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Updated Results of a Phase I Study of Pasireotide (SOM230) in Combination with Everolimus in Patients (pts) with Advanced Neuroendocrine Tumors (NET)

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Background: Octreotide and the mTOR inhibitor 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: Pts received escalating doses of pasireotide and everolimus. Treatment was continued until tumor progression, unacceptable toxicity, or withdrawal of consent. Dose-limiting toxicity (DLT) was defined within the first 56 days of therapy.

Dose Level	No. Evaluable Pts	Pasireotide sc (mcg, Twice daily, Days 1-42)	Pasireotide LAR, intramuscularly (mg, Day 29 and q 4 weeks thereafter)	Everolimus (mg, Daily beginning Day 1)
1	3	600	40	5
2	3	900	60	5
3	6 + 6	900	60	10
4	3	1200	80	10

Results: Among 22 enrolled pts, 21 were evaluable for toxicity. Enrolled pts had the following characteristics: M/F = 14/8; median age 60 (range 35-76); ECOG PS 0/1/2 = 16/5/1; carcinoid/pancreatic NET = 18/4. Pts have received a median of 6 cycles of treatment (range 1-29). No pts at dose level (DL) 1 and DL 2 experienced DLT. DLT was experienced by 1 pt at DL 3 (gr 3 rash) and 1 pt at DL 4 (gr 3 diarrhea). Dose escalation was halted at DL 4 to further assess safety and toxicity at DL 3; no further DLT was observed in 6 additional patients treated at DL3.

Other gr 3 or higher treatment-related adverse events across all cycles included hyperglycemia (n=8; 1 at DL1, 1 at DL2, 4 at DL3, 2 at DL4), hypophosphatemia (n=6; 1 at DL1, 1 at DL2, 3 at DL3, 1 at DL4), thrombocytopenia (n=3; 2 at DL3, 1 at DL4), lymphopenia (n=2; 1 at DL1, 1 at DL3), elevated alkaline phosphatase (n=2; 1 at DL2, 1 at DL3), mucositis (n=1 at DL3), prolonged QTc (n=1 at DL3), and joint pain (n=1 at DL4). Independently-reviewed best objective responses in 21 evaluable pts revealed partial response in 1 pt, stable disease in 19 pts, and progressive disease in 1 pt.

Conclusion: Combination therapy with pasireotide and everolimus is feasible and associated with preliminary evidence of antitumor activity in NET. Pasireotide 60 mg IM monthly combined with everolimus 10 mg daily should be further investigated in future NET studies.