



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

W. McGuire¹, U. Matulonis², H. Hirte³, A. Husain⁴, R. Penson⁵, A. Chiang⁶, C. Aghajanian⁶, D. Young⁷, J.A. Fox⁷, M. Bolton⁷ and G. Michelson⁷

¹Weinberg Cancer Center, Baltimore, MD; ²Dana Farber Cancer Center, Boston, MA; ³Juravinski Cancer Center, Hamilton, ON, Canada; ⁴Stanford University, Palo Alto, CA; ⁵Massachusetts General Hospital, Boston, MA; ⁶Memorial Sloan Kettering Cancer Center, NY; ⁷Sunesis Pharmaceuticals, Inc., South San Francisco, CA

ABSTRACT (Updated March 2008)

Background: SNS-595 is being evaluated 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 novel naphthyridine analog, structurally related to the quinolones which have not been used previously for the treatment of cancer. SNS-595 is a specific, saturable DNA intercalator and topoisomerase II poison, causing replication-dependent site-selective double strand DNA damage, irreversible G2 arrest and rapid apoptosis. SNS-595 is not a substrate for P-glycoprotein, thereby evading a common drug resistance mechanism, and has low potential for CYP450-mediated drug-drug interactions. A phase 2 study of single agent SNS-595 in this population was initiated based on clinical activity observed in patients with ovarian cancer in phase 1, including one partial response (PR).

Methods: SNS-595 was administered IV over 10 minutes, Day 1 of a 21 day cycle to patients with advanced platinum resistant epithelial ovarian cancer with progressive disease after 1 or 2 prior platinum containing regimens; patients could have received an additional biologic or non-platinum therapy after becoming platinum-resistant. Women had to have an ECOG PS of 0-1 and have adequate hematologic, hepatic and renal status.

Results: To date 65 women have been enrolled and treated; 45 have sufficient follow-up to yield useful safety results. The pts have a median age of 57 y (range 33-82 y) and the majority were Caucasian. Median number of prior platinum therapies is 2 (range 1-2) with 19 pts having previously failed pegylated liposomal doxorubicin (PLD) therapy in addition to platinum therapy. Dose reductions/delays were primarily due to neutropenia. The most common AEs thus far include nausea, fatigue, and alopecia. Of the 65 pts currently treated, 35 are evaluable for best response: 1 CR and 4PR have been observed (2PR are unconfirmed), 26 are SD, and 4 with PD. Both platinum-resistant and doxorubicin-resistant patients responded to SNS-595 therapy. Nonclinical data established SNS-595 as a potent inhibitor of proliferation of tumor cells derived from ovarian biopsies.

Conclusions: SNS-595 has demonstrated clinical activity in patients with platinum-resistant ovarian cancer, several of whom have failed prior therapy with PLD as well. Safety data to date supports an increased dose to 60 mg/m² and accrual to this dose level is ongoing.

STUDY OBJECTIVES AND METHODS

- Primary Endpoint: ORR using RECIST criteria
- Secondary Endpoints: Safety, TTP, PFS, OS
- Treatment: SNS-595 48 mg/m² IV q3 weekly for up to 6 cycles followed by possible extension 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 powered to distinguish 8% ORR from 22% ORR
- Study has been amended to increase dose to 60 mg/m² and extend cycle length to 28 days

PATIENTS

Table 1: Patient Demographics

| | |
|------------------------|----------|
| Total, n | 45 |
| Age, yrs | |
| median | 57 |
| range | 33 - 82 |
| Race, n (%) | |
| Asian | 4 (9%) |
| Black or African | 3 (7%) |
| White or Caucasian | 38 (83%) |
| Ethnicity, n (%) | |
| Not Hispanic or Latino | 44 (96%) |

Table 2: Patient Baseline Characteristics

| | | | |
|---------------------------------|----------|----------------------------|------------|
| Disease Duration | mos | CA-125 at baseline | U/mL |
| median | 26.2 | median | 500 |
| range | 8 - 71 | range | 20 - 13178 |
| Metastases at Entry? | n (%) | # Prior Platinum Therapies | n (%) |
| yes | 43 (96%) | one | 20 (44%) |
| no | 1 (2%) | two | 25 (56%) |
| missing | 1 (2%) | | |
| Pathology | n (%) | Prior Doxil Trt? | n (%) |
| serous cystadenocarcinomas | 30 (67%) | yes | 17 (38%) |
| poorly differentiated carcinoma | 2 (4%) | no | 28 (62%) |
| clear cell tumors | 4 (9%) | | |
| papillary serous | 3 (7%) | | |
| endometrioid tumors | 2 (4%) | | |
| adenocarcinomas | 2 (4%) | | |
| Mullerian-type | 1 (2%) | | |
| missing | 1 (2%) | | |

SAFETY

Table 3: Frequent (≥ 7%) 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=45 | only | Preferred Term | N=45 | only |
| # Pts who reported one or more AE | 22 | 13 | | | |
| Blood & Lymphatic System | | | Nervous system | | |
| febrile neutropenia | 4 | 4 | dysgeusia | 6 | 0 |
| neutropenia | 5 | 4 | headache | 6 | 0 |
| Gastrointestinal | | | General | | |
| nausea | 12 | 2 | fatigue | 12 | 4 |
| vomiting | 9 | 1 | mucosal inflammation | 3 | 0 |
| Psychiatric | | | Metabolism & Nutrition | | |
| depression | 4 | 1 | anorexia | 4 | 0 |
| Skin & Subcutaneous system | | | | | |
| alopecia | 8 | 0 | | | |

- Most common AEs ≥ 10% (all grades) were fatigue, nausea, vomiting, alopecia, dysgeusia, headache and neutropenia
 - 4 of 45 (9%) pts: febrile neutropenia (FN)
 - 13 of 45 (29%) pts: reported G3/4 toxicities
- 21 pts had AE-related dose delays and/or dose reductions
 - 14 pts: dose-delayed or reduced due to hematologic toxicity (11 for neutropenia, 1 for thrombocytopenia and 2 for anemia)
 - 1 patient had a dose reduction for depression
 - The most common dose delays were due to G2 neutropenia at D21

PRELIMINARY EFFICACY RESULTS

SNS-595 shows evidence of clinical activity in platinum resistant ovarian cancer.

Figure 1. Waterfall plot of best response (GOG-RECIST) of 35/45 Ovarian cancer patients treated with SNS-595, for whom evaluation data were available

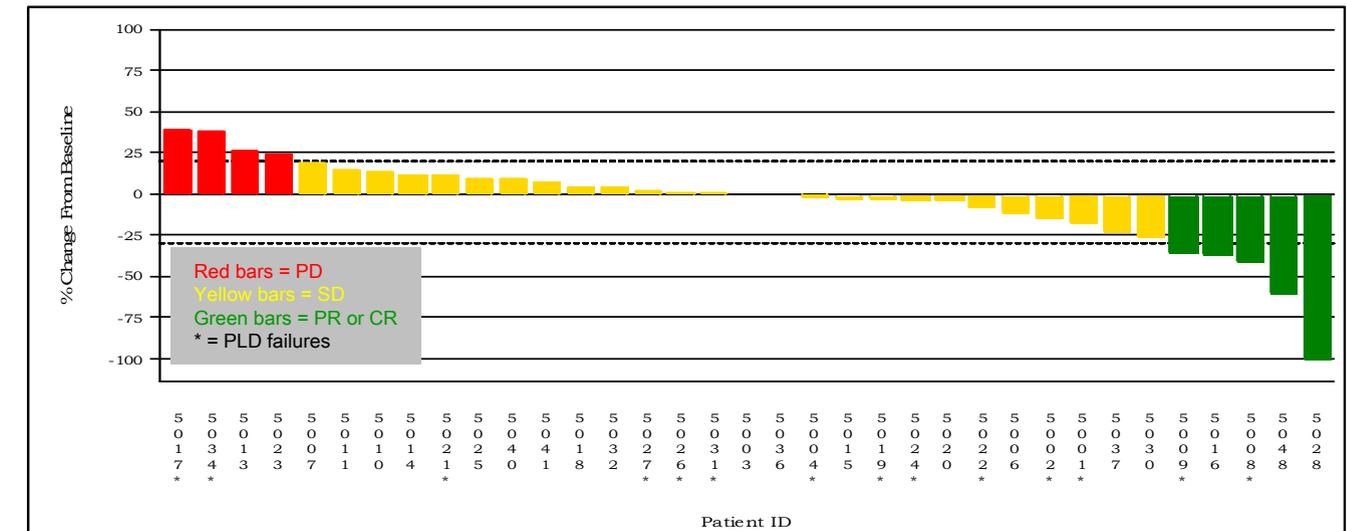


Table 4: Responder Characteristics

| ID | OR | Responder Characteristics | Cy |
|------|----|---|-----|
| 5008 | PR | 2 nd line platinum resistance, gemcitabine, PLD; off-study due to PD | 13 |
| 5009 | PR | 2 nd line platinum resistance, PLD unconfirmed; off-study due to AE | 2 |
| 5016 | PR | Primary platinum resistance, carboplatin/paclitaxel/bevacizumab | 12+ |
| 5028 | CR | 2 nd line platinum (HSR), gemcitabine | 2+ |
| 5048 | PR | Primary platinum resistant (clear cell) | 4+ |

CONCLUSIONS AND FUTURE DIRECTIONS

- ✓ SNS-595 demonstrates single agent activity in advanced platinum resistant ovarian cancer patients with 1CR, 4PR (2 unconfirmed) and 26 SD out of 35 evaluable patients.
- ✓ Platinum resistant patients including those who had failed PLD responded to SNS-595, with no bias thus far towards either population.
- ✓ The rate of febrile neutropenia in this study is low (9%, 4/45) indicating that SNS-595 is a generally well-tolerated drug in this population.
- ✓ Given the safety profile to date, as well as encouraging indications of activity, the dose of SNS-595 has been increased to 60 mg/m² and the study is continuing to accrue patients.
- ✓ 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.