ORIGINAL ARTICLE

Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors

Martyn E. Caplin, D.M., Marianne Pavel, M.D., Jarosław B. Ćwikła, M.D., Ph.D.,
Alexandria T. Phan, M.D., Markus Raderer, M.D., Eva Sedláčková, M.D.,
Guillaume Cadiot, M.D., Ph.D., Edward M. Wolin, M.D., Jaume Capdevila, M.D.,
Lucy Wall, M.D., Guido Rindi, M.D., Ph.D., Alison Langley, M.Sc.,
Séverine Martinez, B.Sc., Joëlle Blumberg, M.D.,
and Philippe Ruszniewski, M.D., Ph.D., for the CLARINET Investigators*

ABSTRACT

From Royal Free Hospital, London
(M.E.C.); Charité University Medicine
Berlin, Berlin (M.P.); University of Warmia
and Mazury, Olsztyn, Poland (J.B.Ć.);
University of Texas M.D. Anderson Can-
cer Center, Houston (A.T.P.); University
Hospital, Vienna (M.R.); Department of
Oncology of the First Faculty of Medicine
and General Teaching Hospital, Prague,
Czech Republic (E.S.); Robert-Debré Hos-
pital, Reims (G.C.), Ipsen, Les Ulis (A.L.,
S.M., J.B.), Beaujon Hospital, Clichy (P.R.),
and Paris Diderot University, Paris (P.R.)
— all in France; Samuel Oschin Cancer
Center, Cedars–Sinai Medical Center, Los
Angeles (E.M.W.); Vall d'Hebron Univer-
sity Hospital, Barcelona (J.C.); Western
General Hospital, Edinburgh (L.W.); and
Università Cattolica del Sacro Cuore,
Rome (G.R.). Address reprint requests to
Dr. Caplin at the Department of Gastro-
enterology, Royal Free Hospital, Pond St,
London NW3 2QG, United Kingdom, or
at m.caplin@ucl.ac.uk.

*Additional investigators in the Controlled
Study of Lanreotide Antiproliferative
Response in Neuroendocrine Tumors
(CLARINET) are listed in the Supplemen-
tary Appendix, available at NEJM.org.

BACKGROUND

Somatostatin analogues are commonly used to treat symptoms associated with hormone hypersecretion in neuroendocrine tumors; however, data on their antitumor effects are limited.

METHODS

We conducted a randomized, double-blind, placebo-controlled, multinational study of the somatostatin analogue lanreotide in patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor–positive neuro-endocrine tumors of grade 1 or 2 (a tumor proliferation index [on staining for the Ki-67 antigen] of <10%) and documented disease-progression status. The tumors originated in the pancreas, midgut, or hindgut or were of unknown origin. Patients were randomly assigned to receive an extended-release aqueous-gel formulation of lanreotide (Autogel [known in the United States as Depot], Ipsen) at a dose of 120 mg (101 patients) or placebo (103 patients) once every 28 days for 96 weeks. The primary end point was progression-free survival, defined as the time to disease progression (according to the Response Evaluation Criteria in Solid Tumors, version 1.0) or death. Secondary end points included overall survival, quality of life (assessed with the European Organization for Research and Treatment of Cancer questionnaires QLQ-C30 and QLQ-GI.NET21), and safety.

RESULTS

Most patients (96%) had no tumor progression in the 3 to 6 months before randomization, and 33% had hepatic tumor volumes greater than 25%. Lanreotide, as compared with placebo, was associated with significantly prolonged progression-free survival (median not reached vs. median of 18.0 months, P<0.001 by the stratified log-rank test; hazard ratio for progression or death, 0.47; 95% confidence interval [CI], 0.30 to 0.73). The estimated rates of progression-free survival at 24 months were 65.1% (95% CI, 54.0 to 74.1) in the lanreotide group and 33.0% (95% CI, 23.0 to 43.3) in the placebo group. The therapeutic effect in predefined subgroups was generally consistent with that in the overall population, with the exception of small subgroups in which confidence intervals were wide. There were no significant between-group differences in quality of life or overall survival. The most common treatment-related adverse event was diarrhea (in 26% of the patients in the lanreotide group and 9% of those in the placebo group).

CONCLUSIONS

Lanreotide was associated with significantly prolonged progression-free survival among patients with metastatic enteropancreatic neuroendocrine tumors of grade 1 or 2 (Ki-67 <10%). (Funded by Ipsen; CLARINET ClinicalTrials.gov number, NCT00353496; EudraCT 2005-004904-35.)

NEUROENDOCRINE TUMORS ARE RARE neoplasms,[1,2] with an annual incidence of 5 cases per 100,000 people in the United States.[1] More than 50% of cases involve tumors originating in the gastrointestinal system or pancreas, and patients commonly have distant metastases at diagnosis.[1] Since many of these patients have inoperable disease, medical therapy is often initiated to control disease progression. Treatment may also be required to relieve symptoms arising from the overproduction of amines or peptide hormones in functioning tumors.

Few medical treatments for advanced neuroendocrine tumors have been approved on the basis of their antiproliferative effects (i.e., efficacy in inhibiting tumor growth). Compelling data show that newer molecularly targeted therapies can prolong progression-free survival among patients with progressive, metastatic pancreatic neuroendocrine tumors.[3,4] In contrast, although somatostatin analogues have a favorable safety profile and are commonly used to treat symptoms associated with hormone hypersecretion,[5-7] evidence of their antiproliferative effects is limited. Most of the clinical data are from retrospective or prospective open-label studies,[7-10] with just a single randomized, controlled trial involving 85 patients with midgut tumors that were low-grade tumors according to a proliferation index (the percentage of cells that were positive for the Ki-67 antigen, determined by immunostaining of the primary tumor) of less than 2%.[11]

In the Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors (CLARINET), we investigated the antiproliferative effects of the long-acting somatostatin analogue lanreotide in more than 200 patients with nonfunctioning, somatostatin receptor–positive, enteropancreatic neuroendocrine tumors with Ki-67 values of less than 10%.

METHODS

PATIENTS

Eligible patients were adults (≥18 years of age) with sporadic neuroendocrine tumors that were confirmed centrally to be well differentiated or moderately differentiated and measurable according to the Response Evaluation Criteria in Solid Tumors (RECIST), version 1.0.[12] The tumors had a centrally assessed proliferation index (on staining for the Ki-67 antigen) of less than 10% (or a mitotic index of ≤2 mitoses per 10 high-power fields, if the Ki-67 index could not be quantified reliably). Primary tumors were located in the pancreas, midgut (defined as the small intestine and appendix), or hindgut (defined as the large intestine, rectum, anal canal, and anus) or were of unknown origin. Tumors were nonfunctioning, except for gastrinomas that had been adequately controlled by means of proton-pump inhibitors for 4 months or longer. Other inclusion criteria were the following: unresectable locally advanced tumor or metastatic disease (or the patient declined surgery), target lesion or lesions that were classified on somatostatin-receptor scintigraphy as grade 2 or higher (on a scale ranging from 0 [no uptake by tumor] to 4 [very intense uptake by tumor])[13] within the previous 6 months, and a score of 2 or less on the World Health Organization (WHO) performance scale (on a scale of 0 to 4, with 0 indicating no symptoms and 4 indicating complete disability).[14] A biopsy of the neuroendocrine tumor within 6 months before study entry was required for patients who had previous cancer and those with evidence of clinical progression.

Patients were excluded if they had received treatment with interferon, chemoembolization, or chemotherapy within 6 months before study entry, a radionuclide at any time, or a somatostatin analogue at any time (unless they had received it >6 months previously and for <15 days). Other exclusion criteria were the following: major surgery related to the neuroendocrine tumor within 3 months before study entry, multiple endocrine neoplasia, previous cancer (except in the case of patients with treated or untreated in situ cervical or uterine carcinoma or basal-cell skin carcinoma or patients with other cancers who had been treated with curative intent and had been disease-free for >5 years), and baseline abnormalities or medical conditions that could jeopardize the patient's safety or interfere with the study.

Patients were withdrawn from the study if tumor progression according to RECIST, version 1.0, was evident in a central review of an imaging scan from a study visit or from unscheduled imaging prompted by clinical or biologic signs of disease progression. Patients could also be withdrawn on the basis of the investigator's judgment, the patient's request, or an adverse event that could jeopardize the patient's safety.

STUDY OVERSIGHT

The study was designed, funded, and conducted by Ipsen in collaboration with the European Neuroendocrine Tumor Society and the UK and Ireland Neuroendocrine Tumour Society. The blinded database was held at a third-party contract clinical research organization, whose statisticians performed the analyses as defined in the statistical-analysis plan. The work of the statisticians, who were employed by the clinical research organization, was overseen by the sponsor's biostatistics department. All parties vouch for the data and analyses. A professional medical writer paid by the sponsor provided assistance with the preparation of drafts of the manuscript under the guidance of all the authors. All authors made the final decision to submit the manuscript for publication and assume responsibility for the completeness and integrity of the data and adherence to the study protocol. The protocol and statistical-analysis plan are available with the full text of this article at NEJM.org.

TRIAL DESIGN AND INTERVENTIONS

In this 96-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter, phase 3 study, an extended-release aqueous-gel formulation of lanreotide (Autogel [known in the United States as Depot]), at a dose of 120 mg, or placebo (sodium chloride) was administered, without dose adjustment, by means of deep subcutaneous injection every 28 days (to a maximum of 24 injections).

Computer-generated randomization lists were created by a statistician employed by the sponsor who was independent of the study. These lists were used to assign patients to lanreotide or placebo in four strata (based on the presence or absence of tumor progression at baseline and receipt or nonreceipt of previous therapies). Investigators enrolled patients and obtained randomization codes through a telephone-based system. Since lanreotide and placebo differed in appearance, the investigators maintained the study blinding by appointing independent health professionals to prepare and administer injections. Sealed envelopes prepared by the sponsor for breaking the randomization code were held confidentially by the sponsor and study centers, and (according to the protocol) they were opened only when patients had centrally assessed disease progression.

Patients who had disease progression while receiving placebo or who received either study drug for 96 weeks and had stable disease were eligible for the extension study (ClinicalTrials.gov number, NCT00842348). Patients who had previously received placebo crossed over to lanreotide.

The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements. Trial documentation was approved by the institutional review board at each study site. (Protocol amendments made after the beginning of the study are described in the Supplementary Appendix, available at NEJM.org.) All patients provided written informed consent.

ASSESSMENTS AND OUTCOMES

Study visits were scheduled during the screening period and at weeks 1 (baseline), 12, 24, 36, 48, 72, and 96. Multiphase computed tomography or dynamic contrast-enhanced magnetic resonance imaging of the chest, abdomen, and pelvis was performed twice during screening to determine the baseline disease-progression status. Results of the second imaging test, which was performed 12 to 24 weeks after the first imaging test, were considered to be the baseline findings and were used to determine target-lesion sizes. Randomization was performed within the following 4 weeks. The screening period was shortened if scanning had been performed once or twice in the previous 24 weeks. Single scans were obtained at all post-baseline visits. If a patient was withdrawn from the study prematurely for reasons other than death or centrally assessed disease progression, further imaging tests were required unless the previous test had taken place within the last 4 weeks. Disease progression was assessed centrally according to RECIST, version 1.0. Assessment of baseline hepatic tumor volumes, measurement of serum chromogranin A and lanreotide levels, and antibody testing are described in the Supplementary Appendix. Two European Organisation for Research and Treatment of Cancer quality-of-life questionnaires — QLQ-C30 and QLQ-GI.NET21 — were completed at post-screening visits. Safety assessments included monitoring for adverse events, physical examination and monitoring of vital signs (assessed at all visits), electrocardiography and ultrasonography of the gallbladder (assessed at baseline and at

weeks 48 and 96, as well as at withdrawal [electrocardiography only]), and clinical laboratory tests (assessed at screening, baseline, and at weeks 48 and 96 or at the time of withdrawal, in the case of patients who did not complete the study).

The primary end point was progression-free survival, defined as the time to disease progression (centrally assessed according to RECIST) or death within 96 weeks after the first injection of the study drug. Progression-free survival was also examined in prespecified subgroups; these included subgroups for tumor origin, tumor grade, and hepatic tumor volume.

Secondary end points included the proportion of patients who were alive without disease progression at 48 and 96 weeks (a measure of progression-free survival that differed from the primary end point because it was assessed at discrete time points and patients were considered to have treatment success or failure), the time to tumor progression, overall survival, quality of life, level of chromogranin A, pharmacokinetic data, and safety. Analyses of data on other tumor biomarkers were exploratory and are not reported here. Overall survival was defined as the time from randomization to death from any cause; in accordance with the protocol, information regarding deaths after the end of the study was sought by the investigators.

STATISTICAL ANALYSIS

Efficacy analyses were conducted in the intention-to-treat population (all patients who underwent randomization). We calculated that we would need to randomly assign 100 patients to each group for the study to have 90% power to detect a significant between-group difference in the primary end point at the 0.05 level, assuming rates of disease progression or death after 2 years of 60% (with lanreotide) and 80% (with placebo) and a constant hazard ratio of 0.57 over time. A preplanned blinded reestimation of the sample size, performed when the first 100 patients had received a study drug for 1 year, did not indicate that the sample size should be changed.

We analyzed between-group differences in progression-free survival in the overall population (the primary end point) using the stratified log-rank test (with stratification for the presence or absence of baseline tumor progression and receipt or nonreceipt of previous therapy). The

hazard ratio and confidence intervals were estimated with the use of the Cox proportional-hazards model. Data for the primary analysis of the primary outcome consisted of deaths and progression events that were assessed centrally; data for all other outcomes were censored according to guidance from the Food and Drug Administration.[15] (Results of associated supportive and sensitivity analyses are provided in Table S1 in the Supplementary Appendix.) Progression-free survival in predefined subgroups was examined with the use of a Cox proportional-hazards model. For hepatic tumor volume, the predefined variable comprising five categories was simplified post hoc as a dichotomous variable: a volume of 25% or less versus a volume greater than 25%. Missing data for the primary end point were not imputed.

Statistical methods for the secondary end points are summarized in Table S2 in the Supplementary Appendix. Descriptive statistics on the safety population (all randomly assigned patients who received at least one injection of study medication) were compiled for the safety end points. Statistical analyses were performed with SAS software, version 9.3 (INC Research).

RESULTS

PATIENTS

The study was conducted between June 2006 and April 2013. A total of 204 patients at 48 secondary or tertiary care centers in 14 countries (12 European countries, the United States, and India) were randomly assigned to an extended-release aqueous-gel formulation of lanreotide (101 patients) or placebo (103 patients). The median study-drug exposure was 24.0 months (range, 1.0 to 25.3) in the lanreotide group and 15.0 months (range, 1.0 to 25.2) in the placebo group. More patients in the lanreotide group than in the placebo group completed the treatment period without events (death or centrally assessed disease progression): 53 patients (52%) vs. 26 patients (25%) (Fig. S1 in the Supplementary Appendix).

The study groups were generally well matched with respect to baseline characteristics (Table 1, and Table S3 in the Supplementary Appendix). Most patients had not received previous treatment (84%) and did not have disease progression

Table 1. Baseline Demographic and Disease Characteristics of the Patients (Intention-to-Treat Population).*

Variable	Lanreotide (N = 101)	Placebo (N = 103)
Male sex — no. (%)	53 (52)	54 (52)
Age — yr	63.3±9.8	62.2±11.1
Time since diagnosis — mo		
Mean	32.6±46.1	34.4±41.4
Median	13.2	16.5
Prior treatment for neuroendocrine tumor — no. (%)	16 (16)	16 (16)
Primary tumor resected — no. (%)	40 (40)	39 (38)
Origin of neuroendocrine tumor — no. (%)†		
Pancreas	42 (42)	49 (48)
Midgut	33 (33)	40 (39)
Hindgut	11 (11)	3 (3)
Unknown or other	15 (15)	11 (11)
Tumor progression — no. (%)	4 (4)	5 (5)
Tumor grade — no. (%)‡		
1: Ki-67 0–2%	69 (68)	72 (70)
2: Ki-67 3–10%	32 (32)	29 (28)
Data missing	0	2 (2)

* Plus–minus values are means ±SD. Additional baseline data are provided in Table S3 in the Supplementary Appendix. Post hoc analyses confirmed that there were no significant between-group differences at baseline. The midgut was defined as the small intestine and appendix, and the hindgut was defined as the large intestine, rectum, anal canal, and anus.
† Two patients in each group had gastrinomas.
‡ Ki-67 thresholds for the tumor grade index were based on the World Health Organization 2010 classification.[16] Patients who had Ki-67 values greater than 2% and up to 10% in the present study were classified as having grade 2 disease.
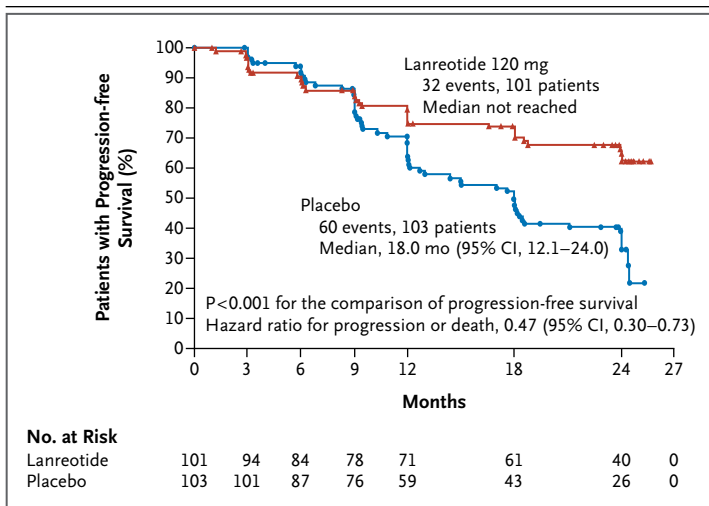
Figure 1. Progression-free Survival (Intention-to-Treat Population).

Shown are estimates of progression-free survival among patients who received lanreotide at a dose of 120 mg and patients who received placebo. Kaplan–Meier curves were compared with the use of a stratified log-rank test, with stratification according to the presence or absence of tumor progression at baseline and the receipt or nonreceipt of previous therapy. The hazard ratio was derived from a Cox proportional-hazards model with terms for study treatment, the presence or absence of tumor progression at baseline, and the receipt or nonreceipt of previous therapy.

according to RECIST in the 3 to 6 months before randomization (96%).

EFFICACY

Progression-free Survival (Primary End Point)

More patients in the placebo group than in the lanreotide group had centrally assessed disease-progression events (58 vs. 30 patients), and 2 patients in each group died. Progression-free survival was significantly prolonged with lanreotide as compared with placebo in the primary analysis (median progression-free survival, not reached vs. 18.0 months, P<0.001 by the stratified log-rank test; hazard ratio for progression or death with lanreotide vs. placebo, 0.47; 95% confidence interval [CI], 0.30 to 0.73) (Fig. 1). At 24 months, the estimated rates of progression-free survival were 65.1% (95% CI, 54.0 to 74.1) in the lanreotide group and 33.0% (95% CI, 23.0 to 43.3) in the placebo group. All supportive and sensitivity analyses corroborated the primary analysis (Table S1 in the Supplementary Appendix).

Hazard ratios for disease progression or death generally favored lanreotide over placebo in the predefined subgroups (Fig. 2, and Fig. S2
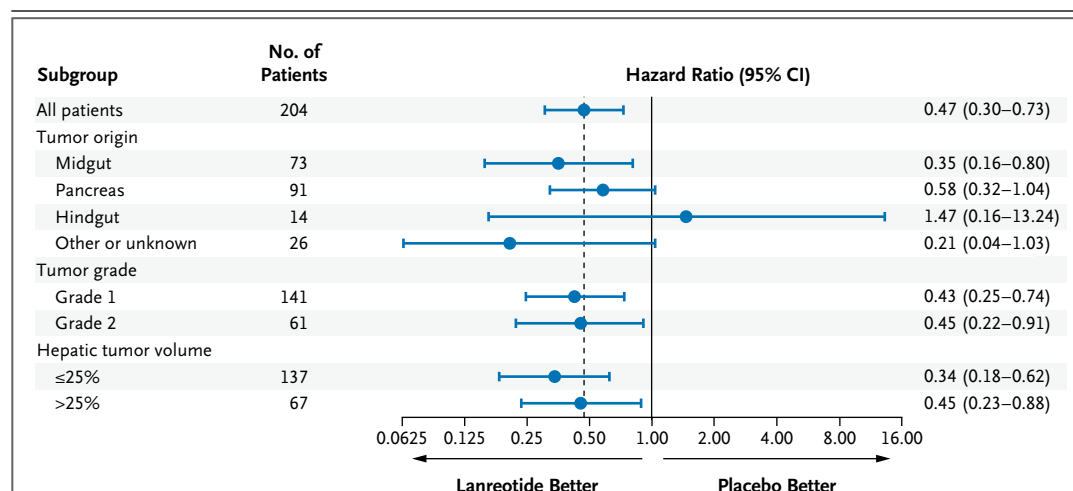
Figure 2. Progression-free Survival, According to Subgroups (Intention-to-Treat Population).

Shown are the hazard ratios for centrally assessed disease progression or death in subgroups defined according to baseline tumor origin and grade and hepatic tumor volume. Subgroup variables were predefined in all cases, although the number of categories for hepatic tumor volume was simplified post hoc from five (estimated hazard ratios ranging from 0.24 to 0.54) to two. The hazard ratio for "all patients" was derived from a Cox proportional-hazards model with terms for study treatment, presence or absence of tumor progression at baseline, and receipt or nonreceipt of previous therapy. The hazard ratio for each subgroup was derived from a Cox proportional-hazards model with a single term for study treatment.

and S3 in the Supplementary Appendix). The exceptions were the smaller subgroups (e.g., the subgroup of patients with tumors originating in the hindgut [Fig. 2]), for which the hazard ratios had wide confidence intervals and the findings were imprecise.

Other End Points

The odds ratio for being alive without centrally assessed disease progression at weeks 48 and 96 (an additional measure of progression-free survival), as well as the time to tumor progression, significantly favored lanreotide over placebo at each time point (Table 2). Although overall survival did not differ significantly between the study groups, the analysis was complicated by crossover from the placebo group to the lanreotide group and uncertainty over treatments after progression (Fig. S4 in the Supplementary Appendix).

Between-group differences with respect to quality of life were not significant (Table 2, and Table S4 in the Supplementary Appendix). Among patients with baseline levels of chromogranin A that exceeded the upper limit of the normal range, the odds of at least a 50% reduction in these levels were significantly greater with lan-

reotide than with placebo (Table 2). Pharmacokinetic data are provided in Table S5 in the Supplementary Appendix.

SAFETY

Similar proportions of patients in the two groups had adverse events (88% in the lanreotide group and 90% in the placebo group) (Table 3). Most of these patients had mild events (17% in each group) or moderate events (44% in the lanreotide group and 43% in the placebo group). Half the patients in the lanreotide group had adverse events related to the study drug (vs. 28% in the placebo group), most commonly diarrhea (26% vs. 9%). Study drug–related adverse events included hyperglycemia (in 5 patients who received lanreotide vs. no patients who received placebo, although 2 patients who received lanreotide also had a history of diabetes) and cholelithiasis (in 10 patients who received lanreotide and 3 patients who received placebo); among the patients with cholelithiasis, 4 patients had new gallbladder sludge (3 in the lanreotide group and 1 in the placebo group) and 10 patients had new lithiasis (7 and 3 patients, respectively).

Six patients had adverse events leading to withdrawal from the study, with only 1 event

Table 2. Secondary Efficacy End Points (Intention-to-Treat Population).*

End Point	Lanreotide (N=101)	Placebo (N=103)	Between-Group Comparison (95% CI)	P Value
Patients alive without disease progression — no./total no. (%)†				
At wk 48	67/101 (66)	50/103 (49)	2.11 (1.19 to 3.76)	<0.05
At wk 96	53/101 (52)	26/103 (25)	3.27 (1.81 to 5.93)	<0.001
Median time to tumor progression (95% CI) — mo‡	Not reached	18.0 (12.1 to 24.0)		<0.001§
EORTC QLQ-C30 global health status score — least-squares mean change from baseline to last post-baseline value available¶	−5.18±3.73	−4.87±3.7	−0.31±2.74 (−5.73 to 5.10)	
Patients with ≥50% reduction in level of chromogranin A from baseline to last post-baseline level available — no./total no. (%)‖	27/64 (42)	3/64 (5)	15.20 (4.29 to 53.87)	<0.001

* Plus–minus values are means ±SE. Odds ratios are reported for all between-group comparisons except the score on the European Organisation for Research and Treatment of Cancer quality-of-life questionnaire QLQ-C30, for which the least-squares mean difference is reported. CI denotes confidence interval.
† Values shown are measures of progression-free survival; however, they differ from the primary end point in that they are measurements at discrete time points and with patients counted as having treatment success or failure at each assessment. (Any patient who withdrew from the study before the visit was counted as having disease progression or having died.) As with the primary end point, disease-progression events were assessed centrally. Odds ratios were calculated with the use of a logistic-regression model with terms for study treatment, presence or absence of centrally assessed progression at baseline, and receipt or nonreceipt of previous therapy.
‡ There were 30 events in the lanreotide group and 58 events in the placebo group.
§ The between-group difference was analyzed with the use of the log-rank test.
¶ Data are from an analysis of covariance with fixed-effect terms for study treatment, presence or absence of progression at baseline, receipt or nonreceipt of previous therapy, and baseline quality-of-life score; quality-of-life scores were transformed before analysis to a range of 0 to 100, with a higher transformed score indicating better quality of life. There were 95 patients in the lanreotide group and 98 patients in the placebo group.
‖ Data are shown for the subgroup of patients with a baseline chromogranin A level higher than the upper limit of the normal range (see Table S3 in the Supplementary Appendix) who also had data that could be evaluated after baseline (64 patients in each group). Results were calculated with the use of a logistic-regression model with terms for study treatment and receipt or nonreceipt of previous therapy. The upper limit of the normal range was 98.1 μg per liter.

considered by the investigator to be related to the study drug (Table 3). A total of 57 patients had 122 serious adverse events; 8 events (7 in the lanreotide group and 1 in the placebo group) were considered to be related to the study drug. Data on antibodies are provided in the Supplementary Appendix. No clinically significant trends were observed in other safety assessments.

DISCUSSION

In this randomized, double-blind study, an extended-release aqueous-gel formulation of lanreotide at a dose of 120 mg, as compared with placebo, was associated with significantly prolonged progression-free survival among patients with metastatic enteropancreatic neuroendocrine tumors of grade 1 or 2 (Ki-67 <10%). In fact, on the basis of the hazard ratio for the primary end point (0.47), the risk of disease progression within 96 weeks after the first dose of the study drug was reduced by 53%. Lanreotide was associated with more gastrointestinal adverse events and a higher rate of study drug–related adverse events (50%, vs. 28% with placebo). Few patients in either group, however, withdrew because of adverse events.

Before these results, the antiproliferative effects of somatostatin analogues in advanced neuroendocrine tumors were principally shown in in vitro studies,[17,18] uncontrolled prospective and retrospective clinical studies,[10,19,20] and one randomized, controlled trial involving 85 patients (Placebo-Controlled, Double-Blind, Prospective,

Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients with Metastatic Neuroendocrine Midgut Tumors [PROMID]).[11] Although PROMID showed a significantly prolonged time to tumor progression with octreotide long-acting release therapy as compared with placebo in patients with midgut tumors, the study was narrowly focused so that it was made up almost entirely of patients with grade 1 tumors and few patients had hepatic tumor volumes greater than 10%.[11] Our study showed an antiproliferative effect of lanreotide in a study population of patients with enteropancreatic tumors, with Ki-67 values extending into grade 2 (Ki-67 <10%) and with larger hepatic tumor volumes. Although detailed comparisons of the findings from these two studies must be made with caution, it seems likely that the patients in our study, as compared with those in PROMID, had, in general, more indolent tumors, since the median time to diagnosis was longer in our study than in PROMID (14.7 months vs. 4.3 months). In addition, almost all the patients in our study had stable disease at baseline, and it seems unlikely, considering the shorter time to disease progression in the PROMID placebo group than in the CLARINET placebo group, that PROMID had such a predominance of patients with stable disease. However, since disease-progression status was not documented in PROMID, this cannot be confirmed. Moreover, disease progression was assessed differently in the two studies: the bidimensional WHO criteria were used in PROMID and the unidimensional RECIST, version 1.0, criteria were used in our study. Since a bidimensional measure shows a larger percentage increase in tumor size than a unidimensional measure of the same tumor response, WHO-based assessments might show a shorter progression-free survival. These differences notwithstanding, the two studies are aligned in affirming clinically relevant antiproliferative effects with long-acting somatostatin analogues in patients with neuroendocrine tumors.

Current clinical practice guidelines regarding the use of somatostatin analogues for control of advanced enteropancreatic neuroendocrine tumors are based largely on findings from PROMID.[5,21] However, in cases in which evidence from clinical trials is lacking or individual circumstances dictate, current guidelines suggest that a period of deferred treatment (a "wait and see" policy) may be appropriate. The placebo group in our study may be considered a surrogate for deferred treatment, and the long period of progression-free survival in this group may appear to support this approach. However, our study principally examined the prevention of dis-

Table 3. Adverse Events (Safety Population).*

Event	Lanreotide (N=101)	Placebo (N=103)
	no. of patients (%)	
Any adverse event	89 (88)	93 (90)
Any adverse event related to study treatment	50 (50)	29 (28)
Any adverse event according to intensity†		
Severe	26 (26)	32 (31)
Moderate	44 (44)	44 (43)
Mild	17 (17)	17 (17)
Any serious adverse event	25 (25)	32 (31)
Serious adverse event related to study treatment‡	3 (3)	1 (1)
Withdrawal from study because of any adverse event§	3 (3)	3 (3)
Withdrawal because of adverse event related to study treatment	1 (1)	0
Study treatment–related adverse events in ≥5% of patients		
Diarrhea	26 (26)	9 (9)
Abdominal pain	14 (14)	2 (2)
Cholelithiasis	10 (10)	3 (3)
Flatulence	8 (8)	5 (5)
Injection-site pain	7 (7)	3 (3)
Nausea	7 (7)	2 (2)
Vomiting	7 (7)	0
Headache	5 (5)	2 (2)
Lethargy	5 (5)	1 (1)
Hyperglycemia	5 (5)	0
Decreased level of pancreatic enzymes	5 (5)	0

* Adverse events were defined according to the *Medical Dictionary for Regulatory Activities,* version 16.0.
† For patients with multiple adverse events, events with the maximum intensity are shown; data are missing for two patients in the lanreotide group.
‡ There were seven events (hyperglycemia, diabetes mellitus, nausea, vomiting, abdominal pain, biliary fistula, and cholelithiasis) in the lanreotide group and one event (bile duct stenosis) in the placebo group.
§ Intestinal obstruction, sepsis, hypoglycemia, esophageal carcinoma, and circulatory collapse were not considered to be related to the study treatment. "Liver decompensation" (the term used by the investigator) was considered by the investigator to be related to the study treatment because of the timing of the event (the day after the first injection); the event was concurrent with an episode of food poisoning, and the patient recovered without sequelae after 3.5 months.

ease progression, and the data indicated that progression is significantly delayed with the use of lanreotide in patients with grade 1 or 2 (Ki-67 <10%) enteropancreatic tumors and stable disease, irrespective of the hepatic tumor volume. Early treatment with lanreotide in such patients may be further facilitated by its favorable safety profile; this favorable safety profile was evident both in our study and in long-term experience with the agent in patients with functioning tumors.[7] Indeed, the adverse-event profiles of somatostatin analogues generally compare favorably with those of alternative treatments such as molecularly targeted therapies[3,4,22] or chemotherapy.[23,24] These arguments notwithstanding, individualized treatment remains the cornerstone of disease management, and deferred treatment will continue to be appropriate for some patients. It will be important to determine the durability of the antiproliferative effects of lanreotide, which is being examined further in the CLARINET extension study. In addition, for patients with a higher risk of progression than the risk among patients in the CLARINET study, investigations are ongoing to assess whether clinical benefits are enhanced by concomitant treatment with somatostatin analogues and molecules that have potentially complementary mechanisms of action.

Although CLARINET is a large and rigorous study, it has limitations. First, 96% of the patients had stable disease at baseline. Such patients are likely to have fewer tumor-related events (disease progression or death) than those with progressive disease. Data are lacking from controlled trials involving patients with documented progressive disease. Second, no significant between-group difference in overall survival was apparent at 2 years, probably because of the long life expectancy for patients with slow-growing tumors[25] and crossover from placebo to active treatment with disease progression. Other studies involving patients with neuroendocrine tumors have reported similar outcomes.[3,11] Finally, our study included only patients with nonfunctioning tumors, whereas PROMID did include some patients with mildly functioning tumors and showed similar treatment effects on time to tumor progression in patients with nonfunctioning tumors.[11]

In summary, lanreotide was associated with prolonged progression-free survival among patients with advanced, grade 1 or 2 (Ki-67 <10%) enteropancreatic, somatostatin receptor–positive neuroendocrine tumors with prior stable disease, irrespective of the hepatic tumor volume.

REFERENCES

1. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol 2008;26:3063-72.

2. van der Zwan JM, Trama A, Otter R, et al. Rare neuroendocrine tumours: results of the Surveillance of Rare Cancers in Europe project. Eur J Cancer 2013;49:2565-78.

3. Yao JC, Shah MH, Ito T, et al. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med 2011;364:514-23.

4. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med 2011;364:501-13. [Erratum, N Engl J Med 2011;364:1082.]

5. Kulke MH, Benson AB III, Bergsland E, et al. Neuroendocrine tumors. J Natl Compr Canc Netw 2012;10:724-64.

6. Öberg K, Knigge U, Kwekkeboom D, Perren A. Neuroendocrine gastro-enteropancreatic tumors: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2012;23:Suppl 7:vii124-vii130.

7. Khan MS, El-Khouly F, Davies P, Toumpanakis C, Caplin ME. Long-term results of treatment of malignant carcinoid syndrome with prolonged release lanreotide (Somatuline Autogel). Aliment Pharmacol Ther 2011;34:235-42.

8. Bajetta E, Catena L, Procopio G, et al. Is the new WHO classification of neuroendocrine tumours useful for selecting an appropriate treatment? Ann Oncol 2005;16:1374-80.

9. Martín-Richard M, Massutí B, Pineda E, et al. Antiproliferative effects of lanreotide autogel in patients with progressive, well-differentiated neuroendocrine tumours: a Spanish, multicentre, open-label, single arm phase II study. BMC Cancer 2013;13:427.

10. Palazzo M, Lombard-Bohas C, Cadiot G, et al. Ki67 proliferation index, hepatic tumor load, and pretreatment tumor growth predict the antitumoral efficacy of lanreotide in patients with malignant digestive neuroendocrine tumors. Eur J Gastroenterol Hepatol 2013;25:232-8.

11. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the PROMID Study Group. J Clin Oncol 2009;27:4656-63.

12. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. J Natl Cancer Inst 2000;92:205-16.

13. Krenning EP, Kwekkeboom DJ, Pauwels S, Kvols LK, Reubi JC. Somatostatin receptor scintigraphy. In: Freeman LM, ed. Nuclear medicine annual. New York: Raven Press, 1995:1-5.

14. Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-55.

15. Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics. Rockville, MD: Food and

Drug Administration, 2007 (http://www .fda.gov/downloads/Drugs/Guidance ComplianceRegulatoryInformation/ Guidances/ucm071590.pdf).

16. Rindi G, Arnold R. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman F, Carneiro F, Hruban R, Theise N, eds. World Health Organization classification of tumours of the digestive system. Lyon, France: IARC Press, 2010:13-4.

17. Susini C, Buscail L. Rationale for the use of somatostatin analogs as antitumor agents. Ann Oncol 2006;17:1733-42.

18. Grozinsky-Glasberg S, Shimon I, Korbonits M, Grossman AB. Somatostatin analogues in the control of neuroendocrine tumours: efficacy and mechanisms. Endocr Relat Cancer 2008;15:701-20.

19. Toumpanakis C, Caplin ME. Update on the role of somatostatin analogs for the treatment of patients with gastroen-teropancreatic neuroendocrine tumors. Semin Oncol 2013;40:56-68.

20. Sidéris L, Dubé P, Rinke A. Antitumor effects of somatostatin analogs in neuroendocrine tumors. Oncologist 2012;17: 747-55.

21. Pavel M, Baudin E, Couvelard A, et al. ENETS Consensus Guidelines for the management of patients with liver and other distant metastases from neuroendocrine neoplasms of foregut, midgut, hindgut, and unknown primary. Neuroendocrinology 2012;95:157-76.

22. Pavel ME, Hainsworth JD, Baudin E, et al. Everolimus plus octreotide long-acting repeatable for the treatment of advanced neuroendocrine tumours associated with carcinoid syndrome (RADIANT-2): a randomised, placebo-controlled, phase 3 study. Lancet 2011;378:2005-12.

23. Sun W, Lipsitz S, Catalano P, Mailliard JA, Haller DG. Phase II/III study of doxo-rubicin with fluorouracil compared with streptozocin with fluorouracil or dacarbazine in the treatment of advanced carcinoid tumors: Eastern Cooperative Oncology Group Study E1281. J Clin Oncol 2005;23:4897-904.

24. Kouvaraki MA, Ajani JA, Hoff P, et al. Fluorouracil, doxorubicin, and streptozocin in the treatment of patients with locally advanced and metastatic pancreatic endocrine carcinomas. J Clin Oncol 2004; 22:4762-71. [Erratum, J Clin Oncol 2005; 23:248.]

25. Kulke MH, Siu LL, Tepper JE, et al. Future directions in the treatment of neuroendocrine tumors: consensus report of the National Cancer Institute Neuroendocrine Tumor clinical trials planning meeting. J Clin Oncol 2011;29:934-43.

Copyright © 2014 Massachusetts Medical Society.