

INCREASED DURATION OF TIME WITHOUT TRANSFUSION RELIANCE (TWiTR) FOR PATIENTS WITH LOWER-RISK MYELODYSPLASTIC SYNDROMES TREATED WITH IMETELSTAT VERSUS PLACEBO IN THE IMERGE TRIAL

Mikkael A. Sekeres,¹ Valeria Santini,² Amer M. Zeidan,³ Uwe Platzbecker,⁴ Rami S. Komrokji,⁵ María Díez-Campelo,⁶ Pierre Fenaux,⁷ Michael R. Savona,⁸ Yazan F. Madanat,⁹ David Valcárcel,¹⁰ Antoine Regnault,¹¹ Flora Mazerolle,¹¹ Libo Sun,¹² Ying Wan,¹² Tymara Berry,¹² Faye Feller,¹² Shyamala Navada,¹² Esther Natalie Oliva¹³

¹Sylvester Comprehensive Cancer Center, University of Miami, Miami, FL, USA; ²MDS Unit, Hematology, DMSC University of Florence, AOUC, Florence, Italy; ³Yale School of Medicine and Yale Cancer Center, Yale University, New Haven, CT, USA; ⁴National Center for Tumor Diseases (NCT), University Hospital Carl Gustav Carus, TU Dresden, Dresden, Germany; ⁵Moffitt Cancer Center, Tampa, FL, USA; ⁶University Hospital of Salamanca, Salamanca, Spain; ⁷Hôpital Saint-Louis, Université de Paris 7, Paris, France; ⁸Vanderbilt-Ingram Cancer Center, Vanderbilt University Medical Center, Nashville, TN, USA; ⁹Harold C. Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; ¹⁰Hospital Universitario Vall d'Hebron, Barcelona, Spain; ¹¹Modus Outcomes, a company of THREAD, Lyon, France; ¹²Geron Corporation, Foster City, CA, USA; ¹³Grande Ospedale Metropolitano Bianchi Melacrino Morelli, Reggio Calabria, Italy

Background

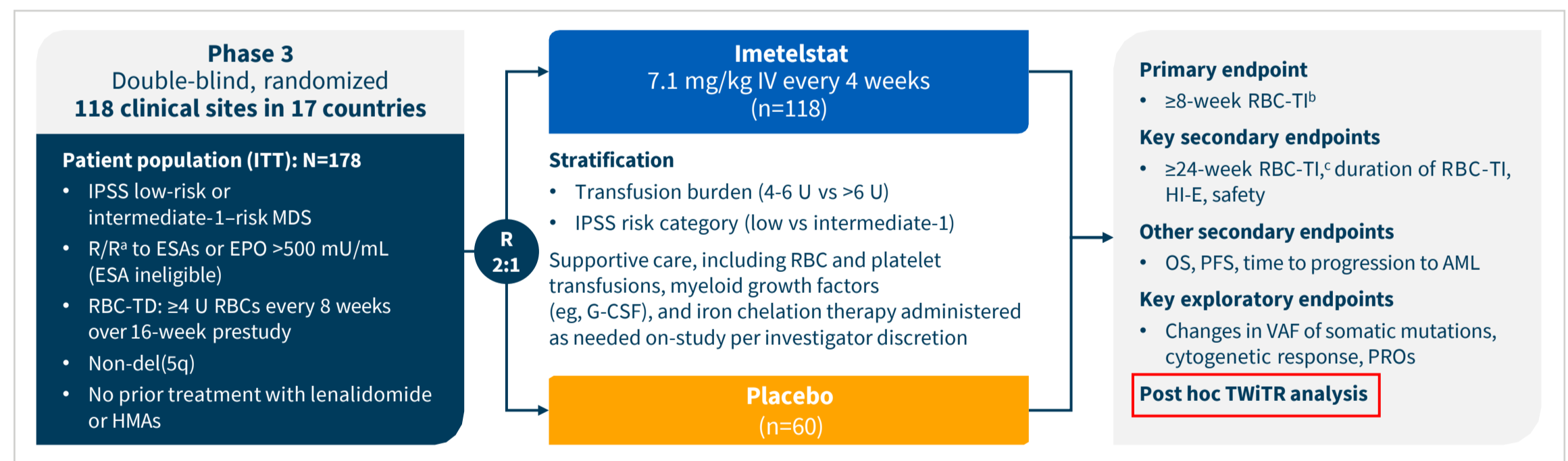
- For patients with lower-risk myelodysplastic syndromes (LR-MDS), the need for frequent red blood cell (RBC) transfusions negatively affects quality of life (QOL), is costly, and is associated with additional risks, including iron overload and alloimmunization¹
- Imetelstat is a first-in-class, oligonucleotide inhibitor of telomerase activity recently approved in the United States and Europe for certain adult patients with LR-MDS with RBC transfusion-dependent (TD) anemia who have relapsed or refractory/unsatisfactory response to or ineligible for erythropoiesis-stimulating agents (ESAs), based on the pivotal, Phase 3 IMerge trial (NCT02598661)^{2,4}
 - The Phase 3 primary analysis of IMerge found higher rates of ≥8-week, ≥24-week, and ≥1-year RBC transfusion independence (TI) with imetelstat (n=118) versus placebo (n=60) in the intention-to-treat population: 39.8% versus 15.0% (P=.0008), 28.0% versus 3.3% (P=.0001), and 17.8% versus 1.7% (nominal P=.0023), respectively
 - The most common adverse events were neutropenia and thrombocytopenia, which were generally reversible and manageable with dose modifications
 - Based on exploratory analysis, more imetelstat-treated patients experienced maintenance of QOL and MDS-related symptoms (eg, anemia) compared with worsening with placebo⁵
- Commonly used QOL measures have limitations, such as the inability to distinguish between improvement of anemia symptoms from treatment versus continued RBC transfusions; this has prompted the development of alternative measures such as time without transfusion reliance (TWiTR)
- TWiTR measure is a validated, composite, patient-centered metric that includes follow-up after treatment discontinuation and combines the clinical outcomes of overall survival and disease progression with RBC-TD⁶**

Here, we present results from a post hoc TWiTR analysis comparing imetelstat and placebo arms in the intention-to-treat population of the Phase 3 IMerge trial

Methods

- In IMerge, patients with RBC-TD LR-MDS who provided informed consent were randomized to 7.1 mg/kg imetelstat active dose (equivalent to 7.5 mg/kg imetelstat sodium) or placebo administered as 2-hour intravenous infusions every 4 weeks (Figure 1)

Figure 1. IMerge Phase 3 Study Design



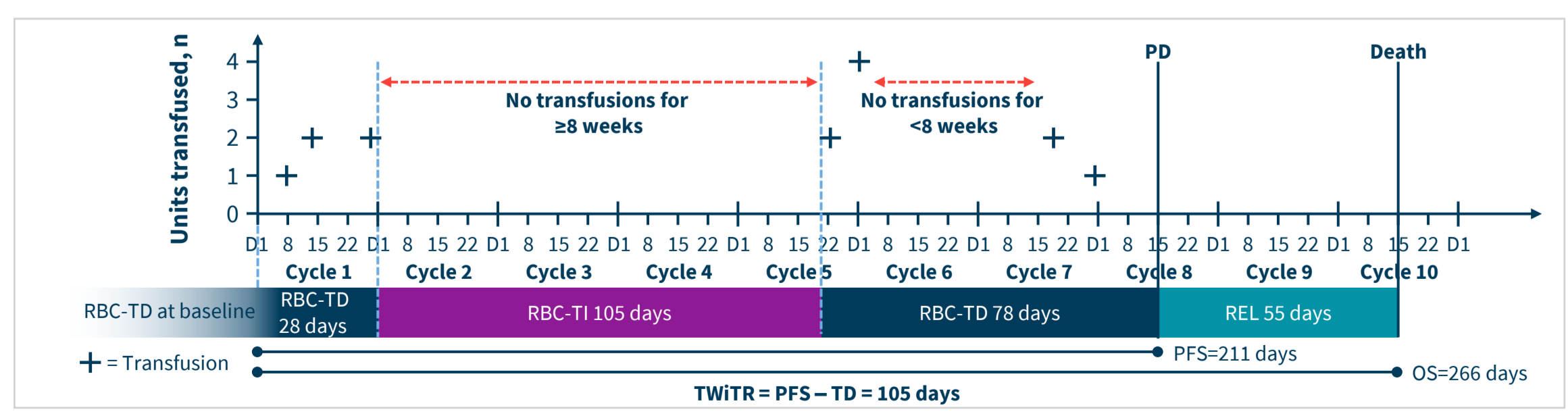
AML, acute myeloid leukemia; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony stimulating factor; Hi-E, hemoglobin; Hi-E, hematologic improvement erythroid; HMAs, hypomethylating agents; IPSS, International Prognostic Scoring System; ITT, intention-to-treat; LR, lower-risk; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; PRO, patient-reported outcome; R, relapsed; RBC, red blood cell; R/R, relapsed or refractory; TD, transfusion dependent; TI, transfusion independence; TWiTR, time without transfusion reliance; VAF, variant allele frequency. *Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U, or darbepoetin alfa 150 µg or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U every 8 weeks or RBC-TD or reduction in Hb by ≥1.5 g/dL after hematology improvement from ≥8 weeks of ESA treatment. †Proportion of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (≥8-week RBC-TI). ‡Proportion of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (≥24-week RBC-TI).

- In the post hoc TWiTR analysis, 3 health states were defined as follows:

TD state	REL state	TWiTR state
Sum of all TD periods experienced by the patient, ending at disease progression, death, or censoring for progression (eg, PFS analysis)	Time between disease progression and death or OS censoring • Calculated as OS minus PFS	Time without TD or REL • Calculated as PFS minus TD

- An example of how the states for the TWiTR analysis were assigned is shown in Figure 2

Figure 2. Example of TWiTR Calculation for a Hypothetical Patient Who Was TD at Baseline, Had 1 Period of TI, Then Another Period of TD Before PD and Death



- Two complementary censoring rules were applied to TD periods as follows:
 - TD state censored according to PFS censoring rules (TD was an event when PFS was an event and censored when PFS was censored) as the primary analysis
 - TD state always considered an event (participants who had TD were never censored) as a sensitivity analysis
- Health states were calculated using Kaplan-Meier estimates; the mean duration in each state was estimated by the area under each survival curve obtained with Kaplan-Meier estimates
 - A bootstrap approach was applied to estimate the 95% CI for the mean TWiTR for each arm and mean TWiTR difference between arms
- These analyses were exploratory, with no prespecified formal statistical hypothesis testing

Results

Patient Population

- A total of 178 patients (imetelstat, n=118; placebo, n=60) in the intention-to-treat population from the final data analysis of IMerge (January 5, 2024) were included in the TWiTR analysis (Table 1)
 - Baseline characteristics were similar across arms

Table 1. Baseline Demographic and Disease Characteristics

Characteristic	Imetelstat (n=118)	Placebo (n=60)
Age, median (range), y	72 (44-87)	73 (39-85)
Male, n (%)	71 (60)	40 (67)
Time since diagnosis, median (range), y	3.5 (0.1-26.7)	2.8 (0.2-25.7)
WHO classification, n (%)		
RS+	73 (62)	37 (62)
RS-	44 (37)	23 (38)
IPSS risk category, n (%)		
Low	80 (68)	39 (65)
Intermediate-1	38 (32)	21 (35)
Pretreatment Hb, median (range), ^a g/dL	7.9 (5.3-10.1)	7.8 (6.1-9.2)
Prior RBC transfusion burden, median (range), RBC U/8 weeks	6 (4-33)	6 (4-13)
Prior RBC transfusion burden, n (%)		
≥4 to ≤6 RBC U/8 weeks	62 (53)	33 (55)
>6 RBC U/8 weeks	56 (48)	27 (45)
sEPO, median (range), mU/mL	174.9 (6.0-4460.0)	277.0 (16.9-5514.0)
sEPO level, n (%) ^b		
≤500 mU/mL	87 (74)	36 (60)
>500 mU/mL	26 (22)	22 (37)
Prior ESA, n (%)	108 (92)	52 (87)
Prior luspatercept, n (%) ^c	7 (6)	4 (7)

ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IPSS, International Prognostic Scoring System; RBC, red blood cell; RS, ring sideroblast; sEPO, serum erythropoietin; WHO, World Health Organization. ^aAverage of all Hb values in the 3 weeks before the first dose date, excluding values within 14 days after a transfusion, which was considered to be influenced by transfusion. ^bData missing for 5 patients in the imetelstat group and 2 in the placebo group. ^cInsufficient number of patients previously treated with luspatercept to draw conclusions about the effect of imetelstat treatment in such patients.

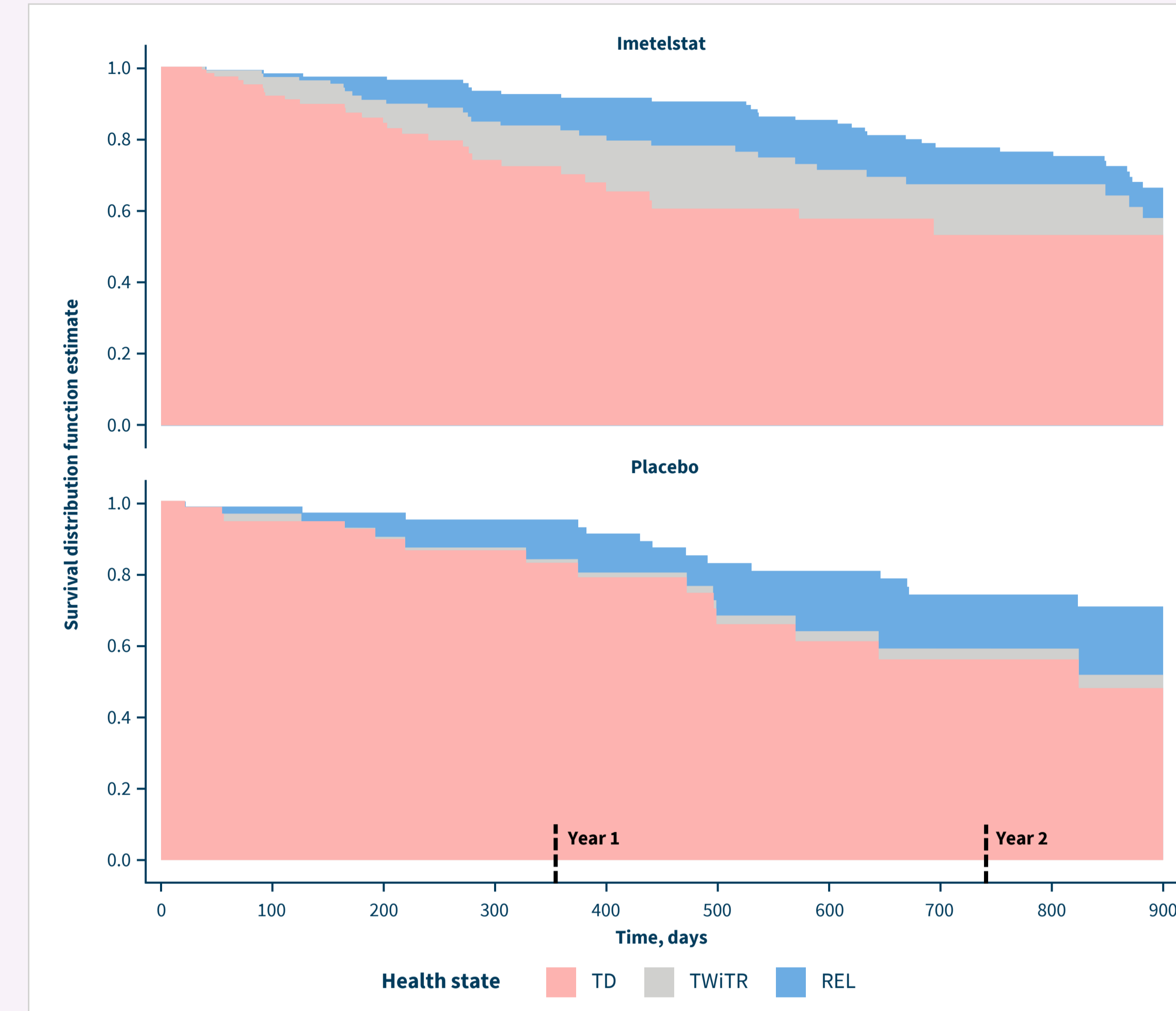
- Post hoc TWiTR analyses in which TD was censored according to PFS censoring rules (assuming that the duration of TD periods was unknown for participants who were censored for PFS) showed that (Table 2, Figure 3):
 - after 2.6 years of follow-up, overall mean TWiTR was longer in the imetelstat arm than in the placebo arm by ~3 months
 - mean TD was almost 1.5 months shorter in the imetelstat arm than in the placebo arm
 - mean time in the REL state was almost 1 month shorter in the imetelstat arm than in the placebo arm
- Results for the TWiTR analysis considering TD an event were similar (Table 3)
- TWiTR in RBC-TI responders is shown in Table 4 and Figure 4
 - In ≥8-week RBC-TI responders, mean TWiTR was longer with imetelstat than placebo, regardless of censoring rules; this analysis was limited by the small number of responders in the placebo group
 - The small number of ≥24-week responders did not allow to perform the TWiTR analysis in these patients
- As nonresponders do not have TWiTR periods by definition, TWiTR results in RBC-TI nonresponders were not interpretable

Table 2. Mean Duration of Health States: Censoring TD According to PFS Censoring Rules (ITT Population)^a

Health state	Imetelstat (n=118)	Placebo (n=60)	Difference (95% CI)
TD (95% CI), d	659.76 (575.93, 750.55)	701.05 (594.52, 814.83)	-41.29 (-196.5, 120.19)
TWiTR (95% CI), d	102.44 (55.84, 149.60)	19.00 (1.92, 47.93)	83.44 (25.46, 135.18)
Relapse (95% CI), d	79.43 (24.40, 122.09)	106.40 (9.91, 194.02)	-26.97 (-147.4, 82.36)

ITT, intention-to-treat; RBC, red blood cell; TD, transfusion dependent; TWiTR, time without transfusion reliance. ^aEstimations were restricted to 966 days to ensure comparability across health states and treatment arms, and were defined as the minimum of the end of the last observed TD event between arms.

Figure 3. TWiTR Analysis Based on PFS Censoring (ITT Population)



ITT, intention-to-treat; PFS, progression-free survival; REL, relapse; TD, transfusion dependent; TWiTR, time without transfusion reliance.

Table 3. Mean Duration of Health States: Always Considering TD an Event (ITT Population)^a

Health state	Imetelstat (n=118)	Placebo (n=60)	Difference (95% CI)
TD (95% CI), d	289.63 (241.69, 339.68)	339.07 (271.80, 412.32)	-49.44 (-141.3, 44.83)
TWiTR (95% CI), d	472.58 (409.68, 534.01)	380.99 (294.83, 489.74)	91.59 (-37.19, 209.40)
Relapse (95% CI), d	79.43 (24.40, 122.09)	106.40 (9.91, 194.02)	-26.97 (-147.4, 82.36)

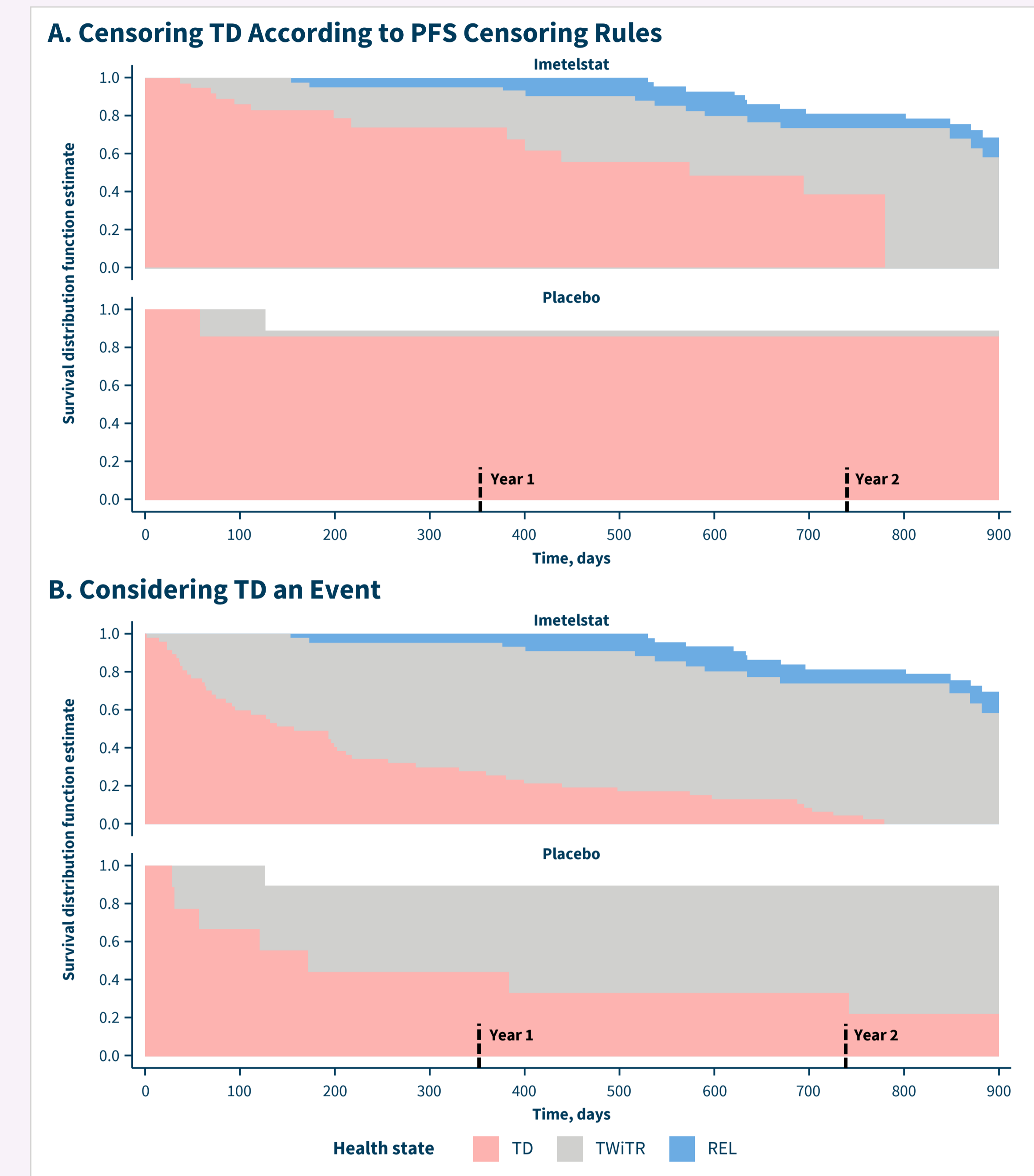
ITT, intention-to-treat; TD, transfusion dependent; TWiTR, time without transfusion reliance. ^aEstimations were restricted to 966 days to ensure comparability across health states and treatment arms, and were defined as the minimum of the end of the last observed TD event between arms.

Table 4. Mean Duration of Health States for ≥8-Week RBC-TI Clinical Responders: Using the Different Censoring Rules (ITT Population)^a

Health state	Imetelstat (n=47)	Placebo (n=9)	Difference (95% CI)
Censoring: TD censored according to PFS censoring rules			
TD (95% CI), d	595.01 (500.93, 664.08)	836.29 (739.00, 865.11)	-241.3 (-347.8, -144.5)
TWiTR (95% CI), d	234.49 (162.20, 338.54)	36.71 (7.89, 134.00)	197.77 (97.99, 299.53)
Relapse (95% CI), d	61.09 (40.65, 85.18)	0	61.09 (40.65, 85.18)
Censoring: TD as an event			
TD (95% CI), d	249.55 (185.70, 321.64)	385.11 (160.22, 601.11)	-135.6 (-380.5, 95.31)
TWiTR (95% CI), d	579.94 (507.94, 648.18)	487.89 (271.89, 712.78)	92.05 (-143.4, 329.10)
Relapse (95% CI), d	61.09 (40.65, 85.18)	0	61.09 (40.65, 85.18)

ITT, intention-to-treat; RBC, red blood cell; TD, transfusion dependent; TWiTR, time without transfusion reliance. ^aEstimations were restricted to 966 days to ensure comparability across health states and treatment arms, and were defined as the minimum of the end of the last observed TD event between arms.

Figure 4. TWiTR Analysis Among ≥8-Week RBC-TI Responders



PFS, progression-free survival; RBC, red blood cell; REL, relapse; TD, transfusion dependent; TWiTR, time without transfusion reliance.

Conclusions

- In this post hoc analysis, patients with LR-MDS in the imetelstat arm had a longer mean duration of time without transfusion reliance or relapse compared with placebo
 - The difference between arms in the time spent without transfusion reliance and TD was fairly stable across the specification of the TWiTR analyses as follows: 49 days fewer in TD and 92 days more in TWiTR when TD was always considered an event, and 41 days fewer in TD and 83 days more in TWiTR when the PFS censoring rule was applied to TD
 - Among ≥8-week RBC-TI responders, TWiTR was longer and TD was shorter in the imetelstat arm compared with the placebo arm; however, this analysis was limited by the small number of responders in the placebo group
- Because of the negative association between health-related QOL and TD,^{7,8} these findings suggesting the ability of imetelstat to lessen TD may be clinically meaningful to patients
- These results should be interpreted with caution, given the analyses were exploratory, with no formal statistical testing applied, and the statistical uncertainties associated with the different censoring rules employed

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