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

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BACKGROUND

- Response Evaluation Criteria In Solid Tumors (RECIST) used to assess response to anticancer drugs in solid tumors is an accepted metric of efficacy in neuroendocrine tumors.
- Estimation of tumor growth rate TGR is a novel approach to assess treatment efficacy and has been explored in several studies in solid tumors in a safety-NET trial.
- The CLARINET study demonstrated long-term safety and efficacy of lenvatinib tablet formulation in patients with non-functioning endocrine tumors.

METHODS

- We analyzed a dataset of patients treated with lenvatinib in the phase 1b/2 CLARINET study.
- Tumor measurements from CT scans were reviewed as the time of longest diameter, with initial stable lesions noted to start data.
- Enrolment was at study sites, and data of safety and efficacy were collected.
- Progression was determined according to RECIST 1.0, and PFS was determined by local investigators.

RESULTS

- Four growth regression models were used, which change in tumor quantity during therapy is assessed by a decreasing exponential model, an exponential growth or regression of the tumor.

Figure 1. Model for tumor growth and regression.

- The model maintained that the tumor quantity at t = 0 time is t = 0 the rate of growth, and the rate of growth is a parameter of the model.
- As the growth decreases, the tumor quantity decreases over time, and the model is maintained using a constant rate of decrease.

Figure 2. Examples of curve fits.

- The fourth-order polynomial model contains an additional parameter, p1, which represents the proportion of tumor that undergoes cell death due to therapy. In this model, a rate of progression or decay of the tumor is calculated.
- The model evaluates the effect of the therapy-resistant tumor fraction at t = 0.

Figure 3. Distributions of g and their associated p-values.

- The Leverkusen-based algorithm was used to calibrate the tumor-specific linear model.
- Among models, where parameters were significant predictors, the models that minimized the Akaike Information Criterion (AIC) were selected to plot the estimates of tumor growth and regression rates.
- Growth rates with insufficiently long data or with sufficient data but where the model failed to converge were excluded from the analysis.
- The results were tested for normal distribution and the p-values were determined individually in each model and summarized in model outputs. A descriptive $p$-value was calculated.

Figure 4. Comparison of $g$ estimates between lenvatinib and placebo groups.

- The distribution of g and growth rates were compared between lenvatinib and placebo groups using different statistical tests (t-test, ANOVA).
- There was a clear trend between treatment differences in g, with lenvatinib treatment showing a higher rate of tumor growth.

Figure 5. Stability of the growth rate while on lenvatinib therapy.

- To demonstrate the stability of the growth rate – that is, it is a constant g – the estimated standard error is the standard deviation of the data available at each point in time.

Figure 6. Values of g and their standard error.

- The tumor growth and regression rate constant of the patients treated with lenvatinib were significantly underestimated.

Figure 7. Example of the model.

- Table 1. Summary of data analysis

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- The statistical significant difference between lenvatinib and placebo was seen in g ($p < 0.05$) (Figure 4). This effect was not almost demonstrated, showing the differential effect of lenvatinib on these aspects of tumor growth.

- No significant difference was observed at all time points – placebo: 786.7 (95% CI: 0.05 to 0.07) (median value).

LIMITATIONS

- The current analysis is limited as it is based on mathematical modeling, which includes estimates of survival based on lifetime estimates.

CONCLUSIONS

- The growth rate constant g has the potential to elucidate differences in treatment efficacy in NETs and in NET-related tumor growth.
- Consistently with principal mechanism of action, lenvatinib primarily slows tumor growth, thus accelerating tumor regression in the treatment of NETs.
- The growth-related effects with lenvatinib in this study were sustained over time, suggesting that tumor resistance to therapy did not develop over the period of observation in the majority of patients.
- Serial analysis of tumor growth rate could be used to monitor continuous and to response to therapy in patients with a very slow tumor growth where the evidence includes stability, correlation of lenvatinib may be expected to provide ongoing benefit.

References


Conflicts of interest

Some of the authors have provided financial support to conduct this study. The authors declare that they have no conflicts of interest. The funding bodies for this study include Merck Serono, a subsidiary of Merck KGaA, Darmstadt, Germany. The authors report no competing interest.

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BACKGROUND

- Response Evaluation Criteria In Solid Tumors (RECIST) used to assess response to antitumor drugs in patients with solid tumors.1,2 It is an accepted metric of efficacy in neuroendocrine tumors.3,4
- 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.2,5
- The CLARINET study demonstrated long-term safety and efficacy of lanreotide depot/subcut 200 mg every 4 weeks in patients with non-functioning neuroendocrine paraneoplastic compared to placebo.6
- 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 of treatment.7
- Measuring the absolute change in tumor volume following cancer-related therapy may not reflect the subtle of simultaneous occurrence of regrowth of the treatment-sensitive fraction and growth of the treatment-resistant fraction. Here we estimate exponential rate constants for tumor growth and regression rates 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 II CLARINET registration trial (NCT010353915), comparing lanreotide with placebo, have previously been published.8
- This post hoc analysis used anonymized data, including: treatment measurements from CT scans recorded as the sum of longest diameter of target lesions, with evaluation dates (delta 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, which change in tumor quantity during therapy is assumed to result from 2 independent component processes: an exponential decrease or regression, d(t), and an exponential growth or regrowth of the tumor, g(t), Figure 1.

![Figure 1. Model theory for regression and growth](image)

- The model labeled gd assumes F(t) is the tumor quantity at time t in days, normalized to the tumor quantity at 0 days, t0, as the rate of decay, and g(t) is the rate of growth: F(t) = e^{-gt}, g = g(t).
- For data showing continuous decrease from the start of treatment, g is eliminated as shown below labeled dl:
  \[ F(t) = e^{-dt} \]
- Similarly, dl is eliminated when data show a continuous growth from the start of treatment as shown below labeled lg:
  \[ F(t) = e^{gt} \]
- The fourth model (labeled gpdl) contains an additional parameter, phi, which represents the proportion of tumor cells that undergo cell death due to therapy. In this model, d(t), rate of regression or decay of the fraction of the tumor that is sensitive to the therapy, phi(t), while g(t) is rate of growth of the therapy-resistant tumor fraction (1-phi(t)).
- The Levenberg-Marquardt algorithm was used to solve the non-linear regression models.
- Among models where all parameters were significant predictors, the model that maximized 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(t) were compared between lanreotide and placebo groups using Wilcoxon signed-ranks test (two-tailed p-value).
- Where there was an overall difference between treatment groups, a Dunn’s test for pairwise difference was conducted with Bonferroni adjustment for multiple comparisons.

RESULTS

- Analysis and graphical output was generated using R (https://www.R-project.org) and the tumour package (Tumor Growth Rate Analysis, R package version 0.4.4, https://CRAN.R-project.org/package-tumgr).
- To demonstrate the stability of the growth rate – that it is actually a constant – g was estimated separately using data available at each point in time. The first calculation used the first three data points, after which d and its 95% CI were estimated by adding the value for each new data point to the cumulative data and repeating the analysis.

Table 1. Summary of data analysis

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Figure 2. Examples of curve fits

- The distributions of g and d constants are shown graphically along with the corresponding distributions of the parameter p-values (Figure 3).
- While the cutoff for each individual patient was set at a p-value of 0.1, p-values for the overwhelming majority of the fits were much lower.

Figure 3. Distributions of g and d and their associated p-values

Figure 4. Comparison of g estimates between lanreotide and placebo groups

A statistically significant difference between lanreotide and placebo was seen for g (p=0.0128, Figure 4) but not d (not shown), demonstrating the differential effect of lanreotide on these aspects of tumor growth.

No significant difference was observed in d (lanreotide: 8.3e−4 day⁻¹ vs placebo: 7.9e−4 day⁻¹; p=0.3751, median values).

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IQR: interquartile range; LAN: lanreotide; PBO: placebo; LAN: doubled data set.

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Stability of g during treatment

- Representative examples for patients with stable g during study-drug treatment are shown in Figure 5 (left), g values calculated with the available data to that point in time, curve depicting the selected model.
- Serial g values for 58 of 69 patients who had a g value calculated are depicted in Figure 6 (the remaining 11 patients had fewer than 3 analyzable tumor measurements). Clustering of g values at the bottom indicates that in most patients the value of g does not change appreciably even during treatment durations of up to 2 years or more.
- A stable g value therefore not that the quantity of tumor is not increasing, but rather that it is increasing at a stable exponential rate during a prolonged duration of therapy suggests that resistance to treatment either does not develop or is slow to develop.

Figure 5. Stability of the growth rate while on lanreotide therapy

Figure 6. g values in n=58 patients who had a g value calculated

LIMITATIONS

- The current analysis is limited as it is based on mathematical modeling, which includes estimates of survival based on literature estimates.

CONCLUSIONS

- 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, lanreotide primarily slows tumor growth rather than accelerating tumor regression in the treatment of NETs.
- The growth-retarding effects seen with lanreotide in this study were sustained over time, suggesting that tumor resistance to lanreotide did not develop over the period of observation in the majority of patients.
- Serial estimates of a tumor’s growth rate could be used to monitor continued response to treatment. In patients with a very slow rate of tumor growth where the evidence indicates stability, continuation of lanreotide may be expected to provide ongoing benefit.

REFERENCES


CONFLICTS OF INTEREST

Ipsen Biopharmaceuticals provided financial support for this study.

ALB: consultant/advisor for Astellas, Bayer, and Massimo R. member of speakers' bureau for Curis, LifeSciences, Gelseine, and Guardant Health; institute received research funding from Ipsen.

ATF: consultant/advisor for Curvacean Pharma; received a very small amount of royalties from the federal government from a long-standing agreement to conduct. This has now ended. TRB: employee of Ipsen.

BR: employee of Ipsen; stock/stockholder ownership in interests in Bristol-Myers Squibb CD.

PM: nothing to disclose.

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