Tumor growth and regression rate constants from the CLARINET study as surrogate endpoints: A novel assessment approach in cancer therapy

Clarisse Dromain,[1] Arturo Loaiza-Bonilla,[2] Thomas Beveridge,[3] Beloo Mirakhur,[3] Julia Wilkerson,[4] Antonio Tito Fojo[5]

[1]*Centre Hospitalier Universitaire Vaudois, Lausanne, Vaud, Switzerland;* [2]*Cancer Treatment Centers of America, Boca Raton, FL, USA;* [3]*Ipsen Biopharmaceuticals, Basking Ridge, NJ, USA;* [4]*National Institutes of Health, Bethesda, MD, USA;* [5]*Columbia University Medical Center, New York, NY, USA*

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93

BACKGROUND

- Response Evaluation Criteria In Solid Tumors (RECIST), used to assess response to anticancer drugs in patients with solid tumors,[1-3] is an accepted metric of efficacy in neuroendocrine tumors (NETs).[1,4,5]
- Estimation of tumor growth rate (TGR) is a novel approach to assess treatment efficacy and has been explored in several studies in solid tumors, including NETs.[6-9]
- The CLARINET study demonstrated long-term safety and efficacy of lanreotide depot/autogel 120 mg every 4 weeks in patients with non-functioning enteropancreatic NETs compared to placebo.[10]
- A *post hoc* analysis of TGR, expressed as percentage change in tumor volume over 1 month, showed that in a substantial proportion of patients in CLARINET, tumors were actively growing during the pre-treatment period. Antitumor efficacy of lanreotide in terms of reduced TGR was evident in some patients as early as 12 weeks into treatment.[11]
- Measuring the absolute change in tumor volume following cancer-related therapy may not reflect the subtlety of simultaneous occurrence of regression of the treatment-sensitive fraction and growth of the treatment-resistant fraction. Here we estimate exponential rate constants for tumor regression/decay (***d***) and growth (***g***) in CLARINET using four mathematical models and explore their potential utility as efficacy endpoints by reference to tumor measurements.

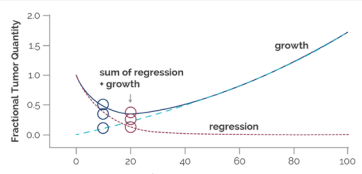
METHODS

- Results and details of the design of the phase III CLARINET registration trial (NCT00353496), comparing lanreotide with placebo, have been previously published.[10]
- This *post hoc* analysis used anonymized data, including:
  - tumor measurements from CT scans recorded as the sum of longest diameter of target lesions, with evaluation dates (days relative to start date);
  - enrollment and off-study dates, and date of death;
  - responses and progressions assessed according to RECIST 1.0, and PFS determined by local investigators.

Growth/regression models

- Four growth/regression models were used, in which change in tumor quantity during therapy is assumed to result from 2 independent component processes: an exponential decrease or regression, ***d***, and an exponential growth or regrowth of the tumor, ***g*** (**Figure 1**).

Figure 1. Model theory for regression and growth



- The model (labeled ***gd***) assumes f(t) is the tumor quantity at time t in days, normalized to the tumor quantity at time 0, ***d*** is the rate of decay, and ***g*** is the rate of growth:

$$f(t) = e^{-dt} + e^{gt} - 1$$

- For data showing continuous decrease from the start of treatment, ***g*** is eliminated as shown below (labeled ***dx***):

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- Similarly, ***d*** is eliminated when data show a continuous growth from the start of treatment as shown below (labeled ***gx***):

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- The fourth model (labeled ***gdphi***) contains an additional parameter, phi (***Ø***), which represents the proportion of tumor cells that undergo cell death due to therapy. In this model, ***d*** is rate of regression or decay of the fraction of the tumor that is sensitive to the therapy (***Ø***), while ***g*** is rate of growth of the therapy-resistant tumor fraction (***1 – Ø***):

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- The Levenberg-Marquardt algorithm was used to solve the 4 non-linear regression models.
- Among models where all parameters were significant predictors, the model that minimized the Akaike information criterion (AIC) was selected to provide the estimates of tumor growth and regression rates.
- Patients with insufficient/missing data, or with sufficient data but where the model did not converge with the data, were excluded and noted individually in results and summarized in model outputs. A stepwise selection method was utilized.

Statistical analyses

- Distributions of ***g*** and ***d*** were compared between lanreotide and placebo groups using Wilcoxon 2-sided tests (cut off *p*-value 0.1).
- Where there was an overall difference between treatment groups, a Dunn's test for pairwise difference was conducted with Bonferroni adjustment for multiple comparisons.
- Analysis and graphical output was generated using R (https://www.R-project.org) and the *tumgr* package (Tumor Growth Rate Analysis. R package version 0.0.4. https://CRAN.R-project.org/package=tumgr).
- To demonstrate the stability of the growth rate – that it is actually a constant – ***g*** was estimated serially using the data available at each point in time. The first calculation used the first three data points, after which ***g*** and its 95% CI were estimated by adding the value for each new data point to the cumulative data and repeating the analysis.

RESULTS

Values for *g* and *d* rates were estimated in a majority of patients.

- In the CLARINET study, a total of 204 patients were randomly assigned to lanreotide (101 patients) or placebo (103 patients).[10]
- Datasets were reviewed for N=97 patients randomized to lanreotide and N=101 patients randomized to placebo.
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  - For these patients we did not calculate ***g*** or ***d***.
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Arm	Total	Type	Selected Fit	Count	Percent	
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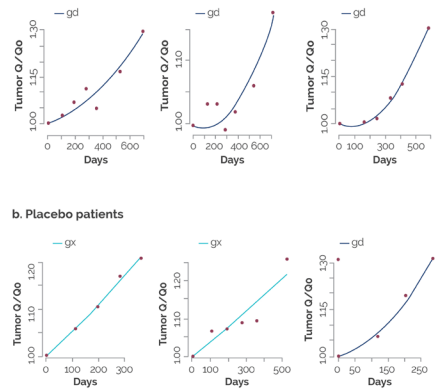

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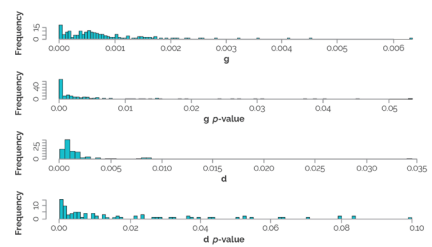

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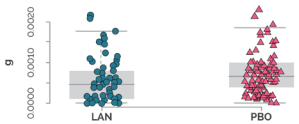

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IQR, inter-quartile range; LAN, lanreotide; PBO, placebo; SD, standard deviation

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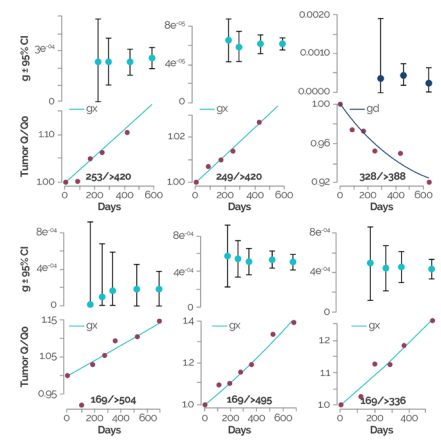

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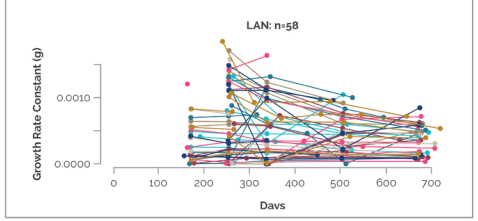

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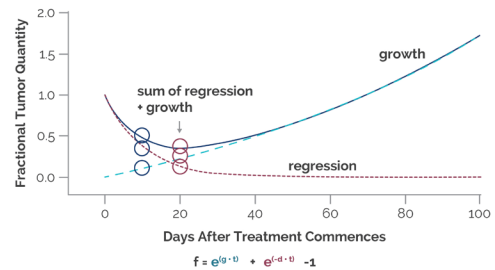

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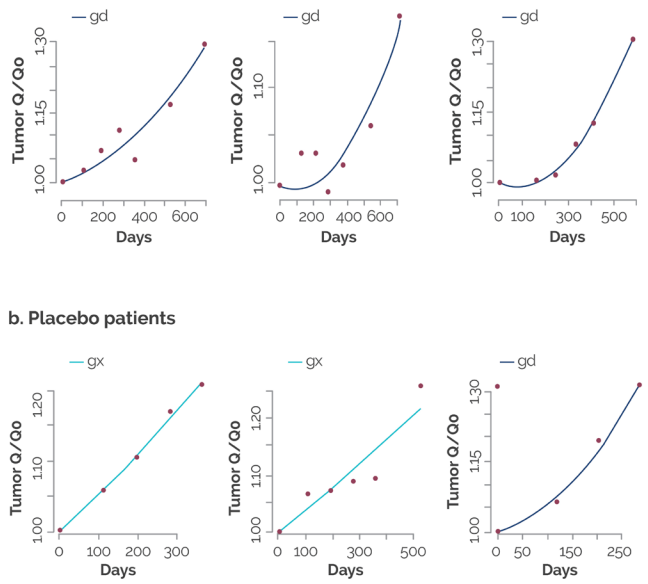

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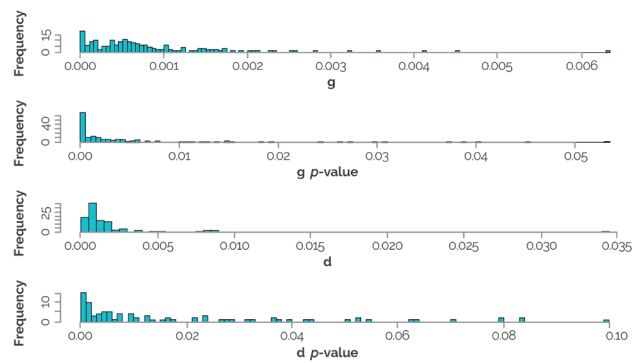

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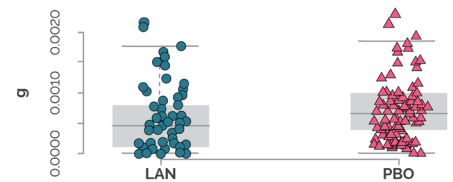

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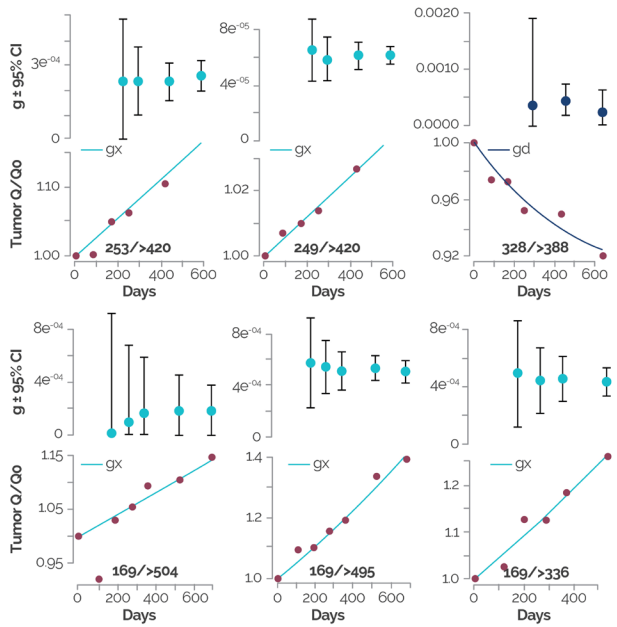

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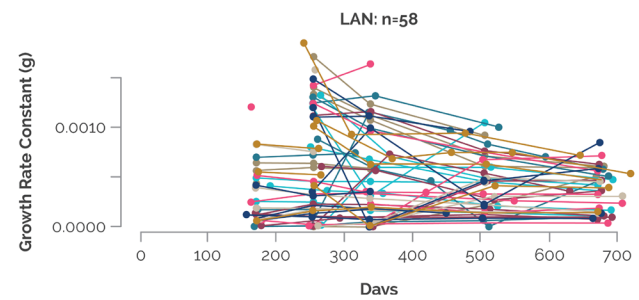

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ALB: consultant/advisor for AstraZeneca, Bayer, and Massive Bio; member of speakers' bureau for Caris Life Sciences, Celgene, and Guardant Health; institution received research funding from Ipsen. **ATF:** consultant/advisor for Cerulean Pharma; received a very small amount of royalties from the federal government from a long-standing agreement on taxol. This has now ended. **TB:** employee of Ipsen. **BM:** employee of Ipsen; stock/other ownership interests in Bristol-Myers Squibb. **CD** and **JW:** nothing to disclose.

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