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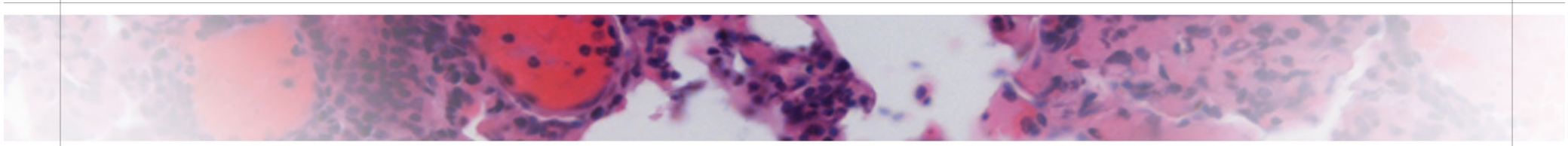

Efficacy of Imetelstat in Achieving Red Blood Cell Transfusion Independence Across Different Risk Subgroups in Patients With Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis-Stimulating Agents in IMerge Phase 3 Study

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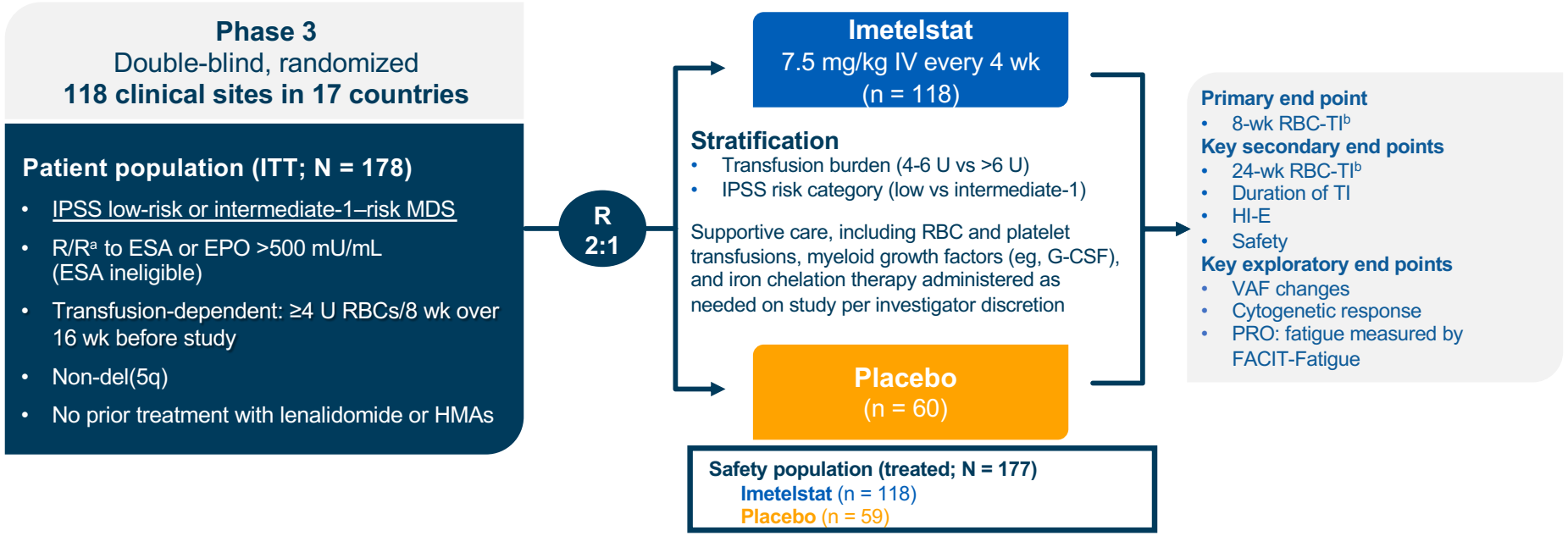
Background

- Patients with RBC-TD LR-MDS R/R to or ineligible for ESAs remain in need of safe and effective treatments
- Imetelstat is a first-in-class, potent, and competitive inhibitor of telomerase activity that selectively induces apoptosis of malignant hematopoietic progenitor cells while sparing the normal counterparts, thus enabling recovery of bone marrow function and erythropoiesis[1,2]
- IMerge (NCT02598661) is a multinational phase 2/3 study comparing imetelstat with placebo in patients with LR-MDS that were heavily RBC-TD, ESA relapsed/refractory or ineligible, non-del(5q), and naive to lenalidomide and HMA
- In phase 3 of IMerge, rates of RBC-TI for ≥8 weeks, ≥24 weeks, and ≥1 year were significantly higher with imetelstat than placebo[3]
- The most common treatment-emergent AEs were neutropenia and thrombocytopenia. AEs were generally of short duration and were reversible. Rates of grade ≥3 bleeding and infection with imetelstat were similar to placebo[3]
- Here, we report the clinical efficacy of imetelstat across different IPSS, IPSS-R, IPSS-M, and IPSS-R cytogenetic risk categories

AE, adverse event; ESA, erythropoiesis-stimulating agent; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IPSS-M, IPSS-molecular; IPSS-R, revised IPSS; LR-MDS, lower-risk MDS; MDS, myelodysplastic syndrome; RBC, red blood cell; R/R, relapsed/refractory; TD, transfusion-dependent; TI, transfusion independence.

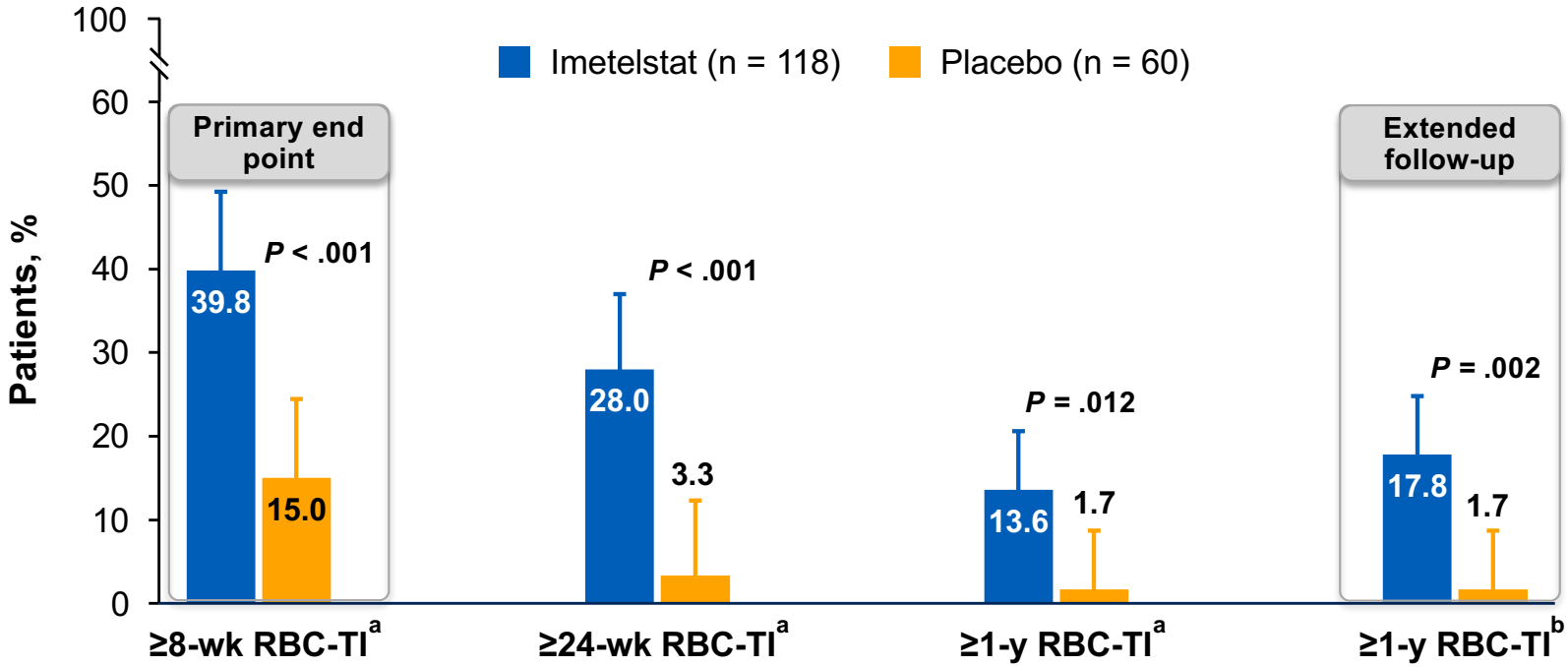
1. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939.2. Wang X, et al. *Blood Adv.* 2018;2(18):2378-2388. 3. Platzbecker U, et al. *Lancet.* Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.

IMerge Phase 3 Trial Design



[a]Received ≥8 weeks of ESA treatment (epoetin alfa ≥40,000 U, epoetin beta ≥30,000 U, darbepoetin alfa 150 µg, or equivalent per week) without Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement ≥4 U/8 wk or transfusion dependence or reduction in Hb by ≥1.5 g/dL after HI-E from ≥8 weeks of ESA treatment. [b]Percentage of patients without any RBC transfusion for ≥8 consecutive weeks since entry to the trial (8-week TI); percentage of patients without any RBC transfusion for ≥24 consecutive weeks since entry to the trial (24-week TI).
EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; FACIT, Functional Assessment of Chronic Illness Therapy; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HI-E, hematologic improvement–erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; ITT, intent-to-treat; IV, intravenous; MDS, myelodysplastic syndromes; PRO, patient-reported outcome; R, randomization; RBC, red blood cell; R/R, relapsed/refractory; TI, transfusion independence, VAF, variant allele frequency.
Platzbecker U, et al. *Lancet.* Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.

Overall Population: Higher Rates of Longer-Term Duration of RBC-TI With Imetelstat vs Placebo[1,2]



[a]Data cutoff date: October 13, 2022. [b]Data cutoff date: January 13, 2023.
The *P* value was determined by the Cochran-Mantel-Haenszel test, with stratification for prior RBC transfusion burden (≥4 to ≤6 vs >6 RBC U/8 wk during a 16-week period before randomization) and baseline IPSS (low-risk vs intermediate-1–risk) applied to randomization.
IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.
1. Zeidan A, et al. ASCO 2023. Abstr 7004. 2. Platzbecker U, et al. *Lancet.* Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.

Risk Classification at Baseline

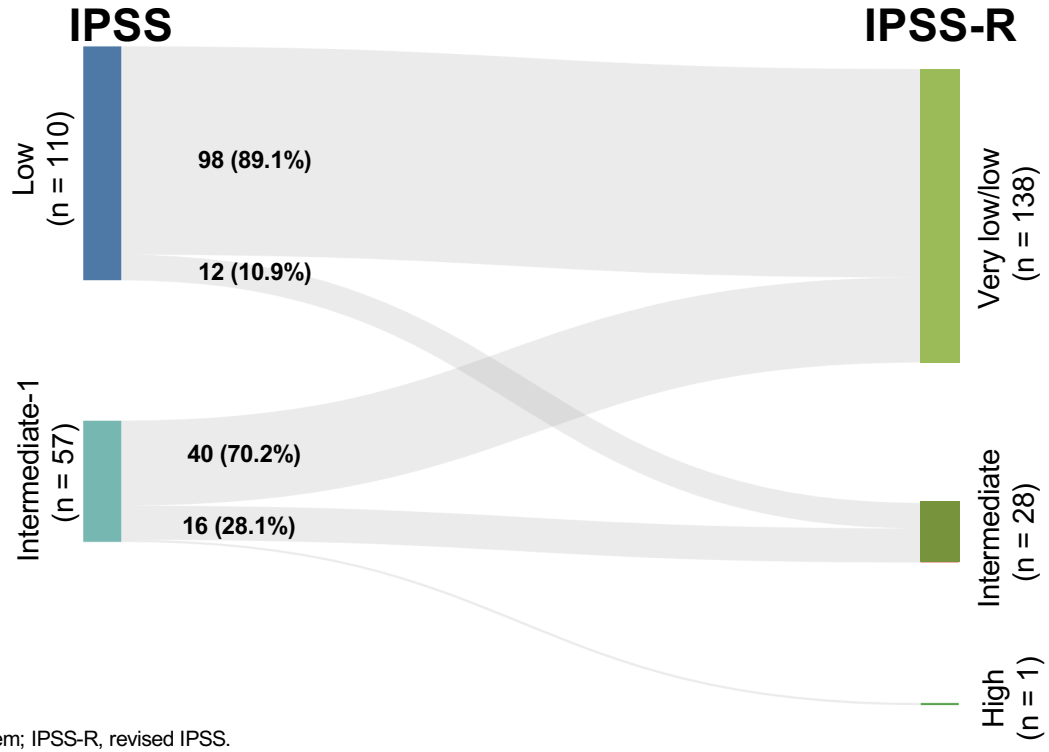
Risk group, n (%)		Imetelstat	Placebo	Total
IPSS[a]	Low	80 (67.8)	39 (65.0)	119 (66.9)
	Intermediate-1	38 (32.2)	21 (35.0)	59 (33.1)
IPSS-R[a,b]	Very low	3 (2.5)	2 (3.3)	5 (2.8)
	Low	87 (73.7)	46 (76.7)	133 (74.7)
	Intermediate	20 (16.9)	8 (13.3)	28 (15.7)
	High	1 (0.8)	0	1 (0.6)
IPSS-M[c]	Very low	4 (3.9)	0	4 (2.6)
	Low	65 (63.1)	33 (63.5)	98 (63.2)
	Moderate low	22 (21.4)	10 (19.2)	32 (20.6)
	Moderate high	7 (6.8)	6 (11.5)	13 (8.4)
	High	4 (3.9)	3 (5.8)	7 (4.5)
	Very high	1 (1.0)	0	1 (0.6)

Data cutoff date: October 13, 2022. [a]Based on the ITT population: 118 imetelstat; 60 placebo. [b]Data were missing for a total of 11 patients (7 imetelstat; 4 placebo). [c]For IPSS-M, the mutation biomarker analysis set included all the patients who received ≥1 dose of study drug and had baseline mutation data and central cytogenetic data available: 103 imetelstat; 52 placebo. Molecular data for *MLL-PTD*, *BCORL1*, *GNB1*, *PPM1D*, and *SETBP1* were not assessed in the study.

BCORL1, BCL6 corepressor-like 1; *GNB1*, G protein subunit beta 1; IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS; ITT, intent-to-treat; *MLL-PTD*, mixed lineage leukemia partial tandem duplication; *PPM1D*, protein phosphatase, Mg2+/Mn2+ dependent 1D; *SETBP1*, SET-binding protein 1.

Patient Reclassification Between Risk Groups

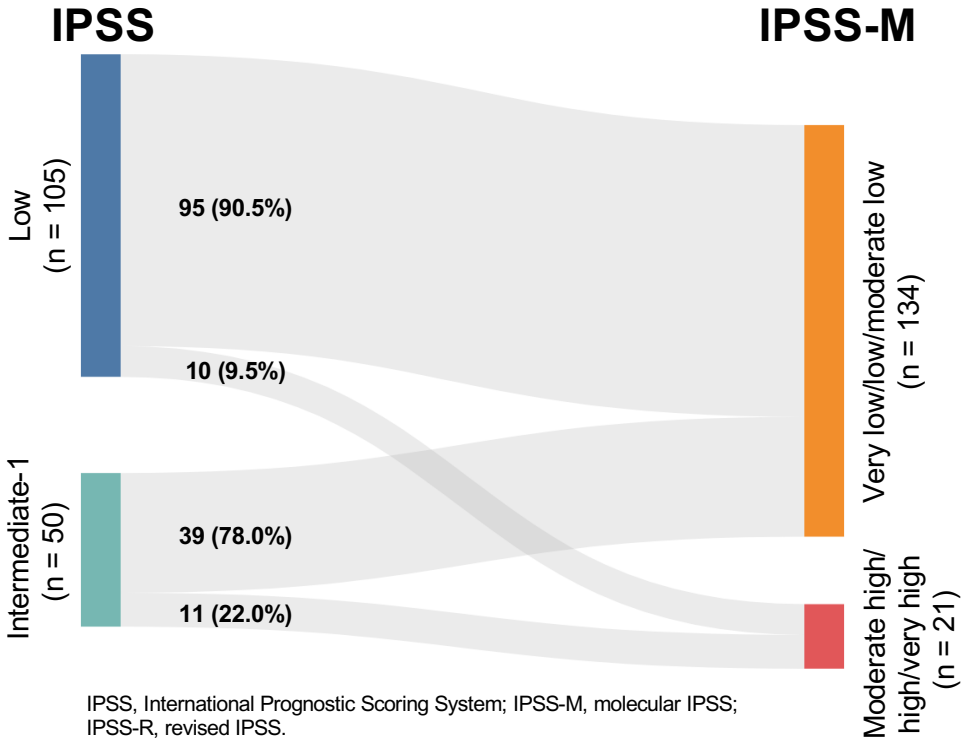
- Approximately 11% of patients classified as low risk by IPSS were reclassified as intermediate risk by IPSS-R
- Approximately 28% of patients classified as intermediate-1 risk by IPSS were reclassified as intermediate risk by IPSS-R

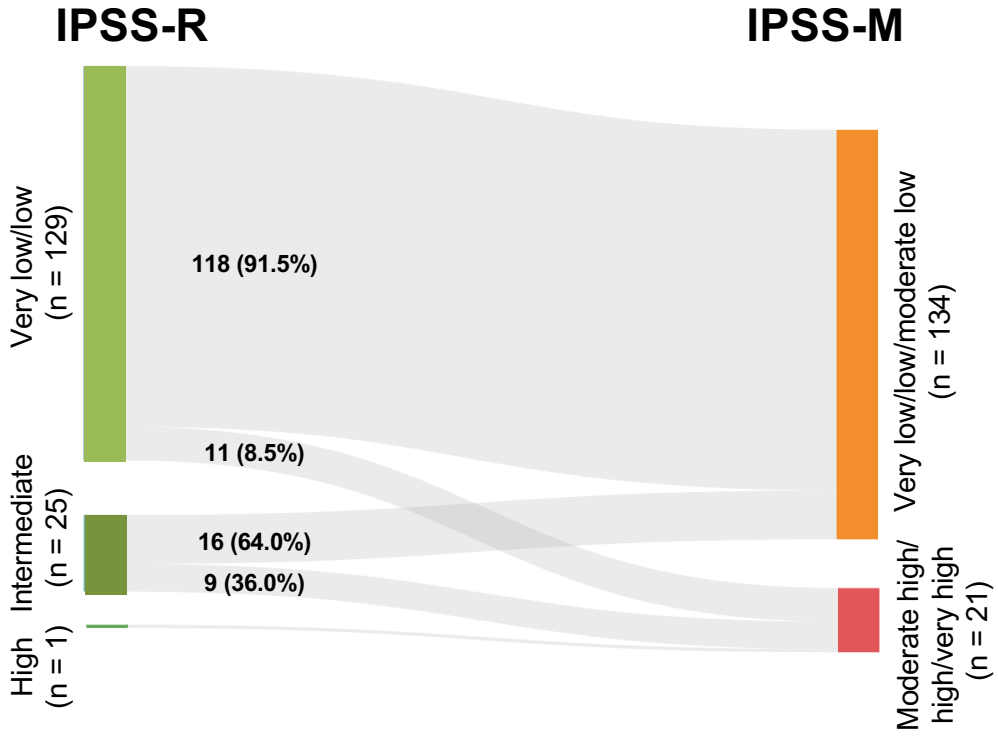


IPSS, International Prognostic Scoring System; IPSS-R, revised IPSS.

Patient Reclassification Between Risk Groups (cont.)

- Approximately 14% of patients classified as low or intermediate-1 risk by IPSS and 13% of those classified as very low/low or intermediate risk by IPSS-R were reclassified as higher-risk disease (moderate high/high/very high risk) by IPSS-M

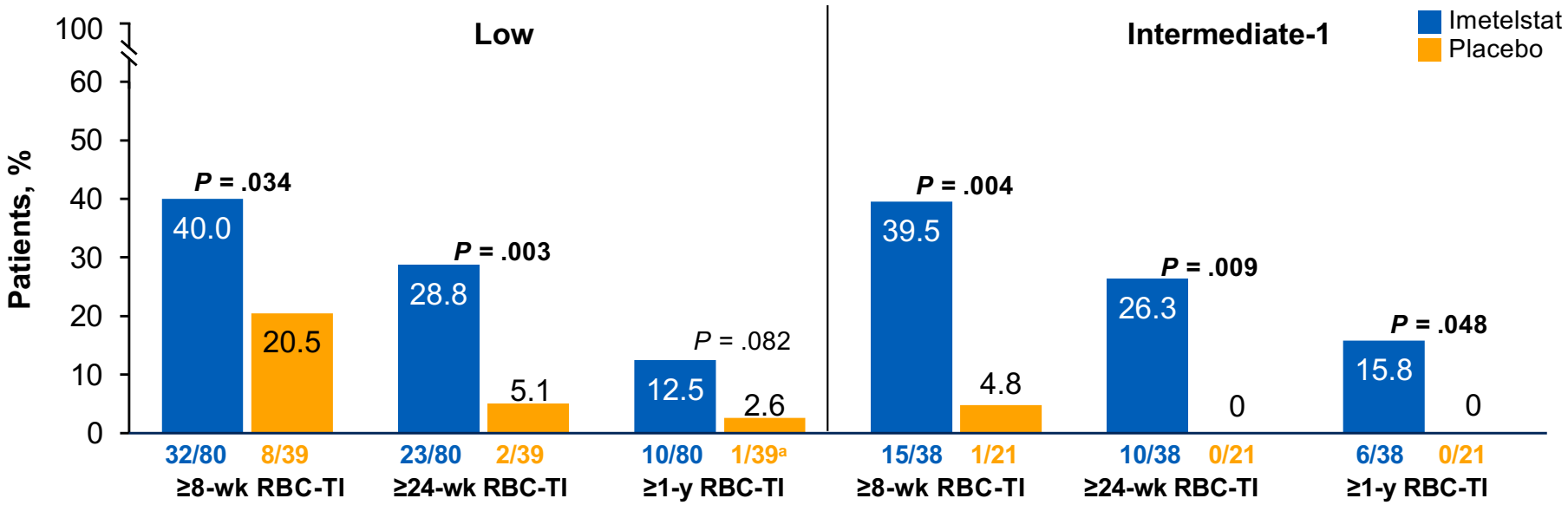




IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS.

RBC-TI by IPSS Subgroup

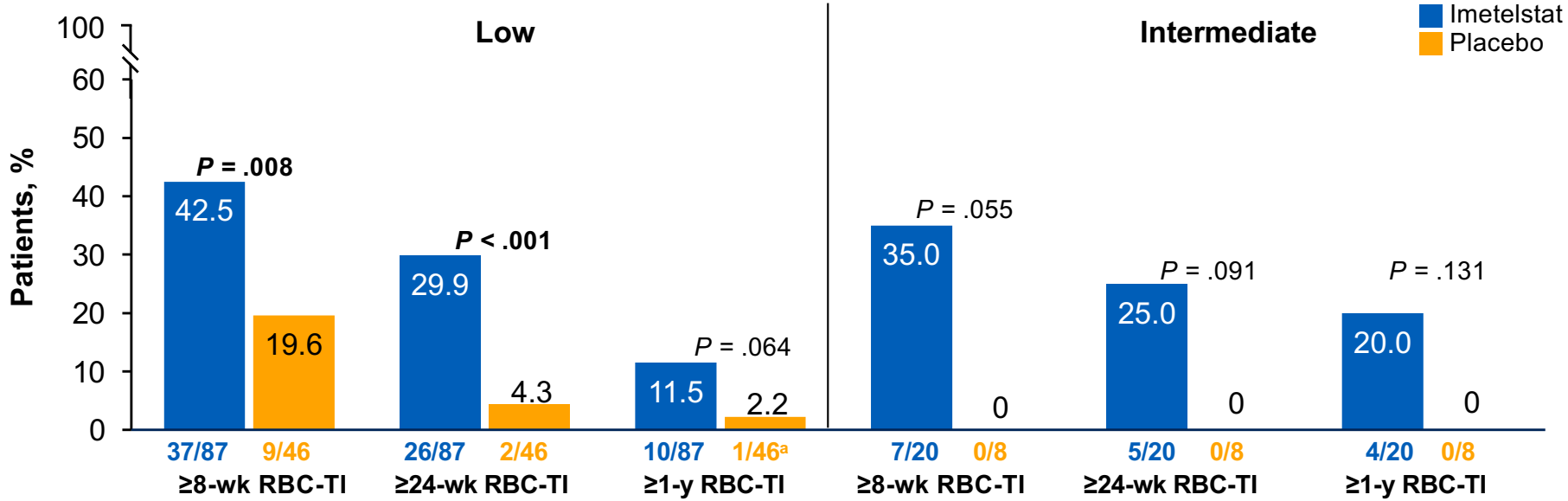
- Imetelstat treatment resulted in significantly higher 8- and 24-week RBC-TI response rates than did placebo, regardless of IPSS risk group



Data cutoff date: October 13, 2022. [a]For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period
Hb, hemoglobin; IPSS, International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

RBC-TI by IPSS-R Subgroup

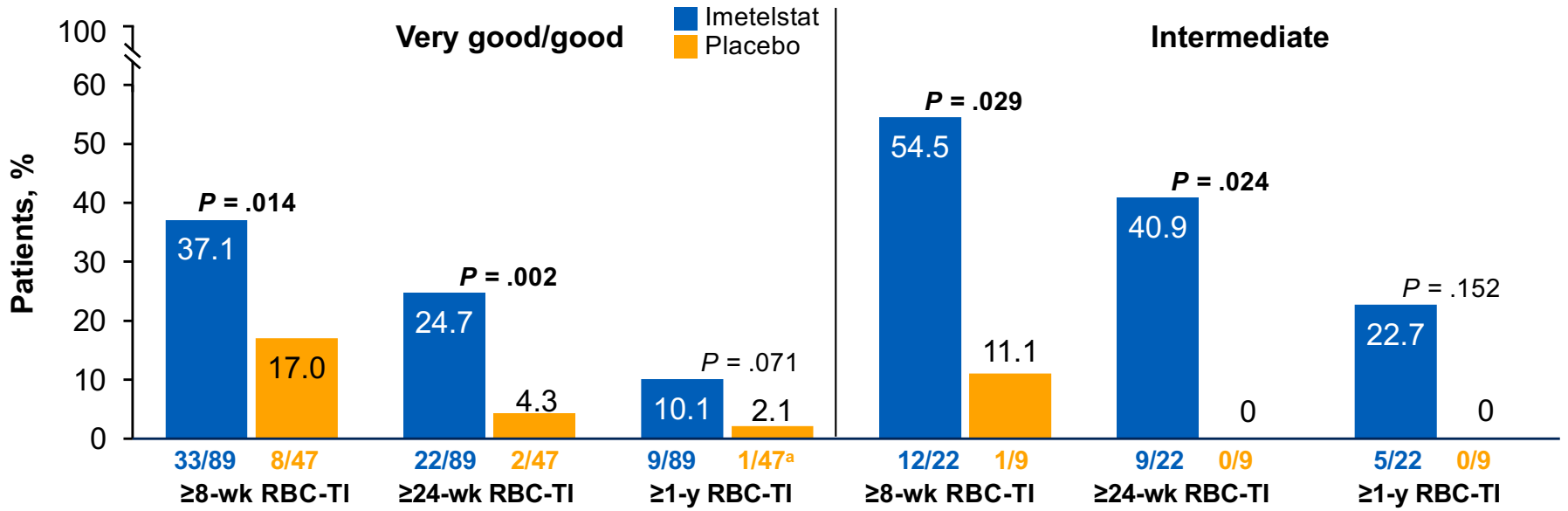
- Imetelstat treatment had higher RBC-TI response rates than did placebo, regardless of IPSS-R risk group
- Among imetelstat-treated patients reclassified as intermediate risk by IPSS-R, response rates were similar to those reclassified as low risk; no response was noted in placebo-treated patients reclassified as intermediate risk
- For the very low and high IPSS-R categories, the number of patients was too low (≤3 patients) in both groups to assess differences in RBC-TI response



Data cutoff date: October 13, 2022. [a]For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period
Hb, hemoglobin; IPSS-R, revised International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

RBC-TI by IPSS-R Cytogenetic Subgroup

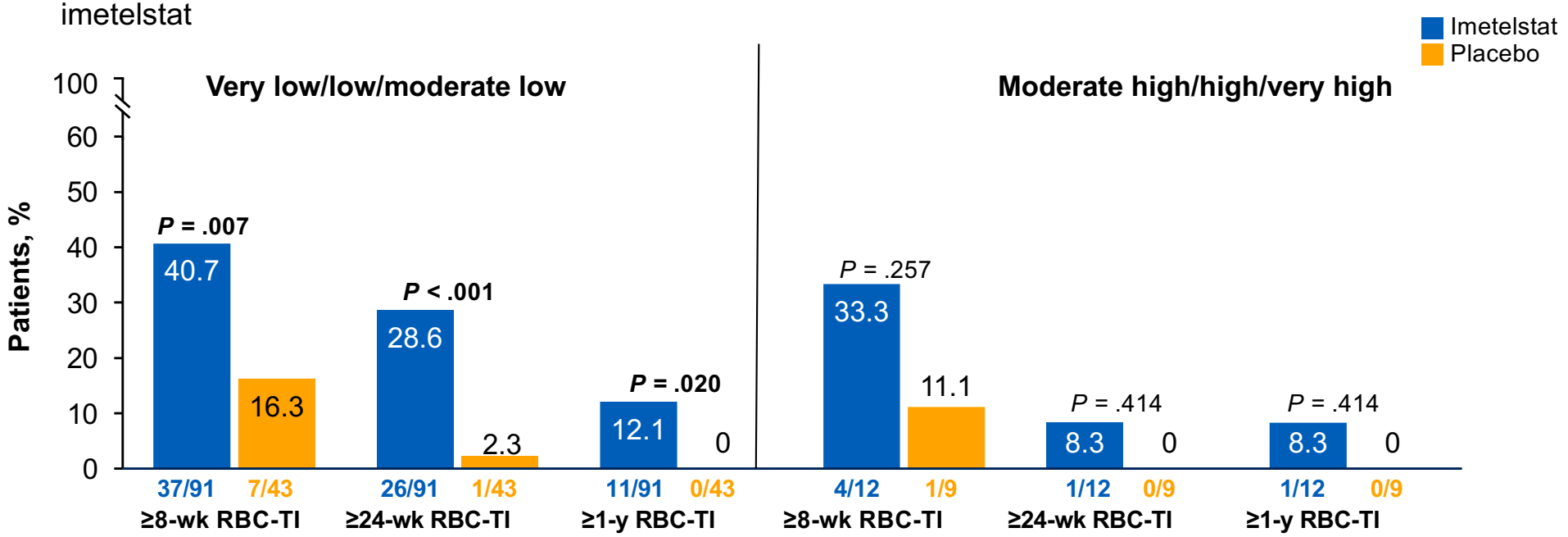
- Imetelstat treatment resulted in significantly higher 8- and 24-week RBC-TI rates than did placebo, regardless of IPSS-R cytogenetic risk group



Data cutoff date: October 13, 2022. [a]For the patient on placebo: pretreatment Hb was 6.2 g/dL and transfusion burden was 5 U/8 weeks; while on-study, Hb was <6.5 g/dL during majority of TI period
Hb, hemoglobin; IPSS-R, revised International Prognostic Scoring System; RBC, red blood cell; TI, transfusion independence.

RBC-TI by IPSS-M Subgroup

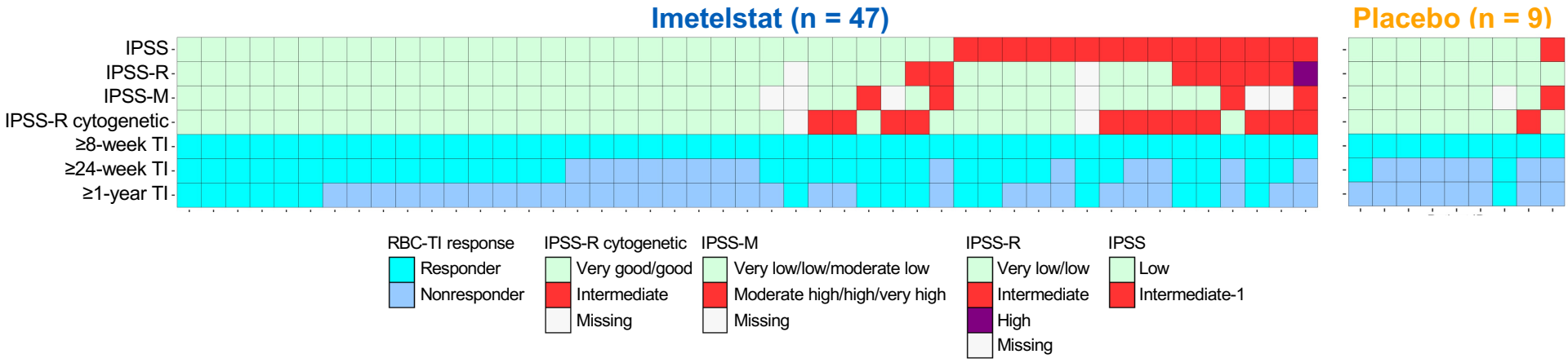
- Imetelstat treatment had higher RBC-TI response rates than did placebo, regardless of IPSS-M risk group
- 4 out of 12 patients (33%) reclassified as having higher risk MDS by IPSS-M had ≥8-week RBC-TI with imetelstat



Data cutoff date: October 13, 2022.
Hb, hemoglobin; IPSS-M, molecular International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.

Risk Classifications and TI Responses: 8-week RBC-TI Responders

- RBC-TI response with imetelstat treatment was achieved in patients across all risk subgroups defined per IPSS, IPSS-R, IPSS-M, and IPSS-R cytogenetic
- Among the 47 patients who achieved the primary end point of 8-week RBC-TI with imetelstat, 15 responders (32%) who had intermediate/higher risk, across all the classification systems used, also achieved long-term TI responses of ≥24 weeks and ≥1 year
- None of the two ≥8-week TI responders with intermediate/higher risk in the placebo group achieved durable TI responses of ≥24 weeks and ≥1 year



IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS; RBC, red blood cell; TI, transfusion independence.

Conclusions

- In the IMerge clinical trial, 16% of patients were intermediate risk by IPSS-R
- IPSS to IPSS-M reclassification upstaged a total of 21 patients (10 with low and 11 with intermediate-1) to moderate high, high, or very high risk
- The results of this subgroup analysis of IMerge showed that imetelstat consistently had higher RBC-TI response rates than did placebo across different risk subgroups defined per IPSS, IPSS-R, IPSS-M, and IPSS-R cytogenetic
- Overall, durable RBC-TI responses of ≥24-week and ≥1-year were observed with imetelstat in all lower- and higher-risk subgroups
- Reclassifying patients by IPSS-M revealed that one-third of the patients identified as higher-risk IPSS-M derived RBC-TI benefit from imetelstat for ≥8 weeks
- In contrast, higher-risk subgroups receiving placebo failed to achieve long-term RBC-TI, regardless of the risk classification scheme used
- In summary, in heavily transfused patients with LR-MDS R/R to ESAs or ineligible for ESAs, the clinical efficacy of imetelstat was maintained irrespective of risk category

ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System; IPSS-M, molecular IPSS; IPSS-R, revised IPSS; LR-MDS, lower-risk myelodysplastic syndromes; RBC, red blood cell; R/R, relapsed/refractory; TI, transfusion independence.

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- ClinicalTrials.gov: NCT02598661
- For more information on IMerge phase 3, please check our posters 4603 and 4605 presented here, at ASH 2023, and our recent publication by Platzbecker U, et al. *Lancet*. Published Online December 1, 2023. https://doi.org/10.1016/S0140-6736(23)01724-5.