423PD

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

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BACKGROUND

- Neuroendocrine tumors (NETs) are a heterogeneous group of neoplasms arising in a variety of anatomic sites, most frequently the bronchopulmonary tree and small intestine. Other common sites include the pancreas and other areas of the gastrointestinal (GI) tract.[1]
- Preclinical data have suggested that targeted inhibition of heat shock protein 90 (Hsp90) may have an antiproliferative effect on neuroendocrine tumor cells.[2-5]
- SNX-5422 is an orally bioavailable pro-drug of SNX-2112, a highly potent and selective inhibitor of Hsp90.[6]
- In a prior clinical study, prolonged stable disease was observed in 2 of 2 patients with refractory NETs who received 8 cycles of SNX-5422 at doses of 42-100 mg/m^2 every other day.[7]
- Everolimus, an mTOR (mammalian target of rapamycin) kinase inhibitor, is used for the treatment of progressive pancreatic NETs as well as progressive, well-differentiated, nonfunctional GI and pulmonary NETs that are unresectable, locally advanced or metastatic.[8]
- In preclinical studies, the effects of SNX-2112 and everolimus (EVR) appear at least additive.[9]

OBJECTIVES

Primary

- To determine the maximally tolerated dose (MTD) of SNX-5422 when given in combination with everolimus in patients with unresectable NETs and <5 prior lines of systemic anti-cancer treatment.

Secondary

- To investigate the effects of SNX-5422 plus everolimus on tumor response.

METHODS

Study Design

- Phase 1, open-label, multicenter, 3+3 dose-escalation study. Each dosing cycle was 28 days.
- SNX-5422 dosing was started at 50 mg/m^2. The actual dose administered was based on body surface area, calculated using body weight measured at the start of each cycle and height at Screening. The calculated dose was then rounded to nearest mg on the dosing chart. SNX-5422 was available in 5, 20, 75, and 150 mg capsules.
- Everolimus (EVR) was dosed at 10 mg once daily; dose reduction was allowed based on EVR toxicity.
- Ophthalmological examination: visual acuity, visual field, ophthalmoscopy, Low Luminance Questionnaire-23 (LLQ-23), and Optical Coherence Tomography (OCT); performed at Screening, end of Cycle 1, and study end.

Dosing Schedule and Times

- For each 28-day dosing cycle:
  - SNX-5422: Once daily by mouth every other day (QOD) in the morning for 21 days (total of 11 doses) followed by a 7-day drug-free period; no food 2 hours before and 1 hour after dosing.
  - Everolimus: Once daily by mouth every evening (at least 8 hours after SNX-5422 dosing) for 28 out of 28 days, and taken consistently either with or without food.

Key Inclusion Criteria

- Males or non-pregnant, non-breastfeeding females ≥18 years-of-age with pathologic evidence of locally advanced or metastatic NET of gastro-entero-pancreatic, pulmonary (other than small cell lung cancer), or thymic origin.
- Less than 5 lines of previous systemic anti-cancer therapy.
- Karnofsky performance score ≥70, life expectancy ≥3 months, adequate baseline laboratory values
- All adverse events from previous anti-cancer therapy (with the exception of alopecia) recovered to ≤Grade 1 toxicity.

Safety and Efficacy Analysis

- Safety: Adverse event data, laboratory parameters, ECG, vital signs, ophthalmological examination.
- Efficacy: At a minimum, tumor response was assessed at the end of every 2 cycles ± 2 weeks, using RECIST 1.1 criteria.

Key Exclusion Criteria

- Contraindication to EVR, or prior failed treatment with mTOR inhibitors (current EVR use permitted for subjects still receiving treatment benefit).
- Prior treatment with any Hsp90 inhibitor.
- Clinically significant interstitial lung disease, or obstructive disease without sufficient reserve (Forced Expiratory Volume in one second <50% of predicted).
- Neuroendocrine tumor with uncontrolled hormone related symptoms, particularly those symptoms that may mimic toxicity of SNX-5422 such as diarrhea (diarrhea ≥4 stools per day).
- Neuroendocrine cancer of the thyroid.
- Conventional chemotherapy or radiation within 4 weeks or palliative radiation within 2 weeks before study start.
- Treatment with other anti-cancer drugs (except EVR or somatostatin analogues) or any other investigational drug within 30 days prior to the first dose of SNX-5422 and throughout the study.
- Gastrointestinal diseases or conditions (including chronic diarrhea) that could affect drug absorption or alter safety assessments.
- Glaucoma, retinitis pigmentosa, macular degeneration, or any retinal changes detected by ophthalmological examination.

RESULTS

Table 1. Study Population

Population	Number (%) of Patients
All enrolled patients	20 (100%)
Evaluable for efficacy[a]	17 (85%)
Evaluable for safety	20 (100%)

[a]Three patients with small cell lung cancer (SCLC) were enrolled prior to SCLC being an exclusion criterion; these patients were not included in the efficacy evaluable population.

Table 2. Baseline Characteristics

Parameter	N=17
Age, median (range), years	59 (36-70)
Age >65 years, n (%)	3 (18%)
Males, n (%)	10 (59%)
Race, n (%)	
White	11 (65%)
Asian	1 (6%)
Black	1 (6%)
Other	4 (23%)
Primary diagnosis, n (%)	
Pulmonary NET	4 (24%)
Pancreatic NET	3 (18%)
Gastrointestinal NET	2 (12%)
Gastrointestinal carcinoid	2 (12%)
Atypical pulmonary carcinoid	2 (12%)
Unknown carcinoid	2 (12%)
Pulmonary carcinoid	1 (6%)
Unknown NET	1 (6%)
Prior treatments, n (%)	
Prior systemic anti-cancer therapy regimens	
0	1 (6%)
1	5 (29%)
2	5 (29%)
3	2 (12%)
4	1 (6%)
≥5[a]	3 (18%)

[a]Radiotherapy (2 patients) and preventive sandostatin (1 patient) not considered by the investigator as prior systemic anti-cancer therapy.

SAFETY

Table 3. SNX-5422 Dosing Cohorts

Cohort	SNX-5422 Dose (mg/m^2)	Number of Patients Assigned to Cohort (N=17)	DLT (Cycle 1)
1	50	3	
2	75	14	n=1 (diarrhea)

Maximum Tolerated Dose

- One subject experienced a DLT of Grade 3 diarrhea after 5 doses of SNX-5422 75 mg/m^2 QOD and daily EVR 10 mg. No further SNX-5422 dose escalation was attempted due to the observed adverse GI events with combined therapy. This patient continued in the study with SNX-5422 dose de-escalation to 50 mg/m^2 QOD and EVR dose reduction to 5 mg daily.
- The MTD of SNX-5422 was therefore determined to be 75 mg/m^2 QOD in combination with EVR.
- Everolimus-related toxicities resulted in EVR dose reduction in 9 of 17 (53%) patients.

Table 4. Most Frequent Treatment-Related Adverse Events (Safety Population)[a]

Adverse Event (AE)	SNX-5422-related	Everolimus-related	Combination therapy-related	Total N=20
	Number of Patients			
Diarrhea	3 (n=1, Grade 3)	1 (Grade 3)	9 (n=1, Grade 3)	13
Blurred vision	2	0	1	3
Anemia	1	1 (Grade 3)	3	5
Hypokalemia	1	0	1	2
Hyponatremia	1	2 (Grade 3)	2 (Grade 3)	5
Mucositis	0	4	2	6
Thrombo-cytopenia	0	2	3	5
Fatigue	0	0	4	4
Creatinine increased	0	3 (n=1, Grade 3)	0	3
Maculopapular rash	0	2	2	4
Nausea	0	0	3	3
Vomiting	0	1	2	3
Anorexia	0	1	2	3
Dehydration	0	1	1	2
Weight loss	0	2	0	2

All AEs were mild or moderate in severity, unless otherwise noted.
[a]Events considered by the investigator to be possibly treatment-related, and reported for ≥2 patients in total.

- All patients experienced at least 1 adverse event.
- There were 3 deaths (occurred during the study or within 30 days of stopping study drug); all attributed to disease progression.

EFFICACY

Antitumor Activity

- Best response in the 17 patients evaluable for efficacy:
  - Partial response: 2 patients
  - Stable disease: 12 patients
  - Progressive disease: 3 patients
- 4 patients are ongoing, and 2 of these have completed >26 cycles

Figure 1. Best Response in Each Patient

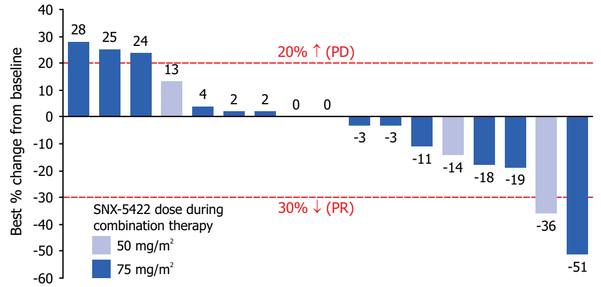
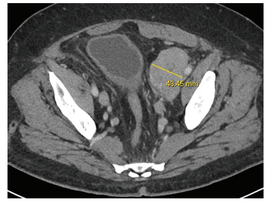
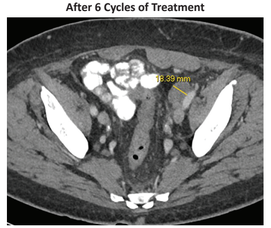


Figure 2. Partial Response in Patient with Pulmonary Carcinoid

Baseline



After 6 Cycles of Treatment



- This patient has achieved a 51% reduction in target lesions.

CONCLUSIONS

In patients with unresectable NETs and <5 prior lines of systemic anti-cancer therapy:

- The MTD of SNX-5422 was established at 75 mg/m^2 QOD in combination with everolimus.
- SNX-5422 at doses up to 75 mg/m^2 QOD was generally well-tolerated when combined with everolimus.
- Diarrhea was the most common AE during SNX-5422 + everolimus combined therapy, and the cause of DLT.
- SNX-5422 in combination with everolimus showed promising signs of clinical activity in patients with advanced NETs.

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