# Are We Making Progress in the Treatment of Neuroendocrine Tumors?

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Abstract

During the past decade, treatment options for well-differentiated neuroendocrine tumors (NETs) have improved significantly. Beginning with the PROMID study, a total of 9 phase III trials of systemic drugs have been completed, 7 of which met their primary endpoint. While some new treatments are active across multiple subsets of NETs, others are designed to target very specific populations. At the current time, few predictive biomarkers can help guide selection of treatment, resulting in therapeutic choices that are often determined based on clinical factors, clinical experience, and judgment. Challenges of the next decade will be to learn how to best combine and sequence treatments, and how to match the appropriate patient with the optimal therapy.

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## Introduction

The past decade has been remarkably productive in the history of neuroendocrine tumor (NET) research. Since 2009, results of 9 prospective phase III studies have been published, 7 of which met their primary endpoint (**Table**).[1-9] These studies have dramatically altered the treatment landscape. The field of NET research, formerly dominated by anecdotal information, is now guided by principles of evidence-based medicine.

When considering these innovations, it is important to recognize that NETs are a highly diverse family of neoplasms that can be categorized using multiple criteria. These include primary site (eg, small intestinal, pancreatic, colorectal, or bronchopulmonary), tumor grade (low, intermediate, and high), morphologic differentiation, hormonal output (functioning or nonfunctioning), extent of disease (localized, liver-dominant, or widely metastatic), and somatostatin receptor expression.[10,11] While some therapies have been studied in broad categories of NETs, others have been designed to target very specific populations.

The somatostatin analogs (SSAs) octreotide and lanreotide remain the cornerstone treatment for most well-differentiated, somatostatin-receptor–expressing metastatic NETs.[6,9,12] Initially designed to palliate hormonal symptoms such as flushing and diarrhea associated with the carcinoid syndrome, both SSAs were subsequently found to inhibit tumor growth. This property, also known as the "antiproliferative effect" of SSAs, was demonstrated in 2 landmark studies: the PROMID study, which randomized patients with well-differentiated midgut NETs to receive octreotide long-acting release (LAR) versus placebo, and the CLARINET study, which evaluated lanreotide versus placebo in a more heterogeneous population of patients with nonfunctioning enteropancreatic NETs.

In this review, we will focus on subsequent lines of therapy: mammalian target of rapamycin (mTOR) inhibition, using everolimus; antiangiogenic therapy, with a focus on sunitinib and bevacizumab; peptide receptor radiotherapy, using $^{90}$yttrium- and $^{177}$lutetium-labeled somatostatin analogs; temozolomide-based cytotoxic chemotherapy; and telotristat, a novel serotonin synthesis inhibitor. Although liver-directed therapy remains highly important for patients with liver-dominant metastases, it is outside the scope of this review.[13-17]

## mTOR Inhibitor Therapy

Inhibition of mTOR, a serine-threonine kinase that regulates cell growth, proliferation, metabolism, and angiogenesis, has been shown to have antiproliferative effects.[18-20] Discrete mutations in mTOR pathway enzymes such as PTEN and PIK3CA are found in approximately 15% of pancreatic NETs.[21] Similar mutations are substantially rarer in midgut NETs.[22] However, even tumors that lack identifiable mTOR pathway mutations are frequently found to have phosphorylation of downstream markers, suggesting pathway activation as a common feature of NETs regardless of primary site.[23] Altered protein levels of key inhibitors of the Akt/mTOR pathway, including TSC2 and PTEN, have been seen in more than 80% of pancreatic NETs.[24] Low expression of these tumor-suppressor genes was associated with significantly shortened time-to-tumor progression.

The oral mTOR inhibitor everolimus has been studied extensively in well-differentiated NETs. Based on the promising results of a phase II study in pancreatic NETs, the RADIANT-3 trial compared everolimus 10 mg versus placebo in 410 patients with advanced, radiographically progressing, low- or intermediate-grade pancreatic NETs.[3] Crossover was allowed for patients progressing on placebo. Treatment with everolimus resulted in

significantly longer median progression-free survival (PFS) of 11 months compared with 4.6 months with placebo (HR, 0.35; 95% CI, 0.27-0.45; *P* <.001). Response rates were modest, with partial response observed in 5% of the patients receiving everolimus versus 2% of patients receiving placebo; stable disease was evident in 73% of patients receiving everolimus versus 51% in the placebo group. Although no significant overall survival (OS) benefit was observed (44.02 months vs 37.68 months; HR, 0.94; *P* = .300), it is important to consider that the study was not powered to evaluate survival and that nearly all placebo patients crossed over to active treatment. Everolimus was approved for treatment of pancreatic NETs based on the results of this study.

The RADIANT-2 trial was a randomized, placebo-controlled, phase III study that assessed the combination of everolimus plus octreotide LAR versus placebo plus octreotide LAR in patients with advanced, progressive NETs and history of carcinoid syndrome.[5] The eligibility criterion requiring history of carcinoid syndrome (thus supporting the use of octreotide use in both arms) resulted in a preponderance of midgut NET patients in the trial population of 429 individuals. The primary endpoint was PFS by central radiology review. Crossover was permitted upon progression on the placebo arm. Median PFS was 16.4 months for the everolimus combination group compared with 11.3 months in the placebo plus octreotide LAR group (HR, 0.77). With a *P* value of .026 and a significance threshold of .024, the trial fell slightly short of statistical significance. It is possible that imbalances in baseline prognostic factors, including primary site and tumor marker elevations, may have contributed to the lack of statistical significance.[25] OS was once again not significantly different, with a hazard ratio of 1.05 numerically favoring the placebo group (*P* = .594). As a result of lack of statistical significance for improvement in PFS, everolimus was not approved for treatment of hormonally functioning nonpancreatic NETs.

After a phase II study demonstrated high rates of disease stability with everolimus in nonfunctioning NETs,[26] the phase III RADIANT-4 trial further evaluated this remaining group of NETs: hormonally

**TABLE. Prospective Phase III Studies.**

| Study | Primary Endpoint | Population | Study Arms | Primary Endpoint Results | Hazard Ratio/ *P* Value |
|---|---|---|---|---|---|
| PROMID[9] | Time-to-tumor progression | Metastatic midgut NETs | Octreotide LAR 30 mg every 4 weeks vs placebo | 14.3 vs 6 months | HR, 0.34; *P* = .000072 |
| Sunitinib vs placebo[7] | PFS | Advanced pancreatic NETs | Sunitinib vs placebo | 11.4 vs 5.5 months | HR, 0.42; *P* <.001 |
| RADIANT-2[5] | PFS | Advanced NETs with carcinoid syndrome | Everolimus 10 mg daily vs placebo (both with 30 mg octreotide LAR every 28 days) | 16.5 vs 11.3 months | HR, 0.77; *P* = .026 |
| RADIANT-3[3] | PFS | Advanced pancreatic NETs | Everolimus 10 mg daily vs placebo (both with best supportive care) | 11 vs 4.6 months | HR, 0.35; *P* <.001 |
| RADIANT-4[4] | PFS | Advanced nonfunctioning NETs of the lung or gastrointestinal tract | Everolimus 10 mg daily vs placebo | 11 vs 3.9 months | HR, 0.48; *P* <.00001 |
| CLARINET[6] | PFS | Metastatic enteropancreatic NETs | Lanreotide 120 mg every 4 weeks vs placebo | Median PFS not reached vs 18 months | HR, 0.47; *P* <.001 |
| SWOG S0518[1] | PFS | Advanced carcinoid tumors | Bevacizumab 15 mg/kg every 3 weeks vs interferon-alpha-2b 5 million units 3 times/week (both with octreotide LAR 20 mg every 21 days) | 16.6 vs 15.4 months | HR, 0.93; *P* = .55 |
| TELESTAR[8] | Change from baseline in BM frequency per day | Carcinoid syndrome | Telotristat 250 mg 3 times a day vs telotristat 500 mg 3 times a day vs placebo | −1.7 vs −2.1 vs −0.9 (mean BM reductions at week 12) | *P* <.001 |
| NETTER-1[2] | PFS | Metastatic midgut NETs | $^{177}$Lu-Dotatate 7.4 gigabecquerel every 8 weeks plus best supportive care with octreotide LAR vs octreotide LAR 60 mg every 4 weeks | Median PFS not reached vs 8.4 months | HR, 0.21; *P* <.0001 |

BM indicates bowel movement; LAR, long-acting release; NET, neuroendocrine tumors; PFS, progression-free survival.

nonfunctioning NETs of the gastrointestinal (GI) tract and lungs (including unknown primary).[4] Patients were randomized to everolimus versus placebo with concurrent somatostatin analogs prohibited on entry. Crossover was not included in the study design. In total, 302 patients were enrolled with diverse primary sites, including lung, gastroduodenum, and colorectum. The RADIANT-4 trial demonstrated substantial benefit associated with everolimus in this group of relatively aggressive tumors: Median PFS was 11.0 months in the everolimus group versus 3.9 months in the placebo group (HR, 0.48; $P$ <.00001); interim OS analysis was encouraging (HR, 0.64; $P$ = .037).

Based on the RADIANT-4 trial, everolimus was approved by the FDA for the treatment of advanced nonfunctioning NETs of the gastrointestinal tract and lungs. However, while hormonal status is a criterion for drug use in the product label, it is not clear that functional status is truly a predictive factor for benefit with everolimus. Rather, it is more likely that patients with highly indolent NETs (eg, many functional tumors of midgut primary) experience less benefit and more risk with everolimus treatment, thus accounting for the relative lack of efficacy observed in the RADIANT-2 trial compared with the RADIANT-3 and RADIANT-4 studies.

Side effects of everolimus include oral aphthous ulcers, rash, diarrhea, immunosuppression resulting in atypical infections, pneumonitis, hyperglycemia, and hyperlipidemia. Consequently, prescribers need to carefully weigh risk versus benefit when considering this drug and select patients with clinically significant disease progression. With appropriate supportive measures, such as dexamethasone mouth rinse for oral ulcer prevention, and appropriate dose reductions, most patients can tolerate long-term everolimus treatment.

### Angiogenesis Inhibitors

NETs are highly vascular tumors, and many express both VEGF and its receptors. Thus, antiangiogenic agents have shown significant promise in management of advanced NETs.[27,28] To date, sunitinib, an oral tyrosine-kinase inhibitor, is the only angiogenesis inhibitor to gain approval. Its efficacy was demonstrated in a phase III trial of 171 patients with low- to intermediate-grade progressive pancreatic NETs, randomized to receive sunitinib 37.5 mg daily versus placebo.[7] There was statistically significant improvement in PFS on sunitinib when compared with placebo (11.4 versus 5.5 months; HR, 0.42; $P$ <.001), a result that was very similar to that of the RADIANT-3 study, which enrolled a very similar patient population. Additionally, the response rate of 9.3% was similar to the response rate of 5% observed in RADIANT-3. Five years after study closure, the median OS was 38.6 months for sunitinib and 29.1 months for placebo, a result that was not statistically significant ($P$ = .094).[29] Primary side effects of sunitinib include hypertension, cytopenias, diarrhea, nausea, vomiting, asthenia, and fatigue. At this time, there are no studies comparing everolimus with sunitinib, and thus few reasons to select one drug versus the other in pancreatic NET patients. Often, patient comorbidities and physician preference guide treatment choice.

Several phase II trials have investigated other antiangiogenic agents, including pazopanib, axitinib, and bevacizumab. Pazopanib combined with octreotide LAR was evaluated in a study of 52 patients with advanced, low- to intermediate-grade NETs.[30] Tumor responses were observed only in the pancreatic NET cohort. Axitinib was evaluated in 30 patients with well-differentiated NETs of the GI tract and lungs.[31] Although objective response (OR) was only observed in 1 patient (3%), median PFS was relatively prolonged at 26.7 months. Despite promising phase II data with bevacizumab in gastrointestinal NETs, a phase III trial of bevacizumab and octreotide versus interferon and octreotide failed to show a difference in PFS.[1] Thus far, there has been no placebo-controlled study of bevacizumab. Results of a randomized phase II study comparing pazopanib with placebo in NETs of the GI tract and lungs are pending.

Combinations of mTOR inhibitors and anti-VEGF agents show promise, particularly in pancreatic NETs. The first phase II trial to show that high response rates may be achieved with this combination used bevacizumab and temsirolimus. This combination was associated with an overall response rate of 41% and a median PFS of 13.2 months in 56 patients with pancreatic NETs.[32] When everolimus was compared with everolimus plus bevacizumab in a randomized study of 150 pancreatic NET patients, response rates with the everolimus-bevacizumab combination were 31% (vs 12 % with everolimus, $P$ = .005). However, the improvement in PFS was more modest: 16.7 months median PFS with the combination, in comparison with 14 months median PFS with the everolimus ($P$ =.12).[33] Thus, it appears that combining an mTOR inhibitor with bevacizumab can substantially improve response rates, but will only modestly affect PFS.

### Radiolabeled Somatostatin Analog Therapy

Radiolabeled somatostatin analog therapy, also known as peptide receptor radionuclide therapy, is a targeted form of systemic radiotherapy facilitating the delivery of radionuclides with high therapeutic index directly to tumors that express somatostatin receptors. Since 1992, this technique has shown promise as an effective therapeutic modality for inoperable or metastatic NETs. Nonrandomized trials with $^{90}$Y-DOTA0-Tyr3-octreotide (Dotatoc) and $^{177}$Lu-DOTA0-Tyr3-octreotate ($^{177}$Lu-Dotatate) showed exceptionally long durations of median PFS.[34,35] Adverse events have included nephrotoxicity, which can be significantly mitigated with pre- and posttreatment amino acid infusions, and hematotoxicity, which is typically mild and transient. Long-term myelotoxic events, including myelodysplastic syndrome and acute leukemia, are thought to occur in roughly 1% to 2% of patients.

The safety and efficacy of $^{177}$Lu-Dotatate was investigated in the phase III NETTER-1 trial of 229 patients with metastatic midgut NETs who had experienced radiographic progression on

standard doses of octreotide therapy.[2] Patients were randomized to receive a standard fixed dose of $^{177}$Lu-Dotatate (4 doses of 200 mCi every 8 weeks) combined with standard-dose octreotide LAR 30 mg, compared with high-dose octreotide (60 mg every 4 weeks). Primary endpoint was PFS by blinded central radiology review. At the time of primary data analysis, median PFS was 8.4 months on the control arm of the study, and had not been reached on the $^{177}$Lu-Dotatate arm (HR, 0.21; $P$ <.0001). Response rate was 18% in the $^{177}$Lu-Dotatate group compared with 3% in the control group ($P$ <.001). Although mature analysis of OS has not yet been performed, interim OS analysis demonstrated a hazard ratio of 0.4 for death ($P$ = .004). Grade 3 or 4 myelosuppression occurred in less than 10% of patients receiving $^{177}$Lu-Dotatate and there was no evidence of nephrotoxicity during the observed timeframe.

Although $^{177}$Lu-Dotatate is not yet approved by the FDA, it is now available through a compassionate use program sponsored by the manufacturer. Data from the NETTER-1 study suggest that it should be strongly considered in patients with somatostatin-receptor–expressing metastatic midgut NETs progressing on conventional SSAs. Data from single-arm studies and institutional series strongly point to the activity of this radiopharmaceutical in a diverse population of gastroenteropancreatic NETs. Indeed, response rates are generally observed to be higher in pancreatic NETs than in midgut NETs. Several randomized clinical studies are now comparing $^{177}$Lu-labeled somatostatin analogs with the targeted agents everolimus and sunitinib in patients with pancreatic NETs, and these will hopefully provide important guidance on the sequencing of systemic treatments in pancreatic NETs.

### Cytotoxic Chemotherapy

Chemotherapeutic regimens using the alkylating agent streptozocin were studied extensively in the 1980s and 1990s and were found to be particularly active in metastatic pancreatic NETs.[36,37] During the past decade, another alkylating drug, temozolomide, has emerged as a potentially less toxic and more convenient oral alternative. Data on use of temozolomide in NETs derive primarily from small subsets of phase II studies and from retrospective series, showing activity predominantly in pancreatic NETs and relative lack of activity in NETs of the GI tract.[38-41] Interestingly, nearly all studies have evaluated temozolomide in combination with another drug: examples include thalidomide, bevacizumab, capecitabine, and everolimus. Data on the combination of temozolomide with capecitabine have attracted particular interest due to the relative lack of additive toxicity associated with low-dose capecitabine and the preclinical evidence of synergy.[42,43] Although the exact mechanism of synergism is unknown, a possible rationale is depletion of the DNA-repair enzyme O$^6$-methylguanine-DNA methyltransferase (MGMT) by capecitabine, thus potentiating the effect of temozolomide.[44]

Although high-level evidence supporting use of capecitabine/temozolomide is still lacking, encouraging response rates of approximately 50% have led to the endorsement of this regimen by the National Comprehensive Cancer Network. An ECOG-sponsored randomized phase II study comparing capecitabine/temozolomide versus temozolomide monotherapy in patients with progressive pancreatic NETs has completed accrual (NCT01824875); initial results are anticipated in the next year. As a general principle, temozolomide-based regimens are used primarily in patients with relatively aggressive pancreatic NETs based on tumor volume, proliferative activity, or tumor-related symptoms. However, at this time, there are limited data to prove that markers such as Ki-67 index or mitotic rate predict response to temozolomide in patients with well-differentiated tumors. It is also unclear whether tumoral deficiency of the DNA-repair enzyme MGMT predicts response to temozolomide.[45]

### Telotristat Ethyl

Carcinoid syndrome occurs predominantly in patients with metastatic midgut NETs and is characterized by diarrhea, flushing, and the development of right-side cardiac valvular fibrosis, potentially leading to heart failure.[46,47] While flushing is multifactorial, both diarrhea and carcinoid heart disease appear to be related primarily to secretion of serotonin. Telotristat ethyl is an oral inhibitor of tryptophan hydroxylase, a rate-limiting step in the conversion of the amino acid tryptophan into serotonin. Two early-stage clinical studies of telotristat demonstrated a favorable safety profile and evidence of clinical activity in carcinoid syndrome.[48,49] In the multicenter, placebo-controlled, phase III TELESTAR trial, the safety and efficacy of telotristat ethyl was evaluated in patients with well-differentiated metastatic NETs with carcinoid syndrome and diarrhea refractory to SSA therapy.[8] The primary endpoint was the mean change from baseline in daily bowel movement frequency averaged over a 12-week period. Telotristat 250 mg versus 500 mg versus placebo was administered orally 3 times per day over the 12-week double-blind treatment period, followed by open-label treatment. There was an estimated daily reduction in bowel movements of –0.81 for 250 mg ($P$ <.001) and –0.69 for 500 mg ($P$ <.001). There was also significant (≥30%) reduction in urinary 5-hydroxyindoleacetic acid (78% of patients in the 250-mg arm and 87% in the 500-mg arm). The drug was safe and well tolerated.

The FDA approved telotristat at a dose of 250 mg 3 times daily in February 2017 for control of diarrhea related to carcinoid syndrome in patients with suboptimal control of diarrhea on an SSA. When considering use of this drug, it is important to recall that diarrhea may be multifactorial and that other causes, such as pancreatic malabsorption from SSA use, or bile salt malabsorption from ileocecectomy, may contribute to abnormal bowel movements in carcinoid syndrome patients. At this time, limited clinical evidence supports the hypothesis that telotristat reduces the risk of carcinoid heart disease; however, it is likely that reduction in circulating blood serotonin can delay progression of carcinoid heart disease in patients with elevated serotonin levels and early signs of valvular fibrosis.

## Discussion

New, targeted treatments for control of tumor growth and hormonal output have transformed the treatment landscape for patients with advanced NETs. While SSAs remain the appropriate first-line treatment for most somatostatin-receptor–expressing tumors, multiple systemic and liver-directed options now exist for treatment at time of radiographic or symptomatic progression. Currently, few predictive biomarkers can help guide selection of treatment, resulting in therapeutic choices that are often determined based on clinical factors, clinical experience, and judgment. Challenges of the upcoming decade will be to learn how to best sequence treatments and select the appropriate therapy for the appropriate patient. Fortunately, several randomized clinical trials have opened that directly compare therapies with each other rather than with a placebo control. These include the SEQTOR trial (NCT02246127), comparing sequencing of streptozocin-5-FU followed by everolimus versus the reverse order of treatment, and the COMPETE trial (NCT03049189), comparing $^{177}$Lu-Edotreotide versus everolimus in progressive gastroenteropancreatic NETs. An important randomized phase II trial comparing temozolomide monotherapy with combination of capecitabine and temozolomide in pancreatic NETs (NCT01824875) has completed accrual and will provide much-needed prospective data on the risks versus benefits of combination versus monotherapy. In addition, early-phase trials are currently exploring novel agents, including CDK4/6 inhibitors and immune checkpoint inhibitors, which may result in the further expansion of therapeutic options for advanced NET patients.

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