**Review**

**Everolimus in Advanced Pancreatic Neuroendocrine Tumors: The Clinical Experience**

James C. Yao¹, Alexandria T. Phan¹, Valentine Jehl³, Gaurav Shah⁴, and Funda Meric-Bernstam²

**Abstract**

The incidence of neuroendocrine tumors (NET) has increased dramatically in the past 30 years. This information has revitalized basic and clinical research into the molecular biology of NET and has resulted in the recent approval of new therapies for pancreatic NET (pNET), including the oral inhibitor of the mTOR everolimus. Everolimus significantly improved progression-free survival among patients with pNET in the phase III RADIANT-3 study. Here, we review the clinical studies showing the efficacy of everolimus in pNET and summarize the translational science from these studies. To understand the mechanisms of resistance and cause of treatment failure, we compared the type of progression events observed in the everolimus and placebo arms of the RADIANT-3 study. Comparison of the everolimus arm to the placebo arm indicated the fractions of progression events due to new metastasis only (21% vs. 22%), growth of preexisting lesions (24% vs. 27%) were similar. These results suggest that although everolimus delays disease progression in patients with pNET, patients who experience disease progression while on everolimus do not appear to have a more aggressive metastatic phenotype than those whose disease progresses while on placebo. Cancer Res 73(5): 1449-53.

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**Introduction**

Pancreatic neuroendocrine tumors (pNET) occur at an incidence of 3 per 1 million persons per year and account for a small fraction of all pancreatic malignancies (1). However, because patient survival with pNET is longer than with pancreatic adenocarcinoma, the prevalence of pNET is higher, accounting for 10% of pancreatic malignancies (2). In treating these patients, physicians are faced with the parallel challenges of controlling the often dramatic manifestations of both hormone hypersecretion and cancer growth.

Results from 2 phase III trials of oral targeted agents for pNET have recently been published. Table 1 summarizes the data from a diverse group of clinical trials. No direct comparison can be made among trials conducted over a period of 2 decades with different enrollment criteria given the recent approval of new therapies for pancreatic NET (pNET), including the oral inhibitor of the mTOR everolimus. Everolimus significantly improved progression-free survival among patients with pNET in the phase III RADIANT-3 study. Here, we review the clinical studies showing the efficacy of everolimus in pNET and summarize the translational science from these studies. To understand the mechanisms of resistance and cause of treatment failure, we compared the type of progression events observed in the everolimus and placebo arms of the RADIANT-3 study. Comparison of the everolimus arm to the placebo arm indicated the fractions of progression events due to new metastasis only (21% vs. 22%), growth of preexisting lesions only (54% vs. 49%), and new metastasis along with growth of preexisting lesions (24% vs. 27%) were similar. These results suggest that although everolimus delays disease progression in patients with pNET, patients who experience disease progression while on everolimus do not appear to have a more aggressive metastatic phenotype than those whose disease progresses while on placebo. Cancer Res 73(5): 1449-53.

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Recent advances have significantly improved our understanding of the molecular biology underlying pNET (Fig. 1; ref. 9). Genetic cancer syndromes associated with pNET include multiple endocrine neoplasia type 1, tuberous sclerosis, neurofibromatosis, and von Hippel-Lindau syndrome (10). Tuberous sclerosis complex (TSC) is the direct inhibitor of mTOR. Loss of the neurofibromatosis 1 gene leads to constitutive mTOR activation. A recent study (11) using an exome sequencing approach among patients with sporadic pNET identified 3 key groups of somatic mutations involving MEN1, DAXX/ATRX, and the mTOR pathway. Evidence suggests that MEN1 mutation or deletion leads to the downregulation of p27 and p18, driving cell cycling and proliferation (12, 13). Loss of DAXX/ATRX is associated with alternative lengthening of telomeres, allowing for unlimited replication without senescence (14). mTOR pathway abnormalities, on the other hand, are reported to be associated with increased aggressiveness (Fig. 2; refs. 15, 16). Low protein expression of the mTOR pathway components TSC2 and PTEN was associated with shortened progression-free survival (PFS) and overall survival among patients with pNET (17). Thus, clues from germline mutations, somatic mutations, and protein level expression support the conduct of clinical studies of the mTOR inhibitor everolimus in patients with pNET.

Everolimus has been studied in the largest development program in pNET. Three human phase II or III studies included 600 patients with advanced pNET (5, 18, 19). In this article, we review the knowledge gained from clinical data and translational science thus far and analyze the pattern of failure in the large placebo-controlled RADIANT (RAD001 in Advanced Neuroendocrine Tumors)-3 study.
Patients and Methods

Published data from 2 phase II studies and 1 phase III randomized trial, which included patients with advanced pNET, were reviewed (5, 18, 19). Associated translational and correlative studies that have been published or presented in abstract form were summarized. All patients gave informed consent. All studies were approved by relevant institutional review committees and followed the tenets of the Declaration of Helsinki and Good Clinical Practice guidelines.

University of Texas MD Anderson Cancer Center phase II study

In the initial open-label phase II study conducted at The MD Anderson Cancer Center (Houston, TX), patients with advanced pNET with or without progression were treated with octreotide long-acting repeatable (LAR) 30 mg intramuscularly (IM) every 4 weeks along with everolimus at 5 or 10 mg/d orally (18). Response Evaluation Criteria in Solid Tumors (RECIST) profiles were monitored by multiphasic computed tomography or MRI every 12 weeks. Patients consenting to the optional correlative studies underwent image-guided core needle biopsy of metastatic lesions before and after 2 weeks of everolimus therapy.

RADIANT-1 study

RADIANT-1 was an open-label phase II study that screened 186 patients from 51 sites and enrolled 160 patients from 36 sites in 11 countries. One hundred fifteen patients not undergoing treatment with octreotide at study entry were assigned to stratum 1 (everolimus 10 mg/d orally), and 45 patients undergoing treatment with octreotide LAR were assigned to stratum 2 [everolimus 10 mg/d orally and octreotide LAR IM every 28 days at the prestudy dose (/C27)](18). All patients had advanced pNET with progressive disease documented by RECIST during or after cytotoxic chemotherapy.

RADIANT-3 study

RADIANT-3 was a double-blind, placebo-controlled, randomized phase III study that enrolled 410 patients from 82 centers in 18 countries. Patients with advanced pNET and progressive disease were randomly assigned to treatment with everolimus or matching placebo (5). Octreotide LAR could be used as concurrent medication for the management of symptoms related to hormone secretion.

Results

University of Texas MD Anderson Cancer Center phase II study

Among 30 evaluable patients with pNET, a response rate of 27% (according to RECIST) and a median PFS of 11.6 months [95% confidence interval (CI), 7.1–16.1] were observed (18). From the larger sample of 60 patients, which advanced pNET with or without progression were treated with octreotide long-acting repeatable (LAR) 30 mg intramuscularly (IM) every 4 weeks along with everolimus at 5 or 10 mg/d orally (18). Response Evaluation Criteria in Solid Tumors (RECIST) profiles were monitored by multiphasic computed tomography or MRI every 12 weeks. Patients consenting to the optional correlative studies underwent image-guided core needle biopsy of metastatic lesions before and after 2 weeks of everolimus therapy.

Table 1. Summary of data from published phase III studies in pNET

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>Median overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moertel et al. (3)</td>
<td>Streptozocin</td>
<td>42</td>
<td>16.5 mo</td>
</tr>
<tr>
<td>Moertel et al. (3)</td>
<td>Streptozocin + fluorouracil</td>
<td>42</td>
<td>26 mo</td>
</tr>
<tr>
<td>Moertel et al. (4)</td>
<td>Streptozocin + fluorouracil</td>
<td>33</td>
<td>1.4 y (16.8 mo)</td>
</tr>
<tr>
<td>Moertel et al. (4)</td>
<td>Streptozocin + doxorubicin</td>
<td>36</td>
<td>2.2 y (26.4 mo)</td>
</tr>
<tr>
<td>Yao et al. (5), Lombard-Bohas et al. (6)</td>
<td>Everolimus + BSC</td>
<td>207</td>
<td>Not reached (estimated &gt;36 mo)</td>
</tr>
<tr>
<td>Yao et al. (5), Lombard-Bohas et al. (6)</td>
<td>Placebo + BSC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>203</td>
<td>36.6 mo</td>
</tr>
<tr>
<td>Raymond et al. (7), Vinik et al. (8)</td>
<td>Sunitinib + BSC</td>
<td>86</td>
<td>30.5 mo</td>
</tr>
<tr>
<td>Raymond et al. (7), Vinik et al. (8)</td>
<td>Placebo + BSC&lt;sup&gt;b&lt;/sup&gt;</td>
<td>85</td>
<td>24.4 mo</td>
</tr>
</tbody>
</table>

Abbreviation: BSC, best supportive care.
<sup>a</sup>Planned crossover to everolimus at progression.
<sup>b</sup>Crossover to sunitinib allowed by separate study.

included an additional 30 patients with carcinoid tumors (i.e., non-pNET), a higher response rate was observed among patients treated with 10 mg/d everolimus (30%) than with 5 mg/d everolimus (13%). Everolimus treatment was associated with dose- and time-dependent increases in blood lactate dehydrogenase (LDH). Larger increases in LDH from baseline and longer PFS were associated with the 10-mg dose level. Evaluation from paired pre- and posttreatment biopsy specimens showed that everolimus slowed tumor proliferation, as shown by reduced Ki-67 labeling (18).

One consequence of mTOR inhibition is the downregulation of p-S6K, which may lead to Akt activation, at least in part, by feedback loop activation through an insulin receptor substrate–dependent mechanism (20, 21). Such activation has been proposed to lead to increased tumor aggressiveness and may be a possible resistance mechanism. We therefore evaluated the effect of mTOR inhibition on Akt/mTOR signaling in vitro in xenograft models and in paired biopsies from patients before and after treatment with everolimus. In vitro, cell lines that had greater rapamycin sensitivity had greater feedback loop activation of Akt with treatment (20). Akt phosphorylation was observed in a neuroendocrine xenograft model on treatment with everolimus, along with significant in vivo growth inhibition compared with vehicle only (20). In paired tumor biopsy specimens obtained in the clinical trial, treatment with everolimus was associated with decreases in p-S6 S240/244 (P = 0.003 compared with pretreatment baseline) and p-S6 235/236 (P = 0.02) levels and increases in p-Akt levels. Patients who experienced response per RECIST after everolimus therapy were more likely to have increased p-Akt T308 levels from baseline than patients who did not achieve radiologic response (P = 0.01; ref. 20).

RADIANT-1 study

Among patients with progressive disease during or after previous cytotoxic chemotherapy, the response rate was 9.6% (95% CI, 4.9%–16.5%) for patients receiving everolimus and 4.4% (95% CI, 0.5%–15.1%) for patients receiving everolimus plus octreotide LAR (19). Median PFS by central radiology review was 9.7 months (95% CI, 8.3–13.3) for those receiving everolimus and 16.7 months (95% CI, 11.1–NA) for those receiving the combination of everolimus and octreotide LAR.

Biomarker analyses showed high baseline chromogranin A and neuron-specific enolase to be prognostic of inferior PFS and overall survival (22). Furthermore, early biomarker response, defined as a 30% decrease at week 4 from baseline, was associated with significantly improved PFS.
RADIANT-3 study

RADIANT-3 is the largest clinical trial thus far conducted in patients with pNET. In this randomized phase III study, everolimus therapy was associated with a 2.4-fold improvement in median PFS compared with placebo (5). Median PFS was 11 months in the everolimus arm compared with 4.6 months in the placebo arm (HR, 0.35; 95% CI, 0.27–0.45; log-rank test, \(P < 0.0001\)). Everolimus also significantly reduced tumor-secreted hormones associated with functional syndromes among patients with functional pNET (5, 23, 24).

This large randomized phase III study also assessed circulating blood markers associated with angiogenesis. Everolimus treatment was associated with reductions in VEGF pathway markers, including soluble VEGF receptor 2, and placent al growth factor 1, suggesting that everolimus may also have an antiangiogenic effect in patients with pNET (25). The prognostic and predictive relevance of baseline and treatment-induced change in VEGF pathway biomarkers is undergoing further investigation. Although paired biopsy specimens were not feasible in this large international phase III study, an effort was made to collect paraffin-embedded archival tumor material. An analysis of collected samples is also planned.

Although everolimus clearly inhibited tumor growth and delayed time to progression among patients with pNET, the presence of a placebo control arm afforded an opportunity to examine the pattern of treatment failure. At the end of the final PFS analysis, 98 progression events were reported in the everolimus arm and 161 progression events were reported in the placebo arm (Table 2). Percentages of progression events attributed to the emergence of new metastasis as the only cause of progression were similar (21% in the everolimus arm vs. 22% in the placebo arm). The appearance of new metastasis concurrent with the progression of preexisting lesions occurred in 24% of progression events in the everolimus arm and 27% in the placebo arm. Lesion growth at baseline without the appearance of new metastasis occurred in 54% of progression events in the everolimus arm and 49% in the placebo arm.

These data suggest that everolimus delayed tumor progression without changing the pattern of progression among patients with advanced pNET.

Discussion

Recent years have seen significant improvement in our understanding of the molecular biology underlying genetic cancer syndromes involving pNET and the somatic mutations associated with sporadic pNET. These advances have supported the successful development of everolimus as a new drug for advanced pNET.

Although cell lines, xenograft models, and rodent models recapitulate to some degree the behavior of human pNET, they cannot fully model the behavior of well-differentiated pNET in humans and are less desirable for attempts at understanding the mechanisms of resistance. Fundamentally, well-differentiated NET in humans are slow growing, have a Ki-67 of 1% to 20%, and have a doubling time in the range of 5 to 12 months. Existing neuroendocrine cell lines, on the other hand, are aggressive, rapidly proliferative, and have a Ki-67 well more than 70% (26). They can also harbor genetic abnormalities that do not frequently occur in human pNET. For example, the BON line has been described to carry a PIK3CA mutation that is rare (1.8%) in human pNET (11). Another example is the RIPI-Tag2 transgenic mouse model, which introduces the T-antigen that binds to p53 and pRb (27) pathways generally thought to be intact in human pNET.

Our experience with human studies suggests that although baseline Akt activation is associated with a more aggressive clinical course, increases in p-Akt are expected consequences of successful mTOR inhibition and are not markers of drug resistance (20). Our analyses of the pattern of failure in RADIANT-3 showed that everolimus delayed tumor progression compared with placebo and delayed a similar fraction of progression that ultimately occurred due to new or newly detected metastasis. These analyses do not show an increased metastatic phenotype to be a principal mechanism of resistance to or failure of everolimus.

Efforts to further build on the successful approval of everolimus in pNET are under way. Clinical studies combining everolimus with drugs that may modulate the insulin-like growth factor 1 pathway (e.g., pasireotide and cixutumumab) are ongoing. The PI3K/Akt/mTOR pathway can also be blocked at multiple points using serine–threonine kinase inhibitors that simultaneously inhibit phosphoinositide 3-kinase (PI3K) and mTOR (e.g., BEZ235). Studies combining everolimus with VEGFR inhibitors also hold promise.

Disclosure of Potential Conflicts of Interest

J.C. Yao has served as a consultant to Ipsen, Lexicon, Novartis, and Pfizer and has received research funding from Novartis. A.T. Phan has received research support from Novartis, Ipsen, Lexicon, and OSI. No potential conflicts of interest were disclosed by the other authors.

Authors’ Contributions

Conception and design: J.C. Yao, G. Shah, F. Meric-Bernstam
Development of methodology: J.C. Yao, G. Shah, F. Meric-Bernstam

Table 2. Disease progression in RADIANT-3 by treatment arm, per investigator

<table>
<thead>
<tr>
<th>Number of patients with PD</th>
<th>Everolimus arm</th>
<th>Placebo arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of PD events</td>
<td>98</td>
<td>161</td>
</tr>
<tr>
<td>Growth of preexisting target and/or nontarget lesions; no new metastases</td>
<td>53 (54%)</td>
<td>79 (49%)</td>
</tr>
<tr>
<td>New metastases only</td>
<td>21 (21%)</td>
<td>36 (22%)</td>
</tr>
<tr>
<td>New metastases plus growth of preexisting target and/or nontarget lesions</td>
<td>24 (24%)</td>
<td>43 (27%)</td>
</tr>
<tr>
<td>RECIST PD not met</td>
<td>0 (0%)</td>
<td>3 (2%)</td>
</tr>
</tbody>
</table>

Abbreviation: PD, progressive disease.
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): J.C. Yao, A.T. Phan, F. Meric-Bernstam

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.C. Yao, A.T. Phan, V. Jelh, F. Meric-Bernstam

Writing, review, and/or revision of the manuscript: J.C. Yao, A.T. Phan, V. Jelh, G. Shah, F. Meric-Bernstam

References


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