Clinical Roundtable Monograph

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Recent Advances in the Management of Gastroenteropancreatic Neuroendocrine Tumors: Insights From the 2017 ASCO Gastrointestinal Cancers Symposium

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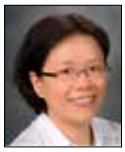

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Abstract: Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are rare malignancies that originate in the gastrointestinal system. GEP-NETs are typically indolent, but tumors known as "functional" secrete hormones that can lead to a complex of symptoms, including flushing, diarrhea, bronchospasm, and valvular heart disease. Management of patients with GEP-NETs requires a multidisciplinary approach, as treatment modalities include surgery, radiology, and pharmacotherapy. The available pharmacologic agents have increased in recently, and now include cytotoxic chemotherapies, somatostatin analogues, multitargeted tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors, and radioisotopic radiotherapies. The optimal sequencing of treatments is unknown. Advances in the management of GEP-NETs have been based on the results of recently completed clinical trials that have shown improvement in disease outcome and symptom management. The amount of positive data that has emerged from these studies is unprecedented in the GEP-NETs field. At the 2017 American Society of Clinical Oncology Gastrointestinal Cancers Symposium, several abstracts provided subanalyses of previous trials and new data for emerging treatments. Management will likely evolve as these therapies are incorporated into clinical care.

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Target Audience

This activity has been designed to meet the educational needs of oncologists and nurses involved in the management of patients with gastroenteropancreatic neuroendocrine tumors (GEP-NETs).

Statement of Need/Program Overview

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) are typically indolent. Some tumors secrete hormones that can lead to a complex of symptoms, including flushing, diarrhea, bronchospasm, and valvular heart disease. Treatment options have greatly increased in recent years. Modalities include surgery, radiology, and pharmacotherapy. Patients who can have their disease extirpated surgically live the longest. The somatostatin analogue lanreotide depot/autogel has been shown to increase progression-free survival and improve symptom control. Octreotide long-acting release and telotristat ethyl also alleviate symptoms. Other systemic options include inhibitors of tyrosine kinase and mammalian target of rapamycin. Peptide receptor radionuclide therapy is used in Europe and will likely be approved by the US Food and Drug Administration. The optimal sequence of therapy remains unknown. Management requires a multidisciplinary approach, with input from the medical oncologist, surgeon, nuclear medicine specialist, pathologist, gastroenterologist, and nutritionist. At the 2017 American Society of Clinical Oncology Gastrointestinal Cancers Symposium, several abstracts provided subanalyses of previous trials and new data for emerging treatments.

Educational Objectives

After completing this activity, the participant should be better able to:

- Discuss strategies to refine the management of patients with GEP-NETs
- Describe the incorporation of emerging treatment options into the standard of care for patients with GEP-NETs
- Discuss the role of multidisciplinary care in the treatment of GEP-NETs
- Analyze results from clinical trials presented at the 2017 American Society of Clinical Oncology Gastrointestinal Cancers Symposium

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Refining the Management of Patients With Gastroenteropancreatic Neuroendocrine Tumors

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Neuroendocrine tumors (NETs) are epithelial neoplasms that arise from neuroendocrine cells. These cells can originate in nearly any anatomic location, but the most common locations are the gastrointestinal (GI) tract and the pancreas.[1,2] These tumors are known as gastroenteropancreatic (GEP) NETs. NETs are often slow-growing, indolent tumors, but they can metastasize. NETs known as "functional" secrete amines and/or peptides that can lead to clinical symptoms.[3-5] Approximately 40% of NETs arising in the pancreas and 10% of those arising in the small intestine are functional.[3-5] The most common symptom is carcinoid syndrome, which consists of flushing, diarrhea, bronchospasm, and valvular heart disease. Carcinoid syndrome is caused by the overproduction of serotonin, and it can be diagnosed by measuring the urinary metabolite 5-hydroxyindoleacetic acid (5-HIAA).

Locally advanced and unresectable or metastatic GEP-NETs are considered incurable. Instead, the primary treatment goal is to prolong progression-free survival (PFS), which may then help to extend overall survival. Another goal of therapy is symptom management. Treatment modalities include surgery, radiology, and pharmacotherapy. Recent years have seen an increase in the available pharmacologic agents, to now include cytotoxic chemotherapies, targeted therapies, biologic agents, and radioisotope therapies. Three classes of targeted agents have received approval from the US Food and Drug Administration (FDA) for the treatment of pancreatic NETs: somatostatin analogues, multitargeted tyrosine kinase inhibitors (TKI), and mammalian target of rapamycin (mTOR) inhibitors.

Somatostatin analogues include lanreotide depot/autogel, which is approved for the treatment of patients with unresectable, well- or moderately differentiated, locally advanced or metastatic GEP-NETs; and octreotide long-acting release (LAR) depot, which is approved for symptom control of severe diarrhea/flushing episodes associated with metastatic, midgut, well-differentiated NETs (carcinoid tumors) or functional pancreatic NETs producing vasoactive intestinal peptide.[6-7] Somatostatin analogues control the symptoms associated with hormone hypersecretion in GEP-NETs, which often overexpress receptors for the inhibitory hormone somatostatin.[8-10] Clinical trials have shown that somatostatin analogues have an antiproliferative effect in these tumor types.[9,10]

The multitargeted TKIs include sunitinib, which is approved by the FDA for progressive, advanced, unresectable, metastatic pancreatic NETs.[11] The mTOR inhibitor everolimus is approved for the treatment of progressive NETs, regardless of the site of origin.[12]

Telotristat ethyl is a novel tryptophan hydroxylase inhibitor that was approved by the FDA in February 2017 in combination with somatostatin analogue therapy for the treatment of adults with diarrhea related to carcinoid syndrome that is not adequately controlled by somatostatin analogues alone.

Updates of Completed Studies

Recent advances in the management of GEP-NETs have been based on the results of several completed clinical trials. The amount of positive data that has emerged from these studies is unprecedented in the GEP-NETs field. Presentations at the 2017 American Society of Clinical Oncology Gastrointestinal Cancers (ASCO GI) Symposium included updates of clinical trials, as well as new analyses.

Lanreotide Depot/Autogel

The somatostatin analogue lanreotide depot/autogel has been evaluated in phase 3 trials for the treatment of patients with GEP-NETs. CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuro-

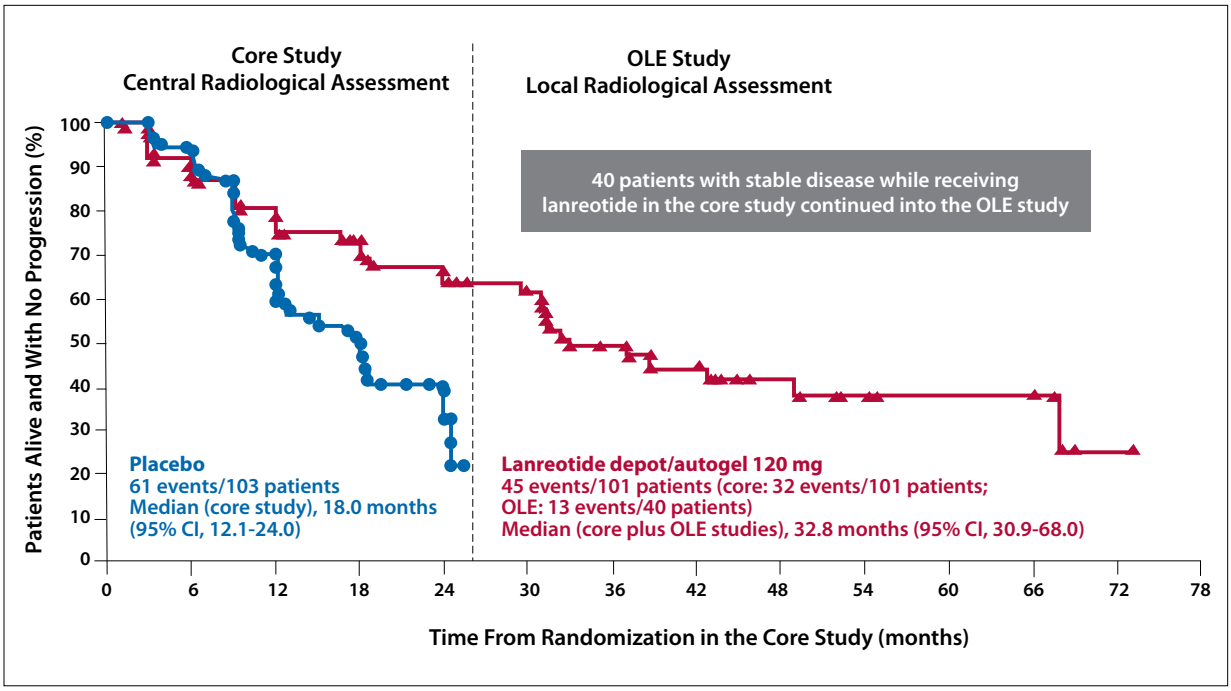

Figure 1. The OLE phase of the CLARINET trial continued to show improvement in progression-free survival for lanreotide depot/autogel vs placebo. CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors; OLE, open-label expansion. Adapted from Caplin ME et al. *Endocr Relat Cancer*. 2016;23(3):191-199.[15]

endocrine Tumors) was a 96-week, randomized, double-blind, placebo-controlled, parallel-group, international study in 204 patients with locally advanced or metastatic GEP-NETs.[9] All patients had either well-differentiated or moderately differentiated, nonfunctioning, unresectable tumors. CLARINET demonstrated that lanreotide depot/autogel (120 mg administered subcutaneously once every 4 weeks) was associated with a significant improvement in PFS, the primary study endpoint. The median PFS was not reached among patients treated with lanreotide depot/autogel vs 18.0 months among patients treated with placebo (P<.001). Lanreotide depot/autogel significantly reduced the risk of disease progression or death within 96 weeks of the first dose (hazard ratio [HR], 0.47; 95% CI, 0.30-0.73). An open-label expansion phase continued to show improvement (Figure 1). The PFS benefit was apparent in many of the predefined patient subgroups, such as tumor origin (midgut, pancreas, or other), tumor grade (1 or 2), and hepatic tumor volume (>25% or ≤25%). Data from the CLARINET study served as the basis for FDA approval of lanreotide depot/autogel in the treatment of GEP-NETs.

The phase 3 ELECT trial (A Double-Blind, Randomized Placebo-Controlled Clinical Trial Investigating the Efficacy and Safety of Somatuline Depot [Lanreotide] Injection in the Treatment of Carcinoid Syndrome) compared lanreotide depot/autogel (120 mg administered subcutaneously once every 4 weeks) vs placebo in patients with GEP-NETs.[13] ELECT differed from CLARINET in 2 ways: it was shorter (16 weeks of a double-blind phase, followed by a 32-week, open-label extension phase), and the primary endpoint was control of hormonal symptoms associated with carcinoid syndrome. Given the difficulty in measuring symptom control, the ELECT study utilized a novel primary endpoint, the mean percentage of days requiring rescue medication. Lanreotide depot/autogel was associated with a significant decrease in this endpoint vs placebo at 16 weeks (34% vs 49%; P=.017). The study authors estimated that this decrease translated to use of a rescue medication on approximately 5 fewer days, a clinically significant difference.

At the 2017 ASCO GI symposium, Phan and colleagues reported on a safety analysis evaluating clinical data from studies of lanreotide depot/autogel in the treatment of GEP-NETs.[14] This analysis pooled safety data from: (1) the 96-week double-blind portion of the CLARINET study and its long-term, open-label, extension phase (which lasted up to 8 years)[9,15]; (2) the 16-week double-blind phase of the ELECT study and its 2 open-label extension phases (an initial extension phase of 32 weeks followed by a long-term extension phase of 2 years)[13,16]; (3) a randomized study lasting 7 to 8 months[17]; (4) a 6-month, open-label, multicenter, dose-titration study[18]; and (5) a 92-week, open-label, single-arm study.[19]

Table 1. Most Common Treatment-Related Adverse Events in a Pooled Analysis of Clinical Trials Evaluating Lanreotide

	Lanreotide in Double-Blind and Open-Label Extension Studies (n=378; %)	Lanreotide in a Double-Blind Study (n=159; %)	Lanreotide in an Open-Label Extension Study (n=127; %)	Placebo in Double-Blind Studies (n=160; %)
Abdominal pain	36 (9.5)	15 (9.4)	16 (12.6)	2 (1.3)
Cholelithiasis	32 (8.5)	10 (6.3)	5 (3.9)	3 (1.9)
Injection site pain	30 (7.9)	9 (5.7)	7 (5.5)	4 (2.5)
Nausea	21 (5.6)	10 (6.3)	8 (6.3)	3 (1.9)

Data from Phan AT et al. ASCO GI abstract 398. *J Clin Oncol.* 2017;35(suppl 4S).[14]

The overall pooled population consisted of 378 patients (mean age, 60.7 years). Just over half of these patients (55.0%) were naive to somatostatin analogues at the time of study enrollment, and slightly more than half (57.9%) had functioning GEP-NETs. Patients were grouped according to whether they had received lanreotide depot/autogel in a double-blind study (n=159), lanreotide depot/autogel in an open-label study (n=127), or placebo in a double-blind study (n=160).

An adverse event leading to study withdrawal was reported in 6.1% of patients.[14] The overall incidence of adverse events was similar in patients who had received more than 12 months of treatment and those who had received 6 months or less of treatment (92.1% vs 88.1%). The rates of adverse events were relatively similar among patients treated with lanreotide depot/autogel in the double-blind (74.8%) and open-label (88.2%) studies and with placebo in the double-blind studies (78.8%). However, the incidence of treatment-related adverse events was higher with lanreotide depot/autogel (37.1% in the double-blind studies and 59.1% in the open-label studies) vs placebo (20.6% in the double-blind studies).

GI-related events were the most frequently reported adverse events, occurring in 55.8% of all patients.[14] Abdominal pain was the most common (23.0%), followed by vomiting (14.6%), headache (13.5%), nausea (13.0%), fatigue (12.2%), upper abdominal pain (11.9%), cholelithiasis (10.8%), asthenia (10.8%), back pain (10.6%), and constipation (10.1%). The most frequent treatment-related adverse events were abdominal pain, cholelithiasis, pain at the injection site, and nausea (Table 1).

The study authors noted that diarrhea and flushing were evaluated as part of the efficacy outcomes in the ELECT study, so they did not include these symptoms in the overall tabulation of adverse events.[14] Diarrhea was reported in 27.7% of patients, and considered related to treatment in 19.0%. More than 1 flushing event was reported in 6.6% of patients and thought to be related to treatment in 1.5%.

Quality of life (QoL) was also measured in this pooled analysis.[14] No deterioration in QoL occurred with lanreotide depot/autogel. Instead, there was a trend toward a modest improvement in QoL in some of the studies.

Phan and colleagues concluded that the results of this pooled analysis, which included data from long-term studies, were consistent with the already reported safety profile of lanreotide depot/autogel.[14] The authors stated that this well-tolerated safety profile supported the long-term use of lanreotide depot/autogel for the treatment of GEP-NETs.

A multicenter, single-arm, phase 2 study by Ito and colleagues, reported at the 2017 ASCO GI symposium, evaluated the safety and efficacy of lanreotide depot/autogel for the treatment of GEP-NETs in Japanese patients.[20] Patients received a fixed dose of lanreotide depot/autogel at 120 mg, administered subcutaneously once every 4 weeks for a total duration of 48 weeks. All patients had either locally advanced or metastatic NETS (most of which were GEP-NETs).[20] The study included 32 patients in the safety analysis and 28 patients in the efficacy analysis.

Among the patients in the efficacy analysis, the mean age was 61.7 years, and 78.6% had received prior treatment. The most common tumor sites were the pancreas (42.9%) and the rectum (28.6%). Less common sites were the duodenum (3.6%), the jejunum (3.6%), and the lungs (3.6%). The origin was unknown in 17.9%. Patients had either grade 1 (32.1%) or grade 2 (67.9%) disease, and most (64.2%) had a hepatic tumor load of 10% or less.

The primary study endpoint was the clinical benefit rate, defined as the proportion of patients who achieved a complete response, a partial response, or durable stable disease.[20] At 24 weeks, the clinical benefit rate in the efficacy population was 64.3% (95% CI, 44.1-81.4). By 60 weeks, 75% of patients had achieved stable disease as their best overall response, and 3.6% had achieved a partial response as their best overall response. No patient achieved a complete response.

Several secondary endpoints were also reported.[20] The median PFS was 9.1 months (equal to 36.3 weeks;

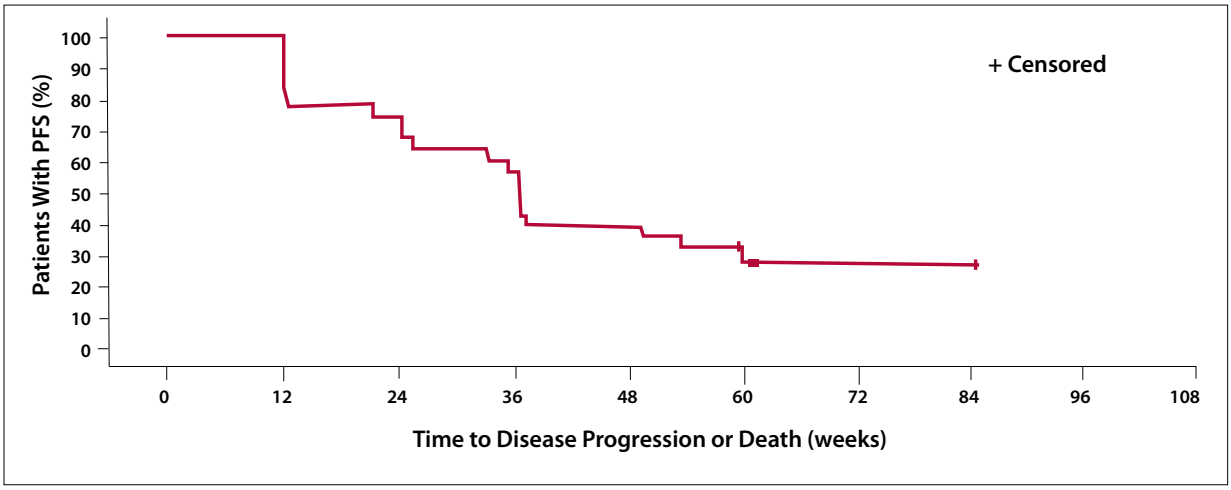

Figure 2. PFS in a phase 2 study of lanreotide depot/autogel for the treatment of GEP-NETs in Japanese patients. GEP-NETs, gastroenteropancreatic neuroendocrine tumors; PFS, progression-free survival. Data from Ito T et al. ASCO GI abstract 471. *J Clin Oncol.* 2017;35(suppl 4S).[20]

95% CI, 24.1-53.1; Figure 2). Notably, the median PFS was twice as long in the subpopulation of patients without progressive disease at baseline (53.1 weeks; 95% CI, 24.1 to not calculable) than in the subpopulation with baseline progressive disease (25.1 weeks; 95% CI, 12.0-37.1). The overall response rate (complete responses plus partial responses) at 60 weeks was 3.6% (95% CI, 0.1-18.3). Among 17 patients with elevated levels of serum chromogranin A at baseline, 15 (88.2%) experienced a decrease in these levels of at least 50%. QoL, another secondary endpoint, did not change from baseline.

The tumor growth rate (defined as the percent change in tumor volume throughout 1 month) in the efficacy population was also reported as a post-hoc analysis.[20] Before administration of the study drug, the mean tumor growth rate reported among the patients was 25.3% ±35.7%. This rate decreased to 5.4% ±10.7% from baseline to the last observation in the study.

The most frequent treatment-related adverse events of any grade reported in the safety population were injection site induration (28.1%), pale feces (18.8%), flatulence (12.5%), and diabetes mellitus (12.5%).[20] Treatment-related adverse events of grade 3 or higher occurred in 18.8% of patients, and included upper abdominal pain, pancreatitis, diabetes mellitus, hyperglycemia, inadequately controlled diabetes mellitus, increased blood glucose, and hypertension.

Ito and colleagues concluded that treatment with lanreotide depot/autogel was beneficial and safe for this group of Japanese patients with NETs.[20] Following completion of the study, patients were eligible for enrollment onto a 48-week extension study, which is ongoing. Although this study was limited to a small group of patients, it suggests that Japanese patients experience benefits with lanreotide depot/autogel that are similar to those of Western patients.

Refining Existing Therapy

Several abstracts presented at the 2017 ASCO GI symposium focused on refining existing therapies used in the management of GEP-NETs. Zhao and colleagues discussed a preliminary analysis evaluating the addition of the anti–vascular endothelial growth factor (VEGF) antibody bevacizumab to folinic acid/fluorouracil/irinotecan (FOLFIRI) for the second-line treatment of patients with metastatic GEP-NETs.[21] This single-center, retrospective study included 11 patients (median age, 51 years) who had received first-line chemotherapy within 2 years prior to study enrollment. Of these patients, 72.7% had received an etoposide/cisplatin combination as their first-line regimen. Other patients received a capecitabine-based regimen or gemcitabine plus nab-paclitaxel. All 11 patients received FOLFIRI as their second-line regimen (median, 8 courses; range, 3-36). Six patients also received bevacizumab. The overall disease control rate was 63.7%. Three patients had a partial response, and 4 patients had stable disease. Among the 6 patients who were treated with bevacizumab, the disease control rate was 66.7% (3 patients with a partial response and 1 patient with stable disease). The median PFS among all patients was 3.77 months (95% CI, 1.77-24.07). Among bevacizumab-treated patients, the median PFS was 4.77 months (95% CI, 1.83-24.07).

The most severe adverse event was grade 3 neutropenia (27.2%). More mild adverse events included anemia, transient elevations in transferases, and proteinuria. The

study authors concluded that FOLFIRI was a potentially beneficial second-line treatment regimen in patients with GEP-NETs, and that the addition of bevacizumab could possibly enhance and/or prolong the efficacy achieved with FOLFIRI.

An ongoing, multinational, single-arm, open-label, phase 4 clinical trial of sunitinib in patients with advanced, well-differentiated, pancreatic NETs was presented by Raymond and colleagues.[22] This study was conducted to satisfy, in part, postapproval commitments to the FDA to further evaluate the efficacy and safety of sunitinib in pancreatic NETs. Among the 106 enrolled patients, previous treatment included somatostatin analogues (in 48.1%) and chemotherapy (in 42.5%). Patients' median age was 54.6 years. The tumors were nonfunctioning in 60.4% and functioning in 17.9%. (The functional status was unknown for the remainder.) Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of either 0 (64.2%) or 1 (35.8%). Most patients had either 1 (31.1%) or 2 (38.7%) involved disease sites. The liver was involved in 92.5%, and the pancreas in 44.3%. Patients received sunitinib at a dosage of 37.5 mg once daily on a continuous regimen. If a treatment response was not seen after 8 weeks, then a dose escalation to 50 mg once daily was permitted in patients with minimal treatment-related adverse events (grade ≤1 nonhematologic or grade ≤2 hematologic). The investigator-assessed median PFS was 13.2 months (95% CI, 10.9-16.7), and was similar in the treatment-naive cohort (13.2 months; 95% CI, 7.4-16.8) and the previously treated cohort (13.0 months; 95% CI, 9.2-20.4). The median PFS by independent review was 11.1 months (95% CI, 7.4-16.6). The overall response rate by investigator assessment was 24.5% (95% CI, 16.7-33.8). The partial response rate was 21.7%. Neutropenia (55.7%), diarrhea (50.9%), and leukopenia (43.4%) were the most common all-grade, treatment-related adverse events. A dose reduction was required by 24.6% of treatment-naive patients and 11.1% of previously treated patients. The study authors concluded that the efficacy data reported in this phase 4 trial support the previously reported outcomes in the pivotal phase 3 trial of sunitinib in pancreatic NETs.[23] Additionally, no new safety signals were observed.

A post-hoc analysis of patients with GEP-NETs enrolled in the phase 3 RADIANT-4 trial (RAD001 in Advanced Neuroendocrine Tumors) was reported by Singh and colleagues.[24] The RADIANT-4 trial demonstrated that everolimus plus best supportive care resulted in significantly improved PFS vs placebo plus best supportive care in 302 patients with advanced, progressive, nonfunctional NETs of GI or lung origin. This analysis evaluated health-related quality of life (HRQoL) in the cohort of 211 patients with well-differentiated advanced NETs of GI origin only. HRQoL was assessed using the Functional Assessment of Cancer Therapy: General (FACT-G) questionnaire, which includes 27 items that assess well-being across 4 health subscales: physical, social/family, emotional, and functional. Higher scores on the FACT-G indicate improved HRQoL.

Overall, FACT-G scores were maintained throughout the course of the study, with only minor differences observed between the everolimus and placebo arms. At baseline, the mean total FACT-G score was 81.6 for everolimus and 83.1 for placebo. At week 8, the mean total FACT-G score was 79.9 for everolimus (95% CI, 77.7-81.1) and 79.9 for placebo (95% CI, 77.0-82.8). At week 48, these scores declined to 77.1 for everolimus (95% CI, 73.9-80.4) and 78.7 for placebo (95% CI, 73.4-83.9). Similar results were obtained for each of the FACT-G subscales. The authors concluded that despite the toxicities associated with everolimus, HRQoL is maintained in patients with NETs of GI origin. The authors noted that their conclusions were limited by the fact that these were patient-reported outcomes.

Chan and colleagues presented the results of a systematic review on the use of dose escalation with somatostatin analogues in NETs.[25] The analysis included 12 prospective studies and 7 retrospective studies, for a total of 981 patients. For octreotide, doses ranged from 48 mg every 28 days to 160 mg every 14 days. Doses for lanreotide depot/autogel ranged from 180 mg every 28 days to 420 mg every 28 days. Response rates ranged from 0% to 14%, and disease control rates ranged from 30% to 100%. Overall, rates of biochemical and symptomatic response exceeded 50%.

Importantly, the authors noted that no randomized trials studied dose-escalation of somatostatin analogues in NETs. No pharmacokinetic data were reported in the trials. The authors therefore concluded that well-designed, randomized trials of dose-escalated somatostatin analogues in patients with NETs are warranted. How best to extrapolate these results to clinical practice is currently unclear.

Symptom Control

There were several studies on symptom control in patients with GEP-NETs. Pommier and colleagues presented results from a subanalysis of patient-reported symptoms from the phase 3 ELECT study.[26] As previously discussed, the ELECT study demonstrated that lanreotide depot/autogel significantly reduced the need for octreotide as a rescue medication among patients with symptomatic carcinoid syndrome.[13] This subanalysis focused on diarrhea and flushing symptoms. In ELECT, 115 patients with a history of carcinoid syndrome (evidenced by diarrhea

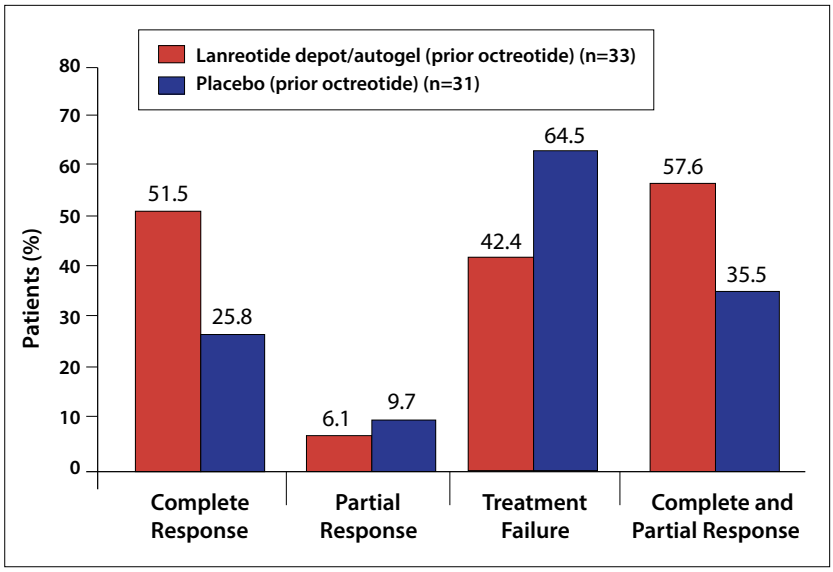

Figure 3. Treatment response, based on the use of short-acting octreotide rescue medication for symptomatic control of carcinoid syndrome, was improved with the use of lanreotide depot/autogel vs placebo in a subanalysis of the phase 3 ELECT study. Data for patients with prior exposure to octreotide are shown. ELECT, A Double-Blind, Randomized Placebo-Controlled Clinical Trial Investigating the Efficacy and Safety of Somatuline Depot (Lanreotide) Injection in the Treatment of Carcinoid Syndrome. Data from Pommier RF et al. ASCO GI abstract 378. *J Clin Oncol.* 2017;35(suppl 4S).[26]

and/or flushing) were randomly assigned to lanreotide depot/autogel or placebo for 16 weeks. Patients recorded the frequency and severity of diarrhea, flushing, and other symptoms via a voice/web response system each day for a month before the study and then for a month during it. Patients in the study were either currently responding to rescue therapy with octreotide (n=64) or had never received it before (n=51).

Treatment response, based on the use of short-acting octreotide rescue medication for symptomatic control of carcinoid syndrome, was improved with the use of lanreotide depot/autogel vs placebo (Figure 3). Compared with placebo, lanreotide depot/autogel reduced the frequency of moderate to severe diarrhea and/or flushing in both octreotide-naive patients and those with prior exposure to octreotide.[26] The least square mean percentage of days with moderate or severe diarrhea and/or flushing was significantly decreased among lanreotide depot/autogel–treated patients vs placebo-treated patients (23.4% vs 35.8%, respectively; *P*=.004).

Among patients receiving lanreotide depot/autogel, levels of 5-HIAA dropped by at least 30% by week 12 in 35% of octreotide-naive patients and 29% of patients with prior octreotide exposure.[26] In the placebo arm, 5-HIAA levels decreased by 15% in octreotide-naive patients and 7% of patients with prior exposure. These findings suggest that the symptom benefit seen in patients treated with lanreotide depot/autogel can be attributed to this agent's inhibitory mechanism of action.

Treatment Patterns

The increasing therapeutic options for patients with GEP-NETs prompted an analysis of treatment patterns among patients treated at a tertiary referral center.[27] This cohort analysis included 682 patients (mean age, 58.5 years), who were treated between July 2003 and May 2015 at the GI Cancer Centers of the Dana-Farber Cancer Institute or the Brigham and Women's Hospital. Treatment strategies were classified as either cytotoxic agents, angiogenesis inhibitors, mTOR inhibitors, interferons, somatostatin analogues, experimental therapies, or other. The tumors were located in the midgut in 45% of patients, the pancreas in 29%, and other locations in 26%. Functional GEP-NETs were identified in 38.9% of patients upon diagnosis of metastatic disease.

Most patients (87.0%) began treatment with at least 1 therapy throughout the follow-up period.[27] Somatostatin analogues, the most common treatment, were used by 77.4% of patients (Figure 4). Sustained use of somatostatin analogues was common, with 82.2% of patients still receiving treatment when they died or when the study ended. Somatostatin analogue combination therapy was increasingly common in later lines of therapy. Among patients with pancreatic NETs, the median duration of first-line somatostatin analogue therapy was 532 days (95% CI, 395-677 days) vs 1066 days among patients with midgut NETs (95% CI, 843-1374 days).

NCCN Guidelines

The guidelines for the treatment of NETs from the National Comprehensive Cancer Network (NCCN) may be updated to reflect some of the advancements discussed here.[28] The guidelines already recommend the use of lanreotide depot/autogel and other systemic therapies to slow disease progression and address symptom control. The guidelines will likely now recommend the novel

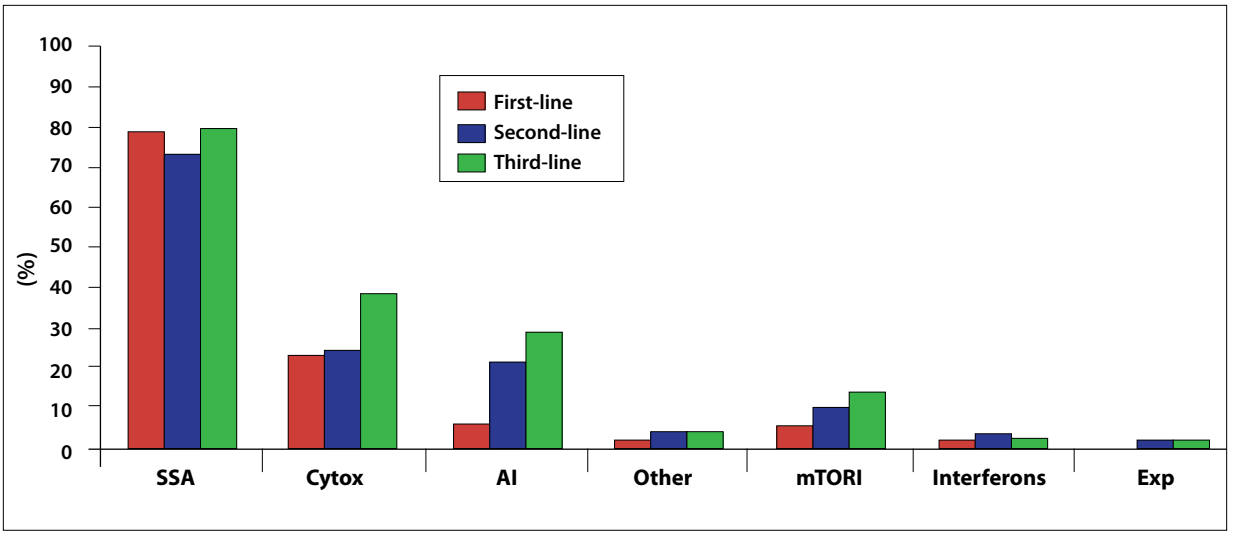

Figure 4. In a cohort analysis of patients with GEP-NETs, SSAs were the most common treatment strategy. AI, angiogenesis inhibitors; Cytox, cytotoxic agents; Exp, experimental therapies; GEP-NETs, gastroenteropancreatic neuroendocrine tumors; mTORI, mTOR inhibitors; SSA, somatostatin analogues. Data from Jalbert JJ et al. ASCO GI abstract 397. *J Clin Oncol*. 2017;35(suppl 4S).[27]

agent telotristat ethyl (discussed in the next article) for symptom control.

Another potential upcoming change to the guidelines will be the inclusion of the gallium-68 (GA-68) DOTATATE positron emission tomography (PET)/computed tomography (CT) scan.[29] Because the GA-68 agent robustly binds to the somatostatin receptors 2 and 5 (expressed by neuroendocrine cells), the GA-68 PET/CT is a higher-resolution alternative to the currently used magnetic resonance imaging and CT scans. The expected approval of peptide receptor radionuclide therapy (PRRT), discussed in a later article, will also likely warrant an update to the NCCN guidelines. Radiopeptides consisting of a somatostatin analogue combined with a radionuclide have shown efficacy in the treatment of NETs.[30]

Disclosure

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References

1. Cives M, Strosberg J. An update on gastroenteropancreatic neuroendocrine tumors. *Oncology (Williston Park)*. 2014;28(9):749-756, 758.
2. Lawrence B, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am*. 2011;40(1):1-18, vii.
3. Moertel CG, Sauer WG, Dockerty MB, Baggenstoss AH. Life history of the carcinoid tumor of the small intestine. *Cancer*. 1961;14:901-912.
4. Ito T, Tanaka M, Sasano H, et al; Neuroendocrine Tumor Workshop of Japan. Preliminary results of a Japanese nationwide survey of neuroendocrine gastrointestinal tumors. *J Gastroenterol*. 2007;42(6):497-500.
5. Panzuto F, Nasoni S, Falconi M, et al. Prognostic factors and survival in endocrine tumor patients: comparison between gastrointestinal and pancreatic localization. *Endocr Relat Cancer*. 2005;12(4):1083-1092.
6. Somatuline depot [package insert]. Basking Ridge, NJ: Ipsen Biopharmaceuticals, Inc; 2014.
7. Sandostatin LAR depot [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.
8. Wolin EM, Manon A, Chassaing C, et al. Lanreotide depot: an antineoplastic treatment of carcinoid or neuroendocrine tumors. *J Gastrointest Cancer*. 2016;47(4):366-374.
9. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med*. 2014;371(3):224-233.
10. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. 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: a report from the PROMID Study Group. *J Clin Oncol*. 2009;27(28):4656-4663.
11. Sutent [package insert]. New York, NY: Pfizer Labs; 2015.
12. Afinitor [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2016.
13. Vinik AI, Wolin EM, Liyanage N, Gomez-Panzani E, Fisher GA; ELECT Study Group. Evaluation of lanreotide depot/autogel efficacy and safety as a carcinoid syndrome treatment (ELECT): a randomized, double-blind, placebo-controlled trial. *Endocr Pract*. 2016;22(9):1068-1080.
14. Phan AT, Wolin EM, Fisher GA, et al. Safety and tolerability of lanreotide autogel/depot (LAN) in patients (pts) with neuroendocrine tumors (NETs): pooled analysis of clinical studies [ASCO GI abstract 398]. *J Clin Oncol*. 2017;35(suppl 4S).
15. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Anti-tumour effects of lanreotide for pancreatic and intestinal neuroendocrine tumours: the CLARINET open-label extension study. *Endocr Relat Cancer*. 2016;23(3):191-199.
16. Vinik A, Fisher G Jr, Kunz P, et al. Long-term safety/tolerability of lanreotide autogel/depot (LAN) in neuroendocrine tumors (NETs) patients with carcinoid syndrome (CS): the ELECT long-term open-label extension. Presented at: the 2016 North American Neuroendocrine Tumor Society meeting; September 30-October 1; Jackson, Wyoming. Abstract 147.
17. Johanson V, Wilson B, Abrahamsson A, et al. Randomized crossover study in patients with neuroendocrine tumors to assess patient preference for lanreotide autogel(®) given by either self/partner or a health care professional. *Patient Prefer Adherence*. 2012;6:703-710.
18. Ruszniewski P, Ish-Shalom S, Wymenga M, et al. Rapid and sustained relief from the symptoms of carcinoid syndrome: results from an open 6-month study

of the 28-day prolonged-release formulation of lanreotide. *Neuroendocrinology*. 2004;80(4):244-251.
19. Martín-Richard M, Massutí B, Pineda E, et al; TTD (Tumores del Tracto Digestivo) Study Group. Antiproliferative effects of lanreotide autogel in patients with progressive, well-differentiated neuroendocrine tumours: a Spanish, multicentre, open-label, single arm phase II study. *BMC Cancer*. 2013;13:427.
20. Ito T, Hisamatsu S, Nakajima A, Shimatsu A. A single-arm, multicenter phase II study of lanreotide autogel in Japanese patients with neuroendocrine tumors [ASCO GI abstract 471]. *J Clin Oncol*. 2017;35(suppl 4S).
21. Zhao X, Wang CC, Zhang W, Zhu X, Guo W, Chen Z. Preliminary analysis of FOLFIRI regimen with or without bevacizumab as second-line systemic therapy in patients with metastatic gastroenteropancreatic neuroendocrine carcinoma [ASCO GI abstract 469]. *J Clin Oncol*. 2017;35(suppl 4S).
22. Raymond E, Kulke MH, Qin S, et al. The efficacy and safety of sunitinib in patients with advanced well-differentiated pancreatic neuroendocrine tumors [ASCO GI abstract 380]. *J Clin Oncol*. 2017;35(suppl 4S).
23. Raymond E, Dahan L, Raoul JL, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med*. 2011;364(6):501-513.
24. Singh S, Strosberg JR, Pacaud L, et al. Health-related quality of life (HRQoL) in patients with advanced neuroendocrine tumors (NET) of gastrointestinal origin in the phase 3 RADIANT-4 trial [ASCO GI abstract 285]. *J Clin Oncol*. 2017;35(suppl 4S).
25. Chan DL, Ferone D, Albertelli M, Singh S. Escalated dose somatostatin analogues (SSAs) in management of neuroendocrine tumors (NETs): a systematic review [ASCO GI abstract 422]. *J Clin Oncol*. 2017;35(suppl 4S).
26. Pommier RF, Fisher GA, Wolin EM, et al; ELECT Study Investigators. Efficacy of lanreotide depot (LAN) for symptomatic control of carcinoid syndrome (CS) in patients with neuroendocrine tumor (NET) previously responsive to octreotide (OCT): subanalysis of patient-reported symptoms from the phase III ELECT study [ASCO GI abstract 378]. *J Clin Oncol*. 2017;35(suppl 4S).
27. Jalbert JJ, Casciano R, Tao B, et al. Treatment patterns among patients with metastatic GEP-NET treated at a tertiary referral center [ASCO GI abstract 397]. *J Clin Oncol*. 2017;35(suppl 4S).
28. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Neuroendocrine tumors. Version 1.2017. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Updated February 21, 2017. Accessed March 16, 2017.
29. Mojtahedi A, Thamake S, Tworowska I, Ranganathan D, Delpassand ES. The value of (68)Ga-DOTATATE PET/CT in diagnosis and management of neuroendocrine tumors compared to current FDA approved imaging modalities: a review of literature. *Am J Nucl Med Mol Imaging*. 2014;4(5):426-434.
30. Severi S, Grassi I, Nicolini S, Sansovini M, Bongiovanni A, Paganelli G. Peptide receptor radionuclide therapy in the management of gastrointestinal neuroendocrine tumors: efficacy profile, safety, and quality of life. *Onco Targets Ther*. 2017;10:551-557.

Emerging Treatment Options for Patients With Gastroenteropancreatic Neuroendocrine Tumors

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Since the results of the CLARINET and PROMID trials (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) were published,[1,2] therapeutic advancement in NETs has dramatically changed the treatment landscape for these patients. Somatostatin analogues are now recognized as a class of agents with antiproliferative effects on the tumor. By the end of the summer of 2017, 5 classes of agents will be FDA-approved or recognized for the management of GEP-NETs. However, there remain several areas of unmet need in the management of patients with GEP-NETs.

Unmet Needs

The optimal sequence of therapy remains unknown, particularly for patients with pancreatic NETs, who have the most treatment options. It is unlikely that sequencing will be evaluated in clinical trials because it will be difficult to find patients who have not already received certain treatments. More likely, sequencing will be addressed through expert opinion and consensus in published guidelines.

Clinicians must learn how to integrate PRRT into management. FDA approval of PRRT is expected in 2017, although it will not be widely available throughout the United States. It remains unknown whether PRRT will have application as a cytoreductive procedure in the neoadjuvant setting, or whether the best use of this modality will be to treat minimal residual disease after surgical resection in the adjuvant setting.

A better clinical understanding of high-grade NETs is another unmet need. The definition of a high-grade NET is evolving, with the recent inclusion of different subgroups. Better management of these tumors will require an improved understanding of how they differ on a molecular level, which may also better predict response to treatment.

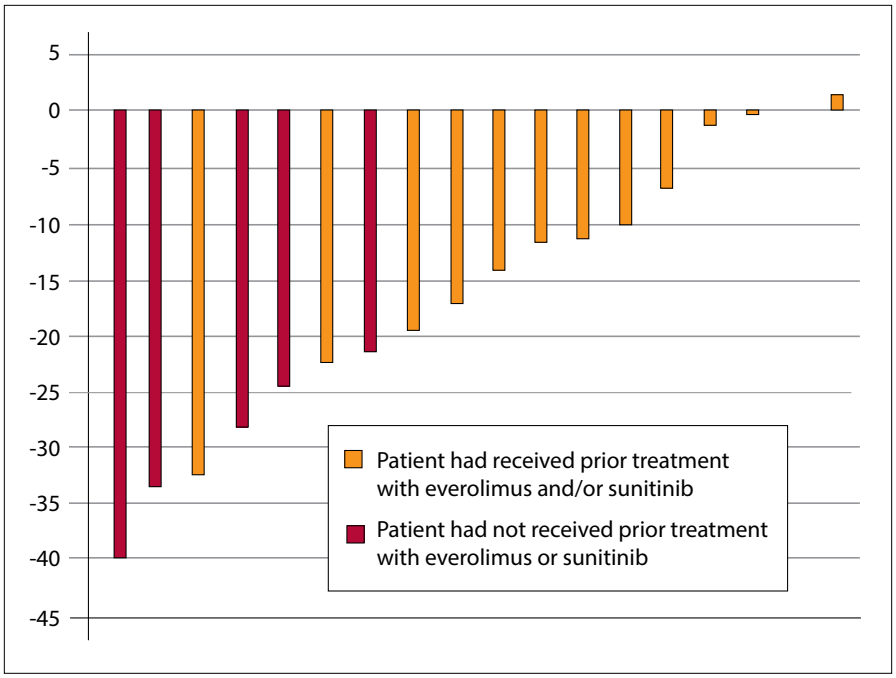

Figure 5. Response rate, as assessed by the RECIST criteria, among patients with pancreatic neuroendocrine tumors treated with cabozantinib. RECIST, Response Evaluation in Solid Tumors. Adapted from Chan JA et al. ASCO GI abstract 228. *J Clin Oncol.* 2017;35(suppl 4S).[4]

The optimal dosages and schedule for somatostatin analogues in combination with other therapies (either targeted treatment or PRRT) remain to be elucidated. Even the therapeutic dosage needed to achieve an antiproliferative effect is unknown. It is possible that these questions will be answered when a new somatostatin analogue is brought into the market.

Future research is needed to focus on the more rare NETs, such as those arising in the lungs or rectum. It has been difficult to enroll significant numbers of these patients into clinical trials, although recently there has been increased recruitment of patients with lung cancer. Rectal NETs occur mainly in Southeast Asia, and recruitment remains a challenge.

The emerging role of immunotherapy is currently an active focus in clinical research. Another unmet need in the treatment of NETs is to better define outcomes of treatment for clinical trials. Overall survival has not been used as a primary endpoint in these trials because historically it was considered unachievable. However, the recently published NETTER-1 trial (Phase III in Patients With Midgut Neuroendocrine Tumors Treated With ^{177}Lu-DOTATATE) of PRRT has proven that improvement in overall survival is an achievable goal in these patients.[3] It will be important to move clinical trials in this direction, which is the gold standard endpoint for many other malignancies.

Finally, it has become increasingly important to consider the cost effectiveness for the treatment of any disease, particularly chronic diseases requiring long-term therapy, such as NETs.

New Therapies

Data for the new agent cabozantinib were presented by Chan and colleagues at the 2017 ASCO GI symposium.[4] This TKI targets VEGF receptors, as well as other kinases, including MET, AXL, and RET. VEGF pathway inhibition has previously been shown to be an effective mechanism with demonstrated activity in NETs.[5-7] More recently, it has been suggested that MET expression and activation play a role in NET growth.[8] In preclinical NET models, cabozantinib has shown evidence of benefit with inhibition of cell viability and decreased metastatic potential.[9,10]

This phase 2 study enrolled 20 patients with pancreatic NETs and 41 with carcinoid tumors.[4] Patients had well-differentiated, grade 1 to 2, locally advanced, unresectable or metastatic NETs. All patients showed radiographic progression within 12 months before study entry, and had been receiving a stable dose of a somatostatin analogue for at least 2 months. Patients were treated with cabozantinib at 60 mg daily in continuous 28-day cycles until disease progression or unacceptable toxicity. At baseline, the median age for patients with pancreatic NETs was 55 years, and patients had received a median of 3 prior therapies (range, 0-8).

The primary study endpoint was the response rate, as assessed by the Response Evaluation in Solid Tumors (RECIST) criteria.[4] Among the 20 patients with pancreatic NETs, 3 (15%) had a partial response and 15 (75%) had stable disease (Figure 5). The median PFS was 21.8 months (95% CI, 8.5-32.0) among patients with pancre-

atic NETs and 31.4 months (95% CI, 8.5 to not reached) among patients with carcinoid tumors. Among the entire population of 61 patients, the most frequently reported treatment-related adverse events of any grade were fatigue (67%), increase in aspartate aminotransferase (59%), diarrhea (54%), thrombocytopenia (44%), and hypertension (41%). The most common grade 3/4 treatment-related adverse events were hypertension (13%), hypophosphatemia (11%), and diarrhea (10%).

Based on these results, the study authors determined that cabozantinib showed potential clinical activity in patients with advanced pancreatic NETs, producing objective responses and durable PFS.[4] The adverse event profile observed in this study was consistent with previous experiences with cabozantinib. A randomized, phase 3 trial of cabozantinib in a similar patient population is in development.

Libutti and colleagues reported on the use of combretastatin A4 phosphate (CA4P) for the treatment of unresectable or metastatic GEP-NETs that were well-differentiated, low to intermediate grade, and locally advanced.[11] CA4P is considered to be a vascular-disrupting agent that acts by binding to and depolymerizing tubulin. This results in a change in the shape of the endothelial cell that leads to occlusion of tumor blood vessels. CA4P has previously demonstrated activity in preclinical GEP-NET models.[12-14]

In this phase 2, single-arm, open-label study, 18 patients with GEP-NETs were treated with CA4P (60 mg/m^2 on days 1, 8, and 15 of a 21-day cycle) for 3 cycles.[11] The patients had pancreatic NETs (22%) or another type (78%). All patients exhibited elevated biomarker levels, and had relapsed while receiving standard treatment or afterward. The tumors were well-differentiated in 94% of patients. Patients' median age was 58 years. They had an ECOG performance status of either 0 (33%) or 1 (67%).

The study's primary endpoint was to determine the biochemical response to CA4P. An improvement was noted in 0% to 15% patients, stabilization in 61% to 83%, and worsening in 17% to 33% over time.[11] Stable disease was reported in 39% of patients, and 53% of patients had an improvement in QoL. After 3 months in the primary study, 7 patients were eligible for continuation in a rollover study. While on the rollover study, 3 of these patients received 6 or more cycles of continued CA4P. Overall, patients tolerated CA4P well. Grade 3 to 5 adverse events occurring in 10% or more of patients were anemia, abdominal pain, fatigue, hypertension, and increases in levels of alanine transaminase and aspartate aminotransferase. There was 1 death, from underlying carcinoid syndrome. The authors concluded that CA4P showed clinical benefit and good tolerability in patients with GEP-NETs. An ongoing, follow-on, investigator-led study is evaluating CA4P in combination with everolimus for patients with GEP-NETs.

Telotristat ethyl is a novel tryptophan hydroxylase inhibitor that was approved by the FDA in February 2017 in combination with somatostatin analogue therapy for the treatment of adults with diarrhea related to carcinoid syndrome that is not adequately controlled by somatostatin analogue therapy alone. The phase 3 TELESTAR trial (Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome) evaluated telotristat ethyl in 135 patients with carcinoid syndrome who were experiencing 4 or more bowel movements per day despite stable doses of somatostatin analogues at enrollment.[15] Patients were randomly assigned to receive telotristat ethyl at 250 mg or 500 mg, or placebo, all administered 3 times daily during a 12-week double-blind treatment period. In the open-label extension study, 115 patients subsequently received telotristat ethyl at 500 mg.

The primary endpoint was change from baseline in bowel movement frequency.[15] Results were reported by Hudgens and coworkers at the ASCO GI meeting and subsequently published.[15,16] Estimated differences in daily bowel movement frequency (averaged over 12 weeks) were –0.81 for the low dose of telotristat ethyl (P<.001 vs placebo) and –0.69 for the high dose of telotristat ethyl (P<.001 vs placebo; Figure 6). At week 12, the mean reduction in bowel movement frequency was –0.9 and –1.7 for the low and high doses of telotristat ethyl, respectively, vs –2.1 for placebo. Both doses of telotristat ethyl significantly decreased mean 5-HIAA levels compared with placebo at week 12 (P<.001). Mild nausea and asymptomatic increases in gamma-glutamyltransferase were reported in some patients receiving telotristat ethyl. No new safety signals were revealed in the open-label extension study.

Biologic or Genetic Signatures

The use of biologic or genetic signatures in the management of patients with NETs was another subject of research at the 2017 ASCO GI symposium. Raj and colleagues showed apparent differences in the genetic signature of well-differentiated pancreatic NETs with whole genome sequencing.[17] The researchers used the Memorial Sloan Kettering–Integrated Mutation Profiling of Actionable Cancer Targets assay, which includes a signature of more than 400 genes, to evaluate the tumors for genomic abnormalities, including abnormal copies of genes and genome rearrangement. Overall, the analysis included 89 tumor samples from 78 patients.

The study authors reported changes in the chromatin remodeling gene that could be used to distinguish between well-differentiated and poorly differentiated tumors.[17] Alterations in *DAXX* and *ATRX* were noted in

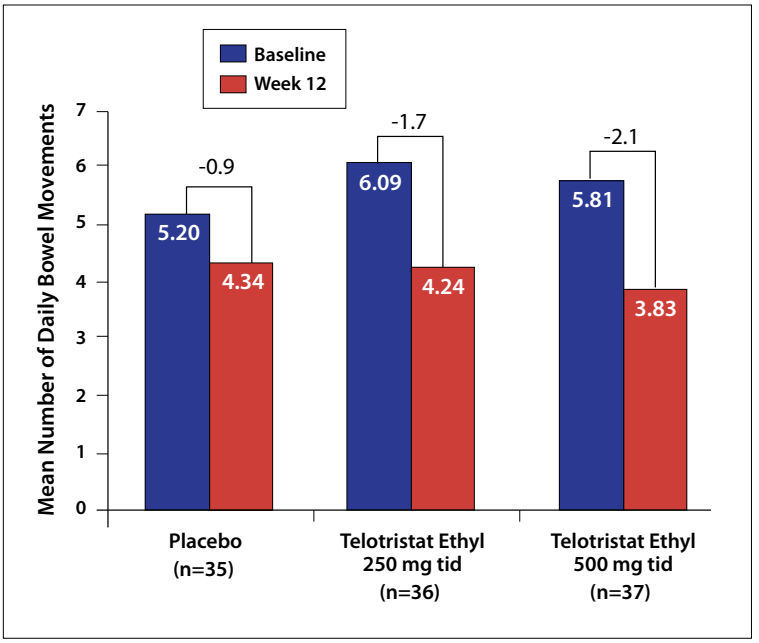

Figure 6. Mean number of daily bowel movements in the TELESTAR trial. Data include patients with assessments at both baseline and week 12. The arithmetic mean reduction in daily bowel movement frequency from baseline to week 12 was –0.9 with placebo, –1.7 with telotristat ethyl 250 mg, and –2.1 with telotristat ethyl 500 mg. TELESTAR, Telotristat Etiprate for Somatostatin Analogue Not Adequately Controlled Carcinoid Syndrome. Adapted from Kulke MH et al. *J Clin Oncol.* 2017;35(1):14-23.[15]

well-differentiated tumors. Additionally, a new alteration in *SETD2* was also reported, as were *TP53* mutations or alterations. Alterations in the *RB1* gene were identified in only 3 tumors, but all of these tumors were high grade. The authors concluded that only poorly differentiated NETs show *RB1* gene changes, which potentially suggests a unique way to aid in the future classification of NETs.

Chromogranin A has often been investigated as a biomarker, but this use has not been confirmed. Raoof and colleagues evaluated chromogranin A as a prognostic marker in small (<2 cm), nonfunctional, pancreatic NETs.[18] Patients with these characteristics were identified from the National Cancer Database throughout a 10-year period.

The researchers grouped tumors according to whether they had high or low chromogranin A levels, using a value of 420 ng/mL as a threshold.[18] Among the 445 patients eligible for analysis, 149 were deemed to have a low level of chromogranin A, and 296 patients had a high level of the marker. In a multivariate analysis, chromogranin A was shown to be a significant and independent marker of overall survival (P<.001) after controlling for tumor size, grade, and clinical nodal status. Therefore, the authors suggested that in this very specific group of patients with small, nonfunctional pancreatic NETs, chromogranin A was a predictor of overall survival. Additionally, patients with high levels of chromogranin A were found to benefit more from surgical resection than monitoring alone.

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.

References

1. Rinke A, Müller HH, Schade-Brittinger C, et al; PROMID Study Group. 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: a report from the PROMID Study Group. *J Clin Oncol.* 2009;27(28):4656-4663.
2. Caplin ME, Pavel M, Ćwikła JB, et al; CLARINET Investigators. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. *N Engl J Med.* 2014;371(3):224-233.
3. Strosberg J, El-Haddad G, Wolin E, et al; NETTER-1 Trial Investigators. Phase 3 trial of (177)Lu-dotatate for midgut neuroendocrine tumors. *N Engl J Med.* 2017;376(2):125-135.
4. Chan JA, Faris JE, Murphy JE, et al. Phase II trial of cabozantinib in patients with carcinoid and pancreatic neuroendocrine tumors (pNET) [ASCO GI abstract 228]. *J Clin Oncol.* 2017;35(suppl 4S).
5. Raymond E, Dahan L, Raoul J-L, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. *N Engl J Med.* 2011;364(6):501-513.
6. Grande E, Capdevila J, Castellano D, et al. Pazopanib in pretreated advanced neuroendocrine tumors: a phase II, open-label trial of the Spanish Task Force Group for Neuroendocrine Tumors (GETNE). *Ann Oncol.* 2015;26(9):1987-1993.
7. Phan AT, Halperin DM, Chan JA, et al. Pazopanib and depot octreotide in advanced, well-differentiated neuroendocrine tumours: a multicentre, single-group, phase 2 study. *Lancet Oncol.* 2015;16(6):695-703.
8. Krampitz GW, George BM, Willingham SB, et al. Identification of tumorigenic cells and therapeutic targets in pancreatic neuroendocrine tumors. *Proc Natl Acad Sci U S A.* 2016;113(16):4464-4469.
9. Reuther C, Heinzle V, Spampatti M, et al. Cabozantinib and tivantinib, but not INC280, induce antiproliferative and antimigratory effects in human neuroendocrine tumor cells in vitro: evidence for 'off-target' effects not mediated by c-Met inhibition. *Neuroendocrinology.* 2016;103(3-4):383-401.
10. Sennino B, Ishiguro-Oonuma T, Wei Y, et al. Suppression of tumor invasion and metastasis by concurrent inhibition of c-Met and VEGF signaling in pancreatic neuroendocrine tumors. *Cancer Discov.* 2012;2(3):270-287.
11. Libutti SK, Anthony LB, Chaplin DJ, Sosa JA. A phase II study of combretastatin A4-phosphate (CA4P) in the treatment of well-differentiated, low- to intermediate-grade, unresectable, recurrent, or metastatic pancreatic, or GI neuro-

endocrine tumors/carcinoid (GI-NETs/PNETs) with elevated biomarkers [ASCO GI abstract 432]. *J Clin Oncol*. 2017;35(suppl 4S).
12. Chaplin DJ, Pettit GR, Hill SA. Anti-vascular approaches to solid tumour therapy: evaluation of combretastatin A4 phosphate. *Anticancer Res*. 1999;19(1A):189-195.
13. Galbraith SM, Chaplin DJ, Lee F, et al. Effects of combretastatin A4 phosphate on endothelial cell morphology in vitro and relationship to tumour vascular targeting activity in vivo. *Anticancer Res*. 2001;21(1A):93-102.
14. Vincent L, Kermani P, Young LM, et al. Combretastatin A4 phosphate induces rapid regression of tumor neovessels and growth through interference with vascular endothelial-cadherin signaling. *J Clin Invest*. 2005;115(11):2992-3006.
15. Kulke MH, Hörsch D, Caplin ME, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. *J Clin Oncol*. 2017;35(1):14-23.
16. Hudgens S, Gable J, Kulke MH, et al. Evaluation of meaningful change in bowel move frequency for patients with carcinoid syndrome [ASCO GI abstract 583]. *J Clin Oncol*. 2017;35(suppl 4S).
17. Raj NP, Klimstra D, Shah R, et al. Next-generation sequencing (NGS) in pancreatic neuroendocrine tumors (panNETs): defining differentiation and grade genetically [ASCO GI abstract 291]. *J Clin Oncol*. 2017;35(suppl 4S).
18. Raoof M, Jutric Z, Melstrom LG, et al. Prognostic significance of chromogranin A in small pancreatic neuroendocrine tumors [ASCO GI abstract 375]. *J Clin Oncol*. 2017;35(suppl 4S).

Surgical Approaches for Patients With Gastroenteropancreatic Neuroendocrine Tumors

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Many current options for the treatment of GEP-NETs were not available just a few years ago. Some of the newer therapies, even for advanced and metastatic disease, could be considered "quasi-surgical." Several aspects to GEP-NETs are important to remember when selecting among the newer treatment options. Chief among these is that GEP-NETs can be effectively managed with surgery, at least in patients with well-differentiated disease. Patients who can have their disease extirpated surgically live the longest. Mounting evidence also suggests a benefit even when there is metastatic disease that cannot be completely resected.

In addition to resection of related liver tumors, there are now several methods that allow for ablative therapy, such as microwave ablation, radiofrequency ablation, and irreversible electroporation. Ablative techniques can be performed laparoscopically as well as percutaneously under cross-sectional imaging guidance. Many tools are available to facilitate liver resection, making it a relatively bloodless procedure as compared with historical methods. Ablative therapy is most effective for tumors that are 3 cm or less.

There are options for patients who are not candidates for surgical cytoreduction. Embolic therapy for the liver can consist of bland embolization or chemoembolization. Chemoembolization uses the hepatic artery as a pathway to the tumors, as the blood supply is derived primarily from the arterial side. The liver has a dual blood supply, and thus can survive using the portal vein even when the hepatic artery has been compromised. Radioembolic therapies, such as microsphere embolization (using most commonly the yttrium-90 isotope), typically do not sacrifice or occlude the artery. For this reason, radioembolization is an attractive modality that does not preclude the use of subsequent therapies.

One of the newer treatments in the United States is a relatively older therapy in Europe. Peptide receptor radionuclide therapy (PRRT) can be used for liver disease and extrahepatic disease. With PRRT, a molecule that binds to a receptor on the tumor is conjugated to a radionuclide, such as indium, lutetium, or yttrium. Of these, lutetium seems to be the most widely favored.

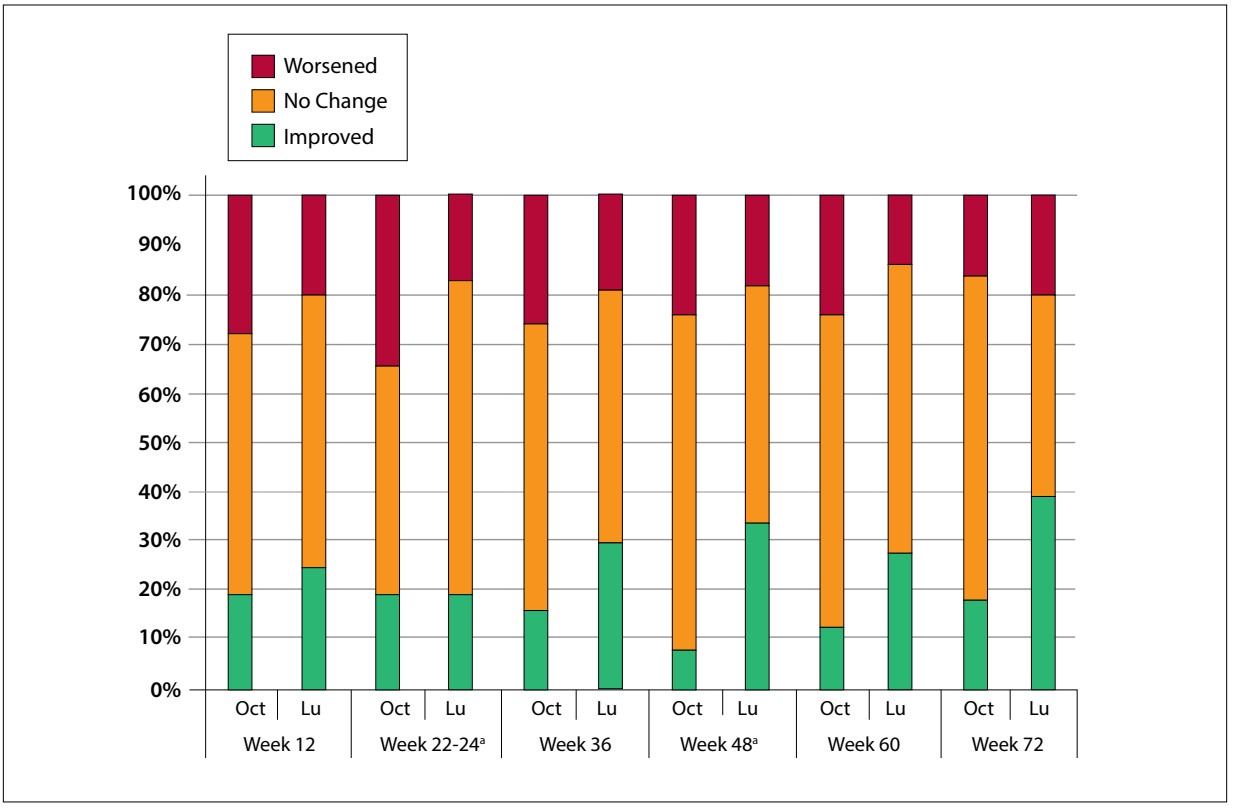

Figure 7. Global health status among patients receiving ^{177}Lu-DOTATATE or octreotide in the phase 3 NETTER-1 trial. [a]The difference between the arms was statistically significant ($P \leq .05$). Lu, ^{177}Lu-DOTATATE; NETTER-1, Phase III in Patients With Midgut Neuroendocrine Tumors Treated With ^{177}Lu-DOTATATE; Oct, octreotide. Adapted from Strosberg J et al. ASCO GI abstract 348. *J Clin Oncol*. 2017;35(suppl 4S).[1]

Challenges in Surgical Resection

Several challenges remain in the surgical resection of GEP-NETs. Mesenteric vascular encasement, often the consequence of an unresected primary gut tumor, can result in intestinal ischemia, intestinal angina, gut failure, and multiple bowel obstructions. These patients have few options, which begs the question of why the primary tumor was not resected earlier.

Other challenges include how to identify the best candidates for resection. It is also not known how much tumor burden in the liver should be debulked. In general, we strongly consider patients for debulking when less than half of their liver is replaced by the tumor. If 70% or more of the hepatic tumor burden can be debulked, we recommend surgery. Many times, ablative therapies are used in combination with surgical extirpation. By decreasing hormone production, cytoreductive therapy controls disease, alleviates symptoms, and improves QoL in patients who have functional tumors. In rare circumstances, particularly if dominant bulky tumors are causing significant symptoms, we will consider surgery for patients who have more than half of the liver involved. Unresected pancreatic primary tumors often result in complications, such as splenic vein thrombosis, retroperitoneal nerve invasion and pain, gastric varices, upper GI hemorrhage, and gastric outlet obstruction. It is preferable to intervene before these issues arise, even when the liver cannot be debulked.

Nutrition

When considering surgery, it is necessary to evaluate a patient's overall state of health. Addressing malnutrition in these patients is an unmet need. Pancreatic insufficiency often goes unrecognized. Somatostatin analogues lead to more diarrhea from exocrine suppression in up to 30% of patients. These factors must be considered when evaluating patients and creating a management plan. Surgery may need to be postponed in order to improve the patient's nutrition. Malnutrition is associated with a higher complication rate and poorer outcome.

Sequencing Treatment

With so many options available, it is a challenge to determine sequencing. In Europe, where PRRT is more

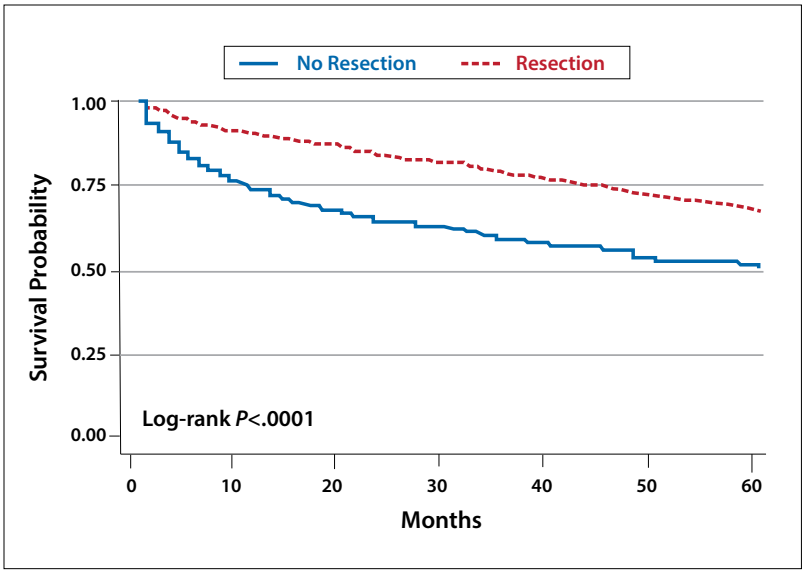

Figure 8. In a study evaluating the role of aggressive debulking in older patients (≥70 years) with GEP-NETs, resection of the primary tumor was associated with improved survival. GEP-NETs, gastroenteropancreatic neuroendocrine tumors. Adapted from Jutric Z et al. ASCO GI abstract 377. *J Clin Oncol.* 2017;35(suppl 4S).[2]

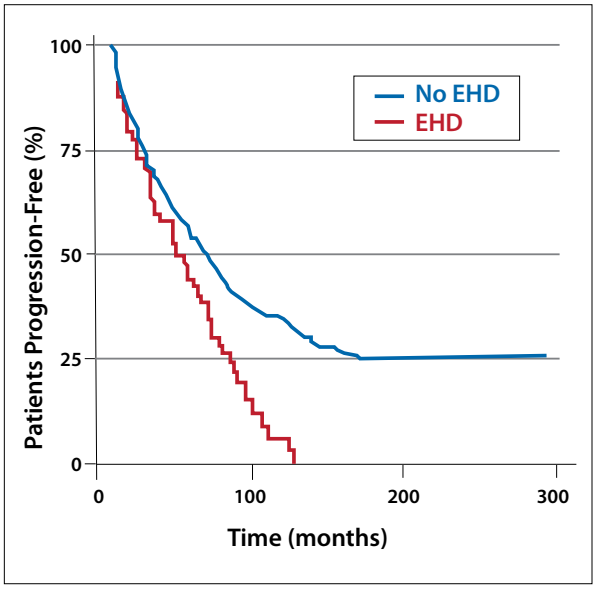

Figure 9. Among patients undergoing liver-directed therapy for neuroendocrine and liver metastases, EHD was associated with shorter progression-free survival. EHD, extrahepatic disease. Adapted from Ejaz A et al. ASCO GI abstract 277. *J Clin Oncol.* 2017;35(suppl 4S).[6]

established, it is often one of the first treatments initiated. In the United States, PRRT is not yet approved or widely used, and it is an option only for patients with significant financial resources.

When considering treatment sequencing, the importance of early surgery is paramount. Patients with GEP-NETs who do not undergo surgical intervention typically do not achieve long-term survival. Eventually, a GEP-NET will obstruct, hemorrhage, and/or perforate.

The best management is modeled by centers in which clinicians meet on a weekly basis and discuss all aspects of the care of these patients. This multidisciplinary approach ensures the consideration of viewpoints from the medical oncologist, surgeon, nuclear medicine specialist, pathologist, gastroenterologist, and nutritionist.

Study Updates

Strosberg and colleagues examined QoL among patients treated with PRRT from the phase 3 NETTER-1 trial.[1] The trial randomly assigned patients to treatment with ^{177}Lu-DOTATATE or high-dose octreotide LAR. Global health status improved in 28% of patients receiving ^{177}Lu-DOTATATE vs 15% of patients receiving octreotide (Figure 7). Global health status was less likely to worsen in the ^{177}Lu-DOTATATE arm vs the high-dose octreotide arm (18% vs 26%). Diarrhea improved in 39% of ^{177}Lu-DOTATATE–treated patients vs 23% of octreotide-treated patients. Diarrhea worsened in 19% of the ^{177}Lu-DOTATATE arm vs 23% of the octreotide arm. There was a trend toward improved pain control with ^{177}Lu-DOTATATE, but it did not reach statistical significance (perhaps owing to the limited number of patients).[1] Flushing improved compared with baseline in both groups, but there was not a clear advantage with either treatment. Overall, it appeared that ^{177}Lu-DOTATATE was associated with a meaningful increase in QoL compared with high-dose octreotide in patients with advanced, midgut NETs.

A study by Jutric and colleagues evaluated the role of aggressive debulking in older patients (≥70 years) with GEP-NETs.[2] This study reviewed a tumor registry

in California that included 2000 patients. Among these patients, 1660 without liver metastases had undergone resection of their primary tumor. Resection of the primary tumor was associated with improved survival (HR, 0.50; *P*<.0001; Figure 8). In a subgroup of 360 patients with liver metastases, those who underwent liver-directed therapy alone (n=37) did not demonstrate significantly different overall survival vs the remainder of the subgroup. However, resection of their primary tumor, either with or without liver-directed therapy, was associated with significantly improved overall survival (HR, 0.14; *P*<.001). The authors concluded that surgical management significantly improved survival, and that aggressive surgical debulking should be considered among older adults. My colleagues and I concur with that statement. We recently published a study evaluating 1001 cytoreductive procedures in patients with metastatic NETs.[3] Patients experienced improved survival at all time points. We also examined the degree of cytoreduction. Reduction of 90% or higher improved symptom control and survival across all forms of NETs. For midgut tumors, a 70% or better cytoreduction improved survival.[4]

Tsukamato and colleagues examined the impact of PET/CT with gallium-68 DOTATATE in NETs at a private institution in Brazil.[5] This analysis confirmed earlier studies, showing that the gallium scan was sensitive in detecting NETs. Among a series of 28 patients, the uptake of gallium 68 was 82%. Uptake was 53.6% among patients with low Ki-67 (≤20%) expression vs 21.4% in patients with high Ki-67 expression (>20%). The authors concluded that poorly differentiated tumors do not uptake gallium 68 as efficiently as well-differentiated tumors, which is not an unexpected finding.

Ejaz and coworkers reported on the impact of extrahepatic disease among patients undergoing liver-directed therapy for neuroendocrine and liver metastases.[6] This multi-institutional analysis evaluated data from a variety of European and North American institutions. A total of 612 patients underwent liver-directed therapy. Overall survival and PFS were compared among 70 patients with or without extrahepatic disease. Most primary tumors originated from the pancreas (41%) and the small bowel (31%). After a mean follow-up of 51 months, the mortality rate was 28%, with a median survival of 140 months. Median overall survival was 87 months for patients with extrahepatic disease and not reached for those without (*P*=.002). PFS was shorter in patients with extrahepatic disease (46.8 months vs 68.6 months, respectively; Figure 9). The authors concluded that the presence of extrahepatic disease was independently associated with increased risk of death and progression of disease. In general, it appeared that patients with extrahepatic disease had more aggressive tumors.

Disclosure

Dr Boudreaux serves on the advisory board and as a speaker and consultant for Ipsen Biopharmaceuticals, Inc.

References

1. Strosberg J, Wolin E, Chasen B, et al. Quality-of-life findings in patients with midgut neuroendocrine tumors: results of the NETTER-1 phase III trial [ASCO GI abstract 348]. *J Clin Oncol*. 2017;35(suppl 4S).

2. Jutric Z, Raoof M, Lewis AG, et al. Role of aggressive surgical debulking in older adults with gastrointestinal neuroendocrine tumors [ASCO GI abstract 377]. *J Clin Oncol*. 2017;35(suppl 4S).

3. Wang YZ, Chauhan A, Rau J, et al. Neuroendocrine tumors (NETs) of unknown primary: is early surgical exploration and aggressive debulking justifiable? *Chin Clin Oncol*. 2016;5(1):4.

4. Woltering EA, Voros BA, Beyer DT, et al. Aggressive surgical approach to the management of neuroendocrine tumors: a report of 1,000 surgical cytoreductions by a single institution [published online January 11, 2017]. *J Am Coll Surg*. doi: 10.1016/j.jamcollsurg.2016.12.032.

5. Tsukamoto JS, Wassano NS, Barbosa LDR, et al. The clinical impact of PET/CT with ^{68}Ga-DOTATATE in neuroendocrine tumors (NETs): the experience of a private institution in Brazil [ASCO GI abstract 271]. *J Clin Oncol*. 2017;35(suppl 4S).

6. Ejaz A, Reames B, Maithel S, et al. The impact of extrahepatic disease among patients undergoing liver-directed therapy for neuroendocrine liver metastasis: a multi-institutional analysis [ASCO GI abstract 277]. *J Clin Oncol*. 2017;35(suppl 4S).

Recent Advances in the Management of Gastroenteropancreatic Neuroendocrine Tumors: Discussion

J. Philip Boudreaux, MD, FACS, Renuka Iyer, MD, and Alexandria T. Phan, MD

J. Philip Boudreaux, MD, FACS I was intrigued by the abstract using FOLFIRI for pancreatic NETs.[1] In what types of patients would you consider this approach?

Renuka Iyer, MD The study by Zhao and colleagues used FOLFIRI in patients with grade 3 neuroendocrine carcinoma.[1] Clinically, though, we tend to rely on biology when selecting treatment. Sometimes, the histology does not match what is happening in the patient. A patient known to have intermediate-grade disease can still have an aggressive course. In these situations, a biopsy may or may not show progression to a higher grade. I might consider FOLFIRI when all other options are exhausted, for example, after platinum and etoposide in a patient with a high-grade tumor.

J. Philip Boudreaux, MD, FACS How often do you rebiopsy these patients?

Renuka Iyer, MD I occasionally rebiopsy. In some cases, the lesion is high grade, and the rest of the disease is low grade.

Alexandria T. Phan, MD Irinotecan plus cisplatinum is an active regimen in high-grade NETs. The challenge is how to define high-grade tumors. A response to chemotherapy is typically seen in patients with a high-grade NET who have a Ki-67 level exceeding 50%. In the setting of pancreatic NETs, options include fluorouracil, gemcitabine, and temozolomide. These agents are more convenient to administer than FOLFIRI. FOLFIRI is not the standard of care. I would limit the use of FOLFIRI or folinic acid/fluorouracil/oxaliplatin (FOLFOX) regimens to patients who have no other treatment options or high-grade NETs. The caveat is how to define high-grade disease. Specialists in pancreatic NETs are already redefining high grade, by introducing more subgroups.

Renuka Iyer, MD The Nordic Neuroendocrine Tumour Group study used a Ki-67 level exceeding 55% to define high-risk disease.[2] Current guidelines state that management of high-grade NETs should follow that used in patients with small-cell lung cancer.[3] It can be difficult to obtain approval for a drug that is not included in the compendia for the NCCN guidelines or that has not been evaluated in small-cell lung cancer. There are studies for FOLFOX in NETs originating from outside the lungs.[4,5]

Optimal sequencing, as well as personalization of therapy according to comorbidities, prior therapies, disease burden, and disease location, will be based on clinical judgment and multidisciplinary discussion. Access to novel therapies will need to be improved. However, this is a very exciting time for patients with NETs.

J. Philip Boudreaux, MD, FACS I would echo those remarks. Patients can be divided in many ways: symptomatic vs asymptomatic, high tumor burden vs low tumor burden, functional tumors vs nonfunctional tumors. These characteristics dictate the types of therapy that should be initiated. Symptoms should be addressed, regardless of whether patients have high-volume or low-volume disease. The cause of symptoms can be difficult to discern. For example, symptoms can arise from a bowel obstruction or pancreatic insufficiency in patients treated with a somatostatin analogue. A patient's nutritional fitness also dictates the treatment approach. The tolerability of their physiology must be a consideration.

PRRT will likely be approved by the FDA in 2017. How will this modality fit in the management plan? Are you more inclined to use it upfront or later?

Alexandria T. Phan, MD It will depend on access, which may be limited for many patients. Ideally, I would use PRRT upfront as much as possible, particularly for midgut NETs. Data from Europe support the use of PRRT in pancreatic NETs,[6] but those rates are similar to those seen with systemic chemotherapy. It also depends on what the patient can tolerate.

Renuka Iyer, MD I agree with Dr Phan. PRRT is administered differently in the United States than in Europe. The role of chemotherapy and systemic therapy will likely remain the same.

J. Philip Boudreaux, MD, FACS Is there any reason that PRRT cannot be administered concurrently with chemotherapy and systemic therapy?

Renuka Iyer, MD There are no data for this approach. Safety would be a consideration, as well as approval from insurance.

J. Philip Boudreaux, MD, FACS The hardest group of patients to treat are those with pancreatic NETs. They have a different disease that advances more quickly than other GEP-NETs, such as those originating in the small bowel.

Alexandria T. Phan, MD Although patients with pancreatic NETs have many more treatment options, it is not yet known how to best sequence and use them.

Disclosures

Dr Boudreaux serves on the advisory board and as a speaker and consultant for Ipsen Biopharmaceuticals, Inc. Dr Iyer is a consultant for Ipsen Biopharmaceuticals, Inc, and Novartis. She has received grant funding from Ipsen Biopharmaceuticals, Inc. 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.

References

1. Zhao X, Wang CC, Zhang W, Zhu X, Guo W, Chen Z. Preliminary analysis of FOLFIRI regimen with or without bevacizumab as second-line systemic therapy in patients with metastatic gastroenteropancreatic neuroendocrine carcinoma [ASCO GI abstract 469]. *J Clin Oncol*. 2017;35(suppl 4S).
2. Sorbye H, Welin S, Langer SW, et al. Predictive and prognostic factors for treatment and survival in 305 patients with advanced gastrointestinal neuroendocrine carcinoma (WHO G3): the NORDIC NEC study. *Ann Oncol*. 2013;24(1):152-160.
3. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Neuroendocrine tumors. Version 1.2017. National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf. Updated February 21, 2017. Accessed March 16, 2017.
4. Faure M, Niccoli P, Autret A, Cavaglione G, Mineur L, Raoul JL. Systemic chemotherapy with FOLFOX in metastatic grade 1/2 neuroendocrine cancer. *Mol Clin Oncol*. 2017;6(1):44-48.
5. Hadoux J, Malka D, Planchard D, et al. Post-first-line FOLFOX chemotherapy for grade 3 neuroendocrine carcinoma. *Endocr Relat Cancer*. 2015;22(3):289-298.
6. van der Zwan WA, Bodei L, Mueller-Brand J, de Herder WW, Kvols LK, Kwekkeboom DJ. GEPNETs update: radionuclide therapy in neuroendocrine tumors. *Eur J Endocrinol*. 2015;172(1):R1-R8.

Highlights in GEP-NETs From the 2017 ASCO Gastrointestinal Cancers Symposium

January 19-21, 2017 • San Francisco, California

Safety and Tolerability of Lanreotide Autogel/Depot in Patients With Neuroendocrine Tumors: Pooled Analysis of Clinical Studies

The phase 3 trials CLARINET and ELECT compared lanreotide depot/autogel vs placebo in patients with NETs. Lanreotide depot/autogel was associated with a significant improvement in PFS among patients with advanced GEP-NETs in the CLARINET trial. ELECT found that patients treated with lanreotide depot/autogel were less likely to need short-acting rescue medication for certain symptoms of carcinoid syndrome. At the ASCO GI Cancers Symposium, Dr Alexandria Phan presented results from a pooled analysis evaluating safety and tolerability in these trials, their quality-of-life extensions, and 3 additional open-label studies (abstract 398). The analysis included 378 patients treated with lanreotide depot/autogel and 160 patients treated with placebo. The overall incidences of adverse events and serious adverse events were similar among patients, regardless of treatment. The most common treatment-related adverse event was abdominal pain, reported in 9.5% of patients who received lanreotide depot/autogel vs 1.3% of those who received placebo. Other common treatment-related adverse events were cholelithiasis (8.5% vs 1.9%), injection site pain (7.9% vs 2.5%), and nausea (5.6% vs 1.9%). Some of the studies showed that lanreotide depot/autogel was associated with a trend toward improved quality of life, particularly among patients with functioning NETs receiving treatment for symptoms associated with carcinoid syndrome.

Quality-of-Life Findings in Patients With Midgut Neuroendocrine Tumors: Results of the NETTER-1 Phase III Trial

The phase 3 NETTER-1 trial of patients with advanced, progressive midgut NETs found that ^{177}Lu-DOTATATE was superior to high-dose octreotide long-acting release in terms of progression-free survival (not reached vs 8.4 months; $P<.0001$) and overall response rate (18% vs 3%; $P=.0008$). An interim analysis of overall survival also favored ^{177}Lu-DOTATATE, but results must be confirmed. Quality-of-life data were reported by Dr Jonathan Strosberg (abstract 348). Global health status improved in 28% of patients receiving ^{177}Lu-DOTATATE vs 15% of patients receiving octreotide. Flushing/sweats improved in 42% of the ^{177}Lu-DOTATATE arm vs 38% of the octreotide arm, and worsened in 22% vs 19%, respectively. In the ^{177}Lu-DOTATATE arm, pain improved in 41% and worsened in 17%. These rates were 28% vs 17% in the octreotide arm. Improvements in diarrhea were seen in 39% of the ^{177}Lu-DOTATATE arm vs 23% of the octreotide arm. Diarrhea worsened in 19% vs 23%, respectively. The authors concluded that ^{177}Lu-DOTATATE is associated with more benefits than high-dose octreotide in several quality-of-life domains.

Treatment Patterns Among Metastatic GEP-NET Patients Treated at a Tertiary Referral Center

Treatment options for patients with GEP-NETs have increased in recent years. A cohort study presented by Dr Jessica Jalbert evaluated management strategies for patients with GEP-NETs treated at the Dana-Farber Cancer Institute (abstract 397) between 2003 and 2015. This analysis included 682 patients, among whom 45% had midgut GEP-NETs, 29% had pancreatic GEP-NETs, and 26% had other types. Throughout the follow-up analysis, 87.0% of patients initiated at least 1 type of treatment. Treatment with a somatostatin analogue (as monotherapy or in combination) was the most common strategy for metastatic GEP-NETs. More than three-quarters of patients (77.4%) were treated with a somatostatin analogue. Combination therapy including a somatostatin analogue was increasingly common in later treatment lines. The median duration of treatment with a somatostatin analogue in the first-line setting was 783 days, compared with 349 days in the second-line setting and 259 days in the third-line setting. Continued use of a somatostatin analogue was common, and 82.2% of patients were receiving treatment when they died or when the study ended.

Phase II Trial of Cabozantinib in Patients With Carcinoid and Pancreatic Neuroendocrine Tumors (pNET)

Cabozantinib inhibits the vascular endothelial growth factor receptor 2 and c-MET, which have been associated with the growth of NETs. A phase 2 trial evaluated cabozantinib in patients with carcinoid or pancreatic NETs. Dr Jennifer Chan presented the results (abstract 228). Among the 20 patients with pancreatic NETs, the overall response rate was 15%, consisting entirely of partial responses among the 20 patients with pancreatic NETs and the 41 patients with carcinoid tumors. Rates of stable disease were 75% and 63%, respectively. Median progression-free survival was 21.8 months in patients with pancreatic NETs and 31.4 months in patients with carcinoid tumors. The toxicity data were consistent with previous reports. The most common grade 3/4 treatment-related adverse events were hypertension (reported in 13%), hypophosphatemia (11%), and diarrhea (10%). Development of a phase 3 trial is underway.

An Open-Label, Single-Group, Multicenter Phase II Study of Lanreotide Autogel (LAN) in Japanese Patients (pts) With Neuroendocrine Tumors (NET)

Dr Tetsuhide Ito presented results from an open-label, single-group, phase 2 trial of lanreotide depot/autogel among Japanese patients with grade 1 or 2 NETs that were unresectable and metastatic or locally advanced (abstract 471). The trial enrolled 32 patients from 10 sites. Progressive disease was reported at baseline in 39.3%. Patients were treated with lanreotide depot/autogel at a dose of 120 mg once every 4 weeks for 48 weeks. Patients who completed this study were enrolled in a long-term extension trial. The primary endpoint was the clinical benefit rate, which encompassed complete response, partial response, and stable disease at 24 weeks. Among the 28 patients in the full analysis set, the clinical benefit rate was 64.3%. The median PFS was 36.3 weeks. Median PFS was more than double in patients without baseline progressive disease vs those with progressive disease (53.1 weeks vs 25.1 weeks). During the 60-week extension study, there was 1 partial response, for an overall response rate of 3.6%. Levels of serum chromogranin A decreased by at least 50% in 88.2% of the 17 patients who had elevated levels at baseline. The most common adverse reactions related to treatment were injection site induration (28.1%), pale stools (18.8%), flatulence (12.5%), and diabetes (12.5%).

Preliminary Analysis of FOLFIRI Regimen With or Without Bevacizumab as Second-Line Systemic Therapy in Patients With Metastatic Gastroenteropancreatic Neuroendocrine Carcinoma

A retrospective analysis by Dr Xiaoping Zhao evaluated the use of FOLFIRI in patients with GEP-NETs (abstract 479). The study included 11 patients who required further treatment after first-line chemotherapy consisting of etoposide/cisplatin combinations (n=8), capecitabine-based regimens (n=2), or gemcitabine with nab-paclitaxel (n=1). All patients had metastatic disease. The median number of FOLFIRI cycles was 8 (range, 3-36). In 6 patients, bevacizumab was added to FOLFIRI. The median PFS was 3.77 months among all patients and 4.77 months among the patients who also received bevacizumab. Among all patients, a partial response occurred in 3 (27.3%), stable disease in 4 (36.4%), and tumor progression in 4 (36.4%). The addition of bevacizumab increased the disease control rate to 66.7%, with 3 partial responses (50.0%) and 1 report of stable disease (16.7%). Among all patients, the most common toxicities were grade 1/2 anemia (occurring in 63.7%), grade 1/2 thrombocytopenia (27.2%), and grade 3/4 neutropenia (27.2%).

Efficacy of Lanreotide Depot (LAN) for Symptomatic Control of Carcinoid Syndrome (CS) in Patients With Neuroendocrine Tumor (NET) Previously Responsive to Octreotide (OCT): Subanalysis of Patient-Reported Symptoms From the Phase III ELECT Study

A subanalysis of the ELECT study evaluated whether treatment with lanreotide depot/autogel improved flushing and diarrhea. Dr Rodney Pommier presented the results (abstract 378). All patients had NETs and a history of carcinoid syndrome. Patients could be octreotide-naive (n=51) or responsive to octreotide (either long-acting [n=56] or short-acting [n=24]). The least square mean percentage of days with moderate or severe diarrhea and/or flushing was significantly lower for patients treated with lanreotide depot/autogel (23.4%) than placebo (35.8%; *P*=.004). This subanalysis also measured levels of 5-HIAA. Among the lanreotide depot/autogel arm, levels dropped by 30% or more to normal by week 12 in 35% of octreotide-naive patients and 29% of patients previously treated with octreotide. In the placebo arm, decreases in levels of 5-HIAA were reported in 15% of octreotide-naive patients and 7% of patients who had previously received octreotide.

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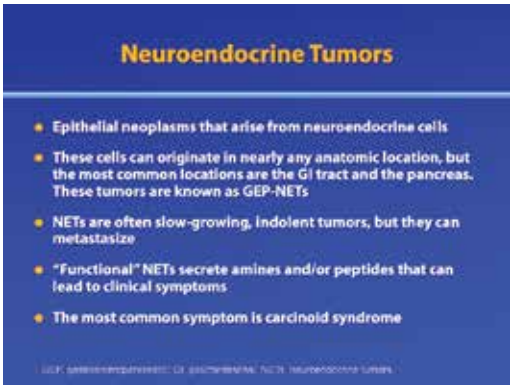

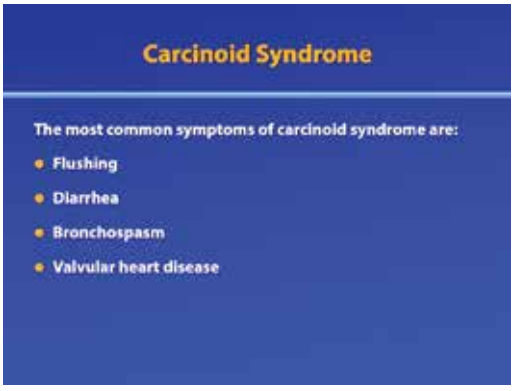

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Recent Advances in the Management of Gastroenteropancreatic Neuroendocrine Tumors: Insights From the 2017 ASCO Gastrointestinal Cancers Symposium

CME Post-Test: *Circle the correct answer for each question below.*

1. Which symptom is not a common component of carcinoid syndrome?

   a. Bronchospasm
   b. Cholelithiasis
   c. Diarrhea
   d. Valvular heart disease

2. In the CLARINET trial, what was the median PFS associated with lanreotide depot/autogel?

   a. 14.7 months
   b. 16.5 months
   c. 18.0 months
   d. Not reached

3. In a phase 4 trial of sunitinib, what was the median PFS?

   a. 11.1 months
   b. 12.6 months
   c. 13.2 months
   d. Not reached

4. In a cohort analysis of patients with GEP-NETs treated at the GI Cancer Centers of the Dana-Farber Cancer Institute or the Brigham and Women's Hospital, what was the most frequently used treatment?

   a. Angiogenesis inhibitors
   b. Cytotoxic agents
   c. mTOR inhibitors
   d. Somatostatin analogues

5. Which agent is a tryptophan hydroxylase inhibitor?

   a. Cabozantinib
   b. Combretastatin A4 phosphate
   c. Everolimus
   d. Telotristat ethyl

6. A study of the genetic signature of well-differentiated pancreatic NETs showed that changes in which gene were seen only in poorly differentiated NETs?

   a. *ATRX*
   b. *DAXX*
   c. *RB1*
   d. *SETD2*

7. In a phase 2 trial of cabozantinib, what was the progression-free survival among patients with pancreatic NETs?

   a. 6.8 months
   b. 18.7 months
   c. 21.8 months
   d. 31.2 months

8. Left untreated, a GEP-NET will eventually:

   a. Hemorrhage
   b. Obstruct
   c. Perforate
   d. All of the above

9. In a quality-of-life analysis from the NETTER-1 trial, diarrhea improved in __ of patients treated with ^{177}Lu-DOTATATE.

   a. 22%
   b. 27%
   c. 35%
   d. 39%

10. In a study of patients undergoing liver-directed therapy for neuroendocrine and liver metastases, what was the PFS among patients with extrahepatic disease?

    a. 46.8 months
    b. 52.3 months
    c. 57.1 months
    d. 63.9 months

Evaluation Form: Recent Advances in the Management of Gastroenteropancreatic Neuroendocrine Tumors: Insights From the 2017 ASCO Gastrointestinal Cancers Symposium

If you wish to receive acknowledgment for completing this activity, please complete the post-test by selecting the best answer to each question, complete this evaluation verification of participation, and fax to: (303) 790-4876. You may also complete the post-test online at www.cmeuniversity.com. On the navigation menu, click on "Find Post-tests by Course" and search by **project ID 12281**. Upon successfully registering/logging in, completing the post-test and evaluation, your certificate will be made available immediately.

1. What degree best describes you?

❒ MD/DO ❒ PA/PA-C ❒ NP ❒ RN ❒ PharmD/RPh ❒ PhD
❒ Other, please specify:

2. What is your area of specialization?

❒ Oncology, Medical ❒ Surgery/Surgical Oncology ❒ Oncology, Radiation

3. Which of the following best describes your *primary* practice setting?

❒ Solo Practice ❒ Group Practice ❒ Government
❒ University/teaching system ❒ Community Hospital
❒ HMO/managed care ❒ Non-profit/community ❒ I do not actively practice
❒ Other, please specify:

4. How long have you been practicing medicine?

❒ More than 20 years ❒ 11-20 years ❒ 5-10 years ❒ 1-5 years
❒ Less than 1 year ❒ I do not directly provide care

5. Approximately how many patients do you see each week?

❒ Less than 50 ❒ 50-99 ❒ 100-149 ❒ 150-199 ❒ 200+
❒ I do not directly provide care

6. How many patients do you currently see each week who have neuroendocrine tumors?

❒ Fewer than 5 ❒ 6-15 ❒ 16-25 ❒ 26-35 ❒ 36-45 ❒ 46-55
❒ 56 or more ❒ I do not directly provide care

7. Rate how well the activity supported your achievement of these learning objectives:

Discuss strategies to refine the management of patients with GEP-NETs
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Describe the incorporation of emerging treatment options into the standard of care for patients with GEP-NETs
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Discuss the role of multidisciplinary care in the treatment of GEP-NETs
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

Analyze results from clinical trials presented at the 2017 American Society of Clinical Oncology Gastrointestinal Cancers Symposium
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

8. Rate how well the activity achieved the following:

The faculty were effective in presenting the material
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The content was evidence based
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The educational material provided useful information for my practice
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity enhanced my current knowledge base
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The activity provided appropriate and effective opportunities for active learning (e.g., case studies, discussion, Q&A, etc.)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

The opportunities provided to assess my own learning were appropriate (e.g., questions before, during or after the activity)
❒ Strongly Agree ❒ Agree ❒ Neutral ❒ Disagree ❒ Strongly Disagree

9. Based upon your participation in this activity, do you intend to change your practice behavior? *(choose only one of the following options)*

❒ I do plan to implement changes in my practice based on the information presented
❒ My current practice has been reinforced by the information presented
❒ I need more information before I will change my practice

10. Thinking about how your participation in this activity will influence your patient care, how many of your patients are likely to benefit?

Please use a number (for example, 250):

11. If you plan to change your practice behavior, what type of changes do you plan to implement? *(check all that apply)*

❒ Apply latest guidelines ❒ Choice of treatment/management approach
❒ Change in pharmaceutical therapy ❒ Change in current practice for referral
❒ Change in nonpharmaceutical therapy ❒ Change in differential diagnosis
❒ Change in diagnostic testing ❒ Other, please specify:

12. How confident are you that you will be able to make your intended changes?

❒ Very confident ❒ Somewhat confident ❒ Unsure ❒ Not very confident

13. Which of the following do you anticipate will be the primary barrier to implementing these changes?

❒ Formulary restrictions ❒ Insurance/financial issues ❒ Time constraints
❒ Lack of multidisciplinary support ❒ System constraints
❒ Treatment-related adverse events ❒ Patient adherence/compliance
❒ Other, please specify:

14. Was the content of this activity fair, balanced, objective and free of bias?

❒ Yes ❒ No, please explain:

15. Please list any clinical issues/problems within your scope of practice you would like to see addressed in future educational activities:

Request for Credit (*required fields)

Name* _____

Degree* _____

Organization _____

Specialty* _____

City, State, ZIP* _____

Telephone _____ Fax _____

E-mail* _____

Signature* _____ Date* _____

For Physicians Only:

I certify my actual time spent to complete this educational activity to be:

❒ I participated in the entire activity and claim 1.50 credits.
❒ I participated in only part of the activity and claim _____ credits.

Post-test Answer Key

1	2	3	4	5	6	7	8	9	10

Project ID: **12281**