5 Minute JournalClub

POST-ASH Issue 5, 2015

Results from the Phase II SWOG-S1117 Trial in Higher-Risk MDS and CMML and the Phase III MDS-005 Trial in Lower-Risk MDS without del(5q)

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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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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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Results from the Phase II SWOG-S1117 Trial in Higher-Risk MDS and CMML and the Phase III MDS-005 Trial in Lower-Risk MDS without del(5q)

Presentations discussed in this issue

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

Santini V et al. **Efficacy and safety of lenalidomide (LEN) versus placebo (PBO) in RBC-transfusion dependent (TD) patients (Pts) with IPSS low/intermediate (Int-1)-risk myelodysplastic syndromes (MDS) without del(5q) and unresponsive or refractory to erythropoiesis-stimulating agents (ESAs): Results from a randomized phase 3 study (CC-5013-MDS-005).** *Proc ASH* 2014;**Abstract 409**.

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

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.

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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.

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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.

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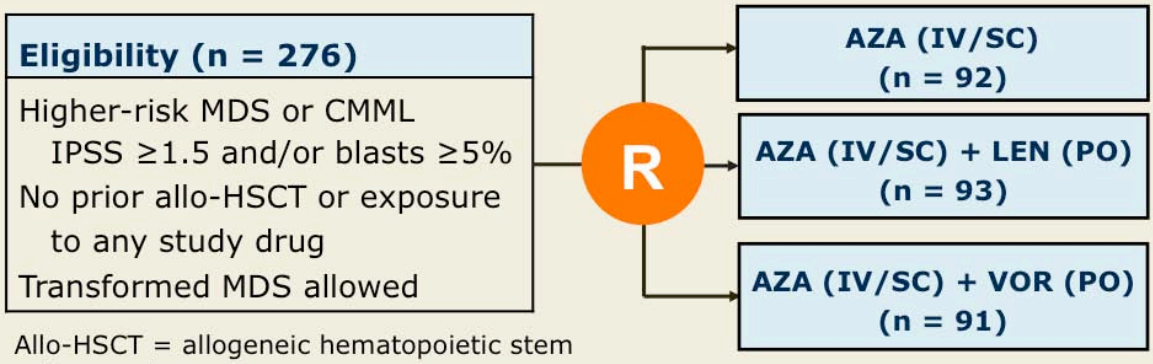
Phase II SWOG-S1117 Trial Design



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%

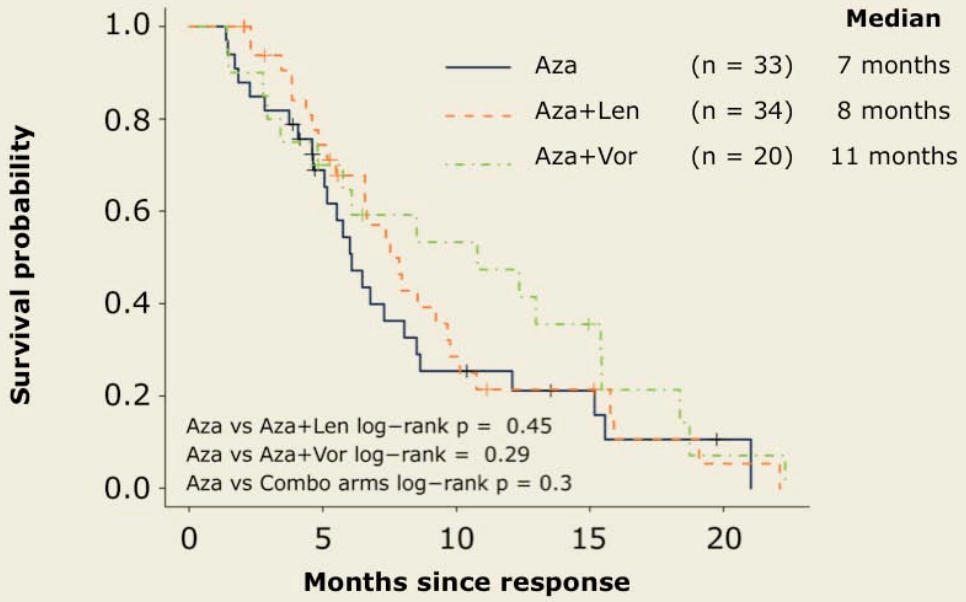
* Versus AZA

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

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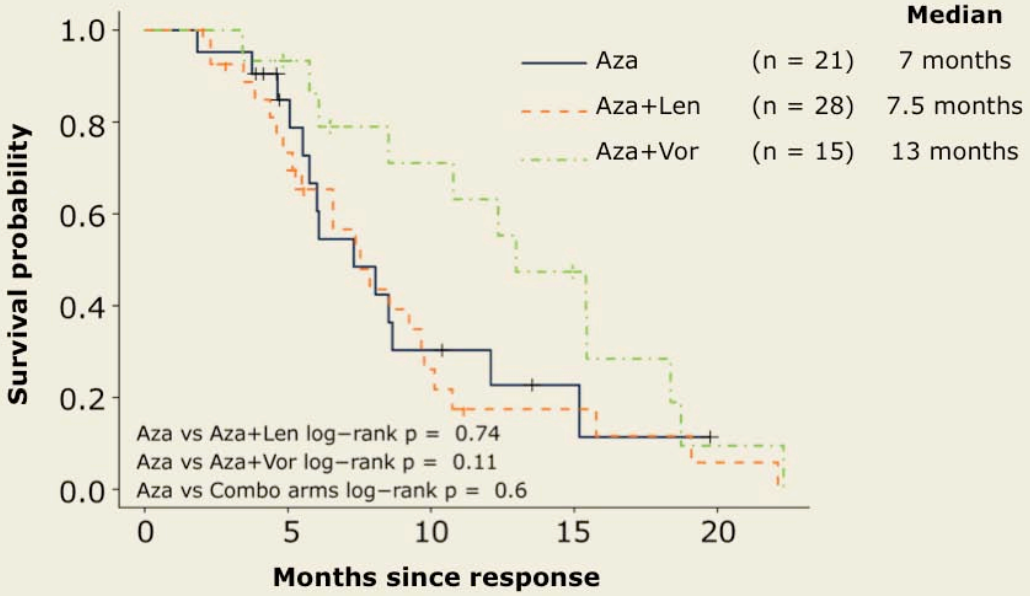
RFS: All Responders on Therapy for More Than 6 Months



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

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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.

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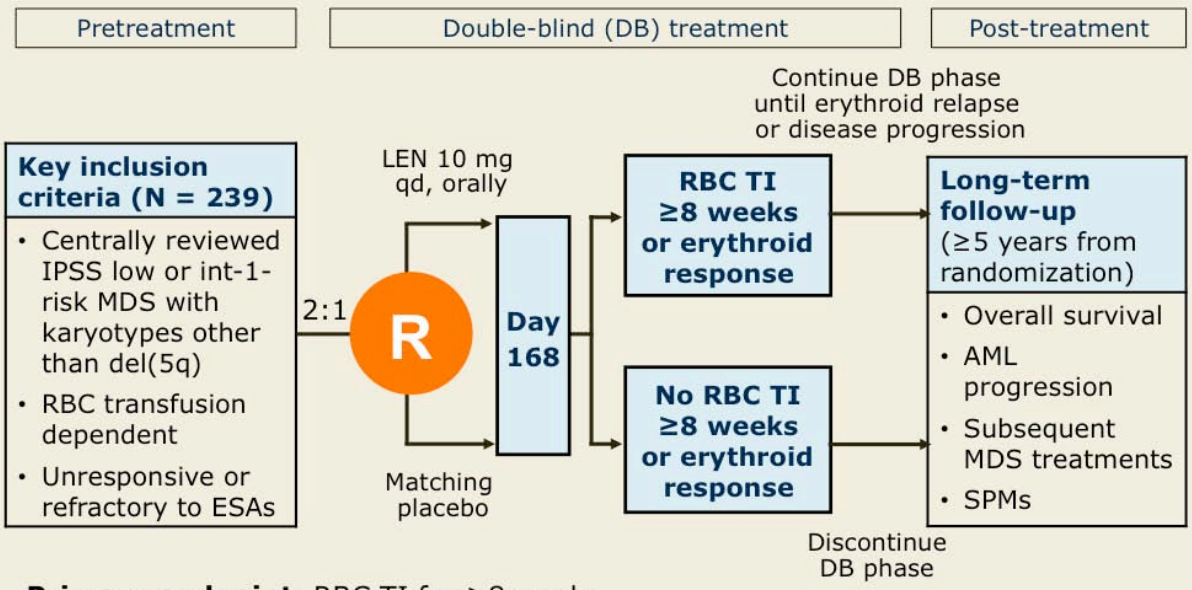
Phase III MDS-005 Trial Design



Primary endpoint: RBC TI for ≥8 weeks

AML = acute myeloid leukemia; SPM = second primary malignancy

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

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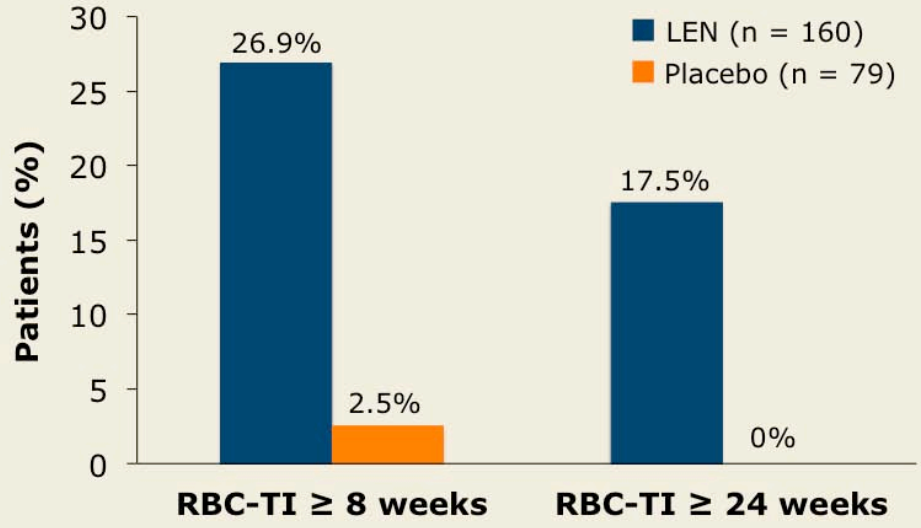
RBC TI at ≥8 Weeks and ≥24 Weeks



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

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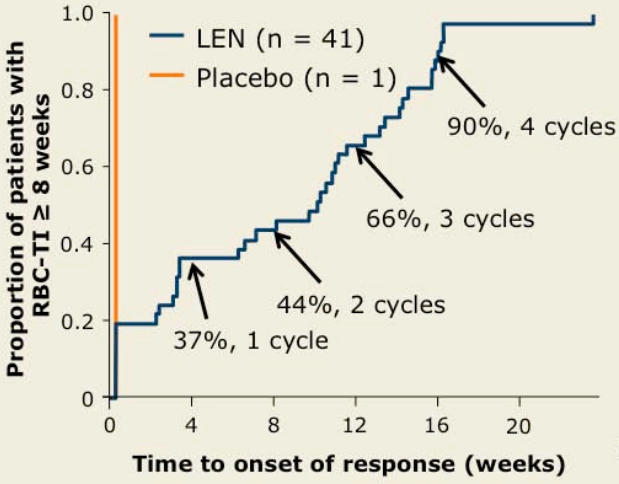
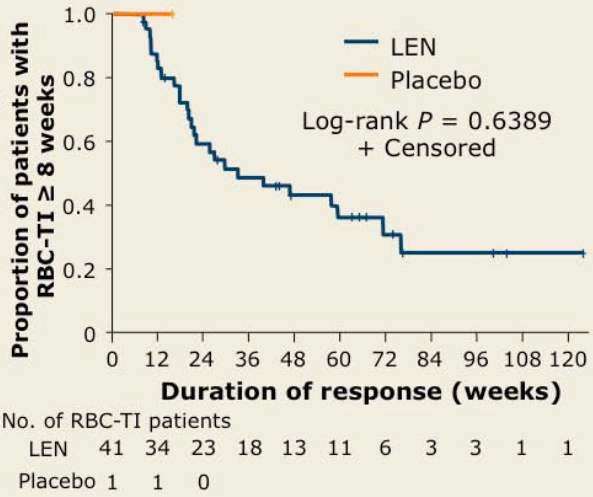
Time to and Duration of RBC TI Achieved at ≥8 Weeks





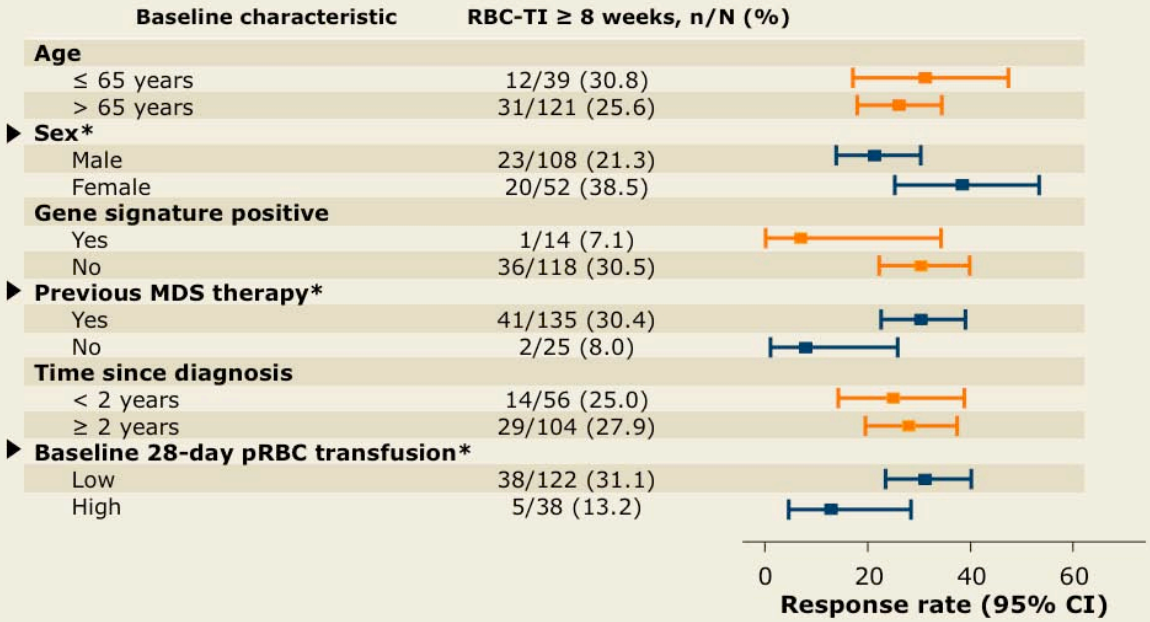
No. of RBC-TI patients

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



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

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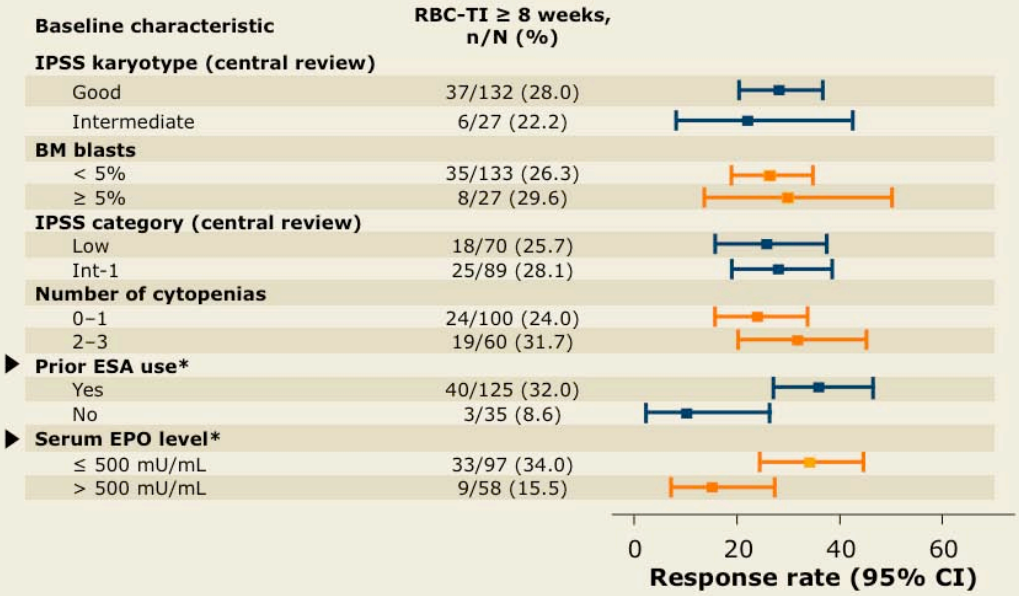
Subgroup Analysis of Patients Who Achieved RBC TI at ≥8 Weeks with LEN (continued)



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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.

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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.

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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