

A SPECIAL MEETING REVIEW EDITION

**Highlights in GEP-NETs From the 2016
NANETS Symposium**

A Review of Selected Presentations From the 2016 North American
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Special Reporting on:

- NETTER-1 Phase III in Patients With Midgut Neuroendocrine Tumors Treated With ¹⁷⁷Lu-Dotatate: Efficacy, Safety, QoL Results and Subgroup Analysis
- Efficacy of Lanreotide Depot/Autogel for Symptomatic Control of Carcinoid Syndrome (CS) in Neuroendocrine Tumor Patients: Follow-Up Analysis of the ELECT Prospective, Randomized, Double-Blind and Open-Label Phases
- Efficacy and Safety Results of Telotristat Ethyl in Patients With Carcinoid Syndrome During the Double-Blind Treatment Period of the TELECAST Phase 3 Clinical Trial
- The Efficacy and Safety of Sunitinib in Patients With Advanced Well-Differentiated Pancreatic Neuroendocrine Tumors
- Lanreotide Autogel/Depot (LAN) Post-Octreotide Long-Acting Release (OCT) for Safe and Tolerable Treatment of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)
- Long-Term Efficacy, Survival and Safety of [¹⁷⁷Lu-DOTA0,Tyr3] Octreotate in Patients With Gastroenteropancreatic and Bronchial Neuroendocrine Tumors

PLUS Meeting Abstract Summaries

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NETTER-1 Phase III in Patients With Midgut Neuroendocrine Tumors Treated With ^{177}Lu -Dotatate: Efficacy, Safety, QoL Results and Subgroup Analysis

Somatostatin analogs were initially approved for controlling carcinoid syndrome associated with neuroendocrine tumors (NETs), but they have subsequently demonstrated antiproliferative activity in moderately or well-differentiated NETs.^{1,2} The efficacy of somatostatin analogs is predicated on binding to somatostatin receptors, particularly somatostatin receptor subtype 2, which is expressed on the majority of well-differentiated NETs. Limited therapeutic options are available for patients with inoperable or metastatic NETs of the gastrointestinal tract and those who progress on first-line somatostatin analogs. Peptide receptor radionuclide therapy (PRRT) provides targeted delivery of radiation to tumor cells and has shown promise in treating refractory and metastatic gastroenteropancreatic (GEP) NETs.^{3,4} Radioactivity is typically supplied by ^{90}Y or ^{177}Lu covalently bound to the somatostatin analog. Octreotate is a modified form of octreotide with improved affinity for somatostatin receptor subtype 2. It is modified with ^{177}Lu , an isotope that emits β and γ , to generate the therapeutic molecule known as ^{177}Lu -DOTATATE (or ^{177}Lu -octreotate).

The phase 3 NETTER-1 trial (Phase III in Patients With Midgut Neuroendocrine Tumors Treated With ^{177}Lu -DOTATATE) was the first randomized, prospective study to examine the safety and efficacy of PRRT using ^{177}Lu -DOTATATE in patients with NETs.⁵ Enrolled patients had inoperable midgut NETs with positive somatostatin receptor expression that progressed during treatment with octreotide long-acting release (LAR; 30 mg). Patients were randomly assigned to receive 4 cycles of ^{177}Lu -DOTATATE

(7.4 GBq every 8 weeks) or high-dose octreotide (60 mg every 4 weeks). Patients in the ^{177}Lu -DOTATATE arm were also treated with octreotide LAR (30 mg every 4 weeks) to control NET symptoms. High-dose octreotide was recommended as the comparator treatment by both the US Food and Drug Administration (FDA) and the European Medicines Agency, reflecting the lack of standard second-line treatments for this patient population. The primary endpoint was progression-free survival (PFS) based on the Response Evaluation Criteria In Solid Tumors (RECIST) by blinded review.⁶ Other endpoints included overall survival (OS), safety, and quality of life. Global health status was assessed by the European Organisation

for Research and Treatment of Cancer (EORTC) quality-of-life questionnaire (QLQ) C30, which assesses health in cancer patients, and by the EORTC QLQ-GINET21, which is designed specifically for patients with NETs.

The intent-to-treat population included 116 patients in the ^{177}Lu -DOTATATE arm and 113 in the octreotide LAR arm. The patients' mean age was approximately 64 ± 9 years. The primary tumor site was the ileum in about 74% of patients. Approximately two-thirds of tumors were grade 1 and one-third were grade 2, reflecting low and intermediate mitotic counts, respectively. Somatostatin receptor expression was strong in most of the tumors. The most common sites of metastasis included

ABSTRACT SUMMARY Long-Term Safety/Tolerability of Lanreotide Autogel/Depot in Neuroendocrine Tumor Patients With Carcinoid Syndrome: The ELECT Long-Term Open-Label Extension

As part of the ELECT trial, a long-term open-label extension study of 57 NET patients was conducted to evaluate the safety and tolerability of lanreotide depot/autogel for controlling symptoms associated with carcinoid syndrome (Abstract 147). In the ELECT trial, patients were randomly assigned to receive lanreotide depot/autogel (120 mg) or placebo every 4 weeks during the double-blind phase, and all continuing participants received lanreotide depot/autogel (120 mg) every 4 weeks thereafter. During the extension phase, median treatment exposure was 110 weeks (interquartile range, 64-135 weeks), and 29 patients (51%) received short-acting octreotide. AEs were observed in 27 patients (84%) who received lanreotide depot/autogel during the double-blind phase and extension phases, and in 21 patients (84%) who received placebo followed by lanreotide depot/autogel. Serious AEs occurred in 31% of patients treated with lanreotide depot/autogel first and in 20% of patients treated with placebo first. One patient in each group experienced a serious, treatment-related AE. Five patients discontinued study drug treatment and 5 patients died, but none of these events were considered related to treatment. The most frequently reported class of AE was gastrointestinal disorders. An increase in blood triglycerides in 1 patient receiving lanreotide depot/autogel occurred throughout the study and was considered treatment-related. Four patients (7%) experienced cholelithiasis during the extension study. No new safety concerns were identified during the extension study. Long-term safety data were consistent with previous reports.

the liver (83%-84%), lymph nodes (58%-66%), and bone (11%). Urinary levels of 5-hydroxyindoleacetic acid (5-HIAA) were generally high, consistent with the presence of midgut NETs.

The final analysis of PFS demonstrated superior outcomes in the ^{177}Lu -DOTATATE arm vs the octreotide LAR arm (HR, 0.21; 95% CI, 0.13-0.33; $P<.0001$), with a 79% reduction in the risk of disease progression or death. Median PFS in the control arm was 8.4 months and was not reached in the investigational arm (Figure 1). The estimated median PFS for patients in the ^{177}Lu -DOTATATE arm was approximately 40 months. Forest plot analysis demonstrated superior outcomes with ^{177}Lu -DOTATATE treatment for all patient subpopulations, including those with vs without extrahepatic metastases; men vs women; tumors of grade 1 vs 2; and patients with high vs normal or low levels of alkaline phosphatase, 5-HIAA, chromogranin A, and somatostatin receptor expression. The objective response rate (ORR) was 18% in the investigational arm vs 3% in the control arm ($P=.0008$). Interim analysis of OS yielded an HR of 0.398 (95% CI, 0.21-0.77; $P=.0043$).

^{177}Lu -DOTATATE yielded a favorable safety profile. The most common adverse events (AEs) of any grade were nausea, which occurred in 59% of the treatment arm vs 12% in the placebo arm, and vomiting, which occurred at rates of 47% vs 10%, respectively. The majority of these AEs were associated with the amino acid infusions that are given concurrently with ^{177}Lu -DOTATATE to provide renal protection, and most resolved when these infusions ended. The study protocol mandated use of a commercial formulation containing 18 to 21 amino acids. In contrast, in Europe, a formulation consisting of only arginine and lysine is used, and nausea and vomiting are rare. In the investigational vs the control arm, hematotoxicities of any grade included thrombocytopenia (25%

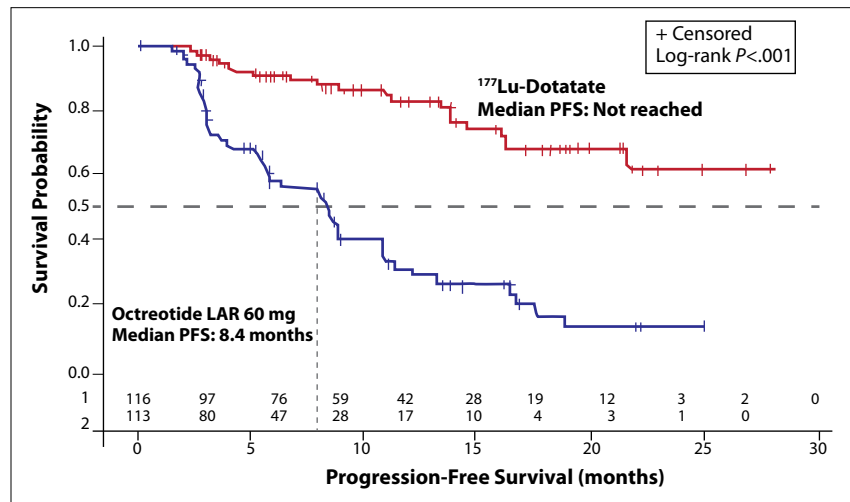


Figure 1. Median PFS in the NETTER-1 trial of ^{177}Lu -DOTATATE vs octreotide LAR. LAR, long-acting release; NETTER-1, Phase III in Patients With Midgut Neuroendocrine Tumors Treated With ^{177}Lu -DOTATATE; PFS, progression-free survival.

Adapted from Strosberg J et al. NANETS abstract 144.⁵

vs 1%), lymphopenia (18% vs 2%), anemia (14% vs 5%), leukopenia (10% vs 1%), and neutropenia (5% vs 1%), respectively. Grade 3/4 hematotoxicities were not observed in the octreotide LAR arm. Grade 3/4 lymphopenia occurred in 9% of the ^{177}Lu -DOTATATE arm, with rates of 0% to 2% for all other hematotoxicities. Renal function is a concern with therapeutic somatostatin analogs. However, based on rates of creatinine clearance, renal function remained stable during a median follow-up of 14 months, with no grade 3/4 increases in creatinine clearance.

Preliminary quality-of-life findings suggested that ^{177}Lu -DOTATATE improved key issues that are relevant to patients with midgut NETs, including global health and frequency of diarrhea. Global health status was assessed through the EORTC QLQ-C30, which asks patients to rate their quality of life and overall health. Mean outcomes were measured every 12 weeks during the study. Global health status improved in 28% of patients in the ^{177}Lu -DOTATATE arm vs 15% in the octreotide LAR arm. It worsened in 18% vs 26% of patients, respectively. The EORTC QLQ-C30 also queried the occurrence of diarrhea, pain, and

flushing/sweats. On average during the study, diarrhea improved in 39% of patients in the ^{177}Lu -DOTATATE arm vs 23% in the octreotide LAR arm and worsened in 19% vs 23%, respectively. Pain improved in 41% vs 39% and worsened in 17% vs 25%, respectively. Flushing/sweats improved in 42% vs 38% and worsened in 22% vs 19%.

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Efficacy of Lanreotide Depot/Autogel for Symptomatic Control of Carcinoid Syndrome (CS) in Neuroendocrine Tumor Patients: Follow-Up Analysis of the ELECT Prospective, Randomized, Double-Blind and Open-Label Phases

NETs arising in the gastrointestinal tract, lung, or thymus may secrete any of several hormones and vasoactive peptides. Carcinoid syndrome most commonly arises from carcinoid tumors of the digestive tract and is caused by the secretion of serotonin and other vasoactive substances by NETs. The syndrome consists of a group of symptoms that usually includes diarrhea and flushing and may also include abdominal pain and carcinoid heart disease.^{1,2} Treatment guidelines recommend

long-acting somatostatin analogs as first-line therapy to control symptoms associated with carcinoid syndrome in patients with NETs.^{3,4} Lanreotide depot/autogel is a long-acting somatostatin analog that is administered by deep subcutaneous injection. The multinational phase 3 ELECT study (An Efficacy and Safety Study of Somatoline Depot [Lanreotide] Injection to Treat Carcinoid Syndrome) evaluated the efficacy and safety of lanreotide depot/autogel (120 mg every 4 weeks) vs placebo for the control of carcinoid

syndrome symptoms in patients with NETs.⁵ The study included adult patients with histologically confirmed NETs or NETs of unknown location with liver metastases, and a history of carcinoid syndrome that included diarrhea and/or flushing. Eligible patients were either previously untreated with somatostatin analogs or had shown a prior response to either short- or long-acting octreotide.

The trial included a 1-month screening phase, a 16-week double-blind treatment phase, and a 32-week initial open-label phase. A long-term open-label extension study lasted at least 2 years. Patients were randomly assigned to receive lanreotide depot/autogel (120 mg) or placebo every 4 weeks. Patients were allowed to self-treat with short-acting subcutaneous octreotide as rescue medication to control carcinoid syndrome symptoms throughout the double-blind and open-label phases. The primary outcome measure was use of short-acting octreotide rescue medication. The study met its primary endpoint, demonstrating a significant improvement in the control of carcinoid syndrome symptoms in the lanreotide depot/autogel arm compared with the placebo arm based on the percentage of days requiring use of rescue medication (34% vs 49%; $P=.02$).

Post hoc analyses were performed to evaluate patient-reported symptom data from the 16-week double-blind and the 32-week initial open-label phases of the ELECT study and to assess levels of urinary 5-HIAA and

ABSTRACT SUMMARY Association of Disease Progression, Health-Related Quality of Life (HRQoL), and Utility in Patients With Advanced, Nonfunctional, Well-Differentiated Gastrointestinal (GI) or Lung Neuroendocrine Tumors (NET) in the Phase 3 RADIANT-4 Trial

The phase 3 RADIANT-4 study (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) yielded a significant improvement in PFS with everolimus plus best supportive care vs placebo plus best supportive care in patients with advanced, progressive, nonfunctional gastrointestinal or lung NETs (Yao JC et al. *Lancet*. 2016;387[10022]:968-977). A study was conducted to assess the relationship between disease progression and health-related quality of life and utility based on pooled data from 282 patients in the 2 RADIANT-4 treatment arms (Abstract 137). Health-related quality of life was assessed by the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire, which covers physical, social, emotional, and functional well-being. FACT-G values were converted to the utility score using 2 published mapping algorithms. Based on the entire study population, FACT-G scores were significantly lower after progression vs before progression in total and in all subscale scores. The difference in FACT-G total score before vs after progression was 4.91, which may be clinically relevant based on a minimally important difference of 3 to 7 points. With the exception of the social score, the differences before vs after progression remained significant when analyzed according to subgroups of NETs originating in the gastrointestinal tract or lung. Disease progression was also associated with a decline in utility, but the difference in utility before vs after progression was not clinically relevant.

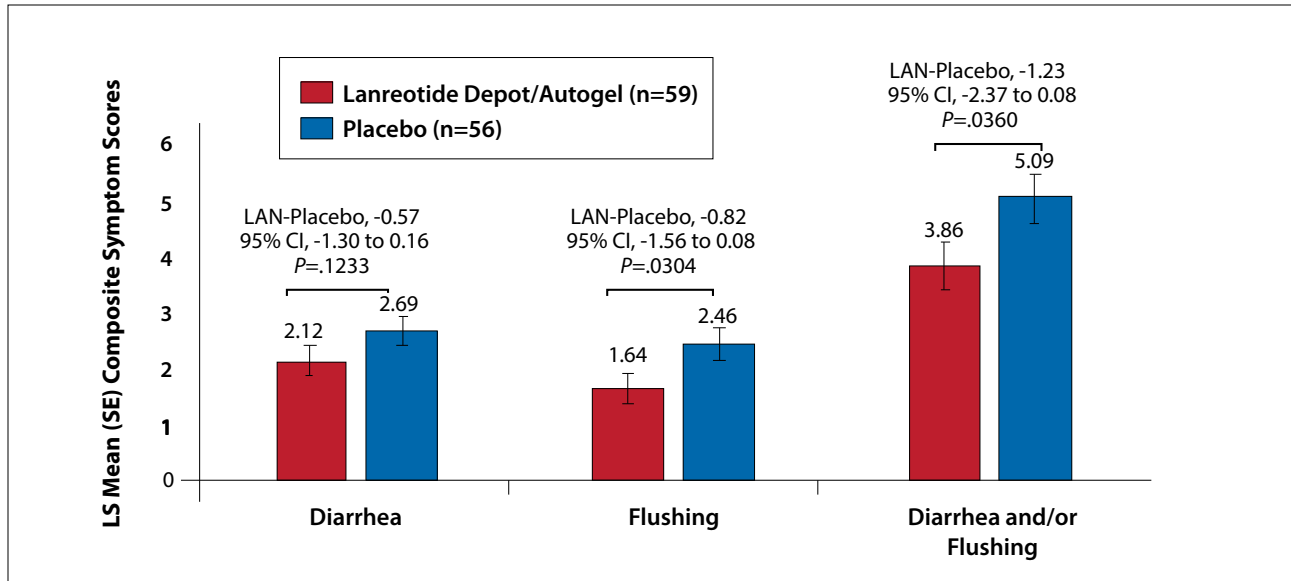


Figure 2. Least square mean daily composite symptom scores for lanreotide depot/autogel and placebo in the intent-to-treat population during the double-blind phase of the ELECT trial. ELECT, An Efficacy and Safety Study of Somatoline Depot (Lanreotide) Injection to Treat Carcinoid Syndrome; LAN, lanreotide depot/autogel; LS, least square; SE, standard error.

Adapted from Fisher GA et al. NANETS abstract 155.⁶

safety during the latter phase.⁶ Patients recorded the presence, frequency, and severity of diarrhea and flushing events using an interactive voice/web response system. Urinary 5-HIAA was assessed at baseline and every 12 weeks for a total of 48 weeks. The post hoc analyses included all patients in the intent-to-treat population. Patient-reported daily symptom frequency and severity were combined to generate an average daily composite score.

For the 16-week double-blind phase, 59 patients were randomly assigned to lanreotide depot/autogel and 56 to placebo. Fifty-six of the lanreotide depot/autogel patients and 45 of the placebo patients continued to the initial open-label phase. The 101 patients who entered the initial open-label phase had a mean age of approximately 58 ± 11 years, and approximately 60% had prior exposure to octreotide. The time since the first symptoms to treatment start was 1 year or longer in 66.7% to 76.8% of patients, and the time since first diagnosis to treatment start was 1 year or longer in 60.0% to 67.9% of patients

in the 2 arms. Approximately half of the patients had used short-acting octreotide during screening.

The proportion of patient-reported days with severe diarrhea was 5.13% in the lanreotide depot/autogel arm vs 3.35% in the placebo arm, and the proportion of patient-reported days with severe flushing was 2.21% vs 4.84%, respectively, with no significant differences between the 2 arms. Adjusted average daily composite symptom scores for diarrhea only, flushing only, and diarrhea and/or flushing showed greater improvements in patients treated with lanreotide depot/autogel vs placebo during the 16-week double-blind phase. Comparing the 2 arms, least squares mean daily composite symptom scores showed superior carcinoid symptom control with lanreotide depot/autogel compared with placebo for diarrhea (2.12 vs 2.69; $P=0.1233$), flushing (1.64 vs 2.46; $P=0.0304$), and diarrhea and/or flushing (3.86 vs 5.09; $P=0.0360$; Figure 2). Lanreotide depot/autogel was also superior based on the mean proportion of days with moder-

ate or severe diarrhea (15.8% vs 24.6%; $P=.016$), moderate or severe flushing (13.2% vs 21.7%; $P=.012$), moderate or severe diarrhea and/or flushing (23.4% vs 35.8%; $P=.004$), and severe diarrhea and/or flushing (3.9% vs 7.6%; $P=.023$). In patients treated with lanreotide depot/autogel, mean daily composite symptom scores for diarrhea improved significantly from the 16-week double-blind phase to the initial open-label phase (mean difference, -0.71; 95% CI, -1.20 to -0.22; $P=.0054$; Figure 3). However, mean composite symptom scores for flushing only or for diarrhea and/or flushing remained stable during the same time. Patients who received placebo treatment during the 16-week double-blind phase followed by lanreotide depot/autogel during the initial open-label phase experienced improvements in mean composite symptom scores for diarrhea (-1.07; $P=.0005$), flushing (-1.06; $P=.0179$), and diarrhea and/or flushing (-2.13; $P=.0010$).

During the double-blind treatment phase, lanreotide depot/autogel yielded a 36% greater decrease in

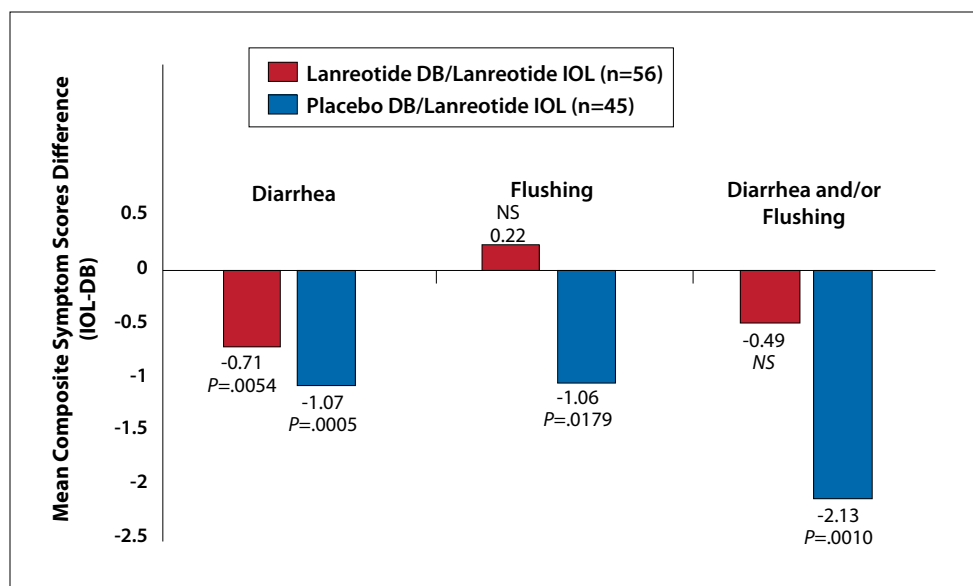


Figure 3. Mean daily composite symptom scores for diarrhea and flushing with lanreotide depot/autogel vs placebo in the ELECT trial. DB, double-blind; ELECT, An Efficacy and Safety Study of Somatuline Depot (Lanreotide) Injection to Treat Carcinoid Syndrome; IOL, initial open-label; NS, not significant.

Adapted from Fisher GA et al. NANETS abstract 155.⁶

adjusted absolute logarithmic urinary 5-HIAA levels at week 12 vs placebo (relative mean ratio, 0.64; 95% CI, 0.39-1.04). 5-HIAA levels were generally stable during the initial open-label phase in patients who were also treated with lanreotide depot/autogel during the 16-week double-blind phase. In patients who initially received treatment with placebo, treatment with lanreotide depot/autogel during the initial open-label phase yielded decreases in 5-HIAA levels at week 24 (-81.5; 95% CI, -149.7 to -13.0), week 36 (-75.2; 95% CI, -151.9 to 1.5), and week 48 (-71.3; 95% CI, -150.4 to 7.8).

Lanreotide depot/autogel was generally well-tolerated. The AE profile was similar during the 16-week double-blind phase and the 32-week initial open-label phase, indicating a favor-

able safety profile with sustained use. Among patients treated with lanreotide depot/autogel during the double-blind phase, the most common AEs during the initial open-label phase were abdominal pain (14.3%), weight loss (10.7%), dyspnea (10.7%), and hypertension (10.7%). For patients who had initially received placebo, the most common AEs of any grade included nausea, fatigue, and headache, each occurring in 11.1% of patients. Most AEs were mild to moderate in severity.

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Efficacy and Safety Results of Telotristat Ethyl in Patients With Carcinoid Syndrome During the Double-Blind Treatment Period of the TELECAST Phase 3 Clinical Trial

Somatostatin analogs are indicated for the control of symptoms associated with carcinoid syndrome.¹⁻³ Some patients, however, may require additional treatment for certain symptoms. Carcinoid syndrome is associated with increased levels of serotonin, a key driver of the diarrhea associated with the syndrome.⁴ Telotristat ethyl (formerly referred to as *telotristat etiprate*) is an oral inhibitor of tryptophan hydroxylase, the rate-limiting enzyme that catalyzes serotonin biosynthesis.⁵ Two early-stage clinical trials of telotristat ethyl yielded evidence of clinical activity

in patients with carcinoid syndrome as well as a favorable safety profile.^{6,7} The phase 3 TELESTAR (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) trial reached its primary endpoint by demonstrating that telotristat ethyl significantly reduced the frequency of bowel movements in patients with carcinoid syndrome who were receiving somatostatin analogs.⁸ The drug was also associated with reductions in urinary levels of 5-HIAA, the primary metabolite of serotonin. Telotristat ethyl has been designated an orphan drug by both the FDA and the European Medicines

Agency, with fast track status granted by the FDA.

The double-blind, placebo-controlled, randomized, phase 3 TELECAST trial (Telotristat Ethyl for Carcinoid Syndrome Therapy) evaluated the efficacy and safety of telotristat ethyl in patients with carcinoid syndrome.⁹ TELECAST was designed as a companion study to TELESTAR to provide further safety and efficacy data. TELECAST enrolled patients with histopathologically confirmed, well-differentiated metastatic NETs. While TELESTAR required enrolled patients to have an average of at least 4 bowel movements a day, TELECAST enrolled patients on a stable dose of a somatostatin inhibitor with an average of fewer than 4 bowel movements per day. Additionally, patients in TELECAST were required to have at least 1 of the following symptoms: daily stool consistency of 5 or greater on the Bristol Stool Form Scale for at least 50% of the run-in period; daily flushing occurring at least twice daily; daily pain rated at 3 or greater on a scale of 0 to 10; nausea present on at least 20% of days; and urinary 5-HIAA level above the upper limit of normal.¹⁰ Patients not taking a somatostatin inhibitor were eligible if they had an average of 4 or more bowel movements per day or 1 of the previously mentioned signs and symptoms. Patients were excluded from the trial if they had undergone tumor-directed therapy within 12 weeks prior to screening; had more than 12 bowel movements a day associated with volume contraction, dehydration, or hypotension; showed

ABSTRACT SUMMARY Pharmacokinetic (PK) Differences Between Subcutaneous and Intramuscular Administration of Lanreotide: Results From a Phase I Study

Lanreotide depot/autogel (120 mg) is approved as a deep subcutaneous injection. In a study of intended gluteal intramuscular injections of octreotide depot, appropriate injection was associated with improved control of flushing among patients with carcinoid syndrome, but only 52% of injections were successfully delivered (Boyd AE et al. *Pancreas*. 2013;42[5]:878-882). Given the pharmacokinetic implications of different injection methods, a randomized, parallel, double-blind, phase 1 study was conducted to evaluate the pharmacokinetic parameters associated with intramuscular vs subcutaneous administration of lanreotide depot/autogel (Abstract 112). Healthy volunteers ages 18 to 45 years were enrolled into 7 groups of 3 male and 3 female subjects. Eleven subjects received injections of lanreotide depot/autogel (60 mg) in a formulation of 0.246 mg/mg, including 6 by intramuscular injection and 5 by subcutaneous injection. For the subcutaneous vs intramuscular injections, pharmacokinetic results were similar in terms of mean C_{max} ($5.8 \pm 4 \mu\text{g/L}$ vs $6.8 \pm 3 \mu\text{g/L}$), mean $t_{1/2}$ (33 ± 14 days vs 23 ± 9 days), and last measured mean residence time (30 ± 6 days vs 23 ± 11 days), respectively. However, significant differences were observed in the last measured area under the curve ($1651 \pm 54 \text{ h}\cdot\mu\text{g/L}$ vs $2007 \pm 172 \text{ h}\cdot\mu\text{g/L}$; $P=.006$) and the area under the curve extrapolated to infinity (1843 ± 134 vs $2100 \pm 193 \text{ h}\cdot\mu\text{g/L}$; $P=.03$). Based on the slight increase of available lanreotide in the late-release phase after subcutaneous injection, the results support the use of subcutaneous injection.

evidence of enteric infection, such as *Clostridium difficile*; had a history of short bowel syndrome; had diarrhea related to any condition other than carcinoid syndrome; or had a Karnofsky performance status of 60% or lower.

Enrolled patients were randomly assigned to 1 of 3 arms. During the double-blind treatment period, 26 patients received placebo (arm 1), 25 received telotristat ethyl (250 mg 3 times daily; arm 2), and 25 received telotristat ethyl (500 mg 3 times daily; arm 3). Primary endpoints were evaluated during the double-blind treatment period. The incidence of treatment-emergent AEs was the primary safety endpoint, and the change in 24-hour urinary 5-HIAA from baseline to week 12 was the primary efficacy endpoint. Other endpoints included daily bowel movement frequency, stool consistency, cutaneous flushing, abdominal pain, and quality of life. A durable response to treatment was defined as a reduction of 30% or greater in daily bowel movement frequency for at least 50% of the double-blind treatment period. Following the double-blind treatment period, patients were permitted to enter the 36-week open-label extension period, in which they received telotristat ethyl (500 mg 3 times daily).

Baseline patient characteristics were generally similar in the 3 arms. Patients had a median age of 63 ± 11 years, and approximately 55% were male. More than two-thirds of patients had a urinary 5-HIAA level above the upper limit of normal. Across the 3 arms, the mean daily bowel movement frequency ranged from 2.2 to 2.8, and the mean weekly stool consistency score ranged from 5.0 to 5.3. The mean number of daily flushing episodes ranged from 1.8 to 3.7, and the mean weekly abdominal pain rating ranged from 1.2 to 1.8. The study met its primary safety and efficacy endpoints. In the entire

Table 1. GI-Related Treatment-Emergent AEs in the TELECAST Trial

AE	Placebo (n=26)	Telotristat Ethyl 250 mg tid (n=25)	Telotristat Ethyl 500 mg tid (n=25)
Any GI-related treatment-emergent AE, n (%)	15 (57.7)	16 (64.0)	9 (36.0)
Abdominal pain, n (%)	4 (15.4)	8 (32.2)	0 (0.0)
Diarrhea, n (%)	5 (19.2)	4 (16.0)	2 (8.0)
Nausea, n (%)	4 (15.4)	3 (12.0)	2 (8.0)
Constipation, n (%)	1 (3.8)	4 (16.0)	3 (12.0)

AEs, adverse events; GI, gastrointestinal; TELECAST, Telotristat Ethyl for Carcinoid Syndrome Therapy; tid, 3 times daily.

Adapted from Pavel M et al. NANETS abstract 174.⁹

ABSTRACT SUMMARY Tumor Growth Rate (TGR) in Intestinal/Pancreatic Neuroendocrine Tumors: Post Hoc Exploratory Analysis of Data From the CLARINET Study

NETs generally exhibit slow growth. Although clinical trials of somatostatin analogs have demonstrated improved PFS rates in patients with NETs, the tumors commonly respond by cessation of growth rather than shrinkage; thus their progression and response to therapy may not be adequately characterized by RECIST evaluation. In the phase 3 CLARINET study, patients with metastatic GEP-NETs received lanreotide depot/autogel (120 mg) or placebo every 4 weeks for 96 weeks. The trial demonstrated a significant improvement in PFS for patients treated with the somatostatin analog (not reached vs 18.0 months; HR, 0.47; 95% CI, 0.30-0.73; $P < .001$). In a post hoc analysis of data from the CLARINET study, tumor growth rate was evaluated as a method for assessing tumor progression and as a prognostic factor for progression prior to treatment (Abstract 149). Tumor size was determined from existing CLARINET data using the sum of longest diameters, and tumor growth rate was expressed as the percentage change in tumor volume over 1 month. After 12 weeks of treatment, 94% of patients in the lanreotide depot/autogel arm and 96% in the placebo arm were classified with stable disease by RECIST criteria; however, the mean tumor growth rate was significantly reduced in patients receiving lanreotide depot/autogel at week 12 (1.2% vs 4.1%; $P = .008$). A reduction in mean tumor growth rate was observed in the lanreotide depot/autogel arm through week 96. In the overall study population, a pretreatment tumor growth rate of greater than 4% was associated with a 4.1-fold greater risk of progression compared with a pretreatment tumor growth rate of 4% or lower. Treatment with lanreotide depot/autogel significantly reduced the likelihood of disease progression or death, regardless of growth rate, compared with placebo. In patients with NETs, tumor growth rate may provide an earlier indication of treatment activity than RECIST criteria.

study group, 67 patients (88.2%) experienced 1 or more treatment-emergent AEs during the double-blind treatment period. In arms 1, 2, and 3, the most common treatment-related

AEs were gastrointestinal disorders (57.7%, 64.0%, 36.0%), general disorders (23.1%, 28.0%, 16.0%), and infections and infestations (19.2%, 32.0%, 16.0%), respectively.

Gastrointestinal disorders included abdominal pain, diarrhea, nausea, and constipation (Table 1). Among patients receiving telotristat ethyl at 250 mg or 500 mg 3 times daily, urinary tract and influenza infections occurred in 12.0% of patients and 8.0%, respectively, vs 0% in the placebo group. Other AEs of interest occurring in arms 1, 2, and 3, respectively, included depression-related treatment-emergent AEs (7.7%, 4.0%, 4.0%) and hepatic enzyme elevations (0.0%, 8.0%, 12.0%). Treatment-related treatment-emergent AEs occurred in 30.8%, 40.0%, and 44.0% of patients in arms 1, 2, and 3, respectively. Serious treatment-emergent AEs were more common in the placebo arm and were observed in 19.2%, 4.0%, and 8.0% of patients in the 3 arms, respectively. Study discontinuations owing to a treatment-emergent AE were uncommon in each of the 3 arms. No patients died from a treatment-emergent AE.

At week 12 of the double-blind treatment period, levels of urinary 5-HIAA improved significantly from baseline in patients who received treatment with telotristat ethyl compared with placebo. In the placebo arm, urinary levels of 5-HIAA increased by a mean 97.7%. In patients

receiving the lower or higher dose of telotristat ethyl, levels were reduced by 33.2% and 76.5%, respectively. Based on the Hodges-Lehmann estimator of treatment differences, the reduction in urinary 5-HIAA levels at week 12 was significant for both telotristat ethyl treatment arms compared with placebo ($P < .001$ for both). In arms 1, 2, and 3, reductions in 5-HIAA levels were observed in 36%, 88%, and 100% of patients, respectively. The mean reduction in bowel movement frequency during the treatment period also favored telotristat ethyl, with significant improvements for both 250 mg ($P = .004$) and 500 mg ($P < .001$). Compared with placebo, frequency at week 12 was reduced by 24.4% in the 250-mg arm and 29.5% in the 500-mg arm. Durable responses were observed in 40% of patients in each of the telotristat ethyl treatment arms vs 0% of patients in the placebo arm ($P = .001$ for both doses).

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The Efficacy and Safety of Sunitinib in Patients With Advanced Well-Differentiated Pancreatic Neuroendocrine Tumors

Most patients with pancreatic NETs are diagnosed after the tumor has metastasized, at which point there are limited treatment options. Because pancreatic NETs are highly vascular, efforts are underway to treat the tumors by abrogating the activity of molecules that promote angiogenesis. Strong expression of vascular endothelial growth factor (VEGF) has been observed in pancreatic NETs. Sunitinib is an oral tyrosine kinase inhibitor with high affinity to the VEGF tyrosine kinase domain. Sunitinib (37.5 mg daily) was compared with placebo in a phase 3 trial of 171 patients with well-differentiated advanced NETs.¹ An interim analysis demonstrated superior median PFS in the sunitinib arm (11.4 months vs 5.5 months; $P < .001$), as well as superior OS ($P = .02$). The trial was terminated early owing to a greater proportion of serious AEs and deaths in the placebo group. Sunitinib is currently approved by the FDA and the European Medicines Agency for the treatment of patients with progressive, locally advanced and/or metastatic, well-differentiated, unresectable pancreatic NETs.

A multinational, single-arm, open-label, phase 4 trial is being conducted to provide further evidence of the efficacy and safety of sunitinib in patients with pancreatic NETs.² The primary endpoint is investigator-assessed PFS based on RECIST 1.0.³ Secondary endpoints include PFS assessed by independent radiologic review, time to tumor progression, ORR, OS, and safety. Eligible patients had histologically or cytologically confirmed advanced and/or metastatic, well-differentiated,

unresectable pancreatic NETs with documented progression within 12 months of enrollment and disease that was considered incurable by surgery, radiation, or combined modality therapy. Patients had at least 1 measurable target lesion based on RECIST 1.0, an Eastern Cooperative Oncology Group performance status of 0 or 1, no preexisting uncontrolled hypertension, and no prior treatment with tyrosine kinase inhibitors or angiogenesis inhibitors. Patients received sunitinib at 37.5 mg once daily. The sunitinib dose could be increased to 50 mg daily after 8 weeks of initial treatment in patients who showed no response and experienced grade 2 or lower hematologic or grade 1 nonhematologic treatment-related AEs. For patients who experienced severe toxicity, the sunitinib dose could be temporarily interrupted or reduced to 25 mg daily. Use of

somatostatin analogs was permitted for control of symptoms.

Patients could be treatment-naïve ($n = 61$) or previously treated ($n = 45$), and were enrolled at 24 centers in 15 countries. Patients had a median age of 54.6 ± 9.0 years, and 49% were male. Thirty percent of patients had 3 or more involved disease sites. Tumors were nonfunctioning in 60.4% of patients and functioning in 17.9%. (The status was unknown in the remaining patients.) Previous locoregional treatments included transarterial chemoembolization (used in 18.9%), radiofrequency ablation (used in 3.8%), transarterial embolization (used in 2.8%), percutaneous injections (used in 2.8%), and microwave ablation (used in 2.8%). Median treatment duration was 357.5 days (range, 7 to 1092 days) and was longer in treatment-naïve vs previously treated patients (371 vs 309 days). As deter-

ABSTRACT SUMMARY Everolimus for Advanced, Progressive, Non-functional Neuroendocrine Tumors (NET) of the Gastrointestinal (GI) Tract: Efficacy and Safety From a RADIANT-4 Subgroup Analysis

In the phase 3 RADIANT-4 study, everolimus (10 mg daily) yielded an improvement in PFS of 7.1 months over placebo in patients with advanced, well-differentiated progressive, nonfunctional NETs of the lung or gastrointestinal tract (Yao JC et al. *Lancet*. 2016;387[10022]:968-977). Subgroup analysis was conducted to determine the efficacy and safety of everolimus in patients with gastrointestinal NETs in the RADIANT-4 trial (Abstract 127). Of 302 patients with gastrointestinal NETs, 118 had received everolimus and 57 had received placebo. Patients had a median age of 63 years, 55% were female, and all had a World Health Organization performance status of 0 (78%) or 1 (22%). The most common sites of NET were the ileum (41%), rectum (23%), and jejunum (13%). By central review, median PFS was 13.1 months for everolimus (95% CI, 9.2-17.3 months) vs 5.4 months for placebo (95% CI, 3.6-9.3 months). The estimated risk reduction with everolimus was 44% (HR, 0.56; 95% CI, 0.37-0.84). The most common grade 3/4 AEs were diarrhea, hypertension, and stomatitis.

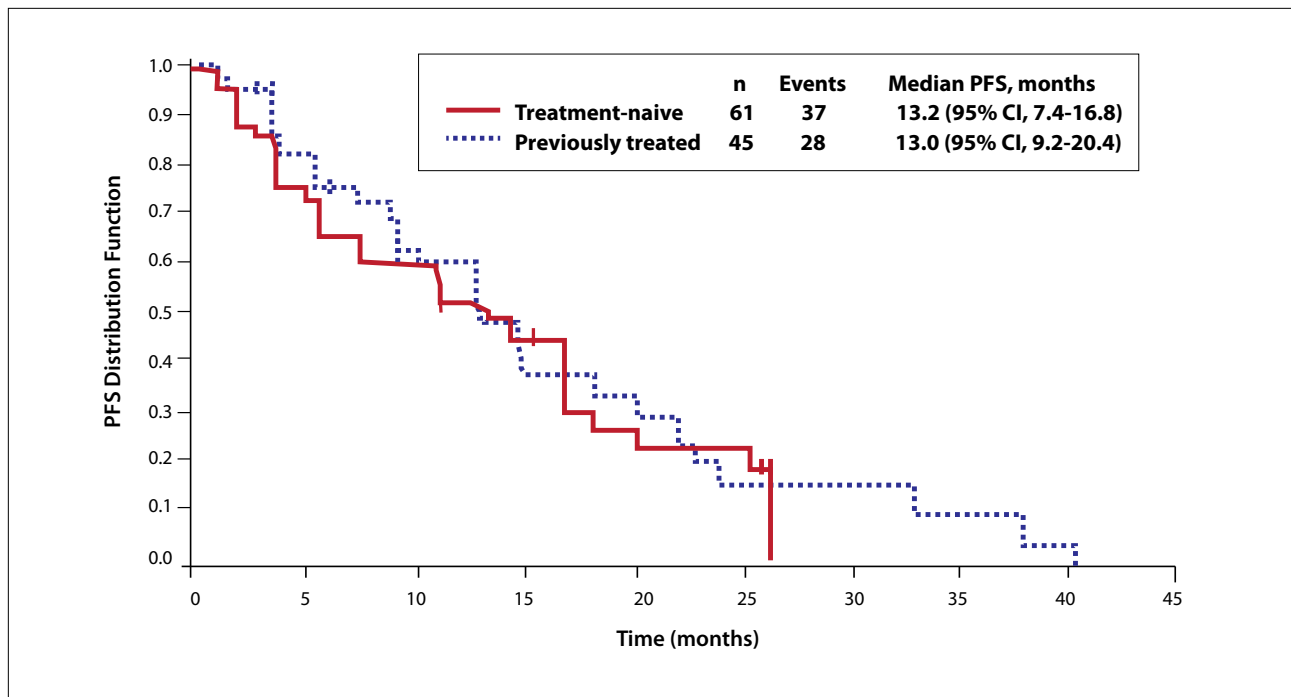


Figure 4. In a phase 4 trial of sunitinib, median PFS as determined by investigators was similar in treatment-naive and previously treated patients. mPFS, median progression-free survival.

Adapted from Raymond E et al. NANETS abstract 151.²

mined by investigators, median PFS was 13.2 months (95% CI, 10.9-16.7 months) in the overall study population and was similar in treatment-naive and previously treated patients (Figure 4). As assessed by independent radiologic review, median PFS was 11.1 months (95% CI, 7.4-16.6 months) for the entire study population and was higher in treatment-naive patients compared with previously treated patients (11.1 months vs 9.5 months). Based on investigator assessment, the ORR was 24.5% (95% CI, 16.7%-33.8%). The median time to tumor progression was 14.5 months (95% CI, 11.0-16.7 months) and was similar in the treatment-naive and treatment-experienced patient groups. Prelimi-

nary OS data yielded a median OS of 37.8 months (95% CI, 33.0 months - not estimable).

The safety profile was consistent with previous reports of sunitinib in this setting. The most common treatment-emergent AEs of any grade were neutropenia (56%), diarrhea (51%), and leukopenia (43%). Most AEs occurred with similar frequencies in treatment-naive and previously treated patients, with the exceptions of dyspepsia (11% vs 31%), nausea (18% vs 31%), and neutropenia (61% vs 49%). Rates of grade 3/4 AEs and serious AEs were similar in treatment-naive and previously treated patients. Sunitinib dose reductions owing to an AE occurred in 25% of treatment-

naive patients and 11% of previously treated patients. Discontinuation of treatment owing to an AE occurred in 13% and 22%, respectively.

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Lanreotide Autogel/Depot (LAN) Post-Octreotide Long-Acting Release (OCT) for Safe and Tolerable Treatment of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

The mean 5-year survival rate of patients with NETs in the United States is 68% and the median OS is 75 months, highlighting the need for improved therapies.¹ In the randomized, double-blind, placebo-controlled, phase 3 CLARINET trial (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors), treatment with lanreotide depot/autogel improved median PFS compared with placebo in patients with NETs (not reached

vs 18.0 months; HR, 0.47; 95% CI, 0.30-0.73; $P < .001$).² The estimated 24-month PFS rates were 65.1% (95% CI, 54.0%-74.1%) for lanreotide depot/autogel vs 33.0% (95% CI, 23.0%-43.3%) for placebo. However, the tolerability of sequential use of somatostatin analogs in patients with GEP-NETs has not been established.

Retrospective chart review was conducted to evaluate the safety and tolerability of lanreotide depot/autogel in patients with GEP-NETs following

disease progression or lack of tolerance to octreotide.³ Serologic tumor markers were evaluated at each visit to the physician. Twenty-four hour urinary 5-HIAA samples were collected every 3 to 6 months. Radiologic imaging was performed every 3 months. Patients who received liver-directed therapy underwent magnetic resonance imaging within 8 to 12 weeks after the procedure. An octreotide scan was performed at baseline and then 6 to 12 months later. The study included 16 patients with nonfunctional cecal or pancreatic NETs of grade 1 or 2. All patients had stage III (12.5%) or stage IV (87.5%) disease. Sixty-nine percent were female, and the mean age was 64.25 years (range, 43-81 years). All patients had initially received octreotide (30-60 mg). Treatment was switched to lanreotide depot/autogel owing to injection discomfort or pain (37.5%), patient decision (37.5%), progressive disease (18.75%), or poor tolerance (6.25%; Table 2). Patients received lanreotide depot/autogel every 28 days. The starting dose of lanreotide depot/autogel was adjusted owing to renal dysfunction. The doses were 120 mg in 81.25%, 90 mg in 6.25%, and 60 mg in 12.5% of patients. Patients received a median 5.25 doses of lanreotide depot/autogel (range, 2-10 doses). AEs that occurred after initiation of lanreotide depot/autogel were all grade 1 or 2 and were observed in 6 patients (37.5%).

In 15 patients (93.75%), the chromogranin level decreased after the start of treatment with lanreotide depot/autogel, with the greatest decreases seen in patients who had the

ABSTRACT SUMMARY Impact of Prior Treatment on Progression-Free Survival (PFS) in Patients (Pts) With Advanced, Nonfunctional NETs of Lung or Gastrointestinal (GI) Origin: Secondary Analyses From the Phase 3 RADIANT-4 Study

The phase 3 RADIANT-4 trial demonstrated a 7.1-month improvement in PFS with everolimus vs placebo in patients with advanced, progressive, nonfunctional NETs of the lung or gastrointestinal tract (Yao JC et al. *Lancet*. 2016;387[10022]:968-977). The association between prior chemotherapy or prior somatostatin analog use and disease progression was evaluated by subset analyses of patients in the RADIANT-4 trial (Abstract 130; Abstract 131) Among the 302 patients randomly assigned to treatment, 25% had received prior chemotherapy, including 54 patients in the everolimus arm and 23 in the placebo arm, and 54% of patients had received prior treatment with a somatostatin analog. For the group of patients who had previously received chemotherapy, median PFS was 9.2 months (95% CI, 5.6-11.7 months) vs 2.1 months (95% CI, 1.9-3.7 months) in patients treated with everolimus vs placebo, respectively (HR, 0.35; 95% CI, 0.19-0.64). For the chemotherapy-naive group, median PFS was 11.2 months (95% CI, 9.2-16.6 months) in the everolimus group vs 5.4 months (95% CI, 3.7-9.0 months) in the placebo group (HR, 0.60; 95% CI, 0.42-0.86). In patients who had received prior treatment with a somatostatin analog, median PFS was 11.1 months (95% CI, 9.2-13.3 months) with everolimus vs 4.5 months (95% CI, 3.6-7.9 months; HR, 0.56; 95% CI, 0.37-0.85) with placebo. In patients who had not received prior treatment with a somatostatin analog, median PFS was 9.5 months with everolimus (95% CI, 8.2-16.7 months) vs 3.7 months with placebo (95% CI, 2.4-8.1 months; HR, 0.57; 95% CI, 0.37-0.89). Everolimus improved the PFS in patients with advanced, progressive, nonfunctional NETs of the lung or gastrointestinal tract irrespective of prior chemotherapy or prior somatostatin analog use.

Table 2. Characteristics of Patients Who Switched From Octreotide to Lanreotide Depot/Autogel

Patient	Last OCT Dose (mg)	Reasons for Switching to LAN	LAN Starting/Current Dose (mg)	Total LAN Doses	Adverse Events
1	30 IM	Patient decision	120	9	G1 fatigue
2	30 IM	Patient decision	120	5	None
3	30 IM	Patient decision	120	8	None
4	30 IM	Patient decision	60 ^a	8	None
5	30->40 IM	Increased serologic marker + new liver lesion	120	8	None
6	30 IM	Patient decision	120	3 ^b	None
7	40 IM	Diarrhea and abdominal pain	120	2 ^c stopped	G1 tremor, G2 hyperglycemia, G1 fatigue, G2 nausea, G1 blurred vision
8	30->40 IM	PD (liver)	120	3	G1 nausea, G1 abdominal pain
9	20 IM	Cost, GI pain, possible nausea	120	10	None
10	20 IM	Radiologic and serologic PD	90 ^a	5	None
11	30->60 IM	GI upset, bone progression (stable liver)	120	3	None
12	40 IM	Serologic marker	120	3	None
13	20->40 IM	Patient decision	120	5	G1 diarrhea
14	30 IM	Intolerance, low muscle mass (anorexia)	120	3	None
15	Unknown	Serologic progression	120	3	G1 fatigue
16	30 IM	Buttock pain	60 ^a	6	G1 constipation

G, grade; GI, gastrointestinal; IM, intramuscular; LAN, lanreotide depot/autogel; OCT, octreotide; PD, progressive disease.

^aPatients #4 and #10 were successfully escalated to the full dose without any adverse effects. In patient #16, the dose was escalated to 90 mg but not higher, as his kidney function remained moderately impaired owing to diabetic nephropathy.

^bPatient had past intolerance to octreotide owing to diarrhea.

^cPatient received an unknown number of additional doses after 1 confirmed dose.

Adapted from Saif M et al. NANETS abstract 146.³

highest chromogranin levels prior to initiating treatment with lanreotide. Levels of 5-HIAA were available for 7 patients and ranged from 3.3 mg/L to 23 mg/L before treatment with lanreotide depot/autogel vs 3.1 mg/L to 16.0 mg/L after. The maximum serum serotonin level decreased from 1290 ng/mL to 533 ng/mL. Eight patients received concomitant therapies that included chemotherapy (18.75%), radiofrequency ablation (18.75%), and surgery (12.5%).

Radiologic responses included complete response (6.25%), partial response (31.25%), stable disease (56.25%), and progressive disease (6.25%). Decreases were also observed in levels of gastrin, pancreatic polypeptide, and adrenocorticotrophic hormone. The authors are undertaking a study to evaluate the efficacy and safety of lanreotide depot/autogel in a real-world setting and to provide additional information on the use of lanreotide depot/autogel following treatment with octreotide.

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Long-Term Efficacy, Survival and Safety of [177Lu-DOTA0,Tyr3] Octreotate in Patients With Gastroenteropancreatic and Bronchial Neuroendocrine Tumors

The medium-energy β -emitter ^{177}Lu has a half-life of 6.7 days and penetrates tissue to a depth of 2 mm.¹ The relatively short range traversed by the β particles provides a good source of radiation for small tumors and has demonstrated efficacy in treating NETs. A study of patients treated between 2000 and 2015 was conducted to evaluate the efficacy of PRRT with ^{177}Lu -DOTATATE in patients with bronchial NETs or GEP-NETs.² Patients had histologically proven, inoperable NETs with octreotide uptake greater in the tumor vs the liver. No prior treatment with other radiolabeled somatostatin analogs was allowed, and patients were required to

have adequate blood counts, creatinine clearance, and performance status. Patients initially received prophylactic treatment with granisetron or ondansetron and then received 200 mCi of ^{177}Lu -DOTATATE plus an infusion of 2.5% arginine/2.5% lysine. Four treatment cycles were scheduled, with 6 to 10 weeks between infusions.

Of 1214 patients who received at least 100 mCi of ^{177}Lu -DOTATATE, 696 had bronchial NETs or GEP-NETs. The safety analysis included 610 patients. The efficacy and survival analysis included 443 patients who had been treated with at least 600 mCi of ^{177}Lu -DOTATATE prior to 2013. The safety population showed a 0.7% rate of acute leukemia and a 1.5% rate

of myelodysplastic syndrome as long-term side effects of treatment. Renal failure occurred in 1.0% of patients, but was considered unlikely to be related to PRRT therapy. No liver failures occurred.

Among the 443 patients included in the efficacy analysis, the ORR was 39%. Tumor responses included CR in 2%, partial response in 37%, stable disease in 43%, and progressive disease in 12%. Five percent of patients were not evaluable. ORRs for the specific tumor types were 31% for midgut, 33% for hindgut, 55% for pancreas, 30% for bronchus, 41% for other foregut, and 35% for unknown origin. For the entire study population, the PFS was 29 months, and the time to tumor progression was 36 months. For specific tumor types, PFS ranged from 20 months for bronchial tumors to 30 months for midgut and pancreatic tumors. Time to progression ranged from 25 months for bronchial NETs to 42 months for midgut NETs. The rates of median OS were 71 months (95% CI, 56-86 months) for patients with NETs of the pancreas, 60 months (95% CI, 49-55 months) for those with NETs of the midgut, 52 months (95% CI, 49-55 months) for those with NETs of the bronchus, and 53 months (95% CI, 44-62 months) for those with NETs of unknown origin (Figure 5).

Several factors were associated with median OS. Patients without liver metastases had a median OS of 119 months vs 57 months for those with liver metastases (HR, 0.46; 95% CI, 0.34-0.62; $P < .001$). OS was 69 months for patients without bone metastases vs 47 months for those

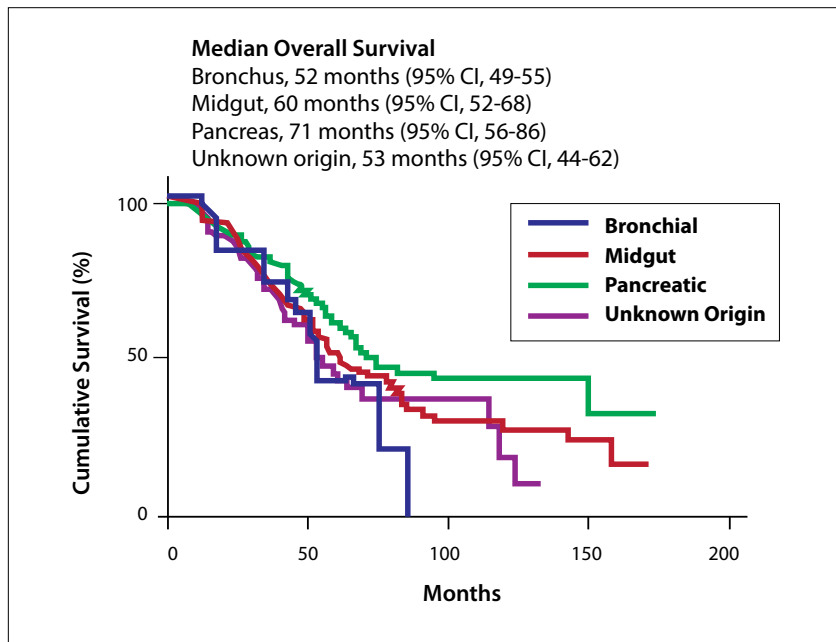


Figure 5. Rates of median overall survival in a study of ^{177}Lu -DOTATATE.

Adapted from Brabander T et al. NANETS abstract 142.²

ABSTRACT SUMMARY Tumor Growth Rate (TGR) in Intestinal/Pancreatic Neuroendocrine Tumors: Post Hoc SPINET: a Randomized, Double-Blind, Placebo-Controlled Phase III Study of Lanreotide Autogel/Depot (LAN) in Patients With Advanced Lung Neuroendocrine Tumors

The multinational, randomized, double-blind, placebo-controlled, phase 3 SPINET (Efficacy and Safety of Lanreotide Autogel/Depot 120 mg vs. Placebo in Subjects With Lung Neuroendocrine Tumors) study is evaluating the safety and efficacy and lanreotide depot/autogel in patients with advanced, well-differentiated, typical or atypical lung NETs that demonstrate positive somatostatin receptor imaging (Abstract 156). The trial will randomly assign 216 patients 2:1 to receive best supportive care plus lanreotide depot/autogel (120 mg every 28 days) or placebo until disease progression, death, or unacceptable toxicity. Patients in the placebo arm who experience progressive disease will be allowed to switch to lanreotide depot/autogel during an open-label extension phase. The primary endpoint is PFS based on central review using RECIST 1.1 criteria. Main secondary endpoints include PFS based on local review, ORR, OS, chromogranin levels, pharmacokinetics, quality of life, and safety. SPINET is the first prospective, placebo-controlled, randomized study designed to assess outcomes from lanreotide depot/autogel in patients with typical and atypical carcinoid lung NETs.

with bone metastases (HR, 0.56; 95% CI, 0.38-0.83; $P < .01$). In patients with an alkaline phosphatase level of less than 120 IU/L vs greater than 120 IU/L, median OS was 83 months vs 47 months (HR, 0.45; 95% CI, 0.35-0.59; $P < .001$). In patients with a Karnofsky performance score of 100, 90, 80, or less than 70, median OS was 81 months, 65 months, 50 months, and 27 months, respectively ($P < .01$).

Both the current study and the NETTER-1 study evaluated PRRT with ^{177}Lu -DOTATATE in patients with NETs.³ However, the outcomes from the 2 studies must be considered in context of the specific tumor characteristics in the different patient populations. The patients in the current study had a lower mean Karnofsky performance index (85.8% vs 88.6%; $P < .05$). The current study

enrolled more patients with a mean somatostatin receptor scintigraphy score of 3 (70% vs 29%; $P < .01$), and fewer patients with a mean somatostatin receptor scintigraphy score of 4 (23% vs 61%; $P < .01$). The distribution of tumor grades, based on Ki67 immunoreactivity, also differed between the studies. In the current study, 41 of patients were grade 1, 55% were grade 2, and 4% were grade 3. In the NETTER-1 study, these percentages were 66%, 34%, and 0%, respectively. In the current study, median PFS was 24 months, and median OS was 46 months. Both of these endpoints were not reached in NETTER-1.

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Highlights in GEP-NETs From the 2016 NANETS Symposium: Commentary

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The 2016 North American Neuroendocrine Tumor Society (NANETS) Annual Symposium was held on September 30 and October 1 in Jackson, Wyoming. The management of gastroenteropancreatic neuroendocrine tumors (GEP-NETs) and lung NETs was examined in oral presentations and posters. Symptom control, an important aspect of treatment, was the focus of several studies. Other analyses evaluated the impact of prior treatments and provided data on existing therapies.

Symptom Control

Disease control requires long-term therapy. Primary endpoints of therapeutic trials are typically radiographic disease control, but given the significant symptoms from biochemical activity of neuroendocrine cancers, there is increased interest in how existing therapies control symptoms. Furthermore, decisions regarding treatment modification are based on symptom control. Rational management choices can be made by knowing how a particular treatment might improve symptoms, as well as how any associated toxicities might impair quality of life. Focus on these aspects of care is much needed. The following abstracts provide useful information for clinicians as they select therapies.

Dr George A. Fisher presented data from the phase 3 ELECT study (An Efficacy and Safety Study of

Somatuline Depot [Lanreotide] Injection to Treat Carcinoid Syndrome), which evaluated the efficacy and safety of lanreotide depot/autogel in controlling symptoms of carcinoid syndrome.¹ The CLARINET trial (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) assessed the impact of lanreotide depot/autogel on disease control in patients with intestinal and pancreatic NETs, finding a significant improvement in median PFS compared with placebo (not reached vs 18.0 months; hazard ratio [HR], 0.47; 95% CI, 0.30-0.73; $P < .001$).² ELECT was a small study that randomly assigned patients with carcinoid syndrome to receive lanreotide depot/autogel ($n=59$) or placebo ($n=56$).³ A double-blind phase was followed by an open-label phase, with 56 patients receiving lanreotide depot/autogel and 45 patients receiving placebo. The analysis by Dr Fisher found that the frequency of adverse events was similar in both arms.¹ The events were mild to moderate, and consisted primarily of abdominal pain, weight loss, hypertension, dyspnea, nausea, fatigue, and headache. Symptom control, as assessed by the need for breakthrough medication (rescue shots of octreotide) was improved among patients treated with lanreotide depot/autogel. This study did not evaluate quality of life, but it can be assumed that patients were happier to receive fewer shots of octreotide.

Another analysis of the ELECT

trial, by Dr Aaron Vinik, assessed the safety and tolerability of lanreotide depot/autogel during a long-term extension phase.⁴ At a median treatment exposure of 110 weeks, the long-term safety was consistent with that seen in earlier studies of lanreotide depot/autogel. Treatment-related severe adverse events occurred in 23% of patients. In conclusion, both analyses from the ELECT trial showed that lanreotide depot/autogel was associated with some initial toxicities, but they are mild and very manageable. These toxicities did not compel patients to leave the study.

Dr Jonathan Strosberg presented results from preliminary analyses of safety and quality of life from the NETTER-1 trial (Phase III in Patients With Midgut Neuroendocrine Tumors Treated With ¹⁷⁷Lu-DOTATATE).⁵ Previous data from the NETTER-1 trial showed that ¹⁷⁷Lu-DOTATATE improved progression-free survival (PFS) as compared with high-dose octreotide long-acting release (LAR).⁶ It is still too early to assess overall survival endpoints in NETTER-1. In the analysis by Dr Strosberg, ¹⁷⁷Lu-DOTATATE improved safety, global health scores, and frequency of diarrhea as compared with octreotide LAR.⁵ The most common adverse events seen with ¹⁷⁷Lu-DOTATATE—nausea and vomiting—are likely associated with the amino acid infusions given concurrently for renal protection. Global health status improved in 28% of the

patients receiving ^{177}Lu -DOTATATE vs 15% of those receiving octreotide LAR, and worsened in 18% vs 26%, respectively. Throughout the study, on average, diarrhea improved in 39% of patients in the ^{177}Lu -DOTATATE arm vs 23% in the octreotide LAR arm.

Telotristat ethyl (formerly referred to as *telotristat etiprate*) is an oral tryptophan hydroxylase inhibitor that has been studied in refractory carcinoid syndrome. In the TELESTAR trial (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome), telotristat ethyl reduced the average number of daily bowel movements from baseline over a 12-week period.⁷ There was no significant effect on other carcinoid-related symptoms, such as hot flushing. The TELECAST trial (Telotristat Etiprate for Carcinoid Syndrome Therapy) was a companion study to TELESTAR that evaluated safety and efficacy. Dr Marianne Pavel presented the results at the NANETS meeting.⁸ A quality-of-life analysis showed that the study met its primary safety endpoint, incidence of treatment-emergent AEs, as well as its primary efficacy endpoint, the change in 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) from baseline to week 12. Telotristat ethyl significantly reduced levels of 5-HIAA and bowel movement frequency. Durable response, defined as a reduction of 30% or more in daily bowel movement frequency for at least 50% of the double-blind treatment period, was seen in 40% of patients.

A study by Dr Simron Singh evaluated whether disease progression impacted quality of life in the RADIANT-4 trial (Everolimus Plus Best Supportive Care vs Placebo Plus Best Supportive Care in the Treatment of Patients With Advanced Neuroendocrine Tumors [GI or Lung Origin]).^{9,10} Everolimus is administered to treat disease progression and, to a lesser extent, symptom progression. The analysis found that radiographic disease progression had a clinical

component that was perceivable by patients and decreased quality of life. When disease was controlled, quality of life either remained stable or improved. There was a consistent correlation between disease progression and worsened quality of life. These findings are not surprising and confirm clinical experience.

All patients enrolled in the RADIANT-4 trial had radiologically documented disease progression within 6 months before randomization. Most of the patients had progressed within 3 months before enrolling in the study. These patients were no longer receiving treatment with somatostatin analogs. It is not known whether their disease progression could be attributed to hormonal changes or if it reflected a shift to a more aggressive phenotype. It is therefore unknown whether the analysis by Dr Singh applies to all patients receiving everolimus, or just those with the most aggressive disease. In clinical practice, disease progression does not always decrease quality of life.

Lung NETs

Dr Tessa Brabander presented results from a study of lutetium-177 octreotate in European patients with gastroenteropancreatic and bronchial NETs.¹¹ The long-term benefit of radiopeptide therapy is of great interest given that the NETTER-1 data have not yet reached maturity. A strength of the study from Dr Brabander is that it provides data for patients who were enrolled more than 15 years ago, in 2000. It is important to consider long-term toxicity and characteristics of long-term responders following such therapies to help guide treatment decisions. It should be noted that the NETTER-1 trial evaluated a different isotope, ^{177}Lu -DOTATATE, and sequencing of therapies will be a topic of interest in the coming years as these agents are increasingly studied and/or used.⁶ The patient population was similar to that in the NETTER-1 trial, although the study by Dr Bra-

bander included a few patients with higher-grade tumors. Liver metastases were reported in 92% of patients with midgut tumors, compared with 84% in NETTER-1. Bone metastases were slightly more common (13% vs 11%).

For all patients in the study, the median time to tumor progression was 36 months. Median overall survival was 71 months in patients with pancreatic NETs, 60 months in those with midgut tumors, 53 months in those with NETs of unknown origin, and 52 months in those with bronchial NETs. Patients with bronchial NETs have only recently been included in NET clinical trials, and hence have limited long-term follow-up, so this information is especially valuable.

Overall survival in a trial is impacted by the use and availability of other treatment options beyond those in the study. It is necessary to consider the adjunctive therapies patients received before or after disease progression. Accrual into the NETTER-1 trial is more contemporary, and patients had access to several oral agents that were not available during the study by Dr Brabander.^{6,11} In addition, the study by Dr Brabander was conducted in Europe, where patients have access to multiple other radioisotopes. The overall survival data are therefore not easy to compare. In the NETTER-1 trial, overall survival, as well as time to tumor progression, have not yet been reached.⁶ At this point, it is impossible to know how lutetium-177 octreotate compares with ^{177}Lu -DOTATATE.

The phase 3 SPINET trial (Efficacy and Safety of Lanreotide Autogel/Depot 120 mg vs. Placebo in Subjects With Lung Neuroendocrine Tumors) is currently enrolling patients with advanced lung NETs to evaluate lanreotide depot/autogel.¹² The role of radiolabeled somatostatin analogs has been studied, but the role of somatostatin analogs by themselves remains unclear. The SPINET study will address this question. It will include patients with atypical carcinoids in

the lung, which are difficult to treat. It is unclear whether somatostatin analogs will play a role in these patients. Importantly, this study will also assess quality of life.

Pancreatic NETs

Dr Eric Raymond presented results of a multinational, single-arm, open-label phase 4 trial conducted to provide further evidence of the efficacy and safety of sunitinib in patients with pancreatic NETs.¹³ The overall response rate was 24.5%, and the median time to tumor progression was 14.5 months. The safety profile was similar to previous reports.

Dr Nitya Raj examined how next-generation sequencing can be used to define genetic mutations in pancreatic NETs.¹⁴ The study found that next-generation sequencing can identify common mutations and provide information about the evolution of the tumor. Among the 5 patients with poorly differentiated, high-grade neuroendocrine carcinomas, genetic alterations were seen in *TP53* (80%), *RBI* (60%), *MEN1* (20%), and *ARID1A* (20%). No alterations were observed in *DAXX*, *ATRX*, *SETD2*, or *ARID1A*. In 62 patients with well-differentiated disease, none had mutations in *RBI*. These well-differentiated pancreatic NET samples had mutations in *MEN1* (50%), *DAXX* (33%), *ATRX* (19%), *SETD2* (12%), and *ARID1A* (10%).

Other Studies of Approved Therapies

Patients with NETs have limited treatment options. Both octreotide and lanreotide depot/autogel have reasonable tolerability. The strong data from recent reports of lanreotide depot/autogel might tempt clinicians to see if a switch from octreotide to lanreotide depot/autogel can offer clinical benefit. Dr M. Wasif Saif presented a retrospective case series of 16 patients who switched to lanreotide depot/

autogel after treatment with octreotide LAR led to disease progression or intolerance.¹⁵ Lanreotide depot/autogel was well-tolerated in these patients. Levels of chromogranin A decreased in all patients but one. The greatest reductions occurred among patients with the highest levels before treatment with lanreotide depot/autogel. Almost all patients experienced an overall reduction in serologic markers. A radiologic response to lanreotide depot/autogel was seen in 94% of patients. These included one complete response, which I have not seen before in this setting. Patient-reported quality of life was not provided. This approach of switching agents must still be studied in a prospective clinical trial.

A phase 1 study presented by Dr Amandine Manon evaluated whether there were any pharmacokinetic differences between subcutaneous vs intramuscular administration of lanreotide depot/autogel.¹⁶ Results from this small study were also presented at the 13th Annual European Neuroendocrine Tumor Society (ENETS) conference.¹⁷ Lanreotide depot/autogel should be administered subcutaneously, according to the manufacturer. Office staff, however, may be more familiar with intramuscular injection. The study by Dr Manon found that the pharmacokinetics did not differ between the 2 modes of administration. The pharmacokinetic results were similar in terms of mean C_{max} , mean $t_{1/2}$, and last measured mean residence time. Intramuscular administration of lanreotide depot/autogel can be expected to achieve the same therapeutic results as subcutaneous administration.

A post hoc analysis of the CLARINET trial examined whether tumor growth rate could be used to assess tumor response.^{2,18} The study found that a pretreatment tumor growth rate exceeding 4% was associated with a 4.1-fold greater risk of progression compared with a pretreatment tumor

growth rate of 4% or lower. The data suggest that tumor growth rate may be superior to the Response Evaluation Criteria In Solid Tumors (RECIST) in assessing treatment outcome.

Impact of Prior Therapies

Two analyses from the RADIANT-4 trial suggested that prior therapy with chemotherapy or somatostatin analogs does not impact response to everolimus. Dr Rodney Pommier evaluated the impact of prior chemotherapy on PFS.¹⁹ Among patients treated with everolimus, median PFS was 9.2 months among those who had received prior chemotherapy vs 11.2 months in patients who had not received prior chemotherapy. The placebo arm of the prior-chemotherapy group had a median PFS of 2.1 months, indicating that these patients had aggressive disease. Among patients who had not received prior chemotherapy, PFS in the placebo arm was 5.4 months. This finding suggests that tertiary referral centers are correctly identifying those patients who are appropriate candidates for chemotherapy. In a study by Dr Roberto Buzzoni, everolimus was associated with a median PFS of 11.1 months among patients previously treated with somatostatin analogs vs 9.5 months in patients who had not received previous treatment.²⁰

Disclosure

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