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A Phase II Study to Evaluate the Safety and Efficacy of RAD001 plus Erlotinib in Patients with Well-Differentiated Neuroendocrine Tumors (NET)

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Background: Building on strong preclinical data, we hypothesized that concomitantly targeting mammalian target of rapamycin (mTOR) and epidermal growth factor receptor (EGFR) signaling pathways will inhibit neuroendocrine tumors (NET) more effectively than targeting either pathway alone (thus improving likelihood of shrinkage). We initiated a prospective, phase II study to assess the safety and efficacy of RAD001 plus erlotinib in patients (pts) with advanced NET.

Methods: Pts with well-differentiated NET were enrolled using a Simon 2-stage design with 2 groups: pancreatic NET (PNET) and other low-grade NET/ carcinoid (CARC). Eligibility criteria included histological diagnosis of a well- to moderately-differentiated NET and no prior mTOR- or EGFR-inhibitor. Pts treated with RAD001 5 mg PO QD and erlotinib 100 mg PO QD without scheduled breaks (1 cycle = 28 d). Pts followed for toxicity and radiographic response, with first planned analysis after 8 evaluable pt / group.

Results: Since 6/09, 17 pt enrolled: M/F 9/8; PNET/CARC 8/9. Pts on octreotide remained on drug. All pt had PD at enrollment. Median # cycles: 12 in CARC (range 2-20)**;** 5.5 (to date) in PNET (range 0.5-18). Excessive toxicity in first 7 pts prompted reduction in starting erlotinib dose from 150 to 100 mg/d, resulting in improved tolerability: Gr 3 stomatitis in 3/7 initial pts (43%) vs 1/10 (10%) after new starting dose. Overall, the most common side effects include diarrhea, stomatitis, rash, anorexia, and fatigue. Enrollment to CARC cohort stopped after first stage due to insufficient efficacy (7/9 SD, 2/9 PD; 0 PR).

Conclusions: RAD001 plus erlotinib appears to be associated with radiographic stability, but not shrinkage, in CARC. Combining the two agents has proven challenging; toxicity precludes administration of either agent at full dose. Interim efficacy analysis for PNET stratum pending. Correlation with expression of mTOR pathway components in archived tissue planned.

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