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REVIEW

# Safety and Efficacy of Everolimus in Adult Patients with Neuroendocrine Tumors

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**Abstract:** Neuroendocrine tumors (NETs) consist of a diverse family of tumors which are derived from the neuroendocrine system. Most NETs are well or moderately differentiated tumors with a relatively indolent growth pattern. However, these tumors can cause significant clinical disease due to release of functional products that mediate the carcinoid syndrome and other diverse sequela. They also can grow progressively and cause symptoms from local invasion or distant metastasis. NETs are optimally treated with surgery and somatosatin analogs (SSA's) to control symptoms but are relatively insensitive to systemic chemotherapy. As a result, patients with advanced unresectable NETs have a poor prognosis. In 2011, two targeted therapies, sunitinib and everolimus were approved in the subset of progressive pancreatic NETs (pNETs). Everolimus is an oral inhibitor of the growth stimulatory mTOR pathway.
In Phase 2 trials in NETs and pNETs, everolimus was well tolerated and associated with some response and widespread disease stabilization. In follow-up, randomized Phase 3 trials, everolimus was compared to placebo. In the RADIANT-2 trial, everolimus and a somatostatin analog were used in patients with functional NETs and treatment was associated with an an improvement in progression-free survival (PFS). In the RADIANT-3 trial, patients with pNET were randomized to receive everolimus or placebo along with best supportive care. Everolimus was again associated with improvement in PFS compared to placebo and it has been approved by the FDA for patients with progressive pNET. Everolimus is associated with frequent low grade toxicity but is also notable for increased rates of infection as well as non-infectious pneumonitis. mTOR inhibition with everolimus represents a significant advance in the treatment of advanced neuroendocrine tumors.

**Keywords:** neuroendocrine tumors, pancreatic neoplasms, molecular targeted therapy, drug safety

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## Background

### Neuroendocrine tumors

Neuroendocrine tumors (NETs) consist of a diverse family of tumors which are derived from the neuroendocrine system. This heterogeneous population of tumors frequently arise from embryonal neural crest cells, which are abundant in the epithelium of the gastrointestinal tract and bronchopulmonary system.[1] However NETs can arise in other sites throughout the body. NETs have a wide range of morphologic, functional and behavioral characteristics.[2] In general NETs are more indolent than epithelial tumors, though small cell and large cell morphology are associated with aggressive proliferation.

The majority of NETs are low to intermediate grade and are often termed carcinoid tumors. Carcinoid tumors represent a heterogeneous group of lesions but their incidence has markedly increased in the last 30 years. An analysis of SEER data from a 25 year period[3] revealed that the incidence of carcinoid tumors had risen from 8.5 to 38.4 per million persons between 1973 and 1997. The reason for this increase is not clear but may be related to greater standardization of the pathologic diagnosis and increased awareness of this disease. A subset of NETs are of pancreatic origin[4] and are termed islet cell carcinomas or pancreatic NETs (pNETs) and will be discussed separately in this review paper.

Within the GI tract, carcinoids are subclassified based on their tissue of origin and this relates to the associated clinical symptoms. Foregut carcinoids have low serotonin and rarely secrete active peptides but can metastasize, midgut tumors invariably secrete serotonin and cause the classic carcinoid syndrome,[5] hindgut tumors secrete a variety of gastrointestinal hormones.

"Functional" NETs may synthesize and release a variety of hormones and active peptides that are associated with clinical symptoms. Most notably, this may lead to the carcinoid syndrome which consists of flushing, diarrhea, and other symptoms including wheezing and cardiac symptoms.[5,6] Somatostatin is an endogenous 14 amino acid peptide which binds to somatostatin receptors and has a predominately inhibitory effect on the release of many gastrointestinal hormones.[7] The clinical utility of utilizing somatostatin is limited by the short half-life of this peptide in the circulation (less than three minutes). Octreotide is a synthetic peptide that mimics the effect of somatostatin but remains stable and active for a longer time in the circulation. Octreotide and other somatostatin analogs are useful in reducing symptoms in patients with carcinoid syndrome. One early study found rapid relief of symptoms in 22 of 25 patients with prolonged response in the majority of patients treated with octreotide.[8] Long acting formulations are associated with prolonged relief in many patients[9,10] and are the standard of care for symptomatic tumors. The PROMID study,[11] looked at the use of long acting octreotide to control symptoms of functional NETs. Active treatment was effective in reducing symptoms compared to placebo and additionally was associated with delayed time to tumor progression (from 6 months to 14.3 months, HR = 0.34, $P \leq 0.0001$) even among patients without functional tumors.

Despite the ability to utilize symptomatic treatment, the definitive therapy for functional or non-functional NETs is surgical resection. Once tumors are locally advanced or metastatic their management becomes increasingly challenging. Some metastatic lesions remain suitable for resection[12] but in general patients with advanced NETs require definitive medical therapy. The more common, well to moderately differentiated tumors have a lower proliferation rate but are often unresponsive to chemotherapy. This is in noted contrast to poorly differentiated NETs such as small cell and large cell tumors which are more responsive to cytotoxic chemotherapy.[13,14] Cytotoxic therapy has been studied for the treatment of advanced well-differentiated NETs but has generally been disappointing.[15] High dose paclitaxel was given in a Phase 2 trial[16] which included 24 patients, 14 with carcinoid and 9 with pNET, there was response in only 2 patients (8%) with substantial toxicity. A phase 2/3 trial looked at the combination of 5-FU with either doxorubicin or streptozocin for patients with advanced, unresectable NETs.[17] Both regimens were associated with similar but modest response rates (15.9 and 16% respectively) and progression free survival intervals; with an improvement in overall survival in the 5-FU/streptozocin arm (24.3 months vs. 15.7 months with 5-FU/doxorubicin, $P = 0.0267$). This benefit was countered by an increase in renal toxicity in addition to baseline hematologic toxicity; given the modest response rates, chemotherapy has traditionally been infrequently used in the treatment of metastatic carcinoid lesions.

## Pancreatic NET

In the pancreas, NET's arise from the islets and are often referred to as islet cell carcinoma but now more commonly known as pNET (pancreatic neuroendocrine carcinoma). Pancreatic neuroendocrine tumors (pNET) represent a small percentage of all pancreatic tumors:[4] 1.3% (with a 9.9% prevalence); but their incidence is rising. Between 1977–1981 to 2002–2005, the incidence rate of endocrine cancer of the pancreas rose more than 100% and advanced stage disease increased by 137%.[18] This increase in pNET parallels the increasing frequency in NETs in general and likely relates to increased pathologic awareness and standardization of diagnosis. As with NETs in general, the definitive treatment of pNETs is surgical. When pNETs cause carcinoid symptoms, these can be controlled with somatostatin analogs.[10] The majority of patients are unresectable as pNETs are frequently diagnosed at an advanced stage, with approximately 65% of patients presenting with unresectable or metastatic disease.[19]

Prior to 2011 the only chemotheraputic agent approved for use in pNETs was Streptozocin which is an alkylating agent isolated from streptomyces acromogenes in the 1950s. The first study of its activity in pNET was reported in 1973 when Broder et al[20] reported a response rate of 50% in a single arm study with 52 patients, which represented a significant advance given the absence of effective therapy prior to this time. Streptozocin was approved by the FDA for this indication in 1976. Subsequent studies reported less robust response rates in pNET with streptozocin both when used alone[21] and in combination with doxorubicin.[22] Some of the disparity in reported response is likely due to non-uniform response criteria utilized in some studies. Using radiographic response criteria McCollum et al,[23] reported a response rate of only 6% among a series of 16 patients with advanced pNET (1 of 16 patients). In contrast a retrospective review of a three drug regimen, doxorubicin, 5-FU, streptozocin, was associated with a 39% response rate.[24]

Although there may be benefit with streptozocin combination regimens, the lack of prospective data has made it difficult to determine the most beneficial therapy in this disease. Prior to 2011, no therapy had been approved by the FDA since the approval of Streptozocin in 1976. As a result patients with unresectable pNETs have a poor prognosis. The median survival time for patients with distant metastatic disease is 24 months;[19] the 5-year survival rate of patients with metastatic disease is 30% to 40%[25] and has not changed for 20 years.[26] This previously poor landscape has been significantly altered in 2011. We will report here on everolimus, an oral mTOR inhibitor which has now been approved for progressive pNET. Additionally, in 2011 another targeted agent, the multitarget tyrosine kinase inhibitor, sunitinib, was approved for progressive pNET.[27]

## NETs in hereditary syndromes point to mTOR as a therapeutic target

The search for novel active agents that would have potential use in NETs was enhanced by the association of NETs with several hereditary cancer syndromes.[28] NETs and especially pNETs are classically found in at least 4 hereditary cancer syndromes; multiple endocrine neoplasia type 1 (MEN1),[29,30] tuberous sclerosis (TS),[31] neurofibromatosis type 1 (NF1),[32] and von Hippel-Lindau syndrome (vHL).[33] In general, there is a specific increase in pNETs in these syndromes, though some are also associated with carcinoid from other sites.[34] Interestingly the putative genes involved in these disorders are associated with constitutive activation of the mTOR pathway. Mammalian target of rapamycin, or mTOR, is a serine threonine tyrosine kinase that plays a critical role in cellular growth, proliferation, and apoptosis.[35,36] mTOR is part of the PI3K/AKT pathway in which active signaling results in an increase in translation of proteins that are important in regulating cell cycle progression and maintaining proliferation. In the setting of reduced nutrients or other cellular signals to limit growth, mTOR is inhibited and this leads to increased levels of CDK2 and cell cycle inhibition.[37] In many human cancers mTOR signaling is dysregulated through several mechanisms including mutations in the pathway kinases,[38] loss of inhibitory proteins (such as PTEN),[39] or activating mutations in the signaling pathway.[40] Besides mutations in the specific genes associated with the above mentioned cancer syndromes,[41,42] upstream components of this signaling pathway such as insulin like growth factor-1[43] (IGF-1) and the IGF receptor,[44] as well as vascular endothelial growth factor (VEGF) are overexpressed in NETs.[45,46] Finally in support of the role of mTOR pathway in NETs, a global gene expression analysis of pNETs[47] revealed that two important genes in the

mTOR pathway (tuberous sclerosis 2 and PTEN) were downregulated in most of the primary tumors. Altered levels of one or both of these proteins were identified in 85% of pNETs in this survey, strongly supporting the role of the mTOR pathway in tumorogenesis. Thus targeting the mTOR complex downstream of these growth factors (IGF-1, IGFR and VEGF) may result in clinical benefit.

### Inhibition of mTOR with everolimus

Early efforts to modulate aberrant mTOR activity in malignancy utilized rapamycin (sirolimus). Rapamycin is a macrolide antibiotic which binds to the cytosolic protein, FK binding protein 12 (FKBP-12), which interacts with the mTOR complex and prevents downstream signaling.[48] Mice that are deficient in PTEN (a tumor suppressor gene which is a negative regulator of the mTOR signaling pathway) are susceptible to developing a variety of malignancies.[50] In this model, treatment with rapamycin was successful in normalizing protein function and reducing the rates of tumor development. Inhibitors of the mTOR pathway have been tested in a number of malignancies that are associated with aberrant activation of the mTOR signaling pathway,[35] including breast cancer, head and neck malignancies, and lymphoma. Moreno and colleagues utilized this clinical rationale and demonstrated the clinical potential of blocking the mTOR pathway in NET.[51] Rapamycin significantly inhibited cell proliferation in carcinoid cell lines and was associated with significant tumor suppression in vivo.

Based on the above data, early clinical trials looked at the role of mTOR inhibition in NETs. The first rapamycin analog to be reported in this disease was temsirolimus. This drug was evaluated in 36 patients with progressive, unresectable NETs, 21 with carcinoid and 15 with pNET,[52] but only 2 patients (5.6%) experienced an objective response to therapy. Everolimus, (originally known as RAD001) is an orally active mTOR inhibitor that blocks the mTOR pathway by binding with high affinity to its intracellular receptor FKBP-12 in a fashion similar to rapamycin.[49] Preclinical studies show that everolimus inhibits proliferation of a variety of human solid tumors in vitro and in vivo.[36] Everolimus has demonstrated efficacy in renal cell carcinoma[53] and is approved for this indication. The initial phase I trial of everolimus involved 92 patients with solid tumors[54] (there was no report of patients with NETs on this trial). A MTD was not achieved but doses up to 10 mg/day were tolerated and the recommendation was to begin trials at doses of at least 5 mg/day.

In addition to everolimus, which is the focus of this review, there is ongoing interest in novel agents that target diverse components of the mTOR signaling pathway. These include GDC-0980,[55] a class I PI3K and mTOR inhibitor, as well as pp242,[56] an inhibitor of the active site of the mTOR complex.

## Efficacy of Everolimus in NET

On the basis of the above preclinical data, Yao et al[57] conducted a single institution, Phase II trial of everolimus in patients with advanced NETs. They treated each patient with a combination of everolimus at either 5 or 10 mg/day and long acting octreotide (Sandostatin LAR 30 mg every 28 days). Prior treatment was permitted; patients were required to have adequate bone marrow, renal, and hepatic function as well as ECOG performance status of 2 or less (ie, active for >50% of the day and capable of self-care). 60 patients were treated on this protocol, 30 with carcinoids and 30 with pNET. There were 13 partial responses (22%) and 42 patients with stable disease (70%), there were no complete responses. The median progression free survival of patients was 60 weeks (95% CI, 54 to 66 weeks). The encouraging results in this single institution, Phase II trial, led to additional trials in advanced functional NETs, in which everolimus was combined with octreotide; and in pNET, where everolimus was used alone or in combination with octreotide depending on patient symptoms. These trials are summarized below and in Table 1.

### RADIANT-1

An open label Phase II trial was initiated to look at everolimus in patients with pNET. This trial, RAD001 in advanced neuroendocrine tumors-1 (or RADIANT-1), was a multinational, single-arm, Phase II trial.[58] All patients had advanced pancreatic NETs who had progression despite prior use of cytotoxic chemotherapy. All patients were treated with everolimus 10 mg/day; in addition patients who had previously been receiving a somatostatin analog were continued on these agents. The study enrolled 160 patients, and demonstrated a response rate of 8.7% (PR), 84.7% of patients achieved at least stable disease. Median PFS

**Table 1.** Phase II/III studies of everolimus in NET.

| Study | Intervention | Efficacy outcomes | Toxicity grade 3 and higher, >5% | Other |
|---|---|---|---|---|
| **Phase 2: Single arm**<br>N = 60<br>Well differentiated, Advanced NET<br>Carcinoid, n = 30<br>pNET, n = 30<br>Yao et al, 2008[57] | Everolimus 5 or 10 mg + Sandostatin LAR | RR-22%<br>mPFS-60 weeks<br>(95% CI- 54–66 weeks) | Diarrhea- 11%<br>Hyperglycemia- 9%<br>Hypophosphatemia- 11%<br>Leukopenia- 6% (10 mg group)<br>Thrombocytopenia- 6%<br>Pneumonitis in 9% of patients (1 was grade 3) | RR was higher in pt's with pNET (27%) compared to carcinoids (17%) |
| **RADIANT-1**<br>Phase 2: Single Arm<br>N = 160, Progressive pNET<br>Outcomes for 115 who received everolimus alone<br>Yao et al, 2010[58] | Everolimus 10 mg | RR-8.1%<br>mPFS- 9.7 months<br>mOS- 24.9 months | Asthenia- 5.2%<br>Lower grade toxicity was common and included:<br>Stomatitis- 45%<br>Rash- 40%<br>Diarrhea- 39% | 45 patients also received Sandostatin LAR with mPFS-16.7 m and mOS- not reached |
| **RADIANT-2**<br>Phase 3: randomized, placebo-controlled<br>N = 429, Advanced NET<br>Pavel at al, 2011[60] | Everolimus 10 mg vs. placebo + Sandostatin LAR (all patients) | RR- not reported<br>mPFS 16.4 vs. 11.3 months<br>HR = 0.77; 95% CI, 0.59–1.00; $P = 0.026$ | Stomatitis- 7% (vs. 0% in placebo)<br>Fatigue- 7% (vs. 3%)<br>Diarrhea- 6.0% (vs. 2%)<br>Hyperglycemia- 5.1% (vs. 0.5%)<br>Infections- 5% (vs. 0.5%)<br>Pulmonary events- 12% (2% were grade 3 or 4) | PFS survival benefit did not meet prespecified statistical significance |
| **RADIANT-3**<br>Phase 3: randomized, placebo-controlled<br>N = 410, advanced pNET<br>Yao et al, 2011[63] | Everolimus 10 mg | RR- 5% vs. 2%<br>mPFS 11.4 vs. 5.4 months<br>HR- 0.34; 95% CI, 0.26–0.44, $P < 0.001$<br>mOS- not significant<br>HR-1.05 | Stomatitis- 7%<br>Anemia- 6%<br>Hyperglycemia- 5%<br>Lower grade toxicity was common and included:<br>Stomatitis- 64%<br>Rash-49%<br>Infection-23% (vs. 6%)<br>Pneumonitis- 17% (vs. 0%) | 73% of patients treated with placebo received everolimus on progression. |

**Abbreviations:** NET, neuroendocrine tumor; pNET, pancreatic NET; LAR, long acting release; RR, response rate; mPFS, median progression free survival; mOS, median overall survival; HR, hazard ratio.

was 9.7 months in patients who received everolimus alone (n = 115) and 16.7 months in patients who received everolimus and octreotide. Median overall survival was 24.9 months in the first group and had not been reached in the second group. The differences between the 2 groups were not statistically significant. These results confirmed the robust rates of stable disease and a small percentage of objective responses seen in the earlier study and led to the initiation of 2 large randomized, multi-center Phase III trials.

## RADIANT-2

The RADIANT-2 trial looked at the role of adding everolimus or placebo to treatment with long-acting release (LAR) octreotide in patients with advanced NETs with carcinoid syndromes. This was a large, multi-national, randomized, placebo-controlled, Phase III trial. This study included 429 patients, all patients received octreotide LAR 30 mg IM every 28 days and were randomized to receive everolimus 10 mg/day or placebo. The most frequent primary site of disease was the small intestine (52%), followed by the lung (10%), 6% of patients had a pancreatic primary site. All patients had well to moderately differentiated progressive NETs with secretory symptoms. Among the 429 patients, mPFS was 16.4 months in the everolimus group compared to 11.3 months in the placebo group.[60,61] Though the trial demonstrated that everolimus is associated with a reduced risk of progression of 23%, the hazard ratio (HR: 0.77; $P = 0.026$) fell just short of the prespecified boundary of statistical significance (0.0246). Subset analysis by Anthony et al[62] revealed that there was an improvement in mPFS among patients who had received somatostatin analogs prior to enrollment (79% of patients, mPFS was 14.3 vs. 11.1 months) and among those who had not received prior therapy with somatosatin analogs (21% of patients, mPFS was 25.2 vs. 13.6 months). However neither subgroup reached statistical significance.

## RADIANT-3

The most robust data for everolimus was obtained in a randomized phase III study in 410 patients with progressive advanced pancreatic NETs (RADIANT-3). This study demonstrated significant improvements in PFS associated with everolimus as compared to placebo[63] (11 months versus 4.6 months). Patients were included if they had low or intermediate grade NET defined as "advanced" (unresectable or metastatic), ECOG performance status of 2 or less (meaning they were ambulatory, able to care for themselves and active for more than 50% of the day); they could have received prior chemotherapy or other treatment but not previous treatment with an mTOR inhibitor. The trial was double-blinded, patients received either 10 mg oral everolimus daily or placebo. In addition to study drug, patients received best supportive care which included somatostatin analogs in 40% of patients. The patient's treatment was concealed until progression at which time they could cross-over to everolimus if they were previously receiving placebo. 410 patients were randomized; most had well differentiated disease (80%), 90% had evidence of liver metastasis. Patients were continued on treatment until they had progression of disease or unacceptable toxicity. The median duration of treatment in the everolimus group was 8.79 months, compared to 3.74 months in the placebo group.

PFS as determined by the local investigators was 11.0 months vs. 4.6 months (hazard ratio for disease progression or death with everolimus, 0.35; $P < 0.001$). Response rates (using standardized radiographic criteria- Response Evaluation Criteria in Solid Tumors-RECIST)[64] were low, 10 patients on the everolimus arm (5%) compared to 4 patients (2%) in the placebo arm. Most patients experienced stable disease as their best response (73 vs. 51%), and progressive disease as best response was seen in 14% of patients on everolimus compared to 42% of patients on placebo. Ultimately there was significant crossover with 73% (148 of 203) of the placebo arm patients receiving everolimus on progression. At the time of report, no difference was seen in median OS between the two groups. Subset analysis of the RADIANT-3 trial was reported in abstract form. Shah et al,[65] reported that equal patients received somatostatin analogs (SSAs) on each arm (39 vs. 40%) and that there was a significant improvement in PFS regardless of the use of SSAs. Pommier and colleagues[66] found that PFS was improved in patients regardless of whether they received prior chemo (50%) or had no prior chemotherapy. In multivariate analysis (reported along with ASCO 2011- J Clin Oncol 29: 2011 (suppl; abstr e21091) performance status of 0, non-elevated baseline neuron specific enolase (NSE) and absence of liver involvement were associated with improved PFS.

These results in RADIANT-3 compare to the results achieved with use of sunitinib in advanced pNET. In a randomized Phase III trial,[27] sunitinib demonstrated improvement in progression free survival of 11.4 months compared to 5.5 months for placebo ($P < 0.001$).

## Toxicity of Everolimus Therapy in NETs

As with any new drug it is important to evaluate the expected toxicity profile of this agent and to maintain awareness that long term data is lacking and vigilance is needed to identify emerging toxicities. In general studies in available mTOR inhibitors have shown similar dose limiting toxicities which are primary related to GI disturbance (including stomatitis), weakness, fatigue, and thrombocytopenia at high doses.[67] The first widely studied use of everolimus and mTOR inhibitors in general is in attenuating rejection in the solid organ transplant setting. In phase I studies, the most commonly reported toxicities included hypercholesterolemia, hypertriglyceridemia, and mild hematologic toxicity with leukopenia and thrombocytopenia.[68] In both the cardiac[69] and renal transplant setting,[70] everolimus has shown benefit and safety at daily doses of 1.5 or 3 mg. In the initial Phase I trials of everolimus in solid tumors a higher daily dose was ultimately used. The most commonly[54] identified toxicities were fatigue (34%), rash (48%), and GI toxicities (66%) which included stomatitis, nausea, vomiting, anorexia. Dose limiting toxicity was only seen in 2 of 92 patients (2.1%), one with stomatitis, and one with hyperglycemia. A maximum tolerated dose was not established but the mean dose used for further trials has been 10 mg/day.

Prior to its approval for pNET, everolimus was approved for the treatment of renal cell carcinoma. In this indication toxicity was comparable to that seen in solid organ transplant patients. For example, in the Phase III trial that demonstrated efficacy for everolimus,[53,71] common toxicities which were more frequent in the everolimus arm compared to placebo, included fatigue (20%), stomatitis (40%), rash (25%), and hyperglycemia (50%). Additionally, pneumonitis has been reported with mTOR inhibitors and this was seen in 8% of patients, though all of the above side effects were rarely grade 3 or higher. Similar toxicity was seen with temsirolimus,[72] suggesting that this toxicity is a class effect of mTOR inhibitors.

### Toxicity of mTOR inhibitors in NETs

In the previously described Phase II study of temsirolimus,[52] the most frequent adverse events were: fatigue (78% of patients), hyperglycemia (69% of patients), and rash/desquamation (64% of patients). Seven patients (of 37) developed pneumonitis considered as possibly related to temsirolimus, three of whom required drug discontinuation. Similar toxicities were seen in all trials utilizing everolimus in NETs. In the single institution study[57] by Yao et al, grade 1 or 2 toxicity was common but grade 3 toxicity was generally uncommon; pneumonitis was seen in 9% of the patients on the 10 mg dose. In the phase 2, RADIANT-1 trial,[58] pneumonitis was seen in 8% of patients, all events were grade 1 or 2. In the phase 3, RADIANT-2 trial[60] the most common side effects were similar and included frequent grade 1–2 toxicities including stomatitis (62 vs. 14%), rash (37 vs. 12%), and fatigue (31 vs. 23%). The most frequent drug-related grade 3–4 adverse events were fatigue, diarrhea, and hyperglycemia. Pulmonary events, including pneumonitis, were seen in 12% of patients on everolimus versus 0% of patients on the placebo arm.

Similar toxicity was noted in the phase 3, RADIANT-3 trial in which patients with pNET were randomized to everolimus at a dose of 10 mg/day or placebo. Adverse effects were common in the everolimus group with 64% of patients reporting stomatitis (vs. 17% in the placebo arm), 49% with rash (vs. 10%), 34% with diarrhea (vs. 10%) and 23% with infections (vs. 6%). Notably 12% of patients in the everolimus arm developed pneumonitis (vs. 0% in placebo). Atypical infections such as pulmonary tuberculosis, bronchopulmonary aspergillosis, and reactivation of hepatitis B (each of which occurred in one patient) were also observed in association with everolimus therapy and 5 patients (2%) were felt to have grade 3–4 non-infectious pneumonitis or ILD.

### Rare side effects

In previous experience with everolimus and other mTOR inhibitors, rare side effects have been observed and caution must be taken to be alert for these. Among the serious side effects reported are development of bronchiolitis obliterans with organizing pneumonia

(BOOP) which required drug discontinuation and steroid therapy.[54] In the transplant setting, everolimus has rarely been associated with severe pneumonitis,[73] diffuse alveolar hemorrhage,[74] and other pulmonary complications.[75] Pneumonitis has also been observed with everolimus therapy for renal cell carcinoma (14% of patients vs. 0% with placebo).[76]

## Monitoring during therapy

Since some common side effects are metabolic, patients who begin therapy with everolimus should have cholesterol, triglyceride, and glucose levels monitored at baseline and during therapy. In addition hematologic parameters should be monitored regularly. There is an increased risk of infection, possibly owing to the immunosuppressive effect of everolimus and patients should be monitored for signs of infection. In the event of infection, the product manufacturer recommends discontinuation of the drug. There is varying practice regarding checking hepatitis B and C prior to treatment depending on patient's risk factors for infection. In the event of positivity, anti-viral treatment should be administered with therapy or at least viral serologies should be monitored and treatment adjusted accordingly. Respiratory toxicity can be substantial. Patients should be alerted to this possibility as the presentation of interstitial lung disease may be insidious. In some trials in renal cell cancer[71] (RECORD-1) patients were routinely screened with chest imaging but this was not done in the large trials in NETs. Patients should know to alert the physician with signs of worsening lung function such as cough, dyspnea with exertion, or fatigue and imaging should be pursued in these cases. Interstitial pneumonitis can often be reversed with prompt discontinuation of the drug and steroid treatment when necessary.

## Conclusions

In 2 large randomized controlled trials in NETs, everolimus has demonstrated benefit in patients with advanced, unresectable NETs. To date the benefit has been in increased time to progression, there are no reported trials (or abstracts) that suggest overall survival benefit. Although prolonged follow up from these large trials may be informative, it is possible that a survival benefit will not be achieved due to substantial cross-over at the time of progression (73% in RADIANT-3). It is also possible that the benefit of everolimus is not associated with survival benefit, only prolonging the time to disease progression. Objective response rates in the RADIANT-3 trial were low, suggesting that the primary benefit of everolimus is in stabilizing disease. In pancreatic NETs everolimus was approved by the FDA for the treatment of progressive pancreatic neuroendocrine tumors that are unresectable, locally advanced, or metastatic. We await further analysis of the RADIANT-2 trial to determine the role of this agent in other unresectable, advanced carcinoid tumors.

Everolimus is effective in patients who have previously received somatostatin therapy as well as patients who have received cytotoxic therapy. Subset analysis suggests that patients with elevated levels of chromogranin (CgA) and neuron-specific enolase (NSE) at baseline have improved outcomes, some tumor subsets are also predictive of improved response though these subsets must be validated in dedicated studies.

Everolimus is generally well tolerated though grade 1 or 2 toxicity is common and should be expected. The most common side effects are rash and stomatitis, metabolic abnormalities in glucose, phosphate, and lipid metabolism are also common and these parameters should be monitored regularly during therapy. Medical management is usually sufficient to handle these abnormalities and rarely requires discontinuation of therapy. Infection and non-infective pneumonitis are potentially more severe toxicities that may necessitate discontinuation of everolimus. Signs of these toxicities should be monitored closely. In addition, long term follow up of everolimus in solid tumors is lacking and clinicians should remain vigilant for unexpected toxicity.

The success of mTOR therapy in neuroendocrine tumors and the low rate of serious toxicity raise the possibility that everolimus may be suitable for combination therapy with cytotoxic therapy or other inhibitors of the aberrant signaling cascade. Recent studies have been initiated to test the combination of everolimus with the VEGF inhibitor, bevacizumab. Additional trials are looking at the combination of everolimus and sorafenib, a multi-kinase inhibitor that also modulates downstream effectors in the mTOR pathway. There is also ongoing research in alternative somatostatin analogs (pasireotide) which may have greater efficacy than currently available somatostatin analogs.

In summary, the mTOR pathway appears to play an important role in neuroendocrine tumors which are identified in several hereditary syndromes that are associated with aberrant mTOR signaling. This has been validated specifically in the case of pancreatic NETs in which everolimus, an oral mTOR inhibitor, demonstrated marked improvements in progression free survival in patients who were heavily pre-treated and had progressive disease. Everolimus is the first new drug approved for this disease in more than 30 years and with the recently approved sunitinib,[27] provides hope that this disease can be managed and prolonged periods of stable disease can be reliably achieved.

## Clinical Highlights

- Neuroendocrine tumors (NETs) and especially pancreatic NET (pNETs) are difficult to treat when they are advanced and unresectable.
- Treatment of advanced functional NETs with everolimus plus octreotide demonstrated an improvement in PFS compared to palcebo (16/4 vs. 11.3 months, $P = 0.026$).
- pNETs generally have reduced overall survival compared to other NETs.
- Although pNET only represents 1.3% of pancreatic tumors the incidence is rising.
- 65% of pNETs are advanced at diagnosis and the median overall survival for these patients is 24 months with no improvement in the last 20 years.
- Recently 2 agents were approved by the FDA for advanced pNET; everolimus and sunitinib.
- Everolimus increased PFS in advanced pNET from 4.6 to 11 months compared to placebo ($P < 0.001$).
- Patients tolerated everolimus with concomitant somatostatin analog therapy.
- Patients with PS-0 had the largest benefit in multivariate analysis.
- Stomatitis, rash, and diarrhea are common but manageable toxicities of everolimus therapy. Patients should be monitored for hyperglycemia and hypertriglyceridemia.
- Caution is required to monitor for infections (23% of patients) and pneumonitis (12%) which can become severe and limit therapy.

## Abbreviations

SSA, somatostatin analogs; PFS, progression free survival; NET, neuroendocrine tumor; pNET, pancreatic neuroendocrine tumor; mTOR, mammalian target of rapamycin; LAR, long acting release; mOR, median overall survival.

## Disclosures

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