

# Voreloxin Single-Agent Treatment of Older Patients (≥ 60 Years) With Previously Untreated Acute Myeloid Leukemia: Results From a Phase 2 Study With 3 Schedules



RT Stuart<sup>1</sup>, F Ravandi<sup>2</sup>, LD Cripe<sup>3</sup>, MB Maris<sup>4</sup>, MA Cooper<sup>5</sup>, SR Dakhlil<sup>6</sup>, RM Stone<sup>7</sup>, F Turturro<sup>8</sup>, JA Fox<sup>9</sup>, G Michelson<sup>9</sup>

<sup>1</sup>Medical University of South Carolina, Charleston, SC; <sup>2</sup>Univ of Texas MD Anderson Cancer Center, Houston, TX; <sup>3</sup>Indiana University Cancer Center, Indianapolis, IN; <sup>4</sup>Rocky Mountain Blood and Marrow Transplant Program, Denver, CO; <sup>5</sup>St. Francis Hospital, Indianapolis, IN;

<sup>6</sup>Cancer Center of Kansas, Wichita, KS; <sup>7</sup>Dana Farber Cancer Institute, Boston, MA; <sup>8</sup>LSUHSC Feist Weiller Cancer Center, Shreveport, LA; <sup>9</sup>Sunesis Pharmaceuticals, Inc, South San Francisco, CA

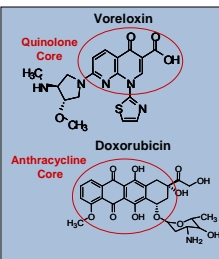
## ABSTRACT - UPDATED

**Background:** Voreloxin is a first-in-class anticancer quinolone derivative that intercalates DNA and inhibits topoisomerase II, inducing apoptosis. REVEAL-1, a phase 2 dose regimen optimization study of 3 schedules of single-agent voreloxin, was conducted in patients age ≥ 60 with newly diagnosed acute myeloid leukemia (AML) and ≥ 1 additional adverse risk factor (age ≥ 70, secondary AML, intermediate or unfavorable cytogenetics, or PS ≥ 2). These patients were thought to be unlikely to benefit from standard induction therapy. However, recent publications (Lewenberg 2009, Juissoum 2009) and NCCN 2010 guidelines indicate that many patients age ≥ 60 are eligible for conventional therapies. Response and safety results of REVEAL-1 are presented for each cohort (N = 113).

**Methods:** Three voreloxin schedules were studied: A 72 mg/m<sup>2</sup> qw x 3, N = 29 or B 72 mg/m<sup>2</sup> qw x 2, N = 35 or C 72 mg/m<sup>2</sup> on d1, 4, N = 29 or C 90 mg/m<sup>2</sup> on d1, 4, N = 20. Eligibility: newly diagnosed AML (de novo or secondary), patients age ≥ 60 with ≥ 1 additional adverse risk factor. Patients were allowed up to 2 cycles of induction and up to 2 additional cycles for consolidation (4 cycles total). Plasma and urine PK was evaluated in a patient subset in cycle 1. **Results:** Schedule A was established in a phase 1 study in relapsed/refractory leukemia patients (Proc ASH 2007), and showed good activity but was less well-tolerated in this older, newly diagnosed population. Across all cohorts, most patients were male (65%) with a median age of 74 (70% were ≥ 70), 82% had ECOG PS 0-1, and 30% had AML from AHD such as MDS. Most patients had intermediate (46%) or unfavorable (42%) cytogenetics; 82% had 2 or more risk factors. Schedule was optimized in successive cohorts, after real-time review, to improve tolerability and maintain efficacy after review of schedule A data indicated good activity but excessive toxicity (Proc ASH 2009). The 2-dose schedules, B and C72, maintained activity with improved tolerability, with cohort C72 demonstrating the best overall outcome with 38% ORR, ANC recovery at 30 days, median OS of 7.7 months, 1 year survival of ~38%, and 30- and 60-day all-cause mortality of 7% and 17%, respectively. Overall incidence of adverse events (AE) and serious adverse events (SAE) of infections and mucositis was reduced in B and C72. Voreloxin PK was similar to PK in the phase 1 study and in an ongoing phase 2 study in combination with cytarabine, and voreloxin clearance is nonrenal with < 5% of total dose recovered in urine (Proc ASH 2007 and 2009). **Conclusions:** In REVEAL-1, voreloxin demonstrated clinical activity in older patients with AML and multiple risk factors. C72 d1, 4 is appropriate for further development based on ORR (38%), good median OS of 7.7 months, 30- and 60-day all-cause mortality (7% and 17%, respectively) and an improved safety profile with lower rates of AE and SAE of infection and mucositis than for A. Further studies are planned for voreloxin administered on a days 1 and 4 schedule as a single agent as well as in combination with cytarabine and other agents. A multinational, randomized, double-blind, placebo-controlled, pivotal phase 3 study of voreloxin or placebo in combination with cytarabine in relapsed or refractory AML is planned.

## VORELOXIN: AN ANTICANCER QUINOLONE DERIVATIVE (AQD) (PLAS ONE, 2010)

- Novel, stable scaffold offers advantages over anthracyclines
- Intercalates DNA and inhibits topoisomerase II
- Evades common drug resistance mechanisms
  - Not a P-glycoprotein substrate
  - Activity unaffected by p53, p63 or p73 status
- Unlike anthracyclines, does not produce in vitro substantial reactive oxygen species implicated in cardiotoxicity



## STUDY DESIGN

Population	Previously untreated patients with AML 60 years or older with one or more risk factors:
	<ul style="list-style-type: none"> <li>• Age ≥ 70 years</li> <li>• AHD (t-AML allowed)</li> <li>• ECOG PS 2</li> <li>• Intermediate or unfavorable cytogenetics</li> </ul>
Design	Single arm, sequential groups
Endpoints	Overall remission rate (CR + CRp) per IWG criteria Safety, early mortality, PK, leukemia-free survival

## DOSE AND SCHEDULE OPTIMIZATION

Schedule	Dose	Rationale
A: d1, 8, 15	72 mg/m <sup>2</sup>	<ul style="list-style-type: none"> <li>• Dose regimen identified in phase 1 in relapsed/refractory AML</li> </ul>
B: d1, 8	72 mg/m <sup>2</sup>	<ul style="list-style-type: none"> <li>• Implemented to reduce duration of myelosuppression seen in A</li> <li>• More closely aligned with AML treatment paradigm</li> </ul>
C: d1, 4	72 mg/m <sup>2</sup>	<ul style="list-style-type: none"> <li>• Explore if more intensive dose schedule maintained improved safety of B</li> <li>• Aligned with voreloxin/cytarabine combination schedule</li> </ul>
C: d1, 4	90 mg/m <sup>2</sup>	<ul style="list-style-type: none"> <li>• Safety at 72 mg/m<sup>2</sup> supported escalation to explore therapeutic window</li> <li>• Aligned with voreloxin/cytarabine combination dose</li> </ul>

## DEMOGRAPHICS

Schedule and Dose mg/m <sup>2</sup>	A72 d1, 8, 15	B72 d1, 8	C72 d1, 4	C90 d1, 4	All
N	29	36	30	22	117
Male	66%	67%	50%	82%	65%
Median age (range)	75 (61-89)	74 (64-87)	71 (61-84)	77 (62-88)	74 (61-89)
≥ 70 years	76%	75%	50%	80%	70%
ECOG PS 0-1	86%	86%	70%	81%	82%
ECOG PS 2	14%	14%	30%	19%	18%
AHD	38%	28%	23%	30%	30%

## BASELINE CHARACTERISTICS

Schedule and Dose mg/m <sup>2</sup>	A72 d1, 8, 15	B72 d1, 8	C72 d1, 4	C90 d1, 4	All	
N	29	36	30	22	117	
Cytogenetics	Favorable	0%	6%	7%	0%	4%
	Intermediate	52%	37%	45%	55%	46%
	Unfavorable	41%	46%	48%	30%	42%
NCCN 2010	Not available	7%	11%	0%	15%	8%
	0	0%	3%	0%	0%	1%
	1	10%	17%	24%	10%	16%
Risk Factors	≥ 2	90%	80%	76%	85%	82%

## NONHEMATOLOGIC GRADE 3 OR HIGHER ADVERSE EVENTS ≥ 15%

• Grade 3 and Higher AEs generally decreased in other schedules relative to Schedule A

Schedule and Dose mg/m <sup>2</sup>	A72 d1, 8, 15	B72 d1, 8	C72 d1, 4	C90 d1, 4
N	29	35	29	20
Febrile neutropenia	35%	60%	52%	45%
Upper GI mucositis*	31%	14%	28%	15%
Pneumonia*	31%	34%	28%	15%
Sepsis/bacteremia*	52%	34%	21%	40%
Infections*	21%	6%	7%	15%
Fatigue	17%	20%	7%	5%
Hypokalemia	41%	20%	21%	5%
Anorexia	28%	9%	10%	0%
Hypophosphatemia	21%	3%	7%	10%
Dyspnea	24%	9%	3%	0%
Hypotension	17%	3%	0%	5%

\*Includes multiple preferred terms.

## COMPLETE REMISSIONS ACROSS VORELOXIN DOSE REGIMENS

Schedule and Dose mg/m <sup>2</sup>	A72 d1, 8, 15	B72 d1, 8	C72 d1, 4	C90 d1, 4
N	29	35	29	20
CR + CRp %	41%	29%	38%	25%
CR (CRp) No.	9 (3)	7 (3)	9 (2)	5 (0)
Hematologic recovery, days				
ANC > 1000/μL (range)	35 (29-70)	34 (22-60)	30 (20-43)	27 (21-28)
Pits > 100,000/μL (range)	43 (34-81)	27 (20-145)	26 (7-50)	24 (21-27)

## OVERALL SURVIVAL AND EARLY MORTALITY ACROSS VORELOXIN DOSE REGIMENS

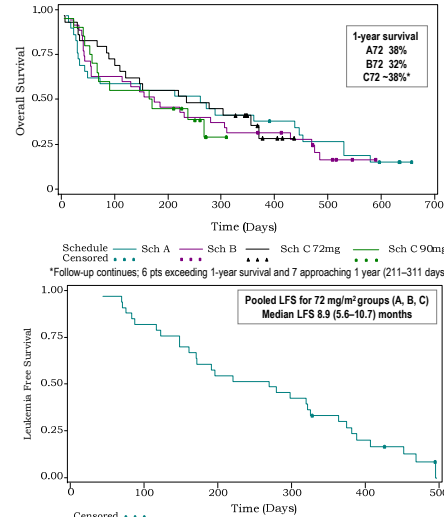
Schedule and Dose mg/m <sup>2</sup>	A72 d1, 8, 15	B72 d1, 8	C72 d1, 4	C90 d1, 4
N	29	35	29	20
Median overall survival months (95% CI)	8.6 (1.5, 14.7)	5.7 (1.9, 10.2)	7.7 (3.6, 12.2)	5.5 (1.91, nr)
1-Year survival %	38%	32%	~38%*	TETE
30-day all-cause mortality	17%	9%	7%	10%
60-day all-cause mortality	38%	37%	17%	30%

nr is not reached; TETE is too early to evaluate.

\*Follow-up continues; 6 pts exceeding 1-year survival and 7 approaching 1 year (211-311 days).

[http://www.sunesis.com/products-in-development/presentations\\_and\\_publications.php](http://www.sunesis.com/products-in-development/presentations_and_publications.php)

## KAPLAN-MEIER CURVES FOR OVERALL SURVIVAL AND LEUKEMIA FREE SURVIVAL (LFS)



## CONCLUSIONS

- Voreloxin demonstrated favorable clinical activity in older patients (≥ 60 years) with one or more additional risk factors
- The recommended single-agent dose regimen of voreloxin in this population is 72 mg/m<sup>2</sup> on days 1, 4 based on safety and activity
  - 38% ORR with median overall survival of 7.7 months
  - ~38% 1-year survival with patients remaining in follow-up
  - Improved safety profile relative to schedule A
  - Low 30-day and 60-day all-cause mortality
    - Decreased rate of infections
    - Manageable adverse events
    - More rapid hematologic recovery
- Voreloxin day 1 and 4 schedule aligns with dose regimen for voreloxin in combination with cytarabine in patients with relapsed or refractory AML
  - Voreloxin 90 mg/m<sup>2</sup> administered day 1 and 4 in combination with 1 g/m<sup>2</sup>/day cytarabine 2-hour IV infusion daily for 5 days
- Continued development of voreloxin is planned in older patients with previously untreated AML, and in combination with cytarabine in relapsed or refractory AML (Abstract No. 6526)

This poster and poster no. 6526, board no. 18 (voreloxin in combination with cytarabine in relapsed or refractory AML) will be discussed: RM E354a 5 - 6PM.