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Phase I / II Study of Everolimus (RAD001) in Combination with Temozolomide (TMZ) in Patients with Advanced Pancreatic Neuroendocrine Tumors (NET)

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Background: Both the mTOR inhibitor RAD001 and TMZ have antitumor activity in NETs. We performed a phase I/II study to evaluate tolerability and efficacy of RAD001 in combination with TMZ in patients with advanced pancreatic NETs.

Methods: Patients were enrolled at 2 dose levels: TMZ 150 mg/m^2 daily, administered for 7 consecutive days every other week, in combination with RAD001 5 mg daily (Cohort 1) or RAD001 10 mg daily (Cohort 2). TMZ with RAD001 10 mg daily was established as the phase II dose. TMZ was administered in combination with RAD001 for a maximum of six 4-week treatment cycles, at which point patients with response or stable disease continued treatment with RAD001 alone. Patients received prophylaxis with trimethoprim-sulfamethoxazole. Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent.

Results: In Phase I, 1 patient in cohort 1 experienced DLT consisting of grade 4 thrombocytopenia, and the cohort was expanded to 6 patients. No further DLTs have been observed. A total of 27 patients have been enrolled; 7 in cohort 1 (6 evaluable) and 20 in cohort 2 (19 evaluable). Enrolled patients have the following characteristics: M:F =15:12; median age 52 (range 29-87); ECOG PS 0/1= 13/14. Patients received a median of 5 cycles of treatment. Observed grade 3/4 toxicities included thrombocytopenia (n=5), lymphopenia (n=7), neutropenia (n=2), diarrhea (n=1), hyperglycemia (n=1), elevated transaminases (n=2), elevated triglycerides (n=2), skin rash (n=1), fatigue (n=1), hyper/hypokalemia (n=1/1), and hyponatremia (n=1). 22

patients were evaluable for response. Responses include 7 patients with PR (32%), 13 with SD (59%), and 2 with PD (9%). 17/22 patients had elevated CGA levels (>225 ng/ml) at baseline; 5 (29%) experienced CGA decreases of >50% from baseline on 2 consecutive assessments.

Conclusions: The combination of RAD001 and TMZ can be safely administered and shows promising activity in patients with advanced pancreatic NET. Further enrollment is planned.