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Effect of prior therapy on the clinical activity of imetelstat in patients with transfusion-dependent, ESA-relapsed or -refractory/-ineligible LR-MDS

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Lower-risk (LR) myelodysplastic syndromes (MDS) are myeloid neoplasms characterized by ineffective hematopoiesis, abnormal blood cell development, and a relatively low risk of progression to acute myeloid leukemia or death [1]. Anemia is a hallmark of LR-MDS and often leads to chronic red blood cell (RBC) transfusion dependence (TD), which is a reflection of further bone marrow failure, increased disease burden, and shortened survival (~3–9 years) [1, 2]. These patients present with a clinical challenge, in that the primary therapeutic goal is to improve the cytopenias and manage their symptoms (typically through supportive care and targeted pharmacotherapeutics) rather than controlling the malignant hematopoiesis [3–5]. There is an unmet need for improvements in therapies for LR-MDS that can target the underlying cause of the disease.

Most commonly used recommended first-line treatments for LR-MDS include erythropoiesis-stimulating agents (ESAs) or luspatercept (preferred for patients with serum erythropoietin levels >200 to ≤500 mU/mL) for non-del(5q) disease, and lenalidomide for del(5q) disease [6, 7]. Hypomethylating agents (HMAs) are typically used in patients with higher-risk MDS and rarely indicated in earlier lines of treatment. The direct and competitive inhibitor of telomerase activity, imetelstat, demonstrated clinically meaningful and durable efficacy, a generally manageable safety profile, and potential for disease modification in the Phase III IMerge study (NCT02598661), leading to its regulatory approval in the United States (June 2024) and EU (March 2025) for the treatment of certain patients with LR-MDS and RBC-TD anemia who are relapsed, refractory, or ineligible for ESAs [8]. As new agents become available, it is essential to evaluate how initial therapeutic choices may influence the efficacy of subsequent therapies to inform optimal sequencing strategies. This is particularly relevant in LR-MDS, given its protracted disease course [4, 9]. To that end, we conducted a post hoc analysis to investigate the effects of prior therapies on the clinical activity of imetelstat.

Patient data were pooled ($N = 226$) from the following 3 parts of the IMerge study: Phase II [10], Phase III [8], and a ventricular repolarization Cardiac Safety substudy (regulatory requirement for new agents, which concluded no evidence of QTc prolongation effects with imetelstat) [11]. Patients were not included in >1 part of IMerge. Additional details related to study design, treatments, assessments, and statistical analysis are provided in the Supplementary Methods. Imetelstat was administered intravenously every 4 weeks at 7.1 mg/kg (equivalent to 7.5 mg/kg imetelstat sodium) over 2 h. Patients were not permitted to receive any anticancer, ESAs, or erythropoiesis maturation agent therapy while on study treatment. Use of prior therapies was collected from the patients' case report forms with no minimum exposure dose or duration required, and prior treatment was not exclusive.

At baseline, most patients were ≥65 years of age, had ring sideroblast (RS)–positive disease, International Prognostic Scoring System LR disease, a high transfusion burden, and had received several prior therapies (Supplementary Tables 1, 2, and 3). The median treatment duration of imetelstat was 33.6 weeks and most patients received ≥7 cycles of imetelstat therapy (Supplementary Table 4). Most patients had prior ESA exposure, while fewer had prior lenalidomide, luspatercept, or HMA therapy, which may have been administered before/after treatment with ESAs (Supplementary Fig. 1; patients may be reflected in multiple subgroups). The ESA-ineligible subgroup was comprised of 13 patients who were treatment naive (i.e., no prior ESAs or other therapies) and 9 who had received non-ESA–based therapies.

Efficacy results in the current analysis of the overall pooled population treated with imetelstat were comparable to the IMerge Phase III results (Fig. 1A) [8]. Data from IMerge Phase III, published in *The Lancet*, are plotted as green lines on the graphic for comparison. The median duration of ≥8-week RBC transfusion independence (TI) for the pooled population was 55 weeks (95% confidence interval: 42–70) (Supplementary Table 5). Overall survival data were not mature at the time of this analysis.

Of those patients ineligible for ESA therapy (i.e., no ESA exposure) due to baseline serum erythropoietin >500 mU/mL ($n = 22$), 36%, 14%, and 9% achieved ≥8-week, ≥24-week, and ≥1-year RBC-TI, respectively (Fig. 1B); median (range) hemoglobin rises were 3.66 g/dL (−0.07 to 9.28), 6.87 g/dL (4.17–9.28), and 6.72 g/dL (4.17–9.28) during the ≥8-week, ≥24-week, and ≥1-year RBC-TI periods, respectively. In the subset of patients who were ineligible for ESA therapy and were treatment-naive (13/22), 54%, 23%, and 15%, respectively, met these same RBC-TI endpoints. Achievement of ≥8-week, ≥24-week, and ≥1-year RBC-TI and median hemoglobin rises after prior ESA (Fig. 1C), prior luspatercept (Fig. 1D), and prior lenalidomide (Fig. 1E) show clinically meaningful activity of imetelstat after common LR-MDS therapies but little activity after prior HMAs (Fig. 1F). There were 6 patients who had received all 4 prior therapies (prior HMA, ESA, lenalidomide, and luspatercept), 2 (33%) of whom achieved ≥8-week RBC-TI and 1 (17%) who achieved ≥24-week RBC-TI. The median time to onset of the 8-week RBC-TI interval, as well as durations of ≥8-week, ≥24-week, and ≥1-year RBC-TI for all the prior therapy subgroups are presented in Supplementary Table 5. Outcomes by RS status are listed in Supplementary Table 6.

Clinical activity was observed with imetelstat regardless of prior response to ESAs (Fig. 2A). Clinical activity of imetelstat decreased

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Fig. 1 Efficacy of imetelstat in patients with prior therapy. A Clinical response with imetelstat in the overall patient population. **B** Clinical response with imetelstat in patients who were ESA ineligible. **C** Clinical response with imetelstat in patients with prior treatment with ESA. **D** Clinical response with imetelstat in patients with prior treatment with luspatercept. **E** Clinical response with imetelstat in patients with prior treatment with lenalidomide. **F** Clinical response with imetelstat in patients with prior treatment with HMA. ESA erythropoiesis-stimulating agent, Hb hemoglobin, HI-E hematologic improvement-erythroid, HTB high transfusion burden, IWG International Working Group, LTB low transfusion burden, LUSP luspatercept, n/N number with event/number in population, RBC red blood cell, TI transfusion independence. [a]Hb rise is defined as the increase from the pretreatment Hb level to the peak Hb value during the TI period, excluding values within the first 2 weeks after transfusion (this ensures no impact of transfusions on Hb rise outcome). [b]LTB is defined as 3–7 RBC U in 16 weeks in ≥2 transfusion episodes, and a maximum of 3 in 8 weeks. [c]HTB is defined as ≥8 RBC U in 16 weeks, or ≥4 RBC U in 8 weeks. [d]ESA ineligibility per inclusion criteria was defined as erythropoietin >500 mU/mL, which included 13 patients who were treatment naive and 9 who had received non-ESA–based therapy. [e]Of patients with any prior LUSP, 31 had ring sideroblast–positive status, and all but 4 patients had also received prior ESA.

with the number of prior lines of therapy but was still clinically meaningful when used in later lines of therapy (Fig. 2B). More than half (54%, 7/13) of patients who received imetelstat as first-line therapy (i.e., treatment-naive patients) achieved ≥8-week RBC-TI and 23% (3/13) achieved ≥24-week RBC-TI. Of patients treated with imetelstat in the second-line setting, 42% (60/142) and 30% (43/142) achieved ≥8- and ≥24-week RBC-TI, respectively. Imetelstat in the third-line setting showed 31% (22/71) and 24% (17/71) of patients achieving ≥8- and ≥24-week RBC-TI, respectively.

In the 98% of patients treated with imetelstat who experienced a treatment-emergent adverse event (TEAE) of any grade, and the 88% who experienced a Grade ≥3 TEAE, neutropenia and thrombocytopenia were the most common (Supplementary Table 7 and Supplementary Table 8). Most cytopenia events occurred in earlier treatment cycles/months and resolved to Grade ≤2 in <4 weeks. (Supplementary Table 9). In the overall pooled population treated with imetelstat, rates of cycle delay, dose reduction, and infusion interruptions were comparable to those observed in the Phase III portion of IMerge (Supplementary Table 4) [8].

In this analysis, imetelstat demonstrated meaningful clinical activity in patients with LR-MDS regardless of prior therapy with ESA, lenalidomide, or luspatercept (much less after HMA) or line of treatment (first line through third line and beyond). Although clinical activity was evident across all lines of therapy, efficacy appeared to be greater in earlier lines. These data, together with recent evidence supporting the disease modification potential of imetelstat (Santini, et al. accepted for publication, *Leukemia* 2025), may suggest that use of imetelstat earlier in the LR-MDS treatment paradigm could help maximize its clinical benefit [8]. Further prospective studies in a larger patient population are needed to validate the observations from this pooled study.

Reducing a patient's transfusion burden is a key therapeutic target [12, 13]. A real-world evidence analysis of the OPTUM database ($n = 6531$) showed that 46% of patients with LR-MDS continued to receive ≥1 RBC transfusion during any 8-week period of their first-line treatment [14]. The current study demonstrates that imetelstat has clinical activity, including RBC-TI and hematologic improvement (HI-E response criteria) in patients previously treated with ESAs,

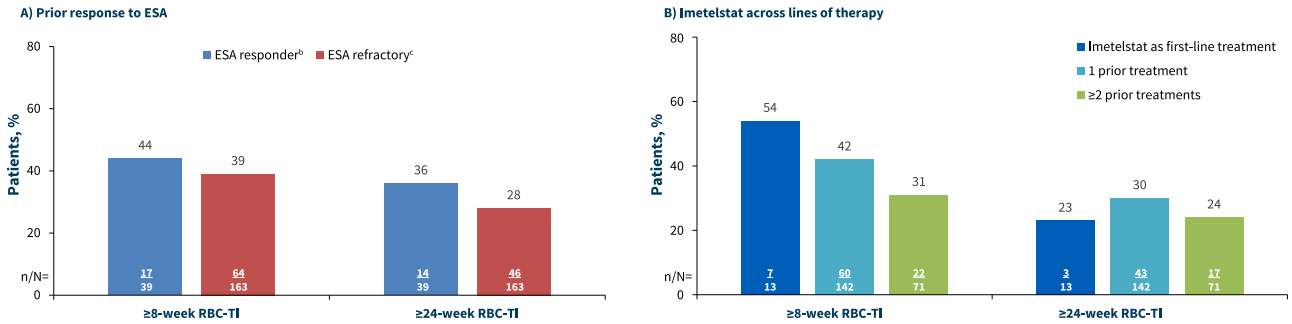

Fig. 2 Achievement of RBC-TI in patients with prior treatment. A RBCI-TI responses with imetelstat in prior ESA responders and ESA-refractory patients. **B** RBCI-TI responses with imetelstat in patients across lines of therapy. EPO erythropoietin, ESA erythropoiesis-stimulating agent, HI-E hematologic improvement-erythroid, n/N number with event/number in population, RBC red blood cell, TI transfusion independence. [a]Two patients with prior ESA but missing best response to ESA were excluded. [b]Response included RBC-TI and HI-E response. [c]Received ≥8 weeks of ESA treatment (EPO alfa ≥40,000 U, EPO beta ≥30,000 U, or darbepoetin alfa 150 μg or equivalent per week) without having achieved an Hb rise ≥1.5 g/dL or decreased RBC transfusion requirement by ≥4 U every 8 weeks or having transfusion dependence or reduction in Hb by ≥1.5 g/dL after hematologic improvement from ≥ 8 weeks of treatment with therapies.

luspatercept, or lenalidomide, comparable to patients treated with imetelstat in the pivotal IMerge Phase III study population. Prior results from IMerge Phase III show a reduction in transfusion burden (≥ 4 units RBC reduction/8 weeks) for patients (86%, 6/7) treated with imetelstat after prior ESA and luspatercept despite not achieving RBC-TI [8]. The present analyses in a larger patient subgroup also showed that patients who had prior treatment with ESA and luspatercept had a high rate of transfusion reduction (72%, 23/32).

Limitations of this analysis include small subgroup sizes and potential confounding due to the timing of luspatercept approval during IMerge enrollment. Mutational samples for disease assessment were not available for some IMerge study parts; therefore, the scoring system used may not reflect the updated mutational risk scoring system, which may more accurately reflect modern paradigms in MDS. Healthcare resource utilization data were not available for assessment.

In conclusion, these results show that imetelstat had clinical activity in patients with LR-MDS and anemia who were either treatment naive or had prior exposure to therapies typically used in the frontline setting, with no new safety signals identified. As the therapeutic landscape for LR-MDS with anemia continues to evolve, these findings support the potential of imetelstat to provide meaningful clinical benefit to patients irrespective of prior treatment history.

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DATA AVAILABILITY

De-identified study data will be made available upon request to qualified researchers after approval of imetelstat in myelodysplastic syndromes, 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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AUTHOR CONTRIBUTIONS

R.S.K., V.S., A.M.Z., M.A.S., P.F., A.R., M.M., S.T., R.B., U.G., Y.F.M., M.D.-C., D.V., A.J., M.R.S., and U.P. were involved in data acquisition, data interpretation, and manuscript writing and revisions. S.D., S.S., Q.X., L.B., S.N., and F.F. were involved in study design/conception, data acquisition, data analysis, data interpretation, and manuscript writing and revisions. All authors approved submission of the final draft.

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COMPETING INTERESTS

R.S.K. reports consultancy/speaker bureau fees from AbbVie, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Geron Corporation, Jazz Pharmaceuticals, PharmaEssentia, Rigel Pharmaceuticals, Servier, Sobi, and Sumitomo Pharma; received research funding from Bristol Myers Squibb/Celgene. V.S. reports participation on advisory board for Ascentage Pharma, AbbVie, Bristol Myers Squibb, CTI BioPharma, Geron Corporation, Gilead, Novartis, Servier, and Syros Pharmaceuticals. A.M.Z. reports research funding from, AbbVie, ADC Therapeutics, Aprea Therapeutics, Astex, AstraZeneca, Boehringer Ingelheim, Cardiff Oncology, Bristol Myers Squibb/Celgene, Genentech, Geron Corporation, Novartis, Pfizer, Shattuck Labs, and Takeda; has served on the Board of Directors, advisory committees, or clinical trial committees for AbbVie, Agios, ALX Oncology, Amgen, Aprea Therapeutics, Astellas Pharma, Astex, BeyondSpring, BioCryst, Bristol Myers Squibb/Celgene, Chiesi, Daiichi Sankyo, Epizyme, Genentech, Gilead, Ionis Pharmaceuticals, Janssen, Jazz Pharmaceuticals, Kura Oncology, Mendus, Notable Labs, Novartis, Orum, Otsuka, Pfizer, Regeneron, Seattle Genetics, Syndax, Takeda, and Taiho Pharmaceutical. M.A.S. reports research funding from Bristol Myers Squibb and has served on the Board of Directors or advisory committees of Bristol Myers Squibb, Kurome Therapeutics, and Schrödinger. P.F. reports honoraria from AbbVie and Bristol Myers Squibb and research funding from AbbVie, Astex, Bristol Myers Squibb, Novartis, and Servier. A.R. reports patents and royalties from/has served on the Board of Directors or advisory committees of TFC Therapeutics. M.M. reports consultancy/speaker bureaus fees from BioConvergence, Dr. Reddy, FibroGen, and research funding from AbbVie, Bristol Myers Squibb, Johnson & Johnson, Novartis, and Roche; holds equity in Cannalean. S.T. received advisory board fees or honoraria from AbbVie, Astellas Pharma, Bristol Myers Squibb/Celgene, Gilead, and Takeda. R.B. reports honoraria/consulting fees from Bristol Myers Squibb, Keros Therapeutics, and Taiho Pharmaceutical and research funding from Bristol Myers Squibb and Taiho Pharmaceutical. Y.M.F. reports consultancy fees from Blueprint Medicines, Bristol Myers Squibb, Geron Corporation, and Kura Oncology; travel expenses from Blueprint Medicines, MD Education, and MorphoSys; has served on advisory boards for Blueprint Medicines, Cogent Biosciences, Geron Corporation, MorphoSys, Novartis, Rigel Pharmaceuticals, Sierra Oncology, Sobi, Stemline Therapeutics, and Taiho Pharmaceutical. M.D.-C. reports consultancy fees/honoraria from Agios Pharmaceuticals, Blueprint Medicines, Bristol Myers Squibb/Celgene, GlaxoSmithKline, and Novartis; travel expenses from Gilead and Otsuka; has served on the Board of Directors or advisory committees of Agios Pharmaceuticals, Bristol Myers Squibb/Celgene, Curis, GlaxoSmithKline, Hemavan, Keros Therapeutics, Novartis, Otsuka, and Syros Pharmaceuticals. D.V. reports honoraria and consultancy/speaker bureau fees with AbbVie, Agios Pharmaceuticals, Amgen, Astellas Pharma, Bristol Myers Squibb, Gebro Pharma, Grifols, Janssen, Jazz Pharmaceuticals, Kite/Gilead, MSD, Novartis, Pfizer, Sanofi, Servier, Sobi, and Takeda; travel expenses from AbbVie, Agios Pharmaceuticals, Amgen, Bristol Myers Squibb, Grifols, Jazz Pharmaceuticals, Novartis, Sanofi, and Sobi; research funding from Bristol Myers Squibb; has served on the Board of Directors/advisory committees for Amgen, Bristol Myers Squibb, Grifols, Jazz Pharmaceuticals, Novartis, Servier, and Sobi. M.R.S. reports consultancy fees from AbbVie, Bristol Myers Squibb, CTI BioPharma, Geron Corporation, GlaxoSmithKline, Rigel Pharmaceuticals, Taiho Pharmaceutical, and Treadwell Therapeutics; grants or contracts with Astex and Incyte; patents/royalties from Boehringer Ingelheim and Empath Biosciences; holds equity at Empath Biosciences, Karyopharm Therapeutics, and Ryvu Therapeutics; has served on the Board of Directors or advisory committees for the MDS Foundation. U.P. received honoraria and research funding from AbbVie and Geron Corporation. S.D., S.S., Q.X., L.S., and F.F. report employment at Geron Corporation. S.N. reports current employment at/holds stock options from Geron Corporation. U.G. and A.J. have nothing to disclose.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by institutional review boards and ethics committees at all sites, following International Conference on Harmonization, Good Clinical Practice, and local standard operating procedures. Written informed consent was obtained from all patients or their legal representatives if unable to consent.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41408-025-01444-0.

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