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Vosaroxin plus cytarabine versus placebo plus cytarabine in patients with first relapsed or refractory acute myeloid leukaemia (VALOR): a randomised, controlled, double-blind, multinational, phase 3 study

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Declaration of interests

FR reports grants and advisory fees from Sunesis during the conduct of the study, and grants from Sunesis outside the submitted work. NV reports advisory fees from Sunesis during the conduct of the study. SAS and AW report advisory fees from Sunesis outside the submitted work. HPE reports grants and consulting fees from Sunesis during the conduct of the study, and reports fees from Novartis, Incyte, Celgene, Ariad, and Seattle Genetics and grants from Millennium, Seattle Genetics, Celator, Amgen, and Astellas, outside the submitted work. CR reports advisory fees from Sunesis during the conduct of the study, and reports grants from Amgen, Chugai, and Celgene and advisory fees from Celgene outside the submitted work. VMK and GJR report clinical trial support from Sunesis during the conduct of the study and advisory fees from Sunesis outside the submitted work. JC reports grants from Ambit, Arog, Astellas, Celator, Novartis and consulting fees from Novartis and Astellas, outside the submitted work. OO reports grants from Sunesis during the conduct of the study, and reports fees from Sunesis, Algeta, and Spectrum Pharmaceuticals and grants from Astex, MEI-Pharma, Topotarget, Lilly, and Celgene outside the submitted work. MH reports grants and consulting fees from Sunesis during the conduct of the study. LD reports research funds from Sunesis during the conduct of the study, and reports consulting fees from Maxygen and research funds from Celator outside the submitted work. GG reports fees from Amgen, Celgene, GlaxoSmithKline, Janssen, Novartis, and Roche, outside the submitted work. RKS reports grants and advisory fees from Sunesis during the conduct of the study. CM is an employee of Cytel Inc. and receives no remuneration other than his Cytel salary; he has nothing to disclose. ARC, JAF, RW, JAS, and GA were employed by Sunesis Pharmaceuticals during the conduct of the study. EKR, HS, JEL, MEC, GJS, EJ, AP, H-AH, XT, VH, JM, H-GD, BLP, A-MC, and DH have nothing to disclose.

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Summary

Background—Safe and effective treatments are urgently needed for patients with relapsed/refractory acute myeloid leukaemia (AML). We investigated the efficacy and safety of vosaroxin, a first-in-class anticancer quinolone derivative, plus cytarabine in patients with relapsed/refractory AML.

Methods—VALOR was a phase 3, double-blind, placebo-controlled trial conducted at 101 international sites. Patients were randomised 1:1 to vosaroxin (90 mg/m^2 IV days 1,4) plus cytarabine (1 g/m^2 IV days 1–5) (vos/cyt) or placebo plus cytarabine (pla/cyt) using a permuted block procedure stratified by disease status, age, and geographic location. All participants were blind to treatment assignment. Primary endpoints were overall survival (OS) and 30- and 60-day mortality. Efficacy analyses were by intention-to-treat; safety analyses included all treated patients. This study is registered at clinicaltrials.gov (NCT01191801).

Findings—Between December 2010 and September 2013, 711 patients were randomised to vos/cyt (n=356) or pla/cyt (n=355). Median OS was 7·5 months with vos/cyt and 6·1 months with pla/cyt (hazard ratio 0·87; unstratified log-rank p=0·061; stratified p=0·0241) and was supported by a sensitivity analysis censoring for subsequent transplant (6·7 and 5·3 months; p=0·0243). Complete remission (CR) rate was higher with vos/cyt vs pla/cyt (30·1% vs 16·3%, p<0·0001). Early mortality rates were equivalent (vos/cyt vs pla/cyt: 30-day, 7·9% vs 6·6%; 60-day, 19·7% vs 19·4%). Treatment-related deaths occurred at any time in 18 patients (5·1%) with vos/cyt and 8 (2·3%) with pla/cyt. Grade ≥3 adverse events more frequent with vos/cyt included febrile neutropenia (167/355 [47%] vs 117/350 [33%]), stomatitis (54 [15%] vs 10 [3%]), hypokalaemia (52 [15%] vs 21 [6%]), sepsis (42 [12%] vs 18 [5%]), and pneumonia (39 [11%] vs 26 [7%]).

Interpretation—Addition of vosaroxin to cytarabine prolonged survival in patients with relapsed/refractory AML, increasing CR rates with equivalent early mortality. These results support vos/cyt as an option for salvage therapy in AML patients.

Funding—Sunesis Pharmaceuticals

Introduction

The prognosis of patients with relapsed or refractory acute myeloid leukaemia (AML) is poor; median survival is less than 1 year.[1,2] High-dose cytarabine monotherapy or cytarabine-based combination regimens are often used as salvage therapy with limited efficacy; in a recent randomised trial, salvage therapy with the investigator's choice of one of seven commonly used regimens (including high-dose cytarabine) produced complete remission (CR) in 12% of patients and a median survival of 3.3 months, with no significant difference between regimens.[3] Toxicity is also a concern, particularly in patients over 60 years of age, who constitute the majority of the AML population.[1,4–6]

Vosaroxin is an anticancer quinolone derivative that intercalates DNA and inhibits topoisomerase II activity.[7] In contrast to traditional topoisomerase inhibitors, vosaroxin is minimally metabolised due to its stable core quinolone structure and is not associated with significant formation of free radicals, reactive oxygen species, or toxic metabolites.[7–9] Vosaroxin is not a substrate of P-glycoprotein and can induce apoptosis independent of p53.[7,10] Vosaroxin and cytarabine exhibit non-overlapping primary mechanisms of action and demonstrate synergistic antiproliferative activity in preclinical assays.[10,11] In a phase 2 study, vosaroxin plus cytarabine demonstrated clinical activity and good tolerability in patients with relapsed/refractory AML, producing a 25% CR rate with low (2·5%) 30-day all-cause mortality.[12]

These results supported the initiation of a phase 3 trial. The cytarabine dose and schedule selected was based on several factors, including the phase 2 study results, regimens used in recent clinical registration studies,[4] results from ex vivo studies,[13] and published clinical studies[14–17] suggesting that intermediate-dose cytarabine may provide similar clinical benefit with less toxicity than high-dose cytarabine. The phase 3 VALOR ("Vosaroxin and Ara-C combination evaLuating Overall survival in Relapsed/refractory AML") study was designed to assess whether the addition of vosaroxin to cytarabine confers a survival benefit in patients with relapsed/refractory AML, compared with cytarabine alone.

Methods

Study Design

VALOR was a phase 3, randomised, double-blind, placebo-controlled trial conducted at 101 sites in North America, Europe, South Korea, and Australia/New Zealand. The study protocol was approved by an ethics review board at each participating institution. The study was conducted in accordance with the Declaration of Helsinki.

Patients

Written informed consent was provided by all patients. Eligible patients were ≥18 years of age with a diagnosis of AML, as defined by World Health Organization criteria,[18] and were in first relapse or had refractory disease. Patients with acute promyelocytic leukaemia were excluded. Relapse was defined as reemergence of ≥5% leukaemia blasts in bone marrow or ≥1% blasts in peripheral blood 90 days to 24 months after first CR or CR without complete platelet recovery (CRp). Refractory AML was defined as persistent disease ≥28 days after initiation of induction therapy or relapse <90 days after first CR or CRp. All patients must have received prior induction therapy with an anthracycline (or anthracenedione) plus cytarabine; no more than two prior induction cycles were allowed. Additional inclusion criteria included Eastern Cooperative Oncology Group performance status of 0–2 and adequate liver (total bilirubin ≤1·5 × the upper limit of normal [ULN], aspartate aminotransferase ≤2·5 × ULN, alanine aminotransferase ≤2·5 × ULN), renal (serum creatinine ≤2·0 mg/dL) and cardiac (left ventricular ejection fraction ≥40%) function. Patients were excluded if they had received cytarabine-containing treatment at a total dose ≥5 g/m^2 within 90 days of randomisation. Other AML therapies were not permitted while the patient was receiving study medication. Hydroxyurea was permitted up to 24 hours prior to randomisation. (See Supplementary Appendix for complete exclusion criteria.)

Randomisation and masking

Patients were assigned to a treatment group using a permuted block randomisation procedure. Randomisation was stratified by disease status (refractory, first relapse at ≥90 days and <12 months, or first relapse at ≥12 months and ≤24 months), age (<60 years or ≥60 years), and geographic location (US sites or non-US sites). The study sponsor and all participants were blinded to treatment group assignment; only the data and safety monitoring board (DSMB) and independent statistics provider (ISP) had access to unblinded data in a controlled and limited manner during the study. Treatment assignments remained blinded until follow-up was completed for the final analysis.

Procedures

Patients were randomised 1:1 to receive vosaroxin (90 mg/m^2 in cycle 1 and 70 mg/m^2 in subsequent cycles by short [within 10 minutes] intravenous [IV] infusion on days 1 and 4) or placebo in combination with cytarabine (1 g/m^2, 2-h infusion on days 1–5) (Supplementary Figure S1). A second induction cycle could be initiated between 14 days and 8 weeks after initiation of cycle 1, at the discretion of the investigator, in patients with residual leukemia upon bone marrow assessment during initial induction, provided all drug-related toxicity had resolved to grade ≤1. Up to two additional cycles could be administered as consolidation therapy in patients who achieved CR or CRp within 12 weeks after therapy initiation, at the discretion of the investigator. Growth factor support and/or transfusions were permitted according to institutional guidelines.

Results of cytogenetic and molecular marker assessments were collected if available at screening, but were not required. Complete blood counts were obtained at least weekly to monitor haematologic recovery. Bone marrow biopsy or aspirate was obtained at screening, approximately day 15 during induction, and at haematologic recovery (to absolute neutrophil

count >1000 cells/μL) or by day 57 of induction cycles for response assessment. Safety, including documentation of adverse events (AEs), was assessed at each visit; severity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events, version 4·0.

Outcomes

Primary endpoints were overall survival (OS) and all-cause mortality at 30 and 60 days. The secondary endpoint was CR rate; tertiary endpoints included combined CR rate (CR/CRp/CR with incomplete recovery of platelets or neutrophils [CRi]), overall remission rate (ORR; CR/CRp/CRi plus partial response); event-free survival (EFS), leukaemia-free survival (LFS), rate of post-treatment allogeneic stem cell transplant (alloSCT), and safety/tolerability. Responses were categorised based on revised International Working Group response criteria[19] and were reviewed by a blinded, independent review panel.

Statistical analysis

This was an event-driven study incorporating an innovative adaptive trial design that permitted a prespecified, one-time increase in OS events, to ensure adequate statistical power to detect a clinically meaningful survival benefit over a range of potential outcomes. Initial target accrual was 375 OS events in 450 patients, providing 90% power (at two-sided level α=0·05) to detect an improvement in median survival from 5 months in the placebo/cytarabine group to 7 months in the vosaroxin/cytarabine group (hazard ratio [HR], 0·71). A formal interim survival analysis was performed by the ISP after 173 events (approximately 50% of required events) according to predefined statistical procedures stipulated and evaluated by the DSMB. Based on this interim analysis, the DSMB could recommend: 1) study termination based on efficacy or futility; 2) continuation as planned; or 3) a 50% increase in planned OS event accrual (to 562 events), with a corresponding increase in sample size (to 675 patients). After reviewing the interim results, the DSMB recommended option 3.

Primary efficacy analyses were conducted after 562 deaths using an unstratified log-rank test. A stratified log-rank test using factors at randomisation was pre-specified as supportive of efficacy. Because the adaptive trial design resulted in a data-dependent increase in the total number of events, a weighted log-rank statistic was employed for both unstratified and stratified tests to control type I error. The independent statistic at stage 1 (prior to interim analysis) was combined with its independent increment at stage 2 (post-interim analysis) using prespecified weights of $\sqrt{(187/375)}$ (i.e., equal to the square root of the planned proportion of events expected if there were no adaptation in design).[20,21] The use of the weighted statistic ensured that the type 1 error α=0·05 would be preserved notwithstanding the adaptive increase in total events. Additional log-rank tests were performed within each stratum defined at randomisation. Kaplan-Meier methods and Cox proportional hazard modeling were used to analyse the time-to-event endpoints, both overall and within subsets of patients defined by randomisation strata. All p values were two-sided.

OS was defined as the time between randomisation and death; surviving patients were censored from the OS analysis at the analysis cutoff date or the last date known to be alive,

whichever occurred first. In the primary OS analysis, patients were not censored for administration of subsequent nonprotocol AML therapy, including transplantation. A preplanned sensitivity analysis was performed for OS in which patients were censored at the start of a transplant conditioning regimen; patients with subsequent non-transplant AML therapy were not censored. EFS was defined as the time from randomisation to treatment failure, relapse, or death due to any cause. LFS was defined as the time from CR to relapse or death due to any cause.

Response rates and all-cause mortality rates were calculated for each treatment group and corresponding 95% CIs were calculated using the Clopper-Pearson method. Rates were compared between treatment groups using a chi-square test and by Cochran-Mantel-Haenszel tests stratified by factors used at randomisation, and corresponding 95% CIs were calculated using the normal approximation to the binomial distribution.

The intent-to-treat population consisted of all randomised patients, and was used for the analysis of efficacy endpoints. The safety population comprised all patients who received any amount of study drug.

Role of the funding source

This study was sponsored by Sunesis Pharmaceuticals. Sunesis employees were involved in the trial design, were responsible for all data collection, management, and analysis, and were involved in the writing of the report. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

Results

Between December 16, 2010 and September 25, 2013, 711 patients were enrolled and randomised to receive vosaroxin plus cytarabine (vos/cyt; n=356) or placebo plus cytarabine (pla/cyt; n=355) (Supplementary Figure S2). Baseline characteristics were well balanced between treatment arms (Table 1).

Nearly all patients (99%) completed a first induction cycle; 148 (21%) completed a second induction cycle (70 [20%] in the vos/cyt arm and 78 [22%] in the pla/cyt arm). Twenty-seven percent of patients in the vos/cyt arm and 14% in the pla/cyt arm completed at least one consolidation cycle; 13% and 6%, respectively, received two consolidation cycles. Discontinuation prior to maximum allowed treatment was primarily attributed to treatment failure (n=434; 50% vos/cyt; 73% pla/cyt); patient/physician decision (n=76; 13% vos/cyt; 8% pla/cyt); death (n=42; 9% vos/cyt; 3% pla/cyt); or AEs (n=17; 3% vos/cyt; 2% pla/cyt).

Median OS was 7·5 months (95% CI: 6·4–8·5) for vos/cyt vs 6·1 months (95% CI: 5·2–7·1) for pla/cyt (HR 0·87 [95% CI: 0·73–1·02]; unstratified log-rank p=0·0610) (Figure 1A). Notably, OS was significantly prolonged in a predefined secondary analysis that stratified by factors used in randomisation (stratified log-rank p=0·0241). In a predefined analysis censoring for subsequent alloSCT, median OS was improved with vos/cyt (6·7 vs 5·3 months; HR 0·81 [95% CI: 0·67–0·97]; p=0·0243; stratified p=0·0270) (Figure 1B). Overall, 210 patients (29·5%) underwent alloSCT following the study. Transplant rates were

comparable between treatment arms (30·1% vos/cyt; 29·0% pla/cyt), but markedly higher in younger patients (119/260 [45·8%] <60 years; 91/451 [20·2%] ≥60 years). Median time to transplantation was similar between arms (3.3 months [95% CI 3.0, 4.0] with vos/cyt and 3.1 months [95% CI 2.8, 3.5] with pla/cyt). Any subsequent non-protocol AML therapy (including transplant) was administered in 68.6% of patients (80.0% of patients <60 years and 62.1% of patients ≥60 years; Supplementary Table S1).

Prespecified subgroup analyses according to randomisation strata demonstrated that OS benefit with vosaroxin was greatest in patients age ≥60 years (7·1 months vs 5·0 months with pla/cyt; HR 0·75; p=0·0030) (Figure 1C) and those with early relapse (6·7 months vs 5·2 months with pla/cyt; HR 0·77; p=0·0388) (Figure 1E). Median OS was not significantly different between treatment arms in patients age <60 years (HR 1·08; p=0·60) (Figure 1D), nor in patients with late relapse (HR 0·98; p=0·96) (Figure 1F) or refractory disease (HR 0·87; p=0·23) (Figure 1G). HRs for OS by subgroup are presented in Figure 2. The heterogeneity p value for treatment by subgroup interaction approached significance for the age group stratum (p=0·0501). In post-hoc, exploratory analyses, OS benefit was observed in patients with unfavorable cytogenetic risk (Supplementary Table S2) and FLT3 mutations (Supplementary Table S3).

CR was achieved in 30·1% of patients treated with vos/cyt vs 16·3% treated with pla/cyt (p<0·0001) (Table 2). ORR was 37·9% and 18·9% for the vos/cyt and pla/cyt treatment arms, respectively (a difference of 19.0% [95% CI: 12.6, 25.5; p<0·0001). Prespecified subgroup analyses demonstrated significantly higher response rates for vos/cyt-treated patients across all randomisation strata except for those less than 60 years of age (Table 2), with the most pronounced improvement in patients aged ≥60 years (CR: 31·9% for vos/cyt vs 13·8% for vos/pla; p<0·0001). A higher proportion of patients in the vos/cyt arm achieved CR with study drug prior to transplant (48% [51/107] vos/cyt; 32% [33/103] pla/cyt). In patients with CR, median LFS was 11·0 months with vos/cyt vs 8·7 months with pla/cyt (HR 0·89 [95% CI: 0·57–1·40]; p=0·63). Median EFS was significantly prolonged in vos/cyt-treated patients: 1·9 months vs 1·3 months in patients receiving pla/cyt (HR 0·67 [95% CI: 0·57–0·79]; p<0·001).

Thirty-day and 60-day all-cause mortality was similar in the two treatment arms (30-day: 7·9% vs 6·6%; 60-day: 19·7% vs 19·4% for vos/cyt vs pla/cyt, respectively). Grade 3 and higher AEs were primarily related to myelosuppression, infection, and gastrointestinal events (Table 3). Granulocyte colony-stimulating factors use was more frequent in the vos/cyt arm (40.8% vs 22.0% of patients in the pla/cyt arm). Importantly, there was no increase in the incidence of organ-specific toxicity (cardiac, renal, hepatic, or pulmonary) in the vos/cyt arm compared to the pla/cyt arm. Serious AEs attributed to study drug were more frequent in the vos/cyt arm (Supplementary Table S3), including febrile neutropenia, infections, and gastrointestinal mucosal toxicity.

At the time of last follow-up, 273 (76·9%) and 288 (82·3%) deaths were recorded in the vos/cyt and pla/cyt arms, respectively. Progressive disease was the primary cause of death (65·9% and 79·5% for vos/cyt and pla/cyt arms, respectively). Deaths attributed to serious AEs occurred in 14% (n=50) and 7% (n=26) of patients (considered related to therapy by the

investigator in 5·1% and 2·3%) in the vos/cyt and pla/cyt treatment arms, respectively. In both arms, most deaths attributed to serious AEs occurred within 60 days (80% with vos/cyt and 77% with pla/cyt).

Discussion

In the past 40 years, little progress has been achieved in prolonging survival in patients with relapsed/refractory AML. Median survival with current salvage options, including high-dose cytarabine or anthracycline- or anthracenedione-based combination regimens, is less than 1 year, ranging from 3.3 to 9.0 months in recent phase 2/3 clinical trial reports.[3, 4, 23, 28] Many investigational agents have failed to improve survival in randomised trials in this setting, despite promising early clinical data.[3,4,22–25] Two of these agents, laromustine and clofarabine, improved response rates (producing CR rates of 20% and 35%, respectively, vs 16% and 18% in the control arms); however, improvements in response did not translate into improved survival, in part due to higher early mortality than in the control arms.[4,22,23]

In contrast, the VALOR trial demonstrated that the addition of vosaroxin to cytarabine prolonged survival in patients with relapsed/refractory AML. Considering the rapidity of progression and death in patients with relapsed/refractory AML, a one month improvement in median survival should be considered clinically significant. In the primary analysis, the statistical significance of OS was borderline according to the standard criteria of $p<0·05$ (unstratified, log-rank $p=0·0610$). An OS benefit was supported, however, by two additional, preplanned analyses: a stratified log-rank test, and a sensitivity analysis in which OS was censored for subsequent alloSCT due to the potential to confound survival analyses.[26] In both of these analyses, statistical significance was observed ($p=0·0241$ and 0.0243). The near significance of the primary endpoint together with the additional analyses support the conclusion that the addition of vosaroxin to cytarabine provides clinical benefit. The survival benefit was particularly compelling in patients older than 60 years, one of the most treatment-resistant groups. In these patients, a 2 month improvement in median survival was observed, corresponding to a 25% reduction in the risk of death. There are a number of factors that could underlie the difference in the treatment effect between younger and older patients, including differences in disease biology and chemosenstivity. Among patients <60 years of age, a survival benefit with vosaroxin may not have been detected due to higher transplant rates and the ability to effectively salvage younger patients with more aggressive subsequent therapies.

The CR rate was nearly doubled in the vos/cyt arm compared with the pla/cyt arm (30·1% vs 16·3%, $p<0·0001$). The CR rate was significantly higher in all subgroups analysed except patients <60 years of age, and the combined CR rate was significantly improved in all subgroups, including younger patients. Similar to survival, the improvement in response was most compelling in patients ≥60 years. Responses in both arms were durable, as indicated by median LFS of 11·0 months with vos/cyt and 8·7 months with pla/cyt.

Despite a significantly higher CR rate in the vosaroxin arm, rates of transplantation were similar between treatment arms. Among transplanted patients, a higher proportion achieved CR with vos/cyt prior to transplant than with pla/cyt; however, a considerable number of

patients were transplanted either without remission, or after achieving remission with subsequent non-protocol therapy.

Importantly, the combination of vosaroxin and cytarabine increased OS and CR rates without an appreciable increase in 30- or 60-day mortality, supporting the conclusion that the benefit associated with vosaroxin in combination with cytarabine outweighs the toxicity. AEs observed in this study are consistent with those in prior studies of vosaroxin, including myelosuppression and gastrointestinal toxicities. Rates of neutropenia, neutropenic fever, and infection were higher in the vosaroxin arm as would be expected with the addition of a second cytotoxic agent. Although the number of deaths within 60 days was not increased, the number of deaths within 60 days due to AEs, mainly infection, was higher in the vos/cyt arm. Careful management of infections is critical. Stomatitis was also more common in the vosaroxin arm, as expected from phase 1/2 trials. Oral mucositis typically resolves within a few weeks of therapy and is thus unlikely to delay transplantation; however, it should also be managed attentively. Significantly increased cardiac, renal, neurologic, and hepatic AEs with vosaroxin were not observed.

The VALOR study represents one of the largest datasets available in the relapsed/refractory AML setting. Vosaroxin plus cytarabine is the first new regimen to show an improvement in survival in patients with relapsed/refractory AML. The toxicity observed with the addition of vosaroxin is acceptable in light of the benefit conferred. VALOR data support the use of this combination as a new option for salvage therapy in patients with relapsed/refractory AML and as a standard of care in patients older than 60 years of age.

Panel: Research in context

Evidence before this study

There is no generally accepted standard of care for patients with relapsed/refractory AML. The benefit of current treatment options is limited, and enrolment in a clinical trial is recommended when possible.[2,27] We searched PubMed for randomised trials in patients with relapsed/refractory AML in the decade prior to the initiation of the VALOR trial (January 1, 2000, through December 31, 2010) using the following search string: (‘acute myeloid leukemia’ or ‘acute myeloid leukaemia’ or ‘AML’) AND (‘relaps*’ OR ‘refractory’ OR ‘second-line’ OR ‘salvage’) AND (‘randomized’ or ‘randomised’). Dose-finding trials, trials evaluating transplant or maintenance therapy, and trials in populations other than patients with relapsed and/or refractory AML were excluded. In the previous decade, none of the novel agents or regimens studied in a randomised trial of relapsed/refractory AML patients demonstrated an overall survival benefit.[22–24,28–30] Since the initiation of the VALOR study, three additional randomized studies conducted in this population have demonstrated no improvement in survival over controls.[3,4,25]

Added value of this study

VALOR is a phase 3 trial assessing vosaroxin, a first-in-class anticancer quinolone derivative that represents a new therapy for patients with relapsed or refractory AML. VALOR is one of the largest studies to be conducted in the relapsed/refractory AML setting. Vosaroxin plus cytarabine is the first regimen to show a survival benefit in relapsed/refractory AML, with

the greatest benefit observed in patients older than 60 years, a population with limited treatment options.

Implications of all the available evidence

VALOR data support the use of vosaroxin plus cytarabine as a treatment option for patients with relapsed/refractory AML and as a new standard of care in patients 60 years of age or older.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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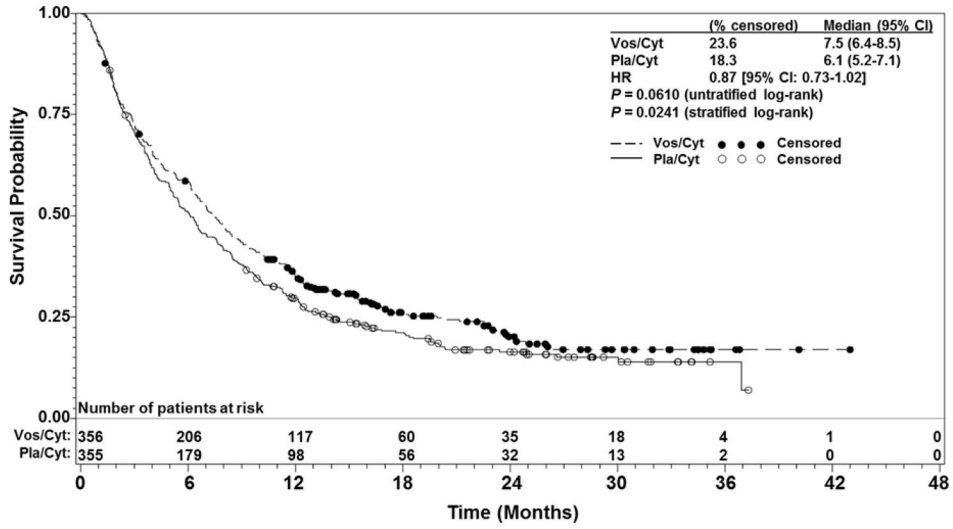
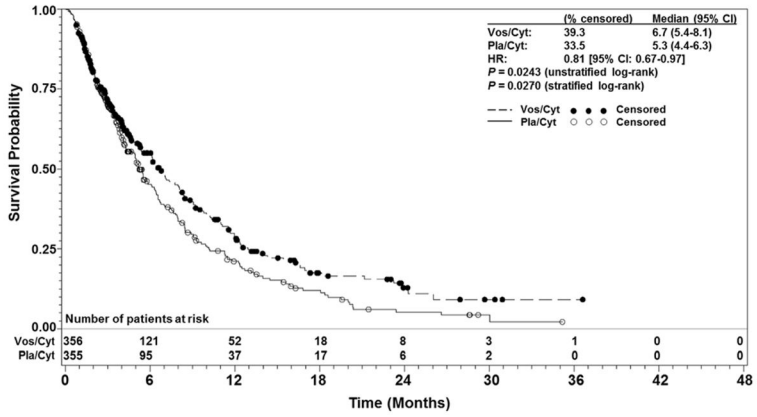
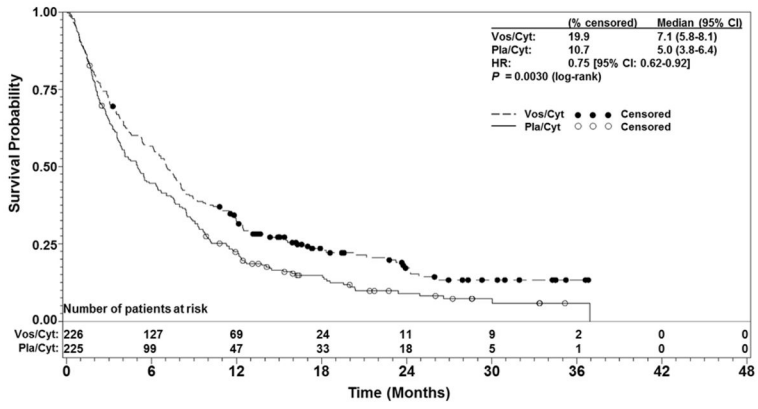
A. OS by treatment arm (N=711)



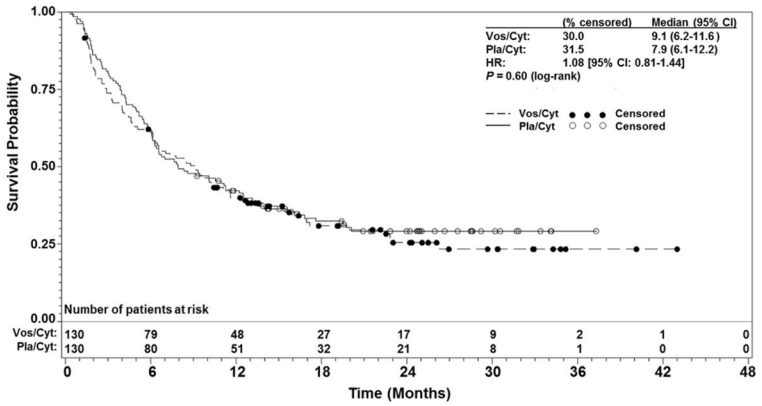
B. OS (censored for alloSCT), by treatment arm (N=711)



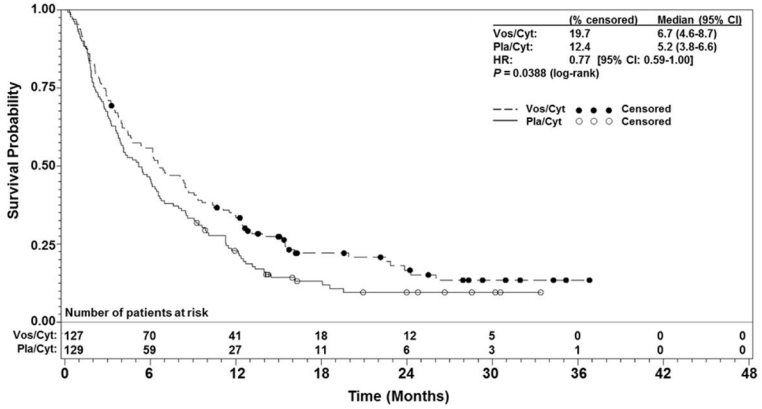
C. OS in patients aged ≥60 years, by treatment arm (n=451)



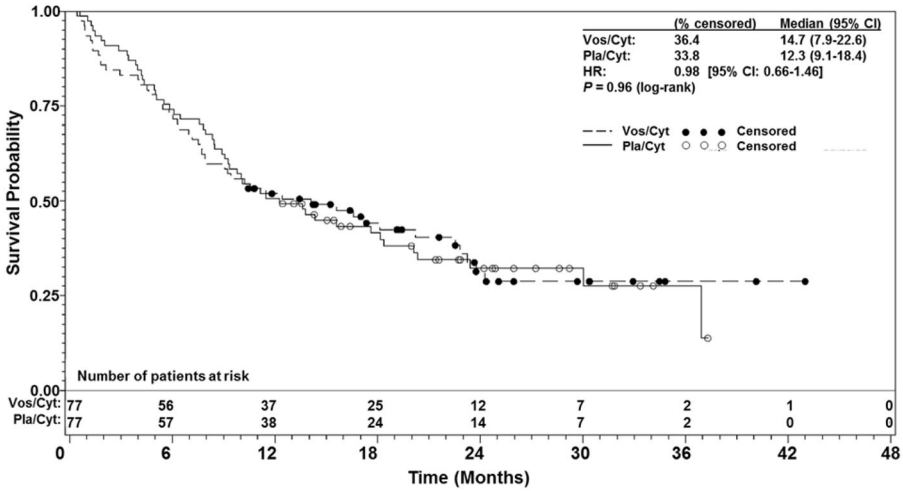
D. OS in patients aged <60 years, by treatment arm (n=260)



E. OS in patients with early (within 12 months) relapse, by treatment arm (n=256)



F. OS in patients with late (12 months or later) relapse, by treatment arm (n=154)



G. OS in patients with refractory AML, by treatment arm (n=301)

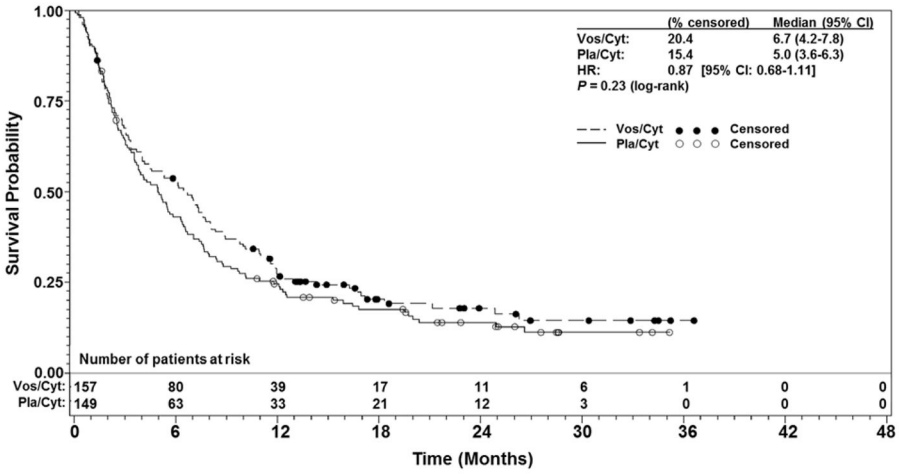
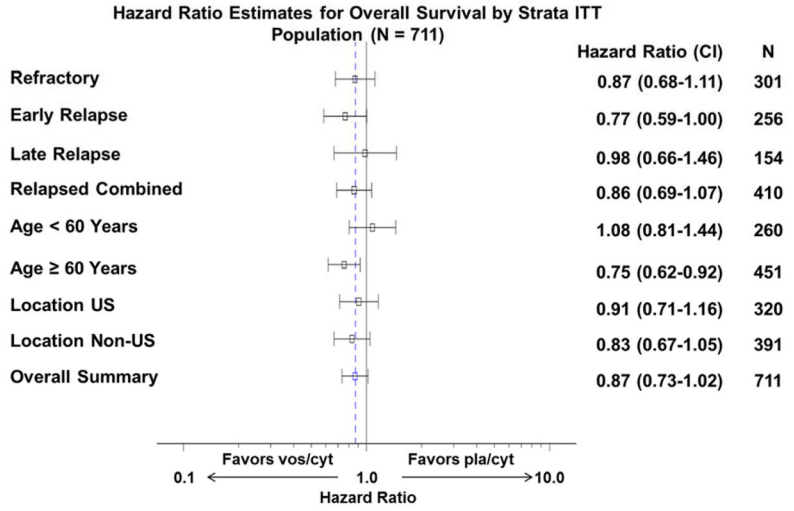


Figure 1.

Overall survival (OS) in patients with relapsed and refractory acute myeloid leukaemia treated with vosaroxin or placebo in combination with cytarabine, for all patients (A), censored for allogeneic stem cell transplant (alloSCT) (B), patients aged ≥60 years vs <60 years (C, D); and early relapsed vs late relapsed vs refractory patients (E, F, G).

CI= confidence interval; HR=hazard ratio; Pla/Cyt=placebo+cytarabine; Vos/Cyt=vosaroxin +cytarabine.



Stratification factor	Sample size	Hazard ratio	Confidence interval (95%)	Heterogeneity p value
Overall	711	0·87	(0·73, 1·02)	NA
First relapse status				
Refractory	301 (42%)	0·87	(0·68, 1·11)	
90 d to 12 mo	256 (36%)	0·77	(0·59, 1·00)	0·57
12 mo to 24 mo	154 (22%)	0·98	(0·66, 1·46)	
Age group				
<60 y	260 (37%)	1·08	(0·81, 1·44)	0·0501
≥60 y	451 (63%)	0·75	(0·62, 0·92)	
Location				
US	320 (45%)	0·91	(0·71, 1·16)	0·55
Non-US	391 (55%)	0·83	(0·67, 1·05)	

Figure 2.

Forest plot of overall survival in subgroups of patients treated with vosaroxin or placebo in combination with cytarabine.

The vertical dashed line indicates the hazard ratio in the overall population. CI= confidence interval; ITT=intention-to-treat.

Table 1

Baseline characteristics of patients treated with vosaroxin plus cytarabine or placebo plus cytarabine (N=711)

	Vosaroxin + cytarabine (n=356)	Placebo + cytarabine (n=355)
Sex, n (%)		
Male	202 (56·7)	192 (54·1)
Female	154 (43·3)	163 (45·9)
Age, yr		
Mean	61·0	60·2
Median (range)	64 (20–80)	63 (18–82)
Age subgroup [*], n (%)		
<60	130 (36·5)	130 (36·6)
≥60	226 (63·5)	225 (63·4)
Disease status [*], n (%)		
Early relapse [†]	127 (35·7)	129 (36·3)
Late relapse [‡]	77 (21·6)	77 (21·7)
Refractory	152 (42·7)	149 (42·0)
Region [*], n (%)		
US	161 (45·2)	159 (44·8)
Outside US	195 (54·8)	196 (55·2)
Race, n (%)[§]		
White	253 (71·1)	242 (68·2)
Black	21 (5·9)	11 (3·1)
Asian	20 (5·6)	18 (5·1)
Other	4 (1·1)	7 (2·0)
Multiple	0	3 (0·8)
Type of AML, n (%)[¶]		
AML not otherwise specified	188 (52·8)	180 (50·7)
AML with myelodysplasia-related changes	103 (28·9)	93 (26·2)
AML with recurrent genetic abnormalities	54 (15·2)	71 (20·0)
Myeloid sarcoma	2 (0·6)	1 (0·3)
Therapy-related myeloid neoplasm	9 (2·5)	10 (2·8)
ECOG PS, n (%)[#]		
0	156 (44·1)	143 (40·5)
1	158 (44·6)	162 (45·9)
2	40 (11·3)	48 (13·6)
Cytogenetic risk, n (%)[^]		
Favorable	7 (2·9)	9 (3·8)
Intermediate	175 (72·9)	155 (64·9)
Unfavorable	58 (24·2)	75 (31·4)
Number of prior induction cycles, n (%)		

	Vosaroxin + cytarabine (n=356)	Placebo + cytarabine (n=355)
1	274 (77·0)	259 (73·0)
2	82 (23·0)	95 (26·8)
>2	0	1 (0·3)

* Pre-planned randomisation strata.

† First complete remission duration of 90 days to 12 months.

‡ First complete remission duration of 12 months to 24 months.

§ Race not reported in 132 patients

¶ Per World Health Organization 2008 criteria.[18]

ECOG PS missing in 4 patients.

^ Per National Comprehensive Cancer Network Treatment Guidelines, AML, 2014; cytogenetic risk not available in 232 patients.

AML=acute myeloid leukaemia; ECOG PS=Eastern Cooperative Oncology Group performance status.

Table 2

Response in all patients and pre-defined subgroups by treatment arm (N=711)

	CR, % (95% CI)				Combined CR (CR/CRp/CRi), % (95% CI)			
	vos/cyt	**pla/cyt**	**difference**	**p value**	**vos/cyt**	**pla/cyt**	**difference**	**p value**
Overall	30·1 (25·3, 35·1)	16·3 (12·6, 20·6)	13.7 (7.6, 19.8)	<0·0001	37·1 (32·0, 42·3)	18·6 (14·7, 23·0)	18.5 (12.0, 24.9)	<0·0001
By age, years								
<60	26·9 (19·5, 35·4)	20·8 (14·2, 28·8)	6.2 (−4.2, 16.5)	0·24	34·6 (26·5, 43·5)	23·1 (16·1, 31·3)	11.5 (0.6, 22.5)	0·0400
≥60	31·9 (25·8, 38·4)	13·8 (9·6, 19·0)	18.1 (10.5, 25.6)	<0·0001	38·5 (32·1, 45·2)	16·0 (11·5, 21·5)	22.5 (14.5, 30.4)	<0·0001
By disease status								
Early relapse *	27·6 (20·0, 36·2)	12·4 (7·3, 19·4)	15.2 (5.5, 24.8)	0·0024	34·6 (26·4, 43·6)	15·5 (9·7, 22·9)	19.1 (8.8, 29.5)	0·0004
Late relapse †	53·2 (41·5, 64·7)	33·8 (23·4, 45·4)	19.5 (4.1, 34.8)	0·0148	59·7 (47·9, 70·8)	36·4 (25·7, 48·1)	23.4 (8.0, 38.7)	0·0037
Refractory	20·4 (14·3, 27·7)	10·7 (6·3, 16·9)	9.7 (1.5, 17.8)	0·0210	27·6 (20·7, 35·5)	12·1 (7·3, 18·4)	15.6 (6.7, 24.4)	0·0007
By region								
US	28·0 (21·2, 35·6)	14·5 (9·4, 20·9)	13.5 (4.7, 22.3)	0·0032	35·4 (28·0, 43·3)	17·0 (11·5, 23·7)	18.4 (9.0, 27.8)	0·0002
Outside US	31·8 (25·3, 38·8)	17·9 (12·8, 23·9)	13.9 (5.5, 22.4)	0·0014	38·5 (31·6, 45·7)	19·9 (14·5, 26·2)	18.6 (9.7, 27.4)	<0·0001

* First complete remission duration of 90 days to 12 months.

† First complete remission duration of 12 months to 24 months.

CR=complete remission; CRi=CR with incomplete recovery of platelets or neutrophils; CRp=CR with incomplete recovery of platelets; cyt=cytarabine; pla=placebo; vos=vosaroxin

Table 3

Grade 3, 4, and 5 treatment-emergent adverse events occurring in >5% of patients treated with vosaroxin or placebo in combination with cytarabine

n (%)	Grade 3		Grade 4		Grade 5	
	vos/cyt (n=355)	pla/cyt (n=350)	vos/cyt (n=355)	pla/cyt (n=350)	vos/cyt (n=355)	pla/cyt (n=350)
Any AE	133 (37·5)	140 (40)	151 (42·5)	129 (36·9)	50 (14·1)	26 (7·4)
Haematologic events						
Febrile neutropenia	163 (45·9)	115 (32·9)	4 (1·1)	2 (0·6)	0	0
Thrombocytopenia	6 (1·7)	8 (2·3)	78 (22)	79 (22·6)	0	0
Anaemia	72 (20·3)	76 (21·7)	6 (1·7)	5 (1·4)	0	0
Neutropenia	9 (2·5)	5 (1·4)	57 (16·1)	44 (12·6)	0	0
Nonhaematologic events						
Stomatitis	48 (13·5)	10 (2·9)	6 (1·7)	0	0	0
Diarrhoea	19 (5·4)	7 (2·0)	1 (0·3)	0	0	0
Pneumonia	23 (6·5)	16 (4·6)	3 (0·8)	1 (0·3)	13 (3·7)	9 (2·6)
Sepsis	8 (2·3)	5 (1·4)	20 (5·6)	7 (2·0)	14 (3·9)	6 (1·7)
Bacteraemia	39 (11·0)	14 (4·0)	4 (1·1)	1 (0·3)	0	1 (0·3)
Hypokalaemia	41 (11·5)	19 (5·4)	11 (3·1)	2 (0·6)	0	0
Hypophosphataemia	25 (7·0)	11 (3·1)	3 (0·8)	0	0	0
Hyperglycaemia	18 (5·1)	15 (4·3)	1(0·3)	0	0	0
Decreased appetite	20 (5·6)	7 (2·0)	0	0	0	0
Hypertension	21 (5·9)	12 (3·4)	0	0	0	0

AE=adverse event; ALT=alanine aminotransferase; AST=aspartate aminotransferase; cyt=cytarabine; pla=placebo; vos=vosaroxin.