Durable Overall Survival Benefit in Patients ≥ 60 Years With Relapsed or Refractory AML Treated With Vosaroxin/Cytarabine vs Placebo/Cytarabine: Updated Results From the VALOR Trial

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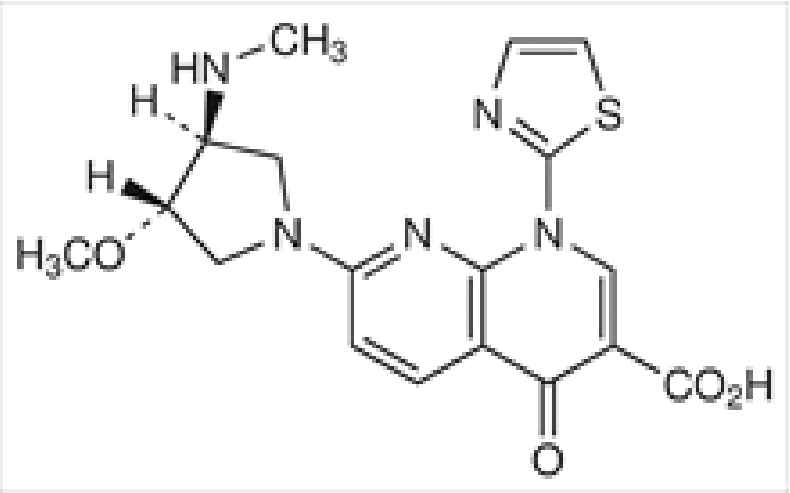
Presentation Overview

- Updated survival shows consistent durable vosaroxin/cytarabine benefit
- Additional sensitivity analyses confirm robustness of benefit in older patients
- Consistent survival benefit in age subgroups over 60

Vosaroxin: Background

- First-in-class anticancer quinolone derivative (AQD)
- Intercalates DNA and inhibits topoisomerase II[1]
- Stable quinolone core



  - No metabolites, free radicals, or reactive oxygen species[2]
  - Low likelihood for off-target organ damage and cardiotoxicity

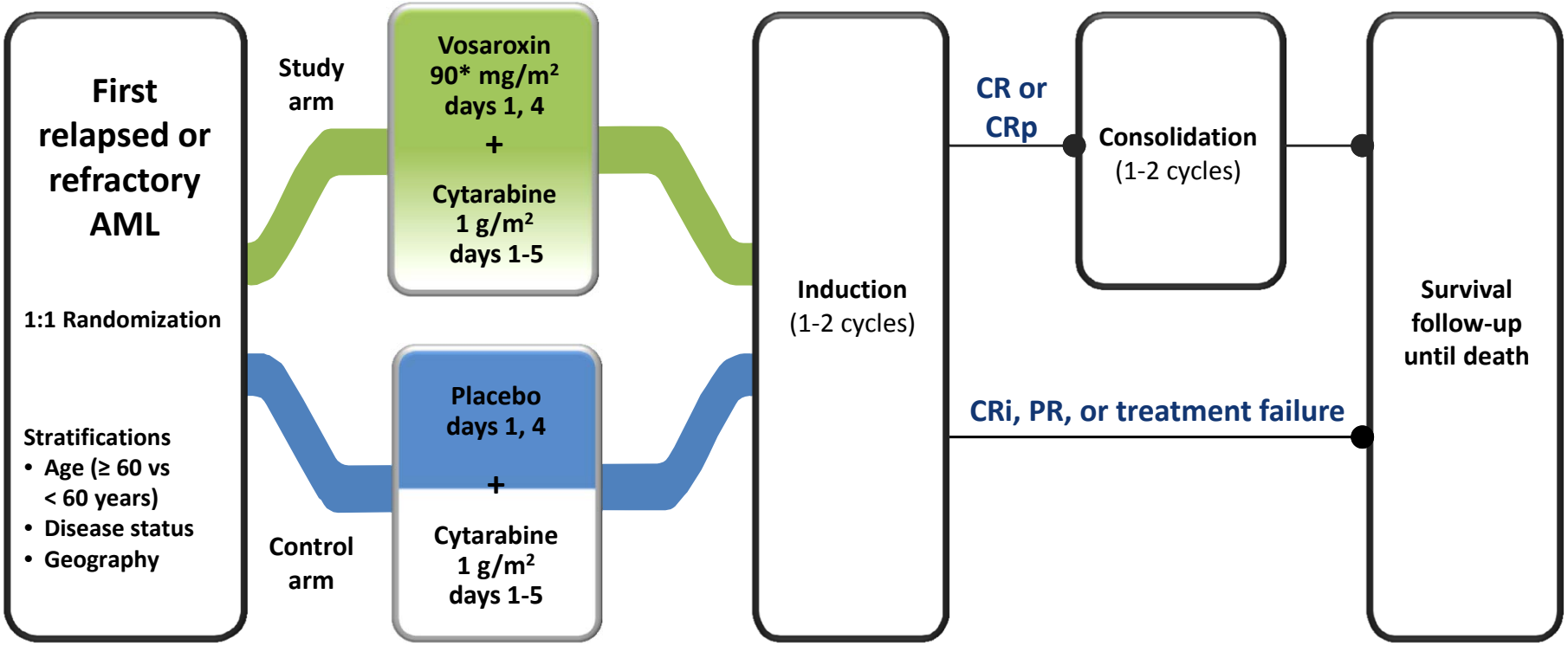
- Evades common mechanisms of drug resistance[1,3]:
  - Not a substrate for P glycoprotein
  - Activity independent of p53 status

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: Eligibility Criteria

- **Inclusion Criteria**
  - AML diagnosis by WHO criteria
  - ≥ 18 years
  - Refractory or first relapsed
    - Failure to achieve remission after up to 2 cycles of induction or CR1 duration < 90 days
    - Relapse ≥ 90 days to ≤ 24 months after first CR or CRp
  - **≤ 2 Cycles of induction (at least 1 cycle of cytarabine + anthracycline [or anthracenedione])**
  - ECOG Performance Status 0, 1, or 2
  - Adequate cardiac, renal and hepatic function
- **Exclusion Criteria**
  - Acute promyelocytic leukemia
  - **Completion of treatment containing ≥ 5 g/m^2 cytarabine within 90 days of randomization**
  - Allogeneic or autologous SCT within 90 days of randomization
  - Active immunosuppressive therapy for GVHD

VALOR: Study Design



*70 mg/m² vosaroxin on days 1, 4 in all subsequent cycles after cycle 1

Endpoints

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

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

Original Analysis: Patients ≥ 60 Years (N = 451)

- Prespecified analysis of OS and CR rates by age
- **OS and CR significantly improved with vosaroxin**

	Vosaroxin/ Cytarabine		Placebo/ Cytarabine
Efficacy endpoints (ITT population)	**n = 226**		**n = 225**
Median OS, months	7.1		5.0
(95% CI)	(5.8-8.1)		(3.8-6.4)
Hazard ratio		**0.75**	
P value		**0.003**	
CR rate, %	31.9		13.8
(95% CI)	(25.8-38.4)		(9.6-19.0)
P value		**< 0.0001**	
Safety endpoints (safety population)	**n = 226**		**n = 221**
30-day all-cause mortality, %	10.2		9.0
60-day all-cause mortality, %	20.4		22.6

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

Grade ≥ 3 Adverse Events

System Organ Class Preferred Term	Vosaroxin/Cytarabine (n = 226), n (%)	Placebo/Cytarabine (n = 221), n (%)
Any grade ≥ 3 AE	213 (94)	189 (86)
Blood and lymphatic system disorders		
Febrile neutropenia	96 (43)	67 (31)
Thrombocytopenia	55 (24)	56 (25)
Anemia	52 (23)	54 (24)
Neutropenia	42 (19)	31 (14)
Gastrointestinal disorders		
Stomatitis	**36 (16)**	**9 (4)**
Diarrhea	12 (5)	6 (3)
Infections and infestations		
Pneumonia	24 (11)	18 (8)
Sepsis	**28 (12)**	**13 (6)**
Bacteremia	21 (9)	9 (4)
Metabolism and nutrition disorders		
Hypokalemia	33 (15)	15 (7)
Hypophosphatemia	17 (8)	9 (4)
Decreased appetite	14 (6)	3 (1)
Vascular disorders		
Hypertension	15 (7)	10 (5)

Grade ≥ 3 events occurring in at least 5% of patients.

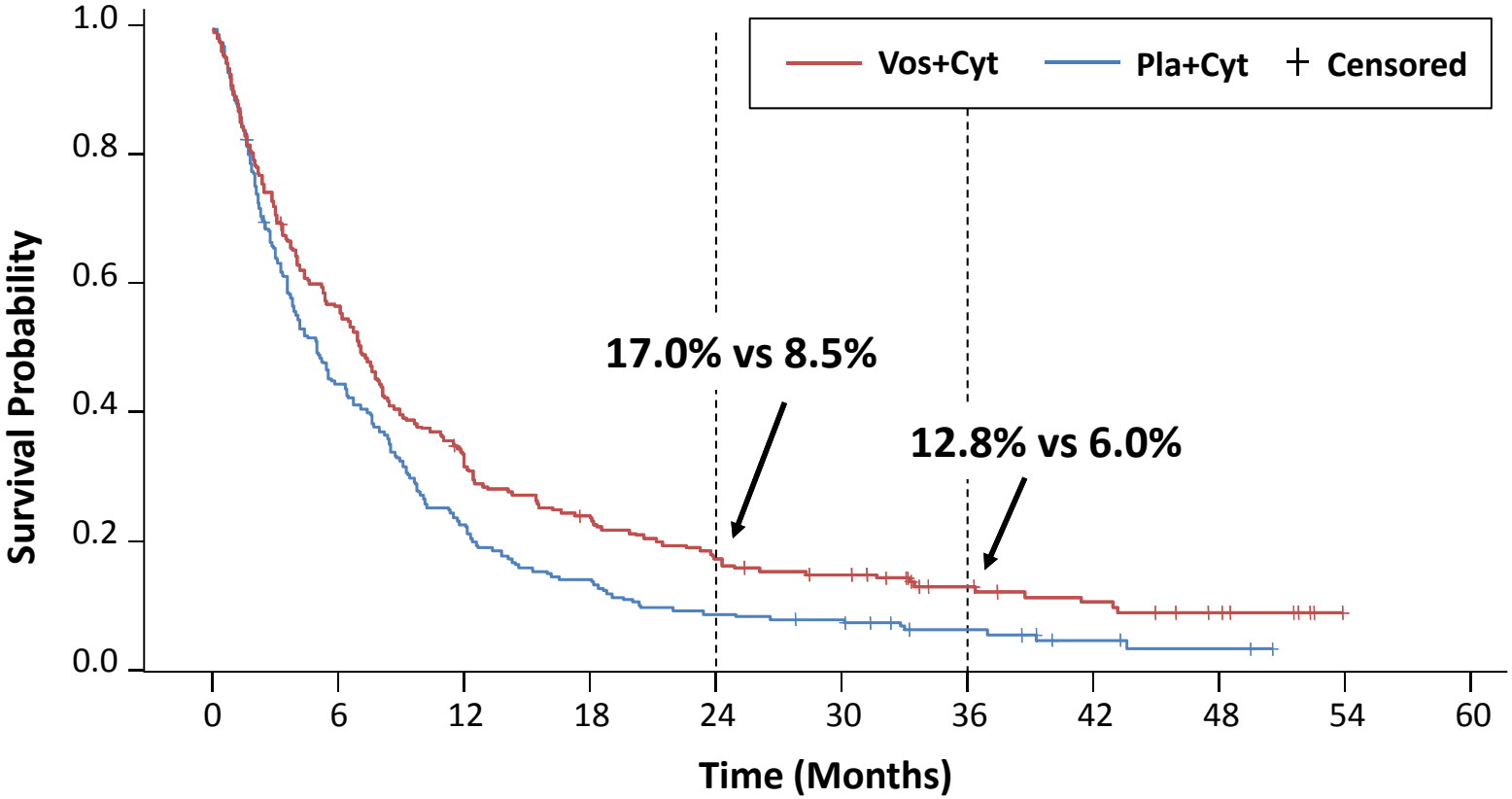
Updated OS Analysis

- Updated with 16 months longer follow-up
- Twice as many patients alive on vosaroxin arm

	Primary Analysis (September 2014)	Updated Survival Analysis (January 2016)
Median duration of follow-up, months[a]	24.4	**39.9**
Patients ≥ 60 years remaining in follow-up, n (%)		
All patients ≥ 60 years (N = 451)	63 (14)	33 (7)
Treated with vos/cyt (n = 226)	42 (19)	**23 (10)**
Treated with pla/cyt (n = 225)	21 (9)	**10 (4)**

[a] Estimated by the reverse Kaplan-Meier method.

Durable Separation of Survival Curves



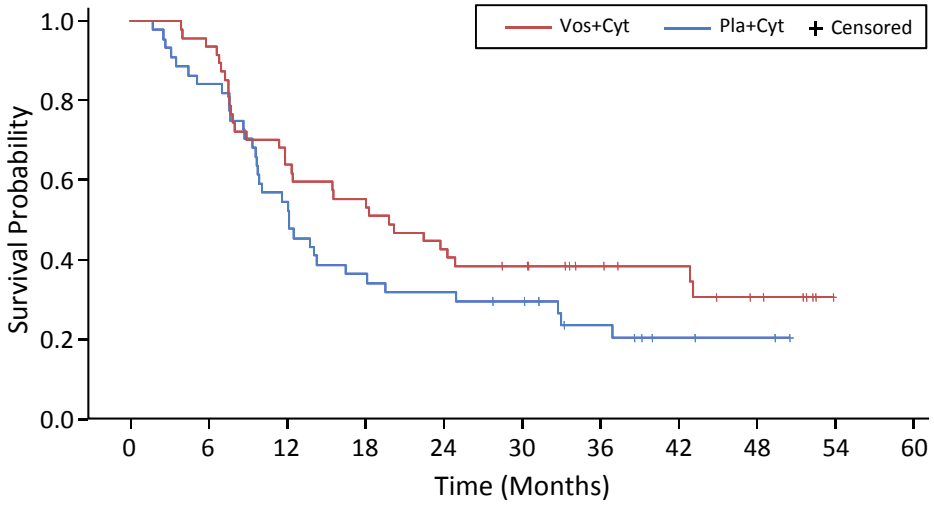
At Risk:										
Vos+Cyt	226	127	70	52	37	30	17	12	7	0
Pla+Cyt	225	99	50	31	19	16	9	4	2	0

Treatment arm	Patients, n	Median OS (95% CI)	HR (95% CI)	*P* value
Vos+Cyt	226	7.1 (5.8-8.1)	0.75 (0.62-0.91)	**0.002**
Pla+Cyt	225	5.0 (3.8-6.4)		

OS ± Post-Treatment Transplantation

- OS benefit demonstrated in both transplanted and non-transplanted patients

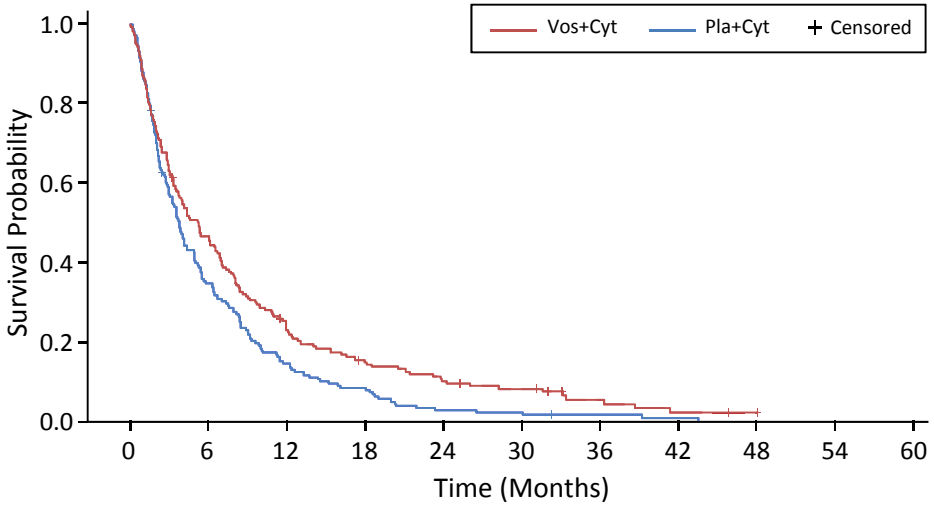
Patients ≥ 60 Years With Subsequent Transplantation (n = 91)



At Risk:										
Vos+Cyt	47	44	30	26	20	17	12	10	6	0
Pla+Cyt	44	37	24	16	14	12	7	3	2	0

HR = 0.70 (95% CI: 0.43-1.13)

Patients ≥ 60 Years Without Subsequent Transplantation (n = 360)



At Risk:										
Vos+Cyt	179	83	40	26	17	13	5	2	1	
Pla+Cyt	181	62	26	15	5	4	2	1	0	0

HR = 0.75 (95% CI: 0.60-0.92)

OS – IPCW Analysis

- Use crossover methodology to estimate treatment effect in the absence of transplant

IPCW Analysis	Patients ≥ 60 Years		
	HR for OS	95% CI	*P* value
Final model adjusted for baseline covariates	0.63	0.48-0.82	**< 0.001**

IPCW, inverse probability of censoring weights

Consistent OS Benefit in Age Subgroups

- OS benefit with the addition of vosaroxin was observed **in all age subsets above 60 years**

Patient Age	Median OS, months		HR (95% CI)
	Vosaroxin/ Cytarabine	Placebo/ Cytarabine	
60-64 years (n = 124)	8.1	5.2	**0.72 (0.49-1.06)**
65-74 years (n = 293)	7.0	5.0	**0.76 (0.60-0.97)**
75-84 years (n = 34)	5.5	3.3	**0.72 (0.36-1.45)**

Conclusions

- VALOR demonstrates continued durable survival benefit with vosaroxin/cytarabine in patients ≥ 60 years
- Sensitivity analyses in patients ≥ 60 years show a robust OS benefit
- Consistent OS benefit among all older patients, including those ≥ 75 years of age
- **These data support vosaroxin/cytarabine as a treatment option in patients ≥ 60 years of age with R/R AML**

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