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A SPECIAL MEETING REVIEW EDITION

Highlights in GEP-NETs From the 2016 American Society of Clinical Oncology Gastrointestinal Cancers Symposium

January 21-23, 2016 • San Francisco, California

Special Reporting on:

- Rare Tumors of the Upper GI Tract: Neuroendocrine Tumors
- New Options for Neuroendocrine Tumors: Results of Recent Trials
- Tumor Response in the CLARINET Study of Lanreotide Depot/Autogel vs Placebo in Patients With Metastatic Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)
- NETTER-1 Phase III: Progression-Free Survival, Radiographic Response, and Preliminary Overall Survival Results in Patients With Midgut Neuroendocrine Tumors Treated With ^{177}Lu-Dotatate
- Peptide Receptor Radiation Therapy for Neuroendocrine Tumors
- Treatment Patterns and Clinical Outcomes of Patients With Metastatic Gastroenteropancreatic Neuroendocrine Tumors (mGEP-NETs)

PLUS Meeting Abstract Summaries

With Expert Commentary by:

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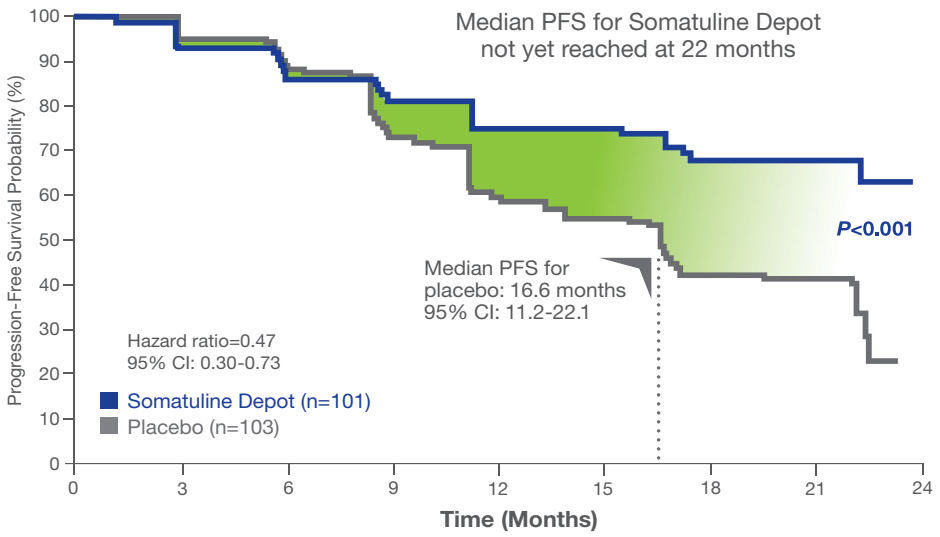
HOLD BACK PROGRESSION

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

SIGNIFICANTLY IMPROVED PROGRESSION-FREE SURVIVAL (PFS)[1]



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® 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.

IPSEN Innovation for patient care

SOMATULINE DEPOT SIGNIFICANTLY EXTENDED PFS IN LOCALLY ADVANCED OR METASTATIC GEP-NETs[1]

A 53% REDUCTION IN THE RISK OF DISEASE PROGRESSION OR DEATH VS PLACEBO[1]

IMPORTANT SAFETY INFORMATION (Continued)

Warnings and Precautions (Continued):

- Cardiac Abnormalities: Somatuline Depot may decrease heart rate. In 81 patients with baseline heart rates of ≥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

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

Somatuline® 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 ≥ 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 † (%)
Any Adverse Reactions	**88**	**26**	**90**	**31**
Abdominal pain[1]	34*	6*	24*	4
Musculoskeletal pain[2]	19*	2*	13	2
Vomiting	19*	2*	9*	2*
Headache	16	0	11	1
Injection site reaction[3]	15	0	7	0
Hyperglycemia[4]	14*	0	5	0
Hypertension[5]	14*	1*	5	0
Cholelithiasis	14*	1*	7	0
Dizziness	9	0	2*	0
Depression[6]	7	0	1	0
Dyspnea	6	0	1	0

[1] Includes preferred terms of abdominal pain, abdominal pain upper/lower, abdominal discomfort

[2] Includes preferred terms of myalgia, musculoskeletal discomfort, musculoskeletal pain, back pain

[3] 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.

[4] Includes preferred terms of diabetes mellitus, glucose tolerance impaired, hyperglycemia, type 2 diabetes mellitus

[5] Includes preferred terms of hypertension, hypertensive crisis

[6] 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.

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Highlights in GEP-NETs From the 2016 American Society of Clinical Oncology Gastrointestinal Cancers Symposium: Commentary
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Rare Tumors of the Upper GI Tract: Neuroendocrine Tumors

At the 2016 American Society of Clinical Oncology Gastrointestinal Cancers Symposium (ASCO GI), Dr Jennifer Eads discussed gastroenteropancreatic neuroendocrine tumors (GEP-NETs) as part of her presentation on gastrointestinal stromal tumors and NETs. GEP-NETs are a heterogeneous group of neoplasms, with varying behavior and degrees of malignancy.[1,2] Most NETs are gastrointestinal in origin, arising in the foregut, midgut, or hindgut. NETs are characterized based on the primary site of origin and the degree of differentiation, and both characteristics are used to determine treatment. Patients with tumors that are well or moderately differentiated often have an indolent disease course and a significantly better overall survival (OS) compared with patients harboring poorly differentiated tumors. NETs that produce hormones are considered functional. The median age at diagnosis is approximately 60 years, and most patients present with metastatic disease. The disease is inoperable in many patients, and there is a need for the development of therapies to control or reverse tumor growth.

Several pathways play a role in the pathogenesis and function of NETs. The somatostatin, vascular endothelial growth factor (VEGF), and mammalian target of rapamycin (mTOR) pathways provide rational targets for the development of new therapies. Somatostatin receptors are expressed on 80% to 100% of GEP-NETs, with the higher levels of expression observed with tumors that have greater differentiation.[3] Somatostatin analogs such as octreotide reduce hormone production induced by activated somatostatin receptors, and thereby improve hormone-related symptoms in patients with functional NETs. Antiproliferative activity has also been demonstrated for octreotide against different cell types in vitro. Several studies in patients showed antiproliferative activity against NETs (although these studies lacked a control arm).[4]

The PROMID and CLARINET Trials

These promising results led to a randomized, placebo-controlled trial evaluating the antitumor activity of octreotide in patients with NETs.[5] The phase 3 PROMID (Study to Investigate the Antiproliferative Effect of Octreotide in Patients With Metastasized Neuroendocrine Tumors of the Midgut) trial enrolled treatment-naive patients with well-differentiated, metastatic midgut NETs. Eighty-five patients were randomly assigned to receive octreotide long-acting release (LAR; 30 mg) or placebo every 28 days. Octreotide LAR significantly reduced tumor growth, yielding a median time to tumor progression of 14.3 months in patients treated with the somatostatin analog vs 6 months in patients who received placebo (hazard ratio [HR], 0.34; 95% CI, 0.20-0.59; *P*=.000072). After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group vs 37.2% of patients who received placebo. Both functional and inactive tumors responded. The trial definitively established the antiproliferative activity of a somatostatin analog in patients with well-differentiated, metastatic midgut NETs. Long-term follow-up demonstrated similar median OS for patients treated with octreotide LAR or placebo (HR, 0.83; 95% CI, 0.47-1.46; *P*=.51).[6] The median OS was

ABSTRACT SUMMARY Clinicopathological Features and Response to Platinum-Based Chemotherapy in Pancreatic Neuroendocrine Carcinoma: A Retrospective Multicenter Study of 70 Patients

Pancreatic neuroendocrine carcinomas (NECs) may consist of different subtypes with distinct genetic profiles, as suggested by patients' variable responses to platinum-based chemotherapy. A study was therefore conducted to clarify the clinicopathologic and molecular characteristics of NECs (Abstract 298). Case slides from 100 patients were reassessed by expert pathologists and reclassified as well differentiated (NET-G3), small cell NEC, or large cell NEC based on morphologic features. Thirty cases were not included owing to spurious initial classification. Among the remaining 70 cases, 30% were NET-G3, 44.3% were small cell NEC, and 25.7% were large cell NEC. Median Ki-67 labeling index levels were 29% for NET-G3, 85% for small cell NEC, and 70% for large cell NEC. Rb expression was detected in 100%, 41%, and 53% of tumors, respectively, and *KRAS* mutations were observed in 0%, 48%, and 50%. Response rates to platinum-based chemotherapy were 0% for NET-G3, 60% for small cell NEC, and 44% for large cell NEC. Median OS was 1255 days, 340 days, and 196 days, respectively. Predictive factors for response to first-line platinum-based chemotherapy included loss of Rb expression and presence of *KRAS* mutation. Platinum-based chemotherapy was ineffective in all patients with tumors showing a Ki-67 labeling index of less than 50% and all patients with NET-G3 tumors.

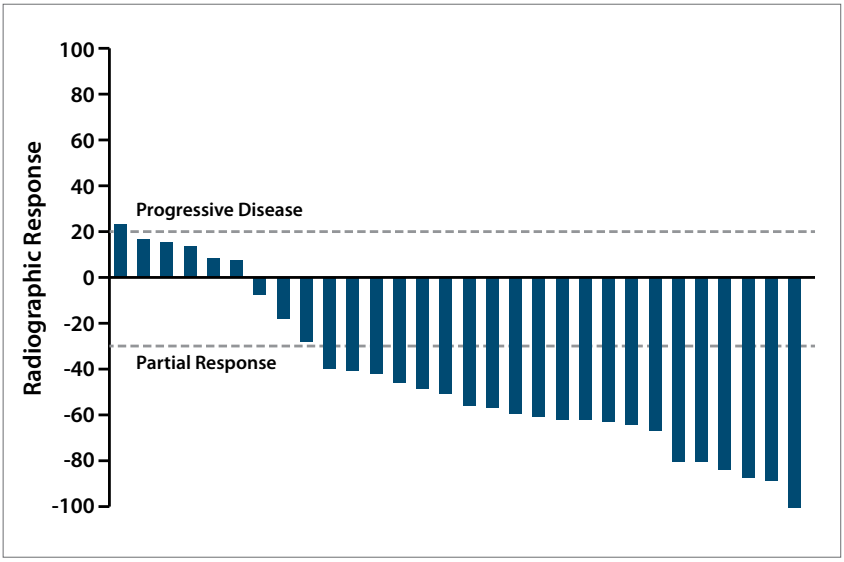

Figure 1. Best radiographic response among patients with metastatic pancreatic endocrine carcinomas receiving first-line chemotherapy with capecitabine and temozolomide.

Adapted from Strosberg JR et al. *Cancer*. 2011;117(2):268-275.[12]

shortened among patients with high tumor burden (*P*=.002). In addition, the majority of patients in the placebo arm crossed over to the octreotide LAR arm, which may have confounded survival data.

One limitation of the PROMID study was that nearly all of the patients had tumors with a proliferation index of 2% or less, based on Ki-67 detection, and the primary tumor site was restricted to the midgut. The CLARINET (Controlled Study of Lanreotide Autogel in Non-Functioning Entero-Pancreatic Endocrine Tumours) study investigated lanreotide depot/autogel—the extended-release, aqueous gel formulation of the somatostatin analog—in a broader patient population.[7] The study included patients with NETs of the pancreas, midgut, or hindgut, as well as those of unknown origin. All patients had metastatic disease. Tumors were well or moderately differentiated and nonfunctional, with a proliferation index of 1 or 2, indicating Ki-67 staining in less than 10% of cells. The study randomly assigned 101 patients to receive lanreotide depot/autogel (120 mg) and 103 to placebo given every 28 days for 96 weeks. One-third of patients had hepatic tumor volumes greater than 25%. Lanreotide depot/autogel was associated with a significantly prolonged median progression-free survival (PFS) compared with placebo (not reached vs 18.0 months; HR for progression or death, 0.47; 95% CI, 030-0.73; *P*<.001). Estimated 24-month PFS rates were 65.1% for lanreotide depot/autogel vs 33.0% for placebo. The most common treatment-related adverse event (AE) was diarrhea, occurring in 26% of patients who received lanreotide depot/autogel and 9% of patients who received placebo.

VEGF and mTOR Inhibition

Inhibitors of the VEGF and mTOR pathways have been explored in NETs, as monotherapy and in combination regimens. Studies investigating sunitinib or everolimus as monotherapy in patients with advanced, progressive pancreatic NETs demonstrated significant improvements in PFS compared with placebo.[8,9] More recently, results of the RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) trial underscored the potential of mTOR inhibition.[10] The randomized, double-blind, placebo-controlled phase 3 trial enrolled 302 patients diagnosed with advanced, progressive, well-differentiated, nonfunctional NETs of lung or gastrointestinal origin. Patients were stratified by tumor origin, performance status, and previous treatment, and were then randomly assigned 2:1 to receive either everolimus (10 mg daily) or placebo. Patients in both arms also received supportive care. Median PFS was 11.0 months with everolimus vs 3.9 months with placebo. Everolimus was associated with a 52% reduction in the estimated risk of progression or death (HR, 0.48; 95% CI, 0.35-0.67; *P*<.00001). Grade 3/4 drug-related AEs were consistent with the known side effect profile of everolimus.

Another study evaluated the combination of everolimus monotherapy or everolimus plus bevacizumab added to octreotide in 147 patients with pancreatic NETs.[11] The addition of bevacizumab was associated with a nonsignificant increase in PFS (16.7 months vs 14.0 months; *P*=.12) and a significant improvement in objective response rate (31% vs 12%; *P*=.005). Rates of grade 3/4 toxicity were higher among patients receiving everolimus plus bevacizumab.

Cytotoxic Therapies

Cytotoxic treatments, including streptozotocin and temozolomide, remain an important option for treating pancreatic NETs. However, few randomized, controlled trials have evaluated these agents. In a retrospective study of 30 treatment-naive patients with metastatic and moderately or well-differentiated pancreatic NETs, the cytotoxic combination of temozolomide plus capecitabine yielded an overall response rate of 70%, PFS of 18 months, and 2-year survival of 92% (Figure 1).[12] The Eastern Cooperative Oncology Group is conducting a prospective trial comparing temozolomide with or without capecitabine in pancreatic NETs.[13]

Peptide Receptor Radionuclide Therapy

Peptide receptor radionuclide therapy (PRRT) delivers radiation directly to tumor cells. ^{177}Lutetium-DOTA^{0},Tyr^{3}-octreotrate (^{177}Lu-octreotate; also called ^{177}Lu-DOTATATE) is a radiolabeled derivative of octreotide that binds to somatostatin receptors and delivers localized radiation therapy to NETs. It has been studied extensively in Europe and has a favorable safety profile. In a single-arm study of 310 patients with GEP-NETs, the radiolabeled somatostatin analog achieved a median OS of 46 months and a median PFS of 32 months.[14] Based on the promising results of this study and others, the NETTER-1 (A Study Comparing Treatment With ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumors) trial was conducted to evaluate octreotide vs ^{177}Lu-octreotate in patients with metastatic midgut NETs.[15] The study was conducted in 230 patients and yielded a significant improvement in PFS among patients who received PRRT therapy (8.4 months vs not reached; $P<.0001$).

Treatment of Poorly Differentiated Carcinoid Tumors

Poorly differentiated carcinoid tumors are rare, accounting for approximately 10% of all NETs.[16] Limited clinical trial data are available to guide treatment of poorly differentiated carcinoid tumors. However, based on histologic similarities with small cell lung cancer tumors, treatment for poorly differentiated carcinoid tumors has been extrapolated from trials in small cell lung cancer. The combination of cisplatin and etoposide has emerged as the preferred first-line treatment for these tumors, but median OS remains poor and is measured in months.

The ideal second-line treatment for poorly differentiated neuroendocrine carcinoid tumors has yet to be determined, and only a limited number of studies in the second-line setting have been conducted. Four retrospective studies yielded response rates ranging from 0% to 33% and OS times ranging from 3.5 months to 22 months, with regimens including agents such as irinotecan, oxaliplatin, and temozolomide.[17-20] The best results were obtained in a study of 25 patients treated with the combination of temozolomide alone or in combination with capecitabine and bevacizumab, which yielded a 33% overall response rate and an OS of 22 months.[20]

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New Options for Neuroendocrine Tumors: Results of Recent Trials

The number of approved drugs for treating GEP-NETs has expanded dramatically in the past several years. In 2011, everolimus and sunitinib were approved for pancreatic NETs, and lanreotide depot/autogel was approved in 2014 for treatment of GEP-NETs.[1] Recent phase 3 trials have demonstrated the efficacy and safety of telotristat, everolimus monotherapy, and PRRT.

At the 2016 ASCO GI symposium, Dr Pamela Kunz discussed the management of patients with NETs, with a focus on treatment paradigms, results from recent clinical trials, and ongoing clinical trials.[2] Five key tumor characteristics should be evaluated when determining treatment: primary tumor site, disease burden and extent, tumor grade, pace of growth, and hormone function. Treatment choice also should take into consideration side effects and likely outcomes, particularly delayed progression and the potential for tumor shrinkage.

Ongoing clinical trials are evaluating new therapies and testing existing treatments in expanded patient populations. The phase 3 PROMID and CLARINET trials evaluated somatostatin analogs in patients with NETs. The phase 3 PROMID trial enrolled 85 patients with midgut tumors of grade 1 proliferation that were restricted to 2% active cells, and included both functional and nonfunctional NETs.[3] Few patients had a hepatic tumor volume greater than 10%. More recently, the CLARINET study examined lanreotide depot/autogel in a more diverse patient population.[4] The study enrolled 204 patients with tumors of the pancreas, midgut, hindgut, or unknown primary site. Only nonfunctional tumors were included, and all tumors showed less than 10% proliferation based on Ki-67 staining. In addition, the CLARINET trial included patients with greater hepatic tumor volume: in 33%, the hepatic tumor volume was 25% or greater. Lanreotide depot/autogel improved PFS over placebo (Figure 2).[4] The RADIANT-4 trial evaluated everolimus in patients with advanced, nonfunctional neuroendocrine tumors of the lung or gastrointestinal tract.[5] Everolimus was associated with an improved PFS compared with placebo (Figure 3).[5]

Telotristat etiprate recently demon-

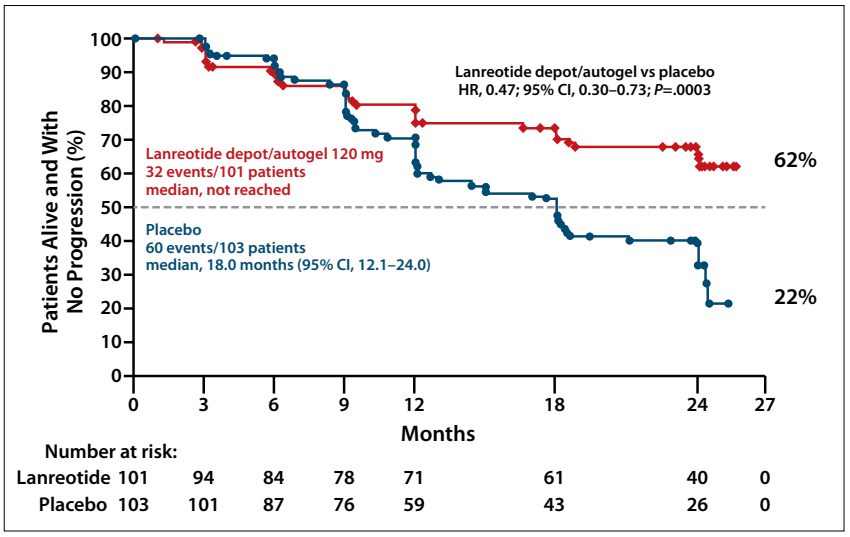

Figure 2. Progression-free survival among the intent-to-treat population in the CLARINET trial, which enrolled patients with grade 1 or 2 GEP-NETs that were well-differentiated or moderately differentiated, nonfunctioning, and locally inoperable or metastatic.

CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors. GEP-NETs, gastroenteropancreatic neuroendocrine tumors. Adapted from Caplin ME et al. *N Engl J Med.* 2014;371(3):1556-1557.[4]

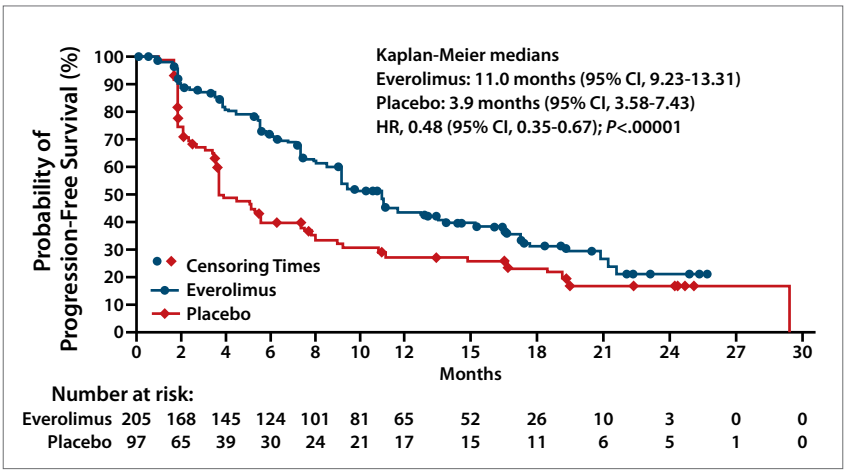

Figure 3. Progression-free survival in the RADIANT-4 trial of patients with advanced, nonfunctional neuroendocrine tumors of the lung or gastrointestinal tract.

RADIANT-4, Everolimus Plus Best Supportive Care vs Placebo Plus Best Supportive Care in the Treatment of Patients With Advanced Neuroendocrine Tumors (GI or Lung Origin). Adapted from Yao JC et al. *Lancet.* 2015 Dec 15. doi:10.1016/S0140-6736(15)00817-X.[5]

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

A pivotal, double-blind, phase 3 study of patients with advanced, well-differentiated pancreatic NETs demonstrated a median PFS of 11.4 months for sunitinib (37.5 mg daily) vs 5.5 months for placebo (HR, 0.42; 95% CI, 0.26-0.66; *P*<.001; Raymond et al. *N Engl J Med*. 2011;364[6]:501-513). Two years after study closure, survival was statistically similar between the 2 arms (*P*=.115). To determine the long-term benefit of sunitinib, final OS at 5 years after study closure was evaluated in the intent-to-treat population (Abstract 309). In the placebo arm, 69% of patients crossed over to the sunitinib arm. An analysis that did not adjust for this crossover found that the median OS at 5 years was 29.1 months for placebo vs 38.6 months for sunitinib (HR, 0.73; 95% CI, 0.50-1.06; *P*=.094). After adjusting for crossover, median OS for the placebo arm was reduced to 13.2 months (HR, 0.34; 95% CI, 0.14-1.28; *P*=.094). With censoring for crossover, median OS for patients treated with placebo was 16.3 months (HR, 0.40; 95% CI, 0.23-0.71; *P*=.001). The authors concluded that the unadjusted differences in OS are in fact significant, but that the analysis was confounded by the relatively small size of the study population and the effect of patients crossing over from placebo to sunitinib.

strated efficacy in controlling symptoms in patients with carcinoid syndrome whose symptoms persisted after treatment with long-acting somatostatin analog therapy. Telotristat etiprate is an orally delivered drug with a novel mechanism of action. It acts by inhibiting the enzyme tryptophan hydroxylase, which catalyzes the rate-limiting step in serotonin biosynthesis. The double-blind, phase 3 TELESTAR (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) trial evaluated 2 different dose levels of telotristat etiprate vs placebo in patients with carcinoid syndrome.[6] Enrolled patients were required to have well-differentiated, metastatic NETs with documented carcinoid syndrome and 4 or more bowel movements per day. Patients were required to have received somatostatin therapy for at least 3 months before enrollment. The primary endpoint was daily bowel movement frequency averaged over the 12-week treatment period.

The study randomly assigned 135 patients into 3 arms to receive telotristat etiprate (250 mg or 500 mg administered 3 times daily) or placebo. The initial 12-week, double-blind treatment period was followed by an extension period during which patients received open-label telotristat etiprate (500 mg, 3 times daily). At baseline, patients were having approximately 5 to 6 bowel movements per day. The majority of patients were receiving daily octreotide, with the remainder receiving lanreotide depot/autogel. Urinary levels of 5-hydroxyindoleacetic (5-HIAA) acid were above the upper limit of normal in 58% of patients.

During the initial 12-week treatment period, patients receiving telotristat etiprate experienced reductions in mean daily bowel movement frequency of 0.81 in the 250-mg arm and 0.69 in the 500-mg arm (*P*<.001 for both). From baseline compared with week 12, there was a reduction in mean daily bowel movements of 17% in the placebo group vs 29% to 35% in the telotristat etiprate groups. Patients in the telotristat etiprate arms showed a reduction in urinary 5-HIAA, the main metabolite of serotonin. AEs of interest included nausea and depression. Nausea was reported in 11.1% of the placebo arm, 13.3% of the low-dose arm, and 28.9% of the high-dose arm, and depression was reported in 6.7%, 2.2%, and 17.7% of patients, respectively.

Ongoing Clinical Trials

Several clinical trials are currently underway or will begin recruitment. A phase 2 trial will evaluate temozolomide with or without capecitabine in patients with advanced pancreatic NETs.[7] The study will enroll 145 patients for up to 13 courses of treatment. The primary endpoint is PFS, with secondary outcomes of response rate, OS, and toxicity. Another phase 2 trial will test the combination of temozolomide plus capecitabine vs cisplatin plus etoposide in patients with metastatic GEP-NETs.[8] The study will enroll 126 patients. The primary endpoint is PFS, with secondary endpoints of response rate, OS, and toxicity.

The phase 2/3 REMINET (A Study Evaluating Lanreotide as Maintenance Therapy in Patients With Non-Resectable Duodeno-Pancreatic Neuroendocrine Tumors) study is currently recruiting patients with metastatic or locally advanced, nonresectable, duodenopancreatic NETs to evaluate lanreotide maintenance vs placebo.[9] After 3 to 6 months of double-blind first-line treatment, 118 patients will be randomly assigned to receive lanreotide (120 mg every 28 days) or placebo. If the phase 2 results are promising, the trial will be expanded to include 222 patients in a phase 3 trial. The primary endpoint is PFS rate at 6 months, with secondary endpoints of toxicity and PFS rate at 12 months.

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Tumor Response in the CLARINET Study of Lanreotide Depot/Autogel vs Placebo in Patients With Metastatic Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs)

The CLARINET study met its primary endpoint by demonstrating a significant improvement in PFS for lanreotide depot/autogel (not reached vs 18.0 months; HR, 0.47; 95% CI, 030-0.73; *P*<.001) as well as a favorable safety profile.[1] The study included patients with metastatic or locally advanced disease and well or moderately differentiated, nonfunctional NETs with Ki-67 staining in less than 10% of cells. Patients were randomly assigned to receive lanreotide (120 mg) or placebo once every 28 days for 96 weeks. Tumor response was evaluated centrally using Response Evaluation Criteria In Solid Tumors 1.0 criteria.[2] Tumors were measured by the sum of the longest diameter of target lesions, and change in lesion size was calculated by comparing the baseline value with the last available postbaseline value.

Dr Alexandria Phan presented results from a follow-up analysis.[3] Among the 101 patients treated with lanreotide depot/autogel, 65 patients (64%) demonstrated stable disease, and 2 (2%) achieved a partial response. In the placebo arm, 44 patients (43%) achieved stable disease.[3] Lanreotide depot/autogel was associated with a significant increase in the chance of achieving a complete response, a partial response, or stable disease (relative risk, 1.55; 95% CI, 1.19-2.02; *P*=.0011). Lanreotide showed a significant benefit over placebo among patients with midgut NETs (relative risk, 1.52; 95% CI, 1.05-2.18; *P*=.03). Among patients with pancreatic NETs, the difference in relative risk was not significant (relative risk, 1.49; 95% CI, 0.94-2.36; *P*=.09).

Urinary 5-HIAA is a metabolite of serotonin. It serves as an indicator of serotonin overproduction by carcinoid tumors and as a marker of carcinoid syndrome. At baseline, 81 patients had levels of urinary 5-HIAA that were above the upper limit of normal. Urinary 5-HIAA concentration fell by a median 39.0 µmol/day in the lanreotide group, and increased by a median

ABSTRACT SUMMARY Efficacy and Safety of Everolimus in Advanced, Progressive, Nonfunctional Neuroendocrine Tumors (NET) of the Gastrointestinal (GI) Tract and Unknown Primary: A Subgroup Analysis of the Phase III RADIANT-4 Trial

The phase 3 RADIANT-4 trial compared everolimus (10 mg daily) vs placebo in 302 patients with advanced, progressive, well-differentiated, nonfunctional NETs. It demonstrated a 7.1-month increase in PFS with everolimus (*P*<.00001; Yao JC et al. *Lancet*. 2015. doi: 10.1016/S0140-6736(15)00817-X). Although the RADIANT-4 study included tumors of the lung, a post-hoc analysis was conducted in 175 patients with NETs of the gastrointestinal tract and 36 with NETs of unknown primary origin (Abstract 315). In patients with gastrointestinal NETs, median PFS was 13.1 months with everolimus vs 5.4 months with placebo (HR, 0.56; 95% CI, 0.37-0.84). In patients with NETs of unknown primary origin, median PFS was 13.6 months with everolimus vs 7.5 months with placebo (HR, 0.60; 95% CI, 0.24-1.51). In patients with midgut disease, median PFS was 17.28 months with everolimus vs 10.87 months with placebo (HR, 0.71; 9% CI, 0.40-1.26). In patients with nonmidgut NETs, median PFS was 8.11 months with everolimus vs 1.94 months with placebo (HR, 0.27; 95% CI, 0.15-0.51). Patients appeared to benefit from everolimus, regardless of prior treatment. The AE profile was consistent with prior reports.

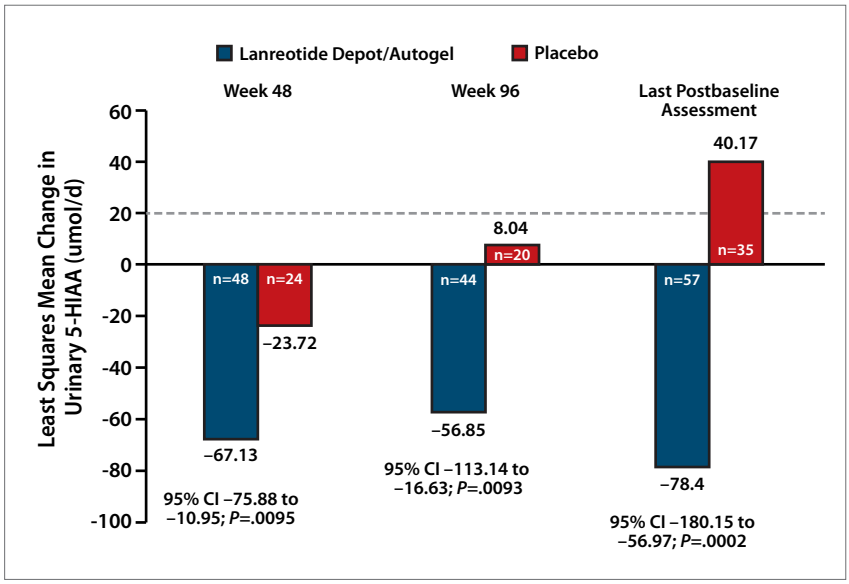

Figure 4. A subanalysis of the CLARINET trial showed reductions in urinary 5-HIAA levels among patients who achieved a complete response, a partial response, or stable disease with lanreotide depot/autogel.

CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors; 5-HIAA, 5-hydroxyindoleacetic acid; LS, least squares. Adapted from Phan AT et al. ASCO GI abstract 434. *J Clin Oncol.* 2016;34(suppl 4S).[3]

ABSTRACT SUMMARY A New Immunohistochemistry Prognostic Score (IPS) for Recurrence and Survival in Pancreatic Neuroendocrine Tumors

A retrospective study aimed to identify prognostic biomarkers for recurrence and survival after surgical resection of pancreatic NETs (Abstract 241). The study included 92 patients, and median follow-up exceeded 24 months. The analysis evaluated the expression of *N-myc* downstream-regulated gene 1 (*NDRG1*), O^6-methylguanine DNA methyltransferase (*MGMT*), and Pleckstrin homology-like domain family A member 3 (*PHLDA3*) by immunohistochemistry and methylation analysis in resected pancreatic NETs. Results were used to develop an immunohistochemistry prognostic score. Length of disease-free survival was significantly shorter in patients with tumors that lacked *MGMT* expression vs tumors that had any grade of expression (HR, 2.31; 95% CI, 1.19-4.48; *P*=.013). A moderate or high score for *NDRG1* expression was also associated with reduced disease-free survival (HR, 6.37; 95% CI, 1.45-27.9; *P*=.005), as was increased expression of *PHLDA3* (HR, 1.94; 95% CI, 1.05-3.6; *P*=.036). Increased *NDRG1* expression level also correlated with increased OS (HR, 4.05; 95% CI, 0.5-32.6; *P*=.013). In multivariate analyses, Ki-67 score and immunohistochemistry prognostic score were independent prognostic factors for disease-free survival (*P*≤.01 for both), whereas age and immunohistochemistry prognostic score were independent prognostic factors for OS (*P*=.0017 and *P*=.03, respectively).

117.6 µmol/day in the placebo group (*P*<.0001; Figure 4). In the patients with midgut tumors and elevated baseline urinary 5-HIAA, mean urinary 5-HIAA concentration also decreased after treatment with lanreotide compared with placebo (*P*=.0001).

Least square mean analysis showed that reductions in urinary 5-HIAA occurred in patients treated with lanreotide who experienced a partial response or stable disease. Among patients who experienced a clinical benefit from lanreotide, least square mean differences between lanreotide and placebo were significant at week 48, week 96, and the last available assessment (*P*<.05). Urinary 5-HIAA levels did not decline in patients who experienced progressive disease, regardless of the treatment arm. A similar correlation between tumor response and urinary 5-HIAA levels was observed for the subset of patients with midgut NETs who experienced a clinical benefit vs progressive disease.

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NETTER-1 Phase III: Progression-Free Survival, Radiographic Response, and Preliminary Overall Survival Results in Patients With Midgut Neuroendocrine Tumors Treated With ^{177}Lu-Dotatate

Treatment options are limited for patients with gastrointestinal NETs who progress on first-line somatostatin analog therapy.[1] During the past decade, PRRT has been used in thousands of patients, mostly in Europe.[2] By attaching a radioactive isotope to a somatostatin analog, radiation is targeted directly to tumor cells that express somatostatin receptors. This strategy is applicable to many patients with NETs, because a large majority of well-differentiated NETs express high levels of somatostatin receptors. For the PRRT used in NETs, the most common somatostatin analog is octreotate, a modified form of octreotide that has an enhanced affinity to somatostatin-receptor subtype 2. ^{177}Lu is a β- and γ-emitting isotope and has a favorable therapeutic index.

Early single-arm studies of ^{177}Lu-octreotate showed a prolonged median PFS in patients with progressive disease at baseline. These findings led to the phase 3 NETTER-1 (A Study Comparing Treatment With ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumors) study.[3] Patients were recruited from 36 sites in 8 European countries and 15 centers in the United States. The study included patients with NETs that had progressed on octreotide LAR (30 mg). Patients had metastatic or locally advanced, well-differentiated midgut NETs, with a Ki-67 index of 20% or less. Somatostatin expression was required. Tumors could be functional or nonfunctional.

Patients were randomly assigned to receive high-dose octreotide LAR (60 mg every 4 weeks) or ^{177}Lu-octreotate (7.4 GBq every 8 weeks) for a total of 4 courses followed by treatment with a somatostatin analog for symptom control. The use of a high-dose octreotide arm was recommended by the US Food and Drug Administration (FDA) based on the drug's possible efficacy and the lack of standard second-line treatment options for this patient population. The primary endpoint was PFS by central radiologic review, with secondary objectives of response rate, OS, safety, and quality of life.

The study enrolled 229 patients with a mean age of 64 ± 9 years. The ileum was the primary site of 74% of tumors. The liver was the most common site of metastasis, observed in 83% of patients. Approximately two-thirds of patients had grade 2 Ki-67 expression, and the majority of tumors demonstrated strong expression of somatostatin receptors. Many of the patients had carcinoid syndrome, as evidenced by very high levels of chromogranin and 5-HIAA.

After a median follow-up of nearly 1.5 years, patients who received high-dose octreotide achieved a median PFS of 8.4 months (95% CI, 5.8-11.0 months), whereas the median PFS was not reached in the ^{177}Lu-octreotate arm (Figure 5). Risk of progression was reduced by 79% after treatment with ^{177}Lu-octreotate vs high-dose octreo-

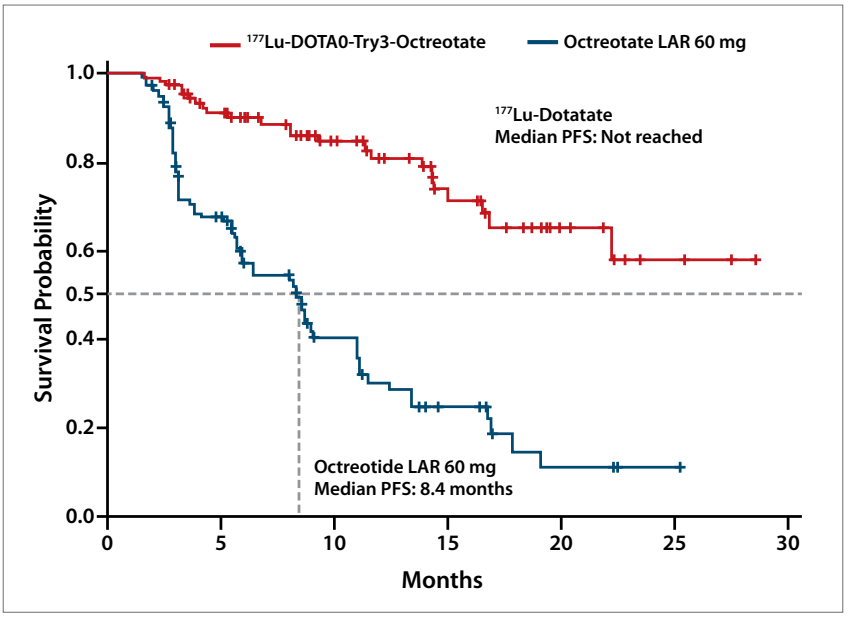

Figure 5. Progression-free survival (PFS) in the NETTER-1 phase 3 trial of patients with midgut neuroendocrine tumors.

LAR, long-acting release; NETTER-1, A Study Comparing Treatment With ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumors. Adapted from Strosberg JR et al. ASCO GI abstract 194. *J Clin Oncol.* 2016;34(suppl 4S).[3]

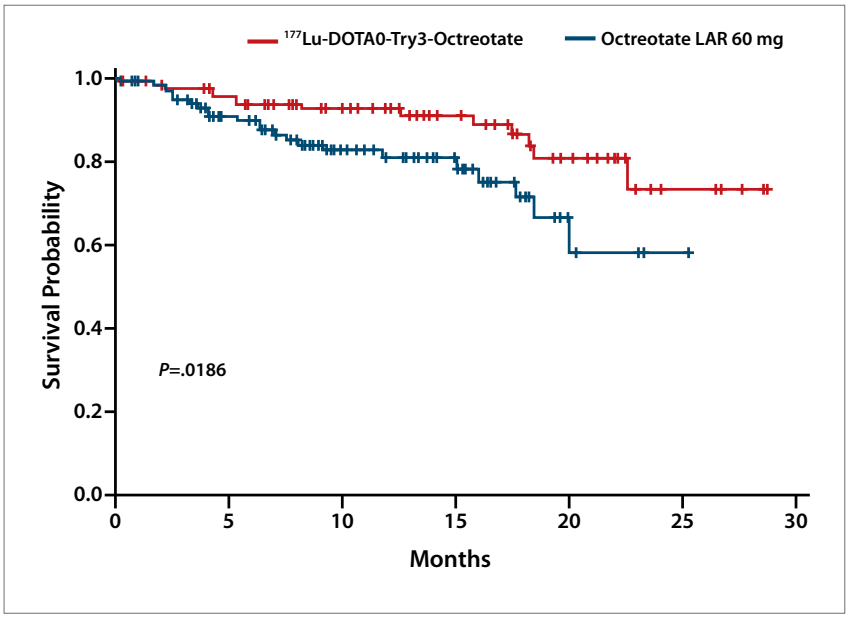

Figure 6. An interim analysis of overall survival in the NETTER-1 phase 3 trial of patients with midgut neuroendocrine tumors.

LAR, long-acting release; NETTER-1, A Study Comparing Treatment With ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumors. Adapted from Strosberg JR et al. ASCO GI abstract 194. *J Clin Oncol.* 2016;34(suppl 4S).[3]

tide (HR, 0.21; 95% CI, 0.13-0.34; *P*<.0001). The projected median PFS for the ^{177}Lu-octreotate treatment arm was greater than 3 years. The trial also showed notable results in obtaining a response rate of 18% for treatment with ^{177}Lu-octreotate vs 3% with high-dose octreotide (*P*=.0006). PRRT therapy also appeared to improve median OS based on preliminary analysis, with deaths occurring in 13% of patients in the ^{177}Lu-octreotate treatment arm vs 22% in the high-dose octreotide arm (*P*=.0186; Figure 6). This difference, however, did not reach the prospectively determined threshold for significance, which was set at *P*=.001.

Among the patients in the ^{177}Lu-octreotate arm, 77% of patients completed all 4 courses of treatment. Toxicities requiring dose modification were observed in 5% of patients. In the population evaluated for safety, treatment-related AEs of any grade occurred in 86% of patients in the ^{177}Lu-octreotate arm and 31% in the octreotide LAR arm. Rates of serious treatment-related AEs were 26% vs 24%, respectively. Grade 3/4 AEs were elevated in the ^{177}Lu-octreotate arm, with the most common ones being lymphopenia (9%), vomiting (7%), and nausea (4%). One patient experienced an opportunistic infection; however, the patient was receiving immunosuppressive treatment for arthritis, and the infection was considered unrelated to therapy. Most nausea and vomiting events occurred in the setting of amino acid infusions that were given as nephroprotective agents during the ^{177}Lu-octreotate infusions (which were given every 8 weeks and lasted approximately 4 to 6 hours). Most of these events quickly subsided after the infusion ended. The gastrointestinal events were also impacted by the use of commercial formulations including 18 or 19 amino acids, which was mandated by the FDA. These events could be reduced by using formulations that contain fewer amino acids. Cytopenias were generally minor. Counts of lymphocytes, neutrophils, leukocytes, and platelets initially showed a mean reduction from baseline but returned to baseline after cessation of treatment. Although these initial NETTER-1 results have demonstrated that cytopenias are transient, a few studies have suggested that long-term myelodysplastic syndrome and acute leukemia can occasionally occur in patients treated with ^{177}Lu-octreotate.[4]

Hepatotoxicity is of concern in this patient population, given the frequency of liver metastases in patients with gastrointestinal NETs and possible deleterious effects from previous liver-directed therapy or radioembolization. However, patients in the ^{177}Lu-octreotate arm experienced a low rate of grade 3/4 hepatic abnormalities, and many of these AEs were considered unrelated to treatment. Increased levels of alanine transaminase or aspartate transaminase were observed in 4% of patients, and bilirubin increased in 2% of patients. In contrast, no patients treated with high-dose octreotide exhibited any of these laboratory abnormalities. At baseline, γ-glutamyl transferase levels were elevated in 11% of patients in the ^{177}Lu-octreotate arm and 9% of patients in the high-dose octreotide arm, and these rates increased to 18% and 13%, respectively, with study treatment. Nephrotoxicity is also a concern with PRRT. However, creatinine clearance was generally consistent throughout the study, and no grade 3/4 nephrotoxicity events were reported.

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Peptide Receptor Radiation Therapy for Neuroendocrine Tumors

Dr Dik Kwekkeboom presented a review of recent trials of PRRT in patients with NETs.[1] PRRT is predicated on directly delivering radioactivity to tumor cells by exploiting selective binding between extracellular receptors and analogs of their ligands.[2] The therapeutic agent consists of a radionuclide, such as ^{90}Y or ^{177}Lu, attached to a peptide that has high binding specificity for the target. For specific targeting of NETs, the radionuclide is linked to a somatostatin analog. ^{177}Lu-octreotate and ^{90}Y-octreotide are the most commonly used compounds today. The resulting radiolabeled somatostatin analog is injected intravenously. It binds with high specificity to the somatostatin receptors expressed on the tumor cells, after which it is internalized and metabolized. The radioactive moiety is trafficked to the lysosome, where it remains for weeks, continuously damaging the tumor cells.

For ^{177}Lu-octreotate therapy, most treatment centers adhere to common inclusion criteria. Patients should have inoperable disease proven by pathology. Uptake of radiolabeled octreotide by the tumor must be detectable by octreotide scanning. Patients may not have received prior therapy with other radiolabeled somatostatin analogs. Patients must have sufficient bone marrow reserve, as indicated by hemoglobin levels of at least 6 mmol/L, white blood cell counts of at least 2×10^9/L, and platelet counts of at least 80×10^9/L. Patients should have functional kidneys that can tolerate the exposure to radiation, as indicated by a serum creatinine level of no more than 150 µmol/L. A Karnofsky performance status of at least 50 is necessary.

The practice protocol is as follows. The patient receives an infusion of amino acids beginning approximately 30 minutes before infusion of ^{177}Lu-octreotate. In Europe, a commonly used amino acid formulation in this setting includes 2.5% lysine and 2.5% arginine. The amino acid infusion lasts 4 hours and is given in conjunction with granisetron (3 mg), a serotonin 5-HT$_3$ receptor antagonist and antiemetic. The ^{177}Lu-octreotate infusion is administered throughout 30 minutes. One night of hospitalization is required.

Acute side effects include nausea and vomiting, which occur in approximately 25% and 10% of patients, respectively. Vague abdominal pain occurs in approximately 10% of patients and is more common among those with hepatic enlargement. Temporary, limited hair loss may occur in approximately two-thirds of patients. Grade 3/4 toxicities include reductions in hemoglobin (0.4%), white blood cells (1.5%), and platelets (2.6%). In aggregate, treatment-related grade 3/4 toxicities of any type occur in approximately 3.6% of drug administrations. In a retrospective analysis of 279 patients with NETs treated between 2000 and 2010 at a single center in Rotterdam, serious AEs included 2 cases of renal insufficiency, 1 case each of chronic myelogenous leukemia and acute myeloid leukemia, 1 case of pancytopenia lasting more than 6 months, and 4 cases of myelodysplastic syndrome. These cases yielded an overall long-term toxicity rate of approximately 3%.

In a retrospective analysis of 263 Dutch GEP-NET patients treated between 2000 and 2007, 3 CRs occurred, all in patients with pancreatic primary disease. Because most of the treated patients had widely metastatic disease at baseline, the low rate of CRs is not surprising. PRs were observed in 93 patients (35%), minor responses in 53 (20%), and stable disease in 68 (26%). In most patients, the maximum reduction in tumor size is reached at approximately 6 months after the final course of therapy. Approximately 15% of patients continue to experience reductions in tumor size afterward. In the 263 Dutch patients treated from 2000 to 2007, no difference in OS was observed for patients who achieved stable disease vs those who achieved a partial response or complete response; however, OS was reduced in patients whose disease progressed during treatment (Figure 7). Improvement in overall quality of life was observed after treatment with ^{177}Lu-octreotate in 36% of patients with available data (Figure 8). In studies by other groups, renal insufficiency has been observed in 1% to 4% of patients treated with ^{90}Y-DOTATOC and is an important long-term AE, but rates of renal insufficiency are considerably lower with ^{177}Lu-octreotate. Cases of myelodysplastic syndrome have also been reported in patients treated with PRRT.[3]

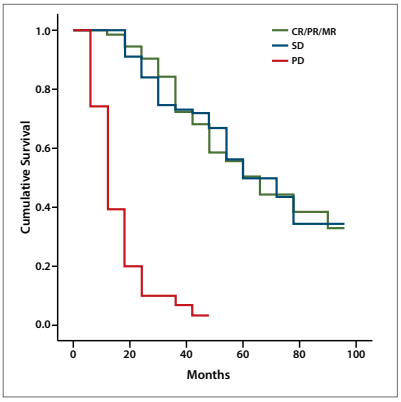

Figure 7. Overall survival among patients with GEP-NETs treated with ^{177}Lu-octreotate therapy.

CR, complete response; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease. Adapted from Kwekkeboom DJ. Peptide receptor radiation therapy for neuroendocrine tumors. Paper presented at: 2016 ASCO Gastrointestinal Cancers Symposium; January 21-23, 2016; San Francisco, CA.[1]

The NETTER-1 study compared ^{177}Lu-octreotate vs high-dose octreotide

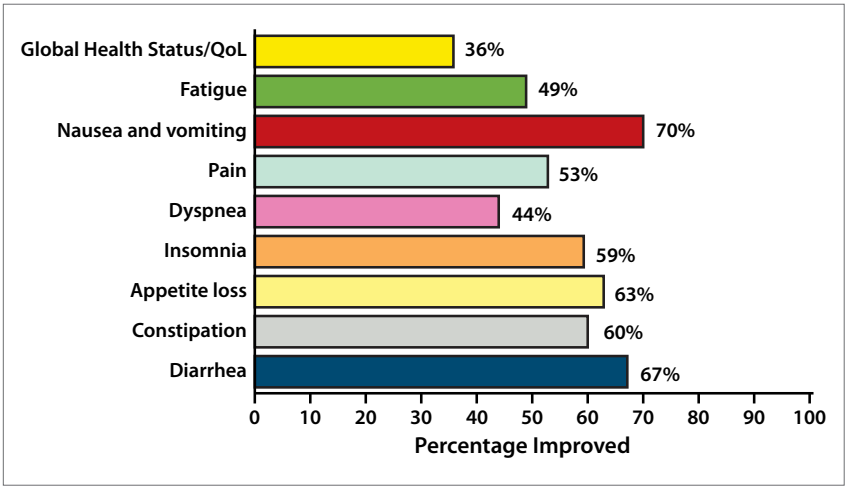

Figure 8. Improvement in quality of life and symptoms among patients with GEP-NETs treated with ^{177}Lu-octreotate therapy.

CR, complete response; MR, minor response; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease. Adapted from Kwekkeboom DJ. Peptide receptor radiation therapy for neuroendocrine tumors. Paper presented at: 2016 ASCO Gastrointestinal Cancers Symposium; January 21-23, 2016; San Francisco, CA.[1]

LAR in patients with midgut NETs whose disease progressed during treatment with octreotide LAR.[4] The initial analysis demonstrated a PFS of 8 months in patients who received high-dose octreotide LAR vs not reached in the ^{177}Lu-octreotate arm. Based on the HR of 0.2, the final PFS for the ^{177}Lu-octreotate arm is projected to extend to approximately 40 months, which compares favorably to PFS rates reported with biologics. The available safety data confirmed the results obtained in Rotterdam, demonstrating a favorable safety profile for PRRT therapy with ^{177}Lu-octreotate.

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Treatment Patterns and Clinical Outcomes of Patients With Metastatic Gastroenteropancreatic Neuroendocrine Tumors (mGEP-NETs)

Although the reported incidence of GEP-NETs has increased throughout the past decade, these tumors are rare, representing approximately 1% of all cancers.[1] Limited data have been published on the real-world clinical management of these tumors. A retrospective study was conducted to understand the treatment patterns and clinical outcomes of patients with metastatic GEP-NETs treated in the community oncology setting.[2] Information was collected from the database of the US Oncology Network, a large network of integrated, community-based oncology practices that provide care to approximately 12% of cancer patients in the United States. Included patients were adults diagnosed from January 1, 2008 to December 31, 2012, with follow-up through October 31, 2014. Patients had at least 2 recorded visits to the treatment center and an initial diagnosis of metastatic GEP-NETs or presented with metastatic disease after the initial diagnosis. The study excluded patients who enrolled in a clinical trial and those diagnosed with other primary cancers or poorly differentiated tumors.

The study enrolled 229 patients with a median age of 64.0 years. Reporting of tumor characteristics and tumor-related laboratory values was inconsistent. Primary tumor sites included small bowel (47.6%), pancreas (31.4%), and other (21.0%). Tumor histology was unknown or missing for approximately 9.5% of patients. Information on tumor differentiation was unknown or missing for approximately 40% of patients. For patients with available data, tumors were either well- or moderately differentiated. Levels of serum chromogranin A and urinary 5-HIAA were reported for 34.9% and 32.8% of patients, respectively. Among the 80 patients with available data on serum chromogranin A levels, this value decreased after treatment in 75%, remained stable in 4%, and increased after treatment in 21%. Data regarding urinary 5-HIAA levels were available for 75 patients, with 60%

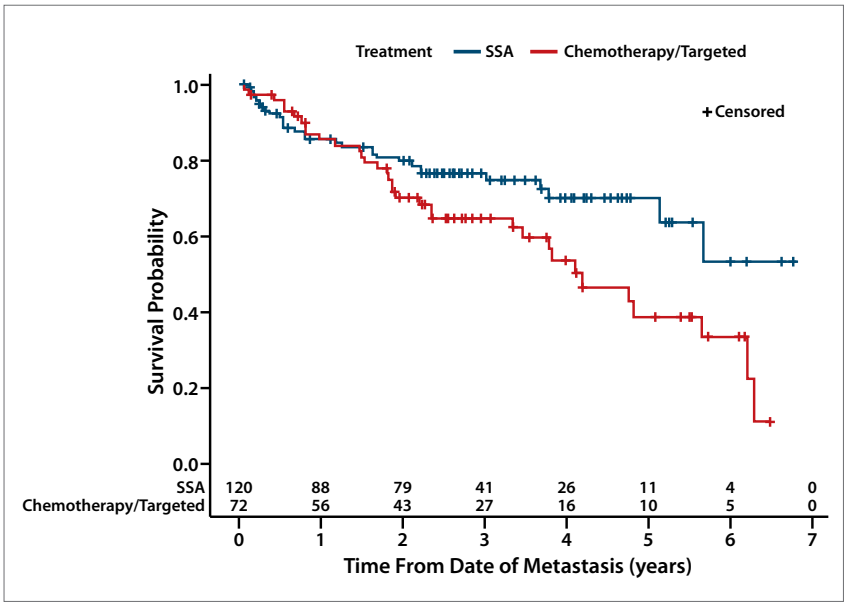

Figure 9. Overall survival according to treatment in a retrospective analysis of patients with metastatic gastroenteropancreatic neuroendocrine tumors.

SSA, somatostatin analog. Adapted from Jiao X et al. *J Clin Oncol*. 2016;34(suppl 4S).[2]

ABSTRACT SUMMARY Next-Generation Sequencing (NGS) in Advanced Well Differentiated Pancreatic Neuroendocrine Tumors (WD pNETs): A Study Using MSK-IMPACT

The Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets (MSK-IMPACT) test provides full exon sequencing of 410 cancer-related genes, using next-generation sequencing to detect base substitutions, small insertions and deletions, copy number, and some gene rearrangements. A prospective study was conducted in 39 patients to identify mutations in tumor DNA from patients with well-differentiated pancreatic NETs (Abstract 246). Actionable alterations were identified in 33.3% of patients and included *BRAF V600E* (5.1%) plus mutations in *TSC1* (2.6%), *TSC2* (12.8%), *ARID1A* (12.8%), *PTEN* (10.3%), *CDKN1B* (5.1%), *CDKN2A* (5.1%), *CDKN2B* (5.1%), and *CDKN2C* (2.6%). Other recurrently altered genes included *MEN1* (59.0%), *DAXX* (33.3%), and *ATRX* (25.6%). Seven patients with metastatic liver disease had alterations in the histone methyltransferase *SETD2*. Six of these tumors were intermediate grade, and 1 was high grade. All 7 patients received treatment with temozolomide plus capecitabine, which induced tumor shrinkage in 6 patients and stable disease in 1 patient. The clinical significance of *SETD2* in patients with pancreatic NETs is unknown, and further evaluation using tissue microarrays is ongoing.

showing a level greater than or equal to 8 mg/day; however, the timing of these measurements (before vs after treatment) was not reported. Based on urinary 5-HIAA levels or physicians' notes, 57% of NETs were functional.

Thirty-seven patients (16.2%) were under observation only. For the 192 patients who received systemic treatment, the median time to first systemic treatment after diagnosis was 2.7 weeks, with a wide range of 0.1 week to 256 weeks. Most patients (75%) started therapy by 9.4 weeks after diagnosis. Approximately half of patients (52.4%) received somatostatin analogs alone, with 98.0% receiving octreotide LAR for a median length of treatment of 374 days. The dose of somatostatin therapy was reduced in 3.1% of patients and increased in 28.5%. Dosing frequency remained unchanged in 31.9% of patients, was increased in 38.7%, and was decreased in 29.4%. Most treatment discontinuations were attributed to loss during follow-up (12.8%), followed by death (10.8%) and disease progression (4.1%). The most common AEs were diarrhea (18.2%), abdominal pain (16.9%), and fatigue (13.5%).

Median OS for the overall population was 68.0 months (95% CI, 57.1 months–not reached). Median OS was 68.0 months among patients with small-bowel NETs (95% CI, 57.7 months–not reached), 49.1 months among patients with pancreatic NETs (95% CI, 40.0-75.5 months), and not reached among patients with other NETs (95% CI, 26.5 months–not reached). Based on unadjusted analysis, patients treated with somatostatin analogs tended to have longer survival than patients treated with chemotherapy or targeted therapies (P=.027; Figure 9).

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Highlights in GEP-NETs From the 2016 American Society of Clinical Oncology Gastrointestinal Cancers Symposium: Commentary

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The 2016 American Society of Clinical Oncology Gastrointestinal Cancers Symposium featured several abstracts on gastroenteropancreatic neuroendocrine tumors. New data were presented on peptide receptor radionuclide therapy (PRRT). Follow-up analyses were provided for studies of lanreotide depot/autogel, sunitinib, and everolimus. Other studies provided real-world data.

Dr Jonathan Strosberg presented results from the phase 3 NETTER-1 trial (A Study Comparing Treatment With ^{177}Lu-DOTA^{0}-Tyr^{3}-Octreotate to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumors), which evaluated PRRT. This therapy is frequently used in Europe.[1] PRRT is not approved by the US Food and Drug Administration (FDA), and access is limited in the United States.

In the NETTER-1 trial, median progression-free survival (PFS) was 8.4 months in the high-dose octreotide arm and not reached in the ^{177}Lu-octreotate arm.[1] The investigators projected that the median PFS for the ^{177}Lu-octreotate treatment arm was greater than 3 years. A preliminary analysis suggested that PRRT improved median overall survival, with deaths occurring in 13% of patients in the ^{177}Lu-octreotate treatment arm vs 22% in the high-dose octreotide arm. (This difference was not significant according to the study's threshold.) NETTER-1 is the first prospective study to suggest that PRRT can improve overall survival. It is also the first study to show an objective response rate exceeding 10% for midgut NETs.

These results suggest that PRRT will remain a component of management for patients with midgut carcinoid tumors in Europe and will likely gain FDA approval in the United States. However, more than just FDA approval will be required to make this therapy feasible in the United States. Facilities will be needed to produce and administer PRRT, and also to provide follow-up care and monitoring to patients receiving it. The use of PRRT will require a new discipline in the management of patients with NETs: nuclear medicine.

The NETTER-1 study is the first to suggest that tumor disease regression is associated with improved survival. There has been some debate regarding whether treatment with therapies such as sunitinib, everolimus, and lanreotide improves overall survival. Clinical trials of these agents incorporate a crossover design, which may skew the study results. An important aspect of the NETTER-1 study is that it did not permit patients from one arm to cross over to the other.

Follow-up data were provided for 3 trials in NETs. I presented an analysis of tumor response in the CLARINET (Controlled Study of Lanreotide Autogel in Non-Functioning Entero-Pancreatic Endocrine Tumours) study, which investigated lanreotide depot/autogel

ABSTRACT SUMMARY Does Receptor Status Impact Survival of Patients With Mid-Gut Neuroendocrine Tumors?

A study was undertaken to determine whether somatostatin receptor status, as determined by ^{111}In-pentetreotide scan (octreoscan) and ^{123}I-metaiodobenzylguanidine (MIBG) imaging, is associated with survival in patients with small-bowel NETs (Abstract 227). The study included 110 patients from a single database with histologically confirmed ileal, jejunal, or small-intestinal NETs, who had octreoscan and MIBG imaging results. Patients were diagnosed between July 1994 and September 2013. Patients with a negative octreoscan as well as a negative MIBG scan demonstrated the longest survival, with 5- and 10-year survival rates of 95% for both timeframes. Unexpectedly, survival rates were lowest among patients who had a positive octreoscan and a positive MIBG scan, with 5- and 10-year survival rates of 89% and 62%, respectively.

in patients with metastatic GEP-NETs.[2,3] In the treatment arm, 64% of patients demonstrated stable disease, compared with 43% in the placebo arm. Treatment with lanreotide depot/autogel increased a patient's chance of achieving a complete response, a partial response, or stable disease. A post-hoc analysis of the RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) trial excluded patients with tumors of the lung to focus on patients with advanced, progressive NETs of the GI tract or of unknown origin.[4,5] The improvement with everolimus seen in the overall analysis was maintained among these patients. Dr Eric Raymond presented results from a 5-year follow-up analysis of a phase 3 trial of sunitinib in patients with advanced, well-differentiated pancreatic NETs.[6,7] In the placebo arm of this trial, 69% of patients crossed over to the sunitinib arm. In a 5-year analysis that did not adjust for this crossover, the median overall survival was not significantly improved for sunitinib vs placebo. The authors attributed this lack of significance to the crossover and the small population size.

The original phase 3 trials showed objective tumor response rates of approximately 10% to 30%,[2,6,8] which was enough to improve PFS and will likely also translate into improved overall survival. The improved overall survival is an extrapolation because in these studies, more than 50% of patients crossed over from the placebo arm to the treatment arm. It is not known whether a minimal response rate will translate into improved overall survival in a randomized, controlled study without crossover. However, the robust response rates in the NETTER-1 trial suggest that disease control may be equivalent to improved overall survival. Another difference is that these 3 studies used a placebo arm, whereas the NETTER-1 trial compared PRRT vs an active treatment, octreotide LAR. These studies were in different patient populations as well. The conclusion is that for midgut NETs and pancreatic NETs, treatment options should not be restricted to cytostatic agents. Cytoreduction is also possible.

Dr Xiaolong Jiao presented a retrospective analysis of treatment patterns and clinical outcomes of patients with metastatic GEP-NETs in real-world settings.[9] Median overall survival was 68.0 months among patients with small-bowel NETs, 49.1 months among patients with pancreatic NETs, and was not reached among patients with other NETs. An unadjusted analysis showed that patients treated with somatostatin analogs had a longer survival than patients treated with chemotherapy or targeted therapies.

This study examined several biomarkers known to be useful in monitoring disease in patients with GEP-NETs and provided proof-of-concept data suggesting that biomarkers can be used to predict response and prognosis. 5-HIAA levels greater than or equal to 8 mg/day were seen in 60% of patients. A concern, however, with the measurement of 5-HIAA is that the values can vary. Eating seeds, for example, is known to raise levels. In addition, the most frequently used 5-HIAA tests require patients to collect urine for 24 hours, which can be difficult. Therefore, I question whether the use of 5-HIAA analysis can be translatable into the community practice. There is now a serum 5-HIAA test that may prove more convenient than the urine-based test.

Disclosure

Dr Phan is a member of the speakers bureaus of Lilly, Genentech, Celgene, Ipsen, and Novartis. She has received research grants from Novartis, Lexicon, and Ipsen. She is a consultant for Novartis and Ipsen.

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