

A Phase 2 Trial of SNS-595 in Women with Platinum Resistant Epithelial Ovarian Cancer

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ABSTRACT (Updated October 2007)

Background: SNS-595 is under clinical investigation in acute leukemia and ovarian cancer. Clinical responses have been observed in these indications, as well as in non-small cell (NSCLC) and small cell lung cancers. SNS-595 is a replication-dependent DNA damaging agent that causes irreversible G2 arrest, and rapid apoptosis. A secondary mechanism for SNS-595 is a unique inhibition of topoisomerase II that causes highly selective DNA damage with low dependence on topoisomerase II for its potent anti-tumor activity. A phase 2 study of single agent SNS-595 in ovarian cancer was initiated based on clinical activity observed in patients (pts) with ovarian cancer in phase 1, including one partial response (PR), and supported by preclinical studies in several human ovarian cancer xenograft mouse models. A translational medicine study of SNS-595 activity in ovarian tumor biopsies was undertaken in parallel. **Methods:** SNS-595 was administered to pts with advanced platinum resistant epithelial ovarian cancer who had progressive disease after 1 or 2 prior platinum containing regimens; pts could have received an additional biologic or non-platinum therapy after becoming platinum-resistant. Platinum resistance was defined as progression during or relapse within 6 months of platinum-based chemotherapy. The drug was delivered as an IV infusion over 10 minutes on Day 1 of a 21-day cycle. Women had to have an GOG PS of 0-1 and have adequate hematologic, hepatic and renal status. The translational study evaluated the activity of SNS-595 towards cancer cells harvested from 20 ovarian tumor biopsies, using the Extreme Drug Resistance (EDR®) cell proliferation assay developed and performed by Oncotech. Activity of SNS-595 was compared with doxorubicin, etoposide and carboplatin. **Results:** To date 27 women have been enrolled and treated; 19 have sufficient follow-up to yield useful safety results. The pts have a median age of 56.1 y (range 33-78 y) and the majority were Caucasian (16), with 1 African American and 2 women of Asian family origin. Median number of prior therapies is 3 (range 1-4) with 8 pts having previously failed liposomal doxorubicin therapy in addition to platinum therapy and 11 pts being liposomal doxorubicin -naïve. SNS-595 infusions were well tolerated. Dose reductions/delays were primarily due to neutropenia. Of the 27 pts currently treated, best response data are available on 17: one is a confirmed PR, one is an unconfirmed PR, and thirteen have stable disease (SD). Both pts who achieved a PR had failed 2 prior platinum-containing regimens and both had failed liposomal doxorubicin within 6 months as well. Nonclinical EDR® data established that SNS-595 is a potent inhibitor of ovarian tumor cell growth. Activity exceeded that of etoposide and carboplatin and was comparable with doxorubicin.

BACKGROUND

A prior Phase 1 dose-escalation study in 41 advanced solid tumor patients of SNS-595 administered by 10 min IV push q3 week demonstrated that:

- The primary dose limiting toxicity of SNS-595 observed was neutropenia
- Grade 3 or higher neutropenia occurred in 34% of patients with 1 reported febrile neutropenia

STUDY OBJECTIVES, METHODS AND SCHEMA

- Primary Endpoint: ORR using RECIST criteria
- Secondary Endpoints: Safety, TTP, PFS, OS
- Treatment: SNS-595 48 mg/m² IV q3 weekly for up to 8 cycles
- The study is being conducted with IRB approval at each participating center and all patients were enrolled following informed consent
- Patient population: platinum resistant ovarian cancer pts that have failed 1-2 prior platinum regimens and may have received up to one additional non-platinum cytotoxic therapy or a biologic
- Single-arm two-stage Green-Dahlberg design with a total of 55 pts, powered to distinguish 8% ORR from 22% ORR

PATIENTS

Table 1: Patient Demographics

Total, n	19
Age, yrs	
median	56.1
range	33 - 78
Race, n (%)	
Asian	2 (11%)
Black or African	1 (5%)
White or Caucasian	16 (84%)
Ethnicity, n (%)	
Not Hispanic or Latino	19 (100%)

Table 2: Patient Baseline Characteristics

Disease Duration	mos	CA-125 at baseline	U/mL
median	20	median	473
range	8 - 51	range	52 - 12089
missing		missing	15
Metastases at Entry?	n	# Prior Platinum Therapies	n
yes	17 (89%)	one	11 (58%)
no	1 (5%)	two	8 (42%)
missing	1 (5%)		
Pathology	n	Prior Doxil Trt?	n
serous cystadenocarcinomas	13 (68%)	yes	8 (42%)
poorly differentiated carcinoma	2 (11%)	no	11 (58%)
clear cell tumors	1 (5%)		
papillary serous	1 (5%)		
endometrioid tumors	1 (5%)		
missing	1 (5%)		

SNS-595 IS CYTOTOXIC FOR CELLS DERIVED FROM OVARIAN TUMOR BIOPSIES

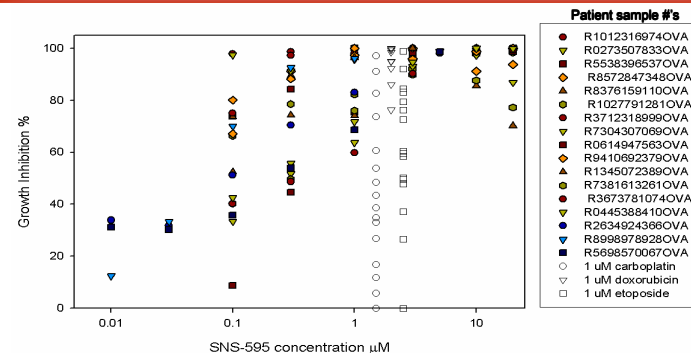


Figure 1. EDR® assay results with cells from 17 ovarian cancer biopsies obtained from the Oncotech repository. SNS-595 concentration range was 0.01-20µM; carboplatin, doxorubicin and etoposide concentration was 1µM.

- SNS-595 causes dose-dependent cell killing of primary ovarian tumor cells at clinically relevant plasma concentrations
 - 1µM SNS-595 causes >50% killing in all samples
- None of the ovarian cancer samples tested by EDR® were resistant to SNS-595 in this study
- Activity at 1µM is comparable with that of doxorubicin and exceeds that of carboplatin and etoposide

SAFETY

Table 3: Frequent (≥10%) Adverse Events for all NCI CTCAE Grades

System Organ Class	All Grades	Grade 3 or 4	System Organ Class	All Grades	Grade 3 or 4
Preferred Term	N=19	only	Preferred Term	N=19	only
# Pts who reported one or more AE					
Blood & Lymphatic System			Nervous system		
febrile neutropenia	2	2	dysgeusia	3	0
neutropenia	2	2	headache	2	0
Gastrointestinal			General		
nausea	6	1	fatigue	6	2
vomiting	2	0	mucosal inflammation	2	0
Psychiatric			Metabolism & Nutrition		
depression	4	1	anorexia	2	0
Skin & Subcutaneous system					
alopecia	5	0			

SNS-595 is generally well tolerated with a clinically manageable adverse event profile and few (4/19) dose reductions.

- Most common AEs were nausea and fatigue with an incidence of 32% (6/19).

- Incidence of neutropenia and febrile neutropenia were both 11% (2/19).

EFFICACY RESULTS

SNS-595 shows evidence of clinical activity in ovarian cancer patients

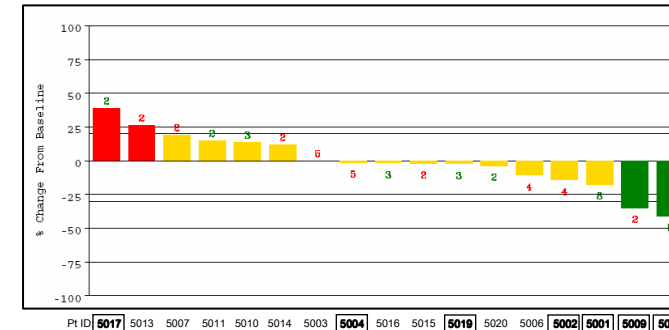


Figure 2. Waterfall plot of best response (RECIST) of 17/19 Ovarian cancer patients treated with SNS-595, for whom evaluation data were available

Red = Progressive Disease (PD)
Yellow = Stable Disease (SD)
Green = Partial Response (PR)

Bar labels signify # completed cycles; red for pts who have withdrawn, green for those who are ongoing

Bold Pt IDs indicate previous Doxil use [association with tumor response, p=0.07]

CONCLUSIONS AND FUTURE DIRECTIONS

- ✓ SNS-595 demonstrates single agent activity in advanced platinum resistant ovarian cancer patients with 88% (15/17) of patients having stable disease or better, including 2 PRs in patients previously resistant to Doxil.
 - 38% (5/13) of patients with stable disease have received three or fewer cycles of SNS-595 and remain on study.
- ✓ The rate of febrile neutropenia in this study is low (11%, 2/19) indicating that SNS-595 is a generally well-tolerated drug in this population.
- ✓ SNS-595 will proceed to Stage 2 of this study having already achieved the pre-specified criterion (2 or more responses) set for Stage 1.
- ✓ No resistance to SNS-595 was observed in 17 historical ovarian cancer biopsy specimens tested by EDR® assay for extreme drug resistance.
- ✓ Further study of SNS-595 in combination and single agent settings is supported by evidence of clinical activity as well as nonclinical studies that showed additivity or synergy in combination with other chemotherapeutic agents.