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

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Background: Voreloxin (formerly SNS-595) is being evaluated in acute leukemias and ovarian cancer. Clinical responses have been observed in these indications, as well as in non-small cell (NSCLC) and small cell lung cancers. Voreloxin is a novel naphthyridine analog, structurally related to the quinolines which have not been previously used previously for the treatment of cancer. Voreloxin intercalates DNA and poisons topoisomerase II, causing replication-dependent, site-selective double strand DNA damage, irreversible 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. Based on clinical activity observed in patients with ovarian cancer in phase 1, including one partial response (PR), a phase 2 study of single agent voreloxin in patients with advanced platinum-resistant ovarian cancer was initiated.

Methods: For the 48 mg/m² dose group, voreloxin has been administered IV within 10 minutes on Day 1 of a 3 week cycle. Patients had 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. An ECOG PS of 0-1 and adequate hematologic, hepatic and renal status were required.

Results: To date 65 women have been treated at 48 mg/m² and are evaluable for safety. 62 are evaluable for efficacy. The patients have a median age of 60 (range 33-82 y) and the majority are Caucasian. Median number of prior platinum therapies is 2 (range 1-3) with 26 patients having previously failed pegylated liposomal doxorubicin (PLD) therapy in addition to platinum therapy. Dose reductions/delays have been primarily due to neutropenia. The most common non-hematologic G3/4 voreloxin-related AEs have been fatigue, nausea and vomiting. Of the 62 patients evaluable for efficacy 1 CR and 5 PR have been observed (1 PR was unconfirmed), 45 with SD, and 11 with PD as best response. Median duration of response for patients with an objective response is 95 days (range 33-260 days); 4 of 6 responders at 48 mg/m² remain on study. Twenty-four patients have had SD for ≥ 90 days. Overall, disease control (SD for ≥ 90 days + CR + PR) has been achieved in 48% of patients, with median progression-free survival of 13 weeks. Twenty-three patients remain on study at this dose level. Both platinum-resistant and PLD-resistant patients have responded to voreloxin therapy. Conclusions: Voreloxin has demonstrated clinical activity in patients with platinum-resistant ovarian cancer, several of whom have failed prior platinum therapy with PLD as well. Safety data at 48 mg/m² supported increasing the dose to 60 mg/m². 34 of 35 planned patients have been accrued to the 60 mg/m² dose level. Of 8 patients currently evaluable for efficacy, 1 PR has been observed thus far. Safety in 23 patients at 60 mg/m² has been similar to that at 48 mg/m² and is supportive of increasing the dose, the study has been amended to further increase the dose to 75 mg/m² q4 weeks.

Voreloxin is a well-tolerated drug in this population: Cycle Length extended to 28 days, Neutropenia (from laboratory data) 45 (69%), 15 (75%) at 48 mg/m² and 60 mg/m², respectively. AEs ≥ Grade 3/4 in ≥ 5% of 65 patients at 48 mg/m²: Neutropenia 44 (67%), 14 (70%); Anemia 3 (5%), 1 (5%); Vomiting 3 (5%), 0; Fatigue 8 (12%), 0. Based on the low incidence of Grade 3/4 AEs, the dose has been further escalated to 75 mg/m² q4 weeks.

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