Effect of Everolimus Treatment on Markers of Angiogenesis in Patients With Advanced Pancreatic Neuroendocrine Tumors: Results From the Phase III RADIANT-3 Study

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BACKGROUND

Pancreatic neuroendocrine tumors (pNET) account for 1.3% of all pancreatic cancers and 4% to 7% of all NET.1 Identification of novel treatment options and prognostic and predictive biomarkers for patients with pNET is necessary to improve outcomes in these patients.1 Two highly vascularized and often overexpressed vascular endothelial growth factor (VEGF) and its receptors2−4—Circulating VEGF levels are elevated in patients with NET and are significantly associated with tumor progression.5−7 The phosphatidylinositol-3-kinase/Akt/mammalian target of rapamycin (mTOR) pathway, which is important for the regulation of cell growth, proliferation, and angiogenesis, may be involved in the molecular pathogenesis of sporadic pNET.8−10 In the recent phase II RADIANT-3 trial involving 410 patients with pNET, everolimus, an oral inhibitor of mTOR, provided a clinically and statistically significant 6.4-month improvement in progression-free survival (PFS) compared with placebo (11.0 months vs 4.6 months; hazard ratio, 0.35; 95% confidence interval, 0.27-0.45; P < 0.001).8 Everolimus was approved by the US Food and Drug Administration in May 2011 and by the European Union Committee for Medicinal Products for Human Use in September 2011 for the treatment of progressive pNET that is unresectable, locally advanced, or metastatic.11

METHODS

RADIANT-3 was an international, multicenter, double-blind, placebo-controlled, phase III study (Figure 1). Accrual between August 2007 and May 2009. Treatment cycles were 28 days, and the study duration was 12 months. The primary endpoint was the Kaplan-Meier estimate of median progression-free survival (PFS) in patients receiving everolimus vs placebo. Other endpoints included the overall response rate, the time to disease progression, and the incidence of treatment-related adverse events. Patients were stratified by WHO performance status (PS) (1-4), region (North America vs Europe), and percentage of disease progression occurring in the liver (≥50% vs <50%). After cycles 2 through 4, patients were allowed to cross over and receive the treatment they did not receive in cycles 1 and 2. *Best supportive care

RESULTS

Treatment Effect on Markers of Angiogenesis

Biomarker data were available in 198 patients in the everolimus arm and 195 patients in the placebo arm. vVEGFR2. Everolimus was associated with a significant reduction in sVEGFR2 compared with placebo (P = 0.001).—Mean fold changes from baseline in sVEGFR2 were significantly greater with everolimus than with placebo (Figure 2).—Cycle 3, day 1: 0.73 vs 0.92, P = 0.001.—Cycle 4, day 1: 0.89 vs 0.95, P = 0.001.—This effect was independent of potential prognostic factors, including WHO-PS and previous chemotherapy.

Other Angiogenesis Biomarkers

No significant differences were observed between treatment arms in changes in sVEGFR1 (P = 0.62) or VEGF (P = 0.35).—All samples were analyzed by a central laboratory using ELISA.

CONCLUSIONS

• In the large phase III RADIANT-3 trial, everolimus provided a clinically and statistically significant 6.4-month improvement in median PFS compared with placebo in patients with advanced pNET (HR, 0.35; 95% CI, 0.27-0.45).• Everolimus significantly reduced levels of angiogenic biomarkers, including VEGFR, PDGF, and IFN-γ, in patients with advanced pNET; the reductions in PDGF and IFN-γ with everolimus were not sustained.†• No significant differences were observed in circulating levels of VEGF or sVEGFR1 between treatment arms.†• These data, together with earlier in vitro and in vivo study results, provide support for the angiogenic properties of everolimus.9−11

REFERENCES