5 Minute JournalClub

POST-ASH Issue 5, 2015

For more visit ResearchToPractice.com/5MJCASH2015

Research To Practice®

CME Information

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.

CME Information (Continued)

- 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).

CREDIT DESIGNATION STATEMENT

Research To Practice designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

HOW TO USE THIS CME ACTIVITY

This CME activity contains slides and edited commentary. To receive credit, the participant should review the slide presentations, read the commentary, complete the Post-test with a score of 75% or better and fill out the Educational Assessment and Credit Form located at ResearchToPractice.com/5MJCASH2015/5/CME.

CME Information (Continued)

FACULTY DISCLOSURES
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:

Mikkael A Sekeres, MD, MS
Professor of Medicine
Director, Leukemia Program
Cleveland Clinic Taussig Cancer Institute
Cleveland, Ohio

Advisory Committee: Amgen Inc, Boehringer Ingelheim Pharmaceuticals Inc, Celgene Corporation.

5 MinuteJournalClub

POST-ASH Issue 5, 2015

Leukemias and Myelodysplastic Syndromes Think Tank Faculty
January 29, 2015

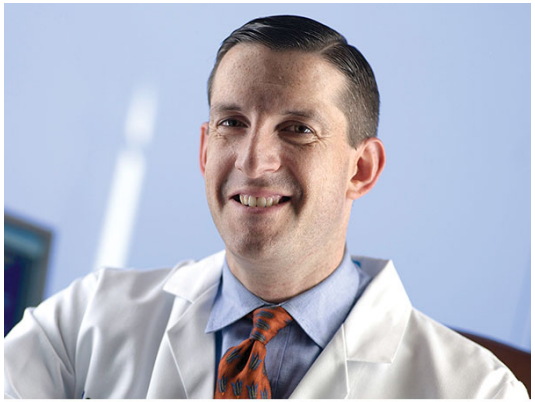
Jennifer R Brown, MD, PhD
Hagop M Kantarjian, MD
Charles A Schiffer, MD
B Douglas Smith, MD
David P Steensma, MD
Wendy Stock, MD, MA

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.

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
Research To Practice
Miami, Florida

Sorafenib versus Placebo in Addition to Standard Therapy in Younger Patients with Newly Diagnosed Acute Myeloid Leukemia: Results from 267 Patients Treated in the Randomized Placebo-Controlled SAL-SORAML Trial

Rollig C et al.

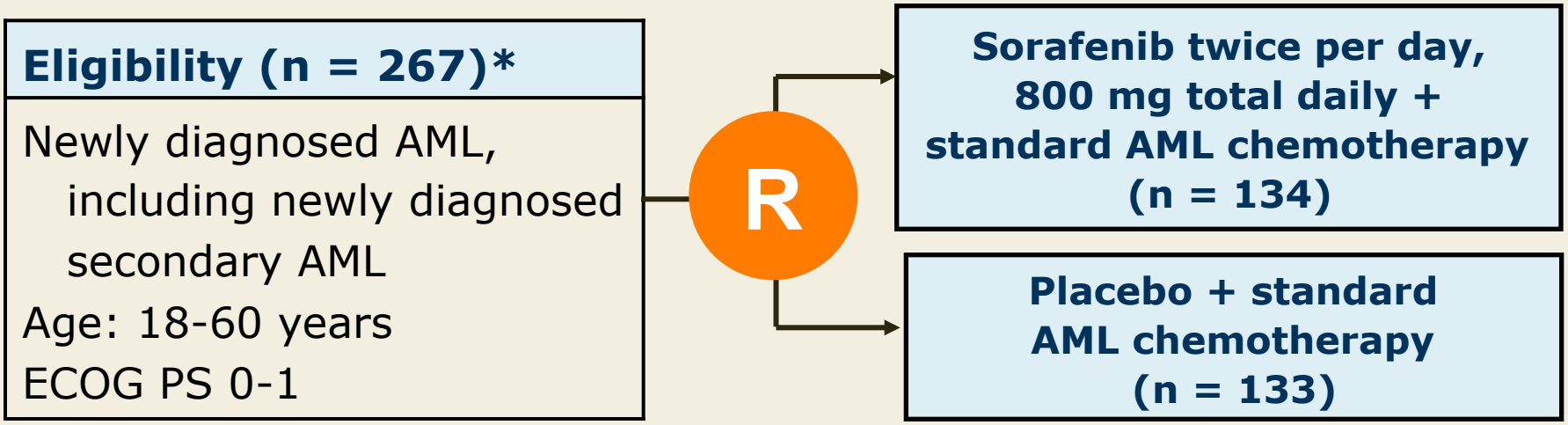
Proc ASH 2014;Abstract 6.

Background

- Sorafenib is a multikinase inhibitor with activity against several oncogenic kinases that may play a role in the pathogenesis of acute myeloid leukemia (AML).
- Data from in vitro studies and nonrandomized clinical trials suggest that sorafenib might be an effective drug for the treatment of AML (*Biol Blood Marrow Transplant* 2014;20:1687; 2042).
- **Study objective:** To determine the efficacy of sorafenib added to standard primary induction and consolidation therapy for patients ≤60 years of age with newly diagnosed AML.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

Phase II SORAML Trial Design (NCT00893373)



* Out of 276 enrolled patients, 267 received the study treatment.

- **Primary endpoint:** Event-free survival (EFS)
- Treatment plan for all patients included 2 cycles of induction with DA (daunorubicin 60 mg/m^2 d3-5 + cytarabine 100 mg/m^2 continuous IV d1-7)
  → 3 cycles of high-dose cytarabine consolidation (3 g/m^2 BID d1, 3, 5).
- Patients without response after DA I received second induction with HAM (cytarabine 3 g/m^2 BID d1-3 + mitoxantrone 10 mg/m^2 d3-5).
- Allogeneic stem cell transplantation was scheduled for all patients with intermediate-risk AML in first complete remission with a sibling donor and for all patients at high risk with a matched related or unrelated donor.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

Patient Demographics and Treatment Characteristics

- Demographic and disease characteristics were equally distributed between the 2 arms.
  - The incidence of the FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutation was 17% in both arms.
- Among 46 patients with FLT3-ITD-positive AML, there was no difference in EFS:
  - A trend in favor of sorafenib was observed for prolonged relapse-free survival and overall survival.
- The median follow-up time was 36 months.
- The median cumulative dose of administered study medication was similar in both arms.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

Clinical Outcomes

Outcome	Sorafenib	Placebo	*p*-value
Complete response (CR)	60%	59%	0.764
Median EFS* 3-year EFS	20.5 mo 40%	9.2 mo 22%	0.013
Median RFS 3-year RFS	NYR 56%	23 mo 38%	0.017
Median OS 3-year OS	NYR 63%	NYR 56%	0.382

RFS = relapse-free survival; NYR = not yet reached; OS = overall survival

* An event is defined as failure to achieve CR after induction, relapse or death.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

Adverse Events

- The most common reported Grade ≥3 adverse events were:
  - Fever (40%)
  - Infections (22%)
  - Bleeding events (2%)
- The risk for fever, bleeding events and hand-foot syndrome was significantly higher in the sorafenib arm.
- The incidence of all other adverse events showed no significant differences.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

Author Conclusions

- For younger patients with AML, the sequential addition of sorafenib to standard chemotherapy is feasible and associated with antileukemic efficacy.
- A higher incidence of infections and bleeding events was associated with sorafenib therapy.
- Although overall survival in both treatment arms was similar, sorafenib treatment resulted in significantly prolonged event-free and relapse-free survival.

Rollig C et al. *Proc ASH* 2014;Abstract 6 (Abstract only).

Investigator Commentary: Results from the Phase II SORAML Trial of Sorafenib in Patients with Newly Diagnosed AML

The results from the SORAML trial were presented at the plenary session at ASH 2014. Patients received sorafenib or placebo in addition to primary induction and consolidation therapy. Induction included treatment with 2 cycles of DA followed by 3 cycles of high-dose cytarabine consolidation therapy. The CR rates in both arms were identical at 59% with placebo versus 60% with sorafenib. All patients were followed for 36 months. A statistically significant difference was reported in median EFS, which was 9.2 months in the placebo arm versus 20.5 months in the sorafenib arm. The 3-year relapse-free survival was statistically different at 38% in the placebo arm and 56% with sorafenib.

Importantly, among the 46 patients with FLT3-ITD abnormalities, no difference was reported in EFS between the 2 treatment arms. Overall, there appears to be an advantage for patients who received sorafenib versus placebo regardless of FLT3-ITD status. However, no overall survival data are available because the median had not yet been reached. The 3-year overall survival was 63% with the addition of sorafenib versus 56% in the placebo arm.

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

continued

Investigator Commentary: Results from the Phase II SORAML Trial of Sorafenib in Patients with Newly Diagnosed AML (continued)

The "money page" in AML is overall survival, and historically we've always been able to get better results with more therapy earlier on, but this is usually at the cost of some toxicity that limits survival. We need to see how the survival data with the addition of sorafenib in this study mature. It's perplexing that we didn't see more of a signal with sorafenib therapy in those patients who had FLT3-ITD abnormalities.

The addition of sorafenib during induction and consolidation therapy did not add much toxicity. As a side note, assessing adverse events in patients who are receiving intensive induction chemotherapy is mind-bogglingly difficult because by design we're creating side effects. We're even creating a measurable amount of mortality associated with therapy. In this study the most common adverse events of Grade 3 or higher included fever, which is usually observed in leukemia studies, and, not surprisingly, infections and bleeding events. The rates of fever, bleeding events and hand-foot syndrome were significantly higher in the sorafenib arm. Overall, there was not much of a difference in the observed adverse events between the treatment arms.

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

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)

Ravandi F et al.

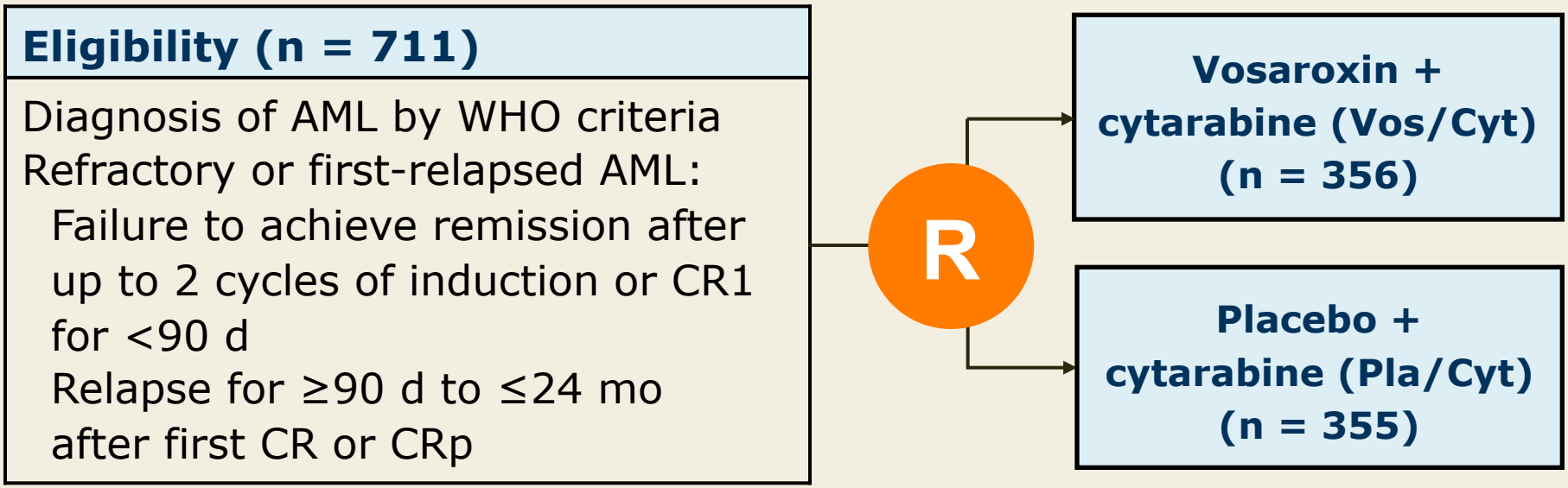
Proc ASH 2014;Abstract LBA-6.

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.

Phase III VALOR Trial Design (NCT01191801)

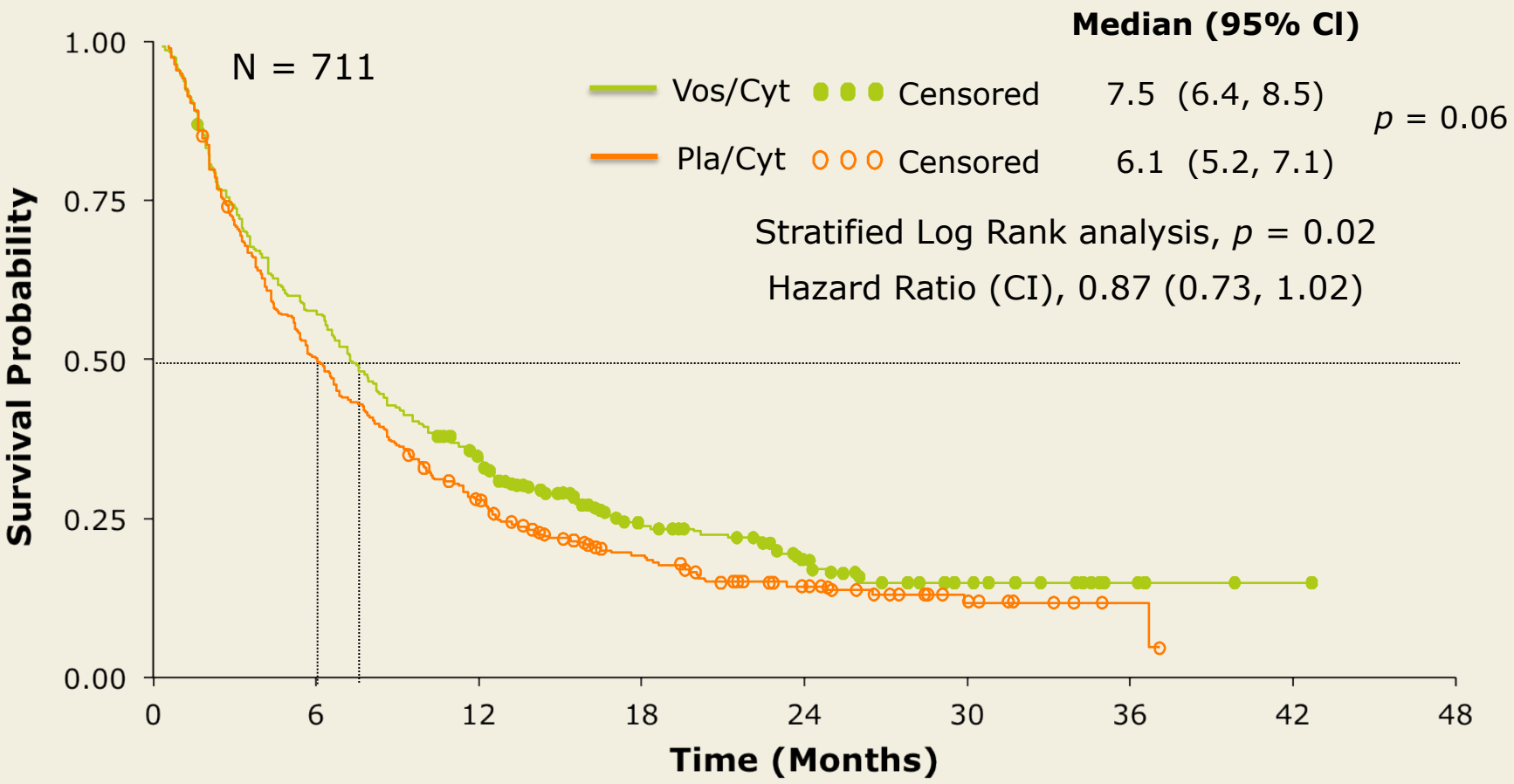


CR = complete response; CRp = CR with incomplete platelet recovery

- 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

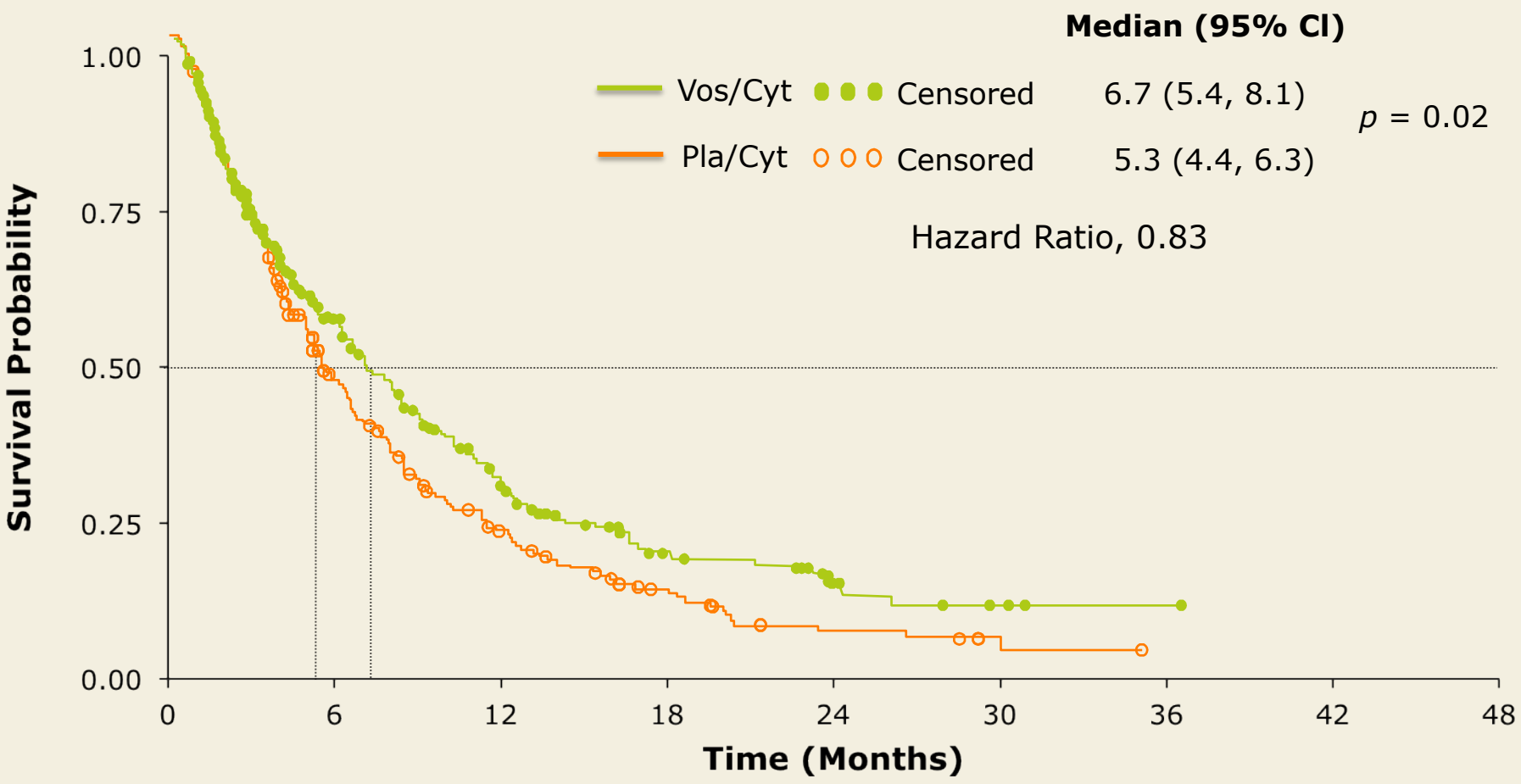
Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

Overall Survival: Intent-to-Treat



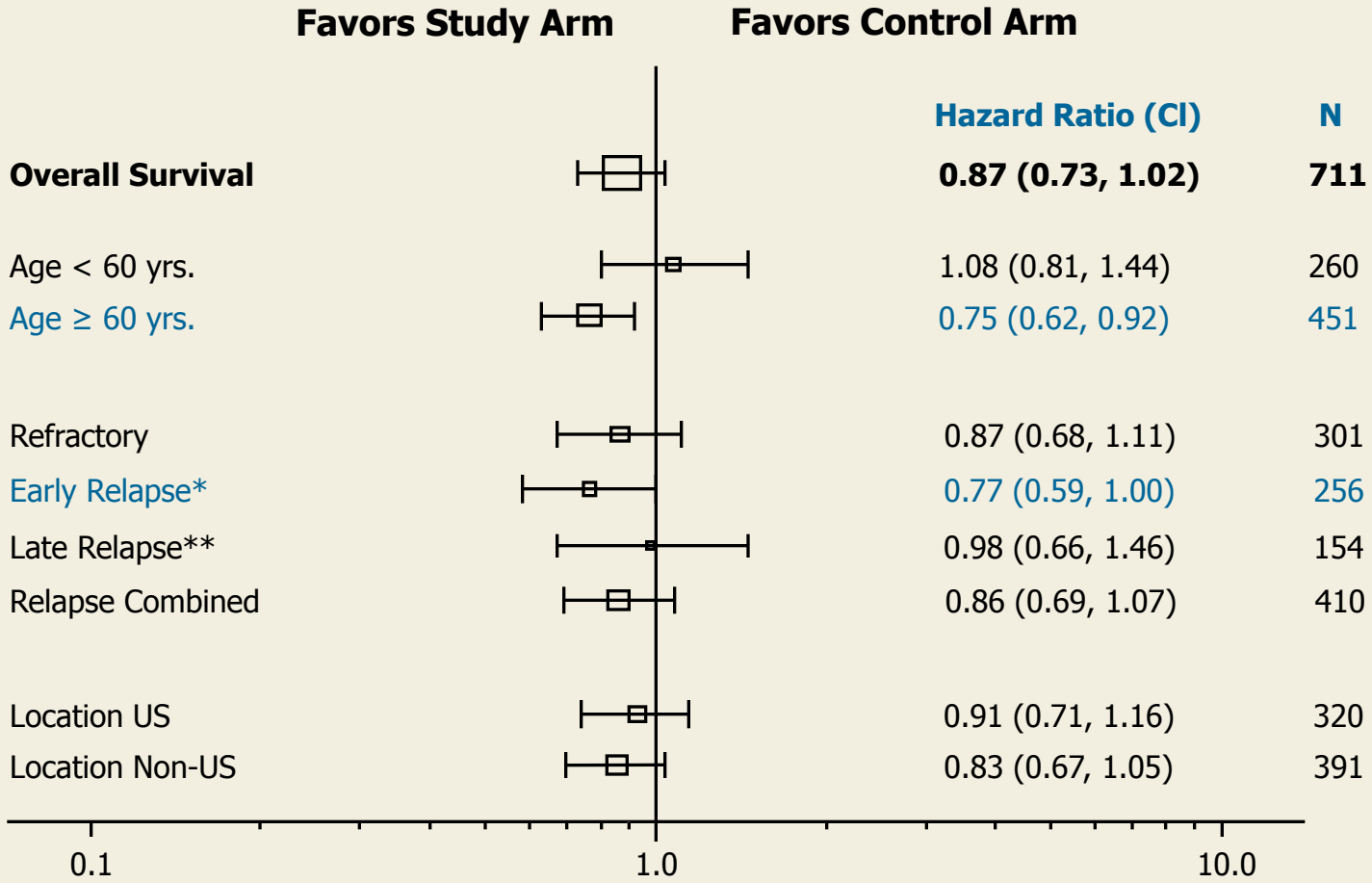
With permission from Ravandi F et al. *Proc ASH* 2014;Abstract LBA-6.

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



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

Overall Survival by Strata

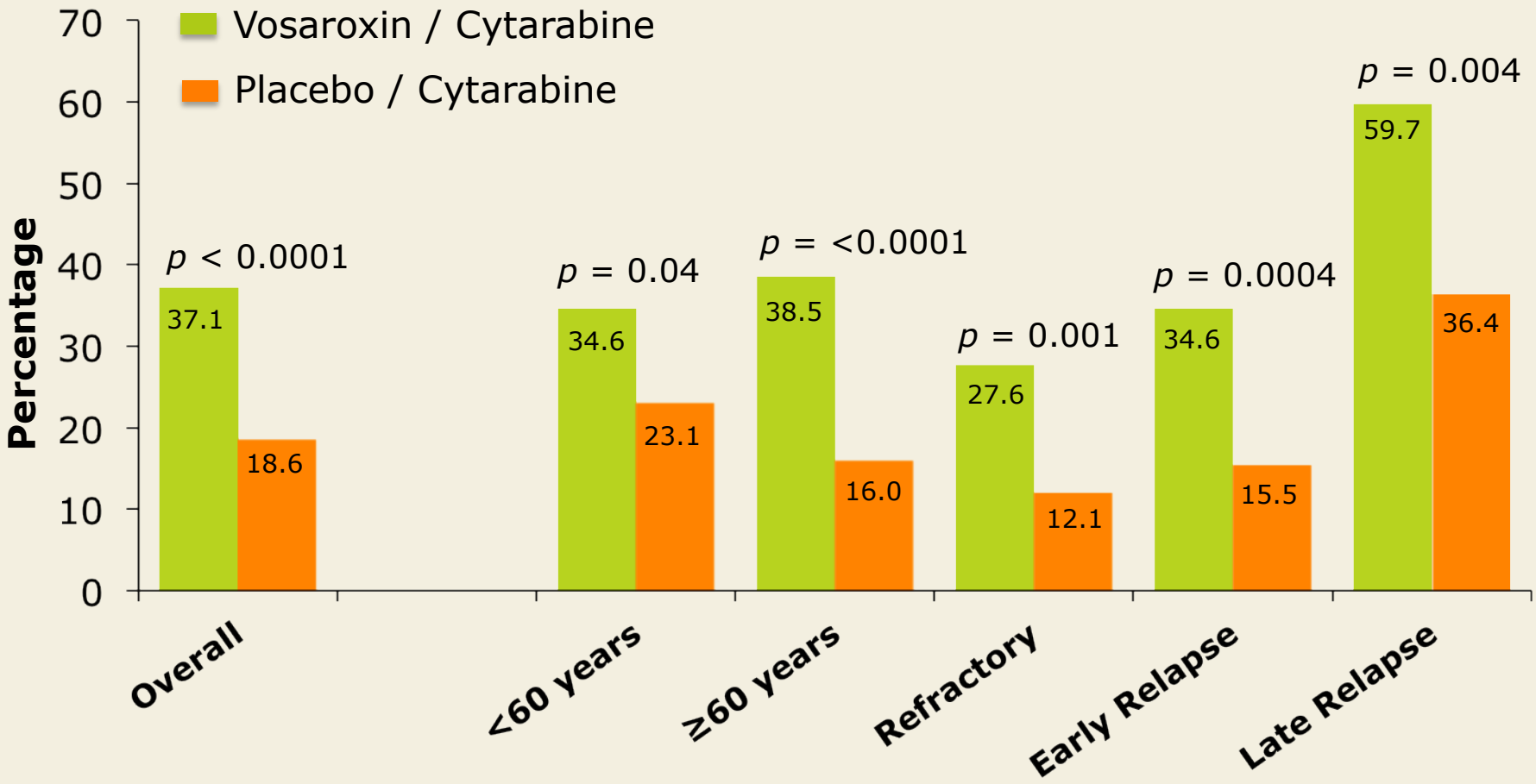


* Early relapse: relapse between 90 days and 12 months from previous response

** 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

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

Clinical Outcomes

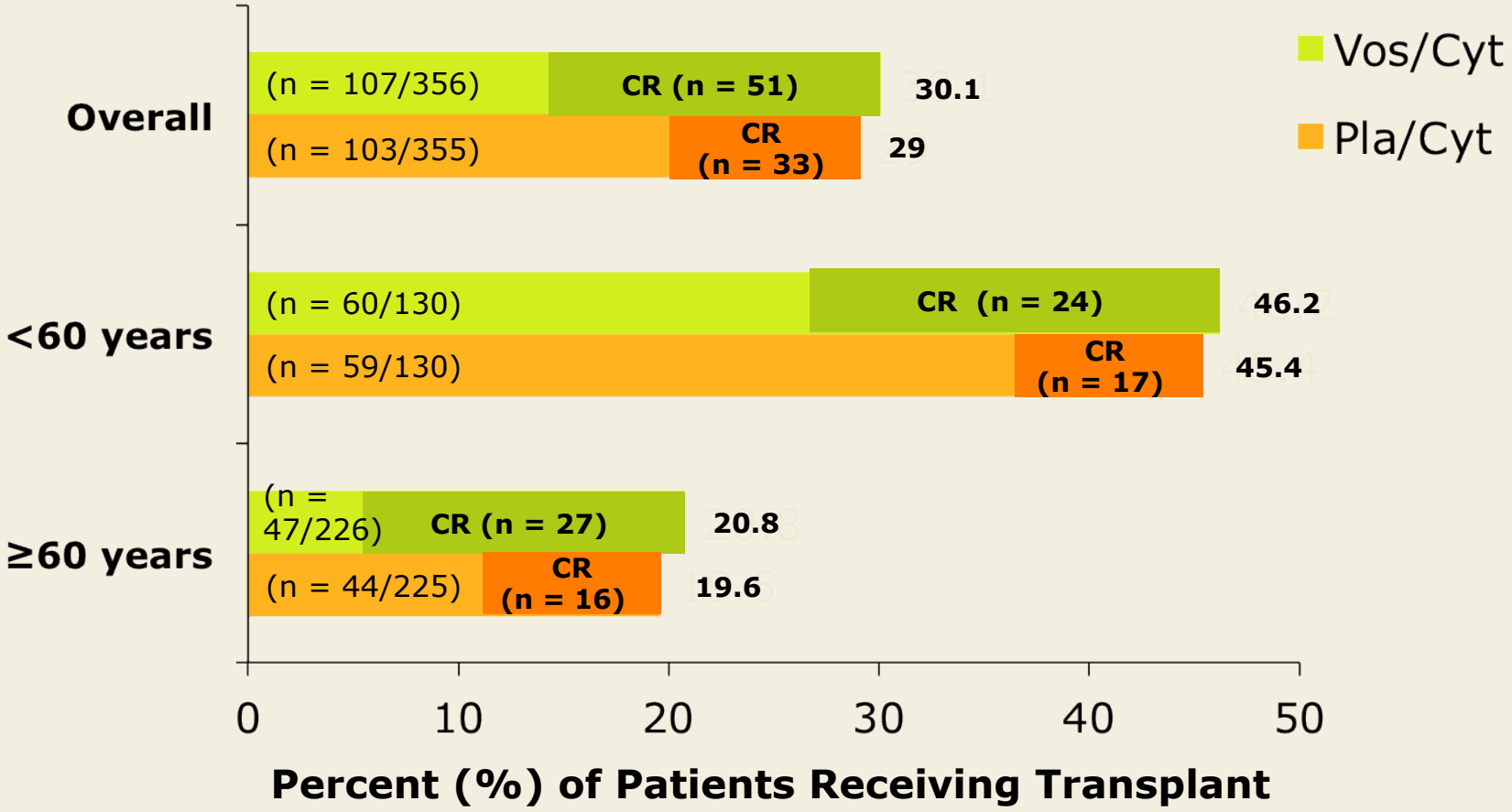
EFS	Vos/Cyt (n = 356)	Pla/Cyt (n = 355)	Hazard ratio	*p*-value
Median EFS	1.9 mo	1.3 mo	0.67	<0.0001
LFS	**Vos/Cyt (n = 107)**	**Pla/Cyt (n = 58)**	**Hazard ratio**	***p*-value**
Median LFS	11.0 mo	8.7 mo	0.89	0.63

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.

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.

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.

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

A Randomized Phase II Study of Azacitidine Combined with Lenalidomide or with Vorinostat vs Azacitidine Monotherapy in Higher-Risk Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML): North American Intergroup Study SWOG S1117[1]

Efficacy and Safety of Lenalidomide versus Placebo in RBC-Transfusion Dependent Patients with IPSS Low or Intermediate-1-Risk Myelodysplastic Syndromes without Del(5q) and Unresponsive or Refractory to Erythropoiesis-Stimulating Agents: Results from a Randomized Phase 3 Study (CC-5013-MDS-005)[2]

[1] **Sekeres MA et al.**
Proc ASH 2014;Abstract LBA-5.

[2] **Santini V et al.**
Proc ASH 2014;Abstract 409.

A Randomized Phase II Study of Azacitidine Combined with Lenalidomide or with Vorinostat vs Azacitidine Monotherapy in Higher-Risk Myelodysplastic Syndromes (MDS) and Chronic Myelomonocytic Leukemia (CMML): North American Intergroup Study SWOG S1117

Sekeres MA et al.

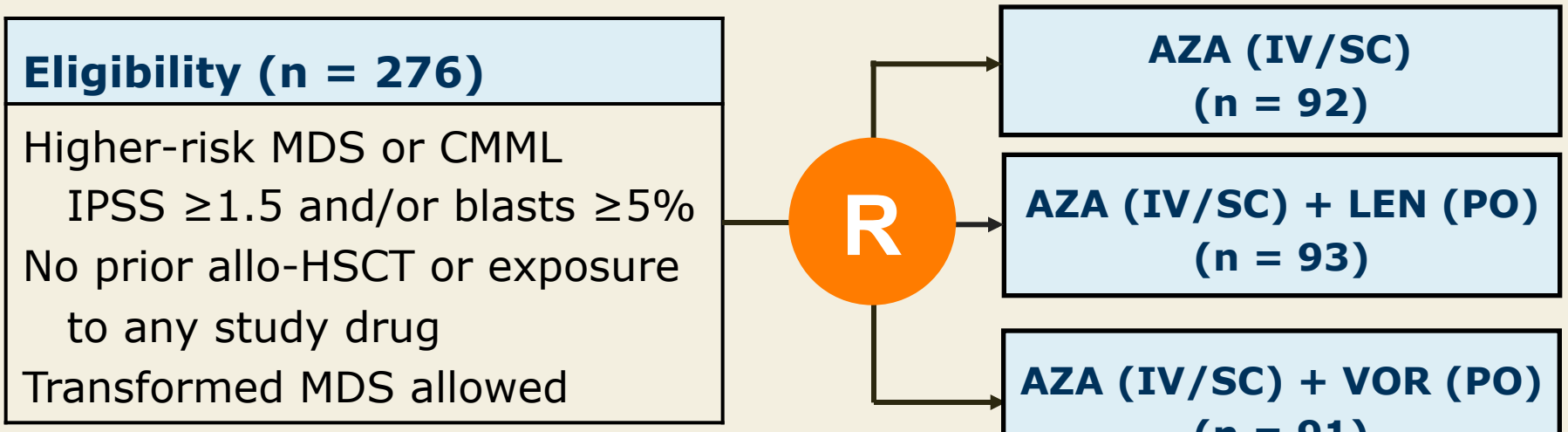
Proc ASH 2014;Abstract LBA-5.

Background

- Higher-risk MDS and CMML comprise a spectrum of disorders associated with cytopenias, high risk of transformation to acute myeloid leukemia (AML) and truncated survival (*Blood* 2009;114:937).
- Initial treatment with a hypomethylating agent such as azacitidine (AZA) is considered to be the standard practice.
- It is not known if the histone deacetylase inhibitor vorinostat (VOR), which acts synergistically with AZA to reactivate epigenetically silenced genes, or the addition of lenalidomide (LEN), which impacts the bone marrow microenvironment, improves response rates in comparison to AZA monotherapy.
- **Study objective:** To determine the efficacy and safety of AZA with or without LEN or VOR for patients with higher-risk MDS or CMML.

Sekeres MA et al. *Proc ASH* 2014;Abstract LBA-5.

Phase II SWOG-S1117 Trial Design



Allo-HSCT = allogeneic hematopoietic stem cell transplant

AZA: 75 mg/m^2 per day on days 1-7; LEN: 10 mg/d for 21 days; VOR: 300 mg BID on days 3-9

- Dose reductions were allowed for unresolved Grade ≥3 adverse events or delayed count recovery.
- **Primary endpoint:** 20% improvement in overall response rate (ORR).
- **Secondary endpoints** included overall survival (OS), relapse-free survival (RFS) and leukemia-free survival.

Sekeres MA et al. *Proc ASH* 2014;Abstract LBA-5.

Response

All patients	AZA	AZA + LEN (*p*-value*)	AZA + VOR (*p*-value*)	Total (n = 260)
ORR	37%	39% (1.0)	24% (0.07)	33%
CR	24%	18%	15%	19%
PR	0%	1%	1%	1%
HI	13%	19%	7%	13%
CMML	**n = 15**	**n = 19**	**n = 16**	**n = 50**
ORR	33%	59% (0.15)	13% (0.41)	34%

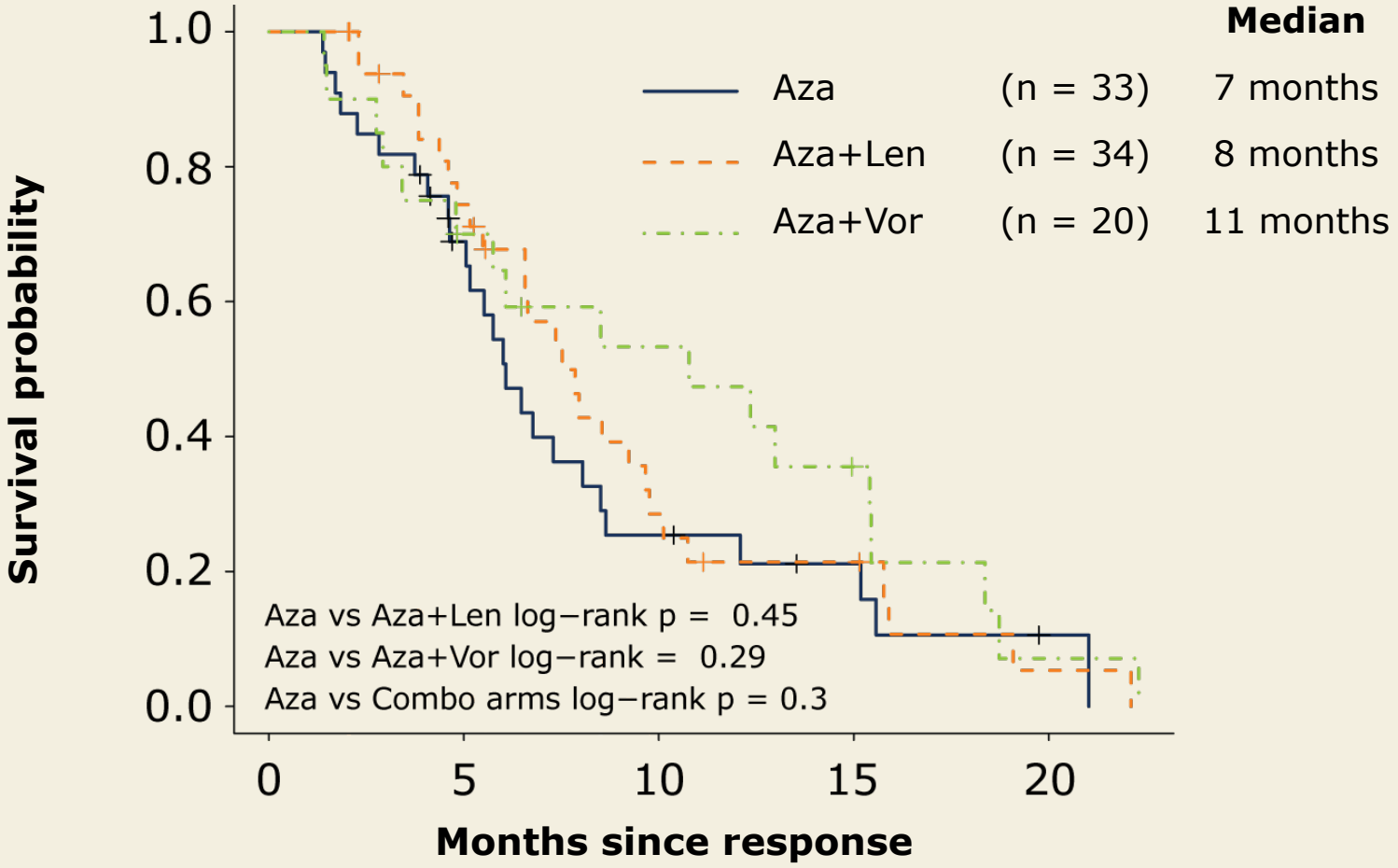
* Versus AZA

CR = complete response; PR = partial response; HI = hematologic improvement

- Median duration of treatment: 25 wk (AZA) vs 24 wk (AZA + LEN) vs 20 wk (AZA + VOR)

Sekeres MA et al. *Proc ASH* 2014;Abstract LBA-5.

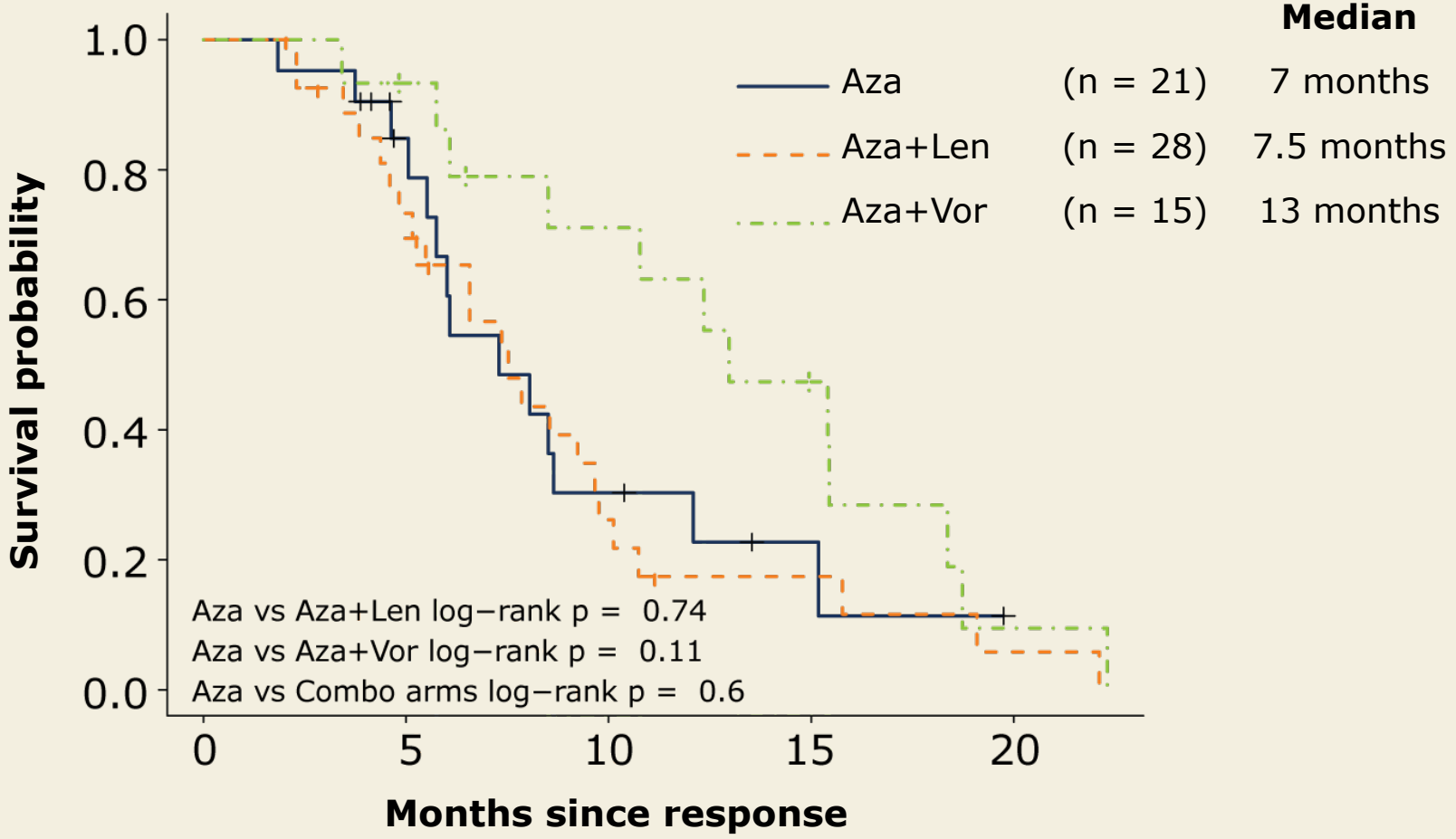
RFS: All Responders



- Median RFS in all responders: 7 months

With permission from Sekeres MA et al. *Proc ASH* 2014;Abstract LBA-5.

RFS: All Responders on Therapy for More Than 6 Months



- Median RFS in all responders on therapy for >6 months: 8.5 months

With permission from Sekeres MA et al. *Proc ASH* 2014;Abstract LBA-5.

Adverse Events (AEs)

Grade ≥3 (n)	AZA	AZA + LEN (*p*-value*)	AZA + VOR (*p*-value*)	Total (n = 260)
Febrile neutropenia	10	13 (0.66)	13 (0.51)	36
GI toxicity	4	11 (0.10)	23 (<0.001)	38
Rash	2	12 (0.01)	1 (1.0)	15

* Versus AZA

- Patients who discontinued treatment due to AEs: 9% (AZA) vs 23% (AZA + LEN) vs 24% (AZA + VOR); all patients, 19%
  - *p*-values vs AZA: 0.04 (AZA + LEN); 0.03 (AZA + VOR)
- Patients with nonprotocol-defined dose modifications: 23% (AZA) vs 41% (AZA + LEN) vs 36% (AZA + VOR); all patients, 33%
  - *p*-values vs AZA: 0.01 (AZA + LEN); 0.05 (AZA + VOR)

Sekeres MA et al. *Proc ASH* 2014;Abstract LBA-5.

Author Conclusions

- There was no difference in ORR between AZA + LEN or AZA + VOR and AZA monotherapy.
  - Some subgroups of patients may have benefited from AZA-based combinations.
- There was a signal of RFS improvement with AZA + VOR therapy.
- Mature data analyses for event-free survival and OS according to cytogenetic subgroups are pending.
- Some questions remain:
  - Are combination regimens in MDS too toxic?
  - Is there a need to manage toxicities better?
- ORR is not the right endpoint for large MDS trials.
  - It is important to focus on durable responses and on OS.

Sekeres MA et al. *Proc ASH* 2014;Abstract LBA-5.

Investigator Commentary: Phase II SWOG-S1117 Trial of AZA with or without LEN or VOR for Higher-Risk MDS or CMML

SWOG-S1117 is the largest prospective study in higher-risk MDS ever conducted in North America. The use of AZA + LEN capitalizes on the different mechanisms of action of the 2 drugs. Accrual to the study was much faster than we anticipated. ORR was defined as a combination of CR, PR and HI, and no difference across arms was observed, with an ORR of 37% for AZA, 39% for AZA + LEN and 24% for AZA + VOR. Although the CR rates were numerically higher for AZA at 24% versus 18% for AZA + LEN and 15% for AZA + VOR, this is an artifact of patients not getting to their first bone marrow biopsy to assess response. Patients on the AZA + LEN arm were significantly more likely to experience HI. There was a signal for improvement in ORR for patients with CMML who received AZA + LEN: 59% versus 33% for AZA only. RFS appeared to be slightly higher for patients on the combination arms versus AZA only. With a focus on patients who received therapy for more than 6 months, an attempt to correct for those on the combination arms who were prematurely removed from the study, RFS for patients receiving AZA + VOR was 13 months compared to 7 months for AZA only, with a *p*-value with a trend toward significance.

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

continued

Investigator Commentary: Phase II SWOG-S1117 Trial of AZA with or without LEN or VOR for Higher-Risk MDS or CMML

In terms of toxicity, the rates of febrile neutropenia were similar across arms. Patients who received AZA + VOR were more likely to experience gastrointestinal toxicities, whereas those who received AZA + LEN were more likely to develop a rash. Interestingly, patients on the combination arms were statistically significantly more likely to come off the study because of toxicities or complications than those who received AZA only. More importantly, those on the combination arms were significantly more likely to undergo nonprotocol-defined dose modifications.

Many of the data are still maturing. We don't have OS data yet. Because of the Intergroup mechanism we don't yet have analysis to detect any signal within cytogenetic subgroups. Also, I'm not convinced that ORR is the right endpoint for large MDS trials. We need to focus on durable responses and on OS. I believe that the use of more drugs is better for higher-risk MDS because of the biology of the disease with the number of steps involved before the disease becomes manifest. I don't believe that a single strategy will be the answer for MDS. Targeted therapy works somewhat but probably not as well as we would like in isolation for hematologic cancers.

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

Efficacy and Safety of Lenalidomide versus Placebo in RBC-Transfusion Dependent Patients with IPSS Low or Intermediate-1-Risk Myelodysplastic Syndromes without Del(5q) and Unresponsive or Refractory to Erythropoiesis-Stimulating Agents: Results from a Randomized Phase 3 Study (CC-5013-MDS-005)

Santini V et al.

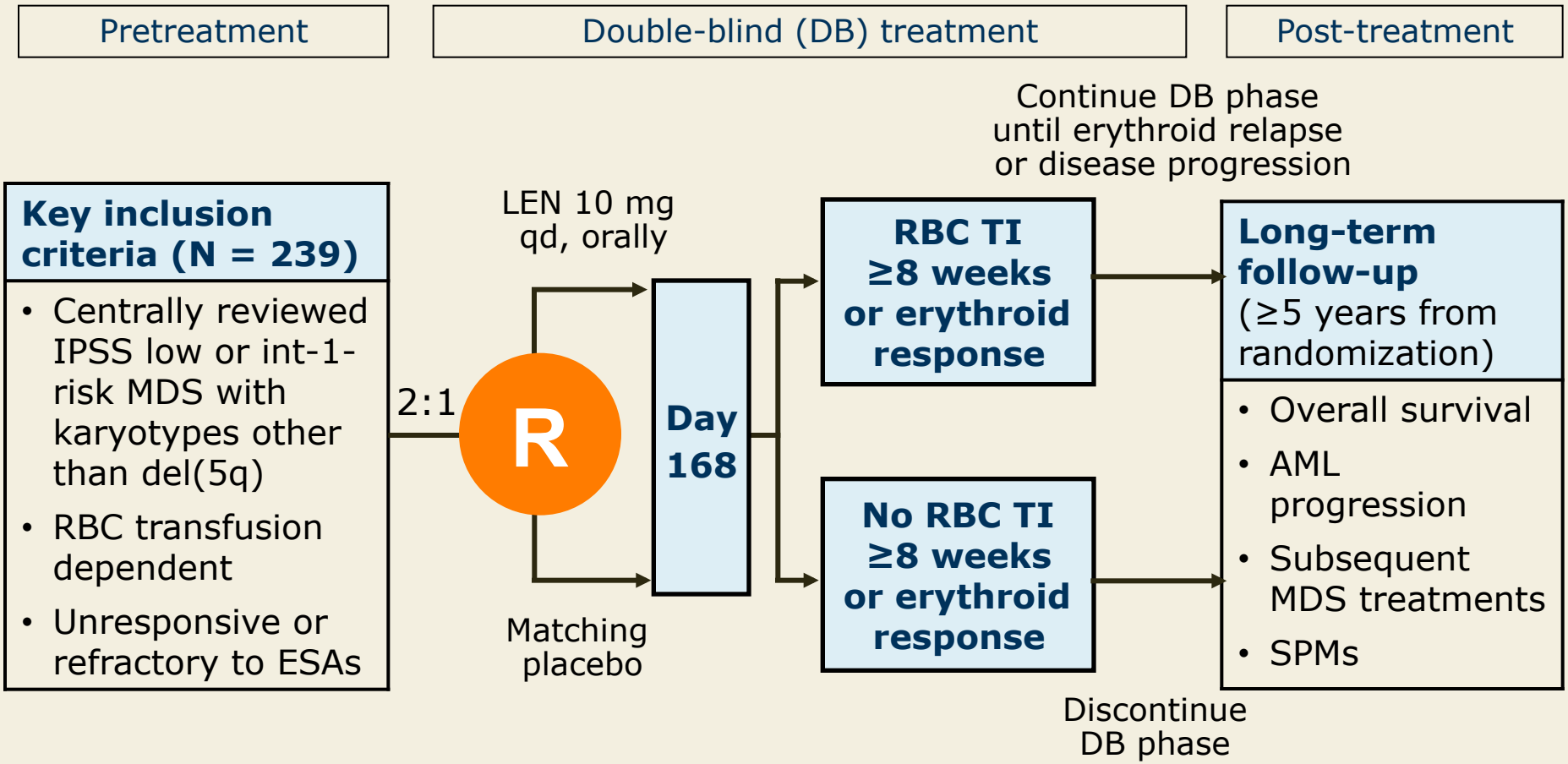
Proc ASH 2014;Abstract 409.

Background

- The majority of patients with lower-risk (LR) myelodysplastic syndromes (MDS) present with anemia at diagnosis (*Blood* 2013;121:4280).
- Erythropoiesis-stimulating agents (ESAs) remain the first-line treatment option for anemia in LR MDS without del(5q).
- Most responses to ESAs are transient, relapse of anemia is common and transfusions are often required.
- In the Phase II MDS-002 trial, lenalidomide (LEN) was associated with RBC transfusion independence (TI) ≥8 weeks in 26% of patients with LR MDS without del(5q) (*Blood* 2008;111:86-93).
- A retrospective analysis of MDS-002 identified a gene expression signature predictive of LEN response in patients without del(5q) (*PLoS Med* 2008;5:e35).
- **Study objective:** To determine the efficacy and safety of LEN in RBC transfusion-dependent patients with low- or intermediate-1 (Int-1)-risk MDS without del(5q).

Santini V et al. *Proc ASH* 2014;Abstract 409.

Phase III MDS-005 Trial Design

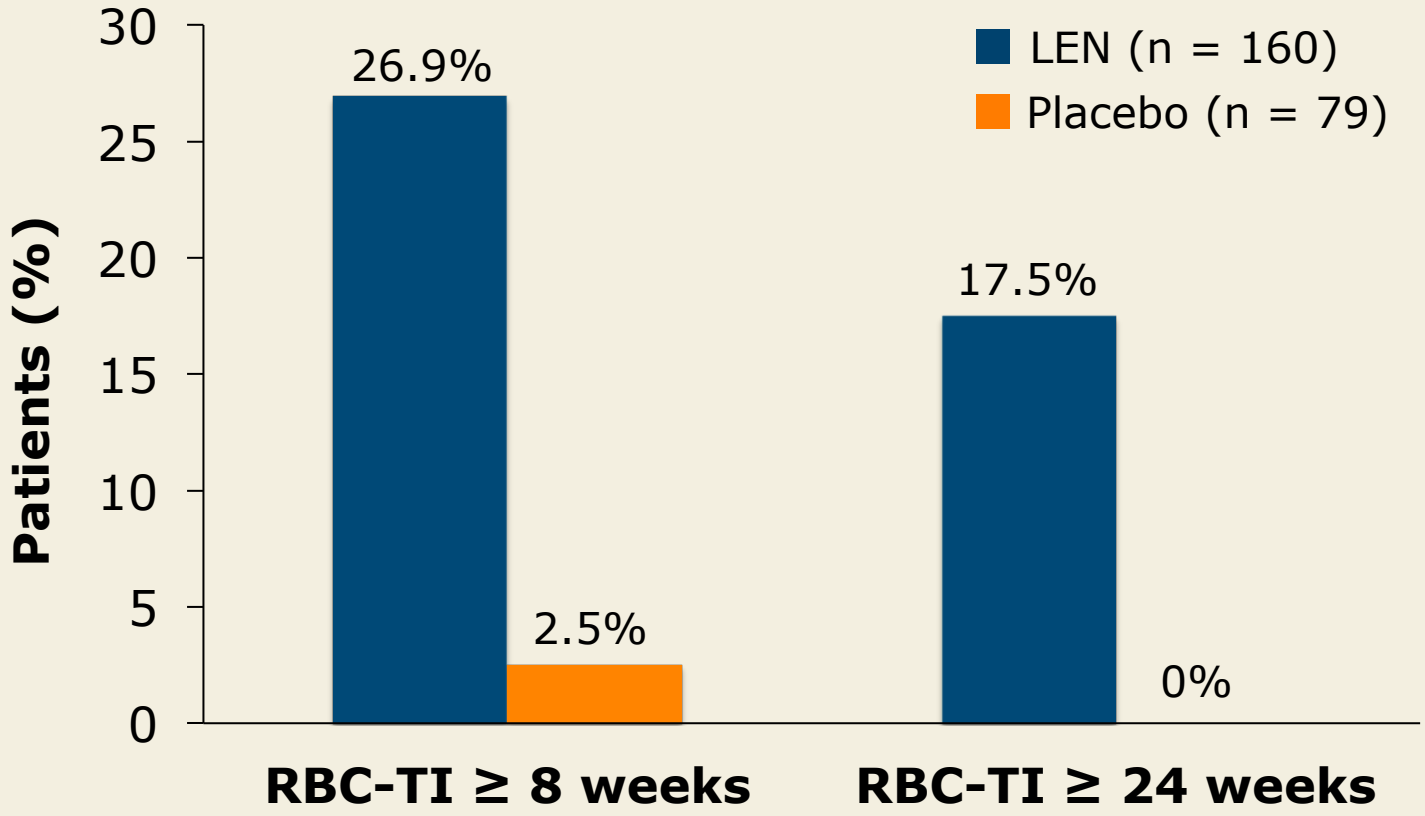


Primary endpoint: RBC TI for ≥8 weeks

AML = acute myeloid leukemia; SPM = second primary malignancy

Santini V et al. *Proc ASH* 2014;Abstract 409.

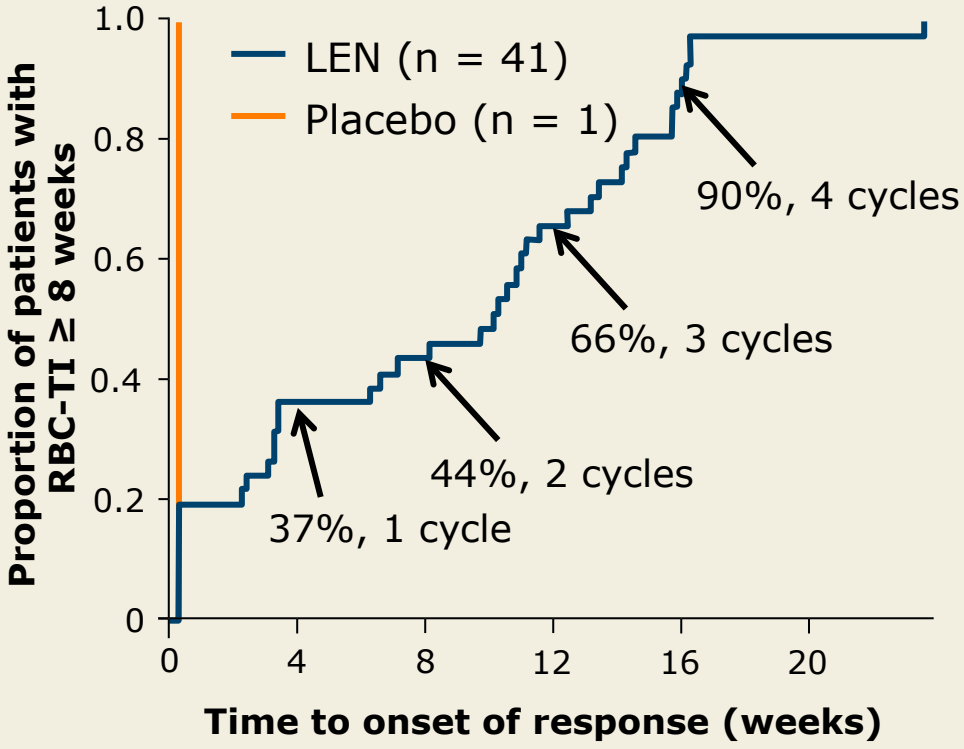
RBC TI at ≥8 Weeks and ≥24 Weeks

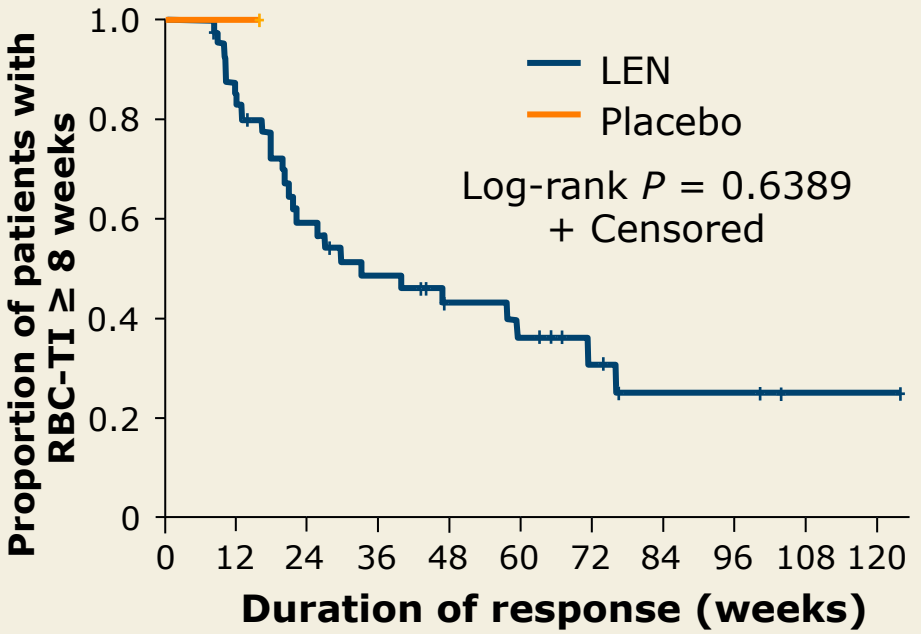


- Significantly more patients who received LEN achieved RBC TI at ≥8 weeks versus placebo ($p<0.001$)

With permission from Santini V et al. *Proc ASH* 2014;Abstract 409.

Time to and Duration of RBC TI Achieved at ≥8 Weeks





No. of RBC-TI patients

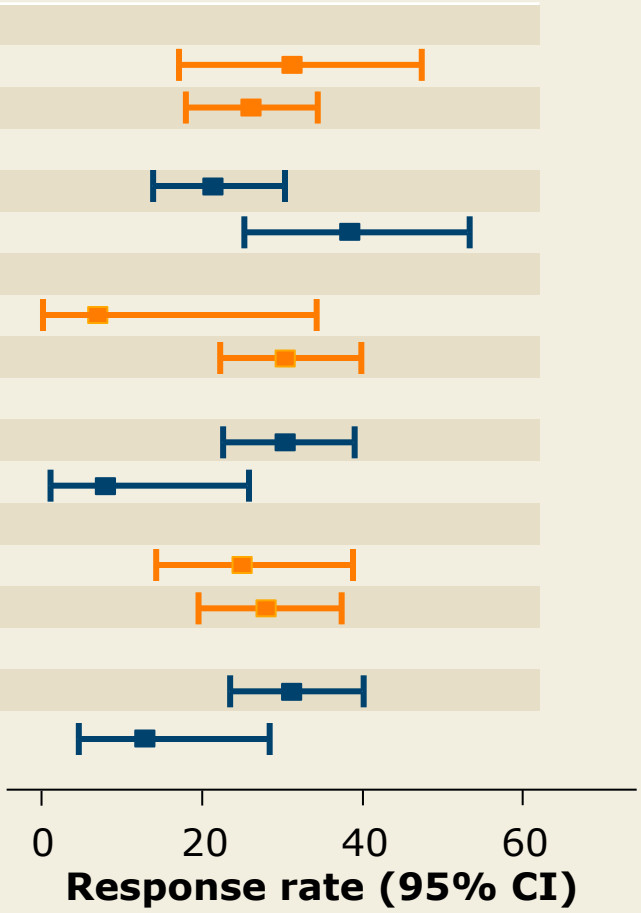
LEN	41	34	23	18	13	11	6	3	3	1	1
Placebo	1	1	0								

- 90% of patients with RBC-TI at ≥8 weeks responded within 4 cycles of tx
- The median duration of response was 32.9 weeks among RBC-TI ≥8-weeks responders with LEN

With permission from Santini V et al. *Proc ASH* 2014;Abstract 409.

Subgroup Analysis of Patients Who Achieved RBC TI at ≥8 Weeks with LEN

Baseline characteristic	RBC-TI ≥ 8 weeks, n/N (%)
Age	
≤ 65 years	12/39 (30.8)
> 65 years	31/121 (25.6)
Sex*	
Male	23/108 (21.3)
Female	20/52 (38.5)
Gene signature positive	
Yes	1/14 (7.1)
No	36/118 (30.5)
Previous MDS therapy*	
Yes	41/135 (30.4)
No	2/25 (8.0)
Time since diagnosis	
< 2 years	14/56 (25.0)
≥ 2 years	29/104 (27.9)
Baseline 28-day pRBC transfusion*	
Low	38/122 (31.1)
High	5/38 (13.2)

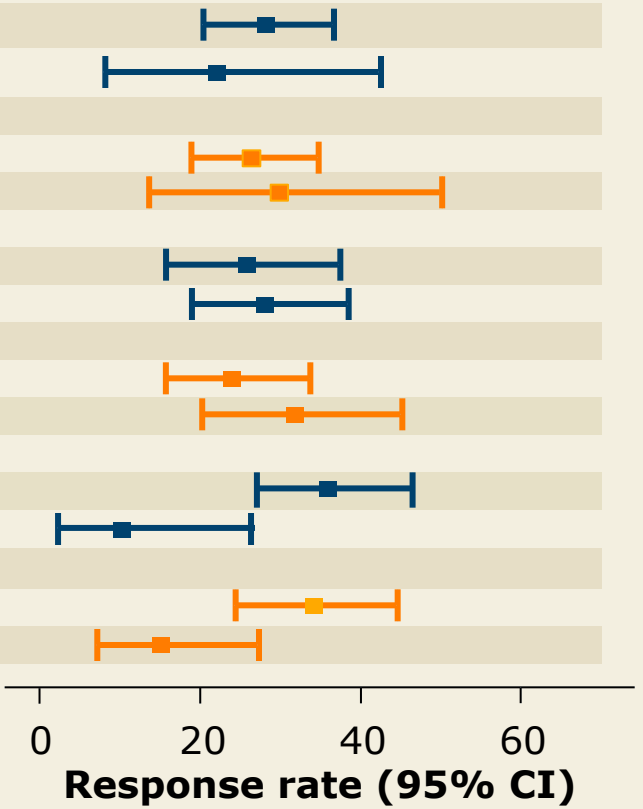


* Indicates a statistically significant difference in rates within subgroup ($p<0.05$)

With permission from Santini V et al. *Proc ASH* 2014;Abstract 409.

Subgroup Analysis of Patients Who Achieved RBC TI at ≥8 Weeks with LEN (continued)

Baseline characteristic	RBC-TI ≥ 8 weeks, n/N (%)
IPSS karyotype (central review)	
Good	37/132 (28.0)
Intermediate	6/27 (22.2)
BM blasts	
< 5%	35/133 (26.3)
≥ 5%	8/27 (29.6)
IPSS category (central review)	
Low	18/70 (25.7)
Int-1	25/89 (28.1)
Number of cytopenias	
0–1	24/100 (24.0)
2–3	19/60 (31.7)
Prior ESA use*	
Yes	40/125 (32.0)
No	3/35 (8.6)
Serum EPO level*	
≤ 500 mU/mL	33/97 (34.0)
> 500 mU/mL	9/58 (15.5)



* Indicates a statistically significant difference in rates within subgroup ($p<0.05$)

With permission from Santini V et al. *Proc ASH* 2014;Abstract 409.

Incidence of AML and SPMs and Correlation of a Gene Expression Signature with LEN Therapy

Events per 100 person-years	LEN (n = 160)	Placebo* (n = 79)
AML† progression	1.91	2.46
SPM	2.19	2.27

* One patient in the placebo group with AML at baseline was excluded from the analysis of AML progression.

† AML is not considered an SPM in this population.

- The median duration of follow-up was 1.6 years (range 0-3.6 years) in the LEN group and 1.3 years (range 0-4.0 years) in the placebo group.
- The MDS-005 trial demonstrated that the erythroid differentiation signature gene set was not predictive for a response of RBC-TI at ≥8 weeks.
  - This result is based on 139 intent-to-treat patients who received LEN and had baseline bone marrow expression of erythroid differentiation using the 30-gene set data.

Santini V et al. *Proc ASH* 2014;Abstract 409.

Treatment-Emergent Adverse Events in ≥10% of Patients

Event	LEN (n = 160)		Placebo (n = 79)	
	Any	Grade 3-4	Any	Grade 3-4
Neutropenia	64.4%	61.9%	12.7%	12.7%
Infections	51.9%	14.4%	43.0%	3.8%
Thrombocytopenia	39.4%	35.6%	7.6%	3.8%
Hemorrhage	20.6%	1.9%	10.1%	0%
Diarrhea	42.5%	2.5%	22.8%	0%
Constipation	22.5%	0%	12.7%	2.5%
Hepatic disorder	14.4%	5.0%	5.1%	2.5%
Cardiac arrhythmia	11.3%	1.3%	8.9%	5.1%
Cutaneous reactions	10.0%	1.3%	1.3%	0%

- Deep vein thrombosis (DVT) was rare; Grade 3 or 4 DVT was reported in 1.9% of patients on the LEN arm.

Santini V et al. *Proc ASH* 2014;Abstract 409.

Author Conclusions

- LEN was associated with a significant achievement of RBC TI at ≥8 weeks in 26.9% of patients with LR MDS without del(5q):
  - Median duration of RBC TI was 32.9 weeks
  - 90% responded in ≤16 weeks with LEN therapy
- RBC TI at ≥24 weeks was observed in 17.5% of patients who received LEN.
- The results from this study are consistent with the MDS-002 response rates (Raza et al. *Blood* 2008;111:86-93).
- The gene expression signature was not predictive for a response of RBC TI at ≥8 weeks.
- The overall safety data are consistent with the known safety profile of LEN.
- These data support the use of LEN therapy for patients with IPSS low- or intermediate-1-risk MDS without del(5q) who are unresponsive or refractory to ESAs.

Santini V et al. *Proc ASH* 2014;Abstract 409.

Investigator Commentary: Efficacy and Safety Results from the Phase III MDS-005 Trial of LEN in Low- or Int-1-Risk MDS without Del(5q)

The results of a single-arm Phase II study of LEN in patients with LR MDS without del(5q) were published in 2008 (Raza et al. *Blood* 2008;111(1):86-93). There were 214 patients on the Phase II study, and 26% of these patients achieved TI. Since that publication the question was, how would these results hold up in a Phase III trial? Hence, the Phase III trial by Santini and colleagues has the same inclusion criteria, by which transfusion-dependent patients with LR MDS without del(5q) were randomly assigned in a 2-to-1 ratio to receive LEN or placebo.

The primary endpoint of RBC TI by 8 weeks or longer was 26.9% with LEN versus 2.5% for patients on the placebo arm. It is interesting that the TI rate lasting 8 weeks or more was almost identical to that obtained in the original Phase II study. That resonated with me. You don't often see these sort of response rates repeated from the Phase II to the Phase III setting.

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

continued

Investigator Commentary: Efficacy and Safety Results from the Phase III MDS-005 Trial of LEN in Low- or Int-1-Risk MDS without del(5q)

The incidence of AML progression was similar between the 2 arms. The durability of response is the one thing that wasn't quite as long as in the Phase II study. In the Phase II study the median duration of TI was 41 weeks. Here, it was 32.9 weeks on the LEN arm. My take-home message from this is that it was a proof of concept. It basically supported what was seen in the Phase II study. We have to wait to see whether these results are enough to gain approval for this indication both in the European Union and the United States.

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

Improved Outcome with ATRA-Arsenic Trioxide Compared to ATRA-Chemotherapy in Non-High Risk Acute Promyelocytic Leukemia — Updated Results of the Italian-German APL0406 Trial on the Extended Final Series

Platzbecker U et al.

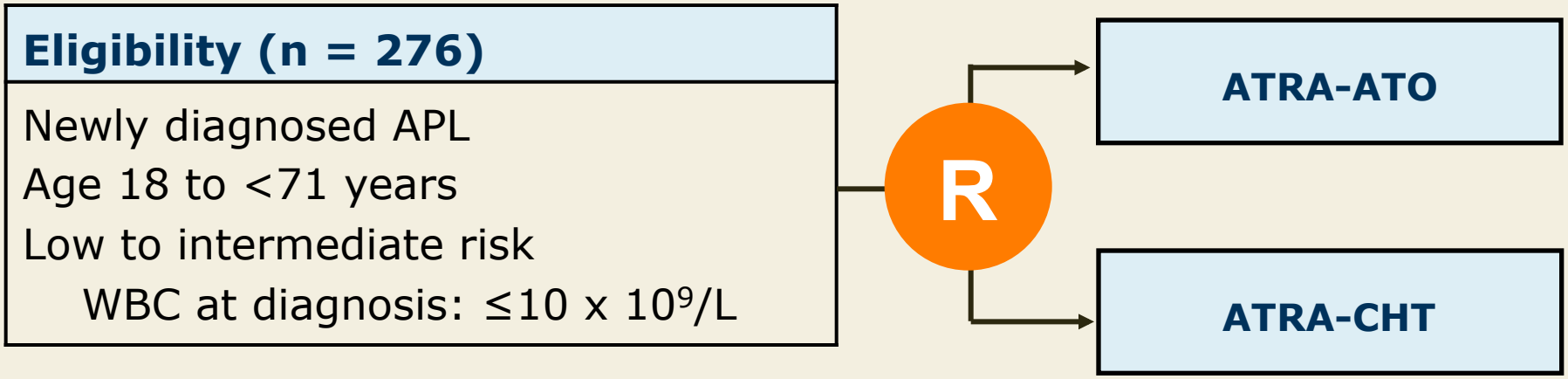
Proc ASH 2014;Abstract 12.

Background

- Results from the Phase III APL0406 trial showed that the combination of all-trans retinoic acid (ATRA) and arsenic trioxide (ATO) is at least not inferior and possibly superior to standard ATRA and chemotherapy (CHT) in the front-line management of low-to intermediate-risk acute promyelocytic leukemia (APL) (*NEJM* 2013;369(2):111-21):
  - 2-year event-free survival (EFS): 97% (ATRA-ATO) vs 86% (ATRA-CHT); $p < 0.001$ for noninferiority and $p = 0.02$ for superiority
  - 2-year overall survival (OS): 99% (ATRA-ATO) vs 91% (ATRA-CHT); $p = 0.02$
- **Study objective:** To report the updated efficacy results from the extended and final series of 276 patients with newly diagnosed nonhigh-risk APL.

Platzbecker U et al. *Proc ASH* 2014;Abstract 12.

Phase III APL0406 Trial Design



- ATRA: 45 mg/m^2 per day; ATO: 0.15 mg/kg per day
- Patients on the ATRA-ATO arm received ATRA-ATO induction until complete response (CR), then ATO 5 days/week, 4 weeks on, 4 weeks off for a total of 4 courses and ATRA 2 weeks on, 2 weeks off for a total of 7 courses.
- Patients on the ATRA-CHT arm received the standard ATRA + idarubicin induction followed by 3 cycles of anthracycline-based consolidation together with ATRA and low-dose CHT and ATRA for maintenance.
- **Primary endpoint:** 2-year EFS

Platzbecker U et al. *Proc ASH* 2014;Abstract 12;
LoCoco F et al. *N Engl J Med* 2013;369(2):111-21.

Survival Outcomes

Outcome	ATRA-ATO (n = 122)	ATRA-CHT (n = 132)	*p*-value
Two-year EFS	98%	84.9%	0.0002
Two-year cumulative incidence of relapse	1.1%	9.4%	0.005
Two-year OS	99.1%	94.4%	0.01

- Median follow-up period = 36 months.
- Four patients died during induction therapy on the ATRA-CHT arm.

Platzbecker U et al. *Proc ASH* 2014;Abstract 12 (Abstract only).

Response to Induction Therapy

	ATRA-ATO (n = 122)*	ATRA-CHT (n = 132)*	*p*-value
CR rate	100%	97%	0.12

* Number of patients evaluable for response to induction

Platzbecker U et al. *Proc ASH* 2014;Abstract 12 (Abstract only).

Author Conclusions

- The data on this extended cohort demonstrate a significantly augmented survival benefit coupled to a higher antileukemic efficacy provided by ATRA-ATO compared to ATRA-CHT for patients with low- to intermediate-risk APL.
- These results further support ATRA-ATO as the new standard therapy in this clinical setting.

Platzbecker U et al. *Proc ASH* 2014;Abstract 12 (Abstract only).

Investigator Commentary: Updated Results of the APL0406 Trial of ATRA-ATO versus ATRA-CHT in Newly Diagnosed APL

The original results of the APL0406 trial were presented at a plenary session at ASH 2012 and were published in 2013. I believe that the updated results are practice changing. Patients had to have low- to intermediate-risk APL to be eligible. Neither of the treatment arms included cytarabine, which continues to be somewhat controversial in the treatment of APL. The primary endpoint was EFS at 2 years.

When the results were initially presented the median follow-up was 2 years, and we thought the results were provocative but we were eager to see the data after a longer follow-up period. With 3 years of follow-up the CR rate is 100% with ATRA-ATO versus 97% with ATRA-CHT. These results were not statistically different. Four patients died on the ATRA-CHT arm. The CR rate for APL is higher than 90%. Those patients who do not achieve a CR die: There is no middle ground in APL. The 2-year EFS and OS rates were 98% and 99% with ATRA-ATO versus 84.9% and 94.4% with ATRA-CHT. Based on these data, our standard for patients with lower-risk APL at the Cleveland Clinic is induction ATRA-ATO in postremission therapy, and we exclude chemotherapy altogether. We did not make this change after the initial presentation because we were not convinced by the results after just 2 years of follow-up.

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

Favorable Outcomes for Older Adolescents and Young Adults (AYA) with Acute Lymphoblastic Leukemia (ALL): Early Results of US Intergroup Trial C10403

Stock W et al.

Proc ASH 2014;Abstract 796.

Background

- ALL is relatively rare among the AYA population of patients but is the most commonly diagnosed form of leukemia in childhood.
- Retrospective analyses have demonstrated significantly improved survival for AYA patients with ALL aged 16-20 years when treated on pediatric versus adult US NCI Cooperative group regimens (*Blood* 2008;112:1646).
- **Study objective:** To evaluate the feasibility and effectiveness of administering treatment to patients with AYA ALL aged 16-39 years with the standard arm of the successful Children's Oncology Group regimen (COG AALL0232) (*Proc ASCO* 2011;Abstract 3).

Stock W et al. *Proc ASH* 2014;Abstract 796.

US Intergroup Phase II C10403 Trial Design (NCT00558519)

Eligibility (n = 296)

Newly diagnosed B- or T-precursor ALL

Age 16-39 years

No Burkitt-type leukemia

No Ph+ ALL known at diagnosis

→

4 intensive courses including chemotherapy and radiation therapy:

- Remission induction (I) Tx
- Remission consolidation (C) Tx
- Interim maintenance (IM) Tx
- Delayed intensification (DI) Tx
- Prolonged maintenance (M) Tx

- Patients with M2 marrow response (>5% but <25% lymphoblasts) after remission induction received an extended remission induction course of Tx.
- **Primary endpoints** include event-free survival (EFS), overall survival (OS) and safety.
- Key correlative science studies in a subset of patients included the assessment of minimal residual disease (MRD).

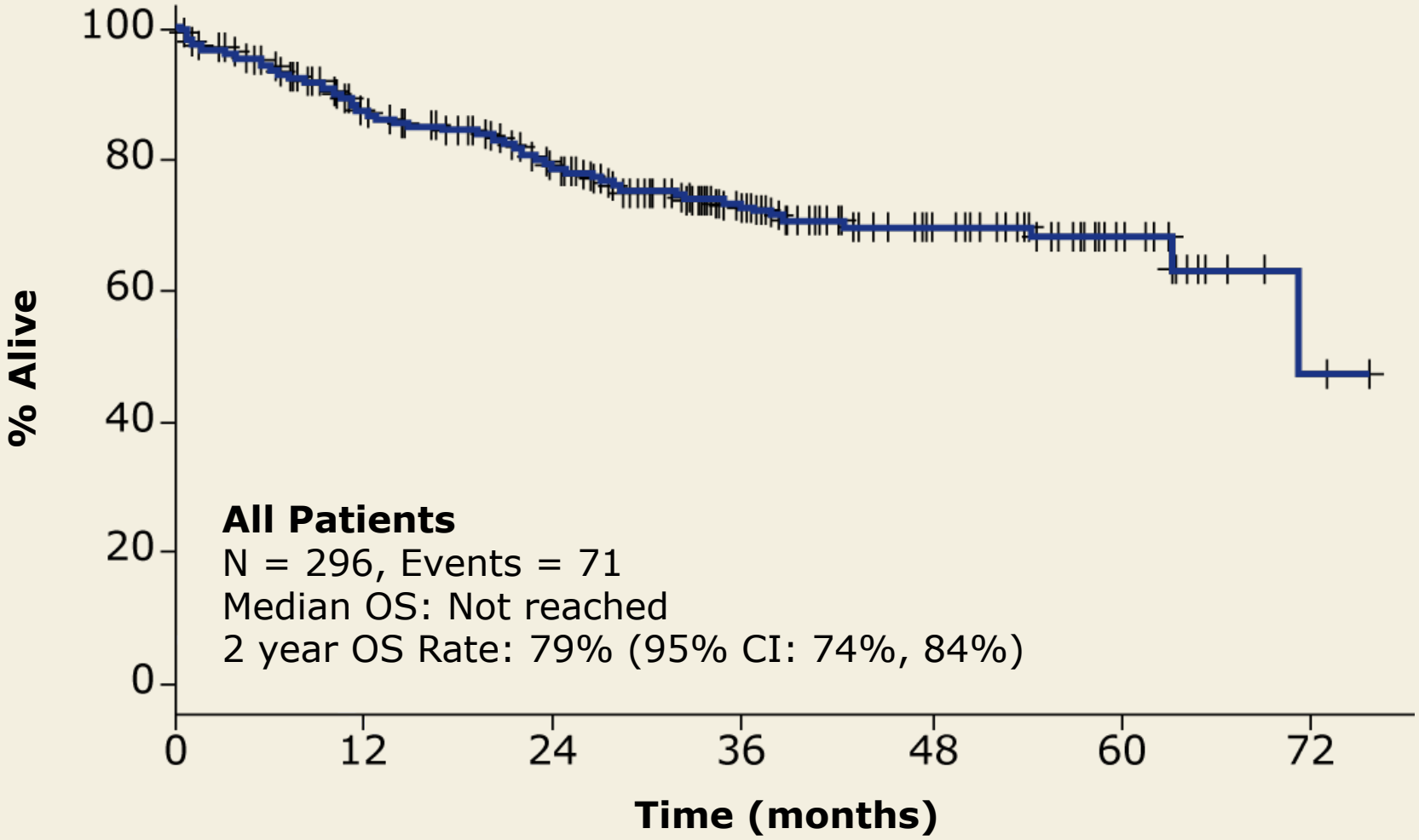
Stock W et al. *Proc ASH* 2014;Abstract 796.

US Intergroup Study C10403 Chemotherapy Regimen

I	C	IM	DI	M
DNR	Cyclo	MTX	DOX	DEX
VCR	VCR	VCR	Cyclo	VCR
Pred	Dex	Peg-ASP	Dex	6MP
Peg-Asp	Peg-Asp	IT-MTX	Peg-Asp	MTX
IT-MTX	Ara-C		Ara-C	IT-MTX
IT-AraC	6MP		6-TG	
	IT-MTX		IT-MTX	

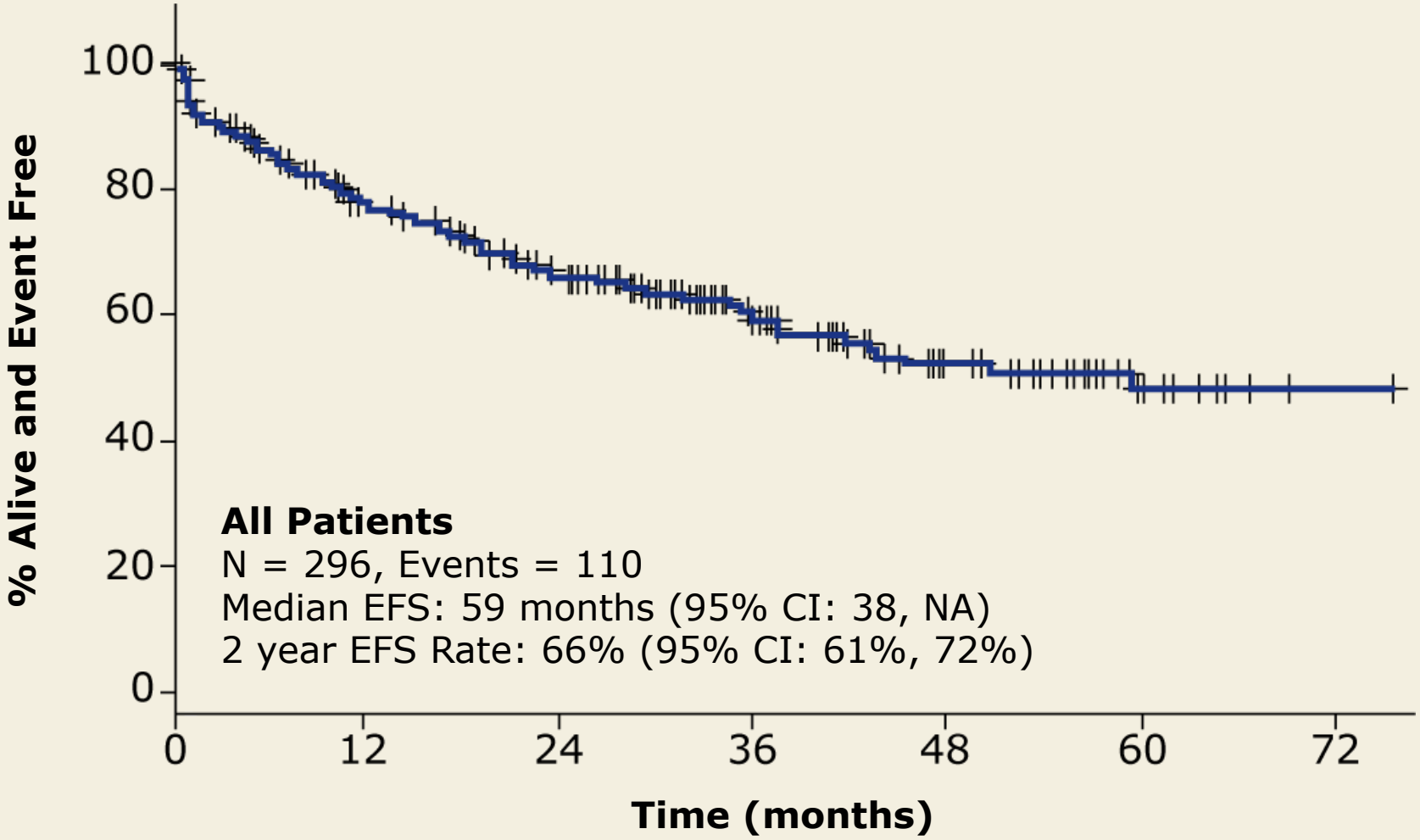
Patients with T-precursor ALL receive prophylactic radiation therapy after DI.
Maintenance therapy continues for 2 to 3 years.

Overall Survival (All Patients)



With permission from Stock W et al. *Proc ASH* 2014;Abstract 796.

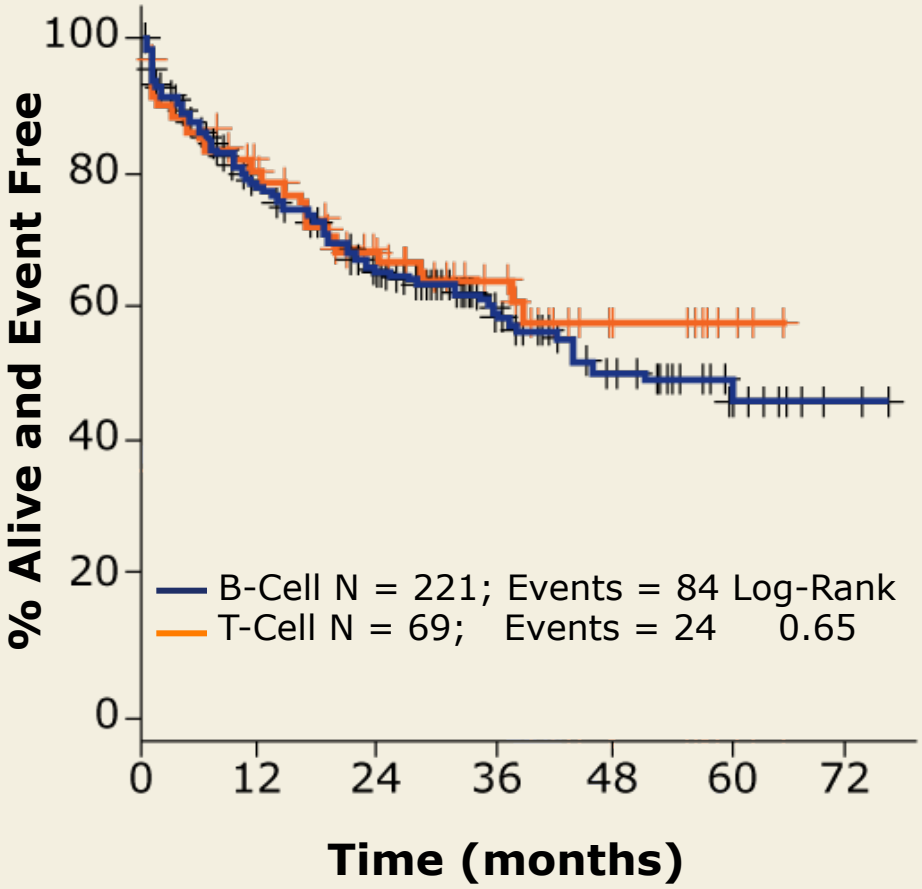
Event-Free Survival (All Patients)



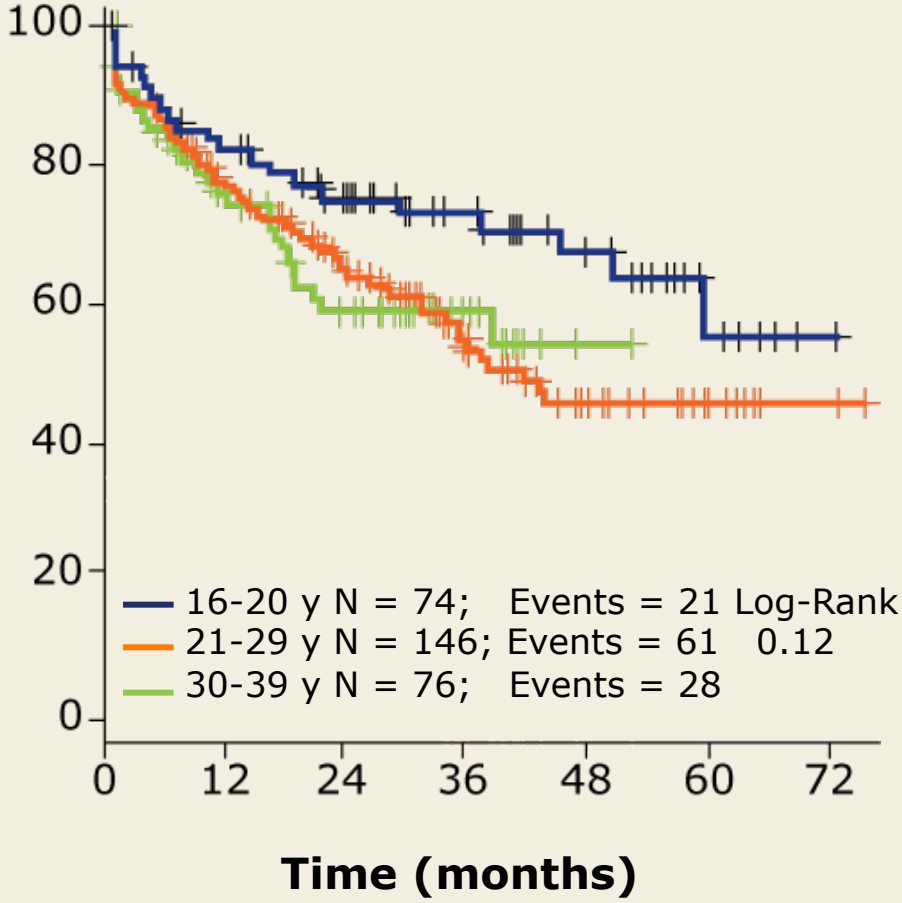
With permission from Stock W et al. *Proc ASH* 2014;Abstract 796.

Event-Free Survival: Subgroup Analysis

By Subtype of ALL

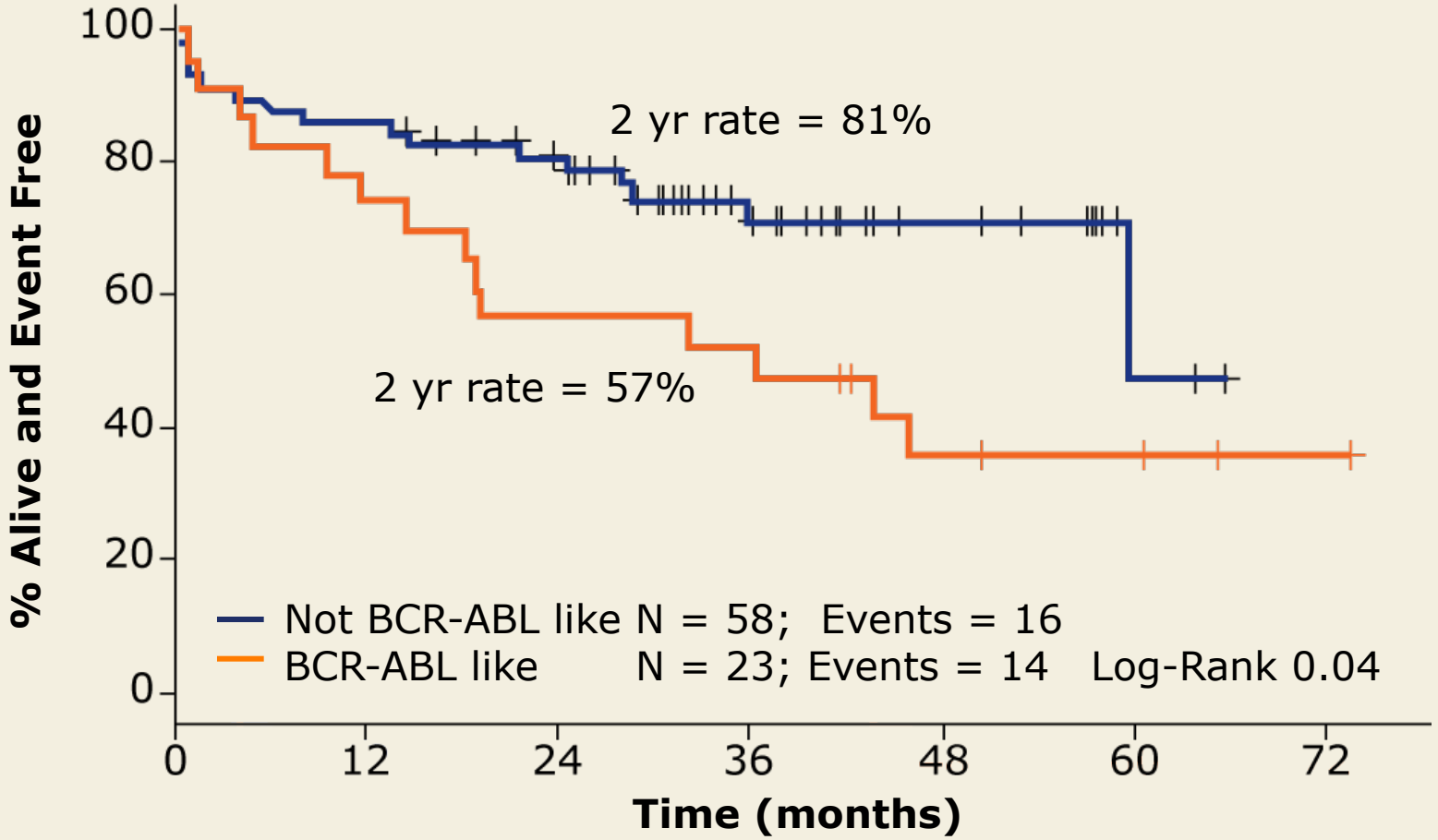


By AYA Age Group



With permission from Stock W et al. *Proc ASH* 2014;Abstract 796.

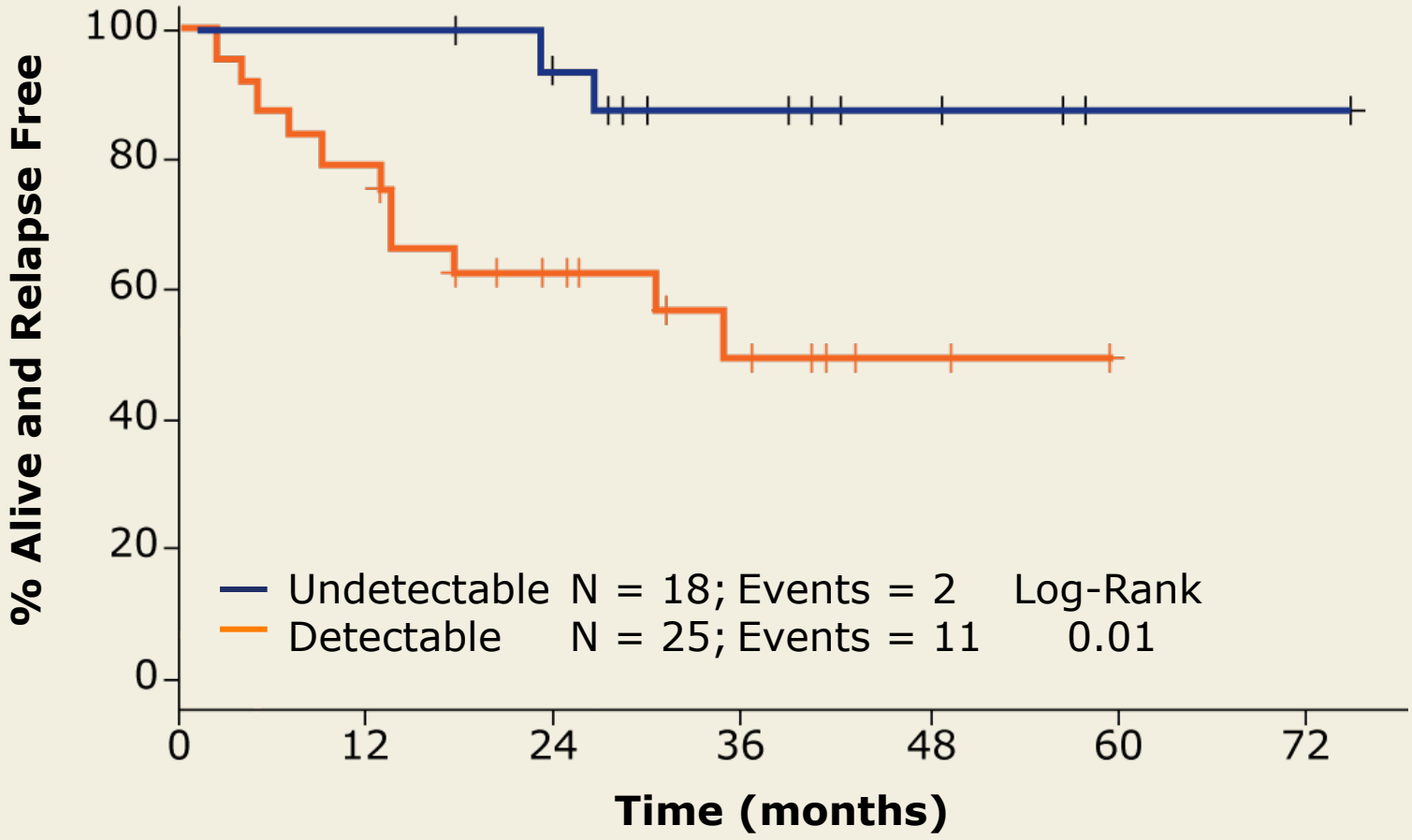
Correlation of BCR-ABL1-Like Signature with EFS



- The BCR-ABL1-like signature occurred in 28% of patients and is associated with poor EFS.

With permission from Stock W et al. *Proc ASH* 2014;Abstract 796.

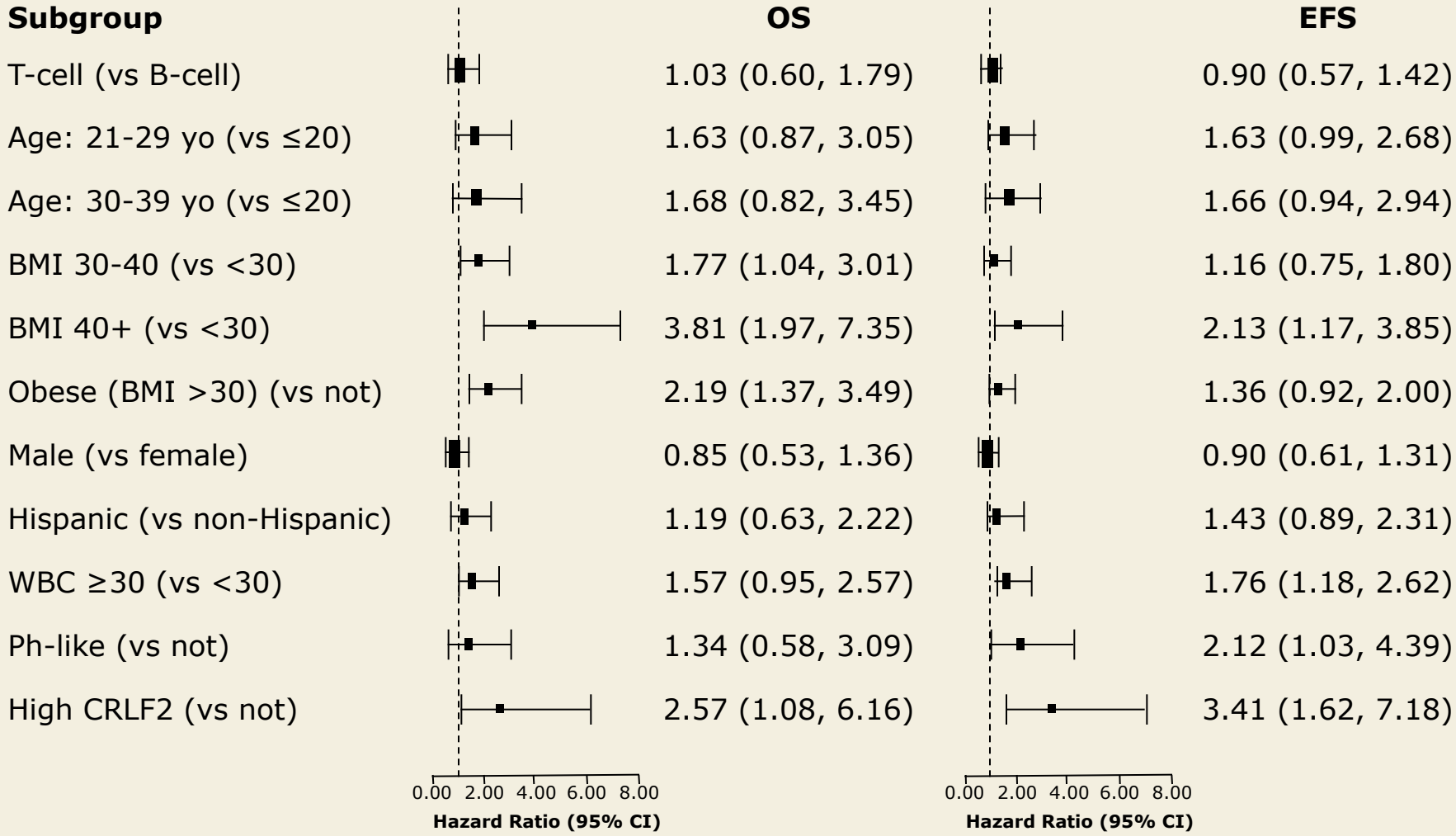
Correlation of MRD After Induction Therapy with Disease-Free Survival (DFS)



- The absence of MRD after induction therapy was associated with excellent DFS.

With permission from Stock W et al. *Proc ASH* 2014;Abstract 796.

Univariate Analyses of OS and EFS According to Subgroups



Stock W et al. *Proc ASH* 2014;Abstract 796.

Comparison of Grade 3 to 5 Adverse Events with the COG AALL0232 Study

Event	Induction only		All treatments	
	C10403	AALL0232	C10403	AALL0232
Hyperglycemia	29.2%	22.0%	N/A	N/A
Abnormal bilirubin	16.4%	6.7%	25.7%	25%
Abnormal ALT/AST	26.6%	N/A	54.3%	49%
Thrombosis	3.0%	1.5%	N/A	N/A
Pancreatitis	1.1%	0.5%	4.2%	3.8%
CNS hemorrhage	1.0%	N/A	N/A	N/A
Neuropathy	N/A	N/A	15.7%	11.4%
Hypersensitivity	N/A	N/A	9.6%	19%
Osteonecrosis	N/A	N/A	2.5%	3.2%

- Overall, treatment-related mortality in the C10403 study was 3%

Stock W et al. *Proc ASH* 2014;Abstract 796.

Author Conclusions

- The pediatric ALL regimen administered by adult patient hematologists/oncologists was validated in this large North American Intergroup trial.
- The study showed significant improvements in survival outcomes in comparison to a 34% EFS for historical controls in CALGB trials (*Blood* 2008;112:1646).
  - 2-year EFS rate: 66%
  - 2-year OS rate: 79%
- A median EFS of 59 months allows for the rejection of the null hypothesis in this trial that the true EFS was 32 months.
  - However, a longer follow-up period is needed to confirm the observed survival improvement.
- The outcomes are similar to other prospective international trials of pediatric regimens in AYA patients (*Proc ASH* 2013;Abstract 839; *JCO* 2009;27:911; *JCO* 2008;26:1843).

Stock W et al. *Proc ASH* 2014;Abstract 796.

Author Conclusions (Continued)

- The presence of the BCR-ABL1-like signature and CRLF2 overexpression (data not shown) are common and associated with significantly worse survival outcomes.
- The absence of MRD after induction therapy was associated with excellent DFS.
- Future directions include the use of a C10403 pediatric regimen as the foundation for future studies for AYA patients with ALL in US Intergroup trials, representing a shift in approach to treating AYA ALL.
- The goal of future studies is to incorporate new targeted antibodies/kinase inhibitors into treatment, eradicate MRD and improve survival in AYA ALL.

Stock W et al. *Proc ASH* 2014;Abstract 796.

Investigator Commentary: Results of the Phase II C10403 Trial for Older AYA Patients with ALL

This is one of the more exciting studies to come out of ALL in a while. This was a huge effort across the US Intergroups to answer a fundamental question that's been circulating for a few years. Retrospective studies have reported that adolescents and young adults, defined variably as patients from age 16 to 39 years, seem to perform better when treated with pediatric protocols compared to adult protocols. Was this due to the fact that different agents were being used in the pediatric protocols or that adult patient oncologists were not as rigorous in keeping patients on therapies or were not dose reducing?

Patients (ages 16-39) received treatment using a Children's Oncology Group regimen, but treatment was administered by adult oncologists through the adult cooperative groups. We do not yet have a head-to-head comparison of similarly aged patients treated by pediatricians as opposed to adult oncologists, but the study reported that toxicities were similar to those reported in the standard arm of the pediatric COG AALL0232 protocol, with an increase in thrombosis and hyperbilirubinemia.

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

continued

Investigator Commentary: Results of the Phase II C10403 Trial for Older AYA Patients with ALL

The median EFS was 59 months and the 2-year EFS was 66%. The 2-year OS rate was 79% and the median OS has not yet been reached. Notably, the 2-year EFS and OS rates were high. The predictors for worse outcome were age greater than 20, initial white blood cell counts greater than 30,000, the presence of MRD at day 28 after induction therapy and Ph +-like gene expression. The assessment of MRD after induction therapy in order to make treatment decisions is increasingly becoming the standard for ALL therapy. In the Cleveland Clinic, our standard in this age group of patients has now become to administer treatment on this protocol. Anyone who walks into the Cleveland Clinic to our adult group aged 17 to 39 years is receiving this regimen. We're impressed by the outcomes so far, with limited follow-up, and now it is also our standard practice to assess MRD in patients.

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

CD19-Targeted 19-28z CAR Modified Autologous T Cells Induce High Rates of Complete Remission and Durable Responses in Adult Patients with Relapsed, Refractory B-Cell ALL[1]

BLAST: A Confirmatory, Single-Arm, Phase 2 Study of Blinatumomab, a Bispecific T-Cell Engager (BiTE®) Antibody Construct, in Patients with Minimal Residual Disease B-Precursor Acute Lymphoblastic Leukemia (ALL)[2]

[1] **Park JH et al.**
Proc ASH 2014;Abstract 382.

[2] **Goekbuget N et al.**
Proc ASH 2014;Abstract 379.

CD19-Targeted 19-28z CAR Modified Autologous T Cells Induce High Rates of Complete Remission and Durable Responses in Adult Patients with Relapsed, Refractory B-Cell ALL

Park JH et al.

Proc ASH 2014;Abstract 382.

Background

- Relapsed adult acute lymphoblastic leukemia (ALL) is associated with high reinduction mortality, chemotherapy resistance and dismal prognosis:
  - Median overall survival (OS) <6 months
  - 5-year OS ≤10%
- High antitumor activity of autologous T cells genetically modified to express 19-28z chimeric antigen receptor (CAR) targeting CD19 was previously reported in adult patients with CLL and ALL (*Blood* 2011;118:4817; *Sci Transl Med* 2014;6(224):224ra25).
- **Study objective:** To report long-term outcomes with 19-28z CAR in adult patients with relapsed/refractory (R/R) ALL, including analysis of the potential predictive markers of response and neurologic toxicities.

Park JH et al. *Proc ASH* 2014;Abstract 382.

Ongoing Phase I Trial Design (NCT01044069)

Eligibility (Target accrual: n = 40)

R/R B-cell ALL

Age: ≥18 years

Patients with minimal residual disease (MRD) or in first complete response (CR)

Karnofsky PS >70

→ **19-28z CAR therapy**

24 patients have received treatment

- Eligible patients underwent leukapheresis, and T cells were transduced with a retrovirus encoding a CAR construct composed of anti-CD19 scFV linked to CD28 and CD3ζ signaling domains (19-28z).
- All patients received lymphodepleting chemotherapy followed 2 days later by infusion with 1 x 10^6 to 3 x 10^6 19-28z CAR T cells/kg.
- **Primary endpoints:** Safety and antitumor activity of 19-28z CAR T cells
- Post-treatment MRD was assessed at day 14 to 28 in the bone marrow samples.

Park JH et al. *Proc ASH* 2014;Abstract 382; www.clinicaltrials.gov, accessed May 2015.

Patient Characteristics

Characteristic	n = 24
Median age (range)	56 years (23-74)
Ph+ B-cell ALL BCR-ABL T315I mutation	25% 8%
Prior allo-HSCT	25%
≥3 prior lines of ALL therapy before receiving 19-28z CAR T-cell therapy	46%

Allo-HSCT = allogeneic hematopoietic stem cell transplant

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

Responses

At time of 19-28z CAR T infusion	n = 22*
Patients with morphologic disease†	12 (54.5%)
Patients with MRD	10 (45.5%)
After 19-28z CAR T infusion	**n = 22***
Patients in CR	20 (91%)
Achieved MRD-negative CR	18 (82%)
Transplant-eligible patients (after infusion)	**n = 13**
Successfully underwent allo-HSCT	10 (77%)

* Evaluable patients; † 6%-97% blasts in the bone marrow

- As of July 1, 2014, the median follow-up was 7.4 months (range, 1-34)
- Patients with ≥6 months of follow-up (n = 13)
- Responses appeared to be durable with 6 patients disease free >1 year

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

Outcomes

- Median OS was 9 months
- Patients who relapsed during follow-up (n = 5)
  - This includes patients with CD19-negative relapse (n = 1)
  - Patients re-treated with CAR T cells (n = 3)
    - Patients who achieved a second CR (n = 2)
- For responders versus nonresponders, there was no association between response and:
  - Age (<60 vs ≥60 years)
  - Prior allo-HSCT
  - Number of prior therapies
  - Pretreatment blast percentage

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

Treatment-Related Adverse Events

- None of the 10 patients with MRD at the time of T-cell infusion developed cytokine release syndrome (CRS).
- 9 of 13 (69%) patients with morphologic disease at the time of T-cell infusion developed CRS with or without neurological symptoms that required intervention with an interleukin (IL)-6R antagonist or corticosteroid.
- A detailed analysis of serum cytokines demonstrated a consistent peak of IL-6 (22.2- to 553-fold increase) immediately prior to the development of neurological toxicities.
- Based on these data, a multidisciplinary CRS management algorithm was developed for patients at high risk in order to reduce the severity of CRS and improve safety of the 19-28z CAR T-cell therapy.

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

Author Conclusions

- While longer follow-up is needed to confirm the durability of the observed responses, the potent induction of MRD-negative responses and the successful long-term outcomes, including subsequent allo-HSCT without apparent additional post-transplant toxicities, strongly support the use of 19-28z CAR T cells in adult patients with B-ALL.
- A temporal relationship between serum IL-6 levels and neurological toxicities indicates that early intervention with IL-6-directed therapy may be more effective in ameliorating neurological toxicities in patients with morphologic disease at the time of T-cell infusion.
- These findings need to be evaluated systematically and confirmed in a larger Phase II trial.

Park JH et al. *Proc ASH* 2014;Abstract 382 (Abstract only).

Investigator Commentary: Efficacy and Safety Results from a Phase I Trial of CAR T Cells in R/R B-Cell ALL

CAR T-cell therapy has been a hot topic for the past couple of years. The median age of patients on the study was 56 years, so young and old patients were included (range 23-74). Remarkably, of 22 evaluable patients, 20 achieved CR after the infusion of CAR T cells, and 18 of these patients achieved MRD-negative CR. Of 13 transplant-eligible patients, 10 underwent allo-HSCT after CAR T-cell therapy.

With a median follow-up of 7.4 months, 6 patients remain disease free beyond 1 year. This is interesting, but interpretation depends on whether one is a "glass-half-full" or a "glass-half-empty" kind of person. Although the investigators state that the responses were durable, I don't know if I would call 6 out of 22 evaluable patients remaining disease free beyond a year "durable." We will have to wait to see how CAR T-cell therapy will be incorporated into the treatment algorithm, but it appears to have a role as a bridge to transplant.

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

continued

Investigator Commentary: Efficacy and Safety Results from a Phase I Trial of CAR T Cells in R/R B-Cell ALL

In terms of toxicity, 9 out of 13 patients with morphologic disease at the time of infusion developed CRS. You have to administer this type of therapeutic approach either in a bone marrow transplant unit with intensive care capacity or in an intensive care unit. This is not a foreign concept because patients who have received IL-2 therapy for other types of cancer have had to go through this. It's a doable approach, but it's not doable at every treatment center. It is a specialized, "boutique" approach to the treatment of lymphoid cancers. Also, some patients developed neurologic toxicities, and this is probably related to the CRS observed.

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

BLAST: A Confirmatory, Single-Arm, Phase 2 Study of Blinatumomab, a Bispecific T-Cell Engager (BiTE®) Antibody Construct, in Patients with Minimal Residual Disease B-Precursor Acute Lymphoblastic Leukemia (ALL)

Goekbuget N et al.

Proc ASH 2014;Abstract 379.

Background

- Patients with ALL with persistent/recurrent minimal residual disease (MRD) after induction therapy have a higher risk of relapse than those with no detectable MRD.
- Treatment for patients with MRD aims to avoid hematologic relapse, reduce MRD load and provide a bridge to subsequent hematopoietic stem cell transplant (HSCT).
- Blinatumomab is a recently approved, bispecific T-cell-engaging monoclonal antibody construct that redirects CD3-positive T cells to CD19-positive target cells, resulting in the serial lysis of CD19-positive B cells.
- In a Phase II study of first-line blinatumomab in 21 patients with MRD-positive ALL, 80% of evaluable patients achieved a complete MRD response (*JCO* 2011;29(18):2493-8).
- **Study objective:** To confirm whether blinatumomab is effective, safe and tolerable in patients with MRD-positive ALL.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379.

Phase II BLAST Trial Design (NCT01207388)

Eligibility (n = 116)

B-precursor ALL in hematologic complete response (<5% blasts in bone marrow) after ≥3 intensive chemotherapy treatments

MRD $\geq 10^{-3}$

No prior allo-HSCT; not eligible for tyrosine kinase inhibitor therapy

→

Blinatumomab (IV)

15 µg/m² per day for 4 weeks → 2 weeks off

(for ≤4 cycles or ≥1 cycle → HSCT)

- Responders could receive ≤4 cycles of treatment or undergo HSCT after ≥1 cycle; patients with hematologic relapse discontinued treatment.
- **Primary endpoint:** Rate of complete MRD response within the first treatment cycle
- **Secondary endpoints** include overall survival, relapse-free survival, duration of complete MRD response, incidence and safety of adverse events
- As of Feb 2014, 106 patients had ended treatment: 74 completed and 32 discontinued

Goekbuget N et al. *Proc ASH* 2014;Abstract 379.

Efficacy

- Patients excluded from study (n = 3)
  - No central laboratory assay results (n = 1)
  - Assay results with a sensitivity of 5×10^{-4} (n = 2)
- Patients included in efficacy analysis (n = 113)
  - Patients who achieved complete MRD response after 1 cycle of treatment: 88 (78%)
    - The lower confidence interval limit exceeded 44% (the null hypothesis for response rate)
  - Patients who achieved complete MRD response after >1 cycle of treatment: 80%
- The rate of complete MRD response did not differ significantly across age, sex, line of treatment and MRD burden categories.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379 (Abstract only).

MRD Response with Blinatumomab Therapy

Complete response in which treatment was administered (n = 116, 113)	Baseline n (%)	MRD response % (95% CI)
First	75 (65%)	82% (72%-90%)
Second	39 (34%)	71% (54%-85%)
Third	2 (2%)	50% (1%-99%)
Baseline MRD level*	**n (%)**	**MRD response**
$\geq 10^{-1}$ to <1	9 (8%)	67% (30%-93%)
$\geq 10^{-2}$ to $<10^{-1}$	45 (39%)	82% (67%-92%)
$\geq 10^{-3}$ to $<10^{-2}$	52 (45%)	78% (65%-89%)

* 10 (9%) patients had MRD $<10^{-3}$, below the lower limit of quantitation, or unknown MRD status.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379 (Abstract only).

Select Adverse Events (AEs)

AE	Occurring in ≥20% (All grades)	Occurring in ≥5% (Serious AEs)
Pyrexia	88%	15%
Headache	38%	Not reported (NR)
Tremor	29%	7%
Chills	25%	NR
Fatigue	24%	NR
Nausea	22%	NR
Vomiting	22%	NR
Aphasia	NR	5%
Encephalopathy	NR	5%

- All patients experienced ≥1 AE; 60% experienced serious AEs; 2 fatal AEs occurred on treatment.
- 5% of patients experienced overdose.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379 (Abstract only).

Author Conclusions

- This is the largest prospective trial with an experimental compound in MRD-positive ALL.
- Blinatumomab treatment resulted in complete MRD response across multiple patient demographics, including patients in second-line treatment and those with high MRD burden.
- With a complete MRD response rate of 78%, the study met its primary objective.
- Among patients with a complete MRD response, 98% had a response within the first treatment cycle.
- After intensive therapy for patients with MRD-positive ALL, rapid MRD response induced by blinatumomab has the potential to improve patient outcomes.

Goekbuget N et al. *Proc ASH* 2014;Abstract 379 (Abstract only).

Investigator Commentary: Efficacy and Safety Results from the Phase II BLAST Trial of Blinatumomab in B-Precursor ALL

On December 3, 2014 the FDA granted accelerated approval for blinatumomab for Philadelphia chromosome-negative relapsed or refractory precursor B-cell ALL. It's a clever strategy to use such a drug to kill leukemia cells. Of 113 patients, 88 (78%) achieved a complete MRD response after 1 cycle of treatment with blinatumomab. This is a high response rate, including a low disease burden. Across all cycles beyond cycle 1, the MRD response rate was 80%. Adverse events occurring in 20% or more of patients included pyrexia (88%), headache, tremor, chills and fatigue.

In my experience, an infusion-related reaction is associated with blinatumomab, and our approach is to hospitalize patients for 9 days, take them through an initial dose-escalation period, discharge them and administer the agent in an outpatient setting. Blinatumomab is administered continuously over 28 days, and the FDA recommends changing the infusion bag every 48 hours. It is an intensive approach that requires a specialty center and that patients live close to the center. The current approval in the relapsed/refractory setting is based on patients previously achieving MRD, and the goal is to eliminate MRD-positive ALL while focusing on longer-term outcomes.

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