C-8

Phase I, Open-label, Dose-Escalation Study of SNX-5422 Plus Everolimus in Neuroendocrine Tumors (NETs)

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BACKGROUND: SNX-5422 is an orally bioavailable pro-drug of SNX-2112, a highly potent and selective heat shock protein 90 (Hsp90) inhibitor. In preclinical studies, the effects of SNX-2112 and everolimus appear at least additive. Previously, at doses of 42-100 mg/m2 of SNX-5422 every other day (qod), 2 of 3 subjects with refractory NETs achieved stable disease (SD) for >8 cycles.

METHODS: Eligible subjects had unresectable gastro-entero-pancreatic or pulmonary NETs and <5 prior lines of anti-cancer treatment. Each cycle was 28 days: SNX-5422 was dosed qod each morning for 21/28 days, starting at 50 mg/m2 with standard 3+3 dose escalation, and everolimus was dosed 10 mg each evening for 28 days, with dose de-escalation allowed based on everolimus toxicity.

RESULTS: Enrolled subjects(n=17; 10 males; 36-70 yrs)had pulmonary, GI, pancreatic, or other NETs (59% were refractory [≥3 prior lines, large tumor size at entry]). The MTD of SNX-5422 was determined to be 75 mg/m2 in combination with everolimus. Dose limiting toxicity was 1 case of G3 diarrhea.

Other adverse events in ≥2 subjects possibly related to either or both agents included: anemia, anorexia, blurred vision (3 subjects, all mild, all continued

SNX-5422), diarrhea, fatigue, hyponatremia, mucositis, nausea, increased creatinine (everolimus), dehydration (everolimus), maculopapular rash (everolimus), thrombocytopenia (everolimus), and weight loss (everolimus). All events were G1/G2, except for G3 diarrhea (1 SNX-5422, 1 everolimus, 1 both), increased creatinine (1, everolimus), hyponatremia (2, everolimus).

Best responses are presented in Table 1. Two subjects had prolonged benefit and remained on study for 30 and 35 cycles before progressive disease. Final outcome for the 17 subjects: 3 withdrew from the study (1 personal reasons, 2 for tolerability), 2 discontinued due to intercurrent illness, and 12 had progressive disease.

CONCLUSION: Combining SNX-5422 with everolimus in subjects with advanced NETs warrants further study.

Table 1:
Best Response

Subjects	Partial Response	Stable Disease	Progressive Disease
All subjects (N=17,%)	3(18%)	8(47%)	6(35%)
Subjects with ≤2 prior lines (N=11,%)	3(27%)	5(45%)	3(27%)