

**A SPECIAL MEETING REVIEW EDITION**

**Highlights in GEP-NETs From the 13th Annual ENETS  
Conference for the Diagnosis and Treatment of  
Neuroendocrine Tumor Disease**

March 9-11, 2016 • Barcelona, Spain

**Special Reporting on:**

- Tumor Growth Rate (TGR) as an Indicator of Antitumor Activity With Lanreotide Autogel/Depot (LAN) Versus Placebo (Pbo) in Intestinal/Pancreatic NET: Post Hoc Analysis of CLARINET Data
- NETTER-1 Phase III in Patients With Midgut Neuroendocrine Tumors Treated With <sup>177</sup>Lu-DOTATATE: Efficacy and Safety Results
- Budget Impact of Somatostatin Analogs (SSAs) as Treatment for Metastatic Gastroenteropancreatic Neuroendocrine Tumors (mGEP-NETs) in US Hospitals
- Everolimus for Advanced, Progressive, Nonfunctional Neuroendocrine Tumors (NET) of the Gastrointestinal (GI) Tract: Efficacy and Safety From a RADIANT-4 Subgroup Analysis
- Interim Results on the Influence of Lanreotide on Uptake of [<sup>68</sup>Ga]-DOTATATE in Patients With Metastatic or Unresectable NET: No Evidence for Discontinuation of Lanreotide Before [<sup>68</sup>Ga]-DOTATATE PET/CT
- Pharmacokinetic (PK) Differences Between Subcutaneous and Intramuscular Administration of Lanreotide: Results From a Phase I Study

**PLUS Meeting Abstract Summaries**

**With Expert Commentary by:**

Renuka Iyer, MD  
Associate Professor of Oncology  
Co-Director, Liver and Pancreas Tumor Center  
Section Chief for Gastrointestinal Oncology  
Roswell Park Cancer Institute  
Buffalo, New York

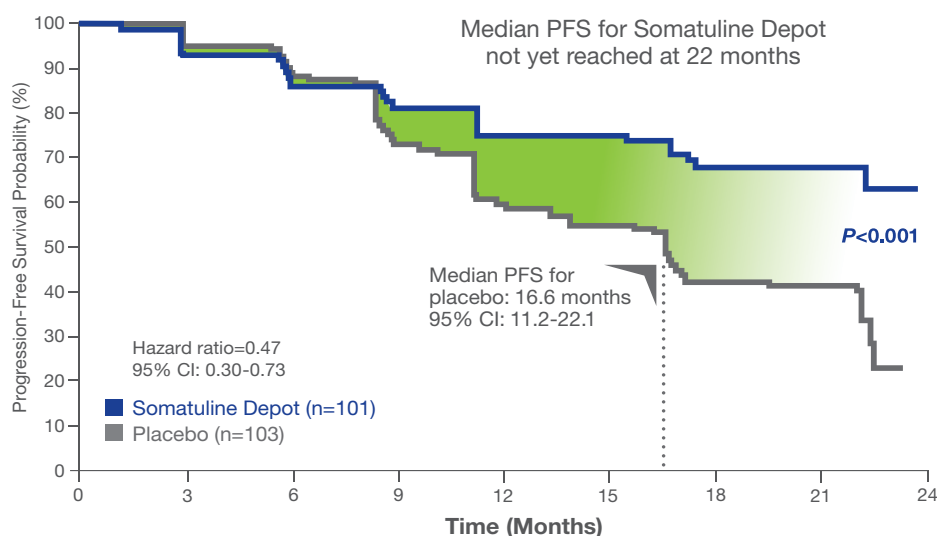
Hassan Hatoum, MD  
Assistant Professor of Medicine  
Hematology-Oncology  
Stephenson Cancer Center  
University of Oklahoma Health Sciences Center  
Oklahoma City, Oklahoma

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# HOLD BACK PROGRESSION

In patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastrointestinal and pancreatic neuroendocrine tumors (NETs)

## SIGNIFICANTLY IMPROVED PROGRESSION-FREE SURVIVAL (PFS)<sup>1</sup>



Somatuline Depot vs placebo reduced risk of progression or death by **53%**

**Study design:** Randomized, double-blind, placebo-controlled, multicenter, 96-week study of Somatuline Depot 120 mg vs placebo administered every 28 days. Patients had unresectable, well- or moderately differentiated, nonfunctioning, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Primary endpoint was time to disease progression or death.

### INDICATION

Somatuline<sup>®</sup> Depot (lanreotide) Injection 120 mg is indicated for the treatment of adult patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.


### IMPORTANT SAFETY INFORMATION

#### Contraindications:

Somatuline Depot is contraindicated in patients with hypersensitivity to lanreotide. Allergic reactions (including angioedema and anaphylaxis) have been reported following administration of lanreotide.

#### Warnings and Precautions:

- **Cholelithiasis and Gallbladder Sludge:** Somatuline Depot may reduce gallbladder motility and lead to gallstone formation. Periodic monitoring may be needed.
- **Hypoglycemia or Hyperglycemia:** Pharmacological studies show that Somatuline Depot, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Blood glucose levels should be monitored when Somatuline Depot treatment is initiated, or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.



**SOMATULINE DEPOT  
SIGNIFICANTLY  
EXTENDED PFS IN  
LOCALLY ADVANCED OR  
METASTATIC GEP-NETS<sup>1</sup>**

**A 53% REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH VS PLACEBO<sup>1</sup>**

#### **IMPORTANT SAFETY INFORMATION (Continued)**

##### **Warnings and Precautions (Continued):**

- **Cardiac Abnormalities:** Somatuline Depot may decrease heart rate. In 81 patients with baseline heart rates of  $\geq 60$  beats per minute (bpm) treated with Somatuline Depot in the GEP-NETS clinical trial, the incidence of heart rate  $< 60$  bpm was 23% (19/81) with Somatuline Depot vs 16% (15/94) with placebo; 10 patients (12%) had documented heart rates  $< 60$  bpm on more than one visit. The incidence of documented episodes of heart rate  $< 50$  bpm or bradycardia reported as an adverse event was 1% in each treatment group. Initiate appropriate medical management in patients who develop symptomatic bradycardia. In patients without underlying cardiac disease, Somatuline Depot may lead to a decrease in heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to treatment, sinus bradycardia may occur. Care should be taken when initiating treatment in patients with bradycardia.
- **Drug Interactions:** The pharmacological gastrointestinal effects of Somatuline Depot may reduce the intestinal absorption of concomitant drugs. Concomitant administration of Somatuline Depot may decrease the relative bioavailability of cyclosporine and may necessitate the adjustment of cyclosporine dose to maintain therapeutic levels.

##### **Adverse Reactions:**

In the GEP-NET pivotal trial, the most common adverse reactions (incidence  $> 10\%$  and more common than placebo) in patients treated with Somatuline Depot vs placebo were abdominal pain (34% vs 24%), musculoskeletal pain (19% vs 13%), vomiting (19% vs 9%), headache (16% vs 11%), injection site reaction (15% vs 7%), hyperglycemia (14% vs 5%), hypertension (14% vs 5%), and cholelithiasis (14% vs 7%).

You may report suspected adverse reactions to FDA at 1-800-FDA-1088 or to Ipsen Biopharmaceuticals, Inc. at 1-888-980-2889.

Patient support is available through IPSEN CARES™:  
(866) 435-5677 (8 AM to 8 PM ET)

**Reference:** 1. Somatuline Depot (lanreotide) Injection [Prescribing Information]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; December 2014.

**To learn more, visit [SomatulineDepot.com](http://SomatulineDepot.com)**

Please see Brief Summary of full Prescribing Information on the following page.



**Somatuline<sup>®</sup> Depot**  
(lanreotide) Injection 120 mg



## SOMATULINE DEPOT® (lanreotide) Injection 120 mg

### Brief Summary of Prescribing Information

#### 1 INDICATION

SOMATULINE DEPOT Injection 120 mg is indicated for the treatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NETs) to improve progression-free survival.

#### 4 CONTRAINDICATIONS

SOMATULINE DEPOT is contraindicated in patients with history of a hypersensitivity to lanreotide. Allergic reactions (including angioedema and anaphylaxis) have been reported following administration of lanreotide.

#### 5 WARNINGS AND PRECAUTIONS

##### 5.1 Cholelithiasis and Gallbladder Sludge

Lanreotide may reduce gallbladder motility and lead to gallstone formation; therefore, patients may need to be monitored periodically [see *Adverse Reactions* (6.1)].

##### 5.2 Hyperglycemia and Hypoglycemia

Pharmacological studies in animals and humans show that lanreotide, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Hence, patients treated with SOMATULINE DEPOT may experience hypoglycemia or hyperglycemia. Blood glucose levels should be monitored when lanreotide treatment is initiated, or when the dose is altered, and antidiabetic treatment should be adjusted accordingly [see *Adverse Reactions* (6.1)].

##### 5.3 Thyroid Function Abnormalities

Slight decreases in thyroid function have been seen during treatment with lanreotide in acromegalic patients, though clinical hypothyroidism is rare (<1%). Thyroid function tests are recommended where clinically indicated.

##### 5.4 Cardiovascular Abnormalities

In patients without underlying cardiac disease, SOMATULINE DEPOT may lead to a decrease in heart rate without necessarily reaching the threshold of bradycardia. In patients suffering from cardiac disorders prior to SOMATULINE DEPOT treatment, sinus bradycardia may occur. Care should be taken when initiating treatment with SOMATULINE DEPOT in patients with bradycardia.

In patients with baseline heart rates of  $\geq 60$  beats per minute (bpm) treated with SOMATULINE DEPOT in the GEP-NETs clinical trial, the incidence of heart rate < 60 bpm was 23% as compared to 16% of placebo-treated patients; 12% of patients had documented heart rates < 60 bpm on more than one visit. The incidence of documented episodes of heart rate < 50 bpm as well as the incidence of bradycardia reported as an adverse event was 1% in each treatment group. Initiate appropriate medical management in patients who develop symptomatic bradycardia.

##### 5.5 Drug Interactions

The pharmacological gastrointestinal effects of SOMATULINE DEPOT may reduce the intestinal absorption of concomitant drugs.

Lanreotide may decrease the relative bioavailability of cyclosporine. Concomitant-administration of SOMATULINE DEPOT and cyclosporine may necessitate the adjustment of cyclosporine dose to maintain therapeutic levels [see *Drug Interactions* (7.2)].

#### 6 ADVERSE REACTIONS

##### 6.1 Clinical Studies Experience

The safety of SOMATULINE DEPOT 120mg for the treatment of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs) was evaluated in Study 3, a double-blind, placebo-controlled trial. Patients in Study 3 were randomized to receive SOMATULINE DEPOT (N=101) or placebo (N=103) administered by deep subcutaneous injection once every 4 weeks. Patients treated with SOMATULINE DEPOT had a median age of 64 years (range 30-83 years), 53% were men and 96% were Caucasian. Eighty-one percent of patients (83/101) in the SOMATULINE DEPOT arm and eighty-two percent of patients (82/103) in the placebo arm did not have disease progression within 6 months of enrollment

and had not received prior therapy for GEP-NETs. The rates of discontinuation due to treatment-emergent adverse reactions were 5% (5/101 patients) in the SOMATULINE DEPOT arm and 3% (3/103 patients) in the placebo arm.

**Table 1: Adverse Reactions Occurring in >5% in SOMATULINE DEPOT-Treated Patients and Occurring More Commonly Than Placebo-Treated Patients (>5% higher incidence) in Study 3**

Adverse Reaction	SOMATULINE DEPOT 120 mg (N=101)		Placebo (N=103)	
	Any (%)	Severe † (%)	Any (%)	Severe † (%)
<b>Any Adverse Reactions</b>	<b>88</b>	<b>26</b>	<b>90</b>	<b>31</b>
Abdominal pain <sup>1</sup>	34*	6*	24*	4
Musculoskeletal pain <sup>2</sup>	19*	2*	13	2
Vomiting	19*	2*	9*	2*
Headache	16	0	11	1
Injection site reaction <sup>3</sup>	15	0	7	0
Hyperglycemia <sup>4</sup>	14*	0	5	0
Hypertension <sup>5</sup>	14*	1*	5	0
Cholelithiasis	14*	1*	7	0
Dizziness	9	0	2*	0
Depression <sup>6</sup>	7	0	1	0
Dyspnea	6	0	1	0

<sup>1</sup> Includes preferred terms of abdominal pain, abdominal pain upper/lower, abdominal discomfort

<sup>2</sup> Includes preferred terms of myalgia, musculoskeletal discomfort, musculoskeletal pain, back pain

<sup>3</sup> Includes preferred terms of infusion site extravasation, injection site discomfort, injection site granuloma, injections site hematoma, injection site hemorrhage, injection site induration, injection site mass, injections site nodule, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling.

<sup>4</sup> Includes preferred terms of diabetes mellitus, glucose tolerance impaired, hyperglycemia, type 2 diabetes mellitus

<sup>5</sup> Includes preferred terms of hypertension, hypertensive crisis

<sup>6</sup> Includes preferred terms of depression, depressed mood

\* Includes one or more serious adverse events (SAEs) defined as any event that results in death, is life threatening, results in hospitalization or prolongation of hospitalization, results in persistent or significant disability, results in congenital anomaly/birth defect, or may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed.

† Defined as hazardous to well-being, significant impairment of function or incapacitation

##### 6.2 Immunogenicity

In Study 3, development of anti-lanreotide antibodies was assessed using a radioimmunoprecipitation assay. In patients with GEP NETs receiving SOMATULINE DEPOT, the incidence of anti-lanreotide antibodies was 3.7% (3 of 82) at 24 weeks, 10.4% (7 of 67) at 48 weeks, 10.5% (6 of 57) at 72 weeks, and 9.5% (8 of 84) at 96 weeks. Assessment for neutralizing antibodies was not conducted.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant

medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SOMATULINE DEPOT with the incidence of antibodies to other products may be misleading.

#### 6.3 Postmarketing Experience

The profile of reported adverse reactions for SOMATULINE DEPOT was consistent with that observed for treatment-related adverse reactions in the clinical studies. Those reported most frequently being gastrointestinal disorders (abdominal pain, diarrhea, and steatorrhea), hepatobiliary disorders (cholecystitis), and general disorders and administration site conditions (injection site reactions). Occasional cases of pancreatitis have also been observed.

Allergic reactions associated with lanreotide (including angioedema and anaphylaxis) have been reported.

#### 7 DRUG INTERACTIONS

##### 7.1 Insulin and Oral Hypoglycemic Drugs

Lanreotide, like somatostatin and other somatostatin analogs, inhibits the secretion of insulin and glucagon. Therefore, blood glucose levels should be monitored when lanreotide treatment is initiated or when the dose is altered, and antidiabetic treatment should be adjusted accordingly.

##### 7.2 Cyclosporine

Concomitant administration of cyclosporine with lanreotide may decrease the relative bioavailability of cyclosporine and, therefore, may necessitate adjustment of cyclosporine dose to maintain therapeutic levels.

##### 7.3 Other Concomitant Drug Therapy

The pharmacological gastrointestinal effects of SOMATULINE DEPOT may reduce the intestinal absorption of concomitant drugs. Limited published data indicate that concomitant administration of a somatostatin analog and bromocriptine may increase the availability of bromocriptine.

Concomitant administration of bradycardia-inducing drugs (e.g., beta-blockers) may have an additive effect on the reduction of heart rate associated with lanreotide. Dose adjustments of concomitant medication may be necessary.

Vitamin K absorption was not affected when concomitantly administered with lanreotide.

##### 7.4 Drug Metabolism Interactions

The limited published data available indicate that somatostatin analogs may decrease the metabolic clearance of compounds known to be metabolized by cytochrome P450 enzymes, which may be due to the suppression of growth hormone. Since it cannot be excluded that lanreotide may have this effect, other drugs mainly metabolized by CYP3A4 and which have a low therapeutic index (e.g. quinidine, terfenadine) should therefore be used with caution. Drugs metabolized by the liver may be metabolized more slowly during lanreotide treatment and dose reductions of the concomitantly administered medications should be considered.

#### 8 USE IN SPECIFIC POPULATIONS

##### 8.1 Pregnancy

###### Pregnancy Category C

Lanreotide has been shown to have an embryocidal effect in rats and rabbits. There are no adequate and well-controlled studies in pregnant women. SOMATULINE DEPOT should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Reproductive studies in pregnant rats given 30 mg/kg by subcutaneous injection every 2 weeks (five times the human dose, based on body surface area comparisons) resulted in decreased embryo/fetal survival. Studies in pregnant rabbits given subcutaneous injections of 0.45 mg/kg/day (two times the human therapeutic exposures at the maximum recommended dose of 120 mg, based on comparisons of relative body surface area) shows decreased fetal survival and increased fetal skeletal/soft tissue abnormalities.

**8.3 Nursing Mothers**

It is not known whether lanreotide is excreted in human milk. Many drugs are excreted in human milk. As a result of serious adverse reactions from SOMATULINE DEPOT in animals and, potentially, in nursing infants, a decision should be made whether to discontinue nursing or discontinue the drug, after taking into account the importance of the drug to the mother.

**8.4 Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

**8.5 Geriatric Use**

The GEP-NETs clinical trial did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. No dose adjustment required.

**8.6 Renal Impairment**

No effect was observed in total clearance of lanreotide in patients with mild to moderate renal impairment receiving SOMATULINE DEPOT 120 mg. Patients with severe renal impairment were not studied.

**8.7 Hepatic Impairment**

SOMATULINE DEPOT has not been studied in patients with hepatic impairment.

**10 Overdosage**

If overdose occurs, symptomatic management is indicated.

Up-to-date information about the treatment of overdose can often be obtained from the National Poison Control Center at phone number 1-800-222-1222.

**17 Patient Counseling Information**

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Advise patients to inform their doctor or pharmacist if they develop any unusual symptoms, or if any known symptom persists or worsens.

Advise patients experiencing dizziness not to drive or operate machinery.

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## Tumor Growth Rate (TGR) as an Indicator of Antitumor Activity With Lanreotide Autogel/Depot (LAN) Versus Placebo (Pbo) in Intestinal/Pancreatic NET: Post Hoc Analysis of CLARINET Data

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) grow slowly, thus presenting challenges to established methods for assessing growth.<sup>1</sup> The Response Evaluation Criteria in Solid Tumors (RECIST) describe tumors based on broad categories derived from many tumor types.<sup>2</sup> RECIST categorizes steadily growing tumors that are amenable to treatment as stable disease (SD). In patients receiving treatment, NETs typically stabilize rather than shrink, and the response is often slow compared with other tumor types and treatments.<sup>3</sup> As a result, identification of responders requires more time in patients with NETs. New objective measures of NET tumor response are needed to complement outcome measures based on RECIST. Tumor growth rate (TGR) can provide dynamic and quantitative evaluation of tumor kinetics. Based on phase 1 data in solid tumors, TGR is independently associated with progression-free survival (PFS).<sup>4</sup> A phase 3 study of patients with metastatic renal cell carcinoma demonstrated an independent association between TGR and PFS as well as overall survival (OS).<sup>5</sup>

The phase 3 CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) study demonstrated the efficacy and safety of lanreotide depot/autogel in patients with intestinal and pancreatic NETs.<sup>6</sup> The international, randomized, double-blind, placebo-controlled study enrolled 204 patients with nonfunctional, well or moderately differentiated tumors with demonstrated somatostatin receptor expression and metastatic disease. The tumors had a proliferation index of less than 10% and originated in the midgut, hindgut,

or pancreas or were of unknown origin. Patients received lanreotide depot/autogel (120 mg; n=101) or placebo (n=103) once every 28 days for 96 weeks or until death or progressive disease based on RECIST 1.0.<sup>2</sup> Lanreotide depot/autogel was associated with a significant extension of median PFS (not reached vs 18.0 months; hazard ratio [HR], 0.47; 95% CI, 0.30-0.73;  $P<.001$ ). The study clearly demonstrated an improved PFS for patients treated with the somatostatin analog. However, the majority of patients had SD at baseline by RECIST, and PFS improvements were confirmed only after a prolonged period of therapy.

To assess the potential role of TGR in evaluating patients with GEP-NETs, a post hoc analysis of data from the CLARINET study was conducted.<sup>7</sup> Measures included reevaluation of the tumor response data, as well as assessment of the clinical utility of TGR during the pretreatment screening period and of changes in TGR during the treatment period. TGR was defined as the percentage change in tumor volume throughout 1 month. Tumor size was defined using the sum of the longest diameters of target lesions only.

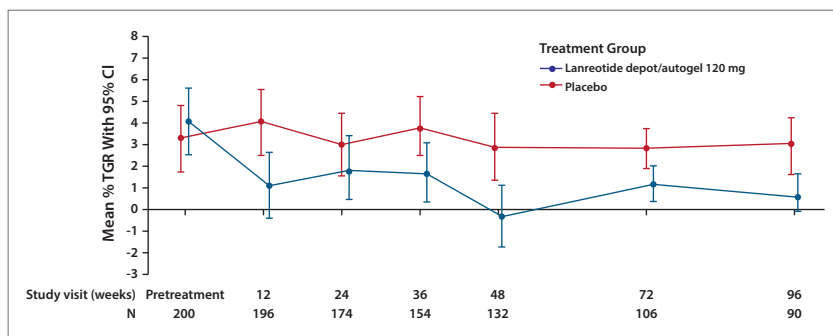
Among the 204 study patients, 84% had received no prior treatment, and 96% had SD at baseline according

### ABSTRACT SUMMARY Sunitinib (SU) in Patients With Advanced, Progressive Pancreatic Neuroendocrine Tumors (pNET): Final Overall Survival (OS) Results From a Phase III Randomized Study Including Adjustment for Crossover

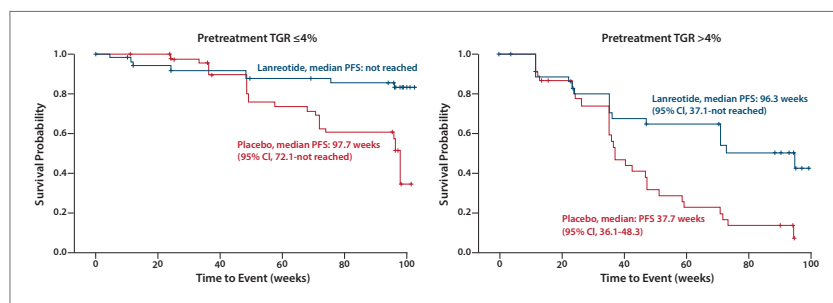
In a phase 3 trial of 171 patients with advanced, well-differentiated pancreatic NETs and progressive disease, daily sunitinib (37.5 mg) was superior to placebo, demonstrating improved median PFS (11.4 months vs 5.5 months;  $P<.001$ ) and a reduced risk of death (HR, 0.41;  $P=.02$ ; Raymond E et al. *N Engl J Med*. 2011;364[6]:501-513). This study, however, permitted crossover to sunitinib treatment, and OS was not reached. Final OS data after 5 years of follow-up demonstrated a significant improvement in OS for patients treated with sunitinib (Abstract L19). An intent-to-treat analysis yielded a median OS of 38.6 months (95% CI, 25.6-56.4 months) with sunitinib vs 29.1 months (95% CI, 16.4-36.8 months) with placebo. This difference was not significant ( $P=.094$ ), despite early separation of the curves on a Kaplan-Meier analysis. With a median follow-up duration of 67.4 months, 69% of patients randomized to placebo had crossed over to sunitinib. By using the rank-preserving structural time model to adjust for crossover, OS for the placebo arm was reduced to 13.2 months (95% CI, 9.2-38.5 months;  $P=.094$ ). Additional analyses demonstrated a significant difference in OS. Censoring at crossover yielded a median OS for the placebo arm of 16.3 months (95% CI, 12.5-24.3 months; HR, 0.40;  $P=.001$ ). Analysis of HR by the time-dependent Cox model yielded an HR of 0.46 ( $P=.004$ ). The authors suggested that the original analysis likely failed to demonstrate significance because of the relatively small size of the study population and the confounding effects of patients crossing over from the placebo arm to the treatment arm.

to RECIST 1.0. The mean time between diagnosis and enrollment was  $33.5 \pm 42.7$  months. Based on Ki-67 staining, 68% of patients had grade 1 tumors and 30% had low grade 2 tumors. Thirty-three percent of patients had hepatic tumor loads in excess of 25%. Primary tumors were found in the pancreas in 45% of patients and in the midgut in 36% of patients. During the screening period, although most patients had SD based on RECIST 1.0, TGR analysis demonstrated that many patients' tumors were actively growing. Assessment with TGR indicated antitumor effects after only 12 weeks of treatment, an earlier time point than shown with RECIST 1.0. At 12 weeks, lanreotide depot/autogel was associated with statistically significant improvements in TGR. The TGR was 1.2 (95% CI, -0.4 to 2.7) with lanreotide depot/autogel vs 4.1 (95% CI, 2.6-5.6) with placebo ( $P=.008$ ; Figure 1). This difference in TGRs was sustained at all intervals and through the final assessment during weeks 72 to 96, which demonstrated a TGR of 0.6 (95% CI, -0.5 to 1.6) with lanreotide depot/autogel vs 3.1 (95% CI, 1.7-4.6) with placebo ( $P=.007$ ). The lanreotide depot/autogel arm also demonstrated a reduction in the sum of the longest diameters of target lesions vs placebo over 96 weeks.

A pretreatment TGR of more than 4% was associated with a 4-fold improvement in risk of progression compared with a TGR of 4% or lower (HR, 4.1; 95% CI, 2.5-6.5;  $P<.001$ ; Figure 2). Lanreotide depot/autogel was significantly more effective than placebo in reducing the risk of progressive disease or death. Risk was reduced by 73% in patients with pretreatment TGRs of no more than 4% and by 63% in patients with pretreatment TGRs of more than 4%. Therefore, pretreatment TGR serves



**Figure 1.** In a subanalysis of the CLARINET trial, lanreotide depot/autogel was associated with statistically significant improvements in tumor growth rate (TGR) compared with placebo. CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors. Adapted from Caplin M et al. ENETS Abstract K2. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>7</sup>



**Figure 2.** Progression-free survival according to tumor growth rate (TGR) in the CLARINET trial. CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors. Adapted from Caplin M et al. ENETS Abstract K2. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>7</sup>

as a prognostic factor for PFS. Prospective validation is needed to confirm the utility of TGR as a novel indicator of tumor progression.

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## NETTER-1 Phase III in Patients With Midgut Neuroendocrine Tumors Treated With $^{177}\text{Lu}$ -DOTATATE: Efficacy and Safety Results

Somatostatin analogs are indicated for the control of carcinoid syndrome and to inhibit disease progression.<sup>1</sup> Both octreotide and lanreotide depot/autogel bind to somatostatin receptors, displacing the activating peptide hormone and preventing downstream events. Patients with NETs of the gastrointestinal tract who progress on first-line somatostatin analogs have limited therapeutic options. Peptide receptor radionuclide therapy (PRRT) delivers radioactivity to tumor cells based on the selective binding between extracellular receptors and analogs of their ligands.<sup>2,3</sup> This strategy is often effective in patients with NETs because a large majority of well-differentiated NETs express high levels of somatostatin receptors. Radioactivity is usually delivered by  $^{90}\text{Y}$ trium (Y) or  $^{177}\text{Lu}$ utetium (Lu) bound to the soma-

tostatin analog. Following intravenous injection, the radiolabeled somatostatin analog binds with high specificity to the somatostatin receptors expressed on tumor cells, triggering internalization. The radioactive moiety is trafficked to the lysosome, where it emits radiation for several days. For PRRT of NETs, the most commonly used somatostatin analog is octreotate, a slightly modified form of octreotide with increased affinity to somatostatin receptor subtype 2.  $^{177}\text{Lu}$  is a  $\beta$ - and  $\gamma$ -emitting isotope with a favorable therapeutic index. The therapeutic radiolabeled somatostatin analog is known as  $^{177}\text{Lu}$ -DOTATATE or  $^{177}\text{Lu}$ -octreotate.

During the past decade, thousands of European patients have been treated with PRRT.<sup>3</sup> In phase 1 and 2 clinical trials of PRRT, median PFS has ranged from approximately 1.5 years

to nearly 3 years in study populations that included a majority of patients with progressive tumors at baseline. Objective response rates (RRs) have generally ranged from 20% to 35% in patients with pancreatic disease.

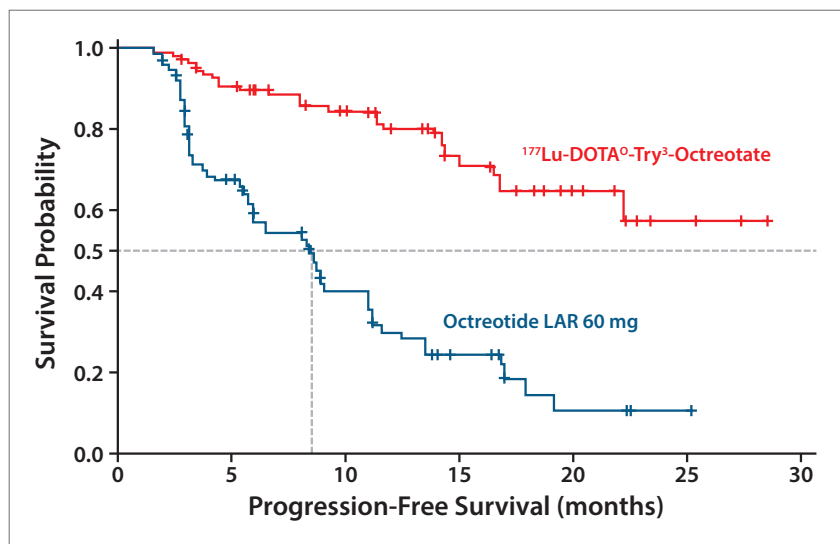
The phase 3 NETTER-1 (Phase III in Patients With Midgut Neuroendocrine Tumors Treated With  $^{177}\text{Lu}$ -DOTATATE) study was the first randomized, prospective trial to investigate the safety and efficacy of PRRT in patients with NETs.<sup>4</sup> Enrolled patients had midgut NETs with progressive disease. Patients were randomized to receive either  $^{177}\text{Lu}$ -DOTATATE (7.4 GBq every 8 weeks) for a total of 4 administrations or high-dose octreotide (60 mg every 4 weeks). Patients receiving  $^{177}\text{Lu}$ -DOTATATE also received octreotide long-acting release (LAR; 30 mg every 4 weeks) for NET symptom control. Although there was a lack of standard alternative therapy, high-dose octreotide was chosen as the comparator arm because it was viewed as safe and tolerable. Moreover, the comparator was recommended by both the US Food and Drug Administration and the European Medicines Agency. The primary endpoint was PFS based on RECIST criteria by blinded radiology review. Secondary endpoints included objective RRs, OS, safety, tolerability, and quality of life. Eligible patients were adults with well-differentiated NETs of low to medium grade with evidence of progressive disease by RECIST at baseline. All patients had tumors that expressed the somatostatin receptor based on octreotide scan, and patients could have functional or non-functional NETs.

The intent-to-treat population of 229 patients had a median age of  $63 \pm 10$  years, and approximately 50% were male. Most primary tumors were

### ABSTRACT SUMMARY Combination of Lanreotide Autogel and Temozolomide in Patients With Progressive Gastro-Entero-Pancreatic Neuroendocrine Tumours (GEPNET) - A Pilot-Study

The ongoing SONNET (Combination of Lanreotide Autogel 120 mg and Temozolomide in Progressive GEP-NET) trial is evaluating the efficacy and safety of lanreotide depot/autogel plus temozolomide in patients with progressive GEP-NETs (Abstract K6). The open-label trial has a planned enrollment of 40 patients. The dosage of lanreotide depot/autogel is 120 mg every 4 weeks. Temozolomide will be given at 150 mg/m<sup>2</sup> daily for 5 days in month 1 followed by 200 mg/m<sup>2</sup> daily for 5 days in months 2 through 6. Patients with functional NETs will then receive lanreotide depot/autogel, whereas patients with non-functional NETs will be randomly assigned to lanreotide depot/autogel or no treatment for 6 months. At the time of this analysis, 36 patients had received the combination treatment, and 9 were withdrawn from the study. During the combination treatment phase, 78% of patients experienced treatment-emergent AEs, mostly grade 1 or 2. Reported AEs were consistent with those observed in prior studies of the 2 therapies. One patient experienced serious treatment-related AEs, including nausea, vomiting, and worsening of general medical condition. This patient was withdrawn from the study and recovered with appropriate treatment. One patient died from cardiac failure that was considered unrelated to treatment. Among the 11 patients who had received at least 4 months of combination treatment, none had progressive disease at the time of data cutoff.





**Figure 3.** Progression-free survival in the NETTER-1 trial. NETTER-1, Phase III in Patients With Midgut Neuroendocrine Tumors Treated With  $^{177}\text{Lu}$ -DOTATATE. Adapted from Strosberg J et al. ENETS Abstract N15. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>4</sup>

in the ileum, and the liver was the site of metastatic disease in approximately 83% of patients. More than two-thirds of patients had grade 1 disease based on Ki-67 staining, and 60% of patients had grade 4 somatostatin receptor expression based on the Krenning scale. Patients in both arms showed high levels of chromogranin A and 5-hydroxyindoleacetic acid (5-HIAA) at baseline.

Kaplan-Meier analysis of PFS showed clear separation between the curves representing the 2 treatment arms (Figure 3). Treatment with  $^{177}\text{Lu}$ -DOTATATE yielded a 79% reduction in the risk of disease progression or death (HR, 0.21; 95% CI, 0.129-0.338;  $P < .0001$ ). The median PFS was approximately 8 months in the high-dose octreotide arm vs not reached in the  $^{177}\text{Lu}$ -DOTATATE arm. The median PFS was estimated to be approximately 40 months for  $^{177}\text{Lu}$ -DOTATATE. The objective response rate was 18%, with 1 complete response, in the PRRT arm vs 3%, with no complete responses, in the high-dose octreotide arm (Table 1). Interim analysis of OS also showed benefit with  $^{177}\text{Lu}$ -DOTATATE ( $P = .0186$ ), with median OS not reached by either arm. The study

protocol defined statistical significance as a  $P$  value of .001 or less. Seventy-seven percent of patients completed all 4 treatments with  $^{177}\text{Lu}$ -DOTATATE, and only 5% required dose modifications. The final OS analysis will occur in 2017.

In the 221 patients available for safety analysis, adverse events (AEs) were considered related to study treatment in 86% of patients who received PRRT vs 31% of patients who received high-dose octreotide. This outcome may have been influenced by the fact that treatment was not blinded. Patients who received high-dose octreotide had more rapid disease progression and therefore more tumor-related AEs. The rates of serious AEs were similar in the 2 arms (24%-26%), as were the rates of withdrawals owing to an AE (6%-9%). The most common AEs of any grade in patients receiving PRRT were nausea (59%), vomiting (47%), and fatigue/asthenia (40%). The majority of nausea and vomiting events were attributed to the amino acid infusions that patients received during the  $^{177}\text{Lu}$ -DOTATATE cycles. Each cycle contained several types of amino acids and was given at a fast rate. In contrast, the European amino acid formulation

**Table 1.** Objective Responses in the NETTER-1 Trial

	$^{177}\text{Lu}$ -DOTATATE (n=101)	Octreotide LAR 60 mg (n=100)
Complete response (n)	1	0
Partial response (n)	17	3
Objective response rate	18%	3%
95% Confidence interval	10%-25%	0%-6%
Statistical significance	$P = .0008$	

Adapted from Strosberg J et al. ENETS Abstract N15. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>4</sup>

typically contains only arginine and is associated with considerably less nausea and vomiting. The most common grade 3/4 events with  $^{177}\text{Lu}$ -DOTATATE were lymphopenia (9%), vomiting (7%), and nausea (4%). Hematologic AEs were manageable, with grade 3/4 AEs including lymphopenia (9%), thrombocytopenia (2%), leukopenia (1%), and neutropenia (1%). Median leukocyte counts decreased with  $^{177}\text{Lu}$ -DOTATATE treatment but returned to normal over time. Lymphocyte counts remained somewhat lower but did not raise any clinical concerns. Renal toxicity was not observed.

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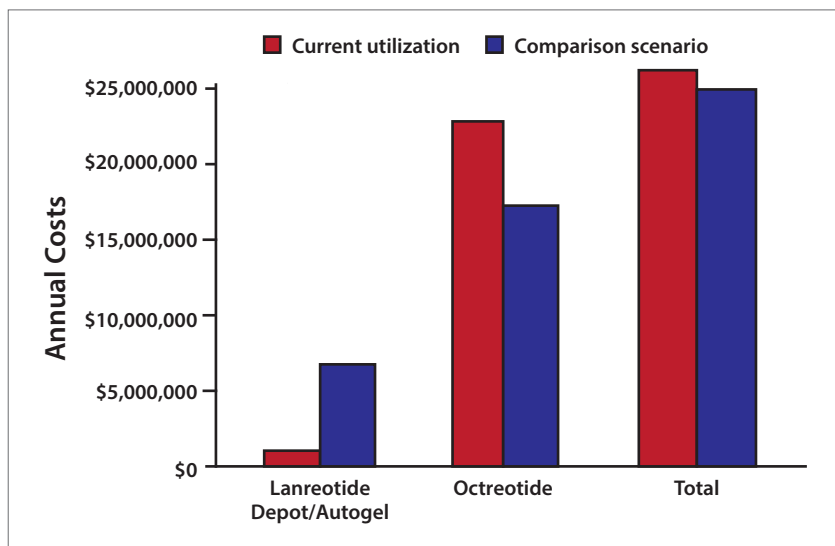
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## Budget Impact of Somatostatin Analogs (SSAs) as Treatment for Metastatic Gastroenteropancreatic Neuroendocrine Tumors (mGEP-NETs) in US Hospitals

First-line systemic therapy for patients with GEP-NETs often includes a somatostatin analog, such as lanreotide depot/autogel or octreotide LAR. In the United States, lanreotide depot/autogel is indicated in patients with GEP-NETs to improve PFS, whereas octreotide LAR is approved to treat symptoms associated with metastatic carcinoid tumors. Clinical trials have demonstrated improved PFS for both therapies compared with placebo.<sup>1-3</sup>

To evaluate real-world costs, a budget impact analysis was conducted based on cost and dosing of lanreotide depot/autogel and octreotide LAR modeled at a single hospital throughout 1 year.<sup>4</sup> The analysis used a deterministic cohort model that incorporated patients eligible for somatostatin analog treatment, product acquisition costs, preparation and mixing costs, and product utilization.

Patients received either lanreotide depot/autogel or octreotide LAR. The model assessed 2 scenarios. In the Current Utilization model, market share was based on current treatment patterns. In the comparator model, market share was hypothetically shifted from octreotide LAR to lanreotide depot/autogel, with a decrease from 95% current utilization of octreotide LAR and 5% lanreotide depot/autogel to 70% vs 30%, respectively. The model population included 500 patients with GEP-NETs at a hypothetical hospital with the assumptions that 80% of patients had metastatic or inoperable disease, and 78% were treated with a somatostatin analog. In the model, patients were treated for the entire 1-year period with 100% medication adherence. Dosing patterns and injection frequencies were held constant



**Figure 4.** Total hospital costs associated with lanreotide depot/autogel vs octreotide in a hypothetical setting. The comparison scenario incorporates a hypothetical change in market share. Adapted from Ortendahl JD et al. ENETS Abstract R9. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>4</sup>

for both scenarios, and patients incurred costs associated with product acquisition and administration. In the base case analysis, total hospital and per-patient costs were estimated for the Current Utilization and Comparator scenarios. Cost assumptions are listed in Tables 2 and 3.

Dosing was assumed to be 120 mg every 4 weeks for lanreotide depot/autogel, based on the product labeling. For octreotide LAR, dosing was variable and based on a real-world analysis.

In the base-case analysis, the cost per patient was \$75,508 with octreotide LAR and \$71,442 for lanreotide depot/autogel. For a hypothetical hospital with 500 GEP-NET patients, a shift from using lanreotide depot/autogel 5% of the time to 30% resulted in a cost savings of \$317,977 (Figure 4). One-way sensitivity analysis demonstrated that results were driven by product acquisi-

tion costs and the proportion of patients treated with octreotide LAR receiving the indicated dosage. The results suggest

**Table 2.** Somatostatin Analog Acquisition Costs

Product	Acquisition Cost Per Syringe (\$)
<b>Lanreotide Depot/Autogel</b>	
60 mg	3328
90 mg	4434
120 mg	5494
<b>Octreotide LAR</b>	
10 mg	2380
20 mg	3118
30 mg	4670

Adapted from Ortendahl JD et al. ENETS Abstract R9. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>4</sup>

**Table 3.** Product Preparation and Administration Costs

Product	Octreotide LAR	Lanreotide Depot/Autogel
Mixing/Preparation Time (seconds)	329	66
Wage Rate (\$)	82.27	82.27
Cost Per Syringe (\$)	7.52	1.51

Adapted from Ortendahl JD et al. ENETS Abstract R9. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>4</sup>

that real-world administration of octreotide LAR at doses higher than indicated contribute to increased costs whereas use of lanreotide depot/autogel at the indicated dosing may result in cost savings.

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

Everolimus (RAD001) is an inhibitor of the mammalian target of rapamycin (mTOR). The drug is approved for the treatment of advanced kidney cancer and for hormone-receptor-positive breast cancer in postmenopausal women (in combination with exemestane). A phase 2 study of patients with low- to intermediate-grade, advanced NETs showed that the combination of everolimus plus octreotide LAR was well-tolerated and yielded promising antitumor activity.<sup>1</sup> The phase 3 RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) study was the largest randomized, controlled trial of NETs evaluating patients with advanced, nonfunctional tumors of the lung or gastrointestinal tract. The trial yielded a PFS improvement of 7.1 months compared with placebo (HR, 0.48; 95% CI, 0.35-0.67;  $P < .00001$ ).<sup>2</sup> The results led to the recent approval of everolimus by the US Food and Drug Administra-

tion for the treatment of adult patients with progressive, nonfunctional NETs of either gastrointestinal or lung origin and with unresectable, locally advanced or metastatic disease.<sup>3</sup>

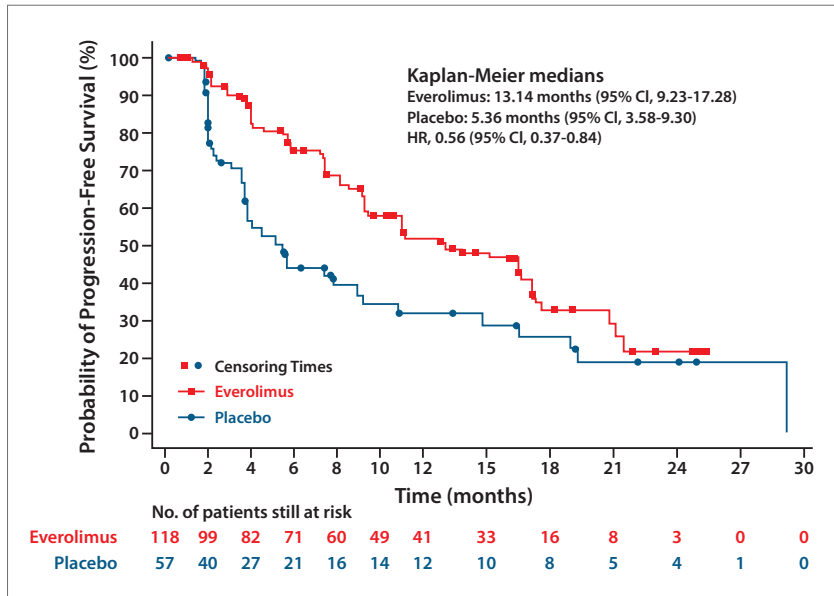
Dr Simron Singh presented an analysis of the subgroup of 175 patients with

gastrointestinal NETs and 36 patients with NETs of unknown primary origin who received treatment with everolimus or placebo in the RADIANT-4 study.<sup>4</sup> The study enrolled patients with well-differentiated, advanced, progressive, nonfunctional NETs of gastrointestinal

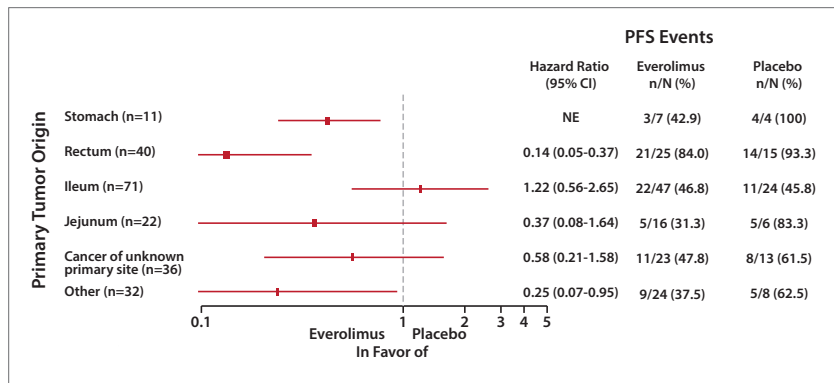
## ABSTRACT SUMMARY Efficacy of Lutetium-177 DOTA Octreotate Peptide Receptor Radionuclide Therapy in Patients With Advanced Neuroendocrine Tumours and Carcinoid Syndrome Refractory to Somatostatin Analogues

A study examined the efficacy of PRRT in patients with carcinoid syndrome and advanced NETs refractory to somatostatin analogs (Abstract L11). The 35 enrolled patients had refractory carcinoid syndrome despite treatment with maximum doses of somatostatin inhibitors. Study patients received PRRT treatment with <sup>177</sup>Lu-DOTATATE. All patients had refractory flushing. After treatment, 22 patients (62.8%) experienced significant improvement (>50%) in the number of flushing episodes. Among the 17 patients who had increased bowel frequency prior to study treatment, 12 (70.5%) reported a significant reduction (>50%) in bowel movement frequency, with frequency decreasing from 4.2 to 1.5 times daily. 5-HIAA data was available for 7 patients. Levels decreased significantly in 1 patient and moderately in 2 patients. One patient experienced a nonsignificant decrease. In 3 patients, 5-HIAA levels increased despite symptom improvement.





**Figure 5.** Progression-free survival among patients with neuroendocrine tumors of the gastrointestinal tract in a subanalysis of RADIANT-4. RADIANT-4, RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial. Adapted from Singh S et al. ENETS Abstract L20. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>4</sup>



**Figure 6.** Progression-free survival according to site of primary tumor origin in a subanalysis of the RADIANT-4 trial. RADIANT-4, RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial. Adapted from Singh S et al. ENETS Abstract L20. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>4</sup>

or lung origin. Patients had experienced progression within the prior 6 months. The trial randomized 205 patients to everolimus (10 mg daily) and 97 to placebo. No crossover was allowed during the trial. The primary endpoint was PFS. For the current analysis, the everolimus arm included 118 patients with gastrointestinal NETs and 23 with NETs of unknown primary origin. The placebo arm included 57 patients with

gastrointestinal NETs and 13 with NETs of unknown primary origin. Most of the tumors of unknown primary origin were thought to be gastrointestinal; however, radiologic evidence was inconclusive.

Within the gastrointestinal NET subgroup, the most common primary tumor sites were the ileum (41%), rectum (23%), and jejunum (13%). More than 65% of patients in the gastrointestinal and unknown primary subgroups

had liver metastasis. Patients had a median age of approximately 62 years, and the majority of patients had a World Health Organization performance status of 0. Approximately 73% of tumors were grade 1. More than half of patients had received prior treatment with a somatostatin analog. Among the 175 patients with NETs of the gastrointestinal tract, PFS improved from 5.36 months with placebo to 13.14 months with everolimus (HR, 0.56; 95% CI, 0.37-0.84; Figure 5). Among the 36 patients with NETs of unknown primary origin, PFS improved from 7.52 months with placebo to 13.63 months with everolimus, but the difference did not reach statistical significance (HR, 0.60; 95% CI, 0.24-1.51). Everolimus treatment effects were most striking in the 40 patients with NETs originating in the rectum (HR, 0.14; 95% CI, 0.04-0.37).

Comparison of the midgut vs nonmidgut subgroups demonstrated a reduction in the risk of disease progression or death by 29% and 73%, respectively. PFS increased from 10.87 months with placebo to 17.28 months with everolimus for patients in the midgut subgroup. In the nonmidgut subgroup, PFS increased from 1.94 months with placebo to 8.11 months with everolimus.

Among patients who had received prior treatment with a somatostatin analog, everolimus was associated with a 46% reduction in the risk of disease progression or death. PFS in this group increased from 4.47 months with placebo to 11.20 months with everolimus (HR, 0.54; 95% CI, 0.32-0.89). Patients who had not had prior treatment with a somatostatin analog experienced a 40% reduction in the risk of disease progression or death, and PFS increased from 7.52 months with placebo to 16.59 months with everolimus (HR, 0.60; 95% CI, 0.34-1.05).

AEs in patients treated with everolimus were manageable and consistent with those previously observed in trials of patients with kidney or breast cancer and. The most common AEs of any grade in these patients were stomatitis, infection,

diarrhea, edema, and fatigue. Grade 3/4 AEs occurring in more than 10% of patients with NETs of gastrointestinal origin included infections (12.8%) and diarrhea (11.1%). In patients with NETs of unknown primary origin, grade 3/4 AEs included stomatitis (13.6%) and abdominal pain (13.6%).

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## Interim Results on the Influence of Lanreotide on Uptake of [<sup>68</sup>Ga]-DOTATATE in Patients With Metastatic or Unresectable NET: No Evidence for Discontinuation of Lanreotide Before [<sup>68</sup>Ga]-DOTATATE PET/CT

Imaging of NETs is often performed by octreotide scan, a process in which radiolabeled octreotide binds to somatostatin receptors 2 and 5 on NETs, allowing tumor visualization. <sup>111</sup>In-octreotide is the standard radiolabel, and planer imaging or single-photon emission computed tomography (SPECT) is

used for tumor visualization. Images must be obtained at 4 and 24 hours, and sometimes as late as 48 hours, after injection of <sup>111</sup>In-octreotide. SPECT imaging has a resolution of approximately 1 cm, a sensitivity of approximately 75%, and a specificity that ranges from 50% to 95%, depending on the tumor type.<sup>1,2</sup>

In an effort to improve NET detection, alternative tumor-labeling agents are being developed. <sup>68</sup>Ga-DOTATATE consists of gallium-68 bound to octreotide by means of 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid (DOTA). The compound binds to somatostatin receptor 2, and imaging can take place within 1 hour after injection. Resolution by positron emission tomography (PET) is as low as 5 mm, with sensitivity and specificity as high as 93% and 91%, respectively.<sup>3,4</sup> Compared with <sup>111</sup>In-octreotide, <sup>68</sup>Ga-DOTATATE reveals many more tumors, even those that are low-grade or small.

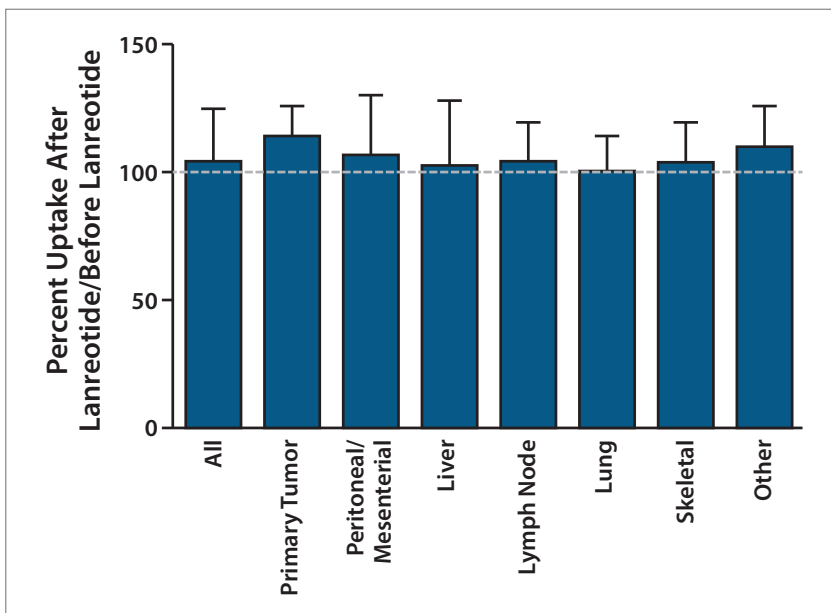
The compounds used for imaging are derived from compounds used for treatment, thus potentially leading to competition for binding to the somatostatin receptor. European and American guidelines recommend that treatment with long-acting somatostatin analogs be suspended for 3 to 6 weeks before imaging. Short-acting somatostatin analogs should be suspended for 24 hours before imaging. However, the true consequences of continuing treatment through imaging remain unclear, and suspending treatment with antiproliferative therapies has obvious medical consequences. A study addressed this issue

### ABSTRACT SUMMARY Peptide Receptor Radionuclide Therapy Prolongs Survival in Neuroendocrine Neoplasms: A Single Centre Study in 1048 Patients Over 10 Years

Results after 10 years of follow-up were presented for 1048 patients with neuroendocrine neoplasms (NENs) treated with PRRT at a single center (Abstract N1). Patients received treatment with <sup>90</sup>Y or <sup>177</sup>Lu bound to DOTATATE, DOTATOC, DOTANOC, or OPS201. Median OS for 1048 patients was 51 months (95% CI, 47.0-54.9 months). Patients treated with a combination of <sup>90</sup>Y and <sup>177</sup>Lu-based PRRT had better median OS compared with those treated exclusively with <sup>90</sup>Y-based PRRT (64 months [95% CI, 51.7-64.3 months] vs 24 months [95% CI, 17.4-30.6 months], respectively). OS was superior in patients with grade 1 tumors (88 months; 95% CI, 69.3-106.6 months) vs grade 3 tumors (23 months, 95% CI, 10.8-35.2 months). Patients with tumors of small intestinal origin had superior OS (69 months; 53.7-84.2 months) compared with other primary tumors, including those of the lung, pancreas, and unknown origin. For the entire study population, median PFS was 28 months according to RECIST and 19 months based on criteria from the European Organisation for Research and Treatment of Cancer. In patients who had experienced a third disease progression, the second treatment with PRRT yielded a median PFS of 8 months (95% CI, 6.4-9.5 months).

### ABSTRACT SUMMARY Netazepide, a Gastrin/CCK2 Receptor Antagonist, Can Eradicate Gastric Neuroendocrine Tumours in Patients With Autoimmune Chronic Atrophic Gastritis

Hypergastrinemia leads to upregulation of various genes involved in cell division, invasion, angiogenesis, and survival in the gastric mucosa. Most gastric NETs (80%) are type 1 and characterized by chronic atrophic gastritis, low levels of gastric acid, and pernicious anemia. Netazepide is a benzodiazepine derivative and antagonist of the gastrin and CCK2 receptors. An open-label, 2-center study evaluated the efficacy of oral netazepide in patients with chronic atrophic gastritis, hypoacidity, hypergastrinemia, increased plasma chromogranin A, and multiple gastric type 1 NETs (Abstract L3). Sixteen patients received netazepide (50 mg once daily) for 12 weeks followed by 12 weeks without treatment. Initial patient assessments were made at this time. After a mean of 14 months without treatment, 13 patients received netazepide (25 mg or 50 mg once daily) for 52 weeks. After the initial treatment and recovery period, which lasted 24 weeks, significant reductions were observed in the number of tumors ( $P<.001$ ), the size of the largest tumor ( $P<.01$ ), and chromogranin A level ( $P<.05$ ). During the mean 14 months without treatment, significant increases occurred in the number of tumors ( $P<.01$ ), the size of the largest tumor ( $P<.05$ ), and chromogranin A level ( $P<.001$ ). After 52 weeks of treatment with netazepide, all tumors were eradicated in 6 of 13 patients, with significant reductions in tumor size observed in the remaining patients. Treatment was safe and well-tolerated.



**Figure 7.** Treatment with lanreotide depot/autogel did not negatively impact uptake of  $^{68}\text{Ga}$ -DOTATATE in an interim analysis of patients with neuroendocrine tumors. Adapted from Aalbersberg E et al. ENETS Abstract I1. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>6</sup>

by assessing the uptake of  $^{68}\text{Ga}$ -DOTATATE in 105 patients with NETs, 35 of whom had been pretreated with octreotide LAR.<sup>5</sup> The maximum stan-

dardized uptake value ( $\text{SUV}_{\text{max}}$ ) was significantly reduced in the liver and spleen of the pretreated patients ( $P<.001$ ). The  $\text{SUV}_{\text{max}}$  in primary tumors did not differ

according to pretreatment with octreotide LAR. There were also no differences in maximum  $^{68}\text{Ga}$ -DOTATATE uptake by liver metastases, lymph nodes, or bones. In 9 patients with available inpatient data, tumor uptake was unaffected by the presence of nonlabeled octreotide ( $P=.93$ ).

To further elucidate the role of treatment during imaging, a study was performed to evaluate the effect of lanreotide depot/autogel on the uptake of  $^{68}\text{Ga}$ -DOTATATE.<sup>6</sup> The study enrolled patients with grade 1 or 2 NETs and metastatic or unresectable disease who had been treated with lanreotide depot/autogel for at least 4 months. Patients received  $^{68}\text{Ga}$ -DOTATATE followed by imaging on day -1, the lanreotide injection for medical treatment on day 0, and another injection of  $^{68}\text{Ga}$ -DOTATATE followed by imaging on day 1. To ensure consistency, the elapsed time between the  $^{68}\text{Ga}$ -DOTATATE injection and the following scan was similar for both scans. The planned enrollment is for 34 patients to provide an  $\alpha$  of 0.05 and a power of 80%. Paired analyses will be performed for primary and metastatic tumors using 3 lesions per metastatic site in patients with multiple metastases. The  $\text{SUV}_{\text{max}}$  will be determined for tumors and for normal tissues, including the spleen and liver, and for the adrenal, pituitary, thyroid, and parotid glands.

Data were available for 17 patients, of whom 1 dropped out of the study after the first scan. Patients had a mean age of 63 years (range, 45-78 years). The primary tumor was located in the small intestine in 11 patients (65%). The primary tumor was visible by scanning in 3 patients. Based on the relative difference in  $\text{SUV}_{\text{max}}$  between the first and second scans, no difference was observed for old tumors, including primary and metastatic lesions. No difference was observed in tumors based on metastatic site (Figure 7). For the normal tissue, the uptake in the liver, the spleen, and the thyroid gland decreased slightly in the second scan, which was taken just after lanreotide injection. These preliminary results



suggest that lanreotide depot/autogel does not negatively impact imaging results of NETs with  $^{68}\text{Ga}$ -DOTATATE.

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

In a study of octreotide LAR, only 52% of intramuscular injections were administered properly.<sup>1</sup> Among the 328 intended intramuscular injections, 62% were correctly administered, and 38% were mistakenly given subcutaneously. The recommended dosing for lanreotide depot/autogel is 120 mg every 4 weeks by subcutaneous injection.<sup>2</sup> Based on the concerns noted with the octreotide LAR injections, a study was undertaken in healthy subjects to determine whether the route of administration had an impact on the pharmacokinetics of lanreotide depot/autogel in healthy volunteers.<sup>3</sup> Data were gathered from a randomized, parallel, double-blind, phase 1 study completed in 1998. Healthy volunteers ages 18 to 45 years were enrolled into 7 groups, each containing 3 men and 3 women. All volunteers received an initial injection of lanreotide depot/autogel at 1 mg/mL. Afterward, they were randomly assigned to receive a second injection of lanreotide depot/autogel at varying doses and concentrations (Table 4). Lanreotide depot/autogel doses of 60 mg, 90 mg, and 120 mg were investigated using a lanreotide concentration of 0.246 mg/mg to establish the linearity of the drug's pharmacokinetics. Lanreotide depot/autogel formulations of 0.205 mg/mg or 0.246 mg/mg were injected intra-

**Table 4.** Lanreotide Depot/Autogel Injections

Cohort Number	1	2	3	4	5	6	7
Preparation Concentration (mg/mg)	0.246	0.246	0.246	0.246	0.287	0.205	0.205
Dose (mg)	60	90	120	60	60	60	60
Route of Administration	IM	IM	IM	SC	IM	IM	SC

IM, intramuscular; SC, subcutaneous.

Adapted from Manon A et al. ENETS Abstract R8. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>3</sup>

muscularly or subcutaneously at a fixed dose of 60 mg to compare the resulting pharmacokinetic profiles. Lanreotide depot/autogel formulated at 0.287 mg/

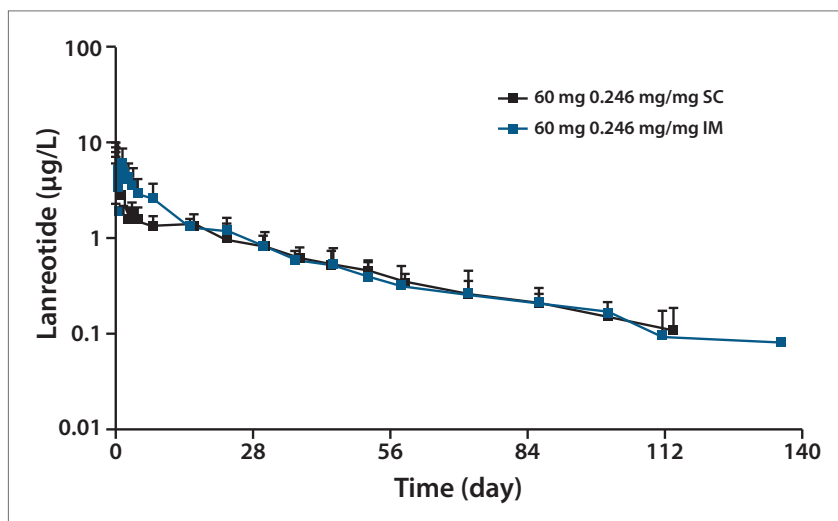
mg was injected only intramuscularly because data on subcutaneous injection were available from a prior phase 1 trial. Between days 14 and 112, serum

## ABSTRACT SUMMARY Evaluation of the Therapeutic Approaches Impacting on the Survival of Patients With an Advanced Pancreatic Neuroendocrine Tumor

A multicenter, retrospective study was conducted to determine whether palliative treatment affects OS in patients with metastatic pancreatic NETs (Abstract O10). The study included 312 consecutive patients with pathologically confirmed, sporadic, well-differentiated, metastatic pancreatic NETs of grade 1 or 2. Patients were diagnosed between 1993 and 2010, and the minimum follow-up was 5 years. Two-thirds of patients had grade 2 tumors, and two-thirds had nonfunctional tumors. Hepatic masses were present in both lobes in 68.9% of patients. Nearly half of patients had undergone surgery, 79.8% had received systemic treatment, and 15.1% had received locoregional treatment. Median OS was 6.67 years (95% CI, 5.82-8.13 years). Median OS rates were 62% (95% CI, 57%-68%) at 5 years and 34% (95% CI, 27%-40%) at 10 years. The univariate analysis suggested that surgery and locoregional treatment, undertaken with either palliative or curative intent, are significant prognostic factors.

### ABSTRACT SUMMARY FOLFOX Chemotherapy: Efficacy and Tolerability in Advanced Digestive Neuroendocrine Neoplasms (NENs)

A retrospective, single-center study assessed the use of folinic acid, 5-fluorouracil, and oxaliplatin (FOLFOX) in patients with digestive neuroendocrine neoplasms (NENs) (Abstract J5). The study included 67 consecutively treated patients with sporadic, advanced digestive NENs. Standard FOLFOX therapy was administered every 14 days. Tumors were functional in 86.6% of patients. Grade 2 and 3 tumors were observed in 40.3% and 58.2% of patients, respectively. The median Ki-67 labeling index was 25% (range, 2%-90%). The primary tumor was located in the pancreas in 64% and in the gastrointestinal tract in 33%. It was of unknown origin in 3%. Nearly all patients (96%) had stage IV disease, and 27% were treatment-naïve. Treatment discontinuations occurred in 32.8% of patients, and 34.3% of patients received a reduced dose. The disease control rate was 76.1%, which consisted of partial responses in 62.7% and stable disease in 13.4%. Based on multivariate Cox regression analysis, PFS was improved in patients who received more than 9 cycles of FOLFOX treatment (HR, 0.79;  $P < .001$ ). Prognostic factors included low serum levels of protein or albumin and a high level of alkaline phosphatase.



**Figure 8.** Mean concentration-time profiles of lanreotide depot/autogel administered intramuscularly (IM) or subcutaneously (SC). Adapted from Manon A et al. ENETS Abstract R8. Abstract presented at: the 2016 European Neuroendocrine Tumor Society Meeting; March 9-11, 2016; Barcelona, Spain.<sup>3</sup>

levels of lanreotide depot/autogel were assessed using a validated radioimmunoassay method.

The 42 healthy volunteers had a mean age of  $25 \pm 5$  years and a mean

weight of  $66 \pm 10$  kg. Lanreotide depot/autogel (60 mg formulated at 0.246 mg/mg) was injected intramuscularly in 6 subjects and subcutaneously in 5 subjects, with 1 subject excluded

from the latter group. Thirty subjects received other doses and/or concentrations of lanreotide depot/autogel and were not included in the analysis. Among the 11 patients who received injections of lanreotide depot/autogel (60 mg formulated at 0.246 mg/mg), the mean concentration-time profiles were similar after the subcutaneous and intramuscular injections.

Pharmacokinetic results following subcutaneous and intramuscular injections were similar for mean  $C_{max}$  ( $5.8 \pm 4 \mu\text{g/L}$  vs  $6.8 \pm 3 \mu\text{g/L}$ ), mean  $t_{1/2}$  ( $33 \pm 14$  days vs  $23 \pm 9$  days), and last measured mean residence time ( $30 \pm 6$  days vs  $23 \pm 11$  days) (Figure 8). After subcutaneous vs intramuscular injection, statistically significant differences were observed based on 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 ( $1843 \pm 134$  vs  $2100 \pm 193 \text{ h}\cdot\mu\text{g/L}$ ;  $P = .03$ ). The median  $T_{max}$  was 8 hours after subcutaneous injection vs 16 hours after intramuscular injection.

In summary, subcutaneous and intramuscular injection led to similar pharmacokinetic profiles based on maximal concentration and terminal half-life. Slightly more lanreotide depot/autogel was available in the late-release phase following subcutaneous injection, thus providing a superior long-term release profile.

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# Highlights in GEP-NETs From the 13th Annual ENETS Conference for the Diagnosis and Treatment of Neuroendocrine Tumor Disease: Commentary

Renuka Iyer, MD, and Hassan Hatoum, MD

The 13th Annual European Neuroendocrine Tumor Society (ENETS) conference was held in Barcelona from March 9 through 11, 2016. Data were presented on several studies evaluating treatments for gastroenteropancreatic neuroendocrine tumors (GEP-NETs), such as lanreotide depot/autogel, octreotide, sunitinib, and radioisotope therapy. In this commentary, we discuss selected abstracts from the meeting that will potentially impact the approach to managing GEP-NETs, as well as abstracts that present promising results from ongoing areas of research.

## Existing Therapies

Lanreotide depot/autogel was approved in 2014 for the treatment of patients with unresectable, well or moderately differentiated, locally advanced or metastatic GEP-NETs based on results from the CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) trial.<sup>1</sup> Median progression-free survival was not reached in the CLARINET trial, after a follow-up of 29 months. At the ENETS conference, a subanalysis of the trial found that tumor growth rate (TGR; defined as percentage change in volume per month) greater than 4% was strongly correlated with progression.<sup>2</sup> A reasonable explanation is that TGR is a radiologic factor that acts as a surrogate for Ki-67, yet is easier to obtain. Measurement of TGR can be easily accomplished with computed tomography scans. We suggest that patients with an increased TGR should be scanned more frequently to optimize surveillance. Guidelines typically do

not indicate which patients require scanning every 3 months vs every 6 months. In the future, increased TGR may be an indication for the use of adjunctive biologic therapies. TGR may challenge the reliability of Ki-67, which in some cases, can be difficult to assess in a heterogeneous tumor and must be evaluated by expert pathologists, which some institutions may lack.

The manufacturer recommends that lanreotide depot/autogel be administered subcutaneously. A study by Dr Amandine Manon evaluated the practical question of whether pharmacokinetics differ when lanreotide depot/autogel is given intramuscularly vs subcutaneously.<sup>3</sup> The study found that the pharmacokinetics did not differ. This finding is important for clinicians to know. Office staff may be in the habit of giving intramuscular injections, and may inadvertently administer lanreotide depot/autogel this way. This study is small, but it provides reassurance that lanreotide depot/autogel administered intramuscularly is still absorbed and can be expected to achieve similar therapeutic results to subcutaneous administration.

A study by Dr Jesse Ortendahl focused on the costs of octreotide vs lanreotide depot/autogel in a US hospital model.<sup>4</sup> Data from case reports have suggested that patients who progress on octreotide can achieve benefit from lanreotide depot/autogel and vice versa.<sup>5,6</sup> In the current healthcare environment, cost-effectiveness is a key driver of decision-making. The study by Dr Ortendahl found that in 64% of patients, octreotide was administered at 30 mg once every 4 weeks.

For the remaining patients, octreotide was given every 3 weeks or at a higher dosage. When compared with this use, lanreotide depot/autogel would be less expensive than octreotide. The study also evaluated mixing time, hospital time, and the effort that goes into preparing these injections, and found that use of lanreotide depot/autogel was associated with reduced costs. It is important to consider these types of issues more seriously moving forward, as we select among treatments known to have similar results.

Sunitinib was approved in 2010 in Europe and in 2011 in the United States for the treatment of progressive pancreatic neuroendocrine tumors. A phase 3 trial showed improvement in progression-free survival but not overall survival.<sup>7</sup> Prescribers have been eager to learn whether sunitinib improves overall survival. An analysis presented by Dr Eric Raymond evaluated data from 5 years of follow-up, which were unadjusted for crossover.<sup>8</sup> In the original trial, patients in the placebo arm were permitted to cross over to active treatment at the time of progression or when the study was unblinded. Even unadjusted for that crossover, the difference in survival was 9 months in favor of sunitinib. However, this difference did not reach statistical significance. Approximately 65% of patients in each arm died. After adjustment for crossover, there was a very significant difference in death, showing improved overall survival with sunitinib.

## Novel Therapies

Type 1 gastric carcinoid tumors are typically managed by an endoscopist,



with frequent ablation or endoscopic management of these small lesions. There are some patients who have multiple lesions, which requires multiple endoscopies and procedures. A study by Dr Malcolm Boyce evaluated the use of netazepide, a novel gastrin CCK2 receptor antagonist, in patients with type 1 gastric carcinoids.<sup>9</sup> Netazepide was efficacious in this small study, eradicating or shrinking most of the tumors. This exciting study suggests that netazepide may have a role in these patients. The cost-effectiveness of netazepide should be compared with that of endoscopic therapies.

The RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) study led to the approval of everolimus for the treatment of advanced carcinoid tumors, regardless of origin.<sup>10</sup> Dr Singh presented a small safety and efficacy subset analysis.<sup>11</sup> An important question is whether previous treatment with somatostatin analogs (SSAs) impacts treatment with everolimus. The RADIANT-2 study allowed patients to continue treatment with an SSA.<sup>12</sup> In contrast, patients in RADIANT-4 discontinued treatment

with SSAs at the time of randomization. The current analysis showed that everolimus benefited both gastrointestinal and nongastrointestinal metastatic gastroenteropancreatic neuroendocrine tumors, regardless of whether patients had received prior treatment with SSAs. This study suggests that everolimus, with its favorable toxicity profile, might be appropriate as first-line therapy, particularly for patients who are unable or unwilling to receive treatment with injectable drugs on one hand. On the other hand, for some oncologists, everolimus might not be an attractive first-line choice compared with an SSA because of the concern of serious side effects, particularly infections and respiratory complications. This strategy challenges our previous approach, which always involved use of SSAs because there was nothing else to offer.

Among the non-antineoplastic therapies, telotristat etiprate is a tryptophan hydroxylase inhibitor, which is basically a synthesis inhibitor for serotonin. Dr Dieter Hörsch provided data from a phase 2/3, randomized, placebo-controlled trial that evaluated 2 dosages of oral telotristat etiprate:

250 mg 3 times daily or 500 mg 3 times daily.<sup>13</sup> The primary endpoint was reduction in the number of daily bowel movements from baseline averaged over a 12-week period. The patients continued SSA treatment. Treatment with both doses of the drug showed significant improvement in the primary endpoint. However, there was no significant effect on other carcinoid-related symptoms, such as hot flushing. Telotristat etiprate represents a new hope for patients whose daily activities are hindered by uncontrolled bowel movements despite the optimal use of an SSA. Needless to say, diarrhea secondary to pancreatic insufficiency caused by SSA use should be identified and treated with pancreatic enzyme supplements. For some patients, this treatment could be as important as controlling the disease burden. In addition, the decrease in the urinary 5-hydroxyindoleacetic acid associated with treatment may present a protective effect against carcinoid-associated cardiac valve disease. Previous data had suggested that telotristat etiprate might cause depression in certain patients. A strong association was not seen in the current study, but larger trials should provide more information.

#### **ABSTRACT SUMMARY Efficacy and Safety of Telotristat Etiprate in Patients With Carcinoid Syndrome Not Adequately Controlled by Somatostatin Analog Therapy: Analysis of the Ongoing TELESTAR Extension Period**

The phase 2/3 TELESTAR (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) trial evaluated 2 dose levels of telotristat etiprate (250 mg or 500 mg 3 times daily) vs placebo in 135 patients with carcinoid syndrome (Abstract M5). During the 12-week, double-blind treatment period, frequency of daily mean bowel movements decreased by 0.81 in the 250-mg arm and by 0.69 in the 500-mg arm. In both telotristat etiprate arms, the daily bowel movement frequency decreased by approximately 1.5 bowel movements daily by week 4 of treatment. Interim data showed that reductions in bowel movement frequency continued at the end of the double-blind treatment period, when 115 patients crossed over to the open-label extension study to receive telotristat etiprate (500 mg 3 times daily). During the 12-week, double-blind treatment period, rates of treatment-related AEs of any grade were 26.7% with placebo, 35.6% in the 250-mg arm, and 66.7% in the 500-mg arm. Patients treated with the higher dosage of telotristat etiprate during the 12-week, double-blind period experienced an increase in depression relative to placebo. However, rates of depression did not increase during the open-label extension study.

#### **Practice-Changing Data**

Dr Jonathan Strosberg presented results of the NETTER-1 (Phase III in Patients With Midgut Neuroendocrine Tumors Treated With <sup>177</sup>Lu-DOTATATE) trial.<sup>14</sup> In Europe, radioisotopes have been used for the treatment of neuroendocrine cancers for several decades. In the United States, lack of FDA approval has made it challenging to incorporate radioisotopes into the treatment algorithm. This early analysis of the NETTER-1 trial has provided data on the use of radioisotopes in patients with advanced midgut neuroendocrine tumors who have progressed on first-line somatostatin therapy. Patients were randomly assigned to receive <sup>177</sup>lutetium

### ABSTRACT SUMMARY Sequential Everolimus and Sunitinib Treatment in Pancreatic Metastatic Well-Differentiated Neuroendocrine Tumors Resistant to Prior Treatments

Alternating treatment between sunitinib and everolimus has been explored in renal cell carcinoma (Davis A et al. *Ann Oncol.* 2015;26[6]:1118-1123). A study was conducted to evaluate the efficacy of alternating sunitinib and everolimus in patients with well- or moderately differentiated, stage IV pancreatic NETs (Abstract L1). Eleven patients received sunitinib followed by everolimus, and 20 received everolimus followed by sunitinib. Median PFS was prolonged in patients who received everolimus first, but the results did not reach statistical significance (16.3 months vs 9 months;  $P=.015$ ). Median PFS based on second-line therapy was similar for everolimus vs sunitinib (15.5 months vs 10.3 months, respectively;  $P=.3$ ). Everolimus was less likely than sunitinib to be discontinued owing to serious AEs.

DOTATATE or high-dose octreotide (60 mg every 4 weeks), which was considered the standard treatment at the time of the trial design. Among the 229 patients in the intent-to-treat population,  $^{177}$ lutetium DOTATATE was associated with a 79% reduction in the risk of death, with a hazard ratio of .21 and a very significant  $P$  value ( $P<.0001$ ), with a favorable safety profile. The short follow-up time permitted only an estimate of progression-free survival, which was approximately 40 months, more than double that of any other treatment currently available. It is expected that radioisotope therapy will be approved in the United States by the end of 2016, and will likely be practice-changing. There are several logistical questions, such as how and where this therapy will be available.

Lanreotide depot/autogel has shown an impressive ability to treat and delay disease progression among patients with advancing NETs,<sup>1</sup> which raises the questions of whether patients will need to remain on biologic therapy or oral chemotherapy indefinitely, and whether lanreotide depot/autogel can provide disease stabilization and control as maintenance therapy in patients with limited exposure to chemotherapy. Dr Markus Raderer presented preliminary safety results from a study that combined lanreotide depot/autogel and temozolomide in patients with progressive GEP-NETs.<sup>15</sup> It found that the adverse events for the combination were consistent with the safety profiles reported for each therapy. I commend the authors for this trial design because it addresses the kinds of questions that need to be asked as we move forward. Traditionally, the approach has been to give chemotherapy indefinitely until progression. There are patients who stop chemotherapy and still have disease control on lanreotide depot/autogel alone. The results of this study have the potential to be practice-changing.

**Disclosure**  
Dr Iyer is a consultant for Ipsen Biopharmaceuticals, Inc. Dr Hatoum has no real or apparent conflicts of interest to report.

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