Clinical Advances in
HEMATOLOGY & ONCOLOGY™
A Peer-Reviewed Journal

September 2020 Volume 18, Issue 9, Supplement 14

A SPECIAL MEETING REVIEW EDITION

Highlights in Myelodysplastic Syndromes From the 2020 American Society of Clinical Oncology Annual Meeting and the 25th European Hematology Association Congress

A Review of Selected Presentations From the 2020 ASCO Annual Meeting and the EHA25 Congress

Special Reporting on:

- Clinical Benefit of Luspatercept in Patients With Lower-Risk MDS and High Transfusion Burden in the Phase III MEDALIST Study
- A Phase III Placebo-Controlled Trial of CC-486 in Patients With Red Blood Cell Transfusion-Dependent Anemia and Thrombocytopenia Due to IPSS Lower-Risk Myelodysplastic Syndromes
- Assessment of Dose-Dependent Response to Luspatercept in Patients With Lower-Risk Myelodysplastic Syndromes With Ring Sideroblasts in the Phase 3 MEDALIST Trial
- Treatment With Imetelstat Provides Durable Transfusion Independence in Heavily Transfused Non-Del(5q) Lower-Risk MDS Relapsed/Refractory to Erythropoiesis-Stimulating Agents
- Longer-Term RBC Transfusion Reduction in the Phase III MEDALIST Study of Luspatercept in Patients With Lower-Risk MDS With Ring Sideroblasts
- Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined With Azacitidine in MDS and AML Patients: Phase Ib Results
- Effects of Luspatercept on Serum Ferritin in Patients With Lower-Risk Myelodysplastic Syndromes With Ring Sideroblasts in the Phase 3 MEDALIST Trial
- Phase 2 Study of Pevonedistat + Azacitidine Versus Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes/Chronic Myelomonocytic Leukemia or Low-Blast Acute Myelogenous 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
University of Texas MD Anderson Cancer Center
Houston, Texas

ON THE WEB:
hematologyandoncology.net

Indexed through the National Library of Medicine
(PubMed/MEDLINE), PubMed Central (PMC), and EMBASE

BRING ERYTHROID MATURATION TO LIFE

REBLOZYL is the first and only erythroid maturation agent FDA approved for anemia

IN MDS

Reblozyl®
(luspatercept-aamt)
for injection 25mg • 75mg

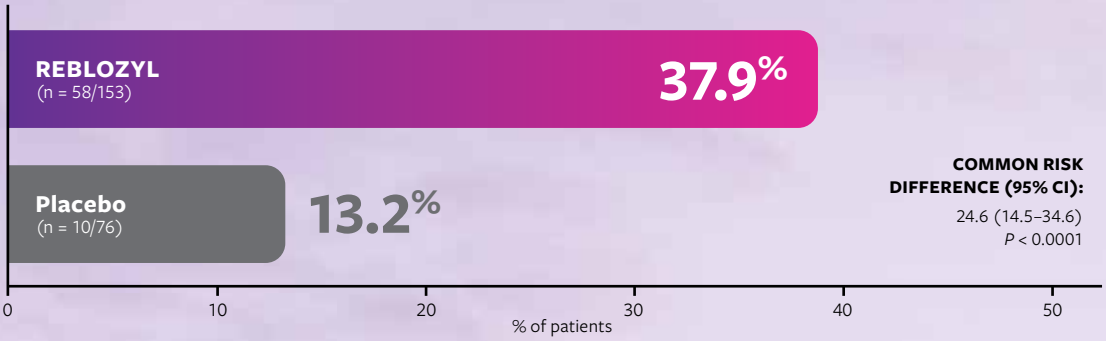
for patients with ring sideroblasts who are failing an ESA and require ≥2 RBC units/8 weeks[1]

REBLOZYL is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

REBLOZYL provided substantial clinical benefit through RBC transfusion independence vs placebo[1]

PRIMARY ENDPOINT: RBC-TI ≥8 WEEKS DURING WEEKS 1 TO 24



CI, confidence interval; ESA, erythropoiesis-stimulating agent; RBC-TI, red blood cell transfusion independence.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Thrombosis/Thromboembolism
In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. TEEs included deep vein thrombosis, pulmonary embolus, portal vein thrombosis, and ischemic stroke. Patients with known risk factors for thromboembolism (splenectomy or concomitant use of hormone replacement therapy) may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients at increased risk of TEE. Monitor patients for signs and symptoms of thromboembolic events and institute treatment promptly.

Hypertension
Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients. Across clinical studies, the incidence of Grade 3 to 4 hypertension ranged from 1.8% to 8.6%. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new or exacerbations of preexisting hypertension using anti-hypertensive agents.

Embryo-Fetal Toxicity
REBLOZYL may cause fetal harm when administered to a pregnant woman. REBLOZYL caused increased post-implantation loss, decreased litter size, and an increased incidence of skeletal variations in pregnant rat and rabbit studies. Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment and for at least 3 months after the final dose.

ADVERSE REACTIONS

Grade ≥3 (≥2%) adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. A fatal adverse reaction occurred in 5 (2.1%) patients.

REBLOZYL provided RBC-TI vs placebo in patients with MDS-RS and MDS/MPN-RS-T[1]

KEY SECONDARY ENDPOINTS: RBC-TI ≥12 WEEKS

Endpoint	REBLOZYL (n = 153)	Placebo (n = 76)	Common risk difference (95% CI)	*P* value
RBC-TI ≥12 weeks during weeks 1–24	**28.1%** (43)	**7.9%** (6)	20.0 (10.9, 29.1)	0.0002
RBC-TI ≥12 weeks during weeks 1–48[a]	**33.3%** (51)	**11.8%** (9)	21.4 (11.2, 31.5)	0.0003

[a]The median (range) duration of treatment was 49 weeks (6–114 weeks) on the REBLOZYL arm and 24 weeks (7–89 weeks) on the placebo arm.

RBC-TI ≥8 WEEKS DURING WEEKS 1 TO 24 BY DIAGNOSIS AND BASELINE TRANSFUSION BURDEN IN MEDALIST

	Responders/N		% Response (95% CI)	
	REBLOZYL	Placebo	REBLOZYL	Placebo
WHO 2016 diagnosis				
MDS-RS	46/135	8/65	**34.1%** (26.1, 42.7)	**12.3%** (5.5, 22.8)
MDS/MPN-RS-T	9/14	2/9	**64.3%** (35.1, 87.2)	**22.2%** (2.8, 60.0)
Other[a]	3/4	0/2	**75.0%** (19.4, 99.4)	**0.0%** (0.0, 84.2)
Baseline RBC transfusion burden				
2–3 units/8 weeks[b]	37/46	8/20	**80.4%** (66.1, 90.6)	**40.0%** (19.1, 63.9)
4–5 units/8 weeks[c]	15/41	1/23	**36.6%** (22.1, 53.1)	**4.3%** (0.1, 21.9)
≥6 units/8 weeks	6/66	1/33	**9.1%** (3.4, 18.7)	**3.0%** (0.1, 15.8)

[a]Includes MDS-EB-1, MDS-EB-2, and MDS-U.
[b]Includes patients who received 3.5 units.
[c]Includes patients who received 5.5 units.

REBLOZYL was studied in the pivotal phase 3 MEDALIST trial of 229 patients with IPSS-R very low-, low-, or intermediate-risk MDS who have ring sideroblasts and require RBC transfusions (≥2 RBC units/8 weeks) who were randomized 2:1 to REBLOZYL (n = 153) or placebo (n = 76). Patients were required to have had an inadequate response to prior treatment with an ESA, be intolerant of ESAs, or be ineligible for ESAs (serum EPO >200 U/L). MEDALIST excluded patients with del 5q MDS, white blood cell count >13 Gi/L, neutrophils <0.5 Gi/L, platelets <50 Gi/L, or with prior use of a disease-modifying agent for treatment of MDS. REBLOZYL was administered 1 mg/kg subcutaneously every 3 weeks. Two dose-level increases were allowed (to 1.33 mg/kg and to 1.75 mg/kg) if the patient had an RBC transfusion within the prior 6 weeks. All patients received best supportive care, which included RBC transfusions as needed.

del 5q, deletion 5q; EPO, erythropoietin; IPSS-R, Revised International Prognostic Scoring System; MDS-EB-1, myelodysplastic syndromes with excess blasts (5%–9% in the bone marrow or 2%–4% in the blood); MDS-EB-2, myelodysplastic syndromes with excess blasts (10%–19% in the bone marrow or 5%–19% in the blood); MDS-U, myelodysplastic syndromes, unclassifiable; RBC, red blood cell; WHO, World Health Organization.

IMPORTANT SAFETY INFORMATION (CONT'D)

ADVERSE REACTIONS (CONT'D)

The most common (≥10%) adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection.

LACTATION

It is not known whether REBLOZYL is excreted into human milk or absorbed systemically after ingestion by a nursing infant. REBLOZYL was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. Because many drugs are excreted in human milk, and because of the unknown effects of REBLOZYL in infants, a decision should be made whether to discontinue nursing or to discontinue treatment. Because of the potential for serious adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for 3 months after the last dose.

Please see the Brief Summary of full Prescribing Information for REBLOZYL on the following pages.

Reference: 1. REBLOZYL [Prescribing Information]. Summit, NJ: Celgene Corporation; 2020.

Learn more, sign up for updates, and find out how to access REBLOZYL at:
REBLOZYLpro.com/discoverMDS

Bristol Myers Squibb™ | ACCELERON

06/20 US-RBZ-20-0260

REBLOZYL® (luspatercept-aamt) for injection, for subcutaneous use
Initial U.S. Approval: 2019

The following is a Brief Summary; refer to full Prescribing Information for complete product information.

1 INDICATIONS AND USAGE

1.2 Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic/ Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia

REBLOZYL is indicated for the treatment of anemia failing an erythropoiesis stimulating agent and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk myelodysplastic syndromes with ring sideroblasts (MDS-RS) or with myelodysplastic/myeloproliferative neoplasm with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T).

1.3 Limitations Of Use

REBLOZYL is not indicated for use as a substitute for RBC transfusions in patients who require immediate correction of anemia.

2 DOSAGE AND ADMINISTRATION

2.2 Recommended Dosage for Myelodysplastic Syndromes with Ring Sideroblasts (MDS-RS) or Myelodysplastic/ Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis (MDS/MPN-RS-T) Associated Anemia

The recommended starting dose of REBLOZYL is 1 mg/kg once every 3 weeks by subcutaneous injection for patients with anemia of MDS-RS or MDS/MPN-RS-T. Prior to each REBLOZYL dose, review the patient's hemoglobin and transfusion record. Titrate the dose based on responses according to Table 3. Interrupt treatment for adverse reactions as described in Table 4. Discontinue REBLOZYL if a patient does not experience a decrease in transfusion burden after 9 weeks of treatment (administration of 3 doses) at the maximum dose level or if unacceptable toxicity occurs at any time.

If a planned administration of REBLOZYL is delayed or missed, administer REBLOZYL as soon as possible and continue dosing as prescribed, with at least 3 weeks between doses.

Dose Modifications for Response

Assess and review hemoglobin results prior to each administration of REBLOZYL. If an RBC transfusion occurred prior to dosing, use the pretransfusion hemoglobin for dose evaluation.

If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose, increase the REBLOZYL dose to 1.33 mg/kg (Table 3). If a patient is not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1.33 mg /kg dose level, increase the REBLOZYL dose to 1.75 mg/kg. Do not increase the dose more frequently than every 6 weeks (2 doses) or beyond the maximum dose of 1.75 mg/kg.

In the absence of transfusions, if hemoglobin increase is greater than 2 g/dL within 3 weeks or if the predose hemoglobin is greater than or equal to 11.5 g/dL, reduce the dose or interrupt treatment with REBLOZYL as described in Table 3. If, upon dose reduction, the patient loses response (i.e., requires a transfusion) or hemoglobin concentration drops by 1 g/dL or more in 3 weeks in the absence of transfusion, increase the dose by one dose level. Wait a minimum of 6 weeks between dose increases.

Dose modifications for response are provided in Table 3.

Table 3: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dose Titration for Response

	REBLOZYL Dosing Recommendation*
Starting Dose	• 1 mg/kg every 3 weeks
Dose Increases for Insufficient Response at Initiation of Treatment	
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at the 1 mg/kg starting dose	• Increase the dose to 1.33 mg/kg every 3 weeks
Not RBC transfusion-free after at least 2 consecutive doses (6 weeks) at 1.33 mg/kg	• Increase the dose to 1.75 mg/kg every 3 weeks
No reduction in RBC transfusion burden after at least 3 consecutive doses (9 weeks) at 1.75 mg/kg	• Discontinue treatment

(continued)

Table 3: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dose Titration for Response

	REBLOZYL Dosing Recommendation*
Dose Modifications for Predose Hemoglobin Levels or Rapid Hemoglobin Rise	
Predose hemoglobin is greater than or equal to 11.5 g/dL in the absence of transfusions	• Interrupt treatment • Restart when the hemoglobin is no more than 11 g/dL
Increase in hemoglobin greater than 2 g/dL within 3 weeks in the absence of transfusions and	
• current dose is 1.75 mg/kg	• Reduce dose to 1.33 mg/kg
• current dose is 1.33 mg/kg	• Reduce dose to 1 mg/kg
• current dose is 1 mg/kg	• Reduce dose to 0.8 mg/kg
• current dose is 0.8 mg/kg	• Reduce dose to 0.6 mg/kg
• current dose is 0.6 mg/kg	• Discontinue treatment

* Do not increase the dose if the patient is experiencing an adverse reaction as described in Table 4.

Dose Modifications for Toxicity

For patients experiencing Grade 3 or higher adverse reactions, modify treatment as described in Table 4.

Table 4: MDS-RS and MDS/MPN-RS-T Associated Anemia - REBLOZYL Dosing Modifications for Adverse Reactions

	REBLOZYL Dosing Recommendation*
Grade 3 or 4 hypersensitivity reactions	• Discontinue treatment
Other Grade 3 or 4 adverse reactions	• Interrupt treatment • When the adverse reaction resolves to no more than Grade 1, restart treatment at the next lower dose level** • If the dose delay is > 12 consecutive weeks, discontinue treatment

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, and Grade 4 is life-threatening.

**Per Table 3 dose reductions above.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Thrombosis/Thromboembolism

In adult patients with beta thalassemia, thromboembolic events (TEE) were reported in 8/223 (3.6%) REBLOZYL-treated patients. Reported TEEs included deep vein thromboses, pulmonary embolus, portal vein thrombosis, and ischemic strokes. Patients with known risk factors for thromboembolism, e.g. splenectomy or concomitant use of hormone replacement therapy, may be at further increased risk of thromboembolic conditions. Consider thromboprophylaxis in patients with beta thalassemia at increased risk of TEE. Monitor patients receiving REBLOZYL for signs and symptoms of thromboembolic events and institute treatment promptly.

5.2 Hypertension

Hypertension was reported in 10.7% (61/571) of REBLOZYL-treated patients. Across clinical studies, the incidence of grade 3-4 hypertension ranged from 1.8% to 8.6%. In adult patients with beta thalassemia with normal baseline blood pressure, 13 (6.2%) patients developed systolic blood pressure (SBP) ≥130 mm Hg and 33 (16.6%) patients developed diastolic blood pressure (DBP) ≥80 mm Hg. In adult patients with MDS with normal baseline blood pressure, 26 (29.9%) patients developed SBP ≥130 mm Hg and 23 (16.4%) patients developed DBP ≥80 mm Hg. Monitor blood pressure prior to each administration. Manage new-onset hypertension or exacerbations of preexisting hypertension using anti-hypertensive agents.

5.3 Embryo-Fetal Toxicity

Based on findings from animal reproductive studies, REBLOZYL may cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during organogenesis resulted in adverse developmental outcomes including increased embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) of 1.75 mg/kg.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use an effective method of contraception during treatment with REBLOZYL and for at least 3 months after the final dose *[see Use in Specific Populations (8.1, 8.3)]*.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Thrombosis/Thromboembolism *[see Warnings and Precautions (5.1)]*
- Hypertension *[see Warnings and Precautions (5.2)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data in the WARNINGS AND PRECAUTIONS reflect exposure to REBLOZYL as a single agent administered across a range of doses (0.125 mg/kg to 1.75 mg/kg) in 571 patients in 4 trials.

Myelodysplastic Syndromes with Ring Sideroblasts or Myelodysplastic / Myeloproliferative Neoplasm with Ring Sideroblasts and Thrombocytosis Associated Anemia

The safety of REBLOZYL at the recommended dose and schedule was evaluated in 242 patients with MDS with ring sideroblasts (n=192) or other myeloid neoplasms (n=50). The safety population included 63% males and 37% females of median age 72 years (range, 30 – 95 years); of these patients, 81% were White, 0.4% Black, 0.4% Other, and race was not reported in 18.2% of patients. The median time on treatment with REBLOZYL was 50.4 weeks (range, 3 – 221 weeks); 67% of patients were exposed for 6 months or longer and 49% were exposed for greater than one year.

Among the 242 patients treated with REBLOZYL, 5 (2.1%) had a fatal adverse reaction, 11 (4.5%) discontinued due to an adverse reaction, and 7 (2.9%) had a dose reduction due to an adverse reaction. The most common (≥10%) all-grade adverse reactions included fatigue, musculoskeletal pain, dizziness, diarrhea, nausea, hypersensitivity reactions, hypertension, headache, upper respiratory tract infection, bronchitis, and urinary tract infection. The most common (≥2%) Grade ≥ 3 adverse reactions included fatigue, hypertension, syncope and musculoskeletal pain. Selected laboratory abnormalities that changed from Grade 0-1 at baseline to Grade ≥ 2 at any time during the studies in at least 10% of patients included creatinine clearance decreased, total bilirubin increased, and alanine aminotransferase increased.

Table 8 shows the most common adverse reactions for patients treated with REBLOZYL or placebo through the first 8 cycles in the MEDALIST trial

Table 8: Adverse Reactions (≥5%) in Patients Receiving REBLOZYL with a Difference Between Arms of >2% in MEDALIST Trial Through Cycle 8

Body System / Adverse Reaction	REBLOZYL (N=153)		Placebo (N=76)	
	All Grades n (%)	Grade 3 n (%)	All Grades n (%)	Grade 3 n (%)
General disorders and administration site conditions				
Fatigue [a, b]	63 (41)	11 (7)	17 (22)	2 (3)
Musculoskeletal and connective tissue disorders				
Musculoskeletal pain [b]	30 (20)	3 (2)	11 (14)	0 (0)
Nervous system disorders				
Dizziness/vertigo	28 (18)	1 (<1)	5 (7)	1 (1)
Headache [b]	21 (14)	0 (0)	5 (7)	0 (0)
Syncope / presyncope	8 (5)	5 (3)	0 (0)	0 (0)
Gastrointestinal disorders				
Nausea [b]	25 (16)	1 (<1)	8 (11)	0 (0)
Diarrhea [b]	25 (16)	0 (0)	7 (9)	0 (0)
Respiratory, thoracic and mediastinal disorders				
Dyspnea [b]	20 (13)	2 (1)	4 (5)	1 (1)
Immune system disorders				
Hypersensitivity reactions [b]	15 (10)	1 (<1)	5 (7)	0 (0)

(continued)

Table 8: Adverse Reactions (≥5%) in Patients Receiving REBLOZYL with a Difference Between Arms of >2% in MEDALIST Trial Through Cycle 8

Body System / Adverse Reaction	REBLOZYL (N=153)		Placebo (N=76)	
	All Grades n (%)	Grade 3 n (%)	All Grades n (%)	Grade 3 n (%)
Renal and urinary disorders				
Renal impairment [b]	12 (8)	3 (2)	3 (4)	0 (0)
Cardiac disorders				
Tachycardia [b]	12 (8)	0 (0)	1 (1)	0 (0)
Injury poisoning and procedural complications				
Injection site reactions	10 (7)	0 (0)	3 (4)	0 (0)
Infections and infestations				
Upper respiratory tract infection	10 (7)	1 (<1)	2 (3)	0 (0)
Influenza / influenza like illness	9 (6)	0 (0)	2 (3)	0 (0)

[a] Includes asthenic conditions.
[b] Reaction includes similar/grouped terms.

Other clinically relevant adverse reactions reported in <5% of patients include bronchitis, urinary tract infection, and hypertension *[see Warnings and Precautions (5.2)]*.

Shifts from Grades 0-1 to Grades 2-4 abnormalities for selected laboratory tests during the first 8 cycles in the MEDALIST trial are shown in Table 9.

Table 9: Selected Grades 2-4 Treatment-Emergent Laboratory Abnormalities Through Cycle 8 in the MEDALIST Trial

Parameter	REBLOZYL		Placebo	
	N[a]	n (%)	N[a]	n (%)
ALT elevated	151	13 (9)	74	5 (7)
AST elevated	152	6 (4)	76	0 (0)
Total bilirubin elevated	140	17 (12)	66	3 (5)
Creatinine clearance reduced	113	30 (27)	62	13 (21)

[a] Number of patients at Grades 0-1 at baseline.
ALT = alanine aminotransferase; AST = aspartate aminotransferase.

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to luspatercept in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

Of 284 patients with beta thalassemia who were treated with REBLOZYL and evaluable for the presence of anti-luspatercept-aamt antibodies, 4 patients (1.4%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 2 patients (0.7%) who had neutralizing antibodies.

Of 260 patients with MDS who were treated with REBLOZYL and evaluable for the presence of anti-luspatercept-aamt antibodies, 23 patients (8.9%) tested positive for treatment-emergent anti-luspatercept-aamt antibodies, including 9 patients (3.5%) who had neutralizing antibodies.

Luspatercept-aamt serum concentration tended to decrease in the presence of neutralizing antibodies. There were no severe acute systemic hypersensitivity reactions reported for patients with anti-luspatercept-aamt antibodies in REBLOZYL clinical trials, and there was no association between hypersensitivity type reaction or injection site reaction and presence of anti-luspatercept-aamt antibodies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on findings in animal reproduction studies, REBLOZYL may cause fetal harm when administered to a pregnant woman. There are no available data on REBLOZYL use in pregnant women to inform a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. In animal

reproduction studies, administration of luspatercept-aamt to pregnant rats and rabbits during the period of organogenesis resulted in adverse developmental outcomes including embryo-fetal mortality, alterations to growth, and structural abnormalities at exposures (based on area under the curve [AUC]) above those occurring at the maximum recommended human dose (MRHD) (*see Data*). Advise pregnant women of the potential risk to a fetus.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data
In embryo-fetal development studies, luspatercept-aamt was administered subcutaneously at 5, 15, or 30 mg/kg on gestation days 3 and 10 (rats) or 5, 20, or 40 mg/kg on gestation days 4 and 11 (rabbits). Effects in both species included reductions in numbers of live fetuses and fetal body weights, and increases in resorptions, post-implantation losses, and skeletal variations (such as asymmetric sternal centra in rats and angulated hyoid in rabbits). Effects were observed at exposures (based on AUC) approximately 7-times (rats) and 16-times (rabbits) the MRHD of 1.75 mg/kg.

In a pre- and postnatal development study, pregnant rats were administered luspatercept-aamt subcutaneously at 3, 10, or 30 mg/kg once every 2 weeks during organogenesis and through weaning, gestation day 6 through postnatal day 20. At all dose levels lower F1 pup body weights and adverse kidney findings (such as membranoproliferative glomerulonephritis, tubular atrophy/hypoplasia, and vessel ectasia occasionally associated with hemorrhage) were observed. These effects were observed at exposures (based on AUC) approximately 1.6-times the MRHD of 1.75 mg/kg.

8.2 Lactation
Risk Summary

Luspatercept-aamt was detected in milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. There are no data on the presence of REBLOZYL in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in the breastfed child, advise patients that breastfeeding is not recommended during treatment with REBLOZYL, and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential
Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential before starting REBLOZYL treatment.

Contraception

Females
REBLOZYL may cause embryo-fetal harm when administered to pregnant women *[see Use in Specific Populations (8.1)]*. Advise female patients of reproductive potential to use effective contraception during treatment with REBLOZYL and for at least 3 months after the last dose.

Infertility

Females
Based on findings in animals, REBLOZYL may impair female fertility *[see Nonclinical Toxicology (13.1)]*. Adverse effects on fertility in female rats were reversible after a 14-week recovery period.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established. Based on findings in juvenile animals, REBLOZYL is not recommended for use in pediatric patients *[see Non-Clinical Toxicology (13.1)]*.

8.5 Geriatric Use
Clinical studies of REBLOZYL in beta thalassemia did not include sufficient numbers of patients age 65 years and older to determine whether they respond differently from younger patients.

Clinical studies of REBLOZYL for treatment of anemia in MDS-RS and MDS/MPN-RS-T included 206 (79%) patients ≥ 65 years of age and 93 (36%) patients ≥ 75 years of age. No differences in safety or effectiveness were observed between older (≥ 65 years) and younger patients.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenicity or mutagenicity studies have been conducted with luspatercept-aamt.

In a repeat-dose toxicity study, juvenile rats were administered luspatercept-aamt subcutaneously at 1, 3, or 10 mg/kg once every 2 weeks from postnatal day 7 to 91. Hematologic malignancies (granulocytic leukemia, lymphocytic leukemia, malignant lymphoma) were observed at 10 mg/kg resulting in exposures (based on area under the curve [AUC]) approximately 4.4 times the maximum recommended human dose (MRHD) of 1.75 mg/kg.

In a combined male and female fertility and early embryonic development study in rats, luspatercept-aamt was administered subcutaneously to animals at doses of 1 to 15 mg/kg. There were significant reductions in the average numbers of corpora lutea, implantations, and viable embryos in luspatercept-aamt-treated females. Effects on female fertility were observed at the highest dose with exposures (based on AUC) approximately 7-times the MRHD of 1.75 mg/kg. Adverse effects on fertility in female rats were reversible after a 14-week recovery period. No adverse effects were noted in male rats.

17 PATIENT COUNSELING INFORMATION

Discuss the following with patients prior to and during treatment with REBLOZYL.

Thromboembolic Events
Advise beta thalassemia patients of the potential risk of thromboembolic events. Review known risk factors for developing thromboembolic events and advise patients to reduce modifiable risk factors (e.g., smoking, use of oral contraceptives) *[see Warnings and Precautions (5.1)]*.

Effects on Blood Pressure
Caution patients that REBLOZYL may cause an increase in blood pressure *[see Warnings and Precautions (5.2)]*.

Embryo-Fetal Toxicity
Advise females of reproductive potential of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception while receiving REBLOZYL and for at least 3 months after the final dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, during treatment with REBLOZYL *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1)]*.

Lactation
Advise females not to breastfeed during treatment with REBLOZYL and for 3 months after the final dose *[see Use in Specific Populations (8.2)]*.

Manufactured by:
Celgene Corporation
86 Morris Avenue
Summit, NJ 07901
U.S. License No. 2114

Jointly Marketed by:
Acceleron Pharma, Inc.
Cambridge, MA 02139

RBZ_HCP_MDS BS_v001_04-2020

Clinical Benefit of Luspatercept in Patients With Lower-Risk MDS and High Transfusion Burden in the Phase III MEDALIST Study

Ineffective erythropoiesis can lead to symptomatic anemia in patients with lower-risk myelodysplastic syndromes (MDS).[1,2] Erythropoiesis-stimulating agents are not effective in a significant proportion of these patients, who therefore must undergo regular red blood cell (RBC) transfusions. Dependence on RBC transfusions is associated with a lower quality of life and reduced overall survival.[1-4] Lenalidomide is an established treatment for RBC transfusion–dependent patients with lower-risk MDS who have del(5q) disease.[1,5] However, alternative therapeutic strategies are needed for patients with non-del(5q) disease.

Luspatercept is a first-in-class erythroid maturation agent that binds to select transforming growth factor beta superfamily ligands.[6] The interaction results in inhibition of downstream Smad2/3 signaling, leading to late-stage erythroblast differentiation and erythroid maturation. In April 2020, the US Food and Drug Administration (FDA) expanded the indication of luspatercept to include the treatment of anemia that did not respond to an erythropoiesis-stimulating agent and that requires 2 or more RBC units over 8 weeks in adult patients with very low- to intermediate-risk MDS with ring sideroblasts or with myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis.[7] This approval was based on results from MEDALIST (A Study of Luspatercept [ACE-536] to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes), a randomized, double-blind, placebo-controlled phase 3 trial that evaluated the safety and efficacy of luspatercept in patients with lower-risk MDS with ring sideroblasts and non-del(5q) disease.[8] (Lower risk was defined per the Revised International Prognostic Scoring System [IPSS-R].)

The trial enrolled patients with MDS who had been receiving regular RBC transfusions and had disease that was refractory to or unlikely to respond to erythropoiesis-stimulating agents or had discontinued these agents owing to an adverse event. At baseline, the average RBC transfusion burden was at least 2 units during the 8 weeks prior to the study. A total of 229 patients were randomly assigned in a 2:1 ratio to treatment every 3 weeks with luspatercept (n=153) or placebo (n=76). Luspatercept was administered at a starting dose of 1.0 mg/kg, and was titrated up to 1.75 mg/kg in patients who did not achieve RBC transfusion independence (RBC-TI).[8]

Fenaux and colleagues recently reported updated results from the MEDALIST trial, with a data cutoff of May 8, 2018.[8] At that time, the primary endpoint of RBC-TI for 8 weeks or longer during weeks 1 through 24 was observed in 38% of patients in the luspatercept arm vs 13% of patients in the placebo arm (P<.001). The key secondary endpoint of RBC-TI for 12 weeks or longer was met by 28% of the luspatercept arm vs 8% of the placebo arm during weeks 1 through 24, and by 33% vs 12%, respectively, during weeks 1 through 48 (P<.001 for both comparisons).

At the 2020 American Society of Clinical Oncology (ASCO) meeting, Zeidan and colleagues presented an updated analysis of the MEDALIST

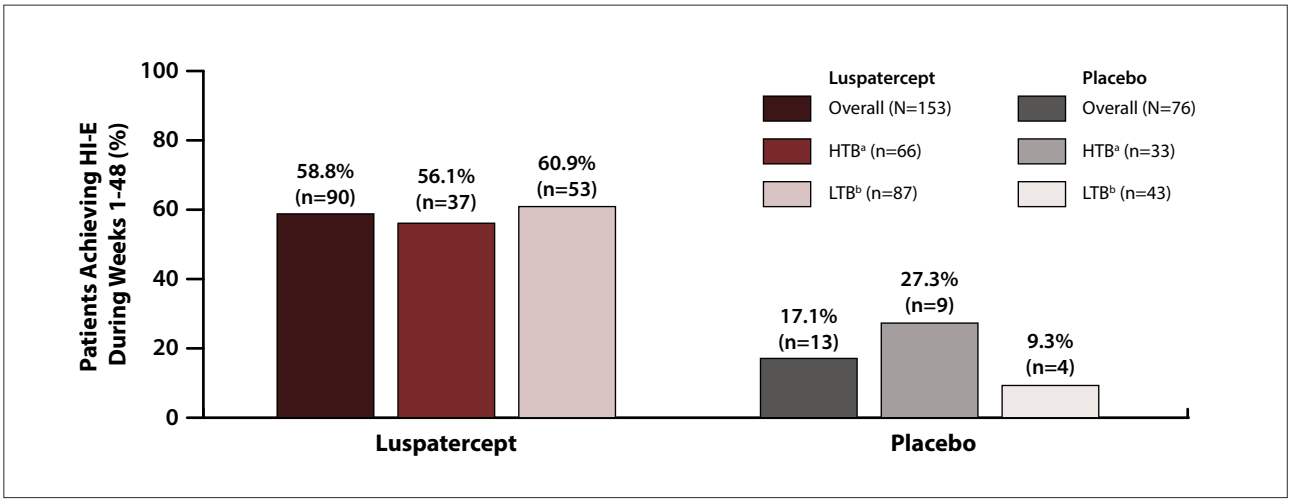


Figure 1. Patients achieving HI-E during weeks 1 to 48 in the MEDALIST trial. [a]HTB referred to patients who received transfusions of ≥6 RBC units within 8 weeks prior to the study. [b]LTB referred to patients who received transfusions of <6 RBC units within 8 weeks prior to the study. HI-E, hematologic improvement–erythroid; HTB, high transfusion burden; LTB, low transfusion burden. Adapted from Zeidan AM et al. ASCO abstract 7554. *J Clin Oncol.* 2020;38(15 suppl).[9]

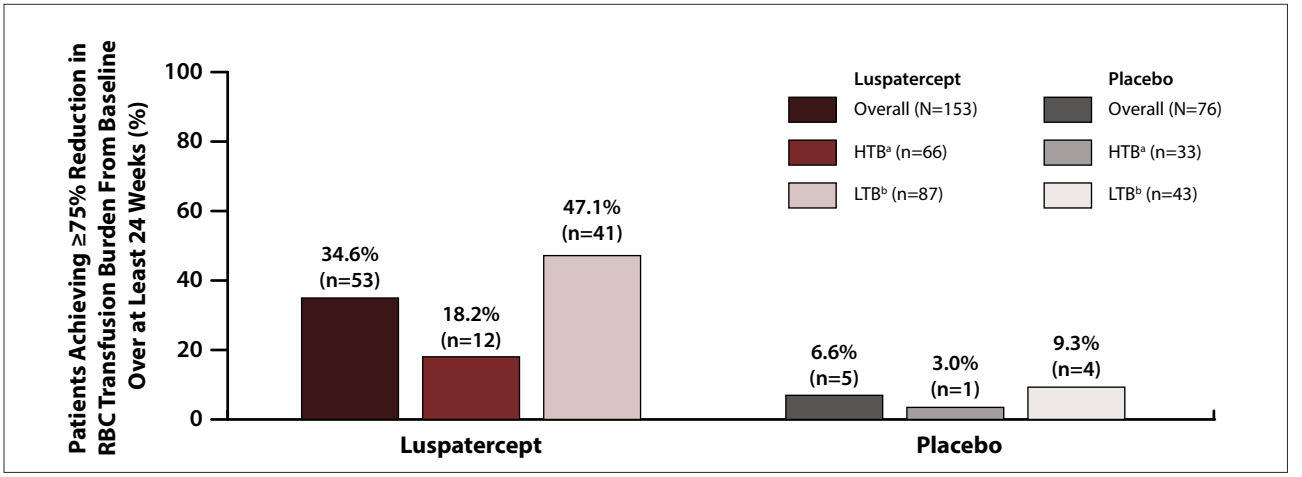


Figure 2. Patients achieving a reduction of 75% or more in RBC transfusion burden from baseline over at least 24 months in the MEDALIST trial. [a]HTB referred to patients who received transfusions of ≥6 RBC units within 8 weeks prior to the study. [b]LTB referred to patients who received transfusions of <6 RBC units within 8 weeks prior to the study. HTB, high transfusion burden; LTB, low transfusion burden; RBC, red blood cell. Adapted from Zeidan AM et al. ASCO abstract 7554. *J Clin Oncol.* 2020;38(15 suppl).[9]

trial, with a data cutoff of July 1, 2019.[9] The median follow-up at this cutoff was 26.4 months in the luspatercept arm and 26.1 months in the placebo arm. The analysis assessed the clinical benefit of luspatercept, with a focus on those patients with a high transfusion burden (HTB).[9] An HTB was defined as transfusion of 6 or more RBC units within the 8 weeks prior to the study. This group encompassed 43% of the study population (n=99). At baseline, the median transfusion burden over 8 weeks among HTB patients was 7.5 RBC units (range, 6-15) in the luspatercept arm and 8.0 RBC units (range, 6-20) in the placebo arm.[9]

Among patients with an HTB, the primary study endpoint of RBC-TI for 8 weeks or longer during weeks 1 to 24 was met by 9.1% of the luspatercept arm vs 3.0% of the placebo arm (*P*=.27). In the overall population, the key secondary endpoint of RBC-TI for 8 weeks or longer during weeks 1 to 48 was met by 45.1% of the luspatercept arm compared with 15.8% of the placebo arm in this updated analysis. Among patients with an HTB, this endpoint was met by 18.2% vs 6.1%, respectively. Among patients with a low transfusion burden, the endpoint was met by 65.5% vs 23.3%.[9]

Among HTB patients, a major hematologic improvement–erythroid (HI-E) response in weeks 1 to 48 was reported in 56.1% of the luspatercept arm vs 27.3% of the placebo arm (*P*=.0071; Figure 1). The secondary endpoint of major HI-E improvement for 8 weeks or longer was achieved by 56.1% of the luspatercept arm vs 27.3% of the placebo arm (*P*=.0071) in the HTB patients. HI-E was defined per International Working Group 2006 criteria as a reduction of at least 4 RBC units from baseline (for patients with baseline RBC transfusion burden of <4 units over 8 weeks) or a mean hemoglobin increase of 1.5 g/dL or more from baseline (for patients with a baseline RBC transfusion burden of <4 units over 8 weeks).[9]

The secondary endpoint of a reduction in RBC transfusion burden of 50% or more from baseline over at least 24 weeks was met by 34.8% in the luspatercept arm vs 9.1% in the placebo arm among HTB patients. A reduction of 75% or more in RBC transfusion burden from baseline over at least 24 weeks was reported in 18.2% vs 3.0%, respectively (Figure 2).[9] HTB patients had long periods of reduction in transfusion burden. Among the 23 HTB patients who responded to treatment with luspatercept, the Kaplan-Meier estimate of the median longest duration of reduction in RBC transfusion burden of 50% or more over at least 24 weeks was 72.3 weeks (95% CI, 29.6 to not estimable). This endpoint was not estimable (95% CI, 27.7 to not estimable) in the 3 HTB patients who responded to placebo.[9]

The most common treatment-emergent adverse events of any grade reported with luspatercept were fatigue (30.1%), diarrhea (28.1%), and asthenia (25.5%). The investigators concluded that luspatercept was associated with clinically significant reductions in RBC transfusion burden, as well as achievement of HI-E. This observation spanned the overall population, as well as HTB patients. The rate of RBC-TI for 8 weeks or longer (the study's primary endpoint) was low in HTB patients. However, luspatercept was associated with improvements in several secondary endpoints among HTB patients, including reductions in the number of transfusion events and the duration of transfusion burden.[9]

References

1. Fenaux P, Adès L. How we treat lower-risk myelodysplastic syndromes. *Blood*. 2013;121(21):4280-4286.
2. Adès L, Itzykson R, Fenaux P. Myelodysplastic syndromes. *Lancet*. 2014;383(9936):2239-2252.

3. Hiwase DK, Kutyna MM, Chhetri R, et al. Transfusion dependency is associated with inferior survival even in very low and low risk IPSS-R patients [ASH abstract 1518]. *Blood.* 2013;122(21).
4. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. *J Clin Oncol.* 2005;23(30):7594-7603.
5. Santini V, Schemenau J, Levis A, et al. Can the revised IPSS predict response to erythropoietic-stimulating agents in patients with classical IPSS low or intermediate-1 MDS? *Blood.* 2013;122(13):2286-2288.
6. Suragani RN, Cadena SM, Cawley SM, et al. Transforming growth factor-ß superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. *Nat Med.* 2014;20(4):408-414.
7. Reblozyl [package insert]. Summit, NJ: Celgene Corporation; 2020.
8. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med.* 2020;382(2):140-151.
9. Zeidan AM, Garcia-Manero G, DeZern AE, et al. Clinical benefit of luspatercept in patients with lower-risk MDS and high transfusion burden in the phase III MEDALIST study [ASCO abstract 7554]. *J Clin Oncol.* 2020;38(15 suppl).

A Phase III Placebo-Controlled Trial of CC-486 in Patients With Red Blood Cell Transfusion-Dependent Anemia and Thrombocytopenia Due to IPSS Lower-Risk Myelodysplastic Syndromes

CC-486, a formulation of oral azacitidine, is an investigational hypomethylating agent with a distinct pharmacokinetic and pharmacodynamic profile compared with injectable azacitidine.[1,2] CC-486 can be administered in extended dosing regimens (for up to 14 or 21 days per cycle), allowing for prolonged therapeutic activity. Clinical activity of CC-486 has been previously demonstrated in multiple hematologic malignancies, including MDS.[2-4] At the 25th congress of the European Hematology Association (EHA25), Garcia-Manero and colleagues provided results from AZA-MDS-003, a phase 3 trial that compared CC-486 with placebo in patients with lower-risk MDS who had RBC-dependent anemia and thrombocytopenia at study entry.[5]

The AZA-MDS-003 trial enrolled adult patients with MDS classified as low or intermediate-1 risk (per the International Prognostic Scoring System [IPSS]). Patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2. All patients were dependent on RBC transfusions, requiring an average of at least 2 RBC units over 28 days for 56 or more days. Patients had no transfusion-free periods of 28 days or longer in the 56 days prior to randomization. Enrolled patients also had thrombocytopenia, defined as a platelet count of 75 × 10^9/L or lower confirmed at 2 visits at least 21 days apart. A confirmatory platelet count was obtained within 14 days before randomization.[5]

The planned enrollment was 386 patients. Review by an independent data monitoring committee revealed an imbalance in early deaths between the treatment groups. Consequently, enrollment was prematurely stopped after 216 patients were randomly assigned to treatment. The study therefore had a 99% power for RBC-TI and a 72% power for overall survival.[5]

Patients were randomly assigned to treatment with CC-486 at 300 mg once daily for 21 days of a 28-day cycle (n=107) or placebo (n=109). Best supportive care was administered to patients in both arms. Response was assessed after cycle 6. At this time, response was defined as RBC-TI or a reduction in transfusion requirements of at least 50%, platelet transfusion independence, HI-E or a hematologic improvement in platelets, and no evidence of disease progression. Patients with evidence of a response continued treatment, whereas patients with no response stopped. Regardless, patients were followed for survival, progression to acute myeloid leukemia (AML), development of second primary malignancies, and subsequent treatments for MDS.[5]

At baseline, the median patient age was 74 years in the CC-486 arm

ABSTRACT SUMMARY APR-246 Combined With Azacitidine in *TP53*-Mutated Myelodysplastic Syndromes and Acute Myeloid Leukemia. A Phase 2 Study by the Groupe Francophone des Myélodysplasies

APR-246 is an investigational agent that reactivates mutant and inactivated TP53 protein by restoring *TP53* conformation and function. Preclinical studies have suggested that APR-246 may act synergistically with azacitidine in *TP53*-mutated MDS and AML. This combination was evaluated in the phase 2 GFM-APR study, in which patients with *TP53*-mutated higher-risk MDS or AML were treated with 6 cycles of APR-246 plus azacitidine (EHA25 abstract S181). After a bone marrow evaluation, patients either continued APR-246 plus azacitidine treatment until relapse, underwent stem cell transplant followed by APR-246 plus azacitidine maintenance therapy, or discontinued the study. The primary study endpoint, objective response rate, was 58% in the intention-to-treat group and 77% in evaluable patients (who had received at least 3 cycles of treatment followed by a bone marrow evaluation). Febrile neutropenia was reported in 37% of patients; all cases were grade 3 or 4 in severity. A neurologic toxicity occurred in 40% of patients. Ataxia was the most common neurologic event (25%).

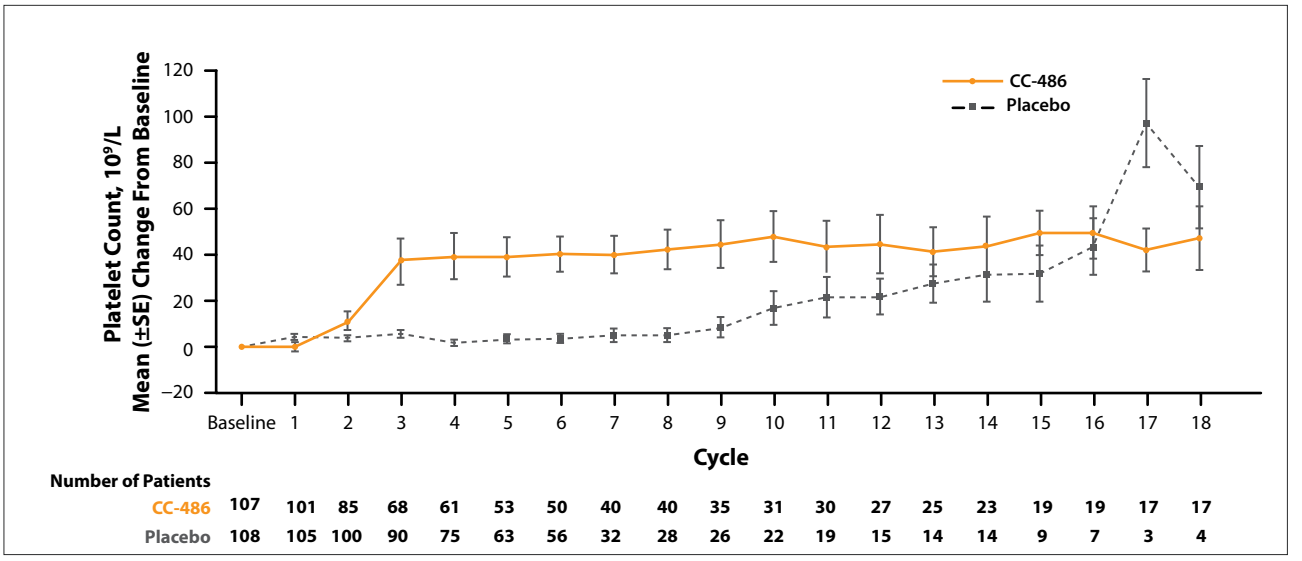


Figure 3. The mean change in platelet count from baseline among patients treated with CC-486 or placebo in the phase 3 AZA-MDS-003 trial. SE, standard error. Adapted from Garcia-Manero G et al. EHA25 abstract S180.[5]

and 73 years in the placebo arm. Nearly all patients in both arms had disease risk categorized as intermediate-1. Good IPSS cytogenetic risk was reported in 81% of the CC-486 arm and 83% of the placebo arm. Approximately one-third of patients (34% in the CC-486 arm and 31% in the placebo arm) had received more than 4 RBC units during the previous 28 days at baseline.[5]

The data cutoff for this primary analysis was January 2019. The primary endpoint was the rate of RBC-TI lasting 56 days or longer. This endpoint was achieved by 30.8% of patients in the CC-486 arm vs 11.1% in the placebo arm (odds ratio [OR], 3.6; 95% CI, 1.7-7.4; *P*=.0002). A key secondary endpoint, RBC-TI lasting at least 84 days, was achieved by 28.0% vs 5.6%, respectively (OR, 6.6; 95% CI, 2.6-16.7; *P*<.0001).[5]

The median duration of RBC-TI, another key secondary endpoint, was 11.1 months in the CC-486 arm vs 5.0 months in the placebo arm, although this difference was not statistically significant (*P*=.42). HI-E was reported in 43.0% of the CC-486 arm vs 31.5% of the placebo arm (OR, 1.6; 95% CI, 0.9-2.9; *P*=.12). Hematologic improvement in platelets was observed in 24.3% vs 6.5%, respectively (OR, 4.6; 95% CI, 1.9-11.2; *P*=.0003).[5] The mean change in platelet count from baseline is shown in Figure 3.

The interim analysis of overall survival found no significant difference between the 2 treatment arms. The median overall survival was 17.3 months with CC-486 and 16.2 months with placebo (hazard ratio [HR], 0.99; 95% CI, 0.70-1.40; log-rank *P*=.9607). At the time of this analysis, progression to AML was observed in 7.5% of the CC-486 arm and 16.7% of the placebo arm.[5]

Adverse events were more frequent with CC-486 compared with placebo. In the study, adverse events were best managed through patient monitoring, supportive care measures, and dose modifications or interruptions. The most common all-grade adverse events in the CC-486 arm were nausea (76%), diarrhea (68%), vomiting (63%), neutropenia (50%), constipation (48%), and pyrexia (34%). Grade 3 or 4 neutropenia occurred in 47% of patients in the CC-486 arm and 12% of patients in the placebo arm. Treatment interruption was required by 62% of the CC-486 arm vs 37% of the placebo arm. Adverse events necessitated dose reductions in 29% vs 4%, respectively. Patients with severe neutropenia at baseline were at higher risk for developing hematologic toxicity early during the course of treatment with CC-486. The investigators suggested that these patients may benefit from a modified dosing regimen.

References

1. Garcia-Manero G, Gore SD, Cogle C, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. *J Clin Oncol.* 2011;29(18):2521-2527.
2. Laille E, Shi T, Garcia-Manero G, et al. Pharmacokinetics and pharmacodynamics with extended dosing of CC-486 in patients with hematologic malignancies. *PLoS One.* 2015;10(8):e0135520.
3. Garcia-Manero G, Gore SD, Kambhampati S, et al. Efficacy and safety of extended dosing schedules of CC-486 (oral azacitidine) in patients with lower-risk myelodysplastic syndromes. *Leukemia.* 2016;30(4):889-896.
4. Savona MR, Kolibaba K, Conkling P, et al. Extended dosing with CC-486 (oral azacitidine) in patients with myeloid malignancies. *Am J Hematol.* 2018;93(10):1199-1206.
5. Garcia-Manero G, Santini V, Almeida A, et al. A phase III placebo-controlled trial of CC-486 in patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk myelodysplastic syndromes. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S180.

Assessment of Dose-Dependent Response to Luspatercept in Patients With Lower-Risk Myelodysplastic Syndromes With Ring Sideroblasts in the Phase 3 MEDALIST Trial

In an analysis of the MEDALIST trial, Platzbecker and colleagues evaluated how the dose of luspatercept impacted clinical activity, as well as the incidence of treatment-emergent adverse events. Responses reported in this analysis were measured within the first 48 weeks of the study, and were reported as of May 8, 2018. The data cutoff for the safety analysis was July 1, 2019.

In the MEDALIST trial, patients randomly assigned to treatment with luspatercept began with a starting dose of 1.0 mg/kg administered subcutaneously every 21 days for 24 weeks or longer. Among patients who did not achieve RBC-TI after 2 or more doses at the same level, the dose was titrated up to 1.33 mg/kg, and then to 1.75 mg/kg.

At baseline, the RBC transfusion burden was 6 or fewer RBC units over 8 weeks in 70.6% of patients in the luspatercept arm and 65.8% of patients in the placebo arm. Baseline RBC transfusion burden was greater than 6 RBC units over 8 weeks in 29.4% of the luspatercept arm and 34.2% of the placebo arm.

The key secondary endpoint of RBC-TI for 8 weeks or longer during weeks 1 to 48 was reached by 45.1% of the luspatercept arm and 15.8% of the placebo arm. Among the 69 patients who responded to luspatercept, 91.3% had a baseline transfusion burden of 6 or fewer RBC units over 8 weeks.

HI-E during weeks 1 to 48 was reported in 58.8% of patients in the luspatercept arm vs 17.1% of patients in the placebo arm. Among the 90 responders, 74.4% had a baseline transfusion burden of 6 or fewer RBC units over 8 weeks.

At the time of this data analysis, 58.8% of luspatercept-treated patients overall had received the maximum dose level of 1.75 mg/kg. Among the 63 luspatercept-treated patients with a baseline transfusion burden of 6 or fewer RBC units over 8 weeks who achieved an RBC-TI response, 39.7% received the maximal dose level of 1.75 mg/kg.

The median time to dose escalation in patients who achieved an RBC-TI response was approximately twice as long as the median time observed in patients without this response. Among patients in the luspatercept arm, responders reached a dose of 1.33 mg/kg by 105 days, vs 43 days for nonresponders. A dose of 1.75 mg/kg was reached in 171 days by responders and 91 days by nonresponders. Factors more frequent among patients who underwent dose escalation included higher erythropoietin levels, an IPSS-R intermediate score, and greater RBC transfusion burden at baseline.

Overall, 68.1% of the RBC-TI responders achieved their first response at the initial dose of 1.0 mg/kg without the need for dose escalation (Figure 4).

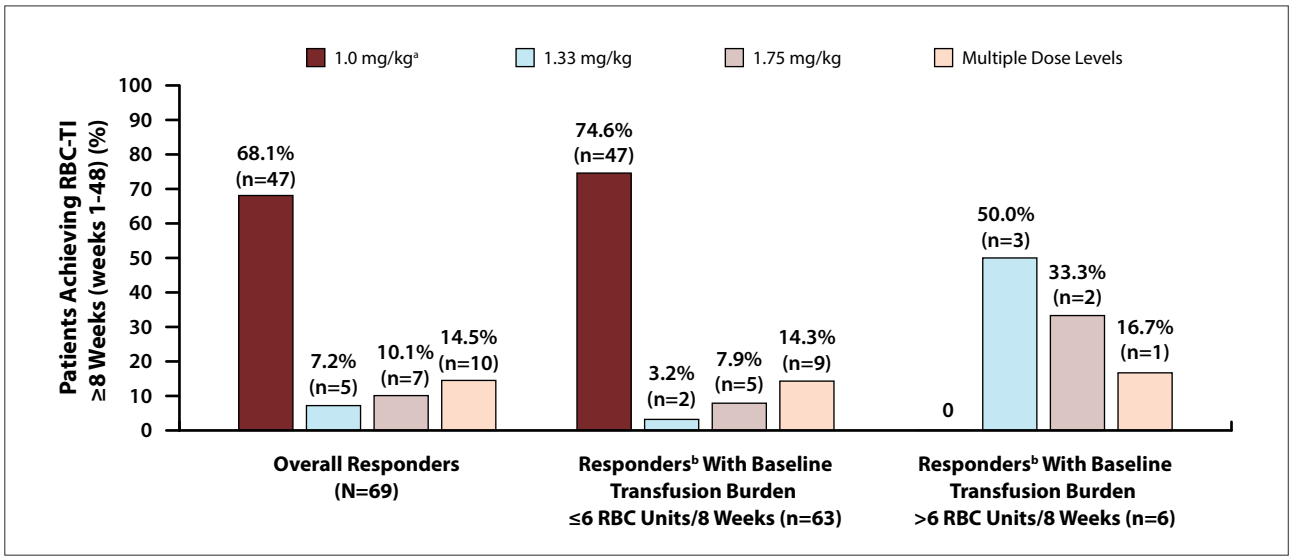


Figure 4. Patients treated with luspatercept at various dose levels who achieved RBC-TI for 8 weeks or longer (during weeks 1 to 48) in the MEDALIST trial. RBC-TI, red blood cell transfusion independence. [a]The category of 1.0 mg/kg includes a limited number of patients treated with 0.8 mg/kg. [b]Patients achieving RBC-TI ≥8 weeks during weeks 1-48 (n=69). Adapted from Platzbecker U et al. EHA25 abstract EP812.[1]

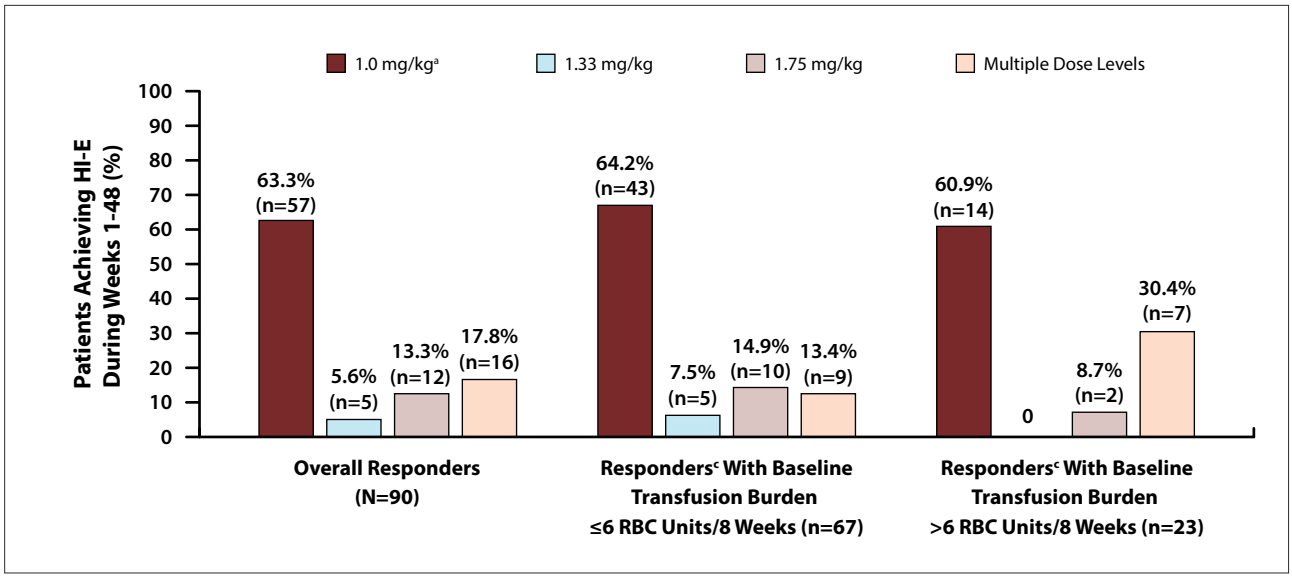


Figure 5. Patients treated with luspatercept at various dose levels who achieved HI-E during weeks 1 to 48 in the MEDALIST trial. [a]The category of 1.0 mg/kg includes a limited number of patients treated at 0.8 mg/kg. [b]Patients achieving RBC-TI ≥8 weeks during weeks 1-48 (n=69). HI-E, hematologic improvement–erythroid; RBC, red blood cell. Adapted from Platzbecker U et al. EHA25 abstract EP812.[1]

Among the RBC-TI responders who had a baseline transfusion burden of 6 or fewer RBC units over 8 weeks, 74.6% achieved their first response at the initial dose of 1.0 mg/kg. In contrast, none of the RBC-TI responders who had a baseline transfusion burden of more than 6 RBC units over 8 weeks achieved their response at the initial dose. Instead, the response was achieved at 1.33 mg/kg in 50.0% and 1.75 mg/kg in 33.3%.

Most patients in the luspatercept arm who achieved HI-E during weeks 1 to 48 did so with the 1.0 mg/kg dose. Among those patients with a low baseline transfusion burden (>6 RBC units over 8 weeks), 64.2% achieved this HI-E outcome at 1.0 mg/kg (Figure 5). In patients with a high baseline transfusion burden (>6 RBC units over 8 weeks), 60.9% achieved this outcome at 1.0 mg/kg.

Luspatercept dose reductions or delays were permitted to manage excessive increases in hemoglobin. Most luspatercept-treated patients with a baseline transfusion burden of 6 or fewer RBC units over 8 weeks who achieved an RBC-TI of 8 weeks or longer within the first 48 weeks achieved their first response at a dose of 1.0 mg/kg. An additional 11% of patients in this group (and approximately 17% of responders overall) achieved their first response only with higher doses of luspatercept (1.33 mg/kg or 1.75 mg/kg). The investigators noted that dose escalations contributed to the maintenance of RBC-TI of 8 weeks or longer and to the achievement of multiple response episodes. The luspatercept dose range of 1.0 mg/kg to 1.75 mg/kg was well tolerated, without dose-dependent increases in treatment-emergent adverse events.

Reference

1. Platzbecker U, Fenaux P, Mufti GJ, et al. Assessment of dose-dependent response to luspatercept in patients with lower-risk myelodysplastic syndromes with ring sideroblasts in the phase 3 MEDALIST trial. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract EP812.

Treatment With Imetelstat Provides Durable Transfusion Independence in Heavily Transfused Non-Del(5q) Lower-Risk MDS Relapsed/Refractory to Erythropoiesis-Stimulating Agents

Telomerase is a ribonuclear protein complex that consists of a reverse transcriptase enzymatic subunit (human telomerase reverse transcriptase), an RNA template, and additional specialized proteins. These molecules work together to extend the length of telomeres, the nucleotide sequences at the end of chromosomes that protect their degradation.[1] Imetelstat, a first-in-class telomerase inhibitor, is a 13-mer oligonucleotide that was designed to be complementary to the template region of the telomerase RNA molecule. Imetelstat binds to the RNA template, competitively inhibiting telomerase activity and preventing maintenance of telomeres.[1,2]

The IMerge study is a phase 2/3 clinical trial evaluating whether imetelstat improves the rate of RBC-TI vs placebo. The phase 2 portion, which incorporates a single-arm, open-label design, enrolled patients with lower-risk MDS. Enrollment into the phase 2 portion has been completed, whereas phase 3 enrollment continues. At the EHA25 congress, Platzbecker and colleagues reported an analysis of the 38 patients enrolled in the phase 2 portion of IMerge. The median follow-up for these patients was 24.0 months (95% CI, 5.6-45.5), at which point 24% of patients remained on study treatment.[2]

The trial population had lower-risk MDS, defined as non-del(5q) cytogenetics or an IPSS of low or intermediate-1 risk. Patients had developed relapsed or refractory disease after treatment with an erythropoiesis-stimulating agent. Patients were transfusion-dependent, requiring 4 or more RBC units over 8 weeks throughout a 16-week prestudy period. The trial excluded patients who had received previous treatment with hypomethylating agents or lenalidomide.

At baseline, the median patient age was 71.5 years (range, 46-83), and 66% were male. Most patients had an ECOG performance status of 0 or 1, and 89% had received previous treatment with an erythropoiesis-stimulating agent. Nearly two-thirds (63%) of this lower-risk population were in the low-risk IPSS category; the remaining patients were in the intermediate-1 category. Patients had a heavy transfusion burden, with 84% requiring 6 or more RBC units over 8 weeks (median of 8 RBC units/8 weeks [range, 4-14]).[2]

All patients received treatment with imetelstat at a dose of 7.5 mg/kg intravenously (IV) every 4 weeks. The primary endpoint of the IMerge study was the 8-week RBC-TI rate. Imetelstat was associated with a clinically meaningful rate of transfusion independence, with an 8-week RBC-TI of 42%. The median time to onset of 8-week RBC-TI was 8.3 weeks (range, 0.1-40.7). Patients across multiple subtypes achieved RBC-TI with imetelstat, including those with or without a ringed sideroblasts phenotype, those with a transfusion burden that was high (4 to 6 RBC units) or very high (>6 RBC units) at baseline, and those with different serum erythropoietin levels (≤500 or >500 mU/mL). A reduction in the *SF3B1* mutation rate correlated with a quicker onset of transfusion independence. Throughout transfusion independence, 32% of patients experienced a rise in their hemoglobin level of 3 g/dL or more from the pretreatment level.[2]

Key secondary endpoints included the rate of 24-week RBC-TI, duration of RBC-TI, and HI-E. The rate of 24-week RBC-TI was 32%. The median duration of RBC-TI was 88.0 weeks (range, 23.1-140.9). A total of 29% of patients remained transfusion-free for at least 1 year—with the longest transfusion-free period reaching 2.7 years—suggesting that imetelstat may have the potential to modify disease (Figure 6). Among patients who achieved RBC-TI, 75% had a rise in their hemoglobin level of 3 g/dL or more from their pretreatment level. The RBC-TI achieved with imetelstat proved durable, lasting a median of 20 months. The rate of HI-E was 68%, and the median duration of HI-E was 21 months.[2]

Cytopenias were the most common adverse event. All-grade cytopenias consisted of thrombocytopenia (66%), neutropenia (58%), and anemia

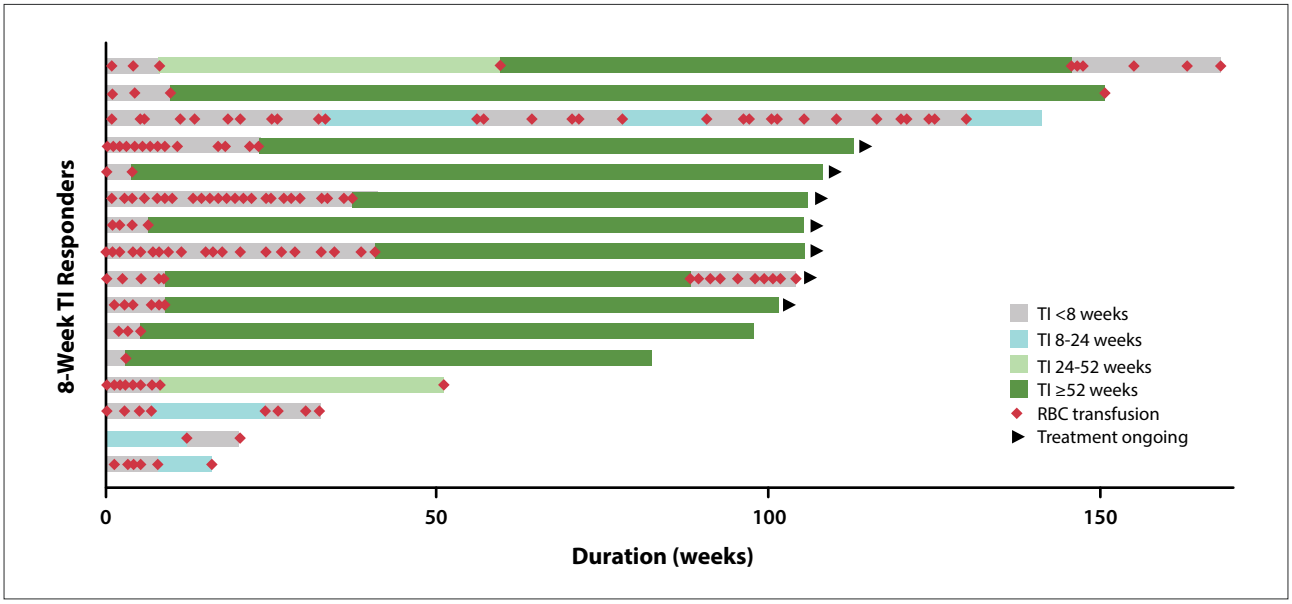


Figure 6. Duration of transfusion independence among patients treated with imetelstat in the phase 2/3 IMerge study. RBC, red blood cell; TI, transfusion independence. Adapted from Platzbecker U et al. EHA25 abstract EP183.[2]

(29%). Grade 3/4 cytopenias consisted of thrombocytopenia (61%), neutropenia (55%), and anemia (21%). These hematologic toxicities lacked significant clinical consequences. Two patients developed febrile neutropenia, and 3 experienced a grade 3 or 4 bleeding event. The cytopenias were largely reversible, as 90% of neutrophil toxicities and 87% of platelet toxicities resolved to grade 2 or better within 4 weeks. Other all-grade adverse events included back pain (24%) and pyrexia (21%).[2]

Based on the results of this analysis, the phase 3 portion of the IMerge trial is continuing and expected to enroll approximately 170 patients. The phase 3 portion follows a randomized, double-blind design, and is randomly assigning patients in a 2-to-1 ratio to imetelstat or placebo.[2]

References

1. Wang X, Hu CS, Petersen B, et al. Imetelstat, a telomerase inhibitor, is capable of depleting myelofibrosis stem and progenitor cells. *Blood Adv.* 2018;2(18):2378-2388.
2. Platzbecker U, Fenaux P, Steensma DP, et al. Treatment with imetelstat provides durable transfusion independence in heavily transfused non-del(5q) lower risk MDS relapsed/refractory to erythropoiesis stimulating agents. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S183.

Longer-Term RBC Transfusion Reduction in the Phase III MEDALIST Study of Luspatercept in Patients With Lower-Risk MDS With Ring Sideroblasts

A study presented by Komrokji and colleagues at the ASCO 2020 virtual meeting evaluated the reduction in long-term transfusion burden among patients treated with luspatercept in the MEDALIST trial. At baseline, the median transfusion burden was 5 RBC units over 8 weeks in both the luspatercept and placebo arms, with ranges of 1 to 15 and 2 to 20, respectively. A reduction in RBC transfusion burden of at least 50% from baseline for 24 weeks or more was reported in 50.3% of the luspatercept arm vs 14.5% of the placebo arm (P<.0001). The median longest episode of reduction in RBC transfusion burden of at least 50% was 131.6 weeks in the luspatercept arm and was not estimable in the placebo arm.

During weeks 9 to 24, the change from baseline in the number of RBC units transfused decreased in the luspatercept arm and increased slightly in the placebo arm. The mean change was –3.0 (95% CI, –3.9 to –2.1) vs +0.4 (95% CI, –0.6 to +1.4), respectively (Figure 7). From weeks 33 to 48, the mean change from baseline in RBC units transfused was –4.9 (95% CI, –5.9 to –3.9) in the luspatercept arm.

During weeks 1 to 24, the mean number of transfusion visits was 5.9 (95% CI, 5.0-6.8) for the luspatercept arm compared with 9.5 (95% CI, 8.3-10.6) for the placebo arm. In the overall population, patients treated with luspatercept had a lower risk of recurrent transfusion visits during weeks 1 to 24 (HR, 0.699; 95% CI, 0.597-0.819).

Treatment with luspatercept was associated with significant improvements in RBC transfusion burden throughout the entire 48-week study period. From weeks 1 to 48, the mean number of RBC units transfused was 22.89 in the luspatercept arm vs 35.98 in the placebo arm (P<.0001). Similarly, the mean number of RBC transfusion visits during this time was 12.95 vs 19.54, respectively (P<.0001).

Luspatercept was associated with statistically significant reductions in serum ferritin levels. The least squares mean (LSM) change in serum ferritin from baseline to weeks 9 to 24 was –2.7 µg/L in the luspatercept arm vs +226.5 µg/L in the placebo arm (LSM difference –229.1 µg/L; P=.0024). From weeks 33 to 48, the LSM change in serum ferritin was –72.0 µg/L vs +247.4 µg/L, respectively (LSM difference –319.5 µg/L; P=.0294).

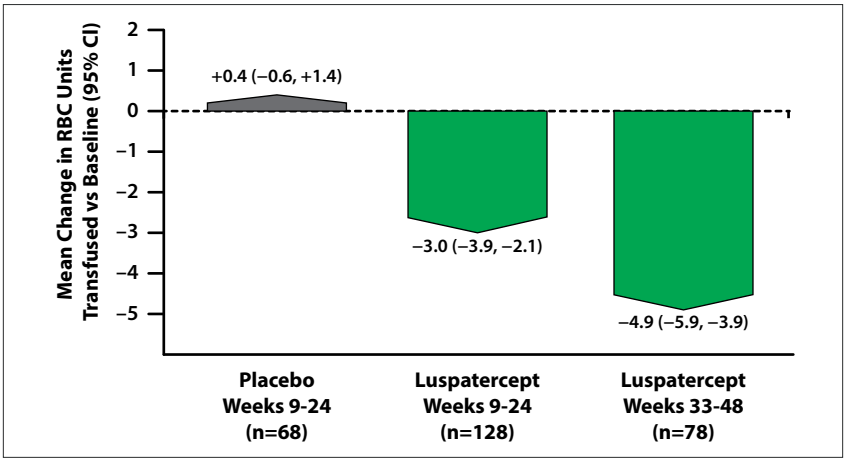


Figure 7. The mean change from baseline in RBC units transfused among patients in the MEDALIST trial. RBC, red blood cell. Adapted from Komrokji RS et al. ASCO abstract 7518. *J Clin Oncol.* 2020;38(15 suppl).[1]

Reference

1. Komrokji RS, Sekeres MA, Zeidan AM, et al. Longer-term RBC transfusion reduction in the phase III MEDALIST study of luspatercept in patients with lower-risk MDS with ring sideroblasts [ASCO abstract 7518]. *J Clin Oncol.* 2020;38(15 suppl).

Tolerability and Efficacy of the First-in-Class Anti-CD47 Antibody Magrolimab Combined With Azacitidine in MDS and AML Patients: Phase Ib Results

The cell surface protein CD47 is a main macrophage immune checkpoint.[1,2] The expression of CD47 in myeloid malignancies enables immune evasion of macrophages, and increased expression portends a worse prognosis among patients with AML.[3] The anti-CD47 monoclonal antibody magrolimab (previously known as 5F9) is a first-in-class macrophage immune checkpoint inhibitor that acts via inhibition of CD47, thereby triggering macrophage-mediated phagocytosis of the tumor cells.[1,4] Preclinical studies identified synergy between magrolimab and azacitidine in AML xenograft models, which might be attributable to increased expression of the phagocytosis-inducing signal calreticulin on cancer cells that is associated with azacitidine.[5]

The 5F9005 trial was an early phase 1b study of magrolimab in combination with azacitidine in patients with MDS or AML. At the EHA25 congress, Sallman and coworkers presented results of this study for the MDS population.[6] A presentation at the 2020 ASCO meeting provided a fuller dataset that included patients with MDS and AML.[7]

The study enrolled patients with untreated MDS with disease risk classified as intermediate, high, or very high based on the IPSS-R (n=39) and patients with untreated AML who were eligible for induction chemotherapy (n=29). The data included outcomes from the dose-expansion portion of the study, during which patients received magrolimab (1 mg/kg priming dose with dose ramp-up to 30 mg/kg) combined with azacitidine (75 mg/m^2 on days 1-7). The priming dose was used to mitigate on-target anemia. The dose was increased from 1 mg/kg to 30 mg/kg by week 2. Then the dose was 30 mg/kg given as maintenance either every week or every 2 weeks starting with cycle 3. After pharmacodynamic studies found similar CD47 receptor occupancy in the peripheral blood and bone marrow between the groups, the every-2-week regimen was selected for further analysis.[6,7]

At baseline, the patients' median age was 70 years (range, 47-80) in the MDS group and 74 years (range, 60-89) in the AML group. Among patients with MDS, 31% had therapy-related disease. Cytogenetic risk was intermediate in 28% and poor in 64%. (Risk was unknown or missing in 8%.) In the MDS group, risk was intermediate in 33%, high in 49%, or very high in 15%. (The risk category was unknown or missing in 3%.) Among the patients with AML, 66% had underlying myelodysplasia (AML with myelodysplasia-related changes), and 45% had *TP53* mutations. In the AML group, cytogenetic risk was intermediate in 7% and poor in 72%. (The category was unknown or missing in 21%.)

In the dose-expansion phase, no maximum tolerated dose was reached. The regimen of magrolimab plus azacitidine had a safety profile that was similar to that of single-agent azacitidine. Although most patients were cytopenic at baseline, there were no reports of significant cytopenias, infections, or immune-related adverse events. Instead, most patients showed an improvement in both neutrophil and platelet counts during therapy. One patient in the combination arm stopped study treatment owing to an adverse event.[6,7]

On-target anemia, which is a pharmacodynamic effect of the combination, was mitigated with an initial

ABSTRACT SUMMARY Randomized Open-Labeled Academic Trial Comparing "G-CSF Prior Aza" With Standard Aza Therapy in High-Risk MDS Patients

In the Prague General Hospital registry of 142 higher-risk MDS patients, those treated with azacitidine who had higher G-CSF consumption showed significantly lower rates of grade 4 neutropenia, as well as prolonged overall survival. Stopka and colleagues compared standard azacitidine (n=27) vs a regimen of G-CSF given before azacitidine (n=35) in a single-center, open-label, randomized study in newly diagnosed patients with higher-risk MDS, AML with fewer than 30% blasts, or CMML II (EHA25 abstract S184). The patients were ineligible for stem cell transplant or intensive chemotherapy. G-CSF was permitted in both arms in cases of febrile neutropenia or grade 4 neutropenia. Therefore, the number of G-CSF injections was also evaluated. The response rate was 71% in patients treated with G-CSF plus azacitidine vs 41% in those treated with standard azacitidine, and the estimated odds of response was approximately 4-fold higher with G-CSF (*P*=.0045). Additionally, overall survival was approximately 8 months longer in patients treated with G-CSF plus azacitidine. The investigators noted that in the group treated with G-CSF plus azacitidine, those patients with the highest rate of G-CSF administration had a significantly higher risk of death compared with patients with lower rates.

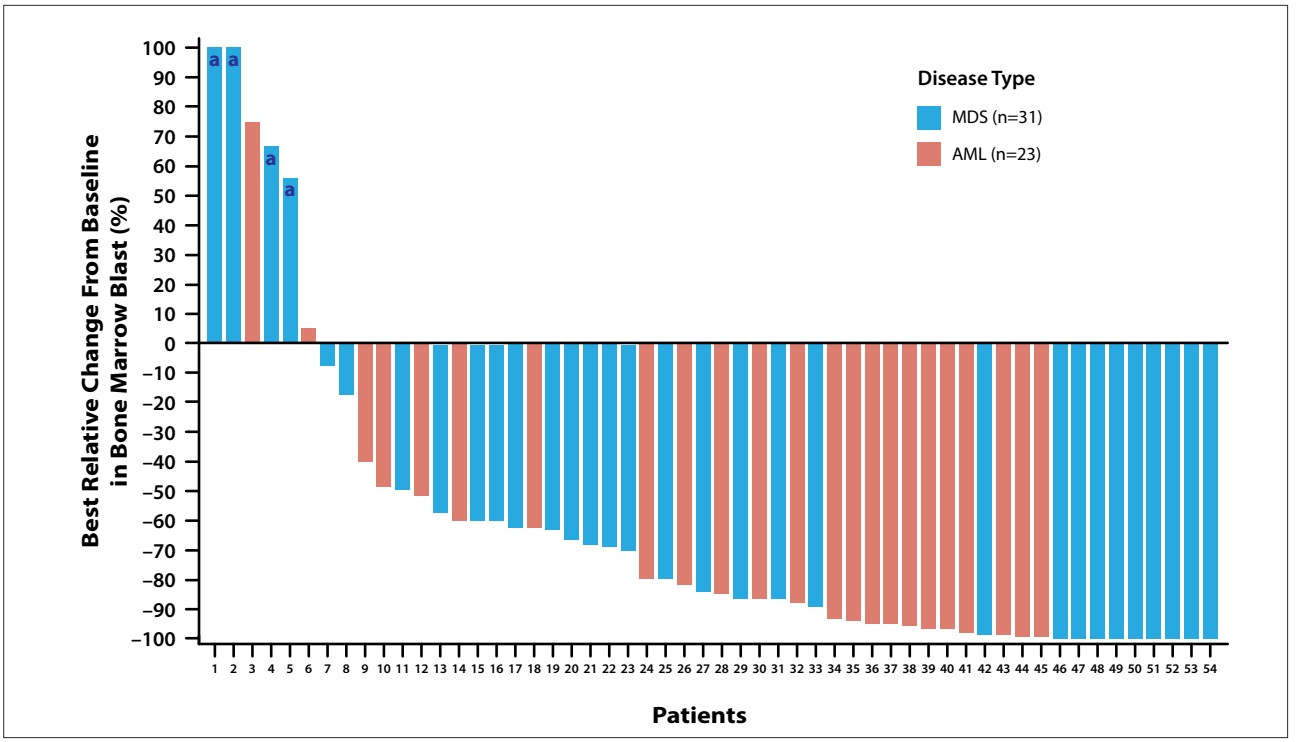


Figure 8. The best relative change from baseline in bone marrow blasts among patients with MDS or AML treated with magrolimab plus azacitidine in the phase 1b 5F9005 study. [a]The baseline bone marrow blasts were ≤5%. AML, acute myeloid leukemia; MDS, myelodysplastic syndromes. Adapted from Sallman DA et al. ASCO abstract 7507. *J Clin Oncol.* 2020;38(15 suppl).[7]

priming dose of magrolimab. This priming dose resulted in a transient mild hemoglobin reduction with the first dose, which then returned to the baseline level. Most patients showed significant hemoglobin improvement and a decrease in transfusion frequency over time.[6,7]

The objective response rate for the combination of magrolimab plus azacitidine was 91% in patients with MDS and 64% in those with AML (Figure 8). The rate of complete remission was 42% in patients with MDS. In patients with AML, the rate of complete remission, including cases of complete remission with incomplete hematologic recovery, was 56%. Responses deepened over time, with a 56% rate of complete remission at 6 months in patients with MDS. The median time to response, 1.9 months, was more rapid than that typically observed with azacitidine alone. After a median follow-up of 5.8 months in the MDS group and 9.4 months in the AML group, the median duration of response was not reached.[6,7]

The rate of RBC-TI was 58% in patients with MDS and 64% in those with AML. Complete cytogenetic responses and minimal residual disease negativity were observed in both groups. The median overall survival had not been reached in either group.[6,7]

A subgroup analysis showed that magrolimab plus azacitidine was active in patients with a *TP53* mutation, resulting in a 75% objective response rate in 4 patients with MDS and 12 patients with AML. The median duration of response was not reached in patients with the *TP53* mutation in either group. Additionally, the combination dramatically reduced the *TP53* mutational burden during treatment.[6,7]

Expansion cohorts are ongoing in both MDS and AML. A registrational study is in progress for MDS and planned for AML patients with the *TP53* mutation.[8]

References

1. Veillette A, Tang Z. Signaling regulatory protein (SIRP)α-CD47 blockade joins the ranks of immune checkpoint inhibition. *J Clin Oncol.* 2019;37(12):1012-1014.
2. Chao MP, Weissman IL, Majeti R. The CD47-SIRPα pathway in cancer immune evasion and potential therapeutic implications. *Curr Opin Immunol.* 2012;24(2):225-232.
3. Majeti R, Chao MP, Alizadeh AA, et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. *Cell.* 2009;138(2):286-299.
4. Sikic BI, Lakhani N, Patnaik A, et al. First-in-human, first-in-class phase I trial of the anti-CD47 antibody Hu5F9-G4 in patients with advanced cancers. *J Clin Oncol.* 2019;37(12):946-953.
5. Feng D, Phung G, McKenna K, et al. Combination treatment with 5F9 and azacitidine enhances phagocytic elimination of acute myeloid leukemia [ASH abstract 616]. *Blood.* 2018;132(suppl 1).
6. Sallman DA, Asch A, Al-Malki M, et al. The first-in-class anti-CD47 antibody magrolimab combined with azacitidine is well-tolerated and effective in MDS patients: phase 1b results. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S187.
7. Sallman DA, Asch A, Al-Malki M, et al. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: phase Ib results [ASCO abstract 7507]. *J Clin Oncol.* 2020;38(15 suppl).
8. ClinicalTrials.gov. Magrolimab monotherapy or magrolimab in combination with azacitidine in patients with hematological malignancies. https://clinicaltrials.gov/ct2/show/NCT03248479. Identifier: NCT03248479. Accessed August 28, 2020.

Effects of Luspatercept on Serum Ferritin in Patients With Lower-Risk Myelodysplastic Syndromes With Ring Sideroblasts in the Phase 3 MEDALIST Trial

Fenaux and colleagues evaluated levels of serum ferritin and use of iron chelation therapy among patients enrolled in the MEDALIST trial. They calculated changes in mean serum ferritin levels and in the mean daily dose of iron chelation therapy through weeks 9 to 24 and weeks 33 to 48. Both outcomes were reported as LSM values, which were estimated post hoc from an adjusted analysis of covariance model. The data cutoff was May 8, 2018.

Among HTB patients, the median serum ferritin level was 1306.1 µg/L in the luspatercept arm and 1492.9 µg/L in the placebo arm. At baseline, iron chelation therapy was reported in 75.8% and 78.8% of these patients, respectively.

Among all patients, from baseline to weeks 9 to 24, levels of mean serum ferritin decreased by 2.7 µg/L in the luspatercept arm but increased by 226.5 µg/L in the placebo arm (P=.0024; Figure 9). From weeks 33 to 48, levels decreased by 72.0 µg/L in the luspatercept arm and increased by 247.4 µg/L in the placebo arm (P=.0294). Among HTB patients, the LSM change from baseline to weeks 9 to 24 was –63.5 µg/L with luspatercept vs 271.2 µg/L with placebo (P=.0103). Both groups had decreases at weeks 33 to 48 (–7.0 µg/L vs –19.0 µg/L, respectively). The number of HTB patients in the placebo arm was small (n=6).

In this post hoc multivariate analysis, the mean serum ferritin levels decreased by 26.1 µg/L in the luspatercept arm but increased by 255.2 µg/L in the placebo arm from baseline to weeks 9 to 24. Over weeks 33 to 48, serum ferritin levels decreased by 132.0 µg/L with luspatercept and increased by 705.8 µg/L with placebo. In HTB patients treated with luspatercept, the LSM change from baseline in mean serum ferritin levels was +0.6 µg/L over weeks 9 to 24 and –178.0 µg/L over weeks 33 to 48.

Among patients with an HI-E response, the LSM change from baseline in serum ferritin levels averaged over weeks 9 to 24 (weeks 1 to 24) was –102.3 µg/L in the luspatercept arm compared with +60.4 µg/L in the placebo arm (P=.3442). Among the HTB patients with an HI-E response, the LSM change from baseline in serum ferritin levels was –111.4 µg/L in the luspatercept arm and +8.6 µg/L in the placebo arm. A significant difference in the mean serum ferritin change from baseline was also observed between treatment arms among HI-E patients who did not respond to therapy, with increases of 73.4 µg/L in patients who received luspatercept vs 244.2 µg/L in

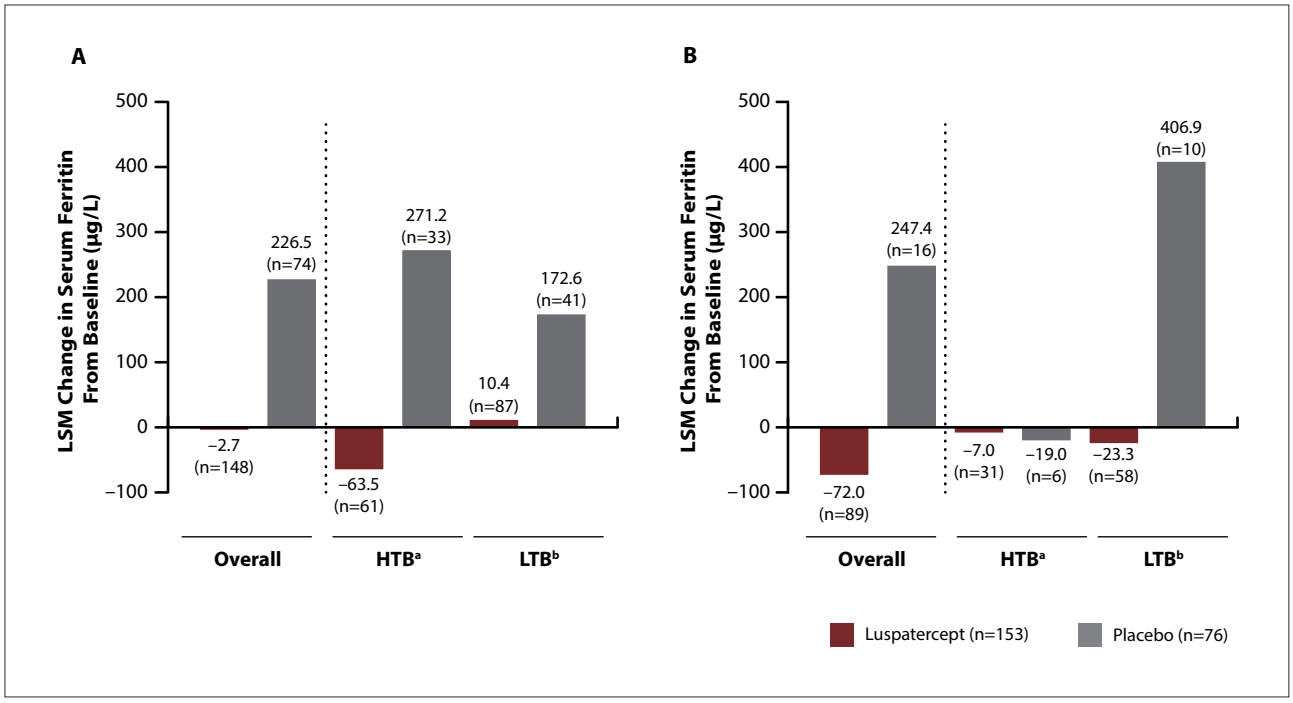


Figure 9. Changes in levels of serum ferritin among patients in the MEDALIST trial. [a]HTB was defined as a baseline transfusion burden of ≥6 RBC units/8 weeks. [b]LTB was defined as a baseline transfusion burden of <6 RBC units/8 weeks. HTB, high transfusion burden; LSM, least square mean; LTB, low transfusion burden. Adapted from Fenaux P et al. EHA25 abstract EP807.[1]

those who received placebo (*P*=.0777).

In the 12 weeks immediately before the first dose of the study drug, the mean daily dose of iron chelation therapy in patients in the luspatercept arm was 1408.9 mg, which decreased to 973.7 mg during the 12 weeks prior to study discontinuation. The LSM change from baseline in the mean daily dose of iron chelation therapy in luspatercept-treated patients was +10.0 mg/day over weeks 9 to 24 and –148.8 mg/day over weeks 33 to 48. Among treated HTB patients who received luspatercept, the LSM change from baseline in the mean daily dose of iron chelation therapy was –68.5 mg/day over weeks 9 to 24 and –327.1 mg/day over weeks 33 to 48.

All luspatercept-treated patients who received iron chelation therapy at baseline developed at least 1 treatment-emergent adverse event of any grade. Of these, 56.3% had at least 1 grade 3/4 treatment-emergent adverse event. Among luspatercept-treated patients who did not receive iron chelation therapy at baseline, 97.6% had at least 1 treatment-emergent adverse event of any grade; the event was grade 3/4 in 53.7%.

Reference

1. Fenaux P, Santini V, Mufti GJ, et al. Effects of luspatercept on serum ferritin in patients with lower-risk myelodysplastic syndromes with ring sideroblasts in the phase 3 MEDALIST trial. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract EP807.

Phase 2 Study of Pevonedistat + Azacitidine Versus Azacitidine in Patients With Higher-Risk Myelodysplastic Syndromes/Chronic Myelomonocytic Leukemia or Low-Blast Acute Myelogenous Leukemia

Pevonedistat is a small-molecule inhibitor of the NEDD8-activating enzyme (NAE). Active NAE in cancer cells allows for ubiquitination and subsequent degradation of select regulatory proteins, which culminates in the cell's ability to maintain growth and survival. Pevonedistat-mediated inhibition of NAE leads to inhibition of several critical cellular processes, including DNA replication, cell cycle progression, and NF-kB signaling. As a result, the cancer cell undergoes apoptosis.[1,2]

Preclinical studies have suggested that pevonedistat works synergistically with decitabine and azacitidine. The combination of pevonedistat plus azacitidine resulted in significantly increased DNA damage and more cell death as compared with either agent alone.[3] An early phase 1b clinical study evaluated pevonedistat combined with azacitidine in patients with treatment-naive AML who were considered unfit for standard induction therapy.[4] The combination was well tolerated. In addition, the timing and frequency of the responses suggested that this combination offered a potential clinical benefit over single-agent azacitidine.[4]

Adés and colleagues conducted a phase 2 clinical study of pevonedistat plus azacitidine in patients with hematologic malignancies.[5,6] The study had a randomized, open-label design and was conducted across multiple centers globally. Enrolled patients had higher-risk MDS (n=67), high-risk chronic myelomonocytic leukemia (CMML; n=17), or AML with low blast percentage (n=36). The trial excluded patients with prior exposure to hypomethylating agents. Enrollment was limited to patients considered ineligible for stem cell transplant.

The trial randomly assigned 120 patients in a 1:1 ratio to receive 28-day cycles of pevonedistat (20 mg/m^2 IV on days 1, 3, and 5) plus azacitidine or azacitidine alone. In both regimens, the dose of azacitidine was 75 mg/m^2 (IV or subcutaneously) on days 1 to 5, 8, and 9. Stratification factors included the IPSS-R risk category (intermediate, high, or very high) for patients with MDS or CMML, as well as low-blast AML. Event-free survival was the original primary endpoint. Overall survival was added as a co–primary endpoint based on regulatory feedback after enrollment. The objective response rate was a secondary endpoint.[5,6]

At baseline, the median age of patients was 74 years (range, 47-91) in the combination arm and 71 years (range, 34-81) in the single-agent arm. Patients with higher-risk MDS were relatively evenly divided across IPSS-R risk groups. The category of refractory anemia with excess blasts was 1 in 38% of patients and 2 in 56% of patients.[5,6]

The primary endpoint of event-free survival was defined as the time to death or transformation to AML in patients with higher-risk MDS/CMML, and by the time of death in patients with low-blast AML. Among patients in the intention-to-treat population, the median event-free survival was 21.0 months with pevonedistat plus azacitidine vs 16.6 months with single-agent azacitidine (HR, 0.665; 95% CI, 0.423-1.047; *P*=.076). A prespecified analysis of event-free survival indicated that the combination of pevonedistat plus azacitidine was favored across nearly all subgroups. The exceptions were patients at intermediate risk and those who had an ECOG performance

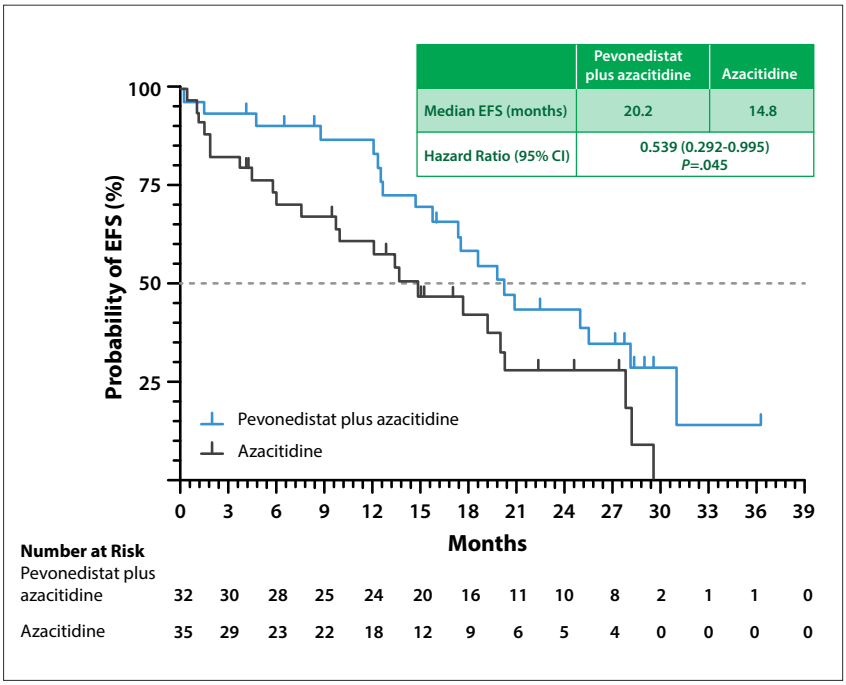


Figure 10. Median event-free survival among patients with higher-risk myelodysplastic syndromes treated with pevonedistat plus azacitidine or single-agent azacitidine in a phase 2 study. EFS, event-free survival. Adapted from Adés L et al. ASCO abstract 7506. *J Clin Oncol.* 2020;38(15 suppl).[5]

status of 2 (although this group had only 5 patients). In the intention-to-treat population, the median overall survival was 21.8 months with the combination vs 19.0 months with monotherapy (HR, 0.802; 95% CI, 0.512-1.256; *P*=.334).[5,6]

Among patients with higher-risk MDS, the median event-free survival was 20.2 months with pevonedistat plus azacitidine vs 14.8 months with single-agent azacitidine (HR, 0.539; 95% CI, 0.292-0.995; *P*=.045; Figure 10). In this patient subgroup, the median overall survival also favored the combination, but the difference was not statistically significant (23.9 vs 19.1 months, respectively; HR, 0.701; 95% CI, 0.386-1.273; *P*=.240). In the patients with low-blast AML, the median event-free survival was 23.6 months with pevonedistat plus azacitidine vs 16.0 months with azacitidine alone (HR, 0.494; 95% CI, 0.220-1.109; *P*=.081). (For patients with AML, the investigators considered event-free survival equivalent to overall survival.) In patients with higher-risk CMML, the combination of pevonedistat plus azacitidine was associated with worse outcomes. Event-free survival was 21.0 months with the combination vs not estimable for monotherapy (HR, 4.302; 95% CI, 0.791-23.407). Overall survival was 21.7 months vs not estimable, respectively (HR, 7.519; 95% CI, 1.362-41.510; *P*=.010).[5,6]

Among patients in the intention-to-treat population who were evaluable for response, the objective response rate was 70.9% with pevonedistat plus azacitidine vs 60.4% with azacitidine alone. Complete remissions occurred in 40.0% vs 30.2%, respectively. The median duration of response was 20.6 months with the combination of pevonedistat plus azacitidine vs 13.1 months for azacitidine alone.[5,6]

The toxicity profiles were relatively similar between the treatment arms. The median azacitidine dose intensity also remained comparable, at 96.9% with the combination and 98.2% with monotherapy. However, the median number of azacitidine treatment cycles was slightly higher with pevonedistat plus azacitidine (13.0) compared with single-agent azacitidine (8.5).[5,6]

An adverse event led to treatment discontinuation in 17% of the combination arm vs 21% of the monotherapy arm. The most common grade 3 or higher adverse events included neutropenia (33% vs 27%), febrile neutropenia (26% vs 29%), neutrophil count decrease (21% vs 10%), anemia (19% vs 27%), thrombocytopenia (19% vs 23%), and pneumonia (12% vs 10%).[5,6]

References

1. Soucy TA, Smith PG, Milhollen MA, et al. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. *Nature.* 2009;458(7239):732-736.
2. Brownell JE, Sintchak MD, Gavin JM, et al. Substrate-assisted inhibition of ubiquitin-like protein-activating enzymes: the NEDD8 E1 inhibitor MLN4924 forms a NEDD8-AMP mimetic in situ. *Mol Cell.* 2010;37(1):102-111.
3. Smith PG, Traore T, Grossman S, et al. Azacitidine/decitabine synergism with the NEDD8-activating enzyme inhibitor MLN4924 in pre-clinical AML models [ASH abstract 578]. *Blood.* 2011;118(21).
4. Swords RT, Coutre S, Maris MB, et al. Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML. *Blood.* 2018;131(13):1415-1424.
5. Adés L, Watts J, Radinoff A, et al. Phase II study of pevonedistat + azacitidine versus A in patients with higher-risk myelodysplastic syndromes/chronic myelomonocytic leukemia, or low-blast acute myelogenous leukemia [ASCO abstract 7506]. *J Clin Oncol.* 2020;38(15 suppl).
6. Adés L, Watts J, Radinoff A, et al. Phase 2 study of pevonedistat + azacitidine versus azacitidine in patients with higher-risk myelodysplastic syndromes/chronic myelomonocytic leukemia or low-blast acute myelogenous leukemia. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S182.

Highlights in Myelodysplastic Syndromes From the 2020 American Society of Clinical Oncology Annual Meeting and the 25th European Hematology Association Congress: Commentary

Guillermo Garcia-Manero, MD

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

The 2020 American Society of Clinical Oncology (ASCO) annual meeting and the 25th European Hematology Association (EHA25) congress were presented in virtual formats. At both meetings, several abstracts provided important data for the management of myelodysplastic syndromes (MDS). Data were presented for luspatercept, imetelstat, venetoclax, and several novel agents.

Luspatercept

Luspatercept is an antibody that modulates transforming growth factor beta signaling in MDS.[1] This drug was recently approved in the United States to treat anemia in adults with MDS with ring sideroblasts or myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis who require regular red blood cell transfusions and have not responded to or cannot receive an erythropoiesis-stimulating agent (ESA).[2] Luspatercept also has an indication for patients with beta thalassemia. In the MDS frontline setting, luspatercept is being compared with ESAs.[3]

At the 2020 ASCO meeting and the EHA25 congress, there were several updates of the ongoing phase 3 MEDALIST trial (A Study of Luspatercept [ACE-536] to Treat Anemia Due to Very Low, Low, or Intermediate Risk Myelodysplastic Syndromes), which compared luspatercept vs placebo among patients with MDS and anemia who were previously treated with ESA and who required red blood cell transfusions. Results of the MEDALIST trial were initially presented at the plenary session of the 2018 American Society of Hematology (ASH) meeting and were recently published in the *New England Journal of Medicine*.[4,5] The primary endpoint was red blood cell transfusion independence of 8 weeks or longer during weeks 1 to 24. This endpoint was met by 38% of patients treated with luspatercept (n=153) vs 13% of those treated with placebo (n=76; $P<.001$). The key secondary endpoint was red blood cell transfusion independence for at least 12 weeks (weeks 1-24 and weeks 1-48). At weeks 1 to 12, this endpoint was met by 28% of patients treated with luspatercept vs 8% of those treated with placebo ($P<.001$). For weeks 1 to 48, this endpoint was met by 33% vs 12%, respectively ($P<.001$).

At the ASCO meeting, Dr Amer Zeidan and colleagues presented an update of the clinical benefit of luspatercept that differentiated between patients with low (LTB) or high transfusion burden (HTB).[6] LTB patients were those who had received less than 6 red blood cell units in the previous 8 weeks before study enrollment, and HTB patients were those who had received 6 or more. The response rates with luspatercept differed based on the transfusion burden before initiation of treatment. Hematologic improvement (erythroid) was achieved by 58.8% of patients in the luspatercept group overall, 56.1% of those with HTB, and 60.9% of those with LTB. An analysis from Dr Rami Komrokji provided longer follow-up for the MEDALIST trial.[7] As of the data cutoff on July 1, 2019, the median follow-up was 26.4 months in the luspatercept arm and 26.1 months in the placebo arm. The primary endpoint of red blood cell transfusion independence of 8 weeks or longer during weeks 1 to 24 was reported in 37.9% of the luspatercept arm vs 13.2% of the placebo arm ($P<.0001$). This transfusion-free period was met at any point during the study by 47.7% of the luspatercept group vs 15.8% of the placebo group ($P<.0001$). A reduction of 50% or more in red blood cell transfusion burden from baseline for at least 24 weeks was met by 50.3% vs 14.5%, respectively ($P<.0001$).

At the EHA25 congress, Dr Uwe Platzbecker and colleagues presented an analysis of the MEDALIST trial that focused on the dose-dependent response.[8] Most luspatercept patients with a baseline transfusion burden of 6 or fewer red blood cell units/8 weeks who achieved transfusion independence of at least 8 weeks within the first 48 weeks achieved their first response at a dose of 1.0 mg/kg. An additional 11% of patients in this group (and approximately 17% of responders overall) achieved their first

response with higher doses of 1.33 mg/kg and 1.75 mg/kg. Dose escalations led to maintenance of transfusion independence of 8 weeks or longer or achievement of multiple response episodes. The study found no dose-dependent increases in treatment-emergent adverse events.

Also at the EHA25 congress, Dr Pierre Fenaux and coworkers reported on the impact of luspatercept on ferritin levels among patients in the MEDALIST trial.[9] Iron accumulation is an important topic for patients with lower-risk MDS who are transfusion-dependent. Ferritin is a surrogate marker for iron accumulation. The analysis showed that patients treated with luspatercept experienced a more profound and deeper decrement in the levels of ferritin as opposed to those who received placebo. A decrease in the mean serum ferritin from baseline was observed with luspatercept, but not placebo, over weeks 9 to 24 (least squares mean, −2.7 µg/L vs +226.5 µg/L; *P*=.0024) and weeks 33 to 48 (least squares mean, −72.0 µg/L vs +247.4 µg/L; *P*=.0294). These results further support the clinical activity of luspatercept in improving anemia.

CC-486

An important issue in low-risk MDS is the role of hypomethylating agents, such as azacitidine and decitabine. Traditionally, these drugs have not been systematically studied in this context. Data from the MD Anderson group have shown that attenuated dose-escalating regimens of decitabine or azacitidine are safe and can have significant activity in patients with low-risk MDS.[10] At the EHA25 congress, I presented the results of a large multicenter phase 3 trial of CC-486 for patients with lower-risk MDS who were dependent on red blood cell transfusion and who had significant thrombocytopenia.[11] The novel agent CC-486 is an oral formulation of azacitidine. This oral formulation is associated with a different pharmacokinetic profile compared with injectable azacitidine.[12] CC-486 has been extensively studied in prior phase 1 and 2 trials. At the 2019 ASH meeting, a study showed a survival benefit with CC-486 among patients with acute myelogenous leukemia (AML) treated with CC-486 as maintenance therapy.[13] The phase 3 trial presented at the EHA25 congress randomly assigned patients with MDS who were dependent on red blood cell transfusions and who had thrombocytopenia to treatment with CC-486 or placebo.[11] This multicenter, international trial enrolled 216 patients. The primary endpoint was the rate of independence from red blood cell transfusions for 56 days or longer. This endpoint was reached by 30.8% of the CC-486 arm vs 11.1% of the placebo arm (*P*=.0002). Platelet levels also improved among patients treated with CC-486. There was not, however, an improvement in overall survival. There was an imbalance in terms of early mortality with CC-486 vs placebo, meaning that there were excess deaths early on in the subset of patients who had significant neutropenia after treatment with this compound.

This study is complex to analyze. The improvements in transfusion independence and platelets did not lead to an increase in overall survival. In addition, CC-486 was associated with myelosuppression. The study targeted a group of patients with low-risk disease but who had a poor prognosis. According to criteria from the Revised International Prognostic Scoring System, many of these patients with thrombocytopenia and significant anemia would be considered at high risk. However, the key message of this trial is that CC-486 can improve hematopoiesis in patients with low-risk disease. Further studies are needed, perhaps with different dose-escalating scenarios to limit toxicity and early mortality, in order to see a benefit in overall survival.

Imetelstat

Dr Uwe Platzbecker and colleagues presented an analysis of the phase 2/3 IMerge trial of imetelstat among patients with relapsed or refractory, lower-risk MDS.[14] Imetelstat modifies polymerase activity. The data that are starting to accumulate suggest that this compound has significant activity in improving the rate of transfusion independence in patients with non-del(5q) MDS that has already been treated with an ESA. There are some data to suggest that imetelstat may also inhibit hematopoiesis. Some patients treated with imetelstat develop early toxicities of neutropenia and thrombocytopenia. Studies of imetelstat in other diseases, such as myelofibrosis, have shown a high rate of response.[15] Longer follow-up studies are needed to provide a better understanding of the molecular mechanism of action of imetelstat. Dr Platzbecker provided results from the phase 2 portion of the study.[14] Imetelstat achieved an 8-week transfusion independence rate of 42%, a high rate of response.

Other Novel Treatments

APR-246 is a prodrug of a compound known as methylene quinuclidinone (MQ) that binds to TP53 protein and stabilizes its function. This agent has significant antileukemia activity when combined with azacitidine.[16] Investigators recently completed a major phase 3 registration trial of azacitidine with or without APR-246.[17] APR-246 is an option specifically for patients with *TP53*-mutated disease. Results from studies of APR-246 plus azacitidine were presented at recent meetings.[18,19] A study conducted in North America was presented at the 2019 ASH meeting.[18] A study conducted in Europe was presented at the EHA25 congress by Dr Thomas Cluzeau.[19] In this study, APR-246 plus azacitidine was associated with a high rate of response, including cytogenetic and molecular responses, in patients with *TP53*-mutated MDS. The overall response rate was 77% among 39 evaluable patients, including a complete response rate of 49%.

Four patients underwent allogeneic stem cell transplant.

Data from the original phase 1/2 studies suggested that survival might be increased among patients with *TP53*-mutated disease treated with hypomethylating agents, but not with APR-246. Results of a phase 3 registration trial are expected later this year or early next year.[17] APR-246 could be one of the first drugs approved for *TP53*-mutated disease, which is currently associated with an almost universally fatal outcome.

Dr David Sallman presented phase 1b results from a study of magrolimab combined with azacitidine in untreated patients with MDS or AML. Results were presented at the EHA25 congress and the 2020 ASCO meeting.[20,21] Magrolimab is a macrophage immune checkpoint inhibitor antibody that targets CD47. This is a new pathway, and an immune checkpoint that modulates macrophages instead of lymphocytes. Magrolimab blocks the antibodies that moderate inhibitory signals in macrophages. Reactivating these macrophages could lead to significant anti-tumor activity. Studies of single-agent magrolimab reported limit activity.[22]

There may be some biologic rationale to combine magrolimab with azacitidine. In this study, the combination led to an overall response rate of 91% in patients with MDS and 64% in AML.[21] This is dramatic activity, particularly in the frontline, high-risk MDS and AML settings. Importantly, magrolimab had significant activity in a group of patients with *TP53*-mutated disease. This group of patients is typically resistant and refractory to treatment. Magrolimab is associated with hemolytic anemia, but it is possible to mitigate this toxicity without major complications for patients. The combination of magrolimab plus azacitidine is moving into registration trials in MDS, and potentially in AML. Data presented at the EHA25 congress and the 2020 ASCO meeting, as well as the 2019 ASH meeting, support the significant activity of this doublet.[20-22]

Pevonedistat inhibits neddylation, a mechanism by which proteins are modified intracellularly.[23] The combination of pevonedistat plus azacitidine is associated with clinical activity in both MDS and AML.[24,25] Dr Lionel Adès and colleagues presented results from a phase 2 study of pevonedistat plus azacitidine in patients with higher-risk MDS, higher-risk chronic myelomonocytic leukemia, or low-blast AML at the 2020 ASCO meeting and the EHA25 congress.[26,27] Among patients with MDS, event-free survival was 20.2 months with the combination vs 14.8 months with azacitidine alone (P=.045). Overall survival was 23.9 months vs 19.1 months, respectively, but this difference was not statistically significant (P=.240). The overall response rate was 79.3% with the combination vs 56.7% with single-agent azacitidine among patients with MDS. The median duration of response was 34.6 months vs 13.1 months. These data are promising. Results of a randomized study of azacitidine with or without pevonedistat are expected next year, and could lead to the approval of this agent for patients with MDS.[28]

At the EHA25 congress, Dr Amer Zeidan presented results from a phase 1b trial of venetoclax plus azacitidine in patients with relapsed/refractory MDS.[29] Data were previously presented at the 2019 ASH meeting,[30] and updated at the EHA25 congress. It is well-known that venetoclax exhibits significant activity when combined with azacitidine in patients with previously untreated AML.[31] Venetoclax is also being studied in frontline and relapsed MDS, including patients with high-risk disease and the so-called hypomethylating agent–failure phenotype. This phenotype is associated with a poor prognosis and a median survival of 4 to 6 months.[32] Currently, no drugs or other interventions are approved for this group of patients. The study by Dr Zeidan evaluated 3 difference doses of venetoclax in combination with azacitidine in 44 patients. The overall response rate was 41%. At 12 months, the median rate of progression-free survival was 31%. The 12-month rate of overall survival was 66%. This survival was longer than expected based on previous studies, such as the randomized trial of rigosertib.[33] These important data may have value for this group of patients with hypomethylating-failure MDS, who are difficult to treat. Venetoclax is already known to have significant activity in AML and frontline high-risk MDS.

MBG453, like magrolimab, represents a new class of immune checkpoint inhibitors. MBG453 targets TIM-3, which regulates immunity in the lymphoid compartment. TIM-3 is an important molecule in the signaling of these cells. At the EHA25 congress, Dr Uma Borate presented results from a phase 1 study of MBG453 plus either decitabine or azacitidine in patients with high-risk MDS and AML.[34] Patients could have treatment-naive or relapsed disease. Previous results were presented at the 2019 ASH meeting.[35]

The doublet was well-tolerated in this study. It did not appear to have some of the toxicities reported with the classic immune checkpoint inhibitors, such as programmed cell death protein 1 (PD-1) or anti–cytotoxic T-lymphocyte–associated protein 4 (CTLA-4). Among the 32 patients with MDS, the overall response rates were 61.1% with MBG453 plus decitabine vs 57.1% with MBG453 plus azacitidine. Patients with a response had been enrolled in the study for a median of 8 months. This level of activity is higher in terms of response and durability of response than would be expected for either of the hypomethylating agents used alone. However, the data are still early. Several ongoing phase 2 studies are further elucidating the clinical activity of these doublets.

Disclosure

Dr Garcia-Manero has received grant or research support from Amphivena, Helsinn, Novartis, AbbVie, BMS, Astex, Onconova, H3 Biomedicine, and Merck. He is a paid consultant for BMS, Astex, and Helsinn.

References

1. Suragani RN, Cadena SM, Cawley SM, et al. Transforming growth factor-ß superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. *Nat Med.* 2014;20(4):408-414.
2. Reblozyl [package insert]. Summit, NJ: Celgene Corporation; 2020.
3. ClinicalTrials.gov. 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 (COMMANDS). https://clinicaltrials.gov/ct2/show/NCT03682536. Identifier: NCT03682536. Accessed August 27, 2020.
4. Fenaux P, Platzbecker U, Mufti GJ, et al. 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 (MDS) with ring sideroblasts (RS) who require red blood cell (RBC) transfusions [ASH abstract 1]. *Blood.* 2018;132(suppl 1).
5. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med.* 2020;382(2):140-151.
6. Zeidan AM, Garcia-Manero G, DeZern AE, et al. Clinical benefit of luspatercept in patients with lower-risk MDS and high transfusion burden in the phase III MEDALIST study [ASCO abstract 7554]. *J Clin Oncol.* 2020;38(15 suppl).
7. Komrokji RS, Sekeres MA, Zeidan AM, et al. Longer-term RBC transfusion reduction in the phase III MEDALIST study of luspatercept in patients with lower-risk MDS with ring sideroblasts study [ASCO abstract 7518]. *J Clin Oncol.* 2020;38(15 suppl).
8. Platzbecker U, Fenaux P, Mufti GJ, et al. Assessment of dose-dependent response to luspatercept in patients with lower-risk myelodysplastic syndromes with ring sideroblasts in the phase 3 MEDALIST trial. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract EP812.
9. Fenaux P, Santini V, Mufti GJ, et al. Effects of luspatercept on serum ferritin in patients with lower-risk myelodysplastic syndromes with ring sideroblasts in the phase 3 MEDALIST trial. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract EP807.
10. Garcia-Manero G, Gore SD, Cogle C, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. *J Clin Oncol.* 2011;29(18):2521-2527.
11. Garcia-Manero G, Santini V, Almeida A, et al. A phase III placebo-controlled trial of CC-486 in patients with red blood cell transfusion-dependent anemia and thrombocytopenia due to IPSS lower-risk myelodysplastic syndromes. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S180.
12. Garcia-Manero G, Gore SD, Cogle C, et al. Phase I study of oral azacitidine in myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. *J Clin Oncol.* 2011;29(18):2521-2527.
13. Wei AH, Döhner H, Pocock C, et al. The QUAZAR AML-001 maintenance trial: results of a phase III international, randomized, double-blind, placebo-controlled study of CC-486 (oral formulation of azacitidine) in patients with acute myeloid leukemia (AML) in first remission [ASH abstract LBA-3]. *Blood.* 2019;134(suppl 1).
14. Platzbecker U, Fenaux P, Steensma DP, et al. Treatment with imetelstat provides durable transfusion independence in heavily transfused non-del(5q) lower risk MDS relapsed/refractory to erythropoiesis stimulating agents. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S183.
15. Tefferi A, Lasho TL, Begna KH, et al. A pilot study of the telomerase inhibitor imetelstat for myelofibrosis. *N Engl J Med.* 2015;373(10):908-919.
16. Maslah N, Salomao N, Drevon L, et al. Synergistic effects of PRIMA-1^{Met} (APR-246) and 5-azacitidine in *TP53*-mutated myelodysplastic syndromes and acute myeloid leukemia. *Haematologica.* 2020;105(6):1539-1551.
17. ClinicalTrials.gov. APR-246 & azacitidine for the treatment of *TP53* mutant myelodysplastic syndromes (MDS). https://clinicaltrials.gov/ct2/show/NCT03745716. Identifier: NCT03745716. Accessed August 31, 2020.
18. Sallman DA, DeZern AE, Garcia-Manero G, et al. Phase 2 results of APR-246 and azacitidine (AZA) in patients with *TP53* mutant myelodysplastic syndromes (MDS) and oligoblastic acute myeloid leukemia (AML) [ASH abstract 676]. *Blood.* 2019;134(suppl 1).
19. Cluzeau T, Sebert M, Rahmé R, et al. APR-246 combined with azacitadine (AZA) in *TP53* mutated myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). A phase 2 study by the Groupe Francophone des Myélodysplasies (GFM). Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S181.
20. Sallman DA, Asch A, Al-Malki M, et al. The first-in-class anti-CD47 antibody magrolimab combined with azacitidine is well-tolerated and effective in MDS patients: phase 1b results. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S187.
21. Sallman DA, Asch A, Al-Malki M, et al. Tolerability and efficacy of the first-in-class anti-CD47 antibody magrolimab combined with azacitidine in MDS and AML patients: phase Ib results [ASCO abstract 7507]. *J Clin Oncol.* 2020;38(15 suppl).
22. Sallman DA, Donnellan WB, Asch AS, et al. The first-in-class anti-CD47 antibody Hu5F9-G4 is active and well tolerated alone or with azacitidine in AML and MDS patients: initial phase 1b results [ASCO abstract 7009]. *J Clin Oncol.* 2019;37(suppl).
23. Zhou L, Jiang Y, Luo Q, Li L, Jia L. Neddylation: a novel modulator of the tumor microenvironment. *Mol Cancer.* 2019;18(1):77.
24. Swords RT, Coutre S, Maris MB, et al. Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML. *Blood.* 2018;131(13):1415-1424.
25. Moyo TK, Watts JM, Skikne BS, et al. Preliminary results from a phase II study of the combination of pevonedistat and azacitidine in the treatment of MDS and MDS/MPN after failure of DNA methyltransferase inhibition [ASH abstract 4236]. *Blood.* 2019;134(suppl 1).
26. Adés L, Watts J, Radinoff A, et al. Phase II study of pevonedistat + azacitidine versus A in patients with higher-risk myelodysplastic syndromes/chronic myelomonocytic leukemia, or low-blast acute myelogenous leukemia [ASCO abstract 7506]. *J Clin Oncol.* 2020;38(15 suppl).
27. Adés L, Watts J, Radinoff A, et al. Phase 2 study of pevonedistat + azacitidine versus azacitidine in patients with higher-risk myelodysplastic syndromes/chronic myelomonocytic leukemia or low-blast acute myelogenous leukemia. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S182.
28. ClinicalTrials.gov. Pevonedistat plus azacitidine versus single-agent azacitidine as first-line treatment for participants with higher-risk myelodysplastic syndromes (HR MDS), chronic myelomonocytic leukemia (CMML), or low-blast acute myelogenous leukemia (AML) (PANTHER). https://clinicaltrials.gov/ct2/show/NCT03268954. Identifier: NCT03268954. Accessed August 27, 2020.
29. Zeidan AM, Pollyea DA, Garcia JS, et al. A phase 1b study evaluating the safety and efficacy of venetoclax in combination with azacitidine for the treatment of relapsed/refractory myelodysplastic syndrome. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S188.
30. Wei AH, Garcia JS, Borate U, et al. A phase 1b study evaluating the safety and efficacy of venetoclax in combination with azacitidine in treatment-naïve patients with higher-risk myelodysplastic syndrome [ASH abstract 568]. *Blood.* 2019;134(suppl 1).
31. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. *N Engl J Med.* 2020;383(7):617-629.
32. Ball BJ, Famulare CA, Stein EM, et al. Venetoclax and hypomethylating agents (HMAs) induce high response rates in MDS, including patients after HMA therapy failure. *Blood Adv.* 2020;4(13):2866-2870.
33. Garcia-Manero G, Navada SC, Fenaux P, et al. Phase 3, multi-center, international, randomized, double-blind, placebo controlled study of oral rigosertib + injectable azacitidine (AZA) versus injectable azacitidine in treatment-naive patients with higher-risk myelodysplastic syndrome (HR-MDS) [ASH abstract 4268]. *Blood.* 2019;134(suppl 1).
34. Borate U, Esteve J, Porkka K, et al. Anti-TIM-3 antibody MBG453 in combination with hypomethylating agents in patients with high-risk myelodysplastic syndrome and acute myeloid leukemia: a phase 1 study. Abstract presented at: the 25th European Hematology Association Congress; June 11-21, 2020. Abstract S185.
35. Zeidan AM, Miyazaki Y, Platzbecker U, et al. A randomized, double-blind, placebo-controlled, phase II study of MBG453 added to hypomethylating agents (HMAs) in patients (pts) with intermediate, high, or very high risk myelodysplastic syndrome (MDS): STIMULUS-MDS1 [ASH abstract 4259]. *Blood.* 2019;134(suppl 1).


H&O