

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

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

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.