IMETELSTAT

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SPONSOR BRIEFING DOCUMENT

ONCOLOGIC DRUGS ADVISORY COMMITTEE

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List of Abbreviations and Terms

Abbreviation/Term	Definition/Explanation
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
AEI	adverse event of interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
CCO	clinical cutoff
CI	confidence interval
C_{max}	maximum observed plasma concentration
$C_{max,u}$	free/unbound maximum observed concentration in plasma
CMH	Cochran-Mantel-Haenszel
CR	complete remission
CTCAE	Common Terminology Criteria for Adverse Events
CV%	coefficient of variation
CYP	cytochrome P450
DDI	drug-drug interaction
DEC-C	decitabine and cedazuridine
DILI	drug-induced liver injury
ECOG	Eastern Cooperative Oncology Group
EPO	erythropoietin
E-R	exposure-response
ESA	erythropoietin stimulating agent
ET	essential thrombocythemia
EU	European Union
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy-Fatigue subscale
FACT-An	Functional Assessment of Cancer Therapy-Anemia Subscale
FDA	Food and Drug Administration
GI	GI
HEC	Hepatic Expert Committee
hERG	Human ether-à-go-go-related gene
Hgb	hemoglobin
HI	hematologic improvement
HI-E	hematologic improvement-erythroid
HMA	hypomethylating agent
HPC	hematopoietic progenitor cell
HR	hazard ratio
HSC	hematopoietic stem cell
HSCT	hematopoietic stem cell transplantation
hTR	human telomerase
hTERT	human telomerase reverse transcriptase
IND	Investigational New Drug
IPSS	International Prognostic Scoring System
IQR	interquartile Range
IRC	independent review committee
IRR	Infusion-related reactions
ITT	Intent-to-Treat
IV	intravenous(ly)

Abbreviation/Term	Definition/Explanation
IWG	International Working Group
LFT	liver function test
LR MDS	lower risk MDS
LS	least squares
LSC	leukemic stem cells
mCR	molecular complete remission
MDS	myelodysplastic syndromes
MF	myelofibrosis
MPN	myeloproliferative neoplasm
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDA	New Drug Application
NE	not estimable
OS	overall survival
PD	pharmacodynamics
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetic
popPK	population PK
PR	partial remission
PRO	patient reported outcome
PT	Preferred Term
q4w	every 4 weeks
QoL	quality of life
QUALMS	Quality of Life in Myelodysplasia Scale
RBC	red blood cell
R/R	relapsed/refractory
RS	ring sideroblasts
SAE	serious adverse event
SOC	system organ class
TD	transfusion-dependent
TI	transfusion independence
UGT1A1	UDP-glucuronosyltransferase 1A1
ULN	upper limit of normal
US	United States
USPI	US Prescribing Information
WHO	World Health Organization

1 EXECUTIVE SUMMARY

1.1 Introduction

Geron Corporation (Sponsor) seeks approval for a first-in-class telomerase inhibitor, imetelstat, for the treatment of transfusion-dependent (TD) anemia in adult patients with low-to-intermediate-1 risk myelodysplastic syndromes (MDS) who have either failed to respond or have lost response to, or are otherwise ineligible for, erythropoiesis-stimulating agents (ESAs). The Phase 3 Study MDS3001 (Section 6) demonstrated clinically meaningful and statistically significant evidence of efficacy, achieving both the primary (Section 7.2.1) and key secondary (Section 7.2.2) endpoints of ≥ 8-week and ≥ 24 -week red blood cell transfusion independence (RBC TI), with long and continuous periods of transfusion independence (TI) unavailable with currently approved treatments for this patient population. Furthermore, imetelstat's safety profile is well characterized and is primarily driven by the manageable risks of neutropenia and thrombocytopenia, the potential risks of which (severe bleeding and infection) are comparable to that seen in placebo treated patients.

The benefit-risk profile of imetelstat in the proposed patient population is favorable. The clinical studies demonstrated substantial evidence of effectiveness, and the safety profile is well characterized and manageable. There is an unmet need in this patient population, with limited approved therapies, restricted to particular subpopulations. For these reasons, and as further discussed below, the Sponsor believes that, if approved, imetelstat would offer a clinically meaningful treatment option for anemia in transfusion dependent low- to intermediate-1 risk MDS patients who have failed to respond, or have lost response to, or are ineligible for, ESAs.

1.2 Background and Unmet Need

Myelodysplastic syndromes are a heterogenous group of bone marrow disorders that are characterized by dysfunctional hematopoiesis resulting in the development of cytopenias and eventual bone marrow failure (Section 2.1.1). Lower risk MDS (LR MDS) is defined as low or intermediate 1 by International Prognostic Scoring System [IPSS] criteria (details on the IPSS criteria are provided in Appendix 11.1). Though the risk categorization is "lower," LR MDS remains a serious, progressive, and life-threatening malignancy.

Approximately 80%-85% of patients with LR MDS have anemia at diagnosis, and most are highly symptomatic (Foran, 2012). In approximately 40% of patients with LR MDS, the anemia has progressed to the point of dependence on red blood cell (RBC) transfusions (RBC TD) (Zeidan, 2013; Ades, 2014). However, over time chronic RBC transfusions significantly correlate with increased risk of clinical complications, including end-organ damage extending to the cardiovascular and hepatic systems (de Swart, 2020; Castelli, 2018; Platzbecker, 2021; Singhal, 2017; Germing, 2019), leading to an overall impairment in quality of life (Platzbecker, 2021). Additionally, many patients with LR MDS who are RBC TD will eventually fail or discontinue ESA therapy, after which time patients

have a life expectancy as estimated by median overall survival (OS) of only 3 years (Consagra, 2023; Kelaidi, 2013; Komrokji, 2023; Park, 2017). Therefore, achieving RBC TI represents an important clinical goal and has been accepted as the primary endpoint for the approval of the few treatments currently approved for TD anemia in LR MDS.

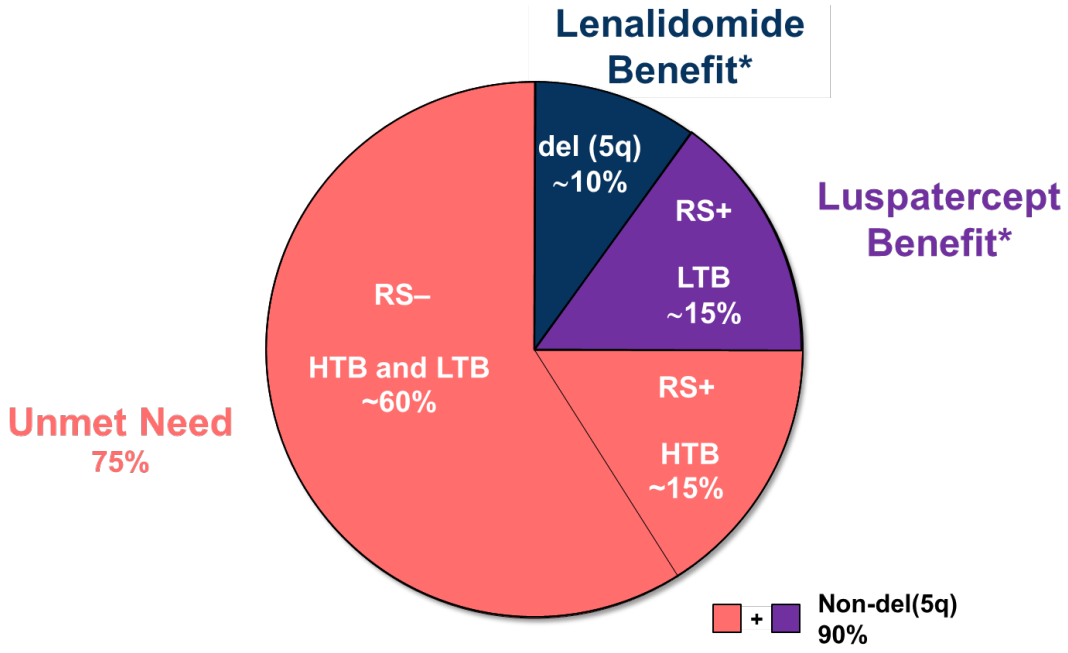
As noted by a recent publication co-authored by the Food and Drug Administration (FDA), there has been a 14-year drought of approvals for MDS treatments between 2006 and 2020, highlighting the need for new treatments (Sekeres, 2023). ESAs and luspatercept (recently approved) represent the two FDA-approved -first line treatments for TD anemia. However, once patients become relapsed/refractory (R/R) to ESA treatment, only two FDA-approved therapies remain for TD anemia: luspatercept and lenalidomide, and both treatments are restricted for use in specific subgroups of patients (Figure 1-1). Lenalidomide approval is restricted to patients with a deletion (5q) abnormality (~10% of the MDS population), and luspatercept is limited to those with ring sideroblast (RS+) dysplastic abnormalities on bone marrow examination (~35% of the MDS population). Furthermore, luspatercept offers less benefit in patients who require ≥ 6 units RBC every 8 weeks, which further increases the unmet need in these heavily transfused RS+ patients.

Lastly, hypomethylating agents (HMAs) are approved for treatment in MDS but are not specifically indicated for TD anemia and generally not recommended as standard of care for LR MDS except in cases with clinically relevant thrombocytopenia or neutropenia (NCCN, 2023).

Altogether, approximately 75% of patients have an unmet need once they become ESA relapsed/ refractory (R/R) (Figure 1-1). Additionally, ~10% of patients with LR MDS have a low likelihood of response to first line ESA therapy due to high serum erythropoietin levels (> 500 mU/mL) and have very limited treatment options at this time.

Thus, there remains a high unmet need in ESA R/R LR MDS patients with currently approved products unable to provide the continuous, durable TI and additional benefits seen with imetelstat in the broader proposed patient population.

Figure 1-1: Unmet Need in Treatment of Anemia in LR MDS after ESA Treatment Failure



Sources: (List, 2018; Patel, 2021)
* Based on Phase 3 studies.
ESA = erythropoiesis-stimulating agents; HTB = high transfusion burden, requiring ≥ 6 RBC units/8 weeks; LTB = low transfusion burden, requiring < 6 RBC units/ 8 weeks; RBC = red blood cell; RS = ring sideroblasts.

1.3 Product Description

Telomeres are repetitive DNA sequences located at the end of chromosomes that are reduced during cell division in somatic cells. After a set number of divisions, telomere length is shortened to a critical length, and further cell division is prevented, leading to cell senescence, or apoptosis (Levy, 1992).

Telomerase is an enzyme that maintains telomere length by the addition of nucleotides to the end of telomeres, preventing telomere shortening during cell division (Dahse, 1997).

Upregulation of telomerase has been demonstrated in > 90% of human cancers (Cong, 2002), enabling the continued and uncontrolled proliferation of malignant cells, driving tumor growth and disease progression. Telomerase is highly expressed in malignant bone marrow cells of patients with MDS while, in contrast, it is generally undetectable in normal somatic cells, making telomerase a relevant and key therapeutic target for LR MDS.

Imetelstat, a 13-nucleotide (13-mer) oligonucleotide with a covalently attached lipid tail, is a first in class telomerase inhibitor with preferential activity in malignant cells that are characterized by the abnormal elevation of telomerase activity compared to normal cells. Imetelstat has a nucleotide sequence that is complementary, and specifically binds with high affinity, to the template region of the RNA component of human telomerase (hTR),

resulting in competitive inhibition of human telomerase reverse transcriptase (hTERT) enzymatic activity, which prevents telomere binding (Asai, 2003; Herbert, 2005).

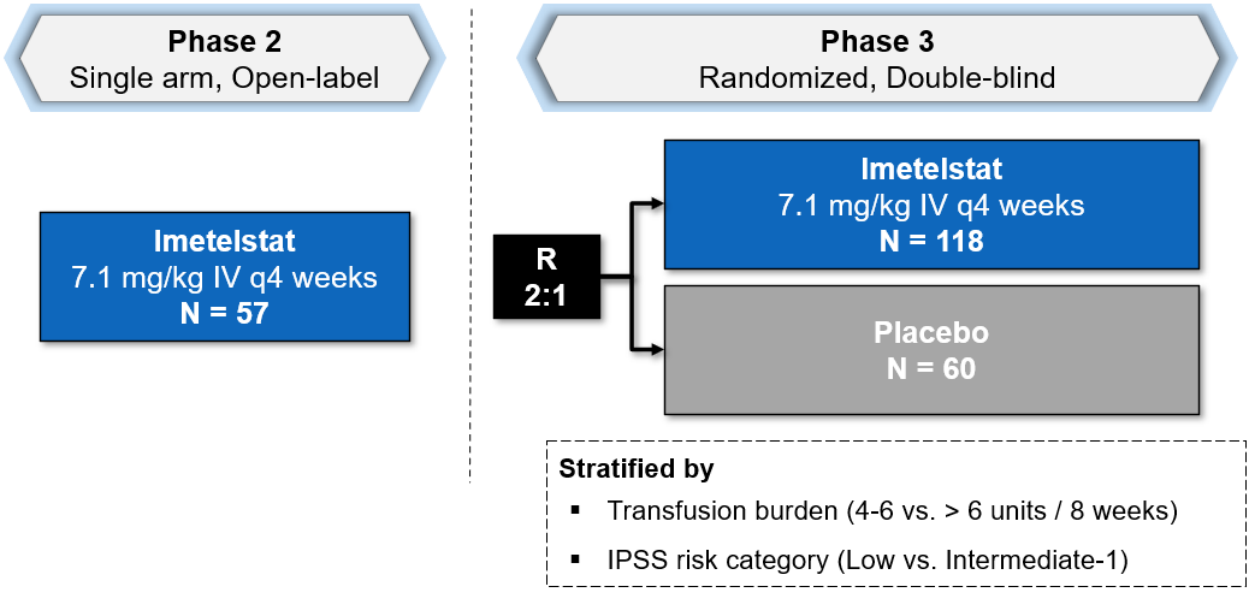
Studies of imetelstat in various cancer cell lines in vitro — and in malignant hematopoietic stem/progenitor cells (HSCs/HPCs) and leukemia stem cells (LSCs) from primary patient samples ex vivo — demonstrate that imetelstat inhibits telomerase activity in a dose-dependent manner, leading to loss of a malignant cell's ability to maintain telomere length. Reduction of telomerase activity results in inhibition of cell proliferation, and induction of apoptosis (or cell death) of malignant cells (Herbert, 2005; Brennan, 2010; Shammas, 2008; Mosoyan, 2017; Baerlocher, 2019; Wang, 2018).

1.4 Development Program

The efficacy and safety of imetelstat have been studied in 15 Sponsor-led Phase 1-3 studies, across various solid tumor and hematologic malignancies, as monotherapy and in combination with other anti-cancer therapy. The efficacy and safety of imetelstat are demonstrated for the treatment for anemia in TD LR MDS patients who are R/R to ESA, by the Phase 2/3 Study MDS3001. MDS3001 was a randomized, controlled, global study conducted at 77 study sites in 17 countries, including the United States (US). The Phase 3 part of Study MDS3001 was the pivotal study in support of registration, with a primary endpoint of ≥ 8 -week RBC TI rate.

Study MDS3001 was a global, 2-part, multicenter, Phase 2/3 study in patients who had TD anemia with IPSS-defined low, or intermediate-1 risk MDS, and who were ineligible for or were relapsed/refractory (R/R) after ESA treatment (Figure 1-2). Treatment was continuous until a patient experienced disease progression, or unacceptable toxicity or withdrew consent, per protocol. The Sponsor and FDA agreed on all aspects of the Phase 3 study design during Type-C interactions prior to the initiation of the study.

Figure 1-2: MDS3001 – Phase 2/3 Study Design



Treatment was continuous until a patient experienced disease progression, or unacceptable toxicity or withdrawal of consent, per protocol.

IPSS = International Prognostic Scoring System; IV = intravenous

Phase 2 was a single arm open label study and Phase 3 was a double blind, randomized and placebo-controlled study. Patients were randomized 2:1 to receive imetelstat or placebo and stratified by transfusion burden and IPSS risk category (Greenberg, 1997); details about the IPSS criteria are provided in Appendix 11.1.

All patients in study MDS3001 received imetelstat 7.1 mg/kg or matched placebo administered intravenously every 4 weeks (q4w) as a 2-hour infusion. The protocol specified dose delays, dose reductions and treatment discontinuation in response to Grade ≥ 3 adverse events (AEs) present at the planned start of a dosing cycle.

Patients in both phases of the study were required to be R/R after at least 8 weeks of ESA treatment or ineligible for ESA treatment due to serum erythropoietin (EPO) level > 500 mU/mL. Patients were TD, defined as requiring at least 4 RBC units transfused over an 8-week period per International Working Group (IWG) 2006 criteria (Cheson, 2006); details about the IWG 2006 criteria are provided in Appendix 11.2. Pre-transfusion hemoglobin (Hgb) should have been ≤ 9.0 g/dL to count towards the 4 units. Additionally, patients had to be non-deletion (5q) and were not previously treated with lenalidomide or HMAs to be enrolled in the randomized Phase 3 part of the study.

Endpoints in the Phase 3 study are listed below. Both the Phase 2 and Phase 3 studies shared the same primary and key secondary endpoints of RBC TI ≥ 8 weeks and RBC TI ≥ 24 weeks, respectively. For the Phase 3 study, in the analyses of the non-key secondary and exploratory endpoints, all p-values are nominal, without multiplicity adjustment.

- **Primary endpoint**: RBC TI ≥ 8 weeks during any consecutive 8 weeks
    - Defined as the proportion of patients without any RBC transfusions during any consecutive 8 weeks (56 days) starting from Study Day 1 until subsequent anti-cancer therapy, if any.
        - The ≥ 8-week RBC TI endpoint has been used as the basis of other drug approvals for the treatment of anemia in LR MDS and was agreed upon with FDA prior to the Phase 3 study; see Section 6.1.3 for additional details.
- **Key Secondary Endpoint**: RBC TI ≥ 24 weeks during any consecutive 24 weeks
    - Defined as the proportion of patients without any RBC transfusion during any consecutive 24 weeks (168 days) starting from Study Day 1 until subsequent anti-cancer therapy if any.
- **Additional Secondary Endpoints**
    - Rate of hematologic improvement-erythroid (HI-E) per IWG 2018 (Platzbecker, 2019).
        - Defined as the proportion of patients who achieved a 50% reduction in transfusion burden over 16 weeks or achieving TI ≥ 16 weeks.
    - Duration of RBC TI.
    - Relative change in RBC transfusion burden.
    - Overall survival (OS); note that OS data is immature and is therefore discussed within the context of safety in Section 8.3.2.8.
    - Rate of progression-free survival (PFS), and time to progression to acute myeloid leukemia (AML).
- Exploratory Endpoints
        - Cytogenetic response.
        - Patient reported outcomes (PROs).
- Ad-Hoc Analysis: Proportion of patients who achieved RBC TI ≥ 1 year.

(Note that, in this document, discussion of the results for the endpoints may be presented in a different order from the list above, based on the relevance to particular topics.)

1.5 Summary of Phase 2 Efficacy and Safety Results

Patients in the Phase 2 study had a baseline transfusion burden of median 8 RBC units per 8 weeks and up to 14 units per 8 weeks.

Key efficacy results for the Phase 2 part of the study included:

- ≥ 8-week RBC TI rate in the target population: 42.1% (95% confidence interval [CI]: 26.3%, 59.2%).
- ≥ 24-week RBC TI rate in the target population: 31.6% (95% CI: 17.5%, 48.7%).

Imetelstat demonstrated similar benefit across key subgroups in the target population, including RS+/RS- status, baseline transfusion burden, and baseline serum EPO levels.

In the open label Phase 2 part of study MDS3001, imetelstat demonstrated an acceptable and manageable safety profile, with no new safety signals or evidence of cumulative toxicity identified. Safety results were generally similar to those in the Phase 3 part of the study; additional details are provided in Section 8.2.

1.6 Summary of Phase 3 Efficacy Results

A total of 178 patients were randomized 2:1 to either imetelstat (118 patients) or placebo (60 patients) treatment respectively (Figure 6-1; Section 6.2.2.1). Randomization was stratified by prior RBC transfusion burden (4–6 units/8 weeks or > 6 units/ 8 weeks and IPSS risk category (low vs intermediate-1). At the time of the clinical data cutoff and primary analysis (13 October 2022) for the Phase 3 study with a median follow up of 18 months, treatment was ongoing in 22.9% of patients in the imetelstat group and 23.7% of patients in the placebo group.

Demographics of patients in MDS3001 were generally representative of the known epidemiology of LR MDS (Table 6-1; Section 6.2.2.2). The median ages were 72 vs 73 years for imetelstat vs placebo, respectively. Both treatment groups had a larger proportion of males (> 60%), and approximately 80% of patients were white, which is representative of LR MDS patient population. The majority of patients were from the European Union, where the epidemiology of MDS, clinical practice, and methods of treatment of anemia are similar to the US and other regions that participated in the study.

Disease characteristics were balanced between the treatment groups and representative of LR MDS patients with anemia (Table 6-2; Section 6.2.2.2). Nearly 50% of patients had a prior RBC transfusion burden of > 6 units/ 8 weeks; 62% of patients in both treatment groups were RS+, and the majority of patients in both groups were categorized as low risk, per IPSS. Ninety percent of patients had received prior ESA treatment and 69% of patients had serum EPO levels of ≤ 500 mU/mL at the time of study entry.

The Phase 3 study met its primary endpoint, with a highly statistically significant and clinically meaningful improvement in ≥ 8-week RBC TI rate in the imetelstat group (39.8% [47/118]) compared to the placebo group (15.0% [9/60]; $p < 0.001$) with a median TI duration of 51.6 weeks in responders (vs 13.3 weeks in placebo responders).

Imetelstat also demonstrated a statistically significant improvement in ≥ 24-week RBC TI rate, meeting the key secondary endpoint. The ≥ 24-week RBC TI rate was 28.0% (33/118) in the imetelstat group versus 3.3% (2/60) in the placebo group ($p < 0.001$), with a median TI duration in these patients of 80 weeks (95% CI: 51.57, not estimable [NE])

with imetelstat treatment. Duration of TI for the 2 patients in the placebo group had not been reached (95% CI: 24.86, NE).

Statistical analyses of the primary and key secondary endpoints passed statistical hierarchical testing. Therefore, all p-values for other secondary and exploratory endpoints are considered nominal.

Subgroup analyses of ≥ 8-week and ≥ 24-week TI responders demonstrated clinical benefit with imetelstat regardless of RS+ or RS- status, prior RBC transfusion burden, or IPSS risk category.

The ≥ 1-year RBC TI rate was 18% (21/118) for patients in the imetelstat group versus 2% (1/60) for patients in the placebo group (p=0.002) and a median TI duration in these patients of over 2.5 years (132 vs 131 weeks for the single placebo patient).

Imetelstat treatment led to a sustained (> 8 weeks) increase in hemoglobin levels (based on central laboratory results) compared to placebo (least squares [LS] mean Hgb increase 1.69 g/dL in imetelstat vs 0.51 g/dL in placebo, LS mean difference 1.18 g/dL, 95% CI: 0.69, 1.67, p < 0.001). There was a median rise in Hgb of 3.6 g/dL in imetelstat-treated, ≥ 8 -week TI responders vs 0.8 g/dL in placebo treated responders.

Per the IWG 2018 Response criteria, the rate of HI-E was 42.2% in patients treated with imetelstat vs 13.3% in patients treated with placebo (p < 0.001). Per IWG 2018 criteria, the proportion of patients who achieved a 50% reduction in transfusion burden over 16 weeks was 44% in the imetelstat group (95% CI: 34.2, 54.8) vs 10% (2.7, 22.6) in the placebo group. The proportion of patients who achieved ≥ 16-week TI was 31.4% (23.1, 40.5) of imetelstat-treated patients vs 6.7% on placebo (1.9, 16.2).

1.7 Summary of Phase 3 Safety Results

The safety profile of imetelstat has been well characterized in the Phase 3 placebo-controlled study. AEs that were recognized as AEs of interest (AEIs) were closely monitored and included the most commonly reported events of neutropenia and thrombocytopenia with the associated potential clinical risks of infections and bleeding events, infusion-related reactions (IRRs), and clinical and laboratory hepatic disorders.

Overall, almost all patients in both imetelstat and placebo groups experienced at least one AE (99.2% vs 100.0%, respectively). The highest incidences of AEs were thrombocytopenia (75.4%) and neutropenia (73.7%) with imetelstat, compared to placebo (10.2% and 6.8%, respectively).

The overall patient incidence rates were higher with imetelstat vs placebo for serious AEs (SAEs; 32.2% vs 22.0%, respectively) and Grade 3/4 events (90.7% vs 47.5%, respectively). However, SAEs and Grade 3/4 events for AEIs of infections, bleeding events, hepatic events, and IRRs occurred with similar incidences in imetelstat compared to placebo. No SAEs were reported for AEIs of neutropenia and thrombocytopenia. A higher patient incidence with imetelstat compared to placebo was reported for Grade 3/4 AEIs of neutropenia (67.8% vs 3.4%, respectively) and thrombocytopenia (61.9% vs.

8.5%, respectively). However, these cytopenias did not translate to higher incidence with imetelstat compared with placebo of severe (Grade 3+) infections (10.2% and 13.6%) or bleeding (2.5% and 1.7%). This comparable incidence could be explained by the short duration of Grade 3/4 neutropenia and thrombocytopenia in imetelstat -treated patients (median event duration < 2 weeks, and > 80% recovering to Grade ≤ 2 within 4 weeks). When excluding neutropenia and thrombocytopenia, the difference in patient incidence of Grade 3/4 events between imetelstat vs placebo decreased significantly (54.2% vs 39.0%).

Treatment-emergent fatal events occurred in 1 patient in each group, and both were considered unrelated to study drug by the investigators.

Rates of IRRs were 7.6% with imetelstat vs 3.4% with placebo, and headache was the only IRR event reported in ≥ 1 patient. Importantly, most IRR events were Grade 1/2, and no severe allergic or hypersensitivity -type reactions were reported.

Hepatic events were closely monitored for both clinical AEs and routine liver function tests assessments. Higher patient incidence with imetelstat versus placebo was reported for laboratory elevations of aspartate aminotransferase (AST; 48.3% vs 22.0%, respectively) and alkaline phosphatase (ALP; 44.9% vs 11.9%, respectively). Similar incidence was reported for laboratory elevations of bilirubin (39.0% in both groups) and alanine aminotransferase (ALT; 39.3% vs 37.3%, respectively). Patient incidence of hepatic AEs overall was higher in the imetelstat group and compared to the placebo group (28.8% vs 16.9%, respectively), but was comparable for Grade ≥ 3 AEs (6.8% vs 5.1%) and SAEs (0.8% vs 0.0%).

A Hepatic Expert Committee (HEC), which reviewed the safety of ongoing clinical studies from a liver toxicity perspective, identified no cases of severe hepatotoxicity or Hy's Law.

Survival analysis was performed with a cutoff date of 05 January 2024, approximately 15 months after the primary analysis. The hazard ratio (HR) based on stratified log-rank test for survival was 0.98 (95% CI: 0.53, 1.82) for imetelstat vs placebo, with a total of 50 events and a median follow-up of 31 months. While still immature, these data suggest no detriment of imetelstat on OS.

1.8 Summary of Dose Justification

Justification of the 7.1 mg/kg q4w imetelstat dosing regimen in the LR MDS population is supported by the observed results of the MDS3001 Phase 3 study. The key clinical efficacy and safety results relevant for the dose justification, as well as related exposure-response (E-R) analyses supporting the dosing regimen, are summarized below.

Dose Justification Based on Efficacy Data

- Efficacy results from Study MDS3001 demonstrated superiority of imetelstat 7.1 mg/kg q4w over placebo with a clinically meaningful and statistically significant RBC TI rate for the primary endpoint, ≥ 8-week RBC TI, and key secondary efficacy endpoint of ≥ 24-week TI.

- Dose intensity and response analyses demonstrated that ≥ 75% of patients received 7.1 mg/kg q4w at the time of onset of ≥ 8-week and ≥ 24-week TI. Further, the mean relative dose intensity (i.e., the average of the actual cumulative dose level received per cycle relative to the 7.1 mg/kg dose) was > 95% and > 93% in imetelstat-treated responders during the period leading up to the achievement of ≥ 8-week TI and ≥ 24-week TI, respectively.
- Exposure-efficacy analyses demonstrated a statistically significant positive E-R relationship for both ≥ 8-week and ≥ 24-week TI rates. These outcomes support that imetelstat doses/exposures < 7.1 mg/kg q4w may result in reduced clinical efficacy.

Dose Justification Based on Safety Data

- Safety results from Study MDS3001 demonstrated a manageable safety profile of imetelstat 7.1 mg/kg q4w that is consistent with Phase 2 and the imetelstat clinical program.
- Dose intensity analyses showed that > 90% mean relative dose intensity (i.e., the average of the actual cumulative dose level received per cycle relative to the 7.1 mg/kg dose) was achieved over the treatment period for all imetelstat-treated patients, despite 49% of patients with dose reductions to 80% of the previous dose, which occurred per-protocol. Dose reductions mitigated the risks of clinical consequences, such as bleeding (thrombocytopenia) and infections (neutropenia), while enabling patients to continue treatment and to derive TI benefit.
- Exposure-safety analyses showed no significant E-R relationship for any grade or Grade 3/4 infection or bleeding events, which together with the low rates of severe infection and bleeding events in imetelstat-treated patients that are similar to the placebo arm, suggest limited clinical significance of neutropenia and thrombocytopenia.
- The imetelstat 4-week (q4w) dosing schedule is supported by disposition properties of imetelstat and the recovery of platelets and neutrophils:
    - Imetelstat is rapidly distributed from blood into tissues and associated with long retention in tissue, consistent with established properties of oligonucleotides (Geary 2009, Geary 2015).
    - The every-4-week dosing allows for recovery of cytopenias, with the majority (> 80%) of Grade 3/4 cytopenias resolving within 4 weeks.

Cumulatively, the clinical efficacy, safety, pharmacokinetic (PK), and E-R relationships, along with the supportive nonclinical data, and clear dose modification guidance in the proposed label, effectively minimize the risks and provide a favorable benefit/risk profile for the recommended imetelstat 7.1 mg/kg q4w dosing regimen for the LR MDS population.

See Section 5.7 for additional information on dose justification.

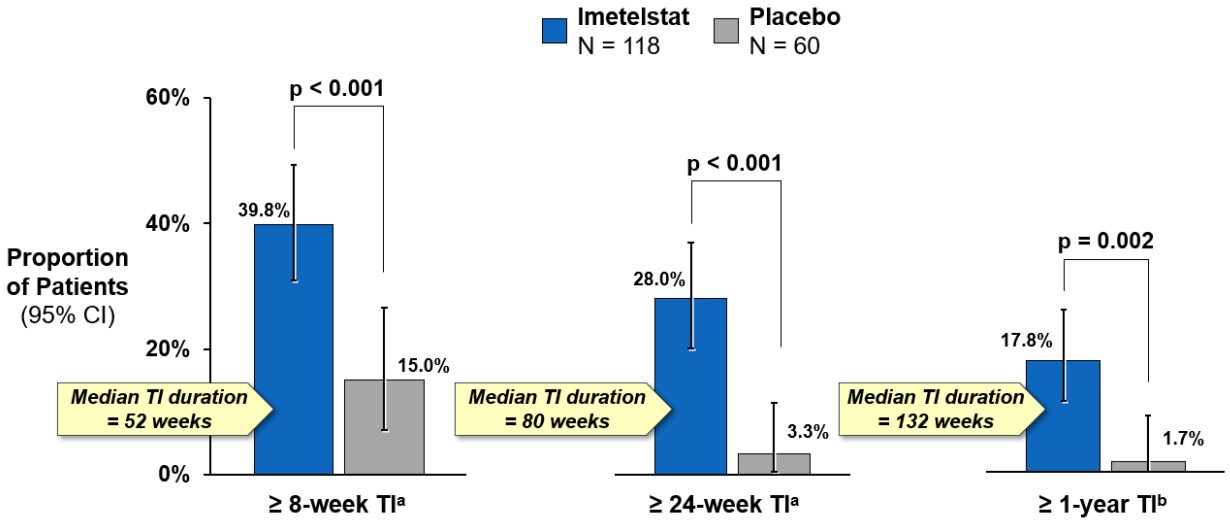
1.9 Benefit-Risk Summary

The intended context of use for imetelstat is ESA R/R/ineligible TD LR MDS which is a debilitating and serious condition with poor prognosis and outcomes. As noted by a recent publication that FDA co-authored, there has been a 14-year drought of approvals for MDS treatments between 2006 and 2020 (Sekeres, 2023) and there few approved treatments and only two (lenalidomide and luspatercept) are approved to treat TD anemia after ESA treatment. The utility of lenalidomide and luspatercept are limited to certain subpopulations, namely del-5q, or RS+. Furthermore, though HMAs are approved for the treatment of LR MDS, recommended use is in patients with multilineage cytopenias or higher risk MDS. There is a need for additional treatments with novel mechanisms of action, that provide alternative options for these underserved patients.

MDS3001 is a pivotal Phase 3 clinical trial designed in concordance with FDA that met its primary endpoint (≥ 8-week RBC TI) and key secondary endpoint (≥ 24-week RBC TI), demonstrating statistically significant, clinically meaningful, and durable improvement in RBC TI compared with placebo (≥ 8-week RBC TI: 39.8% in the imetelstat group compared to 15.0% in the placebo group, $p < 0.001$; ≥ 24-week RBC TI: 28.0% in the imetelstat group compared to 3.3% in the placebo group, $p < 0.001$). Among patients who achieved ≥ 8-week RBC TI, the median length of TI was 51.6 weeks in imetelstat arm and 13.3 weeks in placebo ($p < 0.001$). Durability is further supported by the fact that 17.8% of patients in the imetelstat group had ≥ 1-year RBC TI, versus 1.7% in the placebo group ($p=0.002$).

These data demonstrate continuous RBC TI of long duration in a ≥ 4 units RBC/ 8 weeks TD patient population. These results are particularly important, given that patients who require frequent and chronic RBC transfusions in the R/R-ESA setting have an estimated life expectancy of approximately three years. Thus, achieving RBC TI for one year — one-third of their life expectancy — is considered clinically meaningful for these patients (Figure 1-3).

Figure 1-3: MDS3001 – Rates of Longer-Term Continuous RBC TI



a. Data cutoff: 13 Oct 2022.
b. Data cutoff: 13 Oct 2023.
CI = confidence interval; TI = transfusion independence

Furthermore, the durable, continuous RBC TI was accompanied by sustained improvements in hemoglobin levels, particularly among patients achieving RBC TI.

Regarding the safety profile, the known and well characterized risks of Grade 3 and 4 neutropenia and thrombocytopenia with imetelstat treatment are manageable by hematologists and health care providers who take care of MDS patients. Other agents such as lenalidomide and hypomethylating agents used in the treatment of MDS and other hematologic malignancies have high rates of Grade 3/4 neutropenia and thrombocytopenia. Notably many of these therapies lead to prolonged myelosuppression, and thus have additional risks of severe infections, febrile neutropenia and/or bleeding. Other AEs, including IRRs, liver function test (LFT) abnormalities, and hepatic AEs, were mostly non-severe and non-serious. Overall, the risks associated with imetelstat treatment can be adequately managed through labeling.

Taken together, considering the patient population for which imetelstat will be indicated and the currently limited approved treatment options, the benefit-risk assessment for imetelstat is considered favorable for the treatment of TD anemia in adult patients with low- to intermediate-1 risk MDS who have failed to respond or have lost response to or are ineligible for ESA.

2 BACKGROUND ON TRANSFUSION-DEPENDENT ANEMIA IN MYELODYSPLASTIC SYNDROMES

Summary

- Chronic anemia is the key clinical feature of LR MDS, leading to RBC transfusion dependency that negatively impacts patient quality of life (QoL) and survival.
- There are few approved treatments for patients with LR MDS who are ESA relapsed/refractory or ineligible. Only 2 treatments, lenalidomide and luspatercept, are approved to treat transfusion dependent anemia.
    - Lenalidomide approval is restricted to patients with a del-5q abnormality (~10% of the post ESA MDS population).
    - Luspatercept (post ESA) is limited to those with RS+ disease (~35% of the MDS population) and has limited efficacy in patients requiring ≥ 6 units RBC/ 8 weeks.
    - HMAs (azacitidine, decitabine and decitabine-cedazuridine) are approved for the treatment of MDS and recommended for use in patients with multilineage cytopenias or higher risk MDS
- An unmet need exists for treatments that can provide durable TI with relief from anemia across the broad ESA relapsed/refractory or ineligible population, especially the ~75% that do not qualify for or derive minimal benefit from lenalidomide or luspatercept.

2.1 Overview of Transfusion-Dependent Anemia in MDS

2.1.1 Disease Background

Myelodysplastic syndromes are the most common hematologic malignancy in older people, with a median age at diagnosis of over 70 years old and less than 10% of patients being younger than 50 years old (Neukirchen, 2011; Fenaux, 2021). The age-adjusted incidence rate of MDS in the US in 2019 was estimated to be 3.6 cases per 100,000 persons, with an estimated 13,400 new cases of MDS annually (SEER Cancer Statistics Network, 2020; Zeidan, 2019).

Anemia is the most common peripheral blood abnormality, occurring in approximately 80% to 85% of patients (Foran, 2012). Most patients with anemia are symptomatic and progressive anemia results in the need for RBC transfusions and approximately 40% of patients with LR MDS are dependent on regular RBC transfusions (Zeidan, 2013; Ades, 2014). Over time, patients develop end organ dysfunction, affecting the heart and liver due to persistent anemia and iron overload from RBC transfusions. Importantly, patients have diminished health-related QoL as continuous reliance on transfusions is burdensome to patients and their families and caregivers.

Median OS for LR TD MDS patients after first line treatment with ESA is approximately 3 years (range of 2 to 5.5 years) per retrospective literature reviews (Consagra, 2023; Kelaidi, 2013; Komrokji, 2023; Park, 2017). Given this, an additional and novel treatment option that would allow patients to become free from dependency on RBC transfusions

over long and continuous periods of time would represent an important step forward for these patients.

2.1.2 Transfusion Independence as a Measure of Clinical Benefit

Transfusion independence is considered a clinically relevant endpoint for assessing the efficacy of treatment in providing relief from anemia. Such independence is a direct clinical benefit to LR MDS patients.

Transfusion independence as a primary endpoint has been the basis of approval for other products in similar settings of TD anemia in LR MDS (Table 2-1).

Table 2-1: Primary Endpoint of RBC TI Supporting Approval for TD Anemia in MDS Treatments

Product (Approval Year)	Primary Endpoint	Indication
Imetelstat (Investigational)	RBC TI ≥ 8 weeks during any consecutive 8 weeks	Transfusion-dependent anemia in adult patients with low- to intermediate-1 risk MDS who have failed to respond or have lost response to or are ineligible for ESAs
Lenalidomide (2005)	RBC TI ≥ 8 weeks	Transfusion-dependent anemia due to Low- to Intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities
Luspatercept (2020)	RBC TI ≥ 8 weeks within weeks 1-24	Anemia failing an ESA and requiring 2 or more RBC units over 8 weeks in patients in adult patients with very low- to intermediate-risk MDS with RS or with MDS/MPN-RS-T
Luspatercept (2023)	RBC TI ≥ 12 weeks with mean Hgb increase of 1.5 g/dL within weeks 1–24	Anemia without previous ESA use (ESA-naïve) in adult patients with very low- to intermediate-risk MDS who may require regular RBC transfusions

ESA = erythropoietin stimulating agent; MDS = myelodysplastic syndromes; MPN = myeloproliferative neoplasm; RBC = red blood cell; T = thrombocytosis; TI = transfusion independence; RS = ring sideroblasts

2.2 Current Treatment Options in LR MDS

2.2.1 Erythropoiesis-Stimulating Agents (ESAs)

For the treatment of anemia in LR MDS patients, ESA use results in an overall ≥ 8-week TI rate of 20% to 40%; and rates tend to be higher in those with low baseline serum EPO levels (< 500 U/L, ideally < 100 U/L) and minimal or no RBC transfusion needs (Lucero, 2023). Additionally, responses to ESA have a duration between 17 and 24 months and ultimately, in this progressive disease, patients can relapse, or are refractory. In addition, a proportion of patients with high endogenous EPO levels would not derive benefit from, and are considered ineligible for ESA therapy. Absence of response or short response to ESAs in LR MDS is associated with a higher risk of AML transformation and poorer survival (Kelaidi, 2013).

2.2.2 Lenalidomide

Lenalidomide (Revlimid®) is approved as a treatment for TD anemia in the setting of low- or intermediate-1-risk MDS associated with a del(5q) abnormality. This abnormality is present in approximately 10% to 15% of patients with MDS and is associated with a more favorable prognosis (List, 2006). Lenalidomide is not currently approved to treat patients who are non-del(5q).

Approval of lenalidomide was based on a Phase 2 single-arm study and a 67% RBC-TI rate in del(5q) LR MDS patients (List, 2006; V. Santini, 2016), with a median RBC TI duration of 2 to 3 years (Fenaux, 2013; Ades, 2014). Grade 3/4 neutropenia and thrombocytopenia occurred in 55% and 44% of patients, respectively and dose modifications occurred in 84% of patients most frequently due to cytopenias.

2.2.3 Luspatercept

Luspatercept (Reblozyl®) is approved in the US for the treatment of anemia without previous ESA use and anemia for those with ESA failure and require 2 or more RBC units over 8 weeks, and with very low- to intermediate-risk MDS with ring sideroblasts (MDS-RS+) (Bristol Myers Squibb, 2023a), who comprise ~35% of the MDS patient population. In the pivotal registration study in the ESA failure setting (MEDALIST), treatment with luspatercept resulted in a ≥ 8-week TI rate of 38% with a median TI duration of 30.6 weeks (Fenaux, 2020). Less than half of the patients (43%) in the MEDALIST study had RBC transfusion burden of ≥ 6 units/8 weeks at baseline and the ≥ 8-week RBC TI rate was 9% with luspatercept vs. 3% with placebo in these patients (Fenaux, 2020; NCCN, 2023). The most common adverse reactions were fatigue (41%, Grade 3/4 7%), musculoskeletal pain (20%), and dizziness/vertigo (18%).

2.2.4 Hypomethylating Agents

Hypomethylating agents (HMAs) including azacitidine, decitabine and decitabine-cedazuridine, are primarily used in patients with higher risk MDS, (intermediate 2 and high risk per IPSS), but in the US are approved for use in all patients with MDS who are transfusion dependent and for whom other agents have not been or are no longer effective (NCCN, 2023). However, HMAs are generally indicated for the treatment of MDS and not anemia and are not recommended as standard of care for LR MDS except in cases with clinically relevant thrombocytopenia or neutropenia (NCCN, 2023). With the most frequently used HMA, azacitidine, Grade 3/4 neutropenia and thrombocytopenia occurred in 91% and 85% of patients, respectively (Fenaux, 2009).

Another HMA, an oral combination of decitabine and cedazuridine (DEC-C; Inqovi®), a cytidine deaminase inhibitor, was approved in the US in 2020 for treatment of adult patients with MDS, including previously treated and untreated, de novo and secondary MDS with the intermediate-1, intermediate-2, and high-risk IPSS groups (Inqovi, PI). DEC-C produced clinical responses including a complete remission (CR) rate of ~20% and RBC TI in ~50% in studies of MDS patients that included 44% IPSS intermediate-1 risk patients (Kim, 2022; Garcia-Manero, 2020). Despite the response to DEC-C in MDS

studies that included a portion of lower-risk patients, the National Comprehensive Cancer Network (NCCN) recommends DEC-C for higher-risk patients as an alternative to azacitidine or decitabine or as a bridge to HSC transplantation (HSCT) (NCCN, 2023). With DEC-C, Grade ≥3 neutropenia and thrombocytopenia occurred in 57% and 61% of patients, respectively, febrile neutropenia in 32% of patients and 50% of patients had Grade ≥3 anemia (Otsuka Pharmaceutical Company, 2020; Garcia-Manero, 2024).

2.2.5 Unmet Medical Need

As outlined in Figure 1-1, imetelstat has the potential to address the high unmet need in this patient population that currently approved treatments do not fully address.

There is a need for additional and alternative treatment options given that:

- TD anemia due to LR MDS is debilitating to patient outcomes and lifestyle
- Few treatments are approved for LR-MDS patients who are relapsed or refractory to ESAs and only 2 of which are indicated for the treatment of transfusion dependent anemia
    - Approximately 75% of patients are ineligible for or derive minimal benefit from luspatercept or lenalidomide
    - Neither product provides a broader LR-MDS patient population with extended, continuous durability of TI as seen with imetelstat
    - HMAs, including DEC-C, are not indicated for the treatment of anemia and are recommended for use primarily in higher risk MDS

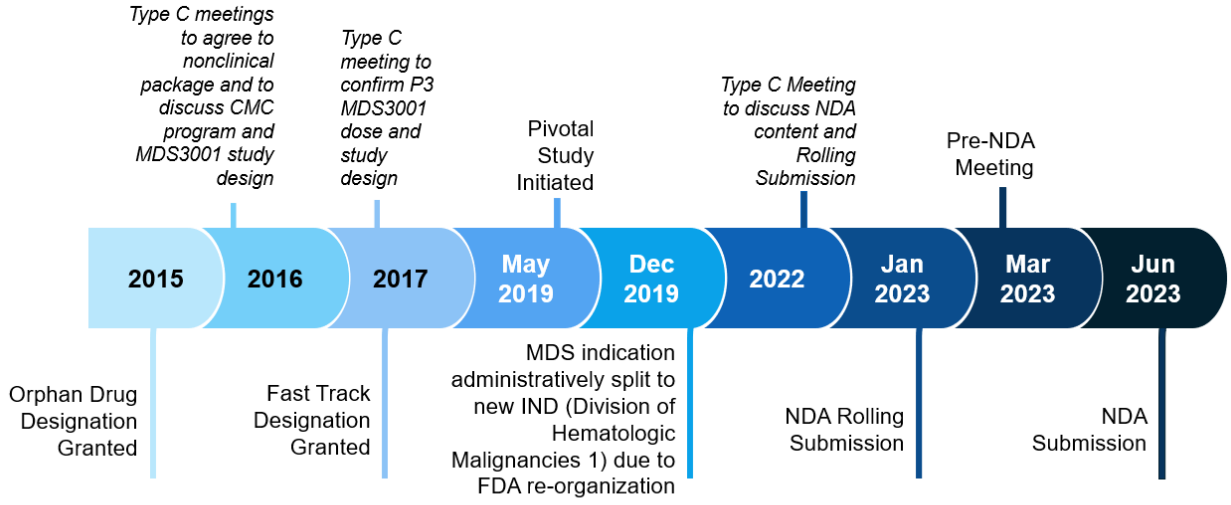
In summary, there is a need for additional alternative therapies for the treatment of TD anemia in non-del(5q) IPSS low- or intermediate-1 risk MDS patients who are R/R or are ineligible for ESA therapy, that can produce continuous long-lasting RBC TI, regardless of RS status or baseline transfusion burden. Imetelstat is a first in class telomerase inhibitor that has demonstrated high rates of and durable RBC TI across all studied LR MDS patient sub-types with TD anemia with a well characterized and manageable safety profile.

3 REGULATORY AND DEVELOPMENT HISTORY

3.1 Regulatory Milestones

Important regulatory milestones in the development of imetelstat in LR MDS are summarized in Figure 3-1. A number of Type C interactions with FDA have occurred during the development of imetelstat to discuss nonclinical, CMC, and clinical aspects of the development program. In particular, in 2016 and 2017 there were two Type C meetings with the Agency to agree on key aspects of the study design and the proposed dosing regimen for the Phase 3 pivotal study MDS3001, which was initiated in May 2019. Following reorganization at FDA, the imetelstat Investigational New Drug (IND) application was administratively split into two, and the IND covering LR MDS development was assigned to the Division of Hematologic Malignances Following a Type C interaction with FDA and submission and acceptance of a formal request for a rolling review, consistent with Appendix 2 of the *Guidance for Industry: Expedited Programs for Serious Conditions – Drugs and Biologics* (FDA, 2014), a rolling submission of non-clinical information was submitted for imetelstat to FDA in January 2023. A Pre-New Drug Application (NDA) meeting followed in March 2023 and the full NDA was submitted in June 2023.

Figure 3-1: Imetelstat US Regulatory Milestones for MDS Development



CMC = Chemistry Manufacturing and Controls; FDA = Food and Drug Administration; IND = Investigational New Drug Application; MDS = myelodysplastic syndromes; NDA = New Drug Application

3.2 Clinical Development Program

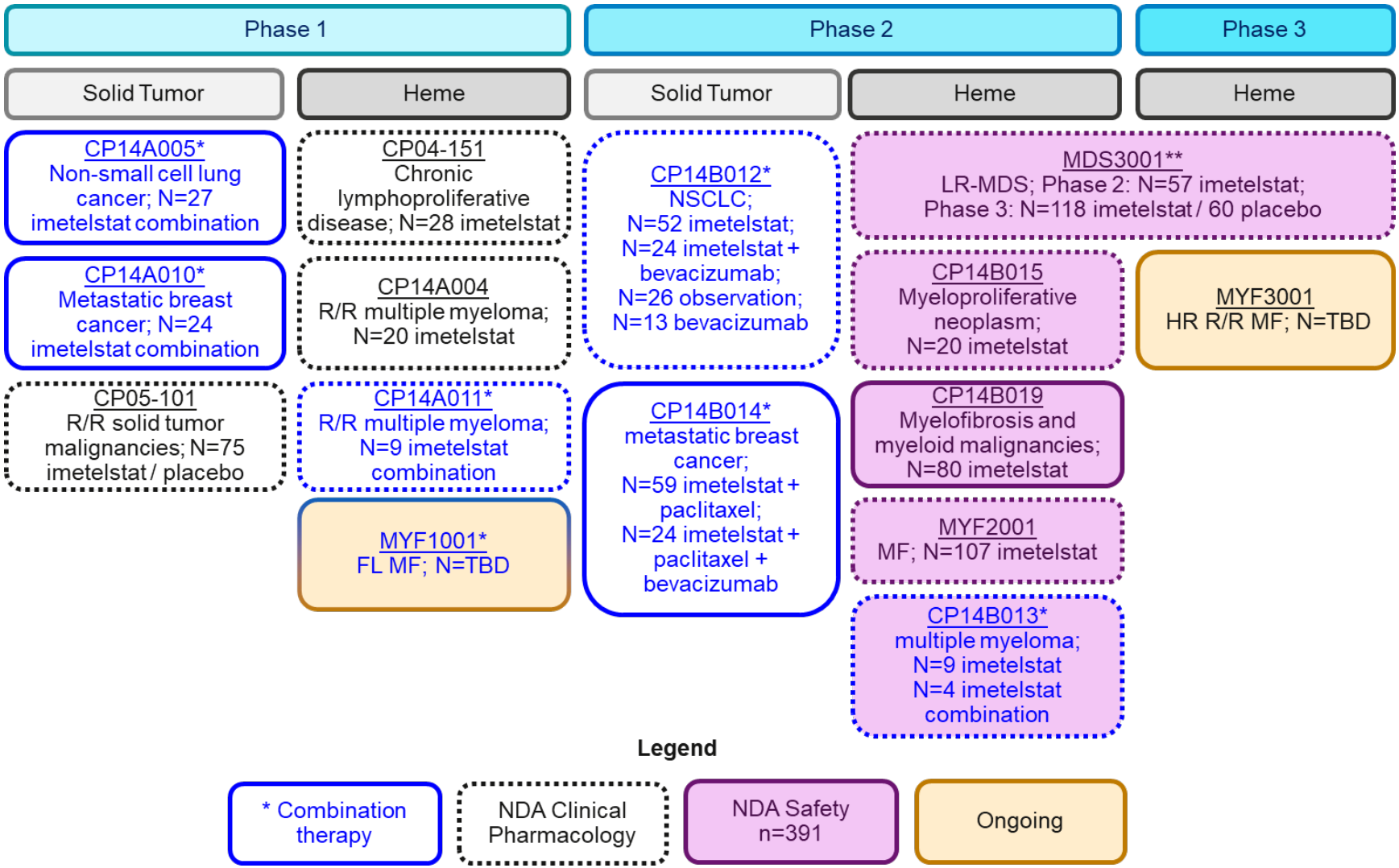
More than 750 patients have been exposed to imetelstat treatment alone or in combination with anti-cancer agents in patients with various solid tumors and hematologic malignancies.

This document focuses on imetelstat as monotherapy for TD anemia in LR MDS. The efficacy and safety of imetelstat as treatment for TD anemia in LR MDS that is relapsed

after, refractory to or ineligible for ESA therapy, are supported by the pivotal Phase 2/3 study (Study MDS3001), with a focus on Phase 3, which is the randomized, double-blind, and placebo-controlled portion of the study. Four additional monotherapy studies in hematology indications (CP14B013, CP14B015, CP14B019, and MYF2001), including MDS, myelofibrosis (MF), essential thrombocythemia (ET) or polycythemia vera and multiple myeloma, were included in the NDA in support of safety of imetelstat.

An overview of clinical studies of imetelstat is provided in Figure 3-2.

Figure 3-2: Summary of Clinical Studies of Imetelstat



FL = frontline; HR = high-risk; LR = lower-risk; MDS = myelodysplastic syndromes; MF = myelofibrosis; NDA = New Drug Application; R/R relapsed/refractory; TBD=to be determined.
**QTc substudy and extension phase ongoing.

4 PRODUCT DESCRIPTION

Summary

- Telomerase is highly expressed in malignant bone marrow cells of patients with MDS. In contrast, telomerase is generally undetectable in normal somatic cells, making it a relevant and key therapeutic target for treatment of LR MDS.
- Imetelstat, a first in class telomerase inhibitor, is a 13-nucleotide oligonucleotide with a sequence that is complementary to and specifically binds with high affinity to the template region of the RNA component of human telomerase.
- Nonclinical studies have shown that imetelstat inhibits telomerase activity and selectively depletes malignant hematopoietic stem and progenitor cells (HSCs/HPCs) by inhibiting cell proliferation and inducing apoptosis, which could facilitate restoration of normal hematopoiesis.

4.1 Proposed Indication

The proposed indication for imetelstat is for the treatment of TD anemia in adult patients with low- to intermediate-1 risk MDS who have failed to respond or have lost response to or are ineligible for ESA.

4.2 Dosing Guidance

The proposed dosing regimen for imetelstat for LR MDS is 7.1 mg/kg (expressed as the active moiety; equivalent to 7.5 mg/kg imetelstat sodium) administered as a 2-hour intravenous (IV) infusion q4w.

Imetelstat is supplied as a sterile, lyophilized powder in a single dose vial containing 188 mg or 47 mg of drug product, for reconstitution with 0.9% sodium chloride for injection. A detailed description for the dose justification is provided in Section 5.7.

4.3 Mechanism of Action

In the human body, normal growth and maintenance of tissues occurs by cell division and the number of divisions is regulated by the length of telomeres, which are repetitions of a DNA sequence located at the end of chromosomes (Counter, 1996). Telomeres serve two primary functions: (i) preserve genomic integrity by protecting the ends of chromosomes to prevent inappropriate degradation by DNA repair mechanisms, and (ii) prevent loss of genetic information during cellular division (Waksal, 2023). Each time a cell divides, the telomeres shorten and eventually shrink to a critically short length, preventing the cell from further division and leading to senescence, or apoptosis (Levy, 1992).

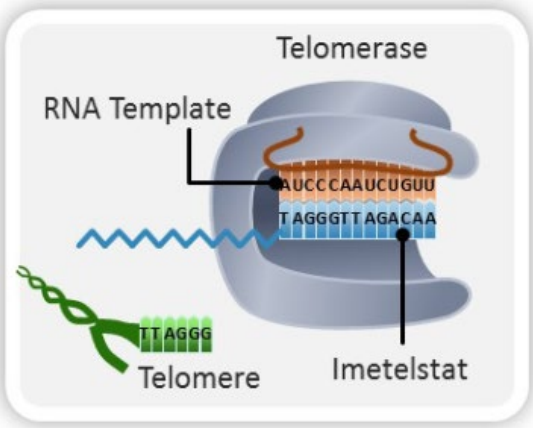
Telomerase is a naturally occurring enzyme involved in synthesizing and maintaining the length of telomeres with the addition of nucleotides to the ends of telomeres, preventing telomere shortening during cell division (Dahse, 1997). In > 90% of human cancers there

is upregulation of telomerase, enabling the continued and uncontrolled proliferation of malignant cells, driving tumor growth and progression (Cong, 2002). This is relevant to LR MDS given that it is characterized by ineffective hematopoiesis due to clonal myeloproliferation arising from malignant HSCs/HPCs, which have high levels of telomerase activity (Briatore, 2009), making telomerase a key therapeutic target in LR MDS.

In contrast, telomerase is undetectable in normal somatic cells, with a few exceptions, including transient expression in hematopoietic stem/progenitor cells (HSCs/HPCs) to allow self-renewal (Hohaus, 1997).

Imetelstat is a 13-nucleotide (13-mer) oligonucleotide with a covalently attached lipid tail to enhance entry into cells (Asai, 2003; Herbert, 2005). Imetelstat has a nucleotide sequence that is complementary, and binds with high affinity and specificity, to the template region of the RNA component of human telomerase (hTR), which lies in the active or catalytic site of human telomerase reverse transcriptase (hTERT) (Figure 4-1). This results in competitive inhibition of hTERT enzymatic activity, which prevents telomere binding (Asai, 2003; Herbert, 2005).

Figure 4-1: Schematic Representation of Imetelstat Binding to the Template Region of the RNA Component of Telomerase

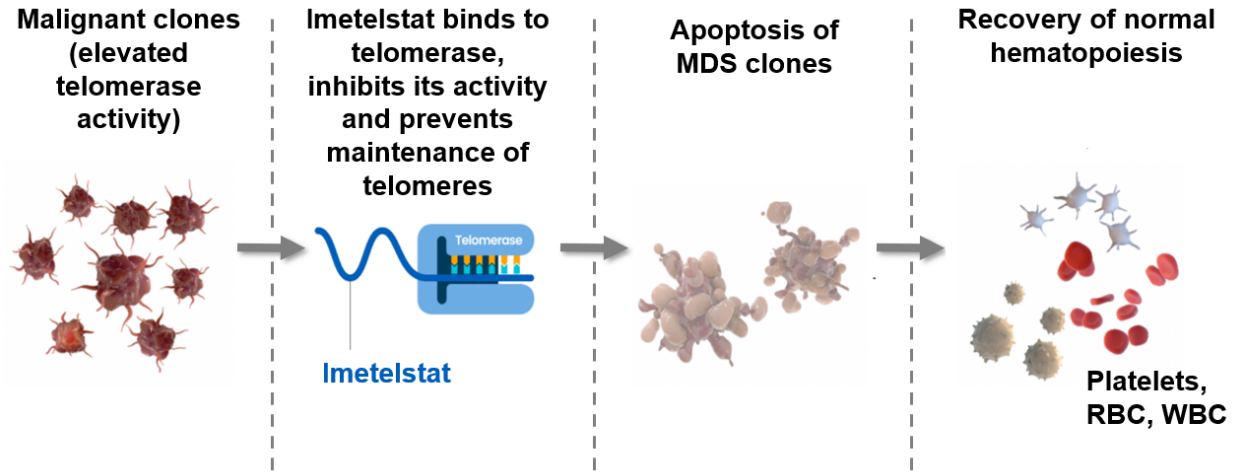


Human telomerase comprises a catalytic subunit with reverse transcriptase activity (hTERT- human telomerase reverse transcriptase), and an RNA template (TERC or hTR - human telomerase RNA component). hTERT synthesizes telomeric sequences using TERC as a template (Greider, 1987). Imetelstat has a complementary nucleotide sequence that binds to the RNA template region which lies in the active or catalytic site of hTERT.

Telomerase inhibition by imetelstat leads to loss of a cancer cell's ability to maintain telomere length, resulting in inhibition of cell proliferation, reduction in colony formation and induction of apoptosis (or cell death) of cancer cells, cancer stem cells, malignant HSCs/HPCs and LSCs, while having minimal effect on normal HSCs/HPCs (Herbert, 2005; Dikmen, 2005; Shammas, 2008; Brennan, 2010; Marian, 2010; Mosoyan, 2017; Ma, 2017; Wang, 2018; Baerlocher, 2019; Bruedigam, 2014). In the context of LR MDS,

such elimination of malignant HSCs/HPCs from the bone marrow could allow for restoration of normal hematopoiesis in these patients, as illustrated in Figure 4-2.

Figure 4-2: Mechanism of Action of Imetelstat in LR MDS



MDS = myelodysplastic syndromes; RBC = red blood cells; WBC = white blood cells

5 CLINICAL PHARMACOLOGY

Summary

- Imetelstat clinical pharmacology was comprehensively characterized across a wide range of doses (0.4 to 11.0 mg/kg) and schedules in patients with solid tumors and hematologic malignancies.
- Peak plasma concentrations occur at the end of infusion and imetelstat does not accumulate between q4w treatment cycles in patients with LR MDS.
- Imetelstat plasma protein binding was approximately 94% in vitro. Following a single 7.1 mg/kg IV dose, the volume of distribution at steady state is 11.5 L.
- The plasma half-life for imetelstat is 4.9 hours in patients with LR MDS, reflecting rapid distribution from plasma to tissues. Once in tissues, imetelstat is associated with a prolonged retention as demonstrated in nonclinical studies.
- Imetelstat, like other oligonucleotides (FDA, 2022b), is metabolized by nucleases in tissue into smaller fragments with component fragments excreted in urine.
- There are no clinically significant effects of age, sex, race, mild to moderate renal impairment, or mild to moderate hepatic impairment on imetelstat pharmacokinetics (PK).
- Based on in vitro data, imetelstat has a low potential for clinically relevant drug-drug interactions (DDIs) with major cytochrome P450 (CYP) enzymes and drug transporters.
- Based on nonclinical and clinical assessments, imetelstat is unlikely to prolong the QT interval.
- In evaluable LR MDS patients, anti-drug antibodies (ADA) occurred at a low incidence of approximately 17%, with median time to onset of 38 weeks. There was no clinically significant effect of ADA on the PK, safety, or efficacy of imetelstat.
- Justification of the imetelstat 7.1 mg/kg q4w clinical dose and dosing regimen in the LR MDS population is supported by the observed clinical efficacy and clinical safety results from the MDS3001 Phase 3 and supportive Phase 2 studies, as well as imetelstat clinical PK data and results from comprehensive exposure-response (E-R) analyses for efficacy and safety.

5.1 Overview of Clinical Pharmacology Studies

The clinical pharmacology of imetelstat has been comprehensively characterized across 9 completed clinical studies with imetelstat administered as a single agent or in combination with various anti-cancer agents across a wide range of doses and dose schedules. The use of healthy volunteers to characterize the clinical pharmacology properties of imetelstat is not considered appropriate due to the specific mechanism of action (i.e., telomerase inhibition) that is relevant to malignant cells, as well as the clinical safety profile. Therefore, the imetelstat clinical pharmacology properties were thoroughly described using studies in adult patients with hematologic malignancies and solid tumors. Cumulatively, the studies have investigated and characterized imetelstat single- and multiple-dose PK properties (Section 5.2), sources of PK variability (Section 5.3), DDI

potential (Section 5.4), proarrhythmic potential (Section 5.5), immunogenicity (Section 5.6), and exposure-response (E-R) relationships (Section 11.7).

5.2 Pharmacokinetics

Following intravenous (IV) administration, imetelstat area under the concentration-time curve (AUC) increases in a more than dose proportional manner over the 0.4 to 11.0 mg/kg dose Per range in patients with solid tumors and hematologic malignancies. In patients with LR MDS receiving the proposed therapeutic dose of 7.1 mg/kg over 2 h IV infusion, peak plasma concentrations are observed at the end of infusion with a geometric mean (coefficient of variation [CV%]) C_{max} of 89.2 µg/mL (27.2%). The geometric mean (CV%) $AUC_{0\text{-}28d}$ is 554 h*µg/mL (43.4%). Imetelstat does not accumulate between treatment cycles following q4w dosing in patients with MDS.

Distribution: Human plasma protein binding of imetelstat is approximately 94% in vitro at clinically relevant concentrations. Following a single dose of 7.1 mg/kg imetelstat over 2 h IV infusion, the geometric mean (CV%) volume of distribution at steady state (V_{ss}) is 11.5 L (26.1%). As reported in nonclinical studies, imetelstat rapidly distributes from plasma to tissue with the highest concentrations detected in the bone marrow (the site of action for myeloid diseases like MDS) and liver, kidney, and spleen.

Metabolism: Consistent with other oligonucleotide therapeutics (Crooke, 2000; Gaus, 1997; Geary, 2001; Geary, 2009; Griffey, 1997; Yu, 2007), imetelstat is likely metabolized by nucleases in tissue into smaller fragments with component fragments excreted in urine. Hepatic CYP enzymes and drug transporters are not expected to be involved in the disposition of oligonucleotides including imetelstat (FDA, 2022a; Geary, 2009).

Elimination: In patients with MDS receiving 7.1 mg/kg imetelstat, the geometric mean (CV%) half-life in plasma is 4.9 h (45.5%), which likely reflects its rapid distribution from plasma to tissues. Nonclinical absorption, distribution, metabolism, and excretion (ADME) studies demonstrated prolonged tissue retention for imetelstat which is line with properties of other oligonucleotide therapeutics which exhibit rapid extravascular distribution followed by longer retention in tissues (Geary, 2009; Geary, 2015). Nonclinical studies demonstrated urine is the primary route of elimination, with 62% to 82% recovery of radiolabeled imetelstat in urine and 12% to 21% recovery in feces after 1 week. Unchanged imetelstat is not detected in the urine of rats administered radiolabeled imetelstat.

5.3 Intrinsic Factors

The influence of intrinsic factors on imetelstat PK was assessed in a comprehensive population PK (popPK) analysis including data from patients across 7 clinical studies (see Table 5-1 for summary of patient demographics). Based on popPK analyses, no clinically significant differences in the PK of imetelstat were detected based on age, sex, race, mild to moderate renal impairment, or mild to moderate hepatic impairment. Body weight was

included as a covariate on imetelstat in the popPK analysis, supporting the use of body weight-based dosing for imetelstat.

Table 5-1. Summary of Demographics of Patients Included in popPK Analysis

Characteristic		Number of Patients (%)[a]
Age (years)	Median (min-max)	67.0 (21.0-87.0)
Weight (kg)	Median (min-max)	75.0 (44.0-161.0)
Sex	Male	247/424 (58.3%)
	Female	177/424 (41.7%)
Race	White/Caucasian	342/424 (80.7%)
	Other[b]	82/424 (19.3%)
Renal Impairment[c]	Normal	156/424 (36.8%)
	Mild	147/424 (34.7%)
	Moderate	115/424 (27.1%)
	Severe	6/424 (1.4%)
Hepatic Impairment[d]	Normal	256/424 (60.4%)
	Mild	119/424 (28.1%)
	Moderate	24/424 (5.7%)
	Severe	3/424 (0.7%)
	Missing	22/424 (5.2%)

[a]All data presented as N of patients (% of total) except age and weight which are presented as median (min-max).
[b]Other category includes Black/African American (N=31), Asian (N=16), Other (N=2), and Unknown (n=33).
[c]Renal impairment categorized according to creatinine clearance (FDA, 2020).
[d]Hepatic impairment categorized according to total bilirubin and aspartate aminotransferase, according to National Cancer Institute Organ Dysfunction Working Group (Ramalingam, 2010).

5.4 Drug-Drug Interactions

Effect of Other Drugs on Imetelstat: Similar to other oligonucleotide therapeutics (FDA, 2022a; Geary, 2009), imetelstat is unlikely to be the victim of DDIs mediated by metabolic enzymes or transporters. Hepatic CYP enzymes and drug transporters are not expected to be involved in the disposition of imetelstat.

Effect of Imetelstat on Other Drugs: Based on in vitro data, imetelstat is not an inhibitor or inducer of CYP enzymes or the P-glycoprotein (P-gp) transporter. Imetelstat is a potential inhibitor of the hepatic uptake transporters OATP1B1 and OATP1B3, the renal transporter OAT1, and the enzyme UDP-glucuronosyltransferase 1A1 (UGT1A1) in vitro.

Based on an integrated assessment of PK characteristics and clinical data, imetelstat has limited risk of clinically relevant DDIs. Imetelstat is dosed infrequently (q4w) and rapidly cleared from plasma (half-life of 4.9 h). There are no clinically meaningful elevations in bilirubin, an endogenous substrate of OATP1B1/OATP1B3 and UGT1A1, in imetelstat treated patients compared to placebo. Further, there is no indication of altered safety profiles when imetelstat is administered with concomitant substrates of OATP1B1, OATP1B3, and UGT1A1. Consistent with other oligonucleotide therapeutics (FDA, 2022a; Adjei, 2003; Geary, 2006; Mani, 2002; Rogers, 2021; Yu, 2009), clinically relevant DDIs for imetelstat via inhibition of transporters and enzymes is unlikely.

5.5 Proarrhythmic Potential

Based on integrated nonclinical and clinical assessments, imetelstat has limited potential to prolong the QT interval. Nonclinical studies demonstrated that imetelstat does not inhibit the Human ether-à-go-go-related gene (hERG) channel at concentrations > 140x unbound C_{max} (C_{max},u) in patients with MDS or cause treatment-related clinical or cardiac signs in monkeys at concentrations > 2.6x C_{max} in MDS. Clinically, there has been no indication of cardiac toxicity in imetelstat-treated patients with hematologic malignancies. A dedicated clinical QT substudy is ongoing in patients with LR MDS to characterize the relationship between imetelstat exposure and the QT/QTc interval. Overall, based on the current knowledge of imetelstat from nonclinical and clinical assessments, and consistent with the limited proarrhythmic potential for other oligonucleotide therapeutics (FDA, 2022a; Noormohamed, 2023), imetelstat is not likely to prolong QT interval.

5.6 Immunogenicity

The overall incidence, titer, and onset of imetelstat ADA, as well as the effects of ADA on efficacy in treatment of patients with MDS, were evaluated in MDS3001. Formation of ADA against imetelstat was assessed using a validated bioanalytical method which included a three-tiered approach: 1) a screening assay which detected anti-imetelstat antibodies; 2) a confirmatory competition assay to assess the specificity of initial positive screening results; and 3) a titration assay for confirmed positive results to obtain semi-quantitative results for titers of detected ADA.

Comprehensive analyses evaluating the incidence of ADA and potential effects of ADA on imetelstat PK, efficacy, and safety were carried out in the 166 ADA-evaluable patients in the combined Phase 2 + Phase 3 portions of MDS3001. ADA developed in 16.9% (28/166) of imetelstat-treated patients with LR MDS, with a median time of onset of 38 weeks (ranging from 12 weeks to 109 weeks). Formal covariate analysis during popPK model development indicated that ADA positivity did not significantly affect imetelstat PK. ADA positivity did not negatively impact the efficacy response rate for ≥ 8-week or ≥ 24-week TI or the duration of TI. There was no apparent effect of ADA positivity on imetelstat safety, with similar rates of AEs, SAEs, and Grade ≥ AEs observed between ADA positive and negative patients. Collectively, these results demonstrate that ADA do not impact the PK, efficacy, or safety of imetelstat in patients with LR MDS. Thus, ADA do not impact the overall benefit/risk profile of imetelstat, consistent with reports for other oligonucleotide therapeutics (Bano, 2022).

5.7 Dose Justification

Justification of the imetelstat 7.1 mg/kg q4w clinical dose and dosing regimen in the LR MDS population is supported by the observed clinical efficacy (Section 7) and clinical safety (Section 8) results from the pivotal randomized placebo-controlled MDS3001 Phase 3 study, as well as the supportive MDS3001 Phase 2 study, along with the cumulative available data on imetelstat clinical PK (Section 5.2) and results from comprehensive exposure-response (E-R) analyses (Section 11.7).

Dose Justification Based on Efficacy Data

- Efficacy results from the Phase 3 portion of Study MDS3001 confirmed the treatment benefit of imetelstat 7.1 mg/kg q4w in the LR MDS population, demonstrating superiority of imetelstat 7.1 mg/kg q4w over placebo on the primary and key secondary endpoints (Section 7.2).
    - Clinical dose intensity and response analysis demonstrated that ≥ 75% received 7.1 mg/kg q4w at the time of onset of ≥ 8-week TI and ≥ 24-week TI.
    - The mean relative dose intensity (i.e., the average of the actual cumulative dose level received per cycle relative to the 7.1 mg/kg dose) was > 95% and > 93% in imetelstat-treated responders in the period leading up to the achievement of ≥ 8-week TI and ≥ 24-week TI, respectively (Section 8.3.2.6).
- Once patients achieved their TI response, if dose reductions were employed per protocol (as discussed below in this section), patients did not lose their response as reflected by a median duration of TI of 47 weeks from time of first dose reduction to end of their longest TI period.
- Exposure-efficacy analysis demonstrated a statistically significant positive E-R relationship for ≥ 8-week TI rate and ≥ 24-week TI rate. These outcomes support that imetelstat doses/exposures lower than imetelstat 7.1 mg/kg q4w may result in reduced clinical efficacy (Section 11.7.1).

Dose Justification Based on Safety Data

- Safety results from the Phase 3 portion of Study MDS3001 demonstrated a manageable safety profile for imetelstat 7.1 mg/kg q4w that is consistent with Phase 2 and the imetelstat clinical program, with Grade 3/4 thrombocytopenia and neutropenia occurring more frequently on imetelstat compared to placebo, the majority (>80%) resolve to Grade 2 within 4 weeks and without Grade 3/4 infections or bleeding events beyond what is seen in the placebo arm (Section 7.2.4.2).
- Per protocol (and as proposed in the US Package Insert), effective management of neutropenia and thrombocytopenia and other events was achieved by providing clear instructions for dose modifications. A total of 68.6% of imetelstat-treated patients had cycle delays and 49.2% had dose reductions due to AEs as specified per protocol.
- Despite the frequency of dose reductions to 80% of the prior dose, the overall mean dose intensity analyses showed that > 90% mean relative dose intensity was achieved over the treatment period for all imetelstat-treated patients (Section 8.3.2.6). Dose reductions enabled management of cytopenias and allowed patients to maintain on treatment and response.
- Exposure-safety analysis demonstrated no significant E-R relationship for Grade 3/4 neutropenia and a positive E-R relationship for Grade 3/4 thrombocytopenia (statistically significant for C_{max} and approaching significance for AUC) (Section 11.7.2).

- Importantly, E-R analyses show no significant relationship between imetelstat exposure and any grade or Grade 3+ infection or bleeding events.
- The 4-week (q4w) dosing schedule is supported by disposition properties of imetelstat and the recovery of platelets and neutrophils.
    - Imetelstat is rapidly distributed from plasma into tissue and associated with long retention in tissue (Section 5.2), consistent with established properties of oligonucleotides (Geary, 2009; Geary, 2015).
    - The majority (> 80%) of Grade 3/4 cytopenia events resolve within 4 weeks, with more recovering in 4 weeks compared to 2 weeks (Section 8.3.2.9, Section 11.7.2).
- Finally, the popPK analysis incorporated body weight with theory-based allometric exponents as a covariate contributing to imetelstat PK variability, supporting the imetelstat body weight-based dosing approach (Section 5.3).

Cumulatively, the clinical efficacy, safety, PK, and E-R relationships along with the supportive nonclinical data, and clear dose modification guidance in the proposed label, effectively minimize the risks and provide a favorable benefit/risk profile for the recommended imetelstat 7.1 mg/kg q4w dosing regimen for the LR MDS population.

6 PHASE 2/3 STUDY MDS3001 DESIGN AND POPULATION

6.1 Phase 2/3 Investigational Plan

6.1.1 Overall Design

The MDS3001 Phase 2/3 study design is summarized in Figure 1-2.

6.1.1.1 Study MDS3001 – Phase 2

The Phase 2 part of Study MDS3001 provides supportive evidence of efficacy and safety. This open label, single-arm study assessed the safety and efficacy of imetelstat. Patients enrolled in Phase 2 part of the study were ineligible to enroll in Phase 3.

All patients in Phase 2 received imetelstat 7.1 mg/kg q4w administered as a 2-hour IV infusion. Review of the efficacy data from the first 32 patients in the Phase 2 study identified a subset of patients with higher hematologic response rates. These were patients with both non-del(5q) LR MDS and no prior exposure to either hypomethylating agents or lenalidomide, hereafter referred to as “target population”. Results in this subset of patients supported further evaluation of imetelstat informing the patient population enrolled in the Phase 3 study.

6.1.1.2 Study MDS3001 – Phase 3

The Phase 3 part of Study MDS3001 was a global study conducted at 77 study sites in 17 countries, including the US. Patients were randomized 2:1 to imetelstat or placebo, respectively. Randomization was stratified according to prior RBC transfusion burden (4–6 or > 6 units RBC/8 weeks) and by IPSS risk category (low vs intermediate-1) to ensure equal distribution across treatment groups.

6.1.2 Randomization

The 2:1 randomization scheme was chosen to limit the number of patients in the placebo group, to increase the likelihood of patients receiving active treatment with imetelstat, and to study the safety of imetelstat in a larger cohort.

6.1.2.1 *Dosing Guidance for Phase 2/3*

Study drug was administered q4w until disease progression, unacceptable toxicity (despite appropriate dose reduction), or withdrawal of consent. Treatment was not mandated for a set number of cycles, and investigators used medical discretion in the determination of when to discontinue a patient from treatment.

Per protocol, study drug dose delay, dose reduction, or dose discontinuation for Grade 3/4 toxicities observed at the time of the planned dose of the next cycle were instituted for hematologic AEs, non-hematologic AEs, hepatic AEs (including LFTs) and IRRs. These instructions were not applicable when toxicities occurred mid-cycle and subsequently resolved to Grade ≤ 2 by the time of the next planned dose.

Dose reduction was to 5.6 mg/kg and subsequently to 4.4 mg/kg as the minimum dose. Patients who experienced repeated Grade ≥ 3 AE at the 4.4 mg/kg dose were instructed

to discontinue study treatment. If a patient was experiencing clinical benefit and without significant toxicity, the investigator could contact the sponsor to discuss continuing treatment.

6.1.3 Efficacy Endpoints

Endpoints in the Phase 3 study are listed below. Both the Phase 2 and Phase 3 studies shared the same primary and key secondary endpoints of RBC TI ≥ 8 weeks and RBC TI ≥ 24 weeks, respectively. For the Phase 3 study, in the analyses of the non-key secondary and exploratory endpoints, all p-values are nominal, without multiplicity adjustment.

- **Primary endpoint**: RBC TI ≥ 8 weeks during any consecutive 8 weeks; (results presented in Section 7.1.1)
    - Defined as the proportion of patients without any RBC transfusions during any consecutive 8 weeks (56 days) starting from Study Day 1 until subsequent anti-cancer therapy, if any.
        - The ≥ 8-week RBC TI endpoint has been used as the basis of other drug approvals for the treatment of anemia in LR MDS and was agreed upon with FDA prior to the Phase 3 study; see Section 6.1.3 for additional details.
- **Key Secondary Endpoint**: RBC TI ≥ 24 weeks during any consecutive 24 weeks; results presented in Section 7.1.2.
    - Defined as the proportion of patients without any RBC transfusion during any consecutive 24 weeks (168 days) starting from Study Day 1 until subsequent anti-cancer therapy, if any.
- **Additional Secondary Endpoints**
    - Efficacy in subgroups, including RS+/- status, prior RBC transfusion burden (4–6 RBC units/ 8 weeks vs > 6 units/ 8 weeks), and IPSS risk category (low vs intermediate-1); results presented in Section 7.2.3.1.
    - Rate of HI-E per IWG 2018 (Platzbecker, 2019); results presented in Section 7.2.3.3.
        - Defined as the proportion of patients who achieved ≥ 50% reduction in transfusion burden over 16 weeks or achieved TI ≥ 16 weeks.
    - Duration of RBC TI; results presented in Section 7.2.3.4.
    - Relative change in RBC transfusion burden; results presented in Section 7.2.3.6.
    - Rate of progression-free survival (PFS), and time to progression to AML; results presented in Section 7.2.3.7.
    - Overall survival (OS); note that OS data is immature, and is therefore discussed within the context of safety in Section 8.3.2.8.

- Exploratory Endpoints
  - Cytogenetic response; results presented in Section 7.2.4.1.
  - Patient reported outcomes (PROs); results presented in Section 7.2.4.2.
- Ad-Hoc Analysis: Proportion of patients who achieved RBC TI ≥ 1 year; results presented in Section 7.2.3.5.

6.1.4 Selection of Study Population

Eligibility criteria for study patients are described below.

Inclusion Criteria:

- Man or woman greater than or equal to (≥) 18 years of age
- Diagnosis of MDS according to World Health Organization (WHO) criteria confirmed by bone marrow aspirate and biopsy within 12 weeks prior to Cycle 1 Day 1 (C1D1) (Phase 2) or randomization (Phase 3)
- IPSS low risk or intermediate-1 risk MDS
- RBC TD, defined as requiring at least 4 RBC units transfused over an 8-week period during the 16 weeks prior to Study Entry; pre-transfusion Hgb should be less than or equal to 9.0 gram per deciliter (g/dL) to count towards the total of 4 units
- Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2
- Had MDS that was relapsed/refractory to ESA treatment as defined by meeting any one of the following criteria:
  - Received ≥ 8 weeks of treatment with a minimum weekly dose of epoetin alfa 40,000 U, epoetin beta 30,000 U, or darbepoetin alfa 150 mcg (or equivalent agent/dose), without having achieved a hemoglobin rise ≥ 1.5 g/dL or decreased RBC transfusion requirement by at least 4 units over 8 weeks
  - Transfusion dependence or reduction in hemoglobin by ≥ 1.5 g/dL after hematologic improvement (HI), in the absence of another explanation
  - Endogenous serum EPO level > 500 mU/mL
- Hematology lab test values within the following limits:
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L independent of growth factor support
  - Platelets ≥ 75 x 10^9/L independent of platelet transfusion
- Biochemical laboratory test values must be within the following limits:
  - AST, ALT and ALP ≤ 2.5 times the upper limit of normal (x ULN)
  - Serum creatinine ≤ 2.0 x ULN

- Total bilirubin ≤ 3 x ULN and direct bilirubin ≤ 2 x ULN (unless due to Gilbert's syndrome, ineffective erythropoiesis due to MDS, or hemolysis due to RBC transfusion)

Exclusion Criteria:

- Patient has known allergies, hypersensitivity, or intolerance to imetelstat or its excipients
- Patient has received an investigational drug or used an invasive investigational medical device within 30 days prior to Study Entry or is currently enrolled in an investigational study
- Prior treatment with imetelstat
- Prior treatment with a hypomethylating agent (e.g., azacitidine, decitabine), lenalidomide, thalidomide, or other thalidomide analogues (Phase 3-specific).
- Patient with del(5q) karyotype (Phase 3-specific).
- Patient with MDS/myeloproliferative neoplasm (MPN) overlap syndrome.
- Have received corticosteroids greater than (>) 30 milligram per day (mg/day) prednisone or equivalent, or growth factor treatment within 4 weeks prior to study entry.
- Has received an ESA or any chemotherapy, immunomodulatory, or immunosuppressive therapy within 4 weeks prior to study entry (8 weeks for long-acting ESAs).

6.1.5 Statistical Analysis

6.1.5.1 General Statistical Considerations

Overview of Analysis Plan

The analysis for MDS3001 Phase 2 was conducted by population type, i.e., overall or target population; the target population was the patients with non-del(5q) MDS and without prior treatment with either HMA or lenalidomide (same population as the Phase 3), and the analysis for Phase 3 data was conducted by treatment group (imetelstat or placebo).

Per protocol and Statistical Analysis Plan, the primary analysis for the Phase 3 study was performed 12 months after the last patient was enrolled (clinical cutoff October 2022). Long term follow-up analyses were performed 1 year later (clinical cutoff October 2023 and January 2024).

General analysis definitions

Unless otherwise specified, all statistical tests were interpreted at a 2-sided nominal significance level of 0.05, and all CIs were calculated at a 2-sided level of 95%. The overall Type-I error rate was 0.05 (2-sided) for the primary and secondary efficacy

hypotheses in each part of the study. Other than the primary and key secondary endpoints (≥ 8-week RBC TI rate and ≥ 24--week RBC TI rate, respectively), the statistical testing does not control familywise alpha; thus, all other p-values are nominal.

Multiplicity was accounted for by a sequential gatekeeping approach for the primary and key secondary endpoints, which were tested sequentially in the prespecified order of 8--week RBC-TI, followed by 24-week RBC TI, then rate of HI-E as per modified IWG 2006 criteria.

No missing data were imputed for primary and secondary endpoints. A transfusion-free period with ≥ 1 missing transfusion assessments was not considered qualifying for an 8-week or 24-week TI period, and patients with no qualifying observation periods were considered non-responders.

The baseline value was defined as the last non-missing value collected on or before the first dose of the trial medication. Baseline RBC transfusion burden was defined as the maximum number of RBC units transfused over an 8-week period during the 16 weeks prior to randomization.

Determination of Sample Size

On the basis of historical data, the 8-week RBC TI rate was expected to be approximately 7.5% in patients with TD anemia in low or intermediate-1 risk MDS without any active treatment (Raza, 2008; Valeria Santini, 2014). The 8-week RBC TI rate with imetelstat treatment was expected to be approximately 30% based on preliminary data from a cohort of 9 patients in Study CP14B019 (Tefferi, 2016).

Using a 2:1 ratio randomization and a 2-group continuity corrected Chi-square test with 0.05 (2-sided) significance level, 150 patients were needed to achieve a power of approximately 88% to detect the difference between an RBC TI rate of 30% in the imetelstat group and an RBC TI rate of 7.5% in the placebo group. To account for a maximum 10% drop-out rate, a total of approximately 170 patients (115 in imetelstat group and 55 in placebo group) was planned.

6.1.5.2 Analysis Sets in Study MDS3001

The analysis sets for Phase 2 and Phase 3 were defined separately, and results are also summarized and presented separately herein. The efficacy analysis for Phase 3 included the following sets:

- **Intent-to-Treat (ITT) Analysis Set** included all patients randomized into the main study. This analysis set was used for all analyses of efficacy and PRO endpoints (except time to the 8- or 24-week RBC TI and duration of RBC TI), analyses of disposition, demographic, and baseline disease characteristics. Patients were classified according to assigned treatment group regardless of the actual treatment received.
- **ITT 8-week (24-week) TI Responder Analysis Set** included all patients in the ITT Analysis Set who did not have any RBC transfusion during at least any consecutive

8 (24) weeks starting from Day 1 until subsequent anti-cancer therapy if any, with the TI starting date between Day 1 and date of last dose of study medication + 30 days or end of treatment visit, whichever occurred first. This analysis set was used for analyses for time to the RBC TI and duration of RBC TI.

- **Safety Analysis Set** included all patients who received at least 1 dose of study drug. This analysis set was used for all safety analyses and analyses of exposure. All patients were analyzed according to the treatment which they received.
- **Patient Reported Outcome (PRO) Analysis Set** included all patients from the ITT Population who completed Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-Fatigue) data at baseline.

6.1.5.3 Efficacy Analyses in Study MDS3001

Summaries of efficacy data in Phase 2 were descriptive and based on the total and target populations. Efficacy data in Phase 3 were compared between the imetelstat and placebo groups based on the ITT Population.

The primary hypothesis of the Phase 3 study was that imetelstat would significantly improve the rate of RBC TI as compared to placebo in TD anemia patients with low or intermediate-1 risk MDS that are R/R to ESA treatment. The hypothesis was tested using a stratified Cochran-Mantel-Haenszel (CMH) test adjusting for the stratification factors at a 2-sided significant level of 0.05.

The RBC-TI rates were summarized with frequencies and percentages along with two-sided 95% exact Clopper- Pearson CIs for the two treatment groups. Difference in TI and its 95% CIs were presented with the Wilson score method. Percentages of patients with a response for the two treatment groups were compared with a stratified Cochran-Mantel-Haenszel test at a two-sided significance level of 0.05, adjusting for stratification factors, previous RBC transfusion burden, and IPSS risk category. The Kaplan-Meier method was used to estimate the distribution of duration of RBC-TI and was compared between groups with the stratified log-rank test. The treatment effect (i.e., hazard ratio [HR]) and its two-sided 95% CIs were estimated with a stratified Cox regression model, with treatment as the sole explanatory variable.

Subgroup analyses were performed, including baseline presence or absence of ring sideroblasts, previous RBC transfusion burden (ie, 4–6 RBC units or > 6 RBC units over 8 weeks), and low or intermediate-1 IPSS risk categories. Peripheral blood hematology, bone marrow evaluation, mutation assessment, and cytogenetic evaluation were performed centrally, and responses assessed by an independent review committee.

6.1.5.4 Safety Analyses in Study MDS3001

All safety summaries and analyses were based on the Safety Analysis Set. Safety variables were tabulated by descriptive statistics.

The verbatim terms used in the eCRF by investigators to identify AEs were coded using MedDRA version 25.0. The severity of AEs was graded using National Cancer Institute (NCI)-Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

Safety was assessed by the evaluation of the incidence, intensity, and type of AEs, clinical laboratory results (hematology and chemistry), and deaths.

6.1.5.5 Patient Reported Outcomes in Phase 3 Study MDS3001

Patient reported outcome (PRO) assessments were exploratory endpoints to be descriptively summarized. One of the instruments utilized in the study was Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-Fatigue), which is based on additional items of the Functional Assessment of Cancer Therapy-Anemia Subscale (FACT-An) and includes 13 items with a 4-point response scale. FACIT-Fatigue score ranges from 0–52, with a higher score meaning less fatigue (better/improvement) (Yellen, 1997; Cella, 1993).

The main PRO objective was to explore the predefined hypothesis that, while on treatment, patients treated with imetelstat were not more likely to experience meaningful deterioration in fatigue, as measured by the FACIT-Fatigue score, than patients treated with placebo, regardless of RBC transfusion status. This is relevant given that LR MDS is a progressive disease and RBC transfusions can reduce fatigue, and therefore becoming TI could potentially worsen fatigue. For each patient, an episode of meaningful deterioration of fatigue was defined as any occurrence of two consecutive assessments with a decrease in the FACIT-Fatigue score of ≥3 points compared to baseline with the threshold based on published literature and confirmed with blinded MDS3001 study data.

Additional exploratory PRO objectives were to describe change over the course of the study in PRO concept of interests that were identified as relevant for patients with LR MDS: physical function, dyspnea, pain, bruising, and systemic symptoms, regardless of their transfusion-dependence status.

6.2 Phase 2/3 Study Patients

6.2.1 Phase 2 MDS3001 Study Population

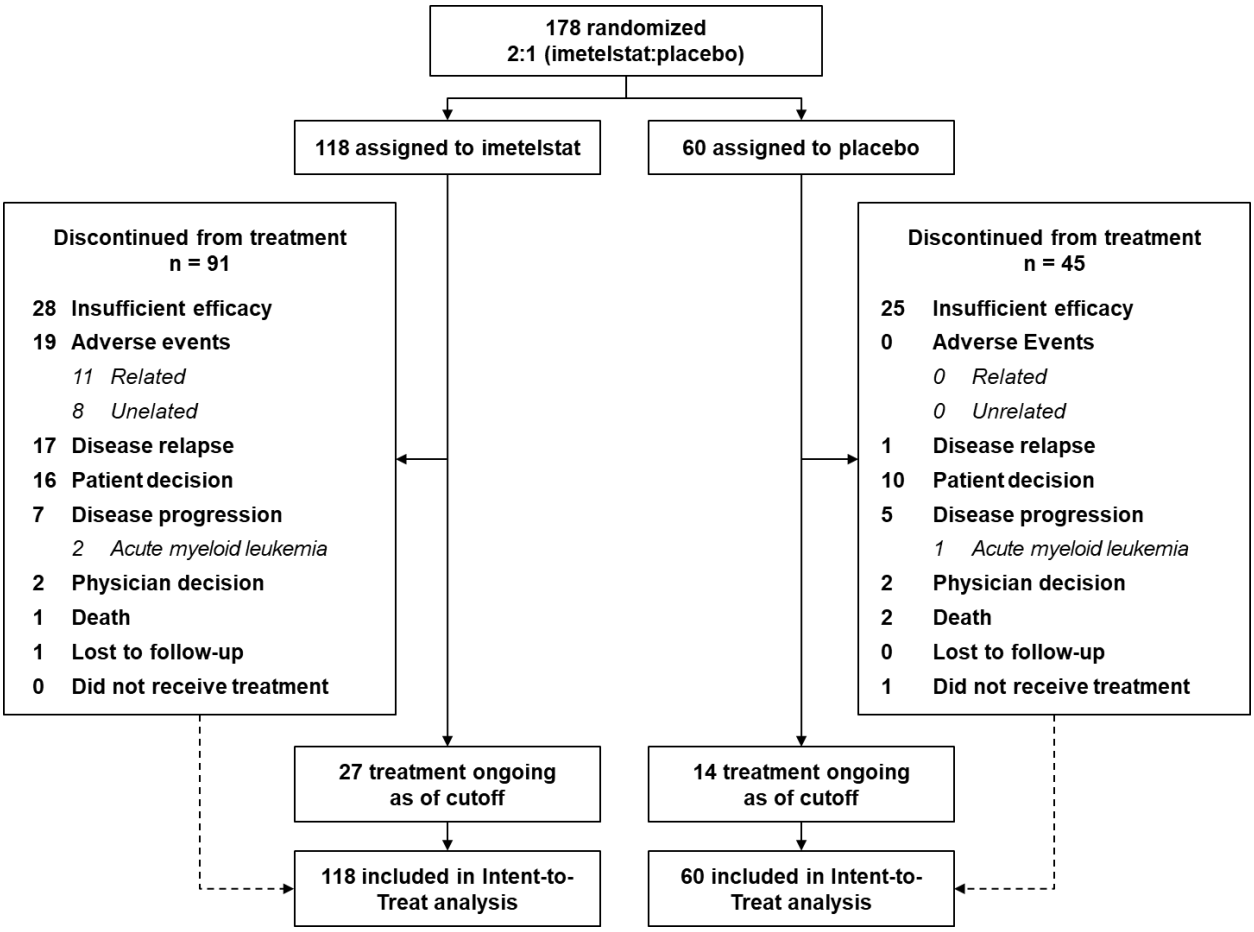
The Phase 2 study enrolled 57 patients, including 38 who met the target population criteria of having neither prior HMA nor lenalidomide use and no del(5q) in karyotype at baseline. The median (range) of prior RBC transfusion burden was 8.0 units per 8 (4–14) weeks and 7.0 (4–14) units per 8 weeks for the target and overall patient populations, respectively. Approximately half of the patients in each population had a prior RBC transfusion burden of > 6 units. Within the target population, 89.5% of patients had prior ESA treatment, and 31.6% had serum EPO > 500 mU/mL at baseline, indicating a low likelihood to respond to or be candidates for further ESA therapy. Seventy nine percent of patients were ≥ 65 years old, and 65.8% were male, consistent with the known demographic population for MDS patients.

6.2.2 Phase 3 MDS3001 Study Population

6.2.2.1 Disposition

A total of 178 patients were randomized 2:1 to imetelstat (N=118) or placebo (N=60), respectively (Figure 6-1). In total, 177 patients received ≥ 1 dose of study drug (118 imetelstat vs 59 placebo). At the time of the clinical data cutoff for the primary analysis (13 October 2022) for Phase 3, after a median follow up of 18 months, treatment was ongoing in 22.9% of patients in the imetelstat group and 23.7% of patients in the placebo group. The median time on treatment was longer for patients in the imetelstat group (7.82 months, range: 0.03 to 32.5 months) compared to patients in the placebo group (6.5 months, range: 0.03 to 26.7 months). The proportion of patients who were discontinued from treatment was similar in the imetelstat and placebo groups (91/118 [77.1%] and 45/59 [76.3%] of patients, respectively). The most common reasons for treatment discontinuation were lack of efficacy, which was higher in the placebo group (25/59 (42.4%)) compared to the imetelstat group (28/118 [23.7%]), followed by a patient refusing further study treatment (10/59 [16.9%] and 16/118 [13.6%] patients, respectively). No patients in the placebo group discontinued treatment due to an AE compared to 19/118 (16.1%) of patients in the imetelstat group. Discontinuations due to AEs in the imetelstat group were mainly due to cytopenias (10/118 [8.5%]). Treatment discontinuation due to disease relapse was higher in the imetelstat group (17/118 [14.4%]) compared to placebo (1/59 [1.7%]), as only patients who initially responded to treatment were eligible to be considered as disease relapse.

Figure 6-1: MDS3001 – Patient Disposition



6.2.2.2 Baseline Demographics and Characteristics

Demographics of patients were representative of the known epidemiology of LR MDS (Table 6-1). The median age of patients was 72-73 years. There was a larger proportion of males and most patients were white. Although most patients were from the European Union (EU), the study population is also representative of US LR MDS patient population since the epidemiology of MDS, clinical practice and methods of treatment are similar in most regions.

Table 6-1: MDS3001 – Phase 3 Demographics

Demographic:	Imetelstat N = 118	Placebo N = 60
Age (years), median (min-max)	71.5 (44-87)	73.0 (39-85)
Female	47 (39.8%)	20 (33.3%)
Male	71 (60.2%)	40 (66.7%)
Race		
White	95 (80.5%)	48 (80.0%)
Asian	8 (6.8%)	2 (3.3%)
Black or African America	1 (0.8%)	2 (3.3%)
American Indian or Alaska Native	0	0
Native Hawaiian or Other Pacific Islander	0	0
Other	1 (0.8%)	1 (1.7%)
Unknown	1 (0.8%)	1 (1.7%)
Not Reported	12 (10.2%)	6 (10.0%)
Region		
North America	13 (11.0%)	12 (20.0%)
European Union	80 (67.8%)	38 (63.3%)
Rest of World	25 (21.2%)	10 (16.7%)

All enrolled patients had their MDS diagnosis confirmed by a central pathologist reviewer and there were no notable differences in disease characteristics or prognostic factors between arms. Baseline pretreatment Hgb levels at which patients received RBC transfusions are similar between arm and between study regions.

Disease characteristics were balanced between treatment groups and representative of LR MDS patients with transfusion dependent anemia (Table 6-2). Of note, nearly half of patients had a prior RBC transfusion burden of ≥ 6 units/ 8 weeks. A majority (> 60%) of patients in both treatment groups were RS+ and categorized as low, per IPSS. Nearly all patients (92% for imetelstat and 87% for placebo) had received prior ESA treatment. Most patients (74% for imetelstat and 60% for placebo) had serum EPO levels ≤ 500 mU/mL at the time of study entry, and more than half had an ECOG score of 1, meaning they were symptomatic but fully ambulatory.

Table 6-2: MDS3001 – Phase 3 Baseline Characteristics

Baseline Characteristic:		Imetelstat N = 118	Placebo N = 60
Prior RBC Transfusion Burden	> 6 units per 8 weeks	56 (47.5%)	27 (45.0%)
	Median (range), units	6 (4, 33)	6 (4, 13)
	Median	6.0	6.0
	Minimum-maximum	4-33	4-13
WHO Classification (2008)	RS+ (RARS/RCMD-RS/MDS/MPN-RS-T)	73 (61.9%)	37 (61.7%)
	RS- (Other)	44 (37.3%)	23 (38.3%)
IPSS Category	Low	80 (67.8%)	39 (65.0%)
	Intermediate-1	38 (32.2%)	21 (35.0%)
Serum Erythropoietin (EPO) Level (mU/mL)	Minimum, maximum	6.0-4460.0	16.9-5514.0
	≤ 500 mU/mL	87 (73.7%)	36 (60.0%)
	> 500 mU/mL	26 (22.0%)	22 (36.7%)
Prior ESA Treatment		108 (91.5%)	52 (86.7%)
Eastern Cooperative Oncology Group (ECOG) Score	0: Asymptomatic	42 (35.6%)	21 (35.0%)
	1: Symptomatic fully ambulatory	70 (59.3%)	39 (65.0%)
	2: Symptomatic in bed < 50% of day	6 (5.1%)	0

ECOG = Eastern Cooperative Oncology Group; EPO = Erythropoietin; ESA = erythropoietin stimulating agent; IPSS = International Prognostic Scoring System; IWG = International Working Group; MDS = myelodysplastic syndrome; MPN = myeloproliferative neoplasm; RARS = RA with ringed sideroblasts; RCMD = Red Cell Membrane Disorder; RS = ring sideroblast; T = thrombocytosis; WHO = World Health Organization

7 PHASE 2/3 EFFICACY RESULTS

Summary

- The pivotal Phase 3 study met its primary and key secondary endpoints, with a highly statistically significant and clinically meaningful improvement in TI.
  - ≥ 8-week RBC TI: 39.8% vs 15.0% for imetelstat vs placebo ($p < 0.001$)
  - ≥ 24-week RBC TI: 28.0% vs 3.3% for imetelstat vs placebo ($p < 0.001$)
- Responses were durable.
  - Median TI durations for ≥ 8-week TI responders were 51.6 vs 13.3 weeks for imetelstat vs placebo ($p < 0.001$)
  - 17.8% of imetelstat vs 1.7% of placebo patients achieved ≥ 1-year TI
- Imetelstat improved TI rates vs placebo across all subgroups assessed, including RS status, prior RBC transfusion burden, and IPSS risk category
- Imetelstat led to a sustained increase in hemoglobin vs placebo: least-square (LS) mean rise = 1.69 vs 0.51 g/dL, $p < 0.001$; LS mean difference = 1.18 g/dL
- Hematologic improvement-erythroid (HI-E), per IWG 2018 criteria, was 42.4% vs 13.3% for imetelstat vs placebo ($p < 0.001$); definition of IWG 2018 criteria provided in Appendix 11.3
- Imetelstat led to a sustained decrease in RBC transfusion burden compared with placebo: mean absolute change from baseline in RBC transfusion burden for the imetelstat group was -4.3 units (range: -24 to +15) and for the placebo group -3.6 units (range: -11 to +2)
- Results from PRO assessments demonstrate that patients receiving imetelstat showed no self-reported worsening in fatigue compared to placebo and a trend toward less fatigue
- In summary, imetelstat is the first therapy for transfusion-dependent anemia in LR MDS patients, who are R/R to or ineligible for ESA treatment, that demonstrates broad and durable benefit by reducing transfusion needs across all major MDS subtypes

7.1 Phase 2 Efficacy Results

Results from the Phase 2 part of study MDS3001 were highly consistent with those from the Phase 3 part (discussed below in Section 7.2).

7.1.1 Phase 2 Primary Efficacy Endpoint: ≥ 8-Week RBC TI Rate

Primary endpoint: The rate of ≥ 8-week RBC TI in the target population was 42.1% (95% CI: 26.3%, 59.2%).

Imetelstat demonstrated similar ≥ 8-week RBC TI rates and clinical benefit across key subgroups in the target population, including RS status (44.4% RS+ and 36.4% RS-),

baseline transfusion burden (47.1% 4- 6 units/ 8 weeks and 38.1% > 6 units/8 weeks), and baseline serum EPO levels (48.0% ≤ 500 mU/mL and 33.3% > 500 mU/mL).

7.1.2 Phase 2 Secondary Efficacy Endpoints

Key secondary endpoint: The rate of ≥ 24-week RBC TI in the target population was 31.6% (95% CI: 17.5%, 48.7%).

Imetelstat demonstrated benefit across all subgroups in the target population, including RS status (37.0% RS+ vs 18.2% RS-), baseline transfusion burden (35.3% ≤ 6 units vs 28.6% > 6 units), and IPSS risk category (20.8% low vs 50.0% intermediate-1).

Additional Secondary endpoints:

- In the target population, ≥ 1-year TI rate was 28.9% (95% CI: 15.4%, 45.9%).
- Median duration of RBC TI among ≥ 8-week RBC TI responders in the target population was 74.5 weeks (95% CI: 17.0, 99.0; range: 8.0 to 162.9 weeks).
- Median duration of RBC TI among ≥ 24-week RBC TI responders in the target population was 85.9 weeks (95% CI: 68.4, 140.9; range: 42.9 to 162.9).
- Imetelstat treatment led to a sustained increase in Hgb levels. The median Hgb rise from pretreatment in the longest RBC TI period for ≥ 8-week RBC TI responders was 3.96 g/dL in the target population.

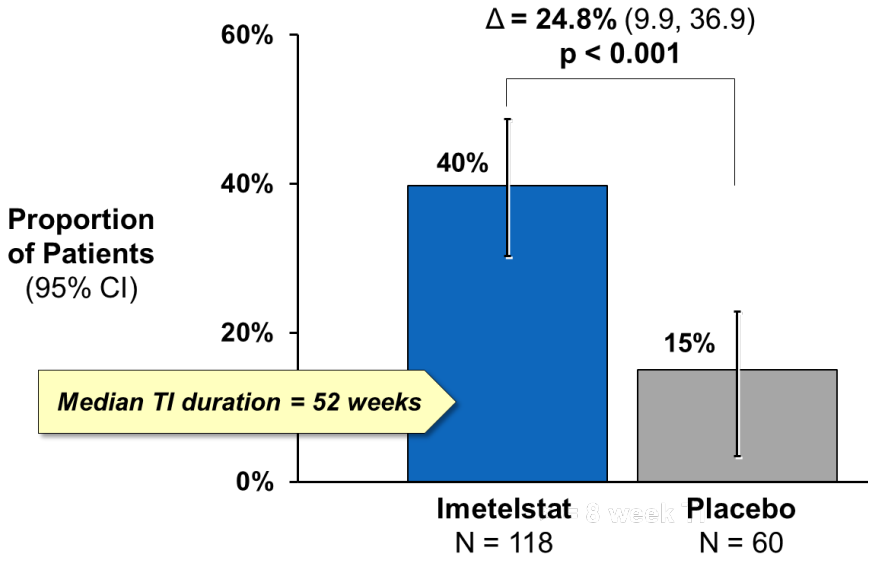
7.2 Phase 3 Efficacy Results

As with the Phase 2 portion of MDS3001, statistical analyses of the primary and key secondary endpoint (≥24-week TI) passed statistical hierarchical testing.

7.2.1 Primary Efficacy Endpoint: ≥ 8-Week RBC TI

The pivotal Phase 3 study met its primary endpoint, with a highly statistically significant and clinically meaningful improvement in ≥ 8-week RBC TI rate in the imetelstat group (39.8% [47/118]) compared to placebo (15.0% [9/60]; p < 0.001; Figure 7-1).

Figure 7-1: MDS3001 – Rate of ≥ 8-Week RBC TI

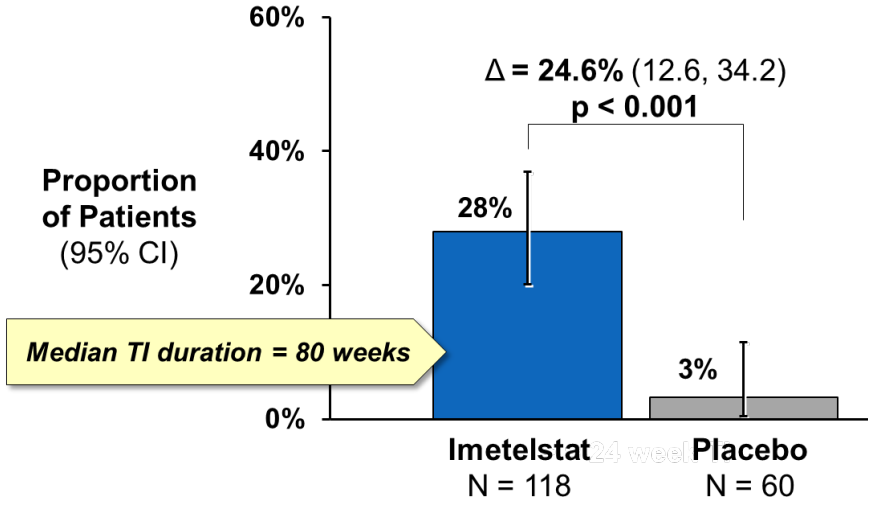


CI = confidence interval; RBC = red blood cell; TI = transfusion independence.

7.2.2 Key Secondary Efficacy Endpoint: ≥ 24-Week RBC TI

Imetelstat also demonstrated a statistically significant improvement in ≥ 24-week TI, meeting the key secondary endpoint. The ≥ 24-week RBC TI rate was 28.0% (33/118) in the imetelstat group vs 3.3% (2/60) for placebo (p < 0.001; Figure 7-2).

Figure 7-2: MDS3001 – Rate of ≥ 24-week RBC TI



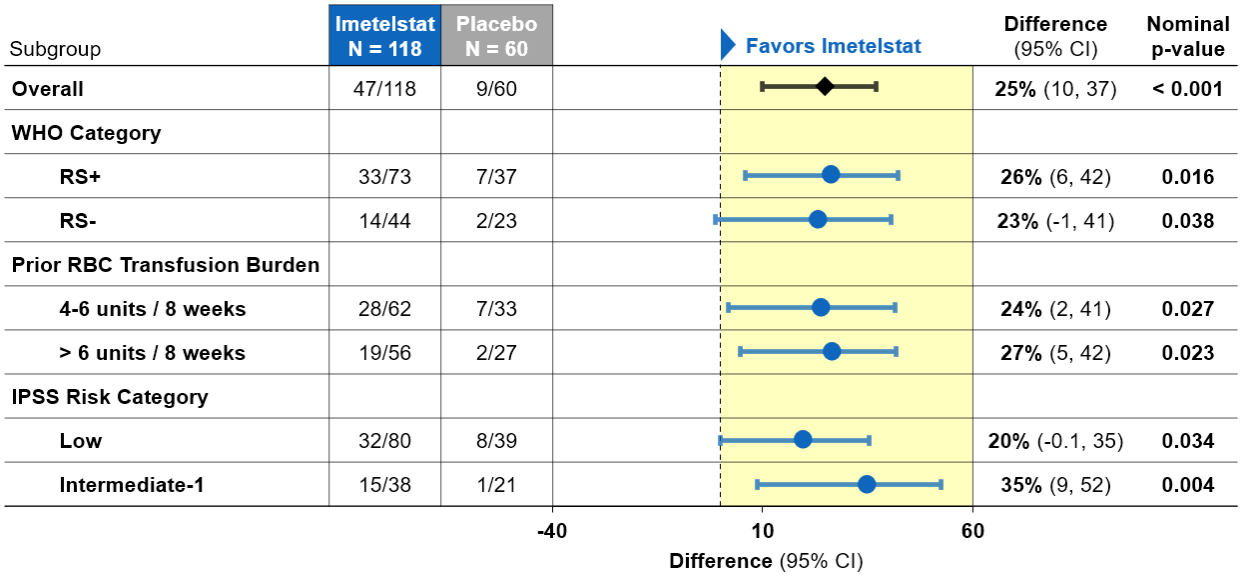
CI = confidence interval; RBC = red blood cell; TI = transfusion independence.

7.2.3 Additional Secondary Efficacy Endpoints

7.2.3.1 Primary Efficacy in Subgroups

Across subgroups, clinical benefit with imetelstat, shown by the proportion of patients who achieved ≥ 8-week RBC TI, was demonstrated regardless of RS status, prior RBC transfusion burden, and IPSS risk category (Figure 7-3).

Figure 7-3: MDS3001 – Primary Endpoint (≥ 8-Week RBC TI) across Subgroups by Disease Characteristics



CI = confidence interval; IPSS = International Prognostic Scoring System; RBC = red blood cells; RS = ring sideroblast; TI = transfusion independence; WHO = World Health Organization.

A clinically meaningful difference in ≥ 24-week RBC TI rates between the imetelstat and placebo groups was also demonstrated across key subgroups, including baseline RS status (27.5%, p=0.003 RS+ vs 20.5%, p=0.019 RS-), baseline RBC transfusion burden (24.6%, p=0.006 4- 6 units vs 25.0%, p=0.012 > 6 units), and IPSS disease category (23.6%, p=0.003 low vs 26.3%, p=0.009 intermediate-1).

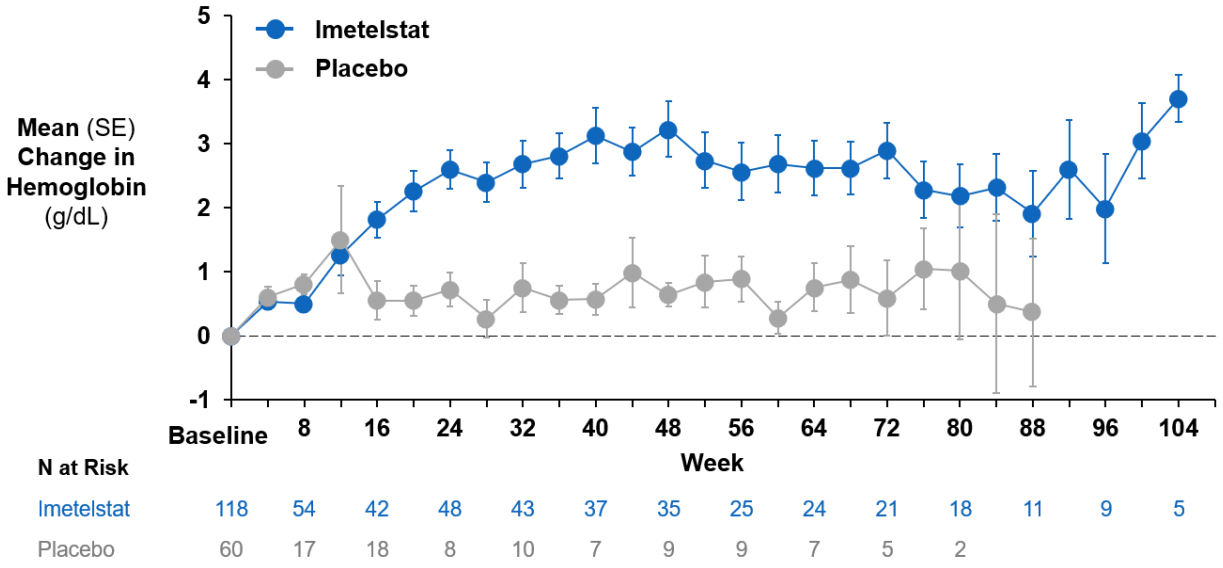
7.2.3.2 Change in Hemoglobin

For efficacy evaluation, changes in hemoglobin were determined based on central laboratory results and excluded hemoglobin values that are considered to be influenced by RBC transfusion (defined as within 14 days after transfusion). Imetelstat treatment led to a sustained increase in Hgb levels compared to placebo (LS mean Hgb increase 1.69 g/dL in imetelstat vs 0.51 g/dL in placebo, LS mean difference in Hgb increase was 1.18 g/dL, 95% CI: 0.69, 1.67, p < 0.001; Figure 7-4).

A figure with the mean change in Hgb, including all Hgb measures, regardless of transfusions, can be found in Appendix 11.5, Figure 11-1. Approximately 34% of imetelstat-treated patients had a ≥ 1.5 g/dL Hgb sustained (≥ 8 weeks) increase for a median duration of 41 weeks.

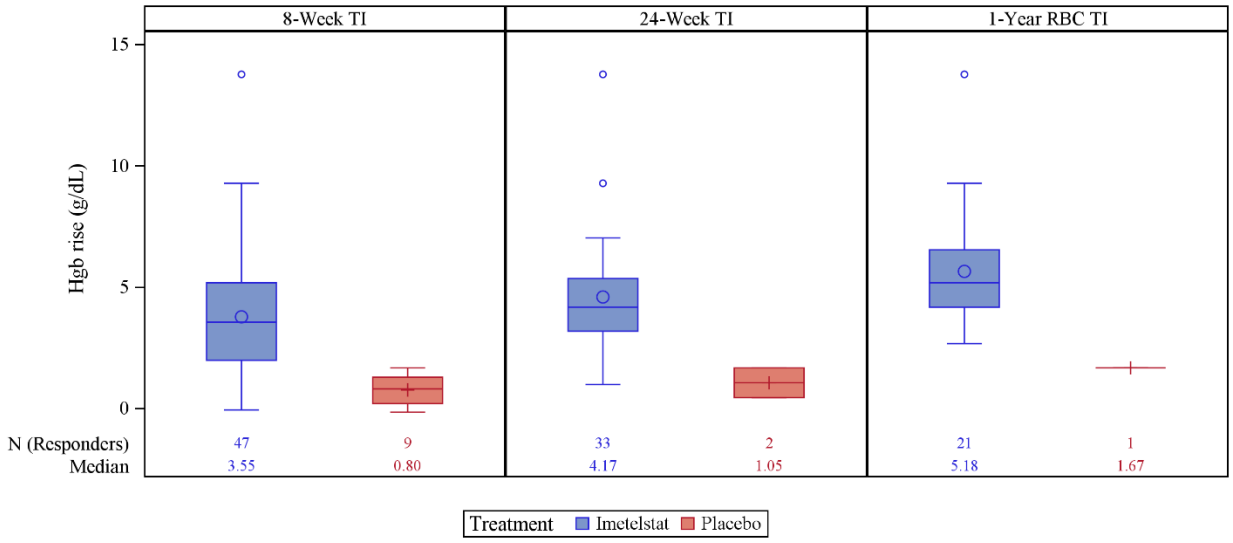
There were meaningful increases in Hgb among patients who achieved TI. Patients who achieved ≥ 8-week and ≥ 24 -week TI on imetelstat had 3.6 g/dL and 4.2 g/dl rises in Hgb respectively, compared to 0.8 g/dL and 1.1 g/dL, respectively, for placebo. Furthermore the 21 patients (17.8%) in the imetelstat group who achieved ≥ 1-year of TI had a median Hgb increase of 5.2 g/dl, compared with one placebo patient (1.7%) who had an Hgb increase of 1.7 g/dL (Figure 7-5).

Figure 7-4: MDS3001 – Change in Hemoglobin among Patients Free from Transfusion for > 14 Days



SE = standard error.
p-value < 0.001.
The mean changes from the minimum Hgb in the 8 weeks prior to the first dose date are shown. Hemoglobin measures within 14 days after a transfusion pre-study and on-study were excluded.
P-value is between treatment arms based on a mixed model for repeated measures with Hgb change as dependent variable, week, stratification factors, min Hgb in 8 weeks prior to first dose, and treatment arm as independent variables with autoregressive moving average (ARMA(1,1)) covariance structure

Figure 7-5: MDS3001 – Change in Hemoglobin for TI Responder, by TI Duration



Hgb = hemoglobin; TI = transfusion independence.
Box-and-whisker plots or Tukey box plots are drawn. The box plot shows the Interquartile Range (IQR) of scores, i.e., the range between the 25th and 75th percentile. Median and mean are shown by the line and circle or plus symbol in the box. The whiskers extend 1.5 times the IQR from the top and bottom of the box. If there are no outliers, then the whiskers extend to the minimum and maximum data values. If there are outliers, they are plotted as circle or plus symbol.

7.2.3.3 Rate of Hematologic Improvement-Erythroid (HI-E)

Analysis of HI-E was also performed using the revised IWG 2018 criteria for HI-E (Platzbecker, 2019) , which is considered more clinically relevant in MDS than the previous IWG 2006 criteria because it emphasizes durability of response over a 16-week interval, versus the 8-week interval used by the IWG 2006 criteria (see Appendix 11.3 for details on the IWG 2018 criteria). This criterion is a standard of LR MDS studies to assess responses beyond TI.

HI-E per IWG 2018 criteria overall was 42.4% (50/118) in patients treated with imetelstat versus 13.3% (8/60) patients treated with placebo ($p < 0.001$; Table 7-1). Among those, 31.4% in the imetelstat group achieved ≥ 16 -week TI vs 6.7% on placebo ($p < 0.001$). For all patients, 43.2% on the imetelstat arm had reduction in the transfusion burden by ≥ 50% over 16 weeks, compared with 15.0% on placebo ($p < 0.001$, per IWG 2018, criteria overall was 42.4% in patients treated with imetelstat vs 13.3% patients treated with placebo ($p < 0.001$; Table 7-1). Among those, 31.4% in the imetelstat group achieved ≥ 16-week TI vs 6.7% on placebo ($p < 0.001$). For all patients, 43.2% on the imetelstat arm had ≥ 50% reduction in the transfusion burden for ≥ 16 weeks, compared with 15.0% on placebo ($p < 0.001$). Additional details on transfusion burden are provided in Section 7.2.3.6.

Table 7-1: MDS3001 – Additional Assessments of Response per IWG 2018

HI-E Response:	Imetelstat N = 118	Placebo N = 60	p-value
Hematologic Improvement-Erythroid (HI-E) per IWG 2018, (95% CI)	50 (42.4%) (33.3, 51.8)	8 (13.3%) (5.9, 24.6)	< 0.001
16-week TI, (95% CI)	37 (31.4%) (23.1, 40.5)	4 (6.7%) (1.9, 16.2)	< 0.001
Transfusion reduction by ≥ 50% / 16 weeks*, (95% CI)	51 (43.2%) (34.1, 52.7)	9 (15.0%) (7.1, 26.6)	< 0.001

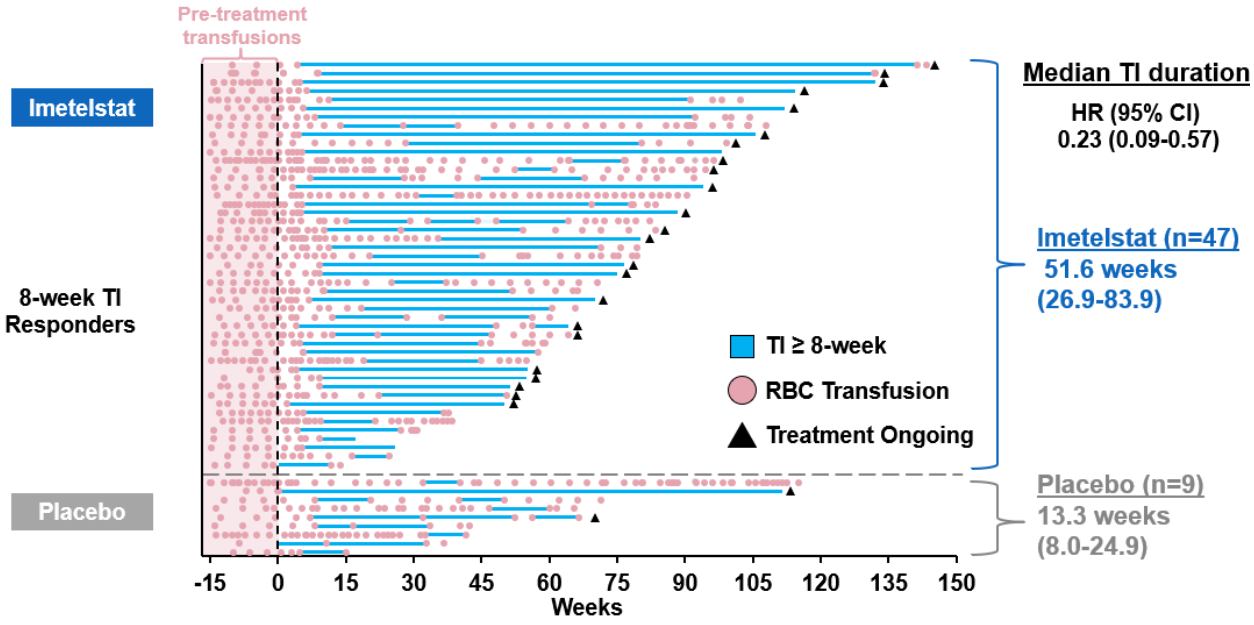
CI = confidence interval; IWG = International Working Group; TI = transfusion independence.
* Modified standard IWG 2018 criteria to consider all patients eligible for transfusion reduction response and not just high transfusion burden (>8 units/ 8 weeks) as per standard definition.

7.2.3.4 Duration of RBC TI

Treatment with imetelstat resulted in highly significant and clinically meaningful durability of RBC TI for patients who achieved ≥ 8-week RBC TI, with a median duration of 51.6 weeks (95% CI: 26.86, 83.86; range: 8.0 to 136.9 weeks) in the imetelstat group vs 13.3 weeks (95% CI: 8.00, 24.86; range: 8.0 to 111.3 weeks) in the placebo group, based on Kaplan-Meier estimates.

The HR for duration of TI between the treatment groups was 0.23 (95% CI: 0.09, 0.57, p < 0.001). Approximately 83% of ≥ 8-week RBC TI responders had a single continuous TI period, further demonstrating the durability of the response (Figure 7-6).

Figure 7-6: MDS3001 – 8-week RBC TI Responders

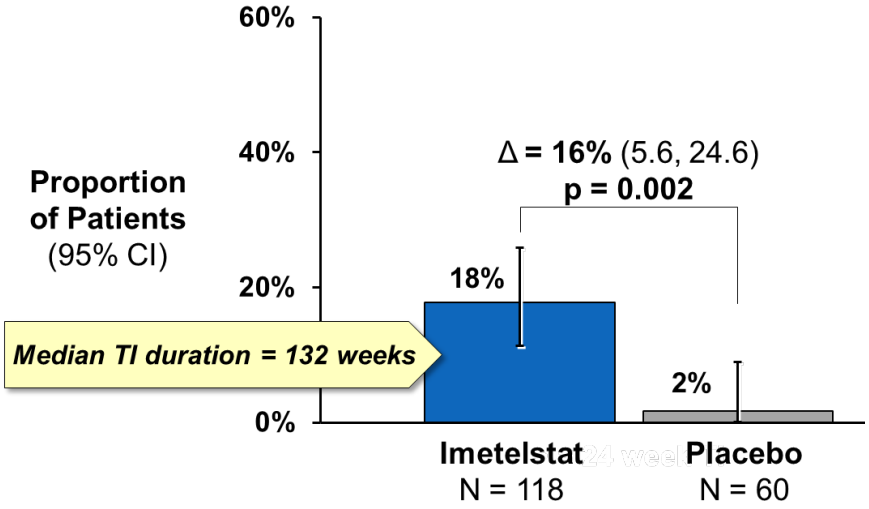


CI = confidence interval; HR = hazard ratio; RBC = red blood cell; TI = transfusion independence

7.2.3.5 Ad Hoc Analysis: ≥ 1-Year RBC TI

An additional ad hoc analysis showed a ≥ 1-year RBC TI rate of 17.8% (21 patients) for patients in the imetelstat group versus 1.7% (1 patient) in the placebo group (p=0.002; Figure 7-7), and a median TI duration of over 2.5 years for the imetelstat group (132 vs 131 weeks for the single placebo patient).

Figure 7-7: MDS3001 – ≥ 1-Year RBC TI



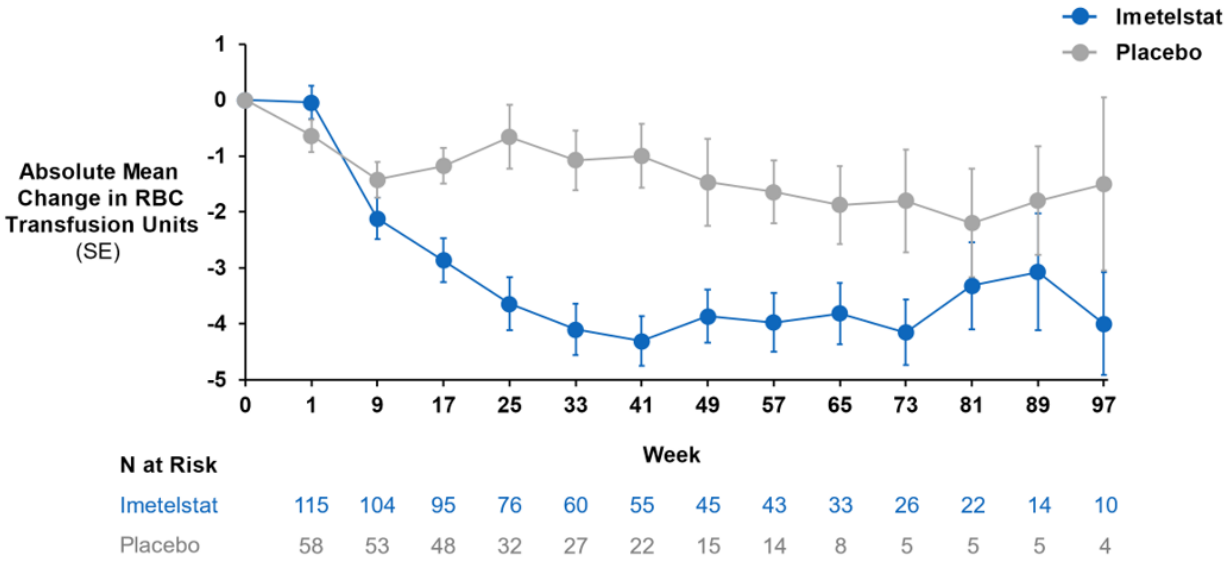
CI = confidence interval; RBC = red blood cell; TI = transfusion independence.

Given the target patient population for imetelstat has an expected median life expectancy of approximately 3 years, a treatment that provides continuous and durable RBC TI for extended periods of time offers an important benefit to patients who would otherwise be dependent on RBC transfusions. (See Figure 7-6; Section 7.2.3.1 for durability of RBC TI.)

7.2.3.6 Relative Change in RBC Transfusion Burden

Imetelstat-treated patients demonstrated a decrease in RBC transfusion burden. Mean absolute change from baseline in RBC transfusion burden during the best 8-week interval (Figure 7-8) for the imetelstat group was -4.3 units (range: -24 to +15) and for the placebo group -3.6 units (range: -11 to +2). Least squares mean absolute change in RBC units from prior transfusion burden for all patients was lower in the imetelstat group versus the placebo group, with the LS mean difference of -0.97 units (p = 0.042).

Figure 7-8: MDS3001 – RBC Transfusion Burden



RBC = red blood cells; SE = standard error.
p = 0.042
The point at a given week represents the absolute change in RBC transfusion units in the post-baseline 8-week interval starting at the given week from the prior transfusion burden (e.g., Week 1 means interval Week 1-9; Week 9 means interval Week 9-17). Prior RBC transfusion burden is defined as the maximum number of RBC units transfused over any consecutive 8 weeks prior to study entry.
P-value is between treatment arms based on a mixed model for repeated measures with change in transfusion reduction as dependent variable, and week, stratification factors, prior transfusion burden, and treatment arm as independent variables with autoregressive moving average (ARMA(1,1)) covariance structure.

7.2.3.7 Progression-free Survival and Time to AML

Additional secondary endpoints included progression-free survival (PFS), and time to AML.

- **Progression-free Survival**: As of the 05 January 2024 cutoff date, with a median (range) of 32.2 (1.4, 47.8) months of follow-up, the median estimated PFS has not been reached in either treatment group. The PFS HR was 0.85 (95% CI: 0.44, 1.64), which indicates an improvement compared to that observed for the primary analysis (0.96 [95% CI: 0.46, 2.04]). At time of the data cut off, 13/118 (11.0%) patients in the imetelstat group and 8/60 (13.3%) patients in the placebo group had reported disease progression to either higher risk MDS or AML.
- **Time to AML**: As of the 05 January 2024 cutoff date, the rate of progression to AML was low in both treatment arms (2/118 [1.7%] with imetelstat vs 2/60 [3.3]% with placebo). The updated HR of progression to AML for imetelstat vs. placebo was 0.45 (95% CI: 0.06, 3.23), which is lower than that observed for the primary analysis (0.86 [95% CI: 0.08, 9.46]), indicating an improvement in the risk estimate for progression to AML with additional follow-up.

7.2.4 Exploratory Endpoints

Exploratory endpoints included cytogenetic responses and PROs. The data cutoff date for Independent Review Committee (IRC)-assessed cytogenetic responses per IWG 2006 was 13 October 2023.

7.2.4.1 Cytogenetic Response

Cytogenetic response criteria, per modified IWG 2006 (Cheson, 2006), by IRC adjudication were assessed for all patients with both ≥ 1 baseline cytogenetic abnormality and ≥ 1 post-baseline bone marrow sample with central reviewer assessment (83/118 for imetelstat arm and 39/60 in the placebo arm).

Of the 22.0% (26/118) and 21.7% (13/60) patients with baseline cytogenetic abnormalities, the overall cytogenetic response rate (complete remission [CR] + PR) was 38.5% (10/26 patients) in the imetelstat group and 15.4% (2/13 patients) in the placebo group (% difference = 23.1% [95% CI: -12.51%, 47.44%]; p-value: 0.160). Complete cytogenetic response was 23.1% (6/26) vs 7.7% (1/13). Partial cytogenetic response was 15.4% (4/26) vs 7.7% (1/13) for imetelstat vs placebo, respectively. Of patients with a complete cytogenetic response, 2/6 (33.3%) vs 0 met the IWG 2023 criteria for CR. (See Appendix 11.4 for definition of response criteria.)

7.2.4.2 Patient Reported Outcome (PRO) Assessments

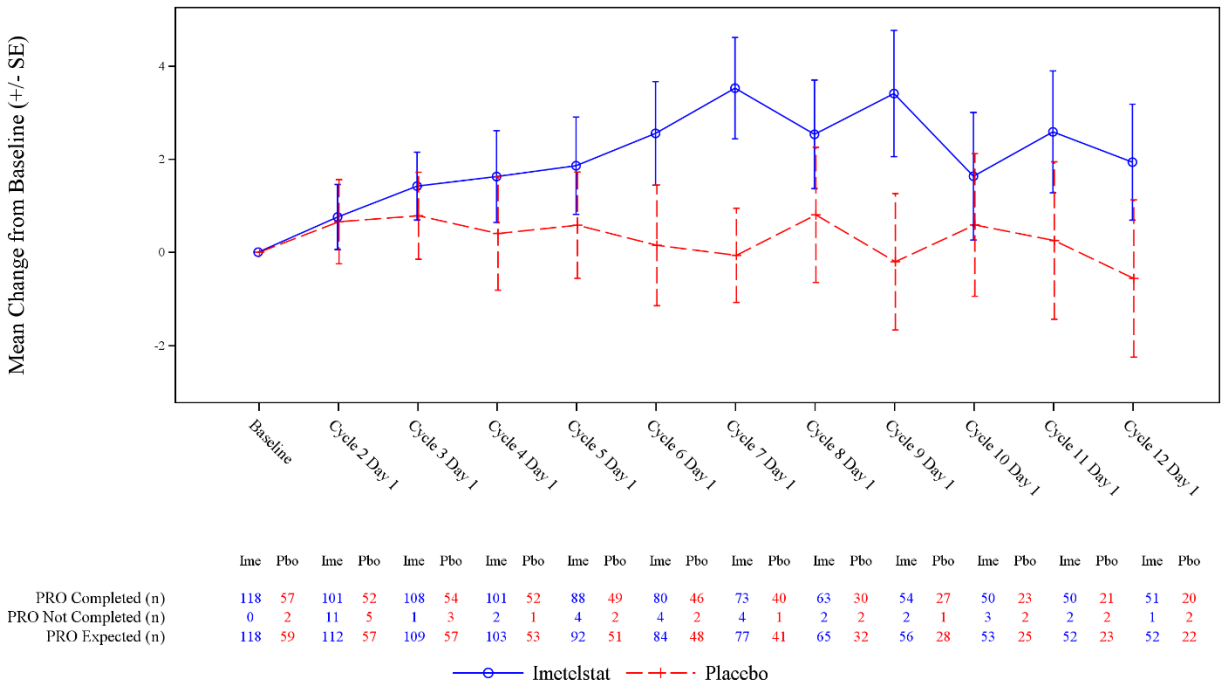
As described in Section 6.1.3, the Phase 3 study utilized multiple validated PRO measures to assess for differences in patient reported symptoms and QoL between imetelstat and placebo. For the main PRO objective, the FACIT-Fatigue score was utilized to assess the predefined hypothesis that while on treatment, patients treated with imetelstat are not more likely to experience a meaningful deterioration in fatigue than patients treated with placebo, regardless of transfusion-dependence status. Additionally, other instruments, including the FACT-An and Quality of Life in Myelodysplasia Scale (QUALMS) total score, assessed if achieving TI and/or reduction in transfusion burden was not accompanied by worsening of fatigue or negative impacts on other important measures of QoL for MDS patients. The PRO population, which includes all patients in the ITT Population who had FACIT-Fatigue data at baseline, included 118 patients in the imetelstat arm and 57 patients in the placebo arm, for a total of 175 patients.

The proportion of patients in the imetelstat group who experienced a sustained, meaningful deterioration in fatigue (defined as a decrease of ≥ 3 points on the FACIT Fatigue score for at least two consecutive non-missing cycles) is comparable to that of the placebo group 43.2% (51/118) in the imetelstat group and 45.6% (26/57) in the placebo group). These results were consistent with sensitivity and supplementary analyses.

This analysis supports the hypothesis that patients treated with imetelstat show no worsening in patient reported fatigue (in the context of receiving fewer transfusions) compared with placebo, in contrast to approved therapy for this target population (Bristol Myers Squibb, 2023a, 2023b). Additionally, the imetelstat group showed a consistent

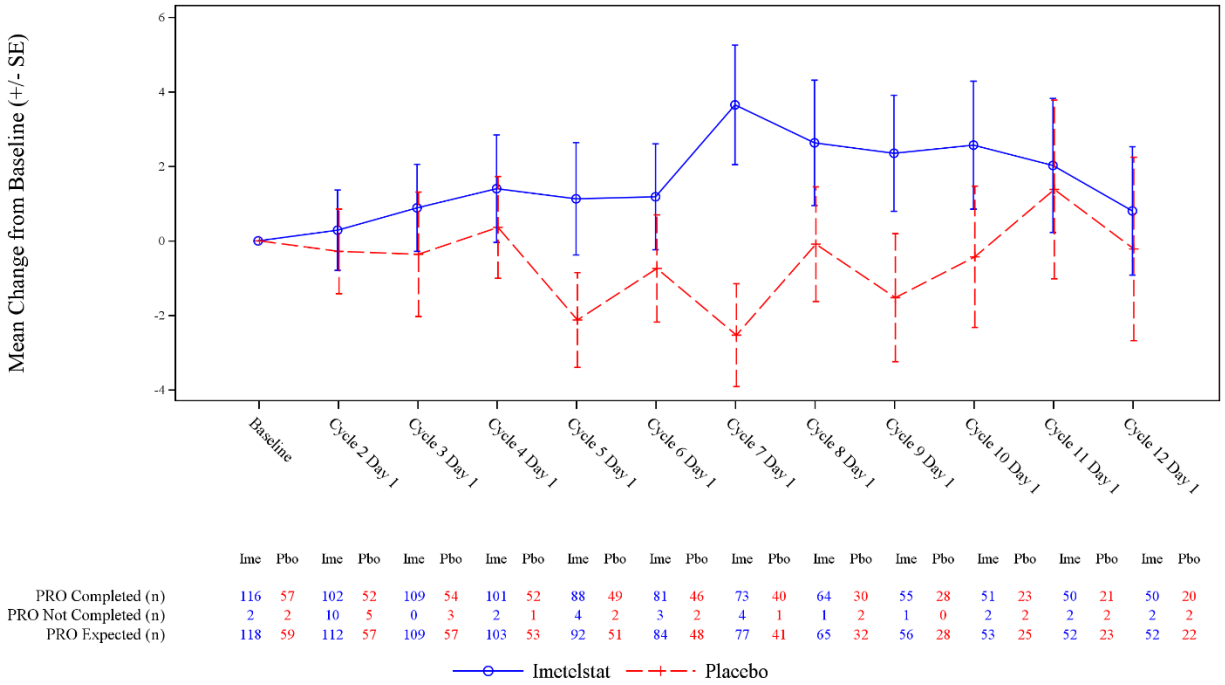
trend towards improvement in mean change from baseline in FACIT- Fatigue score at each cycle while the placebo group showed little change in either direction (improvement or worsening) (Figure 7-9).

Figure 7-9: MDS3001 - Plot of– Change FACIT-Fatigue Scale Change from Baseline at Each Cycle



The QUALMS total score provides an overall perspective on the experience of patients with MDS, beyond fatigue. The description of the QUALMS total score showed a similar pattern as the FACIT-Fatigue and FACT-An anemia score, with improvement over the course of the study in the imetelstat group and stability in the placebo group, suggesting that the QoL improvement trend observed in the imetelstat group extends beyond fatigue (Figure 7-10).

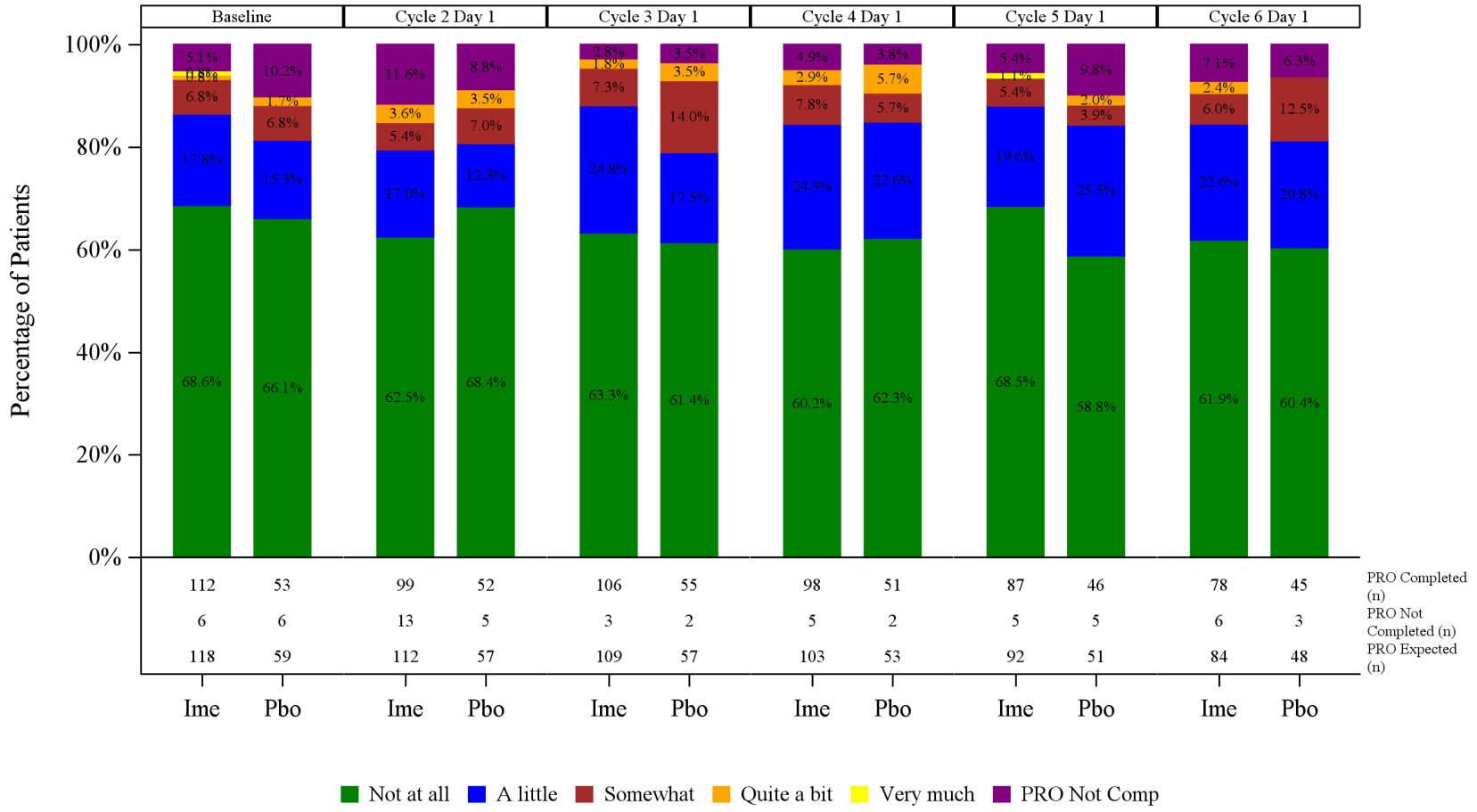
Figure 7-10: MDS3001 – QUALMS Total Score Change from Baseline at Each Cycle



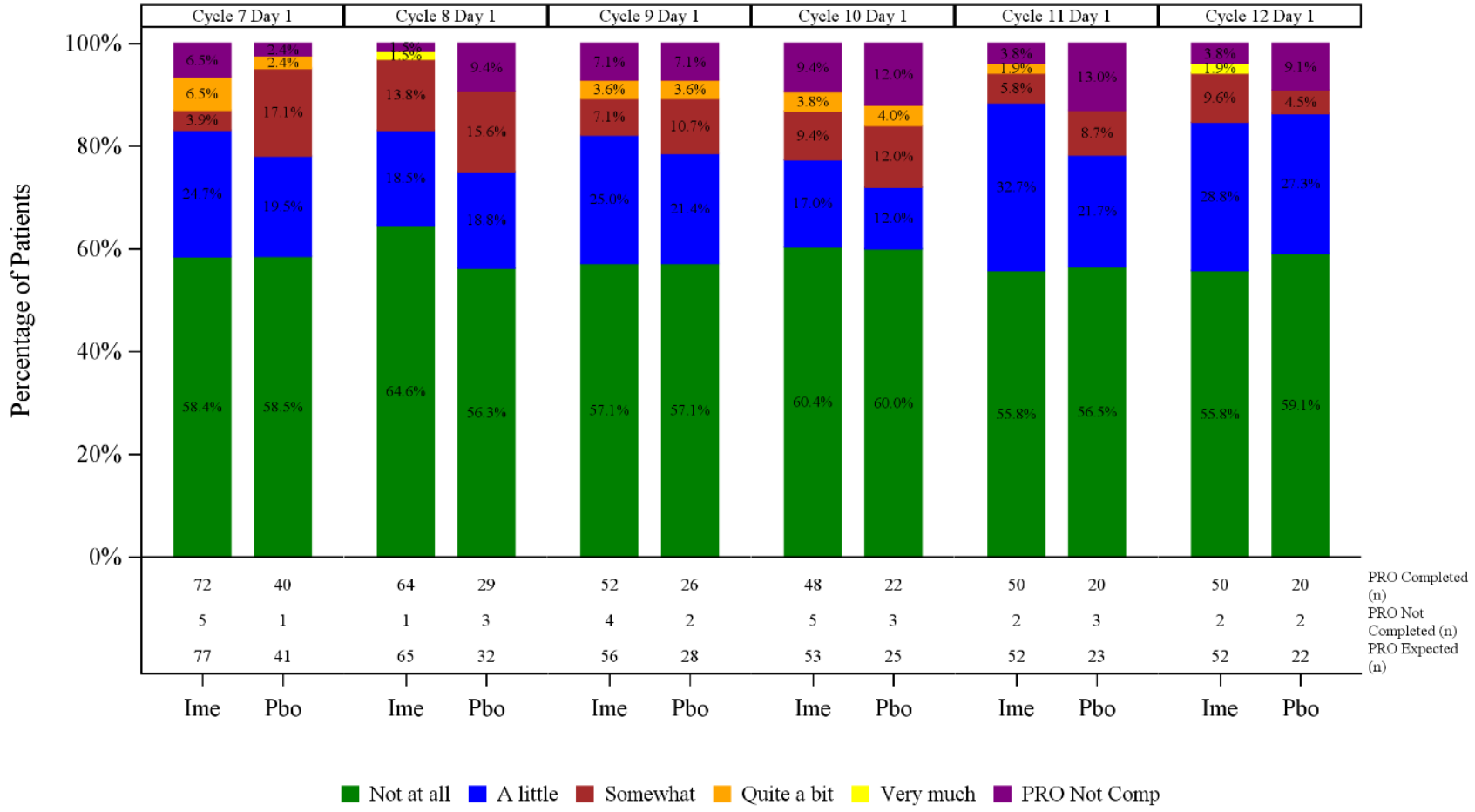
Furthermore, despite the increased frequency of Grade 3/4 neutropenia and thrombocytopenia with imetelstat, these events were short-lived and manageable, and patients reported no additional burden from side effects in the imetelstat arm compared to placebo based on FACT GP5 analysis (Figure 7-11).

Figure 7-11: MDS3001 - Bar plot of Distribution of Categorical Responses for FACT-An Item GP5 (I Am Bothered by Side Effects of Treatment) at Each Cycle

Part A: Cycle 1-Cycle 6



Part B: Cycle 7-Cycle 12



Note: The PRO Expected excludes patients who died, or discontinued from treatment at the visit, or randomized but not treated.
PRO Not Completed includes patients whose PRO assessment is expected but the response for the item is not available at the visit.
PRO Completed includes patients whose response for the item is available at the visit.

In summary, the PRO data demonstrate no worsening in patient reported fatigue and a consistent trend across PROs toward improvement of fatigue and other MDS symptoms. Importantly, patients experienced no additional burden from side effects in the setting of increased frequency of neutropenia and thrombocytopenia. Given the high unmet need in the target population, these PRO data support the overall benefit-risk of imetelstat, without worsening symptoms of anemia.

8 CLINICAL SAFETY

Summary

- Nearly all patients in the imetelstat (99.2%) and placebo (100%) groups had ≥ 1 AE
  - The most frequent AEs were thrombocytopenia (75.4% vs 10.2%) and neutropenia (73.7% vs 6.8%) for imetelstat vs placebo, respectively
- Grade 3/4 AEs were more common with imetelstat vs placebo (90.7% vs 47.5%)
  - Neutropenia (67.8% vs 3.4%) and thrombocytopenia (61.9% vs 8.5%) were the most common Grade 3/4 AEs; however, > 80% resolved to Grade ≤2 within 4 weeks for patients receiving imetelstat
  - The difference between imetelstat vs placebo for Grade 3/4 AEs decreased significantly when excluding neutropenia and thrombocytopenia (54.2% vs 39.0%)
- Incidence of SAEs was higher in the imetelstat group vs placebo (32.2% vs. 22.0%), and no SAE occurred in > 3 patients in either treatment group; one fatal AE occurred in each treatment group, neither was considered related to study drug
- Infections AEs were more common for imetelstat vs placebo (42.4% vs 33.9%); among patients with infection events, most experienced events no higher than Grade 1/2, and the rate of serious infection AEs was comparable between the treatment groups (11.9% in the imetelstat vs 13.6% in the placebo group)
- Bleeding AEs were more common for imetelstat vs placebo (21.2% vs 11.9%); among patients with bleeding events, most experienced events no higher than Grade 1/2, and few experienced serious bleeding AEs (2.5% in the imetelstat vs 1.7% in the placebo group)
- Low-grade headache was the only infusion-related reaction reported in > 1 patient, and there were no severe allergic reactions
- Hepatic AEs were more common for imetelstat vs placebo (28.8% vs 16.9%), and most laboratory abnormalities were elevations of AST (48.3% vs 22.0%) and ALP (44.9% vs 11.9%)
  - Most patients with hepatic AEs experienced events no higher than Grade 1/2, and few patients experienced serious hepatic AEs (0.8% in the imetelstat vs none in the placebo group)
  - There were no cases of severe hepatotoxicity or Hy's Law
- A total of 14.4% vs 0% of imetelstat vs placebo patients had an AE leading to discontinuation, and 49.2% vs 6.8% had a dose reduction; most discontinuations and reductions were driven by Grade 3/4 thrombocytopenia and neutropenia AEs
- While still immature, preliminary data indicate no detriment of imetelstat on OS: HR = 0.98 (95% CI: 0.53, 1.82)

8.1 Introduction

The safety profile of imetelstat has been evaluated in 15 sponsor-led clinical studies (spanning Phase 1 to Phase 3) in which a total of more than 750 patients have been

exposed to imetelstat treatment alone or in combination with other anti-cancer agents in patients with various solid tumors and hematologic malignancies.

The safety analysis focuses primarily on safety data from the randomized, placebo-controlled pivotal Phase 3 study MDS3001.

The well characterized safety profile of imetelstat identified AEs of interest (AEIs), which were closely monitored and included the most commonly reported events of neutropenia and thrombocytopenia with the associated potential clinical risks of infections and bleeding events, infusion-related reactions (IRRs), and hepatic disorders.

8.2 Summary of MDS3001 Phase 2 Safety

In the open label Phase 2 portion of MDS3001, 57 patients with LR MDS were treated for a cumulative 65.3 patient-years. The median (range) duration of treatment for the target population (i.e., patients who matched criteria for Phase 3; N= 38) was 37.1 (0.1 to 179.9) weeks. For all patients in Phase 2, median (range) duration of treatment was 32.3 (0.1 to 260.1) weeks. Patients in the target and overall populations received a median of 9 and 8 cycles of treatment, respectively, and 42.1% and 36.8% of patients in the target and overall populations received > 13 cycles.

Safety findings from the open label Phase 2 part of study MDS3001 were generally similar to those in the controlled Phase 3 portion (Section 8.3). The most commonly reported AEs were neutropenia (66.7%) and thrombocytopenia (61.4%). Similarly, the most common Grade ≥ 3 AEs were neutropenia (59.6%) and thrombocytopenia (54.4%). Five patients (8.8%) had fatal AEs within 30 days of the last dose of imetelstat. However, none of these AEs were considered by the investigator to be related to study drug. Approximately half of patients had an AE leading to dose reduction, with most dose reductions due to neutropenia and thrombocytopenia. Sixteen (28.1%) patients discontinued study treatment due to an AE.

8.3 Phase 3 Safety – MDS3001

8.3.1 Treatment Exposure

A total of 118 patients with LR MDS were treated with imetelstat for a cumulative 105.7 patient-years in the pivotal Phase 3 portion of MDS3001. The median treatment duration was 34 weeks for the imetelstat group and 28 weeks in the placebo group (Table 8-1). Treatment cycles were balanced across groups, with a median of 8 cycles received. Overall, patients receiving imetelstat remained on treatment longer than placebo. A total of 40.7% of imetelstat-treated patients received ≥ 13 cycles vs 28.8% on placebo.

One patient randomized to receive placebo treatment discontinued treatment before Cycle 1 dosing; therefore, a total of 59 patients were considered for safety analysis in the placebo group.

Table 8-1: MDS3001 – Safety Exposures (Safety Population)

Exposure:	Imetelstat N = 118	Placebo N = 59
Treatment duration (weeks), median (min-max)	33.9 (0.1-141.1)	28.3 (0.1-116.1)
Treatment cycles received, median (min-max)	8.0 (1-34)	8.0 (1-30)
1 – 3 cycles	15 (12.7%)	6 (10.2%)
4 – 6 cycles	27 (22.9%)	12 (20.3%)
7 – 12 cycles	28 (23.7%)	24 (40.7%)
≥ 13 cycles	48 (40.7%)	17 (28.8%)

8.3.2 Adverse Events

8.3.2.1 Overall Summary of Safety

Overall, almost all patients in both treatment groups experienced a treatment-emergent AE (Table 8-2). Patient incidence of Grade 3/4 events and SAEs was higher in the imetelstat group compared to placebo. One death occurred in each treatment group during study treatment. During the study, a higher proportion of patients in the imetelstat group had an AE leading to discontinuation, infusion interruption, dose reduction or cycle delay compared to placebo.

Table 8-2: MDS3001 – Overview of Adverse Events (Safety Population)

	Imetelstat N = 118	Placebo N = 59
Any AE	117 (99.2%)	59 (100.0%)
Grade 3 / 4	107 (90.7%)	28 (47.5%)
SAE	38 (32.2%)	13 (22.0%)
Death (during treatment)	1 (0.8%)	1 (1.7%)
AE leading to infusion interruption	7 (5.9%)	0
AE leading to dose reduction or cycle delays	83 (70.3%)	14 (23.7%)
AE leading to discontinuation	17 (14.4%)	0

AE = adverse event; SAE = serious adverse event.

8.3.2.2 Common Adverse Events

Adverse events reported in more than 10% of patients in either arm are summarized in Table 8-3. Thrombocytopenia (Section 8.3.2.9.3.1) and neutropenia (Section 8.3.2.9.2.1) had the highest patient incidences in the imetelstat group.

Table 8-3: MDS3001 – Adverse Events Occurring in ≥ 10% of Patients in Any Study Group (Safety Population)

Preferred Term	Imetelstat N = 118	Placebo N = 59
Any AE	117 (99.2%)	59 (100.0%)
Thrombocytopenia	89 (75.4%)	6 (10.2%)
Neutropenia	87 (73.7%)	4 (6.8%)
Anemia	24 (20.3%)	6 (10.2%)
Asthenia	22 (18.6%)	8 (13.6%)
COVID-19	18 (15.3%)	4 (6.8%)
Headache	15 (12.7%)	3 (5.1%)
ALT increased	14 (11.9%)	4 (6.8%)
Diarrhea	14 (11.9%)	7 (11.9%)
Oedema peripheral	13 (11.0%)	8 (13.6%)
Leukopenia	12 (10.2%)	1 (1.7%)
Hyperbilirubinemia	11 (9.3%)	6 (10.2%)
Constipation	9 (7.6%)	7 (11.9%)
Pyrexia	9 (7.6%)	7 (11.9%)

8.3.2.3 Adverse Events by Severity

Treatment-emergent Grade 3/4 AEs were reported in 107 (90.7%) patients in the imetelstat group and 28 (47.5%) in the placebo group. The most frequently reported Grade 3/4 AEs in imetelstat-treated patients were neutropenia and thrombocytopenia (Table 11-5). Despite higher patient incidence of Grade 3/4 neutropenia and thrombocytopenia, severe (Grade 3+) events of infections or bleedings occurred at a similar patient incidence between imetelstat and placebo arms (10.2% vs. 13.6% and 2.5% vs. 1.7%, respectively). The short duration of Grade 3/4 thrombocytopenia and neutropenia in imetelstat-treated patients (median duration < 2 weeks and > 80% recovering to Grade ≤ 2 within 4 weeks), may account for the lack of severe clinical consequences.

When excluding neutropenia and thrombocytopenia, the overall difference in patient incidence for Grade 3/4 AEs decreased significantly (54.2% vs 39.0%, respectively), and event incidence was generally balanced between arms with the exception of anemia (19.5% vs. 6.8%) and leukopenia (7.6% vs. 0%). Grade 3/4 leukopenia was explained by the high incidence of Grade 3/4 neutropenia. Anemia was present at baseline as all patients were TD at study enrollment (meaning they had Grade 2 or 3 anemia at baseline) and transient decreases in Hgb were observed primarily early in the study treatment period as patients were being monitored for response. Despite the higher rate of anemia reported AEs on imetelstat, median Hgb levels increased overall for patients treated with imetelstat (see Section 7.2.3.2 for additional details).

8.3.2.4 Serious Adverse Events

All reported SAEs by preferred terms are provided in Table 11-15 in Appendix 11.6.2. Treatment-emergent SAEs were reported in 38 (32.2%) patients in the imetelstat group and 13 (22.0%) patients in the placebo group. The 2 most common system organ classes (SOC) with SAEs were SOC Infections and infestations (14 [11.9%] patients in the

imetelstat group and 8 [13.6%] patients in the placebo group) and SOC Cardiac disorders (7 [5.9%] patients in the imetelstat group and 3 [5.1%] patients in the placebo group. SAE events in all SOCs were balanced between arms.

SAE events occurred with similar patient incidence for AEIs of infections, bleeding events, hepatic events, and IRRs. No SAEs were reported for AEIs of neutropenia and thrombocytopenia. Most SAEs in both arms were reported in single patients, and there was no SAE by preferred term reported in more than 3 patients in either group (see Table 11-15 for additional details).

8.3.2.5 Adverse Events Leading to Infusion Interruption

Adverse events leading to infusion interruption were reported in 7 (5.9%) patients in the imetelstat group, including 2 patients with headache and 2 patients with infusion site-related issues (Table 11-6). All other events were reported for 1 patient each. Events leading to infusion interruption were Grade 1/2, except for one patient with medical history of hypertension who had an infusion interruption due to an SAE of Grade 3 hypertensive crisis that was considered an infusion-related reaction. (See Section 8.3.2.9.4 for details on IRRs.) This patient did not experience infusion reactions during subsequent cycles. No patients in the placebo group had an AE that led to infusion interruption.

8.3.2.6 Adverse Events Leading to Cycle Delays or Dose Reductions

Most AEs leading to cycle delays and dose reductions in the imetelstat group were due to neutropenia or thrombocytopenia (Table 8-4). The median time to cycle delays was 7.3 weeks in the imetelstat group and 12.1 weeks in the placebo group, and the median time to dose reductions was 13.9 weeks in the imetelstat group and 20.1 weeks in the placebo group (Table 8-6). A total of 68.6% of imetelstat-treated patients had an AE leading to cycle delays, and 49.2% had an AE leading to dose reductions (Table 8-5), as specified per protocol. Despite the dose reductions to 80% of the previous dose, the overall mean dose intensity was greater than 90% in the imetelstat group, and even higher in the period of time leading up to achievement of ≥ 8-week TI in responders (Table 8-6) (discussed further in Section 5.7). Although the majority of patients had a cycle delay or dose reduction due to AE, treatment discontinuation due to AEs occurred for 14.4% of patients treated with imetelstat (Table 8-7, Section 8.3.2.7), suggesting the protocol-mandated cycle delays and dose reductions allow for recovery from cytopenias, enabling patients to remain on treatment longer and maintain response after having achieved the start of RBC TI while on the recommended dose of 7.1 mg/kg (see Section 5.7).

Table 8-4: MDS3001 – Adverse Events Leading to Cycle Delays or Dose Reductions (Safety Population)

Preferred Term:	Imetelstat N = 118	Placebo N = 59
Any AE leading to cycle delay or dose reduction	83 (70.3%)	14 (23.7%)
Neutropenia	61 (51.7%)	1 (1.7%)
Thrombocytopenia	56 (47.5%)	1 (1.7%)
COVID-19	9 (7.6%)	2 (3.4%)
Leukopenia	4 (3.4%)	0
Pyrexia	3 (2.5%)	0
Urinary tract infection	3 (2.5%)	0
Anemia	2 (1.7%)	1 (1.7%)
Aspartate aminotransferase increased	2 (1.7%)	1 (1.7%)
Epistaxis	2 (1.7%)	0
Fatigue	2 (1.7%)	1 (1.7%)
Renal impairment	2 (1.7%)	0
Alanine aminotransferase increased	1 (0.8%)	2 (3.4%)
Diarrhea	0	2 (3.4%)
COVID-19 pneumonia	0	2 (3.4%)
Gamma-glutamyltransferase increased	0	2 (3.4%)
Gastroenteritis	0	2 (3.4%)

Table 8-5: MDS3001 – Overview of Adverse Events Leading to Cycle Delay or Dose Reduction (Safety Population)

AE Leading to Cycle Delay or Reduction:	Imetelstat N = 118	Placebo N = 59
Any AE leading to cycle delay or dose reduction	83 (70.3%)	14 (23.7%)
Cycle delay	81 (68.6%)	14 (23.7%)
Dose reduction	58 (49.2%)	4 (6.8%)
Treatment discontinuation	14.4%	0

Table 8-6: MDS3001 – Overview of Time to Cycle Delay or Dose Reduction and Dose Intensity (Safety Population)

Parameter of Cycle Delay or Reduction:	Imetelstat N = 118	Placebo N = 59
Median time to cycle delay or dose reduction, weeks	7.4	12.1
Dose reduction, weeks	13.9	20.1
Cycle delay, weeks	7.3	12.1
Dose intensity in all patients, mean	90.5%	98.3%
≥ 8 week TI Responders:	**N = 47**	**N = 9**
Dose intensity up to achievement of ≥ 8-week TI	95.2%	99.0%

TI = transfusion independence

8.3.2.7 Adverse Events Leading to Discontinuation

A total of 14.4% of patients in the imetelstat group discontinued treatment due to an AE, while no patients discontinued in the placebo group due to AEs (Table 8-7). The most common AEs leading to discontinuation in the imetelstat group were neutropenia (5.1% of patients) and thrombocytopenia (3.4% of patients). The remaining AEs leading to discontinuation in the imetelstat group each occurred in only 1 patient.

Table 8-7: MDS3001 – Adverse Events Leading to Discontinuation (Safety Population)

Preferred Term:	Imetelstat N = 118	Placebo N = 59
Any AE leading to discontinuation	17 (14.4%)	0
Neutropenia	6 (5.1%)	0
Thrombocytopenia	4 (3.4%)	0
Anemia	1 (0.8%)	0
Asthenia	1 (0.8%)	0
Atrial fibrillation	1 (0.8%)	0
Cardiac failure	1 (0.8%)	0
Disorientation	1 (0.8%)	0
Dyspnea	1 (0.8%)	0
Gastrointestinal hemorrhage	1 (0.8%)	0
Joint dislocation	1 (0.8%)	0
Lung neoplasm malignancy	1 (0.8%)	0
Myelofibrosis	1 (0.8%)	0
Pruritus	1 (0.8%)	0
Renal abscess	1 (0.8%)	0
Sepsis	1 (0.8%)	0

8.3.2.8 Deaths

The proportion of deaths in the study was similar between the two treatment groups (29.7% and 25.4%, respectively, based on the most recent analysis). Treatment-emergent deaths occurred in 1 patient in each arm (sepsis for imetelstat and aortic stenosis for placebo) at primary analysis (clinical cutoff [CCO] 13 Oct 2022), both reported as not related to study drug. One additional death occurred in each arm at the updated analysis (CCO 05 Jan 2024), myocardial infarction (not related) for imetelstat and pneumonia (related) for placebo. Most deaths during the study occurred in the post-treatment follow-up period, with the majority of deaths occurring ≥ 90 days from the last treatment dose (Table 8-8). All deaths in the post-treatment follow-up period were considered unrelated to study treatment and were confounded by disease progression, subsequent therapies, and comorbidities.

Based on the most recent available data (CCO 05 Jan 2024), after a median follow up of 31 months, the HR for survival was 0.98 (95% CI: 0.53, 1.82) for imetelstat compared to placebo, with a total of 50 events (Table 8-8). At the time of the primary analysis (CCO 13 Oct 2022), the HR was 1.07 (95% CI: 0.46, 2.48), with a total of 27 events and a median follow-up of 18 months. Although the precision of the HR estimates improved, the

survival data remain immature. However, the trend indicates no detriment of imetelstat on OS.

A list of patient deaths due to AEs during treatment (i.e., ≤ 30 days after last dose, or > 30 days if death due to a related AE) is provided in Table 8-9.

Table 8-8: MDS3001 – Deaths (Safety Population)

Parameter:	Primary Analysis[a] (CCO 13 Oct 2022)		Updated Analysis[b] (CCO 05 Jan 2024)	
	Imetelstat N = 118	**Placebo N = 59**	**Imetelstat N = 118**	**Placebo N = 59**
Overall deaths on study	19 (16.1%)	8 (13.6%)	35 (29.7%)	15 (25.4%)
Deaths during treatment (≤ 30 days after last dose or > 30 days if death due to related AE)	1 (0.8%)	1 (2%)	2 (1.7%)	2 (3.4%)
Grade 5 AE	1 (0.8%)	1 (2%)	2 (1.7%)	2 (3.4%)
Deaths in post-treatment follow-up (> 30 days after last dose)[c]	18 (15.3%)	7 (11.9%)	33 (28.0%)	13 (22.0%)
AEs	6 (5.1%)	2 (3.4%)	7 (5.9%)	2 (3.4%)
Progressive disease	1 (0.8%)	3 (5.1%)	4 (3.5%)	4 (6.8%)
Other	11 (9.3%)	2 (3.4%)	22 (18.6%)	7 (11.9%)
Days since last dose until death:	**N = 19**	**N = 8**	**N = 35**	**N = 15**
1–30 days	1 (5.3%)	1 (12.5%)	2 (5.7%)	1 (6.7%)
31–60 days	3 (15.8%)	2 (25.0%)	3 (8.6%)	3 (20.0%)
61–90 days	1 (5.3%)	0	2 (5.7%)	0
91–180 days	5 (26.3%)	0	5 (14.3%)	0
181 days–1 year	6 (31.6%)	4 (50.0%)	11 (31.4%)	5 (33.3%)
> 1 year	3 (15.8%)	1 (12.5%)	12 (34.3%)	6 (40.0%)
Had Subsequent Anti-cancer Therapy	7 (36.8%)	4 (50.0%)	17 (48.6%)	8 (53.3%)
Median OS, months (95% CI)	NE (NE-NE)	NE (NE-NE)	40.4 (37.1–NE)	NE (32.2-NE)
HR (95% CI)	1.07 (0.46, 2.48)		0.98 (0.53, 1.82)	

CCO=clinical cutoff; CI=confidence interval; OS=overall survival; HR=hazard ratio, NE=not estimable.

[a.] As of 13 October 2022, MDS3001 data cutoff date of the primary analysis for the MDS3001 study.

[b.] As of 05 January 2024, MDS3001 data cutoff date for the final analysis for the MDS3001 study.

[c.] Deaths in post-treatment follow-up = overall deaths on study minus deaths during treatment.

Table 8-9: MDS3001 – List of Deaths due to Adverse Events During Treatment (Safety Population)

Treatment	Age/Sex/Race	Study Day of Death	Days Since Last Dose	Cause of Death	Had Subsequent Anti-Cancer Therapy?	Causality
Imetelstat	73/F/White	685	6	AE: Myocardial infarction	No	Not related
Imetelstat	72/M/White	649	30	AE: Sepsis	No	Not related
Placebo	81/M/White	22	21	AE: Aortic stenosis	No	Not related
Placebo	71/F/White	482	55	AE: Pneumonia	No	Related

Death during Treatment include death events that occur after the first dose of study drug, through the treatment phase, and for 30 days following the last dose of study drug or until subsequent anti-cancer therapy if earlier, or any death that is considered study drug-related regardless of the date.

8.3.2.9 Adverse Events of Interest (AEIs)

8.3.2.9.1 Overview of AEIs

Adverse events of interest (AEIs) as defined in the protocol for study MDS3001 included liver function abnormalities based on laboratory data and hepatic AEs. In addition, other selected AEIs, which were not specifically defined in the protocol, were identified based on the safety profile observed to date and were closely monitored throughout the study. These other AEIs included neutropenia, thrombocytopenia, infections, bleeding events, and infusion-related reaction events.

An overview of all AEIs by any grade and by Grade 3/4 is provided in Table 8-10. Thrombocytopenia and neutropenia were the most common AEIs in the imetelstat group. Infections, hepatic events, bleeding events, and IRRs by any grade were more frequently reported in the imetelstat group, but with the exception of thrombocytopenia and neutropenia, Grade 3/4 AEI events were balanced between the treatment groups.

Table 8-10: MDS3001 – Overview of AEIs (Safety Population)

AE of Interest:	Imetelstat N = 118			Placebo N = 59		
	Any Grade	Grade 3 / 4	SAE	Any Grade	Grade 3 / 4	SAE
Thrombocytopenia	89 (75.4%)	73 (61.9%)	0	6 (10.2%)	5 (8.5%)	0
Neutropenia	87 (73.7%)	80 (67.8%)	0	4 (6.8%)	2 (3.4%)	0
Infections	50 (42.4%)	12 (10.2%)	14 (11.9%)	20 (33.9%)	8 (13.6%)	8 (13.6%)
Hepatic AE	34 (28.8%)	8 (6.8%)	1 (0.8%)	10 (16.8%)	3 (5.1%)	0
Bleeding events	25 (21.2%)	3 (2.5%)	3 (2.5%)	7 (11.9%)	1 (1.7%)	1 (1.7%)
Infusion-related reactions	9 (7.6%)	2 (1.7%)	1 (0.8%)	2 (3.4%)	0	0

AE = adverse event; AEI = adverse event of interest; SAE = serious adverse event.

8.3.2.9.2 Neutropenia and Infections

8.3.2.9.2.1 Neutropenia

Neutropenia was common with imetelstat treatment and occurred more frequently during the first few cycles. In the imetelstat group, AEs of neutropenia were reported in 73.7% of patients, and 67.8% of patients had Grade 3/4 neutropenia. In the placebo group, neutropenia was reported in 6.8% of patients, including 2 (3.4%) patients with Grade 3/4 neutropenia (Table 11-7). These neutropenia events were manageable with dose delays

(in 50.8% of patients) and dose reductions (in 33.1% of patients) as well as growth factor support (in 34.7% of patients) when clinically indicated. Six (5.1%) patients discontinued imetelstat due to neutropenia in the imetelstat group. These events were generally reversible. Most (> 80%) of Grade 3/4 neutropenia events resolved to Grade ≤ 2, and > 90% of Grade 4 events resolved to Grade ≤ 3, within 4 weeks. The median time to onset of Grade 3/4 neutropenia was 4.4 weeks, and median duration was 1.9 weeks. An analysis of total time in Grade 3/4 neutropenia showed a median (interquartile range [IQR]) of 2.6 (0.0, 6.9) weeks, including a median (IQR) of 2.1 (0.0, 6.6) weeks for ≥ 8-week TI responders.

There were no Grade 5 or SAE events of neutropenia reported in either treatment group.

8.3.2.9.2.2 Infections

MDS patients have a higher risk for infections due to dysfunctional hematopoiesis. Infections represent the most frequent complications and are the main cause of mortality and morbidity in MDS patients (Poloni, 2021; Leone, 2018).

Infections of any grade occurred in 42.4% of patients in the imetelstat group and 33.9% in placebo, and most were Grade 1 or 2 in severity (Table 8-11). The incidence rate of SAEs (11.9% vs 13.6%, respectively) and Grade 3/4 events (10.2% and 13.6%) was similar between the imetelstat and placebo groups. COVID-19 was the most frequently reported infection in either group and was the only infection event that occurred with a distinct difference between the treatment groups (15.3% [18 patients] with imetelstat versus 6.8% [4 patients] with placebo). However, none of these COVID-19 events was reported as a SAE or with severity Grade 3+, and none was reported as related to imetelstat. Other infection events had similar distribution between groups, and most of them occurred in a single patient each. Analysis of the events of sepsis showed risk factors and alternative explanations, with no definitive evidence for a relationship to imetelstat. A more detailed analysis of infections in patients with neutropenia is provided in Appendix 11.6.3.

The incidence rate was similar between treatment groups for Grade 3/4 infections that occurred within ±7 days of Grade 3/4 neutropenia (2.5% vs 1.7%, respectively). Febrile neutropenia was reported in 1 (0.8%) patient in the imetelstat group and none in the placebo group. All but 1 of the Grade 3/4 AEs were also SAEs. (Additional details on infections are summarized in the appendix in Table 11-8.)

Table 8-11: MDS3001 – Infections by Preferred Term Reported in ≥ 2% of Patients in Either Treatment Group or Reported as Serious in Any Patient (Safety Population)

	Imetelstat (N=118)			Placebo (N=59)		
Preferred Term:	**Any Grade**	**Grade 3/4**	**SAE**	**Any Grade**	**Grade 3/4**	**SAE**
Any AE infection	50 (42.4%)	12 (10.2%)	14 (11.9%)	20 (33.9%)	8 (13.6%)	8 (13.6%)
COVID-19	18 (15.3%)	0	0	4 (6.8%)	0	0
Urinary tract infection	7 (5.9%)	2 (1.7%)	2 (1.7%)	2 (3.4%)	0	0
Pneumonia	4 (3.4%)	3 (2.5%)	3 (2.5%)	2 (3.4%)	1 (1.7%)	1 (1.7%)

Preferred Term:	Imetelstat (N=118)			Placebo (N=59)		
	Any Grade	Grade 3/4	SAE	Any Grade	Grade 3/4	SAE
Gastroenteritis	3 (2.5%)	0	0	2 (3.4%)	1 (1.7%)	1 (1.7%)
Oral herpes	3 (2.5%)	0	0	0	0	0
COVID-19 pneumonia	2 (1.7%)	2 (1.7%)	2 (1.7%)	3 (5.1%)	3 (5.1%)	3 (5.1%)
Erysipelas	2 (1.7%)	0	1 (0.8%)	0	0	0
Sepsis*	2 (1.7%)	1 (0.8%)	2 (1.7%)	0	0	0
Nasopharyngitis	1 (0.8%)	0	0	2 (3.4%)	0	0
Abscess limb	0	0	0	2 (3.4%)	2 (3.4%)	2 (3.4%)
Clostridium difficile infection	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Enterococcal sepsis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Escherichia sepsis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Gastroenteritis clostridial	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Infection	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Neutropenic sepsis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Pneumonia bacterial	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Pseudomembranous colitis	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Arthritis bacterial	0	0	0	1 (1.7%)	1 (1.7%)	1 (1.7%)
Listeriosis	0	0	0	1 (1.7%)	1 (1.7%)	1 (1.7%)

* One patient in the imetelstat group had Grade 5 sepsis.

8.3.2.9.2.3 Conclusions on Neutropenia and Infections

In summary, based on the totality of data, no increased risk for severe infection events has been seen in patients treated with imetelstat as compared to placebo. The incidence rate of SAEs or Grade 3/4 infection events was similar between the treatment groups. Furthermore, the incidence rate was similar between treatment groups for Grade 3/4 infections that occurred within ±7 days of Grade 3/4 neutropenia. Most events were minor Grade 1/2 infections, and most were reported as not related to study drug. Sepsis events occurred in context of established risk factors and comorbidities, and a relationship to imetelstat cannot currently be determined. These results were consistent over time, as demonstrated by an additional 7 months of follow-up data that have been collected (see Appendix 11.6.4 for details). These risks can be addressed adequately in the labeling, and Geron's proposed label includes information and recommendations for the management of neutropenia and potential risk of infections.

8.3.2.9.3 Thrombocytopenia and Bleeding Events

8.3.2.9.3.1 Thrombocytopenia

Thrombocytopenia was common with imetelstat treatment and occurred more frequently during the first few cycles. In the imetelstat group, AEs of thrombocytopenia occurred in 75.4% of patients, and 61.9% of patients had Grade 3/4 thrombocytopenia (Table 11-8). In the placebo group, thrombocytopenia AEs were reported in 10.2% of patients, including 8.5% of patients with Grade 3/4 thrombocytopenia. There were no Grade 5 events of thrombocytopenia and no SAEs of thrombocytopenia reported in either treatment group.

The median time to onset of Grade 3/4 thrombocytopenia in the imetelstat group was 6 weeks. These events were generally reversible. Most (86.3%) of Grade 3/4

thrombocytopenia events resolved to Grade ≤ 2, and > 85% of Grade 4 events resolved to Grade ≤ 3, within 4 weeks. The median time to onset of Grade 3/4 thrombocytopenia was 6 weeks, and median duration was 1.4 weeks. An analysis of total time in Grade 3/4 thrombocytopenia showed a median (IQR) of 2.0 (0.0, 5.1) weeks for the imetelstat arm, including a median (IQR) of 1.0 (0.0, 5.3) week for ≥ 8-week TI responders.

Thrombocytopenia was managed by cycle delays (in 46.6% of patients) and dose reduction (in 22.9% of patients). Four (3.4%) patients discontinued imetelstat treatment due to thrombocytopenia.

8.3.2.9.3.2 Bleeding Events

MDS patients have a higher risk for bleeding events, with thrombocytopenia reported in 45% of patients at diagnosis, including 14% of patients with moderate to severe thrombocytopenia (Cheok, 2019).

Overall, the incidence of bleeding events was 21.2% in the imetelstat group and 11.9% in the placebo group (Table 8-12). The incidence rate of SAEs (1.7% in both groups) and Grade 3/4 events (2.5% and 1.7%, respectively) was similar between the imetelstat and placebo groups. The only bleeding events that occurred with a distinct difference between arms were epistaxis (5.9% [7 patients] with imetelstat versus no patients with placebo) and hematoma (5.1% [6 patients] with imetelstat versus no patient with placebo). None of these events were reported as an SAE or with severity Grade 3+, and only 1 event of epistaxis was reported as related to imetelstat. Other bleeding events had similar distribution between groups and most of them occurred in single patients. Most bleeding events were Grade 1/2, and no Grade 3/4 bleeding events occurred within 7 days before start or after resolution of a laboratory result of Grade 3/4 decreased platelets.

Additional details on bleeding events are summarized in the appendix in Table 11-10, and a more detailed analysis and discussion of bleeding events in patients with thrombocytopenia is presented in Appendix 11.6.3.

Table 8-12: MDS3001 – Bleeding Events by Preferred Term (Safety Population)

	Imetelstat (N=118)			Placebo (N=59)		
Preferred Term:	**Any Grade**	**Grade 3/4**	**SAE**	**Any Grade**	**Grade 3/4**	**SAE**
Any AE Hemorrhage	25 (21.2%)	3 (2.5%)	3 (2.5%)	7 (11.9%)	1 (1.7%)	1 (1.7%)
Epistaxis	7 (5.9%)	0	0	0	0	0
Haematoma	6 (5.1%)	0	0	0	0	0
Ecchymosis	2 (1.7%)	0	0	1 (1.7%)	0	0
Gastrointestinal haemorrhage	2 (1.7%)	1 (0.8%)	1 (0.8%)	0	0	0
Haematuria	2 (1.7%)	1 (0.8%)	1 (0.8%)	0	0	0
Haemorrhoidal haemorrhage	2 (1.7%)	0	0	0	0	0
Contusion	1 (0.8%)	0	0	3 (5.1%)	0	0
Gingival bleeding	1 (0.8%)	0	0	0	0	0
International normalised ratio increased	1 (0.8%)	0	0	0	0	0
Oesophageal varices haemorrhage	1 (0.8%)	1 (0.8%)	1 (0.8%)	0	0	0
Prothrombin time prolonged	1 (0.8%)	0	0	0	0	0
Puncture site haemorrhage	1 (0.8%)	0	0	0	0	0
Melaena	0	0	0	1 (1.7%)	0	0

Preferred Term:	Imetelstat (N=118)			Placebo (N=59)		
	Any Grade	Grade 3/4	SAE	Any Grade	Grade 3/4	SAE
Retinal haemorrhage	0	0	0	1 (1.7%)	0	0
Small intestinal haemorrhage	0	0	0	1 (1.7%)	1 (1.7%)	1 (1.7%)

8.3.2.9.3.3 Conclusions on Thrombocytopenia and Bleeding Events

Overall, and despite a higher incidence of thrombocytopenia with imetelstat, the totality of data showed no increased risk for severe bleeding events in patients treated with imetelstat as compared to placebo. The incidence rate of SAEs or Grade 3/4 bleeding events was similar between groups and there were no Grade 3/4 bleeding events within ±7 days of Grade 3/4 thrombocytopenia in either group. Most events were minor Grade 1/2 bleeding events, and most were reported as not related to study drug. These results were consistent over time, as demonstrated by an additional 7 months of follow-up data that have been collected (see Appendix 11.6.6 for additional details).

These risks can be addressed adequately in the labeling, and Geron's proposed label includes information and recommendations for the management of thrombocytopenia and potential risk of bleeding events.

8.3.2.9.4 Infusion-Related Reactions

The incidence of IRRs was low, occurring in 7.6% of patients in the imetelstat group and 3.4% of patients in the placebo group (Table 11-10). Headache was the only event reported in more than 1 patient, and all were low-grade (Grade 1/2). Of these, 4 patients had single AEs of headache within the first 3 cycles of treatment and one patient had repeated headaches later in treatment. All other infusion-related reaction events occurred in 1 patient each. Most events were Grade 1/2. No severe allergic reactions were reported. To mitigate infusion-related reaction incidence and severity, all patients were premedicated with an antihistamine and a corticosteroid. These results were consistent over time, as demonstrated by an additional 7 months of follow-up data that have been collected (see Appendix 11.6.8 for additional details).

8.3.2.9.5 Hepatic Adverse Events of Interest and LFT Elevations

Hepatic events were closely monitored for both clinical AEs and routine liver function tests monitoring. Higher patient incidence with imetelstat versus placebo was reported for laboratory elevations of AST (48.3% vs 22.0%, respectively) and ALP (44.9% vs 11.9%, respectively). Similar incidence was reported for bilirubin (39.0% in both groups) and ALT (39.3% vs 37.3%, respectively). Most LFT elevations were Grade 1/2 in severity and reversible.

Patient incidence of hepatic AEs overall was higher in the imetelstat group compared to the placebo group (28.8% vs 16.9%, respectively), but was comparable for Grade ≥ 3 AEs (6.8% vs 5.1%) and SAEs (0.8% vs 0.0%). A HEC, which reviewed the safety of ongoing clinical studies from a liver toxicity perspective, identified no cases of severe hepatotoxicity or Hy's Law (Table 11-16; Figure 11-2; Figure 11-3).

Additional details on monitoring of hepatotoxicity and LFT abnormalities are provided in Appendix 11.6.7, which includes the following displays:

- Table 11-16:MDS3001 – Liver Function Test Abnormalities Based on Laboratory Monitoring
- Figure 11-2: MDS3001 – Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analysis
- Figure 11-3: MDS3001 – Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analysis
- Table 11-17:MDS3001 – Selected Events Potentially Representing Liver Injury in the Imetelstat Arm

8.3.2.10 Long-Term Safety

Analysis of long-term safety in the MDS3001 Phase 3 study showed that the incidence of any AEs was consistent over the course of treatment, with no apparent increase in frequency over time and no indication of late onset or cumulative toxicities (additional details are provided in appendix Table 11-13). In general, hematological AEs decreased over time.

9 BENEFIT-RISK CONCLUSIONS

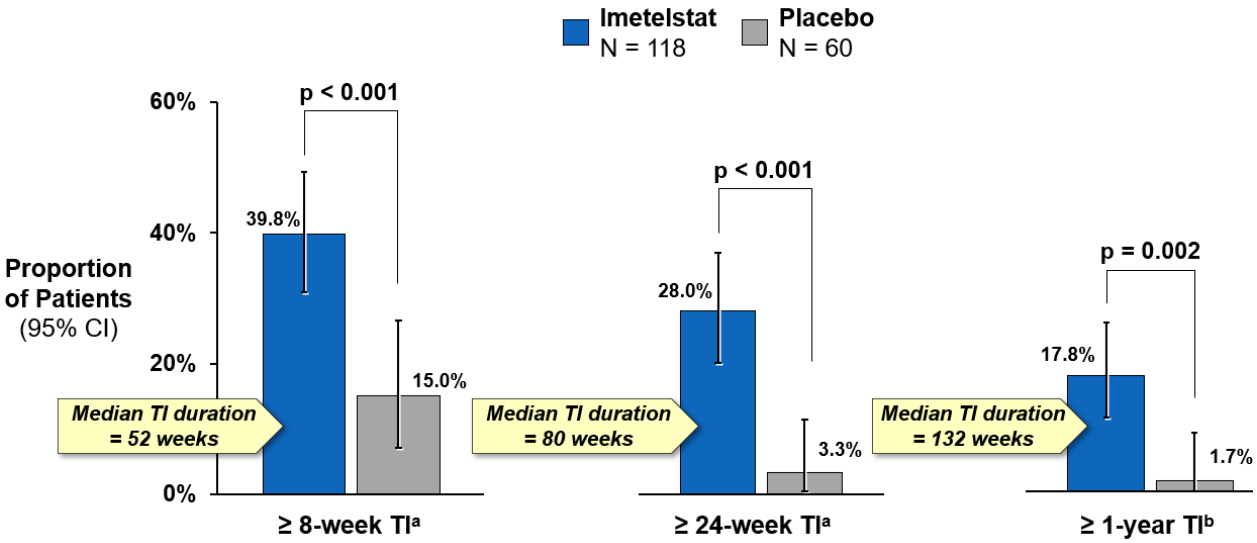
The data support a favorable benefit-risk assessment for imetelstat for the treatment of TD anemia in adult patients with low- to intermediate-1 MDS who have failed to respond or have lost response to or are ineligible for ESAs.

Though characterized as “lower risk” by IPSS, LR MDS is serious and life-threatening, and TD patients have a substantial burden due to the need for frequent RBC transfusions. For these patients who go on to experience ESA treatment failure, their life expectancy, as conservatively estimated by the median OS in LR MDS literature, amounts to approximately only 3 years. Transfusion dependency impacts the daily life of patients and their support systems, and frequent transfusions are associated with development of end organ dysfunction due to iron overload, depletion of already limited supply of blood products, and results in increased burden on patients and caregivers. If approved, imetelstat would represent an important treatment option for this LR MDS patient community.

Currently, the approved treatment options for TD anemia in ESA R/R/ineligible LR MDS are not only limited (with no new drugs approved in the 14 -years between 2006-2020), but also restricted to specific sub-populations. While lenalidomide is indicated for use in del-5q patients, and luspatercept only for those with RS (with limited benefit shown in RS patients with higher transfusion burden), the remainder (75%) of the LR MDS population do not have effective treatment options that provide durable continuous TI. Though HMAs are approved for the treatment of LR MDS, use is reserved for higher risk MDS.

If approved, imetelstat would represent an important treatment option for this high unmet need population. As shown in Figure 9-1, imetelstat treatment demonstrated statistically significant and clinically meaningful improvement in ≥ 8-week RBC TI (40% in the imetelstat group compared to 15% in the placebo group; $p< 0.001$). Among patients who achieved ≥ 8-week RBC TI, the median length of TI was 52 weeks. Imetelstat also demonstrated a statistically significant and clinically meaningful improvement in ≥ 24-week RBC TI (28% in the imetelstat group compared to 3.3% in the placebo group; $p< 0.001$) with a median TI duration of 80 weeks. Durability is further supported by the fact that 18% of patients in the imetelstat group had ≥ 1-year RBC TI, versus 2% in the placebo group ($p=0.002$), and a median TI duration of over 2.5 years (132 weeks).

Figure 9-1: MDS3001 – Rates of Longer-Term Continuous RBC TI



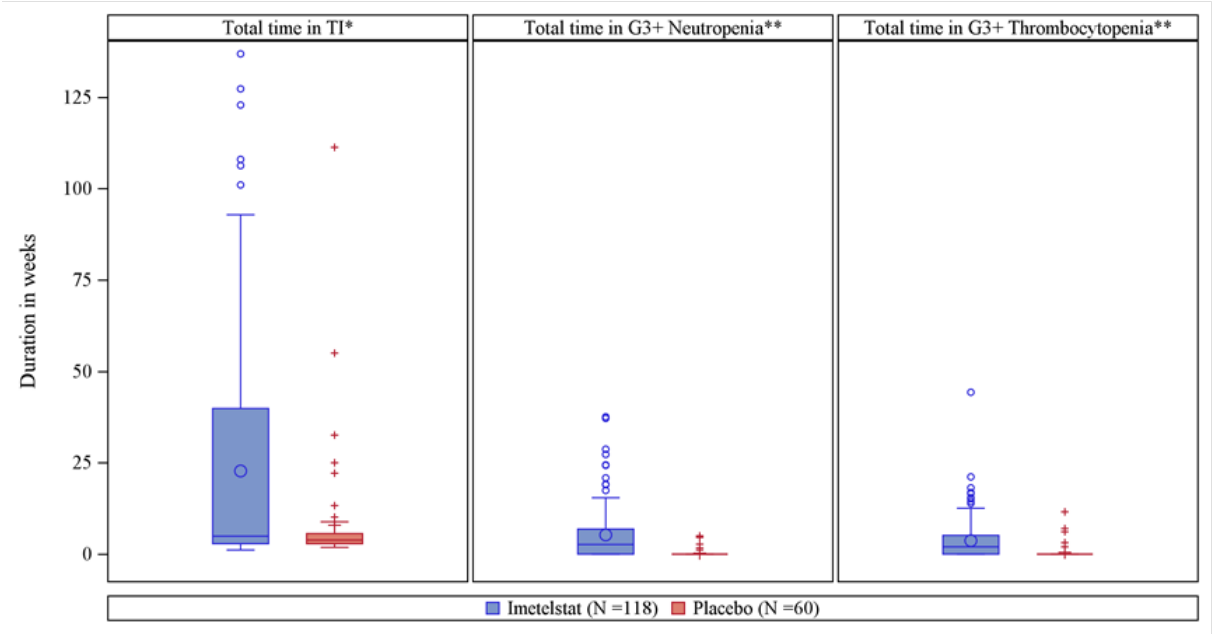
a. Data cutoff: 13 Oct 2022.
b. Data cutoff: 13 Oct 2023
CI = confidence interval; RBC = red blood cell; TI = transfusion independence

(Steensma, 2021)In addition to directly addressing the unmet need for the large proportion of LR MDS patients not currently served by approved therapies, Imetelstat offers additional benefits, including sustained improvements in Hgb levels, no worsening of patient reported symptoms of fatigue, as well as improvements in cytogenetic CR.

Regarding risk, the known and well-characterized risks of Grade 3 and 4 neutropenia and thrombocytopenia with imetelstat treatment are manageable by hematologists and health care providers who take care of MDS patients. In addition, as was done in the MDS3001 study protocol, clear guidance in the proposed US Prescribing Information (USPI) is provided for the effective management of these risks via dose delays and reductions as required. For comparison, other agents commonly used in the treatment of MDS and other hematologic malignancies have high rates of Grade 3/4 neutropenia and thrombocytopenia (Bristol Myers Squibb, 2023b; Otsuka Pharmaceutical Company, 2020). Notably many of these therapies lead to prolonged myelosuppression, and thus have additional risks of severe infections, febrile neutropenia and/or bleeding, which were not observed with imetelstat.

Additionally, when comparing the total time in TI to the total time with Grade 3/4 thrombocytopenia and neutropenia for all imetelstat treated patients (Figure 9-2), the favorable benefit risk profile is confirmed. Time without RBC transfusions for all imetelstat treated patients is longer compared with placebo and importantly, longer than the short duration of time with Grade 3/4 cytopenias.

Figure 9-2: MDS3001 – Total Time in RBC TI and Total Time in Grade 3+ Neutropenia and Thrombocytopenia



AE = adverse event; RBC = red blood cell; TI = transfusion independence.
* Total time in RBC TI intervals of at least 8 weeks or longer for 8-week TI responders or the longest RBC TI interval for 8-week TI non-responders. All RBC TI intervals started before the last exposure to treatment + 30 days and before the first anti-cancer or anti-anemia therapy and terminated with the first anti-cancer or anti-anemia therapy, RBC transfusion, the last adequate transfusion status assessment, or death, whichever is first.
** Total time in AE from first dose to the last dose + 30 days or subsequent anti-cancer therapy or death, whichever is earlier.
One patient who was randomized but not treated had a 0 total time in cytopenia because there was no AE.

Lastly, although the OS data are still immature, the most recent analysis (CCO 05 January 2024) showed a similar number of deaths between the imetelstat and placebo arms with a HR of 0.98, suggesting no detriment for survival.

Overall, given the unmet need in the target population and the rate and durability of RBC TI and associated Hgb increases, the benefit of treatment of TD anemia with imetelstat outweighs the manageable risks for patients with LR MDS.

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11 APPENDICES

11.1 MDS Prognostic Scoring Systems (IPSS)

The IPSS (Table 11-1) uses the following prognostic indicators to predict the MDS disease course for a patient:

- Percentage of leukemic blast cells in marrow.
- Type of chromosomal changes, if any, in marrow cells (cytogenetics).
- Presence of one or more low blood cell counts (cytopenias).

Table 11-1: International Prognostic Scoring System (IPSS) Scoring System Summary

Prognostic Variable	Survival and AML Evolution Score Value				
	0	0.5	1.0	1.5	2.0
Marrow Blasts (%)	<5	5 to 10	n/a	11 to 20	21 to 30
Karyotype[a]	Good	Intermediate	Poor	N/A	N/A
Cytopenias: Neutrophil count <1800/µL Platelets <100,000/µL Hemoglobin <10 g/dL	0 or 1	2 or 3	N/A	N/A	N/A

a Good: normal or any one of the following: -Y, del 5q, del 20q; Intermediate: any other abnormality; Poor: chromosome 7 abnormalities, complex, ≥3 abnormalities

N/A = not applicable.

Risk Category:	Combined Score (Sum of Marrow Blast + Karyotype + Cytopenia Score)
Low	0
Intermediate-1	0.5 to 1.0
Intermediate-2	1.5 to 2.0
High	≥2.5

Source: MDS3001 Protocol

11.2 International Working Group (IWG) Response Criteria 2006

The IWG 2006 criteria are described in Table 11-2.

Table 11-2: International Working Group (IWG) Response Criteria 2006

Category	Response Criteria (responses must last ≥ 4 weeks)
Complete remission (CR)	**Bone marrow**: ≤ 5% myeloblasts with normal maturation of all cell lines[1] Persistent dysplasia will be noted[1,2] **Peripheral blood**[3]: Hgb ≥ 11 g/dL; platelets ≥ 100 x 10^9/L; neutrophils ≥ 1.0 x 10^9/L[2]; blasts, 0%
Partial remission (PR)	All CR criteria if abnormal before treatment except: Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5% Cellularity and morphology not relevant
Marrow CR[2]	**Bone marrow**: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment[2] **Peripheral blood**: if HI responses, they will be noted in addition to marrow CR[2]
Stable disease	Failure to achieve at least PR but no evidence of progression for > 8 weeks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following: Return to pretreatment bone marrow blast percentage Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	**Complete**: Disappearance of the chromosomal abnormality without appearance of new ones **Partial**: At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with: < 5% blasts: ≥ 50% increase in blasts to > 5% blasts 5%–10% blasts: ≥ 50% increase to > 10% blasts 10%–20% blasts: ≥ 50% increase to > 20% blasts 20%–30% blasts: ≥ 50% increase to > 30% blasts Any of the following: ≥ 50% decrement from maximum remission/response in granulocytes or platelets Reduction in Hgb by ≥ 2 g/dL Transfusion dependence
Hematologic Improvement[4]	**Response criteria (responses must last ≥8 weeks)[2]**
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusion units/8 weeks compared with the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a Hgb of ≤ 9 g/dL pretreatment will count in the RBC transfusion response evaluation[2]
Platelet response (pretreatment, <100 x 10^9/L)	Absolute increase of ≥30 x 10^9/L for patients starting with >20 x 10^9/L platelets Increase from <20 x 10^9/L to >20 x 10^9/L and by at least 100%[2]
Neutrophil response (pretreatment, < 1 x 10^9/L)	At least 100% increase and an absolute increase > 0.5 x 10^9/L[2]
Progression or relapse after HI[5]	At least 1 of the following: At least 50% decrement from maximum response levels in granulocytes or platelets Reduction in Hgb by ≥1.5 g/dL Transfusion dependence

[1] Dysplastic changes should consider the normal range of dysplastic changes (modification).

[2] Modification to IWG response criteria.

[3] In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

[4] Pretreatment counts averages ≥ 2 measurements (not influenced by transfusions) ≥ 1 week apart (modification).
[5] In the absence of another explanation such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.
Notes: Deletions to the IWG response criteria are not shown. To convert hemoglobin levels (concentrations) from grams per deciliter to grams per liter, multiply grams per deciliter by 10.
CR = complete remission; DFS = disease-free survival; FAB = French-American-British; Hgb = hemoglobin; HI = hematologic improvement; IWG = International Working Group; MDS = myelodysplastic syndromes; PFS = progression-free survival; PR = partial remission; RBC = red blood cell.
Source: MDS3001 Protocol

11.3 International Working Group (IWG) Response Criteria 2018

The IWG 2018 criteria are described in Table 11-3.

Table 11-3: International Working Group (IWG) Response Criteria 2018

Item	Suggested IWG 2018 criteria	IWG 2006 criteria
Baseline criteria		
Definition of transfusion-burden categories	3 groups: NTD (0 RBCs in 16 wk)* LTB (3-7 RBCs in 16 wk in at least 2 transfusion episodes, maximum 3 in 8 wk)* HTB (≥8 RBCs in 16 wk, ≥4 in 8 wk)	2 groups: TD (at least 4 U of RBC with 8 wk for Hb < 9 g/dL) TID (<4 U of RBC with 8 wk for Hb < 9 g/dL)
Pretreatment RBC transfusion policy	Transfusion policy for the individual patient prior to therapy should be maintained on treatment†	Transfusion threshold of 9 g/dL, no exception for clinical indication
Response evaluation criteria: HI-E		
NTD (0 RBCs in 16 wk)*	At least 2 consecutive Hb measurements ≥1.5 g/dL for a period of minimum 8 wk in an observation period of 16 to 24 wk compared with the lowest mean of 2 Hb measurements (apart from any transfusion) within 16 wk before treatment onset‡; only a response duration of at least 16 wk, however, is considered clinically meaningful	Hb increase by 1.5 g/dL and/or relevant reduction of U of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk; only RBC transfusions given for an Hb of ≤9.0 g/dL pretreatment will count in the RBC transfusion response evaluation
LTB (3-7 RBCs in 16 wk in at least 2 transfusion episodes, maximum 3 in 8 wk)*	HI-E in LTB patients corresponds to transfusion independence, defined by the absence of any transfusions for at least 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment; only a response duration of at least 16 wk, however, is considered clinically meaningful	
HTB (≥8 RBCs in 16 wk, ≥4 in 8 wk)	Major response: Major HI-E response in HTB patients corresponds to transfusion independence, defined by the absence of any transfusions over a period of minimum 8 wk in an observation period of 16-24 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment; only a response duration of at least 16 wk, however, is considered clinically meaningful Minor response: Minor HI-E response in HTB patients is defined as a reduction by at least 50% of RBCs over a minimum of 16 wk with the same transfusion policy (defined below) compared with 16 wk prior to treatment	
On-treatment RBC transfusion policy§	Transfusion policy for the individual patient prior to therapy should be maintained on treatment if not otherwise clinically indicated (documentation by the treating physician required); we suggest a maximum variation between pre- and on-study practice of 1 g/dL (or 0.6 mmol/L) in terms of transfusion threshold	Transfusion threshold of 9 g/dL, no exception for clinical indication
Dose adjustment thresholds for high Hb levels	If the drug under investigation is stopped or its dose reduced in a responding patient for protocol-defined reasons leading to a loss of response, this should not be counted as such if reintroduction at the same or lower dose of the drug induces a new response; if reintroduction of the drug at a lower dose does not reinduce a response, this should be documented as such	NA

Abbreviations are explained in Table 1.

*The coauthors did not fully agree on whether patients who received only 1 or 2 RBC concentrates during the 16-wk screening period should be categorized in the NTB or LTB group. If such patients are included in clinical trials evaluating HI-E, it is recommended that HI-E achievement requires not only transfusion independence but also an increase of Hb by at least 1.5 g/dL (~ 0.9 mmol/L).

†As in IWG 2006 criteria, only RBC transfusions administered for an Hb level below 9 g/dL are taken into account. Exceptions to this rule may be accepted in cases of well-documented moderate or severe angina pectoris, cardiac or pulmonary insufficiency, or ischemic neurologic diseases. In these cases, a higher transfusion trigger level may be established for an individual patient. These patients may require special attention when analyzing responses within clinical trials. Transfusions for intercurrent diseases (bleeding, surgical procedure, etc) are not considered.

‡Oscillations (eg, natural or due to drug intervals) within this period are accepted as long as the patient remains off any transfusions and the same transfusion policy has been maintained. We suggest accepting 1 drop to an increase of between 1.0 and 1.5 g/dL over a period of 8 wk. We recommend that intervals between blood counts do not exceed 2 wk.

§Exceptions to this rule may be accepted in cases of well-documented moderate or severe angina pectoris, cardiac or pulmonary insufficiency, or ischemic neurologic diseases. In these cases, a higher transfusion trigger level may be established for an individual patient. These patients may require special attention when analyzing responses within clinical trials. Transfusions for intercurrent diseases (bleeding, surgical procedure, etc) should not be taken into account.

Source: (Platzbecker, 2019)

11.4 International Working Group (IWG) Response Criteria 2023

Table 11-4: International Working Group (IWG) Response Criteria 2023

Response	IWG 2006	IWG 2023
CR	•BM: ≤5% myeloblasts; dysplasia may persist •PB: Hgb ≥11 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%	•BM: <5% myeloblasts;* dysplasia may persist •PB: Hgb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0%
CR equivalent*	Not included	Patients with <5% BM blasts at baseline •BM: <5% myeloblasts*; dysplasia may persist •PB: Hgb ≥10 g/dL, platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L; blasts 0% •Full cytogenetic clearance of baseline abnormalities (complete cytogenetic response)
mCR	•BM: ≤5% blasts and decrease by ≥50% over pretreatment •No PB responses required	Eliminated as a response criterion‡
PR	All CR criteria except: •BM blasts decreased by ≥50% over pretreatment but still >5% •Cellularity and morphology not relevant	All CR criteria except: •BM blasts decreased by ≥50% over pretreatment but still ≥5% •Cellularity and morphology not relevant
SD	Failure to achieve at least PR, but no evidence of progression for >8 wk	Eliminated as a response criterion‡
CR_L§ (CR_{uni} and CR_{bi})	Not included	•BM: <5% myeloblasts;* dysplasia may persist •PB: blasts 0% •CR_{uni}: PB, not meeting CR but only 1 of the following: Hgb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L •CR_{bi}: PB, not meeting CR but only 2 of the following: Hgb ≥10 g/dL; platelets ≥100 × 10^9/L; neutrophils ≥1.0 × 10^9/L
CRh§	Not included	•BM: <5% myeloblasts;* dysplasia may persist •PB: Not meeting criteria for CR or CR_L, no Hgb threshold required, platelets ≥50 × 10^9/L; neutrophils ≥0.5 × 10^9/L; blasts 0%
HI	HI (responses >8 wk): •Erythroid response (pretreatment, <11 g/dL): Hgb increase by ≥1.5 g/dL and 50% reduction of RBC transfusion •Platelet response (pretreatment, <100 × 10^9/L):absolute increase of ≥30 × 10^9/L for patients starting with >20 × 10^9/L platelets or increase from <20 × 10^9/L to >20 × 10^9/L and by at least 100% •Neutrophil response (pretreatment, <1.0 × 10^9/L): at least 100% increase and an absolute increase >0.5 × 10^9/L	HI defined according to IWG 2018 response criteria: •Not meeting criteria for CR (or CR equivalent) or CRuni or CR_L •$HI_{erythroid}$ (HI-E) •$HI_{platelets}$ (HI-P) •$HI_{neutrophils}$ (HI-N)
ORR	Not defined	ORR = CR (or CR equivalent)* + PR + CR_L + CRh + HI
No response	Not defined	Not meeting criteria for CR (or CR equivalent)*, PR, CR_L, CRh, or HI‡
Not evaluable	Not included	All registered/randomly assigned patients should be reported in the denominator of response assessment analyses in line with the intention-to-treat principle. This category may include patients yet to have a response assessment, suffering early death, exiting the study early, or those with a technically suboptimal BM sample precluding assessment.

Response	IWG 2006	IWG 2023
Cytogenetic response§§	•Complete: disappearance of the chromosomal abnormality without appearance of new ones •Partial: ≥50% reduction of the chromosomal abnormality	•Complete: disappearance of the chromosomal abnormality without appearance of new ones •Partial: ≥50% reduction of the chromosomal abnormality
PD	For patients with: •<5% blasts: ≥50% increase in blasts to >5% blasts •5%-10% blasts: ≥50% increase to >10% blasts •10%-20% blasts: ≥50% increase to >20% blasts •20%-30% blasts: ≥50% increase to >30% blasts Any of the following: •At least 50% decrement from maximum remission/response in granulocytes or platelets •Reduction in Hgb by ≥2 g/dL •Transfusion dependence	Fulfilling any of the criteria below:#** †† •Disease progression by blasts: ≥50% relative increase in blasts and absolute increase of blast percentage by at least 5% from pretreatment sample taken before current line of therapy •Disease progression by worsening cytopenia: new, repeated (more than once and separated by ≥7 days) need for RBC or platelet transfusions within 8 weeks, not related to acute intercurrent illness (eg, sepsis, gastrointestinal tract bleed) or treatment effect, in the absence of HI of at least one other blood lineage as defined above •Progression to AML: ≥50% increase in blasts from baseline assessment to ≥20% blasts
Disease relapse	Any of the following: •Return to pretreatment BM blast percentage •Decrement of 50% from maximum remission/response levels in granulocytes or platelets •Reduction in Hgb concentration by 1.5 g/dL or transfusion dependence	Fulfilling any of the criteria below:# •Disease relapse by blasts: absolute and relative increase in BM blasts by at least 5% and ≥50%, respectively, from prior assessment, or reappearance of blasts in the blood, or development of extramedullary disease (myeloid sarcoma) •Disease relapse by worsening cytopenias: decrement in one or more blood cell lineage counts by ≥50% from maximum remission/response levels for platelets or absolute neutrophil count or a reduction of Hgb by 1.5 g/dL combined with an absolute reduction in the same lineage(s) as follows: Hgb <10 g/dL, platelets <100 × 10^9/L, or absolute neutrophils <1.0 × 10^9/L or repeated (more than once and separated by ≥7 days) need for RBC or platelet transfusions which are not related to acute intercurrent illness (eg, sepsis, gastrointestinal tract bleed) or treatment effect; in the absence of HI of at least one other blood lineage as defined above
Patient reported outcomes (PROs)	Not included	Reporting by means of a validated assessment tool is encouraged‡‡

AML = acute myeloid leukemia; BM = bone marrow; CR = complete remission; CR_{bi} = complete remission bilineage; CR_{uni} = complete remission; unilineage; CR_L = complete remission with limited count recovery; CR_h = complete remission with partial hematologic recovery; Hgb = hemoglobin; HI = hematologic improvement; HI-E = hematologic improvement-erythroid; HI-P = hematologic improvement-platelets; HI-N = hematologic improvement-neutrophils; IWG = International Working Group; mCR = molecular complete remission; ORR = overall response rate; PB = peripheral blood; PD = pharmacodynamics; PR = partial remission; PRO = patient reported outcome; RBC = red blood cell; SD = stable disease; wk = weeks.

∗ Patients require ≥5% blasts before treatment initiation to be considered evaluable for CR, PR, CRh, or CR_L. For patients with <5% blasts who have HR-MDS owing to adverse cytogenetics and/or severe cytopenias, full cytogenetic clearance (complete cytogenetic response) and blood counts that meet CR criteria are considered CR equivalent but should be reported separately. Full trilineage count recovery is defined as Hgb ≥10 g/dL, platelets ≥100 × 10^9/L, and ANC ≥1.0 × 10^9/L independent of baseline PB. Given that molecular clearance has not been validated prospectively, it was not used for CR definition.

‡ A few panelists felt that mCR could still have a value, especially in bridging patients to allo-HSCT, and should therefore, still be reported. If mCR is reported, it should not be included in the ORR. Prolonged SD (≥16 weeks) might have limited benefit in patients with HR-MDS who are not candidates for allo-HSCT. However, SD is a

function of time of stability, and in single-arm studies without a control arm, it is challenging to assess whether SD reflects more indolent MDS biology in some patients vs the impact of therapy. Furthermore, disease stability is included as part of the PFS definition. Therefore, SD should not be included in the ORR.

§ CR_L and CRh are provisional entities that require additional prospective validation. Both CR_L and CRh are included to allow prospective validation of their value in MDS. Similar to CR and PR, both are defined by blood counts at or around the time of response assessment and independently of the baseline blood counts. To be eligible for CR_L, patients need to have achieved PB count levels at or around the time of assessment in 1 or 2 lineages, but not in all 3 lineages, that are at or above the CR threshold for the specific lineage(s). In patients with MDS/AML or MDS with increased blasts as defined by the 2022 International Consensus Classification and the 5th edition of WHO classification, respectively, reporting CRh defined as <5% blasts in the BM, 0% PB blasts, and partial recovery of PB counts (platelets ≥50 × 10^9/L and ANC ≥0.5 × 10^9/L) can be considered to achieve consistency with ELN 2022 AML response criteria. Similar to CRL, CRh is considered a provisional response category in MDS and requires additional prospective validation. If patients meet criteria for both CR_L and CRh, they should be reported as having achieved CR_L for the ORR as it represents a higher threshold for hematologic improvement.

§§ If cytogenetic analyses fail, repeating cytogenetics during a subsequent response assessment is recommended. MRD assessment in MDS is insufficiently validated at this time as a surrogate for OS. MRD-negative response can be reported as a provisional response category, and clinical trial protocols should predefine what techniques are used to detect MRD and what cutoffs are considered to define an MRD response.

BM biopsy to assess for disease progression is recommended. In patients with disease progression/relapse defined by the need for transfusion support, the date of the first unit of RBC and platelet transfusion will be the date of disease progression.

∗∗ Clonal progression (defined as the acquisition of new cytogenetic or molecular abnormalities) can be reported as a provisional progression criterion. This does not necessarily constitute clinical progression unless otherwise specified by the protocol.

†† For patients with <5% BM blasts from pretreatment sample before current line of therapy, the definition of PD might be applied to patients with ≥50% relative BM blast count increase who do not have an absolute increase of ≥5% blasts in the right clinical context (eg, worsening disease-related cytopenias). Similarly, for patients with an absolute BM blast increase to ≥20% but who have <50% relative BM blast count increase from pretreatment before current line of therapy, this could denote progression in the right clinical context where additional therapeutic options may be available with a new diagnosis of AML.

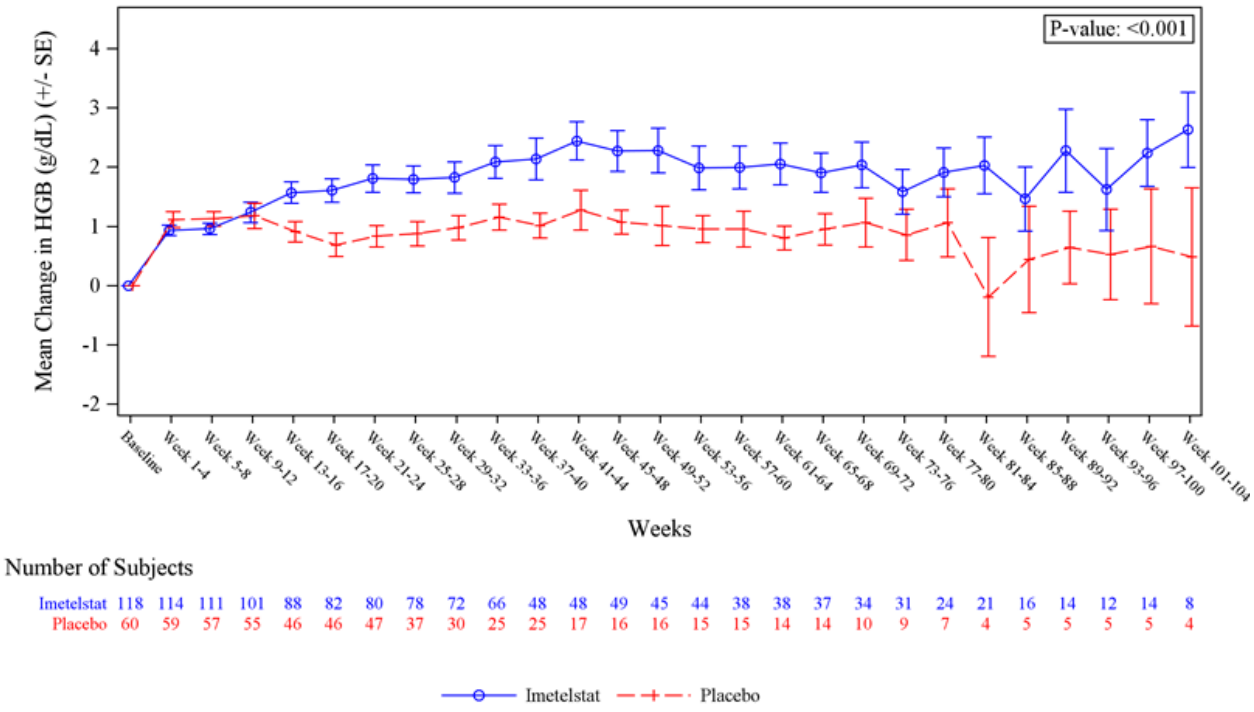
‡‡ The panel recognizes that improvements in PROs (including health-related quality of life or symptoms) can be a meaningful, patient-centered goal of treatment. However, there is not yet sufficient evidence in HR-MDS to support specific recommendations at this point. In any case, rigorous assessment of PROs in clinical trials is recommended.

Source: (Zeidan, 2023)

11.5 Additional Efficacy Information: Change in Hemoglobin over Time

Figure 11-1 below presents change in hemoglobin over time in the MDS3001 Phase 3 study.

Figure 11-1: MDS3001 – Change in Hemoglobin over Time, by ≥ 8-week TI Responders, Without 14-day Rule



HGB = hemoglobin; SE = standard error; TI = transfusion independence.
Note: Data points that have less than 4 patients are not shown.
Note: P-value is between treatment arms based on a mixed model for repeated measures with HGB change as dependent variable, week, stratification factors, min HGB in 8 weeks prior to first dose, and treatment arm as independent variables with autoregressive moving average (ARMA(1,1)) covariance structure.

11.6 Additional Safety Information

11.6.1 Supplemental Safety Tables

Presented in this section are the following tables providing supplemental safety information:

- Table 11-5: MDS3001 – Grade 3 and 4 Adverse Events in ≥ 2 Patients in Any Study Group
- Table 11-6: MDS3001 – Adverse Events Leading to Infusion Interruption
- Table 11-7: MDS3001 – Details on Neutropenia
- Table 11-8: MDS3001 – Summary of Infections
- Table 11-9: MDS3001 – Grade 3-4 Thrombocytopenia

Table 11-5: MDS3001 – Grade 3 and 4 Adverse Events in ≥ 2 Patients in Any Study Group

Preferred Term:	Imetelstat N = 118	Placebo N = 59
Any AE Grade 3 / 4	107 (90.7%)	28 (47.5%)
Neutropenia	80 (67.8%)	2 (3.4%)
Thrombocytopenia	73 (61.9%)	5 (8.5%)
Anemia	23 (19.5%)	4 (6.8%)
Leukopenia	9 (7.6%)	0
Cardiac failure	4 (3.4%)	0*
Alanine aminotransferase increased	3 (2.5%)	2 (3.4%)
Hypertension	3 (2.5%)	0
Pneumonia	3 (2.5%)	1 (1.7%)
Atrial fibrillation	2 (1.7%)	0
COVID-19 pneumonia	2 (1.7%)	3 (5.1%)
Femur fracture	2 (1.7%)	1 (1.7%)
Hyperferritinaemia	2 (1.7%)	0
Lung neoplasm malignant	2 (1.7%)	0
Pyrexia	2 (1.7%)	0
Sepsis	2 (1.7%)	0
Syncope	2 (1.7%)	0
Urinary tract infection	2 (1.7%)	0
Iron overload	0	2 (3.4%)
Abscess limb	0	2 (3.4%)

* One patient in the placebo group (1.7%) also had Grade 3 cardiac failure congestive (SAE).

Table 11-6: MDS3001 – Adverse Events Leading to Infusion Interruption

Preferred Term:	Imetelstat N = 118	Placebo N = 59
Patients experiencing ≥ 1 AE leading to infusion interruption	7 (5.9%)	0
Headache	2 (1.7%)	0
Administration site extravasation	1 (0.8%)	0
Arthralgia	1 (0.8%)	0
Back pain	1 (0.8%)	0
Bone pain	1 (0.8%)	0
Erythema	1 (0.8%)	0
Hypertensive crisis	1 (0.8%)	0
Infusion site extravasation	1 (0.8%)	0

Preferred Term:	Imetelstat N = 118	Placebo N = 59
Malaise	1 (0.8%)	0
Pruritus	1 (0.8%)	0
Urticaria	1 (0.8%)	0

Table 11-7: MDS3001 – Details on Neutropenia

Neutropenia AE:	Imetelstat N = 118	Placebo N = 59
Any neutropenia AE	87 (73.7%)	4 (6.8%)
Grade 3 or 4 neutropenia AE	80 (67.8%)	2 (3.4%)
0 to < 3 months	62/118 (52.5%)	0
3 to < 6 months	26/104 (25.0%)	2 (3.6%)
6 to < 12 months	16/85 (18.8%)	0
≥ 12 months	7/49 (14.3%)	0
Time to onset, median (weeks)	4.4	13
Duration, median (weeks) [range]	1.9 [0-15.9]	2.2 [1.0-4.6]
Percentage of events resolved to ≤ Grade 2 in < 4 weeks	81%	50%

Table 11-8: MDS3001 – Summary of Infections

Parameter:	Imetelstat N = 118	Placebo N = 59
Any infection AE	50 (42.4%)	20 (33.9%)
Grade ≥ 3	13 (11.0%)	8 (13.6%)
Serious	14 (11.9%)	8 (13.6%)
Any infection AE within ± 7 days of Grade 3/4 neutropenia	9 (7.6%)	1 (1.7%)
Grade 1/2 infection AE	6 (5.1%)	0
Grade 3/4 infection AE	3 (2.5%)	1 (1.7%)
Serious infection AE	3 (2.5%)	1 (1.7%)
Febrile neutropenia	1 (0.8%)	0

Table 11-9: MDS3001 – Grade 3-4 Thrombocytopenia

Grade 3/4 Thrombocytopenia:	Imetelstat N = 118	Placebo N = 59
Any thrombocytopenia AE	89 (75.4%)	6 (10.2%)
Grade 3 or 4 thrombocytopenia AE	73 (61.9%)	5 (8.5%)
0 to < 3 months	46/118 (39.0%)	1/59 (1.7%)
3 to < 6 months	20/104 (19.2%)	2/55 (3.6%)
6 to < 12 months	16/85 (18.8%)	2/41 (4.9%)
≥ 12 months	6/49 (12.2%)	0
Time to onset, median (weeks)	6	15
Duration, median (weeks) [range]	1.4 [0.1, 12.6]	2.0 [0.3, 11.6]
Resolved to ≤ Grade 2 in < 4 weeks	183/212 events (86.3%)	4/9 events (44.4%)

Table 11-10: MDS3001 – Summary of Bleeding Events

Parameter:	Imetelstat N = 118	Placebo N = 59
Any bleeding AE	25 (21.2%)	7 (11.9%)
Grade ≥ 3	3 (2.5%)	1 (1.7%)
Serious	3 (2.5%)	1 (1.7%)
Any bleeding AE within ± 7 days of Grade 3/4 thrombocytopenia	9 (7.6%)	0
Grade 1/2 bleeding AE	9 (7.6%)	0
Grade 3/4 bleeding AE	0	0
Serious bleeding AE	0	0

Table 11-11: MDS3001 – Infusion-Related Reactions

	Imetelstat N = 118		Placebo N = 59	
Infusion-Related Reaction:	Any Grade	Grade 3 / 4	Any Grade	Grade 3 / 4
Any Infusion-Related Reactions	9 (7.6%)	2 (1.7%)	2 (3.4%)	0
Headache	5 (4.2%)	0	0	0
Asthenia	1 (0.8%)	0	0	0
Malaise	1 (0.8%)	1 (0.8%)	0	0
Non-cardiac chest pain	1 (0.8%)	1 (0.8%)	0	0
Arthralgia	1 (0.8%)	0	0	0
Back pain	1 (0.8%)	0	0	0
Bone pain	1 (0.8%)	0	0	0
Abdominal pain	1 (0.8%)	0	0	0
Diarrhea	1 (0.8%)	0	0	0
Erythema	1 (0.8%)	0	0	0
Pruritis	1 (0.8%)	0	0	0
Urticaria	1 (0.8%)	0	0	0
Hypertensive crisis	1 (0.8%)	1 (0.8%)	0	0
Chest pain	0	0	1 (1.7%)	0
Cough	0	0	1 (1.7%)	0
Pyrexia	0	0	1 (1.7%)	0

Table 11-12: MDS3001 – LFT Abnormalities

	Imetelstat N = 118		Placebo N = 59	
LFT Abnormality:	Any Grade	Grade 3 / 4	Any Grade	Grade 3 / 4
ALT increased	46 (39.3%)	4 (3.4%)	22 (37.3%)	3 (5.1%)
ALP increased	53 (44.9%)	0	7 (11.9%)	0
AST increased	57 (48.3%)	1 (0.8%)	13 (22.0%)	1 (1.7%)
Bilirubin	46 (39.0%)	1 (0.8%)	23 (39.0%)	1 (1.7%)

Table 11-13: MDS3001 – Long-Term Safety – Adverse Events Over Time

	0 to < 3 Months		3 to < 6 Months		6 to < 12 Months		≥ 12 Months	
Preferred Term:	Imetelstat N = 118	Placebo N = 59	Imetelstat N = 104	Placebo N = 55	Imetelstat N = 85	Placebo N = 41	Imetelstat N = 49	Placebo N = 16
Any AE	95%	83%	86%	56%	79%	59%	84%	50%
Neutropenia	71%	5%	47%	6%	39%	2%	35%	6%

Preferred Term:	0 to < 3 Months		3 to < 6 Months		6 to < 12 Months		≥ 12 Months	
	Imetelstat N = 118	Placebo N = 59	Imetelstat N = 104	Placebo N = 55	Imetelstat N = 85	Placebo N = 41	Imetelstat N = 49	Placebo N = 16
Thrombocytopenia	63%	5%	53%	7%	46%	7%	41%	0
Anemia	14%	7%	7%	4%	9%	7%	0	0
Headache	10%	5%	2%	0	4%	0	4%	0
Leukopenia	9%	2%	5%	0	4%	0	2%	0
Asthenia	9%	9%	6%	2%	4%	10%	14%	19%
ALT increased	8%	3%	5%	0	4%	7%	4%	6%
Dyspnea	8%	5%	0	2%	0	2%	2%	0
Hyperbilirubinemia	7%	5%	1%	4%	5%	5%	0	6%
AST increased	6%	3%	3%	0	2%	5%	4%	0
Fatigue	6%	7%	4%	0	0	2%	4%	0
Diarrhea	5%	7%	3%	0	7%	7%	6%	0
Edema peripheral	3%	5%	5%	4%	4%	5%	4%	6%
Pyrexia	3%	5%	2%	4%	5%	5%	2%	6%
Constipation	3%	10%	2%	4%	1%	0	6%	0%
Arthralgia	3%	3%	2%	0	5%	0	6%	0
Dizziness	3%	7%	1%	0	1%	0	2%	0
COVID-19	2%	3%	2%	2%	6%	2%	18%	0
Hyperkalemia	1%	5%	0	2%	0	0	0	0
Iron overload	0	2%	1%	0	0	0	0	13%

Table 11-14: MDS3001 – Overview of Treatment-emergent Adverse Events – Phase 2 and 3 Imetelstat (Treated Population)

Patients with ≥ 1, n (%):	Imetelstat		
	Phase 2 N = 57	Phase 3 N = 118	Pooled N = 175
AE[a]			
Any	56 (98.2%)	117 (99.2%)	173 (98.9%)
Grade 3/4	50 (87.7%)	107 (90.7%)	157 (89.7%)
Grade 5 (fatal)	5 (8.8%)	1 (0.8%)	6 (3.4%)
Study drug-related AE[b]			
Any	50 (87.7%)	97 (82.2%)	147 (84.0%)
Grade 3/4	43 (75.4%)	85 (72.0%)	128 (73.1%)
Grade 5 (fatal)	0	0	0
Treatment-emergent SAE	27 (47.4%)	38 (32.2%)	65 (37.1%)
Study drug-related treatment-emergent SAE	9 (15.8%)	6 (5.1%)	15 (8.6%)
AE leading to treatment discontinuation	16 (28.1%)	17 (14.4%)	33 (18.9%)
Study drug-related AE leading to treatment discontinuation	9 (15.8%)	11 (9.3%)	20 (11.4%)
AEs leading to infusion interruption/abortion	6 (10.5%)	7 (5.9%)	13 (7.4%)
AEs leading to dose reduction or cycle delays	38 (66.7%)	83 (70.3%)	121 (69.1%)

[a] Treatment-emergent AEs are defined as events that occur or worsen after the first dose of study drug. Treatment-emergent events that were identified for each individual study are used for the pooled analyses.
[b] Study drug relationship is based on investigator assessment.
SAE = serious adverse event; AE = treatment-emergent adverse event.

11.6.2 Summary of All Reported Serious Adverse Events in Study MDS3001

A summary of all reported SAEs in study MDS3001 is presented in Table 11-15.

Table 11-15: MDS3001 – Serious Adverse Events by Preferred Term

Preferred Term	Imetelstat N = 118	Placebo N = 59
Any SAE	38 (32.2%)	13 (22.0%)
Anemia	3 (2.5%)	0
Cardiac failure	3 (2.5%)	0
Pneumonia	3 (2.5%)	1 (1.7%)
Atrial fibrillation	2 (1.7%)	0
COVID-19 pneumonia	2 (1.7%)	3 (5.1%)
Femur fracture	2 (1.7%)	1 (1.7%)
Pyrexia	2 (1.7%)	0
Sepsis	2 (1.7%)	0
Syncope	2 (1.7%)	0
Urinary tract infection	2 (1.7%)	0
Angina pectoris	1 (0.8%)	0
Asthenia	1 (0.8%)	0
Benign prostatic hyperplasia	1 (0.8%)	1 (1.7%)
Bladder papilloma	1 (0.8%)	0
Clostridium difficile infection	1 (0.8%)	0
Deep vein thrombosis	1 (0.8%)	0
Device occlusion	1 (0.8%)	0
Diabetic foot	1 (0.8%)	0
Dyspnea	1 (0.8%)	0
Enterococcal sepsis	1 (0.8%)	0
Erysipelas	1 (0.8%)	0
Escherichia sepsis	1 (0.8%)	0
Faecaloma	1 (0.8%)	0
Febrile neutropenia	1 (0.8%)	0
Gastroenteritis clostridial	1 (0.8%)	0
Gastrointestinal disorder	1 (0.8%)	0
Gastrointestinal hemorrhage	1 (0.8%)	0
Hematuria	1 (0.8%)	0
Hip fracture	1 (0.8%)	0
Humerus fracture	1 (0.8%)	1 (1.7%)
Hypertensive crisis	1 (0.8%)	0
Infection	1 (0.8%)	0
Influenza like illness	1 (0.8%)	0
Joint dislocation	1 (0.8%)	0
Kidney congestion	1 (0.8%)	0
Lung neoplasm malignant	1 (0.8%)	0
Myocardial infarction	1 (0.8%)	0
Nephrolithiasis	1 (0.8%)	0
Neutropenic sepsis	1 (0.8%)	0
Oesophageal varices hemorrhage	1 (0.8%)	0
Pneumonia bacterial	1 (0.8%)	0
Pseudomembranous colitis	1 (0.8%)	0

Preferred Term	Imetelstat N = 118	Placebo N = 59
Pulmonary oedema	1 (0.8%)	0
Abscess limb	0	2 (3.4%)
Aortic stenosis	0	1 (1.7%)
Aortic valve incompetence	0	1 (1.7%)
Arthralgia	0	1 (1.7%)
Arthritis bacterial	0	1 (1.7%)
Atrial flutter	0	1 (1.7%)
Cardiac failure congestive	0	1 (1.7%)
Diverticular perforation	0	1 (1.7%)
Extremity necrosis	0	1 (1.7%)
Gastroenteritis	0	1 (1.7%)
Haemochromatosis	0	1 (1.7%)
Joint effusion	0	1 (1.7%)
Listeriosis	0	1 (1.7%)
Small intestinal hemorrhage	0	1 (1.7%)

11.6.3 Analysis of Infections in Patients with Neutropenia in Study MDS3001

Infections were analyzed at the preferred term (PT) level in order to identify trends for important types of events, such as pneumonia or sepsis. PTs reflecting pneumonia events (Pneumonia, COVID-19 Pneumonia, Pneumonia bacterial) showed an incidence rate of 5.9% (7 patients) with imetelstat versus 8.5% (5 patients) with placebo with corresponding rate of Grade 3/4 events of 5% (6 patients) with imetelstat versus 6.8% (4 patients) with placebo. PTs reflecting events of sepsis (Sepsis, Enterococcal sepsis, Escherichia sepsis, Neutropenic sepsis) showed an incidence rate of 4.2% (5 patients) with imetelstat versus none with placebo. A review of these 5 cases showed presence of significant confounding factors with severe underlying comorbidities and risk factors for infections, including underlying MDS (targeting the malignant clone), diabetes and concomitant corticosteroid treatment. Patient ages were between 74 and 83 years at event onset. In 3 out of the 5 cases the event of sepsis occurred within ±7 days of Grade 3/4 neutropenia. One case had neutrophil count increased at time of the event and another case had no data on neutrophil count at time of event. One case occurred 3 weeks after a single dose of imetelstat and another case occurred in context of disease progression after almost 2 years of treatment. In both cases, a temporal association to imetelstat treatment seems unlikely. Events were reported as not related to imetelstat in 3 cases and as related in 2 cases. The sepsis events had a reasonable infectious explanation in most cases (pulmonary infection, renal abscess, possible contamination during transfusion, and multi-resistant urinary tract infection). One fatal case of sepsis occurred in the setting of disease progression in an ESA R/R LR MDS patient who had been on treatment with 7.1 mg/kg imetelstat (without the need for dose reduction) for almost 2 years and achieved a ≥ 8-week RBC TI response with reduced transfusion burden. This patient developed Grade 3+ neutropenia 11 days prior to the event of sepsis (no additional blood test provided). The patient received methylprednisolone for polymyalgia 11 days before

the sepsis event. The event was reported as not related to the study drug. Per the investigator, the origin of the sepsis was a pulmonary infection of unknown origin.

In summary, based on the totality of data, no increased risk for severe infection events has been seen in patients treated with imetelstat as compared to placebo. The incidence rate of SAEs or Grade 3/4 infection events was similar between the treatment groups. Furthermore, the incidence rate was similar between treatment groups for Grade 3/4 infections that occurred within ±7 days of Grade 3/4 neutropenia. Most events were minor Grade 1/2 infections, and most were reported as not related to study drug. While sepsis was reported more frequently in imetelstat-treated patients, these events occurred in context of established risk factors and comorbidities, and a relationship to imetelstat cannot be determined at this point. These risks can be addressed adequately in the labeling, and Geron's proposed label includes information and recommendations for the management of neutropenia and potential risk of infections.

11.6.4 Neutropenia and Infections: Follow-Up Safety Data

The data from the MDS3001 120-Day Safety Update Report (cut-off date 10 May 2023) are in line with the Phase 3 data submitted in the NDA. The incidence rate of infection events overall at the 120-Day Safety Update Report cut-off was similar to that of the NDA submission cut-off, with 46.6% (n = 55) with imetelstat versus 33.9% (n = 20) with placebo. The additional 5 patients in the imetelstat group had non-serious Grade 1/2 events of infections (PTs: COVID-19 [2 patients], Urinary tract infection, Cystitis, Viral infection, and Wound infection [1 patient each]), all reported as not related to imetelstat.

In summary, based on the totality of data, no increased risk for severe infection events has been seen in patients treated with imetelstat as compared to placebo. The incidence rate of SAEs or Grade 3/4 infection events was similar between the treatment groups. Furthermore, the incidence rate was similar between treatment groups for Grade 3/4 infections that occurred within ±7 days of Grade 3/4 neutropenia. Most events were minor Grade 1/2 infections, and most were reported as not related to study drug. While sepsis was reported more frequently in imetelstat-treated patients, these events occurred in context of established risk factors and comorbidities, and a relationship to imetelstat cannot be determined at this point. These results were consistent over time, as demonstrated by the additional 7-months of data provided in the 120-Day Safety Update Report. These risks can be addressed adequately in the labeling, and Geron's proposed label includes information and recommendations for the management of neutropenia and potential risk of infections.

11.6.5 Analysis of Bleeding Events in Patients with Thrombocytopenia in Study MDS3001

Bleeding events were analyzed at the Preferred Term (PT) level in order to identify trends for important types of events such as cerebral hemorrhage or severe gastrointestinal (GI) bleeding. There were no events reflecting cerebral hemorrhage. PTs reflecting GI bleedings for imetelstat (GI hemorrhage and esophageal varices hemorrhage), and for

placebo (melena and small intestinal hemorrhage) showed an incidence rate of 2.5% (3 patients) with imetelstat versus 3.3% (2 patients) with placebo, with corresponding rate of Grade 3/4 events of 1.7% (2 patients) with imetelstat versus 1.7% (1 patient) with placebo. All these events were reported as not related to study drug by the investigator. The SAE of Grade 4 esophageal varices hemorrhage in the imetelstat group occurred in the context of pre-existing chronic hepatopathy with portal hypertension and ascites, Grade 1 thrombocytopenia, and concomitant treatment with aspirin. The SAE of Grade 4 GI hemorrhage in the imetelstat group occurred in the context of duodenal ulcer, normal platelet count, and concomitant treatment with aspirin. The other GI hemorrhage event in the imetelstat group was reported as Grade 2 and non-serious and occurred in the context of Grade 3 thrombocytopenia (with pre-existing Grade 1 thrombocytopenia) and concomitant treatment with aspirin and apixaban.

Other bleeding events of clinical importance were 1 SAE of Grade 3 hematuria in the imetelstat group and 1 non-serious Grade 1 event of retinal hemorrhage in the placebo group (both reported as not related by the investigators). The hematuria event occurred in the context of bladder papilloma and Grade 2 thrombocytopenia.

In summary, based on the totality of data, no increased risk for severe bleeding events has been seen in patients treated with imetelstat as compared to placebo. The incidence rate of SAEs or Grade 3/4 bleeding events was similar between groups and there were no Grade 3/4 bleeding events in the context of ±7 days Grade 3/4 thrombocytopenia in either group. Most events were minor Grade 1/2 bleeding events, and most were reported as not related to study drug.

Overall, given that the rates and types of severe infection and bleeding events seen with imetelstat were comparable to placebo, there does not appear to be an increased risk of these events associated with imetelstat treatment. This, together with the rate and durability of RBC TI and the associated hemoglobin increases, and the unmet need in the proposed target population, indicates that the benefit of treatment with imetelstat outweighs the risks.

11.6.6 Thrombocytopenia and Bleeding Events: Follow-Up Safety Data

The data from the MDS3001 120-Day Safety Update Report (cut-off date 10-May-2023) are in line with the Phase 3 data submitted in the NDA. The incidence rate of bleeding events overall at the 120-Day Safety Update Report cut-off was similar to the NDA submission cut-off, with 22.0% (n = 26) with imetelstat versus 11.9% (n = 7) with placebo. The additional patient in the imetelstat group had a non-serious Grade 1 event of epistaxis reported as probably related to imetelstat.

In summary, based on the totality of data, no increased risk for severe bleeding events has been seen in patients treated with imetelstat as compared to placebo. The incidence rate of SAEs or Grade 3/4 bleeding events was similar between groups and there were no Grade 3/4 bleeding events in the context of ±7 days Grade 3/4 thrombocytopenia in either group. Most events were minor Grade 1/2 bleeding events, and most were reported

as not related to study drug. These results were consistent over time, as demonstrated by the additional 7-months of data provided in the 120-Day Safety Update Report.

The events of epistaxis and hematoma, that were reported with higher incidence rate with imetelstat are included as adverse reactions in Section 6.1 of the proposed label. The proposed label also includes information and recommendations for the management of thrombocytopenia and potential risk of bleeding events. These events will continue to be closely monitored.

11.6.7 Monitoring for Hepatotoxicity in Study MDS3001

Hepatotoxicity was monitored very closely during the MDS3001 study given that abnormalities in serum aminotransferases (i.e., ALT and AST), ALP, or bilirubin elevations had been observed in patients treated with imetelstat in earlier studies. The protocol defined Grade ≥ 3 elevations in ALT, AST, bilirubin, and ALP, or ALT or AST Grade ≥ 2 (> 3.0 x ULN) with bilirubin Grade ≥ 2 (> 2.0 x ULN), or any hepatic AE as AEIs and all LFTs and hepatic events were monitored by an independent HEC over the course of the study. Of note, the HEC monitors all ongoing sponsor-led imetelstat studies quarterly, has been monitoring these studies since 2015, and continues to monitor all patients on imetelstat treatment in clinical studies.

11.6.7.1 LFT Laboratory Abnormalities

LFT laboratory abnormalities have been routinely monitored in addition to AE reporting. LFT laboratory abnormalities were reported with a higher incidence rate with imetelstat for AST and ALP elevations, while ALT and bilirubin elevations had similar incidence rates between imetelstat and placebo arms (Table 11-16). No Grade 4 LFT abnormalities were reported in any patient in either group, and most events were reversible Grade 1/2 abnormalities.

Hepatocellular and cholestatic drug-induced liver injury (DILI) screening plots for the detection of potential Hy's Law or severe cholestasis cases are provided below (Figure 11-2 and Figure 11-3). For these figures, each patient is plotted based on their maximum on treatment total bilirubin (y-axis) and transaminase (ALT or AST when ALT is not available) or ALP (x-axis). Each value is expressed as multiples of ULN. For a full conservative approach, potential Hy's Law cases were identified based on any post-baseline total bilirubin elevation to ≥ 2 x ULN occurring any time with a post-baseline ALT or AST elevation to ≥ 3 x ULN, independently of any ALP value (Figure 11-2). Two cases meeting these initial criteria were detected on the upper right quadrant of Figure 11-2. Both cases had an alternative etiology for these combined elevations, and therefore, none met the true Hy's Law definition as confirmed following review by the HEC.

Similarly, potential cholestatic DILI cases were identified based on any post-baseline total bilirubin elevation to ≥ 2 x ULN that occurred at any time with a post-baseline ALP elevation to ≥ 2 x ULN (Figure 11-3). Two cases meeting these initial criteria were detected on the upper right quadrant of Figure 11-3. However, none had bilirubin elevations > 2 x ULN within 30 days of ALP elevations > 2 x ULN. No AEs were reported

for these laboratory elevations and no AEs of jaundice or other potential associated clinical consequences were reported. One patient had a medical history of Gilberts' disease with pre-existing ALP and bilirubin abnormalities. The second patient had a single and transient episode of bilirubin elevation at start of treatment that was not concomitant to ALP elevation and resolved for the rest of treatment duration. In both cases, the role of imetelstat appeared to be unlikely.

Table 11-16: MDS3001 – Liver Function Test Abnormalities Based on Laboratory Monitoring

LFT Abnormality	Imetelstat N=118				Placebo N=59			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
ALT increased	36 (30.8%)	6 (5.1%)	4 (3.4%)	0	16 (27.1%)	3 (5.1%)	3 (5.1%)	0
AST increased	50 (42.4%)	6 (5.1%)	1 (0.8%)	0	10 (16.9%)	2 (3.4%)	1 (1.7%)	0
Bilirubin increased	28 (23.7%)	17 (14.4%)	1 (0.8%)	0	15 (25.4%)	7 (11.9%)	1 (1.7%)	0
ALP increased	48 (40.7%)	5 (4.2%)	0	0	7 (11.9%)	0	0	0

Figure 11-2: MDS3001 – Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analysis

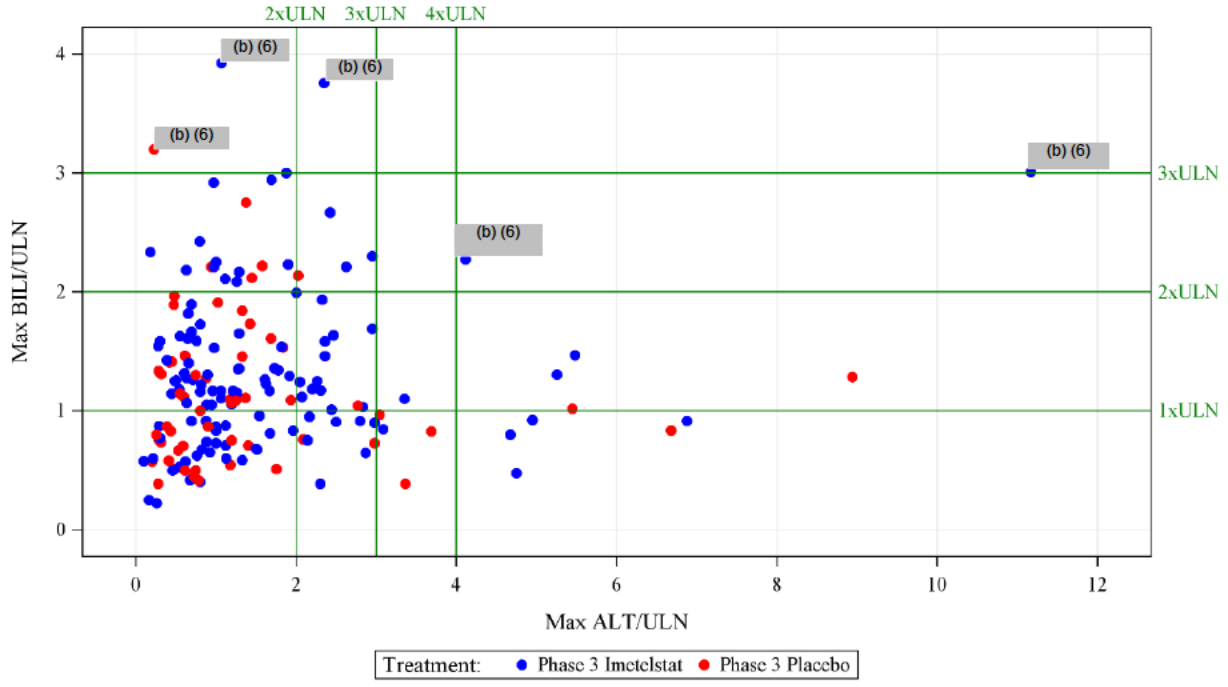
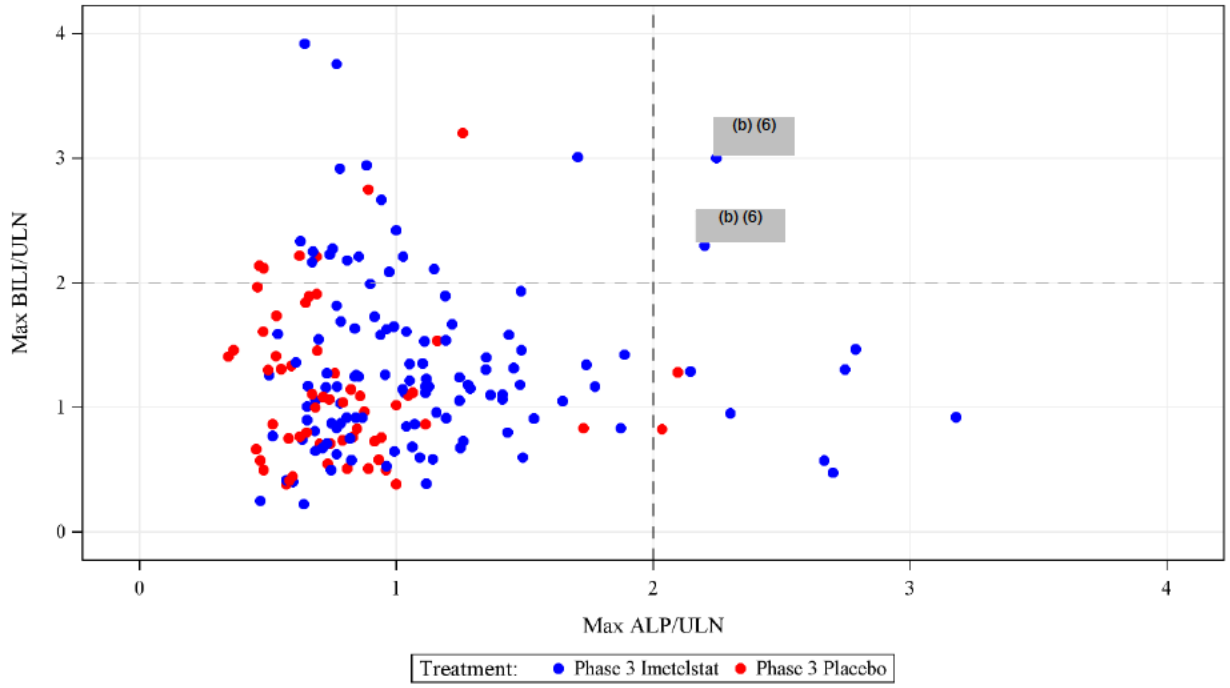


Figure 11-3: MDS3001 – Cholestatic Drug-Induced Liver Injury Screening Plot, Safety Population, Pooled Analysis



11.6.7.2 Hepatic Adverse Events

Hepatic AEs were identified based on the MedDRA SMQ Hepatic disorders. Based on this search strategy, the incidence rate of hepatic events overall was 28.8% (34 patients) with imetelstat versus 16.9% (10 patients) with placebo in the MDS3001 Phase 3 study. Of these, the only hepatic event that occurred with a distinct difference (≥ 5%) between arms was ALT increased (11.9% [14 patients] with imetelstat versus 6.8% [4 patients] with placebo). This difference in AE reporting for ALT increased is not supported by the laboratory data monitoring shown above, which is considered more reliable. None of these events of ALT increased were reported as SAEs or with severity Grade 4. Events of severity Grade 3 ALT increased were reported with similar incidence rates in both arms (2.5% [3 patients] with imetelstat versus 3.4% [2 patients] with placebo). ALT increased events were reported as related for 8.5% (10 patients) with imetelstat and 5.1% (3 patients) with placebo (Table 11-17).

Other laboratory abnormalities were reported with similar rate between imetelstat and placebo with respective incidence rates for imetelstat and placebo as following: AST increased (9.3% [11 patients] and 6.8% [4 patients]), hyperbilirubinaemia and bilirubin conjugated increased (9.3% [11 patients] and 10.2% [6 patients]), Blood ALP increased (4.2% [5 patients] and 1.7% [1 patient], and Gamma-glutamyltransferase increased (3.4% [4 patients] and 3.4% [2 patients]). Other hepatic events had similar distribution between groups and most of them occurred in single patients.

Overall, the majority of hepatic events were Grade 1/2 events, there were no fatal hepatic events, and none led to treatment discontinuation in either group. Most importantly, the incidence rate of SAEs of hepatic events was low and similar between arms (0.8% [1 patient] with imetelstat versus no patients with placebo) and for Grade 3/4 events (6.8% [8 patients] with imetelstat versus 5.1% [3 patient] with placebo). Only 1 event was reported as Grade 4 (PT: esophageal varices hemorrhage) and this event had alternative explanations (see description below). Hepatic events were reported by the investigators as related in 14.4% (17 patient) with imetelstat versus 6.8% (4 patients) with placebo.

Hepatic events were analyzed at the PT level in order to identify trends for important types of events potentially reflecting DILI. The PTs included ascites, bilirubin conjugated increased, hepatic cirrhosis, hepatitis, hepatotoxicity, jaundice hepatocellular, esophageal varices hemorrhage, portal hypertension, and varices esophageal (8 patients total, all in the imetelstat arm). These events occurred in single patients except for ascites and portal hypertension (2 patients each). Events were reported with severity Grade 1/2 except for 3 events reported with severity Grade 3, which had PTs of hepatotoxicity, bilirubin conjugated increased and hepatitis (1 patient each) and 1 event reported with severity Grade 4 (PT: esophageal varices hemorrhage). All events were non-serious except for 1 SAE of Grade 4 esophageal varices hemorrhage reported as not related to imetelstat. This SAE case occurred in context of chronic hepatopathy with portal hypertension and ascites, all reported as not related, non-serious and Grade 2 in severity. Almost all cases were assessed as not related to imetelstat by the investigators except for the events of jaundice hepatocellular (Grade 1), hepatic cirrhosis (Grade 2), and hepatotoxicity (Grade 3). Overall, these cases were all confounded, and were non-serious, with low severity grades and the majority considered not related to imetelstat.

No hepatic event met all Hy's Law criteria. A review of the hepatic AEs/laboratory abnormalities by the independent HEC found no significant hepatic findings without alternative etiology.

Table 11-17: MDS3001 – Selected Events Potentially Representing Liver Injury in the Imetelstat Arm

PT:	Case	SAE	Grade	Related by Investigator
Ascites	1	No	2	No
	2	No	2	No
Bilirubin conjugated increased	1	No	3	No
Hepatic cirrhosis	1	No	2	Yes
Hepatitis	1	No	3	No
Hepatotoxicity	1	No	3	Yes
Jaundice hepatocellular	1	No	1	Yes
Oesophageal varices hemorrhage	1	Yes	4	No
Portal hypertension	1	No	2	No
	2	No	2	No
Varices oesophageal	1	No	2	No

Clinical cutoff: 13 Oct 2022

11.6.7.3 Hepatic Events: Follow-up safety data

The data from MDS3001 120-Safety Update Report (cut-off date 10 May 2023) are in line with the Phase 3 data submitted in the NDA. More specifically, no changes were observed for Grade 3/4 incidence rate of laboratory abnormalities. The incidence rate of hepatic adverse events overall was 28.8% (N= 34) with imetelstat (no change) versus 18.6% (N= 11) with placebo (1 additional patient). Three patients had additional Grade 3/4 events in the imetelstat group (PTs: Gamma-glutamyltransferase increased [2 patients] and Cholestasis [1 patient]). The 2 events of Gamma-glutamyltransferase increased were reported as Grade 3, non-serious and not related to imetelstat. The Cholestasis event was reported as Grade 3, non-serious and probably related to imetelstat. However, clinical evidence was limited for both the diagnosis of cholestasis and its relationship to imetelstat. One additional patient in the placebo group had a non-serious Grade 2 event of direct bilirubin increased (PT: Hyperbilirubinaemia) reported as not related.

In summary, based on the totality of data, no increased risk for severe hepatic events has been seen in patients treated with imetelstat as compared to placebo. The incidence rate of Grade 3/4 LFT abnormalities was low and similar between groups, with no Grade 4 abnormality in either group. The incidence rate of SAEs or Grade 3/4 hepatic AEs was similar between groups. Most events were Grade 1/2 laboratory abnormalities or non-serious Grade 1/2 AEs. There were no cases of Hy's Law and no severe cholestasis cases in relation to imetelstat treatment. These results were consistent over time.

The events of AST increased and ALP increased, that were reported with higher incidence rate with imetelstat based on laboratory data are included as adverse reactions in Section 6.1 of the proposed label. The proposed label also includes information and recommendations for the management of elevated LFTs. These events will continue to be closely monitored.

11.6.8 Infusion-Related Reactions

The events reflecting infusion-related reactions all occurred in single patients with the exception of the events of Headache that occurred in 5 patients, all Grade 1/2. Most IRR events were reported with severity Grade 1/2. There were no serious and no severe events of allergic reactions. To mitigate IRR incidence and severity, all patients were premedicated with an antihistamine and a corticosteroid. IRR events were manageable with pre-medication and dose modifications, which is reflected in the proposed label.

The data from MDS3001 Day 120-Safety Update Report (cut-off date 10-May-2023) was in line with the Phase 3 data submitted in the NDA. No changes were observed for IRR events between the 2 periods.

11.7 Summary of Exposure-Response Analyses in Study MDS3001

The relationships between imetelstat exposure and key efficacy- and safety-related endpoints (Sections 11.7.1 and 11.7.2, respectively) were examined with univariate and multivariate E-R analyses. Exposures were simulated using the popPK model developed

(Section 5.3) and included model-predicted Cycle 1 C_{max}, Cycle 1 AUC, as well as C_{avg} up to the time of the event (or during the entire treatment period for patients who did not have the event), which robustly accounts for individual patient dosing history. The analyses enabled a characterization of the imetelstat exposure-response relationships in the indicated population with the recommended imetelstat 7.1 mg/kg q4w dosing regimen.

11.7.1 Exposure-Efficacy Relationships

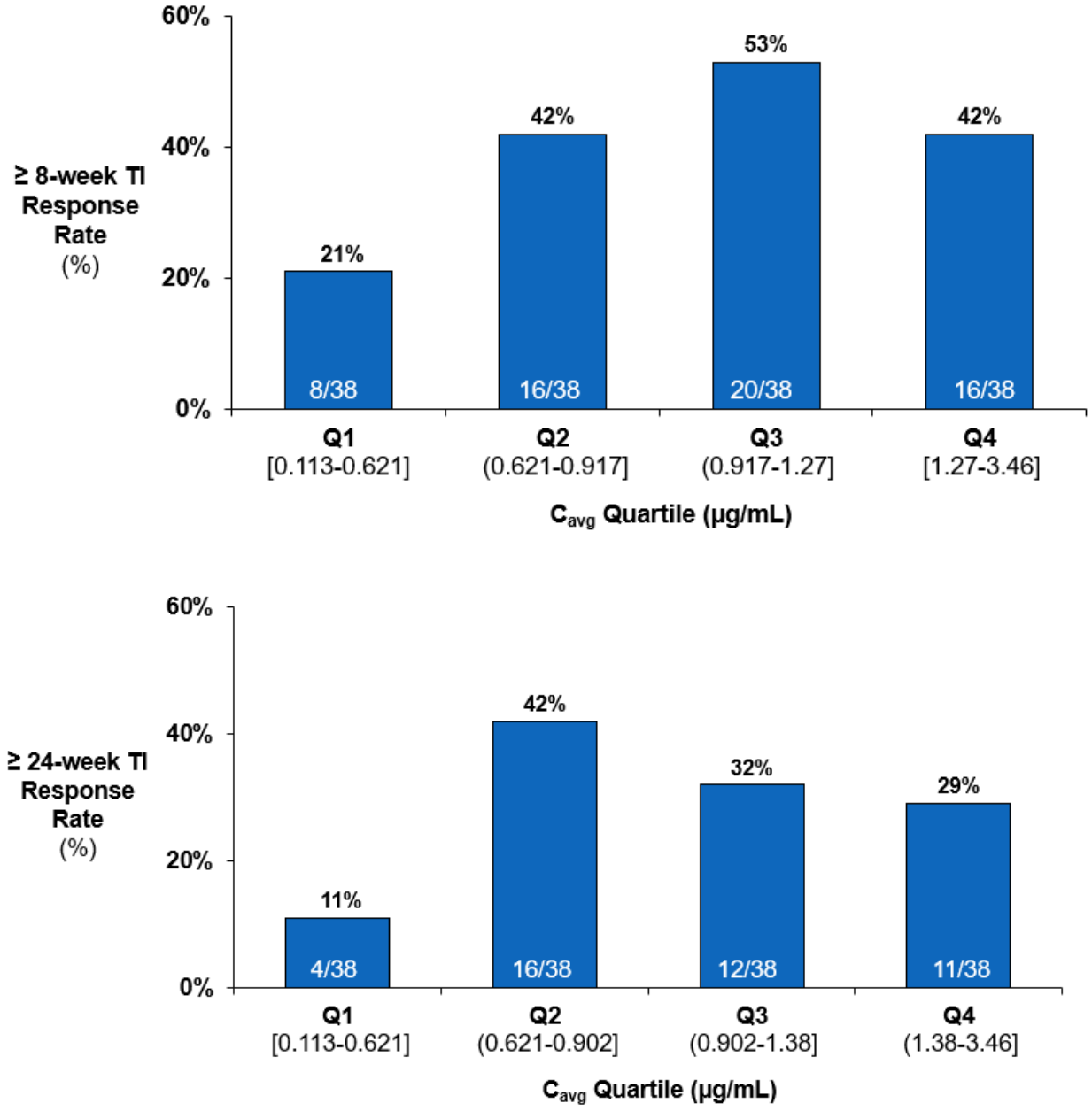
Exposure-response analyses for efficacy explored the relationship between the primary efficacy endpoint, proportion of patients achieving ≥ 8-week TI and the key secondary endpoint, proportion of patients achieving ≥ 24-week TI, and imetelstat exposure. The analyses used efficacy data from patients in the target population [non-del(5q) karyotype and without prior treatment with either hypomethylating agents or lenalidomide] in Phase 2 and all patients in Phase 3 of Study MDS3001 who were included in the popPK analysis (N=152 total).

Results from univariate and/or multivariate logistic regression exposure-response analyses for imetelstat efficacy demonstrated:

- In Study MDS3001, a statistically significant positive exposure-efficacy relationship between the proportion of patients who met the primary efficacy endpoint of ≥ 8-week TI and imetelstat average concentration up to the time of the event (C_{avg}) (Figure 11-4, top figure). Patients in the lowest exposure quartile (Q1) were associated with a lower rate of ≥ 8-week TI response (21%), and the proportion of patients achieving ≥ 8-week TI increased with increasing imetelstat exposure in the upper 3 quartiles (Q2-Q4: 42-53%). The exposure-efficacy relationship for ≥ 8-week TI remained significant in the multivariate analysis, alongside the baseline IPSS risk category.
- In Study MDS3001, there was a statistically significant positive exposure-efficacy relationship between the proportion of patients who met the key secondary efficacy endpoint of ≥ 24 week TI and -C_{avg} (Figure 11-4, bottom figure). Patients in the lowest exposure quartile (Q1) were associated with a lower rate of ≥ 24-week TI response (11%), and the proportion of patients achieving ≥ 24-week TI increased with increasing imetelstat exposure in the upper 3 quartiles (Q2-Q4: 29-42%). The exposure-efficacy relationship for ≥ 24-week TI remained significant in the multivariate analysis, with no additional identified covariates.

Overall, the results from exposure-efficacy analyses suggest that imetelstat doses (and accordingly C_{avg}) lower than 7.1 mg/kg q4w may result in reduced clinical efficacy.

Figure 11-4: MDS3001 – Exposure-Efficacy Analysis: ≥ 8-Week (Top) and ≥ 24-Week TI (Bottom) Response Frequency by Quartile of Imetelstat Exposure (C_{avg})



Includes all patients from combined MDS3001 Phase 2 target population (non-del(5q) and no prior treatment with hypomethylating agent or lenalidomide) and Phase 3 who were included in popPK analysis (N=152). C_{avg} = model-predicted average concentration, calculated up to the time of the achievement of event for responders or until the end of treatment for non-responders.

11.7.2 Exposure-Safety Relationships

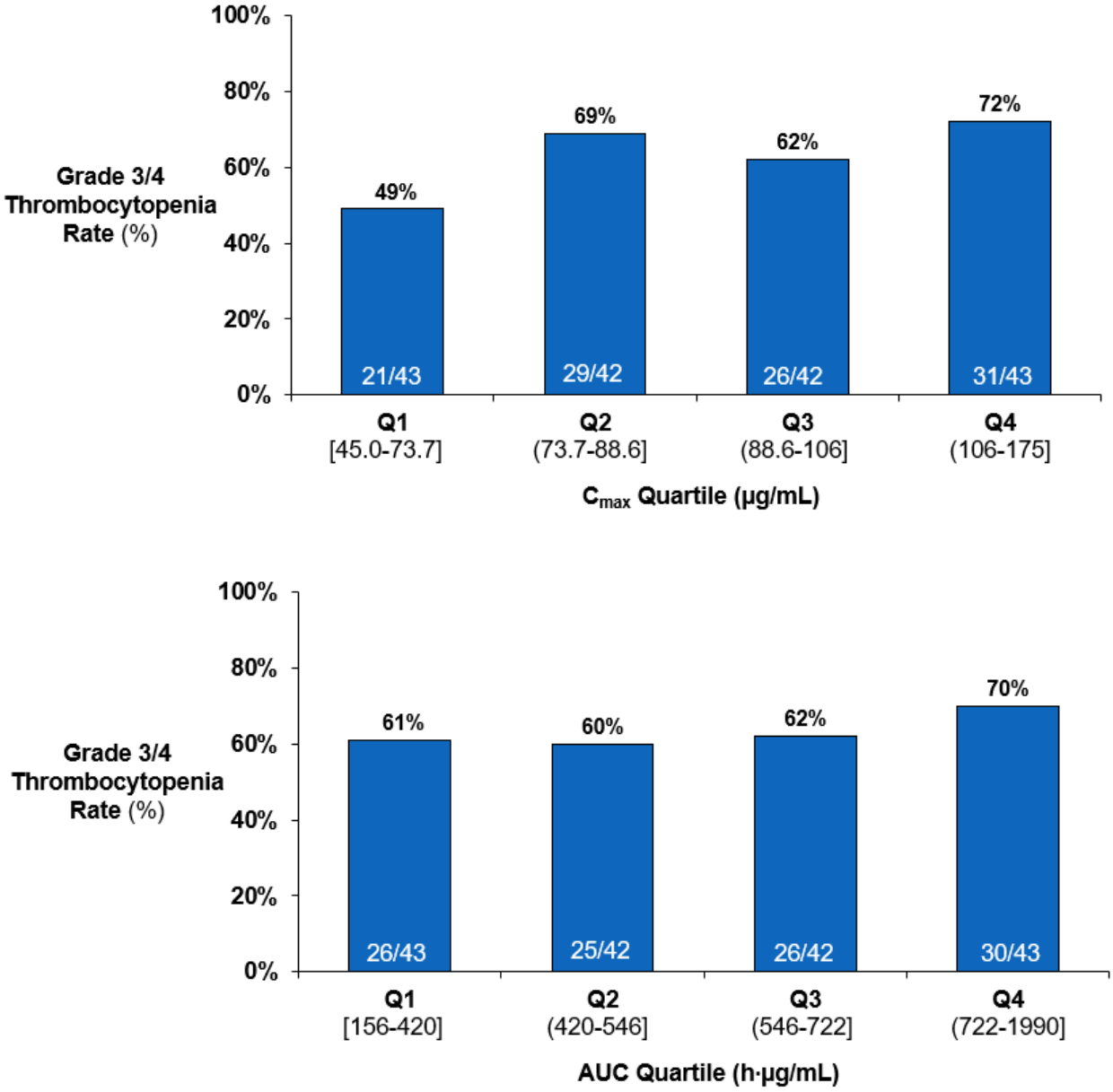
Exposure-response analyses utilized safety data from all patients in Phase 2 and Phase 3 of MDS3001 included in the popPK analysis (N=170). E-R analyses for safety explored the relationship between the proportion of patients with the following safety events and imetelstat exposure: Grade 3/4 neutropenia and Grade 3/4 thrombocytopenia (based on lab values and worsening from baseline); recovery of the first Grade 3/4 neutropenia or thrombocytopenia event to Grade ≤ 2 in less than 2 weeks or in less than 4 weeks; and any grade or Grade 3/4 infection and bleeding events, which are considered the clinical consequences of the cytopenias.

Results from univariate and/or multivariate logistic regression exposure-response analyses for safety in the indicated MDS population from Study MDS3001 show:

- No significant exposure-response relationship for probability of Grade 3/4 neutropenia and no significant exposure-response relationship for the probability of recovery from the first Grade 3/4 neutropenia event to Grade ≤ 2 in less than 2 weeks or in less than 4 weeks, with more patients recovering by 4 weeks than by 2 weeks.
- A positive exposure-response relationship for probability of Grade 3/4 thrombocytopenia (statistically significant for C_{max}, and approaching significance for AUC) (Figure 11-5), while no significant exposure-response relationship for the probability of recovery from the first Grade 3/4 thrombocytopenia event to Grade ≤ 2 in less than 2 weeks or in less than 4 weeks, with more patients recovering by 4 weeks than by 2 weeks.
- Importantly, no exposure-response relationships were identified for the clinical consequences of neutropenia and thrombocytopenia, namely infections and bleeding events. There were no significant E-R relationships for the probability of any grade infection event, Grade 3/4 infection event, any grade bleeding event or Grade 3/4 bleeding event with C_{max} or AUC (Figure 11-6, Figure 11-7). Thus, the clinical consequences of cytopenias and of the apparent positive exposure-response relationship for probability of Grade 3/4 thrombocytopenia are limited, supported by the low rates of high-grade infection and bleeding events in MDS patients.
- Investigations of thrombocytopenia in identified subpopulations with potentially higher imetelstat exposure showed no clear trends between incidence of Grade 3/4 thrombocytopenia and increasing body weight quartiles or between sex.
    - These analyses support that these identified subpopulations based on body weight and sex are not expected to be at increased risk of Grade 3/4 thrombocytopenia, and along with overall low rates of high-grade bleeding events in MDS patients in Study MDS3001, further supporting the limited clinical impact of the characterized exposure-safety relationship.
    - The positive exposure-safety relationship supports the proposed imetelstat cycle delay and dose reduction approach; modifying the dose of imetelstat

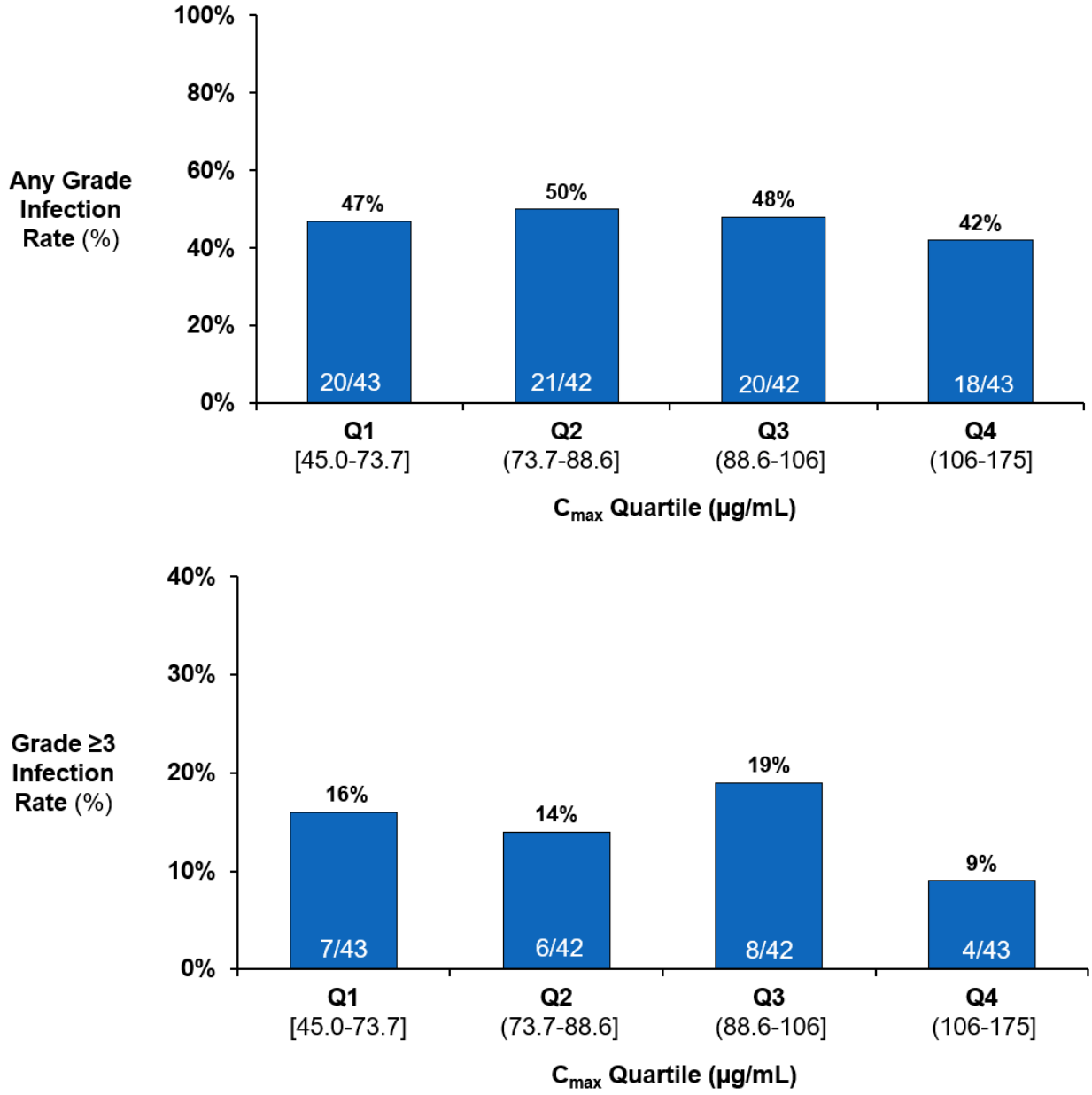
in those patients with increased severity of cytopenias can be an appropriate clinical strategy to manage the risks of associated clinical events.

Figure 11-5: MDS3001 – Exposure-Safety Analysis for Thrombocytopenia: Grade 3/4 Thrombocytopenia Frequency by Quartile of Imetelstat Exposure (C_{max} and AUC)



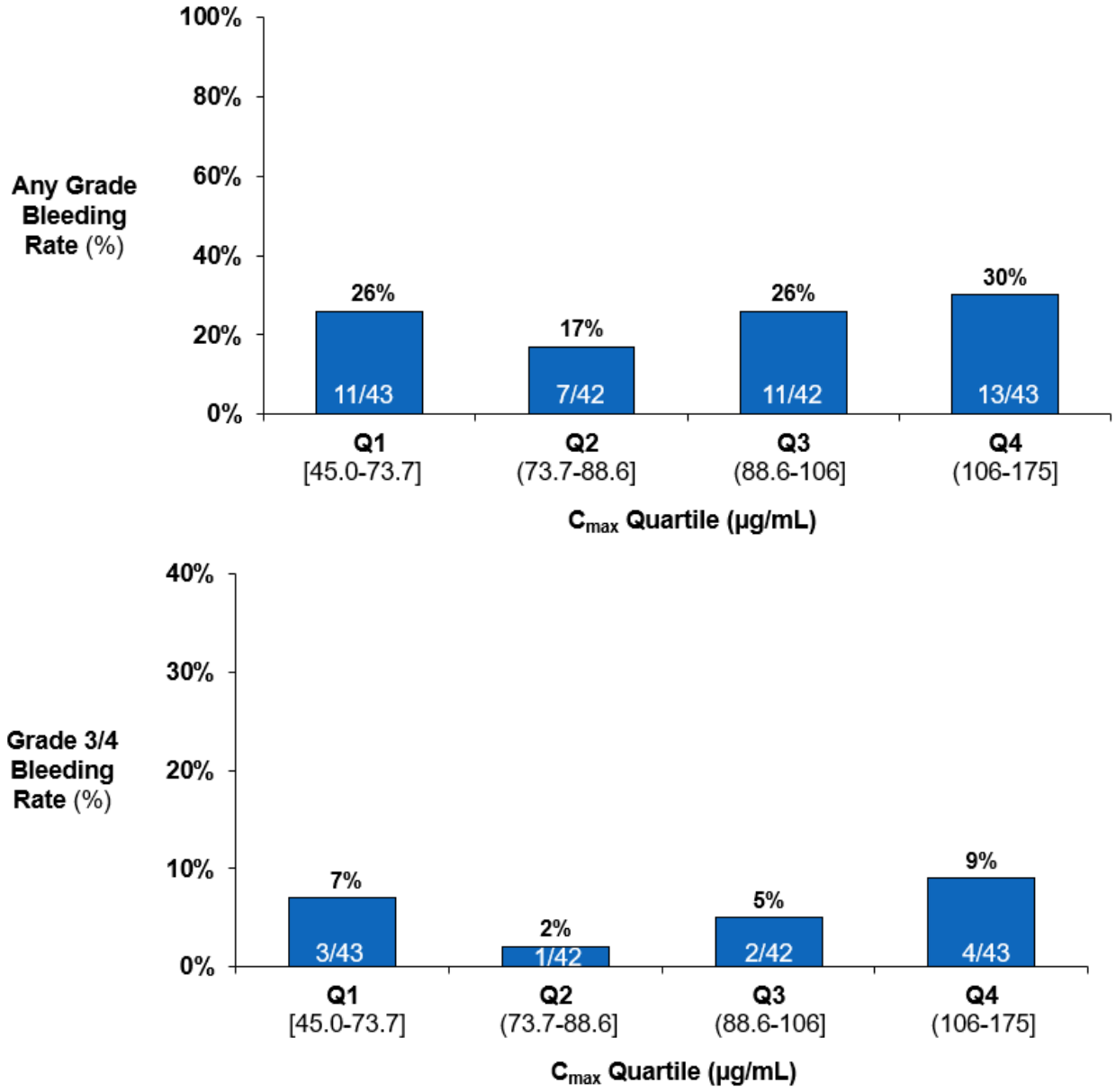
Includes all patients from MDS3001 Phase 2 and Phase 3 included in popPK analysis (N=170). AUC = model-predicted area under the concentration-time curve in Cycle 1; C_{max} = model-predicted maximum concentration in Cycle 1; All patients (with and without safety event) were divided into quartiles of C_{max} or AUC, with Q1 being the lowest quartile of exposure and Q4 being the highest quartile of exposure, and the response rate within each quartile is reported. Grade 3/4 Thrombocytopenia defined based on lab values and worsening from baseline.

Figure 11-6: MDS3001 – Exposure-Safety Analysis for Infections: Any Grade (Top) or Grade 3/4 (Bottom) Infection Frequency by Quartile of Imetelstat Exposure (C_{max})



Includes all patients from MDS3001 Phase 2 and Phase 3 included in popPK analysis (N=170). C_{max} = model-predicted maximum concentration in Cycle 1; All patients (with and without safety event) were divided into quartiles of C_{max}, with Q1 being the lowest quartile of exposure and Q4 being the highest quartile of exposure, and the response rate within each quartile is reported.

Figure 11-7: MDS3001 – Exposure-Safety Analysis for Bleeding: Any Grade (Top) or Grade 3/4 (Bottom) Bleeding Frequency by Quartile of Imetelstat Exposure (C_{max})



Includes all patients from MDS3001 Phase 2 and Phase 3 included in popPK analysis (N=170). C_{max} = model-predicted maximum concentration in Cycle 1; All patients (with and without safety event) were divided into quartiles of C_{max} or AUC, with Q1 being the lowest quartile of exposure and Q4 being the highest quartile of exposure, and the response rate within each quartile is reported.