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No Effect of Immunogenicity on Pharmacokinetics, Efficacy, and Safety of the Oligonucleotide Telomerase Inhibitor Imetelstat in Lower-Risk Myelodysplastic Syndromes

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ABSTRACT

Imetelstat is a first-in-class, 13-mer oligonucleotide telomerase inhibitor approved in the United States and European Union for the treatment of certain adult patients with lower-risk myelodysplastic syndromes (LR-MDS) with red blood cell (RBC) transfusion-dependent anemia. This post hoc analysis evaluated imetelstat immunogenicity and its association with the pharmacokinetics (PK), efficacy, and safety of imetelstat in patients with LR-MDS from the phase II/III IMerge study (NCT02598661). A validated, semi-quantitative 3-tiered method evaluated anti-drug antibodies (ADAs). Graphical and descriptive analyses evaluated ADA incidence and association with clinical outcomes. Of 166 evaluable patients who received 7.1 mg/kg imetelstat via a 2-h intravenous infusion every 4 weeks, 16.9% developed imetelstat ADAs (median [range] time to onset, 38 weeks [12–109]; ~8 treatment cycles). In ADA-positive patients, peak titer was low (median [range], 30 [10–160]). Evaluations showed no association of ADA positivity with imetelstat PK, nor any negative association with efficacy responses, including ≥ 8-week RBC-transfusion independence (TI), ≥ 24-week RBC-TI, hematologic improvement-erythroid, or duration of RBC-TI response. There was no apparent relationship between the onset of ADAs and loss of RBC-TI. The rates of any-grade or grade ≥ 3 treatment-emergent adverse events (TEAEs) were similar for both ADA groups, with no reported serious TEAEs or TEAEs causing death in ADA-positive patients. Infusion-related TEAEs were more frequent in ADA-positive patients, although the sample size was small. Overall, imetelstat ADAs did not appear to impact imetelstat benefit/risk profile in the LR-MDS population of IMerge, although the analysis is limited by the low incidence of imetelstat ADAs, resulting in a small ADA-positive group.

1 | Introduction

Imetelstat (GRN163L; RYTELO) is a novel, first-in-class, 13-mer N3′ → P5′ thio-phosphoramidate oligonucleotide with a covalently attached palmitoyl lipid group [1, 2]. Imetelstat acts by binding with high affinity to the template region of the RNA component of human telomerase, which lies in the active or catalytic site of human telomerase reverse transcriptase (hTERT),

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Study Highlights

- What is the current knowledge on the topic?
  - Imetelstat is a first-in-class, 13-mer oligonucleotide telomerase inhibitor approved in the United States and European Union for the treatment of certain adult patients with lower-risk myelodysplastic syndromes (LR-MDS) with transfusion-dependent anemia. While immunogenicity is a known concern for oligonucleotide therapeutics, data on the clinical impact of anti-drug antibodies (ADA) for this class of drugs remain limited.
- What question did this study address?
  - This post hoc analysis assesses the immunogenic potential of imetelstat to elicit anti-drug antibodies (ADA) in the combined phase II and phase III portions of the IMerge study, along with their association with clinical outcomes of imetelstat.
- What does this study add to our knowledge?
  - The development of imetelstat ADAs in patients with LR-MDS was characterized by low incidence, late response, low titers, and was not associated with meaningful differences in pharmacokinetics, efficacy, or the safety profile of imetelstat.
- How might this change clinical pharmacology or translational science?
  - These results contribute to understanding the clinical outcomes of synthetic oligonucleotides and informing their optimal clinical use. This study supports the continued use of imetelstat in patients with LR-MDS without the need for routine immunogenicity-based monitoring.

resulting in competitive inhibition of hTERT enzymatic activity [1, 2]. Thus, while imetelstat shares structural similarities with other oligonucleotide classes, its mechanism of action is through direct active site enzyme inhibition rather than an antisense-based mechanism. Inhibition of telomerase, which is involved in the regulation of cell division, by imetelstat leads to inhibition of cell proliferation, induction of apoptosis, and elimination of malignant hematopoietic stem and progenitor cells (HSC/HPC) while having minimal effect on normal HSCs/HPCs [2–8]. In preclinical models, imetelstat demonstrated potent in vitro and in vivo activity across various neoplasms, including acute myeloid leukemia [7, 9, 10], multiple myeloma [5], myelofibrosis [8, 11], and essential thrombocythemia [12]. In lower-risk myelodysplastic syndromes (LR-MDS), elimination of malignant HSCs/HPCs from the bone marrow could allow for restoration of normal hematopoiesis and improvement of anemia.

The benefit/risk of imetelstat in the LR-MDS population was established in the randomized, double-blind, phase III IMerge study (NCT02598661) [13, 14]. Patients who received imetelstat at 7.1 mg/kg active dose (equivalent to 7.5 mg/kg imetelstat sodium), administered via 2-h intravenous infusion every 4 weeks, achieved a statistically significant and clinically meaningful improvement in red blood cell (RBC) transfusion independence (TI) compared with placebo as follows: 40% (95% confidence interval [CI] 30.9–49.3) of imetelstat-treated patients had an RBC-TI of ≥ 8 weeks versus 15% [95% CI 7.1–26.6] in the placebo group, with a rate difference of 25% [95% CI 9.9–36.9]; $p = 0.0008$ [13, 14]. Imetelstat also demonstrated an acceptable tolerability profile with transient neutropenia and thrombocytopenia being the most frequent grade 3/4 treatment-emergent adverse events (TEAEs) with imetelstat treatment [13, 14]. Based on these results, imetelstat was recently approved by the United States Food and Drug Administration (FDA) and the European Commission for the treatment of certain adult patients with LR-MDS and RBC transfusion-dependent anemia who were ineligible for erythropoiesis-stimulating agents or had relapsed or refractory/unsatisfactory response to erythropoiesis-stimulating agents [15, 16]. In addition, the randomized, phase III IMpactMF study (NCT04576156) is ongoing to assess the benefit/risk of imetelstat in patients with intermediate-2 or high-risk myelofibrosis who are relapsed/refractory to Janus kinase-inhibitor treatment.

Since synthetic oligonucleotide therapies are an emergent treatment modality, further investigation of their immunogenic potential to elicit anti-drug antibodies (ADAs) is crucial to inform their optimal clinical use [17]. Indeed, recent FDA guidance recommends that clinical and non-clinical immunogenicity assessment for an oligonucleotide therapeutic should be considered based on a product-specific immunogenicity risk assessment [18]. This analysis evaluated the immunogenicity of imetelstat in the combined phase II and phase III portions of the pivotal IMerge study [13, 14], and the association of ADAs with clinical pharmacokinetics (PK), efficacy, and safety.

2 | Methods

2.1 | Clinical Studies

Imetelstat immunogenicity was evaluated using plasma samples from patients with LR-MDS in the combined phase II/phase III IMerge study [13, 14], in which patients had a median treatment duration of 35.1 weeks (primary analysis data cutoff of October 13, 2022) [14]. The starting dosage of imetelstat was 7.1 mg/kg via 2-h intravenous infusion every 4 weeks; dose escalations to 8.9 mg/kg every 4 weeks were allowed in phase II, and dose reductions to 5.6 mg/kg every 4 weeks or 4.4 mg/kg every 4 weeks were employed in both phases to manage adverse events [13, 14]. Samples for evaluation of imetelstat immunogenicity were collected at predose at baseline (cycle 1 day 1), at predose at cycle 4 day 1, then every three cycles until the end of treatment, at the time of dose escalation, at the end of treatment, if an infusion-related reaction (IRR) was observed, and at the first post-treatment follow-up. The study design was reported previously [14], and the study was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Protocols were approved by institutional ethics committees or independent review boards, and all patients provided written informed consent.

2.2 | Immunogenicity Samples and Bioanalysis

Patient plasma samples were assessed for the presence of imetelstat ADAs using a validated electrochemiluminescence immunoassay on the Meso Scale Discovery platform (Meso Scale

Diagnostics; Rockville, MD). The three-tiered bioanalytical approach included a screening assay, which detected anti-imetelstat antibodies, a confirmatory competition assay to assess the specificity of initial positive screening results, and a titration assay for confirmed positive results to obtain semi-quantitative results for titers of detected ADAs. Assays were validated according to regulatory guidelines [19].

Briefly, plasma samples were diluted and incubated with a streptavidin plate coated with biotin-imetelstat. If present, ADAs bound to the immobilized antigen and were detected with a cocktail of SULFO-TAG secondary antibodies (mouse anti-human immunoglobulin G and immunoglobulin M antibodies, and goat anti-rabbit IgG antibody), resulting in an electrochemiluminescence signal proportional to the quantity of ADAs present in the sample. The minimum required dilution (MRD) of the human plasma for this assay was 1/10. The screening and titration cut points were determined in normal and disease-state plasma. A custom affinity-purified rabbit polyclonal anti-imetelstat antibody (designated PANK1, developed by Cambridge Research Biochemicals, lot #6139) was used as the positive control to assess assay sensitivity and performance. This antibody was generated by immunizing rabbits with imetelstat, and immunoglobulin G was purified from the resulting anti-sera. The reported titers are inclusive of the 10-fold MRD.

No acid dissociation or immune complex dissociation step was included in this assay because drug-immune complexes were not expected to interfere with ADA detection. This is supported by the fact that all ADA samples were collected at predose time points when imetelstat concentrations were below the limit of quantification in plasma (0.490 μg/mL or 0.571 μg/mL, depending on the range of the calibration curve and accessory standards used in each validation study) and are therefore considered negligible for complex formation. During the assay validation, imetelstat concentrations < 10.24 μg/mL were established to have no interference on ADA detection; thus, interference was not of concern given immunogenicity samples were collected before dosing. The imetelstat ADA assay had a relative sensitivity of 19.53 ng/mL in the original validated method and 26 ng/mL after a partial re-validation to assess a new plate reader and washer. This change was deemed acceptable, as the relative sensitivity remained within one 2-fold dilution of the original value.

2.3 | PK Samples and Bioanalysis

Patient samples were collected for quantification of imetelstat plasma concentrations at the end of infusion (EOI) and at limited post-dose time points on cycle 1 day 1, and at EOI on day 1 of subsequent cycles. Blood specimens were obtained via lavender-top (K2 EDTA) vacutainers to separate plasma. Total imetelstat in plasma was assessed using a validated hybridization technique performed under regulations for Good Laboratory Practice. This method involved competition of imetelstat with a 3′-labeled digoxigenin analog for binding to a complementary oligonucleotide sequence that features biotin at the 3′ end. Detection was carried out through an enzyme-linked immunoassay, with the formed complex captured on a neutravidin-coated microtiter plate. The digoxigenin-labeled probe was subsequently detected after reacting with an antidigoxigenin antibody conjugated to alkaline phosphatase, which catalyzed the fluorescent substrate system AttoPhos (Promega, Madison, WI). Fluorescence was quantified using a fluorescence plate reader. Since the assay operates on a competitive principle, the signal obtained is inversely related to the amount of imetelstat in the calibration standard, quality control samples, and experimental specimens. To assess potential antibody interference in the validated PK assay for imetelstat, a custom affinity-purified rabbit polyclonal anti-imetelstat antibody (designated PANK1, developed by Cambridge Research Biochemicals, lot #6140) was used as a surrogate ADA reagent. This antibody was produced using the same immunization and purification methods as the reagent used in the ADA method but was generated from a different rabbit and is therefore a different lot. The antibody was spiked into matrix at concentrations up to 1.0 μg/mL and tested for potential impact on imetelstat recovery. No interference was observed across the assay range (0.490 μg/mL–1.96 μg/mL after 100-fold pre-assay dilution). High-concentration samples may be further diluted with blank matrix (up to 500-fold, equivalent to a 50,000-fold when including the MRD) to bring results within the range of the standard curve. Concentrations were reported in terms of imetelstat sodium (molecular weight of 4896 g/mol). The lower limits of quantification of imetelstat in human plasma were 0.490 μg/mL or 0.571 μg/mL, depending on the range of calibration curve and accessory standards used in each validation study.

2.4 | ADAs Assessment

Study patients treated with imetelstat were considered imetelstat ADA evaluable if they had ≥ 1 immunogenicity sample obtained after administration of ≥ 1 dose of imetelstat. ADA-evaluable patients were categorized as ADA positive if they had ≥ 1 positive ADA result at any time after the first dose of imetelstat, as baseline ADA positive if they had a positive ADA result at baseline (cycle 1 day 1), as treatment-induced ADA positive if they had a negative ADA result at baseline and ≥ 1 ADA-positive result any time after the first dose of imetelstat, or as ADA negative if they had no positive ADA results. The rates of ADA incidence and category were summarized overall and by modified dose level throughout the study period.

2.5 | ADA Association With Imetelstat PK, Efficacy, and Safety

The association of ADAs with imetelstat PK was assessed graphically with observed EOI concentrations as well as analyzed in a population PK model considering both time-invariant (patients classified as ADA positive or ADA negative, patient-level) and time-variant (individual records classified as ADA positive or ADA negative, sample-level) ADA status as covariates.

Binary efficacy endpoints analyzed by ADA status included the primary endpoint, proportion of patients who had ≥ 8-week RBC-TI, and key secondary endpoints, rate of ≥ 24-week RBC-TI and rate of hematologic improvement-erythroid (HI-E) per International Working Group 2018 or 2006 criteria. Rates were summarized with counts and percentages, and 95% confidence intervals (CI) were estimated with the Clopper-Pearson

exact method. Duration of RBC-TI was analyzed using the Kaplan–Meier method, with 95% CIs calculated using log–log transformation, and results were stratified by ADA-positive and ADA-negative subgroups. Potential loss of TI response was evaluated graphically by comparing the temporal relationship between RBC-TI with ADA-positive samples. The potential association of imetelstat immunogenicity with safety outcomes was evaluated by comparing the incidence of selected TEAEs between ADA-positive and ADA-negative patients. TEAEs were coded using the Medical Dictionary for Regulatory Activities and graded per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, in ADA-positive patients with those in ADA-negative patients. Exploratory subgroup analyses were conducted by ADA maximum titer category, with patients grouped as ADA negative, ADA positive with maximum titer<median (30), or ADA positive with maximum titer>median (30).

3 | Results

3.1 | Incidence of Imetelstat ADAs

Of the 175 patients treated with imetelstat in the phase II or phase III portions of IMerge, 166 (94.9%) were evaluable for immunogenicity and included in the ADA analysis. A total of 28 patients were ADA positive (16.9%), and no patients had pre-existing immunogenicity before treatment (Table 1). The incidence of ADAs did not appear to differ between patients maintained at the starting dose of 7.1 mg/kg every 4 weeks and those with dose escalations or reductions. The median (range) onset of ADAs was approximately 38 weeks (12–109) (Table 1), or after a median (range) of 8 treatment cycles (3–22). The peak titer of ADAs was low, with a median (range) of 30 (10–160) (Table 1). The time to onset and peak titer did not meaningfully differ between patients maintained on the starting dose and those with dose modifications. The patient demographics and baseline disease characteristics were relatively balanced in the ADA-negative and ADA-positive groups (Table S1).

3.2 | Association of Immunogenicity With Imetelstat PK

Across all ADAs and PK-evaluable patients, graphical evaluation demonstrated similar imetelstat EOI concentrations in ADA-positive and ADA-negative samples at both the starting dose and reduced dose levels (Figure 1A, Figure S1). Within the ADA-positive patients, there was no indication of changes in EOI concentrations after ADA seroconversion (Figure 1B). Formal covariate analysis using a population PK model did not identify a significant covariate effect for either time-invariant or time-variant ADA status on imetelstat clearance [20], and there was no apparent difference in post hoc estimates of individual baseline clearance between ADA-positive and ADA-negative patients (Figure 1C). Model diagnostic plots confirmed no evidence of bias in the overall data when stratified by time-variant ADA status, confirming the results of the covariate analysis (Figures S2 and S3). Among ADA-positive patients, ADA titer did not appear to impact imetelstat concentrations, as EOI concentrations were similar across the range of observed titers (Figure S4).

3.3 | Association of Immunogenicity With Imetelstat Efficacy

The potential association of ADAs with imetelstat efficacy was evaluated by comparing the efficacy response rates, duration of response, and temporal relationship between response and ADA onset in ADA-positive and ADA-negative subgroups. Numerically higher response rates were observed in ADA-positive patients compared with ADA-negative patients for the primary endpoint ≥ 8-week RBC-TI and key secondary endpoints of ≥ 24-week RBC-TI and HI-E per International Working Group 2018 and 2006 criteria (Table 2). Notably, 17 of the 18 ADA-positive patients who achieved ≥ 8-week RBC-TI did so before their first positive ADA sample (Figure 2). The temporal relationship suggests potential for reverse causality—patients deriving clinical benefit are more likely to remain on treatment longer (median [range] treatment duration of 78.6 weeks [13.1–260] for

TABLE 1 | Incidence of imetelstat ADAs, maximum titer, and time to onset of ADAs in patients with LR-MDS.

ADA status, *n* (%)	Escalated to 8.9 mg/kg (*N* = 6)	Maintained at 7.1 mg/kg (*N* = 72)	Reduced to 5.6 mg/kg (*N* = 37)	Reduced to 4.4 mg/kg (*N* = 51)	All evaluable patients (*N* = 166)
Negative	4 (66.7)	61 (84.7)	31 (83.8)	42 (82.3)	138 (83.1)
Positive	2 (33.3)	11 (15.3)	6 (16.2)	9 (17.6)	28 (16.9)
Baseline positive	0	0	0	0	0
Treatment-induced positive	2 (33.3)	11 (15.3)	6 (16.2)	9 (17.6)	28 (16.9)
Maximum titer, median (range)	10 (10–10)	40 (10–160)	20 (10–40)	40 (10–80)	30 (10–160)
Time to onset (weeks), median (range)	38.1 (32.0–44.3)	26.1 (15.1–84.6)	41.9 (12.1–64.1)	46.1 (25.4–109)	38.4 (12.1–109)

Note: Maximum titer and time to onset of ADA are presented for ADA-positive patients only.
Abbreviations: ADA, anti-drug antibody; LR-MDS, lower-risk myelodysplastic syndromes.

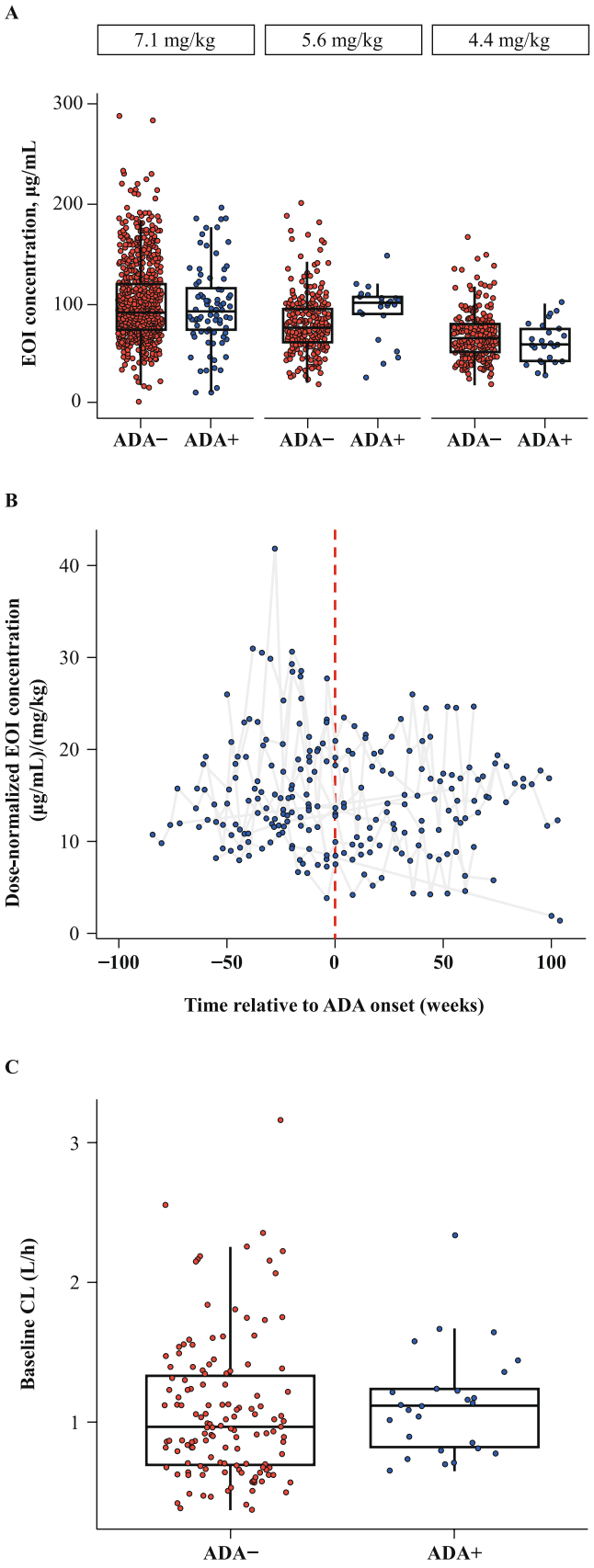

FIGURE 1 | Effect of immunogenicity on imetelstat pharmacokinetics in patients with LR-MDS. (a) Observed EOI PK concentrations were grouped by time-variant ADA (sample-level) status and nominal dose level for patients with available data ($N=161$ patients, $n=1377$ samples). (b) Dose-normalized EOI PK concentrations were plotted for ADA-positive patients over time relative to the onset of ADA ($N=18$ ADA-positive patients with PK data available after seroconversion, $n=261$ samples). Time of 0 corresponds to the time of seroconversion. All nominal dose levels were pooled after dose normalization, and lines represent individual patient profiles. The X-axis was truncated at 105 weeks due to limited data ($N=1$ patient) at late time points. Due to more frequent collection of PK samples than ADA samples, PK samples that lacked an experimentally determined ADA status were imputed to the last available ADA status. The 8.9-mg/kg dose level was excluded in panels A and B due to limited PK samples ($n=4$ samples). (c) Individual post hoc estimates of baseline CL from popPK model [20] by time-invariant ADA (patient-level) status. ADA, anti-drug antibody; CL, clearance; EOI, end of infusion; LR-MDS; lower-risk myelodysplastic syndromes; PK, pharmacokinetics.

TABLE 2 | Summary of efficacy outcomes and duration of response by ADA status in patients with LR-MDS.

Endpoint, *n* (%) [95% CI]	ADA negative ($N=138$)	ADA positive ($N=28$)
≥8-week RBC-TI	48 (34.8) [26.9–43.4]	18 (64.3) [44.1–81.4]
≥24-week RBC-TI	34 (24.6) [17.7–32.7]	13 (46.4) [27.5–66.1]
HI-E per IWG 2018	57 (41.3) [33.0–41.3]	19 (67.9) [47.6–84.1]
HI-E per IWG 2006	84 (60.9) [52.2–69.1]	23 (82.1) [63.1–93.9]
Duration of longest RBC-TI in ≥8-week RBC-TI responders, median (95% CI), weeks	51.9 (26.9–76.3)	68.4 (20.6–136.9)

Abbreviations: ADA, anti-drug antibody; CI, confidence interval; HI-E, hematologic improvement–erythroid; IWG, International Working Group; LR-MDS, lower-risk myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.

≥8-week RBC-TI responders vs. 24.1 weeks [0.14–180] for non-responders), and thus have more opportunity to develop ADAs over time.

To assess whether the onset of ADAs was associated with loss of efficacy, the duration of the longest RBC-TI interval was evaluated. Among ≥8-week RBC-TI responders, the median duration was 68.4 weeks (95% CI 20.6–136.9) in ADA-positive patients and 51.9 weeks (95% CI 26.9–76.3) in ADA-negative patients (Table 2), indicating that ADA positivity was not associated with shortened response. Temporal analysis further supports this conclusion. Among the 18 ADA-positive responders, 10 experienced onset of ADAs during their longest TI interval (Figure 2), yet no consistent pattern of early loss of benefit after detection of ADAs was observed. Efficacy response rates and duration of response were consistent across the range of ADA titers observed in the ADA-positive group, suggesting that titer magnitude did not impact treatment response (Table S2).

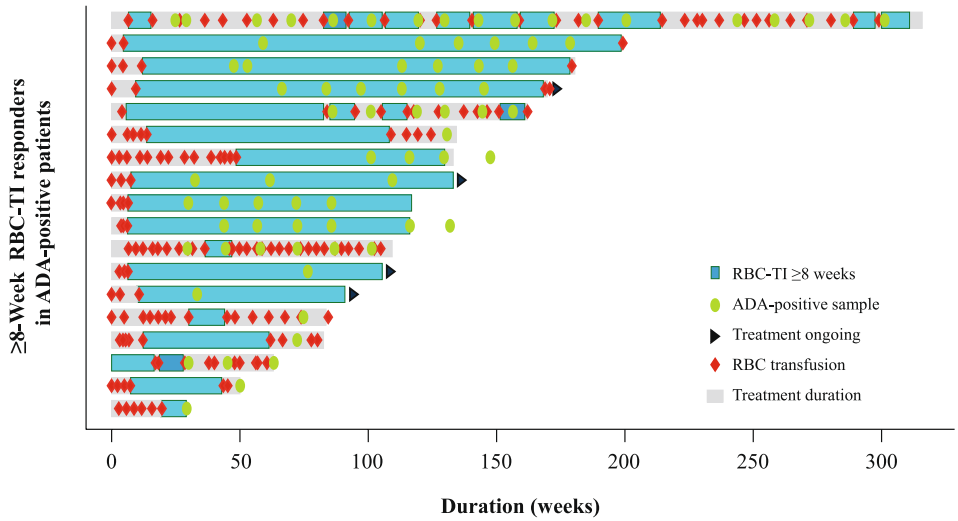

FIGURE 2 | Effect of immunogenicity on imetelstat efficacy in patients with LR-MDS. Swimmer plot of RBC-TI intervals overlaid with positive ADA samples in ≥8-week RBC-TI responders who were ADA positive. Each row indicates a different patient. Gray shading indicates treatment duration, black arrow indicates treatment ongoing at the last assessment as of the primary analysis cutoff (October 13, 2022), blue shading indicates TI intervals, light green dots indicate time points at which ADAs were detected in blood samples, and red diamonds indicate times of RBC transfusions. ADA, anti-drug antibody; LR-MDS; lower-risk myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.

3.4 | Association of Immunogenicity With Imetelstat Safety

The clinical relevance of imetelstat ADAs on safety was evaluated by comparing the incidence of selected TEAEs between ADA-negative and ADA-positive patients with LR-MDS. The incidence of any-grade or grade ≥3 drug-related TEAEs was comparable between the two groups (Table 3). The rate of drug-related serious TEAEs was slightly lower in the ADA-positive group, while there were no drug-related TEAEs of fatal outcomes in either group.

TEAEs considered by the investigator to be an IRR were observed at a higher frequency in ADA-positive patients than in ADA-negative patients (Table 3). None of the infusion-related TEAEs were serious in ADA-positive patients, and few (<10%) were grade ≥3. The time to the first IRR overlapped between the ADA subgroups; median time to the first IRR was 12.7 weeks (range, 0.1–171) in the ADA-negative group and 37.4 weeks (range, 11.1–76.6) in the ADA-positive group. Among the 5 ADA-positive patients with IRRs, ADA onset preceded the first IRR in 1 patient (by 20 weeks), while in the remaining 4 patients, ADAs were first detected 4.0–8.9 weeks after the first IRR event. These findings indicate no clear temporal relationship between IRRs and ADA formation, although interpretation is limited by the every-3-cycle immunogenicity sampling schedule and small sample size. No meaningful differences in the overall incidence of TEAEs were observed between ADA-positive patients with low or high titers (Table S3), although there was a trend for more grade ≥3 IRRs in the high-titer group.

TABLE 3 | Summary of TEAEs by ADA status in patients with LR-MDS.

TEAE category, *n* (%)	ADA negative (*N* = 138)	ADA positive (*N* = 28)
Any TEAE	136 (98.6)	28 (100.0)
Any drug-related TEAE	116 (84.1)	26 (92.9)
Grade ≥3 TEAE	123 (89.1)	26 (92.9)
Drug-related grade ≥3 TEAE	103 (74.6)	21 (75.0)
Serious TEAE	47 (34.1)	13 (46.4)
Drug-related serious TEAE	14 (10.1)	0
TEAE leading to death	4 (2.9)	2 (7.1)
Drug-related TEAE leading to death	0	0
Infusion-related reaction[a]		
Any infusion-related TEAE	10 (7.2)	5 (17.9)
Drug-related infusion-related TEAE	10 (7.2)	5 (17.9)
Infusion-related serious TEAE	1 (0.7)	0
Infusion-related grade ≥3 TEAE	4 (2.9)	2 (7.1)

Abbreviations: ADA, anti-drug antibody; LR-MDS, lower-risk myelodysplastic syndromes; TEAE, treatment-emergent adverse event.
[a]Infusion-related reactions were adverse events considered by the investigator to be infusion-related events and the most common included headache and pain (back, bone, chest, and abdominal).

4 | Discussion

Oligonucleotide therapeutics, though chemically synthesized like small molecules, have a relatively large molecular weight

(approximately 5 kDa) and immunogenic potential more akin to biologics. This includes the potential to induce the formation of ADAs, which may in turn affect PK, pharmacodynamics, efficacy, and safety. Thus, a risk-based immunogenic assessment is recommended for oligonucleotide therapeutics in line with FDA guidance [18, 21, 22]. With the rapidly evolving landscape of novel modalities—including diverse backbone modifications, chemical conjugates, and novel mechanisms of action for oligonucleotide therapeutics—robust immunogenicity testing is becoming increasingly critical to ensure the comprehensive evaluation of safety and therapeutic performance.

This post hoc analysis evaluates the immunogenic potential of the oligonucleotide therapeutic imetelstat by assessing ADAs and their association with imetelstat PK, efficacy, and safety in patients with LR-MDS from the pivotal phase II/phase III IMerge study [13, 14]. Overall, 16.9% of patients with LR-MDS developed imetelstat ADAs, which were characterized by a delayed onset (after prolonged exposure, median of 8 treatment cycles) and low titers. While the incidence of ADAs was limited, no clinically meaningful association was observed between ADA status and imetelstat PK, efficacy, or safety. Both graphical and model-based analyses demonstrated that imetelstat immunogenicity was not meaningfully associated with imetelstat PK.

With respect to imetelstat efficacy, ADA-positive patients achieved comparable or even numerically higher response rates across key endpoints, including ≥ 8-week and ≥ 24-week RBC-TI and HI-E per International Working Group 2018 and 2006 criteria. However, these findings should be interpreted with caution. The apparent differences likely reflect reverse causality, as patients who respond and remain on treatment longer are more likely to develop ADAs due to greater cumulative exposure. Indeed, the temporal analysis demonstrated that ADA onset followed, rather than preceded, clinical benefit. Importantly, there was no evidence of loss of efficacy in terms of shortened RBC-TI intervals in ADA-positive patients and no apparent relationship between the onset of ADAs and loss of TI response. These observations support the conclusion that imetelstat immunogenicity is not detrimental to efficacy.

Consistent with efficacy findings, ADAs did not negatively affect the safety profile of imetelstat. The rates of drug-related grade ≥ 3, serious, or fatal TEAEs were similar or lower in ADA-positive versus ADA-negative patients. While infusion-related TEAEs were more common in ADA-positive patients, these events were generally low grade, not serious, and manageable. Notably, hypersensitivity and IRRs are known adverse effects of several approved oligonucleotide therapeutics [23], although current evidence does not conclusively support a causal relationship between the formation of ADAs and IRRs [24]. For imetelstat, IRRs are mitigated with pre-infusion medications (antihistamines and corticosteroids) and managed through infusion rate adjustments or dose modifications, as outlined in the prescribing information [15, 16]. This approach has markedly reduced IRR incidence for imetelstat (data not shown). With standard premedication and routine infusion monitoring, IRRs remain infrequent and manageable.

Our analyses suggest that imetelstat has a benign immunogenicity profile in LR-MDS, with no evidence of a clinically meaningful association with PK, efficacy, or safety. However, several limitations should be considered. First, the incidence of imetelstat ADAs was low, resulting in a relatively small ADA-positive subgroup ($n = 28/166$), which limits the statistical power of analyses. Although an exploratory analysis stratified by ADA titer category did not identify notable differences in PK, efficacy, or safety across titer levels, the small sample size again limits the strength of interpretation. Second, since ADAs develop after treatment initiation, they cannot be used as a stratification factor, introducing the potential for imbalance in baseline disease characteristics. Although we did not adjust for baseline covariates in our analyses, key baseline disease characteristics and demographics were relatively balanced between ADA-negative and ADA-positive groups. Third, the timing of ADA onset relative to clinical response introduces potential for time-dependent bias, as patients who remain on treatment longer have greater opportunity to develop ADAs. A landmark analysis could help address this by evaluating clinical outcomes beyond a fixed time point; however, this approach was not feasible in our study, as nearly all ADA-positive responders had achieved their response before ADA detection, precluding a meaningful landmark comparison.

Collectively, the development of imetelstat ADAs in the LR-MDS population was characterized by low incidence, late response, low titers, and was not associated with clinical consequences. Therefore, imetelstat immunogenicity does not appear to impact the benefit/risk profile of imetelstat. These findings align with the broader understanding of the immunogenic potential of oligonucleotide therapeutics; while immunogenicity is a theoretical concern for oligonucleotide therapeutics due to their structural complexity and biologic-like properties, clinical experience to date shows that ADA incidence varies widely (4%–72%) across 12 FDA-approved oligonucleotide therapeutics, with no clinically meaningful impact on efficacy, safety, or PK [25]. Unlike therapeutic proteins, where ADA have been reported to alter drug disposition and reduce efficacy [26], no such effects have been reported for oligonucleotide therapeutics to date. These broader class profiles, together with the clinical immunogenicity assessment of imetelstat in LR-MDS, support its continued use without the need for routine immunogenicity-based monitoring. Nevertheless, ongoing ADA surveillance will continue in other patient populations for which imetelstat is being developed, including those with Janus kinase inhibitor relapsed or refractory myelofibrosis, and additional immunogenicity assessments may be conducted as needed in the context of changes to manufacturing or dosing regimens.

Author Contributions

A.L.L., F.H., Y.W., L.S., T.B., F.F., and P.N.M. designed and performed the research, analyzed the data and wrote the manuscript. M.G.-S. performed the research, analyzed the data, and wrote the manuscript.

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Conflicts of Interest

A.L.L., F.H., Y.W., L.S., T.B., and F.F. are employees of Geron Corporation, the sponsor of the work, and may hold stock or stock options. M.G.-S. and P.N.M. are independent consultants and have been paid for the strategic and technical input into the analysis. P.N.M. may hold past or current employment and/or stock options in other organizations.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Data S1:** cts70431-sup-0001-Supinfo.docx.