Everolimus (EVE) for the Treatment of Advanced Pancreatic Neuroendocrine Tumors (pNET): Final Overall Survival (OS) Results of a Randomized, Double-Blind, Placebo (PBO)-Controlled, Multicenter Phase 3 Trial (RADIANT-3)

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Background: EVE significantly improved median progression-free survival vs PBO in patients with pNET by 6.4 months in RADIANT-3 (11.0 vs 4.6 months; HR, 0.35; 95% CI, 0.27-0.45; \( P < 0.001 \)). Here we present final OS results and safety findings.

Methods: Patients with progressive advanced, low- or intermediate-grade pNET were randomized to EVE 10 mg/d (n = 207) or PBO (n = 203); both with best supportive care. Upon disease progression during double-blind phase, crossover from PBO to open-label EVE was allowed. At the time of unblinding (cutoff, June 3, 2010), all ongoing patients transitioned into the extension phase to receive open-label EVE. After 256 events, OS analysis was performed using a stratified log-rank test in the intent-to-treat patient population (N = 410; all randomized patients).

Results: Of 410 patients, 225 switched to open-label EVE; including 85% of patients initially randomized to PBO (172 of 203). Median open-label EVE exposure was 67.1 weeks (range, 1-189) in patients initially randomized to EVE and 44.0 weeks (range, 0-261) in patients randomized to PBO. Median OS (95% CI) was 44.0 (35.6-51.8) months for EVE arm and 37.7 (29.1-45.8) months for PBO arm (HR, 0.94; 95% CI, 0.73-1.20; \( P = 0.30 \); significance boundary, 0.0249). Adverse events reported during the open-label phase (n = 221) were consistent with those observed during blinded treatment; the most common included stomatitis (47%), diarrhea (44%), and rash (40%).
Table 1. Estimated OS rates

<table>
<thead>
<tr>
<th>Kaplan-Meier Estimates (95% CI) at:</th>
<th>EVE 10 mg/d (n = 207)</th>
<th>PBO (n = 203)</th>
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</thead>
<tbody>
<tr>
<td>12 mo</td>
<td>82.6 (76.6-87.2)</td>
<td>82.0 (75.9-86.7)</td>
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<tr>
<td>24 mo</td>
<td>67.7 (60.7-73.8)</td>
<td>64.0 (56.8-70.2)</td>
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<tr>
<td>36 mo</td>
<td>56.7 (49.4-63.3)</td>
<td>50.9 (43.6-57.7)</td>
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<tr>
<td>48 mo</td>
<td>46.9 (39.7-53.8)</td>
<td>41.3 (34.3-48.1)</td>
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<tr>
<td>60 mo</td>
<td>34.7 (27.7-41.7)</td>
<td>35.5 (28.7-42.4)</td>
</tr>
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</table>

**Conclusions:** EVE demonstrated a median OS of 44 months, the longest OS reported in a phase 3 study for patients with progressive advanced pNET. The observed improvement in median OS (6.3 months) was not statistically significant. Crossover of majority of patients (85%) may also have confounded OS. The safety of EVE was consistent with previous experience.