Received: 29 July 2025 | Accepted: 31 October 2025

DOI: 10.1111/bjh.70266

BJHaem
BRITISH JOURNAL OF HAEMATOLOGY

RESEARCH LETTER

Clinical outcomes and safety in patients with lower-risk myelodysplastic syndromes treated with imetelstat: Substudy of the phase 3 IMerge trial

To the Editor,

Imetelstat is a first-in-class, direct and competitive inhibitor of telomerase enzymatic activity approved in the United States and Europe for adult patients with lower-risk myelodysplastic syndromes (LR-MDS) and red blood cell (RBC) transfusion-dependent (TD) anaemia (defined as requiring ≥4 RBC units over 8 weeks) who have relapsed or are refractory to or ineligible for erythropoiesis-stimulating agents (ESAs) based on the results of the pivotal phase 3 IMerge trial (NCT02598661).[1–3] In IMerge, imetelstat demonstrated significant improvements in ≥8- and ≥24-week RBC transfusion independence (TI) rates versus placebo, with a median duration of RBC-TI of 51.6 weeks among imetelstat responders.[1]

In accordance with International Conference on Harmonization guidance,[4,5] a series of nonclinical and clinical assessments of cardiac parameters investigated the proarrhythmic risk of imetelstat. In vitro analyses showed that imetelstat did not inhibit human ether-a-go-go–related gene channel current.[6] In vivo analyses in monkeys showed that imetelstat did not have an effect on cardiac parameters, including corrected QT interval (QTc). Clinical cardiac safety was evaluated in a separate, prespecified, double-blind, randomised, placebo-controlled ventricular repolarisation substudy of the phase 3 IMerge trial, which concluded no evidence of QTc prolongation effects.[6] Here, we report the clinical outcomes and safety results from this IMerge substudy.

The substudy differed from the phase 3 IMerge population by including patients with del(5q) MDS, overlapping myelodysplastic/myeloproliferative neoplasm (MDS/MPN) with ring sideroblasts (RS) and thrombocytosis and those previously treated with lenalidomide or hypomethylating agents (HMA). Furthermore, patients in the substudy could cross over from placebo to imetelstat after two cycles at the investigator's discretion. Adult patients were randomised (2:1) to 7.1 mg/kg imetelstat active dose (equivalent to 7.5 mg/kg imetelstat sodium) or placebo, both administered as 2-h intravenous infusions every 4 weeks. Patients provided prior written informed consent, and the study followed the ethical standards of the responsible committees on human experimentation and the Declaration of Helsinki (October 1996).

The substudy comprised 53 treated patients (imetelstat, $n = 35$; placebo, $n = 18$). As of the data cut-off (10 May 2024), 16/18 placebo recipients crossed over to receive imetelstat. For this entire imetelstat-treated population ($N = 51$), baseline characteristics were generally consistent with the primary IMerge population (Table S1).[1] Of all imetelstat-treated patients ($N = 51$), 57% ($n = 29$) were receiving >6 U RBC/8 weeks; the median pretreatment haemoglobin level was 7.5 g/dL; 76% ($n = 39$) had RS+ LR-MDS; 69% ($n = 35$) and 31% ($n = 16$) were International Prognostic Scoring System (IPSS) risk category low and intermediate-1, respectively; and 78% ($n = 40$) and 22% ($n = 11$) were classified as having a high transfusion burden and low transfusion burden, respectively, as per International Working Group (IWG) 2018 criteria. Eighty-eight percent ($n = 45$) had prior ESA therapy, 27% ($n = 14$) had prior HMA therapy, 45% ($n = 23$) had prior luspatercept and 25% ($n = 13$) had prior lenalidomide. Median treatment duration on imetelstat, including crossover ($N = 51$), was 29 weeks; 37 weeks in the imetelstat group ($n = 35$); and 28 weeks in the crossover group ($n = 16$).

In this post hoc analysis, the proportion of patients with RBC-TI and other binary clinical end-points was summarized with percentage and two-sided exact Clopper–Pearson 95% confidence interval (CI). Kaplan–Meier methodology estimated the distribution of duration of RBC-TI.

In the total imetelstat population including crossover ($N = 51$), 41% ($n = 21$) achieved ≥8-week RBC-TI and 25% ($n = 13$) achieved ≥24-week RBC-TI; haematologic improvement-erythroid as per IWG 2018 criteria was achieved by 41% ($n = 21$), 35% ($n = 18$) had a haemoglobin rise ≥1.5 g/dL lasting ≥8 weeks and 75% ($n = 38$) had a ≥4 U/8 weeks reduction in RBC transfusions (Figure 1). Achievement of ≥8-week RBC-TI with imetelstat was also observed in those with RS+ disease (46% [18/39]) and IPSS intermediate-1–risk disease (56% [9/16]; Figure S1). Of the eight patients with MDS/MPN, three achieved ≥8-week RBC-TI and two achieved ≥24-week RBC-TI. Median duration of RBC-TI among ≥8-week RBC-TI responders ($n = 21$) was 52.6 weeks (95% CI, 40.9 to not estimable); only one patient progressed to acute myeloid leukaemia (AML), a placebo recipient before crossover.

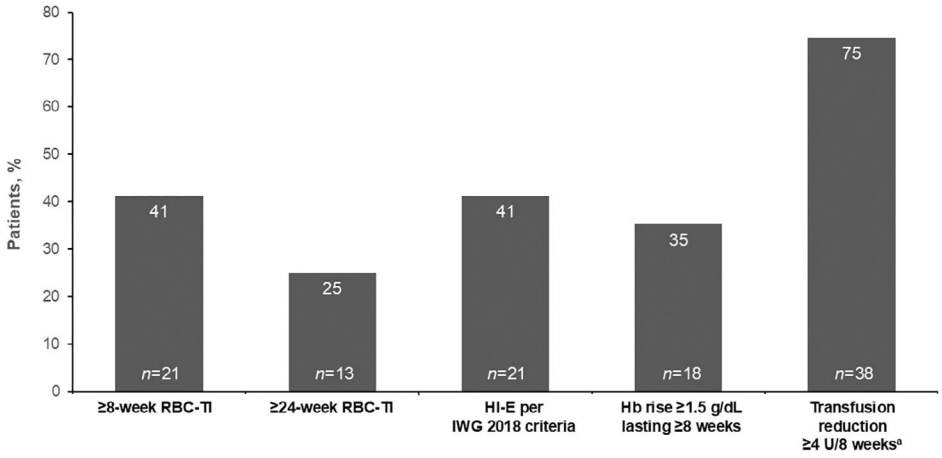

FIGURE 1 Clinical outcomes in the total imetelstat population ($n = 51$). Hb, haemoglobin; HI-E, haematologic improvement-erythroid; IWG, International Working Group; RBC, red blood cell; TI, transfusion independence. [a]Per IWG 2006 criteria.

Figure S2 shows the percent of patients who had received prior therapy and achieved RBC-TI. Of those who had received prior therapy with HMA (azacitidine or decitabine), luspatercept or lenalidomide, 21%, 30% and 38%, respectively, achieved ≥8-week RBC-TI versus 49%, 50%, and 52%, respectively, of patients who had not received these therapies; and 14%, 22%, and 15%, respectively, achieved ≥24-week RBC-TI versus 30%, 29% and 29%, respectively. However, some prior therapy subgroups were small. For patients who received prior ESAs ($n = 45$), 47% ($n = 21$) achieved ≥8-week RBC-TI and 29% ($n = 13$) achieved ≥24-week RBC-TI, and of the six patients who had not received ESA therapy due to erythropoietin >500 mU/mL, no patients achieved ≥8-week RBC-TI. ESA therapy is the most commonly used first-line treatment for LR-MDS, but many patients do not respond and responses are often transient.[7,8] Furthermore, the 5-year cumulative incidence of transformation to AML has been found to be 13% in patients with LR-MDS who experience primary or secondary ESA failure, with median survival of 52 and 60 months for those with primary refractory disease or relapsed disease, respectively.[9] Data on first-line luspatercept failure are limited, but in the pivotal phase 3 COMMANDS trial, 40% of patients did not meet the primary end-point (≥12-week RBC-TI with concurrent haemoglobin rise ≥1.5 g/dL during Weeks 1–24).[10] The overall objective response rate with HMAs in patients with LR-MDS is ~36%, and most patients discontinue therapy due to loss of response or primary resistance.[11] After HMA failure, median overall survival is only ~17 months.[11] Lenalidomide is the standard of care for del(5q) MDS; however, 30%–40% of patients either will not respond or do not tolerate the drug, and after lenalidomide failure, overall survival is only ~23 months, with a 5-year probability of survival of 24%.[12] Thus, the results of the present study are particularly important, since a meaningful proportion of patients who had previously received therapy with ESAs, luspatercept, lenalidomide, or to a lesser extent HMAs, achieved ≥8-week RBC-TI with imetelstat.

No new safety signals emerged in this substudy. Of the 51 total imetelstat-treated patients, 48 (94%) experienced a treatment-emergent adverse event (TEAE), of which the most common were neutropenia and thrombocytopenia, each occurring in 69% (35/51) of patients (all grade; Table 1). Grade 3/4 neutropenia and thrombocytopenia by laboratory evaluation occurred in 65% (33/51) and 49% (25/51) of patients respectively. Of these, 87% and 77%, respectively, resolved to grade ≤2 within 4 weeks. Of the 33 patients who experienced grade 3/4 neutropenia, 5 (15%) had a grade 1/2 infection within 7 days and 3 (9%) had a grade 3/4 infection; of the 25 patients with grade 3/4 thrombocytopenia, 1 (4%) had a grade 1/2 bleeding event within 7 days and none had a grade 3/4 bleeding event. Incidences of these cytopenias were similar to those in the overall phase 3 imetelstat-treated population, where neutropenia and thrombocytopenia were also managed with dose delays and reductions, without any apparent impact on clinical outcomes.[1] Both neutropenia and thrombocytopenia with imetelstat are well characterized, are

TABLE 1 TEAEs occurring in ≥10% of the patients in the IMerge ventricular repolarisation substudy.

	Imetelstat total ($n = 51$)	
TEAE, *n* (%)	**All grades**	**Grade 3/4**
Any TEAE	48 (94)	41 (80)
Neutropenia	35 (69)	33 (65)
Thrombocytopenia	35 (69)	25 (49)
Alanine aminotransferase increased	12 (24)	1 (2)
Diarrhoea	11 (22)	0
Leucopenia	9 (18)	6 (12)
Fatigue	9 (18)	0
Aspartate aminotransferase increased	9 (18)	0
Peripheral oedema	8 (16)	0
Nausea	6 (12)	0
Decreased appetite	6 (12)	0
COVID-19	6 (12)	0
Back pain	6 (12)	1 (2)

Abbreviation: TEAE, treatment-emergent adverse event.

generally manageable and reversible and are associated with low risk of severe clinical consequences, including bleeding and infections. Both of these cytopenias with imetelstat are thought to be related to on-target effects on malignant stem and progenitor cells.[13] A delay in normal megakaryocyte maturation and thereby blood cell production may also contribute to the transient occurrence of thrombocytopenia.[13,14]

Adverse event-related dose reductions occurred in 22/51 (43%) patients due to neutropenia (35% [18/51]), thrombocytopenia (20% [10/51]), sepsis (2% [1/51]) and gamma-glutamyltransferase increased (2% [1/51]). Dose delays due to a TEAE occurred in 39/51 (76%) patients, with the most common (occurring in >5%) due to neutropenia (55% [28/51]), thrombocytopenia (41% [21/51]) and urinary tract infection (6% [3/51]). TEAEs leading to treatment discontinuation occurred in three patients (thrombocytopenia, $n = 2$; pancytopenia, $n = 1$). One (2%) patient experienced a TEAE (pneumonia) that led to death.

In summary, results from this substudy build on the clinical outcomes and safety of imetelstat observed in the phase 3 IMerge population. Here, imetelstat resulted in durable RBC-TI (median duration 1 year), transfusion reduction and clinically meaningful increases in haemoglobin, regardless of baseline disease characteristics and inclusive of exposure to prior therapies. These results suggest that imetelstat has clinical activity when used in early-line and later-line therapy.

Having efficacious treatment options with manageable safety across the spectrum of patients with LR-MDS is important, as it addresses the variability in patient and disease characteristics encountered in real-world practice.[15] As the geographic availability and real-world use of imetelstat expands, future research will further characterize the clinical outcomes, safety and potential disease-modifying capacity of its novel mechanism of action in LR-MDS and beyond.

KEYWORDS

anaemia, clinical trial, efficacy, imetelstat, myelodysplastic syndromes, QTc, safety, transfusions

AUTHOR CONTRIBUTIONS

R.S.K., V.S., U.P., K.V.E., M.D.-C., R.D.P., G.S.S., S.T., M.K., E.N.O., M.A.S., P.F., Y.F.M., M.R.S. and A.M.Z. were involved with data curation, the investigation and writing of the manuscript. J.R. and S.S. were involved with developing the methodology, the investigation and writing of the manuscript. A.L.L., Q.X. and L.S. were involved with conceptualization of the research, developing the methodology, investigation, data curation, formal analysis and validation of the data and writing of the manuscript. T.B. was involved with conceptualization of the research, developing the methodology, validation of the data, project management and writing (reviewing and editing) of the manuscript. All authors reviewed and approved the final version for submission.

ACKNOWLEDGEMENTS

The authors thank all the patients and caregivers for their participation in this study and acknowledge the collaboration and commitment of all investigators and their research support staff. Writing and editorial support were provided by Meredith Rogers, MS, CMPP, of The Lockwood Group (Stamford, CT, USA), funded by Geron Corporation.

CONFLICT OF INTEREST STATEMENT

R.S.K. reports consultancy/speaker bureau fees from AbbVie, Celgene/Bristol Myers Squibb, Daiichi Sankyo, Geron Corporation, Jazz Pharmaceuticals, PharmaEssentia, Rigel Pharmaceuticals, Servier, Sobi and Sumitomo Pharma and received research funding from Celgene/Bristol Myers Squibb. V.S. received travel grants from Janssen and Jazz Pharmaceuticals and participated in Advisory Boards for AbbVie, Ascentage, Bristol Myers Squibb, CTI BioPharma, Geron Corporation, Gilead Sciences, Novartis, Servier and Syros Pharmaceuticals. U.P. received honoraria and research funding from AbbVie and Geron Corporation. M.D.-C. reports honoraria/consultancy fees from Agios Pharmaceuticals, Blueprint Medicines, Celgene/Bristol Myers Squibb, GlaxoSmithKline and Novartis; travel expenses from Gilead and Otsuka; and has served in Board of Directors or advisory committees of Agios Pharmaceuticals, Celgene/Bristol Myers Squibb, Curis, GlaxoSmithKline, Hemavant Sciences, Keros Therapeutics, Novartis, Otsuka and Syros Pharmaceuticals. G.S.S. reports honoraria/consultancy or speaker bureau fees from AstraZeneca, Bristol Myers Squibb, Excelera, GlaxoSmithKline and Novartis; and institutional research funding from Amgen, Bayer, Bristol Myers Squibb, J&J, Menarini Group, Novartis, Pfizer and Takeda. S.T. received advisory board fees or honoraria from Celgene/Bristol Myers Squibb, AbbVie, Gilead, Astellas Pharma and Takeda. E.N.O. reports consultancy/speaker bureau fees from Alexion Pharmaceuticals, BeiGene, Bristol Myers Squibb, Daiichi Sankyo, Janssen, Novartis, Pfizer, Ryvu Therapeutics, Sanofi, Sobi and Syros Pharmaceuticals; and patents and royalties from Amgen, Bristol Myers Squibb, Halia Therapeutics and Ryvu Therapeutics. M.A.S. reports consultancy fees from Bristol Myers Squibb, Schrödinger, Menarini Group and Kurome; research funding from Bristol Myers Squibb; travel expenses from Daiichi Sankyo; and owns stock options in Kurome Therapeutics. P.F. reports honoraria from AbbVie and Bristol Myers Squibb; and research funding from AbbVie, Astex Pharmaceuticals, Bristol Myers Squibb, Novartis and Servier. Y.F.M. reports consultancy fees from Blueprint Medicines, Bristol Myers Squibb, Geron Corporation and Kura Oncology; travel expenses from Blueprint Medicines, MD Education and MorphoSys; and has served in advisory boards for Blueprint Medicines, Cogent Biosciences, Geron Corporation, MorphoSys, Novartis, Rigel Pharmaceuticals, Sierra Oncology, Sobi, Stemline Therapeutics and Taiho Oncology. M.R.S. reports consultancy fees from AbbVie, Bristol Myers Squibb, CTI BioPharma, Forma Therapeutics, Geron Corporation, GlaxoSmithKline, Rigel Pharmaceuticals, Taiho Pharmaceutical and Treadwell Therapeutics; grants or contracts with Astex Pharmaceuticals and Incyte; patents/royalties from Boehringer Ingelheim and Empath Biosciences; holds equity at Empath Biosciences,

Karyopharm Therapeutics and Ryvu Therapeutics; and has served in the Board of Directors or advisory committees for the MDS Foundation. A.M.Z. reports research funding from AbbVie, ADC Therapeutics, Aprea Therapeutics, Astex Pharmaceuticals, AstraZeneca, Boehringer Ingelheim, Cardiff Oncology, Celgene/Bristol Myers Squibb, Genentech, Novartis, Pfizer, Shattuck Labs and Takeda; has served in the Board of Directors, advisory committees, or clinical trial committees for AbbVie, Agios Pharmaceuticals, ALX Oncology, Amgen, Aprea Therapeutics, Astellas Pharma, Astex Pharmaceuticals, BeyondSpring, BioCryst, Celgene/Bristol Myers Squibb, Chiesi, Daiichi Sankyo, Epizyme, Genentech, Gilead, Ionis Pharmaceuticals, Janssen, Jazz Pharmaceuticals, Kura Oncology, Mendus, Notable Labs, Novartis, Orum Therapeutics, Otsuka, Pfizer, Regeneron, Seattle Genetics, Syndax, Takeda and Taiho Pharmaceutical. J.R., S.S., A.L.L., Q.X., L.S. and T.B. are employees of Geron Corporation, the sponsor of the work, and may hold stock or stock options. K.V.E., R.D.P. and M.K. have nothing to disclose at this time.

FUNDING INFORMATION

This study was funded by Geron Corporation.

DATA AVAILABILITY STATEMENT

De-identified study data will be made available upon request to qualified researchers, to the extent permitted by applicable laws and participant informed consent. Approval of such requests is at the discretion of Geron Corporation and is dependent on the nature of the request, the merit of the research proposed, the availability of the data, and the intended use of the data. Data requests should be sent to medinfo@geron.com.

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NCT02598661.

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REFERENCES

1. Platzbecker U, Santini V, Fenaux P, Sekeres MA, Savona MR, Madanat YF, et al. Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2024;403:249–60.
2. RYTELO® (imetelstat) for injection, for intravenous use. Package insert. Geron Corporation. 2024.
3. RYTELO® (imetelstat) summary of product characteristics. Geron Corporation. 2025.
4. United States Food and Drug Administration, Department of Health and Human Services. International Conference on Harmonisation; guidance on S7B nonclinical evaluation of the potential for delayed ventricular repolarization (QT interval prolongation) by human pharmaceuticals; availability. Notice. Fed Regist. 2005;70:61133–34.
5. United States Food and Drug Administration, Department of Health and Human Services. International Conference on Harmonisation; guidance on E14 clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs; availability. Notice. Fed Regist. 2005;70:61134–35.

6. Lennox AL, Sun L, Huang F, Behrs MK, Kleiman R, Xue H, et al. Low proarrhythmic risk of imetelstat, a novel oligonucleotide telomerase inhibitor: a translational analysis. Clin Transl Sci. 2025;18:e70169.
7. Diez-Campelo M, Yucel A, Goyal RK, Parikh RC, Esterberg E, Jimenez M, et al. Treatment characteristics and outcomes in lower-risk, non-del(5q) myelodysplastic syndromes: findings from a medical record review in the USA, Canada and Europe. Future Oncol. 2024;20:1993–2004.
8. Fenaux P, Platzbecker U, Ades L. How we manage adults with myelodysplastic syndrome. Br J Haematol. 2020;189:1016–27.
9. Park S, Hamel JF, Toma A, Kelaidi C, Thépot S, Campelo MD, et al. Outcome of lower-risk patients with myelodysplastic syndromes without 5q deletion after failure of erythropoiesis-stimulating agents. J Clin Oncol. 2017;35:1591–7.
10. Della Porta MG, Garcia-Manero G, Santini V, Zeidan AM, Komrokji RS, Shortt J, et al. Luspatercept versus epoetin alfa in erythropoiesis-stimulating agent-naive, transfusion-dependent, lower-risk myelodysplastic syndromes (COMMANDS): primary analysis of a phase 3, open-label, randomised, controlled trial. Lancet Haematol. 2024;11:e646–e658.
11. Jabbour EJ, Garcia-Manero G, Strati P, Mishra A, Al Ali NH, Padron E, et al. Outcome of patients with low-risk and intermediate-1-risk myelodysplastic syndrome after hypomethylating agent failure: a report on behalf of the MDS Clinical Research Consortium. Cancer. 2015;121:876–82.
12. Prebet T, Cluzeau T, Park S, Sekeres MA, Germing U, Ades L, et al. Outcome of patients treated for myelodysplastic syndromes with 5q deletion after failure of lenalidomide therapy. Oncotarget. 2017;8:81926–35.
13. Wang X, Hu CS, Petersen B, Qiu J, Ye F, Houldsworth J, et al. Imetelstat, a telomerase inhibitor, is capable of depleting myelofibrosis stem and progenitor cells. Blood Adv. 2018;2:2378–88.
14. Mosoyan G, Kraus T, Ye F, Eng K, Crispino JD, Hoffman R, et al. Imetelstat, a telomerase inhibitor, differentially affects normal and malignant megakaryopoiesis. Leukemia. 2017;31:2458–67.
15. Sekeres MA, Schoonen WM, Kantarjian H, List A, Fryzek J, Paquette R, et al. Characteristics of US patients with myelodysplastic syndromes: results of six cross-sectional physician surveys. J Natl Cancer Inst. 2008;100:1542–51.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.