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ABSTRACTS

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Updated Efficacy, Safety, and Exploratory Biomarker Results From RADIANT-2: A Phase III Trial of Everolimus + Octreotide LAR vs. Placebo + Octreotide LAR in Patients With Advanced Neuroendocrine Tumors

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Background: In the large, randomized, double-blind, placebo-controlled, phase III RADIANT-2 trial, everolimus (an oral inhibitor of the mammalian target of rapamycin [mTOR]) + octreotide LAR demonstrated a clinically meaningful increase in progression-free survival (PFS) versus placebo + octreotide LAR in patients with advanced low- or intermediate-grade neuroendocrine tumors (NET) and a history of secretory symptoms (flushing and/or diarrhea). Presented here are updated safety, efficacy, and exploratory biomarker analyses.

Methods: Patients (n=429) were randomly assigned to receive everolimus 10 mg/d orally + octreotide LAR 30 mg IM q28d (E+O; n=216) or placebo + octreotide LAR (P+O; n=213). Primary endpoint was PFS per adjudicated central review (RECIST v1.0). Patients assigned to P+O were allowed to cross over to open-label E+O upon disease progression.

Results: At the April 2, 2010, efficacy data cutoff, median PFS (95% CI) with E+O was 16.4 (13.7-21.2) months versus 11.3 (8.4-14.6) months with P+O (HR=0.77; 95% CI, 0.59-1.00; P=0.026). A benefit in PFS with E+O was observed across all prespecified subgroups (age, sex, performance status, tumor grade, primary site, previous treatment with somatostatin analog, previous chemotherapy). Baseline serum CgA and urinary 5-HIAA were found to be important prognostic markers for progression, with lower levels of the markers associated with reduced risk of progression. For patients with elevated baseline CgA (>2× ULN) versus patients with nonelevated baseline CgA (≤2× ULN): HR, 0.43; 95% CI, 0.32-0.59. For patients with high baseline 5-HIAA levels (>median) versus patients with low baseline 5-HIAA levels (≤median): HR, 0.60; 95% CI, 0.45-0.79. For patients with elevated baseline CgA, median PFS was 13.9 months for E+O and 8.4 months for P+O (HR, 0.66; 95% CI, 0.48-0.89; P=0.003). For patients with nonelevated baseline CgA, median PFS was 31.3 months for E+O and 20.1 months for P+O (HR, 0.74; 95% CI, 0.42-1.28; P=0.14). Median PFS for patients with high baseline 5-HIAA was 13.8 months for E+O and 8.4 months for P+O (HR, 0.66; 95% CI, 0.46-0.96; P=0.015). For patients with low baseline 5-HIAA, median PFS was 21.8 months for E+O and 13.9 months for P+O (HR, 0.70; 95% CI, 0.46-1.08; P=0.051). Mixed-model analysis showed that E+O led to greater fold reductions of both serum CgA and urinary 5-HIAA versus P+O. As of the July 2, 2010, data cutoff for the 90-day safety update, median follow-up was 31.1 months. The primary reason for treatment discontinuation was disease progression. The most frequent drug-related adverse events (AEs) (E+O vs P+O, %) were stomatitis (47.4 vs 10.9), rash (37.2 vs 12.3), and fatigue (31.6 vs 24.2) and were consistent with previous experience. Most frequent drug-related grade 3-4 AEs (E+O vs P+O, %) were fatigue (6.5 vs 2.8), diarrhea (6.0 vs 2.4), and hyperglycemia (5.1 vs 0.5).

Conclusions: In RADIANT-2, the largest trial of patients with advanced NET, treatment with E+O has shown a clinically meaningful increase in median PFS, reductions in tumor and secretory biomarker levels, and an acceptable safety profile. These findings support the benefit of everolimus in patients with advanced NET and a history of secretory symptoms.