

A Phase 2 Study of Voreloxin as Single Agent Therapy for Elderly Patients with Newly Diagnosed Acute Myeloid Leukemia (AML)

F Ravandi¹, R Stuart², M Maris³, R Stone⁴, L Cripe⁵, M Cooper⁶, S Strickland⁷, F Turturo⁸, W Stock⁹, K Mahadoon¹⁰, J Fox¹⁰, G Michelson¹⁰, C Berman¹⁰

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



ABSTRACT - UPDATED

Background: Voreloxin is a first-in-class Anticancer Quinolone Derivative (AQD) that intercalates DNA and inhibits topoisomerase II, inducing apoptosis. Interim results of REVEAL-1, a Phase 2 dose regimen optimization study of three schedules of single agent voreloxin in newly diagnosed elderly AML patients, are reported. The initial dose regimen studied, 72 mg/m² voreloxin q x 3, was established in a Phase 1 dose-escalation study in relapsed/refractory advanced leukemia patients (Lancet ASH 2007). Though the complete remission rate was high (41%), this regimen was less well tolerated in the frontline elderly population. The protocol was amended to optimize the dose regimen in this setting by exploring two alternative voreloxin schedules. Improved tolerability was observed with 72 mg/m² voreloxin q x 2 while maintaining anti-leukemic activity. A more dose intense regimen was then explored, studying 72 mg/m² voreloxin delivered on Days 1 and 4. Another cohort of patients will be enrolled to the Days 1 and 4 schedule at an increased dose of 90 mg/m². The decision to dose escalate was based on safety data from that prior cohort, as well as from an ongoing Phase 1b/2 study with patients who have been treated with voreloxin on Days 1 and 4 at 90 mg/m² in combination with 1gm/m² cytarabine x 5d (Lancet ASCO 2009).

Methods: Phase 2 study of 3 voreloxin schedules (approximately 30 patients/schedule): A, 72 mg/m² q x 3 or B, 72 mg/m² q x 2 or C, 72 mg/m² on Days 1 and 4. C was amended to explore an additional cohort of patients at 90 mg/m² (enrollment target 50 patients). Eligibility: newly diagnosed AML (de novo or secondary AML), patients age ≥ 60 and ≥ 1 additional adverse risk factor (age ≥ 70 , secondary AML, intermediate or unfavorable cytogenetics, or PS 2). PK were evaluated in a patient subset in cycle 1.

Results: Schedules A (29 patients), B (35 patients) and C (30 patients) are fully enrolled. Demographics (N=90): 61% male, 39% female; median age 74 years (range 61 – 89); ECOG PS 0-1-80%, PS 2 17%. Twenty-one % had an antecedent hematologic disorder (AHD) and cytogenetics by SWOG (MDACC: Kantarjian Blood 2006) criteria were favorable in A (28%), intermediate in B (41%), unfavorable in A (52%), unknown in 8% (1%), not yet available for 7% and sample failure for 4%. Final CR + CRp rate was 41% for A and 29% for B. C cohort has not completed response evaluation, but 5 CR + CRp with 2 patients in count recovery of 19 evaluable patients have been observed thus far. Median duration of remission and survival has not been reached for any cohort. A: Five of 12 responders have remained in remission for > 6 months, 3 have withdrawn from remission follow-up and 4 have relapsed. Thirteen of 29 patients are alive and 16 (55%) have survived for > 7 months. B: Nine of 10 responders remain in remission; 2 have exceeded 6 months in duration. Twenty of 35 patients are alive. Fifteen of 29 (52%) patients have survived for > 6 months thus far; an additional 6 patients who survive have been on study for < 6 months. C is too early to evaluate. Safety and tolerability improved markedly in B relative to A, and, although preliminary, the safety profile of C appears similar to B. Thirty-day all-cause mortality was 17%, 9% and 9% (2 of 22 patients) for A, B and C respectively. Infections or PD were the most common causes of early mortality. The incidence of sepsis/bacteremia was also reduced (A: 45%; B: 17%) with the elimination of a 3rd voreloxin dose/cycle, as was the incidence of upper GI mucosal inflammation (A: 31%; B: 11%). B patients were able to receive more consolidation therapy than A. Voreloxin PK were similar to those in an earlier single agent Phase 1 study in relapsed/refractory AML (Lancet ASH 2009). **Conclusions:** In REVEAL-1, voreloxin demonstrates clinical activity with 3 dosing schedules in previously untreated elderly (age ≥ 60) patients with AML who are unlikely to benefit from standard chemotherapy. CR + CRp rate was 41% (12 of 29 patients) for 3 weekly voreloxin doses (A); 29% (10 of 35 patients) for 2 weekly voreloxin doses (B); final CR+CRp remission rate is not available for voreloxin dosed Days 1 and 4, but 6 CR+CRp have been observed thus far. Early mortality was reduced from 17% to 9% tolerability improved in B. Median survival is too early to estimate; > 50% of patients have survived > 6 months on A and B; C enrollment opened too recently to evaluate. Enrollment to 90 mg/m² voreloxin dosed D1 and D4, is pending.

STUDY OBJECTIVES AND TRIAL DESIGN

Study Design	Phase 2 study of patients ≥ 60 years with newly diagnosed AML. Dose regimen optimization
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 Schedule C: 72 mg/m ² voreloxin Days 1 and 4 Schedule C: 90 mg/m ² voreloxin Days 1 and 4
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: BMA evaluated 1 week after voreloxin therapy completed. Reinduction: 1 additional cycle allowed if needed. Consolidation: CR or CRp patients could receive up to 2 additional cycles.
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, and PK.

DEMOGRAPHICS

	Schedule A (Days 1, 8, 15)	Schedule B (Days 1, 8)	Schedule C (Days 1, 4) Preliminary
N	29	36	25
Median Age years (Range)	75 (61-89)	75 (64-87)	69 (61-84)
Male	66%	67%	61%
ECOG PS 0 – 1	86%	86%	64%
ECOG PS 2	14%	14%	24%
AHD	41%	29%	Not available
AML FAB Type			
M0	17%	0%	8%
M1	24%	28%	4%
M2	35%	33%	36%
M4	14%	17%	24%
M5	3%	12%	0%
M6	7%	0%	4%
M7	0%	0%	4%
Cyto-genetics SWOG (MDACC) criteria			
Favorable	0% (0%)	6% (6%)	8% (8%)
Intermediate	48% (38%)	31% (31%)	24% (20%)
Unfavorable	41% (55%)	46% (54%)	36% (48%)
Unknown	7% (3%)	9% (0%)	8% (0%)
Not available	3%	9%	24%

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

NON-HEMATOLOGIC GRADE 3 OR HIGHER AEs $\geq 10\%$

	Schedule A D1,8,15 (N=29)	Schedule B D1,8 (N=35)	Schedule C D1,4 Preliminary (N=20)
Febrile Neutropenia	38%	63%	35%
Pneumonia (bacterial)	28%	31%	25%
Sepsis/Bacteremia	45%	17%	0%
Infections (other)	45%	9%	0%
Upper GI Mucosal Inflammation	31%	11%	15%
Lower GI Diarrhea, Caecitis, Colitis	10%	6%	0%
Fatigue	17%	20%	0%
Anorexia	21%	9%	10%
Hypokalemia	38%	20%	10%
Hypophosphatemia	17%	3%	5%
Hypocalcaemia	10%	6%	10%
Dehydration	14%	0%	0%
Confusional State	14%	0%	0%
Dyspnea	24%	9%	5%
Hypotension	14%	3%	0%

Infection complications comprised the majority of SAEs.

OUTCOME

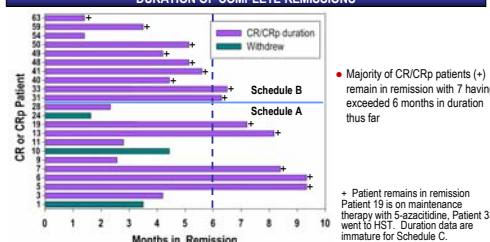
	Schedule A Days 1, 8, 15	Schedule B Days 1, 8	Schedule C (Days 1, 4) Preliminary
Patients enrolled and treated	29	35	28
CR	9*	7*	4#
CRp	3	3	2
Too early to evaluate	0	0	9
30-day all-cause mortality	17%	9%	9% (2 of 23)
Recovery from 1st induction dose:			
ANC > 1000 days (range)	38 (29-63)	60 (26-79)	32 (21-47)
Platelets > 100,000 days (range)	43 (34-64)	46 (21-79)	21 (20-27)
Survival > 6 months N (%)**	55%***	$\geq 52\%^{****}$	too early
Reinduced (N)	4	5	5
CR or CRp after reinduction (N)	2	3	too early
Consolidation cycle 1 (N)	8 of 12 CR/CRp	10 of 10 CR/CRp	too early
Consolidation cycle 2 (N)	0 of 12 CR/CRp	7 of 10 CR/CRp	too early

* 1 patient had blast clearance and full count recovery but confirmatory bone marrow was taken after receiving 5-azacitidine.
Patient qualified for CR by flow cytometry (52% blasts).
** Median survival has not been reached for any cohort.
*** 55% have survived > 7 months.
**** Fifteen patients survived > 6 months with an additional 6 surviving but who have been censored less than 6 months.

PATIENT AND RESPONSE CHARACTERISTICS (SCHEDULES A, B, and C)

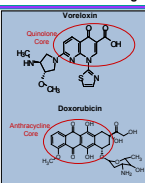
		All Patients (N=81)		CR + CRp	
		N	%	N	%
Age	≥ 70	56	69%	19	34%
	< 70	25	31%	9	36%
	ECOG 2	13	16%	5	38%
Performance Status	ECOG 0-1	69	85%	22	31%
	ECOG 0	21	26%	9	43%
	ECOG 1	46	57%	13	28%
Presence of AHD	Yes	29	36%	9	31%
	No	52	64%	19	37%
Cytogenetics	Int./Unf.	71	88%	23	32%
	Intermediate	25	31%	12	48%
	Unfavorable	46	57%	11	24%
Risk Factors #	Favorable	4	5%	1	25%
	N/A	6	7%	4	67%
	1	13	16%	6	46%
Risk Factors #	2	48	59%	15	33%
	3	16	20%	5	31%
	4	3	4%	1	33%

DURATION OF COMPLETE REMISSIONS



VORELOXIN ANTICANCER QUINOLONE DERIVATIVE (AQD)

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



Voreloxin intercalates DNA and inhibits topoisomerase II, causing site-specific DNA damage and apoptosis.

- Voreloxin-induced DNA damage analogous to quinolone antibiotics in bacterial cells
- Broad therapeutic index due to distribution to normal tissues
- Evades common drug resistance pathways of P-gp and MDR1
- Active in anthracycline-resistant settings
- Low potential for cardiomyopathy
- Low risk of CYP450-mediated drug-drug interaction

CONCLUSIONS

- Voreloxin, a first-in-class Anticancer Quinolone Derivative (AQD), demonstrates clinical activity in poor risk frontline elderly AML with multiple risk factors in the dose-optimization study, REVEAL-1.
- Three dose schedules are investigated: A: 72 mg/m² x 3, B: 72 mg/m² x 2, C: 72 mg/m² Days 1 and 4.
- Though 30-day all-cause mortality in A was acceptable relative to historical references, the tolerability profile supported dose regimen optimization.
- Tolerability was markedly improved with a 2 dose (B) vs 3 dose (A) schedule.
 - 30-day all-cause mortality decreased from 17% to 9% and Grade 3 or higher mucositis decreased from 31% to 11%.
 - Patients were able to receive more consolidation cycles on B
- ORR (CR + CRp) is 41% for A and 29% for B (6 CR + CRp observed thus far for C).
- Durable remissions (> 6 months) have been observed.
- > 50% of patients have survived > 6 months on A and B.
- Current results of REVEAL-1 suggest that voreloxin warrants development as a promising therapy for poor risk frontline elderly AML. A pivotal study is planned with the dose regimen identified in REVEAL-1.

http://www.sunesis.com/medications_and_publications