Effect of Everolimus Treatment on Chromogranin A, Neuron-Specific Enolase, Gastrin, and Glucagon Levels in Patients With Advanced Pancreatic Neuroendocrine Tumors (pNET): Phase III RADIANT-3 Study Results

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BACKGROUND

• Pancreatic neuroendocrine tumors (pNET) account for approximately 1.2% of the incidence of all digestive cancers and 4-5% of all NET, although both incidences are increasing.

• Diagnosis, nearly 40% of patients with NET have advanced, metastatic disease, which carries a median survival time of 24 months.

• Identifications of novel treatment options and prognostic and diagnostic biomarkers for pNET are necessary to improve outcomes in these patients.

• Functional NETs were previously biologically active hormones or peptides, gastrin, insuline, glucagon, pancreatic internal (VIP) polypeptide, which can cause well-established endocrine syndromes.

• Most nonfunctional pNETs can secrete additional substances (eg, chromogranin A (CgA), neuron-specific enolase (NSE), etc. that do not cause specific symptoms but that do indicate the degree of tumor burden.

• Although the molecular pathogenesis of sporadic, pNET is unknown, data suggest that the pheochromocytoma/paraganglioma syndrome (PCC/PGL) pathway, which is important for the regulation of cell growth, proliferation, and angiogenesis, is involved.

• Everolimus, an mTORC1/2 inhibitor has anti-tumor activity in phase II and III studies that included patients with pNET.

• Everolimus has been shown to be a well-tolerated, phase III trial involving 410 patients, to provide clinically and statistically significant 6-month improvement in PFS in patients with pNET compared with placebo (2.5 months vs 1.8 months; hazard ratio, 0.55; 95% confidence interval [CI], 0.47-0.64; P < 0.0001).

• Everolimus has been shown to reduce CgA and NSE levels in a large phase II trial of patients with advanced NET.

OBJECTIVES

• To characterize changes from baseline in serum concentrations of CgA, NSE, gastrin, and glucagon in response to treatment with everolimus or placebo in patients with advanced NET in the phase III RADIANT-3 trial.

PATIENTS AND METHODS

Study Design and Patient Population

• RADIANT-3 was an international, multicenter, double-blind, placebo-controlled, phase III study (Figure 1).

• Figure 1. Phase III RADIANT-3 study design.

Figure 2. Fold change from baseline in (A) CgA, (B) NSE, (C) gastrin, and (D) glucagon levels in the everolimus and the placebo treatment groups.

RESULTS

Table 1. Baseline Patient Assessments

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Everolimus</th>
<th>Placebo</th>
<th>HR (95% CI)*</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CgA</td>
<td>2.05</td>
<td>1.81</td>
<td>1.13 (1.01, 1.26)</td>
<td>0.025</td>
</tr>
<tr>
<td>NSE</td>
<td>2.03</td>
<td>1.79</td>
<td>1.13 (1.01, 1.26)</td>
<td>0.025</td>
</tr>
<tr>
<td>Gastrin</td>
<td>1.45</td>
<td>1.39</td>
<td>1.06 (0.95, 1.19)</td>
<td>0.315</td>
</tr>
<tr>
<td>Glucagon</td>
<td>1.46</td>
<td>1.32</td>
<td>1.07 (0.96, 1.19)</td>
<td>0.189</td>
</tr>
</tbody>
</table>

Table 2. Prolongation of PFS With Everolimus Treatment by Baseline CgA or NSE Level

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Biomarker Analysis

• Everolimus compared with placebo, improved PFS regardless of whether patients had elevated or nonelevated baseline CgA or NSE levels (Table 2).

• In each treatment group, patients with elevated baseline CgA or NSE levels had shorter median PFS than patients with nonelevated baseline CgA or NSE levels (Table 2).

• This analysis explored the impact of elevated biomarkers on PFS as well as changes in biomarker levels over time; patients were excluded from this analysis at the time of crossover.

• For example, for CgA, NSE, gastrin, and glucagon levels stratified by a central laboratory baseline for all patients and on day 1 of each cycle for patients whose baseline level was above the upper limit of normal (ULN).

• Patient population for the analysis only included those who had elevated levels (>2×ULN) at baseline and during treatment.

• Changes from baseline in biomarkers over time were analyzed using a robust non-parametric test that included terms for baseline value, treatment, time, and interaction between time and treatment.

CONCLUSIONS

• In the large phase III RADIANT-3 trial, everolimus provided a clinically and statistically significant 6-month improvement in PFS compared with placebo (2.5 months vs 1.8 months).

• Everolimus provided a significant improvement in PFS regardless of baseline CgA and NSE biomarker levels.

• Everolimus in patients with NET who received everolimus or placebo, suggesting that the improvement in PFS may be related to a broad spectrum of effects on the disease.

• Everolimus treatment resulted in rapid, sustained decreases in the giant phase III RADIANT-3 trial.

• These improvements in gastrin and glucagon levels suggest potential improvements in symptomology as well.

• The relationship between the robustness of these biomarker levels and the observed improvement in PFS in the RADIANT-3 trial warrants further investigation.

• Everolimus was approved by the FDA in May 2011 for the treatment of patients with advanced pNET whose disease progression was not controlled by octreotide and standard care.

REFERENCES


