



A Phase 1 Trial of Weekly SNS-595 in Patients with Refractory Cancer

S. Ebbinghaus¹, M. Gordon², R. Advani³, H. Hurwitz⁴, D. Mendelson², H. Wakelee³, U. Hoch⁵, J. Silverman⁵, N. Havrilla⁵, D. Adelman⁵; ¹Univ of Arizona, Tucson, AZ, ²Premiere Oncology, Scottsdale, AZ, ³Stanford University, Stanford, CA, ⁴Duke University, Durham, NC, ⁵Sunesis Pharmaceuticals, Inc. So. San Francisco, CA

ABSTRACT (Updated March 2006)

Background: SNS-595 is a novel naphthyridine analog with a unique mechanism of action that acts in S phase to induce cell-cycle arrest and apoptosis in vitro and shows broad activity in xenograft and drug resistant tumor models.

Methods: SNS-595 was administered to pts with advanced solid cancers as an IV infusion over 10 minutes once weekly for 3 weeks in a 28-day cycle. Cohorts of 3-6 pts were accrued to doses based on a modified Fibonacci sequence.

Results: 21 pts (9F:12M) were treated in six cohorts ranging from 3-24 mg/m²/week. Tumor types included pancreas (3), colon (3), breast (2), sarcoma (2), mesothelioma (2), ovarian, melanoma, renal, cholangiocarcinoma, neuroendocrine, nasopharyngeal, salivary gland, small-cell lung, spindle cell carcinoma (1 each). The median age was 59.3 years (range 19 to 81) and median ECOG PS was 1 (range 0-1). Dose-limiting toxicity (DLT) of neutropenia was seen in the first patient at the 24 mg/m² level. 5 patients were then treated at 18 mg/m² where 2 developed DLT of neutropenia. The maximum-tolerated dose level was 15 mg/m². Non-hematologic drug-related toxicities were mild and all grade 1/2. Best responses to study therapy were an unconfirmed PR in a patient with mesothelioma treated at 15 mg/m², and stable disease lasting ≥ 4 cycles in 5 additional patients. PK samples were collected on treatment Days 1 and 15 and were assayed using noncompartmental analysis. Plasma SNS-595 concentrations were determined using a validated LC-MS/MS assay. AUC increased proportionally with dose and mean AUC₀₋₂₄ ranged between 1.7 and 15 µg*hr/ml, respectively, for 3 to 24 mg/m² dose levels. The terminal half-life is approximately 18 hours. No evidence of drug-dependent alterations in pharmacokinetic parameters was observed after 3 weekly doses.

Conclusions: In this phase 1 study of SNS-595, the MTD is 15 mg/m² weekly x3 on a 28-day schedule. Isolated neutropenia is the dose-limiting toxicity and combination trials with weekly and q3wk SNS-595 are being developed. A phase 1 trial in AML as well as phase 2 trials in NSCLC and SCLC are underway.

BACKGROUND

SNS 595 is a novel naphthyridine analog, a class of compounds not previously used for cancer treatment, and is a cell cycle-active agent that acts through DNA-PK signaling in the S phase to induce apoptosis and a G2-phase arrest of the cell cycle.

STUDY OBJECTIVES

- To determine the safety and tolerability of IV SNS-595 given weekly x3 in a 28-day schedule
- To assess the PK profile of SNS-595 after single and repeat administration
- To define a recommended dose regimen for subsequent phase 2 efficacy studies
- To obtain preliminary objective tumor response data

METHODS AND SCHEMA

DLT definition

- ANC ≤500 for ≥ 7d or febrile neutropenia
- Platelet nadir <25000 or bleeding
- Non-hematologic AE ≥Grade 3 (CTCAE v3.0)
- AE requiring ≥14 days dose delay

MTD definition

- Dose level below dose level where ≥ 2 of 6 pts experienced DLT

Study schema

- Drug administered by IV bolus, weekly x 3 followed by 14 days of observation
- Starting dose: 3 mg/m²; dose escalation in cohorts of 3: dose doubled to first ≥Grade 2, related AE or abnormal lab value, then by a modified Fibonacci schema
- No mitomycin-C, BCNU, nitrosourea drugs; no MAb therapy w/in 42 d

PATIENTS

Table 1: Patient Demographics

Sex:	Male	9 (43%)
	Female	12 (57%)
Ethnic Background:	Asian	2 (9.5%)
	Black	2 (9.5%)
	White	17 (81%)
Age:	Mean	59.3 years
	Median	61
	Range	19-81
ECOG Performance Status:	Median	1
	Range	0-1
Previous Therapies:	MP	9 (43%)
	HP	12 (57%)

Table 2: Tumor Types

Colon	3
Pancreas	3
Breast	2
Mesothelioma	2
Cholangiocarcinoma	1
Leiomyosarcoma	1
Liposarcoma	1
Melanoma	1
Nasopharyngeal	1
Neuroendocrine	1
Ovarian	1
Renal	1
Salivary Gland	1
Small Cell Lung Cancer	1
Spindle Cell Carcinoma	1

SAFETY DATA

Table 3: Adverse Events Assessed as Related

	Dose (mg/m ²)	3	6	12	15	18	24
No. patients in database		4	3	3	6	4	1
Event	Grade						
Blood and Lymphatic System							
Anemia	1-2		1				
Neutropenia	1-2						1
	3-4						1
Gastrointestinal							
Constipation	1-2						1
Diarrhea	1-2						1
Lip Blister	1-2						1
Nausea	1-2	1	1	1	1	2	1
Vomiting	1-2	1			1	1	
General Conditions							
Aches	1-2				1		
Fatigue	1-2		1	1			1
Nervous System							
Peripheral Neuropathy	1-2			1			
Skin Disorders							
Alopecia	1-2						1

SNS-595 IV qwk x3 is Well Tolerated

- Neutropenia was the only Grade 3/4 toxicity observed and was the dose limiting toxicity
- Low incidence of GI toxicity was observed at biologically active doses
- No study-drug related SAEs were observed

Table 4: Hematologic Effects

Dose	n	Median ANC* (x1000)	Median platelets (x1000)	# ANC ≤ 1000	# ANC ≤ 500	# Febrile Neut.
3 mg/m ²	4	4.5	249	0	0	0
6 mg/m ²	3	3.4	221	0	0	0
12 mg/m ²	3	3.45	241	0	0	0
15 mg/m ²	6	3.3	271.5	0	0	0
18 mg/m ²	4	2.5	179	1	0	0
24 mg/m ²	1	2.4	276	1	0	0

n = number of patients in cohort
* nadir data from first 2 cycles

PHARMACOKINETICS

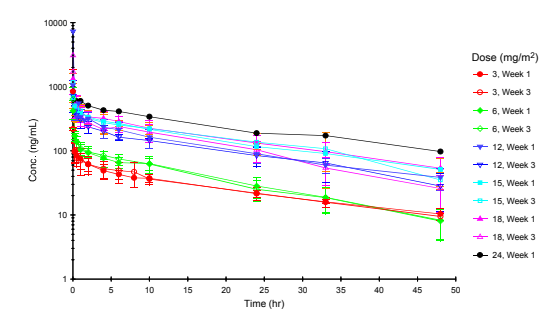
SNS-595 Shows Highly Reproducible Pharmacokinetics

- Low inter-patient variability
- Dose dependent increase in exposure and no change in CL or Vss with dose
- No change in pharmacokinetic parameters after repeat dosing

Table 5: Average of Wk 1 and Wk 3 Pharmacokinetic Parameters

Dose (mg/m ²)	n (Week 1, Week 3)	T _{1/2} (hr)	C _{max} (µg/ml)	AUC _{inf} (µg-hr/ml)	Cl _{obs} (L/hr/m ²)	V _{ss,obs} (L/m ²)
3	7 (4,3)	23.3± 7.2	0.577± 0.795	1.71± 0.20	1.77± 0.23	52.7± 18.2
6	6 (3,3)	13.5± 2.2	0.531± 0.28	2.09± 0.53	3.05± 0.84	51.0± 8.22
12	6 (3,3)	19.9± 5.3	1.84± 2.7	6.81± 1.68	1.87± 0.53	44.6± 8.53
15	10 (5,5)	26.4± 15.2	0.865± 0.318	10.8± 4.7	1.59± 0.56	43.8± 7.90
18	6 (4,2)	15.8± 4.2	1.69± 0.83	8.50± 2.86	2.36± 0.88	47.19± 8.06
24	1 (1,0)	24.2	0.6	15.2	1.58	50.0
Average		18.5± 4.6	---	---	2.22± 0.58	48.9± 4.5
Range		10-33	0.6-1.8	2-15	1.4-4.3	30-75

Mean Concentration-Time Plots



EVIDENCE OF ACTIVITY

Table 6: Evidence of activity (pts receiving ≥4 cycles)

Dose (mg/m ²)	Tumor Type	No. Cycles	Weeks on Therapy	Best response
6	Renal Cell	4	16	SD
12	Leiomyosarcoma	4	16	SD
	Melanoma	4	16	SD
15	Mesothelioma	4	19	PR
	Mesothelioma	5	18	SD
24 ^v	Salivary Gland	6	24	SD

^v Dose reduced to 12 mg/m² during cycle 1

SNS-595 shows evidence of clinical activity

- One patient (mesothelioma, 15mg/m²) achieved a partial response
- 6 of 21 evaluable patients showed a best response of stable disease or better, lasting at least 16 weeks

CONCLUSIONS AND FUTURE DIRECTIONS

- SNS-595 is first-in class, cell-cycle active anti-cancer agent with a unique mechanism of action
- SNS-595 was well tolerated when given as an IV bolus qwk x3
 - The most common drug-related toxicity was neutropenia, which was of short duration and did not appear to be cumulative; non-hematologic toxicity was uncommon and was usually Grade 1-2
 - The recommended phase 2 dose for a qwk x3 dosing schedule for solid tumors is 15 mg/m²
- Since neutropenia is the DLT in the absence of significant GI toxicity, further studies in hematological cancers are warranted; SNS-595 is currently being tested in acute leukemias
- Pharmacokinetics of SNS-595 were predictable with remarkably low inter-individual variability and did not demonstrate changes with repeated dosing
- Evidence of clinical activity was observed: 1 PR and 5 patients with stable disease ≥ 16 wks
- Additional trials of SNS-595 are warranted; trials in NSCLC, SCLC and hematologic tumors are in progress
- Clinical testing in additional tumor types is planned