

# A Phase 2 Trial of Voreloxin (formerly SNS-595) in Women with Platinum-Resistant Ovarian Cancer

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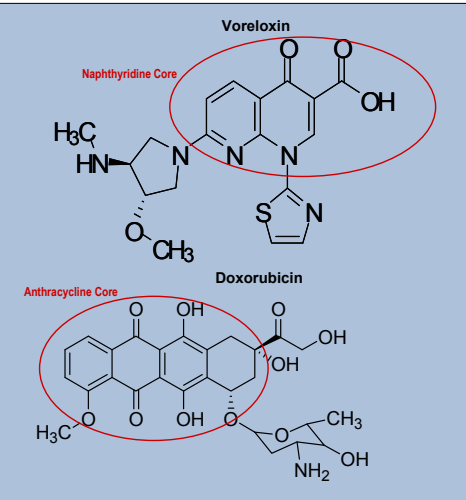


## ABSTRACT - UPDATED (Data as of 16OCT2008)

Voreloxin (formerly SNS-595) has demonstrated clinical activity in acute myeloid leukemia and ovarian cancer. Voreloxin is a novel naphthyridine analog, structurally related to the quinolones which have not been used previously for the treatment of cancer. Voreloxin intercalates DNA and inhibits topoisomerase II, causing replication-dependent, site-selective double strand DNA damage, G2 arrest and apoptosis. Voreloxin is not a substrate for P-glycoprotein and does not require p53 family members for activity, thereby evading common drug resistance mechanisms, and has low potential for CYP450-mediated drug-drug interactions. We report preliminary results from a Phase 2 study of single agent voreloxin in patients with 1<sup>st</sup> or 2<sup>nd</sup> platinum-resistant or refractory ovarian cancer. **Study Design:** Patients may have received up to 3 prior platinum regimens plus one additional non-platinum cytotoxic regimen. PS of 0-1 was required. Patients received 48 mg/m<sup>2</sup> q3weeks (Cohort A, N=65), or 60 mg/m<sup>2</sup> q4weeks (Cohort B, n=35), or 75 mg/m<sup>2</sup> q4weeks (Cohort C, currently enrolling to N=30 patients) by short (<10 min) IV infusion. **Results:** Two CRs and 5 PRs were observed in Cohort A (48 mg/m<sup>2</sup> q3weeks), for an ORR = 11%; 46 patients had SD and 12 had PD as best response. Five of the 7 responding patients did not develop their best response until ≥ cycle 4 (range 2 – 10). Overall, disease control (CR + PR + SD for ≥ 90 days) was achieved in 46% of patients. Seven patients remain on study. The median number of cycles was 4 (range 1 – 17). The preliminary median PFS is 82 days (95% confidence interval 52 – 98 days). Thirty-four patients (52%) experienced a Grade 3 or higher AE. There was a 75% incidence of Grade 3 or 4 neutropenia by laboratory values. Twenty-six patients (40%) experienced a dose delay or reduction due to an AE, most at Cycle 1 and largely due to neutropenia. Common Grade 3 or 4 AEs reported (≥ 5%) were fatigue (14%), and vomiting (6%). Twenty-one SAEs were reported by 15 patients (23%) of which only 5 were for febrile neutropenia (8%). The safety profile at this dose level supported dose escalation. Given that myelosuppression is the primary toxicity, a step-wise approach to dose escalation was taken by first extending cycle length to 4 weeks to allow for marrow recovery along with a dose increase to 60 mg/m<sup>2</sup> to maintain dose intensity (15 mg/m<sup>2</sup>/week). The criterion for ANC requiring dose delay or reduction was also changed from ANC < 1500 to ≥ 1000, to be consistent with standards of practice. Data for Cohort B patients enrolled at 60 mg/m<sup>2</sup> q4weeks are preliminary. Thirty-five patients were treated at this dose level. Early efficacy data are available for 32 patients; responses seen to date include: 1CR at cycle 2, 1PR at cycle 2, and 1PR at cycle 4; 20 patients had SD and 9 patients had PD as best response. Ten patients (31%) thus far with an objective response or stable disease have received > 4 cycles (>16 weeks). Thirteen patients remain on study. Fifteen (43%) of the 35 patients have experienced a Grade 3 or higher AE. There was a 77% incidence of Grade 3 or 4 neutropenia by laboratory values. There have been 2 incidents of febrile neutropenia (6%). Five patients (14%) had a dose delay or reduction, but none were due to neutropenia. Three patients (9%) had a Grade 3 anemia and no patient had a Grade 3 or 4 thrombocytopenia. Other Grade 3 or 4 AEs (≥ 5%) were fatigue (11%) and hypokalemia (9%). Eleven patients (31%) had 16 SAEs. The change in cycle length and the change in minimum ANC criterion were successful at reducing dose delays and reductions. The safety profile supported dose escalation. Both the dose and dose intensity have been increased to 75 mg/m<sup>2</sup> and 19 mg/m<sup>2</sup>/week, respectively. Twenty-two patients have been enrolled at the 75 mg/m<sup>2</sup> q4weeks dose level. Cohort C (target N=30). This cohort is continuing to accrue. **Conclusions:** The safety and efficacy profile for Cohort A (48 mg/m<sup>2</sup> q3weeks) and Cohort B (60 mg/m<sup>2</sup> q4weeks), based on preliminary efficacy data, are similar as anticipated based on comparable dose intensity. Fewer dose reductions and delays have occurred with the 4 week cycle and change in minimum ANC requirement at 60 mg/m<sup>2</sup>. Data analysis is ongoing to identify whether the increase in cycle length and/or ANC criterion allowed patients to receive drug as scheduled. Patients are currently accruing Cohort C (75 mg/m<sup>2</sup> q4weeks), where dose intensity is now increased by more than 25%.

## VORELOXIN BACKGROUND

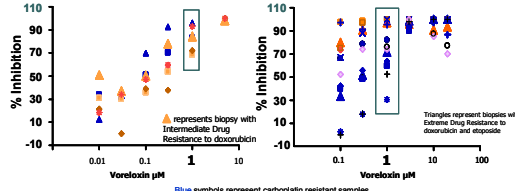
Voreloxin has a Validated Mechanism of Action with Distinct Advantages Over Anthracyclines



- Voreloxin: Novel topoisomerase II inhibitor and DNA intercalator**
- Active in anthracycline-resistant settings
    - Not a P-glycoprotein substrate
    - Unaffected by p53, p63 or p73 status
  - Not a CYP450 inhibitor or inducer
    - Low potential for drug-drug interaction
  - Limited distribution to normal tissues relative to anthracyclines
  - Dose proportional and predictable pharmacokinetics
  - No evidence of QTc prolongation
  - Lower potential for cardiotoxicity than anthracyclines
    - Anthracyclines generate substantial Reactive Oxygen Species (implicated in cardiotoxicity), unlike voreloxin

## VORELOXIN ACTIVITY EX VIVO

Voreloxin Is Active In Ovarian Cancer Biopsies, Including Platinum-Resistant Samples



Blue symbols represent carboplatin resistant samples. Ovarian cancer biopsies were evaluated for response to voreloxin as well as carboplatin, doxorubicin, and etoposide in the EDR<sup>®</sup> assay (OncoTech). Each unique symbol represents a patient biopsy for which a dose response to voreloxin was determined. In this assay, if sample growth is inhibited by < 50% or < 70% by a chemotherapeutic agent at a target concentration, then it is considered Extreme or Intermediate Drug Resistant, respectively.

- Voreloxin is active in carboplatin-resistant ovarian tumor biopsies.
- Voreloxin is active against ovarian tumor biopsies that are resistant to doxorubicin and/or etoposide.
- At 1 µM voreloxin, proliferation was inhibited >80% in 11 of 20 samples and >90% in 7 of 20 samples.
- 1 of 20 samples was EDR to voreloxin. This sample was also EDR to carboplatin, doxorubicin and etoposide.
- 18 of 20 samples were negative for detection of p63 and p73, with no influence on voreloxin activity.

## STUDY DESIGN AND OBJECTIVES

- Primary Objective: ORR using GOG- RECIST criteria
- Secondary Objectives: Safety and median PFS
- Treatment: Voreloxin by IV injection within 10 minutes.

Dose cohorts:

Cohort A (N=65) 48 mg/m<sup>2</sup> q3weeks  
Cohort B (N=35) 60 mg/m<sup>2</sup> q4weeks  
Cohort C (N=30, enrolling) 75 mg/m<sup>2</sup> q4weeks

• Patient population: platinum-resistant ovarian cancer patients who have failed 1-2 prior platinum regimens (Cohort A) and may have received up to one additional non-platinum cytotoxic therapy or a biologic. For Cohorts B and C, patients may have failed 1-3 prior platinum regimens, and an additional non-platinum cytotoxic or biologic after platinum-resistance.

## PATIENT DEMOGRAPHICS

Cohort A (48 mg/m<sup>2</sup> q3weeks) and Cohort B (60 mg/m<sup>2</sup> q4weeks) Prior Treatment History

Prior Tx	48 mg/m <sup>2</sup> N=65	60 mg/m <sup>2</sup> N=35	No. Prior Tx	48 mg/m <sup>2</sup> N=65	60 mg/m <sup>2</sup> N=35
1 <sup>st</sup> platinum-resistant	48%	63%	1	20%	31%
2 <sup>nd</sup> platinum-resistant	52%	37%	2	43%	37%
Doxil <sup>®</sup> (Caelyx <sup>®</sup> )	38%	20%	3	22%	23%
Gemcitabine	25%	17%	≥4	14%	9%
Bevacizumab	6%	6%			
Topotecan	9%	6%			

More primary platinum-resistant patients were enrolled into Cohort B compared to Cohort A, 63% vs. 48%, respectively.

Cohort A (48 mg/m<sup>2</sup> q3weeks) and Cohort B (60 mg/m<sup>2</sup> q4weeks) Histology

Histology	48 mg/m <sup>2</sup> N=65	60 mg/m <sup>2</sup> N=35
Serous Cystadenocarcinoma	63%	54%
Papillary serous	8%	17%
Clear cell	11%	14%
Endometrioid	5%	9%
Adenocarcinoma, NOS	12%	3%
Other	6%	3%

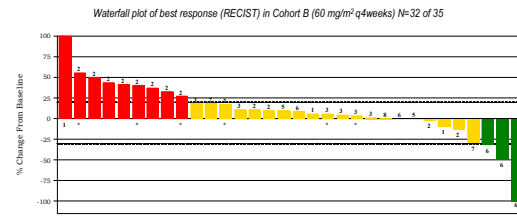
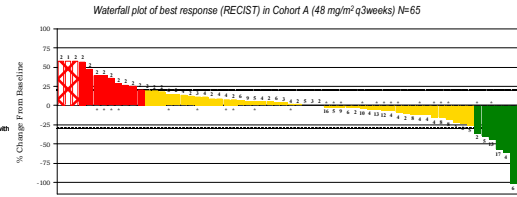
## GRADE 3 OR HIGHER AEs (≥ 5%) AND DOSE DELAYS/REDUCTIONS

	48 mg/m <sup>2</sup> N=65	60 mg/m <sup>2</sup> N=35
Patients Reporting Grade 3 or Higher AEs	34 (52%)	15 (43%)
Febrile Neutropenia	5 (8%)	2 (6%)
Neutropenia	49 (75%)	27 (77%)
Anemia	5 (8%)	3 (9%)
Vomiting	4 (6%)	0
Fatigue	9 (14%)	4 (11%)
Hypokalemia	1 (1.5%)	3 (9%)
Infections	5 (8%)	1 (3%)
Dose Delay or Reduction	26 (40%)	5 (14%)

The safety profile is comparable between Cohort A and Cohort B, albeit proportionally fewer dose delays or reductions were observed in Cohort B. The incidence of febrile neutropenia was also low in Cohort B (5%), which supported the dose increase to 75 mg/m<sup>2</sup> in Cohort C.

## PRELIMINARY EFFICACY

Voreloxin Shows Evidence of Clinical Activity in Platinum-Resistant Ovarian Cancer



Waterfall Plot Legend

- Objective Response: Partial or Complete Response
- Stable Disease
- Progressive Disease
- Progressive Disease, lesion change from baseline unimpeded
- Patient failed treatment with Doxil<sup>®</sup>

\* Number associated with target lesion bar is the number of cycles the patient has received as of October 16, 2008.

## RESPONDER PROFILES

Profiles of Cohort A (48 mg/m<sup>2</sup> q3weeks) Responders

Responder Characteristics	1 <sup>st</sup> or 2 <sup>nd</sup> Platinum Resistant	Best Response	Cycle At Which PR or CR Observed	Cycles
1 <sup>st</sup> line: Carbo/Gemcitabine – Carbo/Taxol				
2 <sup>nd</sup> line: Carbo/Gemcitabine	2 <sup>1</sup>	PR	4	13
3 <sup>rd</sup> line: Doxil BRCA-1 mutation				
1 <sup>st</sup> line: Carbo/Taxol				
2 <sup>nd</sup> line: Doxil	2 <sup>1</sup>	PR	2	2
Unconfirmed PR: off-study due to AE (bowel obstruction)				
1 <sup>st</sup> line: Carbo/Taxol/Avastin	1 <sup>1</sup>	PR	10	17+
1 <sup>st</sup> line: Carbo/Taxol				
2 <sup>nd</sup> line: Carbo/Gemcitabine	2 <sup>1</sup>	CR	6	6
BRCA-2 mutation, off study – pt on holiday				
1 <sup>st</sup> line: Cis/Topotecan Carbo/Taxol	2 <sup>1</sup>	CR	8	10+
2 <sup>nd</sup> line: Carbo/Gemcitabine				
1 <sup>st</sup> line: Carbo/Taxol (Clear cell)	1 <sup>1</sup>	PR	2	4
1 <sup>st</sup> line: Carbo	2 <sup>1</sup>	PR	4	5+
2 <sup>nd</sup> line: Carbo				

+ Indicates patient remains on study receiving voreloxin.

Profiles of Cohort B (60 mg/m<sup>2</sup> q4weeks) Responders

Responder Characteristics	1 <sup>st</sup> or 2 <sup>nd</sup> Platinum Resistant	Best Response	Cycle At Which CR or PR Observed	Cycles
1 <sup>st</sup> line: Carbo/Taxol				
2 <sup>nd</sup> line: Carbo/Taxol	2 <sup>1</sup>	CR	2	6+
1 <sup>st</sup> line: Carbo/Taxol	1 <sup>1</sup>	PR	4	6+
1 <sup>st</sup> line: Carbo/Taxol – Cis/Taxol	1 <sup>1</sup>	PR	2	6+

+ Indicates patient remains on study receiving voreloxin.

## CONCLUSIONS

- Voreloxin in Cohort A (48 mg/m<sup>2</sup> q3weeks) demonstrates single agent activity in advanced platinum-resistant ovarian cancer patients.
  - 2 CR and 5 PR were observed (ORR 11%) with disease control (CR + PR + SD for ≥ 90 days) achieved in 46% and a preliminary median PFS of 82 days (95% confidence interval 52 – 98 days).
  - Most (5 of 7) objective responses occurred at Cycle 4 or later (range 2-10). Seven patients remain on study, including 3 with objective responses.
  - The low incidence of febrile neutropenia (8%) supported dose escalation.
- Given that the primary toxicity at 48 mg/m<sup>2</sup> q3weeks was myelosuppression, a stepwise approach to adjust the dose and schedule was undertaken.
  - The cycle length was increased to 4 weeks to allow for marrow recovery, and the dose was increased to 60 mg/m<sup>2</sup> to maintain dose intensity.
- Preliminary efficacy and safety data for Cohort B (60 mg/m<sup>2</sup> q4weeks) are similar to Cohort A (48 mg/m<sup>2</sup> q3weeks). The data for Cohort B are not yet mature enough to calculate PFS.
  - Thirteen patients remain on study in Cohort B.
  - Proportionally fewer dose delays and reductions observed on Cohort B, allowing patients to receive the full dose on schedule. Low incidence of febrile neutropenia (6%) supported dose escalation.
- The dose has been increased to 75 mg/m<sup>2</sup> on a q4weeks schedule (Cohort C) to increase dose intensity, and 22 of 30 patients have been enrolled. Preliminary results (minimum of 4 cycles) are anticipated in Spring 2009.