Imetelstat for the Treatment of Transfusion-Dependent Anemia in Patients with Lower Risk Myelodysplastic Syndromes who have not Responded to or have Lost Response to or are Ineligible for Erythropoiesis-Stimulating Agents

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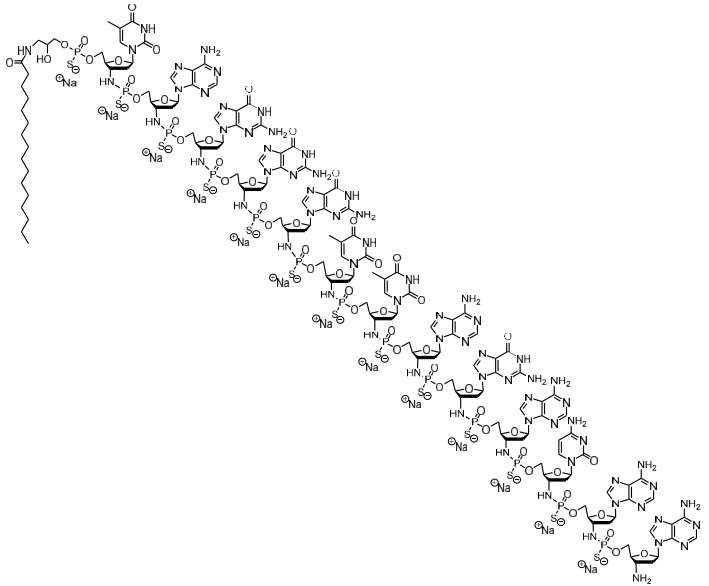
Oncologic Drugs Advisory Committee Meeting
March 14, 2024

Imetelstat: Oligonucleotide Telomerase Inhibitor

- Lipidated 13-mer oligonucleotide
- Targets overexpression of telomerase activity in malignant cells



- April 8, 2005: Investigational New Drug (IND) application submitted
- December 11, 2015: First subject enrolled in Phase 2/3 protocol 63935937MDS3001 (IMerge)
- June 16, 2023: New Drug Application (NDA) submitted

Proposed Indication and Regimen

- Proposed indication:
  - For the treatment of transfusion-dependent anemia in patients with lower risk myelodysplastic syndromes who are ineligible for ESA or after ESA failure
- Treatment regimen:
  - 7.1 mg/kg
  - Intravenous infusion, over 2 hours
  - Every 4 weeks

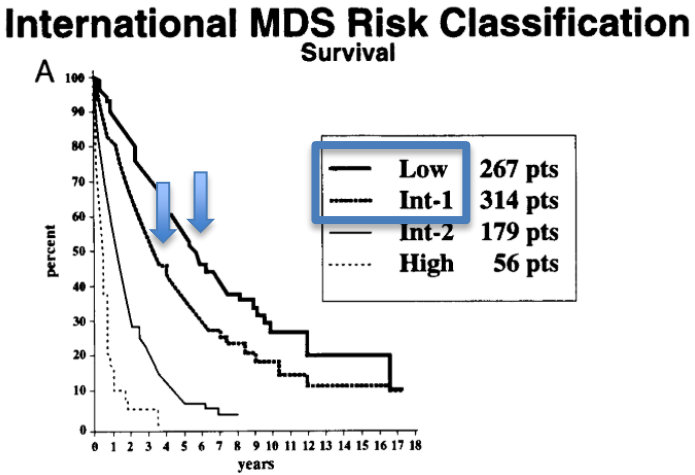
ESA = erythropoiesis-stimulating agents

Evidentiary Criteria for Approval

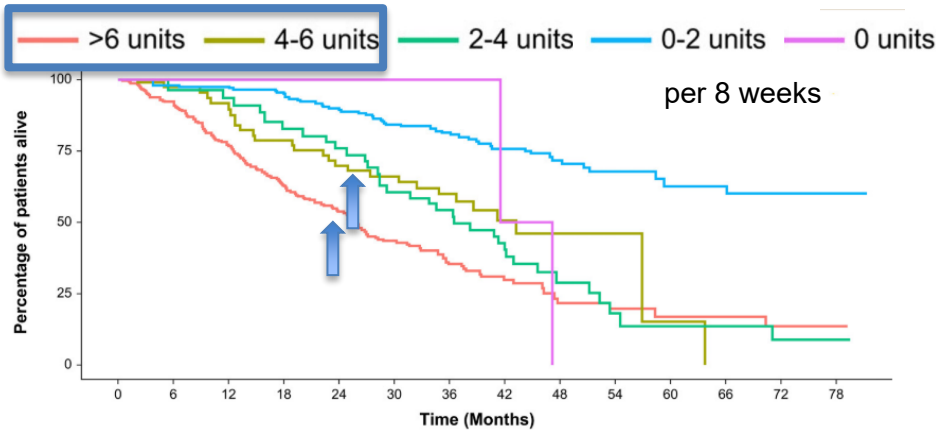
- **Safe and effective**
  - FDA must determine that the drug is safe and effective for use under the conditions prescribed, recommended, or suggested in the product's labeling
- **Benefits must outweigh risks**
  - Demonstration of effectiveness requires substantial evidence that the drug will have the effect it purports or is represented to have
  - Demonstration of safety requires showing that benefits of the drug outweigh its risks

Lower-risk Myelodysplastic Syndrome with Transfusion Dependence

- Heterogeneous disorder from clonal expansion of a hematopoietic progenitor
- Bone marrow dysplasia, ineffective hematopoiesis, risk of transformation to AML



Greenberg et al. Blood 1997



Santini et al. Clin Lymphoma Myeloma Leuk 2022

AML = acute myeloid leukemia; MDS = myelodysplastic syndrome

Treatment Landscape: Transfusion-Dependent Lower-Risk MDS

- ESAs
- Luspatercept
- Lenalidomide*
- HMAs*

* Patients previously treated with HMAs or lenalidomide were excluded from MDS3001-Phase 3

ESA = erythropoiesis-stimulating agents (e.g., epoetin alfa); HMAs = hypomethylating agents (e.g., azacitidine, decitabine)

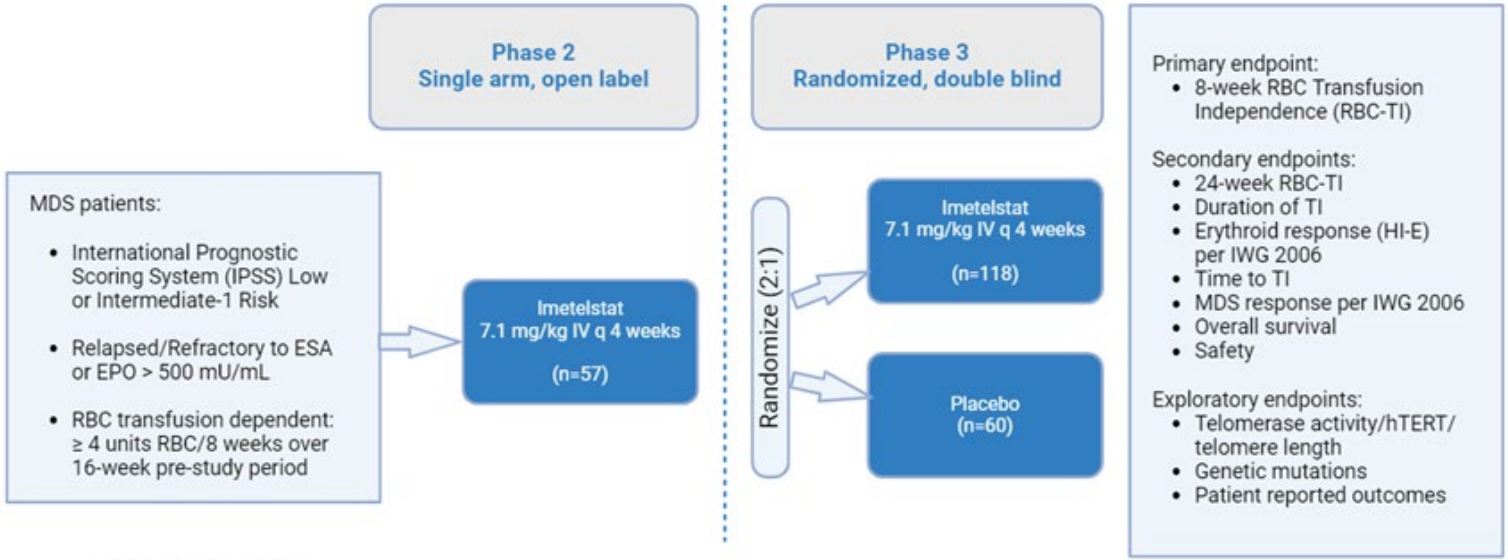
Basis of Approvals in MDS

	Year of initial approval	Population	Basis of approval
Azacitidine	2004	LR-MDS and HR-MDS	CR + PR, OS
Lenalidomide	2005	Anemia in LR-MDS with 5q-	8-week RBC TI
Decitabine	2006	LR-MDS and HR-MDS	CR + PR, DOR
Luspatercept	2020	Anemia in LR-MDS with RS after ESA failure	8-week RBC-TI during weeks 1-24
	2023	Anemia in LR-MDS, ESA-naive	12-week RBC-TI with Hb increase 1.5 gm/dL during weeks 1-24
Decitabine-cedazuridine	2020	LR-MDS and HR-MDS	CR, RBC/platelet-TI
Ivosidenib	2023	R/R MDS with IDH1 mutation	CR + PR, DOR, RBC/platelet-TI

LR-MDS / HR-MDS = lower risk / higher risk myelodysplastic syndrome;
RS = ring sideroblasts, ESA = erythropoiesis-stimulating agents
R/R = relapsed/refractory; IDH1 = isocitrate dehydrogenase 1

CR = complete remission; PR = partial remission;
DOR = duration of response
RBC-TI = red blood cell transfusion independence

MDS3001 (IMerge) Study Design



Supportive care, including transfusions or myeloid growth factors, were administered as needed per investigator discretion and according to local standard practices.

Note: Imetelstat 7.1 mg/kg is equivalent to imetelstat sodium 7.5 mg/kg

Main Topics

- Efficacy: Magnitude and duration of RBC transfusion independence without improvement in survival, response, PROs
- Safety: Myelosuppression, tolerability, dose
- Benefit-Risk Assessment

PROs = patient reported outcomes

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- **Efficacy: Magnitude and duration of RBC transfusion independence without improvement in survival, response, PROs**
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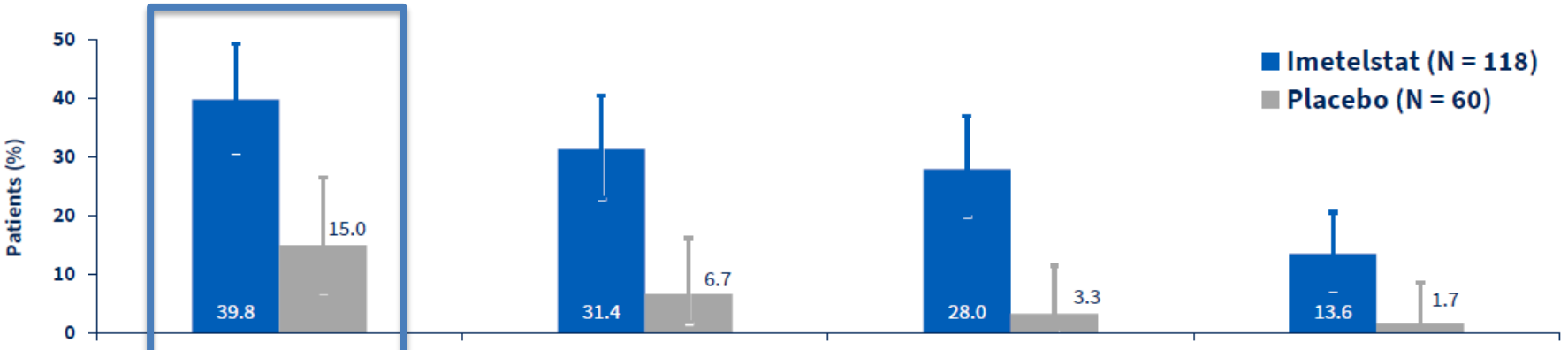
Magnitude and Duration of Red Blood Cell – Transfusion Independence

Primary endpoint



Patients With Response, n (% [95% CI])	8-week TI [a]	16-week TI	24-week TI	1-year TI
Imetelstat	47 (39.8 [30.9–49.3])	37 (31.4 [23.1–40.5])	33 (28.0 [20.1–37.0])	16 (13.6 [8.0–21.1])
Placebo	9 (15.0 [7.1–26.6])	4 (6.7 [1.9–16.2])	2 (3.3 [0.4–11.5])	1 (1.7 [0.0–8.9])

[a] 8-week RBC-TI: 24.8% difference from placebo

RBC-TI = red blood cell transfusion independence

Data cutoff 13 Oct 2022

Source: Applicant's Orientation Meeting Slides

Duration of Longest RBC-TI Interval

Cohort	Treatment group	Median duration of the longest RBC-TI interval in weeks (95% CI)*
All subjects	Imetelstat (N=118)	5.0 (4.0, 7.7)
	Placebo (N=60)	3.9 (3.6, 4.0)
8-week RBC-TI responders	Imetelstat (N=47)	51.6 (26.9, 83.9)
	Placebo (N=9)	13.3 (8.0, 24.9)

*Calculated using the Kaplan-Meier Method

Notes: ITT population; longest RBC-TI interval started after randomization and before end of treatment visit, last dose + 30 days, and date of initiation of subsequent anticancer/antianemia therapy. RBC-TI longest interval terminated with the next RBC transfusion, death, last adequate transfusion status assessment, or date of initiation of subsequent anticancer/antianemia therapy, whichever is first.

Data cutoff 13 Oct 2022

Source: FDA analysis using ADTTEEF dataset

Measures of Clinical Benefit at Primary Analysis

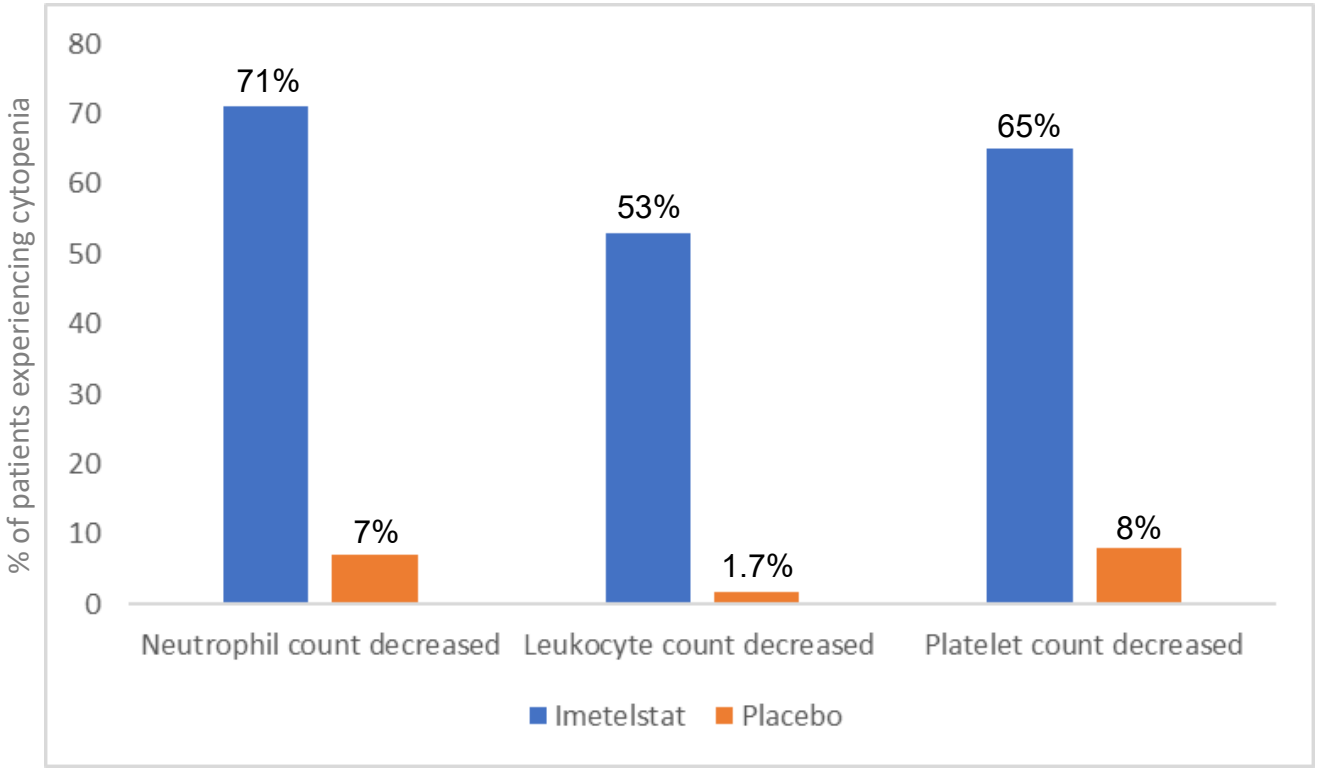
- No benefit demonstrated in:
  - **HI-E**: 64% imetelstat vs. 52% placebo
  - **CR or PR**: 0% imetelstat vs. 0% placebo
  - **OS**: HR 1.07 (95% CI: 0.46, 2.48)
  - **PROs**: Deterioration in FACIT-fatigue: 43% imetelstat vs. 46% placebo

HI-E: hematologic improvement – erythroid, per IWG 2006 criteria
CR: complete response, PR: partial response, OS: overall survival
PROs: patient reported outcomes

Main Topics

- Efficacy: Magnitude and duration of RBC transfusion independence without improvement in survival, response, PROs
- **Safety: Myelosuppression, tolerability, dose**
- Benefit-Risk Assessment

Grade 3-4 Cytopenias



Data cutoff 13 Oct 2022

Source: FDA analysis using ADLB dataset

Interventions for Cytopenias More Common with Imetelstat

	Imetelstat (N=118)	Placebo (N=60)
Subjects requiring myeloid growth factor on-treatment, n (%)	41 (35%)	2 (3%)
Frequency of myeloid growth factor administration, median (range)	3 (1, 23)	-- (1, 7)

	Imetelstat (N=118)	Placebo (N=60)
Subjects requiring platelet transfusion on-treatment, n (%)	21 (18%)	1 (2%)
Number of platelet transfusions, median (range)	1 (1, 10)	-- (1)

Data cutoff 13 Oct 2022

Source: FDA analysis using ADCM and ADTIPR datasets

Consequences of Cytopenias

Adverse event	Imetelstat N=118 (%)		Placebo N=59 (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Infections	42	11	34	14
Hemorrhage	21	2.5	12	1.7

Data cutoff 13 Oct 2022

Source: FDA analysis using ADAE dataset

Main Topics

- Efficacy: Magnitude and duration of RBC transfusion independence without improvement in survival, response, PROs
- Safety: Myelosuppression, tolerability, dose
- **Benefit-Risk Assessment**

Benefit-Risk Assessment

Potential benefit

	Imetelstat (N=118)	Placebo (N=60)	Difference
8-week RBC-TI	40%	15%	+25%
24-week RBC-TI	28%	3%	+25%

- In the context of:
  - Monthly infusion visits
  - No demonstration of CR/PR or OS benefit
  - No clear difference in PROs

Potential risks

	Imetelstat (N=118)	Placebo (N=59)	Difference
Grade 3-4 neutropenia	**71%**	**7%**	**+64%**
Myeloid growth factor requirement	35%	3%	+32%
Infection (any grade)	42%	34%	+9%
Grade 3-4 thrombocytopenia	**65%**	**8%**	**+57%**
Platelet transfusion requirement	18%	2%	+16%
Bleeding (any grade)	21%	12%	+9%

Source: Study MDS3001 Phase 3 CSR & FDA analysis using ADAE, ADCM, ADTIPR datasets

Discussion Question

Discuss the efficacy of imetelstat for patients with lower-risk MDS based on the results of the MDS3001 trial considering the safety profile.

Voting Question

Do the benefits of imetelstat outweigh its risks for the treatment of transfusion-dependent anemia in adult patients with IPSS low- to intermediate-1 risk MDS who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents?

Imetelstat for the Treatment of Transfusion-Dependent Anemia in Patients with Lower Risk Myelodysplastic Syndromes who have Not Responded to or have Lost Response to or are Ineligible for Erythropoiesis-Stimulating Agents

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Oncologic Drugs Advisory Committee Meeting
March 14, 2024

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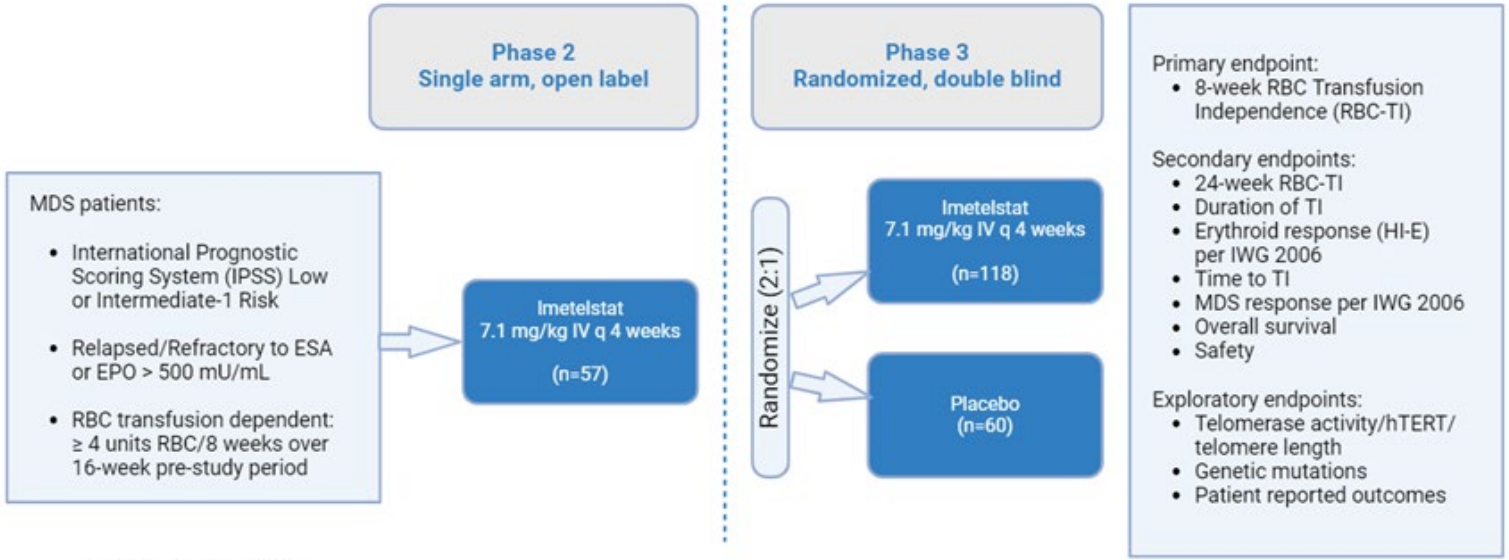
- Nan Zheng, PhD
- Karina Zuck, PhD

FDA Presentation Outline

- Efficacy Issues
  - Magnitude and duration of Red Blood Cell (RBC) Transfusion Independence (RBC-TI)
  - Hematologic improvement (HI), complete remission (CR)/partial remission (PR), and overall survival (OS) results
  - Patient-reported outcomes (PROs)
- Safety Issues
  - Cytopenias
  - Other risks (fractures, arthralgias/myalgias, and fatigue)
  - Dosing concerns
- Benefit-Risk Assessment

MDS3001 (IMerge) Study Design



Stratification factors:
- Prior RBC transfusion burden (Max ≤ 6 or >6 RBC units transfused over an 8-week period during the 16 weeks prior to randomization)
- IPSS risk group (Low- or Intermediate-1 Risk)

Supportive care, including transfusions or myeloid growth factors, were administered as needed per investigator discretion and according to local standard practices.

Note: Imetelstat 7.1 mg/kg is equivalent to imetelstat sodium 7.5 mg/kg

Study MDS3001 Phase 3 Demographics

Demographic parameter	Imetelstat (N=118)	Placebo (N=60)
Sex		
Male	60%	67%
Female	40%	33%
Age group		
< 65 years	23%	15%
≥ 65 years	77%	85%
Race		
White	81%	80%
Black or African American	1%	3%
Asian	7%	3%
Other/Not reported/Missing	12%	2%
Region		
North America	11%	20%
European Union	68%	63%
Rest of world	21%	17%

Source: Study MDS3001 Phase 3 CSR

Study MDS3001 Phase 3 Baseline Characteristics

Baseline characteristic	Imetelstat (N=118)	Placebo (N=60)
IPSS Category		
Low	68%	67%
Intermediate-1	32%	33%
Prior therapies		
ESA	92%	87%
Luspatercept	6%	7%
Hypomethylating agent	0%	<1%
Lenalidomide	<1%	0%
RBC transfusion burden per 8 weeks		
Median RBC units (min, max)	6.0 (4, 33)	6.0 (4, 13)
Median baseline blood counts		
Neutrophils (cells/L)	2.6×10^9	2.7×10^9
Hemoglobin (g/dL)	7.9	7.8
Platelets (cells/L)	230×10^9	239×10^9

Source: Study MDS3001 Phase 3 CSR

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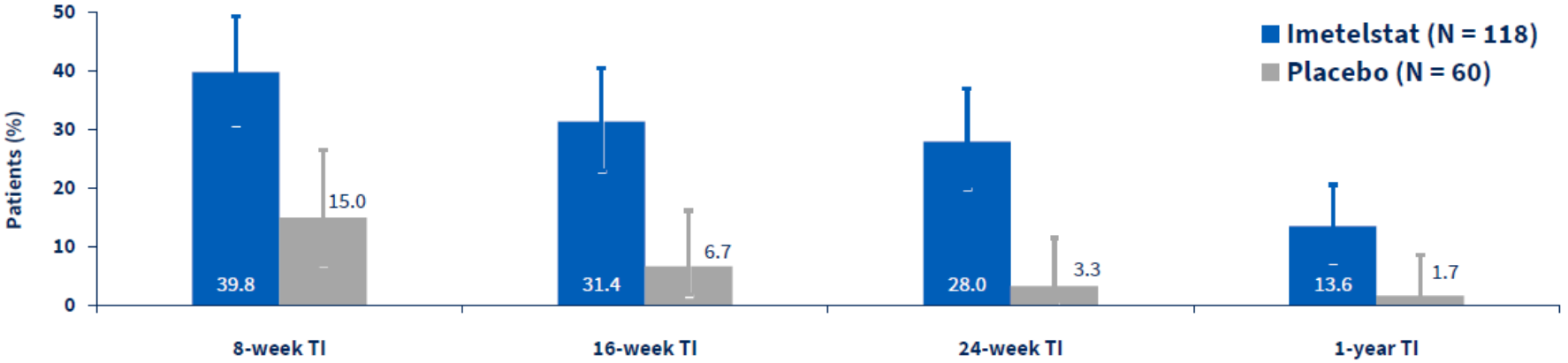
Efficacy Issues

Evidence of Effectiveness

- FDA's review focuses on the Phase 3 results of Study MDS3001
- Treatment with imetelstat was statistically superior to placebo for:
  - 8-week RBC-TI (39.8% vs 15.0%, p <0.001)
  - 24-week RBC-TI (28.0% vs 3.3%, p <0.001)

Magnitude of RBC-TI



Patients With Response, n (% [95% CI])	Transfusion Independence			
Imetelstat	47 (39.8 [30.9–49.3])	37 (31.4 [23.1–40.5])	33 (28.0 [20.1–37.0])	16 (13.6 [8.0–21.1])
Placebo	9 (15.0 [7.1–26.6])	4 (6.7 [1.9–16.2])	2 (3.3 [0.4–11.5])	1 (1.7 [0.0–8.9])

Data cutoff 13 Oct 2022

Source: Applicant's Orientation Meeting Slides

Duration of Longest RBC-TI Interval

Cohort	Treatment group	Median duration of the longest RBC-TI interval in weeks (95% CI)*
All subjects	**Imetelstat (N=118)**	5.0 (4.0, 7.7)
	Placebo (N=60)	3.9 (3.6, 4.0)
8-week RBC-TI responders	**Imetelstat (N=47)**	51.6 (26.9, 83.9)
	Placebo (N=9)	13.3 (8.0, 24.9)

*Calculated using the Kaplan-Meier Method

Notes: ITT population; longest RBC-TI interval started after randomization and before end of treatment visit, last dose + 30 days, and date of initiation of subsequent anticancer/antianemia therapy. Longest RBC-TI interval terminated with the next RBC transfusion, death, last adequate transfusion status assessment, or date of initiation of subsequent anticancer/antianemia therapy, whichever is first.

Data cutoff 13 Oct 2022

Source: FDA analysis using ADTTEEF dataset

CR and PR Results at Primary Analysis

- **Per Independent Review Committee (IRC) assessment:**
  - Only 2 subjects (1 in each treatment arm) were assessed for CR and PR by the IRC
  - **Neither achieved CR or PR**
- **Per investigator assessment:**

	Imetelstat (N=118)	Placebo (N=60)
CR	0	0
PR	0	0
mCR	0	0
SD	69%	68%
Relapse after CR or PR	0	0
Disease progression	6%	3%
Failure	2%	0
Not evaluable*	24%	28%

*Largely due to absent post-baseline bone marrows

Data cutoff 13 Oct 2022

Source: Study MDS3001 Phase 3 CSR

Lack of Hematologic Improvement (HI)

	Imetelstat (N=118)	Placebo (N=60)	P value
Erythroid (HI-E) response rate[a]	64%	52%	0.112
Platelet (HI-P) response rate[a]	0	0	N/A
Neutrophil (HI-N) response rate[a]	None eligible[b]	None eligible[b]	N/A

[a] According to IWG 2006 MDS response criteria

[b] Due to requirement for ANC > 1.5 x 10^9/L at baseline for study eligibility

HI-E definition (per IWG 2006 criteria):

- Hemoglobin increase by ≥ 1.5 g/dL for at least 8 weeks, plus
- Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks. Only RBC transfusions given for a Hgb ≤ 9.0 g/dL pre-transfusion count in the RBC transfusion response evaluation.

Data cutoff 13 Oct 2022

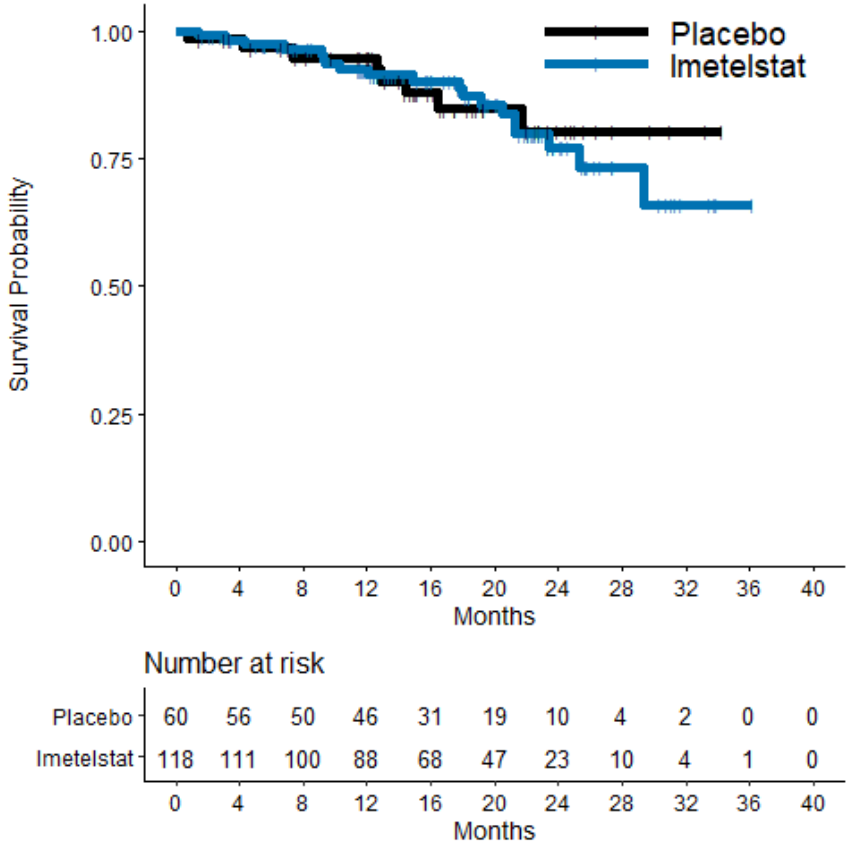
Source: Study MDS3001 Phase 3 CSR

Lack of Overall Survival Benefit (Primary Analysis)

HR = 1.07 (95% CI: 0.46, 2.48)

	Imetelstat (N=118)	Placebo (N=60)
Deaths, n (%)	19 (16%)	8 (13%)
Median Follow-up, months (range)	19.5 (1.4, 36.2)	17.5 (0.7, 34.3)

HR = Hazard Ratio; CI = Confidence Interval; OS = Overall Survival;
NE = Non-estimable



Source: FDA analysis using ADTTEEF dataset; Data cutoff: 13 October 2022

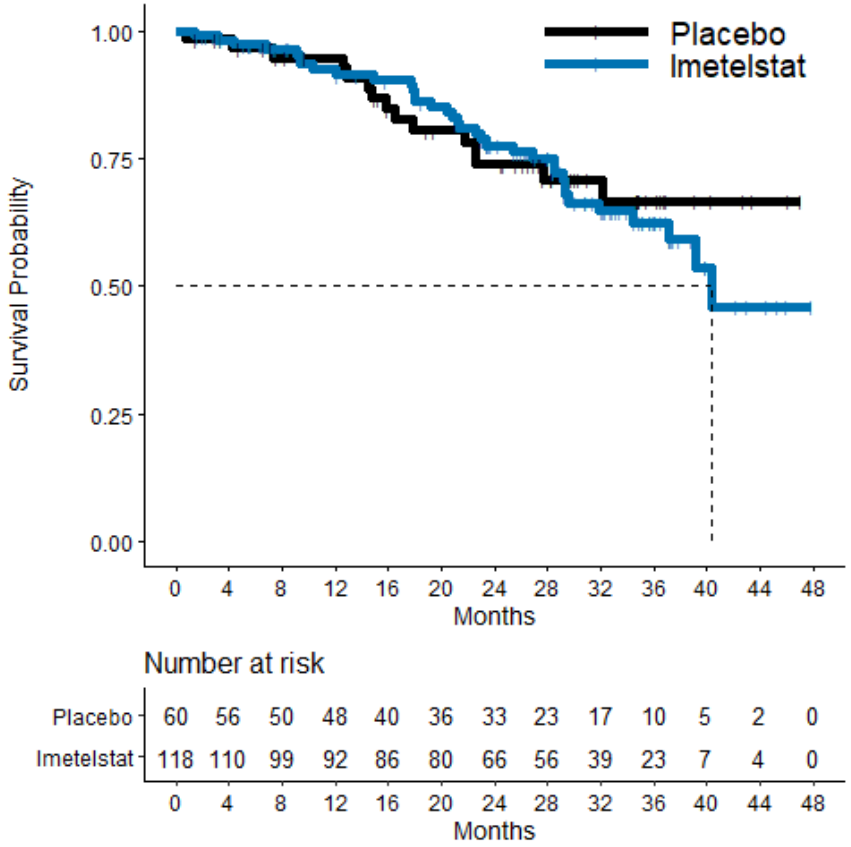
Lack of Overall Survival Benefit (Updated Analysis)

HR = 0.98 (95% CI: 0.53, 1.82)

	Imetelstat (N=118)	Placebo (N=60)
Deaths, n (%)	35 (30%)	15 (25%)
Median OS, months (95% CI)	40.4 (37.1, NE)	NE (32.2, NE)
Median Follow-up, months (range)	32.2 (1.4, 47.8)	28.4 (0.7, 47.0)

HR = Hazard Ratio; CI = Confidence Interval; OS = Overall Survival;
NE = Non-estimable

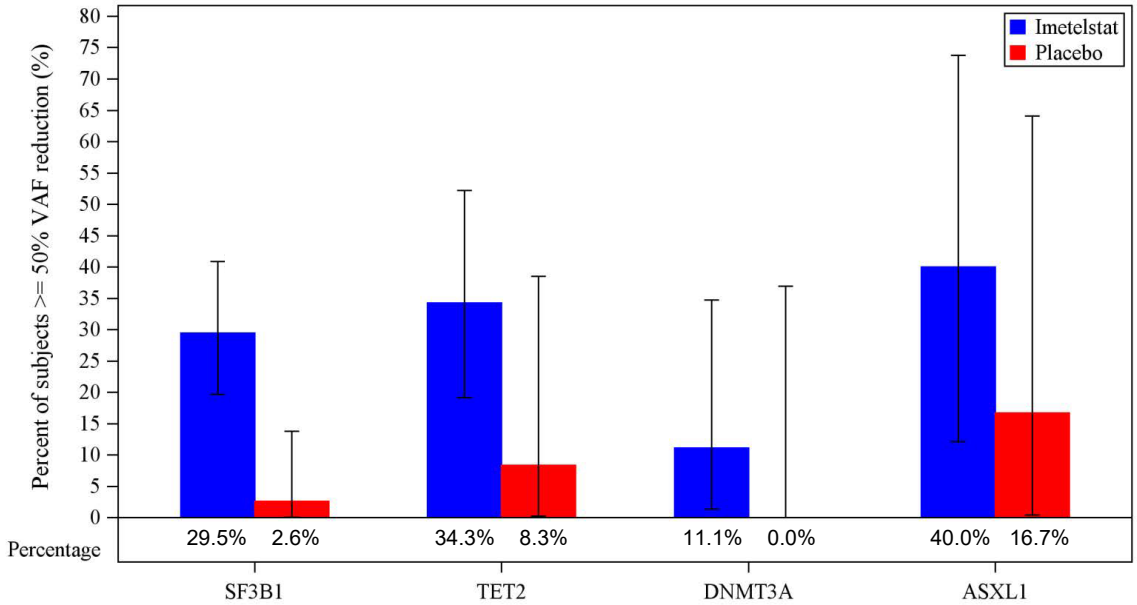
Kaplan-Meier Plot of Overall Survival (ITT set)



Source: FDA analysis using ADTTEEF dataset; Data cutoff: 5 January 2024

Change in Mutational Burden

Subjects Achieving ≥ 50% Reduction from Baseline in SF3B1, TET2, DNMT3A and ASXL1 Variant Allele Frequency (VAF) (Phase 3, Mutation Biomarker Analysis Set)



Number of Patients with ≥50% VAF reduction/Total Evaluable					
	Imetelstat	23/78 (29.5%)	12/35 (34.3%)	2/18 (11.1%)	4/10 (40.0%)
	Placebo	1/38 (2.6%)	1/12 (8.3%)	0/8 (0.0%)	1/6 (16.7%)

Data cutoff 13 Oct 2022

Source: Study MDS3001 Phase 3 CSR

Mutational Burden Interpretation and Conclusions

- Mutation burden analyses were purely exploratory
- Issues with the methodology of data collection:
  - Next Generation Sequencing (NGS) assay utilized was not designed for VAF tracking
  - Only a subset of patients were eligible for analysis
  - Samples were collected by peripheral blood (not marrow) and at relatively sparse timepoints
- Unclear whether a ≥ 50% VAF reduction is clinically significant
- Reduction in mutational burden is not a direct measure of clinical benefit

Patient-Reported Outcomes (PROs)

- PROs were exploratory endpoints, not controlled for multiplicity
- PROs were assessed sparsely: at screening, day 1 of each 4-week cycle, end of treatment, and follow up until start of subsequent therapy
- Compliance rate >85% during first year of treatment, however after cycle 8, available data rate drops below 50% due to attrition
- Applicant PRO endpoint of interest: proportion of patients who experienced deterioration in fatigue
  - No difference noted (43% imetelstat vs. 46% placebo)

PRO Interpretation and Conclusions

- PROs were not prespecified as secondary endpoints with multiplicity adjustment – the results need to be considered purely exploratory
- Additional PRO analyses did not show a large or meaningful improvement in symptoms
- PRO results from MDS3001 are difficult to interpret due a small sample size and available data rate being low after cycle 8
- Durability of fatigue improvement unclear and was not demonstrated

Submitted results are not compelling and do not support that imetelstat improves fatigue compared to placebo

Summary of Efficacy Issues

- Study MDS3001 met the statistical objective for 8-week and 24-week RBC transfusion independence
- The median duration of the longest RBC-TI interval was short when considering all patients
- The secondary endpoints of HI-E, CR, PR, and OS are not supportive of a disease-modifying treatment effect
- PROs do not corroborate the treatment effect

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Safety Issues

Safety Overview

Adverse Event (AE)	Imetelstat (N=118) (%)	Placebo (N=59) (%)
Overall	99	100
Serious adverse events (SAEs)	32	22
Grade 3-4	91	47
Grade 3-4 excluding neutropenia and thrombocytopenia	54	39
Grade 5	0.8	1.7
AE leading to dose modification	86	25
Discontinuation	14	0
Dose reduction	49	7
Dose interruption or delay	78	25

Data cutoff 13 Oct 2022

Source: FDA analysis using ADAE dataset

Treatment Emergent Adverse Events Occurring in >15% of Patients Excluding Laboratory Abnormalities

Adverse event	Imetelstat N=118 (%)		Placebo N=59 (%)	
	All grade	Grade 3-4	All grade	Grade 3-4
Infections[a]	42	11	34	14
Fatigue[b]	29	0	22	1.7
Arthralgia/myalgia[b]	25	2.5	17	5
Anemia[c]	20	20	10	7
Hemorrhage[d]	21	2.5	12	1.7
Arterial occlusive events[b]	3.4	0	15	5

[a]SOC infections and infestations; [b]Custom grouped terms; [c]HLT anemia NEC; [d]Broad SMQ Haemorrhage

AEs of significance reported at <15% and more frequently in the imetelstat arm included hepatic toxicity (14% vs 12%), fractures (5% vs 1.7%), pruritus (6% vs 1.7%), bone pain (3.4% vs 0%)

Data cutoff 13 Oct 2022
Source: FDA analysis using ADAE datasets

Laboratory Abnormalities Occurring in >30% of Patients

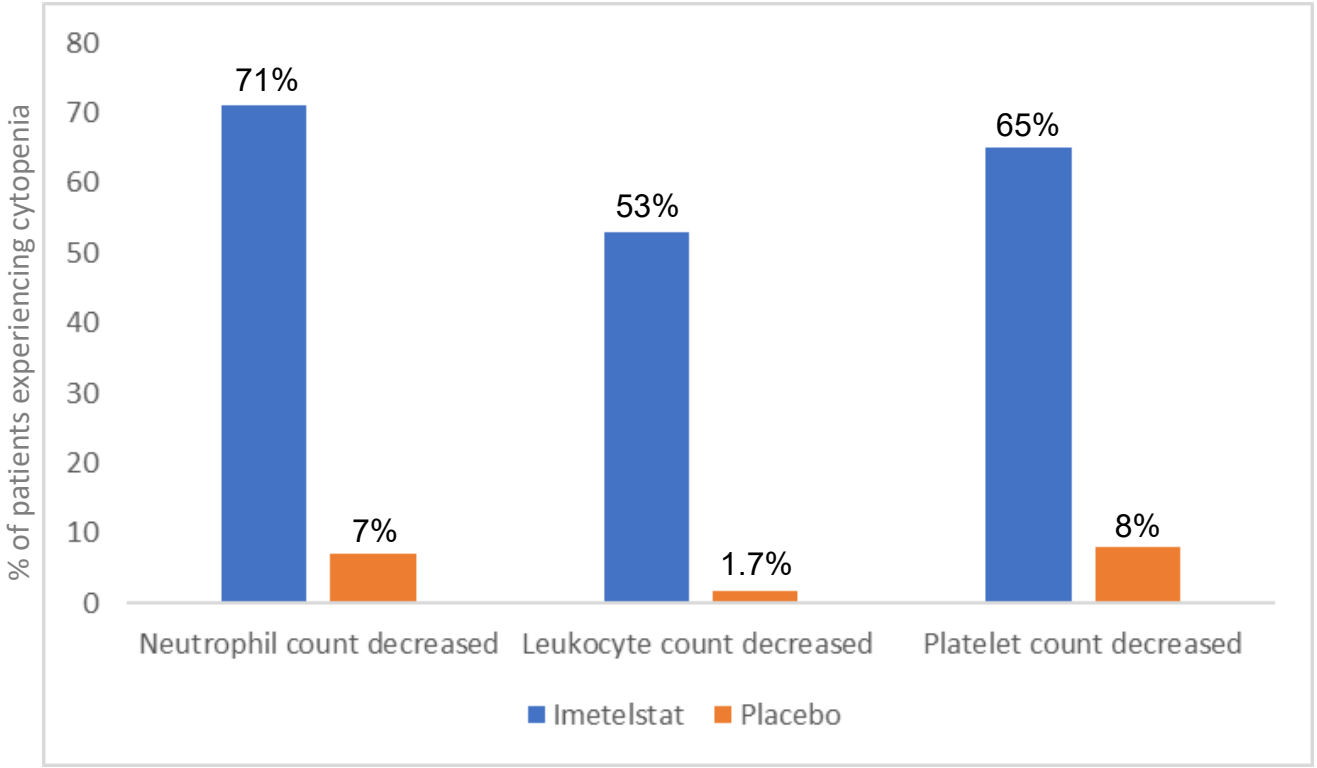
Laboratory abnormality *	Imetelstat N=118 (%)		Placebo N=59 (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Hematology				
Platelets decreased	96	65	34	8
Leukocytes decreased	94	53	58	1.7
Neutrophils decreased	92	71	47	7
Hemoglobin decreased	64	64	64	64
Chemistry				
Creatinine increased	77	0	75	0
Aspartate aminotransferase increased	48	0.8	22	1.7
Alkaline phosphatase increased	45	0	12	0
Alanine aminotransferase increased	40	3.4	37	5
Bilirubin increased	39	0.8	39	1.7

* Worsening from baseline

Data cutoff 13 Oct 2022

Source: FDA analysis using ADLB datasets based on local laboratory values

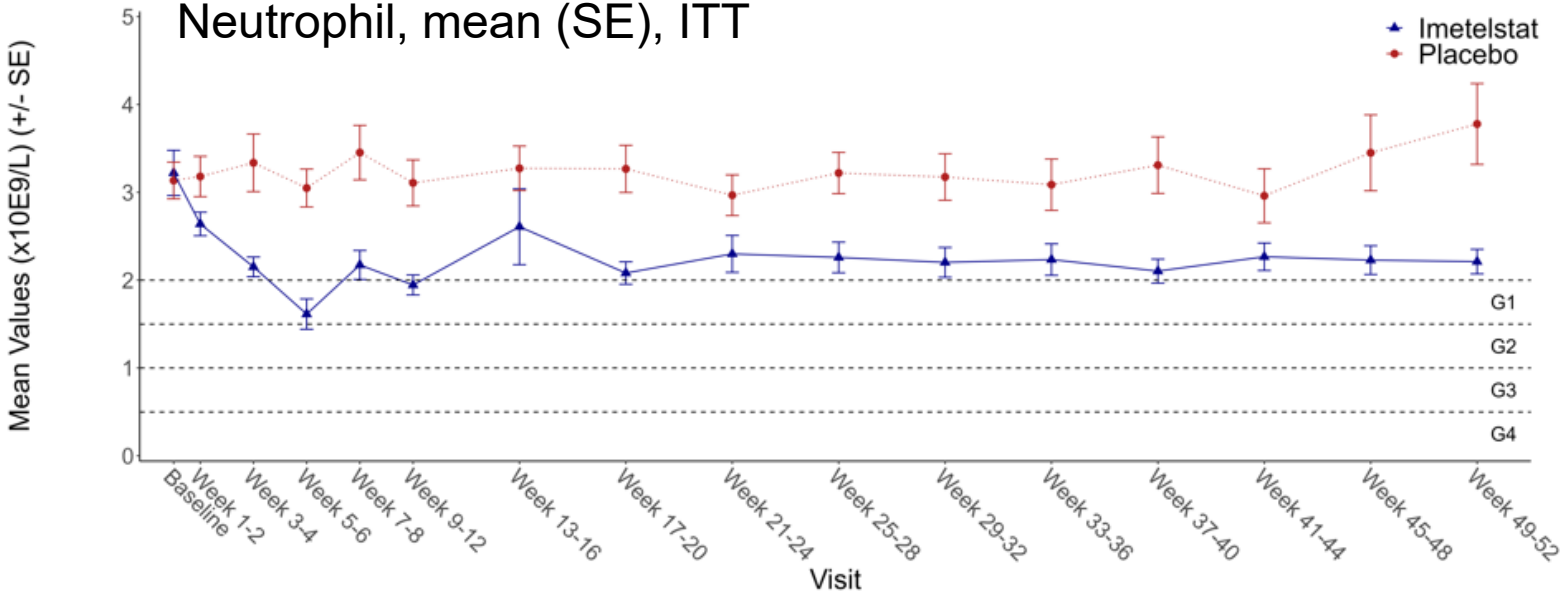
Grade 3-4 Cytopenias



Data cutoff 13 Oct 2022

Source: FDA analysis using ADLB dataset

Neutropenia Persisted Over Time on Imetelstat



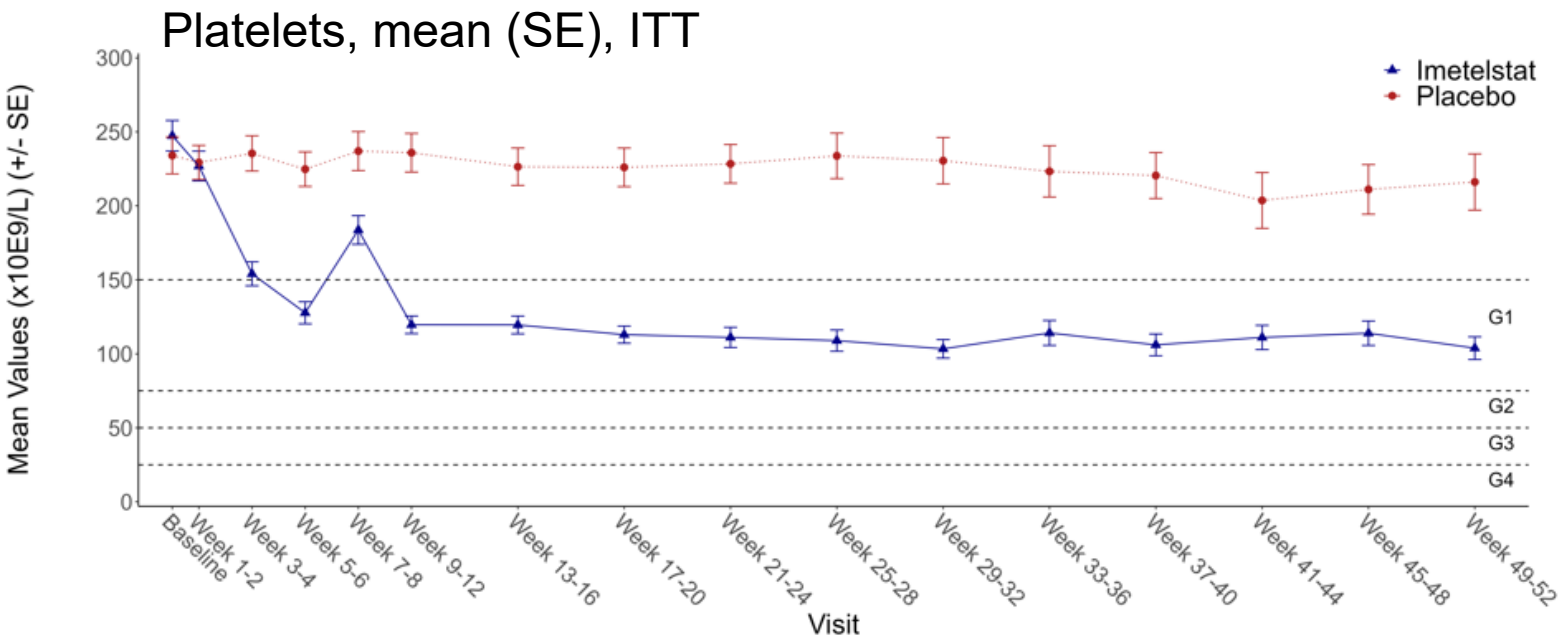
Number of Subjects

	Baseline	Week 1-2	Week 3-4	Week 5-6	Week 7-8	Week 9-12	Week 13-16	Week 17-20	Week 21-24	Week 25-28	Week 29-32	Week 33-36	Week 37-40	Week 41-44	Week 45-48	Week 49-52
Placebo	60	57	55	57	55	52	51	51	43	38	28	25	22	20	19	
Imetelstat	118	116	114	109	107	103	100	91	83	78	67	61	52	51	51	

Data cutoff 13 Oct 2022

Source: FDA analysis using ADLB dataset

Thrombocytopenia Persisted Over Time on Imetelstat



Number of Subjects

	Baseline	Week 1-2	Week 3-4	Week 5-6	Week 7-8	Week 9-12	Week 13-16	Week 17-20	Week 21-24	Week 25-28	Week 29-32	Week 33-36	Week 37-40	Week 41-44	Week 45-48	Week 49-52
Placebo	60	58	58	57	56	55	51	51	43	39	28	26	23	20	19	
Imetelstat	118	116	117	110	107	105	100	94	84	79	68	61	52	53	51	

Data cutoff 13 Oct 2022

Source: FDA analysis using ADLB dataset

Duration of Cytopenias

	Imetelstat (N=118)	Placebo (N=59)
Duration of Grade 3-4 neutropenia		
Number (%) of patients with an event*	86 (73%)	5 (8%)
Median in weeks (range)	1.9 (0, 15.9)	2.2 (1.0, 4.6)
Total number of events	**279**	**6**
Duration of Grade 3-4 thrombocytopenia		
Number (%) of patients with an event*	77 (65%)	5 (8%)
Median in weeks (range)	1.4 (0.1, 12.6)	2.0 (0.3, 11.6)
Total number of events	**212**	**9**

* An event occurred after the last exposure to treatment + 30 days in two patients in the imetelstat arm and one patient in the placebo arm. The duration of Grade 3-4 neutropenia analyses include these patients in imetelstat (N = 84 + 2 = 86) and placebo (N = 4 + 1 = 5) arms.
Note: Median in weeks individual events was defined as the time from onset of worsened Grade 3+ local laboratory result from baseline grade to the day of first subsequent Grade 2 or lower local laboratory result before subsequent anticancer therapy (if any) or study discontinuation. Each subject may have had more than one cytopenia and these results are based on each separate occurrence.

Each subject may have had more than one cytopenia and these results are based on each separate occurrence.

Source: Applicant's Response to FDA Information Request dated 21 December 2023

Interventions for Cytopenias More Common with Imetelstat

	Imetelstat (N=118)	Placebo (N=60)
Subjects requiring myeloid growth factor on-treatment, n (%)	41 (35%)	2 (3%)
Frequency of myeloid growth factor administration, median (range)	3 (1, 23)	-- (1, 7)

	Imetelstat (N=118)	Placebo (N=60)
Subjects requiring platelet transfusion on-treatment, n (%)	21 (18%)	1 (2%)
Number of platelet transfusions, median (range)	1 (1, 10)	-- (1)

Data cutoff 13 Oct 2022

Source: FDA analysis using ADCM and ADTIPR datasets

Infections More Common on Imetelstat Arm

Adverse event	Imetelstat N=118 (%)		Placebo N=59 (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Infections	42	11	34	14
Viral infections	24	1.7	14	5
Bacterial infections	7	3.4	5	3.4
Pathogen not specified	22	7	25	7
Specific infections				
COVID-19*	18	1.7	14	5
UTI	6	1.7	3.4	0
URI*	5	0	5	0
Pneumonia*	4.2	3.4	3.4	1.7
Sepsis*	4.2	4.2	0	0

*Custom grouped terms

Data cutoff 13 Oct 2022

Source: FDA analysis using ADAE dataset

Hemorrhage More Common on Imetelstat Arm

Adverse Event	Imetelstat N=118 (%)		Placebo N=59 (%)	
	All Grade	Grade 3-4	All Grade	Grade 3-4
Any Hemorrhage	21	2.5	12	1.7
Epistaxis	6	0	0	0
Hematoma	5	0	0	0
Contusion	0.8	0	5	0
GI Hemorrhage*	5	1.7	3.4	1.7

*Includes: gingival bleeding, melena, esophageal varices hemorrhage, gastrointestinal hemorrhage, small intestinal hemorrhage, hemorrhoidal hemorrhage

Data cutoff 13 Oct 2022

Source: FDA analysis using ADAE dataset

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Dosing Issues

Dosing Concerns

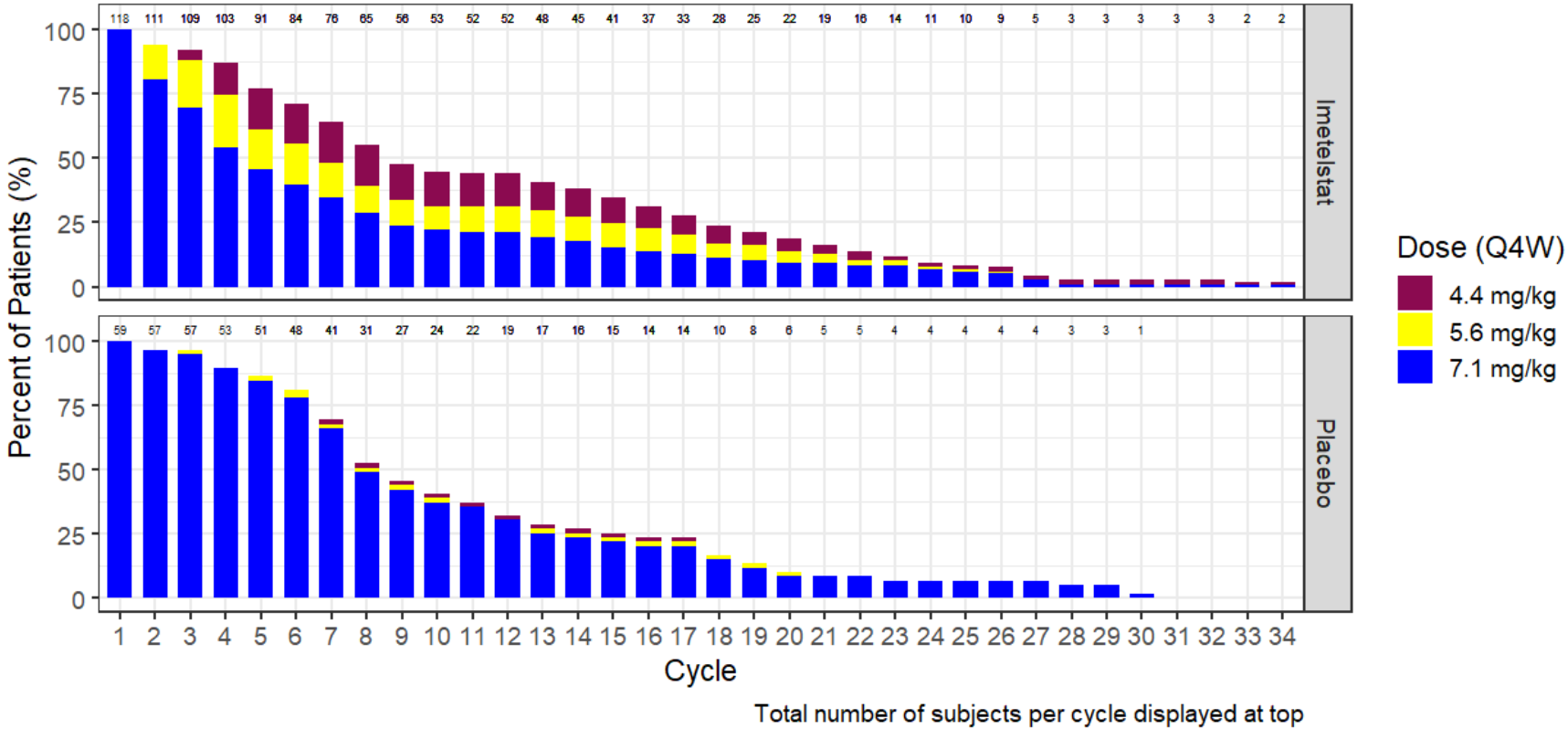
- Lack of dose finding in the target patient population (LR-MDS)
- High dose modification rate with imetelstat, as compared to the placebo group
- High rates and positive exposure-response (E-R) relationship for Grade 3/4 thrombocytopenia

High Dose Modification Rate with Imetelstat Compared to Placebo

	Imetelstat (N=118)	Placebo (N=59)
Dose delay by >3 days	73%	31%
Dose delay by >7 days	64%	22%
Dose reduction due to AE	49%	7%
Infusion interrupted, decreased rate, or aborted due to AE	6%	0
Discontinuation due to AE	14%	0

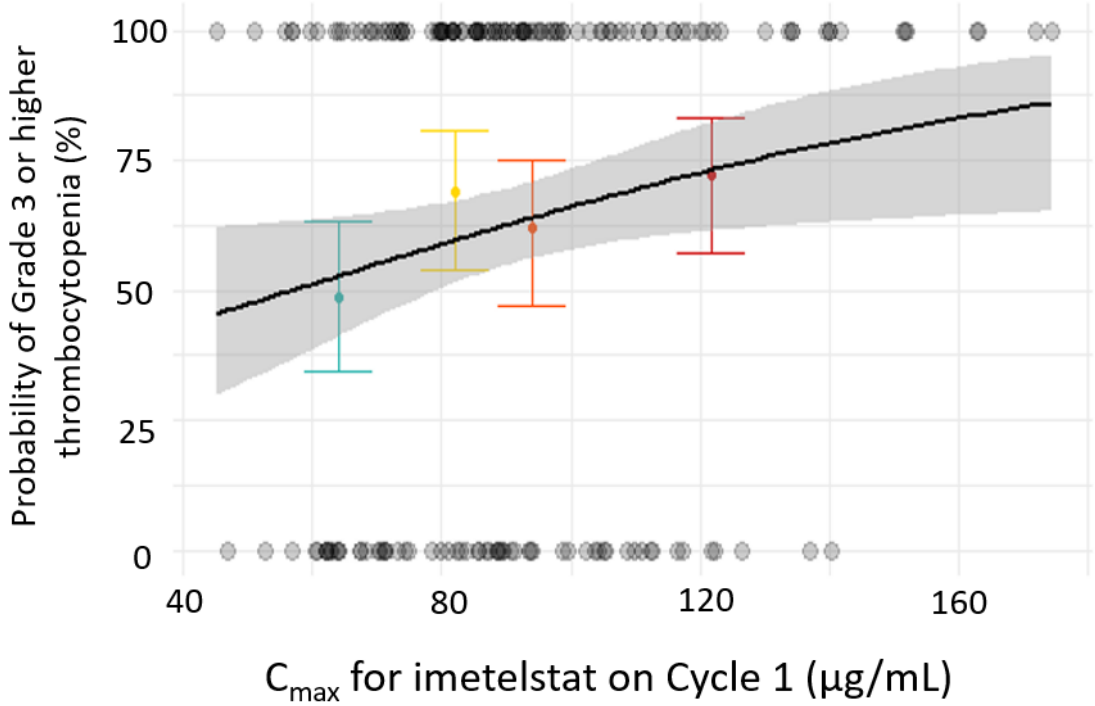
Source: FDA analysis using ADEX dataset

High Dose Reduction Rate with Imetelstat Compared to Placebo



Source: FDA analysis using ADEX dataset

Positive Exposure-Response Relationship between Imetelstat Cmax and Grade 3-4 Thrombocytopenia



C_{max} = maximum serum concentration

Source: FDA analysis using ER_THR.csv dataset

Summary of Safety Issues with Imetelstat

- Higher risk of grade 3+ AEs, SAEs, and AEs leading to treatment modification
- High risk of cytopenias with resultant need for intervention and increased risk of infection and hemorrhage
- Uncertainty about the dose used in lower risk MDS

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Benefit-Risk Assessment

Worsening Grade ≥3 Cytopenias According to Responder Status

	Imetelstat		Placebo	
	8-wk RBC-TI responders (N=47)	8-wk RBC-TI non-responders (N=71)	8-wk RBC-TI responders (N=9)	8-week RBC-TI non-responders (N=51)
Subjects with worsening Grade ≥3 neutropenia on-treatment	72%	70%	0	8%
Subjects with worsening Grade ≥3 thrombocytopenia on-treatment	60%	69%	11%	8%

Source: FDA analysis based on information from Applicant's response to FDA Information Request dated 22 January 2024

Intervention for Cytopenias According to Responder Status

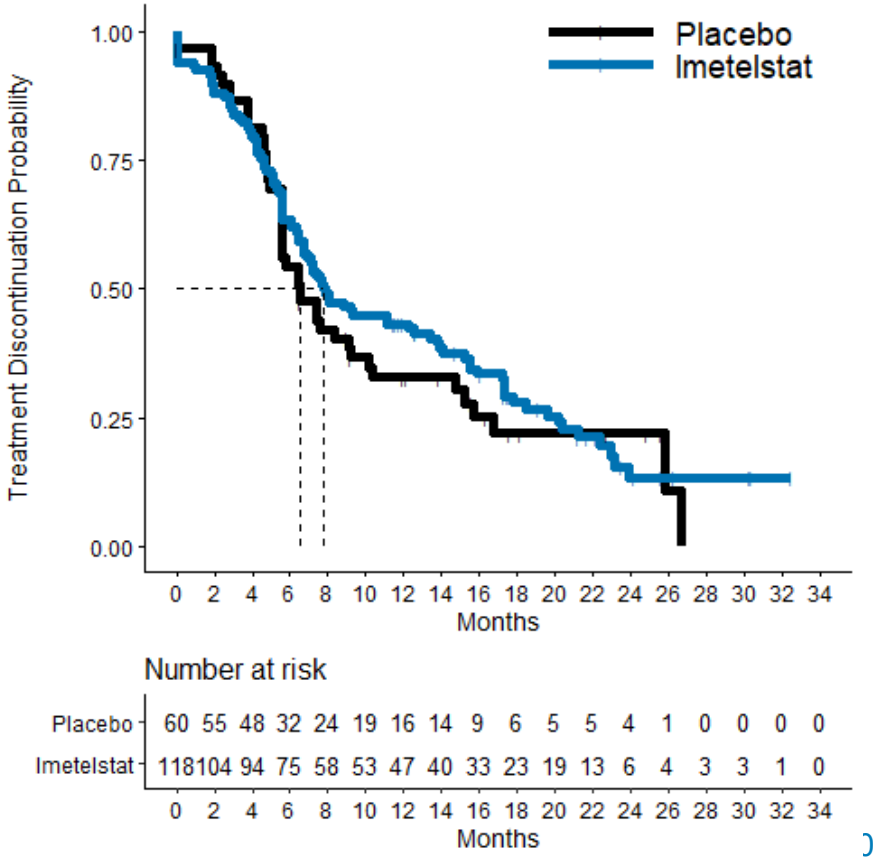
	Imetelstat		Placebo	
	8-wk RBC-TI responders (N=47)	8-wk RBC-TI non-responders (N=71)	8-wk RBC-TI responders (N=9)	8-week RBC-TI non-responders (N=51)
Subjects requiring myeloid growth factor on-treatment	40%	31%	0	2%
Subjects requiring platelet transfusion on-treatment	11%	23%	0	2%

Source: Applicant's response to FDA Information Requests dated 21 December 2023 and 9 January 2024

Treatment Duration

Kaplan-Meier Plot of Treatment Duration (ITT set)

Treatment	Imetelstat (N=118)	Placebo (N=60)
Discontinued **Ongoing** **Untreated**	77% 23% 0%	75% 23% 2%
Median Time to Treatment Discontinuation, months (95% CI)	7.8 (6.5, 13.4)	6.5 (5.6, 9.2)
Median Number of Cycles Received (range)	8.0 (1, 34)	8.0 (1, 30)



CI = Confidence Interval

Source: FDA analysis using ADDISP and ADSL datasets; Data cutoff: 13 October 2022

Reasons for Treatment Discontinuation

Reason	Imetelstat (N=118)	Placebo (N=59)
Lack of efficacy	24%	42%
Subject refused further treatment	14%	17%
Adverse event	16%	0
Disease relapse*	14%	2%
Progressive disease	6%	9%
Physician decision	2%	3%
Death	1%	3%
Lost to follow-up	1%	0

*Disease relapse refers to loss of RBC-TI response in this context

Source: Study MDS3001 Phase 3 CSR, Table 9

Overall Benefit-Risk Assessment

Potential benefit

	Imetelstat (N=118)	Placebo (N=60)	Difference
8-week RBC-TI	40%	15%	+25%
24-week RBC-TI	28%	3%	+25%

In the context of:
- Monthly infusion visits
- No demonstration of CR/PR or overall survival benefit
- No clear improvement in patient-reported outcomes

Potential risks

	Imetelstat (N=118)	Placebo (N=59)	Difference
Grade 3-4 neutropenia	**71%**	**7%**	**+64%**
Myeloid growth factor requirement	35%	3%	+32%
Infection (any grade)	42%	34%	+9%
Grade 3-4 thrombocytopenia	**65%**	**8%**	**+57%**
Platelet transfusion requirement	18%	2%	+16%
Bleeding (any grade)	21%	12%	+9%

+ Other risks (fractures, arthralgias/myalgias, fatigue)
+ Residual uncertainty regarding optimal dose

Source: Study MDS3001 Phase 3 CSR & FDA analysis using ADAE, ADCM, ADTIPR datasets

Discussion Question

Discuss the efficacy of imetelstat for patients with lower-risk MDS based on the results of the MDS3001 trial considering the safety profile.

Voting Question

Do the benefits of imetelstat outweigh its risks for the treatment of transfusion-dependent anemia in adult patients with IPSS low- to intermediate-1 risk MDS who have not responded to or have lost response to or are ineligible for erythropoiesis-stimulating agents?

Thank you

FDA recognizes the time and effort necessary to conduct cancer clinical trials. We would like to thank the patients and their families as well as the investigators and research staff who participated in the research studies discussed today.

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Backup Slides Shown

HI-E per IWG 2006 vs IWG 2018

	Imetelstat – Phase 3	Placebo	P value
HI-E (per IWG 2006)	75/118 (64%)	31/60 (52%)	0.112
HI-E (per IWG 2018)			
LTB subjects	7/21 (33%)	4/18 (22%)	N/A
HTB subjects			
Major HI-E response	30/97 (31%)	0/42 (0%)	N/A
Minor HI-E response	43/97 (44%)	4/42 (10%)	N/A

LTB = low transfusion burden (requiring 3-7 RBC units in a 16-week baseline period in at least 2 transfusion episodes, max 3 units in 8 weeks)
HTB = high transfusion burden (requiring ≥8 RBC units in a 16-week baseline period, or ≥ 4 units in 8 weeks)

Data cutoff 13 Oct 2022
Source: Study MDS3001 Phase 3 CSR

Medical resource utilization (Applicant analysis)

	Imetelstat (N=118)	Placebo (N=60)
Number of subjects with at least 1 medical encounter	66 (56%)	31 (52%)
Number of subjects with at least 1 outpatient encounter*	43 (36%)	24 (40%)
Number of subjects with at least 1 hospitalization	39 (33%)	14 (23%)
Total number of medical encounters (average per patient)	157 (1.3/patient)	96 (1.6/patient)

*Outpatient encounters include emergency room visits, hospital outpatient visits, home care visits, laboratory visits, office visits, other visits

Protocol-mandated procedures, tests, and encounters (e.g., infusion & transfusion visits) were excluded

Data cutoff 13 October 2022

Source: Study MDS3001 Phase 3 CSR

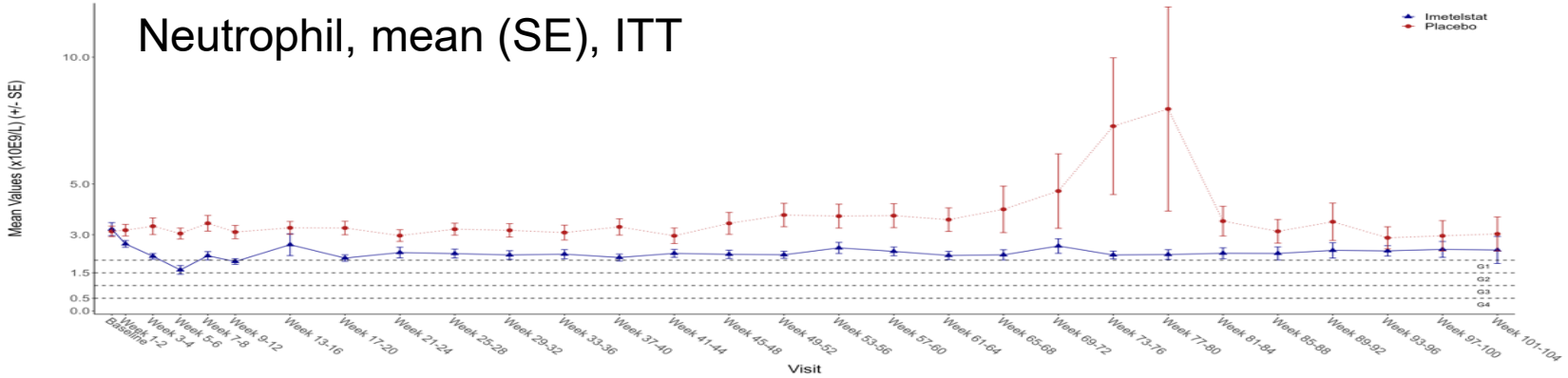
Medical resource utilization (FDA analysis)

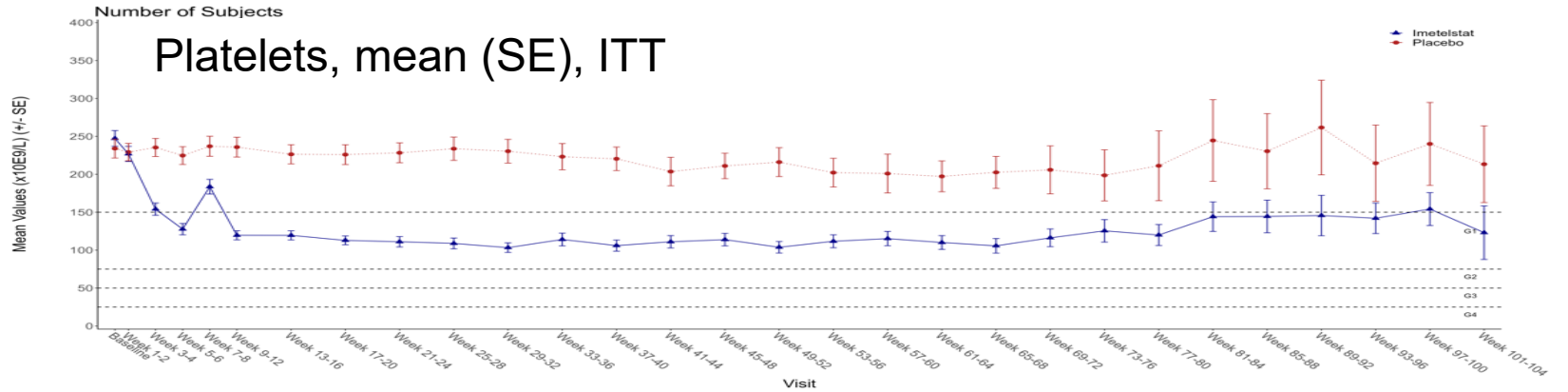
	Imetelstat		Placebo*	
	Responders† (N=47)	**Non-Responders (N=71)**	**Responders† (N=9)**	**Non-Responders (N=50)**
Transfusion encounters[a]	1008 (21/patient)	2735 (39/patient)	207 (23/pt)	1892 (38/pt)
Infusion encounters	832 (18/pt)	520 (7/pt)	140 (16/pt)	486 (10/pt)
Non-protocol mandated encounters	80 (1.7/pt)	77 (1/pt)	21 (2/pt)	75 (1.5/pt)
Total medical encounters[b]	**1920 (41/pt)**	**3332 (47/pt)**	**228 (25/pt)**	**1967 (39/pt)**

*Excluding 1 subject on the placebo arm who was randomized but never treated
†Responders = subjects who achieved 8-week RBC-TI
[a]Includes encounters for whole blood, packed red blood cell, platelet, and fresh frozen plasma transfusions
[b]Excluding infusion visits for the placebo arm, since placebo infusions would not be given in the real world

Data cutoff 13 October 2022
Source: FDA analysis using ADHO, ADTIPR, ADEXSUM, and ADSL datasets

Cytopenias over time





Difference in neutrophil and platelet count by cycle

Neutrophils

Cycle	Grade change	Imetelstat n/N (%)	Placebo n/N (%)
1-3	Any	104/118 (88%)	24/59 (41%)
	1-2	88%	41%
	3-4	36%	0
4-6	Any	71/103 (69%)	11/53 (21%)
	1-2	65%	21%
	3-4	13%	0
7-12	Any	56/76 (74%)	10/41 (24%)
	1-2	72%	24%
	3-4	13%	2.4%
13+	Any	33/48 (69%)	4/16 (25%)
	1-2	69%	25%
	3-4	15%	0

Platelets

Cycle	Grade change	Imetelstat n/N (%)	Placebo n/N (%)
1-3	Any	109/118 (92%)	9/59 (15%)
	1-2	92%	15%
	3-4	41%	0%
4-6	Any	93/103 (90%)	12/53 (23%)
	1-2	90%	23%
	3-4	25%	0%
7-12	Any	71/76 (93%)	7/41 (17%)
	1-2	92%	17%
	3-4	26%	2.4%
13+	Any	42/48 (88%)	5/19 (26%)
	1-2	88%	26%
	3-4	24%	0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