Phase 3 results for vosaroxin/cytarabine in the subset of patients ≥60 years old with refractory/early relapsed acute myeloid leukemia

Refractory/early relapsed (Ref/eRel) acute myeloid leukemia (AML) in patients ≥60 years old is the most important unmet medical need in the salvage setting, where outcomes are exceptionally poor and no standard of care exists.[1] Vosaroxin is a first-in-class anticancer quinolone derivative that intercalates DNA and inhibits topoisomerase II, but has chemical and pharmacologic characteristics that differ from other topoisomerase II inhibitors.[2] The randomized phase 3 VALOR study (*clinicaltrials.gov Identifier: 01191801*) evaluated vosaroxin (90 mg/m^2 cycle 1 [70 mg/m^2 subsequent cycles] by short intravenous [IV] infusion on days 1 and 4) plus cytarabine (1 g/m^2 IV over 2 hours on days 1-5) (vos/cyt) *versus* placebo plus cytarabine (pla/cyt) in 711 patients ≥18 years old with Ref or first relapsed (Rel) AML. A detailed methodology has been published previously.[3] In the primary efficacy analysis, overall survival (OS) was 7.5 months with vos/cyt *versus* 6.1 months with pla/cyt (unstratified P=0.061; stratified P=0.024).[3] The addition of vosaroxin to cytarabine significantly improved the complete response (CR) rate (30% with vos/cyt *vs.* 16% with pla/cyt; P<0.0001). Prespecified subgroup analyses according to randomization strata (age [<60/≥60 years], disease status [Ref/eRel [within 12 months]/late Rel], and geographic location [USA/outside USA]) demonstrated that the treatment benefit was similar by geographic region, but varied considerably by age and disease status.

Table 1. Baseline characteristics in patients ≥60 years of age with Ref/eRel disease (ITT population).

	Patients ≥60 Ref/eRel (n = 364)	
	Vos/Cyt (n = 182)	Pla/Cyt (n = 182)
Sex, n (%)		
Male	102 (56.0)	99 (54.4)
Female	80 (44.0)	83 (45.6)
Median age (range), years	68.0 (60-78)	68.0 (60-78)
Disease status, n (%)		
Refractory	105 (57.7)	105 (57.7)
Early relapsed[a]	77 (42.3)	77 (42.3)
Geographic location, n (%)		
USA	78 (42.9)	76 (41.8)
Outside USA	104 (57.1)	106 (58.2)
Type of AML, n (%)[b]		
AML not otherwise specified	99 (54.4)	73 (40.1)
AML with myelodysplasia-related changes	57 (31.3)	61 (33.5)
AML with recurrent genetic abnormalities	21 (11.5)	41 (22.5)
Therapy-related myeloid neoplasm	5 (2.7)	6 (3.3)
Myeloid sarcoma	0	1 (0.5)
ECOG PS, n (%)[c]		
0	74 (40.9)	55 (30.6)
1	82 (45.3)	90 (50.0)
2	25 (13.8)	35 (19.4)
Cytogenetic risk, n (%)[d]		
Favorable	2 (1.9)	2 (1.7)
Intermediate	76 (70.4)	81 (66.9)
Unfavorable	30 (27.8)	38 (31.4)
Number of prior induction cycles, n (%)		
1	147 (80.8)	141 (77.5)
2	35 (19.2)	41 (22.5)
Total number of prior induction and consolidation/maintenance cycles, n (%)[e]		
1	78 (42.9)	76 (41.8)
2	43 (23.6)	34 (18.7)
>2	61 (33.5)	72 (39.6)

Percentages are based on the number of patients randomized with non-missing data. [a]First complete remission duration of 90 days to 12 months. [b]Per World Health Organization 2008 criteria. [c]ECOG PS missing in three patients. [d]Per National Comprehensive Cancer Network Treatment Guidelines, AML, v2.2010; cytogenetic risk not available in 135 patients. [e]Does not include transplant conditioning cycles (ten patients [five in each treatment arm] received one prior transplant conditioning cycle). AML: acute myeloid leukemia; ECOG PS: Eastern Cooperative Oncology Group performance status; ITT: intent-to-treat; pla/cyt: placebo plus cytarabine; Ref/eRel: refractory and early relapsed disease; vos/cyt: vosaroxin plus cytarabine.

The OS benefit with vos/cyt was most substantial in patients ≥60 years of age (n = 451; hazard ratio [HR] = 0.75 [95% confidence interval [CI]: 0.62-0.92]; *P*=0.0030) and patients with eRel disease (n = 256; HR = 0.77 [95% CI: 0.59-1.00]; *P*=0.039), patient groups that are typically treatment resistant.[3]

These results prompted further analyses in patient subgroups as defined by age and disease status. When results in patients ≥60 years of age were analyzed by disease status, a substantial improvement in the OS and CR rate was observed with vos/cyt *vs.* pla/cyt in patients age ≥60 years with Ref/eRel disease. In contrast, an improvement of OS in patients ≥60 years with late Rel disease was not demonstrated (n = 87; median OS 9.2 months *vs.* 9.8 months, respectively; HR = 1.06; *P*=0.82), despite a significant improvement in the CR rate (vos/cyt: 56.8% *vs.* pla/cyt: 27.9%; *P*=0.0064); small patient numbers and high rates of subsequent therapy, including transplant, may have confounded the OS analysis in this group. Based on the OS and CR benefit observed in patients ≥60 years with Ref/eRel disease, an exploratory analysis of the risk-benefit profile in patients ≥60 years of age with

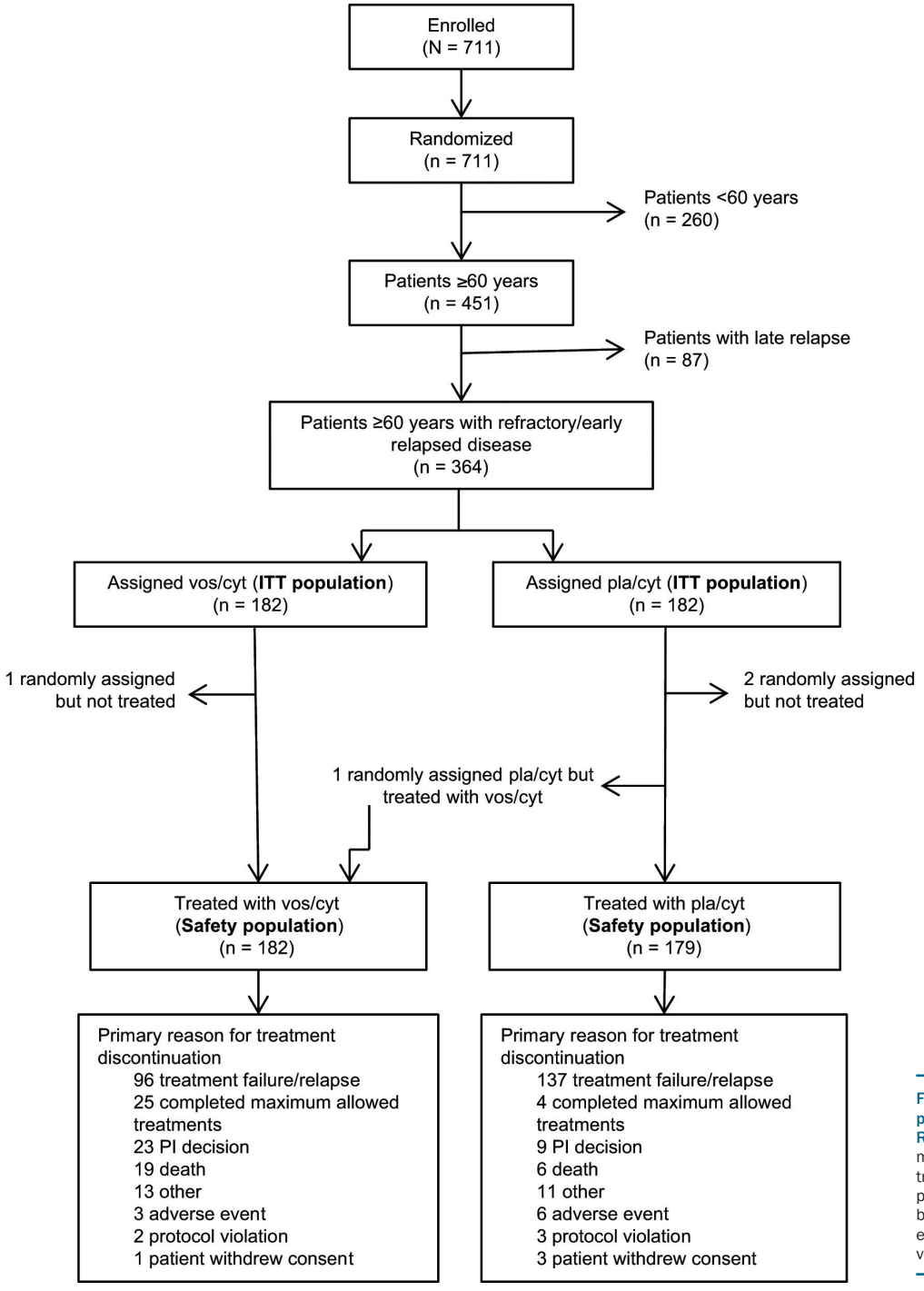

Figure 1. CONSORT diagram of patients ≥60 years old with Ref/eRel AML. AML: acute myeloid leukemia. ITT: intent-to-treat; PI: primary investigator; pla/cyt: placebo plus cytarabine; Ref/eRel: refractory and early relapsed disease; vos/cyt: vosaroxin plus cytarabine.

duration of first CR <12 months or no initial CR was conducted and is reported herein. The VALOR intent-to-treat (ITT) population included 364 patients ≥60 years old with Ref/eRel AML; of these, 361 patients received treatment (Figure 1). Baseline characteristics in this subset were generally well-balanced between treatment arms (Table 1). The median age was 68 years (range 60-78) in both treatment arms. Due to stratified randomization, disease status was evenly distributed: 57.7% Ref and 42.3% eRel disease in both treatment arms. The majority of patients (>75%) in both treatment arms had received only one prior induction cycle; the median number of prior induction and consolidation cycles was two (range 1-9). Five patients (2.7%) in each treatment arm had received prior transplant.

The proportion of patients ≥60 years old with Ref/eRel

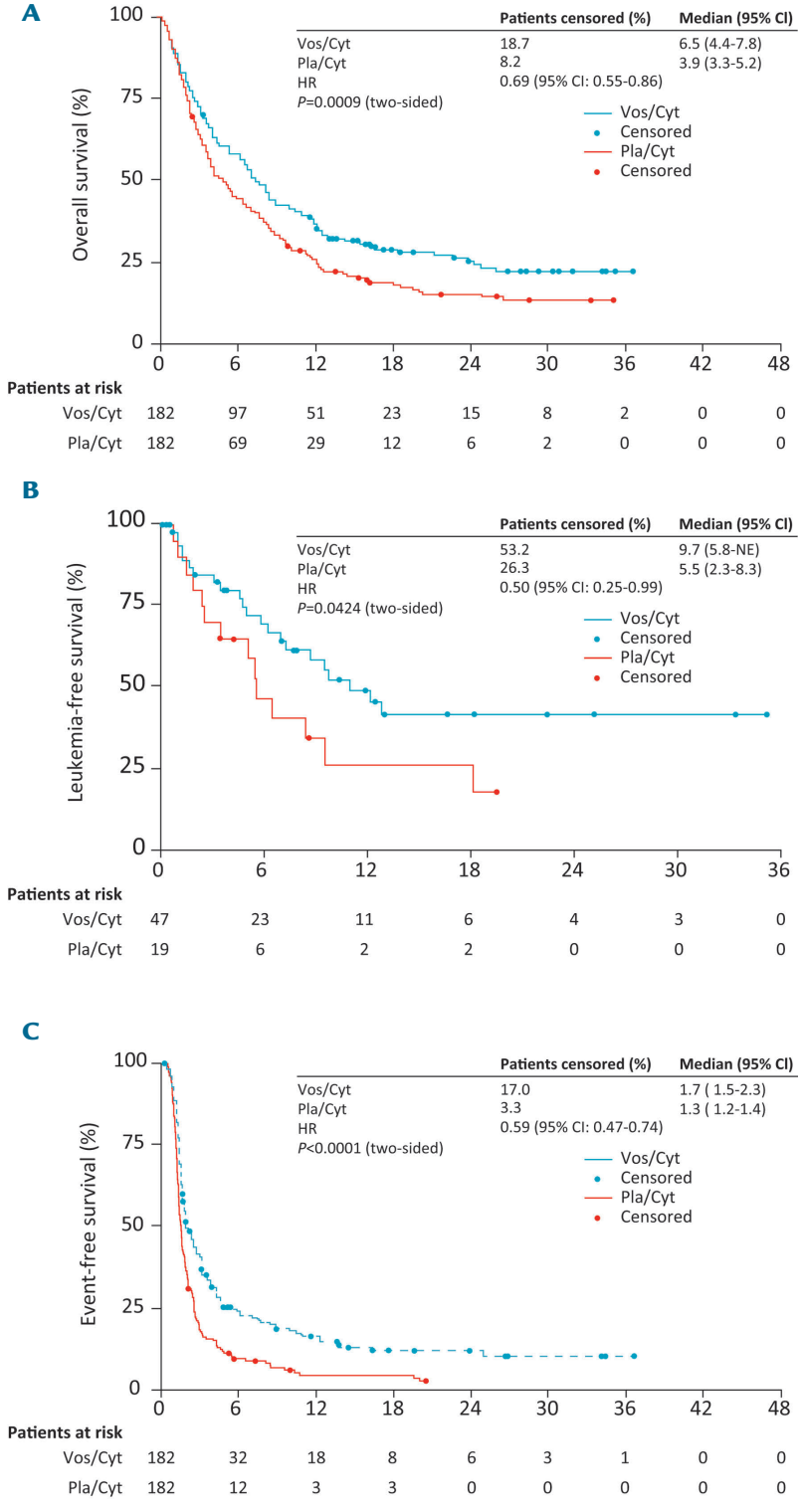

Figure 2. Kaplan-Meier estimates of overall (A), leukemia-free (B), and event-free (C) survival in patients ≥60 years old with Ref/eRel AML. AML: acute myeloid leukemia; HR: hazard ratio; CI: confidence interval; pla/cyt: placebo plus cytarabine; Ref/eRel: refractory and early relapsed disease; vos/cyt, vosaroxin plus cytarabine.

disease who received at least one cycle of study treatment was similar across treatment arms (vos/cyt: 99.5%; pla/cyt: 98.9%). Of these, 31 patients (17.0%) treated with vos/cyt and 39 (21.8%) treated with pla/cyt received a second induction cycle, and 48 (26.4%) and 16 (8.9%) patients, respectively, received at least one consolidation cycle. A median of one treatment cycle was received (range, 1-4 cycles) in both treatment arms. Fewer patients treated with vos/cyt discontinued due to treatment failure or relapse (52.7%) compared with pla/cyt (76.5%) (Figure 1).

The CR rate in patients ≥60 years with Ref/eRel disease was substantially higher with vos/cyt than pla/cyt. The CR rate was 25.8% (47/182; 95% CI: 19.6-32.8) in the vos/cyt arm and 10.4% (19/182; 95% CI: 6.4-15.8) in the pla/cyt arm (P=0.0001). The overall response rate (ORR) was also improved (vos/cyt: 34.1% [62/182] *vs.* pla/cyt: 12.6% [23/182]; P<0.0001).

The addition of vosaroxin to cytarabine substantially increased OS in patients ≥60 years old with Ref/eRel disease (Figure 2). Median OS was 6.5 months (95% CI: 4.4-7.8) with vos/cyt and 3.9 months (95% CI: 3.3-5.2) with pla/cyt (HR = 0.69 [95% CI: 0.55-0.86]; P=0.0009). When patients with subsequent transplant were censored from the OS analysis at the time of transplant, median OS was 6.2 months (95% CI: 4.4-7.4) and 3.9 months (95% CI: 3.3-5.0), respectively (HR = 0.71 [95% CI: 0.56-0.90]; P=0.0047). Vosaroxin plus cytarabine also improved leukemia-free survival (HR = 0.50 [95% CI: 0.25-0.99]; P=0.0424) and event-free survival (HR = 0.59 [95% CI: 0.47-0.74]; P<0.0001) compared with pla/cyt (Figure 2). At the time of database lock, 17.0% of patients in the vos/cyt arm and 7.1% in the pla/cyt arm remained alive and in continued follow-up.

Post-treatment transplantation rates were identical in both treatment arms (17.0% [31/182]; [95% CI: 11.9-23.3]). However, a greater proportion of transplanted patients achieved CR with study therapy prior to transplant in the vos/cyt arm (48.4% [15/31]) than in the pla/cyt arm (32.3% [10/31]) and the 100-day mortality rate after transplant was lower in patients treated with vos/cyt (19.4% [6/31]) than with pla/cyt (25.8% [8/31]). Among transplanted patients, median OS was 18.3 months (95% CI: 11.9-NE) with vos/cyt and 9.9 months (95% CI: 7.7-12.2) with pla/cyt (HR = 0.46 [95% CI: 0.25-0.86]; P=0.0125).

Importantly, the addition of vosaroxin did not increase 30- or 60-day mortality (30-day: 9.9% [18/182] *vs*. 10.6% [19/179]; 60-day: 20.9% [38/182] *vs.* 24.6% [44/179] for vos/cyt *vs.* pla/cyt, respectively). Most patients in both treatment arms experienced at least one adverse event (AE) of any grade (vos/cyt: 99.5% *vs.* pla/cyt: 100%) or grade ≥3 AE (93.4% *vs.* 86.6%, respectively); however, the incidence of discontinuations due to AEs was low (<3.0%) in both treatment arms. Serious AEs (SAEs) were more common with vos/cyt (53.8%) than with pla/cyt (32.4%). Serious AEs leading to death occurred in 15.9% of patients in the vos/cyt arm and 11.2% in the pla/cyt arm. The rates of treatment-related AEs, treatment-related grade ≥3 AEs, and treatment-related SAEs were 91.8%, 72.0%, and 31.3% in the vos/cyt arm compared with 86.0%, 60.9%, and 15.1% in the pla/cyt arm, respectively.

Myelosuppression, infections, and gastrointestinal (GI) toxicities were the most common AEs and SAEs in both treatment arms. Grade ≥3 febrile neutropenia was more common in the vos/cyt arm (40.7%) than the pla/cyt arm (29.1%); however, other grade ≥3 hematologic events occurred with similar frequency in both arms, including (for vos/cyt *vs.* pla/cyt, respectively) thrombocytopenia (23.1% *vs.* 26.8%), anemia (22.5% *vs.* 25.7%), and neutropenia (17.6% *vs.* 16.2%). Differences between treatment arms in grade ≥3 non-hematologic events included higher rates for vos/cyt *vs.* pla/cyt, respectively, of hypokalemia (15.4% *vs.* 7.3%), stomatitis (15.4% *vs.* 4.5%), and sepsis (12.1% *vs.* 5.6%). Vos/cyt therapy was not associated with a higher incidence of other end organ toxicities, such as hepatic, neurologic, renal, and cardiac toxicities.

Overall, this analysis demonstrated that vos/cyt produced clinically meaningful improvements in response and survival compared with pla/cyt in patients ≥60 years old with Ref/eRel AML, without increasing early mortality. The AE profile of vos/cyt in older patients was consistent with the AE profile of the overall VALOR population reported previously.[3] Rates of SAEs were higher in the vos/cyt arm compared with the pla/cyt arm, though this would be expected with the addition of a second cytotoxic agent and has been observed in other trials of cytarabine combination regimens compared to cytarabine alone.[4,5] The toxicities seen with vos/cyt therapy were similar in type and severity to those commonly seen with currently available therapies used to treat Ref/Rel AML patients, and physicians who treat leukemia are accustomed to managing these types of toxicity.

Vosaroxin's activity in patients ≥60 years old with Ref/eRel AML, a generally treatment-resistant population, may be due in part to its ability to evade common drug resistance mechanisms. In older AML patients, there is a higher incidence of unfavorable cytogenetics, resulting in higher resistance to chemotherapy.[6-8] P-glycoprotein (P-gp) expression levels are higher in older patients and those with relapsed disease.[6,7] Similarly, older patients are more likely to have alterations in the *TP53* gene, increased frequency of AML driver gene mutations, and increased probability of *of RAS, Src,* and tumor necrosis factor (TNF) pathway dysregulation.[9,10] Vosaroxin is a broadly active cytotoxic agent that has demonstrated activity in a number of drug-resistant models, including those with breast cancer resistance protein (BCRP) or P-gp transporter-mediated efflux,[11,12] and has activity independent of *TP53* status,[13,14] characteristics that may make it particularly useful in the older Ref/eRel AML population.[15]

As this is a post-hoc subset analysis, a confirmatory study is required. However, the results of this analysis suggest that vosaroxin plus cytarabine represents a potential new treatment option for poor prognosis AML patients ≥60 years old with Ref/eRel AML that merits confirmation with a randomized clinical trial.

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