

A PHASE 2 DOSE REGIMEN OPTIMIZATION STUDY OF THREE SCHEDULES OF VORELOXIN AS SINGLE AGENT THERAPY FOR ELDERLY PATIENTS WITH NEWLY DIAGNOSED ACUTE MYELOID LEUKEMIA



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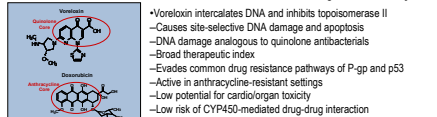
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ABSTRACT - UPDATED

Background: Voreloxin is a first-in-class anticancer quinolone derivative (AQD) 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 newly diagnosed acute myeloid leukemia (AML) patients age ≥ 60 with ≥ 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 (Lowenberg 2009, Juliusson 2009 and NCCN 2010 guidelines indicate that many patients age ≥ 60 are eligible for conventional therapies. Patients age ≥ 75, the vast majority of whom present with at least 1 additional risk factor at diagnosis, are identified as a population with poor outcome to standard treatment by NCCN 2010 AML guidelines as well as in Kantarjian 2006. Preliminary results of REVEAL-1 are presented for each cohort (N=113), as well as results for patients age ≥ 75 (N=49). **Methods:** Phase 2 study of 3 voreloxin schedules: A: 72 mg/m² qw x 3, N=29 or B: 72 mg/m² qw x 2, N=35 or C: 72 mg/m² on D1,4, N=29 or C: 90 mg/m² D1, 4, N=20. **Eligibility:** newly diagnosed AML (de novo or secondary AML), patients age ≥ 60 with ≥ 1 additional adverse risk factor. PK were evaluated in a patient subset in cycle 1. **Results:** A was established in a phase 1 study in relapse/refractory leukemia patients (Lancet et al. Proc ASH 2007), and showed good activity but was less well-tolerated in this frontline elderly population. The 2 dose schedules, B and C, maintained activity with improved tolerability. Overall incidence of infections and mucositis were reduced in B and C. Voreloxin PK were similar to those in the earlier Phase 1 (Lancet et al. Proc ASH 2007). **Conclusions:** In REVEAL-1, voreloxin demonstrates clinical activity with durable CR + CRp observed with 3 dosing schedules in previously untreated elderly (age ≥ 60) AML patients with one or more additional risk factors. ORR (CR + CRp) across 4 dose groups was 34%; the majority (79%) were CR and achieved with 1 cycle (74%). Reinfection resulted in CR(p) in 35% of reinduced patients. Twenty-five of 38 CR + CRp patients are alive, 13 of whom have survived for a year or more thus far. One year survival for A is 38%, all other schedules are too early to evaluate. C D1,4 is appropriate for further development based on ORR (38%), 30 and 60 day all-cause mortality (6% and 16%, respectively) and an improved safety profile with lower rates of infection than for A. In C patients age ≥ 75, unlikely to benefit from standard induction regimens by NCCN 2010 guidelines, ORR was 30% with low 30-day (5%) all-cause mortality.

VORELOXIN ANTICANCER QUINOLONE DERIVATIVE (AQD)

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



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: 1) Age ≥ 70 2) AHD 3) ECOG PS-2-4) Intermediate or unfavorable cytogenetics
Voreloxin Regimen	72 mg/m ² : Schedule A: qw x 3; Schedule B: qw x2; Schedule C: D1, 4; 90 mg/m ² : Schedule C D1, 4
Other Inclusion Criteria	Written informed consent; adequate hepatic, renal and cardiac function
Major Exclusion Criteria	Acute promyelocytic leukemia; CNS involvement, prior treatment for AML; history or recent myocardial infarction or thromboembolic events.
Treatment Paradigm	Up to 4 cycles: induction, reinduction and 2 consolidation cycles allowed.
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

Sch – Voreloxin Dose mg/m ²	Sch A - 72 D1, 8, 15	Sch B - 72 D1, 8	Sch C - 72 D1, 4	Sch C - 90 D1, 4	All	
N Enrolled	29	36	30	22	117	
Male	66%	67%	50%	82%	65%	
Median Age years (Range)	75 (61-89)	75 (64-87)	69 (61-84)	78 (62-88)	74 (61-89)	
≥ 70 years	76%	75%	50%	80%	70%	
ECOG PS 0 – 1	86%	86%	70%	85%	82%	
ECOG PS 2	14%	14%	30%	15%	18%	
AHD	38%	28%	23%	30%	30%	
Cyto-genetics by NCCN 2010 guidelines	Favorable	0%	6%	7%	0%	4%
	Intermediate	52%	37%	45%	55%	46%
	Unfavorable	41%	46%	48%	30%	42%
	Not available	7%	11%	1%	15%	8%
Risk Factors	0	0%	3%	0%	5%	2%
	1	10%	17%	24%	10%	16%
	2	59%	60%	59%	60%	59%
	3	31%	14%	17%	20%	20%
4	0%	6%	0%	5%	3%	

• Majority of patients were AML FAB types M1,M2 or M4.

NON-HEMATOLOGIC GRADE 3 OR HIGHER AEs ≥ 10%

Sch-voreloxin dose mg/m ²	Sch A - 72 D1, 8, 15	Sch B - 72 D1, 8	Sch C - 72 D1, 4	Sch C - 90 D1, 4
N	29	35	29	21
Febriile Neutropenia	38%	60%	52%	38%
Upper GI Mucositis	31%	14%	21%	5%
Lower GI Mucositis	10%	6%	0%	5%
Pneumonia	31%	34%	28%	14%
Sepsis/bacteremia	45%	31%	17%	14%
Infections	28%	9%	14%	10%
Fatigue	17%	20%	7%	10%
Oedema Peripheral	10%	3%	3%	0%
Hypokalemia	41%	20%	17%	5%
Anorexia	24%	9%	10%	0%
Hypophosphatemia	21%	3%	7%	10%
Hyperglycemia	10%	6%	7%	5%
Hypocalcemia	14%	6%	3%	5%
Dehydration	14%	0%	0%	5%
Confusional State	14%	0%	7%	0%
Dyspnea	24%	9%	14%	0%
Hypotension	14%	3%	0%	5%

OUTCOME - OVERALL

Sch – Voreloxin Dose mg/m ²	Sch A - 72 D1, 8, 15	Sch B - 72 D1, 8	Sch C - 72 D1, 4	Sch C - 90 D1, 4
N Treated	29	35	29	20
CR + CRp %	41%	29%	38%	25%
CR (CRp) No.	9(3)	7(3)	9(2)	5(0)
Remission Duration (95% CI) months	10.7 (2.5, N/A)	N/A	N/A	N/A
Reinduction (CR) No.	4(2)	8(3)	10(5)	6(0)
Consolidation 1 (2) No.	9(1)	9(8)	9(7)	3(2) to date
Days to ANC > 1000 (range)	35(29,70)	34(22,60)	30(20,43)	27(26,27)
Days to plds > 3000 (range)	43(34,81)	27(20,145)	26(7,50)	27(26,27)
30-day all-cause mortality	17%	9%	7%	10%
60-day all-cause mortality	38%	37%	17%	30%
Median OS (95% CI) months	8.7 (1.5, 15)	5.8 (1.9, 10)	Preliminary 7.3 (3.4, N/A)	TETE

*1 patient had blast clearance and full count recovery but confirmatory bone marrow was taken after receiving 5-azacitidine.
*2 Patients qualified for CR by flow cytometry and/or investigator assessment. N/A=not achieved.

CHARACTERISTICS OF COMPLETE REMISSIONS

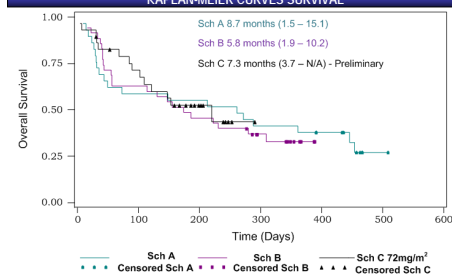
N (%) CR + CRp of Total Patients in Each Risk Category					
Sch – Voreloxin Dose mg/m ²	Sch A - 72 D1, 8, 15	Sch B - 72 D1, 8	Sch C - 72 D1, 4	Sch C - 90 D1, 4	
Age ≥ 70	8 (36%)	9 (33%)	5 (33%)	5 (31%)	
ECOG 2	2 (50%)	1 (25%)	4 (44%)	N/A	
Presence of AHD	5 (45%)	2 (20%)	1 (14%)	1 (17%)	
Cyto. by NCCN 2010	Intermediate	6 (43%)	5 (45%)	4 (40%)	3 (33%)
	Unfavorable	3 (25%)	4 (25%)	3 (21%)	1 (13%)
% of CR + CRp with Risk Factors 1 - 4					
	1	17%	20%	55%	0%
	2	58%	60%	36%	60%
	3	25%	10%	9%	20%
	4	0%	10%	0%	0%

COMPLETE REMISSIONS IN PATIENTS AGE ≥ 75

Sch – Voreloxin Dose mg/m ²	Sch A - 72 D1, 8, 15	Sch B - 72 D1, 8	Sch C - 72 D1, 4	Sch C - 90 D1, 4	
Age ≥ 75 N	13	16	7	13	
ECOG 2 N (%)	1 (8%)	4 (25%)	1 (14%)	2 (15%)	
Presence of AHD N (%)	4 (31%)	4 (25%)	2 (29%)	4 (31%)	
Cyto. by NCCN 2010	Intermediate N (%)	7 (54%)	6 (38%)	1 (14%)	10 (77%)
	Unfavorable N (%)	5 (38%)	9 (56%)	6 (86%)	3 (23%)
CR + CRp N (%)	4 (31%)	3 (19%)	2 (29%)	4 (31%)	
30-day all-cause mortality (%)	3 (23%)	3 (19%)	0 (0%)	1 (8%)	
60-day all-cause mortality (%)	8 (62%)	9 (56%)	2 (29%)	2 (15%)	

• Complete remissions (30%) with acceptable toxicity (5% 30-day all-cause mortality observed with Schedule C D1, 4 in this difficult to treat patient population. 12 of 13 patients who achieved CR or CRp remain alive.

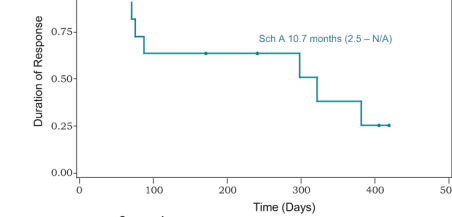
KAPLAN-MEIER CURVES SURVIVAL



Legend: Sch A 8.7 months (1.5 – 15.1), Sch B 5.8 months (1.9 – 10.2), Sch C 7.3 months (3.7 – N/A) - Preliminary

Legend: Censored - alive at time of last follow-up; Data for Schedule C D1,4 90 mg/m² are too early for evaluation.

KAPLAN-MEIER CURVES: DURATION OF COMPLETE REMISSION



Legend: Censored - in remission at time of last follow-up; or at time of subsequent therapy or if died before relapse; Median duration of remission has not been reached for Schedules B and C

CONCLUSIONS

- Voreloxin, a first-in-class Anticancer Quinolone Derivative (AQD), induces durable complete remissions in poor risk frontline elderly AML, with multiple risk factors in REVEAL-1.
 - ORR (CR + CRp) across 4 dose groups was 34%
 - 79% were CR and 47% were achieved with 1 cycle of voreloxin
 - Reinduction resulted in CR or CRp in 35% of reinduced patients
 - Median duration of remission is 10.7 months for Schedule A and has not yet been not achieved for other cohorts
 - Median OS is 8.7 months and 5.8 months for Schedules A and B, preliminary OS is currently 7.3 months for Schedule C
 - One year survival for Schedule A is 38%, all other schedules are too early to evaluate.
- Schedule C D1,4 72 mg/m² is appropriate for further development based on ORR, low 30- and 60-day all cause mortality and tolerability profile
- Voreloxin shows a promising activity and safety profile in patients age ≥ 75 with additional risk factor with Schedule C: CR rate 30%, 30-day all cause mortality 5%. Survival is too early to evaluate in this patient subgroup.
- Voreloxin in combination with cytarabine is being evaluated in a Phase 1b/2 study in relapsed or refractory AML.
 - Monday Dec. 7: Abstract #635; 4:30-5:30 PM session, Presentation Time 5:30 PM, Conv. CR #m 343-345.