Beyond Symptom Control: Continued Advances in Targeting Gastroenteropancreatic Neuroendocrine Tumors

A Review of an Adjunct Symposium of the 2014 European Society for Medical Oncology Congress

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Supported through an educational grant from Ipsen Biopharmaceuticals, Inc.
Target Audience
This activity has been designed to meet the educational needs of physicians, nurses, academicians, researchers, investigators, support staff, and program directors from the field of oncology involved in the care of patients with thyroid carcinoma.

Statement of Need/Program Overview
Although mortality from thyroid cancer has remained relatively low, the proportion of patients dying of the disease is increasing. The pathologic and clinical differences observed across the spectrum of thyroid cancers influence the treatment approach. Risk group stratification is the most important clinical parameter for predicting prognosis and for planning treatment. Thyroid cancer is primarily managed with surgery, but there are cases in which surgery fails or is insufficient. Radioactive iodine (RAI) was established as a standard treatment more than 50 years ago. Soon after, it was recognized that RAI is not effective in all patients. Until recently, there were few options for patients with RAI-refractory disease. The elucidation of key signaling pathways in thyroid cancer has led to the development of targeted therapies that provide needed therapeutic options for these patients. In the past 4 years, the US Food and Drug Administration has approved 3 new treatments, and several other novel agents are in late-phase clinical trials.

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

- Identify thyroid cancer patients who are refractory to radioactive iodine
- Employ risk group stratification to predict prognosis and plan treatment
- Describe the clinical significance of molecular pathways targeted by multikinase inhibitors
- Evaluate the latest clinical trial data supporting the use of tyrosine-kinase inhibitors in iodine-refractory thyroid carcinoma
- Apply strategies to manage the adverse events associated with novel targeted therapies for thyroid carcinoma

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This monograph was authored by an independent medical writer, Mindy Tanzola, PhD, based on presentations given at “New Frontiers and Treatment Paradigms for Thyroid Carcinoma,” an adjunct symposium of the 2014 American Society of Clinical Oncology Annual Meeting, held on June 2, 2014.
Neuroendocrine tumors (NETs) are initially indolent, but they can progress and lead to significant morbidity. Overall survival and outcomes in pancreatic NET patients have slowly improved throughout the past few decades, largely in response to advances in treatment. In the 1980s, significant improvements were seen with the introduction of somatostatin analogs. In 2011, the US Food and Drug Administration (FDA) approved 2 targeted agents for gastroenteropancreatic neuroendocrine tumors (GEP-NETs): sunitinib for the treatment of progressive well-differentiated pancreatic NETs in patients with unresectable, locally advanced, or metastatic disease; and everolimus for the treatment of pancreatic NETs that have progressed and cannot be treated with surgery. Sunitinib and everolimus were both associated with improved progression-free survival in clinical trials. The current treatment landscape also includes liver-directed therapy, surgical interventions, and peptide receptor radionuclide therapy (PRRT), which has been used in Europe but is less common in the United States. There are also effective chemotherapeutic agents. Patients who are diagnosed with pancreatic NETs, or NETs in general, have more treatment options that lead to better prognoses than were expected even 15 years ago.

**Emerging Treatment Approaches**

The latest option in the treatment of GEP-NETs is the somatostatin analog lanreotide depot/autogel. In the United States, lanreotide depot is approved by the FDA for acromegaly. In the European Union, lanreotide autogel is approved for acromegaly and for NET-associated carcinoid syndrome. The phase 3 CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) study evaluated the use of lanreotide depot/autogel in patients with grade 1 or 2 GEP-NETs that were well-differentiated or moderately differentiated, nonfunctioning, and locally inoperable or metastatic. Among the 204 patients enrolled, 91 had pancreatic NETs, 73 had midgut NETs, and 14 had hindgut NETs. (In the remaining 26 patients, the tumor was categorized as “other” or “unknown.”)

The CLARINET trial demonstrated that progression-free survival can be improved with a somatostatin analog alone. The median progression-free survival was not reached with lanreotide depot/autogel vs 18.0 months with placebo. At 2 years, the estimated PFS rate was 65% with lanreotide depot/autogel and 33% with placebo. It is expected that these results will expand the FDA-approved indication for lanreotide to include GEP-NET patients. The CLARINET trial also showed that patients with well-differentiated tumors could benefit from a somatostatin analog. This observation should have been shown in 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) trial, which evaluated the effect of the long-acting release formulation of octreotide in the control of tumor growth in 85 patients with advanced midgut NETs. The median PFS was 14.3
months with octreotide and 6.0 months with placebo. The PROMID study, however, was insufficiently powered and too small to provide data on well-differentiated tumors.

**Areas of Research**

The best use of the many available treatments for NET is currently uncertain. It is not yet known which agent should be used first, how to combine treatments, and which types of patients are most likely to benefit from which agents. Pancreatic NETs can vary in several ways, such as indolence, extent of progression, and amount of volume. Leaders in the field of NET will need to resolve questions about the optimal management approaches.

Research in this area is now focusing on pathways, such as Tec, which might be amenable to targeted therapies. As one example, there is excitement over the use of Tec inhibitors in pancreatic NETs.

Carcinoid tumors are another area of research. In the United States, no therapy is approved for disease control in well-differentiated NETs. Based on the results of the CLARINET trial, lanreotide depot/autogel may become the first agent approved for disease control in carcinoid tumors. In addition, results from the upcoming RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) study may demonstrate a benefit of everolimus for this population. Carcinoid tumors are more indolent than pancreatic NETs. The best that any therapy is likely to achieve is disease control; cytoreduction is unlikely. The optimal outcome will be to keep the disease stable, unless better surgical resection techniques or local therapies become available.

**Presentations at the 2014 ESMO Congress**

There were several abstracts presented at the 2014 European Society for Medical Oncology Congress that offered insight into the management of pancreatic NETs. Dr James C. Yao discussed updated overall survival data for RADIANT-3 (RAD001 in Advanced Neuroendocrine Tumors, Third Trial), the pivotal phase 3 study randomizing patients with pancreatic NETs to either everolimus or placebo. The primary outcome—progression-free survival—was reported in 2011; it more than doubled with everolimus (11.0 months vs 4.6 months). Three years later, almost all enrolled patients met the criteria for survival assessment. Crossover was permitted, and 87% of the placebo arm went on to receive treatment with everolimus. Among the patients with progressions, pancreatic NETs, survival from study entry was 44 months among those initially randomized to everolimus, the longest overall survival in these patients. Among those initially randomized to placebo, the survival was 37.7 months. The log-rank P value was 0.30. The difference failed to meet statistical significance most likely because of the high rate of crossover patients, which essentially condensed the 2 treatment arms into 1 arm. This analysis of RADIANT-3 showed an impressive improvement in overall survival among patients with pancreatic NETs, regardless of the treatment arm. Although the data suggest a benefit from everolimus over placebo, the study design precludes a direct comparison. The results appear to show that patients will benefit from everolimus whether it is given earlier or later in the course of treatment.

**References**

13. Research in this area is now focusing on pathways, such as Tec, which might be amenable to targeted therapies.
Abstract 1132O  Everolimus for the Treatment of Advanced Pancreatic Neuroendocrine Tumors: Final Overall Survival Results of a Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase III Trial (RADIANT-3)

J. Yao

RADIANT-3 3 (RAD001 in Advanced Neuroendocrine Tumors, Third Trial) is a placebo-controlled, phase 3 study that enrolled 410 patients from 18 countries. Patients had well-differentiated histology, documented radiologic progression within 12 months of randomization, and a World Health Organization performance status of 0, 1, or 2. They were randomized to receive everolimus (n=207) or placebo (n=203). The primary endpoint, progression-free survival, was reported in 2011 (N Engl J Med. 2011;364[6]:514-523). In the everolimus group, median progression-free survival was prolonged by 6.4 months, a 2.4-fold increase from 4.6 months to 11 months. At the 2014 European Society for Medical Oncology (ESMO) congress, Dr Yao presented results of the final overall survival and safety update for RADIANT-3.

Everolimus was associated with a nonsignificant improvement in median overall survival of 6.3 months. In the placebo arm, 85% of patients crossed over to everolimus upon disease progression or completion of the core blinded phase of the study. The high crossover rate essentially meant that the main comparison was between early treatment vs late treatment after an additional progression cycle. Among the population of patients with progressive pancreatic neuroendocrine tumors, survival from study entry was 44 months among those initially randomized to everolimus and 37.7 months among those initially randomized to placebo. The log-rank P value was 0.30 and did not achieve statistical significance.

The safety profile of everolimus observed during the open-label extension phase was similar to the known safety profile of everolimus and to that observed during the double-blind phase. The most common adverse event was stomatitis with aphthous ulceration, which occurred among 54% of patients receiving everolimus during the double-blind phase vs 13% of the patients receiving placebo.

Abstract 1134 PD  Treatment Satisfaction, Symptom Control and Quality of Life With Lanreotide Autogel in Neuroendocrine Tumour Patients With Carcinoid Syndrome: Results From the SymNET Study


The SymNET study was an observational trial of patients with NETs and carcinoid syndrome who received treatment with the long-acting somatostatin analog lanreotide. Health-related quality-of-life data were presented at the 2014 ESMO congress.

After treatment, 76% of patients were completely satisfied and 73% were rather satisfied with the primary endpoint, diarrhea control. Slightly fewer patients, 73%, were completely or rather satisfied with flushing control. Cognitive and sexual functioning improved in 80.2% and 68.9%, respectively. Most patients reported improved social functioning and global health status/quality of life. Smaller proportions of patients experienced worse symptoms after treatment, notably fatigue (35.0%), diarrhea (34.0%), insomnia (30.7%), muscle/bone pain (29.4%), GI symptoms (23.0%), and dyspnea (20.4%). Disease-related worries were worse after treatment in 45.5%.

This analysis also included data by physicians gathered at an assessment visit. After treatment, mean daily stool frequency was significantly reduced to 2.1 (95% CI, 1.7-2.5). The percentages of patients reporting stool urgency decreased (from 73% to 41%), as did those with stool leakage (from 21% to 9%), associated pain (from 37% to 14%), and flushing (from 61% to 33%).

1141PD  Gastroenteropancreatic Neuroendocrine Tumors (GEPNET) Registry: Update From an International Collaboration

The GEPNET registry is collecting data on the prevalence, incidence, regional trends in diagnosis, and clinical management of GEP-NET. Enrolled patients are from Turkey and South Africa, as well as the Asian-Pacific and Middle Eastern regions. Enrollment lasted from July 2009 to December 2012. Results from an interim analysis were presented at the 2014 ESMO congress. The registry enrolled essentially equal numbers of men (49%) and women (51%). The median age of diagnosis was 54 years (range, 12-87 years). The median progression-free survival was 57.3 months. The most common primary disease sites were the pancreas (42%) and the stomach (17%). Most patients (70%) had well-differentiated tumors. The most frequent symptoms were abdominal pain and weight loss. Most patients underwent immunostaining for synaptophysin (77%) and chromogranin A (82%). Fewer patients had received proliferative indices, such as the mitotic index (17%) and Ki-67 (50%). Tests used less often included serum chromogranin A testing at diagnosis (11%) and 24-hour urine 5HIAA tests (7%). Computed tomography scanning was the most common technique used for disease evaluation (44%). Surgery (60%) was the most common initial therapy, followed by somatostatin analogs (17%) and chemotherapy (16%).

Abstract 1145P Efficacy of Somatostatin Analogs (SSA) in Gastroenteropancreatic Neuroendocrine Tumors (GEP-NET) According to Ki67 Index: A Single Centre Experience


Dr Marconcini and colleagues presented results from a retrospective analysis of 137 patients with advanced GEP-NETs. The patients received upfront treatment with octreotide LAR or lanreotide LAR until disease progression. There were 87 gastrointestinal NET patients and 50 pancreatic NET patients. Ki-67 information was available for 89%; it was less than 3% in 38 patients, 3% to 5% in 15 patients, 5% to 10% in 15 patients, and more than 10% in 21 patients.

The median time between the diagnosis of NET and initiation of treatment was 5.2 months. Twelve patients (9%) achieved a partial response, and 112 patients (81%) had stable disease. Thirteen patients (10%) had progressive disease. The authors analyzed the progression-free survival data in several different ways. The median progression-free survival was 24.6 months in patients receiving octreotide and 21.83 months in patients receiving lanreotide. Median progression-free survival was 24.73 months in pancreatic NET patients and 21.73 in gastrointestinal NET patients. Median progression-free survival also varied according to the Ki-67 index; it was 27.15 months at less than 2%, 34.77 months at 2% to 5%, 28.3 months at 5% to 10%, and 20 months at greater than 10%.

Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): A Closer Look at the Characteristics of These Diverse Tumors

Ulrich-Frank Pape, MD

Neuroendocrine neoplasias are a heterogeneous group of tumors that can develop in cells throughout the diffuse endocrine system, causing a wide spectrum of clinical manifestations and sequelae. The gastrointestinal tract, as the largest endocrine organ in the body, is a common site for the development of neuroendocrine tumors (NETs). Neoplasms occur in cells that exert effects on digestion and metabolic processes throughout the gastrointestinal system. The remaining tumors are “nonfunctional” and do not cause hormonal symptoms; they must be diagnosed through other methods. Hormone hypersecretion syndromes lead to a broad spectrum of clinical manifestations. The most common hormone hypersecretion syndrome is carcinoid syndrome, which can cause flushing, diarrhea, and edema. The next most common syndromes are insulinoma and gastrinoma, which is associated with peptic ulcer disease and secondary diarrhea (Figure 1). More rare syndromes include glucagonoma, Verner-Morrison syndrome, and Cushing syndrome.
diverse clinical manifestations of NETs require a variety of treatment approaches.

The first classification system for NETs, published in 1963, categorized carcinoid tumors according to their location within the embryonic gastrointestinal tract—the foregut (the thymus, lung, esophagus, stomach duodenum, and pancreas), the midgut (the jejunum, ileum, cecum, and ascending and transverse colon), or the hindgut (the descending and sigmoid colon and rectum). This classification system is no longer used today, and it does not provide guidance regarding prognosis or treatment stratification. It remains useful, however, for considering likely clinical manifestations and potential treatment responses.

The most common primary tumor sites of gastrointestinal NETs in Western populations are the pancreas (16%), bronchus (15%), stomach (15%), jejunum/ileum (15%), appendix (10%), and rectum (10%). There are geographic differences in the distribution of gastroenteropancreatic NETs (GEP-NETs). In Japan, the most common tumor sites are the rectum (56%), followed by the duodenum (17%) and the stomach (15%). Japanese data include a relatively high incidence of small, early-stage tumors that occur primarily in the rectum but also in the pancreas.

The incidence of GEP-NETs has increased in recent decades, as reported in both the US Surveillance, Epidemiology, and End Results (SEER) database and in a population-based study in Europe. Increases have been reported for nearly all organ manifestations. Factors leading to the increased diagnoses include the introduction of statin analogs as a treatment option, which provided an incentive to identify patients; and the introduction of specific immunohistochemical markers—synaptophysin and chromogranin A—which enabled better detection of these tumors.

GEP-NETs predominately affect older adults, but they can also develop in younger people. In one series of patients, the median age at diagnosis was 59 years, but the range spanned from 10 to 99 years. GEP-NETs are also biologically diverse. A prospective study in Austria of all GEP-NETs diagnosed within a 1-year period showed substantial heterogeneity in the biologic characteristics of GEP-NETs according to their location. GEP-NETs in the stomach, appendix, and rectum were classified primarily as benign or uncertain, whereas the majority of GEP-NETs in the small intestine, pancreas, and colon were malignant.

The diagnosis of GEP-NET includes a histopathologic analysis to identify the endocrine origin of the tumor. Markers used to establish neuroendocrine differentiation include synaptophysin (a marker for the small synaptic vesicles that store and secrete biogenic amines, such as serotonin) and chromogranin A (a marker for the large dense-core vesicles that store the peptides or propeptide hormones in endocrine cells).

In 1995, Capella and colleagues published a revised classification system for NETs of the lung, pancreas, and gastrointestinal system. The revised system attempted to account for the morphologic, functional, and biologic features of the tumors. The complexity of this classification system has limited its clinical applicability; however, its emphasis on primary tumor localization and extent of disease is notable, as these characteristics—in particular, the presence of metastatic disease—have been shown to have substantial prognostic importance (Figure 2).

The WHO classification criteria for neuroendocrine neoplasms have evolved substantially since their first publication in 1980. Today, they are widely used for the classification of NETs. In 2000, the World Health Organization (WHO) classified GEP-NETs into 3 categories based on their histologic differentiation. In 2010, the WHO criteria were updated to grade NETs according to their Ki-67 index (using the MIB-1 antibody). Ki-67 has demonstrated significant prognostic value in multiple studies of patients with NETs (Figure 3). German registration data indicate that both disease stage and tumor grade have significant prognostic value in GEP-NETs. Incorporation of Ki-67 into the WHO classification system was an essential update. Ki-67 levels are categorized as follows: 2% or less, grade 1; 3% to 20%, grade 2; higher than 20%, grade 3.

A staging system for GEP-NETs from stage I to stage IV has been developed based on a tumor/lymph node/metastasis (TNM) system specifically defined for each tumor manifestation. First proposed by the European Neuroendocrine Tumor Society (ENETS) and later adopted by the American Joint Committee on Cancer/Union for International Cancer Control, the system accounts for differences in growth patterns based on a tumor’s primary location. Within each tumor location, tumors are staged from T0 to T4 based on the tumor size and invasion into other tissue, as N0 or N1 based on the presence of regional lymph node metastasis, and as M0 or M1 based on the presence of distant metastasis.

Many of the GEP-NET staging systems have been clinically validated. Analysis of a Berlin cohort of 270 GEP-NETs of midgut and hindgut origin found that classification of tumors using the WHO criteria and the ENETS-TNM staging system yielded significant prognostic significance. Overall, 7% of tumors were stage 1, 8% were stage 2, 19% were stage 3, and 66% were stage 4. Five-year survival rates ranged from 100% for stages 1 and 2 to 83% for stage 4. Based on the WHO criteria, 62% of tumors were grade 1, 32% were grade 2, and 6% were grade 3; 5-year survival rates were 95%, 82%,
and 51%, respectively. The prognostic relevance of the classification system has also been validated for foregut NETs,27 gastric NETs,28 and pancreatic NETs.18,29 These studies have confirmed prognostic differences based on the primary tumor location.

Importantly, these outcomes are influenced by the treatments that patients have received. A multicenter analysis of 1072 patients who had undergone surgery for pancreatic NET confirmed the prognostic significance of the ENETS TNM staging system (Figure 4) and found that curative surgery was also independently associated with survival.30 Treatment is an important component of outcome for patients with GEP-NETs, and therapeutic strategies can be guided by the current classification systems.

**References**

New Directions in the Treatment of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs): Shifting From Symptom Management to Targeting Tumors

Matthias Weber, MD

Therapy for patients with NETs is based on 3 main therapeutic principles. The first principle is that surgical therapy is the only curative option for NETs; it is also used for debulking and to treat and prevent complications. The second principle is that symptomatic therapy can be used to control the hormonal symptoms associated with functioning NETs. The third principle is that antiproliferative therapy can be used to control tumor growth and possibly improve survival.

Surgical Therapy

Surgical resection is the only curative option for patients with differentiated (grade 1 or grade 2) GEP-NETs. Curative surgery of liver metastasis should also be considered when R0 or R1 resection is feasible. Surgery may also be undertaken to treat or prevent complications. For example, removal of the primary tumor is recommended in patients with metastatic midgut NETs, as even small tumors in this region can have severe complications. Debulking surgery should be considered when removal of more than 90% of the tumor mass can be achieved, particularly for hormonally active NETs. This approach will likely lead to improved survival, but it is not supported by evidence owing to selection bias.

Local ablative therapies may also have a role in patients with advanced NETs and liver metastases. Techniques include transarterial chemoembolization, radioembolization, and selective internal radiation therapy. These approaches provide symptomatic improvement in the majority of patients with highly vascularized, unresectable metastases, and they may also induce a morphologic response. Percutaneous radiofrequency ablation and cryoablation may be considered as cytoreductive therapy for patients with limited numbers (3-4) of smaller (<3-5 cm) liver metastases. These procedures can supplement surgical resection of liver metastases and provide symptomatic improvement in the majority of patients.

Symptomatic Therapy

The gold standard, first-line approach for symptomatic therapy of functionally active NETs is biotherapy with somatostatin analogs. Most NETs express somatostatin receptors. The somatostatin receptor subtype 2, the most prevalent in GEP-NETs, exerts an inhibitory effect on hormone secretion and proliferation. Treatment with somatostatin can effectively control hormonal symptoms associated with GEP-NETs. Clinical use of somatostatin is limited, however, by its short half-life.

Synthetic derivatives of somatostatin have been developed to overcome the short half-life of the native protein. The development of these agents was a significant advance in the treatment of patients with NETs. The somatostatin analog octreotide is administered by subcutaneous injection 2 to 3 times daily. Long-acting formulations have been developed for both octreotide and lanreotide depot/autogel. The octreotide long-acting release (LAR) formulation is administered once monthly via deep intramuscular injection, and lanreotide depot/autogel is administered once monthly via deep subcutaneous injection. Both octreotide and lanreotide depot/autogel show high affinity for the somatostatin subtype receptor 2 and are approved for antisecretory treatment in NETs.

Symptomatic responses were observed in approximately 65% to 75% of patients receiving lanreotide depot/autogel and octreotide LAR, and biochemical responses were observed in approximately 50% of patients. The symptomatic effect of lanreotide depot/autogel in patients with NETs was further evaluated in the multinational observational SymNET study, which included 273 patients with NET and a history of diarrhea associated with carcinoid syndrome. Patients had received lanreotide depot/autogel for at least 3 months. The majority of patients reported improvements in all symptoms, 76% reported satisfaction with diarrhea control, and 73% were satisfied with flushing control. Patients also reported favorable health-related quality-of-life outcomes, with a high level of ability to conduct activities and low symptom scores. Moreover, patient-reported outcomes were consistent with the investigators’ observations. The
SymNET (A Study to Assess Neuroendocrine Tumour [NET] Patients Currently Treated by Somatuline Autogel for History of Carcinoid Syndrome Associated With Episodes of Diarrhoea) study confirmed in a real-world setting the symptomatic effects of lanreotide depot/autogel in patients with functionally active GEP-NETs.

**Overview of Antiproliferative Therapy**

Antiproliferative therapy for GEP-NETs aims to control tumor growth and ultimately improve survival. It is important to consider the potential antiproliferative effects of therapy in the context of the natural history of GEP-NETs. These tumors generally grow slowly, and patients may demonstrate long phases of apparently stable disease followed by slowly progressive disease. Moreover, spontaneous remissions have been observed in patients with highly differentiated grade 1 or 2 NETs. Rapidly progressing disease is rare and typically observed only in highly aggressive grade 3 neuroendocrine carcinomas.

The typically slow course of NETs has led to the proposal of a fourth treatment principle, which involves watchful waiting for patients with apparently stable tumors who have no hormonal symptoms or clinical sequelae. Antiproliferative therapy is initiated upon disease progression. This strategy, however, has been challenged by recent findings indicating that somatostatin analogs exert an antiproliferative effect in addition to their symptomatic effect.6 This development may shift the therapeutic algorithm from one based on symptom management by somatostatin analogs in functionally active tumors toward a more integrative approach in which the tumor is targeted to control both hormone secretion and tumor growth.

Several mechanisms have been proposed to explain the antiproliferative activity of somatostatin analogs.6 Direct antitumor effects mediated through targeting of the somatostatin receptors on tumor cells may include inhibition of cell growth or cell cycle progression and induction of apoptosis.6 Indirect outcomes may include lowering of growth factors, in particular, insulin-like growth factor 1; inhibition of angiogenesis; and modulation of the immune system.

**The PROMID Study**

The ability of somatostatin analogs to control tumor growth was demonstrated in small studies but remained under debate until publication of the placebo-controlled, double-blind, prospective, randomized 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, which evaluated the effect of octreotide LAR in the control of tumor growth in 85 patients with advanced midgut NETs.8 This randomized, placebo-controlled trial was the first conducted in a well-defined population of patients with NETs. Notably, 41% of patients in the octreotide arm and 37% in the placebo arm had carcinoid syndrome at baseline. Approximately 75% of patients had a hepatic tumor load of less than 10% at baseline. More than 90% of patients had a Ki-67 level of 2% or less.

Octreotide LAR was associated with a significant improvement in progression-free survival (PFS) over placebo. The median PFS was 14.3 months with octreotide LAR and 6.0 months with placebo (Figure 5). The greatest benefit of octreotide LAR was observed in patients with midgut tumors, grade 1 tumors, and a hepatic tumor burden of less than 10%.8 Octreotide had the greatest effect in patients with minimal liver involvement, but this outcome may reflect tumor mass and disease progression. Somatostatin analog therapy failed to achieve an antiproliferative effect in patients with non-midgut tumors, higher liver tumor burden, grade 2 tumors, or progressive disease.

**The CLARINET Study**

The randomized, double-blind, placebo-controlled phase 3 CLARINET (Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors) study was undertaken to evaluate the antiproliferative effect of somatostatin analog therapy—in this case, with lanreotide depot/autogel—in a larger and more advanced patient population than in the PROMID trial.8,9 The CLARINET study enrolled 204 patients with grade 1 or 2 GEP-NETs that were well-differentiated or moderately differentiated (Ki-67 <10%), nonfunctioning, and locally inoperable or metastatic.9 Nearly all patients (96%) had not experienced tumor progression during the 3 to 6 months before randomization. In the study, patients were randomly assigned to receive subcutaneous lanreotide depot/autogel at 120 mg every 28 days or placebo every 28 days, with treatment continuing until tumor progression or death.

Lanreotide depot/autogel was associated with a significant 53% reduction in the risk of progression or death as compared with placebo. The median PFS was not reached with lanreotide depot/autogel vs 18.0 months with placebo (hazard ratio [HR], 0.47; 95% CI, 0.30-0.73; P<.001).9 At the end of 24 months, the estimated PFS rate was 65% with lanreotide depot/autogel and 33% with placebo (Figure 6). The antiproliferative effect of lanreotide depot/autogel demonstrated in the overall population was maintained during an analysis of predefined subgroups, including grade 1 vs grade 2 tumors and low
vs high hepatic tumor load. There was a trend toward improved PFS in patients with midgut and pancreatic NETs; the difference did not reach statistical significance in the pancreatic NET subgroup, although the CIs were wide owing to the small numbers of patients.

The safety analysis confirmed the good tolerability of somatostatin analogs demonstrated in other studies. The most prominent adverse events were diarrhea (reported in 26% of patients in the lanreotide depot/autogel group and 9% in the placebo group) and abdominal pain (reported in 14% and 2%, respectively). Other adverse effects were reported at similar levels with lanreotide depot/autogel and placebo. There were no significant differences in quality of life between the groups.

An open-label extension study evaluated the long-term safety and efficacy of lanreotide depot/autogel for up to 6 years in patients with GEP-NETs. The study included patients with stable disease who continued on lanreotide depot/autogel and patients in the placebo group with or without progressive disease who received open-label lanreotide depot/autogel. The median PFS in the lanreotide depot/autogel group was 32.8 months vs 18.0 months in the placebo group (Figure 7). The core CLARINET trial and the open-label extension phase used different radiologic assessment protocols (use of local vs central radiologic assessment), and therefore a direct comparison of outcomes is precluded. However, the open-label extension study suggests the extent of PFS improvement that might be attained with lanreotide depot/autogel. Among the patients who initially received placebo and switched to lanreotide depot/autogel after documented radiologic disease progression, the median time to second progression after starting lanreotide depot/autogel was 14 months.

In summary, the CLARINET study demonstrated that lanreotide depot/autogel was associated with a 53% reduction in the risk of progression or death in patients with metastatic well-differentiated or moderately differentiated GEP-NETs. This antiproliferative effect was observed in patients with grade 1 and grade 2 tumors, in patients with low and high hepatic tumor load, and, in the open-label extension, in patients with progressive disease. Lanreotide depot/autogel also showed a good tolerability profile that was consistent with previous studies. Overall, these findings support an important role for somatostatin analogs in the treatment of GEP-NETs.

Other Therapeutic Approaches for Patients With Advanced or Progressive Disease

Several alternative antiproliferative therapies might be considered for systemic treatment in patients with advanced or progressive disease. Chemotherapy is generally ineffective in patients with grade 1 or grade 2 cancers of the midgut, yielding overall response rates of less than 20%. However, streptozotocin-based chemotherapy has demonstrated efficacy in patients with grade 1 or grade 2 pancreatic NETs, yielding objective response rates of 40% to 50% and a stable disease rate of 50%. Based on these outcomes, the ENETS guidelines regard streptozotocin-based chemotherapy as first-line treatment in patients with progressive or advanced pancreatic NETs.

Another setting in which chemotherapy has demonstrated benefit is the group of patients with poorly differentiated (grade 3) NETs, in whom etoposide plus cisplatin has demonstrated objective response rates of 40% to 70%. These responses, however, were generally short, and the median survival was approximately 12 to 18 months.

Peptide-receptor–targeted radiotherapy (PRRT) using radiolabeled somatostatin analogs may be a therapeutic option for some patients with unresectable metastatic somatostatin receptor–positive NETs. The approach has primarily been evaluated in small phase 2 studies and retrospective reports, which have yielded objective response rates of approximately 30% to 40%. Moreover, an open-label, phase 2 study suggested a survival benefit with PRRT in patients responding to therapy (Figure 8). Given the limited data available for this approach and the lack of randomized studies, PRRT is considered a second-line therapy by the ENETS guidelines. Use of PRRT is also limited by safety concerns, including hematologic and renal toxicity, and a lack of widespread commercial availability.

The somatostatin analogs are molecularly targeted based on the pathogenesis of NETs. Other molecularly targeted therapies have also been evaluated in the treatment of these tumors, including the multiple tyrosine kinase inhibitor sunitinib and the mammalian target of rapamycin inhibitor everolimus. Sunitinib was evaluated in a randomized, double-blind, placebo-controlled, phase 3 trial in patients with advanced, well-differentiated pancreatic NETs. In this trial, median PFS doubled with sunitinib vs placebo (11.4 months vs 5.5 months, respectively, HR, 0.418; 95% CI, 0.263-0.662; P=.0001). This highly significant improvement in PFS led to the approval of sunitinib for the treatment of advanced pancreatic NETs.

Everolimus was evaluated in the randomized, double-blind, placebo-controlled, phase 3 RAD001 in Advanced Neuroendocrine Tumors, Third Trial) study, which enrolled 410 patients with advanced low-grade or intermediate-grade pancreatic NETs who had experienced radiographic progression in the previous 12 months. Median PFS was 11.0 months with everolimus vs 4.6 months with placebo (HR, 0.35;
95% CI, 0.27-0.45; \( P_c<0.0001 \); Figure 9). Based on these results, everolimus received approval for the treatment of advanced pancreatic NETs.

A combination approach of everolimus plus octreotide LAR has also been evaluated in patients with NETs. The randomized, placebo-controlled, double-blind, phase 3 RADIANT-2 (RAD001 in Advanced Neuroendocrine Tumors, Second Trial) study compared octreotide LAR with everolimus or placebo in patients with advanced, well-differentiated NETs and carcinoid syndrome. As everolimus plus octreotide LAR was associated with a trend toward improved median PFS (16.4 vs 11.3 months) that was clinically meaningful but failed to reach statistical significance.

**Conclusion**

The optimal management of patients with NETs requires a multidisciplinary approach that may involve surgery, localized therapy, somatostatin analogs, targeted therapy, PRRT, or chemotherapy. Given the substantial antisecretory effects of somatostatin analogs, their antiproliferative effects, and their good tolerability profile, these agents should play an important role in the therapeutic armamentarium of NETs.

Although a survival benefit for somatostatin analogs has not been directly demonstrated, data from the SEER program registries indicate that survival has improved in the era of somatostatin analogs, with the median survival increasing from 18 months for patients diagnosed with metastatic NETs from 1973 through 1987 to 38 months for patients diagnosed from 1998 through 2004.

**References**

Clinical Scenario 1: Advanced, Grade 2, Neuroendocrine Tumor in the Midgut

Jaume Capdevila, MD

Case Description
In July 2004, a 40-year-old otherwise healthy man with no relevant family history underwent an abdominal computed tomography (CT) scan following an accident. The CT scan showed no traumatic organ damage, but it revealed a 2-cm mass in the terminal ilium with 3 liver lesions suspicious for metastases. Endoscopic biopsy of the ileum mass showed a grade 2 NET with a Ki-67 of 4% and 3 mitoses per 10 high-power fields. Somatostatin receptor scintigraphy showed an uptake in liver lesions. The patient’s 5-hydroxyindoleacetic acid (5-HIAA) levels and neuron-specific enolase levels were within the normal range. The patient underwent radical resection, had a full recovery, and remained disease-free 5 years after the resection. He was then lost to follow-up.

In 2014, the patient presented with renal colic. An abdominal ultrasound showed multiple liver metastases, and a body CT scan revealed bilobar liver metastases with involvement of mesenteric lymph nodes. Somatostatin receptor scintigraphy showed high uptake in the liver and lymph nodes (Krenning scale, 4). The patient was asymptomatic with no carcinoid syndrome. Laboratory tests were within the normal range, except for an elevated chromogranin A (1450 U/L). The decision was made to start medical treatment with a somatostatin analog.

Criteria for Treatment Decisions in GEP-NETs
Several parameters should be weighed when considering treatment decisions in patients with NETs. First is the histologic assessment, based on the WHO 2010 grading system and/or the differentiation status (which is more commonly used in the United States). Second is the presence of hormonal release, which can lead to potentially significant or even fatal complications (eg, carcinoid syndrome, insulinoma, and gastrinoma) that require treatment. Third is the primary tumor site; currently, the important distinction is to identify pancreatic vs intestinal carcinomas. Other factors to consider include results of somatostatin receptor imaging tests and the degree of tumor burden—in particular, the presence of extrahepatic disease.

Currently, radical surgery of the primary tumor and metastases is recommended if an R0 resection can be achieved. There are no data regarding the use of adjuvant therapy in this setting. However, locoregional liver therapies could be options depending on the tumor size, anatomic location, number of metastases, and presence of extrahepatic disease.

Clinical Guidelines for NETs
Currently, there are 3 major clinical guidelines that address the treatment of NETs: the European Society for Medical Oncology (ESMO) guidelines, updated in 2012; the National Comprehensive Cancer Network (NCCN) guidelines, updated in December 2013; and the ENETS consensus guidelines, updated in 2012.

The ESMO guidelines recommend a variety of approaches based on the tumor location (pancreas vs small intestine), resectability, functionality, and tumor grade. Recommended treatments include somatostatin analogs, interferon, everolimus, sunitinib, chemotherapy, and PRRT.

The NCCN guidelines categorize treatment approaches based on the tumor burden and extent of symptoms. Although the recommendations are similar to those in the ESMO guidelines, the NCCN guidelines also offer watchful waiting as an option for asymptomatic patients with a low tumor burden.

The ENETS guidelines require an update, but they are perhaps the most complete treatment guidelines for NETs. The guidelines stratify the treatment approach based on 2 general categories of functional vs nonfunctional NETs (Figure 10). Therapies for functional NETs include somatostatin analogs or interferon; locoregional treatment and debulking surgery may be used to reduce tumor mass and improve hormone release. For patients with nonfunctional NETs, approaches vary based on the grade and tumor burden and include observation, somatostatin analogs, PRRT, chemotherapy, and everolimus.

Systemic Approaches in NET Therapy
In general, chemotherapy has a limited role in enteric NETs, with overall response rates typically below 20%. Everolimus demonstrated near-positive results in the phase 3 RADIANT-2 trial in patients with advanced NET and a history of secretory symptoms with radiologic progression in the previous 12 months (Figure 11). In most countries, everolimus is not approved for use in extrapancreatic NETs.

A likely factor contributing to the lack of statistical
significance in the RADIANT-2 trial was the inclusion of octreotide in the control arm, as somatostatin analogs have demonstrated antiproliferative effects in this patient population. Ongoing phase 3 trials will help clarify the role of everolimus and other targeted therapies in patients with extrapancreatic NETs. The RADIANT-4 (RAD001 in Advanced Neuroendocrine Tumors, Fourth Trial) study is comparing everolimus vs placebo in patients with nonfunctioning grade 1/2 gastrointestinal or lung NETs with documented disease progression. The Southwestern Oncology Group trial 0518 is comparing octreotide plus bevazuzumab vs octreotide plus interferon-α in patients with grade 2 small intestine NETs with prior disease progression. The NETTER-1 (A Study Comparing Treatment With 177Lu-DOTATATE-Octreotide to Octreotide LAR in Patients With Inoperable, Progressive, Somatostatin Receptor Positive Midgut Carcinoid Tumours) trial is comparing lutetium plus octreotide vs octreotide alone in patients with grade 1/2 small intestine NETs with progression after a somatostatin analog.

Several phase 3 trials have demonstrated the ability of somatostatin analogs to induce an antiproliferative effect. In the phase 3 PROMID study, octreotide LAR was associated with a significant PFS benefit over placebo in patients with well-differentiated functioning or nonfunctioning small-intestine NETs. In the phase 3 CLARINET study, lanreotide depot/autogel was associated with a significant PFS benefit over placebo in patients with nonfunctional, nonprogressive, enteropancreatic grade 1/2 NETs. Subgroup analyses showed similar efficacy with lanreotide depot/autogel regardless of tumor origin, grade, or hepatic tumor volume.

When considering the optimal treatment approach for NETs based on the evidence, it appears that radical surgery for the primary tumor and for all metastatic sites increases survival. Another point to consider is that assessment of disease progression status is not always easy or feasible. Moreover, phase 3 trials with targeted agents include populations with documented disease progression. Finally, the results of the CLARINET study challenge the conventional "wait-and-see" approach.

References

Clinical Scenario 2: Exploring Treatment Options for Patients With Symptomatic, Progressive GEP-NETs

Ulrich-Frank Pape, MD

Case Description: Part 1

In March 2009, a 48-year-old teacher presented with a 6-month history of increasingly troublesome diarrhea and dizzy spells. During the investigations, she developed signs of intestinal obstruction, including abdominal pain and vomiting. Her CT scan was abnormal, revealing small intestinal loops and a tumor mass within the mesentry. The findings suggested an NET with lymph node metastasis. Her urinary 5-HIAA was elevated (120 mg/24 hours), and her chromogranin A was 350 U/L.

The patient underwent laparotomy for impending obstruction and bowel resection, with excision of the tumor mass and involved regional mesenteric lymph nodes. It revealed a 4-cm carcinoid tumor with involved external margin; 4 of 12 nodes contained metastases (stage 3 tumor). Her Ki-67 level was 20%, which indicated a grade 2 tumor.

There was possible residual disease noted on the retroperitoneum. Postoperative somatostatin receptor scintigraphy and 24-hour urinary 5-HIAA were normal. The patient was monitored every 3 to 6 months with urinary 5-HIAA measurements.

In November 2012, she reported symptoms of flushing and diarrhea causing occasional incontinence. At that time, her urinary 5-HIAA level was marginally elevated (20 mg/24 hours). A CT scan revealed 15 to 20 small metastases throughout both liver lobes. Treatment with a somatostatin analog was initiated.

Considerations Regarding the Use of Somatostatin Analog Therapy in NETs

The ENETS guidelines state that the use of somatostatin analogs is standard for patients with functioning NETs, as these agents have demonstrated significant efficacy in treating carcinoid syndrome or other syndromes related to hormone hypersecretion. When considering the use of somatostatin analogs, the indication for using these agents may be antisecretory treatment, proliferation control, or both (as in the current patient).

Upon disease progression, the patient developed carcinoid syndrome despite having marginally elevated 5-HIAA. It is likely that liver metastases bypassed the intrahepatic circulation, resulting in direct release of the hormone into the hepatic veins, which caused systemic effects. If the patient had nonsymptomatic disease rather than carcinoid syndrome, a somatostatin analog would still be the appropriate choice, given the demonstrated efficacy of these agents for controlling tumor proliferation. However, one caveat to consider is that this patient does not reflect the majority of clinical trial participants. The PROMID trial of octreotide enrolled treatment-naive patients, and the CLARINET trial of lanreotide depot/autogel primarily enrolled patients who had stable disease for 3 to 6 months before randomization.

Moreover, in 2012, when the patient’s disease progression was detected, there was not yet evidence supporting the efficacy of somatostatin analogs for highly proliferative grade 2 NETs (as seen in this patient, based on her Ki-67 level of 20%). In 2014, subset analyses from the CLARINET trial supported the use of somatostatin analogs in these patients. It appears that if somatostatin receptors are present on the tumor cell surface, somatostatin analogs are likely to be effective.

One caveat concerning somatostatin analog therapy is that overall survival is difficult to assess. Many patients receive multiple subsequent therapies, and therefore overall survival reflects the total sequential therapeutic strategy. The use of multiple therapies, combined with the slow-growing biology of these tumors, makes survival analyses challenging. Although an overall survival analysis from the PROMID cohort showed a trend toward a survival benefit with octreotide in patients with low hepatic load, the difference did not reach statistical significance. The study, however, was underpowered to detect differences in this subgroup.

For the current patient, somatostatin analog therapy had the potential to extend PFS and control symptoms. A disadvantage of somatostatin analog therapy, as shown in a previous study of octreotate, is the occurrence of progressive disease after a median of 40 months. In the ENETS guidelines, somatostatin analogs are recommended first-line agents for antiproliferative treatment in patients with nonfunctioning, progressive, small intestinal grade 1 NETs. This recommendation will likely need to be revised. ESMO guidelines are less specific but also recommend somatostatin analogs as a first-line treatment in patients with nonfunctioning, progressive, small intestinal grade 1 NETs. The North American Neuroendocrine Tumor Society guidelines broadly recommend considering a somatostatin analog as an option for tumor.
stabilization.7

Case Description: Part 2

The patient begins treatment with lanreotide depot/auto-gel. Her symptoms improve, and her 5-HIAA level normalizes. Follow-up CT scans show stable disease by the Response Evaluation Criteria In Solid Tumors (RECIST) criteria, with necrosis of some metastases. The treatment benefits lasted for 18 months, at which time the patient’s symptoms returned, and a CT scan showed progression of liver metastases.

Options After Somatostatin Analog Therapy

The somatostatin analog provided a benefit that persisted for 18 months. Although this duration is fairly aligned with results from the PROMID trial, in which octreotide was associated with a median PFS of 14.3 months,2 it was inferior to the average results reported in the CLARINET trial of lanreotide depot/auto-gel, in which the median PFS had not been reached in the overall cohort but was 18 months with placebo.3 Considering that the patient has a grade 2 tumor, this result can be considered reasonable.

There are several options for second-line therapy after a first-line somatostatin analog. One approach is to continue the somatostatin analog and add everolimus or sunitinib, although the RADIANT-2 trial missed its primary endpoint of extending PFS.8 A more aggressive approach, such as PRRT, might be appropriate if the tumor has sufficient somatostatin receptor expression. Other options include interferon-α, chemotherapy, or best supportive care, depending on the circumstances.

Influence of the Primary Tumor Site

The primary tumor site can influence the treatment approach. For patients with pancreatic NETs, multiple options are available, including chemotherapy and targeted agents, such as everolimus and sunitinib. The treatment decision may be influenced by the management goals, which can include induction of remission, reduction in tumor mass, and control of proliferation.

Tumor grade must also be a consideration for pancreatic NETs, as it will influence the treatment approach. Importantly, tumor grade may change, and therefore rebiopsy may be necessary. There may be a role for somatostatin analogs to control proliferation of the most slowly progressing pancreatic NETs, although this approach is not yet supported by evidence. Clearly, additional trials are needed to further elucidate the optimal treatment strategy and sequence for these patients.

References

Continued Advances in Targeting Gastroenteropancreatic Neuroendocrine Tumors: General Discussion

Jaume Capdevila, MD, Matthias Weber, MD, and Ulrich-Frank Pape, MD

Jaume Capdevila, MD  Do you recommend removing the wait-and-see option from the guidelines?

Matthias Weber, MD  I would consider use of somatostatin analog therapy within the wait-and-watch strategy.

Ulrich-Frank Pape, MD  It would be easy to move toward the early use of somatostatin analogs in patients who match clinical trial populations. In other patients, we may still consider careful observation, as they will likely soon meet these criteria. Somatostatin analogs may have a broader role in the future. Moreover, given their tolerability, these agents will likely gain wider use. In the field of endocrinology, there is a rather low threshold for long-term use of somatostatin analogs, which is likely a result of experience with other conditions that express somatostatin receptors. In other areas, such as oncology or gastroenterology, the threshold may be higher.

Matthias Weber, MD  One challenge is the lack of overall survival data for these agents. Such data may never be available, given the slow-growing nature of these tumors. The clinical relevance of PFS prolongation in these patients is unclear. However, evidence from the SEER database suggests an overall survival benefit with octreotide.¹

Jaume Capdevila, MD  From a medical oncologist’s perspective, it seems strange to not use a treatment that can produce a 40% difference in the PFS rate at 2 years (62% with lanreotide depot/autogel vs 22% with placebo).² However, other specialists within the multidisciplinary team may have a different perspective of the role of chemotherapy in the treatment of NETs. If the decision is made to delay therapy until disease progression, the option will be there at that point. NETs are slow-growing tumors. Despite the lack of overall survival data, however, many physicians would probably agree that a wait-and-see would not be appropriate for patients with liver metastasis.

In conclusion, neuroendocrine neoplasms are heterogeneous tumors that vary in their hormone functionality, tumor growth rate, and associated symptoms related to hormone...
release and tumor growth. The classification of these tumors is complicated by the use of the ENETS/TNM grading system.

Somatostatin analogs are the cornerstone of therapy based on their symptomatic effects. Results from the phase 3 PROMID and CLARINET studies indicate that these agents also have an antiproliferative effect.²,³ Ongoing studies are continuing to investigate the role of other targeted agents in the treatment of NETs. It will be important to appropriately integrate the various treatment approaches, including targeted therapy, chemotherapy, PRRT, and liver-directed therapies, to attain the best outcomes for patients with NETs.

References

New Frontiers and Treatment Paradigms for Thyroid Carcinoma

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

1. From 2001 to 2010, the proportion of patients with thyroid carcinoma who died from the disease:
   a. Decreased by approximately 33%
   b. Decreased by approximately 16%
   c. Increased by approximately 13%
   d. Increased by approximately 28%

2. Total thyroidectomy is optimal for most patients with tumors ≥1 cm in diameter.
   a. True
   b. False

3. All of the following patient/tumor factors should prompt consideration of radioactive iodine (RAI) therapy, EXCEPT:
   a. Female patient
   b. Tumor size >1 cm
   c. Extrathyroid extension
   d. Presence of metastases

4. Which factor is NOT associated with a high risk of recurrence in patients with differentiated thyroid cancer?
   a. Distant metastases
   b. Inappropriate thyroglobulin elevation
   c. Incomplete tumor resection
   d. Microscopic extrathyroid extension

5. BRAF mutation status should be used to make treatment decisions for patients with thyroid cancer.
   a. True
   b. False

6. What does the National Comprehensive Cancer Network recommend for the treatment of patients with progressive, metastatic, RAI-refractory thyroid cancer?
   a. Clinical trials
   b. Antiangiogenic tyrosine kinase inhibitors
   c. Either clinical trials or antiangiogenic tyrosine kinase inhibitors
   d. Neither clinical trials nor antiangiogenic tyrosine kinase inhibitors

7. Which of the following agents is currently approved in the United States for patients with RAI-refractory differentiated thyroid cancer?
   a. Lenvatinib
   b. Sorafenib
   c. Vandetanib
   d. Vemurafenib

8. Which of the following statements regarding sorafenib and the DECISION trial is FALSE?
   a. Sorafenib significantly improved progression-free survival (PFS) and extended PFS by 5 months vs placebo (10.8 vs 5.8 months)
   b. The most common adverse events associated with sorafenib include hand-foot skin reactions, diarrhea, and alopecia
   c. In the sorafenib arm, dose reductions were required by more than 60%, and almost 20% discontinued therapy
   d. Reductions in target lesions were comparable to placebo

9. Which of the following statements from the phase III SELECT trial (Study 303) of lenvatinib is FALSE?
   a. There was a significant improvement in median PFS by nearly 15 months with lenvatinib over placebo (18.3 vs 3.6 months)
   b. The PFS improvement with lenvatinib was observed only in patients who had not received prior vascular endothelial growth factor–targeted therapy
   c. Lenvatinib was associated with an overall response rate of 65%, including 2% complete responses
   d. The most frequent treatment-related adverse event was hypertension

10. In a phase 2 study comparing vandetanib vs placebo in patients with locally advanced or metastatic RAI-refractory differentiated thyroid cancer (papillary, follicular, or poorly differentiated), what was the PFS associated with vandetanib?
   a. 11.1 months
   b. 12.3 months
   c. 13.2 months
   d. 14.5 months
Evaluation Form: New Frontiers and Treatment Paradigms for Thyroid Carcinoma

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 10149. 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, Hematology/Oncology
   - Oncology, Medical
   - Oncology, Radiation
   - Oncology, Other
   - Other, please specify:

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 with thyroid carcinoma?
   - 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:
   - Identify thyroid cancer patients who are refractory to radioactive iodine
   - Employ risk group stratification to predict prognosis and plan treatment
   - Describe the clinical significance of molecular pathways targeted by multikinase inhibitors
   - Evaluate the latest clinical trial data supporting the use of tyrosine-kinase inhibitors in iodine-refractory thyroid carcinoma
   - Apply strategies to manage the adverse events associated with novel targeted therapies for thyroid carcinoma

8. Rate how well the activity achieved the following:
   - The faculty were effective in presenting the material
   - The content was evidence based
   - The educational material provided useful information for my practice
   - The activity enhanced my current knowledge base

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?

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

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 1.25 credits.
   - I participated in only part of the activity and claim ____ credits.

Figure 2. Primary tumor localization and extent of disease have been shown to have prognostic importance. Adapted from Yao JC et al. *J Clin Oncol*. 2008;26(18):3063-3072.

Figure 3. The Ki-67 index has shown significant prognostic value in patients with neuroendocrine tumors. Adapted from Garcia-Carbonero R et al. *Ann Oncol*. 2010;21(9):1794-1803.

Figure 4. Tumor-related death and ENETS stage in a multicenter analysis of patients who had undergone surgery for pancreatic neuroendocrine tumors. ENETS, European Neuroendocrine Tumor Society. Adapted from Rindi G et al. *J Natl Cancer Inst*. 2012;104(10):764-777.
Figure 5. Progression-free survival in the PROMID trial among patients with advanced midgut neuroendocrine tumors. 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. Adapted from Rinke A et al. J Clin Oncol. 2009;27(28):4656-4663.8

Figure 6. Progression-free survival among the intent-to-treat population in the CLARINET trial in patients with grade 1 or 2 GEP-NETs that were well-differentiated or moderately differentiated, nonfunctioning, and locally inoperable or metastatic. CLARINET, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors. Adapted from Caplin ME et al. N Engl J Med. 2014;371(3):224-233.9

Figure 7. Median progression-free survival in the CLARIENT-OLE trial, which included patients with stable disease who continued on lanreotide and patients in the placebo group with or without progressive disease who received open-label lanreotide. CLARIENT-OLE, Controlled Study of Lanreotide Antiproliferative Response in Neuroendocrine Tumors Open-Label Extension. Adapted from Caplin ME et al. ASCO abstract 4107. J Clin Oncol. 2014;32(5(suppl)).10

Figure 8. An open-label, phase 2 study suggested a survival benefit with PRRT in patients responding to therapy. PRRT, peptide-receptor–targeted radiotherapy. Adapted from Imhof A et al. J Clin Oncol. 2011;29(17):2416-2423.20
Figure 9. Median progression-free survival in the RADIANT-3 trial, which enrolled patients with advanced low-grade or intermediate-grade pancreatic NETs who had experienced radiographic progression in the previous 12 month. RADIANT-3, RAD001 in Advanced Neuroendocrine Tumors, Third Trial). Adapted from Yao JC et al. N Engl J Med. 2011;364(6):514-523.
Figure 10. The ENET guidelines stratify the treatment approach based on 2 general categories of functional vs nonfunctional neuroendocrine tumors. ENET, European Neuroendocrine Tumor Society; IFN, interferon; PD, progressive disease; RFA, radiofrequency ablation; SSA, somatostatin analog. Adapted from Pavel M, et al. *Neuroendocrinology*. 2012;95(2):157-176.4

Figure 11. Median progression-free survival in the RADIANT-2 trial in patients with advanced neuroendocrine tumors and a history of secretory symptoms with radiologic progression in the previous 12 months. Pavel ME et al. *Lancet*. 2011;378(9808):2005-2012.5