# Acute Myeloid Leukemia and Myelodysplastic Syndromes

**Abstract LBA-3**

## The QUAZAR AML-001 Maintenance Trial: Results of a Phase III International, Randomized, Double-Blind, Placebo-Controlled Study of CC-486 (Oral Formulation of Azacitidine) in Patients with Acute Myeloid Leukemia (AML) in First Remission

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**Introduction:** Many older patients (pts) with AML respond to intensive induction chemotherapy (IC), but responses are often short-lived and overall survival (OS) is poor. The benefit of post-remission maintenance treatment (Tx) for pts with AML is unclear, as no therapy has shown to significantly improve OS. CC-486 is an oral hypomethylating agent that allows for prolonged drug exposure during each Tx cycle to sustain therapeutic activity. We hypothesized that prolonged Tx with CC-486 could be effective as post-remission maintenance in AML.

Herein, we report the primary results of QUAZAR AML-001 (NCT01757535), a phase III international, randomized, double-blind, placebo (PBO)-controlled study evaluating CC-486 as maintenance therapy in pts aged ≥55 years with AML in first remission following IC.

**Methods:** Eligible pts had de novo or secondary AML, intermediate- or poor-risk cytogenetics, and Eastern Cooperative Oncology Group performance status (ECOG PS) scores of ≤3; had achieved first complete remission (CR) or CR with incomplete count recovery (CRi) after IC, with or without consolidation chemotherapy; and were not candidates for hematopoietic stem-cell transplant (HSCT). Within 4 months of attaining CR/CRi, pts were randomized 1:1 to receive CC-486 300 mg or PBO once-daily on days 1-14 of repeated 28-day Tx cycles. A 21-day dosing schedule was permitted for pts who experienced AML relapse with 5-15% blasts in blood or bone marrow while on-study. Tx could continue indefinitely until the presence of >15% blasts, unacceptable toxicity, or HSCT. The primary endpoint was OS. Secondary endpoints included relapse-free survival (RFS), health-related quality of life (HRQoL), and safety. Samples were collected for exploratory translational endpoints, including measurable residual disease (MRD). Kaplan-Meier estimates of OS and RFS were compared for CC-486 vs. PBO by stratified log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were generated using a stratified Cox proportional hazards model.

**Results:** Between May 2013 and October 2017, 472 pts were randomized to receive CC-486 (n=238) or PBO (n=234). Baseline characteristics were balanced between Tx arms. Median age was 68 years (range 55-86), 91% of pts had de novo AML, and 86% and 14% of pts, respectively, had intermediate-risk or poor-risk cytogenetics. Following induction, 81% of pts achieved a CR and 19% achieved CRi; 80% of pts had received consolidation chemotherapy (45% received 1 consolidation cycle and 31% received 2 consolidation cycles).

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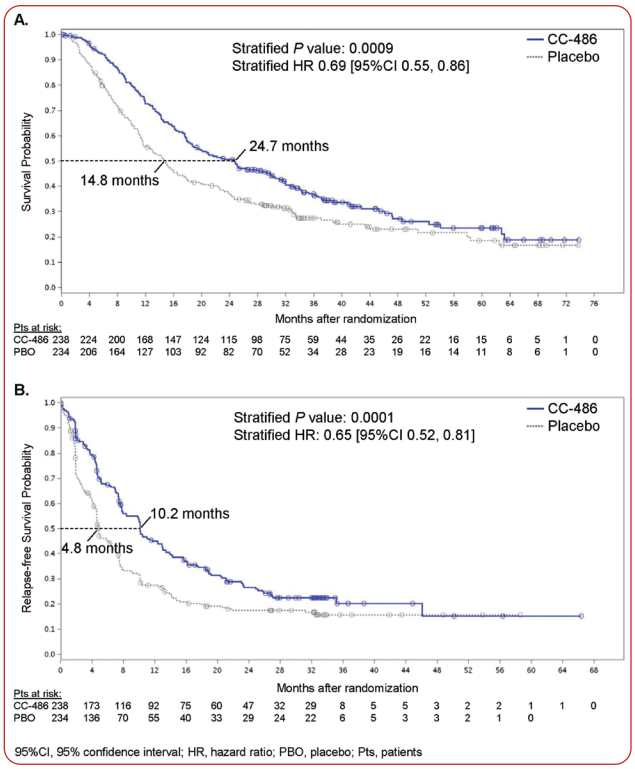


**Figure.** Kaplan-Meier plots of (A) overall survival and (B) relapse-free survival, from time of randomization.

At a median follow-up of 41.2 months, OS was significantly improved with CC-486 vs. PBO: median OS was 24.7 months vs. 14.8 months from time of randomization, respectively (*P*=0.0009; HR 0.69 [95%CI 0.55, 0.86]) (Figure A). RFS was also significantly prolonged: median RFS was 10.2 months in the CC-486 arm, compared with 4.8 months in the PBO arm (*P*=0.0001; HR 0.65 [95% CI 0.52, 0.81]) (Figure B). OS and RFS benefits of CC-486 were demonstrated regardless of baseline cytogenetic risk, the number of prior consolidation cycles received, and CR/CRi status. CC-486 did not adversely impact overall HRQoL vs. PBO, as assessed by mean changes from baseline in HRQoL measures during Tx.

CC-486 had a manageable safety profile generally consistent with that of injectable azacitidine. Median exposure to CC-486 was 12 cycles (range 1-80) and to PBO was 6 cycles (1-73). The most frequently reported adverse events (AEs) with CC-486 and PBO were grade 1 or 2 gastrointestinal (GI) events, including nausea (64% and 23%, respectively), vomiting (59% and 10%), and diarrhea (49% and 21%). The most common grade 3-4 AEs were neutropenia (CC-486, 41%; PBO, 24%), thrombocytopenia (23% and 22%), and anemia (14% and 13%). Serious AEs were infrequent, mainly infections, which occurred in 17% of pts in the CC-486 arm and 8% of pts in the PBO arm. Few AEs led to Tx discontinuation, most often GI events (CC-486, 5%; PBO, 0.4%).

**Conclusions:** CC-486 is the first therapy used in the maintenance setting to provide statistically significant and clinically meaningful improvements in both OS and RFS in pts with AML in remission following induction chemotherapy, with or without consolidation. Oral CC-486 has a manageable safety profile and represents a new therapeutic standard for pts with AML in remission.

## The Advanced Practitioner Perspective: Sandra E. Kurtin, PhD, ANP-C, AOCN®

Managing patients with AML, particularly older patients, is challenging. In this abstract, CC-486, an oral form of the hypomethylating agent azacitadine that is widely used to treat acute leukemia, is being studied as maintenance therapy in patients ≥ 55 years with AML in first remission following induction therapy with intensive chemotherapy who are not eligible for an ASCT.

This study randomized 472 patients with a median age of 68 to one of two arms: either the arm containing CC-486 or placebo. 91% of this population had very high-risk features, either intermediate-1 or high-risk cytogenetics, implying that the risk of relapse is very high in this group.

At a median follow-up of 41 months, the primary endpoint of overall survival favored the group receiving CC-486: 24.7 months vs. 14.8 months in the group receiving placebo. There was also a statistically significant benefit in relapse-free survival among patients receiving CC-486: 10.2 months vs. 4.8 months.

AEs were not uncommon in this population but very similar to those for injectable azacitidine, namely GI toxicities and cytopenias. The primary reason for discontinuation was GI toxicities.

### Allogeneic Hematopoietic Cell Transplants

The diagnosis and treatment of AML in any age group presents a number of challenges. Most newly diagnosed patients move quickly from feeling normal and participating in typical dai-

ly activities to becoming acutely ill, requiring multiple tests and procedures, often hospitalization, and immediate treatment. For the majority of patients, the only potential for cure is an allo-HCT. Historically, patients over the age of 70 were not considered for this transplant.

A recent 2019 study by Atallah and colleagues compared outcomes for 1,280 patients with myelodysplastic syndromes, 688 patients > 65 years of age, and 592 patients ages 55 to 64, undergoing allo-HCT. Many of the patients in both groups had high-risk disease, 24.7% with treatment-related MDS (tMDS) and 77.9% with intermediate- to high-risk disease by the revised international scoring system (R-IPSS) thought to confer a greater risk of leukemic transformation. In multivariate analysis, there was no statistically significant association for age with (hazard ratio [HR], 1.09; 95% CI = 0.94–1.27; $p$ = .23) or without (HR, 1.13; 95% CI = 0.98–1.3; $p$ = .08) adjustment for excess population-based risk of mortality in the older group. Factors independently associated with a greater risk of mortality included high/very high R-IPSS, blasts in bone marrow greater than 11% prior to HCT, non-age–adjusted HCT comorbidity index (HCT-CI) of 4 or greater, and selected regimens for graft-vs.-host disease.

This study reinforces the importance of a complete risk assessment prior to transplant and the caution for exclusion by age alone. A comprehensive geriatric assessment including comorbidities, measures of fitness, instrumental activities of daily living, and gait speed are recommended prior to considering a patient for an HCT to estimate the risk of post-transplant morbidity and mortality (Olin, 2019).

**Azacitidine**

The risk of relapse in the absence of an allo-HCT is high. For patients not eligible for allo-HCT after a full evaluation, hypomethylating agents have been a backbone for treatment. The standard administration of azacitidine requires either intravenous or subcutaneous administration in a clinical setting for 7 days every 4 weeks. Frequent follow-up visits are required for labs and transfusion support in most patients. This places a burden on patients. The ability to provide an oral formulation of a hypomethylating agent (CC-486) will reduce the burden of care for these patients while reducing the risk of relapse.

However, as with all oral antineoplastic agents, the patient and their caregivers are at the core of maintaining consistent and effective treatment. Advanced practitioners play a critical role in educating the patients, preventing and mitigating adverse events, and reinforcing the education needed to keep patients on treatment.

**References**

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Abstract 4268

## Phase 3, Multi-Center, International, Randomized, Double-Blind, Placebo Controlled Study of Oral Rigosertib + Injectable Azacitidine (AZA) Versus Injectable Azacitidine in Treatment-Naive Patients with Higher-Risk Myelodysplastic Syndrome (HR-MDS)

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**Background:** The only approved medications for treatment of first line HR-MDS are HMAs (AZA & decitabine (DEC) in US, AZA only in EU). It is estimated that progression to Acute Myeloid Leukemia (AML) as well as median OS for these pts is <1-3 yrs (Greenberg 2012). Although AZA monotherapy demonstrated improvement in OS in HR-MDS, clinically meaningful & durable responses continue to be limited to a subset of pts (Silverman 2006). One obvious strategy is to identify a novel drug that can be administered effectively in combo with AZA & has minimal overlapping toxicity with AZA. Based on this current approach & favorable results of the Ph2 study (Navada EHA 2019) the 1st pivotal Ph3 randomized study of oral rigosertib in combo with AZA has been developed as part of an effort to increase overall responses as well as reduce risk of transformation to AML for pts with treatment-naive HR-MDS.

Studies have demonstrated that rigosertib binds directly to the Ras-Binding Domains (RBD) found in Ras effector proteins, such as the Raf kinases & PI3K & inhibits the RAS-RAF-MEK & the PI3Ks pathways (Athuluri-Divakar 2016 Cell 2016). In vitro, the combo of rigosertib with AZA synergistically inhibits growth & induces apoptosis of leukemic cells in a sequence-dependent fashion. Sequential exposure with rigosertib followed by AZA achieved maximum synergy with clinically achievable concentrations (Skiddan AACR 2006, Silverman EHA 2019). In a ph2 study (09-08) oral rigosertib at doses ≥ 840 mg/d administered in combo with AZA demonstrated efficacy in HMA-naive MDS pts with an ORR of 90% & a CR rate of 34%. The combo administered in repetitive cycles for more than 2 yrs was well tolerated & the observed GU toxicity was mitigated using specific management guidelines. Based on the efficacy data & favorable safety profile, the pivotal Ph3 trial presented here in treatment-naive HR-MDS population has been developed. (Navada EHA 2019).

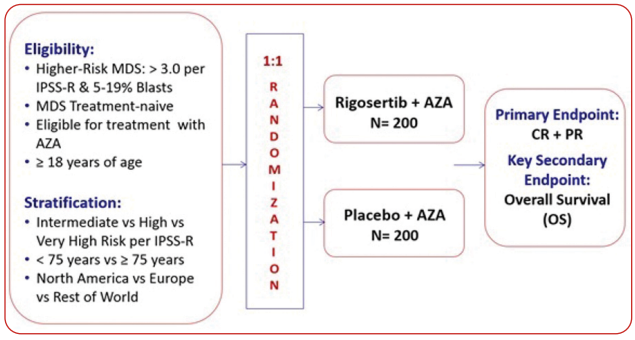


**Figure 1.** Trial design.

**Study Design & Methods:** Ph3, multi-center, international, randomized, double-blind, placebo-controlled study to be conducted in treatment-naive pts with HR-MDS who will receive oral rigosertib 1120mg/d (560 mg morning & 560 mg afternoon) or placebo in combo with AZA 75 mg/m² daily (SC or IV). Pts will take rigosertib/placebo on days 1-21 of a 28-day cycle & starting on Day 8, AZA will be administered by SC injection or IV infusion at a 75 mg/m² daily dose for 7 days of a 28-day cycle according to the approved label. 400 pts are anticipated for enrollment. Major inclusion criteria are shown in Figure 1. Major exclusion criteria are prior treatment with rigosertib or HMA; chronic myelomonocytic leukemia; & prior BMT.

Treatment will continue until disease progression as defined by IWG 2006, or unacceptable toxicity. Treatment will continue until PD as defined by IWG 2006 or unacceptable toxicity, after which pts will be followed for survival every 2 mos until death or 3 yrs, whichever occurs first. The primary analysis of all efficacy endpoints will be in the intention-to-treat population. The safety population will include all pts classified according to the protocol treatment they received, regardless of random assignment. Randomized pts who receive no treatment will be excluded. Management guidelines for treatment emergent adverse events requiring dose adjustments, either dose delay or dose modification at time of AE, is provided in protocol.

The final analysis of response rate will be conducted using IWG 2006.

**Endpoints:** All endpoints for the study are provided in Table 1.

**Conclusion:** This pivotal Phase 3 trial in treatment-naive HR-MDS population has been developed based on efficacy data & favorable safety profile from 09-08. The Intergroup randomized ph2 combo study in pts with HR-MDS treated with AZA + lenalidomide (ORR 49%), or AZA + vorinostat (ORR 27%) had a similar ORR to pts treated with AZA monotherapy (ORR 38%) (Sekeres 2017). In contrast, the ph2 study of oral rigosertib in combo with AZA had an ORR of 90% & a CR rate of 34% (Navada EHA 2019). This proposed study is the 1st ph3 combo study of oral rigosertib with AZA & may provide a potential new treatment for first line in a pt population with poor prognosis & limited therapeutic options.

## The Advanced Practitioner Perspective: Sara Tinsley, PhD, APRN, AOCN®

Currently, there are only two FDA-approved treatments for higher-risk myelodysplastic syndromes (MDS): the hypomethylating agents (HMA) azacitidine and decitabine. Response rates with single-agent azacitidine are low, with 38% overall response rates. Median survival following HMA failure is less than 6 months. There is a need for new treatment options to improve response rates and overall survival by decreasing transformation to acute myeloid leukemia.

This abstract introduces a phase III clinical trial of oral rigosertib in combination with azacitidine in the hopes of improving response rates in higher-risk MDS. In a prior phase II trial, rigosertib in combination with azacitidine yielded an overall response rate of 90%, with a complete response rate of 34%, an improvement over single-agent azacitidine response rates. The adverse events from the phase II study were manageable, primarily genitourinary in nature with dysuria and hematuria. There are mitigation strategies in place for the phase III study.

### Inclusion Criteria

Inclusion criteria for this phase III trial includes treatment-naive higher-risk MDS patients (revised international prognostic score of 3.0 and greater and blasts of 5%–19%) who are 18 years of age and older and eligible for treatment with azacitidine. The trial excludes the participation of patients who have received prior HMA, diagnosis of chronic myelomonocytic leukemia, or prior bone marrow transplant. The trial is designed to be a multicenter international study that is double blinded comparing the overall response rates and overall survival of patients who receive azacitidine in combination with rigosertib to patients who receive azacitidine in combination with placebo. Randomization will occur in a 1:1 fashion. Both arms will receive azacitidine at 75 mg/m$^2$ daily subcutaneously or intravenously for 7 days of a 28-day cycle beginning on day 8. Rigosertib will be dosed at 1,120 mg/day administered at 560 mg in the morning and 560 mg in the afternoon or placebo on days 1–21 of a 28-day cycle.

### Implications for the Advanced Practitioner

Advanced practitioners (APs) are pivotal members of the health-care team who help guide patients when they are making decisions regarding treatment. In order to guide patients in making treatments that align with their goals, APs need to be aware of potential clinical trials, like the one presented here, that could yield a higher response rate if the goal for the patient and caregiver is the best possible response. Potential clinical trials can be found at ClinicalTrials.gov. There is a pressing need for breakthrough therapies discovered through clinical trial participation to improve the treatment options and prognosis of higher-risk MDS.

Abstract 841

## Assessment of Longer-Term Efficacy and Safety in the Phase 3, Randomized, Double-Blind, Placebo-Controlled MEDALIST Trial of Luspatercept to Treat Anemia in Patients (Pts) with Revised International Prognostic Scoring System (IPSS-R) Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes (MDS) with Ring Sideroblasts (RS) Who Require Red Blood Cell (RBC) Transfusions

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**Introduction:** Few treatment options are available to RBC transfusion-dependent pts with lower-risk MDS (LR-MDS) who are refractory/ineligible for erythropoiesis-stimulating agents (ESAs). Luspatercept is a first-in-class erythroid maturation agent that binds select TGF-β superfamily ligands to reduce aberrant Smad2/3 signaling and enhance late-stage erythropoiesis.

In the phase 3, randomized, double-blind, placebo-controlled MEDALIST study (NCT02631070), luspatercept significantly reduced transfusion burden vs placebo. Longer-term efficacy analyses of the MEDALIST study (data cutoff Jan 7, 2019), including multiple responses, and safety are presented here.

**Methods:** Eligible pts were ≥ 18 years of age with IPSS-R-defined Very low-, Low-, or Intermediate-risk MDS with RS (World Health Organization 2016 criteria); were refractory, intolerant, or unlikely to respond to ESAs (serum erythropoietin > 200 U/L); and required regular RBC transfusions. Pts were randomized 2:1 to luspatercept (1.0 mg/kg titrated up to 1.75 mg/kg, if needed) or placebo, subcutaneously every 3 weeks (wks).

This analysis assessed the achievement and number of individual response periods of RBC transfusion independence (RBC-TI) ≥ 8 wks. Clinical benefit, defined as achieving RBC-TI ≥ 8 wks and/or modified hematologic improvement-erythroid (HI-E) response per International Working Group 2006 criteria, was also assessed, along with total duration of clinical benefit (time from achieving clinical benefit to discontinuation due to loss of benefit, adverse events [AEs], or other reasons). Longer-term efficacy and safety were also evaluated.

**Results:** Pts were assessed for RBC transfusion burden/8 wks in the 16 wks before randomization: 66 pts received 2 to < 4 U RBCs (30.1% and 26.3% of pts receiving luspatercept and placebo, respectively), 64 received ≥ 4 to < 6 U (26.8% and 30.2%, respectively), and 99 received ≥ 6 U (43.1% and 43.4%, respectively); both arms had a median baseline burden of 5 RBC U/8 wks.

Compared with our previous analysis and earlier data cutoff of May 8, 2018 (Fenaux P, et al. *Blood*. 2018;132:1), we now report that as of Jan 7, 2019, 72 (47.1%) pts treated with luspatercept and 12 (15.8%) treated with placebo achieved RBC-TI ≥ 8 wks. Analysis of multiple response periods of RBC-TI ≥ 8 wks in the luspatercept responders (i.e. initial RBC-TI ≥ 8 wks, followed by transfusion, followed by another period of RBC-TI ≥ 8 wks) demonstrated that 48 (66.7%) pts had ≥ 2 separate response periods, 22 (30.6%) had ≥ 3, 12 (16.7%) had ≥ 4, and 7 (9.7%) had ≥ 5. Of the 12 pts achieving RBC-TI ≥ 8 wks with placebo, 4 (33.3%) had ≥ 2 responses; none had > 3.

Overall, 48 (31.4%) pts receiving luspatercept and none receiving placebo remained on treatment as of the Jan 7, 2019 data cutoff. Median treatment duration was 50.9 (range 5.9-147.0) wks in pts receiving luspatercept vs 24.0 (range 7.4-103.0) wks in pts receiving placebo. Median duration of the longest period of RBC-TI ≥ 8 wks during Wks 1-48 was 30.6 (95% confidence interval [CI] 20.6-50.9) wks with luspatercept and 18.6 (95% CI 10.9-not evaluable) wks with placebo. Median total duration of clinical benefit was 83.6 and 26.8 wks for pts responding to luspatercept (n = 97) and placebo (n = 20), respectively. Of the 97 luspatercept-treated pts evaluable for clinical benefit, median duration of clinical benefit in pts with baseline transfusion burden of 4 to < 6 U/8 wks was 87.9 (range 13-125) wks, of < 4 U/8 wks was 84.7 (range 21-147) wks, and of ≥ 6 U/8 wks was 64.9 (range 8-122) wks. Twelve luspatercept-treated pts did not require a transfusion after the

first dose of luspatercept up to Wk 48 or until time of analysis; as of Jan 7, 2019 data cutoff, 3 (25%) of those pts maintained response.

AEs occurring more frequently with luspatercept vs placebo (fatigue, diarrhea, asthenia, dizziness) occurred early (Cycles 1-4), were mainly grade 1 or 2, decreased over time, and were not associated with a higher dose level. Progression to acute myeloid leukemia was similar in pts receiving luspatercept (n = 3 [2.0%]) and those receiving placebo (n = 1 [1.3%]).

**Conclusions:** Most lower-risk MDS patients achieving red blood cell transfusion independence and/or hematologic improvement-erythroid response with luspatercept in the MEDALIST study had multiple responses with durable clinical benefit superior to that of pts receiving placebo, including those with a high baseline transfusion burden. Adverse events were mainly grade 1 or 2, decreased over time, and were not correlated with a higher dose level.

## The Advanced Practitioner Perspective: Sara Tinsley, PhD, APRN, AOCN®

Luspatercept was approved in April 2020 by the FDA for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis.

Data in support of luspatercept were presented in this abstract based on the phase III MEDALIST trial, with a data cutoff period of January 7, 2019. The MEDALIST trial is a placebo-controlled trial in which patients diagnosed with very low–, low-, or intermediate-risk MDS (by the revised International Prognostic Scoring System) with ring sideroblasts were randomized 2:1 to luspatercept or placebo.

The dose of luspatercept was 1 mg/kg titrated up to a dose of 1.75 mg/kg if needed or placebo administered subcutaneously every 3 weeks. To qualify for the trial, participants had to be ≥ 18 years old and be refractory, intolerant, or unlikely to respond to erythropoiesis-stimulating agents (serum erythropoietin > 200 U/L), and require regular red blood cell (RBC) transfusions. A key feature of the inclusion criteria was the requirement of ring sideroblasts, a specific type of MDS identified from a bone marrow biopsy report based on criteria established by the 2016 World Health Organization.

This study assessed the achievement of RBC transfusion independence in ≥ 8-week periods comparing luspatercept to placebo. Prior to treatment, both arms had a median baseline RBC transfusion burden of 5 RBC U/8 weeks. The luspatercept arm had a 47% (72) response rate in that time frame compared with 15.8% (12) for the placebo arm. Also reported were multiple ≥ 8-week periods of transfusion independence in both arms, indicating the need for careful monitoring prior to discontinuation to maximize the benefit. The median total duration of benefit in the luspatercept responders was 83.6 weeks. In addition, 12 patients in the luspatercept arm did not require a transfusion after the first dose up to week 48 or until the time of data cutoff on January 7, 2019.

Adverse events (AEs) were reported and occurred more frequently in luspatercept compared to placebo, consisting of fatigue, diarrhea, asthenia, and dizziness. These side effects were reported within cycles 1 to 4, and were limited to grade 1 or 2 toxicity. These AEs were not associated with higher doses of luspatercept. Side effects decreased over time. The rates of progression to acute myeloid leukemia were similar between the two arms.

### Implications for the Advanced Practitioner

Education and symptom management are like bread and butter for the advanced practitioner. This study brings to surface the need for our patients to understand not only whether they have low-risk or high-risk disease, but also the distinct subtype of MDS—ring sideroblasts.

Resources are available online, such as the MDS Foundation, and on smart phones for risk stratification between low- and high-risk MDS using the IPSS-R. Patients also need information regarding response rates and side effects in order to make informed decisions. Fortunately, adverse events are low and decrease over time, and response rates hover around 50%.