Review Article

Biologics in gastrointestinal and pancreatic neuroendocrine tumors

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Abstract: The development of biologic agents has ushered in a new era of precision medicine, opening the door to new therapeutic options designed to intelligently target cancer cells and their promoting factors, while leaving normal cells relatively unharmed. Biologics for the treatment of neuroendocrine tumors (NETs) have followed in the footsteps of regimens targeting pathways upregulated in other cancers, including the vascular endothelial growth factor (VEGF) and the mammalian target of rapamycin (mTOR). Through a number of clinical trials, the mTOR inhibitor everolimus and the receptor tyrosine kinase (RTK) inhibitor sunitinib were recently approved for NETs. Other biologics such as the VEGF-A inhibitor bevacizumab have also demonstrated promising clinical activity in NETs. Interestingly, though trials have demonstrated the efficacy of everolimus and sunitinib in extending progression-free survival (PFS) in NETs, objective response rates (RR) are uniformly low, indicating that the primary effect of these drugs is maintenance of stable disease. Due to the relatively indolent nature of the more common, well-differentiated variety of NETs, stable disease is often a reasonable goal for NET patients. Well-differentiated NETs have been shown to be poor responders to cytotoxic chemotherapy, underlining the important role of biologics in treating and managing NETs and their hormonal symptoms. Ongoing and future trials are investigating a wide variety of biologic compounds in NETs, including other RTK inhibitors, mTOR pathway inhibitors, and immune checkpoint inhibitors. Within this review, we will discuss major trials leading up to the FDA approval of everolimus and sunitinib for NETs, as well as other promising biologics currently under investigation in NET clinical trials.

Keywords: Neuroendocrine tumor (NET); carcinoid; biologic; targeted therapy

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Introduction

When neuroendocrine tumors (NETs) were first documented as a distinct class of neoplasms in 1907, they were described as "carcinoid" for their "cancer-like" properties. It was not until decades later that NETs were recognized for their malignant potential, and likewise, their need for effective chemotherapies. Even so, due to their relatively indolent nature and low rate of incidence, NETs have long remained in the background of the booming field of cancer research. In recent years, a surge in NET research has afforded the medical community a sharper understanding of NET biology, and in following, has opened doors to more effective and varied therapeutic options.

Epidemiologically, NETs occur rarely but are not uncommon when compared to their adenocarcinoma counterparts. While annual incidence in the U.S. is estimated to be between two and five cases per 100,000 people, reports of rising incidence—in part a result of improvements in detection—and the relatively long survival of NET patients has translated into a prevalence greater than that of gastric and pancreatic adenocarcinomas combined (1-3). Over half of NETs originate in the gastrointestinal tract and pancreas,

although the distribution has been found to vary by sex and race (1). While most NETs arise spontaneously, familial diseases such as multiple endocrine neoplasia types 1 and 2, von Hippel-Lindau disease, and neurofibromatosis type 1 are known to cause predisposition to neuroendocrine tumorigenesis (4). Due to their neuroendocrine differentiation, around half of NETs are hormone-secreting, or "functional," and can lead to symptoms of hormone excess. Commonly secreted hormones include serotonin, insulin, gastrin, vasoactive intestinal peptide, and glucagon.

NETs are further classified pathologically by grade via the WHO classification systems for gastroenteropancreatic (GEP) and lung NETs (5,6). Within the GEP system, low-grade (WHO grade 1) NETs are defined by a Ki-67 proliferative index of <3% and mitotic index <2 mitoses/10 high power fields (hpf); intermediate-grade (WHO grade 2), by Ki-67 3–20% and mitotic index 2–20 mitoses/10 hpf; and high-grade (WHO grade 3), by Ki-67 >20% and mitotic index >20 mitoses/10 hpf. The WHO classification system for lung and thymic NETs has some important differences when compared to that for GEP-NETs. Presence or absence of necrosis and mitotic index are the primary data elements; Ki-67 is not routinely included. WHO grade 1 lung NETs are defined by absence of necrosis and mitotic index <2 mitoses/10 hpf; WHO grade 2 lung NETs are defined by presence of necrosis and mitotic index 2–10 mitoses/10 hpf. The pathology and biological behavior of poorly differentiated (grade 3) neuroendocrine carcinomas (NECs) are now recognized to be sharply distinct from those of well-differentiated (grades 1 and 2) NETs, and the therapeutic options reflect as such (7,8). Unlike well-differentiated NETs, poorly differentiated NECs are characterized by extensive necrosis, nuclear pleomorphism, aggressive growth, and poor prognosis (9). While poorly differentiated NECs have demonstrated high response rates (RR) to platinum-based cytotoxic chemotherapies, well-differentiated NETs have been shown to respond poorly (10,11).

Biologic therapies thus play a specifically important role in the treatment and clinical management of well-differentiated NETs, owing to the nuances of their biology and behavior. In light of the relatively indolent nature of the vastly more common well-differentiated NETs and the potential toxicities that accompany cytotoxic chemotherapies, biologics—targeted therapies derived from engineered gene products—have emerged as promising options in treating NETs. The following discussion applies to the treatment of well-differentiated (WHO grades 1 and 2) NETs; there is no known role for biologics in the treatment of poorly differentiated NECs.

Two biologics have been approved by the FDA for NETs upon demonstration of prolonged progression-free survival (PFS) compared to placebo. The multiple receptor tyrosine kinase (RTK) inhibitor sunitinib and the mammalian target of rapamycin (mTOR) inhibitor everolimus were approved for the treatment of advanced, progressive, well-differentiated pNETs in 2011. The indication for everolimus was extended to include advanced, well-differentiated, non-functional gastrointestinal and lung NETs in 2016. A number of ongoing trials for NETs are investigating the clinical activity and therapeutic potential of other biologics, including other RTK and mTOR pathway inhibitors, as well as immune checkpoint inhibitors. This article will review the data supporting the FDA approval of everolimus and sunitinib in NETs, as well as discuss ongoing trials and future directions for biologic therapies in pancreatic and gastrointestinal NETs.

Everolimus and mTOR signaling

mTOR is a serine/threonine protein kinase that is a member of the phosphatidylinositol-3 kinase (PI3K)/protein kinase B (Akt) signaling pathway responsible for cell cycle regulation. Alterations along this pathway are most frequently activating, promoting proliferation while suppressing apoptosis. Negative regulators of the PI3K/Akt/mTOR pathway include phosphate and tensin homolog (PTEN), tuberous sclerosis protein 2 (TSC2), and neurofibromatosis 1 (NF1). mTOR deregulation has been demonstrated in a wide range of cancers, and germline defects in TSC2 and NF1 have been associated with development of NETs (12-15).

While NETs have been shown to be relatively mutationally silent when compared to their more aggressive adenocarcinoma counterparts, Jiao *et al.* found mutations in genes along the mTOR pathway in approximately 15% of pancreatic NETs (16,17). Missiaglia *et al.* observed low expression of PTEN and TSC2 by immunohistochemical (IHC) staining in 41% and 70% of pNETs, respectively (18). Loss of PTEN and TSC2 expression was found to be negatively correlated with prognosis. Preclinical models have validated the upregulation of mTOR pathway signaling in NETs and have demonstrated the efficacy of the mTOR inhibitor everolimus in the NET cell lines INS-1, BON-1, and NCI-H727. Everolimus treatment inhibited cell growth and correlated with an increased G0/G1 peak in flow

cytometric analyses, indicative of cellular quiescence (19,20).

In 2011, the randomized, phase III Everolimus and Octreotide in Patients with Advanced Carcinoid Tumor (RADIANT-2) trial demonstrated the antitumor activity of everolimus in NETs (21). The trial enrolled 429 patients with advanced, low- to intermediate-grade, functional NETs of lung, pancreas, and gastrointestinal origin who had shown radiologic progression of disease within the past 12 months. Patients were randomized to one of two arms: everolimus plus octreotide or placebo plus octreotide, with crossover allowed at progression. Octreotide was administered intramuscularly in 30 mg doses every 28 days, and 10 mg everolimus was orally administered daily. The primary endpoint of the study was median PFS, which favored the everolimus arm at 16.4 months over the placebo arm at 11.3 months (HR, 0.77; 95% CI, 0.59–1.00; P=0.026) by central radiology review. Partial response (PR) as best overall response was noted in 5 (2.3%) patients in the everolimus plus octreotide group and in 4 (1.9%) patients in the placebo plus octreotide group. Stable disease was recorded in 182 patients (84%) in the everolimus arm and in 172 (81%) in the placebo arm. At the time of analysis, median overall survival (OS) was not reached, and the investigators noted no significant difference between the two arms (HR, 1.22; 95% CI, 0.91–1.62). The majority of adverse events (AEs) reported for the everolimus plus octreotide group were limited to grades 1 and 2 in severity, the most common being stomatitis, rash, fatigue, and diarrhea. Though the investigators concluded that, in combination with octreotide LAR, everolimus demonstrated an advantage over placebo, the difference in PFS narrowly missed the pre-specified cutoff (P≤0.0246) for statistical significance due to informative censoring, marking RADIANT-2 as a negative study. Secondary analysis was later conducted on the RADIANT-2 trial, which revealed correlations between response to everolimus and expression of the hormonal NET markers chromogranin A (CgA) and 5-hydroxyindoleacetic acid (5-HIAA) (22). Median PFS was significantly longer for patients with non-elevated CgA (27 *vs.* 11 months; P<0.001) and non-elevated 5-HIAA (17 *vs.* 11 months; P<0.001).

In the same year, the randomized, multinational phase III Efficacy and Safety of Everolimus (RAD001) Compared to Placebo in Patients with Advanced Neuroendocrine Tumors (RADIANT-3) trial established the clinical benefit of everolimus over placebo in advanced pancreatic NETs (23). A total of 410 patients with low- to intermediate-grade, advanced, progressive pNETs were randomized to treatment arms offering best supportive care plus either 10 mg daily everolimus or placebo. PFS, the primary endpoint of the trial, was 11.4 in the everolimus arm versus 5.4 months in placebo arm (HR, 0.34; 95% CI, 0.26–0.44; P<0.001) by central radiology review. Objective tumor response was observed in ten patients on the everolimus arm (5%) and four patients on the placebo arm (2%), while stable disease was seen in 73% and 51% of patients, respectively. Thus, the authors noted that the benefit from everolimus in terms of PFS was seen primarily in stabilization of disease. The survival benefit of everolimus was confounded by high crossover rates (73%) from the placebo group, and while median OS was not reached by the time of analysis, the investigators noted no significant difference between the two arms (HR, 1.05; 95% CI, 0.71–1.55; P=0.59). AEs were mostly grade 1 or 2 in severity and were consistent with the known safety profile of everolimus. Based on the results of the RADIANT-3 study, the FDA approved everolimus for advanced pancreatic NETs in 2011.

The FDA label for everolimus was extended in 2016 to include advanced, well-differentiated, non-functional gastrointestinal (GI) and lung NETs based on the randomized, multinational phase III Everolimus Plus Best Supportive Care *vs.* Placebo Plus Best Supportive Care in the Treatment of Patients with Advanced Neuroendocrine Tumors (GI or lung origin) (RADIANT-4) study (24). The trial enrolled 302 patients, of whom one-third were sorted by double-blind randomization to the placebo arm, while two-thirds were assigned to receive 10 mg everolimus daily. Both groups received best supportive care, and crossover was not permitted until completion of primary analysis. The primary endpoint of PFS was 11.0 months in the everolimus arm and 3.9 months in the placebo arm (HR, 0.48; 95% CI, 0.35–0.67; P<0.00001) by central review. Objective responses (all PRs) by central radiology review were observed in four patients (2%) on the everolimus arm and in one patient (1%) on the placebo arm. While data was insufficient for calculation of median OS, estimates of OS at the 25th percentile were 23.7 and 16.5 months for the everolimus and placebo arms, respectively. AEs aligned with the known safely profile of everolimus and were mostly grade 1 or 2 in severity. RADIANT-4 successfully demonstrated the efficacy of everolimus in improving PFS in both lung and GI NET strata, and results in OS are pending.

Sunitinib and RTKs

RTKs represent a diverse group of cell-surface receptors

responsible for mediating cellular responses to extracellular signals such as growth factors, hormones, and cytokines. RTK activity is tightly regulated in normal cellular processes, and aberrant activation—such as in many cancers—is known to drive cell proliferation, survival, and metastasis (25). RTKs that are frequently upregulated in cancers include the receptor families for epidermal growth factor (EGF), vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), and insulin. RTK activity is mediated by the canonical Ras signaling pathway, which controls processes such as differentiation, proliferation, apoptosis, and cell migration.

Alterations in various growth factors and their cognate receptors have been identified in gastrointestinal and pancreatic NETs (26-30). In particular, VEGFRs and platelet-derived growth factor receptors (PDGFRs) have been widely implicated in driving pancreatic neuroendocrine carcinogenesis. In a study of 44 pNETs by IHC, Gilbert and colleagues observed high expression of the RTKs VEGFR1, TGFBR1, PDGFRA, and IGF1R in 80%, 69%, 65%, and 47% of samples, respectively (31). Fjällskog *et al.* examined 38 resected pNETs by IHC and found that 100% stained positive for PDGFRα, while 74% were positive for PDGFRβ, 92% for c-KIT, and 55% for EGFR (32).

Sunitinib malate is an oral small molecule inhibitor of multiple RTKs including all PDGFRs and VEGFRs, as well as c-KIT. Following the success of a number preclinical and phase II trials in demonstrating the therapeutic potential of sunitinib in pNETs, a multinational, randomized phase III trial established the benefit of sunitinib over placebo in advanced, progressive, well-differentiated pNETs (33,34). The trial enrolled 171 patients whom were assigned in a 1:1 ratio by double-blind randomization to trial arms offering best supportive care plus either placebo or 37.5 mg daily sunitinib. The study was terminated early based on the recommendation of an independent data and safety monitoring committee, which showed more deaths and serious AEs in the placebo arm, in addition to a difference in PFS favoring sunitinib over placebo. In the sunitinib and placebo groups, median PFS—the primary endpoint of the trial—was 11.4 and 5.5 months, respectively (HR, 0.42; 95% CI, 0.26–0.66; P<0.001), and the respective objective RRs were 9.3% and 0%. Most drug-related AEs were grades 1 or 2, the most common of which were nausea, vomiting, diarrhea, asthenia, and fatigue. Based on the findings of this study, the FDA approved sunitinib for advanced, progressive, well-differentiated pancreatic NETs in 2011.

Bevacizumab and the angiogenic VEGF pathway

While sunitinib is the only VEGF pathway inhibitor approved by the FDA for the treatment of NETs, bevacizumab, a monoclonal antibody to VEGF-A ligand, has also shown clinical activity. Bevacizumab received its first FDA approval in 2004 for the treatment of metastatic colorectal cancer in combination with chemotherapy and was the first clinically available angiogenesis inhibitor in the U.S. It has since also been FDA-approved for the treatment of lung cancer, kidney cancer, ovarian cancer, and glioblastoma multiforme. One of the first studies to demonstrate its clinical activity in NETs was a phase II study, in which treatment of advanced NETs with bevacizumab resulted in an objective RR of 18%, as well as reduction of tumor blood flow and an 18-week PFS rate of 95% (35). A recent randomized phase II trial (CALGB 80701) demonstrated the advantage of everolimus plus bevacizumab over everolimus alone in patients with advanced or metastatic pNETs (36). The trial enrolled 150 patients, half of whom were randomized to each arm. Everolimus was given 10 mg daily, and bevacizumab was given 10 mg/kg every 2 weeks. All patients also received depot octreotide acetate. The primary endpoint of the trial was PFS, and secondary endpoints included RR and OS. While patients on the everolimus plus bevacizumab arm did not have significantly longer OS, the combination therapy was associated with significantly higher PFS (16.7 *vs.* 14.0 months; HR, 0.80; 95% CI, 0.55–1.17; P=0.12) and RR (31% *vs.* 12%; P=0.005) over treatment with everolimus alone. Even so, patients receiving everolimus plus bevacizumab experienced more grade 3 AEs, including diarrhea, hyponatremia, hypophosphatemia, proteinuria, and hypertension.

A single-arm phase II trial of bevacizumab plus the mTOR inhibitor temsirolimus in pNETs likewise indicated the therapeutic potential of dually inhibiting the mTOR and VEGFR pathways (37). The trial enrolled 56 patients with progressive, well- to moderately-differentiated pNETs, each of whom received 25 mg intravenous temsirolimus once per week and 10 mg/kg bevacizumab every 2 weeks. The trial had co-primary endpoints of RR and 6-month PFS. Of the 58 patients enrolled, 56 were eligible for response assessment. Objective RR was 41%, though there were no complete responses. PFS at 6 months was 79%, and PFS at 1 year was 43% (95% CI, 41–68%). Median PFS was 13.2 months (95% CI, 11.2–16.6). Median OS was 34.0 months (95% CI, 27.1 to not reached). The most common grade 3 to 4 AEs

noted included hypertension, fatigue, lymphopenia, hyperglycemia, and thrombocytopenia.

Though bevacizumab has shown clinical activity in pNETs when combined with mTOR inhibition, a phase III trial in a patient population of predominantly small bowel NETs showed that octreotide plus bevacizumab is no more effective in extending PFS than octreotide plus interferon alpha (IFNα), a cytokine produced by leukocytes (38). The trial enrolled 427 patients with advanced, well-differentiated, non-pancreatic NETs whom were randomized in a 1:1 ratio to receive either 15 mg/kg bevacizumab every 21 days or 5 million units IFNα 3 times per week. Both arms also received 20 mg octreotide LAR every 21 days. Although differences in median PFS, the primary endpoint of the study, were not statistically significant between the bevacizumab and IFNα arms by central review (16.6 *vs.* 15.4 months; HR, 0.93; 95% CI, 0.73–1.18, P=0.55), median time to failure (TTF) was significantly longer in the bevacizumab arm than in the IFNα arm (9.9 *vs.* 5.6 months; HR, 0.72; 95% CI, 0.58–0.89, P=0.003). RR was 12% in the bevacizumab arm (95% CI, 8–18%) and 4% in the IFNα arm (95% CI, 2–8%). Common adverse effects on the bevacizumab arm included hypertension, proteinuria, and fatigue; and on the IFNα arm, fatigue, neutropenia, and nausea.

In addition, bevacizumab has been studied in multiple small phase II clinical trials in combination with chemotherapies, including CAPOX, FOLFOX, and temozolomide (39-42). Despite its demonstration of clinical activity in NETs in early phase clinical trials, the efficacy has not been confirmed in a requisite prospective, randomized phase III study. Due to the imminently expiring patent on bevacizumab, in 2019 in the U.S. and in 2022 in Europe, this is unlikely to happen, and thus FDA approval in NETs is not anticipated.

Discussion

The recent growth in NET research has yielded various new and promising therapies. In May 2011, everolimus became the first biologic granted FDA approval for the treatment of NETs based on the findings of the phase III RADIANT-3 trial (23). Within the same month, the FDA approved sunitinib for the treatment of advanced, progressive, well-differentiated pancreatic NETs, based on the results of a phase III trial that compared sunitinib to placebo (34). Most recently, in February 2016, the FDA extended the label of everolimus to include progressive, well-differentiated, non-function NETs of GI or lung origin (24). Despite differences in trial design that prevent direct comparison across trials, these studies all demonstrated the advantage of everolimus or sunitinib over placebo in extending PFS in patients with NETs. Upon further analysis, however, the objective RR within each of these trials was found to be relatively low. Combined with high rates of stable disease on the treatment arms, these data indicate that the antitumor activities of these biologics rely largely on their ability to produce tumor stability without necessarily causing tumor shrinkage. Within the more slow-growing subtype of well-differentiated NETs, stable disease is often a reasonable goal of care, though patients with bulky or more rapidly growing well-differentiated NETs or poorly differentiated NECs may require treatments that produce greater objective responses, like cytotoxic chemotherapy.

Although everolimus and sunitinib remain the only two biologics approved by FDA for the treatment of NETs, other inhibitors of the mTOR and VEGF pathways have also demonstrated clinical activity in NETs. Ongoing and upcoming trials are investigating the roles of other biologic inhibitors of targets along the mTOR and VEGF pathways, among other pathways known to drive tumorigenesis (*Table 1*). Most targets are RTKs for important growth factors, including PDGF, FGF, stem cell growth factor (c-KIT), and VEGF. Of note, a phase I/II trial (NCT01465659) evaluating the multi-RTK inhibitor pazopanib plus the DNA methylating agent temozolomide in treating patients with pNETs is ongoing.

Other promising targets currently under study are TORC1 and TORC2, which are two distinct complexes of which mTOR is the catalytic subunit. TORC1 is responsible for regulating protein synthesis and serves as a sensor for nutrient, energy, and redox conditions, while TORC2 controls the cellular cytoskeleton and regulates metabolism and survival through its role in activating Akt signaling (43). Targeting TORC1/2 may potentially serve as a mechanism for overcoming resistance to mTOR inhibition. The dual TORC1/2 inhibitor TAK-228 has demonstrated preclinical activity in some neuroendocrine cancer models; a phase II study of this agent in rapalog-resistant pNETs (EA2161) is expected to start in 2017 (*Table 1*) (44). More recent studies have also demonstrated the expression of the programmed death ligand 1 (PDL-1) on midgut NETs and poorly differentiated NECs by immunohistochemistry (45,46), indicating the potential for targeted immunotherapy in NETs. Further studies characterizing the NET immune environment and the clinical response of NETs to biologic

Table 1 Select ongoing trials using biologics in neuroendocrine tumors (NETs)

Primary Site	Trial name	Phase	NCT#	Biologic(s)	Target
Pancreas	Efficacy and safety of everolimus and (STZ-5FU) given one upfront the other upon progression in advanced pNET (SEQTOR)	III	NCT02246127	Everolimus	mTOR
	Phase III study of sulfatinib in treating advanced pancreatic neuroendocrine tumors	III	NCT02589821	Sulfatinib	VEGFR, FGFR
	Cabozantinib in advanced pancreatic neuroendocrine and carcinoid tumors	II	NCT01466036	Cabozantinib	c-Met, VEGFR
	Regorafenib in treating patients with advanced or metastatic neuroendocrine tumors	II	NCT02259725	Regorafenib	RTKs (e.g., VEGFR, FGFR, PDGFR)
	Phase II study of ibrutinib in advanced carcinoid and pancreatic neuroendocrine tumors	II	NCT02575300	Ibrutinib	Bruton's tyrosine kinase
	Temozolomide and pazopanib hydrochloride in treating patients with advanced pancreatic neuroendocrine tumors that cannot be removed by surgery	I/II	NCT01465659	Pazopanib	RTKs (e.g., c-KIT, VEGFR, FGFR, PDGFR)
	Study of pembrolizumab (MK-3475) in participants with advanced solid tumors (MK-3475-158/KEYNOTE-158)	II	NCT02628067	Pembrolizumab	PD-1
	Phase I, multicenter, dose escalation study of DCR-MYC (pancreatic NET expansion cohort)	I	NCT02110563	DCR-MYC	siRNA to Myc
	A phase II study of MLN0128 (TAK-228) in rapalog-resistant advanced pancreatic neuroendocrine tumors (ECOG-ACRIN 2161)	I	Pending	TAK-228	TORC1/2
Gastrointestinal tract	Phase III study of sulfatinib in treating advanced extrapancreatic neuroendocrine tumors	III	NCT02588170	Sulfatinib	VEGFR, FGFR
	A Randomized Phase II Study of Pazopanib Hydrochloride in Treating Patients With Progressive Carcinoid Tumors (ALLIANCE 021202)	II	NCT01841736	Pazopanib	RTKs (e.g., c-KIT, VEGFR, FGFR, PDGFR)
	Nintedanib in treating patients with locally advanced or metastatic neuroendocrine tumors	II	NCT02399215	Nintedanib	RTKs (e.g., VEGFR, FGFR, PDGFR)
	A study of famitinib in patients with advanced or metastatic gastroenteropancreatic neuroendocrine tumor	II	NCT01994213	Famitinib	RTKs (e.g., c-KIT, VEGFR, PDGFR)
	Regorafenib in treating patients with advanced or metastatic neuroendocrine tumors	II	NCT02259725	Regorafenib	RTKs (e.g., VEGFR, FGFR, PDGFR)
	Cabozantinib in advanced pancreatic neuroendocrine and carcinoid tumors	II	NCT01466036	Cabozantinib	c-Met, VEGFR
	LEE011 in neuroendocrine tumors of foregut origin	II	NCT02420691	Ribociclib (LEE011)	CDK4/6
	Carfilzomib for the treatment of patients with advanced neuroendocrine cancers	II	NCT02318784	Carfilzomib	Proteasome inhibitor
	Safety and pharmacology of SNX-5422 plus everolimus in subjects with neuroendocrine tumors	I	NCT02063958	SNX5422, everolimus	HSP90

mTOR, mammalian target of rapamycin; VEGFR, vascular endothelial growth factor; FGFR, fibroblast growth factor receptor; c-Met, hepatocyte growth factor receptor; RTKs, receptor tyrosine kinases; PDGFR, platelet-derived growth factor receptor; c-KIT, proto-oncogene for mast/stem cell growth factor receptor; PD-1, programmed death receptor 1; TORC, mTOR complex; CDK, cyclin-dependent kinase; HSP90, heat shock protein 90.

immunotherapies are currently in progress (NCT02575300, NCT02628067).

Two other major areas of investigation in NET research involve studying the effects of single-agent versus combination therapies and the sequence in which therapies are administered. Cancers are well known to rapidly develop resistance to single-agent targeted therapies through reactivation of the signaling pathway and through clonal outgrowth of resistant populations (47). The differences in the effects and mechanisms of single-agent biologics versus combination therapies are not yet well understood. Furthermore, the optimum order in which therapies should be administered in NET patients remains unknown. A current phase III trial [Efficacy and Safety of Everolimus and (STZ-5FU) Given One Upfront the Other Upon Progression in Advanced pNET (SEQTOR); NCT02246127] is studying whether the sequence of therapy affects patient outcomes. Patients are randomized to receive either the biologic everolimus or the cytotoxic chemotherapies streptozotocin (STZ) and 5-fluorouracil (5FU) at trial entry. Upon progression, each patient will then switch to the other line of therapy. The primary endpoint of the trial is PFS, and the trial is estimated to be completed in 2018.

The landscape of NET research and therapy has advanced tremendously over the past decade. The clinical success of everolimus, sunitinib, and bevacizumab for pNETs and the expansion of the everolimus label to include GI and lung NETs in 2016 represent major milestones in the field. Despite recent advances, however, many questions remain unresolved. A number of ongoing and upcoming trials aim to study the efficacy of other biologics, such as RTK inhibitors, mTOR pathway inhibitors, cell cycle inhibitors, and immunotherapies, in GI and pancreatic NETs, though it is currently not well understood whether these biologics are more effective as single agents or in combination therapies. Moreover, little is known about the optimal sequence in which therapies should be administered to NET patients. Further prospective studies on novel biologics, as well as retrospective studies of correlative markers, may shine light on future therapies for NET treatment.

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None.

Footnote

Conflicts of Interest: Dr. PL Kunz is the PI on clinical trials with Dicerna, Esanex, Oxigene, Advanced Accelerator Applications, Genentech, Ipsen, Lexicon Pharmaceuticals, Merck and she serves on an Advisory Board for Ipsen and Lexicon. Dr. IH Liu has no conflicts of interest to declare.

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