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Phase I Study of Sorafenib in Combination with Everolimus (RAD001) in Patients with Advanced Neuroendocrine Tumors (NET)

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Background: Both sorafenib and everolimus have activity in NETs. We performed a phase I study to evaluate the safety and feasibility of combining sorafenib and everolimus in patients with advanced NETs.

Methods: Patients were treated with everolimus 10 mg daily in combination with sorafenib (dose level 1: 200 mg BID; dose level 2: 200 mg in the morning, 400 mg in the evening) using a standard phase I dose escalation design. Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent.

Results: Enrolled patients had the following characteristics: M:F = 4:5; median age 56 (range 49-68); ECOG PS 0/1 = 5/4. All 9 patients had low-intermediate grade NETs (midgut, n=6; bronchial, n=2; gastric, n=1). Patients received a median of 2 cycles of treatment (range 1-6). One patient at dose level 1 experienced DLT (grade 3 skin rash); the cohort was expanded to 6 patients with no further DLT. Other ≥ grade 3 treatment-related adverse events at dose level 1 included grade 3 thrombocytopenia (n=2), grade 3 hypokalemia (n=2), grade 3 hypophosphatemia (n=1), grade 4 hypophosphatemia (n=1), grade 4 hypocalcemia (n=1). One patient with gastric carcinoid tumor treated at dose level 1 experienced fatal gastric perforation occurring after the DLT observation period. All 3 patients at dose level 2 experienced DLT (grade 3 thrombocytopenia requiring holding treatment for > 14 days, grade 3 hand-foot skin reaction, grade 3 skin rash/allergic reaction). Grade 3 hypophosphatemia (n=1) was also observed at dose level 2. Independently-reviewed best objective responses in

5 evaluable patients at dose level 1 revealed stable disease in all 5 patients.

Conclusion: Sorafenib 200 mg BID in combination with everolimus 10 mg daily has been established as the MTD in patients with advanced NET. Further enrollment to evaluate safety and antitumor efficacy at this dose level is ongoing.