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Overall survival and long-term outcomes from the randomized, double-blind, placebo-controlled, phase III IMerge trial of imetelstat for lower-risk myelodysplastic syndromes

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PF and FF designed and performed the research, and analyzed and interpreted the data.

MRS designed and performed the research, collected, analyzed, and interpreted the data.

MAS, TB, and RSK performed the research and analyzed and interpreted the data.

QX and LS performed statistical analyses.

YW designed and performed the research, collected, analyzed, and interpreted the data, and performed statistical analyses.

FH designed and performed the research, collected, analyzed and interpreted the data, and outlined the manuscript.

UP designed and performed the research, and collected, analyzed, and interpreted the data.

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Patients with lower-risk myelodysplastic syndromes (LR-MDS) who are red blood cell (RBC) transfusion dependent (TD) have worse prognosis, including shorter overall survival (OS) compared with those who are not RBC-TD.[1] Thus, improving OS represents a recent shift in the paradigm of treatment goals, with RBC transfusion independence (TI) being a key clinical achievement.[2] However, assessing effects of treatment on survival in LR-MDS is complicated by the relatively long natural disease course, older age of patients at diagnosis and associated competing risks of death from comorbidities, and the shorter time horizons of most clinical trials.[1,3] For instance, OS outcomes with frontline luspatercept in erythropoiesis-stimulating agent (ESA)-naive patients in the Phase III COMMANDS trial were recently presented; after >3 years of follow-up, mOS was not reached with luspatercept versus 46 months with epoetin alfa, with median follow-ups of 35.9 months and 30.8 months, respectively.[4] Favorable outcomes are particularly difficult to achieve in patients who previously received treatment with ESAs and lost response.[5]

In the primary analysis of the Phase III IMerge trial (NCT02598661), imetelstat demonstrated greater ≥8-week, ≥24-week, and ≥1-year (primary, secondary, and post hoc endpoints, respectively) RBC-TI versus placebo.[6] At the time of the primary analysis, data were too immature to assess OS (prespecified secondary endpoint). Here, we report long-term OS, progression-free survival (PFS), progression to acute myeloid leukemia (AML), and safety. Although the study was not powered to detect statistical significance for this long-term analysis, imetelstat continued to be well tolerated, with no new safety signals, a low rate of progression to AML, and a favorable trend in OS versus placebo.

IMerge enrolled adults with low- or intermediate-1–risk MDS per International Prognostic Scoring System (IPSS) criteria who were RBC-TD (requiring ≥4 units over an 8-week period during 16 weeks before randomization), had del(5q)-negative disease, relapsed or were refractory to or ineligible for ESAs (due to serum erythropoietin [sEPO] concentration >500

mU/mL) for ESAs, and had not received lenalidomide or hypomethylating agent.[6] Patients were randomized 2:1 to imetelstat (7.1 mg/kg active dose) or placebo. Informed consent and institutional review board/ethics committee approval were obtained; all guidelines and laws regarding the conduct of clinical trials were followed. The primary end point was the proportion of patients who achieved RBC-TI for ≥8 consecutive weeks. Median OS (mOS; interval from randomization to death from any cause), PFS (time from randomization to the first date of disease progression or death from any cause, whichever occurred first), and time to progression to AML (interval from randomization date to the date of AML progression) were prespecified secondary end points. Outcome distributions were compared using a stratified log-rank test for the intention-to-treat (ITT) analysis set. Kaplan-Meier methodology was used to estimate distribution for each treatment. The treatment effect (hazard ratio [HR]) and its two-sided 95% CIs were estimated using a stratified Cox regression model with treatment as the sole explanatory variable. The study was not powered to detect statistical significance in mOS, PFS, or time to progression to AML.

At data cutoff (May 10, 2025), median follow-up was 45 months. The ITT population comprised 178 patients (Table 1). Subsequent anticancer therapy was received by 57/118 (48.3%) of imetelstat-treated patients and 35/59 (59.3%) of placebo recipients, most commonly luspatercept in 41 (34.7%) and 18 (30.5%) patients, respectively, and hypomethylating agents (HMA) in 12 (10.2%) and 12 (20.3%), respectively.

No new safety signals emerged from the primary analysis.[6] Of the 45 imetelstat-treated patients who died, 11 (24.4%) died 6 months to 1 year after their last dose, and 20 (44.4%) died >1 year after their last dose. In the placebo group, 23 patients died (5 [21.7%] patients 6 months to 1 year after their last dose and 14 [60.9%] patients >1 year after their last dose). Two patients in the imetelstat group and 1 patient in the placebo group died from adverse events (sepsis, myocardial infarction, and aortic stenosis, respectively) within 30 days of their last dose.

Progression to AML remained low in both groups at 1.7% (2/118) for imetelstat versus 3.3% (2/60) for placebo (HR=0.45 [95% CI: 0.06-3.23]).

In the ITT population, mOS (95% CI) was 47.8 months (38.3-not estimable [NE]) for imetelstat and 44.8 months (37.4-NE) for placebo (HR=0.82 [95% CI: 0.48-1.38], favoring imetelstat) (Figure 1A). When OS was adjusted for subsequent anticancer therapy by censoring patients at start of subsequent therapy, the HR was 0.84 (95% CI: 0.37-1.94; Figure 1B), with HRs of 0.76 (95% CI: 0.41-1.41) and 0.83 (95% CI: 0.47-1.48) when censored specifically for subsequent luspatercept or HMA, respectively (Figure 1C and 1D). The post hoc landmark mOS analysis of patients reaching ≥42 months (n=63) demonstrated an HR of 0.33 (95% CI: 0.09-1.20; *P*=.077), favoring imetelstat (Supplemental Figure 1). The 42-month landmark captures the onset of clinically meaningful separation between treatment arms, allowing for assessment of emerging long-term survival benefit while maintaining sufficient numbers at risk for reliable estimation. Median (95% CI) PFS in the ITT population was 47.6 months (29.2-NE) for imetelstat and 42.2 months (16.7-NE) for placebo (HR=0.82 [95% CI: 0.43-1.54]), favoring imetelstat.

Among patients who achieved ≥8-week RBC-TI with imetelstat (n=47), mOS (95% CI) was 47.8 months (35.3-NE) versus NE (30.7-NE) in nonresponders (n=71; HR=0.93 [0.51-1.70]; Figure 2A). For those who achieved ≥24-week RBC-TI with imetelstat (n=33), mOS (95% CI) was NE (40.4-NE) versus 45.7 months (29.2-NE) in nonresponders (n=85; HR=0.72 [0.37-1.38]; Figure 2B), and for those who achieved ≥1-year RBC-TI with imetelstat (n=21), mOS (95% CI) was NE (39.1-NE) versus 47.8 months (31.8-NE) in nonresponders (n=97; HR=0.73 [0.35-1.53]; Figure 2C). Among imetelstat-treated patients who achieved a ≥1.5-g/dL central hemoglobin rise from pretreatment lasting ≥8 weeks (International Working Group [IWG] 2006 hematologic improvement-erythroid criteria; n=40), mOS (95% CI) was NE (39.1-NE) versus 47.8 months (29.2-NE) for nonresponders (n=78; HR=0.74 [0.40-1.37]; Figure 2D). By censoring at the start of subsequent anticancer therapy, the same ≥8-week RBC-TI responders vs nonresponders

yielded an HR of 0.51 (95% CI: 0.20-1.32; Supplemental Figure 2A), with HRs of 0.41 (95% CI: 0.16-1.08), 0.58 (95% CI: 0.22-1.56), and 0.38 (95% CI: 0.14-1.00) for those who achieved ≥24-week RBC-TI, ≥1-year RBC-TI, and ≥1.5-g/dL central hemoglobin rise from pretreatment lasting ≥8 weeks vs nonresponders, respectively (Supplemental Figure 2B, 2C, 2D).

Subgroup analyses of mOS trended in favor of imetelstat over placebo for most subpopulations of interest, although the CIs for the HRs were large and crossed 1 (Supplemental Figure 3). Notably, differences in mOS were observed in patients with sEPO >500 mU/mL. This is particularly clinically relevant because numerous studies have shown that patients with higher versus lower sEPO levels are less likely to have a hematologic response and/or shorter survival with ESA, lenalidomide, or luspatercept, leaving hypomethylating agents as the only treatment option for patients with high sEPO levels.[7-10] No significant differences were observed in OS across baseline platelet count subsets (<150 x 10^9/L and ≥150 x 10^9/L) among patients in the imetelstat or placebo groups, indicating that baseline platelet levels do not affect the OS benefit of imetelstat.

In addition, imetelstat-treated patients with *SF3B1*-mutated disease had longer mOS versus those without this mutation (HR=0.32 [95% CI: 0.16-0.64]; nominal *P*<.001); results in placebo recipients with this mutation were nonsignificant (HR=0.88 [95% CI: 0.32-2.45]; nominal *P*=.803). These results are comparable to previous reports showing patients with MDS and *SF3B1* mutations responding better to treatment than those with *SF3B1* wild type.[11]

In summary, after 45 months of follow-up, mOS trended to be longer in imetelstat-treated patients compared with placebo recipients. Median PFS rate also tended to favor imetelstat over placebo, and imetelstat did not appear to cause leukemic progression, supporting the potential disease-modifying properties of imetelstat that were suggested in an exploratory translational analysis of IMerge.[12] Trends toward OS benefit with imetelstat were observed across subgroups of interest, but the numbers of patients in each subgroup were small and results were not statistically significant. These findings are encouraging and warrant additional investigation in a

larger population. Lastly, because OS was generally longer in imetelstat responders versus nonresponders, these results suggest that the durable RBC-TI and increases in hemoglobin observed with imetelstat can potentially lead to improved survival outcomes, as previously described in the literature.[13]

The inclusion criteria of IMerge characterize a population of patients with LR-MDS who presented with poor prognosis, including survival, mainly because of high transfusion burden and because they presented with disease that was refractory, relapsed, or ineligible to ESAs (serum EPO >500 mU/mL). Thus, the patients included in the IMerge study constitute a LR-MDS population very different from that of other trials that enrolled patients with lower transfusion burden or who were ESA naïve.[6,14,15] The significant duration of response in terms of RBC-TI and OS advantage with luspatercept versus EPO was observed in first-line–treated patients; only 35% (64/182) had a transfusion burden ≥4–<6 U/8 weeks.[8]

Here, the survival benefits seen with imetelstat were maintained in patients who received subsequent therapy, including luspatercept and HMAs, suggesting that these responses are attributable to the therapeutic activity of imetelstat rather than to disease progression or the influence of other interventions. Although not statistically powered to detect significance in the long-term time-to-event endpoints, if the observed trends persist, longer follow-up of the IMerge population and/or analyses in larger populations may ultimately demonstrate statistical significance. Thus, these findings support the long-term clinical benefits of imetelstat in the challenging setting of patients with previously treated RBC-TD LR-MDS with a high transfusion burden.

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TABLE 1. Baseline patient and disease characteristics in the ITT population (N=178).

Characteristic	Imetelstat (N=118)	Placebo (N=60)
Age, years, median (range)	71.5 (44-87)	73.0 (39-85)
Male, No. (%)	71 (60.2)	40 (66.7)
WHO classification, No. (%)		
RS+	73 (61.9)	37 (61.7)
RS−	44 (37.3)	23 (38.3)
IPSS risk category, No. (%)		
Low	80 (67.8)	39 (65.0)
Intermediate-1	38 (32.2)	21 (35.0)
Pretreatment Hb, median (range),[a] g/dL	7.9 (5.3-10.1)	7.8 (6.1-9.2)
Transfusion burden per IWG 2018 criteria, No. (%)		
HTB	97 (82.2)	42 (70.0)
LTB	21 (17.8)	18 (30.0)
Prior RBC transfusion burden, No. (%)		
≤6 U/8 weeks	62 (52.5)	33 (55.0)
>6 U/8 weeks	56 (47.5)	27 (45.0)
Serum EPO level, No. (%)[b]		
≤500 mU/mL	87 (73.7)	36 (60.0)
>500 mU/mL	26 (22.0)	22 (36.7)
Mutation status, No. (%)	**n=107**	**n=54**
>1 mutation	76 (71.0)	38 (70.4)
SF3B1 mutation	82 (76.6)	43 (79.6)
TET2 mutation	40 (37.4)	14 (25.9)
ASXL1 mutation	18 (16.8)	6 (11.1)
DNMT3A mutation	19 (17.8)	9 (16.7)
Subsequent anticancer therapy,[c] No. (%)	**n=118**	**n=59**
≥1 anticancer therapy	57 (48.3)	35 (59.3)
Luspatercept	41 (34.7)	18 (30.5)
HMA	12 (10.2)	12 (20.3)
ESA	7 (5.9)	2 (3.4)
Lenalidomide	5 (4.2)	4 (6.8)
Other antineoplastic agent[d]	9 (7.6)	3 (5.1)

[a]Average of all Hb values in the 8 weeks before the first dose date, excluding values within 14 days after a transfusion, which was considered to be influenced by transfusion. [b]Data missing for 5 patients in the imetelstat group and 2 in the placebo group. [c]Safety analysis population. [d]Includes venetoclax, hydroxycarbamide, onametostat, other, selinexor, and imetelstat (placebo group). EPO: erythropoietin; ESA: erythropoiesis-stimulating agent; Hb: hemoglobin; HTB: high transfusion burden; IPSS: International Prognostic Scoring System; ITT: intention-to-treat; IWG: International Working Group; LTB: low transfusion burden; RBC: red blood cell; RS: ring sideroblast; WHO: World Health Organization.

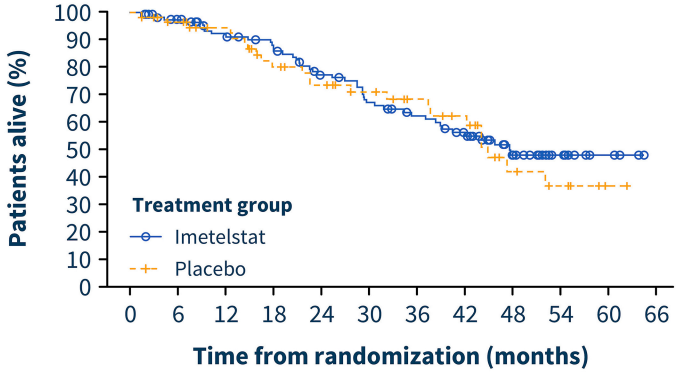
Figure Legends

Figure 1. OS in the ITT population. OS in (A) the total ITT population (N=178), (B) when censoring at start of subsequent anticancer therapy, (C) when censoring at the start of subsequent luspatercept only,[a] and (D) when censoring at the start of subsequent HMAs. Data cutoff: May 10, 2025, 45 months of follow-up. [a]All other subsequent therapies were not censored. HMA: hypomethylating agent; HR: hazard ratio; ITT: intention-to-treat; N/A: not available; NE: not estimable; OS: overall survival.

Figure 2. OS in imetelstat-treated patients. OS in imetelstat-treated patients who achieved (A) ≥8-week RBC-TI, (B) ≥24-week RBC-TI, or (C) ≥1-year RBC-TI and (D) in imetelstat-treated patients who achieved an Hb rise ≥1.5 g/dL lasting ≥8 weeks from pretreatment level per IWG 2006 HI-E criteria. Hb: hemoglobin; HI-E: hematologic improvement-erythroid; HR: hazard ratio; IWG: International Working Group; NE: not estimable; OS: overall survival; RBC: red blood cell; TI: transfusion independence. Data cutoff: May 10, 2025, 45 months of follow-up. [a]Includes patients who achieved ≥8-week but <24-week RBC-TI responders and ≥8-week RBC-TI nonresponders. [b]Includes patients who achieved ≥8-week but <1-year RBC-TI responders and ≥8-week RBC-TI nonresponders. [c]Hb responders = Hb rise ≥1.5 g/dL lasting ≥8 weeks from pretreatment level per IWG 2006 HI-E criteria.

A

OS Analysis, ITT Population	Imetelstat (n=118)	Placebo (n=60)
Deaths, No. (%)	45 (38.1)	23 (38.3)
OS, median (95% CI), months	47.8 (38.3-NE)	44.8 (37.4-NE)
HR (95% CI)	0.82 (0.48-1.38)	

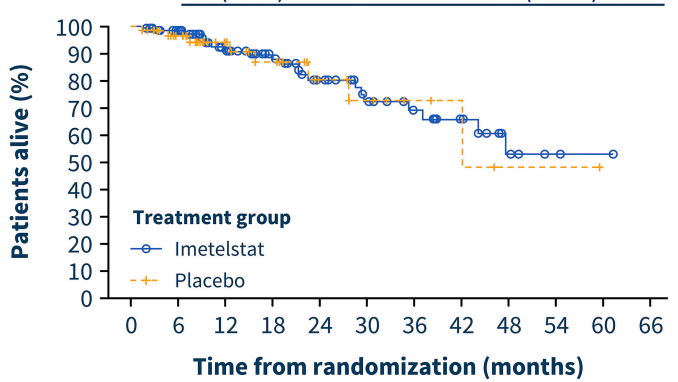


Number of patients at risk

Imetelstat	118	105	92	84	70	60	52	44	27	10	4	0
Placebo	60	54	48	38	33	28	23	19	9	5	1	0

B

OS Analysis, Censored at Subsequent Therapy	Imetelstat (n=118)	Placebo (n=60)
Deaths, No. (%)	21 (17.8)	8 (13.3)
OS, median (95% CI), months	NE (37.1-NE)	42.2 (27.7-NE)
HR (95% CI)	0.84 (0.37-1.9)	

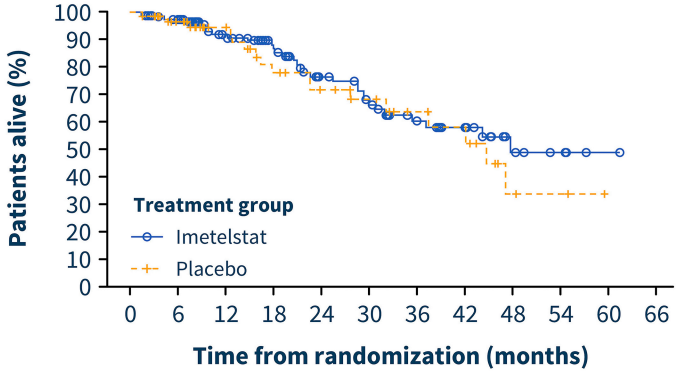


Number of patients at risk

Imetelstat	118	100	69	52	36	27	20	15	7	3	1	0
Placebo	60	45	29	21	11	7	4	3	1	1	0	

C

OS Analysis, Censored at Subsequent Luspatercept	Imetelstat (n=118)	Placebo (n=60)
Deaths, No. (%)	31 (26.3)	17 (28.3)
OS, median (95% CI), months	47.6 (31.8-NE)	44.8 (32.2-NE)
HR (95% CI)	0.76 (0.41-1.41)	

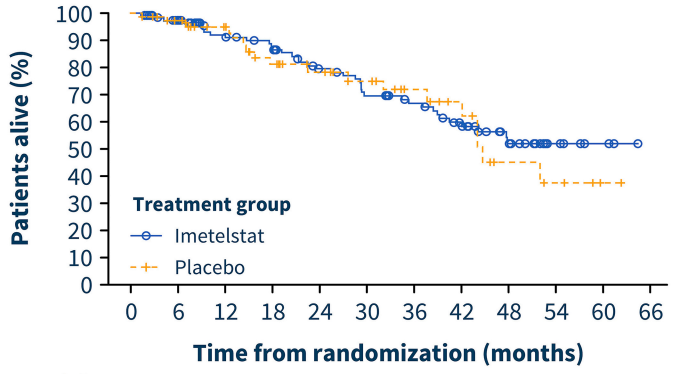


Number of patients at risk

Imetelstat	118	103	78	64	47	38	26	20	9	4	1	0
Placebo	60	49	37	27	22	17	12	10	3	2	0	

D

OS Analysis, Censored at Subsequent HMA	Imetelstat (n=118)	Placebo (n=60)
Deaths, No. (%)	38 (32.2)	18 (30.0)
OS, median (95% CI), months	NE (39.1-NE)	44.8 (37.7-NE)
HR (95% CI)	0.83 (0.47-1.5)	

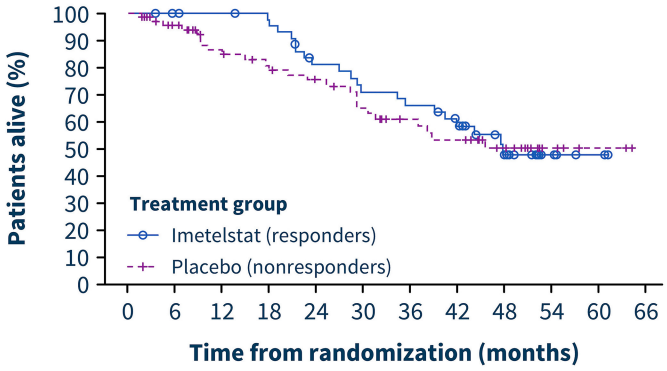


Number of patients at risk

Imetelstat	118	102	85	78	65	56	49	38	24	8	3	0
Placebo	60	53	44	34	28	23	17	13	6	4	1	0

A

	≥8-Week RBC-TI Responders (n=47)	≥8-Week RBC-TI Nonresponders (n=71)
Deaths, No. (%)	45 (38.1)	23 (38.3)
OS, median (95% CI), months	47.8 (38.3-NE)	44.8 (37.4-NE)
HR (95% CI)	0.82 (0.48-1.38)	

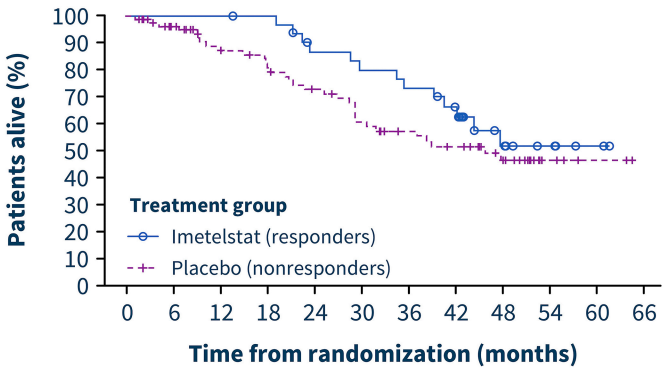


Number of patients at risk

Imetelstat (responders)	47	45	44	42	33	29	27	23	13	5	2	0
Placebo (nonresponders)	71	60	48	42	37	31	25	21	14	5	2	0

B

	≥24-Week RBC-TI Responders (n=33)	≥24-Week RBC-TI Nonresponders[a] (n=71)
Deaths, No. (%)	13 (39.4)	32 (37.6)
OS, median (95% CI), months	NE (40.4-NE)	45.7 (29.2-NE)
HR (95% CI)	0.72 (0.37-1.38)	

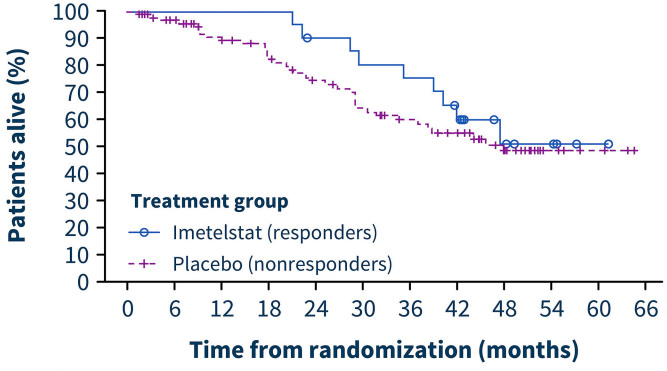


Number of patients at risk

Imetelstat (responders)	33	33	33	32	26	24	22	18	9	5	2	0
Placebo (nonresponders)	85	72	59	52	44	36	30	26	18	5	2	0

C

	≥1-Year RBC-TI Responders (n=21)	≥1-Year RBC-TI Nonresponders[b] (n=71)
Deaths, No. (%)	9 (42.9)	36 (37.1)
OS, median (95% CI), months	NE (39.1-NE)	47.8 (31.8-NE)
HR (95% CI)	0.73 (0.35-1.53)	

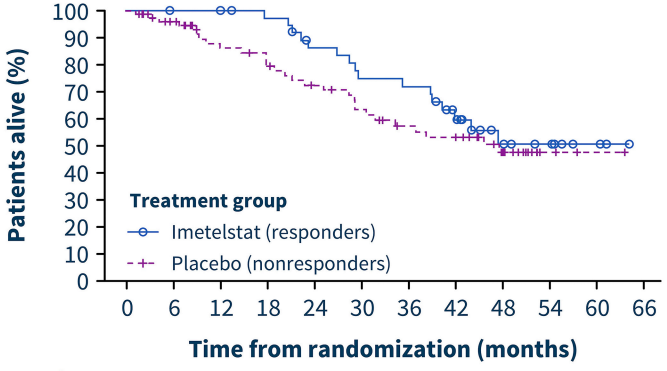


Number of patients at risk

Imetelstat (responders)	21	21	21	21	18	16	15	12	6	4	1	0
Placebo (nonresponders)	97	84	71	63	52	44	37	32	21	6	3	0

D

	Hb Responders[c] (n=40)	Hb Nonresponders (n=78)
Deaths, No. (%)	16 (40.0)	29 (37.2)
OS, median (95% CI), months	NE (39.1-NE)	47.8 (29.2-NE)
HR (95% CI)	0.74 (0.40-1.37)	



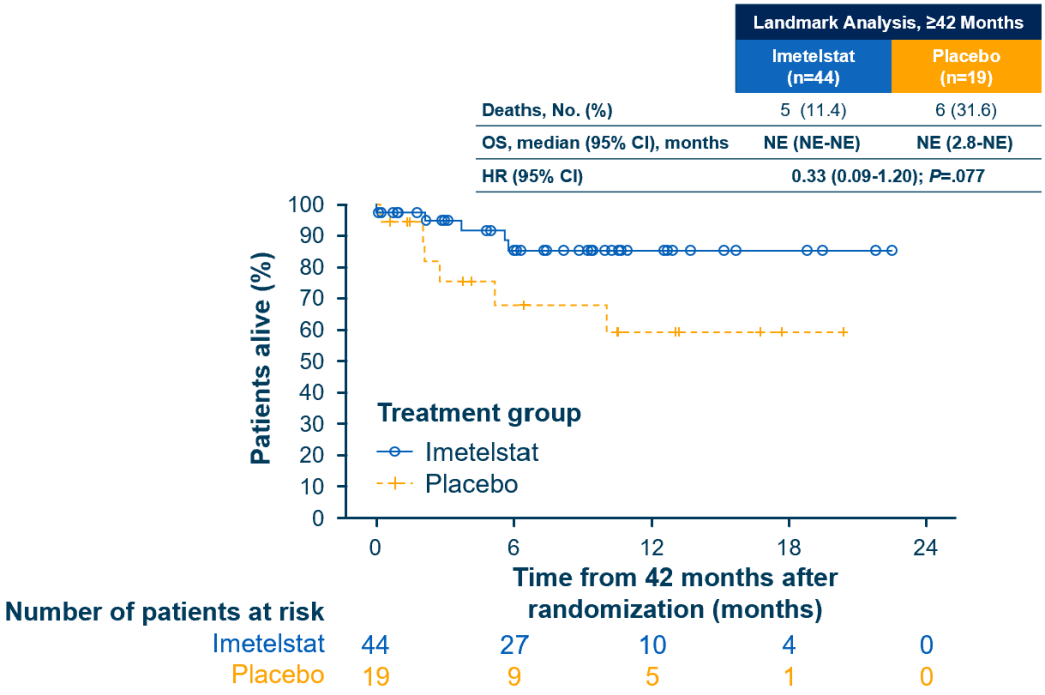
Number of patients at risk

Imetelstat (responders)	40	39	39	36	30	26	25	19	10	7	3	0
Placebo (nonresponders)	78	66	53	48	40	34	27	25	17	3	1	0

Overall survival and long-term outcomes from the randomized, double-blind, placebo-controlled, phase III IMerge trial of imetelstat for lower-risk myelodysplastic syndromes

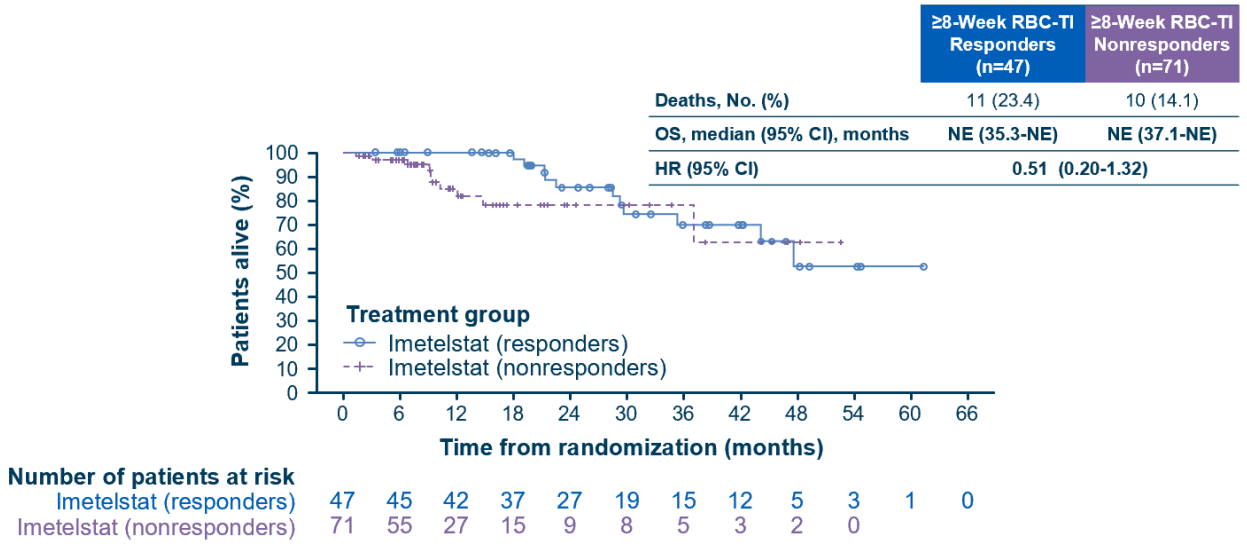
Data Supplement

Supplemental Figure 1. Landmark OS analysis at ≥42 months (n=63).

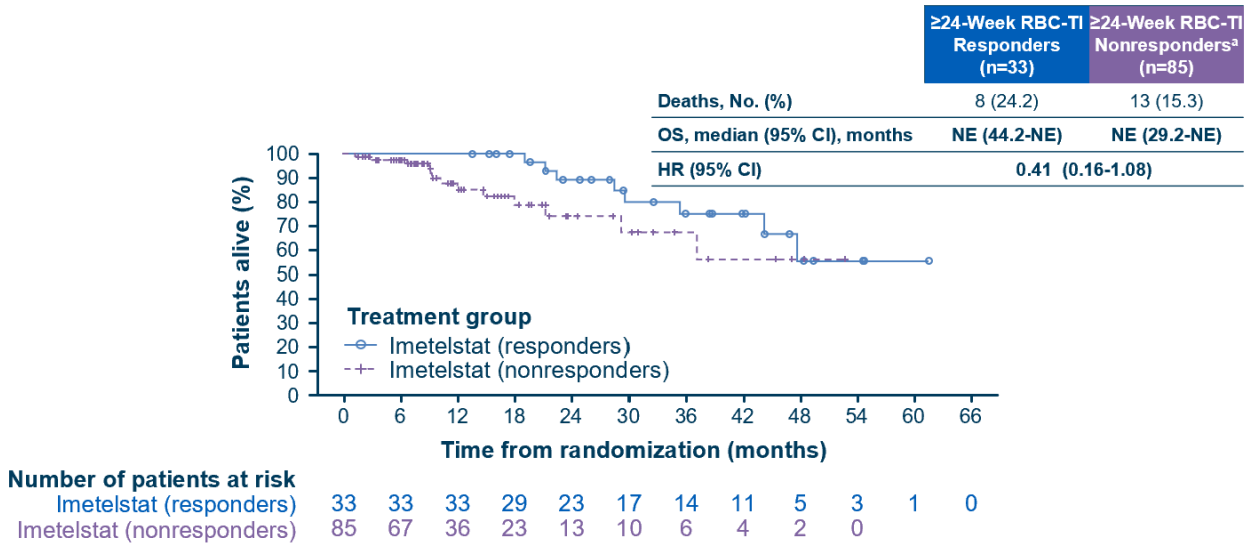


Supplemental Figure 2. OS in imetelstat-treated patients when censored at the start of subsequent therapy. OS in imetelstat-treated patients when censored at the start of subsequent therapy by who achieved (A) ≥8-week RBC-TI, (B) ≥24-week RBC-TI, or (C) ≥1-year RBC-TI and (D) in imetelstat-treated patients who achieved an Hb rise ≥1.5 g/dL lasting ≥8 weeks from pretreatment level per IWG 2006 HI-E criteria versus nonresponders.

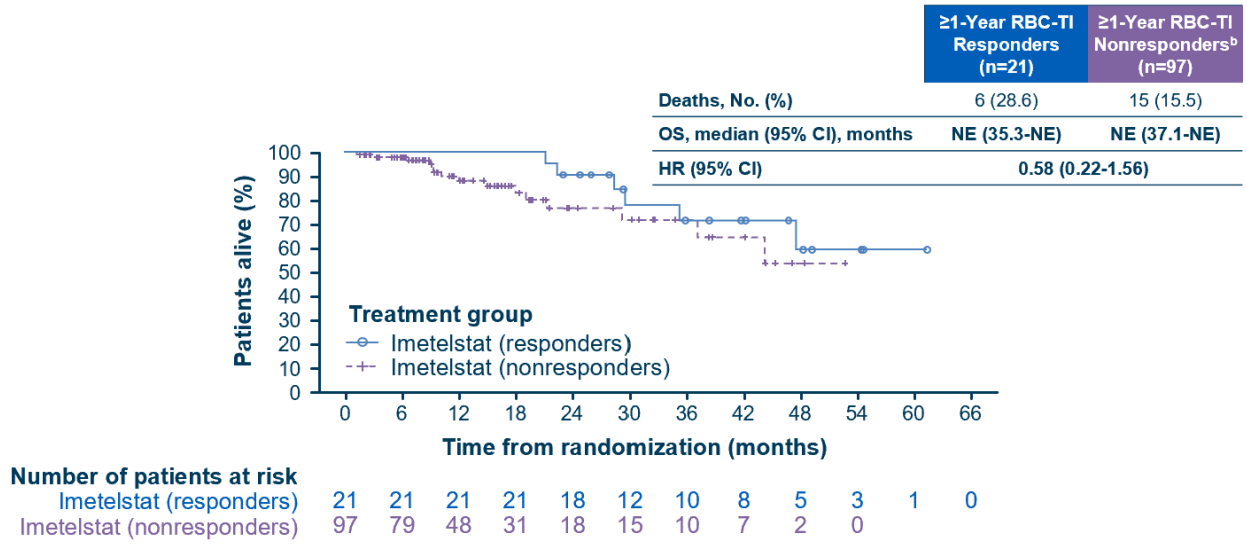
A



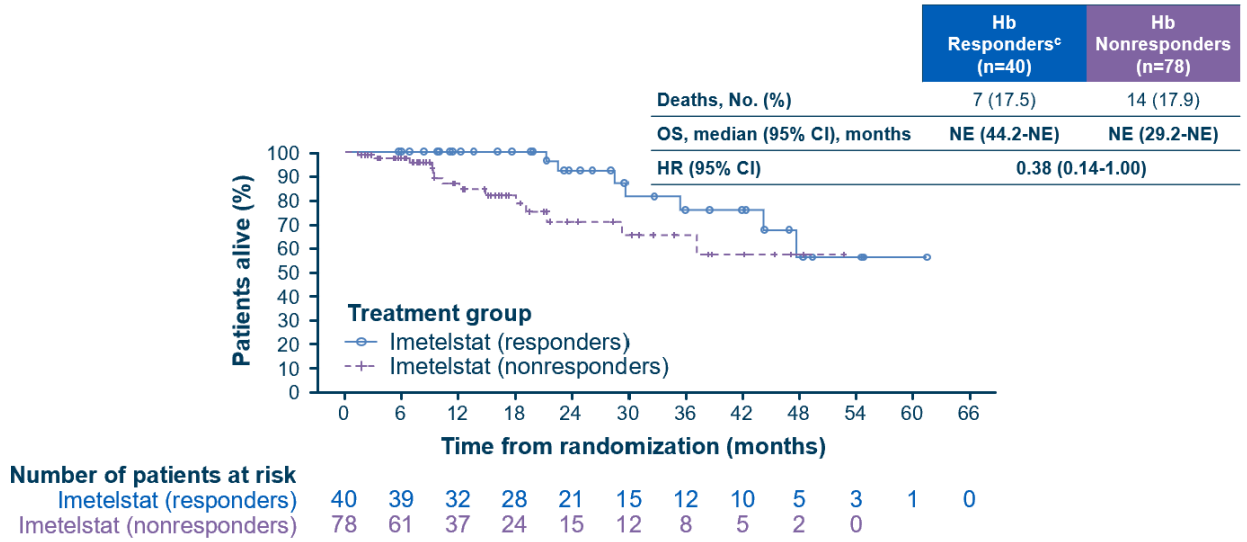
B



C

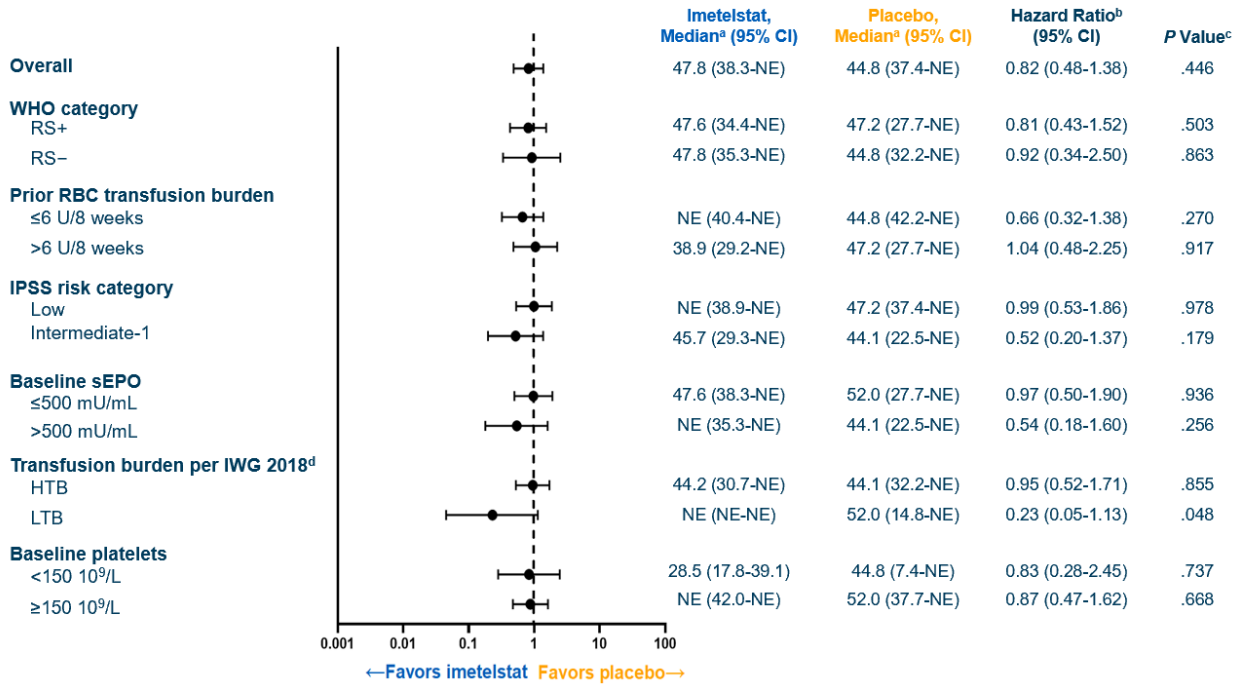


D



Hb: hemoglobin; HI-E: hematologic improvement-erythroid; HMA: hypomethylating agent; HR: hazard ratio; IWG: International Working Group; NE: not estimable; OS: overall survival; RBC: red blood cell; TI: transfusion independence. Data cutoff: May 10, 2025, 45 months of follow-up. [a]Includes patients who achieved ≥8-week but <24-week RBC-TI responders and ≥8-week RBC-TI nonresponders. [b]Includes patients who achieved ≥8-week but <1-year RBC-TI responders and ≥8-week RBC-TI nonresponders. [c]Hb responders = Hb rise ≥1.5 g/dL lasting ≥8 weeks from pretreatment level per IWG 2006 HI-E criteria.

Supplemental Figure 3. OS by baseline subgroup in the ITT population (N=178).



HTB: high transfusion burden; IPSS: International Prognostic Scoring System; LTB: low transfusion burden; NA: not available; NE: not estimable; OS: overall survival; RBC: red blood cell; RS: ring sideroblast; sEPO: serum erythropoietin; WHO: World Health Organization. Data cutoff: May 10, 2025, 45 months of follow-up. [a]Based on Kaplan-Meier product limit estimates. [b]Hazard ratio and 95% CI are from the Cox proportional hazard model, stratified by prior RBC transfusion burden (≤6 vs >6 units RBC) and IPSS risk group (low vs intermediate-1), with treatment as the only covariate. [c]*P* value (two-sided) for superiority of imetelstat versus placebo in hazard ratio, using log-rank test. [d]Per revised IWG 2018, the LTB subject is a subject who received 3 to 7 RBC units in the 16 weeks before study entry in ≥2 transfusion episodes. The HTB subject is a subject who received ≥8 RBC units in the 16 weeks before study entry in ≥2 transfusion episodes.