A SPECIAL MEETING REVIEW EDITION

Highlights in Myelodysplastic Syndromes From the 61st American Society of Hematology Annual Meeting

A Review of Selected Presentations From the 61st ASH Meeting
• December 7-10, 2019 • Orlando, Florida

Special Reporting on:

- Hematologic Improvement–Neutrophil and –Platelet in the MEDALIST Trial: Multilineage Data From a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Anemia in Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes With Ring Sideroblasts Who Require Red Blood Cell Transfusions

- 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 With Revised International Prognostic Scoring System Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes With Ring Sideroblasts Who Require Red Blood Cell Transfusions

- Luspatercept Significantly Reduces Red Blood Cell Transfusion Burden, Regardless of Gene Mutation Frequency, Spectrum, and Prognostic Significance, Among Patients With LR-MDS Enrolled in the MEDALIST Trial

- Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety From a Randomized Cross Over Phase 3 Study (ASCERTAIN Study) of an Oral Hypomethylating Agent ASTX727 (Cedazuridine/Decitabine) Compared to IV Decitabine

- The First-in-Class Anti-CD47 Antibody Magrolimab (5F9) in Combination With Azacitidine Is Effective in MDS and AML Patients: Ongoing Phase 1b Results

- Interim Analysis of a Phase II Study of the Glutaminase Inhibitor Telaglenastat (CB-839) in Combination With Azacitidine in Advanced Myelodysplastic Syndrome

- Phase II Study of Oral Rigosertib Combined With Azacitidine as First-Line Therapy in Patients With Higher-Risk Myelodysplastic Syndromes

- Phase 1b/2 Combination Study of APR-246 and Azacitidine in Patients With *TP53*-Mutant Myelodysplastic Syndromes and Acute Myeloid Leukemia

PLUS Meeting Abstract Summaries

With Expert Commentary by:

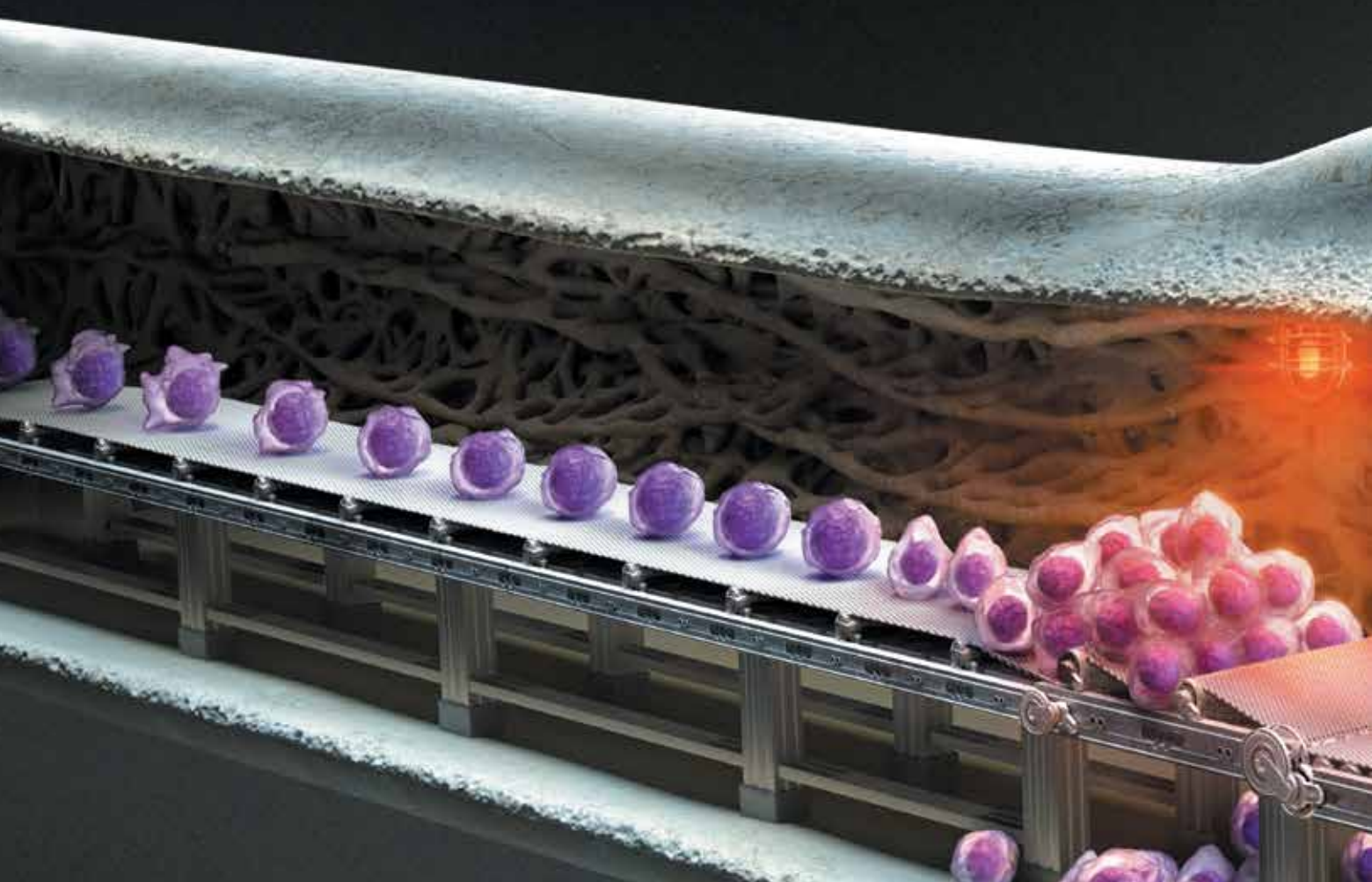### Guillermo Garcia-Manero, MD

Deputy Chair, Translational Research
Professor and Chief, Section of Myelodysplastic Syndromes
Department of Leukemia, The University of Texas MD Anderson Cancer Center
Houston, Texas

ON THE WEB:
**hematologyandoncology.net**

Erythroid Maturation Needs to Stay on Track

Impaired maturation contributes to ineffective erythropoiesis, which can lead to chronic anemia[1,2]

- Ineffective erythropoiesis may be characterized by increased proliferation of erythroblasts, increased erythroid cell death, and impaired erythroid maturation, which may result in chronic anemia[3,4]

- Chronic anemia can have long-term consequences for patients with various blood disorders, such as myelodysplastic syndromes (MDS), β-thalassemia, myelofibrosis, and Diamond-Blackfan anemia[5-8]

Research is expanding what we know.

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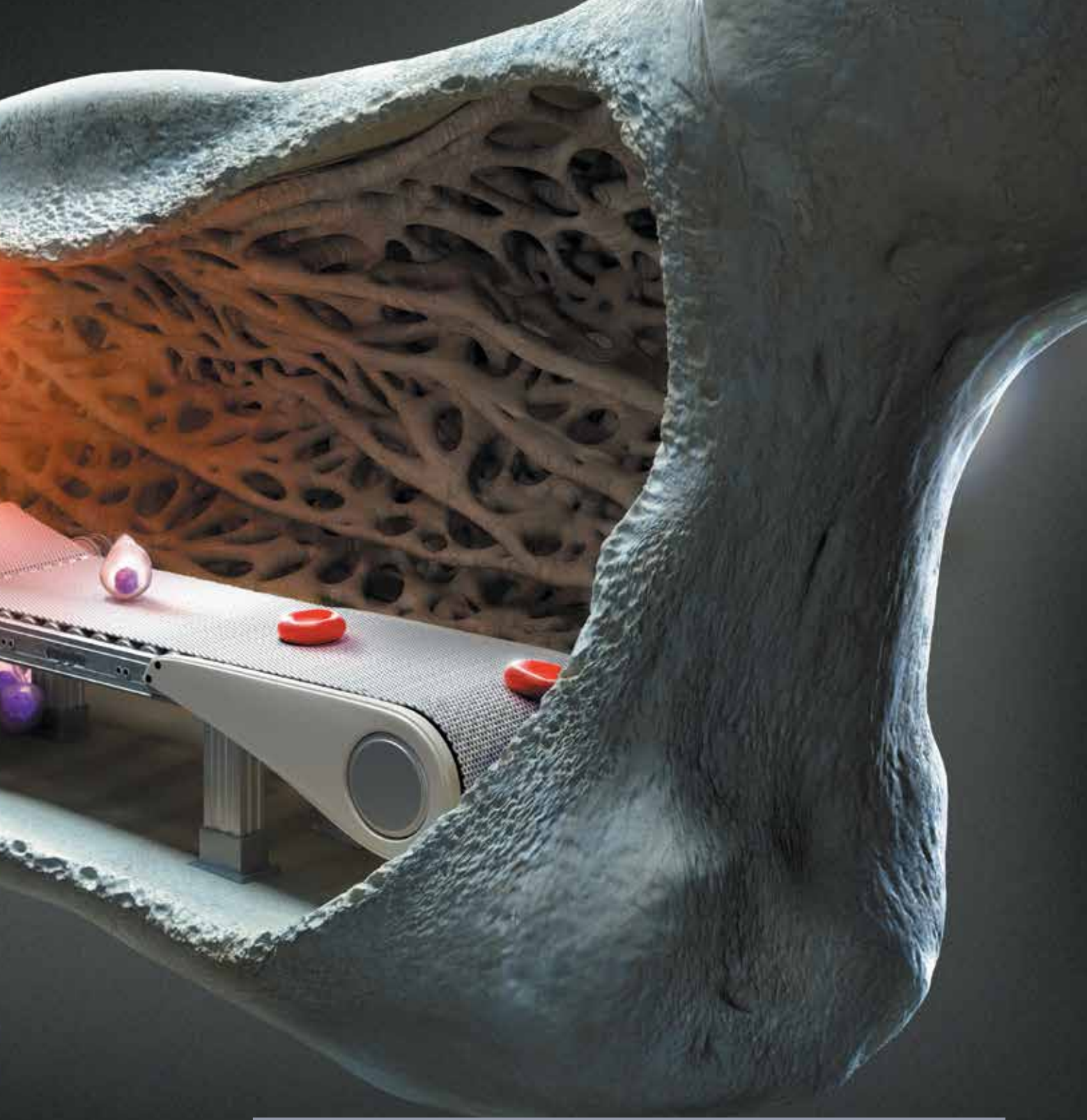
Hematologic Improvement–Neutrophil and–Platelet in the MEDALIST Trial: Multilineage Data From a Phase 3, Randomized, Double-Blind, Placebo-Controlled Study of Luspatercept to Treat Anemia in Patients With Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes With Ring Sideroblasts Who Require Red Blood Cell Transfusions

The randomized, double-blind, placebo-controlled phase 3 MEDALIST trial (A Study of Luspatercept [ACE-536] to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes) showed that luspatercept decreased the need for transfusion among patients with anemia and lower-risk myelodysplastic syndromes (MDS).[1-3] The trial enrolled adult patients with lower-risk MDS and ring sideroblasts who were refractory to or ineligible for erythropoiesis-stimulating agents and dependent on red blood cell (RBC) transfusions. Eligible patients (≥18 years) had very low–, low-, or intermediate-risk MDS, according to the Revised International Prognostic Scoring System (IPSS-R). The patients were randomly assigned 2-to-1 to receive a subcutaneous dose of luspatercept (n=153) at 1.0 mg/kg titrated up to 1.75 mg/kg every 3 weeks or placebo (n=76). Disease and response assessment were conducted after 24 weeks and then every 6 months.

Updated results were presented at the 61st American Society of Hematology (ASH) meeting and published in the *New England Journal of Medicine*.[2,3] The primary endpoint was transfusion independence for 8 weeks or longer. This endpoint was met by 38% of the luspatercept group (n=153) vs 13% of the placebo group (n=76; *P*<.001). A key secondary endpoint, transfusion independence for at least 12 weeks, was assessed during weeks 1 through 24 and weeks 1 through 48. Among patients treated with luspatercept, this endpoint was met by 28% at weeks 1 through 24 and by 33% at weeks 1 through 48. Among patients treated with placebo, this endpoint was met by 8% vs 12%, respectively (*P*<.001 for both comparisons).

Dr Guillermo Garcia-Manero and colleagues presented results for the secondary endpoint of hematologic improvement, categorizing responses in erythrocytes, neutrophils, and platelets throughout any consecutive 56-day period.[4] For platelets and neutrophils, mean changes from baseline were also assessed. At baseline, MDS with refractory cytopenias and ring sideroblasts was reported in 94.8% of the luspatercept arm and 97.4% of the placebo arm. Mean neutrophil counts were 2.8×10^9/L and 2.7×10^9/L, respectively. Mean platelet counts at baseline were 252×10^9/L and 259×10^9/L. Neutropenia ($<1 \times 10^9$/L) was reported in 9.8% of patients in the luspatercept arm and 13.2% of patients in the placebo arm. Baseline thrombocytopenia ($<100 \times 10^9$/L) was reported in 5.2% vs 7.9%, respectively. No patients had received prior platelet transfusions.

During weeks 1 to 48, the luspatercept arm had higher proportions of patients with responses for each measure of hematologic improvement.[4] A response in erythrocytes was reported in 58.8% of patients in the luspatercept arm vs 17.1% in the placebo arm. Among patients evaluable for neutrophil assessment (n=15 in the luspatercept arm and n=10 in the placebo arm), responses were seen in 20.0% of the luspatercept arm vs 10.0% of the placebo arm.

Among the patients evaluable for platelet assessment (n=8 in the luspatercept arm and n=6 in the placebo arm), responses were seen in 62.5% vs

ABSTRACT SUMMARY APR-246 Combined With Azacitidine in *TP53*-Mutated Myelodysplastic Syndrome and Acute Myeloid Leukemia: A Phase 2 Study by the Groupe Francophone des Myélodysplasies (GFM)

In a phase 2 study, the combination of azacitidine and APR-246 demonstrated clinical activity among patients with high-risk or very–high-risk *TP53*-mutated MDS or AML (Abstract 677). Patients (N=53) received APR-246 in combination with azacitidine for 6 cycles. The primary endpoint was response. Among 35 evaluable patients, the ORR at best response was 66%. The CR rate was 49% at best response. The ORR at best response was highest among evaluable patients with MDS (n=24), at 74%. The CR rate was 66% among these patients. ORR was 55% among evaluable AML patients with 20% to 30% blasts and 50% among AML patients with more than 30% blasts. In the study group overall, at a median follow-up of 6.4 months, overall survival was not reached among responders vs 3 months among nonresponders (*P*<.0001). Febrile neutropenia was reported in 36% of patients. All-grade neurologic AEs occurred in 40% of patients. Among the 10 patients who discontinued therapy, all died.
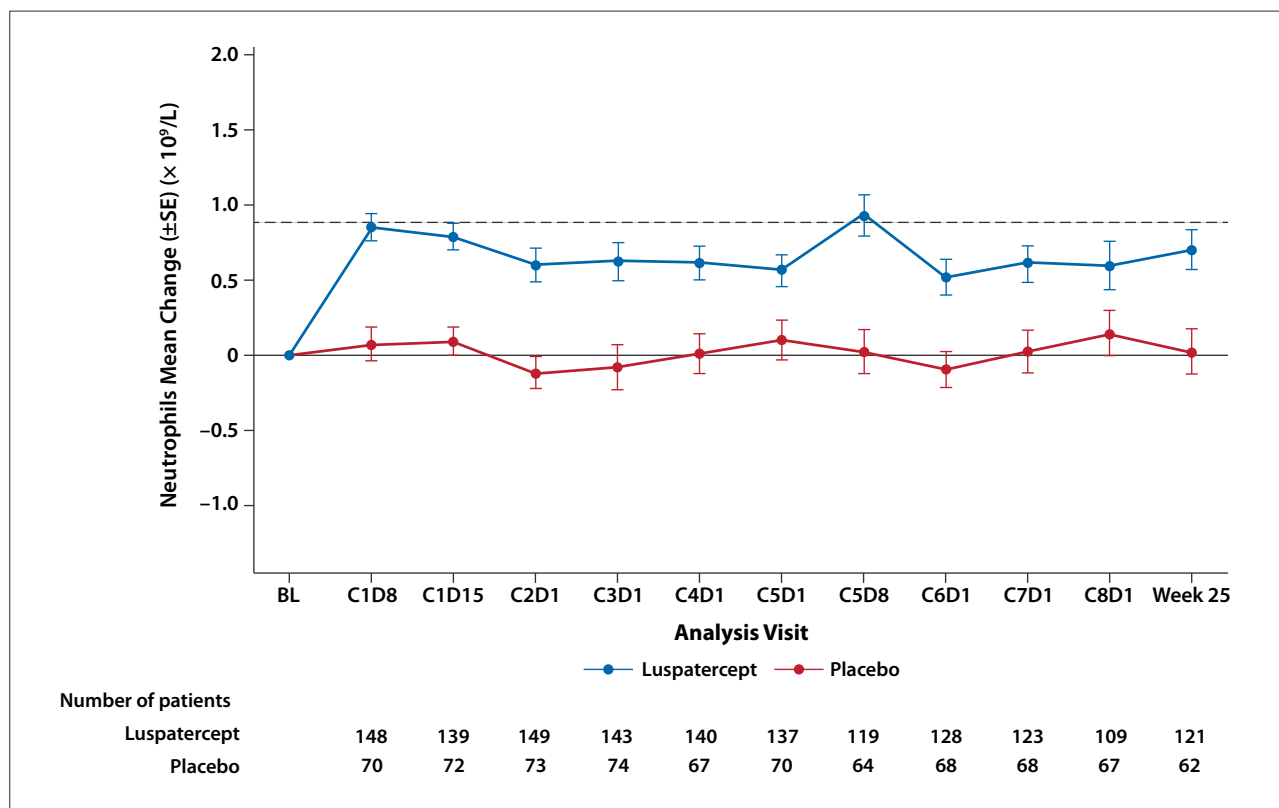
Figure 1. Mean change from baseline in neutrophils over time in the MEDALIST trial. The dotted line indicates a mean change from baseline of 0.9×10^9/L. BL, baseline; C, cycle; D, day; MEDALIST, A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes; SE, standard error. Adapted from Garcia-Manero G et al. ASH abstract 4243. *Blood.* 2019;134(suppl 1).[4]

33.3%, respectively.

By day 8 of cycle 5, the mean change from baseline in neutrophils was 0.95×10^9/L in the luspatercept arm and 0.04×10^9/L in the placebo arm (Figure 1). Early increases with luspatercept were notable by day 8 of cycle 1 (0.86×10^9/L vs 0.08×10^9/L with placebo). A mean absolute increase in neutrophils of at least 0.5×10^9/L was seen in 81.0% of the luspatercept arm vs 51.3% of the placebo arm.

By day 1 of cycle 4, the mean change from baseline in platelets was 28.7×10^9/L in the luspatercept arm vs 0.9×10^9/L in the placebo arm (Figure 2). Early increases were observed by day 8 of cycle 1 with luspatercept (18.3×10^9/L vs 2.9×10^9/L with placebo). A mean absolute increase in platelets of at least 30×10^9/L was seen in 70.6% of the luspatercept arm vs 42.1% of

the placebo arm. None of the patients in the luspatercept arm who achieved an improvement in platelet response received platelet transfusions.

Grade 3 or 4 treatment-emergent neutropenia occurred in 13 patients: 7 in the luspatercept arm (4.6%) and 6 in the placebo arm (7.9%).[4] No cases of grade 3 or 4 treatment-emergent thrombocytopenia occurred. Among patients with thrombocytopenia at baseline, there were no reports of bleeding. Infections occurred in 4 of 9 patients in the luspatercept arm and 3 of 7 patients in the placebo arm who experienced neutropenia during the study.

No patients progressed to acute myeloid leukemia. A single patient in the luspatercept arm progressed to high-risk MDS. This patient had hematologic improvement in neutrophils and platelets.

References

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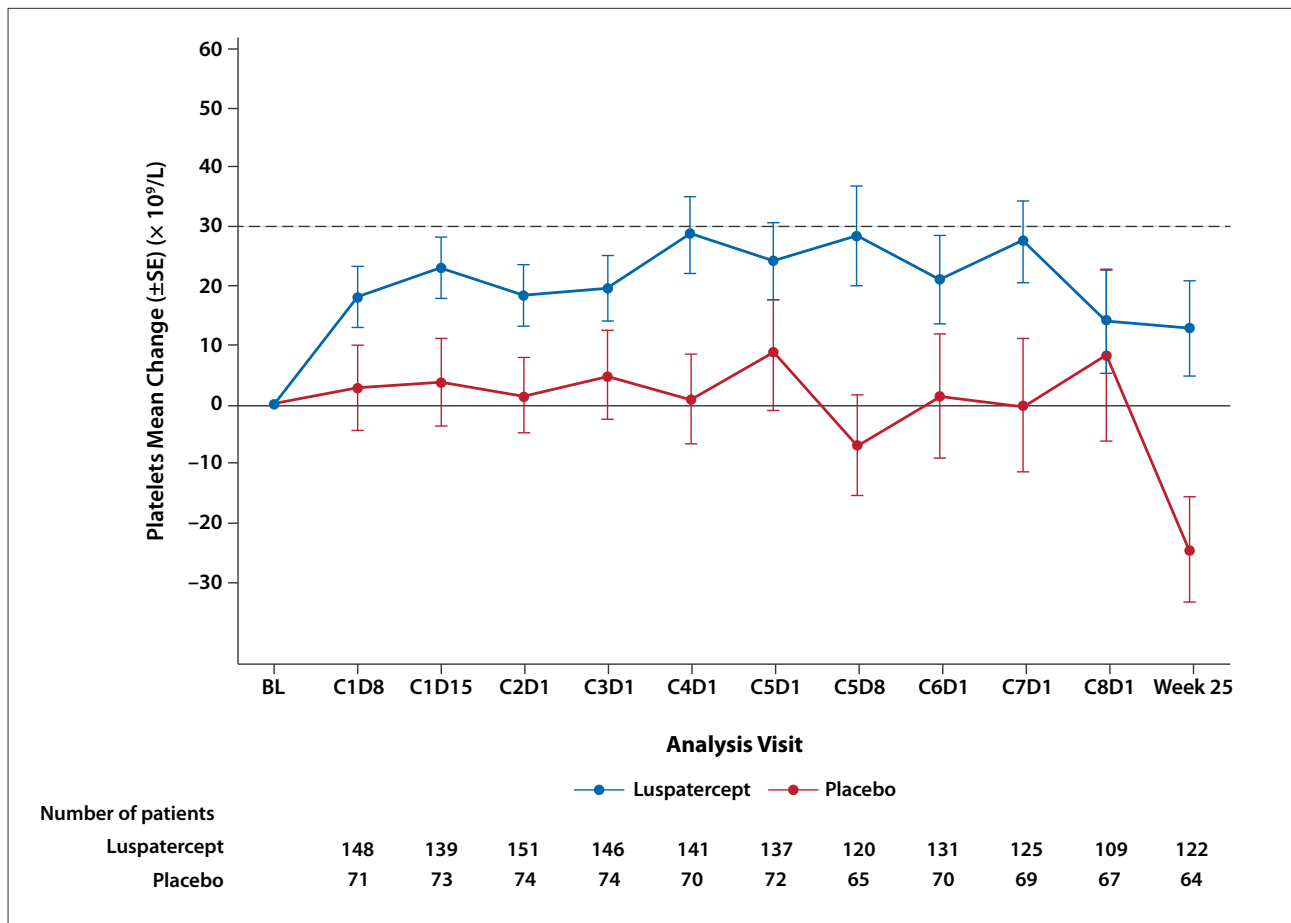
Figure 2. Mean change from baseline in platelets over time in the MEDALIST trial. The dotted line indicates a mean change from baseline of 30×10^9/L. BL, baseline; C, cycle; D, day; MEDALIST, A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes; SE, standard error. Adapted from Garcia-Manero G et al. ASH abstract 4243. *Blood.* 2019;134(suppl 1).[4]

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 With Revised International Prognostic Scoring System Very Low-, Low-, or Intermediate-Risk Myelodysplastic Syndromes With Ring Sideroblasts Who Require Red Blood Cell Transfusions

In the phase 3 MEDALIST study, luspatercept was well tolerated and effective, reducing the need for transfusion among patients with RBC transfusion–dependent, lower-risk MDS with ring sideroblasts.[1-3] Dr Pierre Fenaux and colleagues presented updated results that encompass 14 additional months of follow-up.[3]

The longer follow-up permitted the investigators to evaluate clinical efficacy for several parameters, including the achievement and number of individual response periods of RBC transfusion independence of at least 8 weeks; clinical benefit, defined as RBC transfusion independence (≥8 weeks); modified hematologic improvement–erythroid response; and total duration of clinical benefit, defined as the time from the initial improvement to treat-

ment discontinuation owing to loss of benefit, adverse events (AEs), or other reasons.

Baseline RBC transfusion burden (described as units per 8 weeks) was assessed 16 weeks before patients were randomly assigned to treatment.[1-3] The amount of RBCs given was less than 4 U in 30.1% of the luspatercept arm vs 26.3% of the placebo arm. The amount ranged from 4 U to less than 6 U in 26.8% vs 30.2%, respectively, and was 6 U or more in 43.1% vs 43.4%. The median baseline burden was the same for both arms, at 5 RBC U/8 weeks.

According to the extended follow-up analysis, the endpoint of RBC transfusion independence lasting longer than 8 weeks was reached by 47.7% of the luspatercept arm vs 15.8% of the placebo arm (P<.0001).[2,3] In the earlier analysis, these rates were 37.9% vs 13.2%, respectively (P<.0001).[1]

The benefit of luspatercept was maintained regardless of the baseline transfusion requirement for RBCs. The rate of transfusion independence was 84.8% in patients requiring less than 4 U, 48.8% in those requiring 4 U to less than 6 U, and 21.2% in those requiring 6 U or more. In the placebo arm, these rates were 40.0%, 8.7%, and 6.1%, respectively.

Among patients in the luspatercept arm who achieved RBC transfusion independence during the entire treatment period, discrete episodes of response numbered 2 or more in 69.9%, 3 or more in 38.4%, and 4 or more in 20.5%. Among the 12 patients achieving RBC transfusion independence with placebo, 33.3% had at least 2 response periods. No patients had more than 3.

By the end of the data cutoff, treatment continued in 26.8% of the luspatercept arm. No patients in the placebo arm were receiving treatment at this time. The median treatment duration was 50.9 weeks (range,

6.0-172.0) for luspatercept and 24.0 weeks (range, 7.4-103.0) for placebo. The median cumulative duration of RBC transfusion independence was 79.9 weeks (95% CI, 53.7-112.3) with luspatercept and 21.0 weeks (95% CI, 10.9 to not evaluable) with placebo (Figure 3).

Clinical benefit was seen in 64.1% of the luspatercept arm vs 26.3% of the placebo arm.[2,3] The median total duration of clinical benefit was 92.3 weeks (range, 8-172) for patients in the luspatercept arm and 26.8 weeks (range, 8-103) in the placebo arm. Among patients treated with luspatercept, 7.8% remained RBC transfusion independent through week 48 of the study.

No unexpected AEs occurred.[1-3] The frequency of treatment-emergent AEs was 87.6% in the luspatercept arm and 82.9% in the placebo arm.[3] The frequency of serious AEs was 41.8% with luspatercept vs 30.3% with
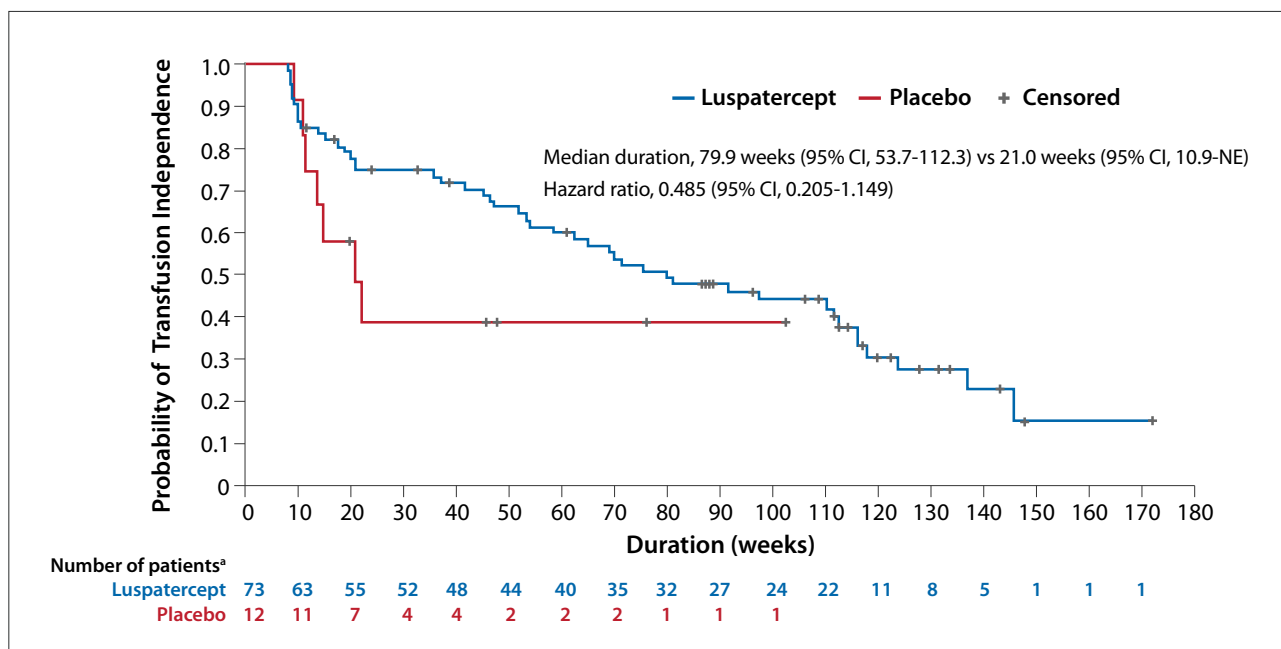

Figure 3. The median cumulative duration of RBC-TI ≥8 in a long-term analysis of the MEDALIST trial. Cumulative duration of RBC-TI ≥8 week is defined as the sum of all durations of RBC-TI for patients achieving RBC-TI ≥8 week during the entire treatment phase. ᵃIn the intention-to-treat population; patients who maintained response were censored from the analysis. MEDALIST, A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes; NE, not estimable; RBC-TI ≥8, red blood cell transfusion independence for 8 weeks or longer. Adapted from Fenaux P et al. ASH abstract 841. *Blood.* 2019;134(suppl 1).[3]

placebo. After adjusting for treatment exposure, the incidence of serious AEs per 100 patient-years was comparable between the treatment arms. The incidence of treatment-emergent AEs appeared to decrease over time in both arms (Figure 4). The most common treatment-emergent AEs that required discontinuation of luspatercept were fatigue (1.3%), asthenia (0.7%), and headache (0.7%). Overall, 13.7% of patients in the luspatercept arm and 7.9% of patients in the placebo arm discontinued treatment owing to at least 1 treatment-emergent AE.

Progression to high-risk MDS was reported in 3.3% of patients in the luspatercept arm vs 2.6% of patients in the placebo arm. Progression to acute myeloid leukemia (AML) occurred in 2.0% vs 2.6%, respectively.

The authors concluded that this longer-term analysis of data from the MEDALIST trial confirmed that luspatercept is a potential new therapy for the treatment of anemia in patients with lower-risk MDS with ring sideroblasts. More patients in the luspatercept arm achieved transfusion independence of at least 8 weeks any time during treatment as compared with the placebo arm. Treatment with luspatercept led to a durable cumulative duration of transfusion independence regardless of the baseline transfusion burden.

The COMMANDS trial (Efficacy and Safety Study of Luspatercept [ACE-536] Versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low, Low or Intermediate Risk
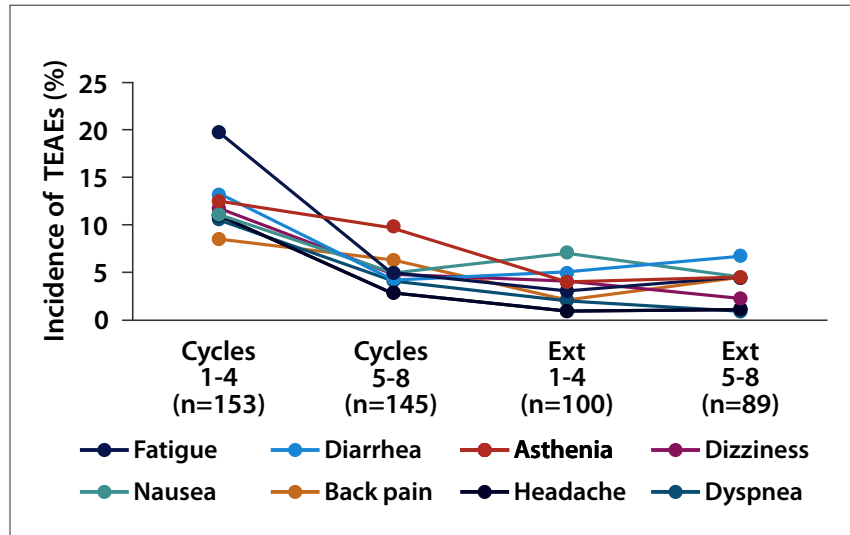

Figure 4. Frequent treatment-emergent adverse events of any grade among patients treated with luspatercept in the MEDALIST trial. Ext, extension cycle; MEDALIST, A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes; TEAEs, treatment-emergent adverse events. Adapted from Fenaux P et al. ASH abstract 841. *Blood.* 2019;134(suppl 1).[3]

Myelodysplastic Syndromes [MDS] in ESA Naïve Subjects Who Require Red Blood Cell Transfusions) will evaluate the efficacy and safety of luspatercept vs epoetin alpha in untreated patients with lower-risk MDS who are dependent on RBC transfusions.[4]

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Luspatercept Significantly Reduces Red Blood Cell Transfusion Burden, Regardless of Gene Mutation Frequency, Spectrum, and Prognostic Significance, Among Patients With LR-MDS Enrolled in the MEDALIST Trial

An analysis of the phase 3 MEDALIST trial assessed the association between genetic mutations relevant to MDS and response to luspatercept, as well as the evolving characteristics of gene mutations during treatment.[1] Researchers isolated DNA from bone marrow mononuclear cells obtained from 222 patients (148 in the luspatercept arm and 74 in the placebo arm). DNA from bone marrow mononuclear cells was isolated at screening and again every 24 weeks when available. Subsequent DNA isolation was obtained from 148 patients in the luspatercept arm and 74 patients in the placebo arm.

Next-generation sequencing of 23 genes relevant to MDS with 1000-fold coverage and a variant allele frequency cutoff of at least 1% revealed no differences in mutations at baseline among patients who responded to luspatercept (n=56) vs those who did not (n=92; Figure 5).[1] The most common baseline mutation was *SF3B1*, occurring in 92.9% of responders and 93.5% of nonresponders. Patients with lower-risk MDS harbored a preponderance of mutations in *SF3B1*. Mutations in genes associated with inferior prognosis were balanced between the treatment arms.

Baseline mutations in luspatercept responders and nonresponders were identified in RNA splicing, DNA methylation, chromatin, transcription, kinase signaling, and p53 functional categories (Figure 6).[1] Baseline cytomorphologic analysis identified erythroid precursors in 33% of responders vs 26% of nonresponders (*P*=.008). Positivity for ring sideroblasts was found in 80% vs 84%, respectively (*P*=.25).

Acquisition of mutations was not significantly different between the treatment arms, occurring in 10.3% of patients receiving luspatercept and 12.5% of those receiving placebo (*P*=.63). Loss of mutations was also similar, occurring in 3.2% vs 7.8%, respectively (*P*=.16).

A total of 58 patients in the luspatercept arm and 19 patients in the placebo arm were evaluable for changes in variant allele frequency in genes associ-
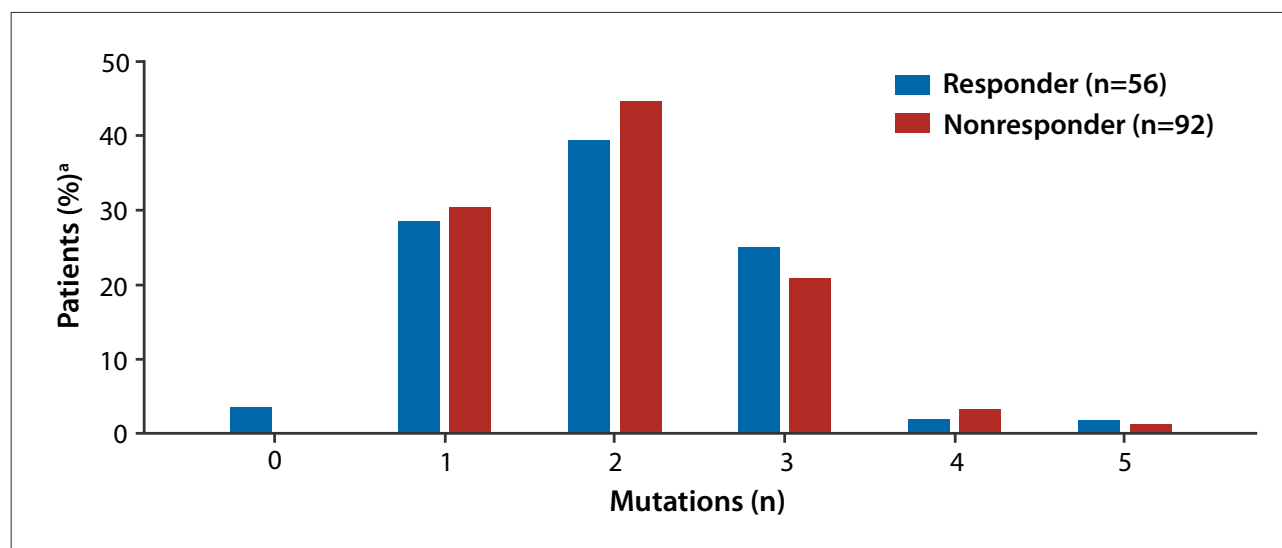

Figure 5. The frequency of the number of mutations at baseline in responders and nonresponders treated with luspatercept in the MEDALIST trial. Response was defined as RBC-TI ≥8 weeks during weeks 1 to 24 of treatment; differences between responders and nonresponders were not statistically different. [a]Frequencies were calculated separately for responders and nonresponders. Frequencies were calculated as the percentage of responding or nonresponding patients with the indicated number of mutations among the total number of responders or nonresponders, respectively. MEDALIST, A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes; RBC-TI, red blood cell transfusion independence. Adapted from Platzbecker U et al. ASH abstract 2999. *Blood.* 2019;134(suppl 1).[1]

ated with a worse prognosis in MDS.[1,4] These genes included *ASXL1*, *SRSF2*, *U2AF1*, *NRAS*, *IDH2*, *GATA2*, *TP53*, *RUNX1*, and *EZH2*. Changes in these genes from baseline to week 25 did not significantly differ between the luspatercept and placebo arms (*P*=.69).

Notably, the ratio of myeloid to erythroid precursors decreased in patients treated with luspatercept vs placebo.[1] In the 125 evaluable patients treated with luspatercept, the ratio decreased by 0.78-fold. Among the 64 evaluable patients receiving placebo, the ratio increased by 1.37-fold (*P*<.0001). These results support the

hypothesis that luspatercept has erythroid activity.

The study investigators concluded that the RBC transfusion independence reported with luspatercept occurred regardless of the patients' allelic burden of *SF3B1*, the number of mutations at baseline, adverse mutations at baseline, and presence of co-mutations.[1]

References

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patients (pts) with LR-MDS enrolled in the MEDALIST trial [ASH abstract 2999]. *Blood*. 2019;134(suppl 1).
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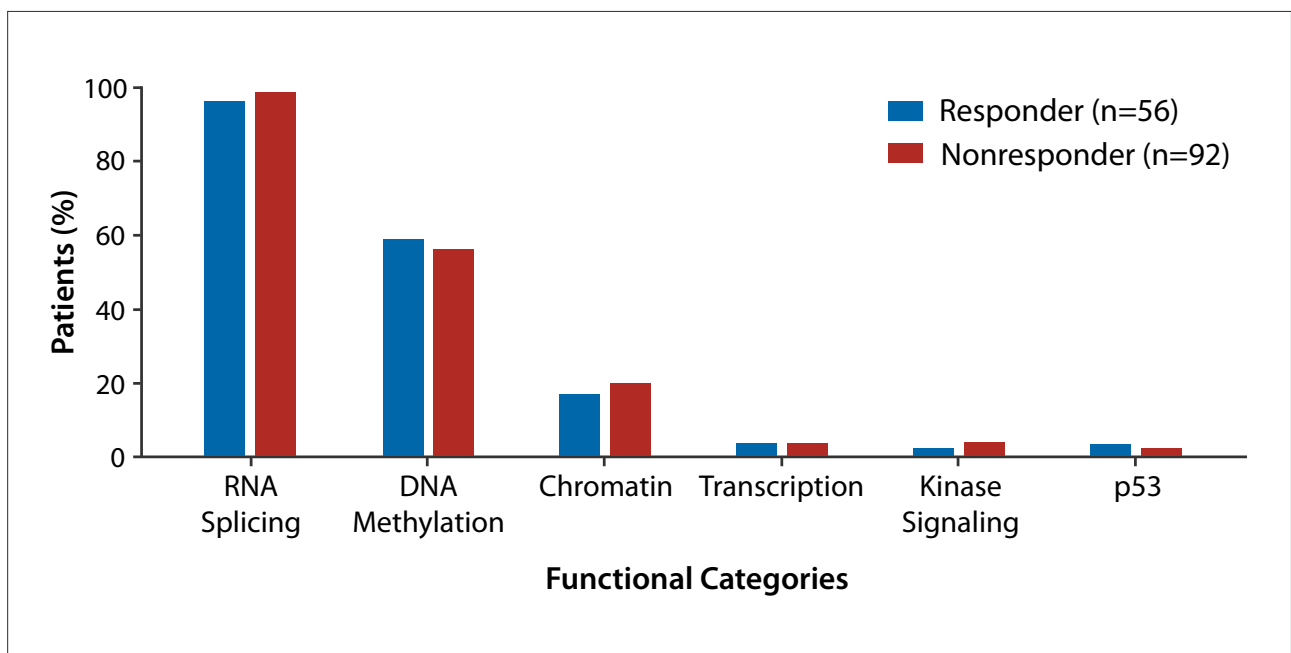

Figure 6. Frequency of mutations according to functional category at baseline among patients treated with luspatercept in the MEDALIST trial. Patients were classified by response, which was defined as RBC-TI ≥8 weeks during weeks 1 through 24 of treatment; differences between responders and nonresponders were not statistically significant in any category (Fisher's exact test). MEDALIST, A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes; RBC-TI, red blood cell transfusion independence. Adapted from Platzbecker U et al. ASH abstract 2999. *Blood*. 2019;134(suppl 1).[1]

Pharmacokinetic Exposure Equivalence and Preliminary Efficacy and Safety From a Randomized Cross Over Phase 3 Study (ASCERTAIN Study) of an Oral Hypomethylating Agent ASTX727 (Cedazuridine/Decitabine) Compared to IV Decitabine

The novel agent ASTX727 is an orally administered tablet containing cedazuridine and decitabine.[1] The phase 3 ASCERTAIN trial (Study of ASTX727 vs IV Decitabine in MDS, Chronic Myelomonocytic Leukemia, and AML) compared the exposure bioequivalence of oral cedazuridine/decitabine with intravenous (IV) decitabine and also generated clinical data for the oral treatment.[1] The trial enrolled patients with MDS (IPSS intermediate-1 or -2, or high-risk) or chronic myelomonocytic leukemia.

The oral treatment consisted of cedazuridine at 100 mg and decitabine at 35 mg.[1] The dose of IV decitabine was 20 mg/m². The trial followed a randomized crossover design. To compare pharmacokinetic exposure, patients were randomly assigned to receive oral cedazuridine/decitabine in cycle 1 followed by IV decitabine in cycle 2, or IV decitabine in cycle 1 followed by cedazuridine/decitabine in cycle 2. From cycle 3 until treatment discontinuation, all patients received cedazuridine/decitabine. The primary endpoint was area under the curve (AUC) equivalence throughout 5 days of dosing and pharmacodynamics of DNA demethylation according to the *LINE-1* assay. The clinical efficacy and safety of cedazuridine/decitabine were also assessed.

In the trial, 133 patients received treatment. The patients' median age was 71.0 years (range, 44-88). Most patients (65%) were male. Patient characteristics in the 2 arms were well balanced at baseline. According to IPSS scoring, 44% of patients were at intermediate-1 risk, 20% were at intermediate-2 risk, and 16% were at high risk. Chronic myelomonocytic leuke-

mia was reported in 12% of patients.

The study met its primary endpoint. The 5-day decitabine AUC_{0-24} (h·ng/mL) geometric mean estimate was 856 with cedazuridine/decitabine and 865 with IV decitabine.[1] The oral/IV AUC was 98.9% (90% CI, 92.7-105.6). This result was confirmed in all sensitivity and secondary exposure analyses.

In the comparison of hypomethylating activity, no significant difference in the percent of *LINE-1* DNA was observed between cedazuridine/decitabine and IV decitabine (Figure 7). The difference was less than 1% in cycles 1 and 2. Therefore, the same pharmacodynamic effect was observed with oral and IV decitabine.

The median follow-up was 5.2 months (interquartile range, 3.5-8.0) for 101 evaluable patients. The overall response rate (ORR) was 64%, and included a complete response (CR) rate of 11.9% and a bone marrow CR rate of 45.5% (including 13.9% with

bone marrow CR with hematologic improvement). Hematologic improvement was reported in 6.9%. Among all treated patients, 12% underwent hematopoietic stem cell transplant.

The safety data were consistent with those expected for decitabine.[1] The most common AE was thrombocytopenia, which occurred in 43.8% of the oral cedazuridine/decitabine arm vs 37.9% of the IV decitabine arm. All-grade anemia was reported in 31.8% vs 36.9%, respectively. Neutropenia occurred in 31.8% vs 35.4%. The incidence of grade 3 gastrointestinal toxicity was less than 1% in both arms.

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ABSTRACT SUMMARY Combined Treatment With Lenalidomide and Epoetin Alfa Leads to Durable Responses in Patients With Epo-Refractory, Lower Risk Non-Deletion 5q MDS: Final Results of the E2905 Intergroup Phase III Study

In a phase 3 trial, lenalidomide enhanced sensitivity to epoetin alfa among patients with lower-risk MDS without 5q deletions and with a poor response to erythropoietic growth factors (Abstract 842). Patients received lenalidomide alone (n=96) or with epoetin alfa (n=99) for 16 weeks. The primary endpoint was the major erythroid response rate. A major erythroid response was reported in 11.5% of the lenalidomide-only arm vs 28.3% of the combination arm (*P*=.004). Among 44 patients who crossed over from lenalidomide to lenalidomide plus epoetin alfa, 25% achieved a major erythroid response. The median duration of major erythroid response was 23.8 months with lenalidomide plus epoetin alfa, compared with 13.0 months for lenalidomide alone. Acute myeloid leukemia was reported in 2.1% of patients in the lenalidomide-only arm and in no patients receiving lenalidomide plus epoetin alfa. Deaths were reported in 2.1% vs 3%, respectively.
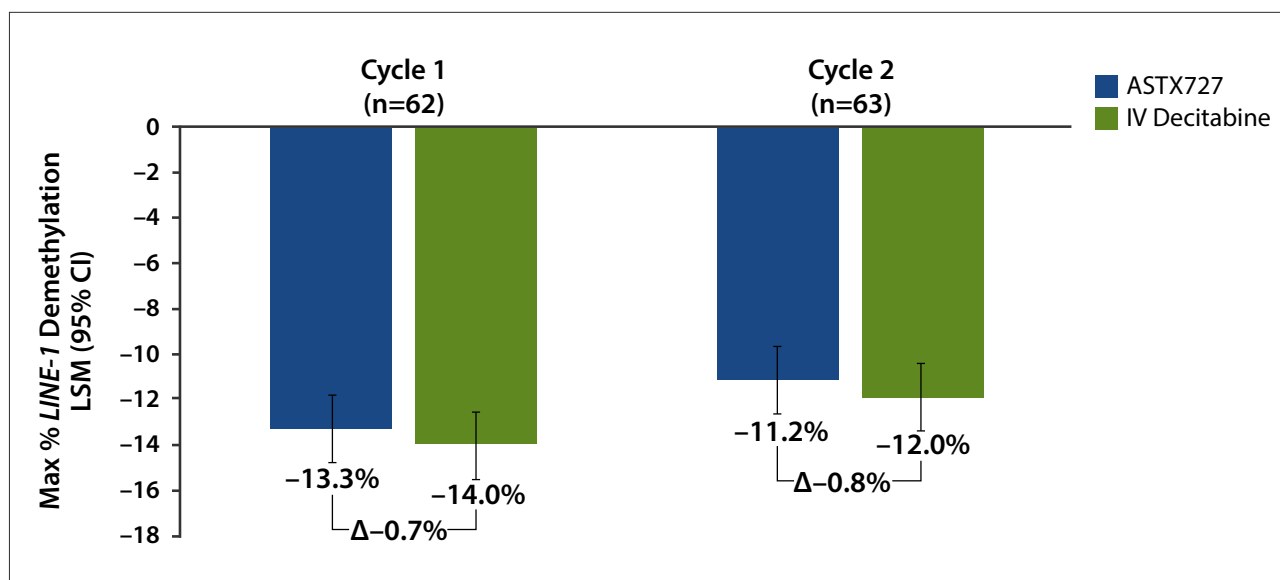
Figure 7. A study comparing ASTX727, an oral tablet containing cedazuridine/decitabine, vs intravenous decitabine found no significant differences in the percent of *LINE-1* DNA demethylation. LSM, geometric least squares means; max, maximum. Adapted from Garcia-Manero G et al. ASH abstract 846. *Blood*. 2019;134(suppl 1).[1]

The First-in-Class Anti-CD47 Antibody Magrolimab (5F9) in Combination With Azacitidine Is Effective in MDS and AML Patients: Ongoing Phase 1b Results

The novel immunotherapy regimen of magrolimab, an anti-CD47 monoclonal antibody, plus azacitidine continues to be well tolerated and exhibits robust activity in patients with MDS and AML, according to updated results from the expansion cohort of the ongoing 5F9005 trial (Hu5F9-G4 Monotherapy or Hu5F9-G4 in Combination With Azacitidine in Patients With Hematological Malignancies).[1] Preliminary results of this phase 1b study, drawn from the safety cohort, demonstrated high response rates in both MDS and AML.[2] The updated report focused on the use of magrolimab combined with azacitidine in untreated patients with intermediate-risk to very–high-risk MDS and AML who were ineligible for induction chemotherapy.[1]

Patients received azacitidine at the standard dose of 75 mg/m², given intravenously or subcutaneously, on

days 1 to 7 of a 28-day cycle.[1] Based on the potential for on-target anemia, magrolimab was first administered as a priming dose starting at 1 mg/kg and then escalated throughout 3 weeks to 30 mg/kg weekly. No maximum tolerated dose was reached. Based on an amendment to the study in cycle 3, patients began to receive the drug every other week.[1,3]

The primary objectives of the study were to assess the safety of magrolimab plus azacitidine in all patients and the efficacy of this combination in untreated MDS/AML.[1,2] Responses were assessed by International Working Group 2006 criteria for patients with MDS and European LeukemiaNet 2017 criteria for patients with AML. The secondary objectives included duration of response, progression-free survival, and overall survival, as well as the pharmacokinetics, pharmacodynamics, and immunogenicity of

magrolimab. An exploratory objective was to assess CD47 receptor occupancy, as well as markers of immune cell activity and molecular profiling in MDS/AML.

At the time of the data presentation, 62 patients had been treated with magrolimab combined with azacitidine.[1] Among these patients, 35 had MDS and 27 had AML. Their median ages were 70 years and 74 years, respectively. Poor-risk cytogenetics were reported in 66% of patients with MDS and 67% of patients with AML. A *TP53* mutation was found in 11% vs 41%, respectively. Among the AML patients, 70% had myelodysplasia.

Overall, 46 patients (24 MDS and 22 AML) were evaluable for efficacy.[1] MDS patients had an ORR of 92%, with a stringent CR in 50%, a marrow CR in 33%, and hematologic improvement in 8%. Stable disease was observed in 8%. In AML, the ORR

was 64%, with a CR rate of 41%, an incomplete CR rate of 14%, and a partial response in 5%. Stable disease was reported in 32% of patients, and progressive disease occurred in 5% of patients. The median response time was 1.9 months, which was more rapid than expected for azacitidine alone.

Among patients with MDS who responded to treatment, a cytogenetic CR was seen in 26%, and minimal residual disease (MRD) negativity was reported in 23%.[1] Among patients with AML, these rates were 60% vs 57%, respectively. The median duration of response and overall survival were not reached for either cohort, at a median follow-up of 6.4 months in patients with MDS and 8.8 months for patients with AML. Allogeneic stem cell transplant was performed in 15% of patients overall.

For patients with AML and a *TP53* mutation, the ORR was 78% (44% CR; 33% incomplete CR), and

67% of responders were MRD-negative. The median duration of response and overall survival for this group were not reached. Thus far, however, data compare favorably with those for current therapies. As a comparison, venetoclax plus azacitidine is associated with an ORR of 47%, a duration of response of 5.6 months, and an overall survival of 7.2 months.[1,4] In most patients treated with magrolimab plus azacitidine in the study, neutrophil and platelet counts improved during therapy (Figure 8).

The combination of magrolimab plus azacitidine depleted putative leukemia stem cells (CD34+ CD38–) in 40% of responding patients.[1] Data produced in collaboration with the Immunotherapy Platform at MD Anderson Cancer Center indicated increased T-cell infiltration in the marrow of patients with AML.

Magrolimab plus azacitidine was well tolerated, with a safety profile

similar to that of azacitidine monotherapy.[1,2] On-target anemia occurred in 37% of patients. There were no significant cytopenias (most patients were cytopenic at baseline), infections, or autoimmune AEs. Only 1 patient in the combination arm discontinued treatment owing to an AE (which was severe infusion-related reaction).

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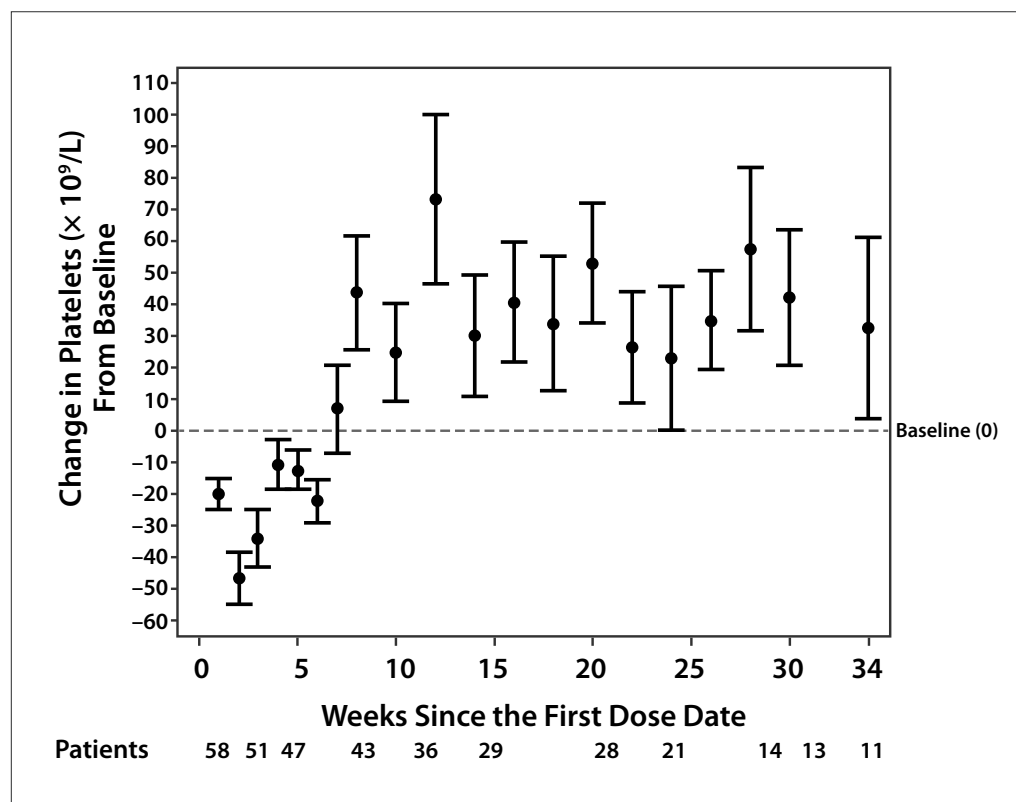
Figure 8. Change in platelets from baseline among patients treated with magrolimab plus azacitidine. Adapted from Sallman DA et al. ASH abstract 569. *Blood*. 2019;134(suppl 1).[1]

Interim Analysis of a Phase II Study of the Glutaminase Inhibitor Telaglenastat (CB-839) in Combination With Azacitidine in Advanced Myelodysplastic Syndrome

The combination of azacitidine with the glutaminase inhibitor telaglenastat shows activity and appears safe for patients with advanced MDS, according to an interim analysis of a phase 2 trial.[1] Glutaminase is involved in the conversion of glutamine to glutamate, and it is frequently upregulated in tumor cells, including in high-risk MDS and AML.[1,2] Glutaminase inhibition can lead to apoptosis, and therefore interrupting glutaminase activity is a target of some cancer treatments.[1-4] The glutaminase inhibitor telaglenastat in combination with azacitidine has been shown to inhibit growth in AML cells.[4]

In this phase 1b/2 trial, eligible patients (N=19) had MDS that was high risk or IPSS intermediate-1 risk with high-risk genetic features.[1] Patients received 75 mg/m²/day of azacitidine on days 1 through 7 of each cycle for 6 cycles, and 600 mg of telaglenastat twice per day on days 1 through 28 of each cycle.

Primary study endpoints included identification of the recommended phase 2 dose and safety.[1,5] Secondary endpoints include ORR, overall survival, and event-free survival.[1,5]

At baseline, 37% of patients had complex cytogenetics.[1] More than half of patients (53%) had *ASXL1* mutations, 37% had *TET2* mutations, and 32% had *TP53* mutations. The patients' median age was 68 years (range, 47-82). For this interim report, the median study follow-up duration was 10.5 months, and the median number of cycles received was 3.

For the entire study population, the ORR was 63%. The CR rate was 11%, and the marrow CR rate was 47%. The median time to best response was 1 cycle. Among the 14 patients receiving frontline treatment, the ORR was 57%. Among the 5 patients who had previously received treatment with a hypomethylating agent, the ORR was 80%. The ORR was 86% in patients with complex cytogenetics (n=7), 60% in those with an *ASXL1* mutation (n=10), and 83% in those with a *TP53* mutation (n=6).

For the entire cohort, the median overall survival time had not been reached (Figure 9). The 1-year overall survival rate was 50%. The median event-free survival was 9.8 months, and the 1-year event-free survival rate was 33%.

Grade 1/2 gastrointestinal events were the most common AEs. Grade 3/4 infections occurred in 47% of patients. Grade 3/4 thrombocytopenia was reported in 42%, and grade 3/4 neutropenia occurred in 37%. There were 7 fatalities, including 2 from infections.

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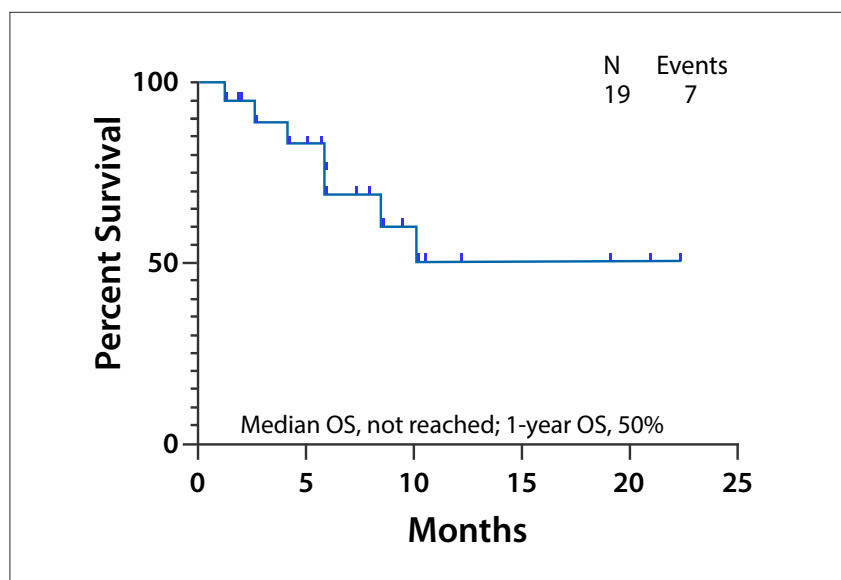|	N	Events
	19	7

Median OS, not reached; 1-year OS, 50%

Figure 9. Overall survival among patients treated with the glutaminase inhibitor telaglenastat in a phase 2 trial. Adapted from Guerra VA et al. ASH abstract 567. *Blood*. 2019;134(suppl 1).[1]

Phase II Study of Oral Rigosertib Combined With Azacitidine as First-Line Therapy in Patients With Higher-Risk Myelodysplastic Syndromes

According to updated results from a phase 2 study, the combination of oral rigosertib with azacitidine as first-line therapy was efficacious and well tolerated in patients with hypomethylating agent–naive, higher-risk MDS.[1,2] Rigosertib acts as a Ras mimetic, blocking Ras-binding domains of proteins involved in multiple dysregulated signaling transduction pathways that are believed to be important in the pathophysiology of high-risk MDS.[1,2] In vitro, the sequential exposure of leukemic cells to rigosertib followed by azacitidine achieved maximum synergy at concentrations that were clinically achievable in patients.[1,3]

In the original study, a dose of single-agent rigosertib at 1120 mg/day yielded the highest response of transfusion independence (44%) in lower-risk MDS patients.[1,2] The study investigators used an expansion cohort to explore the safety and efficacy of this higher dose in patients with high-risk MDS.[1]

The study enrolled patients who had not received hypomethylating agents, as well as patients who developed relapsed/refractory disease after treatment with them (n=55).[1] The report presented at the ASH meeting provided results from patients who had not received hypomethylating agents (n=39). Responses were assessed according to 2006 International Working Group criteria.

In total, 39 treatment-naive high-risk MDS patients received the combination regimen of oral rigosertib and standard-dose azacitidine.[1] Rigosertib was administered at 840 mg/day (560 mg in the morning and 280 mg in the afternoon) or 1120 mg/day (560 mg in the morning and 560 mg in the afternoon or 840 mg in the morning and 280 mg in the afternoon).[1,4] Rigosertib was administered on days 1 to 21 of a 28-day cycle, and azacitidine (75 mg/m^2/day) was administered for 7 days from day 8.

For the hypomethylating agent–naive high-risk MDS patients, the median age was 64 years (range, 42-90). Most patients were male (56%). IPSS-R classification was low in 8%, intermediate in 23%, high in 21%, and very high in 44%. (Risk was unknown in 5%.) According to IPSS-R cytogenetic prognostic scoring, prognosis was very poor in 23%, poor in 18%, intermediate in 23%, and good in 36%. At study entry, 51% of patients were transfusion-dependent.

The median duration of treatment was 7.8 months (range, 0.7-25.1+). Patients evaluable for response had received 3 cycles of therapy. Among these 29 patients, the ORR was 90%, and the CR rate was 34%. There were no partial responses. Hematologic improvement plus a marrow CR was reported in 17%. Hematologic improvement alone occurred in 10%, 28% had a marrow CR alone, and 10% had stable disease. The median duration of response was 12.2 months (range, 0.1-24.2+; Figure 10). The median time to first and best response was one-quarter of a cycle. Responses were observed across all cytogenetic subgroups: 80% of the very-poor group, 100% of the poor group, 88% of the intermediate group, and 92% of the good group. CRs were observed in 42% of patients at very-high risk, 17% of those at high risk, 25% of those at
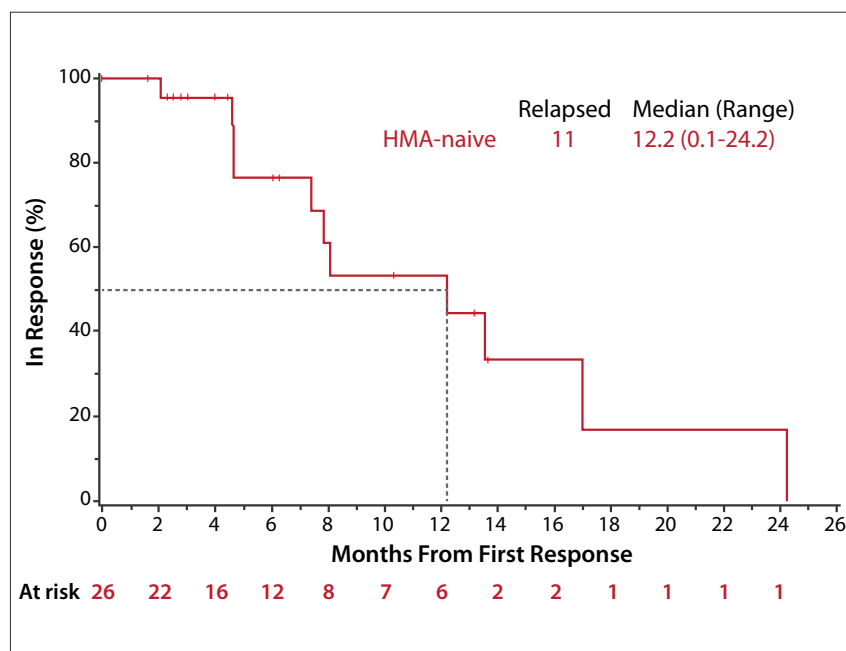

Figure 10. Duration of overall response among patients treated with oral rigosertib and azacitidine. HMA, hypomethylating agent. Adapted from Navada SC et al. ASH abstract 566. *Blood.* 2019;134(suppl 1).[1]

intermediate risk, and 11% of low-risk patients.

All patients developed an AE of grade 1 or higher.[1] The AE was grade 3 or higher in 90%. The most frequent AEs were similar to those associated with each agent alone. Ten AEs required treatment discontinuation; they consisted of urinary tract pain (n=2), urinary retention, hematuria, hydronephrosis, osteolysis, cerebral hemorrhage, reduced white blood cell count, reduced neutrophil count, and abdominal pain (n=1 for each).

These results led to the initiation of a pivotal phase 2/3 adaptive-design trial of oral rigosertib and standard-dose azacitidine in patients with higher-risk MDS who have not received hypomethylating agents.

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Phase 1b/2 Combination Study of APR-246 and Azacitidine in Patients With *TP53*-Mutant Myelodysplastic Syndromes and Acute Myeloid Leukemia

APR-246 is a first-in-class small molecule that stabilizes the p53 protein. A phase 1b/2 study of APR-246 plus azacitidine suggested that the combination is well tolerated and yields high response rates in mutated-*TP53* MDS and AML.[1,2] The results of the phase 2 portion of the study were presented by Dr David Sallman.[1]

Patients enrolled in the trial had not received previous treatment with a hypomethylating agent. The patients had mutated *TP53* higher-risk MDS, MDS/myeloproliferative neoplasm, or oligoblastic AML (≤30% blasts). Patients received APR-246 (4500 mg IV, days 1-4) combined with azacitidine (75 mg/m^2 SC/IV for 7 days, on days 4-10 or days 4-5 and 8-12) in 28-day cycles.

The primary endpoint was the CR rate. The secondary endpoints included ORR, overall survival, outcome following allogeneic hematopoietic stem cell transplant, and clonal suppression and remission depth monitored by both next-generation sequencing and p53 immunohistochemistry.

Among the 55 patients in the trial, 40 had MDS, 11 had AML-myelodysplasia, and 4 had chronic myelomonocytic leukemia, MDS, or a myeloproliferative neoplasm.[1] The patients' median age was 66 years (range, 34-85). Most patients (85%) had complex cytogenetics, and 33% had treatment related-MDS/AML. All patients had mutated *TP53*: 91% had a missense mutation in the DNA-binding domain, and 33% had

ABSTRACT SUMMARY Venetoclax in Combination With Azacitidine in Treatment-Naive or Relapsed/Refractory Myelodysplastic Syndromes

Two phase 1b trials evaluated venetoclax in combination with azacitidine for the treatment of MDS in either the frontline or relapsed/refractory settings. The treatment-naive patients had higher-risk disease (Abstract 568). They were enrolled in an open-label, phase 1b, dose-escalation study. Among 57 patients evaluable for response, 38.6% had a CR, 38.6% had a marrow CR, and 15.8% had stable disease. The median time to a CR was 2.2 months. The 12-month estimate of duration of response after CR was 83.3%. Estimated rates of overall survival were 83.3% for 6 months and 76.9% for 12 months. The trial in the relapsed/refractory setting evaluated venetoclax alone or with azacitidine in 64 patients (Abstract 565). The ORR was 40% for venetoclax plus azacitidine vs 8% for venetoclax monotherapy. Progression-free survival was 9.1 months vs 3.3 months, respectively. The estimated 12-month survival was 65% for patients treated with venetoclax plus azacitidine. The toxicity profile of the combination was considered manageable in the treatment-naive patients and well tolerated in the relapsed/refractory patients.
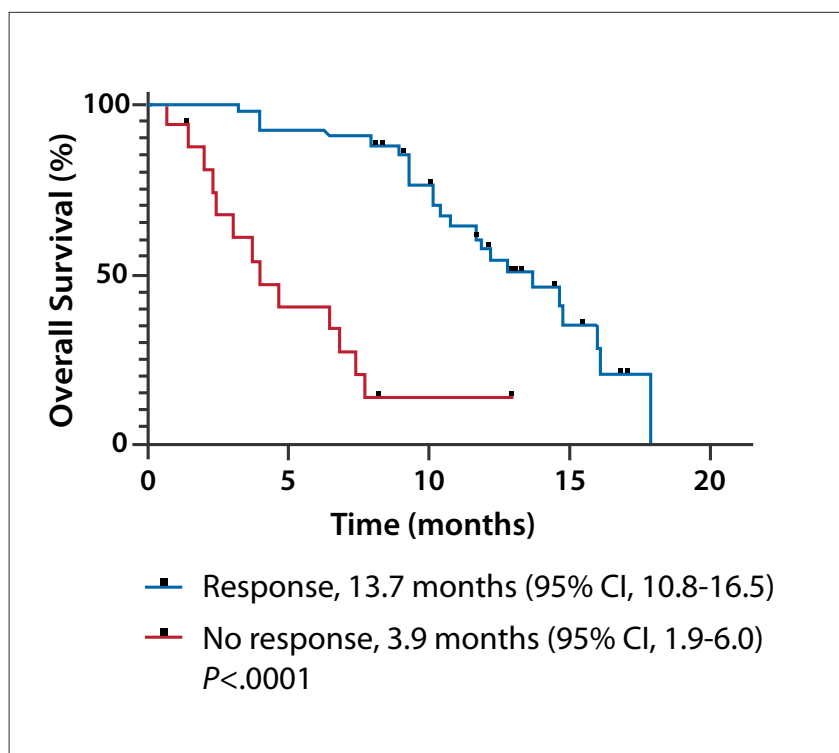
Figure 11. Overall survival among patients who did or did not respond to treatment with APR-246 plus azacitidine. Adapted from Sallman DA et al. ASH abstract 676. *Blood*. 2019;134(suppl 1).[1]

multiple mutations. The median variant allele frequency was 21%. *TP53* was the only gene mutation in 62% of patients.

Forty-five patients were evaluable for response. The median follow-up duration was 10.8 months. The median time to response was 2.1 months (range, 0.1-5.4). The ORR of 87% consisted of a CR in 53%, a bone marrow CR with hematologic improvement in 18%, a bone marrow CR in 9%, and hematologic improvement alone in 7%. Stable disease was reported in 4 patients, and 1 patient developed progressive disease. The median duration of response was 8.0 months (range, 6.5-11.2). Notably, 22 patients (49%) were taken off treatment to undergo allogeneic hematopoietic stem cell transplant.

The CR rate was 69% in patients with a single *TP53* mutation vs 25% in patients with this mutation plus others (*P*=.006). Improvement was associated with a nonsignificant trend toward higher overall survival (93% vs 69%; *P*=.08). The CR rate was 66% among patients with at least 10% p53 staining on immunohistochemistry bone marrow analysis vs 13% in those with a lower amount (*P*=.01). A complete cytogenetic response was reported in 41% of patients, and a partial cytogenetic response occurred in 18% of patients. In 39% of patients, serial *TP53* next-generation sequencing identified MRD negativity, which was associated with improved overall survival (12.8 vs 9.2 months; *P*=.02).

In the intention-to-treat population, the median overall survival was 10.8 months (95% CI, 8.1-13.4). The median overall survival was 13.7 months among responding patients vs 3.9 months among nonresponders (*P*<.0001; Figure 11). The median overall survival was 14.7 months (95% CI, 8.6-20.9) in patients who underwent allogeneic HSCT vs 10.1 months (95% CI, 6.2-14.0) in those who did not (*P*=.10).

The most common AEs related to treatment with APR-246 were nausea (64%), vomiting (45%), dizziness (36%), peripheral sensory neuropathy (31%), ataxia/unsteady gait (24%), and tremor (20%).[1] Severe AEs were consistent with those expected for azacitidine monotherapy, and included febrile neutropenia (25%) and pneumonia (20%). Few patients (5%) discontinued treatment owing to AEs. None of the discontinuations were related to treatment with APR-246. The 30-day mortality was 2%, and the 60-day mortality was 5%.

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Highlights in Myelodysplastic Syndromes From the 61st American Society of Hematology Annual Meeting: Commentary

Guillermo Garcia-Manero, MD

Deputy Chair, Translational Research
Professor and Chief
Section of Myelodysplastic Syndromes
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Abstracts at the 61st American Society of Hematology (ASH) Annual Meeting provided the most relevant data regarding advances in MDS treatment presented at this venue in the past few years. Studies included updated reports on luspatercept. Data on a new oral hypomethylating agent, ASTX727, were presented. In addition, multiple studies provided data for promising new agents.

Luspatercept

Luspatercept is a recombinant human protein that modulates transforming growth factor–ß signaling in MDS, thereby increasing erythropoiesis. Luspatercept is approved by the US Food and Drug Administration (FDA) for the treatment of anemia in adult patients with ß thalassemia who require regular transfusions of red blood cells.[1] The double-blind, placebo-controlled phase 3 MEDALIST trial (A Study of Luspatercept [ACE-536] to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes) evaluated the use of luspatercept to treat anemia among patients with very low–risk, low-risk, or intermediate-risk MDS with ring sideroblasts who had been receiving regular red blood cell transfusions. The risk of anemia was defined according to the Revised International Prognostic Scoring System.[2] Patients had already received growth factor support. My co-investigators and I recently published the results of the MEDALIST trial in the *New England Journal of Medicine*.[3] The primary endpoint—transfusion independence for 8 weeks or longer—was met by 38% of the luspatercept group (n=153) vs 13% of the placebo group (n=76; *P*<.001). The key secondary endpoint of transfusion independence for 12 weeks or longer was assessed during weeks 1 through 24 and weeks 1 through 48. In the luspatercept group, this endpoint was met by 28% at weeks 1 through 24 and by 33% at weeks 1 through 48. Among patients in the placebo group, these rates were 8% vs 12%, respectively (*P*<.001 for both comparisons).

The mechanism of action of luspatercept suggests that it might improve other cytopenias in addition to anemia. My colleagues and I presented results of a subgroup analysis of the MEDALIST trial that evaluated hematologic improvement.[4] The analysis focused on the responses of erythrocytes, neutrophils, and platelets at weeks 1 through 24 and weeks 1 through 48. The study also measured mean neutrophil changes from baseline, absolute increases in neutrophil and platelet counts, and safety.

Hematologic improvement in erythrocytes during weeks 1 to 48 was reported in 58.8% of the luspatercept arm vs 17.1% of the placebo arm. Improvement in neutrophils was seen in 20.0% vs 10.0%, respectively. Improvement in platelets occurred in 62.5% vs 33.3%. An increase in neutrophils from baseline was seen in 81.0% of the luspatercept arm and 51.3% of the placebo arm. For platelets, increases from baseline occurred in 70.6% vs 42.1%, respectively. The mean increases from baseline in neutrophils and platelets associated with luspatercept occurred early and stabilized over time. Among patients with normal baseline levels, the mean increases in neutrophils and platelets associated with luspatercept did not exceed the upper limit of normal and were not clinically meaningful. Among patients with baseline neutropenia or thrombocytopenia, luspatercept did not worsen these cytopenias. None of the patients with improvements in neutrophils or platelets progressed to acute myeloid leukemia (AML). A better understanding of the effect of luspatercept beyond anemia will be important for the optimal use of this compound.

The first report of data from the MEDALIST trial was presented at the 60th ASH meeting.[5] The longer-term analysis presented at the 61st ASH meeting confirmed the original results showing that luspatercept is superior to

placebo in this group of patients. Red blood cell transfusion independence for 8 weeks or longer at any time during the treatment period was achieved by 47.7% of the luspatercept arm vs 15.8% of the placebo arm. In the luspatercept arm, approximately 70% of the patients who responded experienced multiple periods of response. Clinical benefit was reported in 64.1% of the luspatercept arm and 26.3% of the placebo arm. An interesting aspect of the current analysis is that it used consecutive intervals to assess response. The traditional criteria consist of a single measurement of 8-week improvement in transfusions or hematologic response.

The original data suggested that luspatercept is safe, and there was no evidence indicating an increase in the risk of progression to AML. The long-term analysis also provided data regarding safety and the rate of progression to AML. Serious adverse events occurred in 41.8% of the luspatercept arm vs 30.3% of the placebo arm. One or more treatment-emergent adverse events occurred in 87.6% vs 82.9%, respectively, and led to treatment discontinuation in 13.7% vs 7.9%. The rate of progression to AML was 2.0% in the luspatercept arm vs 2.6% in the placebo arm.

Another analysis of data from the MEDALIST trial found that luspatercept significantly reduced red blood cell transfusion burden regardless of gene mutation frequency, spectrum, and prognostic significance.[6] When luspatercept was first developed, it was theorized that splicing mutations could be a biomarker of response. However, most patients with refractory anemia with ring sideroblasts have mutations on the splicing gene *SF3B1*. Luspatercept was associated with transfusion independence regardless of the presence of individual mutations, the number of mutations, mutations in various functional categories, and co-mutations at baseline.

This finding was expected because

a majority of these patients are indeed mutated for *SF3B1*. There was no evidence that any particular gene mutation signature was associated with a response to luspatercept.

A New Oral Hypomethylating Agent

There are currently 2 hypomethylating agents approved for MDS: azacitidine and decitabine. Both of these agents are administered via a parenteral route, either intravenously or subcutaneously. Researchers have been trying to develop oral hypomethylating agents for many years. I presented data on a compound known as ASTX727, which is a combination of oral formulations of cedazuridine and decitabine.[7] Cedazuridine is a cytidine deaminase inhibitor; it inhibits the catabolism of oral decitabine. By doing so, it renders the oral decitabine intact, while potentially allowing for an identical pharmacokinetic profile to intravenous decitabine. Previous studies suggested that the pharmacokinetic profile of ASTX727 was similar or identical to intravenous decitabine.[8,9]

The study presented at the ASH meeting confirmed the earlier data. This phase 3 trial was not randomized; it did not assign patients to different treatment arms. Instead, 133 patients were randomly assigned to treatment with intravenous decitabine or ASTX727 for the first cycle, and then to the other treatment for the second cycle. This design allowed for intra-patient comparison of the pharmacokinetic profile of the compounds. The study showed that the pharmacokinetic profile of intravenous decitabine was identical to that of oral decitabine. These important data suggest that there may be an effective oral hypomethylating agent. Pharmacodynamic endpoints indicated that the effects of the intravenous and oral formulations in terms of *LINE-1* hypomethylation were identical. An early analysis

of clinical activity showed that the intravenous and oral formulations were similar.

Novel Treatment Strategies

Dr David A. Sallman presented results from a phase 1b study that evaluated the first-in-class anti-CD47 antibody magrolimab in combination with azacitidine in patients with MDS and AML.[10] CD47 is an immune checkpoint inhibitor for macrophages. Earlier investigators had hypothesized that blocking CD47 may activate macrophages by inhibiting a "don't eat me" signal.[11,12] Original studies of magrolimab indicated a very high response rate.[13] In this phase 1b study, the response rate was 92% in the MDS patients and 64% in the AML patients.[10] The follow-up was short, at 6.4 months and 8.8 months, respectively. The response rate was especially high among patients with a *TP53* mutation, at 78%. These patients have a poor prognosis, and represent an unmet need. There was also some evidence that the combination eliminated leukemia stem cells.

Magrolimab has one specific toxicity: anemia. This toxicity reflects the fact that red blood cells express CD47. The manufacturer of magrolimab has developed strategies to mitigate this phenomenon. Further follow-up is needed, but these data suggest that magrolimab is a promising treatment for patients with MDS or AML.

My colleague Dr Veronica Guerra presented results from an interim analysis of a phase 2 study of the glutaminase inhibitor telaglenastat in combination with azacitidine in patients with advanced MDS.[14] Telaglenastat is a glutaminase inhibitor for patients with MDS. The overall response rate with the combination was 63%, which is higher compared with single-agent azacitidine. The question is how to position this compound, in view of developments with venetoclax, APR-246, and CD47.

In addition, gastrointestinal toxicity occurred in approximately 75% of patients in the study.

Dr Shyamala C. Navada presented results from a phase 2 study of oral rigosertib combined with azacitidine as first-line therapy in patients with higher-risk MDS.[15] The multikinase inhibitor rigosertib is being tested in both intravenous and oral formulations. The intravenous formulation is undergoing testing in a phase 3 randomized trial for patients with MDS previously treated with hypomethylating agents.[16] The oral formulation was developed by Dr Navada, Dr Lewis Silverman, and colleagues.[17] In phase 1 and 2 trials, oral rigosertib was associated with hematuria, which was mitigated by clinical intervention.[18,19] The phase 3 data show a high overall response rate, 90%, for the doublet of azacitidine and rigosertib. Longer follow-up is needed to assess the impact on survival. However, it appears that the duration of response is longer than expected. Rigosertib has also shown activity among patients with primary refractory MDS,[20] and the doublet might have activity in this setting as well.

Dr David A. Sallman presented phase 1b/2 results of APR-246 plus azacitidine in patients with *TP53*-mutated MDS or oligoblastic AML.[21] As discussed, *TP53* mutations are associated with a dismal prognosis in patients with MDS and AML. These patients are usually resistant to chemotherapy. APR-246 is a prodrug of another compound, methylene quinuclidinone (MQ), which binds to *TP53* and stabilizes it. There is also the possibility that the mechanism of action may alter reactive oxygen species in patients with these myeloid disorders. In a study presented by Dr Sallman at the 2018 meeting of the European Hematology Association, APR-246 in combination with azacitidine had a very high response rate in this group of patients.[22] The data presented at the ASH meeting were drawn from a multicenter phase of the trial and reflected longer follow-up and an increased number of patients. Among the 45 evaluable patients, the overall response rate was 87%, with a complete response rate of 53%. These rates are higher than those seen with hypomethylating agents. A partial or complete cytogenetic response was reported in 59% of evaluable patients.

Another study of APR-246 and azacitidine in patients with *TP53*-mutated disease, presented by Dr Thomas Cluzeau, was performed in France.[23] The data were highly consistent with those from the US study. The overall response rate was 55% in the intention-to-treat cohort and 66% among evaluable patients. A complete response was seen in 39% vs 49%, respectively.

There was a question regarding neurotoxicity with APR-246. In the French study, all-grade neurologic adverse events occurred in 40%, and grade 3/4 events occurred in 6%.[23] In the study by Dr Sallman, all-grade dizziness was reported in 36%, and grade 3 or higher dizziness occurred in 2%.[21] This neurotoxicity appears to be mild, but occasionally it could have significance. The prognosis of patients with the *TP53* mutation is poor. A treatment that could improve overall response rates (including cytogenetic and molecular responses) and increase the number of patients eligible for stem cell transplant would be a fundamental advance for the field. The combination of APR-246 plus azacitidine is being studied in a phase 3 randomized trial in North America that is expected to complete accrual in the next few months.[24]

Dr Alan List presented final results of a phase 3 trial evaluating combined treatment with lenalidomide and epoetin alfa in patients with lower-risk non-deletion 5q MDS that is refractory to erythropoiesis-stimulating agents.[25] Dr List presented initial results of this trial in 2016.[26] The study showed that the addition of lenalido-mide can increase the response rate in these patients who are refractory to erythropoiesis-stimulating agents. The major erythroid response rate was 34.6% with the combination vs 20% with lenalidomide alone. The question is whether these data will impact clinical care. Lenalidomide is not FDA-approved for the treatment of patients with non–deletion 5q MDS. In a study by Santini and colleagues, lenalidomide did not have a significant impact on the natural history of patients with lower-risk MDS without the deletion 5q abnormality.[27]

Dr David P. Steensma presented results of a large, multicenter trial of H3B-8800, a splicing modulator, in patients with MDS, AML, or chronic myelomonocytic leukemia.[28] Splicing mutations are among the most frequent mutations in patients with MDS, and *SF3B1* is a classic example. A drug that could inhibit this pathway would therefore be important. The study was well designed, incorporating important biomarkers. Unfortunately, this compound did not show any significant clinical activity. There were no complete responses or partial responses. There was some evidence of modulation of splicing. I believe that it is important to report on negative data, which will allow the design of new studies, or in this case, perhaps the development of secondary compounds that could target this important pathway in leukemia.

A phase 1/2 study presented by Dr Jorge Cortes evaluated olutasidenib, an IDH1 inhibitor, plus azacitidine in patients with *IDH1*-mutant MDS.[29] Patients with MDS should be evaluated according to their mutational status. The *IDH1* mutation occurs in less than 5% of patients with MDS. Data for this combination were positive. The response rate was 56%. This combination could represent a major improvement for the relatively small subset of patients with MDS who have the *IDH1* mutation.

A multicenter phase 2 trial evalu-

ated enasidenib (AG-221), with or without azacitidine, in the frontline or relapsed/refractory setting for patients with MDS with the *IDH2* mutation.[30] Dr Guillaume Richard-Carpentier presented initial results. The *IDH2* mutation is more frequent than the *IDH1* mutation, occurring in 10% to 15% of patients. In this trial, enasidenib was administered with azacitidine in untreated patients and as monotherapy in patients previously treated with hypomethylating agents. The study showed significant clinical activity in both settings. The overall response rate was 85% for untreated patients and 56% for patients with relapsed/refractory disease.

These positive results are not surprising because enasidenib is approved for patients with relapsed/refractory AML with an *IDH2* mutation. Enasidenib is not yet approved for patients with MDS. The toxicity profile was acceptable. Toxicities were similar to those seen in AML. Grade 3/4 differentiation syndrome occurred in 16% of patients.

Two phase 1b trials evaluated azacitidine and venetoclax in MDS, one in the frontline setting and the other in relapsed/refractory disease.[31,32] Venetoclax is an apoptosis-modulating compound that is approved in combination with azacitidine, decitabine, and low-dose cytarabine for patients with AML. In these phase 1b studies, the combination of azacitidine with venetoclax was highly active, with overall response rates of 100% in the frontline setting[31] and 40% in the relapsed/refractory setting.[32] Importantly, the durability of the responses appeared to be longer than would be expected with single-agent azacitidine. Among treatment-naive patients with a complete response, the 12-month estimated duration of response was 83.3%.[31]

These data will lead to phase 3 randomized trials of azacitidine with or without venetoclax for patients with treatment-naive MDS. It is likely that a BCL2 inhibitor may have an important role in patients with MDS, as it does in AML.

Disclosure

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