Highlights in GEP-NETs From the 2015 American Society of Clinical Oncology Annual Meeting

A Review of Selected Presentations From the 2015 American Society of Clinical Oncology Meeting • May 29-June 2, 2015 • Chicago, Illinois

Special Reporting on:

• Lanreotide Depot/Autogel in Neuroendocrine Tumors: Subgroup Analyses From the CLARINET Study

• Randomized Phase II Study of Everolimus (E) Versus Everolimus Plus Bevacizumab (E+B) in Patients (Pts) With Locally Advanced or Metastatic Pancreatic Neuroendocrine Tumors

• Lanreotide Depot/Autogel (LAN) Vs. Placebo (PBO) for Carcinoid Syndrome (CS) in Patients With Neuroendocrine Tumors (NETs): Subgroup Analysis of the ELECT Study

• Targeted Radionuclide Therapy for NETs

• SWOG S0518: Phase III Prospective Randomized Comparison of Depot Octreotide Plus Interferon Alpha-2b Versus Depot Octreotide Plus Bevacizumab (NSC #704865) in Advanced, Poor Prognosis Carcinoid Patients (NCT00569127)

PLUS Meeting Abstract Summaries

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Houston, Texas

ON THE WEB: hematologyandoncology.net

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**Progresion Hold Back**

**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 gastrointestinal and pancreatic neuroendocrine tumors (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.

**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 (Continued)**

**Contraindications (Continued):**
- 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.
WARNINGS AND PRECAUTIONS (Continued):

- **Cardiac Abnormalities:** Somatuline Depot may decrease heart rate. In 81 patients with baseline heart rates of \( \geq 60 \text{ beats per minute (bpm)} \) treated with Somatuline Depot in the GEP-NETs clinical trial, the incidence of heart rate \(<60 \text{ bpm} \) was 23% (19/81) with Somatuline Depot vs 16% (15/94) with placebo; 10 patients (12%) had documented heart rates \(<60 \text{ bpm} \) on more than one visit. The incidence of documented episodes of heart rate \(<50 \text{ bpm} \) 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.

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 hyperglycemia or hypoglycemia. 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 120 mg 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), 35% were men and 65% were Caucasian. Eighty-one percent of patients (82/103) in the SOMATULINE Depot arm and eighty-two percent of patients (83/101) in the SOMATULINE Depot 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)

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>SOMATULINE Depot 120 mg (N=101)</th>
<th>Placebo (N=103)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Adverse Reactions</td>
<td>88</td>
<td>65</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>34*</td>
<td>6*</td>
</tr>
<tr>
<td>Musculoskeletal pain‡</td>
<td>19*</td>
<td>2*</td>
</tr>
<tr>
<td>Vomiting</td>
<td>19*</td>
<td>2*</td>
</tr>
<tr>
<td>Headache</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>14*</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension§</td>
<td>14*</td>
<td>1*</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>14*</td>
<td>1*</td>
</tr>
<tr>
<td>Dizziness</td>
<td>9</td>
<td>2</td>
</tr>
<tr>
<td>Depression</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

† Includes preferred terms of abdominal pain, abdominal pain upper/lower, abdominal discomfort
‡ Includes preferred terms of myalgia, musculoskeletal discomfort, musculoskeletal pain, back pain
§ Includes preferred terms of infusion site extravasation, injection site discomfort, injection site granuloma, injection site hematoma, injection site hemorrhage, injection site induration, injection site mass, injection site nodule, injection site pain, injection site pruritus, injection site rash, injection site reaction, injection site swelling.

6.2 Immunogenicity
In Study 3, development of anti-lanreotide antibodies was assessed using a radioimmuno precipitation 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 testing method. 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 (cholecytitis), 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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Lanreotide Depot/Autogel in Neuroendocrine Tumors: Subgroup Analyses From the CLARINET Study

The randomized, double-blind CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) trial evaluated the efficacy and safety of the long-acting somatostatin analog lanreotide depot/autogel in patients with metastatic enteropancreatic tumors.1 The trial enrolled 204 patients with advanced, well-differentiated or moderately differentiated, nonfunctioning, somatostatin receptor–positive grade 1 or 2 neuroendocrine tumors (NETs). Patients were randomly assigned to receive lanreotide depot/autogel 120 mg or placebo administered every 28 days for 96 weeks. The trial showed the superior antitumor activity of lanreotide depot/autogel over placebo, with a median progression-free survival (PFS) of 21 months with placebo (hazard ratio [HR], 0.35; 95% CI, 0.30-0.73; P=.001).1 The estimated 2-year PFS rates were 65% and 33%, respectively. The initial publication of the CLARINET trial reported that the effect of lanreotide depot/autogel in predefined subgroups reflected that seen in the overall population, with the exception of small subgroups that showed wide confidence intervals.1

At the 2015 American Society of Clinical Oncology (ASCO) annual meeting, investigators provided additional results of post-hoc subgroup analyses from the CLARINET trial undertaken to further assess the efficacy of lanreotide depot/autogel in various patient populations. The original study was not powered to detect differences among these groups.

Arvind Dasari, MD, and colleagues presented a subgroup analysis of 73 enrolled patients with midgut NETs, including 33 patients who participated in the open-label extension study.2,3 The median PFS was not reached in the lanreotide depot/autogel arm vs 21 months in the placebo arm (HR, 0.35; 95% CI, 0.16-0.80; P=.0091; Figure 1). Within the group of patients with midgut NETs, the response to lanreotide depot/autogel was similar regardless of liver burden or tumor grade.

Safety outcomes confirmed those reported in the overall study. The most common treatment-emergent adverse event (AE) in either arm was diarrhea, reported in 33% of patients receiving lanreotide depot/autogel and 40% of patients receiving placebo. The incidence of serious AEs was low (15% with lanreotide depot/autogel and 18% with placebo), as were withdrawals owing to AEs (0% and 2.5%, respectively). Investigators noted that the highest available dose of lanreotide depot/autogel (120 mg every 4 weeks) appeared to be well tolerated in patients with midgut NETs, and no new safety events were reported. They concluded that the data highlight the positive risk-benefit profile of lanreotide depot/autogel in patients with midgut NETs and support the use of this agent in the frontline setting.2

Dr Dasari also reported on the effects of lanreotide depot/autogel according to patient age.4 Investigators compared outcomes among patients ages 65 years or younger (median age, 57 years; range, 30-65 years) vs those older than 65 years (median age, 71 years; range, 66-92 years). Sites of tumor origin, hepatic tumor load, and disease status did not differ. There was a similar treatment effect of lanreotide depot/autogel regardless of age. The median PFS was not reached with lanreotide depot/autogel among both age groups. Median PFS with placebo was 18.1 months in the younger group (HR,
The median PFS was not reached in any BMI category among patients receiving lanreotide depot/autogel. In the placebo arm, median PFS was 13.0 months for those with the lowest BMIs (18.5 to <25.0 kg/m²), 24.4 months for those at midlevel (25.0 to <30.0 kg/m²), and 17.6 months for those with the highest BMI.

Edward M. Wolin, MD, and colleagues published an abstract evaluating the effect of lanreotide depot/autogel in patients with intestinal and pancreatic NETs.

Alexandria T. Phan, MD, and colleagues provided additional information on the activity of lanreotide depot/autogel in patients with pancreatic NETs in the CLARINET trial. Overall, the CLARINET trial enrolled 91 patients with pancreatic NETs. Their mean age was 64 years; 37% had a hepatic tumor load of 25% or less, 95% had stable disease, 77% had received no prior treatment, and 38% had undergone surgical treatment. The PFS was not reached in the lanreotide depot/autogel arm vs 12.1 months in the placebo arm (HR, 0.58; 95% CI, 0.32-1.04). Treatment-related AEs were reported in 55% of patients in the lanreotide depot/autogel group and 24% of those in the placebo group. The most common AE was diarrhea, occurring in 43% and 37% of patients, respectively. Investigators concluded that lanreotide depot/autogel appeared to have antitumor effects and showed good tolerability, and that this analysis supports the use of lanreotide depot/autogel as a first-line treatment for pancreatic NETs.

Dr Phan also presented a detailed safety analysis of the CLARINET trial. The overall incidence of AEs was similar with lanreotide depot/autogel and placebo (88% vs 90%). The most common AEs were gastrointestinal, occurring in 67% and 63% of patients, respectively. The most common individual AE was diarrhea, occurring in 35% of patients in each arm. The incidence of gastrointestinal AEs, including diarrhea, was not significantly different with lanreotide depot/autogel vs placebo. Researchers found no significant differences in the incidence of any AE reported in at least 5% of patients in either arm. They concluded that the findings highlight the favorable risk-benefit profile of lanreotide depot/autogel in patients with intestinal and pancreatic NETs.

Edward M. Wolin, MD, and colleagues published an abstract evaluating the effect of lanreotide depot/autogel according to body mass index (BMI). The median PFS was not reached in any BMI category among patients receiving lanreotide depot/autogel in the placebo arm, median PFS was 13.0 months for those with the lowest BMIs (18.5 to <25.0 kg/m²), 24.4 months for those at midlevel (25.0 to <30.0 kg/m²), and 17.6 months for those with the highest BMI reported in at least 5% of patients in either arm. They concluded that the findings highlight the favorable risk-benefit profile of lanreotide depot/autogel in patients with intestinal and pancreatic NETs.

Table 1. Prognostic Factors for PFS in the CLARINET Trial

<table>
<thead>
<tr>
<th>Term (reference)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lanreotide depot/autogel (placebo)</td>
<td>0.40 (0.25-0.63)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Progressive disease (no progressive disease)</td>
<td>4.57 (1.67-12.54)</td>
<td>.0032</td>
</tr>
<tr>
<td>Prior therapy (no prior therapy)</td>
<td>1.29 (0.72-2.31)</td>
<td>.3914</td>
</tr>
<tr>
<td>Hepatic tumor load % (0)</td>
<td></td>
<td>.0005</td>
</tr>
<tr>
<td>&gt;0 to ≤10</td>
<td>0.81 (0.42-1.59)</td>
<td></td>
</tr>
<tr>
<td>&gt;10 to ≤25</td>
<td>1.22 (0.59-2.52)</td>
<td></td>
</tr>
<tr>
<td>&gt;25 to ≤50</td>
<td>2.82 (1.41-5.63)</td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>2.47 (1.21-5.03)</td>
<td></td>
</tr>
<tr>
<td>Primary tumor type (pancreas)</td>
<td></td>
<td>.0289</td>
</tr>
<tr>
<td>Midgut</td>
<td>0.80 (0.33-1.94)</td>
<td></td>
</tr>
<tr>
<td>Hind gut</td>
<td>0.53 (0.32-0.88)</td>
<td></td>
</tr>
<tr>
<td>Other/unknown</td>
<td>0.39 (0.17-0.86)</td>
<td></td>
</tr>
<tr>
<td>BMI &gt;median (≤median)</td>
<td>0.64 (0.41-1.00)</td>
<td>.0483</td>
</tr>
</tbody>
</table>

BMI, body mass index; CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors; PFS, progression-free survival.

Adapted from Wolin EM et al. Prognostic factors for progression-free survival (PFS) in CLARINET study of lanreotide depot/autogel (LAN) vs placebo (PBO) in neuroendocrine tumors (NETs) [ASCO abstract e15180]. J Clin Oncol. 2015;33(suppl).

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

Lanreotide depot/autogel, administered as a deep subcutaneous injection, is FDA-approved for the treatment of GEP-NETs. In conjunction with the 2015 ASCO meeting, Amandine Manon, PharmD, and colleagues published results of a phase 1 study comparing the pharmacokinetics of lanreotide depot/autogel administered as deep subcutaneous or intramuscular injection in healthy volunteers (abstract e15186). A total of 42 volunteers ages 18 to 45 years (mean age, 25 years) received 1 mg of lanreotide depot/autogel as an intravenous bolus followed by a dose of 60 mg 0.246 mg/mg deep subcutaneous or intramuscular injection. In the 2 to 16 weeks after the injections, multiple pharmacokinetic parameters, including Cmax, t1/2, Tmax, and residence time in the serum, were comparable between the 2 administration routes. However, the area under the curve (AUC) assessments AUClast and AUCinf were slightly lower with the subcutaneous injections, suggesting a slightly better long-term release.
BMIs (≥30.0 kg/m²). Safety outcomes were similar across BMI categories and treatment arms. The investigators concluded that the antitumor effects and safety profile of lanreotide depot/autogel were maintained regardless of patient BMI.

Dr Wolin also evaluated prognostic factors in CLARINET. In an adjusted model, lanreotide depot/autogel was associated with a 60% reduction in the risk of progression or death vs placebo (HR, 0.40; 95% CI, 0.25-0.63; \( P < .0001 \); Table 1). Factors that increased the risk of progression or death included the presence of progressive disease at baseline (HR, 4.57; 95% CI, 1.67-12.54; \( P = .0032 \)), a hepatic tumor load higher than 25% (HR, 2.5-2.8 compared with no hepatic tumor load; \( P = .0005 \)), and a primary tumor in the pancreas (HR, 0.29). A BMI below the median was associated with a decreased risk of progression or death (HR, 0.64; 95% CI, 0.41-1.00; \( P = .048 \)). Prognosis was not associated with sex, age, race, geographic region, time since diagnosis, Ki-67 level, tumor grade, chromogranin A level, prior chemotherapy, or prior surgery.

Overall, these analyses showed the benefit of lanreotide depot/autogel in multiple patient populations. These benefits were seen regardless of tumor type, age, and BMI. The safety profile seen in the overall study was maintained in the subanalyses.

References

7. Wolin EM, Caplin ME, Pavel ME, et al. Lanreotide depot/autogel (LAN) in intestinal and pancreatic neuroendocrine tumors (NETs) according to body mass index (BMI); subgroup analyses from the CLARINET study [ASCO abstract 4107]. J Clin Oncol. 2015;33(suppl).

Randomized Phase II Study of Everolimus (E) Versus Everolimus Plus Bevacizumab (E+B) in Patients (Pts) With Locally Advanced or Metastatic Pancreatic Neuroendocrine Tumors

Today, patients with advanced pancreatic NETs have a variety of treatment options. Targeted agents, including lanreotide depot/autogel, everolimus, and sunitinib, are associated with significant improvements in PFS but have low response rates, generally less than 10%. In contrast, cytotoxic chemotherapy is associated with higher response rates (30%-40%), but the effects on PFS are not well demonstrated.

It has been hypothesized that combining active targeted agents that inhibit different steps in the vascular endothelial growth factor (VEGF) and PI3K/AKT/mammalian target of rapamycin (mTOR) pathways may enhance treatment efficacy. In a multicenter phase 2 study, a combination of the mTOR inhibitor temsirolimus and the VEGF inhibitor bevacizumab showed activity in patients with advanced pancreatic NETs, yielding a partial response rate of 41%. In another study, James C. Yao, MD, and colleagues showed the feasibility of combining everolimus and bevacizumab, a regimen that yielded a partial response rate of 21% in patients with pancreatic or other NETs.

The randomized phase 2 Cancer and Leukemia Group B 80701 trial, presented by Matthew H. Kulke, MD, was designed to further evaluate the efficacy and safety of combined targeted therapy for the treatment of advanced pancreatic NETs. The trial enrolled 150 patients with advanced pancreatic NETs who were randomly assigned to receive everolimus (10 mg orally each day) with or without bevacizumab (10 mg/kg intravenously every 2 weeks). All patients also received the long-acting release (LAR) formulation of octreotide at standard dosing.

The median age of enrolled patients was 59 years in the single-agent arm and 58 years in the combination arm (range, 21 to 86 years). More than half of patients were male (53% of the single-agent arm and 59% of the combination arm), and more than half had an Eastern Cooperative Oncology Group performance status of 0 (60% and 55%, respectively). Previous treatment included octreotide in 52% of the single-agent arm and 53%
of the combination arm, cytotoxic chemotherapy in 24% (of each arm), and sunitinib in 4% (of each arm).

Patients received a median of 13 cycles in the combination arm vs 12 cycles in the single-agent arm. Study discontinuation owing to disease progression was more common in the single-agent arm than in the combination arm (65% vs 36%). However, rates of discontinuation owing to AEs were higher in the combination arm (28% vs 12%), as were rates of discontinuation for other reasons, including physician or patient discretion (21% vs 5%).

Dose modifications and delays were also more common in the combination arm. Among these patients, dose modifications were required for everolimus in 46% and for bevacizumab in 19%. Dose delays were required for everolimus in 33% of patients and for bevacizumab in 36% of patients. In the everolimus-only arm, dosing was modified in 25% and delayed in 16%.

The median follow-up was 26.7 months in the single-agent arm and 25.7 months in the combination arm. The addition of bevacizumab to everolimus significantly improved PFS. The median PFS was 16.7 months with the combination vs 14.0 months with the single agent (HR, 0.80; 95% CI, 0.55-1.17; P=.12; Figure 2). This difference was considered significant based on a stratified log-rank test with 90% power, with a 1-sided α of 0.15 needed to detect an HR of 0.64. The overall response rate was also significantly superior with everolimus plus bevacizumab vs everolimus alone (31% vs 12%; P=.005).

The median overall survival (OS) was 36.7 months in the combination arm vs 35.0 months in the single-agent arm (HR, 0.72; 95% CI, 0.4-1.28; P=.13). The median time to treatment failure was 12.6 months and 12.2 months, respectively.

Everolimus plus bevacizumab was associated with more toxicity than everolimus alone, including higher rates of grade 3/4 AEs (81% vs 49%), both hematologic (14% vs 8%) and nonhematologic (80% vs 43%). The most common grade 3/4 nonhematologic AEs potentially related to treatment were hypertension (38% vs 8%), hyperglycemia (14% vs 12%), proteinuria (16% vs 1%), diarrhea (11% vs 1%), and hypophosphatemia (10% vs 1%). Less common grade 3/4 AEs included heart failure/myocardial infarction and cardiac arrest, which occurred in 1% and 3%, respectively, of the combination arm, and thromboembolic events, which occurred in 1% of the combination arm.

In her discussion of the study, Diane Reidy, MD, noted that the grade 3/4 AE rate associated with everolimus and bevacizumab was high, at 81%. The investigators suggested that this combination was feasible despite the higher toxicity. They called for further study of regimens combining an mTOR inhibitor and a VEGF pathway inhibitor in patients with advanced pancreatic NETs.
Carcinoid syndrome refers to a group of signs and symptoms that can occur as a result of overproduction of hormones by functional (hormone-secreting) NETs. Control of these signs and symptoms is a treatment goal for patients with NETs. At the 2014 Gastrointestinal Cancer Symposium, results of the randomized, phase 3 ELECT (Efficacy and Safety Study of Somatuline Depot [Lanreotide] Injection to Treat Carcinoid Syndrome) trial demonstrated the efficacy of lanreotide depot/autogel in the treatment of carcinoid syndrome.1 In the ELECT trial, 115 patients with a carcinoid tumor and a history of carcinoid syndrome were randomly assigned to lanreotide depot/autogel 120 mg or placebo administered subcutaneously every 4 weeks for 16 weeks, followed by a 32-week open-label phase, and then by a long-term open-label phase. During the double-blind phase, patients in the lanreotide depot/autogel group required rescue treatment with short-acting octreotide on a mean 34% of days, whereas patients in the placebo group required rescue therapy on 49% of days. In a secondary analysis, 29% of patients in the lanreotide depot/autogel group required no short-acting octreotide compared with 18% of patients in the placebo group.

At the 2015 ASCO meeting, Aaron Vinik, MD, PhD, and colleagues presented results of a subanalysis evaluating the efficacy of lanreotide depot/autogel according to baseline characteristics in the ELECT trial.2 Overall, the mean age of enrolled patients was 59 years, 42% were male, 77% were white, and 72% had experienced symptoms of carcinoid syndrome for at least a year. The only difference in the baseline characteristics was a higher proportion of men in the lanreotide depot/autogel group than the placebo group (46% and 38%, respec-

References
Targeted Radionuclide Therapy for NETs

At a joint session of ASCO and the Society of Nuclear Medicine and Molecular Imaging, Alexander (Sandy) James Baird McEwan, MB, FRCPC, reviewed the role of targeted radionuclide therapy in NETs.1 The general concept behind radioisotope therapy, explained Dr McEwan, is the systemic administration of short-range particles or electron emissions to attain clinically important outcomes for patients with localized or metastatic cancer. Until recently, the primary endpoints of studies evaluating radioisotope therapy have been limited to palliative care because approximately half of patients with NETs who received octreotide analogs experienced symptoms longer. Dr McEwan noted that the confidence interval for the time to first symptomatic event was wide.

Several isotopes, including 90Yttrium and 177Lutetium, have been incorporated into radionuclide therapy. 90Yttrium is a pure ß-emitter incorporated into ibritumomab tiuxetan, a CD20-targeting radiotherapeutic antibody. 90Yttrium is associated with substantial cytopenia.2 The therapeutic isotope 177Lutetium may be an alternative. 177Lutetium has been developed as a peptide receptor radionuclide therapy for NETs as the radiolabeled somatostatin analog [177Lu-DOTA, Tyr3]octreotate.

Clinical Data on Radionuclide Therapy

Before the development of 177Lutetium, radiolabeled metaiodobenzylguanidine (131IImBG) was evaluated for therapeutic use in patients with carcinoid tumors. In a case-controlled study from 2004 involving 58 patients who received 131IImBG and 58 matched control patients, there was a trend toward improved survival in patients who received the treatment.3 Median OS was 7 years in the 131IImBG arm vs 4 years in the control arm. Dr McEwan noted, however, that the study population did not reflect the current standard of care because approximately half of patients received octreotide.

In 2008, Kwekkeboom and colleagues reported results of the first clinical trial evaluating the radiolabeled somatostatin analog 177Lu-octreotate in patients with gastroenteropancreatic (GEP) NETs.4 In this single-arm, unblinded study, 177Lu-octreotate was with placebo (Figure 3). One exception was the 21 patients with a BMI of 30 kg/m² or higher, but the authors noted that the confidence interval for these patients was wide.

The benefit of lanreotide depot/autogel was stronger in men than women. The mean differences in days that required rescue therapy were 24.1% vs 5.4%, respectively. The benefit with lanreotide depot/autogel was slightly less strong among patients who had received prior treatment with octreotide, those with a longer interval since diagnosis, and those who had experienced symptoms longer.

References

evaluated for safety in 504 patients and for efficacy in 301 patients. The median OS of 46 months, and the median PFS of 32 months, were both longer than those seen in historical reports evaluating chemotherapy. The investigators found that survival outcomes did not significantly correspond to reduction in anatomic tumor volume.

More recently, Dutch researchers published an analysis comparing response rates vs PFS and OS in 268 patients with NETs who had received 177Lu-octreotate between January 2000 and April 2007. Both PFS and OS were significantly shorter in patients with progressive disease than in those with an objective response or stable disease (Figure 4). There was no significant difference in outcomes between patients with stable disease and those with an objective response, confirming the findings from the previous study.

In 2014, a phase 2 study was published evaluating the efficacy and safety of 177Lu-octreotate (also referred to as 177Lu-DOTATATE) in the treatment of patients with progressive NETs. Investigators reported a trend toward longer survival with 4 cycles of 177Lu-DOTATATE vs fewer than 4 cycles. Moreover, patients with negative 18F-fluorodeoxyglucose (FDG) scans had better survival outcomes than patients with positive 18F-FDG scans, with no loss of survival in the follow-up period (Figure 5).

In general, 177Lu-DOTATATE is well tolerated. In the large, phase 2 study by Kwak and colleagues, serious AEs were rare. They included several cases of myelodysplastic syndrome and liver toxicity, which Dr McEwan noted was typically observed in patients with extensive intrahepatic metastases. For renal protection, 177Lu-DOTATATE is administered with an infusion of amino acids, which can cause nausea that is relatively manageable.

Based on the available data, Dr McEwan suggested that radionuclide therapy yields outcomes comparable with targeted therapies, such as everolimus or bevacizumab. A 2012 systematic review of multiple radionuclide therapies evaluated for the treatment of NETs found that these agents are generally safe when properly administered. The researchers noted a need for well-designed randomized controlled trials.

Dr McEwan observed that stable disease is a common outcome after
radiopharmaceutical therapy for NETs. He added that the responses are inversely related to tumor burden, and they may be delayed and then sustained for several years. Moreover, palliative responses to radionuclide therapy are common. Toxicity with these agents tends to be minimal and not dose-limiting. Dr McEwan said that there are probable benefits in PFS and OS, although unequivocal evidence is lacking.

Mechanism of Radionuclide Therapy

The mechanism of action of radionuclide therapy remains under debate. Dr McEwan proposed his own hypothesis of how these agents might exert antitumor effects in NETs. While reviewing the characteristics of radioisotope therapy, Dr McEwan noted that these agents are systemically administered, have specific targets, show low toxicity, and are commonly used as retreatment. He noted that the dose rate at which radiation is administered is an important distinction of radionuclide therapy. Whereas external-beam radiation therapy is administered at doses approximating 200 cGy in 2 minutes, β-particle therapies typically deliver a dose of approximately 500 to 700 cGy a day. Dr McEwan explained that traditional models postulated that cell survival declines as the radiation dose increases. Evidence now shows an inverse dose-rate effect identifiable in the part of the curve encompassing lower doses (below -2 Gy/min).10 A possible explanation for this finding is the synchronization of cells in the radiosensitive G2/M phase of the cell cycle. Another explanation, proposed by Marples and Collis, suggests that the treatment induces a low-dose hyperradiosensitivity state, in which there is a substantial increase in killing at low doses, followed by a state of resistance at slightly higher doses.11 Dr McEwan hypothesized that radioisotope therapy may be delivering a dose that is continuously administered at the more effective part of the curve, thereby inducing ultrafractionation.

DNA repair may also contribute to the efficacy of radionuclide therapy. In 2003, Rothkamm and Löbrich reported that exposure of human cells to very low radiation doses was associated with a reduction in the capacity of the cells to undergo DNA double-strand break repair.12 Cells treated at low doses remained unrepaired for days, whereas those exposed to higher doses were efficiently repaired. Similarly, Collis and colleagues reported that DNA damage induced by low-level radiation appears to evade the early cellular response by reducing activation of the ataxia-telangiectasia mutated DNA damage sensor and its downstream target.13 This impairment of DNA repair induced by low-level radiation may contribute to the efficacy of radionuclide therapy.

Optimizing Use of Radionuclide Therapy

Efforts are underway to optimize the use of radionuclide therapy in patients with NETs. Dr McEwan proposed that a period of induction therapy, followed by maintenance therapy, might be feasible. Moreover, appropriate patient selection is important. Kwekkeboom and colleagues found that shorter survival was associated with patient characteristics such as weaker responses to therapy, extensive liver involvement, low Karnofsky performance status, baseline weight loss, bone metastases, and tumor types such as gastrinoma, insulinoma, or VIPoma.4 In an imaging study conducted in 38 patients with NETs, Kayani and colleagues reported a significant association between 18F-FDG and tumor grade as assessed by Ki-67 for patients with a level of 2% or lower (P<.001) and for those with a level higher than 20% (P=.03).14

Clinical Experience

Dr McEwan provided an overview of the clinical experience at his institution with administering 177Lu-octreotate in patients with NETs. Patients first undergo an induction phase, during which they receive 150 mCi every 10 to 12 weeks, followed by a maintenance phase, in which half the initial dose is administered every 6 months and then every 9 months. Treatment is continued until relapse. A total of 169 patients received 776 treatments. The maximum
ABSTRACT SUMMARY Clinicopathologic Considerations of Neuroendocrine Tumors (NETs) in Greece: A Registry Experience

Anna Koumarianou, MD, PhD, and colleagues reported on the clinicopathologic features of NETs in Greece (abstract e15191). The analysis was performed on data collected between October 2010 and November 2012 from 246 patients newly diagnosed with NETs. The median age of patients at diagnosis was 57 years (range, 18-82 years); 49% were male, 94% had sporadic disease, and 6% had multiple endocrine neoplasia. The most common primary sites were the stomach and intestines (49%), followed by the pancreas (15%), head and neck (18%), lung (2%), and adrenal gland (2%). (Ten percent of cases were unknown.) Symptoms related to locally advanced or metastatic disease were present in 61% of patients, whereas 24% had endocrine symptoms and 15% were asymptomatic. Metastases were detected in 25% of patients. More than half of tumors (59%) were well differentiated, and 73% of patients had a Ki-67 of 2 or lower. Magnetic resonance imaging was used to successfully diagnose the NET in 75% of patients, followed by octreo scan in 50%. The most frequently prescribed treatment was a somatostatin analog; lanreotide depot/autogel and octreotide were similarly effective in providing symptomatic relief. Other treatments included chemotherapy, everolimus, and sunitinib.

Dr. McEwan also stated that diagnostic imaging can be useful when giving targeted radionuclide therapy. It is possible to image both the presence of the somatostatin receptors and the distribution of the agent to identify whether all sites of disease are being effectively targeted by the therapy.

Conclusion

Dr. McEwan concluded that radioisotope therapy provides outcomes similar to biologic agents, with a slightly improved safety profile. In contrast, radioisotope therapy has few features in common with external-beam radiation therapy. When considering the future management of patients with NETs, Dr. McEwan noted that multiple effective biologic agents are now available, particularly in pancreatic NETs. He suggested that a prospective trial including radionuclide therapy and biologic agents would be helpful to address questions regarding the optimal sequencing of these therapies and the implications of using one approach before another.

References

Somatostatin analogs have shown significant PFS benefit in clinical trials,1,2 prompting further evaluation of ways to increase efficacy. The randomized, phase 3 Southwest Oncology Group (SWOG) 0518 trial, presented by James C. Yao, MD,3 was designed based on the observed efficacy of 2 approaches: a combination of octreotide and interferon, which was associated with a significant reduction in the risk of tumor progression over octreotide alone (P=.008),4 and single-agent bevacizumab, which showed superior activity vs pegylated interferon in patients with advanced carcinoid tumors.5

SWOG 0518 enrolled patients with advanced grade 1 or 2 NETs with a poor prognosis, defined as having progressive disease, refractory carcinoid syndrome, grade 2 disease with at least 6 lesions, or colorectal or gastric primary tumors. Patients were randomly assigned to receive octreotide LAR 20 mg every 21 days in combination with either bevacizumab 15 mg/kg every 21 days or interferon α-2b 5 MU 3 days/week, with treatment continued until disease progression. Originally, the study was designed to enroll 283 patients in order to detect a difference in PFS from 6 months to 9 months with 90% power. However, after the initial pooled event rate was lower than expected, and the PROMID (Placebo Controlled, Double-Blind, Prospective, Randomized Study on the Effect of Octreotide LAR in the Control of Tumor Growth in Patients With Metastatic Neuroendocrine Midgut Tumors) study reported a longer PFS with single-agent octreotide, the statistical design was amended to enroll 424 patients to detect a difference in PFS from 15 months to 21 months with 84% power.1

A total of 402 eligible patients were enrolled and randomly assigned to bevacizumab (200 patients) or interferon (202 patients), each given with octreotide. Overall, 36% of patients had a primary tumor in the small bowel, cecum, or appendix. Baseline characteristics were well balanced between the 2 treatment arms. In her assessment of the patient characteristics, study discussant Diane Reidy, MD, questioned whether the patients truly represented a poor-prognosis population, given the high prevalence of grade 1 tumors and midgut tumors, which she noted tend to have a better prognosis.

In the primary endpoint analysis, median PFS assessed by central review was not significantly different with bevacizumab vs interferon (16.6 months vs 15.4 months; Figure 6). The PFS analysis by investigator review showed a slightly greater difference between the 2 arms, with a median PFS of 15.4 months and 10.6 months, respectively (Figure 7). Overall response rates were significantly higher with bevacizumab than interferon (12% vs 4%; P=.008). Bevacizumab was also superior to interferon as assessed by the median time to treatment failure (9.9 months vs 5.6 months; HR, 0.72; 95% CI, 0.58-0.89; P=.003).

In her discussion, Dr Reidy noted that interferon is considered a Category 3 recommendation in guidelines from the National Comprehensive Cancer Network,6 and there are conflicting findings regarding its efficacy. The use of interferon as a comparator arm could therefore be questioned.

ABSTRACT SUMMARY Multicenter Prospective Phase II Trial of Bevacizumab (Bev) for Progressive Pancreatic Neuroendocrine Tumor (PNET)

In a multicenter, phase 2 trial, the combination of temsirolimus and bevacizumab had antitumor activity in patients with pancreatic NETs, with a response rate of 41% and an acceptable safety profile (Hobday TJ et al. J Clin Oncol. 2015;33[14]:1551-1556). At the 2015 ASCO meeting, Timothy J. Hobday, MD, presented results of a multicenter, phase 2 study evaluating single-agent bevacizumab in patients with pancreatic NETs (abstract 4096). Enrolled patients had progressive disease within 7 months of study entry, and they could receive ongoing octreotide at stable doses for symptom control. In the 22 eligible patients, bevacizumab monotherapy was associated with a confirmed partial response rate of 9%, a 6-month PFS rate of 95%, a 12-month PFS rate of 54%, and a median PFS of 13.6 months. The only grade 3/4 AE was grade 3 hypertension, reported in 36% of patients. The investigators concluded that the regimen showed promising activity with minimal systemic toxicity.
Adverse events were as expected for the individual agents. The most frequent reason for study discontinuation was disease progression, which accounted for approximately half the discontinuations in each arm. Adverse events accounted for 30% of withdrawals in the bevacizumab arm and 24% in the interferon arm, and withdrawal of consent accounted for 7% and 14%, respectively. Dr Yao concluded that bevacizumab and interferon α-2b have similar antitumor activity in patients with advanced carcinoid tumors. He suggested that the differences in time to treatment failure could be attributable to safety issues and patient tolerance. Dr Yao stated that the treatment of NETs is advancing quickly, and that multiple agents, such as octreotide, lanreotide depot/autogel, sunitinib, and everolimus, have changed the treatment landscape since the SWOG 0518 trial was designed. Dr Yao noted that a recent press release indicated that the phase 3 RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) study showed a significant improvement in PFS with everolimus vs placebo plus best supportive care in the treatment of patients with advanced gastrointestinal or lung NETs, and future studies must consider data from these newer randomized trials.

References

Several abstracts presented at the 2015 ASCO annual meeting examined treatment of patients with GEP-NETs. Subanalyses of the CLARINET trials and ELECT trials showed that lanreotide depot/autogel maintained the antiproliferative benefit seen in the overall study populations. A small, single-center, retrospective analysis suggested that plasma levels of lanreotide depot/autogel are variable based on sex, weight, and BMI. Results from clinical trials evaluating the use of bevacizumab as a single agent and in combination therapy were also presented. An updated analysis of the RADIANT-3 trial examined overall survival adjusted for crossover bias.

**Lanreotide Depot/Autogel**

Lanreotide depot/autogel is approved by the US Food and Drug Administration to improve PFS in patients with GEP-NETS, based on results from the CLARINET trial. Subanalyses focusing on midgut NETs and pancreatic NETs confirmed that lanreotide depot/autogel has antiproliferative effects in these patients. In an analysis presented by Arvind Dasari, MD, of patients with midgut NETs, the median PFS was not reached in the lanreotide depot/autogel arm vs 21 months in the placebo arm (HR, 0.35; 95% CI, 0.16-0.80; P=.0091). The response to lanreotide depot/autogel was similar regardless of liver burden or tumor grade. I presented results from a subgroup analysis of patients with pancreatic NETs. Again, the PFS was not reached in the lanreotide depot/autogel arm vs 12.1 months in the placebo arm (HR, 0.58; 95% CI, 0.32-1.04).

Dr Dasari also presented a subanalysis on the effects of lanreotide depot/autogel according to patient age. There was a similar treatment effect in all age groups.

Edward M. Wolin, MD, presented an analysis of CLARINET data that focused on the benefit of therapy according to BMI. Lanreotide depot/autogel was administered subcutaneously, and there has been some debate regarding whether the treatment effect might vary in patients with high or low BMIs. In the analysis by Dr Wolin and colleagues, the effect of lanreotide depot/autogel did not differ according to BMI. Among patients receiving lanreotide depot/autogel, median PFS was not reached. Among placebo patients, PFS was 13.0 months, 24.4 months, and 17.6 months for BMIs less than 25 kg/m², between 25 to 30 kg/m², and higher than 30 kg/m², respectively. Adiposity, assessed as elevated BMI, has long been associated with increased risk of metabolic syndrome, which traditionally includes cardiovascular disease and diabetes. Calorie-deficient malnutrition is often reflected in decreased BMI. Many studies have documented that decreased BMI has adverse outcomes for patients in general, regardless of the intervention or disease process. The analysis by Dr Wolin only raised the possibility that a move away from ideal BMI, whether above or below, predicts the presence of other comorbid conditions or health factors that might influence the natural history of the disease course, independent of anticancer therapy. Regardless of the BMI group, improved PFS was seen with patients treated with lanreotide depot/autogel compared with placebo.

In another subanalysis of the CLARINET trial, Dr Wolin and colleagues evaluated the prognostic factors linked to PFS. Progressive disease at baseline was found in only 5% of patients in CLARINET. The analysis showed that patients who had no progression of disease at baseline were less likely to die and less likely to progress, which was expected. However, the disproportion of patients with and without progressive disease in this study calls into question the validity of the comparison. This analysis suggests that the study population in CLARINET had a better prognosis than the overall patient population. The patients in CLARINET were not high risk, had more indolent disease, and were treatment-naïve.

Eugene Woltering, MD, and colleagues evaluated the impact of sex, body surface area, and BMI on the plasma levels of lanreotide depot/autogel among 46 patients with NETs treated at a single clinic. The plasma level of lanreotide depot/autogel varied widely according to sex, body surface area, and BMI. The mean level was 8116 pg/mL in men and 8621 pg/mL in women (this difference was not statistically significant). In an analysis adjusted for BMI, the mean level was significantly lower in men than women (284 vs 338 pg/mL/kg/m²; P=.0006). When adjusted for body surface area, the mean level was also significantly lower in men than in women (3740 vs 4810 pg/mL/m²; P=.004). Patients with a higher BMI and body surface area may therefore require higher doses of the drug. This analysis did not attempt to measure any correlation between plasma level and symptom control, overall survival, PFS, or other antiproliferative effect indices. It is important to note that, at present, it is not yet known whether the plasma level of lanreotide depot/autogel or other somatostatin analogs has clinical relevancy to survival outcomes or tumor control.

Aaron Vinik, MD, PhD, presented a subgroup analysis from the ELECT...
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investigators noted that there was a wide confidence interval.

A retrospective, observational 
by Monica Ter-Minassian, 
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compared everolimus vs everolimus 
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and they are standard-of-care treatment 
options for patients with pancreatic NETs. Although these agents 
have different mechanisms of action, 
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the inhibition of angiogenesis via the 
VEGF/VEGFR receptor pathway. The 
rationale of the study was to explore the 
potential benefit of combined targeted 
therapy. The study found a significantly 
improved objective response rate with 
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compared with everolimus alone (31% 
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proof-of-concept study demonstrate 
that 2 agents are probably better than 
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 improved overall response and PFS can 
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it has not been convincingly demonstrated that improved PFS will translate

Combination Therapy

The SWOG 0518 trial, presented by James C. Yao, MD, evaluated octe-
roteotide LAR in combination with either 
bevacizumab or interferon α-2b 5 MU 
in patients with advanced grade 1 or 2 
metastatic midgut NETs. All patients 
were considered to have a poor pro-
gnosis, which was defined as progressive 
disease, refractory carcinoid syndrome, 
grade 2 disease with at least 6 lesions, 
or colorectal or gastric primary tumors. 
It should be mentioned, however, 
that this definition of poor prognosis 
is broad, and the study appeared to 
include patients whose prognosis was 
not poor. The rationale of the study 
was to ascertain whether interferon, 
an immune agent that is used com-
monly in Europe, can improve 
PFS in patients with midgut NETs 
as effectively as the anti–VEGF agent 
bevacizumab. The primary endpoint, 
overall survival. PFS was associated 
with overall survival at 6, 12, 18, and 
24 months. Patients who progressed at 
each of these studied time points had 
a shorter median overall survival than 
patients who did not progress.

The SWOG 0518 trial, presented by 
Matthew H. Kulke, MD, compared 
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 improved overall response and PFS can 
justify the increased toxicity profile will 
require longer follow-up. Additionally, 
it has not been convincingly demonstrated that improved PFS will translate
into longer overall survival duration in well-differentiated NET. This question will likely remain unresolved for this indolent malignancy. Combination therapy, such as everolimus plus bevacizumab, might be an option for patients with a good performance status, when the short-term goal of therapy is cyto-reduction of disease. For any antitumor agent or combination regimen with a narrow therapeutic index, patient selection is important.

Timothy J. Hobday, MD, presented the results of a prospective, proof-of-concept, phase 2 trial of single-agent bevacizumab in patients with progressive pancreatic NETs. Median PFS was 13.6 months with bevacizumab therapy. This promising analysis, median overall survival was 44.02 months with everolimus and 37.68 months with placebo, a difference that was not significant (P = .30). After an adjustment for the crossover bias, everolimus was associated with an overall survival of 82.6% at 12 months and 67.7% at 24 months, vs 74.9% and 55.6%, respectively, with placebo (HR, 0.60; 95% CI, 0.09-3.95). Although this type of statistical manipulation is becoming more common, some question whether it represents a reliable surrogate for overall survival.

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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