

**A SPECIAL MEETING REVIEW EDITION**

## Highlights in Myelodysplastic Syndromes From the 62nd American Society of Hematology Annual Meeting and Exposition

A Review of Selected Presentations From the All-Virtual 62nd ASH Meeting and Exposition • December 5-8, 2020

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**Special Reporting on:**

- Efficacy and Safety of Luspatercept Treatment in Patients With Myelodysplastic Syndrome/Myeloproliferative Neoplasm With Ring Sideroblasts and Thrombocytosis: A Retrospective Analysis From the MEDALIST Study
- Decitabine Versus Hydroxyurea for Advanced Proliferative CMML: Results of the Emsco Randomized Phase 3 DACOTA Trial
- Health-Related Quality of Life Outcomes in Patients With Myelodysplastic Syndromes With Ring Sideroblasts Treated With Luspatercept in the MEDALIST Study
- Efficacy and Safety of Pevonedistat Plus Azacitidine Vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes From Study P-2001
- Effect of Luspatercept on Biomarkers of Erythropoiesis in Patients With Lower-Risk Myelodysplastic Syndromes in the MEDALIST Trial
- Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination With Azacitidine for the Treatment of Patients With Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study
- Duration of Response to Luspatercept in Patients Requiring Red Blood Cell Transfusions With Myelofibrosis – Updated Data From the Phase 2 ACE-536-MF-001 Study
- Phase 3 Study of Lenalidomide vs Placebo in Non-Transfusion Dependent Low Risk del(5q) MDS Patients – Interim Analysis of the European Sintra-REV Trial
- The COMMANDS Trial: A Phase 3 Study of the Efficacy and Safety of Luspatercept Versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low-, Low-, or Intermediate-Risk MDS in Erythropoiesis Stimulating Agent-Naive Patients Who Require RBC Transfusions

**PLUS Meeting Abstract Summaries**

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# BRING ERYTHROID MATURATION TO LIFE

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



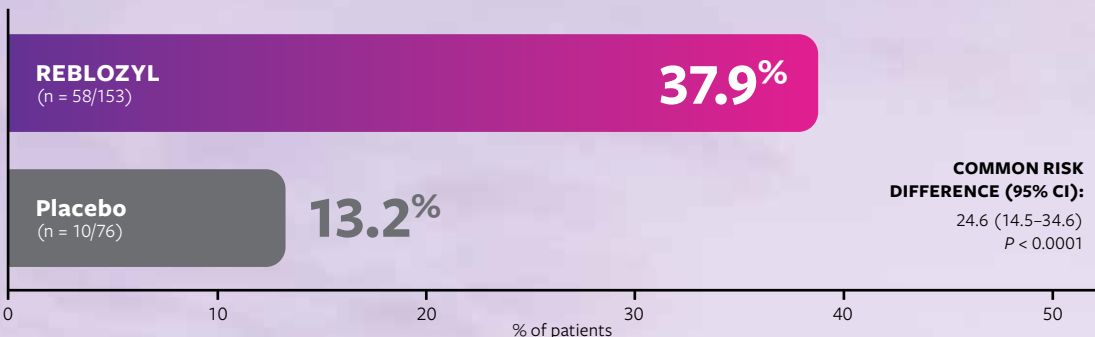
for patients with ring sideroblasts who are failing an ESA and require  $\geq 2$  RBC units/8 weeks<sup>1</sup>

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<sup>1</sup>

PRIMARY ENDPOINT: RBC-TI  $\geq 8$  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  $\geq 130$  mm Hg and 23 (16.4%) patients developed DBP  $\geq 80$  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  $\geq 3$  ( $\geq 2\%$ ) 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<sup>1</sup>

### 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	<b>28.1%</b> (43)	<b>7.9%</b> (6)	<b>20.0</b> (10.9, 29.1)	0.0002
RBC-TI ≥12 weeks during weeks 1–48 <sup>a</sup>	<b>33.3%</b> (51)	<b>11.8%</b> (9)	<b>21.4</b> (11.2, 31.5)	0.0003

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

<sup>a</sup>Includes MDS-EB-1, MDS-EB-2, and MDS-U.

<sup>b</sup>Includes patients who received 3.5 units.

<sup>c</sup>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](https://REBLOZYLpro.com/discoverMDS)



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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**

	<b>REBLOZYL Dosing Recommendation*</b>
<b>Starting Dose</b>	• 1 mg/kg every 3 weeks
<b>Dose Increases for Insufficient Response at Initiation of Treatment</b>	
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**

	<b>REBLOZYL Dosing Recommendation*</b>
<b>Dose Modifications for Predose Hemoglobin Levels or Rapid Hemoglobin Rise</b>	
Predose hemoglobin is greater than or equal to 11.5 g/dL in the absence of transfusions	<ul style="list-style-type: none"> <li>• Interrupt treatment</li> <li>• Restart when the hemoglobin is no more than 11 g/dL</li> </ul>
Increase in hemoglobin greater than 2 g/dL within 3 weeks in the absence of transfusions and <ul style="list-style-type: none"> <li>• current dose is 1.75 mg/kg</li> <li>• current dose is 1.33 mg/kg</li> <li>• current dose is 1 mg/kg</li> <li>• current dose is 0.8 mg/kg</li> <li>• current dose is 0.6 mg/kg</li> </ul>	<ul style="list-style-type: none"> <li>• Reduce dose to 1.33 mg/kg</li> <li>• Reduce dose to 1 mg/kg</li> <li>• Reduce dose to 0.8 mg/kg</li> <li>• Reduce dose to 0.6 mg/kg</li> <li>• Discontinue treatment</li> </ul>

\* 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**

	<b>REBLOZYL Dosing Recommendation*</b>
Grade 3 or 4 hypersensitivity reactions	• Discontinue treatment
Other Grade 3 or 4 adverse reactions	<ul style="list-style-type: none"> <li>• Interrupt treatment</li> <li>• When the adverse reaction resolves to no more than Grade 1, restart treatment at the next lower dose level**</li> <li>• If the dose delay is &gt; 12 consecutive weeks, discontinue treatment</li> </ul>

\* 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 (%)
<b>General disorders and administration site conditions</b>				
Fatigue <sup>a, b</sup>	63 (41)	11 (7)	17 (22)	2 (3)
<b>Musculoskeletal and connective tissue disorders</b>				
Musculoskeletal pain <sup>b</sup>	30 (20)	3 (2)	11 (14)	0 (0)
<b>Nervous system disorders</b>				
Dizziness/vertigo	28 (18)	1 (<1)	5 (7)	1 (1)
Headache <sup>b</sup>	21 (14)	0 (0)	5 (7)	0 (0)
Syncope / presyncope	8 (5)	5 (3)	0 (0)	0 (0)
<b>Gastrointestinal disorders</b>				
Nausea <sup>b</sup>	25 (16)	1 (<1)	8 (11)	0 (0)
Diarrhea <sup>b</sup>	25 (16)	0 (0)	7 (9)	0 (0)
<b>Respiratory, thoracic and mediastinal disorders</b>				
Dyspnea <sup>b</sup>	20 (13)	2 (1)	4 (5)	1 (1)
<b>Immune system disorders</b>				
Hypersensitivity reactions <sup>b</sup>	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 (%)
<b>Renal and urinary disorders</b>				
Renal impairment <sup>b</sup>	12 (8)	3 (2)	3 (4)	0 (0)
<b>Cardiac disorders</b>				
Tachycardia <sup>b</sup>	12 (8)	0 (0)	1 (1)	0 (0)
<b>Injury poisoning and procedural complications</b>				
Injection site reactions	10 (7)	0 (0)	3 (4)	0 (0)
<b>Infections and infestations</b>				
Upper respiratory tract infection	10 (7)	1 (<1)	2 (3)	0 (0)
Influenza / influenza like illness	9 (6)	0 (0)	2 (3)	0 (0)

<sup>a</sup> Includes asthenic conditions.

<sup>b</sup> 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 <sup>a</sup>	n (%)	N <sup>a</sup>	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)

<sup>a</sup> 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  $\geq$  65 years of age and 93 (36%) patients  $\geq$  75 years of age. No differences in safety or effectiveness were observed between older ( $\geq$  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:

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Cambridge, MA 02139

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RBZ\_HCP\_MDS BS\_v001\_04-2020

## Efficacy and Safety of Luspatercept Treatment in Patients With Myelodysplastic Syndrome/Myeloproliferative Neoplasm With Ring Sideroblasts and Thrombocytosis: A Retrospective Analysis From the MEDALIST Study

Some of the myeloid neoplasms that are associated with the erythroid precursors ring sideroblasts (RS) include myelodysplastic syndromes (MDS), myeloproliferative neoplasms (MPN), and MDS/MPN overlap syndromes. MDS/MPN with RS and thrombocytosis (MDS/MPN-RS-T) was officially classified by the World Health Organization in their 2016 revision recommendations.<sup>1,2</sup> One of the primary complications that patients with MDS/MPN-RS-T experience is anemia; in one retrospective analysis, transfusion dependence occurred in approximately half of patients with this disease.<sup>3</sup>

Luspatercept is a first-in-class erythroid maturation agent that binds transforming growth factor- $\beta$  (TGF $\beta$ ) superfamily ligands, thus reducing Smad2/3 signaling and ultimately promoting late-stage erythropoiesis.<sup>4</sup> Luspatercept is indicated for the treatment of anemia failing an erythropoiesis-stimulating agent (ESA) and requiring 2 or more red blood cell (RBC) units over 8 weeks in adult patients with very low- to intermediate-risk MDS-RS or with MDS/MPN-RS-T.<sup>5</sup> In the randomized, double-blind, placebo-controlled, phase 3 MEDALIST study, luspatercept significantly reduced transfusion burden vs placebo in patients with lower-risk MDS.<sup>6</sup> Komrokji and colleagues presented a retrospective analysis of the MEDALIST trial which focused on patients with MDS/MPN-RS-T. The cut-off date for this data analysis was July 1, 2019.<sup>7</sup>

The MEDALIST trial enrolled patients with MDS with at least 15% or more RS or at least 5% or more RS with the *SF3B1* mutation, and fewer than 5% blasts in the bone marrow.

Patients had very low-, low-, or intermediate-risk MDS according to the Revised International Prognostic Scoring System (IPSS-R), and had received no prior treatment with disease-modifying agents such as immunomodulatory drugs or hypomethylating agents. Patients were required to have an average RBC transfusion burden of 2 or more units every 8 weeks, and the primary endpoint of MEDALIST was the achievement of RBC transfusion independence (RBC-TI) for 8 or more weeks during Weeks 1 to 24. Patients were randomized in a 2-to-1 fashion to treatment with either luspatercept (1.0 mg/kg, titrated up to 1.75 mg/kg) or placebo subcutaneously every 21 days.<sup>6</sup>

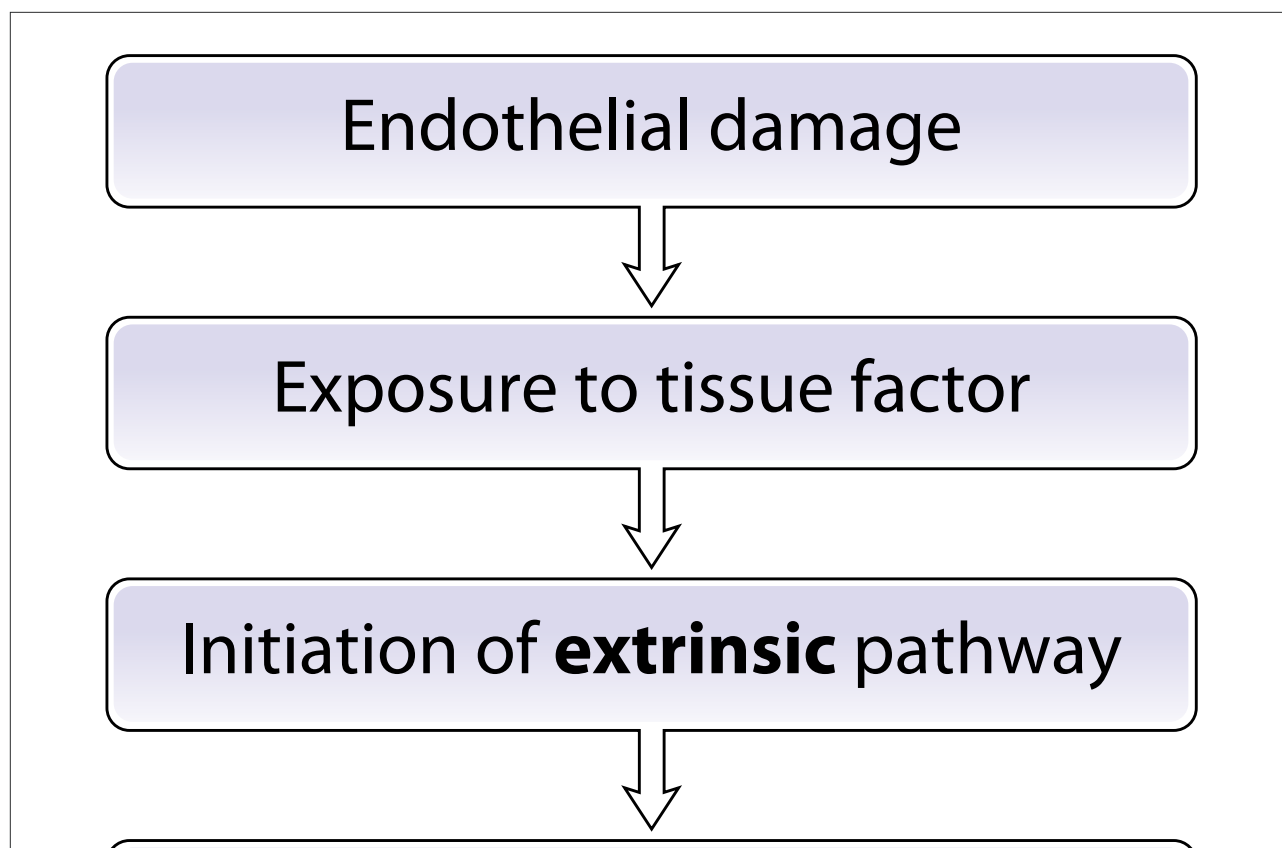
A total of 23 patients in the MEDALIST trial had MDS/MPN-RS-T (14 randomized to luspatercept and 9 to placebo), with a median age of 69.0 years (range: 26.0-83.0). At baseline, 43.5% had a RBC transfusion burden of fewer than 4 units over 8 weeks; 39.1% had a RBC transfusion burden of 4 to fewer than 6 units over 8 weeks; and 17.4% had a RBC transfusion burden of 6 or more units over 8 weeks. A total of 91.3% of patients had received an ESA; 87.0% previously discontinued ESA therapy. The majority (91.3%) of patients harbored a *SF3B1* gene mutation. The median platelet count was  $447.0 \times 10^9/L$  (range: 327.0-892.0), and the median leukocyte count was  $5.1 \times 10^9/L$  (range: 2.5-12.9).<sup>7</sup>

As shown in Figure 1, among patients with MDS/MPN-RS-T, a significantly higher proportion of patients receiving luspatercept achieved the primary endpoint of RBC-TI for 8 or more weeks during Weeks 1 to 24 compared to placebo (64.3% vs 22.2%, respectively,  $P=.028$ ).<sup>7</sup> The study

investigators noted that this was comparable to the results from the entire MEDALIST trial population (38% luspatercept vs 13% placebo).<sup>6</sup> Further, patients who achieved the primary endpoint were more likely to achieve durable RBC-TI for 48 weeks or more at any time during treatment (4 out of 10 luspatercept-treated patients and 0 placebo-treated patients). Among all MDS/MPN-RS-T patients, RBC-TI for 48 weeks or more at any time during treatment was observed in 4 of 14 luspatercept-treated patients (28.6%) compared with 0 of 9 placebo-treated patients ( $P=.084$ ).<sup>7</sup>

The rate of modified hematologic improvement-erythroid (mHI-E) was higher with luspatercept (71.4%) vs placebo (11.1%) in this population of patients with MDS/MPN-RS-T. Patients receiving luspatercept were also significantly more likely to achieve the composite endpoint of clinical benefit (defined as achievement of RBC-TI for 8 or more weeks and/or mHI-E during Weeks 1 to 24) compared with placebo (78.6% vs 33.3%, respectively,  $P=.034$ ). Both of these endpoints are shown in Figure 1.<sup>7</sup>

Compared with high transfusion burden patients (baseline transfusion burden of 4 or more units over 8 weeks), low transfusion burden patients (baseline transfusion burden of fewer than 4 units over 8 weeks), were more likely to achieve the primary endpoint of RBC-TI for 8 weeks or more during Weeks 1 to 24. The primary endpoint was achieved in 5 of 6 luspatercept-treated patients (2 of 4 placebo-treated patients) in the low transfusion burden group, and in 4 of 8 luspatercept-treated patients (0 of 5 placebo-treated patients) in the high transfusion burden group.<sup>7</sup>



**Figure 1.** Rates of clinical benefit, mHI-E, and RBC-TI for 8 weeks or more in patients with MDS/MPN-RS-T during Weeks 1 to 24 in the MEDALIST trial. <sup>a</sup>Unstratified CMH test; OR, 7.3 [95% CI, 1.11-48.26]. <sup>b</sup>CMH test stratified for average baseline RBC transfusion requirement ( $\geq 6$  units vs  $< 6$  units of RBC per 8 weeks), and baseline IPSS-R score (very low or low vs intermediate risk); OR, 11.3 [95% CI, 1.19-106.12]. CB, clinical benefit; CMH, Cochran Mantel Haenszel test; mHI-E, modified hematologic improvement-erythroid; OR, odds ratio; RBC-TI, red blood cell transfusion independence. Adapted from Komrokji RS et al. ASH abstract 3111. *Blood*. 2020;136(suppl 1).<sup>7</sup>

In the luspatercept arm, white blood cell (WBC) count significantly ( $P=.0119$ ) increased from baseline to Week 25 (mean WBC count  $5.3 \times 10^9/L$  at baseline to  $7.8 \times 10^9/L$  at Week 25), while WBC decreased in the placebo arm (mean WBC count  $7.3 \times 10^9/L$  at baseline to  $6.2 \times 10^9/L$  at Week 25). Each of these estimates were based on an ANCOVA model with treatment (luspatercept vs placebo) as the main fact, and baseline of values as a covariate. Platelet count and absolute neutrophil count both showed a trend towards an increase from baseline to Week 25 in the luspatercept arm.<sup>7</sup>

In patients with MDS/MPN-RS-

T, the incidence of treatment-emergent adverse events (TEAE) of any grade was higher in the luspatercept arm. TEAEs of any grade reported in at least 1 patient were dizziness (7 patients in the luspatercept arm vs 0 patients in the placebo arm), nausea (6 vs 2 patients), diarrhea (6 vs 1 patients), dyspnea (3 vs 0 patients), hypertension (3 vs 0 patients), fatigue (1 vs 1 patients), and arthralgia (1 vs 0 patients).<sup>7</sup>

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## Decitabine Versus Hydroxyurea for Advanced Proliferative CMML: Results of the Emsco Randomized Phase 3 DACOTA Trial

**M**yeloproliferative CMML (MP-CMML), defined by a WBC count of  $\geq 13 \times 10^9/L$ , has a poorer prognosis than myelodysplastic CMML.<sup>1,2</sup> In the 1990s, hydroxyurea became the established treatment for MP-CMML in patients with protocol-defined advanced disease, based on its effect on response rate and prolonged overall survival (OS) compared to etoposide.<sup>3</sup> The hypomethylating agents azacitidine and decitabine are both FDA-approved for the treatment of CMML,<sup>4,5</sup> and their efficacy as single agents in patients with advanced MP-CMML has been evaluated.<sup>6,7</sup> Itzykson and colleagues reported on results from the phase 3, randomized, multicenter, open-label DACOTA trial of decitabine (with or without hydroxyurea during the first 3 cycles) vs hydroxyurea in patients with

MP-CMML with protocol-defined advanced disease.<sup>8</sup>

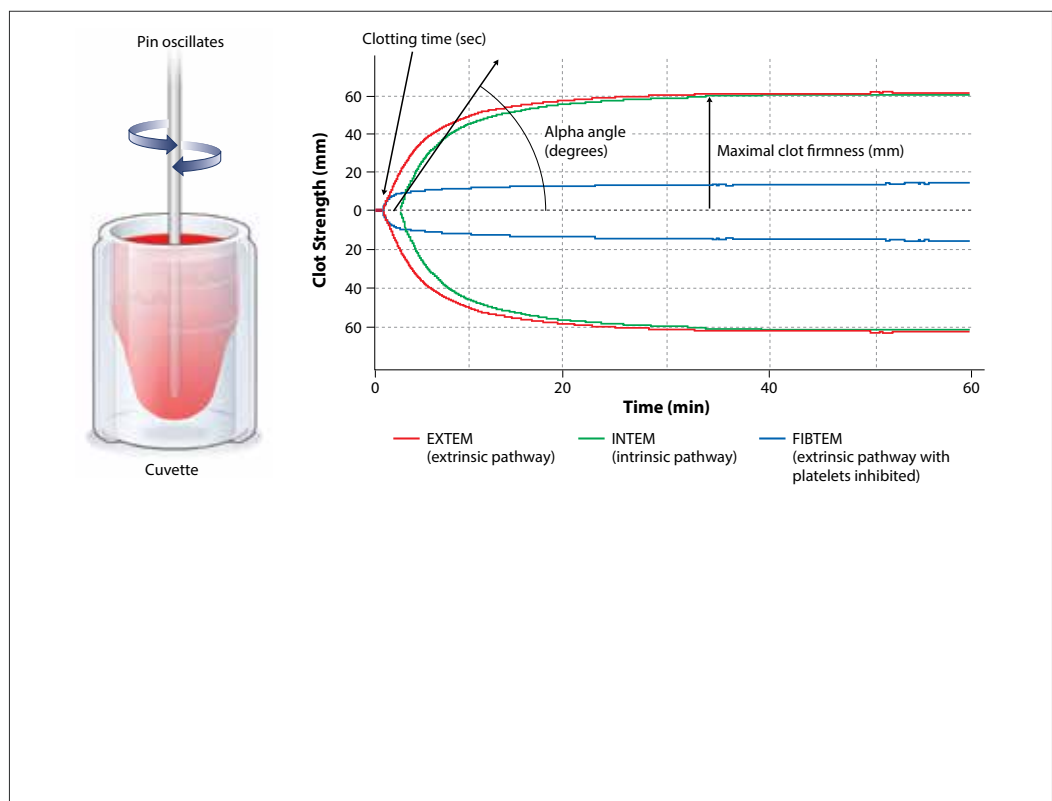
The DACOTA trial enrolled patients with previously untreated (except ESAs or less than 6 weeks of hydroxyurea) MP-CMML. Myeloproliferative disease was defined with a WBC  $\geq 13 \times 10^9/L$ , and advanced disease was defined using previously established criteria,<sup>3,6</sup> either with the presence of documented extramedullary disease (excluding splenomegaly) or 2 or more of the following: 5% or more bone marrow blasts; abnormal clonal karyotype (other than -Y); hemoglobin less than 10 g/dL; absolute neutrophil count of more than  $16 \times 10^9/L$ ; platelet count less than  $100 \times 10^9/L$ ; or splenomegaly greater than 5 cm below the costal margin.<sup>8</sup>

Patients were randomly assigned to treatment with decitabine (n=84)

or hydroxyurea (n=86), and treated until death, acute myeloid leukemia (AML) transformation, or progression. The primary endpoint was event-free survival (EFS). At baseline, 68% of patients had CMML-1 and 32% had CMML-2 disease according to the WHO 2010 criteria. Severe anemia was present in 24% of patients at baseline. Most patients (out of 165 patients) had intermediate-1 (40%) or intermediate-2 (54%) CPSS risk disease; the remainder had low (1%) or high (6%) risk disease.<sup>8</sup>

Overall, 64% (95% CI, 52-73) of patients in the decitabine arm achieved a response, compared to 34% (95% CI, 24-45) of patients in the hydroxyurea arm ( $P=.0002$ ). The benefit in objective response rate was significant as early as after the third cycle (56% vs 30%;  $P=.001$ ) and maintained

**Figure 2.** EFS among patients with MP-CMML in the DACOTA trial. EFS, event-free survival; MP-CMML, myeloproliferative chronic myelomonocytic leukemia. Adapted from Itzykson R et al. ASH abstract 654. *Blood*. 2020;136(suppl 1).<sup>8</sup>



through the sixth cycle (32% vs 17%;  $P=.03$ ).<sup>8</sup>

There was no significant difference in EFS between the 2 arms (Figure 2). With a median follow-up of 13.9 months, the median EFS was 12.6 months in the decitabine arm vs 10.3 months in the hydroxyurea arm (HR, 0.88 [95% CI, 0.61-1.25];  $P=.46$ ). There was also no significant difference in median OS between the 2 arms. (HR, 1.07 [95% CI, 0.73-1.58];  $P=.73$ ).<sup>8</sup>

More patients in the decitabine

arm than in the hydroxyurea arm experienced adverse events requiring hospitalization (55% vs 38%, respectively,  $P=.05$ ).<sup>8</sup>

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## Health-Related Quality of Life Outcomes in Patients With Myelodysplastic Syndromes With Ring Sideroblasts Treated With Luspatercept in the MEDALIST Study

In patients with MDS, RBC transfusions can provide transient relief of anemia-related symptoms and impact their health-related quality of life (HRQoL).<sup>1,2</sup> However, RBC transfusion dependence places a significant burden on these patients, potentially resulting in negative clinical consequences such as iron overload and associated complications of cardiac and hepatic organ failure.<sup>3-5</sup> Further, reducing or stopping RBC transfusions may increase anemia-related symptoms and negatively impact HRQoL. The MEDALIST trial established that luspatercept was associated with a clinically meaningful reduction in transfusion burden in transfusion-dependent patients.<sup>6</sup> An analysis presented by Oliva and colleagues examined the impact of luspatercept treatment on HRQoL from baseline through Week 25 among patients enrolled in the MEDALIST trial.<sup>7</sup>

Several patient-reported outcomes (PROs)/HRQoL endpoints were measured for the HRQoL-evaluable population. The investigators noted that PRO endpoints were not powered in this study and all analyses were considered descriptive. The

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) was used to measure the change in HRQoL at Week 25; the primary domains of interest were global health status/QoL, fatigue, physical functioning, dyspnea, and emotional functioning. All other domains not specified as primary were analyzed as an exploratory endpoint. The Quality of Life Assessment in MDS Questionnaire (QOL-E) was used to measure the change in HRQoL at Week 25 as another exploratory endpoint, in addition to the patient-reported impact of transfusion dependence and side effects. A clinically meaningful change within each treatment arm was defined as a 10 or more point change in PRO score from baseline for all EORTC QLQ-C30 domains, and 0.5 or more standard deviations of the baseline domain score for all QOL-E domains.<sup>7</sup>

At baseline, the 225 patients in the MEDALIST trial had a clinically meaningful worse HRQoL compared with the general population in 5 of 15 EORTC QLQ-C30 domains (physical functioning, role functioning, social functioning, fatigue, and dyspnea).<sup>7</sup>

Through Week 25, there was no clinically meaningful difference in change from baseline between and within the luspatercept and placebo arms in all EORTC QLQ-C30 domain scores. Through Week 25, there was also no clinically meaningful difference in change from baseline between and within the luspatercept and placebo arms in all QOL-E domains. However, compared with the placebo arm (22% at Week 25), a greater proportion of patients in the luspatercept arm (39% at Week 25) reported improvements in daily life from the impact of transfusion dependence.<sup>7</sup>

The study investigators concluded that luspatercept reduced RBC transfusion burden and patient-reported transfusion impact on their daily life, while maintaining other aspects of HRQoL from baseline through Week 25 in the MEDALIST trial. They noted that their analysis had several limitations. For example, in the MEDALIST trial, hemoglobin levels were maintained at a range where HRQoL may be insensitive to changes in hemoglobin. Additionally, PRO data collection was on a fixed schedule at the end of each treatment cycle, independent

of RBC transfusion events. Further, the majority of domains covered by the cancer-specific EORTC QLQ-C30 and the MDS-specific QOL-E were not specific to the effect of luspatercept treatment.<sup>7</sup>

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## Efficacy and Safety of Pevonedistat Plus Azacitidine Vs Azacitidine Alone in Higher-Risk Myelodysplastic Syndromes From Study P-2001

**P**evonedistat is a first-in-class inhibitor of the NEDD8-activating enzyme (NAE). In cancer cells, NAE participates in the ubiquitination and degradation of certain regulatory proteins via a process termed neddylation, a mechanism by which proteins are modified intracellularly. This allows cancer cells to continue their growth and survival.<sup>1,2</sup> Inhibition of NAE by pevonedistat allows for the accumulation of these regulatory proteins, thereby disrupting DNA replication, cell cycle progression, and NFκB signaling. Ultimately, these actions can result in cancer cell death.<sup>2,3</sup> The combination of pevonedistat plus azacitidine is associated with clinical activity in both MDS and AML.<sup>4,5</sup>

Study P-2001 is a phase 2, randomized, open-label, global, multicenter study of pevonedistat plus azacitidine versus azacitidine alone in 120 patients with higher-risk MDS (n=67), higher-risk CMML (n=17), and low-blast AML (n=36). To be eligible, patients could not have previously received hypomethylating agents and were ineligible for allogeneic stem cell transplant. The results from P-2001 for the intention-to-treat (ITT) population have previously been reported.<sup>6,7</sup>

The study was powered to evaluate median EFS as the original primary endpoint. The median EFS was 21.0 months with pevonedistat plus azaciti-

dine vs 16.6 months with azacitidine alone (HR, 0.67 [95% CI, 0.42-1.05];  $P=.076$ ). Based on regulatory feedback, the study's primary endpoint was changed to OS, which was not statistically significantly improved in the ITT population (median OS: 21.8 vs 19.0 months; HR, 0.80 [95% CI, 0.51-1.26];  $P=.334$ ).<sup>6,7</sup>

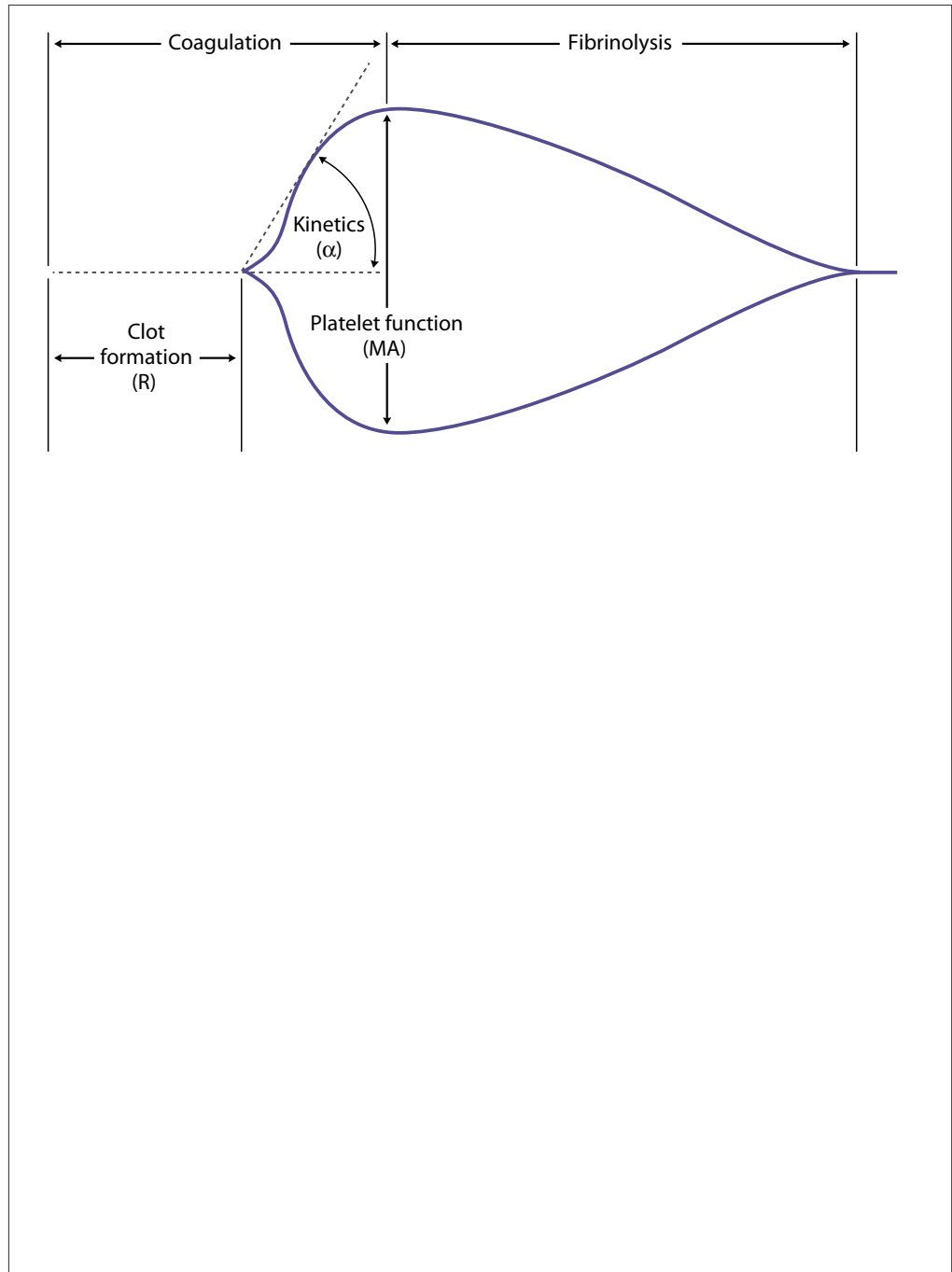
Sekeres and colleagues presented an updated analysis of Study P-2001, which focused on patients with higher-risk MDS. Here, higher-risk MDS was defined as patients with a prognostic risk category of very high (>6 points), high (>4.5 to 6 points), or intermediate (>3 to 4.5 points) according to the IPSS-R. Additionally, patients with intermediate risk disease per IPSS-R were further required to have 5% or more bone marrow blasts. This analysis focused on clinical, cytogenetic, and genetic factors that might impact response rate and duration, as well as EFS and OS.<sup>8</sup>

Among this group of 67 patients with higher-risk MDS, the baseline characteristics were generally well balanced between the treatment arms. The median patient age was 75 years (range: 47-91) in the pevonedistat plus azacitidine arm and 70 years (range: 44-84) in the azacitidine arm. In the combination arm, 34%, 34%, and 31% of patients had intermediate-risk, high-risk, and very high-risk MDS, respectively,

according to IPSS-R. In the azacitidine alone arm, 26%, 29%, and 46% of patients had intermediate-risk, high-risk, and very high-risk MDS, respectively. The vast majority of patients in both arms had de novo disease (100% in the pevonedistat plus azacitidine arm and 97% in the azacitidine arm). The median time from initial diagnosis was 2.30 months (range: 0.2-58.4) in the pevonedistat plus azacitidine arm and 1.74 months (range: 0.6-79.1) in the azacitidine arm.<sup>8</sup>

Both EFS and OS favored pevonedistat plus azacitidine compared with azacitidine in this group of patients with IPSS-R-defined higher-risk MDS (Figure 3). Median EFS, defined as time to death or transformation to AML, was 20.2 months with pevonedistat plus azacitidine vs 14.8 months with azacitidine (HR, 0.539 [95% CI, 0.292-0.995];  $P=.045$ ). The study investigators noted that prolonged EFS was particularly evident in the group of 26 patients with very high-risk MDS, among whom the hazard ratio was 0.47 (95% CI, 0.19-1.18), and the group of 21 patients with high-risk MDS, among whom the hazard ratio was 0.53 (95% CI, 0.17-1.72). Median OS was 23.9 months in the pevonedistat plus azacitidine arm compared with 19.1 months in the azacitidine arm; this difference did not reach statistical significance (HR, 0.701 [95% CI:

**Figure 3.** EFS and OS outcomes among patients with higher-risk MDS according to IPSS-R in Study P-2001. \*EFS was defined as time to death or transformation to AML in higher-risk MDS. CI, confidence interval; EFS, event-free survival; OS, overall survival. Adapted from Sekeres MA et al. ASH abstract 653. *Blood*. 2020;136(suppl 1).<sup>8</sup>



0.386-1.273];  $P=.240$ ).<sup>8</sup>

The study investigators also presented the results of a post hoc analysis of Study P-2001, which focused on patients with MDS assessed as high-risk according to the combined Cleveland Clinic model. This formula incorporates the following weighted clinical and genetic factors significantly

associated with OS: age, IPSS-R score, and mutations in *EZH2*, *SF3B1*, and *TP53*. The calculated score results in 4 risk groups: low (score  $\leq 3$ ), intermediate-1 (3.1 to 3.6), intermediate-2 (3.7 to 4.6), and high ( $\geq 4.7$ ), which correlate to median OS times of 37.4, 23.2, 19.9, and 12.2 months, respectively ( $P < .001$ ).<sup>9</sup> Using this Cleveland Clinic

model, both EFS and OS trended longer in patients treated with pevonedistat plus azacitidine versus azacitidine. In patients with Cleveland Clinic model-defined high-risk MDS, the median EFS was 20.2 months vs 11.7 months (HR, 0.388 [95% CI, 0.166-0.902];  $P=.023$ ). In this same group of patients, the median OS was 24.2

months vs 14.2 months (HR, 0.447 [95% CI, 0.190-1.050];  $P=.056$ ).<sup>8</sup>

Among the patients with IPSS-R-defined higher-risk MDS, the overall response rate was increased with pevonedistat plus azacitidine vs azacitidine (79% vs 57%;  $P=.065$ ). Further, the rate of complete response was almost doubled (52% vs 27%;  $P=.050$ ) and the median duration of response was nearly tripled (34.6 months [95% CI, 11.53-34.60] vs 13.1 months [95% CI, 12.02-not evaluable]) with pevonedistat plus azacitidine vs azacitidine.<sup>8</sup>

Among the patients with IPSS-R-defined higher-risk MDS who were RBC or platelet transfusion-dependent at baseline, the rate and duration of transfusion independence was increased with pevonedistat plus azacitidine (69.2%) versus azacitidine (47.4%; relative risk, 1.46 [95% CI, 0.81-2.65];  $P=.228$ ). The median duration of transfusion independence was 23.3 months with the combination and 11.6 months with azacitidine alone (HR, 0.11 [95% CI, 0.01-0.94];  $P=.016$ ).<sup>8</sup>

The median time to AML transformation was delayed with the combination of pevonedistat plus azacitidine in

patients with IPSS-R-defined higher-risk MDS. Among these patients, the median time to AML transformation was not evaluable in either treatment arm, but the hazard ratio was 0.465 (95% CI, 0.156-1.388;  $P=.159$ ). In the 14 patients who did experience transformation, the median time to transformation was 12.2 months (range: 4.6-12.6;  $n=5$ ) with pevonedistat plus azacitidine and 5.9 months (range: 1.7-14.8;  $n=9$ ) with azacitidine.<sup>8</sup>

The investigators reported that exposure-adjusted rates of adverse events were lower with pevonedistat plus azacitidine, without added myelosuppression.<sup>8</sup>

The combination of pevonedistat plus azacitidine will be further evaluated in the ongoing phase 3 PANTHER trial.<sup>10</sup>

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## Effect of Luspatercept on Biomarkers of Erythropoiesis in Patients With Lower-Risk Myelodysplastic Syndromes in the MEDALIST Trial

Lower-risk MDS is characterized by ineffective erythropoiesis resulting in anemia and RBC transfusion dependence.<sup>1</sup> Luspatercept enhances late-stage erythropoiesis and was approved in patients with very low- to intermediate-risk MDS-RS or with MDS/MPN-RS-T based on the results of the MEDALIST trial.<sup>2</sup> Platzbecker and colleagues investigated the effect of luspatercept on erythropoiesis-associated biomarkers, and their relationship to clinical benefit during Weeks 1 to 24 of the MEDALIST trial.<sup>3</sup> The composite endpoint of clinical benefit (the

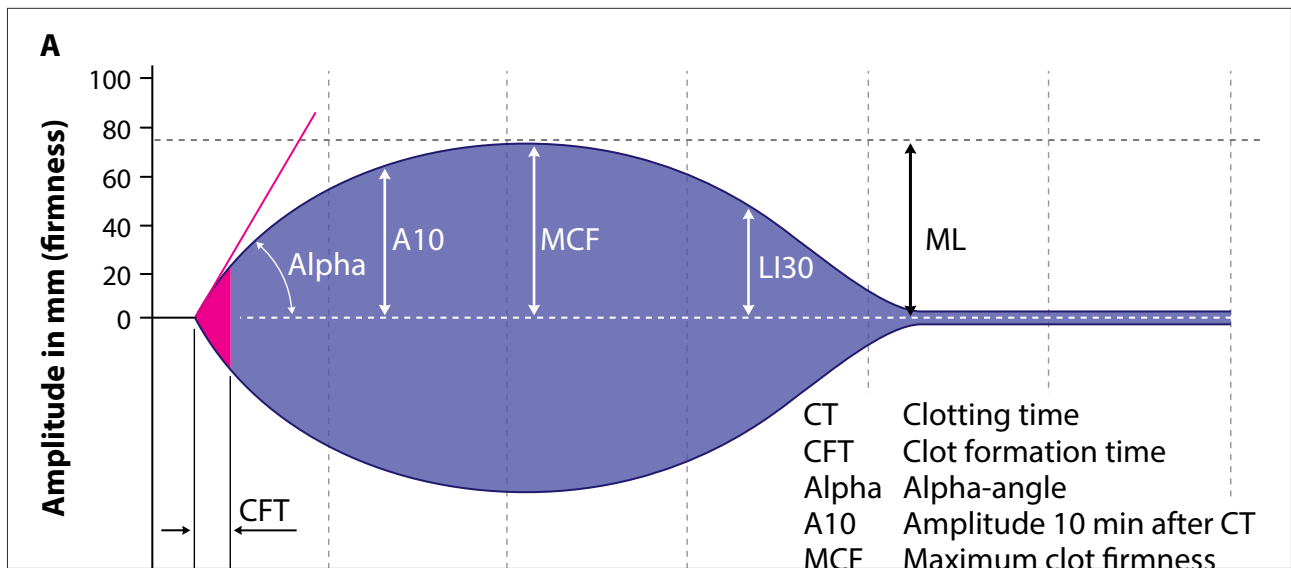
proportion of patients achieving RBC-TI for 8 weeks or more and/or mHI-E) during Weeks 1 to 24 was achieved in 58.2% of luspatercept-treated patients and 21.1% of placebo-treated patients ( $P<.0001$ ).<sup>4</sup>

Increases in several biomarkers associated with erythropoiesis occurred in luspatercept-treated patients, but not placebo-treated patients, in the MEDALIST trial. In the luspatercept arm, beginning at 8 days after the first dose, mean reticulocyte count increased from baseline and remained elevated through Week 25 ( $34.5 \times 10^9/L$  at

baseline vs  $71.9 \times 10^9/L$  at Week 25;  $P<.0001$ ). From baseline, mean serum erythropoietin (EPO) levels increased significantly by cycle 3 and remained elevated through Week 25 ( $220.4 IU/L$  at baseline vs  $662.9 IU/L$  at Week 25;  $P<.0001$ ). Changes from baseline in both reticulocyte count and serum EPO level through Week 25 are shown in Figure 4. The investigators noted that changes in reticulocyte and serum EPO levels increased as early as the first 3 weeks, and remained elevated through Week 25.<sup>3</sup>

Similarly, levels of serum biomark-





**Figure 4.** Reticulocyte count (left) and serum EPO level (right) from baseline through Week 25 in the MEDALIST trial. Data cutoff: July 1, 2019. \* $P < .05$  vs baseline; \*\*\*\* $P < .0001$  vs baseline. C, cycle; D, day; EPO, erythropoietin. Adapted from Platzbecker U et al. ASH abstract 2190. *Blood*. 2020;136(suppl 1).<sup>3</sup>

ers were also significantly increased between baseline and Week 25 in the luspaterecept arm. The mean serum soluble transferrin receptor 1 (sTfR1) increased from 32.7 nM at baseline to 42.8 nM at Week 25 ( $P < .0001$ ). The mean serum erythroferrone (ERFE) level increased from 20.9 ng/mL at baseline to 27.0 ng/mL at Week 25 ( $P < .0001$ ). Mean bone marrow erythroid precursors, as determined by cytomorphology from bone marrow aspirates, increased from 29.3% at baseline to 34.3% at Week 25 ( $P = .0010$ ).<sup>3</sup>

In contrast, in the placebo arm, mean reticulocyte count and mean serum EPO levels remained largely unchanged, while mean levels of serum sTfR1 ( $P < .0001$ ), serum ERFE ( $P = .0431$ ), and bone marrow erythroid precursor ( $P = .0010$ ) were significantly lower at Week 25 relative to baseline.<sup>3</sup>

Among patients treated with luspaterecept, there was a significant difference in the fold change from baseline in mean reticulocyte count for patients with a clinical benefit vs those patients without a clinical benefit (2.72 vs 1.75;  $P = .0017$ ). The fold change in all other

biomarkers were not significantly different between patients who did or did not achieve a clinical benefit.<sup>3</sup>

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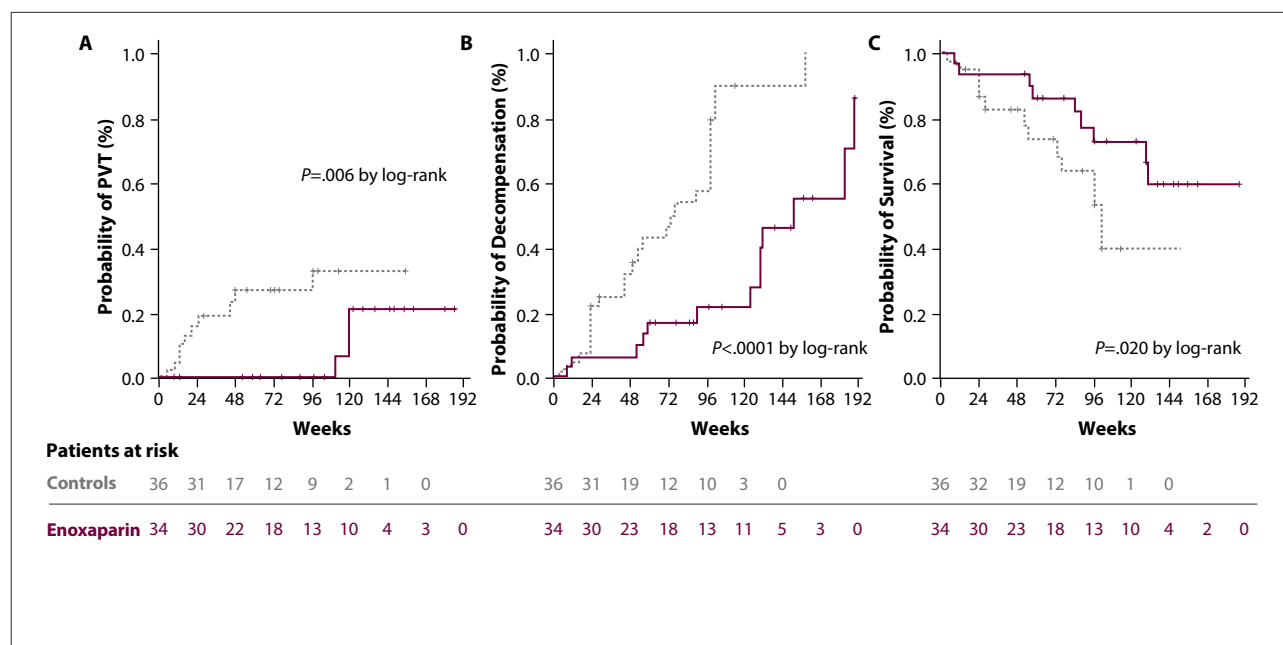
## Safety, Efficacy, and Patient-Reported Outcomes of Venetoclax in Combination With Azacitidine for the Treatment of Patients With Higher-Risk Myelodysplastic Syndrome: A Phase 1b Study

**H**ypomethylating agents are considered a standard of care in patients with higher-risk MDS who are not candidates for allogeneic stem cell transplant. However, despite their activity, both overall response rates and OS are low in patients receiving azacitidine.<sup>1</sup> In pre-clinical and clinical studies of myeloid

malignancies, the BCL-2 inhibitor venetoclax has been shown to act synergistically with hypomethylating agents and has been used in combination with azacitidine, decitabine, or low-dose cytarabine to treat patients with newly diagnosed AML.<sup>2-7</sup>

Garcia and colleagues presented results from M15-531, an ongoing,

phase 1b, dose-escalation, open-label, multicenter study evaluating the combination of venetoclax plus azacitidine for the treatment of patients with higher-risk MDS. A total of 78 patients have been enrolled in this study. Venetoclax was initially given at a dose of 400 mg or 800 mg for 28 days in a 28-day cycle. Due to intolerance, this



**Figure 5.** OS for patients treated with venetoclax plus azacitidine in the M15-531 study. Data cutoff: June 30, 2020. Aza, azacitidine; CI, confidence interval; NR, not reached; OS, overall survival; RP2D, recommended phase 2 dose; Ven, venetoclax. Adapted from Garcia JS et al. ASH abstract 656. *Blood*. 2020;136(suppl 1).<sup>8</sup>

was later amended to an escalating dose (100, 200, and 400 mg) for 14 days in a 28-day cycle. Azacitidine was administered at 75 mg/m<sup>2</sup> subcutaneously or intravenously on Days 1-7 of each 28-day cycle.<sup>8</sup>

The primary study objectives are to evaluate safety and to establish the recommended phase 2 dose of the combination. The secondary objectives include objective response rate and OS. Exploratory objectives included PROs using the EORTC QLQ-C30 scale. This current analysis updated the clinical findings of this trial and evaluated PROs in patients with higher-risk MDS who received the recommended phase 2 dose of the combination.<sup>8</sup>

The most common adverse events included neutropenia (83%), nausea (55%), constipation (54%), febrile neutropenia (49%), diarrhea (49%), thrombocytopenia (49%), vomiting (41%), leukopenia (38%), anemia (29%), fatigue (26%), and hypokalemia (21%). Neutropenia (49%) and febrile neutropenia (45%) were the most common serious adverse events.

The 30-day mortality rate after the first dose was 1%.<sup>8</sup>

In the total study population of 78 patients, the ORR was 79%, including 39.7% complete remission and 39.7% marrow complete remission. The median duration of response was 12.9 months (range: 12.1-16.8), which increased to 13.8 months (range: 6.5-20.9) after achieving complete remission. Among the 51 patients receiving the recommended phase 2 dosing of 400 mg venetoclax, 84% achieved an objective response (47% by Cycle 2 and 78% by Cycle 3) and 35% achieved a complete remission.

Median OS (Figure 5) was 27.5 months (95% CI, 18.2 to not reached), and was not reached among the subset of patients treated with the recommended phase 2 dosing (95% CI, 17.7 to not reached).<sup>8</sup>

This analysis also examined PROs among patients treated at the recommended phase 2 dosing. Clinically meaningful improvements in dyspnea and fatigue were observed to 48 weeks. Among patients who achieved com-

plete remission, there were moderate to large improvements in dyspnea by cycle 3 that were maintained through cycle 13, and there were mild improvements in fatigue by cycle 3, with a large improvement reported at cycle 13. Physical functioning was maintained throughout treatment.<sup>8</sup>

The study authors noted that the phase 3 study VERONA is currently recruiting patients to evaluate the safety and efficacy of venetoclax plus azacitidine in newly diagnosed patients with higher-risk MDS.<sup>8</sup>

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## Duration of Response to Luspatercept in Patients Requiring Red Blood Cell Transfusions With Myelofibrosis – Updated Data From the Phase 2 ACE-536-MF-001 Study

**A**nemia is a significant complication of myelofibrosis (MF). Approximately 60% of patients develop anemia within a year of their diagnosis. Once a patient with MF becomes transfusion-dependent, they are more likely to experience worse survival and quality-of-life outcomes.<sup>1</sup> However, there are currently no therapies specifically approved for the treatment of MF-associated anemia. Luspatercept is under investigation in the ongoing open-label, phase 2 ACE-536-MF-001 trial in subjects with MF and anemia, focusing on response in subjects requiring RBC transfusions. Gerds and colleagues presented updated data from this study which included 79 patients with MF and anemia who had been enrolled by the data cutoff of March 29, 2020.<sup>2</sup>

According to the study design, patients were enrolled into 4 cohorts.

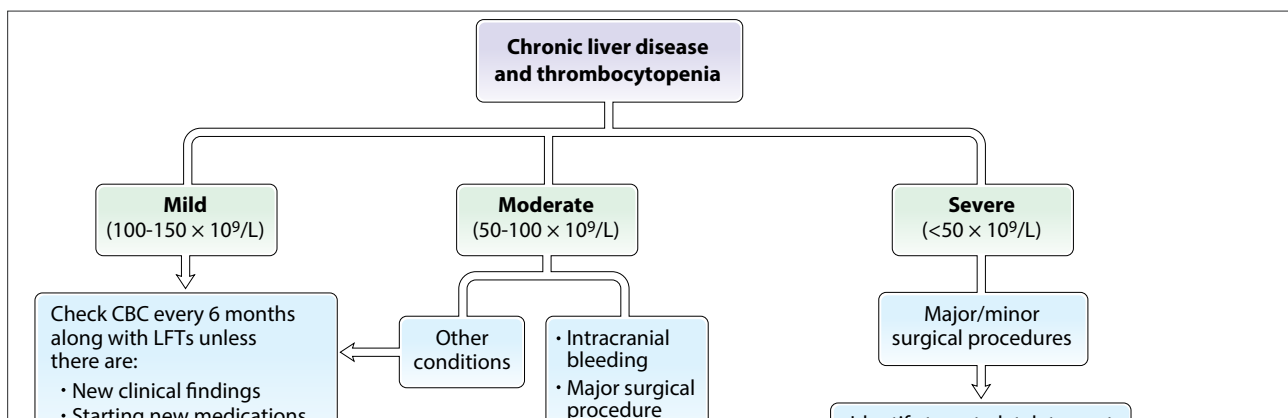
Cohorts 1 (n=22) and 3A (n=14) had no RBC transfusions within the 12 weeks prior to enrollment; Cohort 1 was not receiving ruxolitinib and Cohort 3A was receiving a stable dose of ruxolitinib. Cohorts 2 (n=21) and 3B (n=22) had received RBC transfusions within the 12 weeks prior to enrollment; Cohort 2 was not receiving ruxolitinib and Cohort 3B was receiving a stable dose of ruxolitinib.<sup>2</sup>

During the primary treatment phase, all patients were treated with luspatercept (1.0 mg/kg with titration up to 1.75 mg/kg) subcutaneously every 21 days for 168 days. After a disease response assessment on Day 169, patients with clinical benefit could continue treatment through an extension phase while patients without clinical benefit discontinued treatment. At baseline, the median age among all 79 patients was 71.0 years

(range: 50-89), and 58.2% were male.<sup>2</sup>

Overall, among the patients who reached 24 weeks of treatment, 4 of 15 (27%) in Cohort 2 and 8 of 14 (57%) in Cohort 3B achieved clinical benefit (RBC-TI for 12 or more weeks during Weeks 1 to 24) and therefore continued to receive luspatercept after 24 weeks.<sup>2</sup>

In Cohort 2 (patients receiving RBC transfusion and not receiving ruxolitinib), 2 of 21 patients (10%) achieved a response defined as RBC-TI for 12 or more weeks during Weeks 1 to 24 (Figure 6). The median time to first onset of RBC-TI for 12 or more weeks was 1.5 days (range: 1-2). The median duration of RBC-TI for 12 or more weeks was 49 weeks (range: 16-82). Over the entire treatment period, RBC-TI for 12 or more weeks was achieved in 4 of 21 patients (19%), with a median cumulative duration of



**Figure 6.** Rates of RBC-TI and  $\geq 50\%$  transfusion burden reduction in the phase 2 ACE-536-MF-001 trial. \*Defined as RBC transfusion burden reduction by  $\geq 50\%$  and by  $\geq 4$  RBC units for  $\geq 12$  weeks. RBC, red blood cell; RBC-TI, red blood cell transfusion independence. Adapted from Gerds AT et al. ASH abstract 2992. *Blood*. 2020;136(suppl 1).<sup>2</sup>

all RBC-TI for 12 or more episodes of 59 weeks (range: 24-82). A total of 8 of 21 patients (37%) achieved a 50% or greater reduction in RBC transfusion burden over the entire treatment duration.<sup>2</sup>

In Cohort 3B (patients receiving RBC transfusion who were receiving ruxolitinib), 6 of 22 (27%) of patients achieved a response defined as RBC-TI for 12 or more weeks during Weeks 1 to 24 (Figure 6). The median time to first onset of RBC-TI for 12 or more weeks was 37 days (range: 1-71). The median duration of RBC-TI for 12 or more weeks was 42 weeks (range: 12-111). Over the entire treatment period, RBC-TI for 12 or more weeks was achieved in 8 of 22 patients (36%),

with a median cumulative duration of all RBC-TI for 12 or more episodes of 55 weeks (range: 12-116). A total of 10 of 22 patients (46%) achieved a 50% or greater reduction in RBC transfusion burden over the entire treatment duration.<sup>2</sup>

Safety was assessed among all 79 patients across the 4 cohorts. The most common TEAEs of any grade consisted of diarrhea (23%), hypertension (19%), thrombocytopenia (19%), dyspnea (17%), fatigue (17%), and pyrexia (17%). The most common treatment-related adverse events (TRAEs) were hypertension (13%), bone pain (9%), and diarrhea (5%). Five patients (6%) had Grade 3 or 4 TRAEs, which were diarrhea (n=2),

dehydration (n=1), and hypertension (n=3). Eight patients (10%) experienced a TRAE leading to treatment discontinuation, which included anemia, splenomegaly, fatigue, general physical health deterioration, sepsis, urinary tract infection, diverticular perforation, and hemorrhage.<sup>2</sup>

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## Phase 3 Study of Lenalidomide vs Placebo in Non-Transfusion Dependent Low Risk del(5q) MDS Patients – Interim Analysis of the European Sintra-REV Trial

Lower-risk MDS patients with del(5q) and anemia have a median time to transfusion dependency of about 1.7 years.<sup>1,2</sup> In patients with established transfusion requirements, the immunomodulatory drug lenalidomide has been demonstrated to result in RBC-TI in about two-thirds of patients and improved OS and AML progression outcomes.<sup>3,4</sup> Cadenas and colleagues presented data from an interim analysis of the Sintra-REV trial, which explored the use of early, low doses of lenalidomide to prolong time to transfusion dependence in lower-risk MDS patients with del(5q) who have not yet become transfusion dependent.<sup>5</sup>

Sintra-REV is a phase 3, double-blind, randomized, placebo-controlled, multicenter study which randomizes patients in a 2-to-1 fashion to 108 weeks of treatment with lenalidomide (5 mg/day; n=40) or placebo (n=20)

on days 1 to 28. The primary efficacy objective is to assess the prolongation of the period until disease progression. At baseline, most patients (87.5% and 81% in the lenalidomide and placebo arms, respectively) had IPSS low-risk disease; the remainder had intermediate-1-risk disease. A total of 82.5% and 81% of patients in the lenalidomide and placebo arms, respectively, completed treatment.<sup>5</sup>

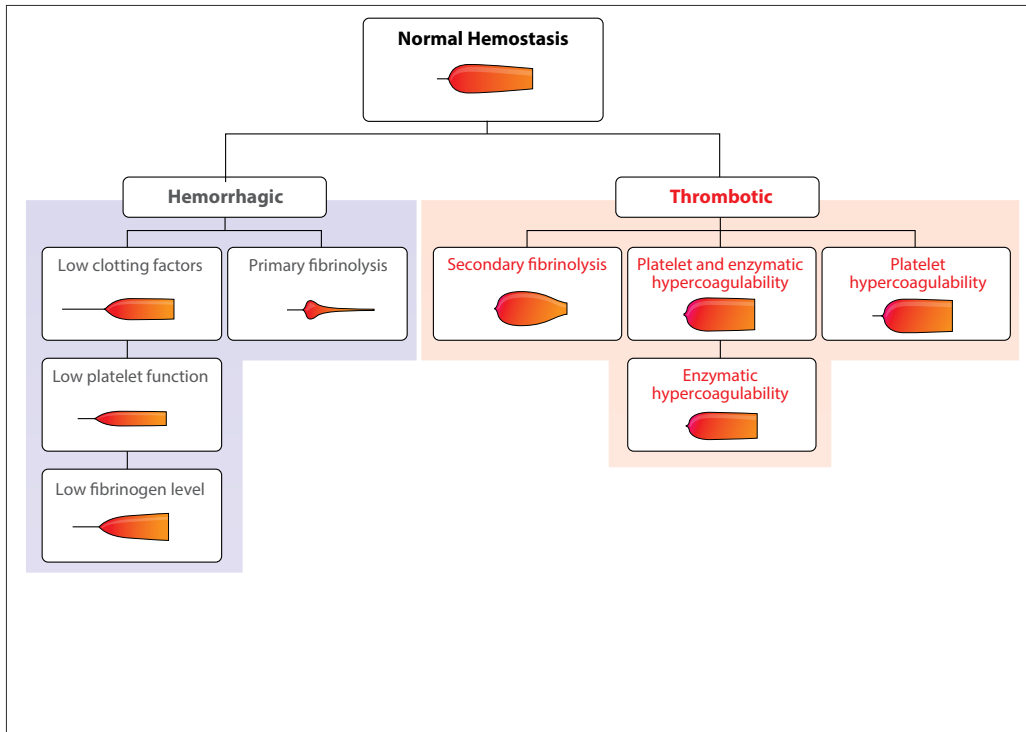
In this interim analysis, low doses of lenalidomide proved to be beneficial to delay disease progression and time to transfusion dependency (Figure 7). Transfusion dependency occurred in a total of 23 patients (37.7%), including 11 in the lenalidomide arm (27.5%) and 12 in the placebo arm (57.1%). The median time to transfusion dependency was more than doubled with lenalidomide vs placebo (6.3 vs 2.8 years). Overall, lenalidomide decreased the risk of transfusion dependency by

61.2% (HR, 0.388 [95% CI, 0.167-0.903],  $P=.028$ ).<sup>5</sup>

Other clinical benefits were also observed with low-dose lenalidomide in these patients with lower-risk MDS with del(5q), including a 72.5% rate of erythroid response and a 80% rate of cytogenetic response. The study investigators reported that the low-dose lenalidomide treatment was associated with an acceptable safety profile (primarily Grade 1 or 2 in severity), with the hematologic toxicities that were observed (including a 46.8% incidence of Grade 3/4 neutropenia) deemed not to be clinically relevant.<sup>5</sup>

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## The COMMANDS Trial: A Phase 3 Study of the Efficacy and Safety of Luspatercept Versus Epoetin Alfa for the Treatment of Anemia Due to IPSS-R Very Low-, Low-, or Intermediate-Risk MDS in Erythropoiesis Stimulating Agent–Naïve Patients Who Require RBC Transfusions

Luspatercept is also being compared with ESAs in the frontline MDS setting. ESAs, including epoetin alfa and darbepoetin alfa, have shown benefit in patients with MDS-related anemia, but their use is limited to only a small subset of patients.<sup>1,2</sup> Luspatercept is currently approved for the treatment of anemia in patients who have failed an ESA and require 2 or more RBC units over 8 weeks in adult patients with very low-to intermediate-risk MDS-RS or with MDS/MPN-RS-T.<sup>3</sup> The COMMANDS trial is designed to evaluate if luspatercept could also be beneficial in the treatment of anemia among ESA-naïve patients requiring

RBC transfusions.<sup>4</sup> Porta and colleagues presented a summary of this currently recruiting study (Figure 8).<sup>5</sup>

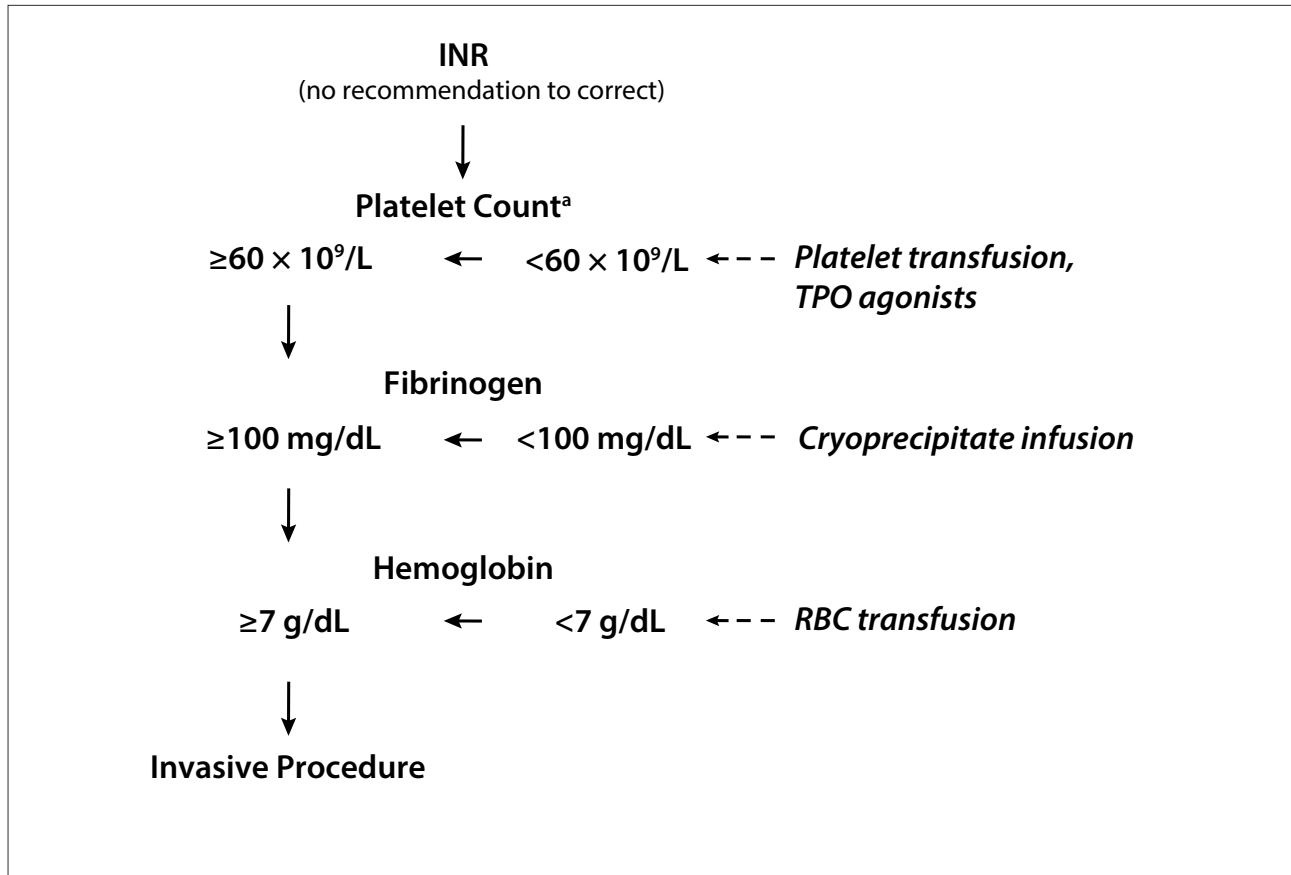
COMMANDS (NCT03682536) is a randomized, open-label, phase 3 trial designed to evaluate the efficacy and safety of luspatercept versus epoetin alfa in anemic patients with IPSS-R-defined lower risk MDS, either with or without 15% or more RS. Eligible patients are ESA-naïve and require regular RBC transfusions.<sup>5</sup>

Inclusion criteria for patients include age 18 years or older at the time of consent, a documented diagnosis of IPSS-R-defined lower-risk MDS with 5% or fewer blasts in the bone marrow,

and serum EPO levels under 500 U/L. Additionally, patients must have an average RBC transfusion requirement of 2 to 6 units of RBCs every 8 weeks for 8 or more weeks immediately prior to randomization.<sup>5</sup>

Exclusion criteria include the previous use of ESAs (1 to 2 doses of prior epoetin alfa were permitted if they were given 8 or weeks prior to the randomization date and serum EPO was confirmed as under 500 U/L). Other exclusion criteria are the prior use of granulocyte colony-stimulating factor or granulocyte macrophage colony-stimulating factor, unless given for the treatment of febrile neutropenia;





**Figure 8.** Design of the COMMANDS study. <sup>a</sup>Crossover between the treatment arms is not permitted during the study treatment period. <sup>b</sup>Individual epoetin alfa doses according to body weight will be rounded up to the next 2,000 IU dose level for starting dose level and dose level -1, and up to the next 4,000 IU for dose level +1 and dose level +2 for doses exceeding a calculated dosing of 56,000 IU according to body weight. AE, adverse event; AML, acute myeloid leukemia; EOT, end of treatment; IP, investigational product; IU, international units; MDS, myelodysplastic syndromes; QW, once every week; Q3W, once every 3 weeks; SC, subcutaneous. Adapted from Porta MD et al. ASH abstract 2198. *Blood*. 2020;136(suppl 1).<sup>5</sup>

and the prior use of disease-modifying agents (such as lenalidomide) or hypomethylating agents. The presence of a del(5q) cytogenetic abnormality also prevents patient enrollment.<sup>5</sup>

Approximately 350 patients are planned to be randomized in a 1-to-1 fashion to receive either luspatercept (at a starting dose of 1.0 mg/kg with titration up to 1.75 mg/kg) subcutaneously once every 3 weeks or epoetin alfa (at a starting dose of 450 IU/kg with titration up to 1,050 IU/kg) subcutaneously once every week. Patients in both arms may receive best supportive care, including RBC transfusions.<sup>5</sup>

Treatment will be continued for a minimum of 24 weeks, at which point patients will engage in a 24-week MDS disease assessment visit. At this

point, treatment may be continued unless discontinued for evidence of progression, death, unacceptable toxicity, patient/physician decision, or withdrawal of consent.<sup>5</sup>

The COMMANDS study enrollment is planned such that between 40% and 60% of randomized patients will be RS-positive, and at least 25% or more will have a serum EPO level >200 U/L. At randomization, patients will be stratified according to the following 3 factors: baseline RBC transfusion burden (<4 vs  $\ge 4$  units RBCs per 8 weeks); RS status (with RS-positive defined as RS  $\ge 15\%$ , or  $\ge 5\%$  if *SF3B1* mutation is present); and baseline serum EPO level ( $\le 200$  U/L vs >200 U/L).<sup>5</sup>

The primary endpoint of the

COMMANDS study is the proportion of patients who achieve RBC-TI for 12 or more weeks within the first 24 weeks on study, with a concurrent mean hemoglobin increase of  $\ge 1.5$  g/dL compared with baseline. Secondary endpoints include RBC-TI for 24 weeks, mean hemoglobin change over 24 weeks, achievement of HI-E response per IWG 2006 criteria, time to achieve HI-E, safety (type, frequency, and severity of adverse events), and progression to AML.<sup>5</sup>

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## Highlights in Myelodysplastic Syndromes From the 62nd American Society of Hematology Annual Meeting and Exposition: Commentary

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The American Society of Hematology (ASH) annual meeting is one of the most important venues for hematologists to share knowledge, and 2020 was no exception. Unfortunately, ASH 2020 was deeply affected by the Covid-19 pandemic, which dealt a negative impact in the sense that we were unable to meet and interact in person. However, surprisingly it also had some positive aspects that I hope remain for future years. One positive note was that all the posters were presented online in a format that was quite well done. This actually allowed for better access to these often-overlooked poster presentations, which many times contain data as important as what is presented during the oral sessions. A second positive outcome from the all-virtual meeting was made

by easing accessibility and allowing the meeting to perhaps be more broadly impactful.

After the exceptional presentations focused on myelodysplastic syndrome (MDS) that were presented at the ASH 2019 meeting, one might think that this year's MDS sessions were not as strong. However, it is important to remember that this past year saw the FDA approval of 2 new drugs for MDS—luspatercept (in April 2020) and oral decitabine/cedazuridine (in July 2020).<sup>1,2</sup> As a result, many of the presentations at ASH 2020 focused on additional data from the label-enabling studies supporting these approvals. Excitingly, other presentations reported on early data from novel agents for this disease, which remain a significant unmet need.

Luspatercept is a recombinant fusion protein that binds select TGFβ superfamily ligands. In this way, luspatercept modulates signaling through TGFβ and diminishes Smad2/3 signaling.<sup>3</sup> The activity of luspatercept is seen not only in MDS but in other conditions such as β-thalassemia, for which it is also FDA-indicated. Specifically in MDS, luspatercept is indicated for the treatment of anemia failing an ESA and requiring 2 or more red blood cell units over 8 weeks in adult patients with very low- to intermediate-risk MDS-RS or with MDS/MPN-RS-T.<sup>4</sup> The efficacy and safety of luspatercept in MDS were established in the MEDALIST trial, first presented in the plenary session at the ASH 2018 meeting,<sup>5</sup> and subsequently published in *The New England Journal of Medicine*.<sup>6</sup> At ASH 2020, there were several abstracts with important updates from this trial.

The phase 3 MEDALIST trial enrolled patients with very-low-risk, low-risk, or intermediate-risk MDS with ring sideroblasts who had been receiving regular red blood cell transfusions. The 229 patients enrolled were randomly assigned to receive either luspatercept or placebo. The primary endpoint, RBC-TI for 8 weeks or longer during weeks 1 through 24, was reached in 38% of the patients in the luspatercept arm compared with 13% of those in the placebo arm ( $P < .001$ ).<sup>6</sup>

Dr. Rami Komrokji, from the

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

The first-in-class telomerase inhibitor imetelstat is under investigation in the open-label, single-arm, phase 2 portion of the IMerge phase 2/3 study (ASH 2020 Abstract 658). All patients had a high transfusion burden, 89% had received prior ESAs, and 32% had a serum EPO level over 500 U/L. As of February 4, 2020, there was a median follow-up duration of 24 months for 38 patients. Treatment with imetelstat achieved an 8-week RBC-TI rate of 42% with a median duration of 20 months. RBC-TI was durable for 1 year or longer in 29% of patients. Imetelstat was also associated with a high rate of HI-E (68% for a median of 21 months). The phase 3 portion of the IMerge placebo-controlled study is currently enrolling.

Moffitt Cancer Center in Florida, presented data focused on the specific subset of patients enrolled in the trial who were diagnosed with MDS/MPN-RS-T. Patients with this overlap syndrome, previously referred to as RARS-T, are characterized by having persistently high platelet counts ( $\geq 450 \times 10^9/L$ ) and anemia.<sup>7-9</sup> MDS/MPN-RS-T is a separate disease entity with distinct survival outcomes, and one that practitioners may not realize was a part of this phase 3 trial. Allowed under the inclusion criteria, this retrospective analysis identified 23 patients with MDS/MPN-RS-T in the MEDALIST trial. In this abstract, Dr. Komrokji and colleagues reported that 64.3% of the 14 luspatercept-treated patients achieved the primary endpoint of RBC-TI, compared to 22.2% of the 9 placebo-treated patients ( $P=.028$ ),<sup>10</sup> a finding consistent with the overall MEDALIST trial population. Several other endpoints were also improved with luspatercept, including the rate of RBC-TI for 48 weeks or longer, the rate of modified hematologic improvement-erythroid, and the composite endpoint of clinical benefit. The safety profile of luspatercept in this subset of patients with MDS/MPN-RS-T was consistent with the overall study population, and adverse events included dizziness, nausea, and diarrhea, among others.<sup>10</sup>

One of the main questions related to the use of luspatercept is whether it improves the quality of life in our patients with MDS. Anemia, one of the most important complications in patients with MDS, causes significant fatigue and weakness, and is associated with a negative impact on the patient's QoL. An abstract by Dr. Esther Oliva from Reggio Calabria in Italy reported on results from an analysis of HRQoL outcomes from the MEDALIST trial. To fully appreciate the findings from this presentation, it is important to understand that in the MEDALIST trial, all patients in both arms received best supportive care as clinically indicated. This treatment could include

RBC transfusions. Overall, the transfusion program in the MEDALIST trial maintained hemoglobin levels at 9.0 g/dL or higher in patients.<sup>6</sup> As a result, patients had a similar degree of anemia-related impact on HRQoL in both arms, making it difficult to see measurable changes in HRQoL. Instead, the analysis by Dr. Oliva and colleagues revealed an improvement in the burden of RBC transfusions on the daily life of patients randomized to luspatercept. A total of 39% of patients in the luspatercept arm reported improvements in their daily life from the impact of RBC-TI, compared to 22% of patients in the placebo arm.<sup>11</sup>

Another question that remains regarding the use of luspatercept (as with many drugs) relates to the identification of predictive biomarkers for response to treatment. Previous studies have explored this topic, but have largely reported negative associations.<sup>12</sup> At ASH 2020, Dr. Uwe Platzbecker from University Hospital Leipzig in Germany presented an analysis of biomarkers of luspatercept response.<sup>12</sup> Unfortunately, no clear biomarker with real-world clinical utility emerged from this analysis. However, we should consider that this study was performed using a dataset from the MEDALIST trial which enrolled a very specific subset of patients with MDS who had disease that was either refractory to or unlikely to respond to ESAs, or who had discontinued ESAs due to an adverse event.<sup>6</sup> It is possible that biomarkers for luspatercept activity may be better identified in the COMMANDS trial, which is designed to enroll patients representative of the overall MDS population.<sup>13</sup>

The randomized COMMANDS study (NCT03682536) is an important phase 3 trial that has now initiated and is currently recruiting patients. Dr. Matteo Della Porta from Humanitas University in Milan, Italy presented the design of this study. This open-label study is planned to randomize patients with lower-risk MDS to treatment with luspatercept or epoetin alfa. Unlike the

MEDALIST trial, which only recruited patients with refractory anemia and RS, the COMMANDS trial will enroll a broader group of patients who are ESA-naïve and RBC transfusion-dependent.<sup>13</sup>

In addition to MDS, luspatercept is also being investigated in other myeloid malignancies, including myelofibrosis. Dr. Aaron Gerds, from the Cleveland Clinic in Ohio, presented updated data from the phase 2 ACE-536-MF-001 study, which is evaluating luspatercept as a treatment for patients with myelofibrosis requiring RBC transfusions.<sup>14</sup>

Continuing with the discussion of interventions for patients with lower-risk MDS, Dr. Félix López Cadenas from the Hospital Clínico Universitario de Salamanca in Spain presented a very interesting interim analysis from the European Sintra-REV trial which evaluated lenalidomide in non-transfusion dependent patients.<sup>15,16</sup> Lenalidomide is approved by the FDA for the treatment of transfusion-dependent anemia due to low- or intermediate-1-risk MDS, only in patients with a del(5q) cytogenetic abnormality with or without additional cytogenetic abnormalities.<sup>15</sup> Based on this indication, lenalidomide is currently only administered to patients once they become RBC transfusion-dependent. The Sintra-REV trial explored the benefit of using lenalidomide earlier in the course of disease, before the patients became transfusion-dependent. Low-dose lenalidomide was associated with a delay in disease progression, as well as a longer time to transfusion dependency (the median transfusion-free survival was 6.3 years in the lenalidomide group compared with 2.8 years in the placebo group).<sup>16</sup> In addition to the impactful clinical results showing the superiority of an earlier initiation of lenalidomide, this study may also lend additional data to support earlier interventions overall in patients with lower-risk MDS.<sup>17</sup> Indeed, these results are not surprising, given the previous studies showing that transfusion-independent

### **ABSTRACT SUMMARY Efficacy and Safety of Sabatolimab in Combination With Hypomethylating Agents in Patients With Acute Myeloid Leukemia and High-Risk Myelodysplastic Syndrome: Updated Results From a Phase 1b Study**

Sabatolimab (MBG453) is a humanized monoclonal antibody targeting TIM-3, an inhibitory receptor involved in the regulation of both adaptive and innate immune responses. TIM-3 is expressed on immune cells and leukemic stem cells and blasts, but not normal hematopoietic stem cells. Inhibition of TIM-3 may restore immune function while also directly targeting leukemic stem cells and blasts. The combination of sabatolimab with a hypomethylating agent (either decitabine or azacitidine) was evaluated in a phase 1b, open-label, multicenter, dose-escalation study in patients with AML or high-risk MDS (ASH 2020 Abstract 657). At the data cutoff of June 25, 2020, the objective response rate was 41.2% among 34 evaluable patients with newly diagnosed AML, and the estimated 6-month duration of response rate was 85.1% (95% CI, 68-100). Among 35 evaluable patients with high-risk MDS, the objective response rate was 62.9% and the estimated 6-month duration of response rate was 90% (95% CI, 73.2-100). The most common Grade 3 or higher TEAEs were thrombocytopenia (45.8% in newly diagnosed AML and 51.2% in high-risk MDS), neutropenia (50% and 46.1%), febrile neutropenia (29.2% and 41%), anemia (27.1% and 28.2%), and pneumonia (10.4% and 5.1%). Possible immune-mediated adverse events were also reported.

patients with lower-risk MDS achieved better outcomes with ESA treatment compared to transfusion-dependent patients.<sup>18</sup> Similarly in luspatercept-treated patients, those with a lower transfusion burden tend to do better with treatment as compared to those with a higher transfusion burden when initiating therapy.<sup>6</sup>

Another important presentation was provided by Dr. Platzbecker on the novel telomerase inhibitor imetelstat. First explored in myelofibrosis,<sup>19</sup> this abstract presented data on this agent in transfusion-dependent lower-risk MDS. In this group of heavily transfused patients, the data were striking, with 42% of patients achieving an 8-week RBC-TI outcome, with a median duration of 20 months.<sup>20</sup> Imetelstat may provide an alternative option with a different mechanism and significant activity in patients with lower-risk MDS.

There were also a number of updates to studies focused on the care of patients with higher-risk MDS. For example, Dr. Jacqueline Garcia from the Dana-Farber Cancer Institute in Massachusetts provided an update to

the phase 1b trial M15-531, which was first presented at ASH 2019.<sup>21</sup> This study evaluated the combination of venetoclax plus azacitidine in patients with higher-risk disease who had not received prior therapy. This combination, considered a standard of care for patients with AML who are not candidates for intensive therapy, is now being explored in patients with higher-risk MDS. The data showed a 79% ORR including 39.7% complete remissions. The median duration of response was 12.9 months, and the median OS was 27.5 months (95% CI: 18.2 to not reached). Neutropenia was the most common adverse event overall (83%), and was also the most common serious adverse event (49%).<sup>22</sup> Though the data were not surprising, the study remains important as it serves as the basis for VERONA, an ongoing randomized phase 3 clinical trial of venetoclax plus azacitidine in newly diagnosed patients with higher-risk MDS.<sup>23</sup>

Another combination regimen investigated in patients with higher-risk MDS was presented as a subset analysis of Study P-2001 by Dr. Mikkael Sekeres from the Cleveland Clinic in

Ohio. Study P-2001 compared pevonedistat plus azacitidine versus azacitidine alone. Pevonedistat is a compound that inhibits neddylation that has been studied in multiple trials encompassing both MDS and AML.<sup>24,25</sup> Study P-2001 enrolled patients with higher-risk MDS, AML, or CMML; this analysis was restricted to the 67 patients with higher-risk MDS. In this group of patients, both EFS and OS favored pevonedistat plus azacitidine compared with azacitidine. One important feature of this regimen is that because pevonedistat is not myelosuppressive, its combination with azacitidine is not associated with excess toxicity.<sup>26</sup> While these data indicate a benefit associated with pevonedistat plus azacitidine, we await the results of the ongoing phase 3 PANTHER trial which will more fully evaluate this combination.<sup>27</sup>

Sabatolimab is an anti-TIM-3 antibody under investigation in myeloid malignancies. TIM-3 is expressed both on immune cells as well as the leukemia stem cell, and therefore this agent may have an anti-leukemia effect as well as an immunomodulatory effect, which would be of great interest. Dr. Andrew Brunner, from Massachusetts General Hospital in Boston, provided an update from a phase 1b study in AML and high-risk MDS which evaluated sabatolimab with an HMA. A 62.9% ORR was reported among patients with high-risk MDS. As opposed to what we have seen with other immune checkpoint inhibitors in myeloid malignancies, the safety profile for sabatolimab is encouraging, with a relatively low rate of immune-related toxicities.<sup>28</sup>

Two abstracts of interest focused on the use of decitabine in high-risk MDS. Dr. Michael Savona from the Vanderbilt University School of Medicine in Tennessee expanded on the clinical data regarding the newly approved oral decitabine/cedazuridine regimen. At ASH 2019, we presented data showing 99% equivalent exposure to standard dose IV decitabine 20 mg/m<sup>2</sup> in the ASCERTAIN phase 3 ran-



domized cross-over study.<sup>29</sup> Here, Dr. Savona and colleagues reported on the clinical outcomes with this oral fixed-dose combination, showing that efficacy and safety were consistent with clinical data from standard IV decitabine.<sup>30</sup> In a separate abstract, Dr. Raphael Itzykson from Saint-Louis Hospital AP-HP in France discussed results from the phase 3 DACOTA trial.<sup>31</sup> To our surprise, the outcomes of this trial suggested there was not a major difference in clinical activity between decitabine and hydroxyurea, the standard of care regimen in the United States. These data are in conflict with data we collected at MD Anderson, showing significant clinical activity for HMAs in CMML.<sup>32</sup>

## Summary

Data presented at ASH 2020 provided important updates in patients with lower-risk MDS, including updated data on luspatercept, the potential for early intervention with lenalidomide, and investigational agents such as imetelstat. In higher-risk MDS, we saw updates from doublets that are quite exciting, providing the groundwork for registration trials that are ongoing. What we are now lacking data on are new options for patients with HMA failure; we hope to see more activity in this setting in future meetings.

## Disclosure

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