VALOR, An Adaptive Design, Pivotal Phase 3 Trial Of Vosaroxin Or Placebo In Combination With Cytarabine In First Relapsed Or Refractory Acute Myeloid Leukemia

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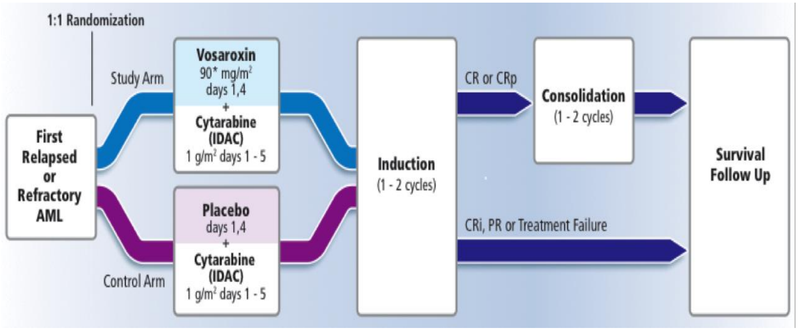
VALOR TRIAL DESIGN

VALOR (NCT01191801), a pivotal phase 3, randomized, controlled, double-blind trial, evaluates vosaroxin and cytarabine versus placebo and cytarabine in patients with first relapsed or refractory acute myeloid leukemia (AML) incorporating an adaptive design. The primary endpoint is overall survival (OS); secondary/tertiary endpoints include complete remission (CR) rates, safety, event free survival (EFS), leukemia free survival (LFS), and transplantation (HSCT) rate.

Figure 1. VALOR Trial Schema



*** After cycle 1, all subsequent cycles at 70 mg/m² vosaroxin on days 1 and 4**

Sample Size	450 evaluable patients
Population	First relapsed or refractory AML
Regimen	IDAC + vosaroxin vs. IDAC + placebo (double-blind)
Study Sites	>110 sites in Europe, North America, AUS/NZ
Interim Analysis	Single, pre-planned evaluation by DSMB
Adaptive Design	At interim analysis, DSMB can recommend adding 225 evaluable patients to the trial

Key Eligibility Criteria

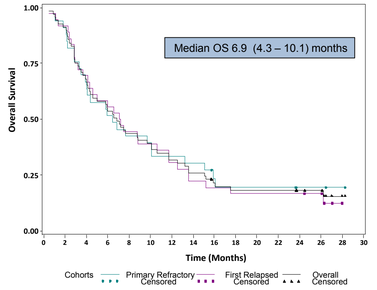
- At least 18 years old with an AML diagnosis by WHO classification
- First relapsed AML with first CR or CRp (CR1) duration of at least 90 days to 24 months OR refractory AML with persistent leukemia after 1 or 2 induction cycles or CR1 less than 90 days
- No more than 2 prior induction cycles that include at least 1 regimen of cytarabine with an anthracycline (or anthracenedione)
- Adequate cardiac, hepatic and renal function
- Refractory to or relapsed within the previous 3 months after therapy with an IDAC- or HIDAC-containing regimen

VALOR ADAPTIVE DESIGN

	Base Case:	Alternative Case:
Power	90% power to detect a 40% survival difference (5 vs. 7 mo.)	90% power to detect a 30% survival difference (5 vs. 6.5 mo.)
Hazard ratio and α	0.71 and 0.05 (2-sided)	0.77 and 0.05 (2-sided)
Resources needed	375 OS events from 450 evaluable patients	616 OS events from 708 evaluable patients
Enrollment	24 months with 6 months follow-up	30 months with 6 months follow-up

- Vosaroxin + cytarabine arm Base Case treatment effect is supported by phase 2 in first relapsed or primary refractory AML(N = 69)
  - Median OS 6.9 mo.
  - Combined CR rate 29% (CR rate 26%)
  - Median LFS (defined as time from CR to relapse or death) 24 mo.
  - 30 and 60 day all-cause mortality 3% and 9%, respectively
  - HSCT rate 26%
- Control arm median OS of 5 mo. is based on published IDAC-based regimens outcomes
- Alternative Case provided a scenario with smaller but meaningful treatment effect
  - Other scenarios adequately powered under VALOR adaptive study design

Figure 2. Phase 2 Kaplan-Meier Survival Curves

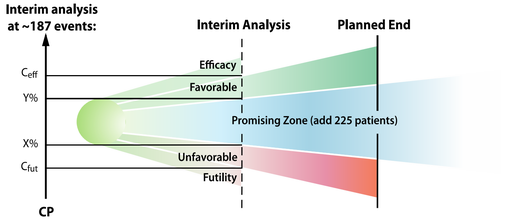


DSMB RECOMMENDATIONS BASED ON INTERIM RESULT

DSMB can recommend based on interim results to:

- Continue the trial to 450 evaluable patients (375 events)
- Adjust sample size to 675 evaluable patients (562 events)
- Stop early for efficacy (p<0.0015) or futility

Figure 3. Outcomes Based on Conditional Power at Interim



CP = Conditional power
The probability of success (statistical significance) at the end of the trial given current data trend

- Interim outcome partitioned into unfavorable, promising, and favorable zones according to observed treatment effect based on conditional power

VALOR RECOVERS POWER BY SAMPLE SIZE INCREASE IF IN PROMISING ZONE

True Hazard Ratio	Base Case Design 450 Patients, 375 Events	Adaptive Design 675 Patients, 562 Events
0.71	91%	98%
0.74	83%	96%
0.77	71%	90%
0.80	58%	84%

- VALOR's adaptive design gains substantial additional power over non-adaptive IF interim outcome falls in the Promising Zone

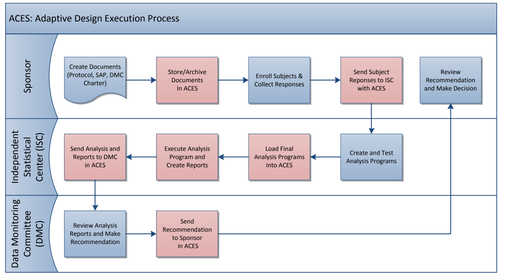
PROTECTING INTEGRITY OF ADAPTIVE DESIGN TRIAL

- Guidance documents by FDA and EMA for DSMB and Adaptive Trial Design:
  - Reference the importance of confidentiality of interim results
  - Suggest "A well-trusted firewall established for trial conduct … can help provide assurance that statistical and operational biases have not been introduced."
  - Requests an accurate recording of trial conduct and documentation – who saw what and when

ACCESS CONTROL EXECUTION SYSTEM (ACES)

- ACES is a secure, web-based system used during the interim analysis to:
  - Centrally store interim analysis reports, meeting agendas and minutes, and DSMB decisions
  - Assign team members to specific roles and grant explicit privileges to securely access data and information

Figure 4. Interim Analysis Process Using ACES



VALOR STATUS AND SUMMARY

- VALOR IS enrolling well with 317 patients as of May 14, 2012
  - On track to conduct pre-specified interim analysis in Q3 2012
  - DSMB recommended VALOR continue as planned after reviewing safety data in Dec 2011
- VALOR is a well-powered study designed to detect a clinically meaningful improvement in OS
  - DSMB may call for sample size increase only if interim result falls into Promising Zone
  - The adaptive design mitigates risk of initial over-investment, and risk of failing to detect a relevant survival benefit
  - This design satisfies both the statistical and operational requirements stipulated in FDA Draft Guidance and in EMA Reflection Paper on Adaptive Design Clinical Trials