Baseline Predictors of Mortality in Patients With Relapsed or Refractory AML Treated With Vosaroxin Plus Cytarabine or Placebo Plus Cytarabine in the Phase 3 VALOR Study

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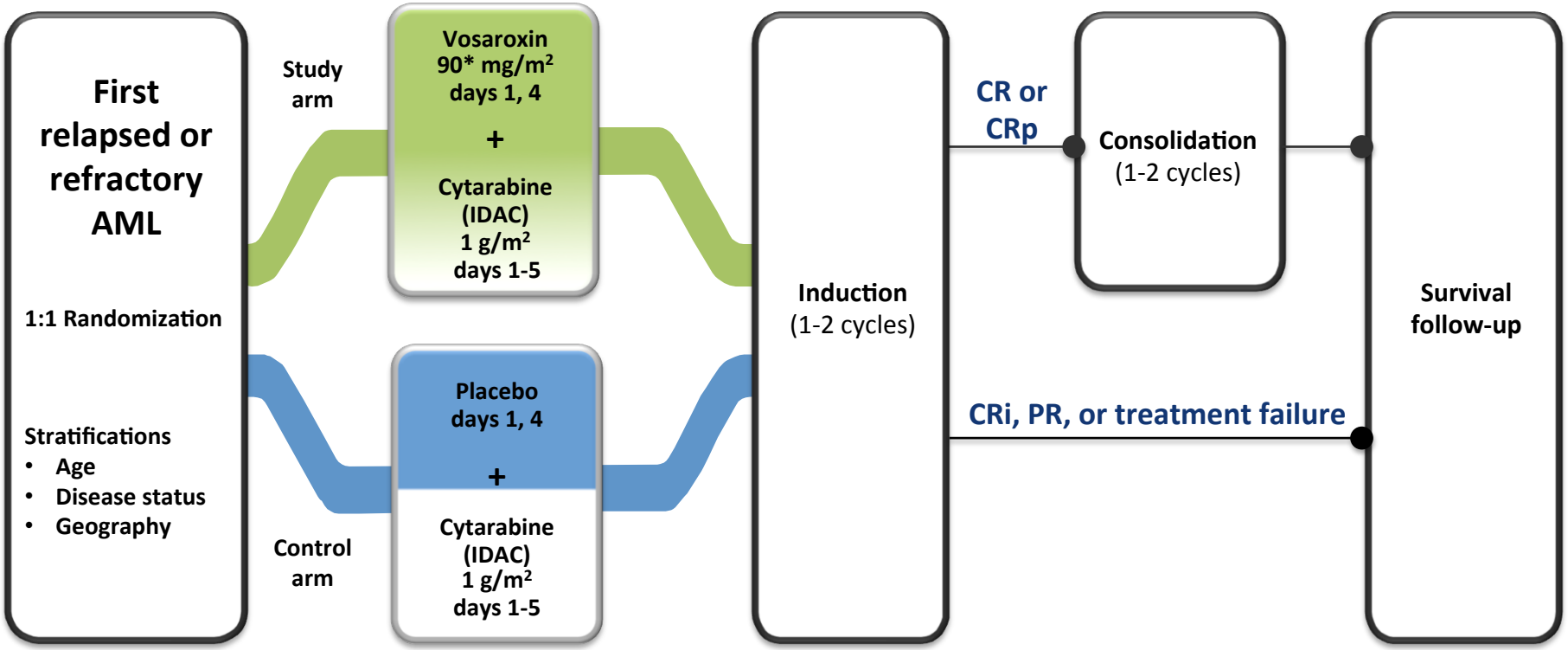
Vosaroxin Background

- First-in-class anticancer quinolone derivative (AQD)
- Intercalates DNA and inhibits topoisomerase II[1]
- Due to its stable quinolone core, vosaroxin is not associated with significant formation of toxic metabolites, free radicals, or reactive oxygen species, which are associated with off-target organ damage and cardiotoxicity[2]
- Not a substrate for P glycoprotein receptor–mediated efflux, and has activity independent of p53 status, thus evading two common mechanisms of drug resistance[1,3]

References: 1. Evanchik MJ et al. *Drug Metab Dispos*. 2009;37:594-601. 2. Hawtin RE, et al. *PLoS One*. 2010;5:e10186.
3. Walsby EJ. *Haematologica*. 2011;96:393-399.

VALOR Study Design
Phase 3 randomized, double-blind, placebo-controlled



*After cycle 1; all subsequent cycles at 70 mg/m^2 vosaroxin on days 1 and 4

Endpoints

- Primary – Overall survival (OS), 30- and 60-day mortality
- Secondary – CR, safety, tolerability
- Tertiary – CR+CRp+CRi, EFS, LFS, transplant rate

AML, acute myeloid leukemia; CR, complete remission; CRi, CR without immunologic recovery; CRp without platelet recovery; EFS, event-free survival; IDAC, intermediate-dose Ara-c; LFS, leukemia-free survival; PR, partial remission.

Reference: Ravandi F et al. *Lancet Oncol*. 2015;16:1025-1036.

VALOR Topline Results

- In VALOR, 30-day mortality was comparable between treatment arms

	Vosaroxin/ Cytarabine		Placebo/ Cytarabine
Efficacy endpoints (intent-to-treat population, n = 711)			
Median OS	7.5 months		6.1 months
Hazard ratio		0.87	
P value		0.0610	
CR rate	30.1%		16.3%
P value		<0.0001	
Safety endpoints (safety population, n = 705)			
30-day all-cause mortality	7.9%		6.6%
60-day all-cause mortality	19.7%		19.4%

Reference: Ravandi F et al. *Lancet Oncol*. 2015;16:1025-1036.

VALOR Post Hoc Analysis: Objective and Methods

Objective

- To identify relapsed/refractory acute myeloid leukemia (AML) patients at higher risk of early mortality with intensive therapy in VALOR

Methods

- A post hoc analysis was performed to assess whether the simplified treatment-related mortality (TRM) score[1] could identify VALOR patients at higher risk of 30-day mortality
  - Simplified TRM scores were retrospectively calculated, according to Walter 2011[1]
  - 30-day mortality by TRM category was summarized and odds ratios calculated
  - Univariate analysis each component of the TRM score was also performed

Reference: 1. Walter RB et al. 2011, *J Clin Oncol* 29:4417-4424.

Background: Simplified TRM Score (Walter et al 2011)

- The simplified TRM score is a prognostic scoring system that predicts risk of 30-day mortality with intensive treatment
- Developed in 3365 newly diagnosed AML patients
- Includes 8 co-variates, each independently predictive of early mortality
- Model yielded a predictive value (AUC) of 0.82

Simplified TRM Model Co-variates
Secondary AML (yes/no)
Age
Performance status
Platelet count
Serum albumin
WBC count
Peripheral blast percentage
Serum creatinine

AUC, area under the curve; WBC, white blood cell.

Reference: Walter RB et al. 2011, *J Clin Oncol* 29:4417-4424.

Relationship Between TRM Score and Probability of Early Mortality in Newly Diagnosed AML (Walter et al 2011)

- In newly diagnosed AML patients, 70% had a score ≤ 9.2
- Patients with higher scores had higher risk of 30-day mortality

Simplified TRM Score Category	Proportion of Patients Within TRM Category	30-day Mortality Probability Within TRM Category
0-1.9	20	1
1.91-3.9	20	2
3.91-6.9	20	7
6.91-9.2	10	7
9.21-13.1	10	12
13.11-22.8	10	20
22.81-100	10	41

Reference: Walter RB et al. 2011, *J Clin Oncol* 29:4417-4424.

Results: Baseline Simplified TRM Scores in VALOR

- A simplified TRM score could be calculated for 554/705 patients in the VALOR safety population
- Median simplified TRM score at baseline was balanced between treatment arms
- Most patients (87%) had a score ≤ 9.2

TRM Score	Vos/Cyt (n = 355)	Pla/Cyt (n = 350)	Total (N = 705)
TRM score available, n	285	269	554
TRM score missing, n	70	81	151
Median TRM score (range)	2.6 (0-21)	2.6 (0-33)	2.6 (0-33)
Score above 9.2, n (%)[a]	34 (12)	36 (13)	70 (13)

[a] Percent calculated based on number of patients with available TRM scores.

Cyt, cytarabine; Pla, placebo; Vos, vosaroxin.

Results: 30-day Mortality by Baseline TRM Score in VALOR

- The risk of 30-day mortality was increased in patients with simplified TRM scores above 9.2

Simplified TRM Score	Treatment	Patients, n (N=705)	30-day Mortality, n (%)[a]	Odds Ratio[b]
0-1.9	Vos/Cyt Pla/Cyt	118 113	2 (1.7) 1 (0.9)	Ref
1.91-3.9	Vos/Cyt Pla/Cyt	66 41	2 (3.0) 1 (2.4)	2.19
3.91-6.9	Vos/Cyt Pla/Cyt	52 65	5 (9.6) 5 (7.7)	7.1
6.91-9.2	Vos/Cyt Pla/Cyt	15 14	1 (6.7) 0	2.71
9.21-13.1	Vos/Cyt Pla/Cyt	23 17	5 (21.7) 4 (23.5)	22.06
13.11-22.8	Vos/Cyt Pla/Cyt	11 14	5 (45.5) 3 (21.4)	35.76
22.81-100	Vos/Cyt Pla/Cyt	0 5	0 2 (40.0)	50.67
Missing	Vos/Cyt Pla/Cyt	70 81	8 (11.4) 7 (8.6)	--

[a]Percent is calculated based on the number of patients in the same treatment arm and TRM score category.
[b]The odds ratio is calculated for all patients in that TRM score category (across both treatment arms) compared with the reference category.

Results: 30-day Mortality by Type of AML in VALOR

- Type of AML (secondary versus primary) is a component of the TRM score
- In univariate analysis, secondary AML was associated with increased risk of early mortality, although not statistically significant

Secondary AML	Treatment	Patients, n (N=705)	30-day mortality, n (%)[a]	Odds Ratio[b]	P Value[b]
No	Vos/Cyt	298	23 (7.7)	Ref	0.2375
	Pla/Cyt	284	16 (5.6)		
Yes	Vos/Cyt	57	5 (8.8)	1.51	
	Pla/Cyt	66	7 (10.6)		

[a]Percent is calculated based on the number of patients in the same treatment arm and type of AML category.
[b]The odds ratio is calculated for all patients in that type of AML category (across both treatment arms) compared with the reference category.

Results: 30-day Mortality in VALOR by Other TRM Components

- Several components of the simplified TRM score were associated with significant increased risk of 30-day mortality in univariate analysis
  - Age
  - Performance status
  - Serum albumin
  - WBC count
  - Platelet count

Results: 30-day Mortality in VALOR by TRM Components (Univariate Analysis)

	Treatment	Patients, n (N=705)	30-day mortality, n (%)[a]	Odds Ratio[b]	P Value[b]
Age					
< 65 years	Vos/Cyt Pla/Cyt	187 195	13 (7.0) 8 (4.1)	Ref	0.0476
65-69 years	Vos/Cyt Pla/Cyt	87 72	7 (8.0) 3 (4.2)	1.15	
70-74 years	Vos/Cyt Pla/Cyt	64 66	6 (9.4) 9 (13.6)	2.24	
≥ 75 years	Vos/Cyt Pla/Cyt	17 17	2 (11.8) 3 (17.6)	2.96	
Baseline ECOG Performance Status					
0-1	Vos/Cyt Pla/Cyt	314 302	18 (5.7) 17 (5.6)	Ref	< 0.0001
2	Vos/Cyt Pla/Cyt	39 46	10 (25.6) 6 (13.0)	3.85	
Missing	Vos/Cyt Pla/Cyt	2 2	0 0	--	

[a]Percent is calculated based on the number of patients in the same treatment arm and type of AML category.
[b]The odds ratio and P value are calculated for all patients in that type of AML category (across both treatment arms) compared with the reference category.

Results: 30-day Mortality in VALOR by TRM Components (Univariate Analysis, Cont'd)

	Treatment	Patients, n (N=705)	30-day mortality, n (%)[a]	Odds Ratio[b]	P Value[b]
Creatinine					
≤ 1.3 mg/dL	Vos/Cyt Pla/Cyt	335 335	25 (7.5) 22 (6.6)	Ref	0.3034
> 1.3 mg/dL	Vos/Cyt Pla/Cyt	19 15	3 (15.8) 1 (6.7)	1.77	
Missing	Vos/Cyt Pla/Cyt	1 0	0 0	--	
Albumin					
≤ 3.6 g/dL	Vos/Cyt Pla/Cyt	161 171	20 (12.4) 15 (8.8)	2.98	0.0015
> 3.6 g/dL	Vos/Cyt Pla/Cyt	165 150	5 (3.0) 7 (4.7)	Ref	
Missing	Vos/Cyt Pla/Cyt	29 29	3 (10.3) 1 (3.4)	--	

[a]Percent is calculated based on the number of patients in the same treatment arm and type of AML category.
[b]The odds ratio and P value are calculated for all patients in that type of AML category (across both treatment arms) compared with the reference category.

Results: 30-day Mortality in VALOR by TRM Components (Univariate Analysis , Cont'd)

	Treatment	Patients, n (N=705)	30-day mortality, n (%)[a]	Odds Ratio[b]	P Value[b]
WBC					
< 25 x10^9/L	Vos/Cyt Pla/Cyt	311 307	24 (7.7) 16 (5.2)	0.47	0.0379
≥ 25 x10^9/L	Vos/Cyt Pla/Cyt	43 43	4 (9.3) 7 (16.3)	Ref	
Missing	Vos/Cyt Pla/Cyt	1 0	0 0	--	
Platelet Count					
< 10 x10^9/L	Vos/Cyt Pla/Cyt	8 11	4 (50.0) 3 (27.3)	17.73	< 0.0001
10-100 x10^9/L	Vos/Cyt Pla/Cyt	264 264	19 (7.2) 20 (7.6)	2.42	
≥ 100 x10^9/L	Vos/Cyt Pla/Cyt	82 75	5 (6.1) 0	Ref	
Missing	Vos/Cyt Pla/Cyt	1 0	0 0	--	

[a]Percent is calculated based on the number of patients in the same treatment arm and type of AML category.
[b]The odds ratio and P value are calculated for all patients in that type of AML category (across both treatment arms) compared with the reference category.

Results: 30-day Mortality in VALOR by TRM Components (Univariate Analysis , Cont'd)

	Treatment	Patients, n (N=705)	30-day mortality, n (%)[a]	Odds Ratio[b]	P Value[b]
Peripheral Blasts					
< 1%	Vos/Cyt Pla/Cyt	106 83	7 (6.6) 2 (2.4)	Ref	0.6397
1-10%	Vos/Cyt Pla/Cyt	65 82	5 (7.7) 4 (4.9)	1.3	
≥ 10%	Vos/Cyt Pla/Cyt	131 129	8 (6.1) 10 (7.8)	1.49	
Missing	Vos/Cyt Pla/Cyt	53 56	8 (15.1) 7 (12.5)	--	

[a]Percent is calculated based on the number of patients in the same treatment arm and type of AML category.

[b]The odds ratio is calculated for all patients in that type of AML category (across both treatment arms) compared with the reference category.

Conclusions

- The previously validated TRM score for predicting early mortality in newly diagnosed AML also predicted mortality in relapsed/refractory patients in VALOR
- In future studies of vosaroxin and other intensive regimens, patient selection based upon these predictors of early mortality should be considered