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# Highlights in Myelodysplastic Syndromes From the 60th American Society of Hematology Annual Meeting

## A Review of Selected Presentations From the 60th American Society of Hematology Annual Meeting • December 1-4, 2018 • San Diego, California

**Special Reporting on:**

- The MEDALIST Trial: Results of 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
- Safety and Efficacy, Including Event-Free Survival, of Deferasirox Versus Placebo in Iron-Overloaded Patients With Low- and Int-1-Risk Myelodysplastic Syndromes: Outcomes From the Randomized, Double-Blind TELESTO Study
- Long-Term Results of a Randomized Phase 2 Dose-Response Study of Guadecitabine, a Novel Subcutaneous Hypomethylating Agent, in 102 Patients With Intermediate- or High-Risk Myelodysplastic Syndromes or Chronic Myelomonocytic Leukemia
- Phase 2 Expansion Study of Oral Rigosertib Combined With Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes: Efficacy and Safety Results in HMA Treatment-Naive and Relapsed/Refractory Patients
- Results of a Phase 2, Open-Label Study of Idarubicin, Cytarabine, and Nivolumab in Patients With Newly Diagnosed Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome
- A Phase II Study of Nivolumab or Ipilimumab With or Without Azacitidine for Patients With Myelodysplastic Syndrome
- Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non-Del(5q) Lower-Risk MDS Relapsed/Refractory to a Erythropoiesis-Stimulating Agent Who Are Lenalidomide- and HMA-Naive
- Phase 3 Study of Lenalidomide Vs Placebo in Non-Transfusion Dependent Low Risk MDS Del(5q) Patients: Preliminary Blinded Analysis of the European SINTRA-REV Trial

**PLUS Meeting Abstract Summaries**

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# The MEDALIST Trial: Results of 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

In patients with lower-risk myelodysplastic syndrome (MDS), red blood cell (RBC) transfusion dependence is associated with a poorer prognosis compared with transfusion independence.[1] Patients with lower-risk MDS who are transfusion-dependent have higher morbidity as well as shorter overall survival, and they are more likely to develop acute myeloid leukemia (AML). Erythropoiesis-stimulating agents are often used as first-line therapy for the treatment of anemia in patients with transfusion-dependent lower-risk MDS who do not have the chromosome 5q deletion. However, erythropoiesis-stimulating agents carry the risk of iron overload and secondary organ complications. Moreover, many lower-risk MDS patients are refractory to erythropoiesis-stimulating agents or stop responding to therapy, underscoring the need for new treatment options. Luspatercept (ACE-536) is a ligand-trapping fusion protein that consists of the modified extracellular domain of human activin receptor type 2B plus a human immunoglobulin G1 Fc domain.[2] By trapping and sequestering select members of the transforming growth factor β ligand superfamily, luspatercept inhibits aberrant signaling by the Smad2/3 pathway, promoting late-stage erythropoiesis and reducing anemia in preclinical models. In a phase 2 study of 58 patients with lower-risk MDS, luspatercept reduced transfusion frequency and promoted transfusion independence.[3]

The double-blind, randomized, 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 luspatercept in patients with MDS with at least 15% ring sideroblasts or at least 5% *SF3B1* mutations.[4] Eligible patients had less than 5% blast cells in the bone marrow and lacked deletion 5q. Patients had very low-, low-, or intermediate-risk disease, as assessed by the revised International Prognostic Scoring System (IPSS-R) for MDS.[5] Patients who had not received previous treatment with erythropoiesis-stimulating agents had an erythropoietin level exceeding 200 U/L. Patients with prior exposure to erythropoiesis-stimulating agents were intolerant to treatment or developed refractory disease. An average RBC transfusion burden of at least 2 units every 8 weeks was

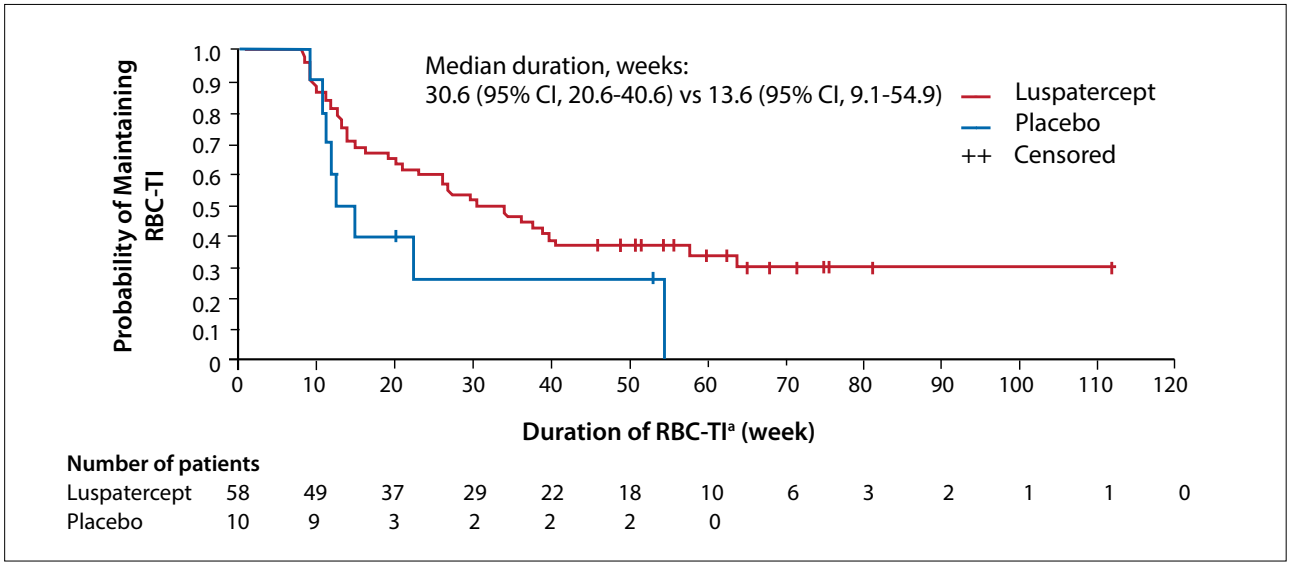


**Figure 1.** The median duration of response in the phase 3 MEDALIST trial, which compared luspatercept vs placebo in patients with myelodysplastic syndromes. [a]During the indicated treatment period. Patients who maintained RBC-TI at the time of the analysis were censored. MEDALIST, A Study of Luspatercept (ACE-536) to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes; RBC-TI, red blood cell transfusion independence. Adapted from Fenaux P et al. ASH abstract 1. *Blood*. 2018;132(suppl 1).[4]

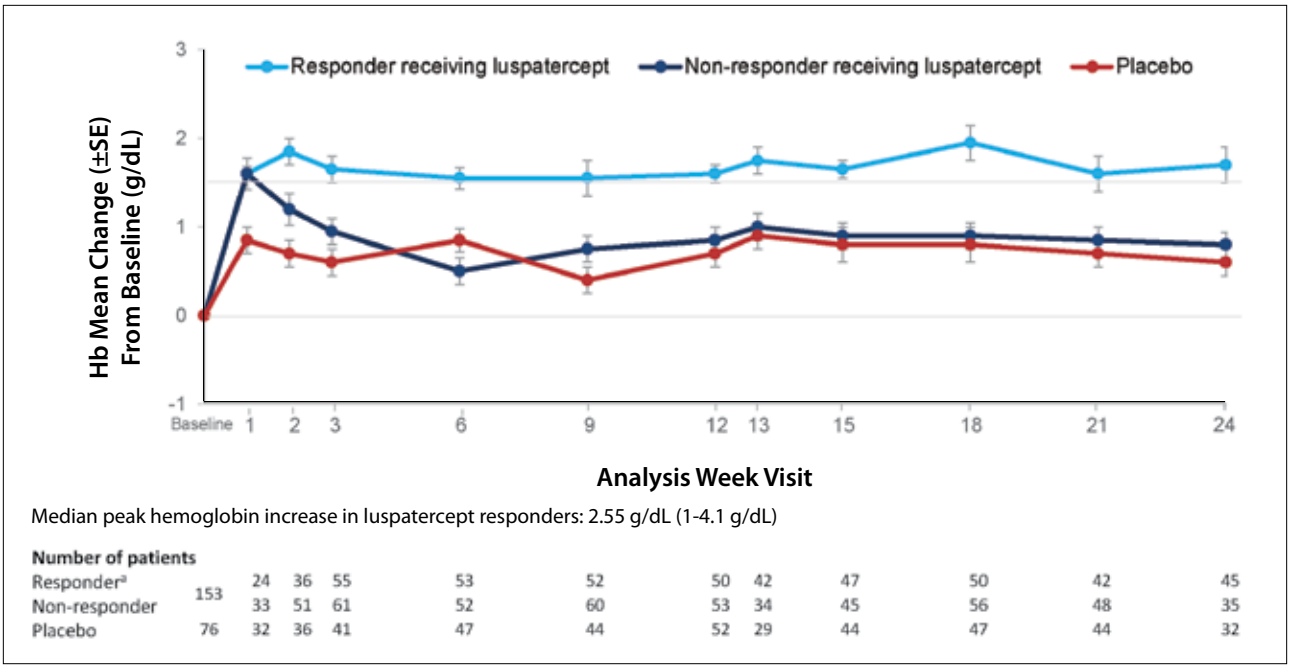


**Figure 2.** The median peak increase in hemoglobin concentration among patients who responded to luspatercept in the phase 3 MEDALIST trial. Data are shown for patients with RBC-TI ≥8 weeks during weeks 1 to 24. [a]The least squares mean difference for luspatercept responders vs placebo was 1.08 (95% CI, 0.84-1.31); *P*<.001). Hb, hemoglobin; 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; SE, standard error. Adapted from Fenaux P et al. ASH abstract 1. *Blood*. 2018;132(suppl 1).[4]

required for enrollment, and no prior treatment with any disease-modifying agents was permitted.

Patients were randomly assigned 2:1 to treatment with luspatercept or placebo. Patients in the active treatment arm received luspatercept at 1.0 mg/kg every 21 days, with a maximum dose escalation to 1.75 mg/kg. Assessments of disease state and response occurred at week 24 and every 6 months thereafter. Treatment was discontinued in patients with no benefit or disease progression based on criteria from the International Working Group. No crossover was allowed. Patients were followed for at least 3 years after the final dose to document progression to AML, subsequent MDS treatment, and overall survival. The primary endpoint was RBC transfusion independence of at least 8 weeks during the first 24 weeks of the trial.

The study randomly assigned 153 patients to luspatercept and 76 to placebo. The patients' median age was 71 years (range, 26-95 years). Patients received a median of 5 RBC transfusion units every 8 weeks (range, 1-20). The median pretransfusion hemoglobin level was 7.6 g/dL (range, 5-10 g/dL). Refractory cytopenia with multilineage dysplasia and ring sideroblasts was seen in 94.8% of the luspatercept arm vs 97.4% of the placebo arm. The proportion of patients with the *SF3B1* mutation was 92.2% in the luspatercept arm vs 85.5% in the placebo arm. The median duration of treatment was 49 weeks (range, 6-114 weeks) vs 24 weeks (range, 7-89 weeks), respectively. At least 48 weeks of treatment were completed by 51.0% of the luspatercept arm vs 15.8% of the placebo arm. The median number of doses received was 16 (range, 2-37) in the luspatercept arm vs 8 (range, 3-30) in the placebo arm. In the active treatment arm, luspatercept was escalated to the maximum dose of 1.75 mg/kg in 58.8% of patients. A higher proportion of patients remained on treatment in the luspatercept arm (45.8% vs 7.9%), and more patients in the placebo arm discontinued treatment owing to a lack of benefit (65.8% vs 33.3%).

The trial met its primary endpoint. The rate of RBC transfusion independence of at least 8 weeks during weeks 1 to 24 was 37.9% with luspatercept vs 13.2% with placebo (*P*<.0001). A greater benefit with luspatercept was seen in most subgroups, including those demarcated by average baseline RBC transfusion requirement, baseline serum erythropoietin levels, age, sex, time since initial diagnosis at baseline, and IPSS-R risk. Patients with a baseline platelet count of at least $100 \times 10^9$/L also showed a greater benefit with luspatercept vs placebo. Luspatercept was also superior to placebo in the key secondary endpoint of RBC transfusion independence of at least 12 weeks during weeks 1 to 24 (28.1% vs 7.9%; *P*=.0002). In addition, more patients in the luspatercept arm were

**ABSTRACT SUMMARY A Clinical Study of Tomaralimab (OPN-305), a Toll-Like Receptor 2 Antibody, in Heavily Pre-Treated Transfusion-Dependent Patients With Lower-Risk Myelodysplastic Syndromes That Have Received and Failed on Prior Hypomethylating Agent Therapy**

Tomaralimab, an antibody against Toll-like receptor 2, was evaluated in a phase 1/2 study of transfusion-dependent lower-risk MDS patients who required treatment after prior HMA therapy (Abstract 798). Forty-seven patients received tomaralimab monotherapy, and 28 patients who did not respond to monotherapy received the antibody plus azacitidine. The ORR with tomaralimab monotherapy was 23.5%, including 11% of patients who achieved transfusion independence. Combination therapy yielded an ORR of 46%, and 21% of patients achieved transfusion independence. After a median follow-up of 13.2 months, the median overall survival was 20.4 months (95% CI, 13.7-27.2 months). Tomaralimab was generally well-tolerated.

RBC transfusion-independent for at least 12 weeks during weeks 1 to 48 (33.3% vs 11.8%; *P*=.0003). Among patients who exhibited a primary endpoint response, the median duration of response was 30.6 weeks (95% CI, 20.6-40.6 weeks) with luspatercept vs 13.6 weeks (95% CI, 9.1-54.9 weeks) with placebo (Figure 1). A larger proportion of patients in the luspatercept arm achieved an erythroid response (based on International Working Group 2006 criteria) during weeks 1 to 24 (52.9% vs 11.8%; *P*<.0001) and during weeks 1 to 48 (58.8% vs 17.1%; *P*<.0001).[6] Among patients who responded to luspatercept, the median peak increase in hemoglobin concentration was 2.55 g/dL (Figure 2).

The rates of treatment-emergent adverse events (AEs), serious treatment-emergent AEs, and grade 3/4 treatment-emergent AEs were similar in the 2 arms. The proportion of patients with treatment-emergent AEs leading to death was 3.3% in the luspatercept arm vs 5.3% in the placebo arm. The proportion of patients with at least 1 treatment-emergent AE leading to discontinuation was 8.5% with luspatercept vs 7.9% with placebo. The most common treatment-emergent AEs in the luspatercept arm were fatigue (26.8%), diarrhea (22.2%), asthenia (20.3%), and nausea (20.3%).

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# Safety and Efficacy, Including Event-Free Survival, of Deferasirox Versus Placebo in Iron-Overloaded Patients With Low- and Int-1-Risk Myelodysplastic Syndromes: Outcomes From the Randomized, Double-Blind TELESTO Study

Most patients with lower-risk MDS eventually require ongoing RBC transfusions owing to impaired hematopoiesis.[1] Ongoing transfusions are associated with iron overload and lead to increased morbidity and mortality. Iron chelation therapy is a cornerstone of treatment for MDS patients with iron overload, although use is based mainly on retrospective and observational studies.[2,3] The TELESTO trial (Myelodysplastic Syndromes [MDS] Event Free Survival With Iron Chelation Therapy Study) was originally designed as a phase 3 trial comparing deferasirox vs placebo in patients with lower-risk MDS.[4] The trial had a planned enrollment of 630 patients. Because of low enrollment, however, TELESTO was modified to a phase 2 trial with a target enrollment of 210 patients. As a result of the decreased enrollment, the trial was no longer powered to make statistical comparisons. Enrolled patients had hematologically stable low-risk or intermediate-1–risk MDS (according to IPSS) confirmed by bone marrow analysis within 6 months prior to study entry.[5] Other

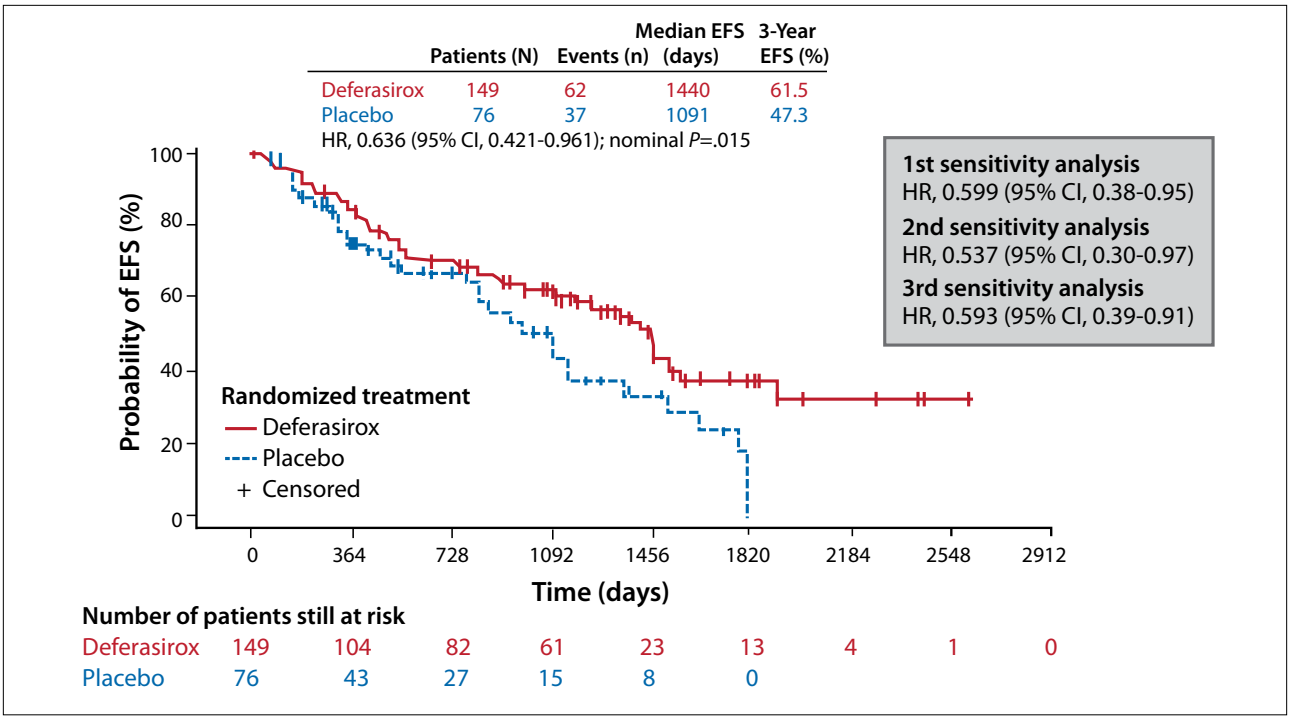


**Figure 3.** Event-free survival in the TELESTO trial, which evaluated iron chelation with deferasirox in patients with myelodysplastic syndromes. EFS, event-free survival; HR, hazard ratio; TELESTO, Myelodysplastic Syndromes (MDS) Event Free Survival With Iron Chelation Therapy Study. Adapted from Angelucci E et al. ASH abstract 234. *Blood*. 2018;132(suppl 1).[4]

enrollment criteria included a serum ferritin level exceeding 1000 ng/mL, a transfusion history of 15 to 75 packed RBC units, adequate organ function, and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or lower. After stratification by IPSS risk and geographic region, patients were randomly assigned 2:1 to receive deferasirox (1040 mg/kg daily) or placebo. The primary objective was event-free survival.

The 225 patients were a median age of 65 years (range, 20-88 years), and 60.9% were male. The deferasirox arm had a higher proportion of patients ages 75 years or older (25.5% vs 17.1%). The IPSS risk score was low in 27.6% of patients and high in 72.4%, and 21.8% of patients had received prior chelation therapy. The most common reasons for treatment discontinuation included AEs (21.5% in the active treatment arm vs 11.8% in the placebo arm), patient or guardian decision (6.7% vs 25.0%), and study termination by the sponsor (24.8% vs 3.9%). The median time on treatment was 587.5 days (range, 1-2599 days) in the deferasirox arm vs 370.5 days (range, 12-1708 days) in the placebo arm. However, the mean dose was lower in the deferasirox arm (14.9 vs 23.5 mg/kg daily). A higher proportion of patients in the placebo arm spent less than 1 year on study treatment (39.2% vs 51.3%), and more patients in the deferasirox arm spent at least 3 years on study treatment (27.0% vs 9.2%).

Patients in the deferasirox arm experienced a 36.4% reduction in the risk of event-free survival compared with placebo (hazard ratio [HR], 0.636; 95% CI, 0.42-0.96; nominal *P*=.015). Three different sensitivity analyses confirmed the risk reduction (Figure 3). As confirmed by the Event Adjudication Committee, deaths during treatment occurred in 32.2% of patients in the deferasirox arm and 32.9% of those in the placebo arm. Progression to AML was seen in 6.7% of the deferasirox arm vs 7.9% of the placebo arm, and congestive heart failure required hospitalization in 0.7% vs 3.9%. Liver impairment developed in 0.7% vs 1.3% of patients, and deterioration in cardiac function was seen in 2.3% vs 2.6%.

The subgroup analysis showed a particular benefit for patients ages 65 years or older (HR, 0.55; 95% CI, 0.32-0.93), patients with favorable cytogenetics (HR, 0.56; 95% CI, 0.34-0.92), and Asian patients (HR, 0.49; 95% CI, 0.25-0.97). The median overall survival was 1907 days with deferasirox vs 1509 days with placebo, but this difference did not reach significance (HR, 0.832; 95% CI, 0.54-1.28; *P*=.200; Figure 4).

No new safety signals were raised. In both arms, the most common AEs included diarrhea (35.8% with deferasirox vs 26.3% with placebo), pyrexia (34.5% vs 22.4%), increased blood creatinine (25.7% vs 1.3%), upper

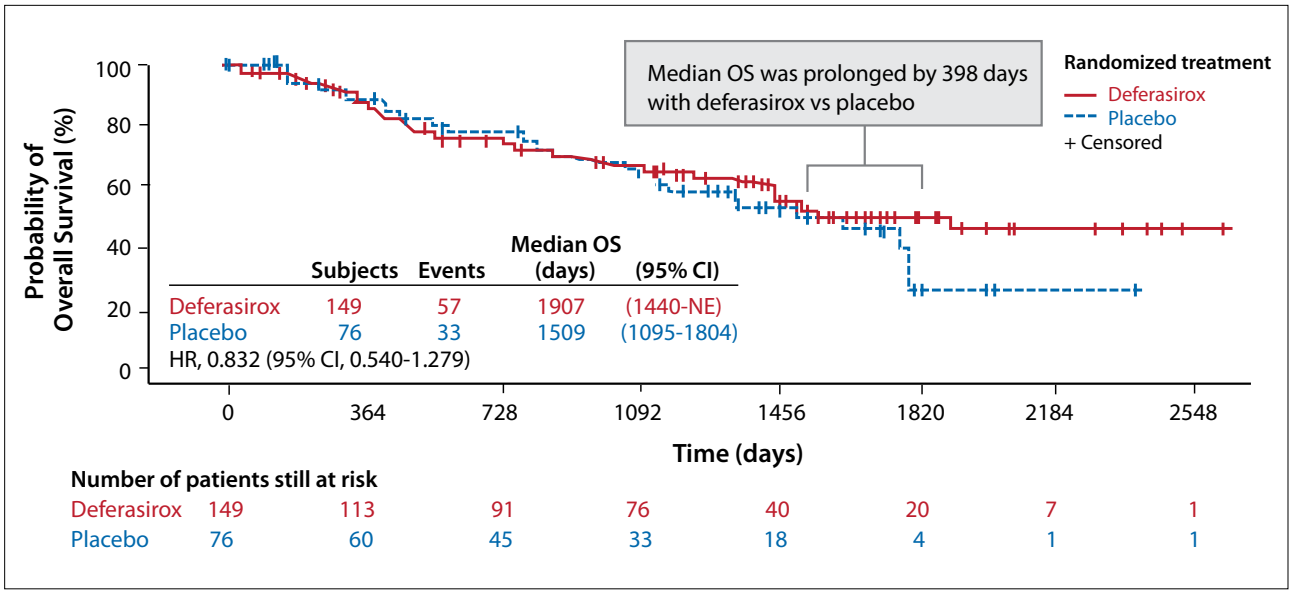


**Figure 4.** Median overall survival in the TELESTO trial, which evaluated iron chelation with deferasirox in patients with myelodysplastic syndromes. The difference was not significant. HR, hazard ratio; NE, not evaluable; OS, overall survival; TELESTO, Myelodysplastic Syndromes (MDS) Event Free Survival With Iron Chelation Therapy Study. Adapted from Angelucci E et al. ASH abstract 234. *Blood*. 2018;132(suppl 1).[4]

respiratory tract infection (25.0% vs 26.3%), and cough (21.6% vs 14.5%).

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# Long-Term Results of a Randomized Phase 2 Dose-Response Study of Guadecitabine, a Novel Subcutaneous Hypomethylating Agent, in 102 Patients With Intermediate- or High-Risk Myelodysplastic Syndromes or Chronic Myelomonocytic Leukemia

The hypomethylating agent (HMA) decitabine is approved for the treatment of MDS.[1] However, it is rapidly inactivated by cytidine deaminase, and most patients eventually lose their initial response to the drug. Guadecitabine (SGI-110) is a dinucleotide of decitabine and deoxyguanosine that is resistant to cytidine deaminase.[2,3] After subcutaneous administration of guadecitabine, decitabine is gradually released, resulting in up to 8 hours of exposure to the active drug. Guadecitabine was evaluated at 2 dose levels in a phase 1 trial of patients with MDS or chronic myelomonocytic leukemia (CMML).[2] Eligible patients had received previous treatment with a first-generation HMA or were treatment-naive. The patients had intermediate-1, intermediate-2, or high-risk disease; an ECOG performance status of 0 to 2; and adequate renal function. Patients were randomly assigned into 2 arms. Patients in arm A received guadecitabine at 60 mg/m$^2$ daily for 5 days, and patients in arm B received guadecitabine at 90 mg/m$^2$ daily for 5 days. The lower dose was considered biologically effective, whereas the higher dose was the highest well-tolerated dose. Responses were assessed according to 2006 International Working Group criteria, and the primary endpoint was the objective response rate (ORR).[4]

The trial included 53 patients in arm A and 49 in arm B. The patients' median age was approximately 72 years

(range, 18-89 years), and approximately two-thirds were male. The IPSS disease category was intermediate-risk MDS in 43% of arm A and 44% of arm B, and high-risk MDS in 28% vs 39%. CMML was the diagnosis in 28% of arm A and 14% of arm B. Bone marrow blast cells exceeding 5% were reported in 38% of arm A vs 67% of arm B. In arm A, 58% of patients were RBC transfusion-dependent, compared with 55% of arm B. Fifty-three patients had received previous treatment, with therapies such as azacitidine in 77% and decitabine in 32%.

Among the previously treated patients, the median number of treatment cycles was 5 (range, 1-37), 40% of patients had received at least 6 cycles of treatment, 47% of cycles were delayed, and 34% of cycles included a dose reduction. Among treatment-naive patients, the median number of cycles was 5 (range, 1-49), 47% of patients had received at least 6 cycles of treatment, 35% of cycles were delayed, and 37% of cycles included a dose reduction.

After a median follow-up of 3.2 years, the ORR among previously treated patients was 43% and included a complete response (CR) rate of 4%. Among the treatment-naive patients, the ORR was 51% and included a CR rate of 22%. RBC transfusion independence was achieved in 15% of previously treated patients and 42% of treatment-naive patients. The median overall survival was 9.1 months in arm A vs 12.3 months in arm B ($P$=.88; Figure 5). In both arms, treatment-naive patients had a median overall survival of 23.4 months. The median overall survival was 22.7 months in patients without the *TP53* mutation vs 7.4 months in those with the mutation (HR, 0.16; 95% CI, 0.08-0.32; $P$<.001). Treatment-related AEs of grade 3 or higher were more common in arm B (88% vs 60%; $P$=.003), mostly owing to a higher rate of thrombocytopenia (51% vs 30%; $P$=.043).

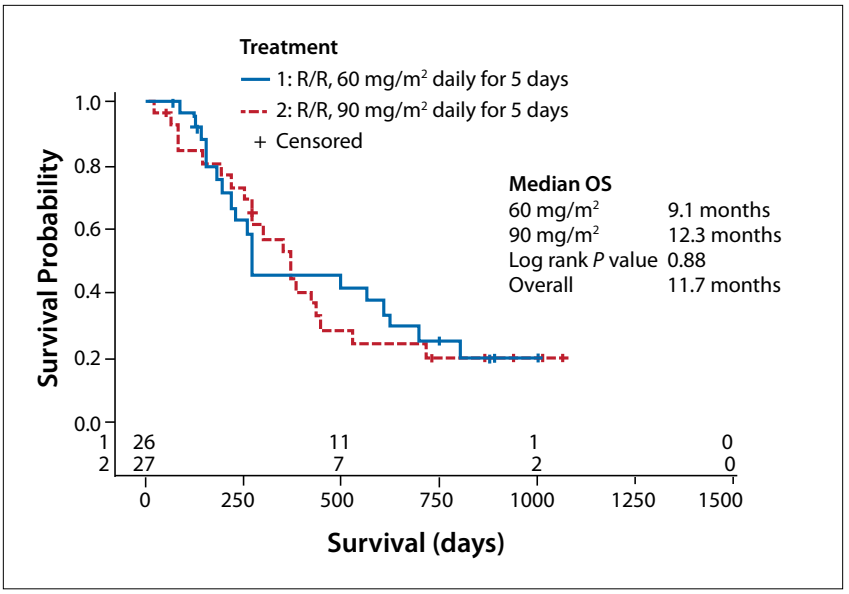


**Figure 5.** Median overall survival in a randomized phase 2 dose-response study of guadecitabine in patients with myelodysplastic syndromes or chronic myelomonocytic leukemia. HMA, hypomethylating agent; OS, overall survival; R/R, relapsed/refractory. Adapted from Garcia-Manero G et al. ASH abstract 231. *Blood*. 2018;132(suppl 1).[2]

**ABSTRACT SUMMARY A Randomized Phase II Study of Azacitidine Alone or With Lenalidomide, Valproic Acid, or Idarubicin in Higher-Risk MDS: GFM "Pick a Winner" Trial**

A phase 2 study randomly assigned 322 patients with higher-risk MDS to receive azacitidine alone or combined with lenalidomide, valproic acid, or idarubicin (Abstract 467). Rates of early study discontinuation were similar across the 4 treatment arms. Rates of hospitalization were lowest with azacitidine monotherapy (38.0%) and highest with azacitidine plus idarubicin (59.7%; $P$=.028). The response rates were similar across the 4 treatment arms, with no added benefit observed with combination treatment vs azacitidine monotherapy. After 6 treatment cycles, ORRs were 41.9% with azacitidine alone, 40.0% with azacitidine plus lenalidomide, 41.2% with azacitidine plus valproate, and 38.3% with azacitidine plus idarubicin. The rates of CR were 35.8%, 31.2%, 36.2%, and 35.8%, respectively. After a median follow-up of 15.1 months, the median event-free survival was 16.6 months, 15.1 months, 14.5 months, and 13.2 months ($P$=.74). The median overall survival was 24.5 months, 17.5 months, 18.9 months, and 20.1 months ($P$=.5).

A separate phase 2 trial evaluated guadecitabine in treatment-naive patients with MDS or CMML.[3] Eligible patients had higher-risk disease and at least 10% blast cells. Guadecitabine at 60 mg/m$^2$ was administered on days 1 through 5 of every 28-day cycle. The primary endpoint was the CR rate. The 97 patients were a median age of 69 years (range, 22-90 years), and 61% were male. The median white blood cell count was 2.6 × 10$^9$/L (range, 0.7-29.3 × 10$^9$/L), the median platelet count was 56 × 10$^9$/L (range, 2-881 × 10$^9$/L), and the median hemoglobin level was 9.4 g/dL. The proportion of

**ABSTRACT SUMMARY Interim Analysis of a Phase II Study of Venetoclax With 10-Day Decitabine in Acute Myeloid Leukemia and Myelodysplastic Syndrome**

A phase 2 study evaluated decitabine plus venetoclax in elderly patients with newly diagnosed AML and in patients with relapsed or refractory AML or MDS/CMML (Abstract 286). Among the 48 patients, the median follow-up was 5.2 months (range, 0.7-8.9 months), and the median number of treatment cycles was 3 (range, 1-7 cycles). The ORR in patients with treatment-naive AML was 96% (26/27), including a CR rate of 59% and an incomplete CR of 27%. Half of patients were negative for minimal residual disease. Among patients with relapsed, refractory, or previously treated disease, the ORR was 52%, including a CR rate of 14% and an incomplete CR rate of 38%. The most common treatment-emergent AEs of grade 3 or higher included infection with grade 3/4 neutropenia (46%) and febrile neutropenia (15%).

blast cells was a median of 10% (range, 0%-20%), and 64% of patients had MDS with excess blasts according to disease classification from the World Health Organization. Risk according to IPSS criteria was intermediate-2 in 77% of patients and very high in 52%. The karyotype was normal in 24% of patients and complex in 40%.

Among 94 evaluable patients, the ORR was 65%, including a CR rate of 26%. The median number of cycles to response was 3 (range, 1-11). The stopping rule for response was not met. After a median follow-up of 11.1 months (range, 1-46 months), the median overall survival was 17.2 months (95% CI, 10.3-24.1 months), and the median event-free survival was 7.0 months (95% CI, 6.2-7.8 months). Based on the multivariate analysis, a response was associated with improved survival (HR, 0.17; *P*<.001). The median overall survival was 32.5 months among patients with wild-type *TP53* (n=63) vs 11.1 months in those with mutated *TP53* (n=32; *P*=.002).

Infectious AEs of grade 3 or higher included pneumonia (31%) and neutropenic fever (30%). The most common hematologic toxicity of grade 3 or higher was thrombocytopenia (12%).

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# Phase 2 Expansion Study of Oral Rigosertib Combined With Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes: Efficacy and Safety Results in HMA Treatment-Naive and Relapsed/Refractory Patients

Azacitidine is standard treatment for patients with higher-risk MDS.[1] Recent studies have failed to demonstrate a benefit with the addition of other agents to azacitidine in this setting.[2,3] Many patients with higher-risk MDS present with refractory disease, and nearly all patients with an initial response ultimately relapse. The prognosis for these patients is poor, with a median overall survival of less than 6 months and a 2-year survival of 15%.[4] Rigosertib is a RAS mimetic that blocks several cellular signaling pathways involved in cancer, including those activated in higher-risk MDS.[5,6] Moreover, the drug is active in azacitidine-resistant cell lines and has shown synergistic activity when paired with azacitidine.[7]

The combination of azacitidine plus rigosertib was evaluated in a phase 1/2 study of 74 patients with higher-risk MDS.[8] Rigosertib was administered at 1120 mg daily, divided into 2 doses, along with standard azacitidine. The patients' median age was 69 years (range, 42-90 years), and 59% were male. Sixty-three percent of patients had IPSS intermediate-2 or high-risk MDS, and 76% had high- or very high-risk disease by IPSS-R classification. Prior HMA therapies included azacitidine (35%), decitabine (8%), and both (4%). Evaluable data were available for 13 HMA-naive patients and 16 patients who required further treatment after HMA therapy.

Based on International Working Group 2006 criteria, the ORR was 92% in HMA-naive patients vs 50% in those with previous exposure to HMA

treatment.[9] The rates of combined CR plus partial response (PR) were 31% vs 6%. HMA-naive patients had a longer median duration of response (13.5 vs 9.2 months) and a longer median duration of treatment (6.7 vs 3.6 months). Among 29 HMA-naive patients who received rigosertib at 840 mg daily or higher, the ORR was 90% and included a CR/PR rate of 34%. Among 26 patients previously exposed to HMA treatment who received at least 840 mg a day of rigosertib, the ORR was 54%, with an 8% rate of CR/PR. The median duration of response was 12.2 months (range, 0.1-24.2 months) in HMA-naive patients vs 10.8 months (range, 0.1-11.8 months) in patients previously treated with HMA therapy (Figure 6).

The most common AEs of any grade were hematuria (45%), constipation (43%), diarrhea (42%), and fatigue (42%). The most common grade 3 or higher AEs were neutropenia (27%), thrombocytopenia (26%), dysuria (9%), and hematuria (9%). The most common reason for treatment discontinuation was progressive disease (28%), followed by toxicity (19%). Based on the efficacy and safety results, azacitidine plus rigosertib will be evaluated in HMA-naive patients in a phase 3 trial.

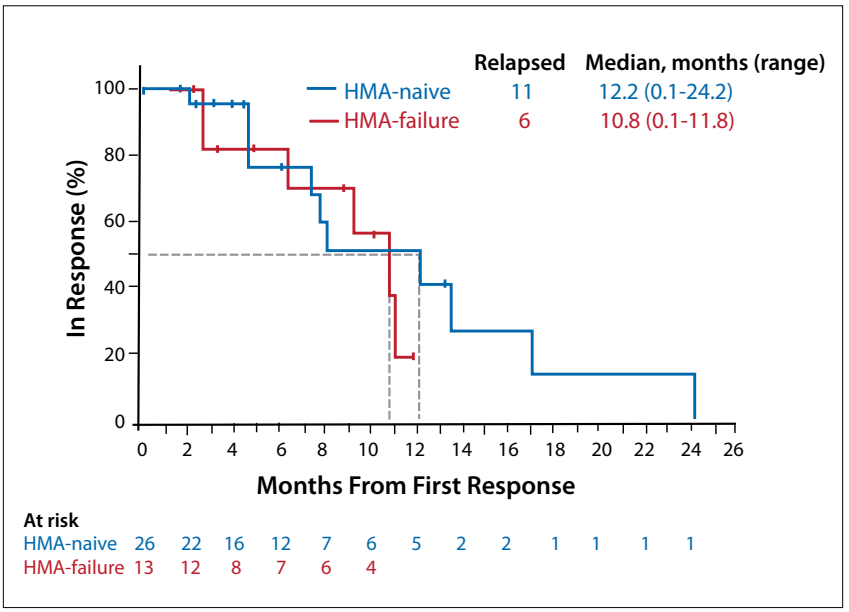


**Figure 6.** Median duration of response among patients with higher-risk myelodysplastic syndromes in a phase 2 expansion study of oral rigosertib combined with azacitidine. Data are shown for patients who were HMA treatment-naive or relapsed/refractory. HMA, hypomethylating agent. Adapted from Navada S et al. ASH abstract 230. *Blood*. 2018;132(suppl 1).[8]

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# Results of a Phase 2, Open-Label Study of Idarubicin, Cytarabine, and Nivolumab in Patients With Newly Diagnosed Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome

Nivolumab is an antibody that binds to the programmed death 1 (PD-1) receptor, thereby reversing T-cell exhaustion and reinstating the ability of T cells to attack cancer cells.[1] In a phase 2 study of 70 patients with relapsed or refractory AML, the combination of nivolumab plus azacitidine had an ORR of 33%, with a CR rate of 22%.[2] A single-center, open-label, phase 2 trial investigated the hypothesis that adding nivolumab to standard treatment would improve outcomes in young AML patients.[3] The trial

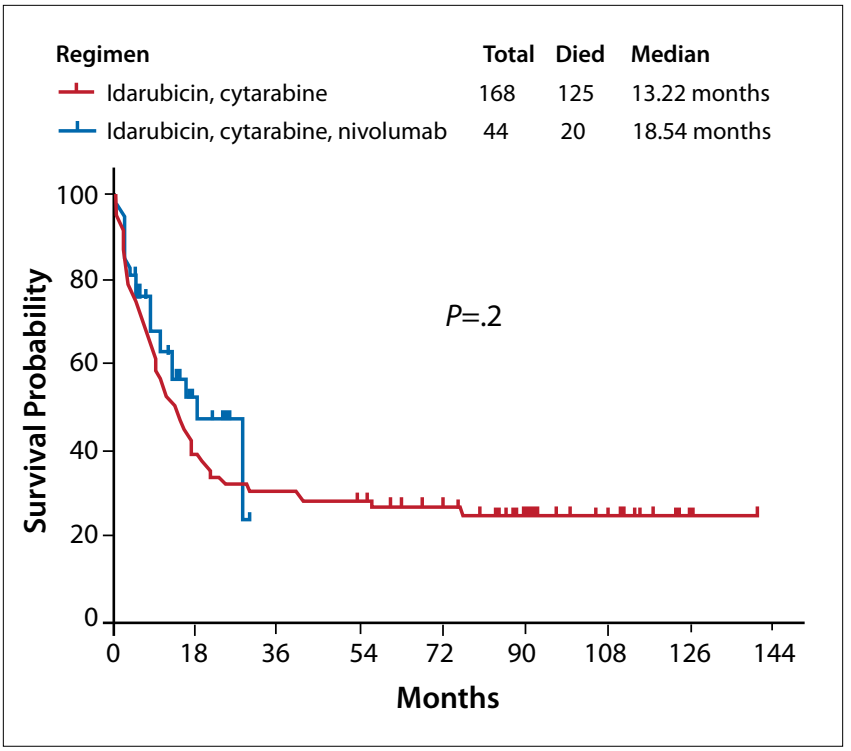


**Figure 7.** Overall survival among patients in a phase 2 trial who received idarubicin plus cytarabine, with or without nivolumab. Patients had newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. The difference was not statistically significant (*P*=.2). Adapted from Assi R et al. ASH abstract 905. *Blood*. 2018;132(suppl 1).[3]

**ABSTRACT SUMMARY Preliminary Results From a Phase II Study of the Combination of Azacitidine and Pembrolizumab in Patients With Higher-Risk Myelodysplastic Syndrome**

Pembrolizumab was evaluated in combination with azacitidine in a phase 2 study of patients with IPSS intermediate-1 or higher-risk MDS (Abstract 464). Eligible patients were treatment-naive or had received HMA therapy, but did not respond to treatment or developed progressive disease. The ORR was 67% (4/6) in treatment-naive patients and 33% (4/12) in those previously treated with HMA therapy. After a median follow-up of 6.2 months, the median overall survival was 10.73 months in treatment-naive patients and 7.95 months in previously treated patients. The most common AEs of grade 3 or higher were neutropenia (n=6) and anemia (n=3). Seven of 18 patients (39%) received corticosteroids for AEs related to pembrolizumab.

enrolled patients with newly diagnosed AML or high-risk MDS; those with MDS could have received prior therapy. Patients were ages 18 to 60 years; fit patients older than 60 years were also enrolled. Treatment included cytarabine (1.5 g/m$^2$ on days 1-4), idarubicin (12 mg/m$^2$ on days 1-3), and nivolumab (3 mg/kg on day 24 ±2 days, then every 2 weeks for up to 1 year). Patients with a CR, incomplete CR, or CR with incomplete platelet recovery could receive up to 5 cycles of attenuated doses of idarubicin plus cytarabine. The primary endpoint was event-free survival.

The 44 patients had a median age of 54 years (range, 26-66 years). Twenty-three percent of patients were older than 60 years, and 61% were female. The median white blood cell count was 4.8 × 10$^9$/L (range, 0.4-46 × 10$^9$/L), and the median bilirubin level was 0.7 g/L (range, 0.2-2.5 g/L). The median percentage of bone marrow blast cells was 42% (range, 15%-96% blast cells). Seventy-three percent of patients had de novo AML, 16% had AML caused by an antecedent hematologic disorder, 7% had therapy-related AML, and 4% had high-risk MDS.

After a median follow-up of 17.25 months (range, 0.5-30.5 months), the median event-free survival was not reached (range, 0.5-13.7+ months). The ORR was 80%, including a CR rate of 64%. The median overall survival with the 3-drug combination was 18.5 months (range, 0.5-30.4 months), and the median relapse-free survival was 18.5 months (range, 1.7-25.8 months). A separate cohort of patients treated with idarubicin plus cytarabine had a shorter overall survival, but the difference was not significant (13.22 vs 18.5 months; *P*=.2; Figure 7).

Among the 19 patients who underwent stem cell transplant, 63% were in continuous CR, 21% died while in CR, and 16% relapsed after a median follow-up of 12.6 months. Graft-vs-host disease developed in 42% at grade 1/2 and in 26% at grade 3/4. Among the entire cohort of 44 patients, the most common grade 3/4 AEs were febrile neutropenia (32%) and diarrhea (16%). Immune-mediated grade 3/4 AEs included rash (5%), colitis (5%), elevated transaminases (2%), pancreatitis (2%), and cholecystitis (2%).

Mass cytometry analysis showed a reduction in AML stem cells and progenitor cells with concomitant recovery of T-cell populations. CD4-positive effector T cells that displayed an exhausted phenotype were observed at higher levels in patients who did not respond to the combination therapy compared with those who had a CR (*P*<.05).

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# A Phase II Study of Nivolumab or Ipilimumab With or Without Azacitidine for Patients With Myelodysplastic Syndrome

Both nivolumab and ipilimumab are immune checkpoint inhibitors.[1] Nivolumab binds to the PD-1 receptor, and ipilimumab binds to cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). By binding to their targets, the antibodies restore T-cell activation, allowing the immune system to recover its ability to attack cancer cells. A phase 2 study evaluated checkpoint inhibitor therapy in patients with MDS.[2] The trial enrolled treatment-naive patients and those with an inadequate response to prior HMA therapy. The most recent cycle of HMA therapy was administered no more than 4 months before enrollment. Patients had received no other treatment after HMA therapy. Patients with a history of inflammatory or autoimmune disease were excluded.

Treatment-naive patients were treated with azacitidine in combination with nivolumab or ipilimumab. Patients who had received HMA therapy were treated with nivolumab or ipilimumab monotherapy. After 6 treatment cycles, azacitidine could be introduced to evaluate the concept of resensitization. Next-generation sequencing was performed using a 28-gene or 81-gene panel to detect mutations in bone marrow cells.

Between 15 and 21 patients were enrolled into each cohort. Forty-one patients were treatment-naive, and 35 had been treated with HMA therapy. The patients' median age was 71 years (range, 39.5-85.7 years). IPSS risk was low in 3 patients (4%), intermediate-1 in 30 (40%), intermediate-2 in 28 (37%), high in 11 (15%), and unknown in 4 (5%). The median proportion of blast cells in the bone marrow was 7% (range, 0%-18%). A complex karyotype was reported in 29 patients (38%), and 17 (22%) had diploid cytogenetics. Based on next-generation sequencing, the most commonly mutated genes across the entire cohort were *TP53* (24%), *ASXL1* (18%), *TET2* (14%), *NRAS* (14%), *DNMT3A* (13%), and *RUNX1* (13%). Patients received a median of 4 treatment cycles (range, 1-29), and the median number of cycles to response was 3 (range, 1-15).

In the treatment-naive patients, the ORR was 70% with nivolumab/azacitidine and 62% with ipilimumab/azacitidine. The CR rates were 40% and 14%, respectively. In patients treated with prior HMA therapy, the ORR was 0% with nivolumab monotherapy and 30% with ipilimumab monotherapy. Survival data were based on a median follow-up of 20.1 months. In patients with newly diagnosed MDS, 1-year overall survival was 68% with ipilimumab/azacitidine and 50% with nivolumab/azacitidine (Figure 8). Median overall survival was not reached in the ipilimumab/azacitidine cohort and 11.8 months in the nivolumab/azacitidine cohort. Among the previously treated patients, the 1-year overall survival was 45% with ipilimumab monotherapy and 25% with nivolumab monotherapy. The median overall survival was 8.5 months vs 8.0 months, respectively.

Among patients in all 4 cohorts, the most common AEs of any grade


**ABSTRACT SUMMARY Treatment of MDS, AML, and CMML Relapse After Allogeneic Blood Stem Cell Transplantation With Azacitidine, Lenalidomide, and Donor Lymphocyte Infusions: Results From the Second Interim Analysis of the Prospective AZALENA Trial**

An open-label, multicenter, single-arm phase 2 trial evaluated the combination of lenalidomide and azacitidine plus donor lymphocyte infusions in patients with MDS, CMML, or AML with myelodysplasia-related changes who had relapsed after their first allogeneic stem cell transplant (Abstract 703). Lenalidomide was administered at 2.5 mg daily or 5 mg daily. Among 24 patients, 71% received at least 1 donor lymphocyte infusion (median, 2; range, 1-11). Based on the interim analysis, the ORR was 74%, including CR rates of 47%, incomplete CR rates of 11%, and partial response rates of 16%. Graft-vs-host disease was acute in 17% of patients and chronic in 21% of patients. No dose-limiting toxicities were observed. The higher dose of lenalidomide was not associated with an increased rate of toxicities, dose reductions, or treatment interruptions.

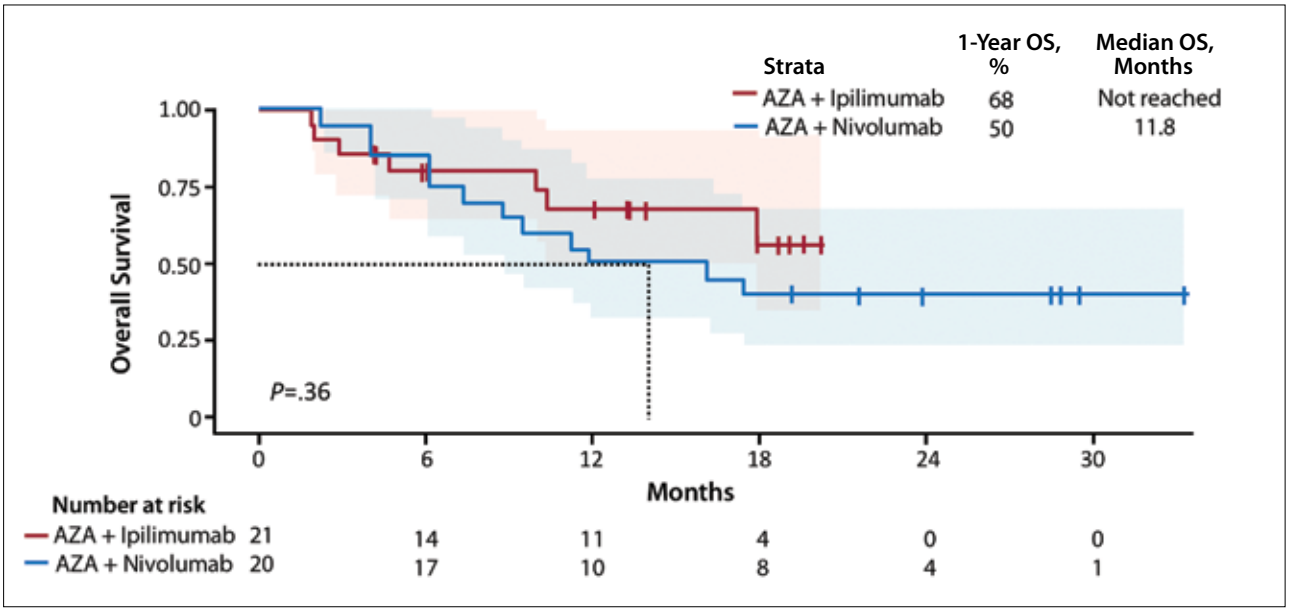


**Figure 8.** Overall survival among patients with newly diagnosed myelodysplastic syndrome treated with azacitidine plus nivolumab or ipilimumab. AZA, azacitidine; OS, overall survival. Adapted from Garcia-Manero G et al. ASH abstract 465. *Blood*. 2018;132(suppl 1).[2]

were infection (32%), rash (27%), and fatigue (24%). The most common grade 3/4 AEs were infection (25%) and transaminitis (8%).

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# Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non-Del(5q) Lower-Risk MDS Relapsed/Refractory to a Erythropoiesis-Stimulating Agent Who Are Lenalidomide- and HMA-Naive

Telomeres protect the ends of chromosomes, and telomere length is an independent prognostic marker in patients with MDS.[1] Increased telomerase activity and expression of the telomerase reverse transcriptase (*TERT*) gene are associated with reduced telomere length and reduced overall survival in patients with lower-risk MDS. Imetelstat is a 13-mer oligonucleotide with modified lipid extensions. The first-in-class molecule binds with high affinity to the template region of telomerase, competitively inhibiting its activity. Imetelstat has demonstrated activity in myeloid malignancies.[2,3] The open-label, single-arm phase 2/3 IMerge trial (Study to Evaluate Imetelstat [JNJ-63935937] in Subjects With International Prognostic Scoring System [IPSS] Low or Intermediate-1 Risk Myelodysplastic Syndrome) evaluated imetelstat among patients with transfusion-dependent lower-risk MDS.[4,5] Patients had an IPSS risk score of low or intermediate-1 and were ineligible for treatment with erythropoiesis-stimulating agents or had developed relapsed or refractory disease after treatment. Transfusion dependence was defined as treatment with at least 4 RBC units within 8 weeks. Patients received imetelstat at 7.5 mg/kg every 4 weeks via a 2-hour infusion. The primary endpoint was RBC transfusion independence for 8 weeks.

The trial enrolled 38 patients who were lenalidomide- and HMA-naive and did not have deletion 5q. The median follow-up was 29.1 months in 13 patients and 8.7 months in 25 patients. Patients received a median of 8.0 treatment cycles (range, 1-34 cycles), and the mean dose intensity for each cycle was 6.9 mg/kg. The median age was 71.5 years (range,

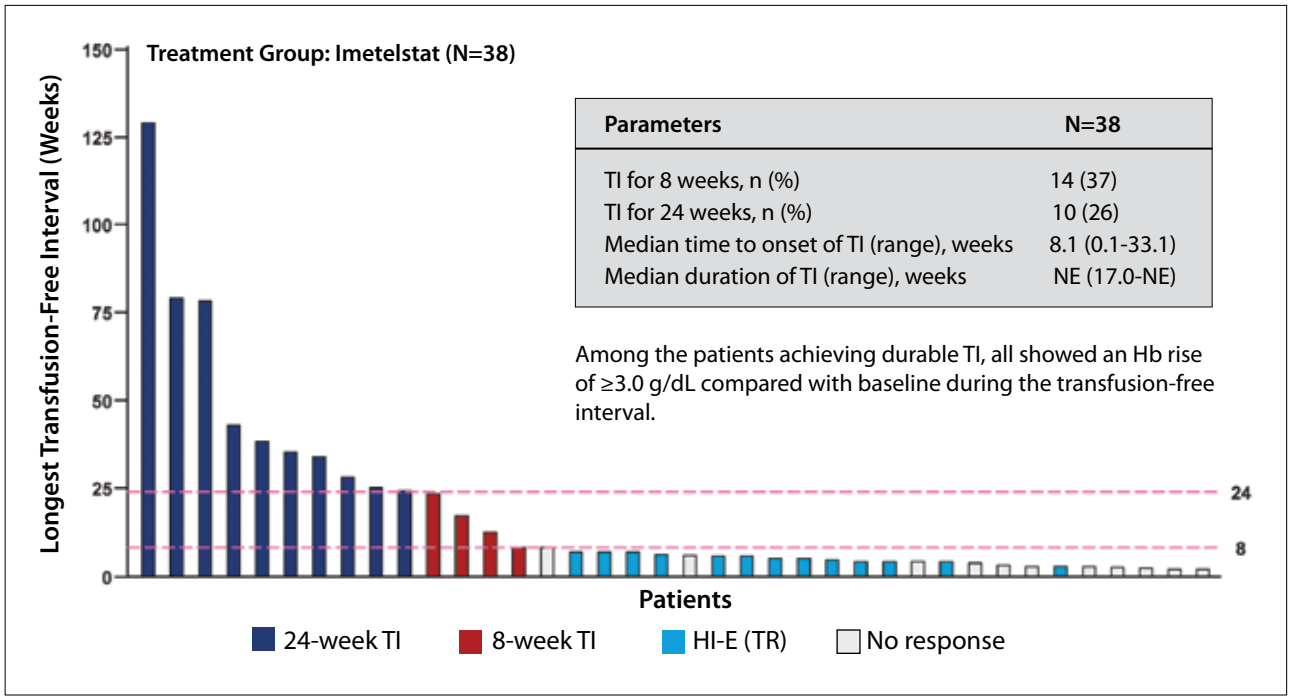


**Figure 9.** Rates of transfusion independence among patients in the phase 2/3 IMerge trial, which evaluated imetelstat in patients with myelodysplastic syndrome. Hb, hemoglobin; HI-E, hematologic improvement–erythroid; IMerge, Study to Evaluate Imetelstat (JNJ-63935937) in Subjects With International Prognostic Scoring System (IPSS) Low or Intermediate-1 Risk Myelodysplastic Syndrome; NE, not evaluable; TI, transfusion independence; TR, transfusion reduction. Adapted from Steensma DP et al. ASH abstract 463. *Blood*. 2018;132(suppl 1).[4]

46-83 years), and two-thirds were male. In 89% of patients, the ECOG performance status was 0 or 1. IPSS low-risk disease was reported in 63%. At baseline, the median number of RBC transfusions every 8 weeks was 8 (range, 4-14), and 89% had prior exposure to erythropoiesis-stimulating agents.

After treatment with imetelstat, 37% of patients were transfusion-free for 8 weeks and 26% were transfusion free for 24 weeks (Figure 9). The median time to onset of transfusion-independence was 8.1 weeks (range, 0.1-33.1 weeks). The median duration of transfusion independence was not estimable. Among patients who achieved durable transfusion independence, all showed an increase in their hemoglobin level of at least 3.0 g/dL compared with baseline during the transfusion-free interval. An erythroid response was reported in 71% of patients, and the mean relative change in transfusion burden from baseline was –68%. In 21% of patients, the best response was a CR, a bone marrow CR, or a partial response.[6]

Dose reductions were required in 50% of patients, and 68% had treatment delays. The most common treatment-emergent AEs of grade 3 or higher were thrombocytopenia (61%), neutropenia (55%), anemia (18%), and leukopenia (18%). Reversible grade 3 liver function test elevations were observed in 8% of patients, but were not considered treatment-related. More than 90% of patients with grade 3/4 neutropenia or thrombocytopenia recovered within 4 weeks. Among the 6 patients with an *SF3B1* mutation at baseline, 2 exhibited a reduction in variant frequency, and both of these patients had durable transfusion independence. One of these patients also had a reduction in the frequency of the *DNMT3A* mutation, and in this patient, the level of ringed sideroblasts in the bone marrow decreased from 75% at baseline to 3% after treatment.

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# Phase 3 Study of Lenalidomide Vs Placebo in Non-Transfusion Dependent Low Risk MDS Del(5q) Patients: Preliminary Blinded Analysis of the European SINTRA-REV Trial

Patients with lower-risk MDS with deletion 5q tend to respond poorly to erythropoiesis-stimulating agents.[1] Lenalidomide has demonstrated efficacy in treating lower-risk MDS patients, showing considerably higher response rates in patients with deletion 5q vs those without.[2,3] In a double-blind, randomized phase 3 trial of RBC transfusion-dependent patients with low- or intermediate-risk MDS and deletion 5q31, treatment with lenalidomide yielded a significantly higher rate of transfusion independence as compared with placebo (*P*<.001). Among patients treated with 2 different doses of lenalidomide, the 3-year overall survival was 56.5%, and the 3-year risk of progression to AML was 25.1%. Most lower-risk MDS/deletion 5q patients are transfusion-independent when first diagnosed. A retrospective study, however, showed that 85% of these patients required transfusions at a median of 20 months after diagnosis.[4]

The double-blind, multicenter, phase 3 SINTRA-REV trial (Study of Revlimid [Lenalidomide] Versus Placebo in Patients With Low Risk Myelodysplastic Syndrome) evaluated lenalidomide vs placebo in patients with lower-risk MDS with deletion 5q and non–transfusion-dependent anemia.[5] Enrolled patients were at low- or intermediate-1 risk, and they did not require RBC transfusion in the context of a hemoglobin level below 12 g/dL.[6] Patients were randomly assigned 2:1 to treatment with lenalidomide or placebo. In the active treatment arm, patients received lenalidomide at 5 mg daily. Treatment cycles were 28 days. The treatment phase continued for 108 weeks, and follow-up was also 108 weeks. Assessment of MDS disease was performed at 12 weeks and every 6 months thereafter. The primary objective was to determine whether lenalidomide prolonged the time until disease progression, as measured by transfusion dependence.

A preliminary blinded analysis at week 12 included 58 patients. The patients' median age was 69.5 years, and 82.8% were female. Deletion 5q disease was observed in 67.2% of patients. IPSS risk was low in 70.7% and intermediate-1 in 29.3%.[7] Based on IPSS-R, 39.7% of patients had very low-risk disease, 56.9% had low-risk disease, and 3.4% had intermediate-risk disease.[8] The median hemoglobin level was 9.8 g/dL (p10-p90, 8.7-11.2 g/dL), the median neutrophil count was 2.1 × $10^9$/L (p10-p90, 1.1-3.6 × $10^9$/L), and the median platelet count was 241 × $10^9$/L (p10-p90, 120-455 × $10^9$/L).

At week 12, an erythroid response was observed in 44.8% of patients (Figure 10). The median hemoglobin level increased from 9.8 g/dL at baseline to 11 g/dL (*P*<.0001), the median platelet count decreased from 237 × $10^9$/L to 175 × $10^9$/L (*P*=.001), and the median neutrophil count decreased from 2 × $10^9$/L to 1.7 × $10^9$/L (*P*=.02). Among patients with an erythroid response, the median hemoglobin level increased by 2.2 g/dL (range, 1-4.4 g/dL). A cytogenetic response was observed in 61.9% of patients.

After a median follow-up of 24 months, 50% of patients had an erythroid response and 60% had a cytogenetic response. Progressive disease was observed in 37.9% of patients, and the median transfusion-free survival was 51 months. Responders exhibited a superior median transfusion-free survival compared with nonresponders (not reached vs 18 months; HR, 0.318; 95% CI, 0.134-0.756; *P*=.006).

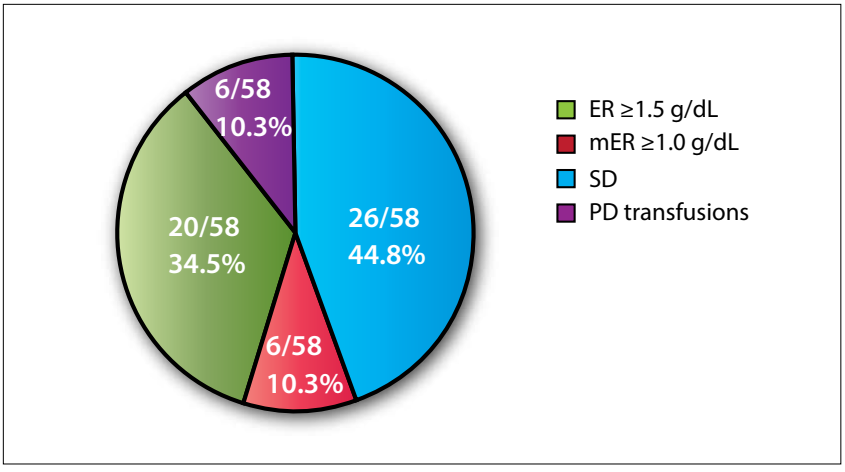


**Figure 10.** Patients with an erythroid response in the phase 3 SINTRA-REV trial, which compared lenalidomide vs placebo in myelodysplastic syndromes. ER, erythroid response; mER, minor erythroid response; PD, progressive disease; SD, stable disease; SINTRA-REV; Study of Revlimid (Lenalidomide) Versus Placebo in Patients With Low Risk Myelodysplastic Syndrome. Adapted from López-Cadenas F et al. ASH abstract 468. *Blood*. 2018;132(suppl 1).[5]

**ABSTRACT SUMMARY Impairment of the Stromal SDF-1–Mediated Hematopoietic Support by GDF-11 in MDS Is Rescued by Luspatercept**

The bone marrow microenvironment plays a key role in mediating MDS. Mesenchymal stem cells were isolated from patients with high-risk or low-risk MDS and age-matched healthy donors (Abstract 939). Mesenchymal stem cells were then treated with GDF-11, a member of the transforming growth factor beta (TGF-β) superfamily of ligands, in the presence or absence of RAP-536, a luspatercept homologue. Treatment with GDF-11 plus RAP-536 did not affect the viability, proliferation, or growth pattern of mesenchymal stem cells. Osteogenic differentiation was improved by treatment with RAP-536 alone, as evidenced by a 2.3-fold increase in alkaline phosphatase activity. RAP-536 treatment also significantly increased the mRNA and protein expression of SDF-1, a chemokine that regulates the interaction and support of hematopoietic stem and progenitor cells ($P<.05$). Further studies showed that the luspatercept homologue modulated mesenchymal stem cells (based on evaluation of the cobblestone-area forming assay), expression of CXCR4, and growth of hematopoietic stem and progenitor cells after co-culture with mesenchymal stem cell monolayers. The results with RAP-536 were validated in a zebrafish model. The authors concluded that these data provide the first evidence that RAP-536 has the capacity to modulate mesenchymal stromal cells, which might contribute to the restoration of hematopoiesis in patients with MDS.

The most common grade 1/2 nonhematologic AEs were infection (28%), asthenia (17%), headache (14%), skin rash (10%), constipation (9%), nausea/vomiting (7%), and diarrhea (5%) Grade 3/4 AEs included skin rash (7%), infection (2%), and asthenia (2%). Hematologic AEs included grade 1/2 thrombocytopenia (44.8%), grade 3/4 neutropenia (37.9%), grade 1/2 neutropenia (29.3%), and grade 3/4 thrombocytopenia (5.2%). Neutropenia of any grade was more common in patients with a response (84.4% vs 46.2%; $P=.002$), as was thrombocytopenia of any grade (68.8% vs 30.8%; $P=.004$).

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# Highlights in Myelodysplastic Syndromes From the 60th American Society of Hematology Annual Meeting: Commentary

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Several important abstracts on the management of myelodysplastic syndromes (MDS) were presented at the 60th American Society of Hematology (ASH) annual meeting. This discussion will divide them based on disease risk.

## Lower-Risk Disease

The highest-ranking abstract at ASH, presented at the plenary session, was a report of the MEDALIST trial (A Study of Luspatercept [ACE-536] to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes).[1] Dr Alan List presented the results of this multicenter trial. This important study evaluated luspatercept, a new agent for patients with lower-risk MDS. Luspatercept is a recombinant human protein that modulates transforming growth factor–ß signaling in MDS and results in increased erythropoiesis. It is administered every 3 to 4 weeks depending on the patient's hemoglobin levels. This randomized phase 3 trial enrolled patients with refractory anemia with ring sideroblasts who required further therapy after failing treatment with an erythroid-stimulating agent.[1] The study met all of the predefined primary and secondary endpoints. The primary endpoint, red blood cell transfusion independence at 8 weeks or longer, was 37.9% with luspatercept vs 13.2% with placebo ($P<.0001$). The median duration of red blood cell transfusion independence response was 30.6 weeks with luspatercept vs 13.6 weeks with placebo. The drug was very well-tolerated, without major significant toxicities. This is the first positive phase 3 trial for patients with MDS in more than a decade.

Luspatercept has also been studied in thalassemia. Results from the BELIEVE trial (An Efficacy and Safety Study of Luspatercept [ACE-536] Versus Placebo in Adults Who Require Regular Red Blood Cell Transfusions Due to Beta [β] Thalassemia), also presented at the ASH meeting, showed that luspatercept significantly reduced the red blood cell transfusion burden in adults with transfusion-dependent β-thalassemia compared with placebo.[2] The primary endpoint was the proportion of patients who achieved a reduction of at least 33% from baseline in red blood cell transfusion burden during weeks 13 to 24. This endpoint was met by 21.4% in the luspatercept arm vs 4.5% in the placebo arm (odds ratio, 5.79; 95% CI, 2.24-14.97; $P<.001$).

Luspatercept may have multiple potential applications. For example, data from the MEDALIST trial has led to the design of a frontline phase 3 trial, COMMANDS (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 Myelodysplastic Syndromes [MDS] in ESA Naïve Subjects Who Require Red Blood Cell Transfusions), comparing luspatercept vs standard growth factor support in the frontline setting for patients with lower-risk MDS.[3] This study is not restricted to refractory anemia with ring sideroblasts. Additional indications for luspatercept may be as a component of combination regimens in higher-risk disease and as supportive care in acute myeloid leukemia (AML) and, potentially, solid tumors.

Dr María Diez-Campelo presented results from the phase 3 SINTRA-REV trial (Study of REVLIMID [Lenalidomide] Versus Placebo in Patients With Low Risk Myelodysplastic Syndrome).[4] This study was designed to evaluate whether lenalidomide, a drug used in patients with MDS and chromosome 5 alterations with anemia, improved outcomes in patients who are transfusion-independent. The standard practice is to use lenalidomide in patients who are transfusion-dependent. This study aimed to assess the impact of early use of lenalidomide in transfusion-independent patients with deletion 5q MDS. The preliminary blinded analysis at week 12 showed erythroid responses in 44.8% of patients and cytogenetic responses in 61.9% of patients. The median transfusion dependency–free survival was not reached among responders (vs 18 months in nonresponders). Among responders, 68.2% experienced a risk reduction in transfusion dependency. A limitation to the study was the small cohort of 58 patients. Based on the limited number of patients, it was not possible to conclude whether there was a true benefit from early intervention. Treatment with lenalidomide did appear safe.

Dr Emanuele Angelucci presented results of the TELESTO trial (Myelodysplastic Syndromes [MDS] Event Free Survival With Iron Chelation Therapy Study), an important study evaluating

the use of iron chelation in patients with MDS.[5] For years, iron chelation has been discussed in the field of MDS, particularly for lower-risk patients who are transfusion-dependent. Deferasirox is approved in this setting, but the approval was based mainly on data for other indications, such as thalassemia, in nonrandomized phase 2 trials. The randomized, double-blind TELESTO study compared deferasirox vs placebo in iron-overloaded patients with low-risk or intermediate 1–risk MDS. The original study was designed with an overall survival objective and planned to enroll several hundred patients. Because of slow enrollment, the study was amended to a randomized phase 2 design, with a target enrollment of 210 patients and event-free survival as the main objective. The primary endpoint of event-free survival was 1440 days with deferasirox vs 1091 days with placebo (hazard ratio [HR], 0.636; 95% CI, 0.42-0.96; *P*=.015). The median overall survival was 1907 days vs 1509 days, respectively (HR, 0.832; 95% CI, 0.54-1.28; *P*=.200). In my opinion, the data indicate that iron chelation was associated with improved outcome in MDS patients with iron overload who were transfusion-dependent. This strategy should therefore be considered an option. Unfortunately, the study was not powerful enough to show improvement in survival and did not clarify how iron chelation results in improved outcomes.

My colleagues and I performed a small, multicenter study of tomaralimab (OPN-305), a monoclonal antibody that blocks the toll-like receptor 2, which is present in the membrane of MDS cells and results in activation of innate immune signalling.[6] This pathway is activated in most patients with lower-risk MDS. We hypothesized that blocking this pathway would lead to clinical improvement. The study enrolled lower-risk MDS patients who required further therapy after receiving a hypomethylating agent. These patients are difficult to treat because there is no drug approved for this indication, and many of the patients are not candidates for stem cell transplant. The study showed that tomaralimab was safe, an important finding because the main activity of this compound is to block innate immunity, which hypothetically could lead to toxicities. The overall response rate was 24%, with mainly erythroid responses. The future development of tomaralimab is uncertain. Tomaralimab may be studied in combination with hypomethylating agents or perhaps in the frontline setting in patients with MDS who have not received hypomethylating agents.

## Higher-Risk Disease

There were several important presentations focusing on higher-risk MDS. Guadecitabine (SGI-110) is a second-generation hypomethylating agent. It is a dinucleotide form of decitabine. Guadecitabine has been studied in AML and MDS. Unfortunately, the study in AML did not meet the primary endpoints.[7] We presented results from two large phase 2 studies of guadecitabine in MDS.[8,9] The first study enrolled patients with intermediate- or high-risk MDS or chronic myelomonocytic leukemia and was part of a multicenter clinical trial in North America.[8] The overall response rate was 43% in previously treated patients and 51% in treatment-naive patients. The response rate with guadecitabine was higher compared with the expectations for azacitidine or decitabine. Long-term follow-up showed that the survival was quite positive, at 11.7 months in previously treated patients and 23.4 months in treatment-naive patients. Survival results were particularly positive for patients without *TP53* mutations.

The second study was performed only at MD Anderson Cancer Center and enrolled only treatment-naive patients with higher-risk MDS.[9] Again, the overall response rate, 65%, was higher than what would be expected with decitabine or azacitidine, and included a 26% complete remission rate. In the MD Anderson study, there was a very high fraction of patients with mutations in *TP53*, a gene that is generally associated with lower response rates and decreased survival regardless of the intervention. In both of the studies, patients without the *TP53* mutation had exceptional outcomes compared with the standard of care. For these patients, the median overall survival was 22.7 months in the North American study and 32.5 months in the MD Anderson study. The toxicity profile was moderate and not dissimilar to what is seen with a standard hypomethylating agent.

A limitation to these 2 studies is that they are not randomized trials. However, the results suggest that guadecitabine could likely improve response rates in frontline MDS as compared with standard-of-care hypomethylating agents. Without head-to-head studies, it is difficult to conclude whether guadecitabine will also improve survival.

A study from Mount Sinai Hospital evaluated oral administration of rigosertib, a multikinase inhibitor, in combination with azacitidine.[10] The intravenous formulation of rigosertib has been studied in a phase 3 trial.[11] A study in primary hypomethylating-agent failure MDS is currently ongoing.[12] The oral formulation is of course easier to administer than the parenteral formulation. Laboratory work found that rigosertib was synergistic with azacitidine, which is the standard of care for patients with high-risk MDS.[13] Initially, there were some problems with urinary toxicity related to rigosertib, but this resolved with appropriate supportive care. As the phase 1 study expanded, it became apparent that the response rate was quite significant with this combination. At a dose of 1120 mg/day, the overall response rate was 92% in patients not previously treated with a hypomethylating agent and 50% in those already treated. At a dose of 840 mg/day or higher, the overall response rates were 90% and 54%, respectively. Although this is a small nonrandomized

study, it may lead to a randomized clinical trial comparing azacitidine with or without oral rigosertib.

Several years ago, my laboratory showed that treatment of AML or MDS cells with a hypomethylating agent upregulates the expression of programmed death 1 (PD-1) and the ligands PD-L1 and PD-L2, as well as the cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4).[14] At the ASH meeting, we presented the results of a phase 1/2 study combining either the PD-1 inhibitor nivolumab or the CTLA-4 inhibitor ipilimumab with azacitidine in MDS patients who were treatment-naive or had relapsed after treatment.[15] This relatively large, proof-of-principle study showed significant increases in the response rates with both nivolumab and ipilimumab. Among treatment-naive patients, the overall response rate was 70% with nivolumab plus azacitidine vs 62% with ipilimumab plus azacitidine. Among patients who had already received a hypomethylating agent, the response rate was 0% with nivolumab alone vs 30% with ipilimumab alone. An intriguing observation was that in the treatment-naive cohort, the median survival was not reached in the azacitidine plus ipilimumab cohort after a median follow-up of 20 months. This outcome was significantly better than what is expected with azacitidine alone. There were toxicity issues with these regimens, so I would not recommend them outside a clinical trial. However, we are excited about these combinations, and we are planning to expand this experience, particularly with the CTLA-4 inhibitor, ipilimumab. We are also studying triple combinations of azacitidine, nivolumab, and ipilimumab in patients with MDS.[16,17] This combination was associated with a very high response rate, but also with significant toxicity.

Dr Lionel Adès presented results of a study from the Groupe Francophone des Myélodysplasies, a network of French investigators.[18] This study incorporated a "pick a winner" design, which is similar to the design followed in a British Medical Research Council for AML.[19] The randomized phase 2 trial by Dr Adès aimed to identify a "doublet" signal that would be studied in subsequent more-definitive trials. Patients were randomly assigned to treatment with azacitidine alone (as the control arm), azacitidine plus lenalidomide, azacitidine plus valproic acid, or azacitidine plus idarubicin. None of the arms appeared to be superior to azacitidine alone. This study is important, however, because it shows the power of the "pick a winner" design. In the future, a trial with this design might replace lenalidomide, valproic acid, or idarubicin with more active compounds, such as venetoclax. This approach might be a good way to develop new combinations in multicenter trials.

Although there were no trials of venetoclax in MDS presented at ASH, a significant amount of data were presented in AML. For example, a phase 2 study combined venetoclax (ABT-199) with decitabine in a 10-day regimen for patients with AML.[20] The rate of complete response/complete response with incomplete blood count recovery was 96% for patients with newly diagnosed AML or untreated secondary AML. This rate was 55% among patients with relapsed/refractory AML or previously treated secondary AML. This study is one of several showing that this combination is extremely potent in terms of response rate.[21,22] This type of combination regimen will likely become the standard of care for patients with AML. In November 2018, the US Food and Drug Administration approved venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine for the treatment of newly diagnosed AML in adults ages 75 years or older who are not candidates for intensive induction chemotherapy. Ongoing clinical trials are evaluating venetoclax in patients with MDS, and it is likely that a subset of MDS patients will also benefit from this type of combination.

***Disclosure***

*Dr Garcia-Manero has performed research for Celgene, Novartis, BMS, Astex, Amgen, and AbbVie. He is an advisor for Celgene and Astex.*

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