PHASE 2 STUDY OF VORELOXIN (SNS-595) AS SINGLE AGENT THERAPY FOR ELDERLY PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA (AML): PRELIMINARY SAFETY AND CLINICAL RESPONSES

F Ravandi[1], R Stuart[2], M. Maris[3], R Stone[4], L Cripe[5], M Cooper[6], S Strickland[7], F Turturro[8], W Stock[9], GC Michelson[10], RE Hawtin[10], L Ericson[10], K Mahadocon[10], JA Fox[10], C Berman[10],

[1]MD Anderson Cancer Center, Houston, TX; [2]Medical University of South Carolina, Charleston, SC; [3]Rocky Mountain Bone Marrow Transplant Program, Denver, CO ; [4]Dana-Farber Cancer Center, Boston, MA; [5]Indiana University Cancer Center, Indianapolis, IN ; [6]St. Francis Hospital, Indianapolis, IN; [7]Vanderbilt University, Nashville, TN; [8]LSU Health Sciences Center, Shreveport, LA; [9]University of Chicago, Chicago, IL; [10]Sunesis Pharmaceuticals, South San Francisco, CA

ABSTRACT - UPDATED

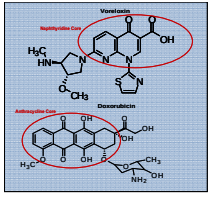
Background: Voreloxin is a first-in-class replication-dependent site-selective DNA damaging agent that causes apoptosis by DNA intercalation and inhibition of topoisomerase II. Voreloxin demonstrated single agent activity in a Phase 1 study of relapsed/refractory acute leukemias (ASH 2007). A Phase 2 study was designed to assess voreloxin's activity in the front line setting for the treatment of elderly AML, the REVEAL-1 study (**R**esponse **E**valuation of **V**or**E**loxin in **A**m**L**). **Objectives:** Overall remission rate (CR plus CRp); safety and tolerability of voreloxin in this patient population; pharmacokinetics; secondary markers of efficacy (leukemia-free survival, overall survival, duration of remission/response, and 30 day all-cause mortality); determine whether ex vivo activity of voreloxin is predictive of response. **Methods:** Open label Phase 2 two-stage study design; 9 CR + CRp are required within the first 30 evaluable patients to complete study enrollment to 55 patients. Eligibility: newly diagnosed AML (either de novo or from an antecedent hematologic disorder, AHD) in patients age 60 and older with a minimum of 1 additional adverse risk factor (age older than 70, AML from AHD, intermediate or poor risk cytogenetics, or ECOG performance status of 2). Study treatment is 72 mg/m^2 voreloxin weekly X 3 doses (Schedule A) or 72 mg/m^2 weekly X 2 doses (Schedule B). Voreloxin is administered by IV push within 10 minutes. Patients achieving a CR or CRp after induction or re-induction may receive up to 2 additional voreloxin courses as consolidation. Response evaluation is per IWG criteria. PK analyses were performed during cycle 1 on a subset of patients. Ex vivo sensitivity to voreloxin was evaluated in baseline bone marrow aspirates (BMA) using the CellTiter-Glo® proliferation assay (assay conducted at Oncotech). **Results**: Preliminary response data are available for all 29 patients enrolled into Schedule A. Demographics: 69% male, 31% female; median age 75 (range: 61-89); ECOG PS: 28% PS 0, 62% PS 1; 10% PS 2. 28% had AHD and cytogenetics were intermediate in 38%, unfavorable in 41%, and unknown in 21%. Eleven patients achieved a CR or CRp. The median duration of response has not been reached. The 30 day all-cause mortality rate was 17%. Infection was the most common cause of early mortality. Most frequent common Grade 3 or higher non-hematologic AEs (≥ 10%) reported include febrile neutropenia, mucosal inflammation, and pneumonia. Although Stage 1 criteria were achieved, in order to reduce duration of myelosuppression and improve treatment tolerability, the protocol was modified with elimination of the day 15 dose (Schedule B) and recommendation for use of prophylactic anti-infectives. Up to 55 patients will be enrolled into Schedule B utilizing the same 2 stage design described above. Thus far, 21 patients were enrolled and treated. Early data for anti-leukemic activity are available for 18 patients. Demographics: 55% male, 45% female; median age 75 (range: 64-83); ECOG PS: 11% PS 0; 78% PS 1; 11% PS 2. 24% patients had AHD and cytogenetics were favorable in 5%, intermediate in 24%, unfavorable in 29%, and unknown in 42%. To date, 18 patients have had a post-induction bone marrow, and of these 1 patient had a CRp, 5 pts are awaiting hematologic recovery; 3 patients are undergoing re-induction, and 3 patients are too early for assessment. Eight patients were treatment failures. The rates of febrile neutropenia were comparable to the day 1,8, and 15 schedule but other Grade 3 or higher non-hematologic AEs reported were less frequent. The 30 day all-cause mortality rate is 6%. **Conclusions**: In the REVEAL-1 study, voreloxin demonstrates clinical activity with 2 dosing schedules in previously untreated elderly (age ≥ 60) patients with AML who are unlikely to benefit from standard chemotherapy. Schedule A (day 1,8, and 15) CR + CRp rate was 38% and met Stage 1 criteria. Schedule B (day 1 and 8) was implemented to reduce duration of myelosuppression and improve tolerability. Early data suggest that Schedule B appears to be better tolerated while maintaining anti-leukemic activity as demonstrated by blast reductions to ≤5% in post-induction bone marrow evaluations. Accrual to this regimen continues.

AML IN THE ELDERLY

- AML is a disease of an aging population: median age at diagnosis is 67.
- Older patients with AML are a difficult population to treat due to patient comorbidities and the intrinsic nature of AML in older patients (adverse cytogenetics, secondary AML).
- These patients have limited therapeutic options: only 1/3 receive chemotherapy because standard induction chemotherapy is associated with lower response rate and increased risk of early mortality, especially age ≥ 70.
- Kantarjian et al (Cancer 2006, 2007) correlated older age and adverse cytogenetics with both lower CR rate and higher risk of early mortality.

VORELOXIN

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
- Lower potential for cardiotoxicity than anthracyclines
  - Anthracyclines generate substantial Reactive Oxygen Species (implicated in cardiotoxicity), unlike voreloxin

STUDY OBJECTIVES AND TRIAL DESIGN

Study Design	Phase 2 study of patients ≥ 60 yo with newly diagnosed AML 2 stage Green-Dahlberg design with interim evaluation at Stage 1. Stage 1: ≥ 9 CR+CRp of 30 patients with adequate safety to enable expansion to 55 patients.
Population	Age ≥ 60 years with AML by WHO criteria (either de novo, secondary, or from AHD) and at least one of the following adverse factors: • Age ≥ 70 • AHD • ECOG PS=2 • Intermediate or unfavorable cytogenetics
Voreloxin Regimen	Schedule A: 72 mg/m^2 voreloxin weekly x 3 Schedule B: 72 mg/m^2 voreloxin weekly x 2
Additional Major Inclusion Criteria	Written informed consent; adequate hepatic, renal and cardiac function, history of and prior treatment for AHD allowed
Major Exclusion Criteria	Acute promyelocytic leukemia; CNS involvement; prior treatment for AML, history or recent myocardial infarction or thromboembolic events
Treatment Paradigm	Induction: Bone marrow biopsy/aspirate (BMA) evaluated 1 week after completion of voreloxin therapy. Patients could receive an additional course of voreloxin as reinduction if needed. Patients who did not achieve a CR after 2 induction cycles were taken off study. Consolidation: Patients with a CR or CRp could receive up to 2 additional cycles of voreloxin therapy.
Objectives	Primary: Overall remission rate (CR+CRp) per IWG criteria Secondary: Safety; 30 day all cause mortality, overall survival, leukemia-free survival, duration of response, pharmacokinetics and ex vivo sensitivity of patient baseline BMA to voreloxin

DEMOGRAPHICS

	Schedule A (days 1, 8 and 15)		Schedule B (days 1 and 8)	
Patients enrolled	29		21	
Median Age in years (Range)	75 (61-89)		75 (64-83)	
Male N (%)	19 (66%)		11 (55%)	
ECOG **PS 0 – 1 (%)** **PS 2**	90 10		89 11	
AML, FAB Type (%)	M_0	14	M_0	6
	M_1	24	M_1	25
	M_2	34	M_2	43
	M_4	17	M_4	13
	M_5	3	M_5	6
	M_6	7	M_6	6
Cytogenetics (%) SWOG criteria	Favorable	0	Favorable	5
	Intermediate	38	Intermediate	24
	Unfavorable	41	Unfavorable	29
	Unknown	21	Unknown	42

SAFETY

	Schedule A (N=29)	Schedule B (N=21)
30-day all-cause mortality	5 (17%)	1 of 17 (6%)
Median days to ANC > 1000	35	Too Early
Median days to platelet > 100,000	39	Too Early

The majority of deaths were due to infection complications.

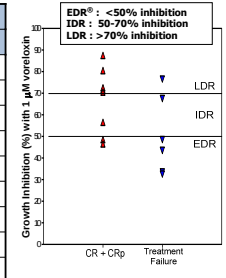
NON-HEMATOLOGIC GRADE 3 OR HIGHER AEs ≥ 10%

	Schedule A (N=29)	Schedule B (N=21)
Febrile Neutropenia	35%	38%
Mucosal Inflammation	24%	13%
Fatigue	17%	0%
Pneumonia	21%	6%
Anorexia	17%	6%
Hypokalemia	14%	0%
Hypophosphatemia	10%	0%
Confusional State	14%	0%
Dyspnea	28%	0%
Hypoxia	10%	0%

Infection complications comprised the majority of SAEs.

PHARMACODYNAMICS: SCHEDULE A EX-VIVO RESPONSE TO VORELOXIN

CR + CRp		Treatment Failure	
Patient No.	**Assay**	**Patient No.**	**Assay**
1	LDR	4	EDR
3	LDR	14	EDR
5	EDR	17	EDR
6	LDR	18	IDR
7	LDR	21	LDR
9	EDR	23	-
11	IDR	26	EDR
19	-	27	-
24	-		
28	LDR		



Ex vivo response to voreloxin does not predict clinical response, however a trend towards ex vivo sensitivity to voreloxin is apparent in the CR vs Treatment Failure patient samples.

EFFICACY

	Schedule A Days 1, 8, 15	Schedule B Days 1 and 8
Patients enrolled and treated	29	21
Patients with post induction Bone Marrow Assessment (BMA)	29	18
CR	8	0
CRp	3	1
Hypoplastic, awaiting heme recovery	1*	5
Reinduction	3	3
Treatment failure	7	8
Median # doses received	3	2

* Peripheral blood counts recovered; induction BMA hypoplastic. Patient declined BMA to confirm remission.

RESPONSE CHARACTERISTICS

		CR or CRp and Risk Factors*				
Patient No.	**Response**	**≥ 70**	**AHD**	**PS 2**	**Intermediate./ Unfavorable Cytogenetics**	**No. Risk Factors**
1	CR	Yes	Yes	No	Intermediate	3
3	CR	Yes	Yes	No	Intermediate	3
5	CR	Yes	No	Yes	Unknown	2
6	CR	Yes	No	No	Unknown	1
7	CRp	Yes	Yes	No	Unknown	2
9	CR	No	Yes	No	Intermediate	2
10	CRp	Yes	No	No	Intermediate	2
11	CR	No	No	No	Unfavorable	1
13	CRp	No	No	No	Intermediate	1
24	CR	Yes	Yes	No	Unknown	2
28	CR	No	No	No	Intermediate	1
33	CRp	No	No	No	Unfavorable	1

*Ref: Kantarjian et al, Cancer 2006, Cancer 2007

CONCLUSIONS

- In the REVEAL-1 study, voreloxin demonstrates clinical activity in poor risk frontline elderly AML in this Phase 2 study.
- **Schedule A (72 mg/m^2 qw x 3)** was identified in a preceding Phase 1 study in a relapsed/refractory population.
  - In the frontline elderly population, 11 complete remissions , 5 marrow ablations to ≤5% blasts, and one marrow ablation to 6% blasts were observed (N=29). CR were observed in patients with multiple risk factors predictive of poor outcome to conventional induction therapy.
  - 30 day all-cause mortality was 17%, which was within historical limits in the literature; the majority of deaths resulted from infectious complications.
- **Schedule B (72 mg/m^2 qw x 2)** was implemented in October. Treatment was limited to 2 weekly doses to reduce duration of myelosuppression and to improve tolerability over Schedule A. 21 patients have enrolled thus far with preliminary activity (induction bone marrows) available for 18.
  - Instituted guidance on prophylactic antibiotics and excluded patients with active infections.
  - CR rate is too early to evaluate.
    - Post induction bone marrow ablations have been observed.
    - In Schedule A, post induction marrow ablation typically resulted in complete remission.
  - 30 day all-cause mortality is currently 6% ; decrease in both morbidity and in Grade 3 and higher AEs (compared to Schedule A) is reported.
- Patients will be followed for outcome, duration of response and survival on both schedules.

http://www.sunesis.com/science/presentations_and_publications.php