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Phase I Study of Pasireotide (SOM230) in Combination with Everolimus (RAD001) in Patients with Advanced Neuroendocrine Tumors (NET)

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Background: Octreotide and everolimus have antitumor activity in NETs. Pasireotide is a novel somatostatin analog with binding affinity to a broader range of somatostatin receptor subtypes than octreotide. We performed a phase I study to evaluate safety and feasibility of combining pasireotide and everolimus in patients with advanced NETs.

Methods: Patients received escalating doses of pasireotide and everolimus (Table 1). Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent. DLT was defined as occurring within the first 56 days of therapy.

Results: Among 16 enrolled patients, 15 were evaluable for toxicity. Enrolled patients had the following characteristics: M:F = 10:6; median age 61 (range 38-76); ECOG PS 0/1/2 = 8/7/1; carcinoid/pancreatic NET = 12/4. Patients received a median of four 28-day cycles of treatment. No patients in cohorts 1 and 2 experienced DLT. 1 patient in cohort 3 experienced DLT (grade 3 rash); the cohort was expanded to 6 patients with no further observed DLTs. 1 patient in cohort 4 experienced DLT (grade 3 diarrhea). Other \geq grade 3 treatment-related adverse events included hyperglycemia (n=8), hypophosphatemia (n=3), elevated alkaline phosphatase (n=2), mucositis (n=1), lymphopenia (n=2), and thrombocytopenia (n=1). Insulin was started in 4 patients due to hyperglycemia. Independently-reviewed best objective

responses in 13 evaluable patients revealed stable disease in all 13 patients.

Conclusion: Combination therapy with pasireotide and everolimus is safe and feasible. Further enrollment with everolimus 10 mg daily in combination with pasireotide LAR 60 mg monthly is planned.

Table 1: Dose Escalation Schema

Cohort	N	Pasireotide sc (Twice daily, Days 1-42)	Pasireotide LAR (IM, Day 29 and q 4 weeks thereafter.)	Everolimus (po, Daily, beginning Day1)
1	3	600 mcg	40 mg	5 mg
2	3	900 mcg	60 mg	5 mg
3	6	900 mcg	60 mg	10 mg
4	3	1200 mcg	80 mg	10 mg