A SPECIAL MEETING REVIEW EDITION

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
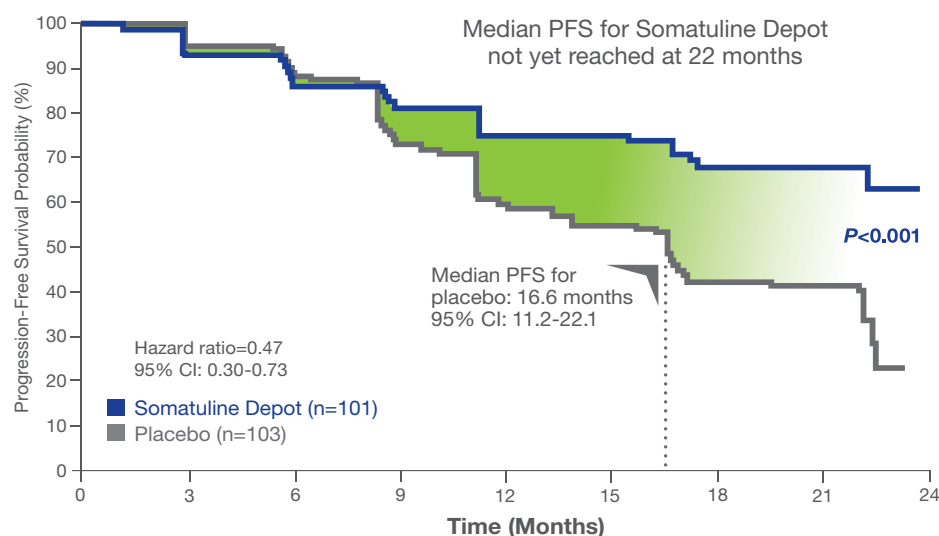
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ON THE WEB:
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HOLD BACK PROGRESSION

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]

Median PFS for Somatuline Depot not yet reached at 22 months

Median PFS for placebo: 16.6 months
95% CI: 11.2-22.1

$P<0.001$

Hazard ratio=0.47
95% CI: 0.30-0.73

Somatuline Depot (n=101)
Placebo (n=103)

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.

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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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) not reached in the treatment group vs 18 months with placebo (hazard ratio [HR], 0.47; 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 lan-
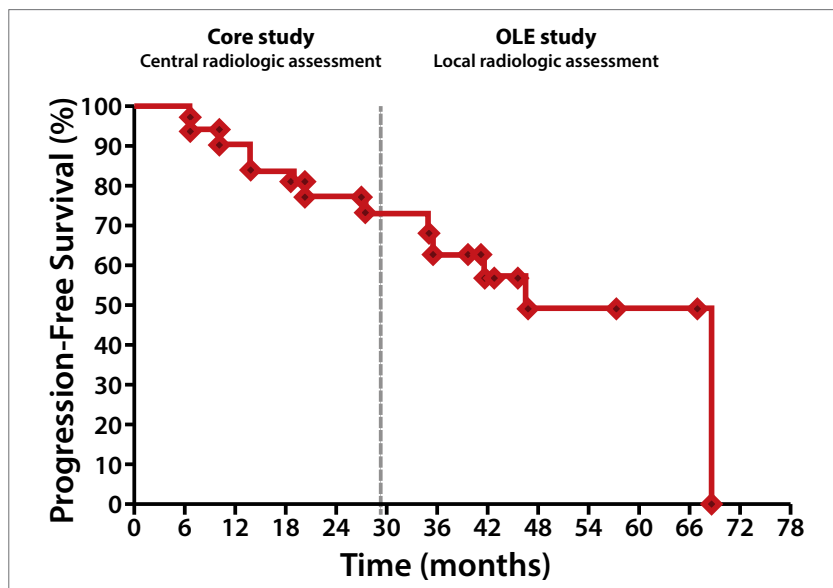

Figure 1. Median progression-free survival among patients with midgut tumors in the CLARINET core study and open-label extension (OLE). CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors. Adapted from Dasari A et al. Lanreotide depot/autogel (LAN) in midgut neuroendocrine tumors (NETs): a subgroup analysis from the CLARINET study [ASCO abstract 4104]. *J Clin Oncol.* 2015;33(suppl).[2]

reotide 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,

0.51; 95% CI, 0.29-0.90) and 12.1 months in the older group (HR, 0.38; 95% CI, 0.19-0.74). Safety outcomes were also similar to those reported in other analyses, with diarrhea being the most common AE. Rates of serious AEs with lanreotide depot/autogel were 24% in the younger patients and 26% in the older patients (vs 23% and 42%, respectively, with placebo).

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.[5] 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.[5]

Dr Phan also presented a detailed safety analysis of the CLARINET trial.[6] 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

ABSTRACT SUMMARY Pharmacokinetic Differences Between Sub-cutaneous 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 C_{max}, $t_{1/2}$, T_{max}, and residence time in the serum, were comparable between the 2 administration routes. However, the area under the curve (AUC) assessments AUC_{last} and AUC_{inf} were slightly lower with the subcutaneous injections, suggesting a slightly better long-term release.

Table 1. Prognostic Factors for PFS in the CLARINET Trial

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

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).[8]

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).[7] 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

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.[8] 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 (P=.029). 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

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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%.[1-3] In contrast, cytotoxic chemotherapy is associated with higher response rates (30%-40%), but the effects on PFS are not well demonstrated.[4,5]

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%.[6] 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.[7]

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.[8] 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%),

ABSTRACT SUMMARY Everolimus in Patients With Advanced, Progressive Pancreatic Neuroendocrine Tumors: Overall Survival Results From the Phase III RADIANT-3 Study After Adjusting for Crossover Bias

In the randomized, phase 3 RADIANT-3 study, everolimus was associated with a significant improvement in PFS over placebo in patients with advanced pancreatic NETs. Median PFS was 11.0 months with everolimus compared with 4.6 months for placebo (HR, 0.35; 95% CI, 0.27-0.45; P<.001; Yao JC et al. *N Engl J Med*. 2011;364[6]:514-523). At the 2015 ASCO meeting, Marianne Pavel, MD, and colleagues presented results from the final OS analysis as well as safety updates from RADIANT-3 (abstract 4091). In an unadjusted analysis, there was no significant difference in median OS between the arms (44 months with everolimus vs 38 months with placebo; P=.30). However, 85% of patients in the placebo arm crossed over to open-label everolimus. In an analysis that adjusted for the crossover bias, everolimus was associated with an OS 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). Investigators noted that safety outcomes were similar to those previously reported. The most common AEs associated with everolimus were stomatitis, rash, diarrhea, and fatigue.
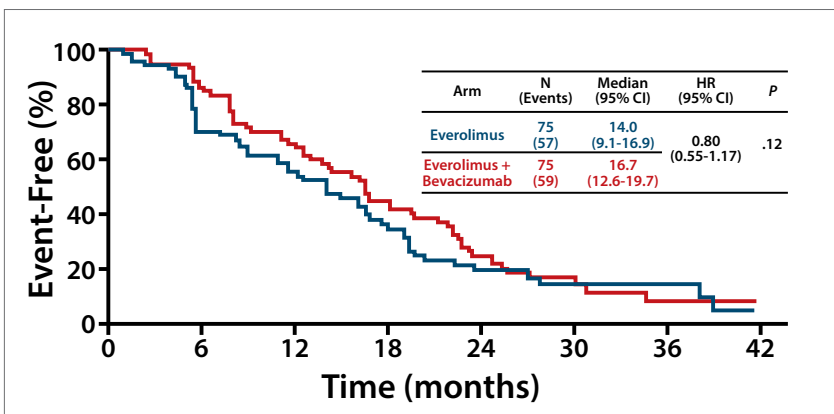
Arm	N (Events)	Median (95% CI)	HR (95% CI)	P
Everolimus	75 (57)	14.0 (9.1-16.9)	0.80 (0.55-1.17)	.12
Everolimus + Bevacizumab	75 (59)	16.7 (12.6-19.7)		

Figure 2. Median progression-free survival in the Cancer and Leukemia Group B 80701 trial. HR, hazard ratio. Adapted from Kulke MH et al. Randomized phase II study of everolimus (E) versus everolimus plus bevacizumab (E+B) in patients (Pts) with locally advanced or metastatic pancreatic neuroendocrine tumors (pNET), CALGB 80701 (Alliance) [ASCO abstract 4005]. *J Clin Oncol*. 2015;33(suppl).[8]

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.

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

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.
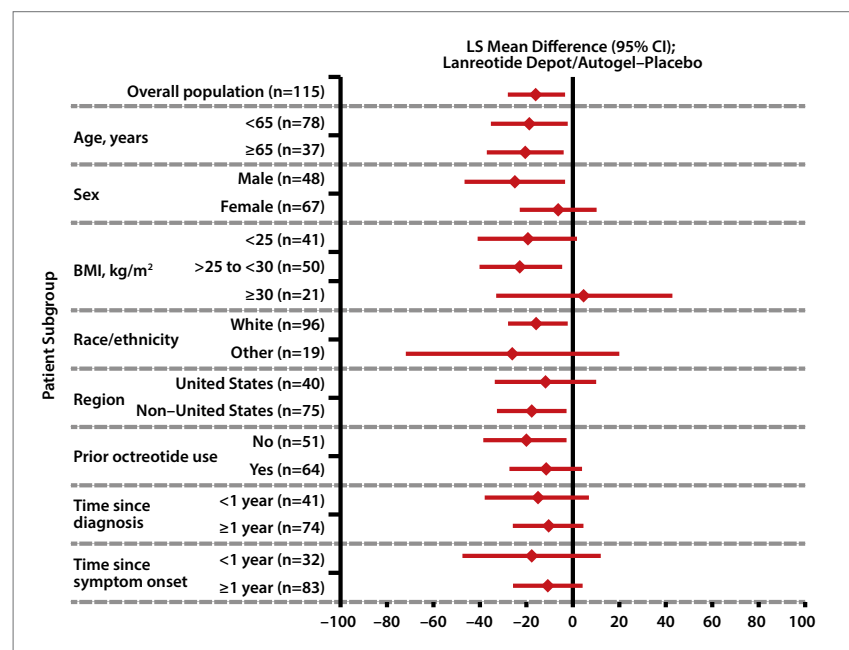
Figure 3. In a subanalysis of the ELECT trial, most subgroups confirmed the trend seen in the overall population that lanreotide depot/autogel reduced the need for rescue therapy as compared with placebo. BMI, body mass index; ELECT, Efficacy and Safety Study of Somatuline Depot [Lanreotide] Injection to Treat Carcinoid Syndrome; LS, least squares. Adapted from Vinik A et al. Lanreotide depot/autogel (LAN) vs. placebo (PBO) for symptom control in patients with neuroendocrine tumors (NETs): subgroup analysis of the ELECT study [ASCO abstract 4103]. *J Clin Oncol.* 2015;33(suppl).[2]

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-

ABSTRACT SUMMARY Association of Progression-Free Survival With Overall Survival (OS) in Patients (pts) With Neuroendocrine Tumor (NET) Treated With Somatostatin Analogs

PFS is commonly used as a primary endpoint in clinical trials of patients with NETs. However, Monica Ter-Minassian, ScD, and colleagues noted that it is uncertain whether PFS is associated with OS in patients with NETs. They conducted a retrospective study analyzing the association between these 2 endpoints in patients with NETs who received somatostatin analogs between 1995 and 2013 (abstract 4090). Landmark analyses were used comparing OS based on the progression status at prespecified times: 6, 12, 18, and 24 months. At all time points, PFS and OS were associated, both in the overall analysis and in subgroup analyses, which included tumor subgroup, functional status, and baseline level of chromogranin A. The strongest associations between PFS and OS were observed in patients with pancreatic NETs, functional NETs, and those with a baseline chromogranin A level greater than twice the upper limit of normal.

tively). Prior treatment with octreotide, which was reported by 56% of patients, included use of the LAR formulation in 49% and the subcutaneous formulation in 21%. The proportion of patients who had received a somatostatin analog was substantially higher in the United States than other countries (41% vs 31%).

In the current analysis, most subgroups, including age, race, and region, confirmed the trend found in the overall population showing that lanreotide depot/autogel reduced the need for rescue therapy as compared with placebo (Figure 3). One exception was the 21 patients with a BMI of 30 kg/m^2 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.

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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 factors, such as symptom control and improved quality of life. Secondary endpoints were based on efficacy responses, such as disease stabilization, partial remission, and complete remission. This paradigm has changed with the development of newer radionuclide therapies that show a survival benefit.

Several isotopes, including [90]Yttrium and [177]Lutetium, have been incorporated into radionuclide therapy. [90]Yttrium is a pure ß-emitter incorporated into ibritumomab tiuxetan, a CD20-targeting radiotherapeutic antibody. [90]Yttrium is associated with substantial cytopenia.[2] The therapeutic isotope [177]Lutetium may be an alternative. [177]Lutetium has been developed as a peptide receptor radionuclide therapy for NETs as the radiolabeled somatostatin analog ^{177}Lu-DOTA[0],Tyr[3]]octreotate.

Clinical Data on Radionuclide Therapy

Before the development of [177]Lutetium, radiolabeled metaiodobenzylguanidine ([131]ImIBG) was evaluated for therapeutic use in patients with carcinoid tumors. In a case-controlled study from 2004 involving 58 patients who received [131]ImIBG 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 [131]ImIBG 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 ^{177}Lu-octreotate in patients with gastroenteropancreatic (GEP) NETs.[4] In this single-arm, unblinded study, ^{177}Lu-octreotate was

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.[4] 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 ^{177}Lu-octreotate between January 2000 and April 2007.[5] 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 ^{177}Lu-octreotate (also referred to as ^{177}Lu-DOTATATE) in the treatment of patients with progressive NETs.[6] Investigators reported a trend toward longer survival with 4 cycles of ^{177}Lu-DOTATATE vs fewer than 4 cycles. Moreover, patients with negative ^{18}F-fluorodeoxyglucose (FDG) scans had better survival outcomes than patients with positive ^{18}F-FDG scans, with no loss of survival in the follow-up period (Figure 5).[6]

In general, ^{177}Lu-DOTATATE is well tolerated. In the large, phase 2 study by Kwekkeboom and colleagues, serious AEs were rare.[4] 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, ^{177}Lu-DOTATATE is administered with an infusion of amino acids, which can cause nausea that is relatively manageable.

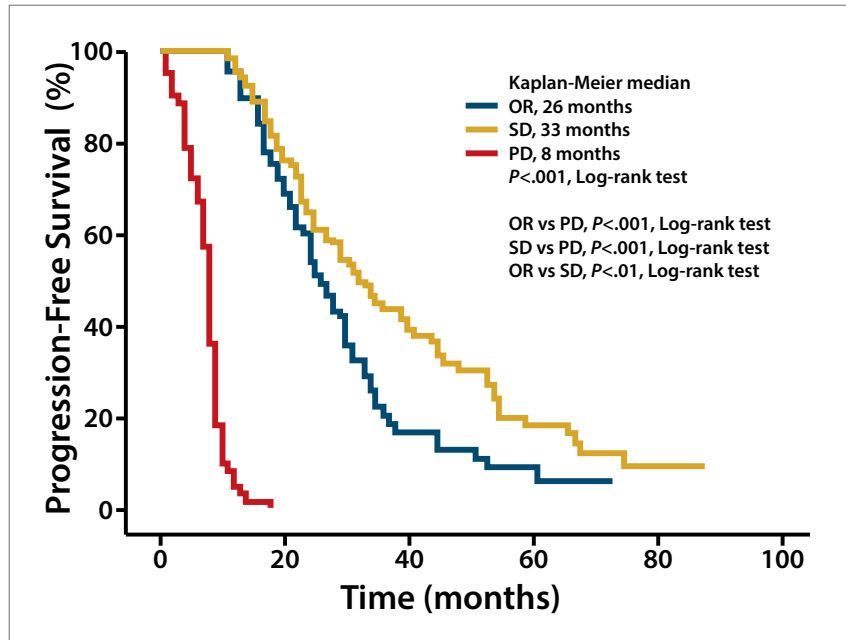Based on the available data, Dr McEwan suggested that radionuclide therapy yields outcomes comparable with targeted therapies, such as everolimus or bevacizumab.[7,8] A 2012 systematic review of multiple radionuclide therapies evaluated for the treatment of NETs found that these agents are generally safe when properly administered.[9]

Figure 4. Progression-free survival, as assessed by RECIST criteria, according to response to ^{177}Lu-octreotate among patients with neuroendocrine tumors. OR, objective response; PD, progressive disease; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease. Adapted from van Vliet EI et al. *J Nucl Med*. 2013;54(10):1689-1696.[5]
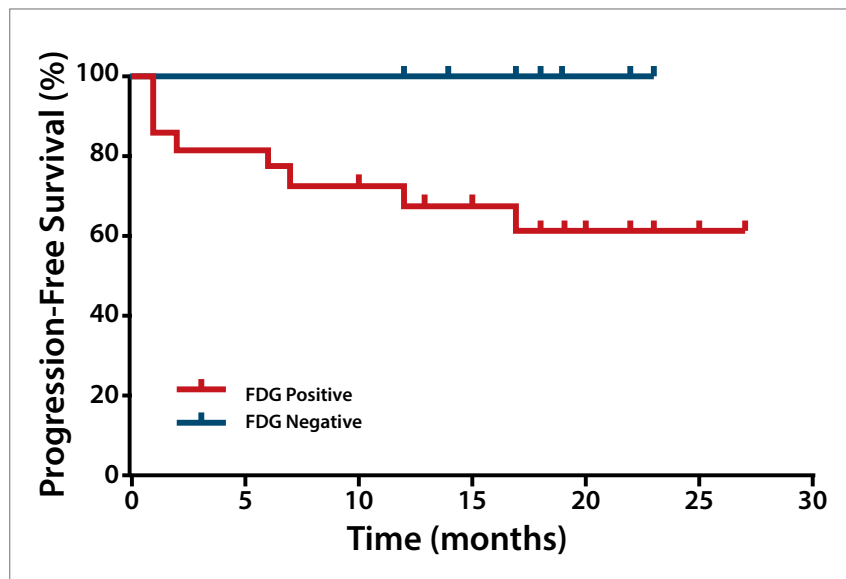
Figure 5. In a phase 2 study evaluating ^{177}Lu-octreotate in progressive neuroendocrine tumors, patients with negative ^{18}F-FDG scans had better PFS than patients with positive ^{18}F-FDG scans, with no loss of survival in the follow-up period. FDG, fluorodeoxyglucose. Adapted from Delpassand ES et al. *Pancreas*. 2014;43(4):518-525.[6]

The researchers noted a need for well-designed randomized controlled trials.[9]

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, ß-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 ^{18}F-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 ^{177}Lu-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 Effect of Sex, Weight, and Body Mass Index on Plasma Lanreotide Levels

Eugene Woltering, MD, and colleagues evaluated the effect of sex, weight, and BMI on plasma lanreotide depot/autogel levels (abstract e15189). The study included 46 patients with NETs treated at a single clinic who had received lanreotide depot/autogel for at least 4 months. The majority of patients (89%) had switched to lanreotide depot/autogel after having an inadequate response to octreotide. Thirty-four patients (72%) received lanreotide depot/autogel 120 mg every 2 weeks, 9 patients (21%) received more than 240 mg/month, and 3 patients (7%) received less than 180 mg/month. The mean plasma lanreotide depot/autogel level in patients receiving 120 mg every 2 weeks was 8324 pg/mL. These levels ranged from 8116 pg/mL in men to 8621 pg/mL in women (this difference was not statistically significant). In an analysis adjusted for BMI, the mean lanreotide depot/autogel level was 306 pg/mL/kg/m²; it was significantly lower in men vs women (284 vs 338 pg/mL/kg/m²; P=.0006). The mean lanreotide depot/autogel level adjusted for body surface area was also significantly lower in men than in women, at 3740 pg/mL/m² vs 4810 pg/mL/m² (P=.004). The investigators concluded that monitoring of plasma lanreotide depot/autogel levels may be a useful guide for dosing.

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 octreoscan 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.

cumulative dose was 1.075 Ci. Dr McEwan noted that researchers have observed almost no myelotoxicity, no renal toxicity, and no decrease in quality of life. Fourteen patients received 9 or more therapies, which Dr McEwan said suggested a fairly extended PFS. A preliminary analysis of the first 3 years showed a clinical response rate of 82%. PFS ranged from 1 to 32 months in patients who received up to 4 treatments, 12 to 54 months with 5 to 8 treatments, and 41 to 54 months with 9 or more treatments. At 1 year, a good partial response or a partial response occurred in 20% of patients (typically observed ≥9 months after starting treatment), stable disease in 65%, and progressive disease in 15%. There were no complete remissions. Biomarker responses were observed in approximately 42% of patients, although Dr McEwan noted that OS and PFS do not appear to be associated with reduction in biomarkers.

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 radio-isotope 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.

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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)

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,[7] and future studies must consider data from these newer randomized trials.

Figure 6. Median PFS as assessed by central review in the Southwest Oncology Group 0518 trial. HR, hazard ratio; LAR, long-acting release; PFS, progression-free survival. Adapted from Yao JC et al. 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) [ASCO abstract 4004]. *J Clin Oncol*. 2015;33(suppl).[3]

Figure 7. Median PFS as assessed by the investigators in the Southwest Oncology Group 0518 trial. HR, hazard ratio; LAR, long-acting release; PFS, progression-free survival. Adapted from Yao JC et al. 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) [ASCO abstract 4004]. *J Clin Oncol*. 2015;33(suppl).[3]

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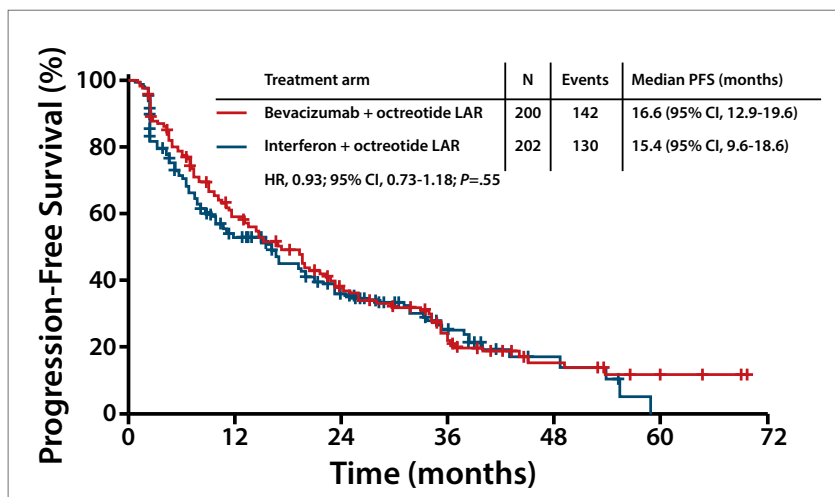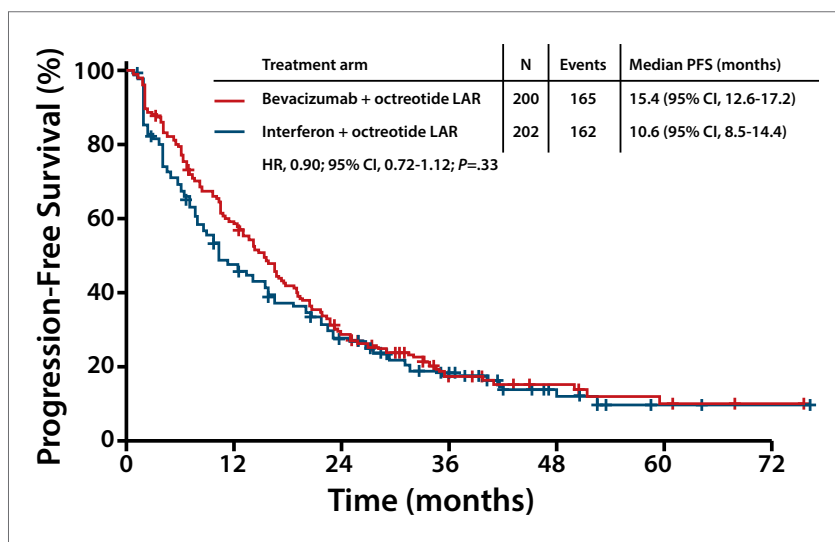5. Yao JC, Phan A, Hoff PM, et al. Targeting vascular endothelial growth factor in advanced carcinoid tumor: a random assignment phase II study of depot octreotide with bevacizumab and pegylated interferon alpha-2b. *J Clin Oncol*. 2008;26(8):1316-1323.
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Highlights in GEP-NETs From the 2015 American Society of Clinical Oncology Annual Meeting: Commentary

Alexandria T. Phan, MD

Several abstracts presented at the 2015 ASCO annual meeting examined treatment of patients with GEP-NETs. Subanalyses of the CLARINET[1-6] and ELECT trials[7-8] showed that lanreotide depot/autogel maintained the antiproliferative benefits 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.[9] Results from clinical trials evaluating the use of bevacizumab as a single agent and in combination therapy were also presented.[10-12] An updated analysis of the RADIANT-3 trial examined overall survival adjusted for crossover bias.[13,14]

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.[1] Subanalyses focusing on midgut NETs and pancreatic NETs confirmed that lanreotide depot/autogel has antiproliferative effects in these patients.[2,3] 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).[2] 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.[3] 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.[6] 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.[4] Lanreotide depot/autogel is 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.[5] 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-naive.

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.[9] 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

trial, which evaluated symptom management in patients randomized to lanreotide depot/autogel or placebo.[7,8] The symptoms—diarrhea and flushing—were evaluated using a novel approach to assessment: the number of rescue dosages of short-acting octreotide. The trial showed that use of rescue therapy was less frequent in the lanreotide depot/autogel arm, an expected finding. In the United States, octreotide LAR has been used for symptom control. Some physicians might have been unaware that lanreotide depot/autogel also improves symptoms of carcinoid syndrome in addition to extending PFS, but the ELECT trial showed that it does. The analysis by Dr Vinik and colleagues showed that lanreotide depot/autogel reduced the need for rescue therapy as compared with placebo in most subgroups, including age, race, and region.[8] One exception was the 21 patients with a BMI of 30 kg/m^{2} or higher. Among these patients, lanreotide depot/autogel had no benefit over placebo; however, investigators noted that there was a wide confidence interval.

A retrospective, observational analysis by Monica Ter-Minassian, ScD, of NET patients receiving somatostatin analogs aimed to identify whether PFS was associated with overall survival.[15] 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.

Combination Therapy

The SWOG 0518 trial, presented by James C. Yao, MD, evaluated octreotide LAR in combination with either bevacizumab or interferon α-2b 5 MU in patients with advanced grade 1 or 2 metastatic midgut NETs.[11] All patients were considered to have a poor prognosis, 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 commonly in Europe,[16,17] can improve PFS in patients with midgut NETs as effectively as the anti–VEGF agent bevacizumab. The primary endpoint, improvement in median PFS as assessed by central radiology review, was not met; neither regimen was superior.[11] By central radiology review, median PFS was 16.6 months for bevacizumab and 15.4 months for interferon (HR, 0.93; 95% CI, 0.73-1.18; P=.55). According to investigator review, the median PFS was 15.4 months for bevacizumab and 10.6 months for interferon (HR, 0.90; 95% CI, 0.72-1.12; P=.33). The investigator review may reflect some biases based on information censoring and investigator reading. When an investigator identifies progression, the patient is typically withdrawn from the study at that particular time point and receives no further protocol scans. During the central radiology review, if the patient's disease does not appear to have progressed, then his or her data are censored at this time point from statistical analysis. This censoring is informative because these patients usually show progression on central radiology sooner than the remaining at-risk cohort. Additionally, the local investigator's assessment of radiologic response or progression may be influenced by the "clinical" benefit of therapy, especially when the treatment arms are not blinded. Although PFS benefit was similar between the treatment arms, time-to-treatment failure, as assessed by the investigators, appeared to be better in the bevacizumab arm. My interpretation of this study is that it did not conclusively demonstrate superiority of either interferon or bevacizumab. Neither of these agents will be incorporated into the standard of care for midgut NETs. Whether interferon is an effective therapy for NETs

will likely remain unanswered. In the United States, use of interferon is less common than in Europe because the drug has side effects that significantly affect quality of life.

A randomized, phase 2 study presented by Matthew H. Kulke, MD, compared everolimus vs everolimus plus bevacizumab in patients with locally advanced or metastatic pancreatic NETs.[12] Both everolimus and sunitinib were approved by the US Food and Drug Administration in 2011, and they are standard-of-care treatment options for patients with pancreatic NETs. Although these agents have different mechanisms of action, their common therapeutic target is the inhibition of angiogenesis via the VEGF/VEGF 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 combined everolimus and bevacizumab compared with everolimus alone (31% vs 12%; P=.005). Median PFS was also improved (16.7 months with the combination vs 14.0 months with the single agent), but with increased toxicity. Everolimus plus bevacizumab was associated with higher rates of grade 3/4 adverse events, such as hypertension (38% vs 8%), hyperglycemia (14% vs 12%), proteinuria (16% vs 1%), diarrhea (11% vs 1%), and hypophosphatemia (10% vs 1%). The median overall survival was 36.7 months with the combination and 35.0 months with the single agent, a difference that was not statistically significant. It was expected that the combination therapy would lead to a higher overall response and better PFS. The results of this proof-of-concept study demonstrate that 2 agents are probably better than 1 in short-term outcomes, such as overall response and PFS. Whether the 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 cytoreduction of disease. For any anticancer 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.[10] Median PFS was 13.6 months with bevacizumab therapy. This promising PFS was expected with an anti-VEGF agent. Similar rates have been seen with other anti-VEGF agents, including pazopanib and sunitinib.[18,19] The results of the study demonstrate that VEGF/VEGF receptor is an actionable and relevant target for therapeutic development in pancreatic NETs. However, it is unlikely that bevacizumab will be further developed as a single agent for pancreatic NETs owing to the approval of similar therapies.

The results presented by Drs Hobday, Yao, and Kulke and confirmed the clinical benefit observed with bevacizumab.[10-12] These studies demonstrated that bevacizumab has activity in pancreatic NETs and possibly even midgut NETs, but they were not designed to show the superiority of bevacizumab as compared with other agents. The studies presented by Drs Yao (octreotide LAR plus bevacizumab or interferon)[11] and Kulke (everolimus plus bevacizumab)[12] are unlikely to be practice-changing, but they show that combination therapy is relatively safe in a select group of patients. The combination of 2 effective therapies can improve response, but the impact on overall survival remained undetermined. Refining the sequence of single-agent therapy may be more effective than combining therapies for the management of patients with indolent well-differentiated NET.

Data from the RADIANT-3 trial were published in 2011.[13] The median PFS was 11.0 months with everolimus and 4.6 months with placebo (*P*<.001). At the 2015 ASCO meeting, Marianne Pavel, MD, presented an updated analysis of overall survival that adjusted for a high crossover: 85% of patients in the placebo arm had crossed over to receive everolimus.[14] In an unadjusted 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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