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ABSTRACTS

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A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Phase III Trial (RADIANT-3) of Everolimus in Patients With Advanced Pancreatic Neuroendocrine Tumors: Updated Safety and Overall Survival Results

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Background: RADIANT-3 represents the largest clinical trial to date in patients with advanced pancreatic neuroendocrine tumors (pNET). In this phase 3, randomized, double-blind, placebo-controlled RADIANT-3 trial, everolimus, an oral inhibitor of the mammalian target of rapamycin (mTOR), was shown to significantly prolong progression-free survival (PFS) compared with placebo (11.0 mo vs 4.6 mo; HR, 0.35; 95% CI, 0.27-0.45; P<0.001) [N Engl J Med 2011]. The US Food and Drug Administration approved everolimus in May 2011 for the treatment of patients with progressive pNET that is unresectable, locally advanced, or metastatic. Presented here are results from the 90-day safety update (cutoff date: June 3, 2010) and an updated survival analysis (cutoff date: February 23, 2011).

Methods: Patients with low- or intermediate-grade advanced pNET were randomly assigned to receive everolimus 10 mg/d (n = 207) or placebo (n = 203) in addition to best supportive care. The primary endpoint was PFS as determined by the local investigator according to RECIST version 1.0 (time from randomization to first documentation of disease progression or death from any cause). Patients assigned to placebo were allowed to cross over to open-label everolimus upon disease progression.

Results: The 90-day safety update contains data from 204 patients in the everolimus arm and 203 patients in the placebo arm. The drug-related adverse event (AE) profile in the safety update was maintained from the primary analysis. Most AEs were grade 1 or 2. The most common drug-related AEs (everolimus vs placebo), based on a median safety follow-up that now extends to 20.1 months, include stomatitis (52.9% vs 12.3%), rash (48.5% vs 10.3%), diarrhea (34.3% vs 10.3%), and fatigue (32.4% vs 14.3%). The most common grade 3-4 AEs include anemia (5.9% vs 0%), hyperglycemia (5.9% vs 2.5%), stomatitis (4.9% vs 0%), and thrombocytopenia (3.9% vs 0%). The number of deaths in the safety update was unchanged from the primary analysis, with 12 deaths (5.9%) occurring in the everolimus arm and 4 deaths (2.0%) occurring in the placebo arm. At the time of the updated safety analysis, 172 (85%) of the 203 patients randomly assigned to receive placebo had crossed over to open-label everolimus. At 40 months of follow-up, median overall survival had still not been reached in the everolimus arm and was 36.6 months in the placebo arm (HR, 0.89; 95% CI, 0.64-1.23).

Conclusions: In the RADIANT-3 trial of patients with advanced pNET, everolimus significantly increased median PFS. Safety results based on longer follow-up are consistent with those from the primary analysis and further support the use of everolimus in the treatment of patients with progressive pNET.