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 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 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 and 70 mg/m² vosaroxin on days 1 and 4

Sample Size 450 evaluable patients
Population First relapsed or refractory AML
Regimen IDAC = Vosaroxin + cytarabine + idarubicin
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 1st CR or CRp1 (CR1) duration of at least 50 days to 24 months CR refractory AML with persistent leukemia after 1 or 2 induction cycles or CR1 less than 50 days
- No more than 2 prior induction cycles that include at least 1 regimen of cytarabine with an anthracycline (or anthracyclineconcurrent chemotherapy with or without additional agents)
- Adequate cardiac, hepatic and renal function
- Refractory to or relapsed within the previous 3 months after therapy with an IDAC- or HIDAC-containing regimen

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

ACES Analysis Interim Analysis Planned End

Interim analysis = <12 months Interim Analysis Planned End

OS (CFD - Conditional Failure Distribution) Median OS is 11.1 vs 8.8 months (p=0.0015). The optimal sample size is 375 events.

INTERIM OUTCOMES:
- Median OS: 11.1 months vs 8.8 months (p = 0.0015)
- OS at 1 year: 41% vs 36%
- Interim outcomes partitioned into unfavorable, promising, and favorable zones according to observed effect treatment on basic conditional power on median OS

Figure 4. Interim Analysis Process Using ACES

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-timed" firewall established for trial conduct... can help provide assurance that statistical and operational biases have not been introduced."
  - Requests an accurate record of trial conduct and documentation -- who saw what and when

ACCESS CONTROL EXECUTION SYSTEM (ACES)

- ACES is a safe, 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

VALOR RECOVERS POWER BY SAMPLE SIZE INCREASE IF IN PROMISING ZONE

True Hazard Ratio Base Case Design Adaptive Design

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

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 fails in 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