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Imetelstat Achieves Meaningful and Durable Transfusion Independence in High Transfusion–Burden Patients With Lower-Risk Myelodysplastic Syndromes in a Phase II Study

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PURPOSE Patients with lower-risk (LR) myelodysplastic syndromes (MDS) who are RBC transfusion dependent and have experienced relapse after or are refractory to erythropoiesis-stimulating agent (ESA) have limited treatment options. High telomerase activity and human telomerase reverse-transcription expression in clonal hematopoietic cells have been reported in patients with MDS. Imetelstat, a first-in-class competitive inhibitor of telomerase enzymatic activity, targets cells with active telomerase. We report efficacy, safety, and biomarker data for patients with LR MDS who are RBC transfusion dependent and who were relapsed/refractory to ESAs.

PATIENTS AND METHODS In this two-part phase II/III study (MDS3001), the primary end point was 8-week RBC transfusion independence (TI) rate, with key secondary end points of 24-week RBC TI rate, TI duration, and hematologic improvement-erythroid.

RESULTS Data from the phase II part of the study are reported. Of 57 patients enrolled and treated (overall population), 38 were non-del(5q) and hypomethylating agent and lenalidomide naïve (subset population). The 8- and 24-week RBC TI rates in the overall population were 37% and 23%, respectively, with a median TI duration of 65 weeks. In the subset population, 8- and 24-week RBC TI rates were 42% and 29%, respectively, with a median TI duration of 86 weeks. Eight-week TI rate was observed across all subgroups evaluated. Cytogenetic and mutational data revealed a reduction of the malignant clones, suggesting disease modification activity. The most common adverse events were cytopenias, typically reversible within 4 weeks.

CONCLUSION Imetelstat treatment results in a meaningful, durable TI rate across a broad range of heavily transfused patients with LR MDS who are ineligible for or relapsed/refractory to ESAs. Biomarker analyses indicated effects on the mutant malignant clone.

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ASSOCIATED CONTENT

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Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Myelodysplastic syndromes (MDS) are characterized by clonal and ineffective hematopoiesis, cytopenias (most commonly anemia), and risk of clonal progression, including evolution to acute myeloid leukemia (AML). Telomere length (TL) is shorter in the blood mononuclear cells of patients with MDS compared with controls.¹ However, despite shortened telomeres, telomerase activity (TA) and expression of human telomerase reverse transcription (hTERT; key catalytic subunit of telomerase) are often increased in MDS cells^{2,3} and may drive the expansion of the malignant progenitor cell clone.⁴ Higher TA and hTERT expression and shorter TL, along with other factors, including RBC transfusion dependence (TD), have been

identified as poor prognostic features for patients with MDS, correlating with International Prognostic Scoring System (IPSS) risk score and associated with shorter overall survival and higher risk of progression to AML.^{3,5-10}

For most patients with IPSS low and intermediate-1 risk MDS—collectively termed lower-risk (LR) MDS—the initial therapeutic approach is typically the use of erythropoiesis-stimulating agents (ESAs) with or without other hematopoietic growth factors and transfusions.¹¹ Among anemic patients with LR MDS treated with ESAs, approximately 40% will achieve International Working Group (IWG)-defined hematologic improvement (HI) for a median duration of 2 years; responses to ESAs are typically restricted to

CONTEXT

Key Objective

Can treatment with the first-in-class telomerase inhibitor imetelstat improve outcomes in patients with lower-risk (LR) myelodysplastic syndromes (MDS) by targeting the malignant clones?

Knowledge Generated

Imetelstat produced meaningful and durable transfusion independence (TI) in heavily transfusion-dependent patients with erythropoiesis stimulating agent–relapsed/refractory non-del(5q) LR MDS. Eight- and 24-week TI and hematologic improvement-erythroid were achieved in different subsets of LR MDS, irrespective of the presence of ring sideroblasts. Biomarker data show a reduction of the malignant clone, suggesting disease-modifying activity of imetelstat.

Relevance

Imetelstat induced durable TI in erythropoiesis stimulating agent–relapsed/refractory patients with LR MDS and reduced neoplastic clone size in some patients.

patients with endogenous serum erythropoietin (sEPO) level of less than 500 mU/mL and especially less than 100 mU/mL.¹²⁻¹⁶ Moreover, early ESA failure, defined by primary ESA resistance or relapse within 6 months of response, is associated with shorter survival in LR MDS.¹⁷ Treatment options for patients with LR MDS who are unlikely to experience a response to or who are ineligible for ESA treatment as a result of high serum erythropoietin level, or after ESA failure—that is, primary resistance or postresponse relapse—are limited and may include hypomethylating agents (HMAs), lenalidomide [approved for the del(5q) MDS subtype but not approved for use in non-del(5q) disease], experimental therapies, and supportive care alone or with chelation therapy.^{11,18} Response rates to HMAs and lenalidomide in ESA-refractory or -ineligible patients have ranged from 15% to 30%, and HMAs are not approved for low and intermediate-1 risk MDS in the European Union and many other countries.¹⁹⁻²¹

Imetelstat, a 13-mer oligonucleotide that specifically targets the RNA template of human telomerase, is a potent, first-in-class, competitive inhibitor of telomerase enzymatic activity^{22,23} and has previously demonstrated clinical activity in myeloid malignancies.²⁴⁻²⁶ A pilot study that focused on primary myelofibrosis also included a cohort of nine patients with MDS with ringed sideroblasts (RS), with or without thrombocytosis; three patients with MDS-RS treated with imetelstat 7.5 mg/kg every 4 weeks achieved transfusion independence (TI) for 8 weeks or longer.²⁶ In addition, 31% of patients with myelofibrosis who were RBC transfusion dependent became transfusion independent for 3 months or longer.²⁵ Targeting MDS clones with imetelstat has the potential to improve outcomes, including anemia and associated symptoms, in patients with MDS. IMerge (MDS3001) is global phase II/III study of imetelstat in RBC TD, ESA-relapsed/refractory LR MDS. The results of the phase II part of the study, including efficacy, safety, and biomarker results, are described here. The phase III part of the study is recruiting.

PATIENTS AND METHODS

Study Design

The phase II part of the study was a multicenter, open-label, single-arm design to assess the efficacy and safety of imetelstat in LR MDS. The study was initially designed to include approximately 30 patients with LR MDS who had experienced relapse or were refractory to ESA treatment. Upon review for efficacy and safety of the first 32 enrolled patients, a subset of 13 patients who were non-del(5q) and HMA/lenalidomide naïve was identified to have higher hematologic response rates. Seven (54%) of 13 patients achieved RBC TI lasting 8 or longer weeks versus 11 (34%) of 32 in all enrolled patients.^{27,28} Therefore, the study was expanded to include an additional 25 patients who were non-del(5q) and HMA/lenalidomide naïve, resulting in 38 patients with these baseline characteristics, hereafter described as the subset population, from a total of 57 patients enrolled in this phase II part of the study (hereafter described as the overall population). The futility criterion was as follows: If four patients or fewer among 30 patients in Part 1 achieved RBC TI lasting 8 weeks or longer, the study would be stopped unless there was compelling clinical evidence of efficacy in one or more other end points (eg, transfusion reduction, erythroid improvement). This study was undertaken only after the independent ethics committee/institutional review board had given full approval of the final Protocol, any amendments, and the informed consent form.

Patients, Investigations, and Treatment

The study enrolled patients who were age 18 years or older and had a diagnosis of MDS according to 2008 WHO criteria confirmed by bone marrow (BM) aspirate and/or biopsy within 12 weeks before study entry, LR MDS that was ineligible for or relapsed/refractory to ESA treatment, RBC transfusion dependent (ie, requiring four or more RBC units transfused over an 8-week period during the 16 weeks

before study entry), and an Eastern Cooperative Oncology Group Performance Status score of 0 to 2. To be considered ESA relapsed/refractory, patients must have received 8 weeks or more of treatment with a minimum weekly dose of epoetin alfa 40,000 U, epoetin beta 30,000 U, or darbepoetin alfa 150 µg (or equivalent agent/dose), either: without having achieved hemoglobin rise of 1.5 g/dL or more or decreased RBC transfusion requirement by four or more units over 8 weeks; or increasing TD or reduction in hemoglobin by 1.5 g/dL or more after HI in the absence of another explanation. Patients were also eligible if they were not considered candidates for ESA treatment as a result of endogenous sEPO level greater than 500 mU/mL. For the expansion cohort, patients were required to have no prior treatment with either an HMA or lenalidomide and to be non-del(5q). Laboratory results requirements were an absolute neutrophil count of $1.5 \times 10^9/\text{L}$ or greater and platelets $75 \times 10^9/\text{L}$ or greater, independent of growth factor or transfusion support before treatment. Local pathology reports for MDS diagnosis were reviewed by the sponsor to determine eligibility for the study.

All patients received imetelstat 7.5 mg/kg as 2-hour intravenous infusion every 4 weeks until disease progression, unacceptable toxicity, withdrawal of consent, or lack of response. Transfusion requirements were assessed at each clinic visit and every 12 weeks at disease evaluation visits until the end of treatment, at which point transfusion monitoring was every 4 to 6 weeks. BM examinations were performed at screening, then every 24 weeks, and at time of suspected IWG response up to and including suspected progressive disease. BM pathology results and response were assessed per modified MDS IWG 2006 criteria by the investigator. Karyotyping and sequencing of BM samples was performed as described in the Appendix (online only). Data review committees included an independent data monitoring committee as well as an independent hepatic expert committee.

Study End Points and Statistical Analysis

The primary end point was 8-week RBC TI rate. Secondary end points included 24-week RBC TI rate, time to onset and duration of TI, HI-erythroid response (HI-E) rate (defined as hemoglobin increase of ≥ 1.5 g/dL or greater above the pretreatment level or reduction of four or more units of RBC transfusions/8 weeks compared with prior RBC transfusion burden), MDS response (complete response [CR], marrow CR [mCR], or partial response, per 2006 IWG criteria), and safety. The total number of RBC units required over rolling 8-week time periods was calculated to identify patients who achieved RBC TI or transfusion reduction. Pretreatment hemoglobin level was defined as the mean of all hemoglobin values in the 8 weeks before entry, including the value on cycle 1 day 1 and excluding values within 14 days after transfusion—if no hemoglobin values met this definition, the last value before treatment initiation was used.

Proportions of patients with 8- and 24-week RBC TI, HI-E, and IWG response were summarized with percentages and 95% 2-sided exact CIs. Times to 8- and 24-week RBC TI were summarized descriptively. We used the Kaplan-Meier method to estimate RBC TI duration.

RESULTS

Patients

Baseline demographic and clinical characteristics for the overall and subset populations who were enrolled and treated with imetelstat are listed in [Table 1](#). Baseline transfusion burden was high, with a median of 7 units/8 weeks (range, 4 to 14 units) in the overall population and 8 units/8 weeks (range, 4 to 14 units) in the subset population. Ninety-three percent and 92% of patients in the overall and subset populations, respectively, received more than 4 units/8 weeks.

At the clinical cutoff of April 30, 2019, median follow up for the overall population ($n = 57$) was 16.4 months (range, 3.9 to 37.5 months) and 15.7 months (range, 5.6 to 16.5 months) for the subset population ($n = 38$). Overall, median treatment duration was 8.2 months (range, 0.02 to 37.5 months), with a median of eight treatment cycles (range, one to 39 cycles). Treatment was ongoing at the time of cutoff in 14 patients in the overall population (25%; including 12 in the subset population), with the 43 treatment discontinuations because of a lack of efficacy ($n = 16$; 28% of overall population), adverse events ($n = 14$; 25%), withdrawal by patient or patient refusal ($n = 6$; 11%), progressive disease ($n = 3$; 5%, including transformation to AML in two patients), death ($n = 2$; 4%), relapse as a result of recurrent TD ($n = 1$; 2%), and physician decision ($n = 1$; 2%).

Efficacy

Efficacy outcomes are summarized in [Table 2](#). The primary end point of 8-week RBC TI rate was 37% in the overall population and 42% in the subset population, with 24-week RBC TI rates of 23% and 29%, respectively. Median time to onset of 8-week RBC TI was 8.3 weeks in both populations (range, 0.1 to 100.6 weeks and 0.1 to 40.7 weeks in overall and subset populations, respectively), with median duration of 65 weeks in the overall population (range, 17 to 140.9 weeks) and 85.9 weeks (range, 8.0 to 140.9 weeks) in the subset population. Of the 8-week RBC TI responders, 62% in the overall population and 75% in the subset population had a hemoglobin rise of 3 g/dL or greater from the pretreatment level. The 8-week RBC TI rate did not differ on the basis of baseline RBC transfusion burden, presence of RS, or baseline sEPO levels ([Fig 1](#)).

HI-E rate per IWG 2006 was 65% in the overall population and 68% in the subset population. Mean relative reduction of RBC transfusion burden from baseline was 63% in the overall population and 68% in the subset population ([Table 2](#) and [Fig 2](#)).

TABLE 1. Baseline Demographic and Clinical Characteristics

Demographic or Characteristic	Overall Population (n = 57)	Subset Population (n = 38)
Median age, years (range)	71.0 (46-83)	71.5 (46-83)
Male	32 (56)	25 (66)
ECOG PS 0-1	52 (91)	34 (89)
IPSS risk		
Low	36 (63)	24 (63)
Intermediate-1	21 (37)	14 (37)
IPSS-revised risk ^a		
Very low	3 (5)	2 (5)
Low	37 (65)	25 (66)
Intermediate	9 (16)	7 (18)
Median RBC transfusion burden, units/8 weeks (range)	7 (4-14)	8 (4-14)
> 4 units/8 weeks at baseline	53 (93)	35 (92)
WHO 2001 category		
RARS or RCMD-RS	35 (61)	27 (71)
RA, RCMD, or RAEB-1	22 (39)	11 (29)
Prior ESA use	51 (90)	34 (89)
sEPO > 500 mU/mL	22 ^b (40)	12 ^b (32)

Note. Data are presented as No. (%) unless otherwise indicated.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group Performance Status; ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System; RA, refractory anemia; RAEB1, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; sEPO, serum erythropoietin.

^aEight patients in the overall (n = 4 in subset) population had missing baseline cytogenetic data and could not be reclassified per IPSS-revised.

^bOf 55 patients in the overall (n = 37 in subset) population with baseline sEPO levels.

Using updated IWG 2018 guidelines, all enrolled patients would be classified as high transfusion burden: eight or more RBCs in 16 weeks, four or more in 8 weeks. A clinically meaningful major response, defined as 16-week RBC TI, per the 2018 guidelines, was achieved by 28% of the overall population and 37% of the subset population. A

TABLE 2. Summary of Efficacy Outcomes

Parameter	Overall Population (n = 57)	Subset Population (n = 38)
8-week TI ^a , No. (%)	21 (37)	16 (42)
Median time to onset, weeks (range)	8.3 (0.1-100.6)	8.3 (0.1-40.7)
Median duration of TI ^b , weeks (range)	65 (17.0-140.9)	85.9 (8.0-140.9)
24-week TI ^a , No. (%)	13 (23)	11 (29)
HI-E per IWG 2006, No. (%)	37 (65)	26 (68)
≥ 1.5 g/dL increase in Hgb lasting ≥ 8 weeks	15 (26)	12 (32)
Transfusion reduction by ≥ 4 units/8 weeks	37 (65)	26 (68)
Response per IWG 2018, No. (%)		
Major response: 16-week TI	16 (28)	14 (37)
Major response: 8-week TI	21 (37)	16 (42)
Minor response ^c	28 (49)	20 (53)

Abbreviations: HI-E, hematologic improvement-erythroid; IWG, International Working Group; TI, transfusion independence.

^aTI rates were assessed for all treated patients.

^bPer Kaplan-Meier method.

^c50% or greater RBC transfusion burden reduction/16 weeks.

FIG 1. Eight-week transfusion independence (TI) in the subset population ($n = 38$): Subgroup analysis. IPSS, International Prognostic Scoring System; RARS, refractory anemia with ringed sideroblasts; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts.

minor response—defined as 50% or greater transfusion reduction in 16 weeks, per the 2018 guidelines—was exhibited by 49% of the overall population and 53% of the subset population (Table 2).

Per modified IWG 2006 criteria, for the overall population, CR was reported for five patients (9%) and mCR for six patients (11%) with no partial responses, for an overall response rate of 19%, per investigator assessment. For the subset population, corresponding CR, mCR, and overall response rates were 10%, 13%, and 24%, respectively. Overall, five (46%) of 11 mCR and CR patients had complete resolution of dysplasia. Mean BM blast percentage at baseline was 2% (range, 0% to 10%) in these patients with LR MDS. Eight CR and mCR patients

demonstrated RS on screening BM aspirate and all had either complete disappearance of BM RS cells—four of eight patients—or 30% or greater reduction of BM RS—four of eight patients—on treatment.

In the subset population, baseline cytogenetic data were available for 34 patients, six of whom were identified as intermediate or poor cytogenetic risk, per IPSS, and five (83%) of six achieved 8-week TI, all with MDS RS WHO subtype. All three patients in the subset population with trisomy 8 achieved 8-week TI, two of whom maintained TI that lasted longer than 18 months. Partial cytogenetic response occurred in two of three patients with available post-treatment cytogenetic data. One patient had a decrease from 45% clone of trisomy 8 from baseline to 5% at week

FIG 2. Reductions in transfusion burden in the subset population ($n = 38$). HI-E, hematologic improvement-erythroid; TI, transfusion independence; TR, transfusion reduction.

FIG 3. (A) Reduction of *SF3B1* mutation variant allele frequency (VAF) post-imetelstat treatment. (*) Remain on treatment. (B) Correlation between percentage reduction of *SF3B1* mutation VAF and the duration of the longest transfusion independence (TI). (C) Correlation between percentage reduction of *SF3B1* mutation VAF and the onset time to achieve the longest TI interval. Data updated with cutoff on February 4, 2020.

24 and another from 100% at baseline to 25% at week 24, and additional reduction to 5% at week 48. In the non-subset population, almost all patients with abnormal cytogenetic data had del(5q). Two of four patients with del(5q) had clonal reduction.

Among 13 patients with pre- and post-treatment mutation analysis, 11 patients had baseline *SF3B1* mutations, and 10 had a reduction (range, 10% to 93%) in *SF3B1* variant allele frequency (VAF) from baseline (Fig 3A). As depicted in Figure 3, the greater the reduction of *SF3B1* VAF

observed, the longer the TI duration; patients achieving 50% or greater VAF reduction remained TI for more than 18 months (Fig 3B). Furthermore, significant correlation (Pearson correlation coefficient $r = 0.646$; $P = .032$) between greater reduction of *SF3B1* VAF and shorter onset time to achieve the longest TI was observed (Fig 3C). *SF3B1* VAF reduction was observed in different hot spots of *SF3B1*: K700E in four patients; R625C in two patients; and R625L, H662Q, E622D, and K666R each in one patient (Fig 3A). VAF reduction in other genes, such as SRSF2

TABLE 3. Most Frequent Hematologic and Nonhematologic Adverse Events

Event	Overall Population		Subset Population	
	All Grades (n = 57)	Grade ≥ 3 (n = 57)	All Grades (n = 38)	Grade ≥ 3 (n = 38)
Hematologic (all grades, ≥ 20% in either arm)				
Thrombocytopenia	35 (61)	31 (54)	25 (66)	23 (61)
Neutropenia	38 (67)	34 (60)	22 (58)	21 (55)
Anemia	13 (23)	11 (19)	10 (26)	8 (21)
Nonhematologic (all grades, ≥ 15% in either arm)				
Back pain	9 (16)	3 (5)	7 (18)	2 (5)
ALT increased	10 (18)	3 (5)	7 (18)	2 (5)
AST increased	8 (14)	3 (5)	6 (16)	3 (8)
Bronchitis	6 (11)	3 (5)	6 (16)	3 (8)
Headache	12 (21)	1 (2)	6 (16)	1 (3)
Nasopharyngitis	6 (11)	0 (0)	6 (16)	0 (0)
Diarrhea	9 (16)	1 (2)	6 (16)	0 (0)
Constipation	8 (14)	0 (0)	6 (16)	0 (0)
Peripheral edema	8 (14)	0 (0)	6 (16)	0 (0)
Asthenia	6 (11)	1 (2)	6 (16)	1 (3)

NOTE. Data are presented as No. (%). Hematologic adverse events were treatment emergent, per reported adverse events (not laboratory values). Frequency of reported grade 3/4 hematologic adverse events was consistent with cytopenias reported through laboratory values. For nonhematologic adverse events, the number and frequency of patients per reported adverse events are shown. Adverse events that occurred in either arm in at least 15% of subjects are reported.

P95L, JAK2-V617F, or DNMT3A-R882H, was also observed in a limited number of patients. Taken together, these data suggest that imetelstat may have disease-modifying activity by reducing the mutated clones.

Biomarkers

To assess the on-target activity of imetelstat, we measured changes in TA and hTERT RNA levels. Of patients with available samples in the overall population, eight (38%) of 21 and 30 (59%) of 51 patients achieved TA and hTERT 50% or greater reduction from baseline postimetelstat treatment, respectively. In the subset population, 50% or greater reduction in TA and hTERT were observed in three (23%) of 13 and 19 (54%) of 35 patients, respectively. The relationship between the optimal target inhibition (hTERT $\geq$ 50% reduction) and clinical response (8-week or 24-week TI) was further explored. In the overall population, compared with patients without TI, a higher proportion of patients who had 50% or greater reduction in hTERT expression achieved 8-week TI (75% [15 of 20] v 48% [15 of 31]; $P = .083$) and 24-week TI (85% [11 of 13] v 50% [19 of 38]; $P = .048$). In the subset population, the proportion of patients who achieved 50% or greater hTERT reductions from baseline was significantly higher among patients with 8-week TI versus without 8-week TI (80% [12 of 15] vs 35% [7 of 20]) and with 24-week TI versus without 24-week TI (91% [10 of 11] v 38% [9 of 24]), with Fisher exact test $P = .016$ and $P = .004$, respectively.

Safety

The safety findings were consistent between the subset and overall populations (Table 3). Within the subset population, 37 patients (94%) and 31 patients (82%) experienced one or more treatment-emergent adverse events (TEAE) and grade 3 or greater TEAE, respectively. All-grade and grade 3 or greater TEAEs were primarily hematologic, including thrombocytopenia, neutropenia, and anemia (Table 3). Only one patient had anemia that was assessed as related to imetelstat. Median duration was 1.7 weeks for grade 3/4 neutropenia and 1.1 weeks for grade 3/4 thrombocytopenia. Ninety percent of grade 3/4 neutropenia events and 88% of grade 3/4 thrombocytopenia events were reversible—that is, resolved to grade 2 or lower—within 4 weeks. Events not reported as resolved within 4 weeks either resolved after 4 weeks or were ongoing at the time of clinical cutoff. There were two patients with febrile neutropenia (5%) and two with grade 3/4 bleeding events (5%), which were not related to imetelstat. One occurred in the setting of thrombocytopenia that was likely a result of imetelstat. The most common grade 3 or greater non-hematologic TEAEs were AST elevation and bronchitis, with incidences of 18%. Reversible grade 3 transaminasetransaminase elevations were observed in three patients (8%), with no cases of liver test elevations consistent with Hy's Law.

DISCUSSION

In this phase II study of imetelstat in 57 heavily TD patients (median, 7 units pRBC/8 weeks) with LR MDS, treatment produced meaningful and durable TI, particularly in the subset population of patients who were non-del(5q) and HMA/lenalidomide naïve for whom the 8-week and 24-week TI rates were 42% and 29%, respectively. TI was durable, with a median duration of approximately 21 months, which is the longest TI reported thus far in the non-del(5q) MDS setting, and was consistently observed across different subgroups, irrespective of baseline disease burden, presence of RS, or baseline EPO levels, unlike recently reported data for luspatercept.²⁹ HI-E rate was 68%, despite the high pretreatment RBC transfusion burden (median, 8 units/8 weeks) of these patients. If the more stringent IWG 2016 criteria are applied, it is evident that imetelstat induces a durable and clinically meaningful major response—28% of the overall population and 37% of the subset population. Imetelstat also demonstrated evidence of disease-modifying activity with reduction in cytogenetically abnormal clones and mutational allele burden in a subset of patients, although only a small number of patients were tested. All three patients with trisomy 8 achieved 8-week TI, two of whom achieved partial cytogenetic response and maintained TI for more than 18 months. Furthermore, substantial *SF3B1* VAF reduction was observed in patients who maintained the longest TI on study. The reduction of cytogenetic and molecular aberrant clones suggests potential disease-modifying activity of imetelstat. This is in contrast to luspatercept, an erythroid maturation agent, for which disease-modification activity has not been observed to date.²⁹

On the basis of the suggested mechanism of action of imetelstat and results from preclinical and previous clinical studies, imetelstat was expected to cause TA inhibition, TL shortening, and hTERT level reduction.²²⁻²⁴ On-target activity was indeed demonstrated by reductions in both TA and hTERT expression. An association between hTERT reduction from baseline and TI response was evident, with patients who achieved 8- or 24-week TI having significantly higher proportions of 50% or greater reduction in hTERT expression, the threshold identified as the pharmacodynamic effect correlating with in vivo antitumor activity in preclinical xenograft models (data on file).

With ongoing follow up, imetelstat has demonstrated a predictable safety profile, with no new safety signal identified in this study. As expected, on the basis of previously reported data in other disease settings,²⁵ reversible cytopenias were the most frequent TEAEs, mostly grade 3 or greater events, but with limited clinical consequences. Febrile neutropenia was uncommon and no patients died of infection or bleeding. The most common grade 3 or greater nonhematologic TEAEs were AST elevation and bronchitis.

In conclusion, in this phase II study, imetelstat induced meaningful and durable TI and a high HI-E rate in a population of heavily RBC-dependent, ESA-relapsed/refractory LR MDS, irrespective of presence of RS. Data suggest

potential disease-modifying activity with imetelstat treatment by reducing the malignant clones driving the disease. An ongoing phase III placebo-controlled trial will provide more definitive insight into the efficacy and safety of imetelstat.

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Imetelstat Achieves Meaningful and Durable Transfusion Independence in High Transfusion–Burden Patients With Lower-Risk Myelodysplastic Syndromes in a Phase II Study

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APPENDIX

Methods

Bone marrow samples were collected at screening to assess the cytogenetic profile at a central laboratory using the standard karyotyping method of G-banding technique. For patients who had cytogenetic abnormalities, follow-up samples at every 24 weeks were evaluated for the change of cytogenetic abnormal clones for cytogenetic response. Blood samples were evaluated centrally using next-generation sequencing with Illumina TruSight Myeloid Sequencing Panel of 54 genes known to be involved in myeloid malignancies. Nonsynonymous variants were further filtered by read depth 1,000 or greater, variant allele frequency of 5% or greater (2% for well-

documented hotspots), variants having a frequency of more than 1% in the 1,000 Genomes database, previously reported by the test laboratory, effect of the amino acid change, and predicted deleteriousness, to characterize mutation status and change of variant allele frequency during the study.

Blood samples were also collected from all patients to analyze telomerase activity using quantitative telomeric repeat amplification protocol technology, telomerase length using high-throughput quantitative fluorescence in situ hybridization technology, and human telomerase reverse transcription levels using Taqman reverse-transcription polymerase chain reaction assay at baseline and during treatment.