Published in final edited form as:

Semin Oncol. 2013 February ; 40(1): 75–83. doi:10.1053/j.seminoncol.2012.11.010.

Systemic Therapy for Advanced Pancreatic Neuroendocrine Tumors

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Abstract

Neuroendocrine tumors (NETs) occur throughout the body, and share similar histologic characteristics. However, it has become increasingly evident that pancreatic NETs tend to respond differently to therapeutic agents than do other NET subtypes. In most cases, systemic therapy has been more effective in NETs of pancreatic origin than in NETs arising from other locations. Traditional systemic treatment options for pancreatic NETs include somatostatin analogs or cytotoxic chemotherapy. Recently, the biologically targeted agents everolimus and sunitinib were approved for use in patients with metastatic disease. Novel agents, as well as novel drug combinations, are currently under investigation.

Surgery remains the mainstay of treatment for patients with localized pancreatic neuroendocrine tumors (NETs); unfortunately, however, the majority of patients with pancreatic NETs present with disease that is already advanced and unresectable.¹ A broad range of systemic therapeutic options can be considered in this setting. Somatostatin analogs, cytotoxic chemotherapy, and, to a lesser extent, interferon, have historically been the main choices. However, in the past few years, targeted biological therapies, including the mammalian target of rapamycin (mTOR) inhibitor everolimus and the tyrosine kinase inhibitor sunitinib, have been shown to be beneficial in the treatment of advanced pancreatic NETs and are now approved for this indication. A number of investigational approaches also have shown promise, including treatment with radiolabeled somatostatin analogs (peptide receptor-targeted therapy) and treatment with novel drug combinations.

SOMATOSTATIN ANALOGS

Octreotide and Lanreotide

Somatostatin analogs are generally the first treatment consideration in patients with pancreatic NETs who demonstrate symptoms of hormonal hypersecretion. Two somatostatin analogs are commonly used: octreotide, which is approved for this indication in North America and Europe, and lanreotide, which is approved in Europe. Approximately one third

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Conflicts of interest: M.H. Kulke has worked as a consultant to Novartis, Ipsen, Pfizer, and Lexicon Pharmaceuticals.

of pancreatic NETs secrete hormones that produce symptoms. These symptoms can be diverse and are dependent on the specific hormone produced.^{1,2}

Patients with excess secretion of vasoactive intestinal peptide (Verner Morrison syndrome) may present with profound secretory diarrhea and electrolyte disturbances that respond rapidly to the administration of somatostatin analogs.³ Excess glucagon secretion associated with glucagonoma results in hyperglycemia and skin rash (necrolytic migratory erythema) that is also usually highly responsive to somatostatin analogs.² Gastrinomas, which arise not only in the pancreas but also in extrapancreatic locations within the “gastrinoma triangle,” are associated with excess gastrin secretion resulting in gastric acid hypersecretion, diarrhea, and refractory peptic ulcer disease. Proton pump inhibitors are generally effective in the first-line treatment of these symptoms; however, administration of somatostatin analogs may further improve symptom control by reducing gastrin levels, and also have been reported to have a direct anti-tumor effect.^{4,5}

The use of somatostatin analogs to treat patients with insulinoma remains somewhat controversial. Insulinomas are often less responsive to somatostatin analogs than are other secretory pancreatic NETs, in part due to their lower expression of somatostatin receptor 2.⁶ Additionally, the administration of somatostatin analogs to patients with insulinoma may decrease levels of endogenous glucagon secretion and can lead to paradoxical hypoglycemia.⁷ For this reason, if used for this indication, somatostatin analogs should be administered to patients with insulinoma with caution and, at least initially, in a monitored setting.

Whether somatostatin analogs also control tumor growth in patients with advanced pancreatic NETs remains uncertain. An antiproliferative effect associated with somatostatin analogs has been demonstrated in patients with advanced small bowel carcinoid tumors. In the PROMID study (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), 80 patients with locally unresectable or meta-static small bowel carcinoid tumors were randomized to receive either treatment with octreotide long-acting release (LAR; 30 mg) or placebo.⁸ Those patients randomized to receive octreotide LAR experienced a median time to tumor progression of over 14 months, as compared with only 6 months for patients receiving placebo ($P < .01$). Based on the results of this study, somatostatin analogs are now commonly used for their antiproliferative effect in patients with advanced carcinoid. Ongoing studies are assessing whether a similar effect also holds in pancreatic NETs.

Novel Somatostatin Analogs

The biological effects of somatostatin analogs are mediated by somatostatin receptors, of which there are five different subtypes (SSTRs 1–5). The two most commonly used somatostatin analogs, octreotide and lanreotide, are thought to exert the majority of their effect by binding to subtype 2.⁹ Pasireotide is a novel somatostatin analog, binding not only to receptor subtype 2 but also to subtypes 1, 3, and 5.¹⁰ Initial clinical studies of pasireotide have shown preliminary evidence of both an antisecretory effect and a cytostatic effect.^{11,12} A phase I study demonstrated that pasireotide, administered at a dose of 60 mg via a

monthly intramuscular injection, can be safely combined with everolimus, administered at a dose of 10 mg daily.¹³ A randomized phase II study is currently being performed to assess whether the addition of pasireotide to everolimus is associated with improved progression-free survival (PFS) duration compared to everolimus alone, in patients with advanced pancreatic NETs.

Radiolabeled Somatostatin Analogs (Peptide Receptor-Targeted Therapy)

Approximately 90% of NETs express somatostatin receptors, and somatostatin scintigraphy with indium 111-labeled somatostatin analogs has been widely used as a diagnostic modality in NET patients. A similar strategy, with different radioisotopes, also can be used for therapeutic purposes in patients with advanced disease and evidence of somatostatin receptor expression. The most frequently used radionuclides for targeted radiotherapy are yttrium (⁹⁰Y) and lutetium (¹⁷⁷Lu).¹⁴ Efficacy results associated with ¹⁷⁷Lu-DOTA, Tyr³-octreotate have been reported in a retrospective series of more than 500 patients. This series suggested good tolerability, and overall tumor response rate of up to 30% in patients with various types of NETs.¹⁵ ⁹⁰Y-DOTA tyr3-octreotide (⁹⁰Y-edotreotide) also has been extensively utilized for the treatment of advanced NETs, and appears to be comparable to ¹⁷⁷Lu-DOTA, Tyr³-octreotate with regard to efficacy.¹⁶ In a retrospective cohort of more than 1,000 patients, treatment with ⁹⁰Y-DOTA tyr3-octreotide (⁹⁰Y-edotreotide) was associated with an overall response rate of 34%.¹⁷ Most recently, the combination of ⁹⁰Y-DOTA tyr3-octreotide (⁹⁰Y-edotreotide) and ¹⁷⁷Lu-DOTA, Tyr³-octreotate was evaluated in 249 patients, and compared retrospectively to results in 237 patients receiving ⁹⁰Y-DOTA tyr3-octreotide (⁹⁰Y-edotreotide) alone.¹⁸ Longer survival durations in patients who were exposed to both agents suggested potential promise associated with this strategy.

While peptide receptor-targeted therapy has been widely used for the treatment of advanced NETs, particularly in Europe, relatively few formal, prospective trials with these agents have been performed. ⁹⁰Y-DOTA tyr3-octreotide (⁹⁰Y-edotreotide) was evaluated in a prospective, phase II study of 90 patients with metastatic carcinoid tumors. The objective tumor response rate, reported to be 4%, was significantly lower than response rates reported in retrospective series, although more than 50% of patients had improvement in symptom control.¹⁹ Differences in outcomes may be in part due to differences in patient selection between trials. Patients treated with peptide receptor therapy are generally selected based on levels of somatostatin receptor expression in octreotide scans, and scan interpretation may vary between sites.

Radioisotope therapy also has been associated with both hematologic and renal toxicity. Among the 1,109 reported patients treated with ⁹⁰Y-DOTA tyr3-octreotide (⁹⁰Y-edotreotide), 12.8% developed transient grade 3 or 4 hematologic toxicity, and 9.2% developed permanent grade 4 or 5 renal toxicity.¹⁷ Myelodysplastic syndrome, although rare, also has been reported following treatment with these agents.¹⁷ Prospective, randomized controlled studies evaluating both the antitumor activity and long-term toxicity of radiolabeled somatostatin analogs are necessary and anticipated.

INTERFERON-ALPHA

Interferon alpha has been used as a treatment for patients with advanced carcinoid tumors for several decades.²⁰ In large retrospective series, low-dose interferon has been reported to both reduce symptoms of hormonal hypersecretion and, in some cases, to result in arrest or slowing of tumor growth.^{21,22} Tumor regression is less common, but has been reported in up to 15% of patients in some studies.²¹ However, whether interferon has similar efficacy in advanced pancreatic NETs is uncertain.

Furthermore, relatively few studies have evaluated interferon prospectively, particularly in advanced pancreatic NETs. The antitumor efficacy of lanreotide, interferon, or combined therapy was evaluated in a prospective randomized trial involving 80 therapy-naive patients with documented progressive metastatic NETs.²³ Objective partial response rates were relatively low in all three groups (4%, 4%, and 7% for lanreotide, interferon, and combined therapy, respectively), although relatively high rates (18%–28%) of tumor stabilization were reported in all groups. Similar findings were noted in a trial in which 109 patients with progressive metastatic gastrointestinal NETs were randomly assigned to octreotide with or without interferon.²⁴

Interferon doses in most studies range from 3–9 mU (million units) subcutaneously, administered from three to seven times per week. Interferon is somewhat myelosuppressive and also can be associated with depression, fatigue, and thyroid function abnormalities. As a result, its routine use in the treatment of advanced NETs (and in particular in pancreatic NETs) is not uniformly accepted.²⁵ An ongoing randomized study is assessing the relative efficacy of octreotide with either interferon or bevacizumab in patients with advanced carcinoid tumors; similar studies in advanced pancreatic NETs have not been performed to date.

CYTOTOXIC CHEMOTHERAPY

Intravenously Administered Alkylating Agents: Regimens Incorporating Streptozocin or Dacarbazine

Alkylating agents have long been used for the treatment of patients with advanced pancreatic NETs, and are clearly associated with antitumor activity in this setting (Table 1). Streptozocin was approved by the US Food and Drug Administration for this indication in 1982. In a subsequent study, a combination of streptozocin and doxorubicin was compared to streptozocin/fluorouracil or another alkylating agent, chlorozotocin. The trial was performed in a relatively limited number of patients, in which 30–40 patients were treated in each arm.²⁶ In this study, treatment with streptozocin/doxorubicin was associated with a 69% rate of tumor regression (defined broadly), as well as a modest survival benefit when compared to streptozocin/fluorouracil. The median duration of response in the streptozocin/doxorubicin arm was estimated to be 18 months.

Interpretation of this study has been limited both by the relatively small size, as well as the use of older response criteria. Two small retrospective analyses of patients receiving the streptozocin/doxorubicin regimen raised questions about the extent of its antitumor activity

in pancreatic NETs, and estimated true response rates, using modern response criteria, to be less than 10%.^{27,28} However, a larger single-institution retrospective series comprising 84 patients with advanced pancreatic NET treated with a three-drug combination of streptozocin, fluorouracil, and doxorubicin found the response rate to be 39%. The median PFS duration in this study was estimated to be 18 months, and median overall survival 37 months.²⁹

Dacarbazine also has been evaluated and shown to be active in advanced pancreatic NETs. The Eastern Cooperative Oncology Group performed a phase II study of dacarbazine in 50 patients with advanced pancreatic NETs and reported an objective response rate of 34%.³⁰ A combination of dacarbazine, 5-fluorouracil, and epirubicin was evaluated in 82 patients with NETs of various sites, and was found to be associated with an overall response rate of 24.4% and a median time to tumor progression of 21 months.³¹

Temozolomide

Despite clear evidence of antitumor activity associated with streptozocin- and dacarbazine-containing regimens, the use of these drugs for the standard treatment for patients with advanced pancreatic NETs has not been adopted universally. Potential concerns associated with the use of these regimens include the risk of renal and hematologic toxicity, cumbersome infusion schedules, and, more recently, inconsistent drug supply. Temozolomide is an alkylating agent that was specifically developed as an oral and less toxic alternative to dacarbazine, and has been widely used for the treatment of glioblastoma and melanoma.³² More recent studies increasingly also support its use for the treatment of pancreatic NETs.

Antitumor activity associated with temozolomide in NETs has been reported in a number of retrospective series. Small retrospective studies evaluating single-agent temozolomide in patients with advanced pancreatic NETs have reported overall response rates of 8%–25%.^{33,34} In a large series that included 53 patients with pancreatic NETs treated with various temozolomide-based regimens, 18 (34%) were reported to have experienced partial or complete responses. The median PFS for temozolomide-treated patients in this study was 13.6 months.³⁵ The most encouraging data to date were reported in a recent single-institution retrospective study in which 30 patients with advanced pancreatic NETs were treated with temozolomide at a dose of 200 mg/m² on days 10–14, together with capecitabine at a dose of 750 mg/m² twice daily on days 1–14.³⁶ In this study, the reported response rate was 70% and the median PFS was 18 months.

Prospective studies of temozolomide in NETs are limited to several single-institution phase II studies, all of which evaluated temozolomide-based combination regimens rather than single-agent temozolomide. In these studies, temozolomide was administered using a dose-intense schedule of 150 mg/m²/d administered for 7 days every other week. In the first study, assessing a combination of temozolomide and thalidomide, 5/11 pancreatic NET patients experienced partial responses. The median PFS was not reached.³⁷ Lymphopenia and opportunistic infections were observed in patients receiving prolonged treatment in this study, prompting the use of prophylactic antibiotics in subsequent studies using similar regimens.³⁸ A follow-up study evaluated the combination of temozolomide and

bevacizumab. Objective tumor responses were observed in 5/15 (33%) patients with pancreatic NETs, and the median PFS for pancreatic NET patients was 14.3 months.³⁹ In a third, prospective study, a regimen of everolimus and temozolomide was associated with an overall tumor response rate of 35% in patients with advanced pancreatic NETs.⁴⁰

The cytotoxic effect of temozolomide has been attributed to its ability to induce DNA methylation at the O-6 position of guanine. The sensitivity of tumor cells to some alkylating agents, including temozolomide, has been associated with decreased levels of the DNA repair protein, O6-methylguanine DNA methyltransferase (MGMT), which restores methylated DNA to its normal state.⁴¹ In patients with melanoma or glioblastoma loss of tumoral MGMT expression has been associated with temozolomide response.^{42–46} In one study evaluating MGMT expression and loss in NETs, over half of pancreatic NETs had loss of MGMT.³⁵ In contrast; MGMT loss was not observed in any carcinoid tumors. Moreover, among 21 patients treated with temozolomide-based regimens, none of the 16 with MGMT expression (including all 13 carcinoid tumors) responded to treatment, whereas four of the five patients whose tumors lacked MGMT expression (all pancreatic NETs) had a radiologic response. Future studies validating the potential predictive value of MGMT in pancreatic NET patients receiving temozolomide therapy are planned.

Oxaliplatin-Based Regimens

Combinations of oxaliplatin and a fluoropyrimidine are widely used and active in gastrointestinal malignancies. Several recent reports have suggested that oxaliplatin-containing regimens may also be active in NETs. An initial study enrolling 11 patients with NETs from various sites explored the antitumor activity of capecitabine and oxaliplatin (XELOX; capecitabine in combination with oxaliplatin). Partial responses were observed in 45% of patients.⁴⁷ In a preliminary report of a subsequent study evaluating the combination of capecitabine, oxaliplatin, and bevacizumab in 20 patients with pancreatic NETs, 30% experienced a partial response.⁴⁸ In a parallel study evaluating fluorouracil, leucovorin, and oxaliplatin (FOLFOX) in combination with bevacizumab, responses were observed in 3/5 (60%) pancreatic NET patients.⁴⁹ (Table 1).

VASCULAR ENDOTHELIAL GROWTH FACTOR PATHWAY INHIBITORS

NETs have high expression of both vascular endothelial growth factor (VEGF) and VEGF receptor (VEGFR).⁵⁰ Additionally, preclinical models of pancreatic endocrine neoplasia have suggested that inhibition of VEGF signaling is a promising therapeutic approach.⁵¹ In pancreatic NETs, the best studied agents in this class have been small molecule tyrosine inhibitors with activity against VEGFR and related tyrosine kinases (Table 2). These agents include sunitinib, pazopanib, and sorafenib.

In an initial phase II trial, sunitinib, administered at a dose of 50 mg daily for 4 out of every 6 weeks was administered to 109 patients with advanced carcinoid or pancreatic NETs.⁵² Among 61 patients with pancreatic NETs, 11 (18%) experienced a partial response. Using a slightly different dosing regimen of 37.5 mg daily, sunitinib was subsequently compared to placebo in a phase III trial of 171 patients with progressing pancreatic NETs.⁵³ Accrual was stopped prior to a pre-planned efficacy analysis; an analysis of the enrolled patients showed

that median PFS was significantly longer with sunitinib as compared to placebo (11.4 v 5.5 months; hazard ratio [HR], 0.42; $P < .001$). A preliminary analysis at the time of study closure also suggested that treatment with sunitinib may be associated with an overall survival benefit. However, an updated overall survival analysis showed no statistically significant differences between the two study arms, possibly due to a substantial number of patients on the placebo arm who subsequently received sunitinib at progression.⁵⁴ Based on the results of this study, sunitinib was approved for use in advanced pancreatic NETs in 2011.

Sorafenib and pazopanib differ from sunitinib to some extent in their specificity for specific tyrosine kinases, but all three drugs share the ability to inhibit VEGFR2. In phase II studies, the antitumor activity associated with sorafenib and pazopanib appears to be similar to that observed with sunitinib. Sorafenib was evaluated in a phase II study that included 43 patients with pancreatic NETs, and produced a response rate of 11%.⁵⁵ Pazopanib was evaluated in a prospective study of 51 patients with advanced NETs, including 29 with pancreatic NETs. The response rate among patients with pancreatic NETs was 17%.⁵⁶ Phase III trials with these two agents have not been performed for this indication to date.

mTOR INHIBITORS

The mTOR inhibitor everolimus also has been evaluated and was recently approved for the treatment of advanced pancreatic NETs.⁵⁷ mTOR functions downstream of a number of receptor tyrosine kinases, and is thought to integrate the signal cascades of several growth factors.⁵⁸ Several lines of evidence support a role for the mTOR pathway in regulating NET growth. mTOR is inhibited, in part, by two tumor-suppressor proteins, TSC2 and PTEN. In a large study performed using archival tissue, low expression of TSC2 or PTEN was both observed and associated with shorter survival times in patients with pancreatic NETs.⁵⁹ Whole-exome sequencing of pancreatic NET revealed mutations in various components of the mTOR pathway, further supporting a role for mTOR in the pathogenesis of this disease.⁶⁰

Clinical studies have confirmed the efficacy of mTOR inhibitors in patients with advanced pancreatic NETs (Table 2). In an initial phase II study evaluating the combination of octreotide and everolimus, 27% of patients with pancreatic NETs experienced partial responses.⁶¹ The activity of everolimus in pancreatic NETs was further explored in an international multi-center phase II trial.⁶² Of the 160 patients enrolled in the study, 45 also received treatment with concurrent octreotide. Among patients receiving everolimus alone, the objective response rate was 9%, and the median PFS was 9.7 months. In patients who received octreotide plus everolimus, only 4% experienced partial responses; however, the median PFS was 17 months. Whether octreotide contributed to the higher PFS in this cohort is unclear, since the study was not randomized.

Everolimus was compared to best supportive care in a placebo-controlled trial that enrolled 410 patients with advanced pancreatic NET.⁶³ Everolimus was associated with a significant prolongation in median PFS (11.6 v 4.6 months; HR = 0.35, log-rank $P < .0001$). Patients receiving placebo on this study received everolimus at the time of progression, and no survival benefit was observed. In addition to its antiproliferative effect, everolimus also has

been reported to improve glycemic control in patients with functioning insulinomas.⁶⁴ Everolimus was approved for use in patients with advanced pancreatic NETs in 2011. (Table 2).

FUTURE DIRECTIONS

With the approval of sunitinib and everolimus, patients with advanced NETs now have multiple potential treatment options. The optimal sequence of therapy at this time remains unknown, and is an open area for future research. Given the demonstrated success of single-agent therapy, several studies have now begun to evaluate combinations of targeted agents in patients with advanced NETs. The combination of the mTOR inhibitor everolimus and the VEGF inhibitor bevacizumab was recently shown to be well tolerated and associated with an overall response rate of 26% in a phase II single-arm study enrolling patients with low- or intermediate-grade NETs.⁶⁵ Cancer and Leukemia Group B (CALGB) 80701 is an ongoing multicenter phase II study in which patients with advanced pancreatic NETs are randomized to receive treatment with everolimus alone or everolimus plus bevacizumab to further assess the efficacy of this regimen (Table 3). A similarly designed study, COOPERATE-2, is comparing the combination of pasireotide and everolimus to everolimus alone. Promising advances in molecular and genetic profiling of pancreatic NET are also likely to influence future clinical developments. The identification of mTOR pathway mutations in pancreatic NET served as a validation for the use of mTOR inhibitors in this indication; however, common mutations in *menin* and in the chromatin remodeling genes *ATRX* and *DAXX* were also reported. Whether these mutations influence the clinical course of pancreatic NET, or whether they may be associated with response to specific therapeutic agents, remains largely unknown.⁶⁰ Future studies, therefore, are likely to not only explore the efficacy of novel agents in pancreatic NET, but to also integrate the analysis of clinical outcomes with the molecular and genetic characteristics of the tumors being treated.

Acknowledgments

M.H. Kulke is supported in part by NIH Grant No. R01 CA151532 and the Dana Farber/Harvard Cancer Center SPORC in Gastrointestinal Cancer P50 CA127003.

The author gratefully acknowledges additional support from the Saul and Gitta Kurlat fund for neuroendocrine tumor research and from Robert and Ann Ramsey. Editorial support for the manuscript was provided by Lindy Morde.

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Table 1
Evaluation of Cytotoxic Chemotherapy in Advanced Pancreatic Neuroendocrine Tumors

Regimen	No. of Patients	Tumor Response Rate (%)	Median PFS	Median Overall Survival	Reference
<i>Prospective Studies</i>					
Streptozocin-based regimens					
Chlorozotocin	33	30	17 mo*	18.0 mo	Moertel et al, 1992 ²⁶
5-FU + streptozocin	33	45	14 mo*	16.8 mo	
Doxorubicin + streptozocin	36	69	18 mo*	26.4 mo	
Dacarbazine and dacarbazine-containing regimens					
Dacarbazine	50	34	NR	19.3 mo	Ramanathan et al, 2001 ³⁰
Dacarbazine, 5-FU, epirubicin	82 (various NETs)	24.4	21 mo	NR	Bajetta et al, 2002 ³⁶
Temozolomide-containing regimens					
Temozolomide + thalidomide	11	45	NR	NR	Kulke et al, 2006 ³⁷
Temozolomide + bevacizumab	17	24	14.3 mo	NR	Kulke et al, 2006 ³⁹
Temozolomide + everolimus	24	35	NR	NR	Kulke et al, 2010 ⁶⁷
Oxaliplatin-containing regimens					
XELOX	11	45	NR	NR	Bajetta et al, 2007 ⁴⁷
XELOX + bevacizumab	20	30	NR	NR	Kunz et al, 2010 ⁴⁸
FOLFOX + bevacizumab	5	60	NR	NR	Bergsland et al, 2008 ⁴⁹
<i>Retrospective Studies</i>					
Streptozocin + doxorubicin + 5-FU	84	39	18 mo	37 mo	Kouvaraki et al, 2004 ²⁹
Temozolomide (diverse regimens)	53	34	13.6 mo	35.3 mo	Kulke et al, 2009 ³⁵
Temozolomide (single agent)	12	8	NR	NR	Ekeblad et al, 2007 ³³
Temozolomide + capecitabine	30	70	18 mo	NR	Strosberg et al, 2010 ³⁶

* Reported as duration of tumor regression.

Abbreviations: PFS, progression-free survival; 5-FU, 5-fluorouracil; NR, not reported.

Table 2
Phase II Studies of Biologically Targeted Therapies in Pancreatic Neuroendocrine Tumors⁵²

Agent	No. of Patients	Tumor Type	Tumor Response Rate (%)	Median TTP or PFS	Reference
VEGF Pathway Inhibitors					
Sunitinib	61	Pancreatic neuroendocrine	13	7.7 mo	Kulke et al, 2008 ⁵²
Sorafenib	43	Pancreatic neuroendocrine	11	11.9 mo	Hobday et al, 2007 ⁵⁵
Pazopanib	29	Pancreatic neuroendocrine	17	11.7 mo	Phan et al, 201 ⁵⁶
mTOR Inhibitors					
Everolimus (RAD001)	30	Pancreatic neuroendocrine	27	50 wk	Yao et al, 2008 ⁶¹
Everolimus	115	Pancreatic neuroendocrine	9	9.7 mo	Yao et al, 2010 ⁶²
	45	Pancreatic neuroendocrine	4	16.7 mo	
Temsirolimus	15	Pancreatic endocrine	7	10.6 mo	Duran et al, 2006 ⁶⁸

Abbreviations: TTP, time to progression; PFS, progression-free survival.

Table 3

Randomized Trials of Targeted Therapies in Neuroendocrine Tumors

Agent	Patients*	Tumor Response Rate (%)	Median TTP or PFS	Reference
Completed Studies				
Sunitinib	86	9	11.4 mo	Raymond et al, 2010 ⁵³
ν				
Placebo	85	0	5.5 mo	
Everolimus	207	NR	11 mo	Yao et al, 2010 (RADIANT-3) ⁶³
ν				
Placebo	203	NR	4.6 mo	
Ongoing Studies				
Everolimus				
ν			CALGB 80701	
Everolimus + bevacizumab				
Everolimus				
ν			COOPERATE-2	
Everolimus + pasireotide				
Lanreotide				
ν			CLARINET	
Placebo				

Abbreviations: TTP, time to progression; PFS, progression-free survival; NR, not reported.