5 Minute JournalClub

POST-ASH Issue 5, 2015

Phase III VALOR Trial of Cytarabine with or without Vosaroxin for Patients with Relapsed/Refractory AML

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CME INFORMATION

OVERVIEW OF ACTIVITY

Each year, thousands of clinicians, basic scientists and other industry professionals sojourn to major international oncology conferences, like the American Society of Hematology (ASH) annual meeting, to hone their skills, network with colleagues and learn about recent advances altering state-of-the-art management in hematologic oncology. As such, these events have become global stages where exciting science, cutting-edge concepts and practice-changing data emerge on a truly grand scale. This massive outpouring of information has enormous benefits for the hematologic oncology community, but the truth is it also creates a major challenge for practicing oncologists and hematologists.

Although original data are consistently being presented and published, the flood of information unveiled during a major academic conference is unprecedented and leaves in its wake an enormous volume of new knowledge that practicing oncologists must try to sift through, evaluate and consider applying. Unfortunately and quite commonly, time constraints and an inability to access these data sets leave many oncologists struggling to ensure that they're aware of crucial practice-altering findings. This creates an almost insurmountable obstacle for clinicians in community practice because they are not only confronted almost overnight with thousands of new presentations and data sets to consider but they are also severely restricted in their ability to review and interrogate the raw findings.

To bridge the gap between research and patient care, this CME activity will deliver a serial review of the most important emerging data sets on up-front and salvage therapeutic options and modalities for the evaluation of treatment response in newly diagnosed and relapsed or refractory acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), acute promyelocytic leukemia (APL) and myelodysplastic syndromes (MDS) from the latest ASH meeting, including expert perspectives on how these new evidence-based concepts may be applied to routine clinical care. This activity will assist medical oncologists, hematologists, hematology-oncology fellows and other healthcare professionals in the formulation of optimal clinical management strategies and the timely application of new research findings to best-practice patient care.

LEARNING OBJECTIVES

- Evaluate the results of the confirmatory Phase II BLAST study of blinatumomab in patients with relapsed/refractory ALL, and consider this information when developing treatment plans for these patients.
- Analyze the efficacy of a more intensive pediatric chemotherapy regimen for older adolescents and young adults with newly diagnosed B- or T-precursor ALL, and determine the feasibility of this approach for patients with ALL in this age group.
- Compare and contrast the benefits and risks reported in the Phase III APL0406 trial of all-trans retinoic acid (ATRA) with arsenic trioxide versus ATRA with chemotherapy, and consider the potential therapeutic benefit of a chemotherapy-free regimen for patients with newly diagnosed nonhigh-risk APL.
- Determine the clinical benefit seen with the addition of the multikinase inhibitor sorafenib to standard primary induction and consolidation therapy for younger patients with newly diagnosed AML.
- Assess the efficacy and tolerability profile of the novel agent vosaroxin combined with cytarabine from the Phase III VALOR trial in patients with relapsed or refractory AML.
- Examine the impact of lenalidomide therapy on the achievement of transfusion independence in red blood cell transfusion-dependent patients with lower-risk MDS without del(5q).

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FACULTY — The following faculty (and their spouses/partners) reported real or apparent conflicts of interest, which have been resolved through a conflict of interest resolution process:

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Hardware/Software Requirements:
A high-speed Internet connection
A monitor set to 1280 x 1024 pixels or more
Internet Explorer 7 or later, Firefox 3.0 or later, Chrome, Safari 3.0 or later
Adobe Flash Player 10.2 plug-in or later
Adobe Acrobat Reader
(Optional) Sound card and speakers for audio

Last review date: May 2015
Expiration date: May 2016

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POST-ASH Issue 5, 2015

To go directly to slides and commentary for this issue, **click here**.

Leukemias and Myelodysplastic Syndromes Think Tank Faculty
January 29, 2015

Jennifer R Brown, MD, PhD
Hagop M Kantarjian, MD
Charles A Schiffer, MD
B Douglas Smith, MD
David P Steensma, MD
Wendy Stock, MD, MA

Not long after this year's American Society of Hematology (ASH) meeting, we gathered 6 clinical investigators for our first ever think tank focused exclusively on leukemias and myelodysplastic syndromes (MDS). Although a lot of the excitement during this closed recording session centered on new agents and therapies — particularly the explosion of encouraging clinical research in acute lymphoblastic leukemia (ALL) with both CAR T-cell immunotherapy and the bispecific T-cell engager antibody blinatumomab (see below) — it was also fascinating to hear that an older drug that has sometimes gotten a bad rap — sorafenib (sor) — may have a new role as part of up-front treatment for acute myeloid leukemia (AML).

ALL is an uncommon disease that many oncologists appropriately triage to tertiary centers, but AML — particularly in elderly patients — is an important part of general oncology practice. As such, even though the randomized, Phase II trial of sor presented at ASH as a plenary was not the "home run" that we are beginning to see more frequently with immunotherapy in many diseases, from a practical clinical perspective the study findings may be among the most important in any cancer this year.

For that reason, we lead off this year's acute leukemia/MDS ASH summary by focusing on that work. But as always, we also created teaching slide sets and obtained perspectives from a noted clinical investigator — in this case Mikkael Sekeres — for a number of the most important presentations, which are outlined below:

Mikkael A Sekeres, MD, MS

AML

Sor up front in AML

About 20% of patients with AML have activating mutations in the FMS-like tyrosine kinase 3 (FLT3), and a number of FLT3 inhibitors are in various states of development. Sor targets this kinase, among others, and for that reason this **Phase II placebo-controlled German trial** evaluated the addition of sor to standard induction and consolidation treatment (followed by maintenance with sor) in 267 adult patients with

newly diagnosed AML age 60 years and younger. Importantly, individuals both with and without FLT3-internal tandem duplication (ITD) mutations were eligible for and enrolled in the study. With a median follow-up of 3 years, the trial met its primary endpoint of event-free survival (EFS), demonstrating a significant improvement in favor of sor (median EFS 20.5 months versus 9.2 months, $p = 0.013$). Interestingly and quite unexpectedly, there was a suggestion that the benefit was, if anything, more impressive in patients without FLT3-ITD mutations. The one sticking point is, to date there is no overall survival (OS) advantage, which is concerning to Dr Sekeres and has informed his current decision not to use up-front sor outside of a clinical trial.

Click here to see Dr Kantarjian's comment

However, at the think tank the reaction to these data was quite different, as Dr Hagop Kantarjian noted that since 2005, he and his MD Anderson colleagues have been routinely using FLT3 inhibitors in patients with FLT3-ITD mutations and that the outcomes appear indirectly to be improved compared to earlier series. The think tank faculty speculated on possible biologic explanations for these compelling findings, including the presence of other kinase targets or inhibition of wild-type FLT3 kinase activation, but most seemed to agree that these new data at the very least deserve careful consideration in patients with and without these abnormalities. To further drive home this point, Dr Kantarjian made an impassioned plea for "leukemia doctors to act more like those focused on solid tumors" and seek small research advances that, when coupled together, create a major positive effect for patients, as seen, for example, in renal cell carcinoma.

VALOR trial of vosaroxin

VALOR is a large, **international Phase III study** evaluating cytarabine with or without vosaroxin, a first-in-class anticancer quinolone derivative, in patients with relapsed/refractory AML. On the surface things look straightforward, as the trial did not reach its primary endpoint of improved OS. However, the data also demonstrated that complete remission rates were improved with vosaroxin/cytarabine, and a preplanned survival subgroup analysis censoring patients at allogeneic transplant showed a statistically significant 1.4-month advantage (hazard ratio 0.83, $p = 0.02$). Dr Sekeres is not convinced these improvements are clinically meaningful, but Dr Kantarjian — whose group has done a lot of this research — believes vosaroxin has important value and should be made available to clinicians.

MDS

Lenalidomide (len) in non-del(5q) disease

While the role of this immunomodulatory agent is well established and approved in patients with del(5q), mainly for management of anemia, a prior Phase II trial

suggested clear-cut benefit in non-del(5q) disease. **This Italian Phase III study** almost duplicated the results seen in the Phase II effort and demonstrated a ≥56-day transfusion independence rate of 27% with len compared to a 2.5% rate with placebo. These findings will undoubtedly lead clinicians to want to use this drug in this situation, and think tank participant Dr David Steensma endorses this approach. However, he cautions that "platelets need to be at a reasonable level" to use len.

Azacitidine (aza) alone or with len or vorinostat (vor) in higher-risk MDS and chronic myelomonocytic leukemia

At ASH Dr Sekeres presented the first results from the largest prospective study in higher-risk MDS ever conducted in North America — **SWOG-S1117** — which demonstrated a modest signal for improvement in disease-related outcomes with the 2 combinations. Unfortunately, a greater likelihood to discontinue treatment due to toxicity was also seen (9% aza, 23% aza/len, 24% aza/vor). In discussing this work, Dr Sekeres pointed out that these data will continue to mature, and he believes it is possible that with better management of side effects, these and other combinations may be successfully incorporated into treatment.

ATRA/arsenic trioxide (AAT) in acute promyelocytic leukemia (APL)

At the 2012 ASH meeting, the initial findings from the landmark Phase III Italian-German APL0406 trial in low/intermediate-risk APL comparing AAT as induction and consolidation to ATRA/idarubicin as induction, consolidation and maintenance therapy grabbed headlines and led many oncologists to change their practices. Dr Sekeres and his Cleveland Clinic group, however, wanted to see more follow-up before following suit. That information came **at this year's meeting** as excellent outcomes (now with 254 patients evaluable for response at 3 years) were observed with both therapies, but there appeared to be a suggestion of greater benefit with AAT (complete response [CR] 100% versus 97%; 2-year EFS rate 98% versus 84.9%, $p = 0.0002$; 2-year OS rate 99.1% versus 94.4%, $p = 0.01$). This has now given Dr Sekeres and his group enough supporting evidence to offer the chemotherapy-free AAT combination as standard induction and postremission therapy to patients with low/intermediate-risk APL.

ALL

Treatment for older adolescents and young adults (AYAs)

For years, a fundamental issue in this disease has been whether more intensive pediatric regimens should be used in AYAs. At ASH we saw relevant findings from the single-arm **US Intergroup trial C10403** of 296 patients age 16 to 39 who received a pediatric regimen administered by adult hematologist-oncologists. The 2-year EFS of 66% seen in this study represents a significant improvement compared to 34% EFS observed in historical controls, and globally the outcomes, including toxicities, were similar to what has been documented in other prospective international studies of pediatric regimens in AYAs.

As a result of these important findings, Dr Sekeres and the think tank faculty, including Dr Wendy Stock, who presented these data at ASH, all support the use of this approach moving forward both in clinical practice and in trials attempting to integrate new agents. It should also be noted that Dr Kantarjian believes that hyper-CVAD is an equivalent alternative.

CD19-targeted 19-28z CAR-modified autologous T cells in adult patients with relapsed, refractory B-cell ALL

A number of our CME programs have helped chronicle the amazing story of CAR T-cell therapy, and we would be remiss to not provide an update coming out of the year's biggest meeting. As previously mentioned, ALL is the locus where this therapy has taken off, and in San Francisco we saw extended follow-up from a **Phase I Memorial Sloan Kettering study** in this disease. Of the 22 patients evaluable for response, many of whom had heavily pretreated disease, an impressive 91% (20 patients) achieved CR after CAR T-cell infusion, with 90% (18 patients) of those being MRD-negative. Ten of the 13 transplant-eligible patients subsequently went on to successfully receive an allogeneic hematopoietic cell transplant.

In terms of complications, patients with MRD at the time of treatment did not experience cytokine release syndrome (CRS), and for those with morphologic disease at the time of T-cell infusion, a temporal relationship between serum IL-6 levels and CRS suggests that early intervention with IL-6-directed therapy might be effective in ameliorating related neurologic toxicities.

In commenting on this study, Dr Sekeres cautions that currently CAR T-cell therapy requires specialized administration logistics and the capability to manage potentially challenging cytokine-mediated toxicities. He also questions the long-term durability of response and envisions a future for this approach as a bridge to transplant but is uncertain as to whether CAR T-cell therapy will one day have a role as a stand-alone treatment or as part of induction.

Blinatumomab

At ASH we saw the presentation of the **Phase II BLAST trial** of 116 patients who were MRD-positive ($\geq 10^{-3}$) after having received at least 3 prior intensive chemotherapy regimens. The MRD CR after 1 cycle of blinatumomab was 78% and did not differ across multiple patient demographics, including those with higher MRD burden. However, the adverse event (AE) profile (mainly related to cytokine release) is not insignificant. Importantly, in this trial serious AEs occurred in 60% of patients, with 2 fatalities.

In discussing the recent FDA accelerated approval of the drug at the think tank, the faculty noted its impressive effectiveness as a salvage therapy but also related the challenges they have faced in managing toxicities. In this regard, Dr Steensma emphasized the role of corticosteroids in mitigating side effects such as fever and impaired mental function. Not surprisingly, a number of current trials combine

blinatumomab with chemotherapy in both the salvage and front-line settings, including a Phase III trial in newly diagnosed ALL (**NCT02003222**).

Be on the lookout for the entire think tank program this summer, but next on this series, we talk about new agents in multiple myeloma, particularly the search for the "rituximab of myeloma" that includes a new wave of monoclonal antibodies such as elotuzumab and daratumumab.

Neil Love, MD
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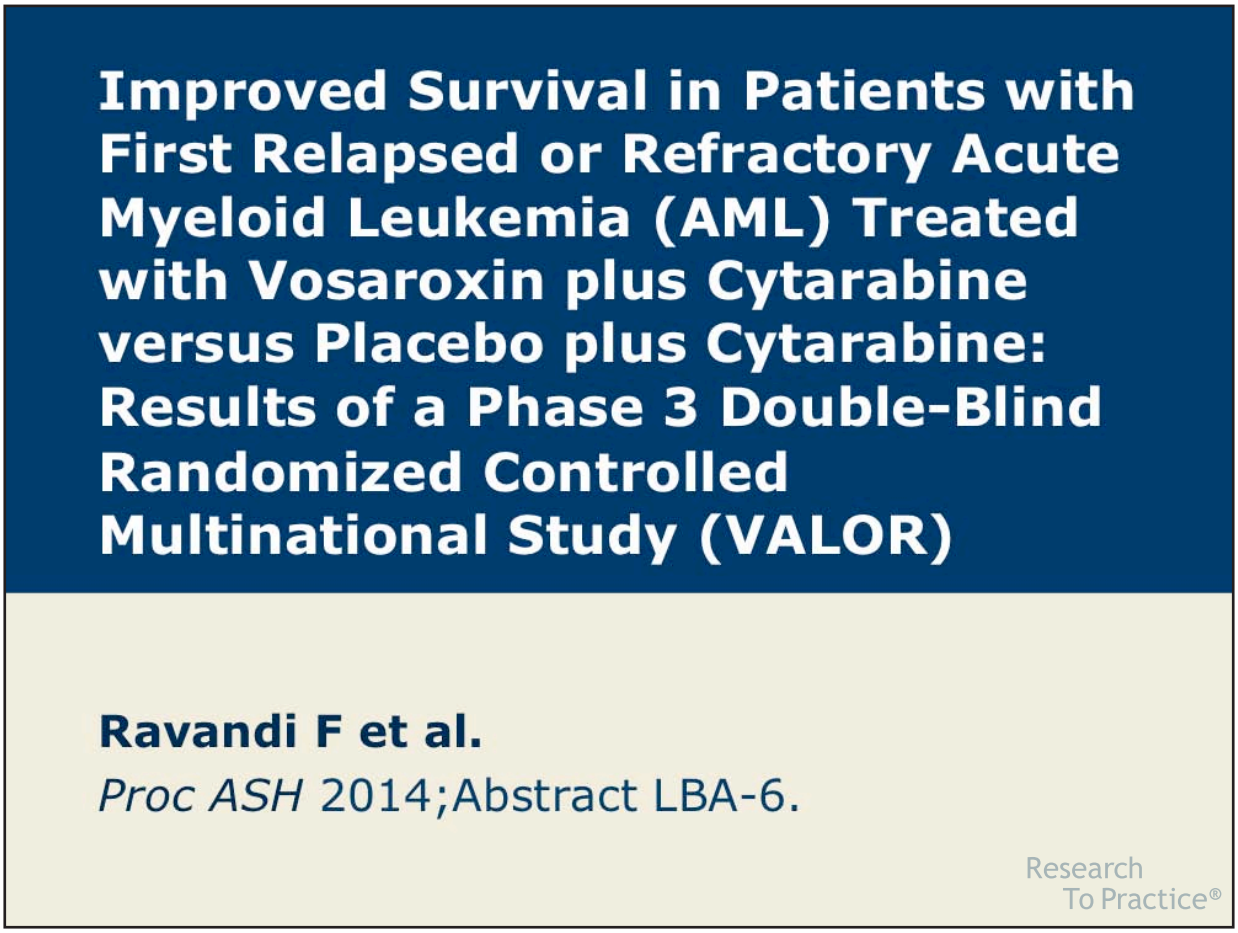
Phase III VALOR Trial of Cytarabine with or without Vosaroxin for Patients with Relapsed/Refractory AML

Presentation discussed in this issue

Ravandi F et al. **Improved survival in patients with first relapsed or refractory acute myeloid leukemia (AML) treated with vosaroxin plus cytarabine versus placebo plus cytarabine: Results of a phase 3 double-blind randomized controlled multinational study (VALOR).** *Proc ASH* 2014;**Abstract LBA-6**.

Slides from a presentation at ASH 2014 and transcribed comments from a recent interview with Mikkael A Sekeres, MD, MS (1/20/15)



Background

- Vosaroxin is a small-molecule and first-in-class anticancer quinolone derivative that is active in AML.
- It is minimally metabolized, evades P glycoprotein receptor–mediated efflux and has activity independent of p53 status.
- In preclinical studies, vosaroxin demonstrated potent cytotoxic activity in AML cell lines and primary tumor samples (*PLoS One* 2010;5:e10186).
- In addition, in a Phase I/II trial, the dosage for the safe combination of vosaroxin with cytarabine was established and found to be effective in relapsed AML (*Haematologica* 2015;100:231).
- **Study objective:** To assess the efficacy and safety of vosaroxin and cytarabine in patients with relapsed or refractory (R/R) AML.

Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

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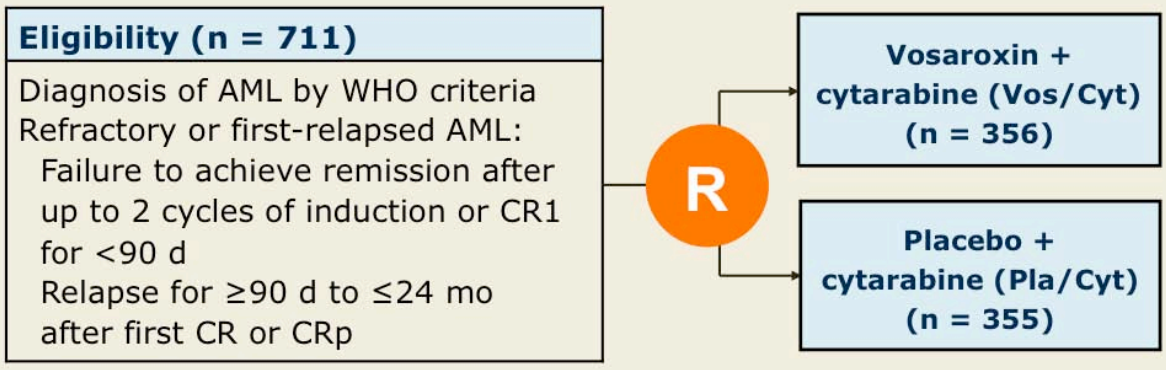
Phase III VALOR Trial Design (NCT01191801)



CR = complete response; CRp = CR with incomplete platelet recovery

- Vosaroxin: 90 mg/m^2 IV over 10 min on days 1, 4; 70 mg/m^2 in subsequent cycles
- Cytarabine: 1 g/m^2 IV over 2 hours on days 1-5
- Patients were stratified by age, disease status and geography before randomization.
- **Primary endpoint:** Overall survival (OS)
- **Secondary endpoints included** CR and safety

Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

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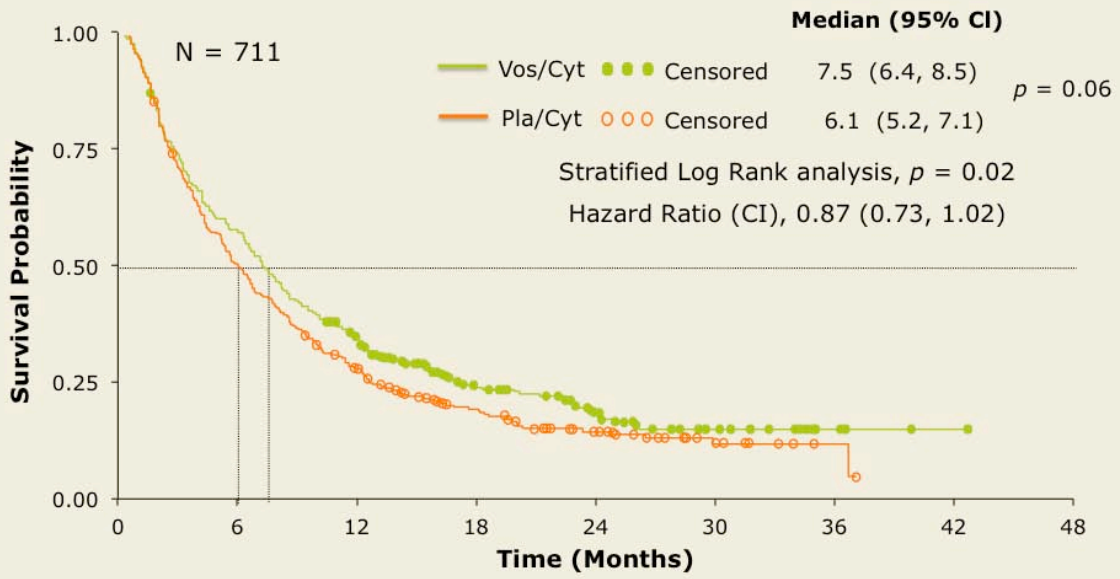
Overall Survival: Intent-to-Treat



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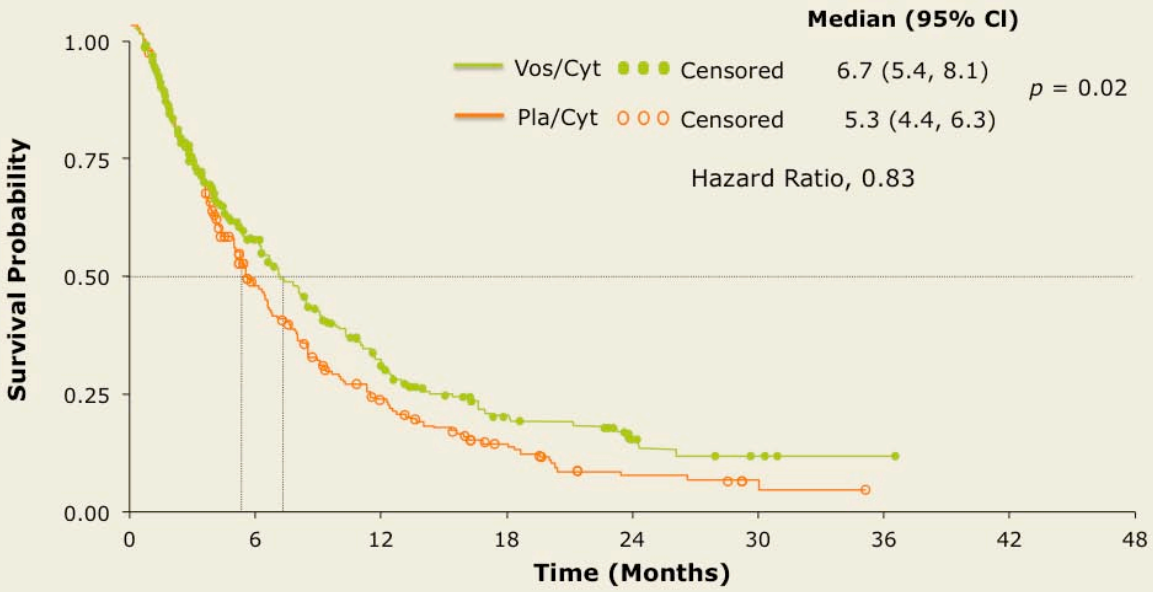
Overall Survival: Censored for Allogeneic Stem Cell Transplantation (Allo-SCT)



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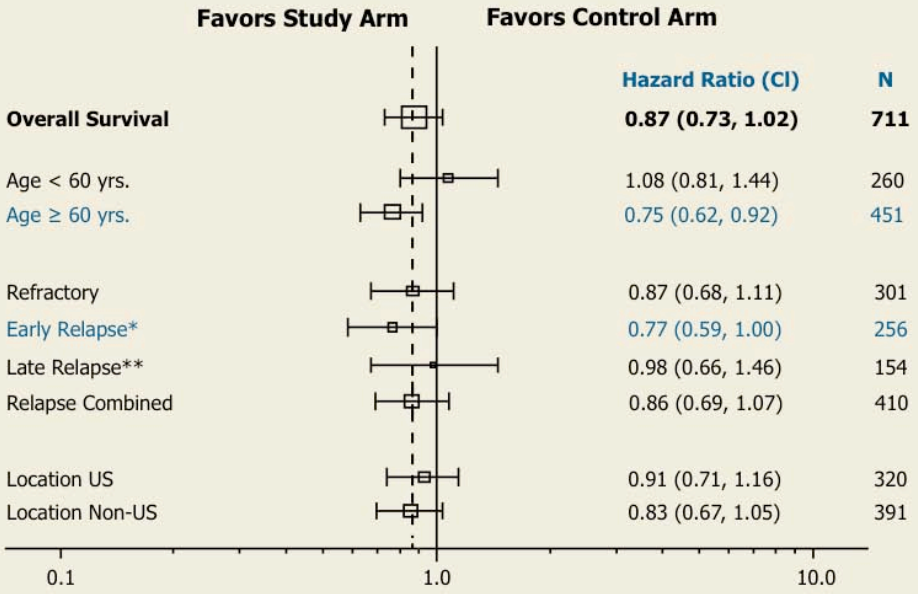
Overall Survival by Strata

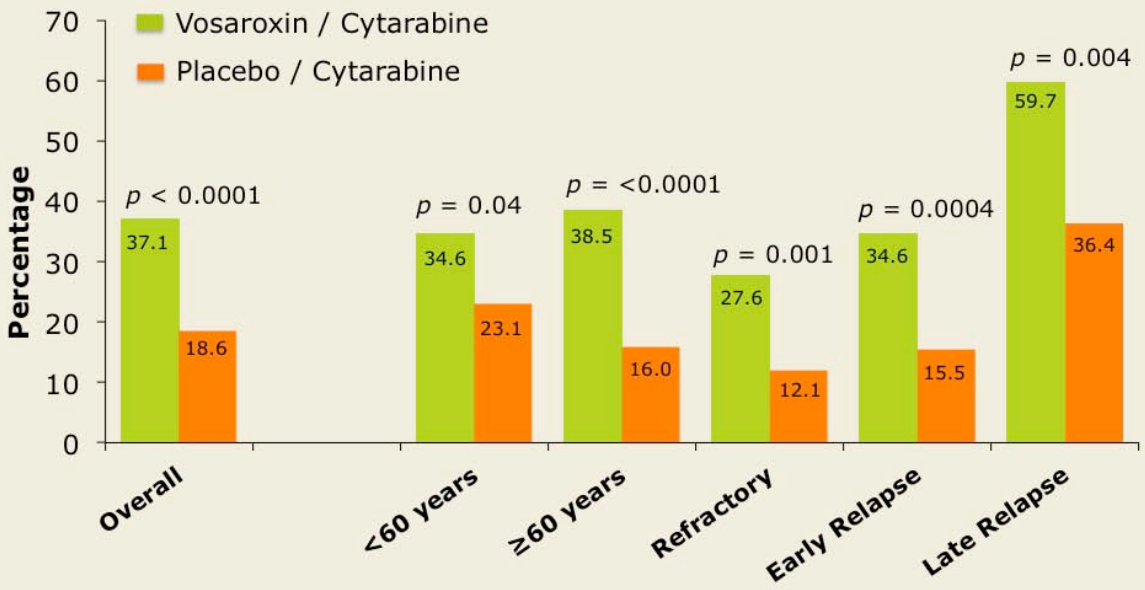


* Early relapse: relapse between 90 days and 12 months from previous response

** Late relapse: relapse between 12 and 24 months following previous response

With permission from Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

CR +CRp + CRi



CRi = CR with incomplete recovery of platelets or neutrophils

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Clinical Outcomes

EFS	Vos/Cyt (n = 356)	Pla/Cyt (n = 355)	Hazard ratio	*p*-value
Median EFS	1.9 mo	1.3 mo	0.67	<0.0001
LFS	**Vos/Cyt (n = 107)**	**Pla/Cyt (n = 58)**	**Hazard ratio**	***p*-value**
Median LFS	11.0 mo	8.7 mo	0.89	0.63

EFS = event-free survival; LFS = leukemia-free survival

- EFS = time from randomization to treatment failure, relapse or death due to any cause
- LFS = time from CR to relapse or death due to any cause, without censoring for subsequent nonprotocol therapy (including hematopoeitic SCT)

Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

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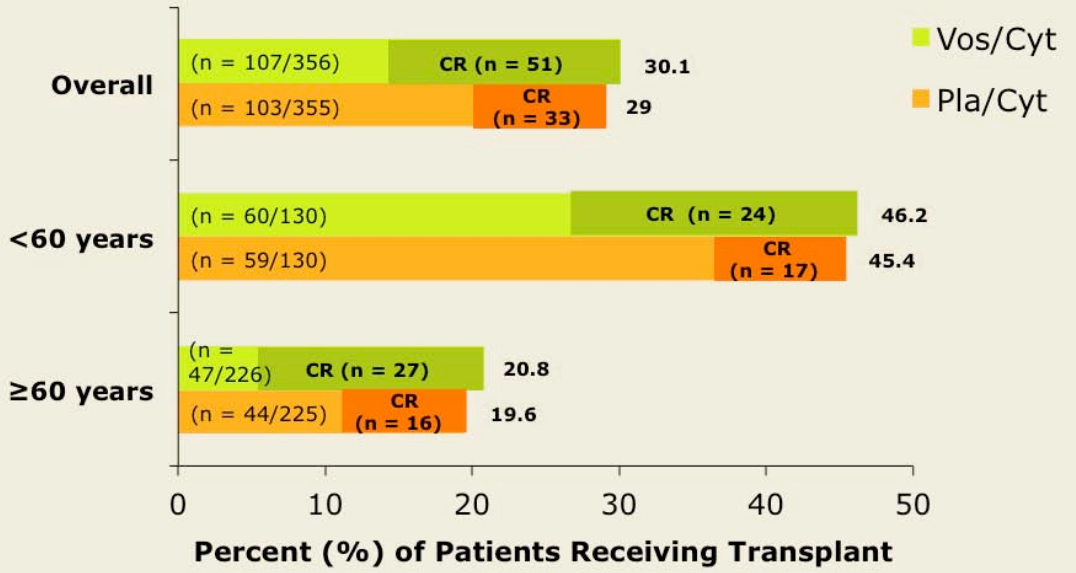
Post-Treatment Transplant Rates



- Overall incidence of Allo-SCT = 210
- Rate for younger patients was approximately double that for older patients

With permission from Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

Adverse Events (AEs) in >10% of Patients

Grade 3/4	Vos/Cyt (n = 355)	Pla/Cyt (n = 350)
Febrile neutropenia	47%	33%
Thrombocytopenia	24%	25%
Anemia	22%	23%
Neutropenia	19%	14%
Hypokalemia	15%	6%
Stomatitis	15%	3%
Pneumonia	11%	7%
Sepsis	12%	5%
Bacteremia	12%	4%

- 30-day mortality: 7.9% (Vos/Cyt) versus 6.7% (Pla/Cyt)
- 60-day mortality: 19.7% (Vos/Cyt) versus 19.4% (Pla/Cyt)

Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

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Author Conclusions

- The VALOR trial provides one of the largest data sets for patients with R/R AML.
- The study demonstrated improvements in OS and higher CR rates without increased early mortality for patients on the vosaroxin/cytarabine arm compared to those who received placebo/cytarabine.
- The clinical benefit from treatment with vosaroxin/cytarabine may be underestimated, particularly for younger patients, due to high transplant rates.
- These data support the use of the vosaroxin/cytarabine combination as a new standard as salvage therapy for older patients with R/R AML.

Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

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Investigator Commentary: VALOR — Efficacy and Safety of Vosaroxin/Cytarabine versus Placebo/Cytarabine in R/R AML

This was a controversial but enormous study. It is an accomplishment in and of itself that this study of 711 patients with R/R AML was completed. The primary endpoint of OS was not significantly improved with vosaroxin/cytarabine at 7.5 months versus 6.1 months with placebo/cytarabine ($p = 0.06$). Even if the difference of 1.4 months had been statistically significant, it would not have been clinically meaningful. It's hard for me to justify exposing my patients to what would probably be an expensive drug with definable side effects for a median OS advantage of 6 weeks.

The investigators focused on a prespecified subgroup of patients. In this population, the rates of hematopoietic SCT were similar between the 2 arms. In terms of OS, censoring for subsequent transplant showed a median OS that was significantly different for patients who received vosaroxin, at 6.7 months versus 5.3 months ($p = 0.02$). However, it is important to focus on the clinical meaning of an OS advantage of 1.4 months. The OS benefit of vosaroxin was greater for patients older than age 60.

Interview with Mikkael A Sekeres, MD, MS, January 20, 2015

continued

Investigator Commentary: VALOR — Efficacy and Safety of Vosaroxin/Cytarabine versus Placebo/Cytarabine in R/R AML (continued)

AEs were increased among patients exposed to vosaroxin. The most common Grade 3 and 4 AEs associated with vosaroxin included febrile neutropenia, stomatitis, pneumonia, sepsis and bacteremia. Although the investigators concluded that vosaroxin and cytarabine demonstrated an improved OS and higher CR rates for patients with R/R AML, it is necessary to question whether those improvements, particularly in subgroup analyses, are clinically meaningful and whether that's the right therapeutic approach for patients with AML.

Interview with Mikkael A Sekeres, MD, MS, January 20, 2015