

Treatment of Pancreatic Neuroendocrine Tumors (pNET) With Everolimus: Improved Progression-Free Survival Compared With Placebo (RADIANT-3)

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Background: The incidence of pNET is increasing steadily; however, there is no established systemic treatment for patients with advanced pNET after chemotherapy failure. Two recent phase II studies demonstrated the antitumor activity of everolimus (RAD001) in patients with advanced NET.

Methods: A multi-center, international, randomized, double-blind, placebo-controlled, phase III trial to evaluate the efficacy and safety of oral everolimus (10 mg/day) plus best supportive care (BSC) [n=207]; compared with placebo plus BSC (n=203) in patients with advanced pNET whose disease has progressed within the past 12 months. The primary endpoint was progression-free survival (PFS). At progression (RECIST), patients could be unblinded and the placebo arm was offered open-label everolimus.

Results: Compared with placebo, everolimus was associated with a 65% reduction in the risk of progression and 6.4-month increase in median PFS (4.6 vs 11.0 months, respectively [HR 0.35; 95% CI: 0.27, 0.45; $P<0.0001$]). Eighteen-month PFS rate was 34% (95% CI: 26, 43) for everolimus versus 9% (95% CI: 4, 16) for placebo. Median PFS by adjudicated central assessment was consistent (HR 0.34; 95% CI: 0.26, 0.44; $P<0.001$). The most common adverse event (AE, all grades) for everolimus versus placebo was stomatitis (64% vs 17%, respectively). The most frequent grade 3/4 AEs for everolimus were: stomatitis (6.9%),

anemia (6%), and hyperglycemia (5%). Treatment discontinuation for AEs was 17.4% in the everolimus arm versus 3.4% in the placebo arm.

Conclusions: Treatment with everolimus met the primary endpoint with a highly statistically significant reduction in the risk of disease progression compared with placebo. Furthermore, everolimus produced a clinically meaningful 6.4-month prolongation in median PFS. The AEs reported for everolimus were consistent with previous reports of everolimus treatment. These results validate earlier trials and represent important progress towards the use of everolimus as an effective treatment alternative for patients with progressive advanced pNET.