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Gastrointestinal Cancer

Novel Tumor Growth Rate Analysis in the Randomized CLARINET Study Establishes the Efficacy of Lanreotide Depot/Autogel 120 mg with Prolonged Administration in Indolent Neuroendocrine Tumors

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Key Words. Computed tomography • Lanreotide depot/autogel • Neuroendocrine tumors • Tumor growth rate • Tumor regression

Abstract

Introduction. Tumor quantity while receiving cancer therapy is the sum of simultaneous regression of treatment-sensitive and growth of treatment-resistant fractions at constant rates. Exponential rate constants for tumor regression/decay (***d***) and growth (***g***) can be estimated. Previous studies established ***g*** as a biomarker for overall survival; ***g*** increases after treatment cessation, can estimate doubling times, and can assess treatment effectiveness in small cohorts by benchmarking to large reference data sets. Using this approach, we analyzed data from the clinical trial CLARINET, evaluating lanreotide depot/autogel 120 mg/4 weeks (LAN) for treatment of neuroendocrine tumors (NETs).

Methods and Materials. Computed tomography imaging data from 97 LAN- and 101 placebo-treated patients from CLARINET were analyzed to estimate ***g*** and ***d***.

Results. Data from 92% of LAN- and 94% of placebo-treated patients could be fit to one of the equations to derive ***g*** and ***d*** ($p < .001$ in most data sets). LAN-treated patients demonstrated significantly slower ***g*** than placebo recipients ($p = .00315$), a difference of 389 days in doubling times. No significant difference was observed in ***d***. Over periods of LAN administration up to 700 days, ***g*** did not change appreciably. Simulated analysis with ***g*** as the endpoint showed a sample size of 48 sufficient to detect a difference in median ***g*** with 80% power.

Conclusion. Although treatment of NETs with LAN can affect tumor shrinkage, LAN primarily slows tumor growth rather than accelerates tumor regression. Evidence of LAN efficacy across tumors was identified. The growth-retarding effect achieved with LAN was sustained for a prolonged period of time. ***The Oncologist*** 2021;26:e632–e638

Implications for Practice: The only curative treatment for neuroendocrine tumors (NETs) is surgical resection; however, because of frequent late diagnosis, this is often impossible. Because of this, treatment of NETs is challenging and often aims to reduce tumor burden and delay progression. A novel method of analysis was used to examine data from the CLARINET trial, confirming lanreotide depot/autogel is effective at slowing tumor growth and extending progression-free survival. By providing the expected rate and doubling time of tumor growth early in the course of treatment, this method of analysis has the potential to guide physicians in their management of patients with NETs.

Introduction

Neuroendocrine tumors (NETs) are a clinically and biologically heterogeneous group of malignancies that arise from neuroendocrine cells whose incidence has been increasing [1–5]. Frequently diagnosed late [6] and with disseminated metastases [2], treatment of NETs is challenging [7]; it primarily aims to reduce tumor burden and associated

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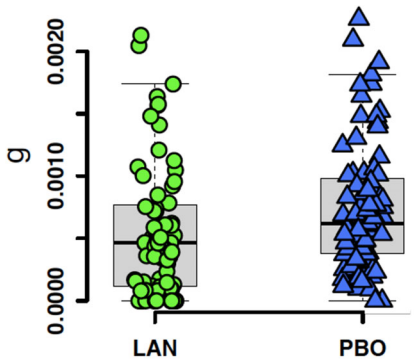
symptoms and to delay progression [8]. Most approved treatments for NETs delay disease progression but fail to improve overall survival (OS) [9–12].

Although regarded as imperfect [13], RECIST guidelines have been used to assess response to anticancer therapies [13–15] and are accepted by regulatory agencies as a metric of efficacy in numerous tumors, including NETs [14, 16, 17]. Estimates of tumor growth rates (TGRs) have been explored in a number of studies involving solid tumors [18–20], including gastroenteropancreatic NETs [8, 21–23]. The clinical value of TGR is supported by its association with progression-free survival (PFS) [19] and OS [20], including PFS in a post hoc analysis from a phase II single-arm trial of lanreotide depot/autogel (LAN) [22], a long-acting somatostatin analogue. However, despite the existence of several tumor growth models, a widely applicable practical tool that can support drug development based on tumor growth kinetics has remained elusive [24–29].

The CLARINET study demonstrated the antitumor efficacy of LAN in patients with nonfunctioning intestinal and pancreatic NETs in comparison with placebo [30], with the CLARINET open-label extension subsequently confirming long-term safety and efficacy [31]. In a post hoc analysis of the CLARINET data, Dromain et al. [21] found that a large proportion of patient tumors, that were actively growing during the pretreatment period, had reductions in TGR, with antitumor efficacy of LAN evident as early as 12 weeks into treatment.

The current study explored the kinetics of tumor growth in the CLARINET study using a novel method of analysis that, unlike other methodologies that only estimate the rate of tumor growth, considers the occurrence of simultaneous regression and growth at constant rates of sensitive and resistant tumor fractions, respectively. The validity of this method of analysis and its correlation with OS has been demonstrated in previous studies [32–38].



Arm	*n*	Mean	SD	Median	IQR	*p* value
LAN	83	0.00067	0.00087	0.00046	(0.00012,0.00077)	.012788
PBO	91	0.00078	0.00062	0.00062	(0.00038,0.00098)	

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

Figure 1. Rates of tumor growth (***g***) in patients randomized to lanreotide depot/autogel 120 mg or placebo. The median value with lanreotide depot/autogel 120 mg (0.00046) was significantly lower (p = .012788) than that with placebo (.00062), demonstrating that lanreotide slowed tumor growth.
Abbreviations: g, tumor growth rate; IQR, interquartile range; LAN, lanreotide depot/autogel 120 mg; PBO, placebo; SD, standard deviation.

Materials and Methods

Clinical Trial and Study Design

Results of the CLARINET study were published in 2014 (ClinicalTrials.gov NCT00353496; EudraCT 2005–004904–35) [30]. The institutional review board of all participating centers approved the original study, and all patients provided written informed consent. Patients were randomized either to LAN or to placebo. Tumor measurements from computed tomography (CT) scans recorded as the sum of the longest diameter of target lesions were determined every 12 and 24 weeks during the first and second year, respectively, of the CLARINET study. Tumor response and progression were assessed according to RECIST v1.0 [14]. For the present analysis, patients' information was anonymized and deidentified.

Model Process

See also supplemental online Information. The rates of tumor growth and regression were estimated using an R package, designated **tumgr**, which uses a regression-growth model previously validated for other types of tumors and treatments [31–38]. This model assumes that change from baseline in tumor quantity during therapy is the result of two independent processes occurring simultaneously: an exponential decay or regression of tumor that occurs at a constant rate, designated as ***d***, and an exponential growth or regrowth of tumor that likewise occurs at a constant rate and is designated as ***g*** (supplemental online Fig. 1). As each new quantity or measurement of tumor burden estimated by summing the values for all individual lesions is accrued, the value of ***g*** can be estimated in series. Previous data have demonstrated that both the rate of tumor decay or regression (***d***) and the rates of growth (***g***) are stable or constant [39, 40]. Four possible models were defined as previously described [31–38] and include (a) ***gd***, in which concomitant regression of the sensitive fraction at rate ***d*** and growth of the resistant fraction at rate ***g*** occur during treatment; (b) ***dx***, in which only decrease in tumor quantity at rate ***d*** occurs during treatment; (c) ***gx***, in which only increase in tumor quantity at rate ***g*** occurs during treatment; and (d) ***gdphi***, similar to the ***gd*** model, in which during treatment there occurs concomitant regression of the sensitive fraction at rate ***d*** and growth of the resistant fraction at rate ***g*** but in which the measurement data are very robust and one can have better estimates using an additional parameter, Ø, which represents the fraction of tumor cells sensitive to therapy

Model Analysis

Excluded from the analysis were (a) patients without tumor measurements; (b) patients with only one data point; (c) patients with two data points differing <20% because these would not have been scored by RECIST as either progression or response; and (d) patients with initial and final measurement values of 0. In some cases, the data could not

be described by any of the four equations, whereas in others, more than one equation could describe the data in a statistically meaningful way (p value for goodness of fit <.1). In these cases, the model with the lowest Akaike information criterion was selected for each patient. Note that in only rare cases were new lesions detected. In such a case, that lesion's value would be added to the total tumor burden.

Statistical Analysis

The Kaplan-Meier method was used to estimate PFS probability. A Cox regression was performed with the log of ***g*** estimated from the data as the single predictor, using the R package **survival** to obtain a measure of concordance (C-index) between ***g*** and PFS [37]. The rate constants can also be expressed in terms of half-lives [ln2 (=0.693)/***d***] and doubling times [ln2 (=0.693)/***g***] [39]. All statistical analyses and graphical output were done in R 3.3.3 (Microsoft, Redmond, WA). Comparisons of model estimate distributions were performed using the two-sided Wilcoxon test of location (Kruskal-Wallis if more than 2 groups) and post hoc analysis of any overall difference detected (>2 groups) using Dunn's test with Bonferroni adjustment for multiple comparisons. All outputs were generated using Base SAS software (version 9.1.3; SAS Institute, Cary, NC) for Windows.

Results

g and *d* Values Were Estimated for Most Patients

Data were available for 198 of 204 patients randomized in the CLARINET study (LAN, n = 97/101; placebo, n = 101/103). Among randomized patients, values for ***d***, ***g***, or both could be estimated in 93% of patients with sufficient data for analysis (Table 1). The ***gd*** and ***gx*** models were the best fit for the majority of the clinical data analysis, implying that most patients experienced concomitant tumor regression and growth during treatment, or a continuous increase in tumor quantity occurred, albeit at a slow rate in these patients. Supplemental Figure 2 demonstrates the strong fit of included cases and the formulas that best fit their data. Supplemental Figure 3 shows distributions of ***g*** and ***d*** and the parameter p values. Although the cutoff for significance was set at p = .1, the majority of these values were ≥ .01. Median ***g*** was significantly lower with LAN (p = .012788 vs. placebo; Fig. 1), whereas ***d*** was not significantly different between study groups (not shown).

Table 1. Summary of data analysis

Type	Selected fit	Count (%)
LAN (n = 97)		
Excluded	2 evaluations <20% different	6 (6.2)
	No fit	8 (8.3)
Included	Model **dx**	14 (14.4)
	Model **gd**	35 (36.1)
	Model **gdphi**	1 (1.0)
	Model **gx**	33 (34.0)
PBO (n = 101)		
Excluded	2 evaluations <20% different	4 (4.0)
	No fit	6 (5.9)
Included	Model **dx**	2 (2.0)
	Model **gd**	36 (35.6)
	Model **gdphi**	1 (1.0)
	Model **gx**	52 (51.5)

Abbreviations: LAN, lanreotide depot/autogel 120 mg; PBO, placebo. (See text for explanation of models.)

g Remains Stable During Treatment

Figure 2 depicts the results of serial estimates of ***g*** values in 58 of 69 patients treated with LAN, in whom a rate of tumor growth (***g***) could be estimated, and who had more than three tumor measurements. In these cases, a ***g*** value could be estimated using the first three measurements, then the first four, then the first five, and so on. The clustering of ***g*** values at the bottom of the figure demonstrates that, for the majority of patients, ***g*** values did not change appreciably even during prolonged duration of treatment. Figure 3 shows representative illustrations of the stability of tumor growth rates (***g***) while on LAN therapy. Note that in an additional 14 patients with only tumor regression observed, the data were best fit by the ***dx*** model and ***g*** did not change. Thus, 72 patients (58 + 14 = 72) randomized to LAN either had no growth of their tumor (no ***g*** value) or prolonged stability of the rate of tumor growth (***g***).

Association of *g* Values with Progression-Free Survival

A statistically significant association between tertiles of ***g*** values and PFS was observed. This association was apparent within each arm of the study but also, more importantly, within the study overall. Figure 4 depicts the results for patients from both arms of the CLARINET trial in whom a ***g*** value could be estimated (158 patients) or in whom the data fit the **dx** model (16 patients), a total of 174 patients, all combined for this analysis since extensive experience has shown ***g*** transcends the administered therapy [41]. The ***dx*** group, comprising 14 patients in whom growth and a ***g*** value could not be discerned, is seen to have a very favorable PFS.

Discussion

We have reanalyzed data from the CLARINET study [30], which supported the registration and approval of LAN by the U.S. Food and Drug Administration and the European Medicines Agency for the treatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic NETs [41, 42]. Unlike previous analyses [21, 23], the current analysis considered the simultaneous occurrence of growth and regression of drug insensitive and drug sensitive tumor fractions, respectively, to more accurately estimate the rates of tumor growth. Our results confirm the principal effect of LAN as slowing of tumor growth, with regression only seen in 14% of tumors. These results coincide with demonstration in the CLARINET study of significant PFS prolongation

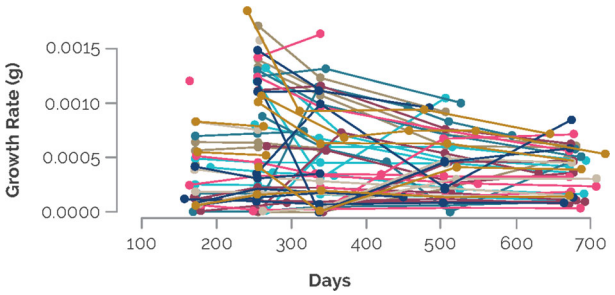


Figure 2. Growth rate (***g***) values for 58 patients treated with lanreotide depot/autogel 120 mg with >3 tumor measurements that allowed for estimates of serial ***g*** values. The value of ***g*** did not change appreciably, even during a prolonged duration of treatment. Eligibility for assessment of ***g*** based on a minimum of three tumor measurements by day 150, with tumor measurement at day 150 used as baseline measurement.

with LAN versus placebo (medians not reached vs. 18.0 months, respectively; $p < .001$) [30]. These data demonstrate an association between the rate of tumor growth (***g***) and PFS, ratifying the value of ***g*** as a biomarker of PFS. The stability of the growth rates indicates that, despite the prolonged administration of LAN, most patients do not develop resistance.

In this post hoc analysis, we were able to estimate the rate of tumor growth (***g***) and/or tumor regression (***d***) for the tumors of most patients. Among the four models describing tumor kinetics, the model describing simultaneous occurrence of growth and regression (***gd***) was most frequently the best fit in those randomized to LAN (36%), followed by the model describing continuous growth (***gx***; 34%). This compared favorably to results in the placebo group, in which the ***gx*** model was the best fit in 52%,

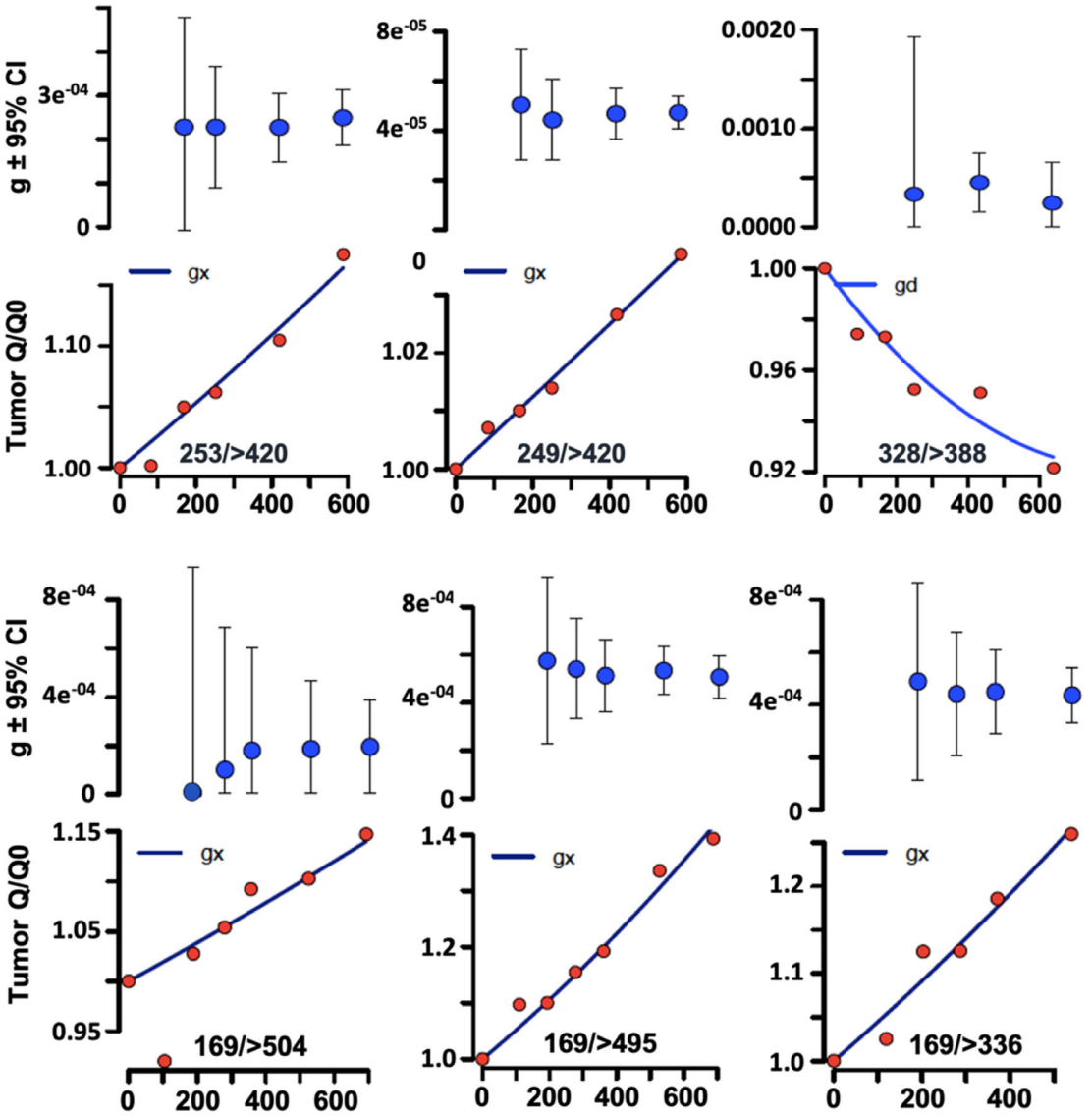


Figure 3. Representative illustrations of the stability of tumor growth rates (***g***) while receiving lanreotide depot/autogel 120 mg therapy. For each pair of graphs, the lower panel depicts a plot of the tumor quantity for a patient while enrolled in the CLARINET study, with the selected model noted in the upper left and the day stability first confirmed and its duration on the bottom. The measured values are displayed as quantity of tumor relative to a quantity of 1 at enrollment. The upper portion of each graph depicts the serial ***g*** values calculated with the available data to that point in time. In these analyses, the value of ***g*** remained stable during treatment for as long as 600 days.
Abbreviations: CI, confidence interval; g, tumor growth rate; Q, quantity; Qo, quantity of 1 (one).

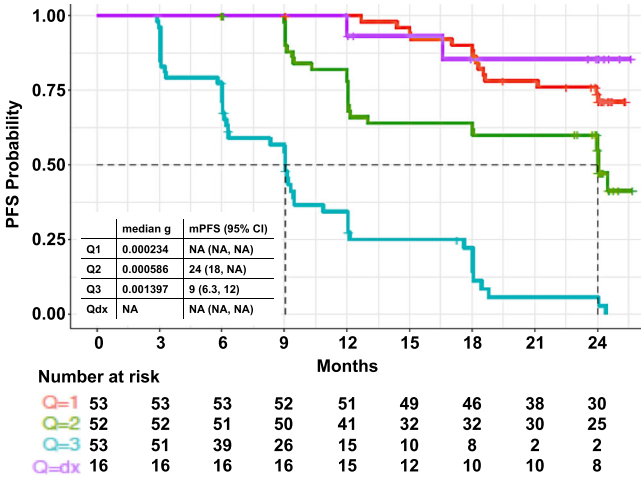


Figure 4. Association between tumor growth rate (***g***) and progression-free survival.
Abbreviations: CI, confidence interval; ***dx***, equation that defines data in which only decrease in tumor quantity at rate ***d*** occurs during treatment; ***g***, tumor growth rate; mPFS, median progression-free survival; NA, not applicable; PFS, progression-free survival; Q, quartiles.

followed by the ***gd*** model in 36%, meaning that measurable rates of regression and decay could be estimated in an additional 18% of patients treated with LAN, with an overall slowing of the rate of growth for the entire cohort of 26%. Additionally, the tumor-quantity data for 14% of patients treated with LAN were best fit by the regression-only model (***dx***), compared with only 2% of patients receiving placebo, a meaningful improvement in the fraction of patients with tumors without measurable rates of growth and only estimable rates of regression. These results confirm that LAN had an impact on tumor kinetics, leading to greater tumor regression with a shift from growth only (***gx***) to regression competing with growth (***gd***), and to regression only (***dx***). Although only a small fraction of patient tumors was scored as having a response, the kinetics of the majority changed favorably, with 60% (50/83) of patient tumors in the LAN group having some component of regression or exclusively regression. This favorable effect of LAN on the majority of tumors, albeit with varying degrees of impact, explains the marked prolongation in PFS observed in the CLARINET study–suggesting that the principal effect of LAN is the slowing of tumor growth, rather than tumor regression, at a magnitude that would score as a response by RECIST.

The clinical application of a drug such as LAN requires its administration for a prolonged period. Our analysis of serial values of ***g*** in the CLARINET study demonstrated that ***g*** remained stable for prolonged periods, with acceleration of that rate seen only rarely. This observation parallels the clinical experience with many patients. It is important to note these results represent stability in the rate at which tumor size increases, not stability in the quantity of tumor size. This stability in tumor growth rate offers the possibility of knowing very early in the course of therapy, and with some certainty, the expected rate of growth and, in turn, the expected tumor doubling time. For example, the median ***g*** value on LAN of 0.00046 day^{-1} translates into a doubling time in excess of 1,500 days (4.12 years). Moreover, this continued stability in the rate of tumor growth indicates that resistance to therapy does not develop or is slow to develop. In practical terms, these results indicate that one can expect the administration of LAN to bring benefit to the majority of patients with NETs, including the regression of tumors in 14% of patients. Among all patients, a 26% reduction in the rate of growth translates into a difference of 389 days in tumor doubling time, a prolongation that may accrue repeatedly because the rate of growth remains stable for very long periods of time. And although tumor regression may occur in some patients after the start of LAN, any narrative with the patient should emphasize the slowing of the rate at which their tumor will grow as the principal attribute of LAN. As to how one addresses the appearance of a "new lesion," that should be a decision left to the clinician. Often, new lesions are lesions now sufficiently large to be reliably measured and one could repeat the estimates of the growth rate (***g***) by including the admittedly less reliable smaller prior values of the new lesion. Alternately, in a patient with a clearly new lesion and a very slow rate of tumor growth (***g***), a decision might be made to address that lesion independently–such as with surgery or with ablation- and continue with a therapy that is otherwise bringing benefit.

This study satisfies all criteria of a "prospective-retrospective" analysis, including (a) data on majority of patients, (b) a valid test (CT measurements), (c) analytical method completely developed before its use [31–38], and (d) results validated in one or more similar data set [43]. However, while the methodology has been validated in other tumors, we do not have a NETs data set for validation.

Conclusion

This reanalysis of CLARINET data provides further insight into the effectiveness of LAN as a therapy in NETs, with some regression or exclusively regression observed in the majority of tumors. Furthermore, in a majority of tumors with growth, the rate of growth (***g***) remained stable for prolonged periods, a result that translates into an extended doubling time. The value of ***g*** as a measure of efficacy is ratified by its association with PFS. Estimations of ***g*** and, in turn, tumor doubling times could help guide physicians in their management of NETs.

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Where patient data can be anonymized, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study

protocol and clinical study report, are not always available. Proposals should be submitted to datasharing@ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

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Disclosures

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