS: 92% of the LAN and 94% of PBO data could be fit to one of the equations to derive g and d values, with P values of <0.001 in most data sets. g in LAN-treated patients was significantly slower versus PBO ($4.6e^{-4}$ day^{-1} vs

$6.2e^{-4}$ day^{-1}; P=0.00315). No significant difference was observed in d (LAN: $8.3e^{-4}$ day^{-1} vs PBO: $7.9e^{-4}$ day^{-1}; P=0.33746). g did not increase over prolonged periods of LAN administration (≤700 days). Simulated sample size analysis with g as the endpoint showed a sample size of 48, sufficient to detect a difference in median g with 80% power.

CONCLUSION: The growth rate constant, g, has the potential to elucidate differences in treatment efficacy in NETs and in many solid tumors. Consistent with its principal mechanism of action, LAN primarily slows tumor growth rather than accelerating tumor regression in the treatment of NETs. The growth-retarding effects seen with LAN in this study were sustained over time.