Safety and Efficacy of Everolimus in Advanced Nonfunctional Neuroendocrine Tumors (NET) of Lung or Gastrointestinal (GI) Origin: Findings of the Randomized, Placebo-Controlled, Double-blind, Multicenter, Phase 3 RADIANT-4 Study

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Background: Everolimus (EVE), a mammalian target of rapamycin inhibitor, is approved in advanced pancreatic NET. Advanced, nonfunctional NET of lung/GI origin remains an area of significant unmet medical need. RADIANT-4 evaluated the efficacy and safety of EVE in this NET population.

Methods: Patients (pts) with advanced, progressive, well-differentiated, nonfunctional lung/GI NET were randomized (2:1) to EVE (10 mg/d) or placebo (PBO), both with best supportive care. Pts were stratified by tumor origin, WHO performance status (PS), and prior somatostatin analogue (SSA) treatment. Primary endpoint was progression-free survival (PFS) assessed by central radiology review (modified RECIST 1.0). Secondary endpoints included overall survival (OS), objective response rate (ORR), disease control rate (DCR), and safety.

Results: 302 pts were randomized to EVE (n=205) or PBO (n=97); median age, 63 y; 53% females; G1/G2: 64%/35%; WHO PS: 0, 74% or 1, 26%; majority (76%) were Caucasian; most common tumor sites: lung (30%), ileum (24%). The two arms were well balanced with respect to prior SSA therapy (53%, EVE vs 56%, PBO), chemotherapy (26% vs 24%), locoregional/ablative therapy (including transarterial embolization, cryoablation or radiofrequency ablation; 11% vs 10%) and radiotherapy (including PRRT; 22% vs 20%). Median PFS by central review was 11.0 mo

(95% CI, 9.2–13.3) in EVE and 3.9 mo (95% CI, 3.6–7.4) in PBO arm (HR, 0.48; 95% CI, 0.35–0.67; *P*<0.001). Investigator assessed PFS was consistent with the central review: 14.0 mo (95% CI, 11.2–17.7) with EVE vs 5.5 mo (95% CI, 3.7–7.4) with PBO (HR, 0.39; 95% CI, 0.28–0.54; *P*<0.001). Subgroup analyses of PFS by stratification factors were consistent with the primary efficacy analysis. Per central review, ORR (all partial responses) was 2% (4 pts) in EVE vs 1% (1 pt) in PBO. DCR was higher in EVE vs PBO (82% vs 65%). 9% in EVE vs 27% pts in PBO arm had progressive disease as best outcome; tumor response was unknown in the remaining pts. A preplanned interim OS analysis showed an HR of 0.64 (95% CI, 0.40–1.05; *P*=0.037) in favor of EVE. The difference in OS does not achieve statistical significance (threshold *P*-value for significance, 0.000213). The most common treatment-related adverse events (AEs) were stomatitis (63%, EVE vs. 19%, PBO), diarrhea (31% vs. 16%), fatigue (31% vs. 25%), infections (29% vs. 4%), rash (27% vs. 8%), and peripheral edema (26% vs. 4%). Grade 3 or 4 drug-related AEs (EVE vs. PBO) were relatively infrequent and included stomatitis (9% vs. 0), diarrhea (7% vs. 2%), infections (7% vs. 0), anemia (4% vs. 1%), fatigue (4% vs. 1%), and hyperglycemia (4% vs. 0).

Conclusions: RADIANT-4, the first large, PBO-controlled, phase 3 study in pts with advanced, progressive, nonfunctional lung/GI NET, provided unequivocal evidence for the efficacy of EVE in this population. Results as per central radiology review demonstrated a statistically significant 52% risk reduction in favor of EVE with a clinically meaningful 7.1-month prolongation of PFS vs PBO. EVE was well tolerated and AEs were consistent with the known safety profile.

This abstract has also been submitted to the European Society for Medical Oncology (ESMO) Congress; 2015; Vienna, Austria.