Imetelstat for the Treatment of Transfusion-Dependent Anemia in Adults with Low to Intermediate-1 Risk Myelodysplastic Syndromes (LR MDS)

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Oncologic Drugs Advisory Committee

Geron Corporation

Introduction

Sharon McBain, BSc

Senior Vice President,
Global Head of Regulatory Affairs
Geron Corporation

Imetelstat for Transfusion-Dependent (TD) Anemia Due to Lower-Risk (LR) MDS After ESA Failure

- TD anemia due to LR MDS is debilitating to patient outcomes and lifestyle
- Only 2 products (luspatercept, lenalidomide) approved post-ESA
  - Both restricted to specific, small sub-populations
  - Neither provide extended, continuous durability of TI
- MDS3001 delivered consistent and robust efficacy meeting primary endpoint and key secondary endpoints
- Safety profile is well characterized and manageable

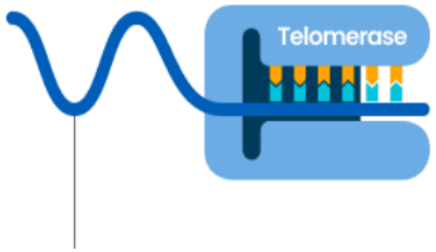
Imetelstat fulfills high unmet need and provides clinical advantages over existing therapies and a positive benefit-risk profile

ESA = erythropoiesis-stimulating agents; TI = transfusion independence

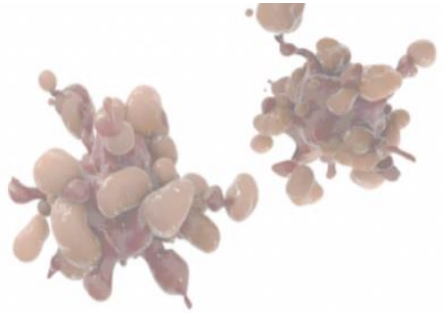
Imetelstat Mechanism of Action for RBC TI

Malignant HSCs/HPCs with elevated telomerase activity

Imetelstat binds to telomerase, inhibits its activity and prevents maintenance of telomeres



Apoptosis of malignant HSCs/HPCs

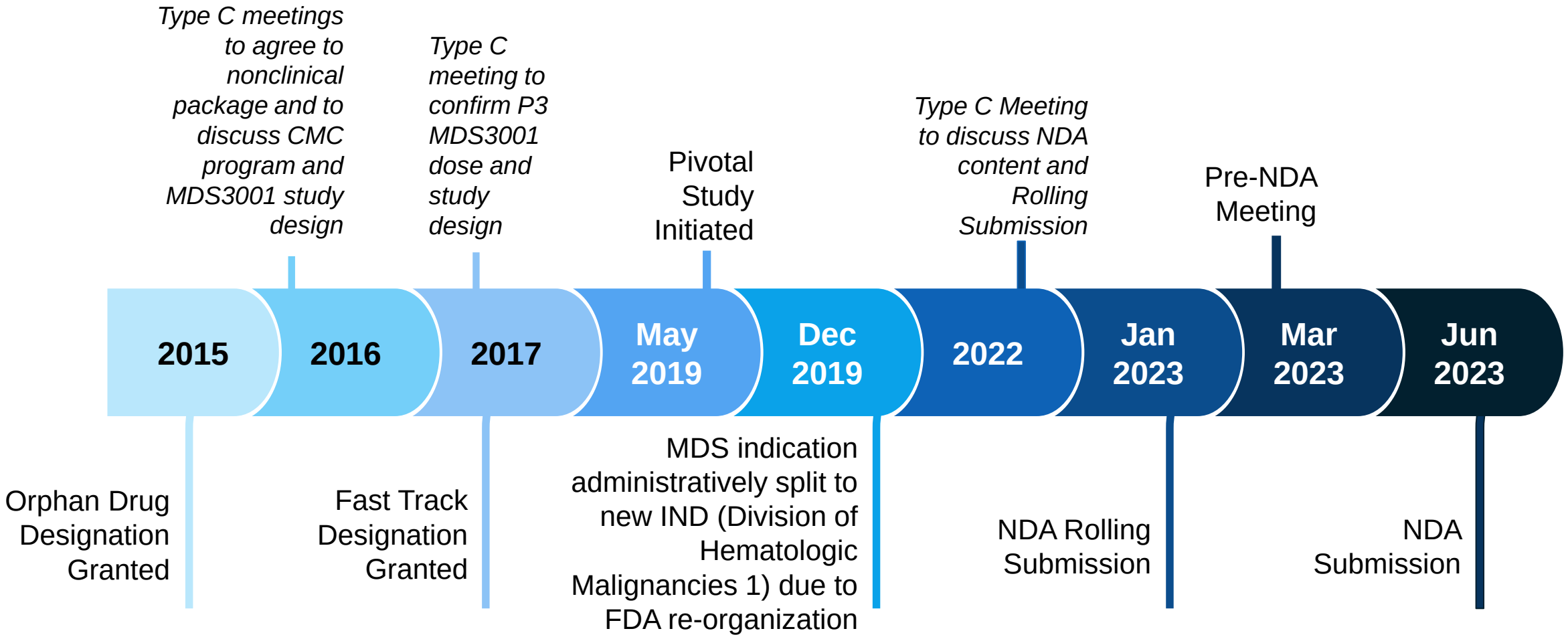


Recovery of erythropoiesis

Increased Hgb leading to RBC TI

HSCs/HPCs = hematopoietic stem/progenitor cells

US Regulatory History for Imetelstat



Seeking conventional approval

Imetelstat Proposed Indication and Dosing Regimen

Proposed Indication

…for the treatment of transfusion-dependent anemia in adult patients with low- to intermediate-1 risk myelodysplastic syndromes who have failed to respond or have lost response to or are ineligible for erythropoiesis-stimulating agents

Proposed Dosing

- 7.1 mg/kg (equivalent to 7.5 mg/kg imetelstat sodium)
- 2-hour IV infusion once every 4 weeks

Key Considerations For Today's Discussion

- Recent FDA publication stated high unmet need in TD anemia in LR MDS patients[1]
- **FDA** briefing document
  - Pivotal Phase 3 study MDS3001 met primary and key secondary TI endpoints
  - HI-E, CR, PR, OS results not supportive of disease-modifying treatment effect
  - PROs not supportive of treatment effect
  - *"To support a marketing application, transfusion independence data should be supported by evidence of direct clinical benefit to the patient (e.g., survival benefit, CR/PR benefit, or improvement in quality of life)."*
- **Geron** position: imetelstat meets regulatory standards for approval
  - Seeking indication in TD anemia
  - TI endpoints represent true clinical benefit and accepted for existing approved products treating TD anemia in absence of disease-modifying effect
  - Study design pre-agreed with FDA through Type C interactions

1. Sekeres, et al 2023; HI-E = hematologic improvement-erythroid

Imetelstat: Positive Benefit-Risk Profile

Benefit

- ✓ Statistically significant, clinically meaningful improvements in TI rate
- ✓ Long, continuous TI
- ✓ Meaningful increases in Hgb
- ✓ Reduced transfusion burden

Risk

- ✓ Well-characterized and manageable
- ✓ Cytopenia events short lived and without severe clinical consequences
- ✓ HCPs experienced in managing cytopenias
- ✓ No OS detriment

Agenda

Unmet Need	**Michael Savona, MD** The Beverly and George Rawlings Director of Hematology Research Professor of Medicine and Cancer Biology Vanderbilt University School of Medicine
Clinical Results	**Faye Feller, MD** Chief Medical Officer Geron Corporation
Clinical Perspective	**Rami Komrokji, MD** Vice Chair, Malignant Hematology Department Lead Clinical Investigator, MDS Program H. Lee Moffitt Cancer Center & Research Institute Professor of Oncologic Sciences, University of South Florida
Conclusion	**Faye Feller, MD** Chief Medical Officer Geron Corporation

Additional Geron Experts

Tymara Berry, MD

Vice President, Clinical Development

Laurence Gamelin, MD, PhD

Vice President, Pharmacovigilance and Drug Safety (PVDS)

Fei Huang, PhD

Executive Director, Translational Research

Ashley Lennox, PhD

Associate Director, Clinical Pharmacology

Ying Wan, MD, PhD

Vice President, Biometrics and Data Management

Unmet Medical Need for Treatment in LR MDS

Michael Savona, MD

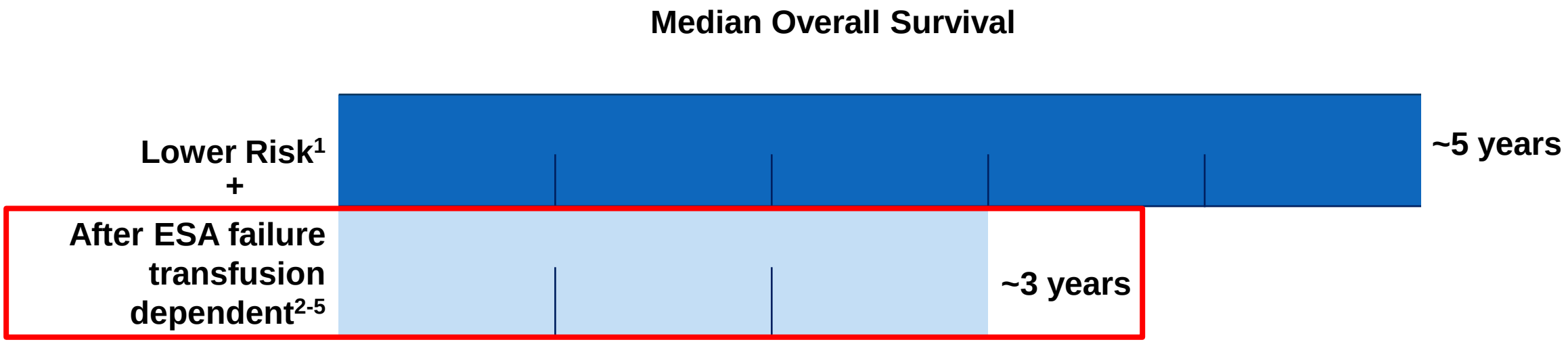
The Beverly and George Rawlings
Director of Hematology Research
Professor of Medicine and Cancer Biology
Vanderbilt University School of Medicine

Myelodysplastic Syndromes Represent a Spectrum of Neoplastic Disease with Variable Risk

- Intimate community of MDS specialists homogenize practice across the world
- Prognosis ranges via International Prognostic Scoring System (IPSS)
  - Very low risk (years of survival) to very high risk (< 1 year survival)
- In US, ~ 45,000 new MDS cases/year[1]
  - Median age of diagnosis ~70 years, majority lower risk
- Patients with LR MDS
  - Considerably diminished OS (~ 1/3 transform to leukemia, ~ 2/3 non-leukemic MDS-related death)
  - Comorbidities (amplification of cardiovascular disease, progressive bone marrow failure resulting in bleeding and infections)
  - Diminished QoL
  - Increased use of healthcare resources

1. Goldberg, 2010

Reduced Life Expectancy in Target Population



1. Neukirchen, 2014; 2. Consagra, 2023; 3. Kelaidi, 2013; 4. Komrokji, 2023; 5. Park, 2017

Anemia is Most Common Presentation of LR MDS

- ~ 85% of patients with symptomatic anemia at diagnosis[1]
  - Vascular events
  - Inflammatory symptoms
  - Severe fatigue
- Decision to transfuse RBCs based on
  - Patient-specific clinical considerations
  - International guidance[2]
  - Hgb threshold of 7-8 g/dL

1. Foran & Shammo, 2012

2. WHO Guidance on Clinical Use of Blood Products and Association for Advancement of Blood & Biotherapies (AABB) principles for RBC Transfusion Thresholds

Transfusion Dependence Associated With Long-Term Consequences

- Frequent RBC transfusions
  - Alloimmunization
  - Risk of transfusion reactions, cardiovascular complications, and infections
  - Iron overload and associated end-organ dysfunction
- Social and psychological burden managing health care
  - Can have diminished health-related quality of life

Transfusion independence is a key therapeutic goal for patients and physicians

Limited Options for Transfusion-Dependent Patients

- First-line treatment with ESAs
  - Given when Hgb falls below threshold
  - Patient response lasts usually 12-18 months on average
  - Not effective for all patients
- TD patients or those with high endogenous serum EPO level have < 10% chance of response with ESAs

EPO = erythropoietin

Current Treatment Options for Transfusion Dependent Anemia in LR MDS

Product (Approval Year)	**Primary Endpoint**	**TD LR MDS Subpopulation**	**TI Rate**	**OS**	**PRO** (Fatigue)
Lenalidomide[1] (2005)	RBC TI ≥ 8 weeks	del(5q)	67%	*Not reported*	*Not reported*
Luspatercept[2] (2020)	RBC TI ≥ 8 weeks within weeks 1-24	After ESA RS+	38% (Δ = 25%)	HR = 0.987[3]	Increased fatigue[4]

- Hypomethylating agents[5-6] (HMAs)
  - Approved for treatment of MDS but not specifically indicated for TD anemia
  - May reduce anemia in higher risk MDS
  - Generally, not used as standard of care for LR MDS

1. List, 2006 2. Fenaux, 2019 3. Platzbecker, 2023; 4. Luspatercept BLA Review, 2019; 5. NCCN, 2022; 6. Azacitidine USPI

Unmet Need for Approved Treatments After ESA Failure

HTB = high transfusion burden
(≥ 6 units/8 weeks)
LTB = low transfusion burden
(< 6 units/8 weeks)
RS = ring sideroblasts

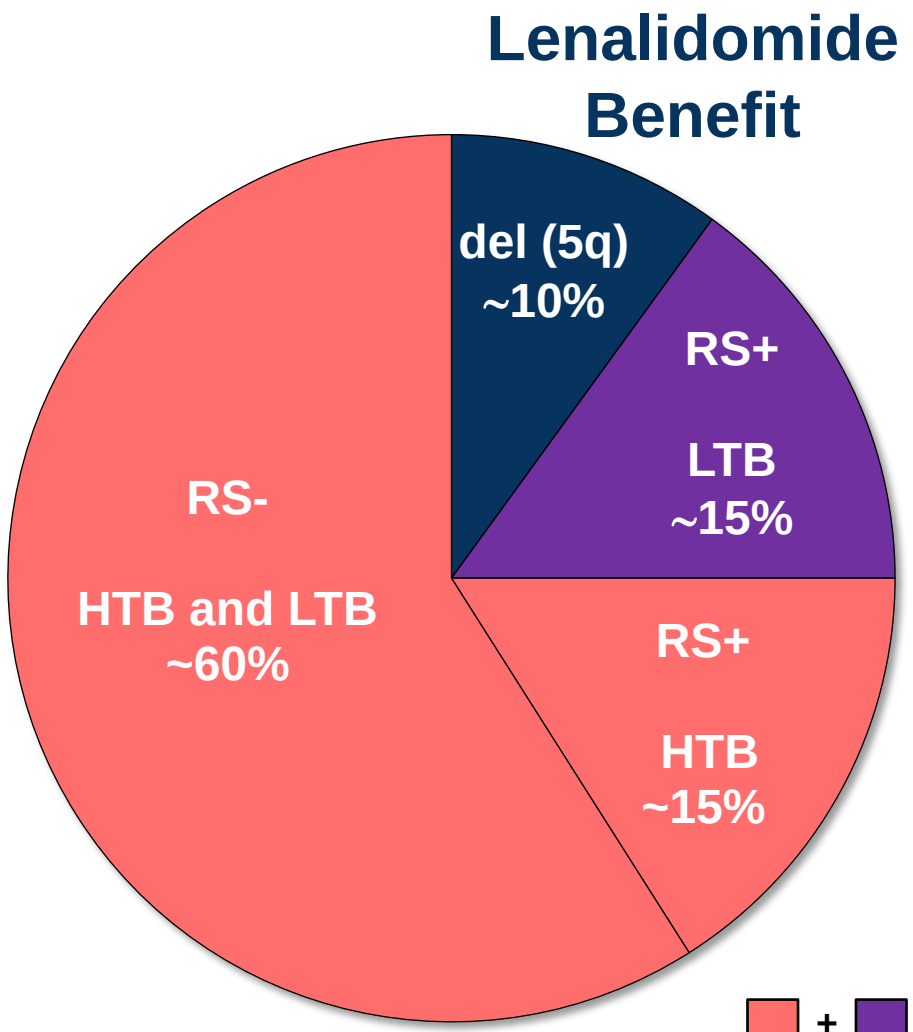


Chart based on: List, 2006; Fenaux, 2019; Patel, 2021

Summary: Patients with LR-MDS and Physicians Have High Unmet Need for Anemia Treatment Options

- MDS is serious and life-threatening
  - Anemia and fatigue key clinical features
- Once patients become ESA relapsed / refractory, only two treatment options exist
  - Current options do not address unmet medical need

Need treatment option that achieves durable transfusion independence in patients with TD anemia

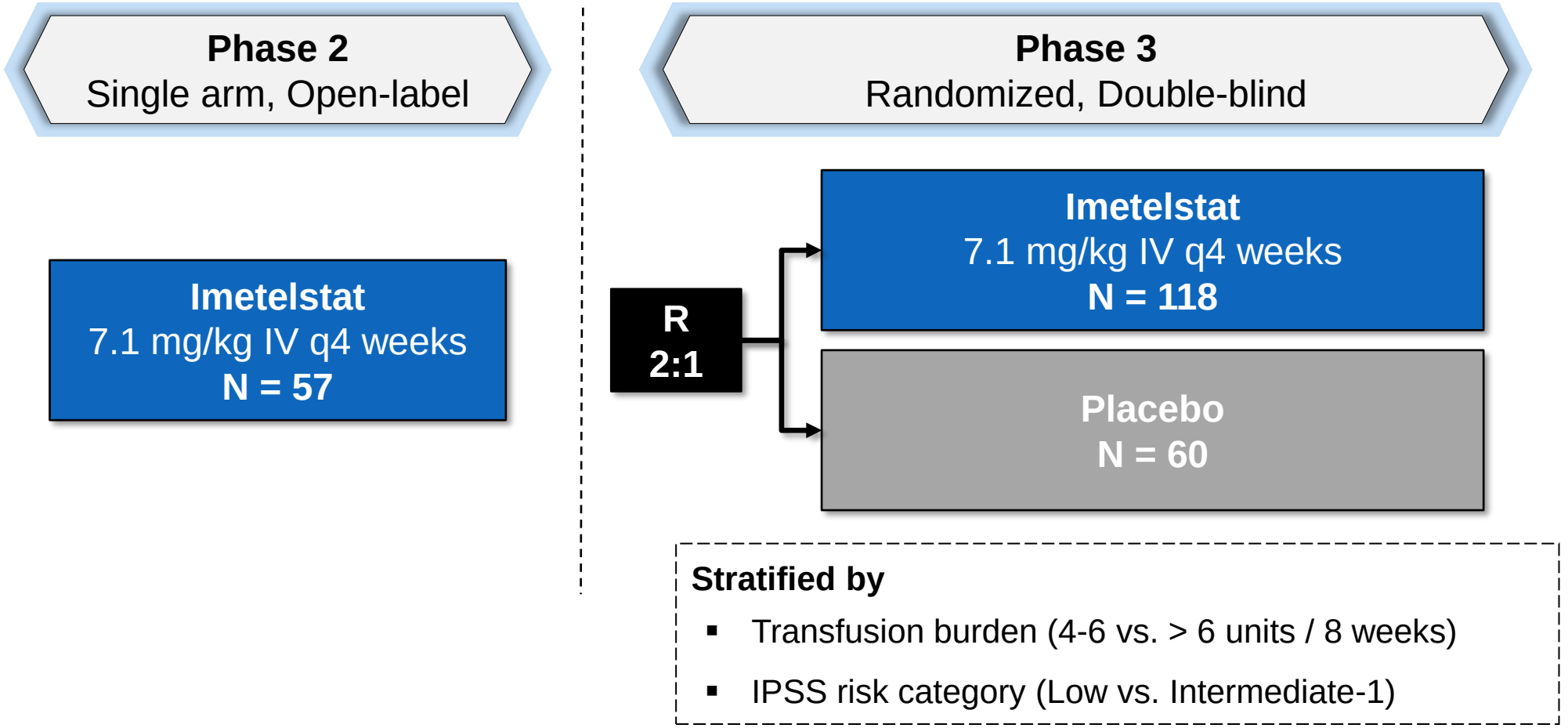
Clinical Results

Faye Feller, MD

Chief Medical Officer

Geron Corporation

MDS3001: Phase 2/3 Study



Treatment continuous until disease progression, unacceptable toxicity or withdrawal of consent, per protocol

Enrolled Patients with Transfusion-Dependent Anemia Relapsed, Refractory, or Ineligible for ESA

- ☑ **IPSS low or intermediate-1 risk MDS (Lower Risk Myelodysplastic Syndromes)**
- ☑ **Relapsed / Refractory to ESA**
  (at least 8 weeks of ESA treatment at protocol specified dose before meeting R/R criteria)
- ☑ **Ineligible for ESA**
  (No prior treatment with ESA and serum EPO > 500 mU/mL at screening)
- ☑ **Transfusion dependent: ≥ 4 units RBC / 8 weeks over 16-week pre-study period**
- ☑ **Non-del(5q) and lenalidomide / HMA-naïve***

*Required for Phase 3 randomization

MDS3001: Phase 3 Endpoints

Primary Endpoint

- RBC TI ≥ 8 weeks (during any consecutive 8 weeks at any time)

Key Secondary Endpoint

- RBC TI ≥ 24 weeks (during any consecutive 24 weeks)

Additional Secondary Endpoints

- Duration of RBC TI for TI responders
- Efficacy in subgroups
- Rate of HI-E per IWG 2006 and 2018 criteria
- Relative change in RBC transfusion burden
- Long-term outcomes (OS)

Statistical Considerations

- Planned to enroll ~ 170 patients
  - ~ 88% power to detect TI rate difference of 22.5%
- Sequential testing procedure for primary and key secondary endpoints at Type I error of 0.05
- No missing data imputed for primary and secondary endpoints

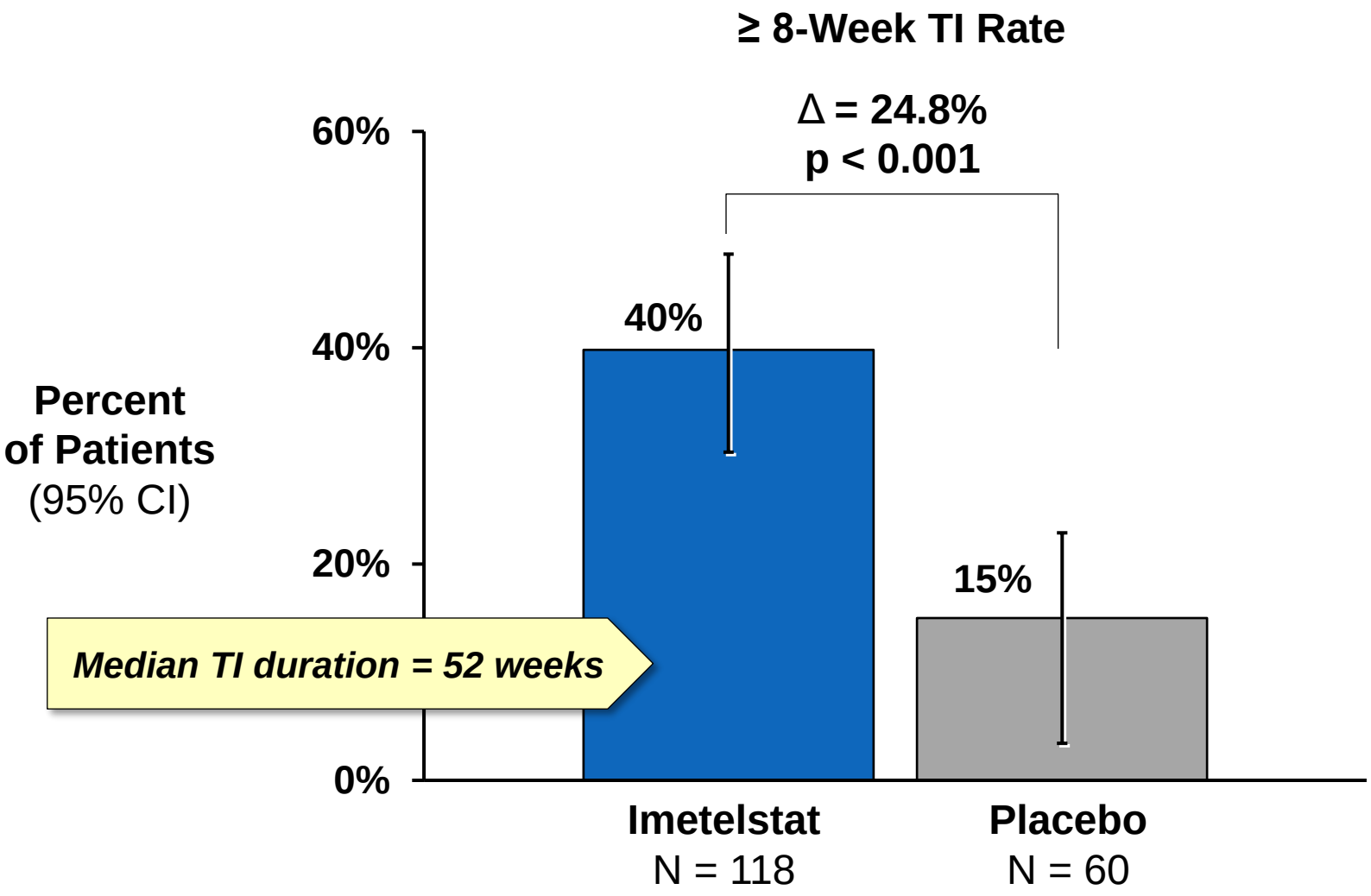
Demographics Representative of Known Epidemiology of LR MDS

	Imetelstat N = 118	Placebo N = 60
Age (years)**, median** (min-max)	**72** (44-87)	**73** (39-85)
Male	**60%**	**67%**
Race		
White	**81%**	**80%**
Black or African American	**1%**	**3%**
Asian	**7%**	**3%**
Region		
North America	**11%**	**20%**
European Union	**68%**	**63%**
Rest of World	**21%**	**17%**

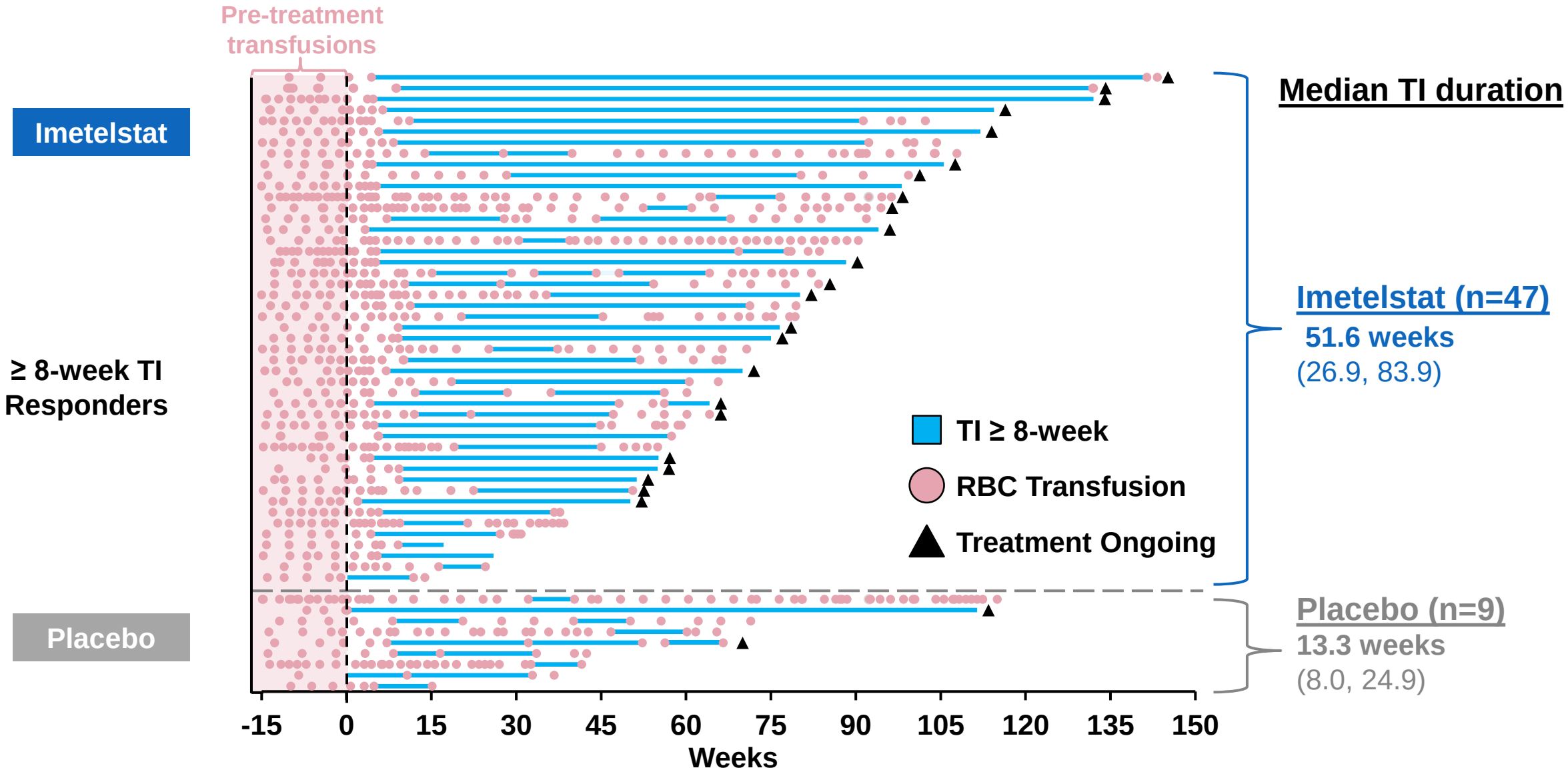
Key Disease Characteristics Balanced Between Groups

		Imetelstat N = 118	Placebo N = 60
Prior RBC transfusion burden	> 6 units / 8 weeks	48%	45%
WHO classification (2008)	RS+	62%	62%
	RS-	37%	38%
IPSS category	Low	68%	65%
	Intermediate-1	32%	35%
Prior ESA treatment		92%	87%
Serum EPO level	> 500 mU/mL	22%	37%
Eastern Cooperative Oncology Group (ECOG) Score	0	36%	35%
	1-2	64%	65%

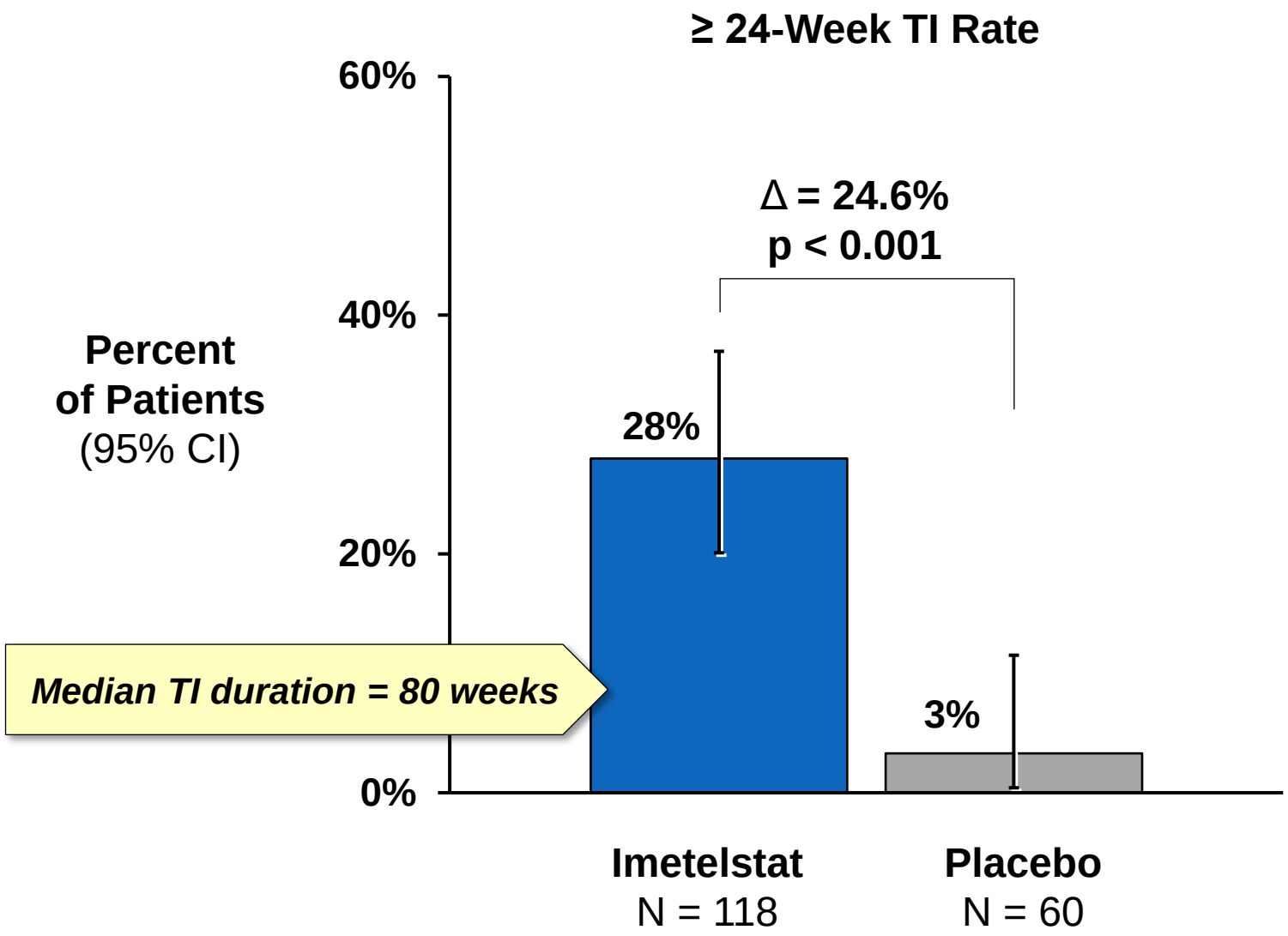
Primary Endpoint: Highly Statistically Significant and Clinically Meaningful Benefit (≥ 8-Week TI)



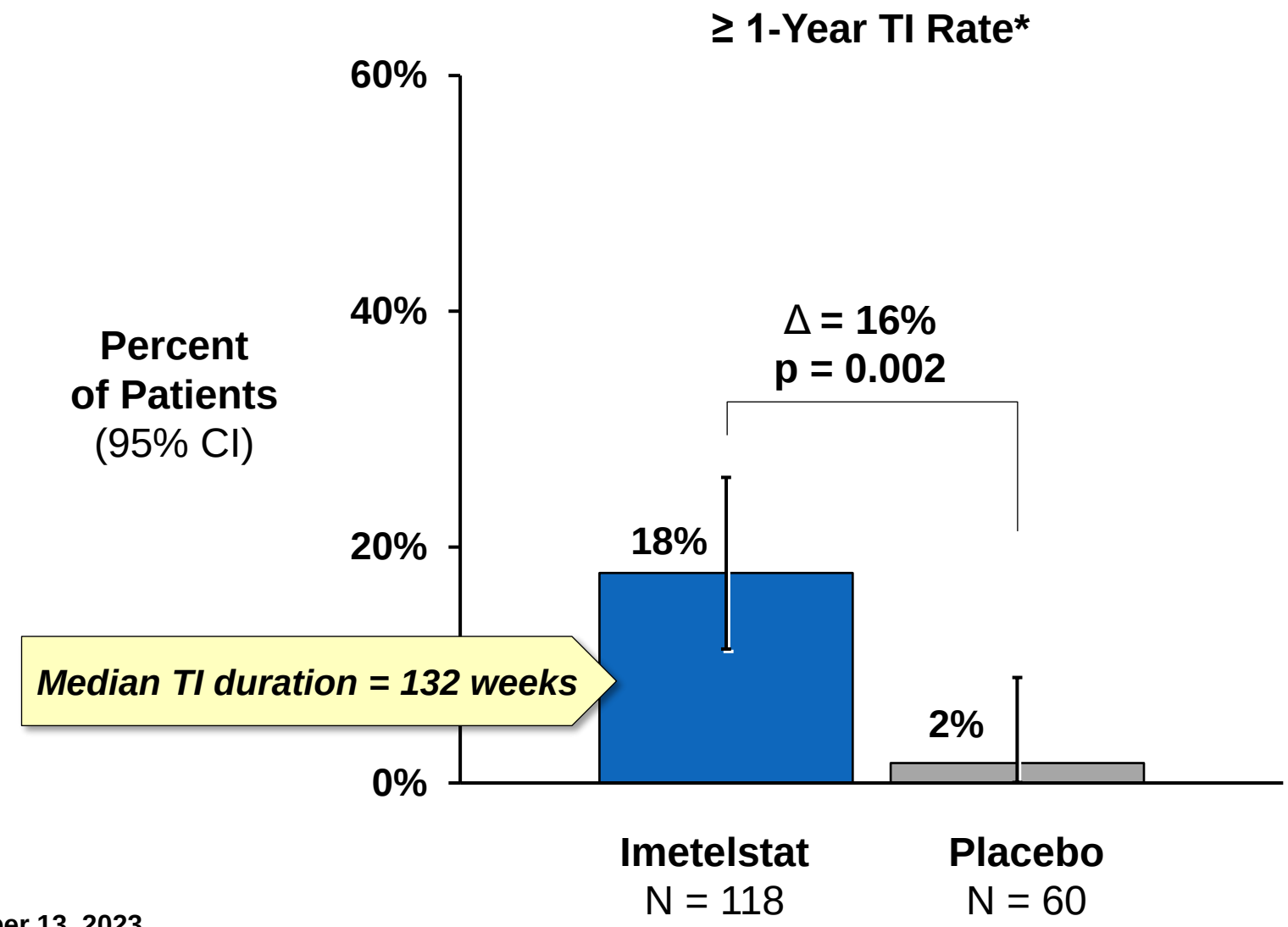
Most Primary Endpoint Responders had Single Continuous TI Period with Median Duration 1 Year



Key Secondary Endpoint: Statistically Significant Improvement (≥ 24-Week TI)

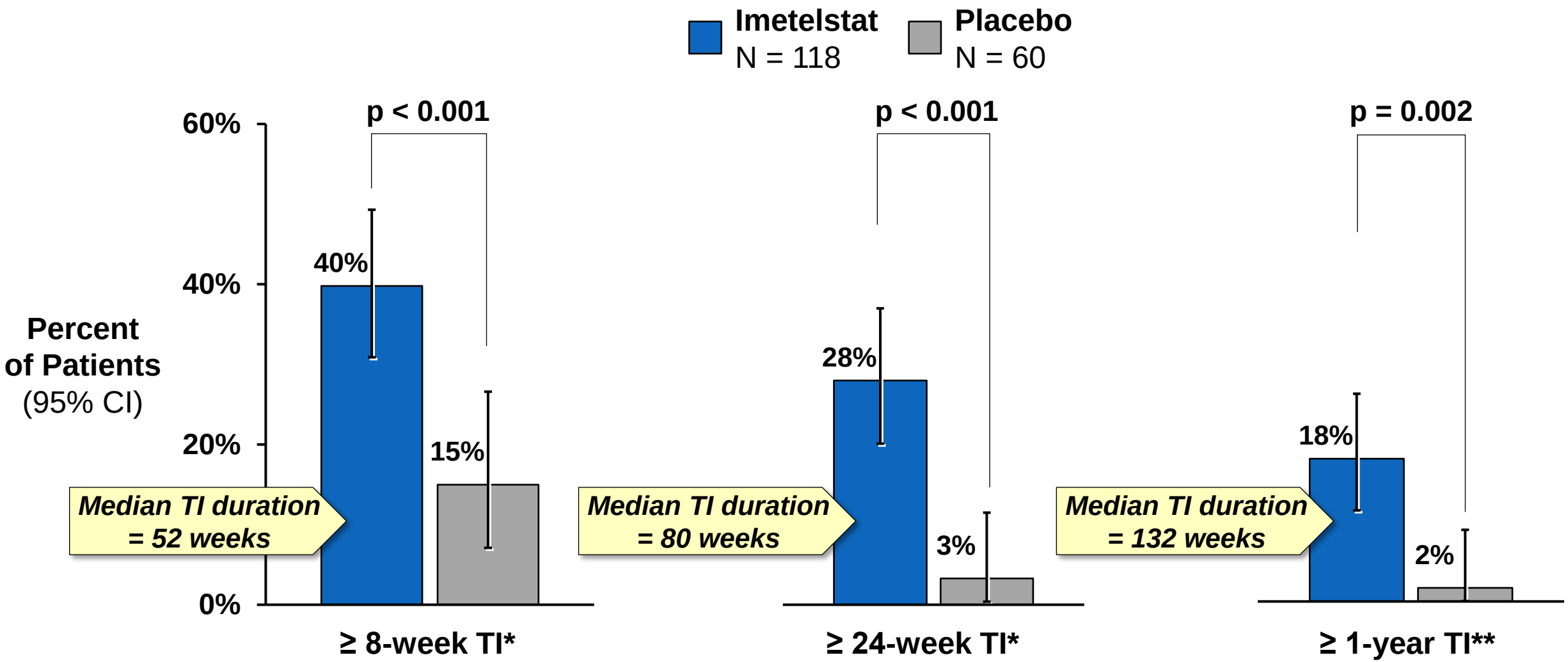


≥ 1 Year TI Rate with Imetelstat Shows Continued Improvement Over Placebo



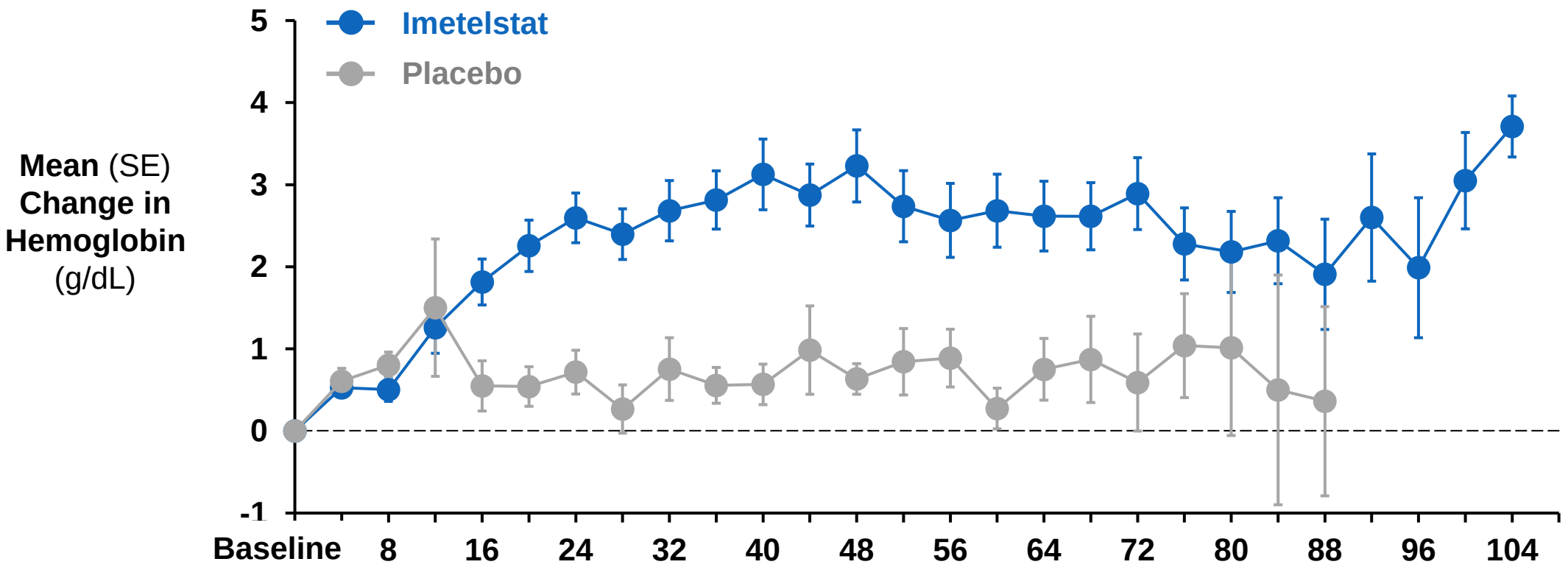
*Data cutoff: October 13, 2023

Higher Rates of Longer-Term Continuous TI Consistently Observed with Imetelstat vs Placebo



*Data cutoff: October 13, 2022; ** Data cutoff: October 13, 2023

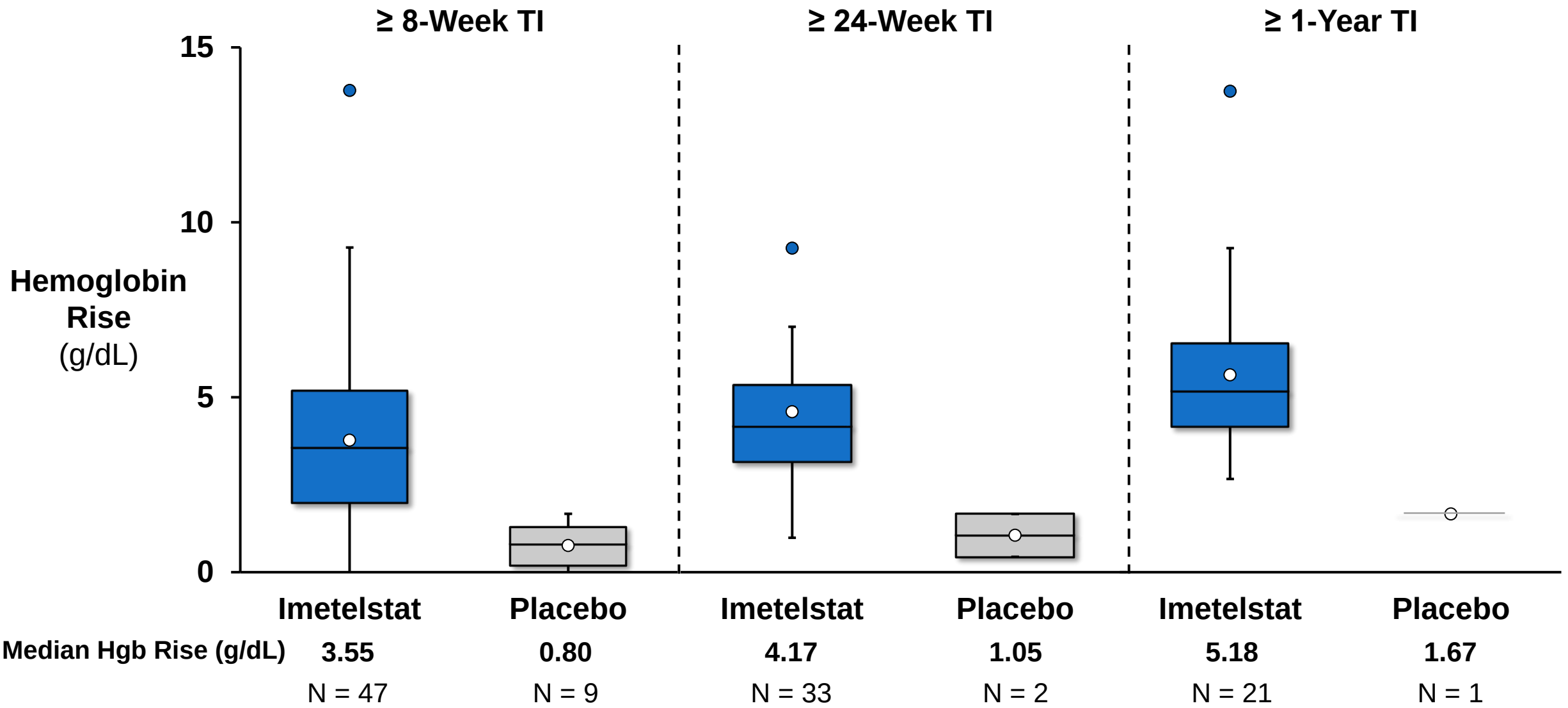
Sustained Increase in Hemoglobin Levels are Objective Indication of Clinical Effect of Imetelstat



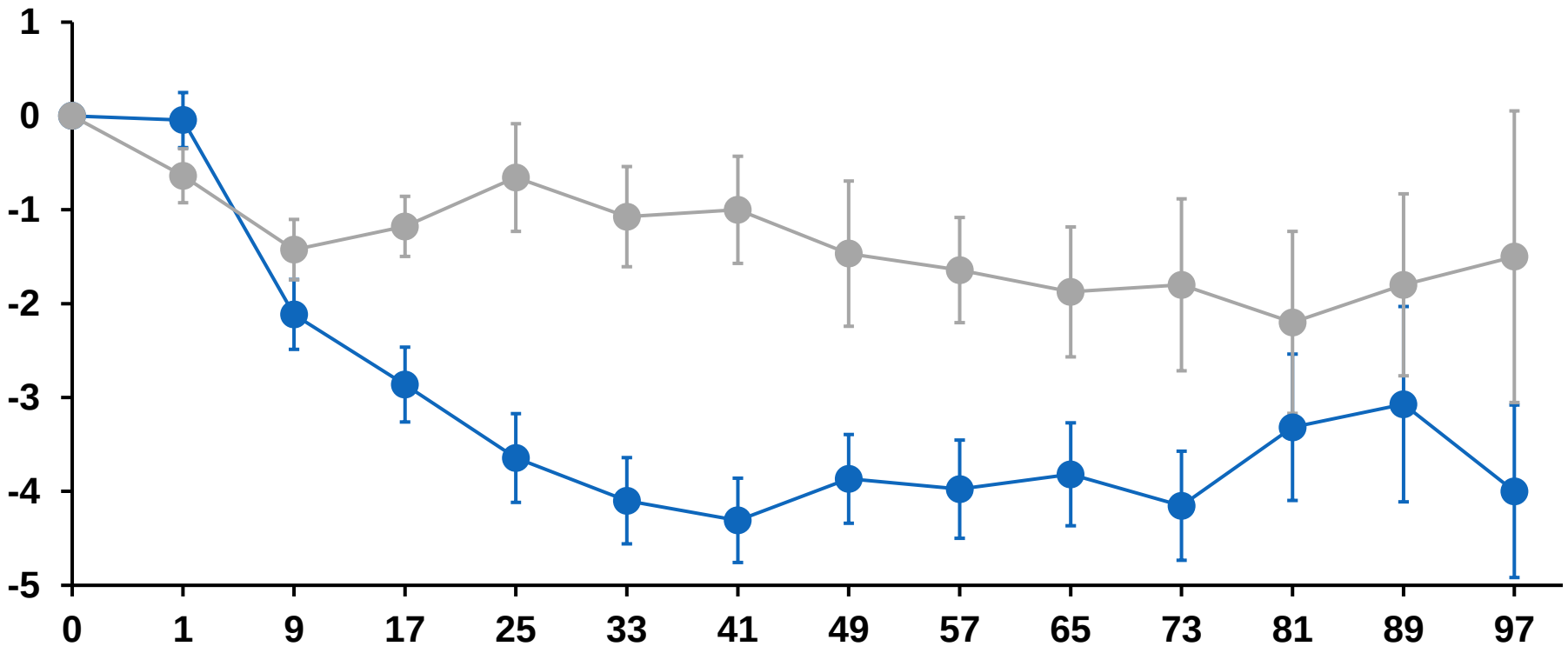
N at Risk	Baseline	8	16	24	32	40	48	56	64	72	80	88	96	104
Imetelstat	118	54	42	48	43	37	35	25	24	21	18	11	9	5
Placebo	60	17	18	8	10	7	9	9	7	5	2			

$p < 0.001$

Meaningful Increases in Hemoglobin Among Imetelstat Responders



Greater Reduction in RBC Transfusion Burden with Imetelstat Treatment



N at Risk														
Imetelstat	118	115	104	95	76	60	55	45	43	33	26	22	14	10
Placebo	60	58	53	48	32	27	22	15	14	8	5	5	5	4

p-value = 0.042

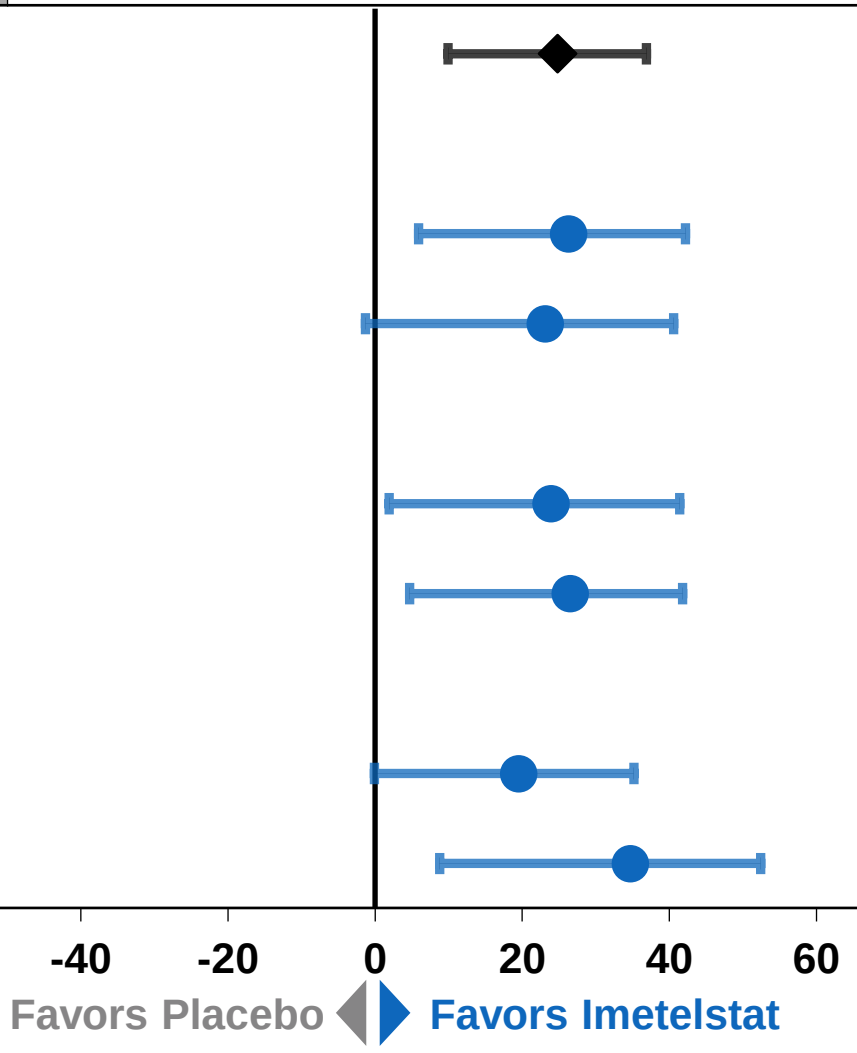
Imetelstat Demonstrated Hematologic Improvement Per IWG 2006 and 2018 Criteria

Hematologic Improvement-Erythroid (HI-E)	Imetelstat N = 118	Placebo N = 60	p-value[3]
HI-E per IWG 2018[1]	**42%**	**13%**	**< 0.001**
16-week TI	**31%**	**7%**	**< 0.001**
Transfusion reduction by ≥ 50% / 16 weeks	**43%**	**15%**	**< 0.001**
HI-E per IWG 2006[2,4]	**64%**	**52%**	**0.112**
≥ 1.5 g/dL increase in Hgb ≥ 8 weeks	**34%**	**10%**	**< 0.001**
Transfusion reduction by ≥ 4 units / 8 weeks	**60%**	**50%**	**0.175**

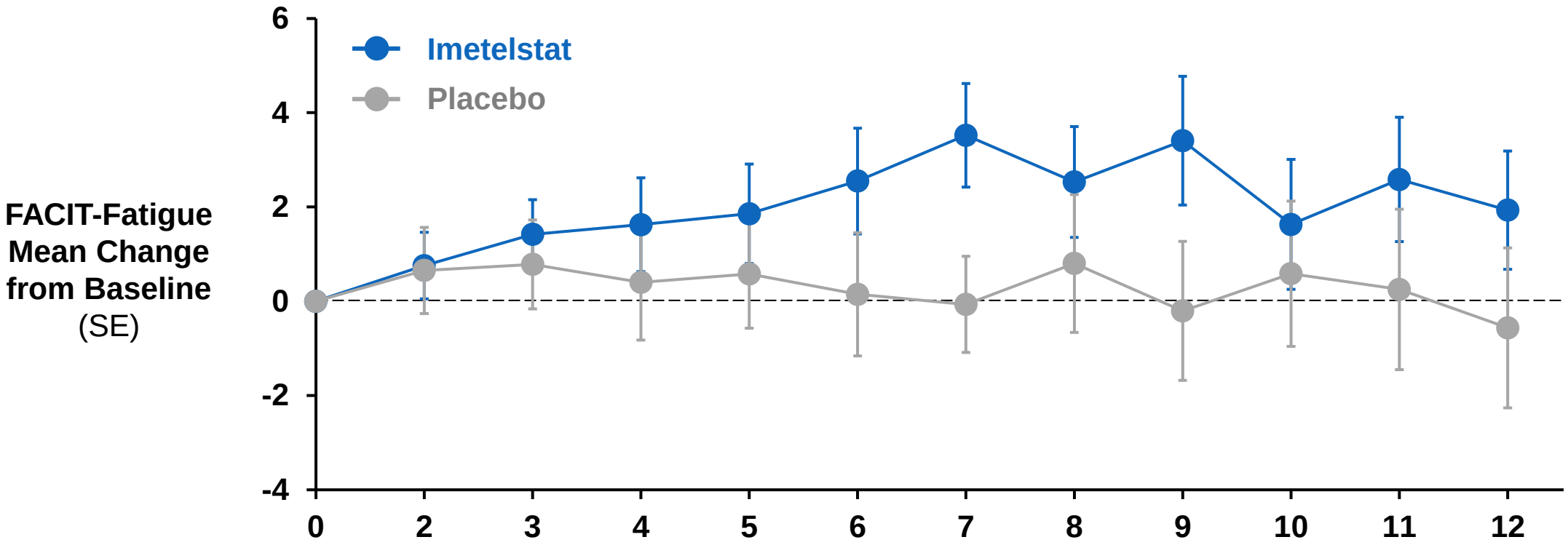
1. Platzbecker, 2019; 2. Cheson, 2006; 3. Cochran Mantel Haenszel test stratified for prior RBC transfusion burden (≤ 6 units or > 6 units of RBC/8 weeks) and baseline IPSS risk score (Low or Intermediate-1); 4. HI-E using protocol-specified IWG 2006 criteria not statistically significant

Comparable and Consistent Clinical Benefit for Primary Endpoint Demonstrated Across Key Subgroups

Subgroup	Imetelstat n/N (%)	Placebo n/N (%)	Difference (95% CI)	Nominal p-value
Overall	47/118 **(40%)**	9/60 **(15%)**	**25%** (10, 37)	**< 0.001**
WHO Category				
RS+	33/73 **(45%)**	7/37 **(19%)**	**26%** (6, 42)	**0.016**
RS-	14/44 **(32%)**	2/23 **(9%)**	**23%** (-1, 41)	**0.038**
Prior RBC Transfusion Burden				
4-6 units / 8 weeks	28/62 **(45%)**	7/33 **(21%)**	**24%** (2, 41)	**0.027**
> 6 units / 8 weeks	19/56 **(34%)**	2/27 **(7%)**	**27%** (5, 42)	**0.023**
IPSS Risk Category				
Low	32/80 **(40%)**	8/39 **(21%)**	**20%** (-0.1, 35)	**0.034**
Intermediate-1	15/38 **(40%)**	1/21 **(5%)**	**35%** (9, 52)	**0.004**



Patient Reported Outcome Endpoints Support TI



PRO Completed												
Imetelstat	118	101	108	101	88	80	73	63	54	50	50	51
Placebo	57	52	54	52	49	46	40	30	27	23	21	20

MDS3001: Phase 3 Endpoints Showed Improvement with Imetelstat Treatment

Primary endpoint: RBC TI ≥ 8 weeks

39.8% vs 15.0% for imetelstat vs placebo ($p < 0.001$)

Key secondary endpoint: RBC TI ≥ 24 weeks

28.0% vs 3.3% for imetelstat vs placebo ($p < 0.001$)

- **Long TI duration for TI responders**
- **Improved TI rates across key subgroups**
- **Improvement in HI-E rates**
  - **Decrease in transfusion burden**
  - **Sustained increase in Hgb**

Imetelstat Safety

Safety Exposures

	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** (1-34)	**8** (1-30)
1 – 3 cycles	**13%**	**10%**
4 – 6 cycles	**23%**	**20%**
7 – 12 cycles	**24%**	**41%**
≥ 13 cycles	**41%**	**29%**

- Monitoring of long-term use will continue in ongoing studies

Based on primary analysis

Overall Safety

	Imetelstat N = 118	Placebo N = 59
AE	**99%**	**100%**
Grade 3/4	**91%**	**48%**
SAE	**32%**	**22%**
AE leading to discontinuation	**14%**	**0**
AE leading to dose reduction or cycle delays	**70%**	**24%**
Deaths during treatment	1 **(0.8%)**	1 **(1.7%)**

Based on primary analysis

Non-Hematologic AEs Generally Low Severity

≥ 10% in either group	Imetelstat N = 118		Placebo N = 59	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Asthenia	**19%**	**0**	**14%**	**0**
COVID-19*	**18%**	**2%**	**15%**	**5%**
Peripheral edema	**11%**	**0**	**14%**	**0**
Headache	**13%**	**< 1%**	**5%**	**0**
Diarrhea	**12%**	**< 1%**	**12%**	**2%**
ALT increased	**12%**	**3%**	**7%**	**3%**
Hyperbilirubinemia	**9%**	**< 1%**	**10%**	**2%**
Constipation	**8%**	**0**	**12%**	**0**
Pyrexia	**8%**	**2%**	**12%**	**0**

***Includes COVID-19, asymptomatic COVID-19, COVID-19 pneumonia**

Hematologic AEs Were Most Frequent

≥ 10% in either group	Imetelstat N = 118		Placebo N = 59	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Thrombocytopenia	**75%**	**62%**	**10%**	**9%**
Neutropenia	**74%**	**68%**	**7%**	**3%**
Anemia	**20%**	**20%**	**10%**	**7%**
Leukopenia	**10%**	**8%**	**2%**	**0**

Serious Adverse Events

> 2% in either group	Imetelstat N = 118		Placebo N = 59	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Any SAE	**32%**	**29%**	**22%**	**20%**
Anemia	**3%**	**3%**	**0**	**0**
Cardiac failure*	**3%**	**3%**	**2%**	**2%**
Pneumonia	**3%**	**3%**	**2%**	**2%**
COVID-19 pneumonia	**2%**	**2%**	**5%**	**5%**
Abscess limb	**0**	**0**	**3%**	**3%**

All SAEs reported as unrelated except 1 SAE of anemia
***Includes cardiac failure and cardiac failure congestive**

Updated Overall Survival Consistent with No Detriment for Imetelstat-Treated Patients

	Primary Analysis (Clinical Cutoff Oct 2022)		Updated OS Analysis (Clinical Cutoff Jan 2024)	
	Imetelstat N = 118	**Placebo N = 60**	**Imetelstat N = 118**	**Placebo N = 60**
Death events	19 **(16%)**	8 **(13%)**	35 **(30%)**	15 **(25%)**
During treatment	1 **(1%)**	1 **(2%)**	2 **(2%)**	2 **(3%)**
In follow up	18 **(15%)**	7 **(12%)**	33 **(28%)**	13 **(22%)**
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** (0.459, 2.476)		**0.98** (0.526, 1.823)	

Dosing Considerations

	Imetelstat N = 118	Placebo N = 59
Any AE leading to cycle delay	**69%**	**24%**
Median time to cycle delay, weeks	**7.3**	**12.1**
Any AE leading to dose reduction	**49%**	**7%**
Median time to dose reduction, weeks	**13.9**	**20.1**
Treatment discontinuation	**14%**	**0**
Mean dose intensity in all patients	**90.5%**	**98.3%**
	N = 47	**N = 9**
Mean dose intensity up to achievement of ≥ 8-week TI	**95.2%**	**99.0%**

Adverse Events of Special Interest

Neutropenia and thrombocytopenia (and associated clinical consequences)

Hepatic events

AESI: Grade 3/4 Neutropenia and Thrombocytopenia Occur Early and Short in Duration

	Neutropenia		Thrombocytopenia	
	Imetelstat N = 118	Placebo N = 59	Imetelstat N = 118	Placebo N = 59
Grade 3/4	**71%**	**7%**	**65%**	**8%**
Occurrence during cycle 1-3	**65%**	**3%**	**48%**	**2%**
Time to onset, median (weeks)	**4.4**	**13**	**6**	**15**
Duration per event, median (weeks) [range]	**1.9** [0-15.9]	**2.2** [1.0-4.6]	**1.4** [0.1-12.6]	**2.0** [0.3-11.6]
Lasting ≤ 4 weeks	**78%**	**98%**	**90%**	**95%**

Based on laboratory data

AESI: Severe Infections Infrequent and Occur at Same Rate as Placebo

	Imetelstat N = 118	Placebo N = 59
Any infection AE	50 **(42%)**	20 **(34%)**
Grade ≥ 3	13 **(11%)**	8 **(14%)**
Serious	14 **(12%)**	8 **(14%)**
Any infection AE within ± 7 days of Grade 3/4 neutropenia	9 **(8%)**	1 **(2%)**
Grade 1/2 infection AE	6 **(5%)**	0
Grade 3/4 infection AE	3 **(3%)**	1 **(2%)**
Serious infection AE*	3 **(3%)**	1 **(2%)**
Febrile neutropenia	1 **(1%)**	0

***SAE: Imetelstat: *Escherichia* sepsis, enterococcal sepsis, neutropenic sepsis; Placebo: listeriosis**

AESI: Severe Bleeding Events Infrequent and Occur at Same Rate as Placebo

	Imetelstat N = 118	Placebo N = 59
Any bleeding AE	25 **(21%)**	7 **(12%)**
Grade ≥ 3	3 **(3%)**	1 **(2%)**
Serious	3 **(3%)**	1 **(2%)**
Any bleeding AE within ± 7 days of Grade 3/4 thrombocytopenia	9 **(8%)**	**0**
Grade 1/2 bleeding AE*	9 **(8%)**	**0**
Grade 3/4 bleeding AE	**0**	**0**
Serious bleeding AE	**0**	**0**

***Grade 1: hematoma (2), epistaxis (2), hematuria, contusion, hemorrhoidal hemorrhage, ecchymosis; Grade 2: gastrointestinal hemorrhage**

Limited Severe Clinical Consequences of Cytopenias

- Low risk of severe bleeding and severe infection
- Short duration and reversibility of cytopenias
- No long-term evidence of bone marrow aplasia or myelosuppression
- Hematologists and HCPs who will administer imetelstat experienced in managing cytopenia
- US Prescribing Information will outline clear risks and monitoring

Use of Supportive Care Infrequent Per Patient and Not a Significant Additional Risk

- Patients on both arms of study received supportive care as clinically indicated per investigator and local standards
- **Growth factor:** 34.7% imetelstat vs 3.4% placebo
  - Median 3 records of treatment per imetelstat patient
- **Platelet transfusions:** 18% imetelstat vs 1.7% placebo
  - Median 1 platelet transfusion instance per imetelstat patient
  - Mostly prophylactic / preventative (for platelet value ≤ 20,000 / μL)

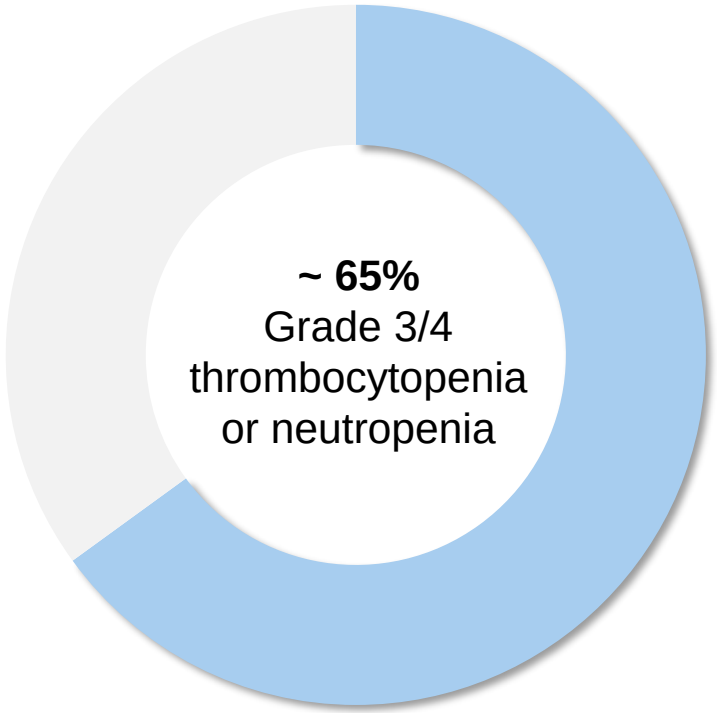
AESI: Most LFT Elevations Grade 1/2 and Reversible; No Hy's Law Cases Identified

	Imetelstat N = 118		Placebo N = 59	
	All Grades	Grade 3/4	All Grades	Grade 3/4
Alanine Aminotransferase (ALT)	**39%***	**3%***	**37%**	**5%**
Alkaline Phosphate (ALP)	**45%**	**0**	**12%**	**0**
Aspartate Aminotransferase (AST)	**48%**	**< 1%**	**22%**	**2%**
Bilirubin	**39%**	**< 1%**	**39%**	**2%**

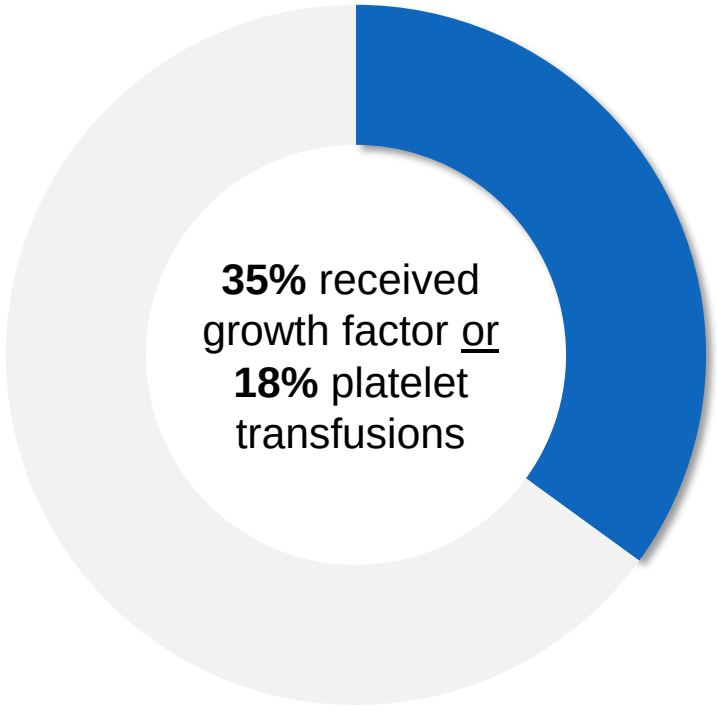
- Primarily low grade and reversible elevations
- No confirmed Hy's Law cases
- Reviewed by Independent Hepatic Expert Committee

*Based on lab results of 117 patients

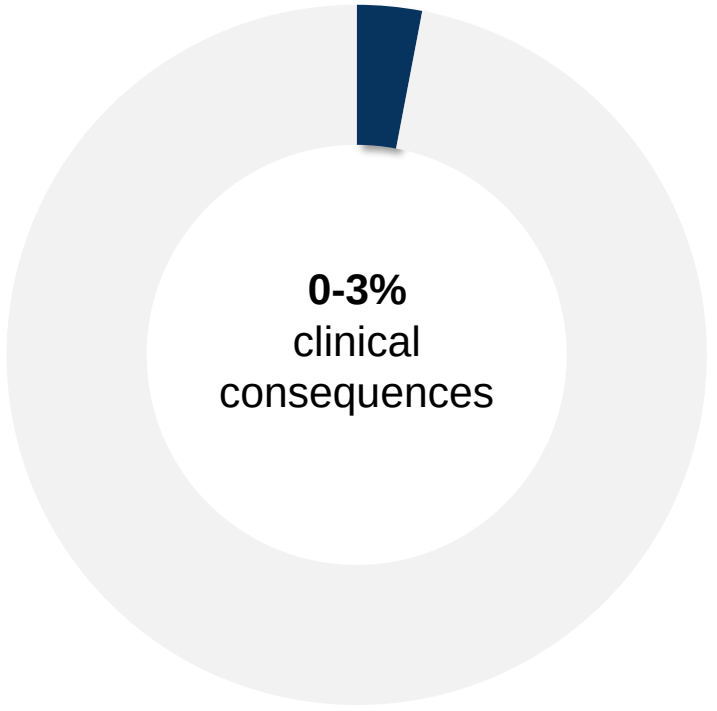
Summary of Clinical Risk: Manageable Cytopenias Without Severe Clinical Consequences



< 2-week median duration



Per clinician discretion, not chronic



No severe bleeding during Grade 3/4 thrombocytopenia

3% severe infection during Grade 3/4 neutropenia, equivalent to placebo

Clinical Perspective

Rami Komrokji, MD

Vice Chair, Malignant Hematology Department
Lead Clinical Investigator, MDS Program
H. Lee Moffitt Cancer Center & Research Institute
Professor of Oncologic Sciences,
University of South Florida

THE LANCET

Imetelstat in patients with lower-risk myelodysplastic syndromes who have relapsed or are refractory to erythropoiesis-stimulating agents (IMerge): a multinational, randomised, double-blind, placebo-controlled, phase 3 trial

Uwe Platzbecker, Valeria Santini*, Pierre Fenaux, Mikkael A Sekeres, Michael R Savona, Yazan F Madanat, Maria Díez-Campelo, David Valcárcel, Thomas Illmer, Anna Jonášová, Petra Bělohlávková, Laurie J Sherman, Tymara Berry, Souria Dougherty, Sheetal Shah, Qi Xia, Libo Sun, Ying Wan, Fei Huang, Annat Ilkin, Shyamala Navada, Faye Feller, Rami S Komrokji†, Amer M Zeidan†*

Summary

Background Unmet medical needs remain in patients with red blood cell transfusion-dependent (RBC-TD) lower-risk myelodysplastic syndromes (LR-MDS) who are not responding to or are ineligible for erythropoiesis-stimulating agents (ESAs). Imetelstat, a competitive telomerase inhibitor, showed promising results in a phase 2 trial. We aimed to compare the RBC transfusion independence (RBC-TI) rate with imetelstat versus placebo in patients with RBC-TD LR-MDS.

Methods In phase 3 of IMerge, a double-blind, placebo-controlled trial conducted in 118 sites including university hospitals, cancer centres, and outpatient clinics in 17 countries, patients (aged ≥18 years) with ESA-relapsed, ESA-refractory, or ESA-ineligible LR-MDS (low or intermediate-1 risk disease as per International Prognostic Scoring System [IPSS] criteria) were randomly assigned via a computer-generated schedule (2:1) to receive imetelstat 7·5 mg/kg or placebo, administered as a 2-h intravenous infusion, every 4 weeks until disease progression, unacceptable toxic effects,

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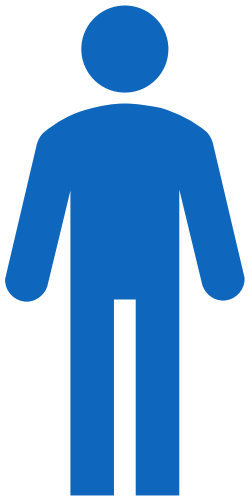
*Joint first authors

†Joint last authors

Department of Hematology, Cellular Therapy, Infectious

Case Presentation of Patient with Anemia in LR MDS

71-yr-old Male



Presented with anemia
(Hgb 8.0 g/dL, platelets 200 /mL, ANC 4000 /mL)
No evidence of bleeding, no nutritional deficiencies

↓

Bone marrow aspirate and biopsy:
> 15% RS and erythroid dysplasia, EPO > 500 mU/mL

↓

Diagnosis: LR MDS, RS+
High transfusion burden: 6-7 units / 8 weeks

↓

Treatment Options

- **ESA** ~ 7%[1]
- **Luspatercept** < 10% (HTB)[2]
- ~~**Lenalidomide**~~
- ~~**HMA**~~

1. Hellström-Lindberg, 2003; 2. Platzbecker, 2023

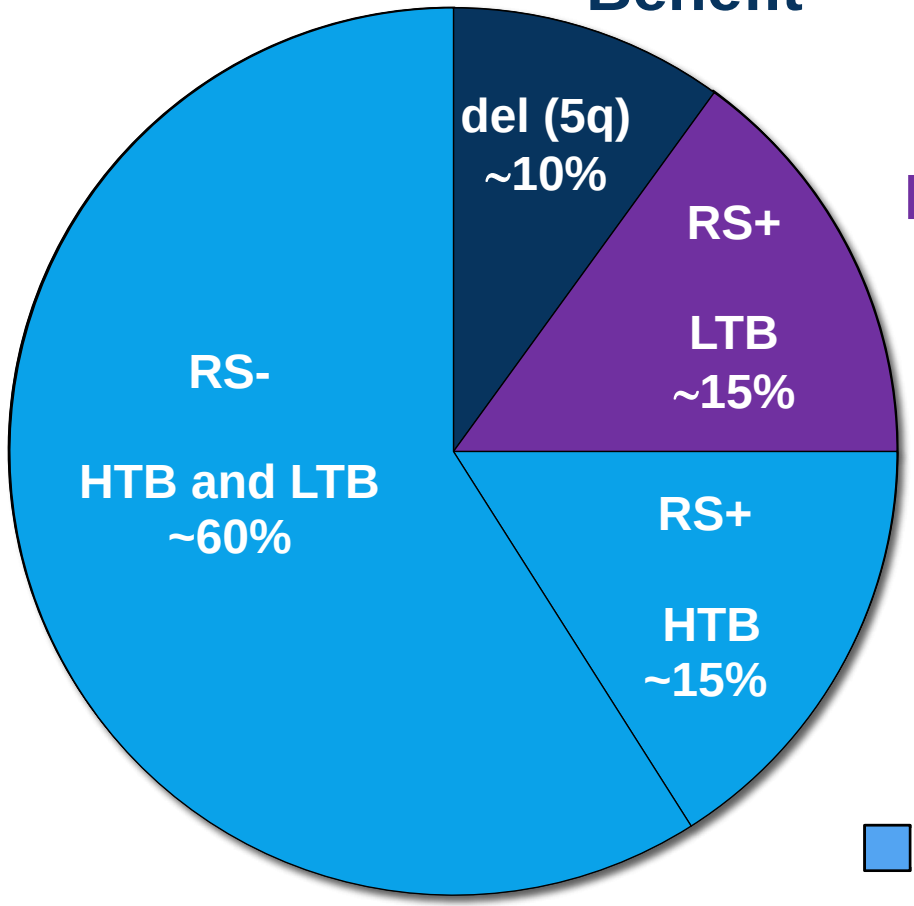
Imetelstat Addresses Unmet Need in Treatment of LR MDS After ESA Treatment Failure

HTB = high transfusion burden
(≥ 6 units/8 weeks)
LTB = low transfusion burden
(< 6 units/8 weeks)
RS = ring sideroblasts

Lenalidomide Benefit

Luspatercept Benefit

Unmet Need Addressed with Imetelstat



Non-del(5q) 90%

Chart based on: List, 2006; Fenaux, 2019; Patel, 2021

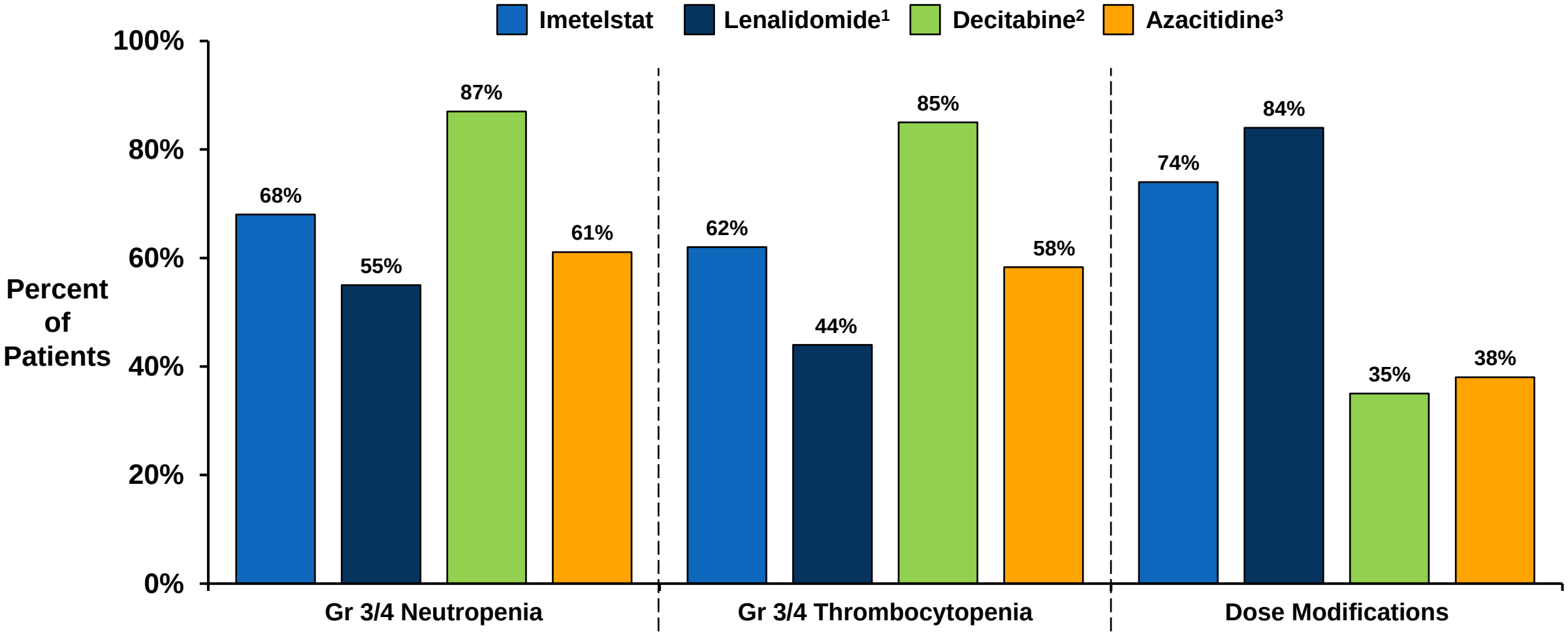
Clinician's Perspective on Imetelstat: Efficacy

- Magnitude and durability of RBC TI
  - Achieving TI is meaningful clinical benefit for TD anemia in LR MDS
  - Duration of response only clinically relevant in responders
    - Pre-specified per protocol as secondary endpoint
    - Imetelstat provides long-term, continuous transfusion-free periods
- Hemoglobin and HI-E
  - Meaningful increases in hemoglobin and HI-E benefits seen with imetelstat

Clinician's Perspective on Imetelstat: Safety

- Cytopenias and associated risks
  - Grade 3-4 or serious infections and bleeding events not increased for imetelstat
  - Grade 1-2 infections and bleeding do not require medical intervention
  - Febrile neutropenia events uncommon
  - Supportive care use in line with other approved treatments in MDS setting
  - Mean neutrophil and platelet levels plateau, do not increase risk of clinical consequences
- Dose modification
  - Rates of dose reductions comparable to other treatment options
  - Safety profile manageable

Hematologists Familiar with Managing Cytopenias in Lower-Risk MDS Clinical Practice



Based on AEs; 1. List, 2006 2. Kantarjian, 2006; 3. Santini, 2016

Clinician's Perspective on Imetelstat

- Current unmet need in TD anemia in LR MDS patients
- Imetelstat fulfills this unmet need
- Favorable benefit-risk profile

Conclusion

Faye Feller, MD

Geron Corporation

Benefits of Imetelstat Outweigh Risks

Benefits

- Statistically significant, clinically meaningful improvement in TI rate
  - **40% achieved ≥ 8-week TI; 52-week duration**
- Long, continuous TI
  - **28% ≥ 24-week TI; 80-week duration**
  - **18% ≥ 1-year TI; 132-week duration**
- Meaningful increases in Hgb
  - **34% ≥ 1.5 g/dL increase ≥ 8-weeks per IWG 2006**
- Reduced transfusion burden
  - **43% transfusion reduction by 50% in 16-week interval per IWG 2018**

Risks

- Well-characterized and manageable
- Grade 3/4 cytopenias with minimal clinical consequences
  - **2-week median duration**
  - **No severe bleeding w/ thrombocytopenia**
  - **3% infection w/ neutropenia, equivalent to placebo**
- Infrequent use of growth factor or platelet transfusions per patient
- HCPs experienced in managing cytopenias
- Non-hematologic AEs infrequent and low-grade
- No detriment in OS
  - **HR = 0.98**

Imetelstat for the Treatment of Transfusion-Dependent Anemia in Adults with Low to Intermediate-1 Risk Myelodysplastic Syndromes (LR MDS)

CLARIFYING QUESTIONS

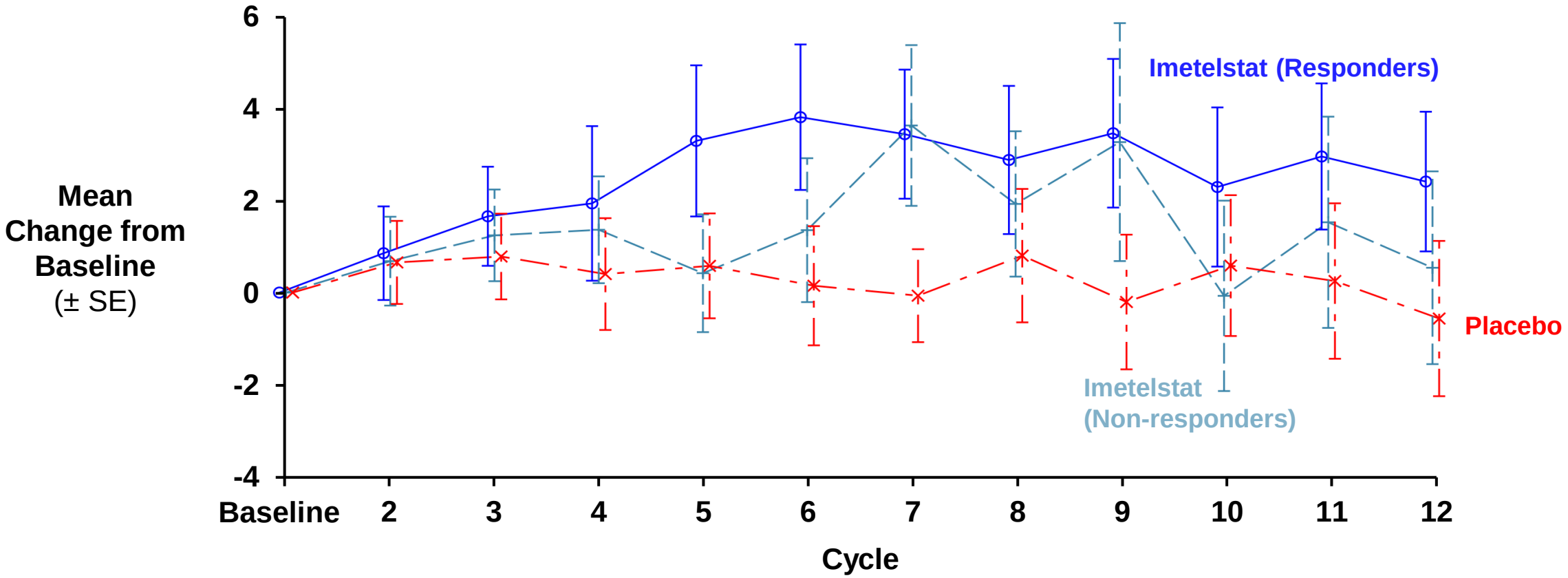
March 14, 2024

Oncologic Drugs Advisory Committee

Geron Corporation

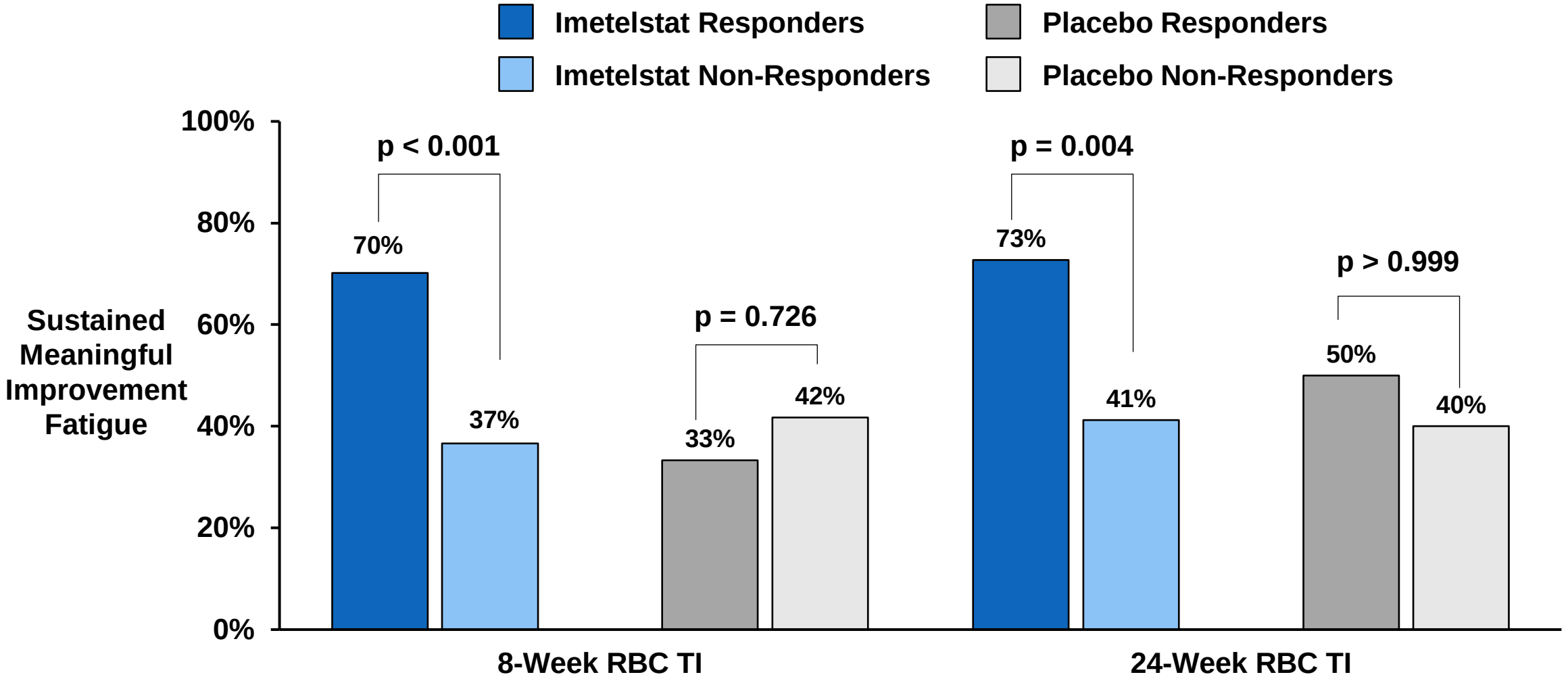
Q&A Slides Shown

FACIT- Fatigue Score by 8-week TI Response Show No Worsening of Fatigue Over Time in Both Imetelstat Groups



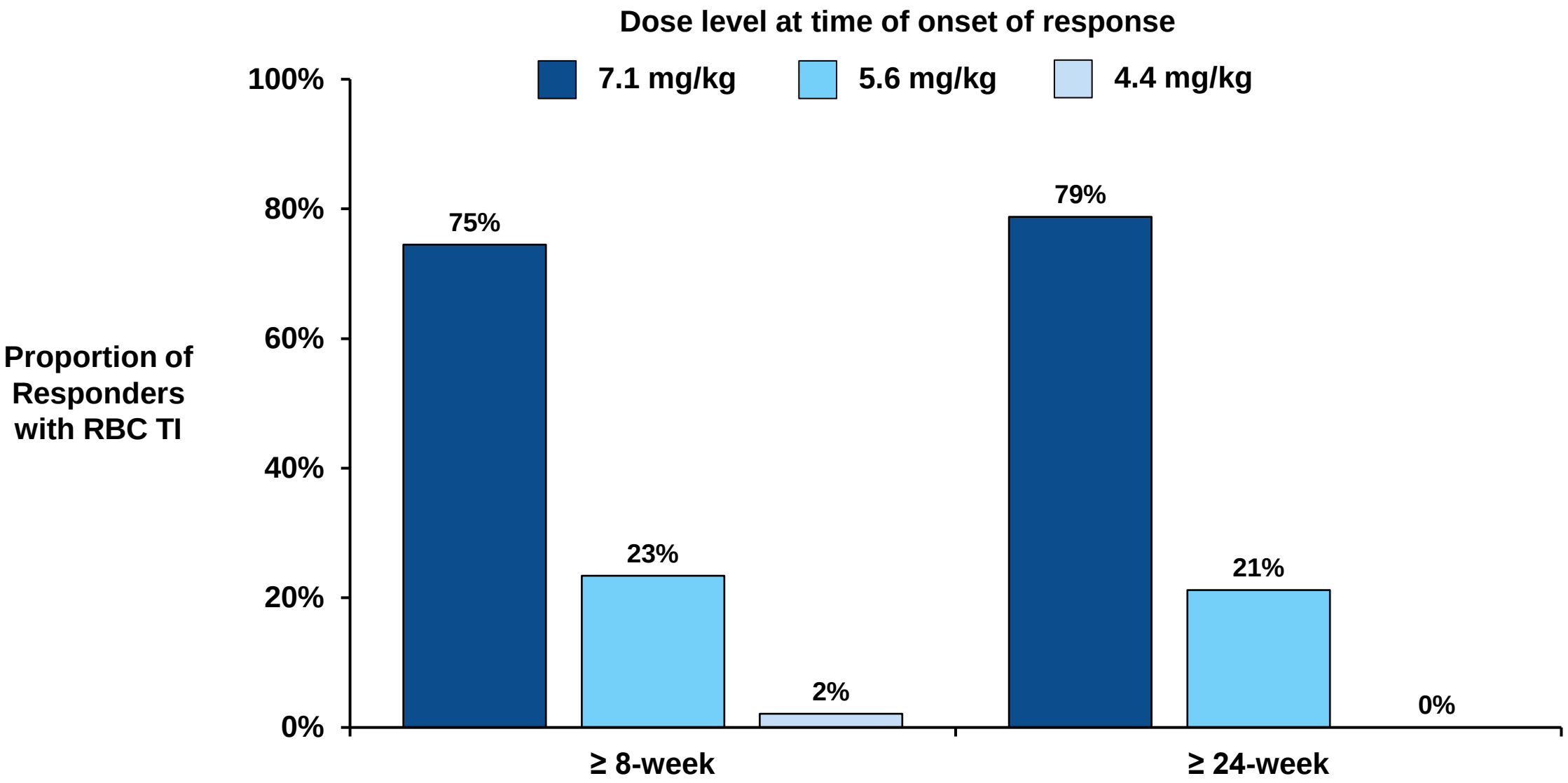
	Baseline	2	3	4	5	6	7	8	9	10	11	12
Imetelstat (Responders)	47	43	46	46	44	39	41	40	39	36	37	38
Imetelstat (Non-responders)	71	58	62	55	44	41	32	23	15	14	13	13
Placebo	57	52	54	52	49	46	40	30	27	23	21	20

Sustained Meaningful Improvement in FACIT-Fatigue Scores Correlated with Imetelstat Response

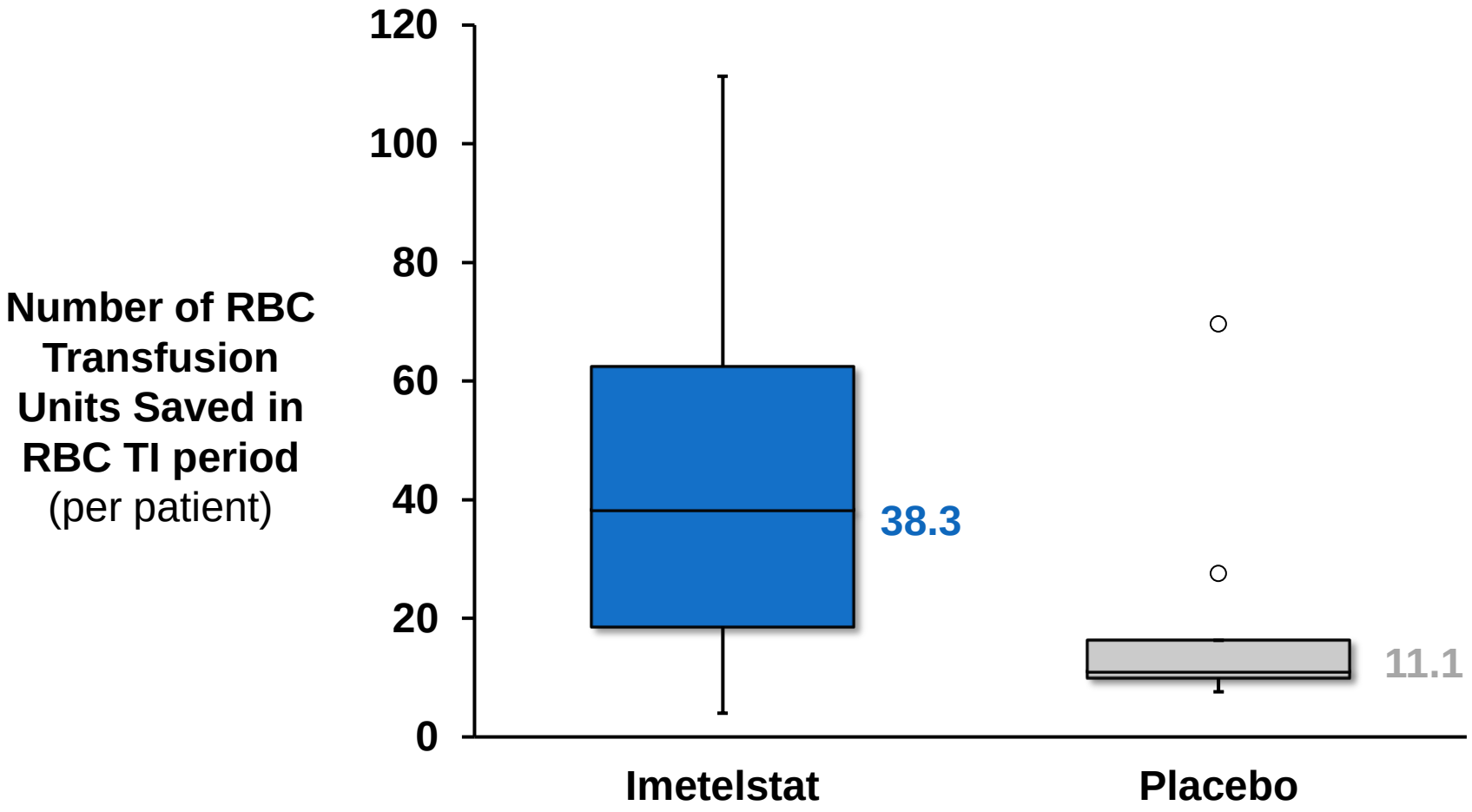


Study MDS3001 CSR (Phase 3)/Figure 20
P value calculated using Fisher exact test P value tests within each treatment goup
HI-E = hematologic improvement erythroid; RBC = red blood cell; TI = transfusion independence

≥ 75% of RBC TI Responders Received 7.1 mg/kg Dose at Time of Onset of Response



Median RBC Transfusion Units Saved Per Patient is Substantial for Primary Endpoint TI Responders on Imetelstat

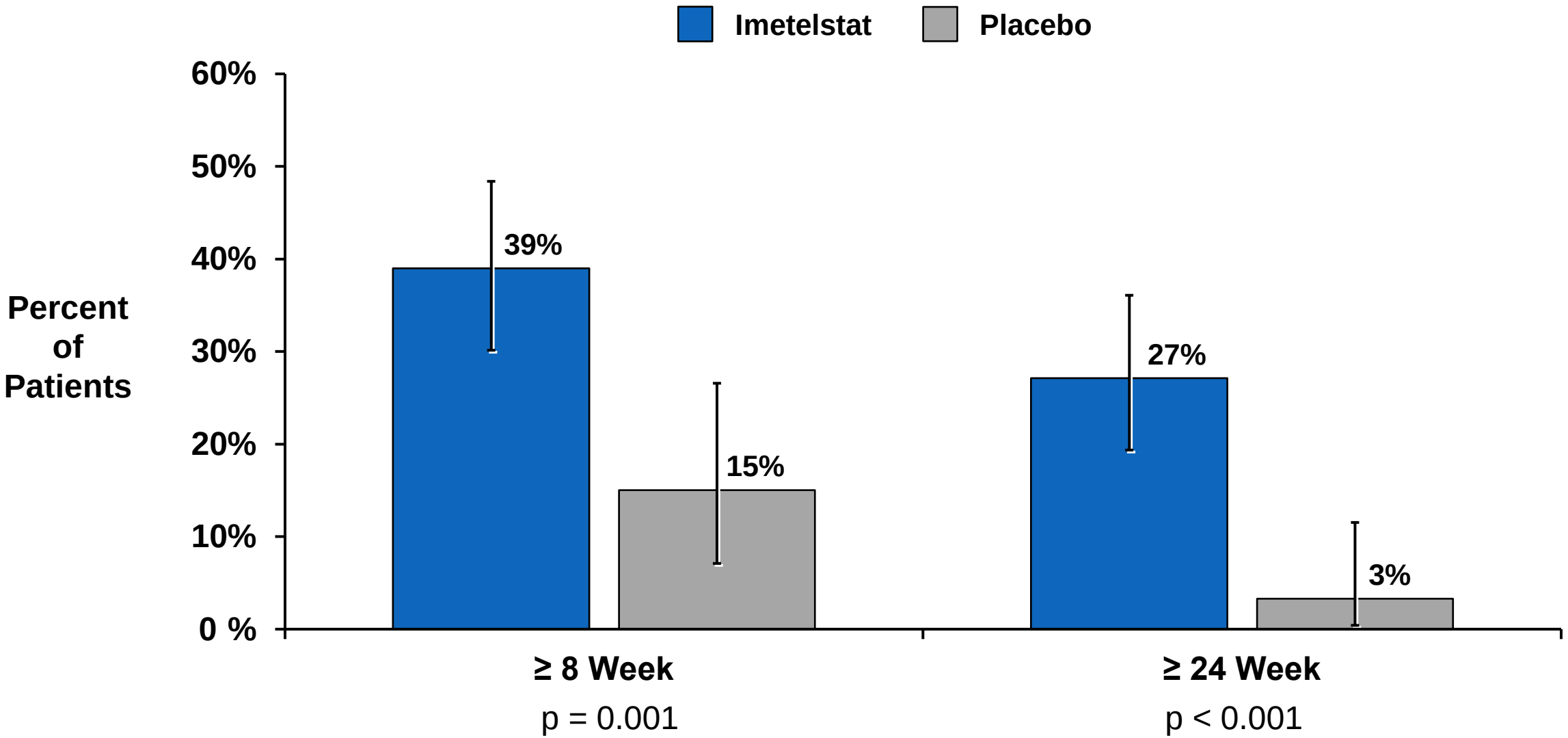


p-value = 0.024

Duration of Hospitalization Shorter on Imetelstat Arm

	Imetelstat N = 118	Placebo N = 59
Number of hospitalized patients	**37 (31%)**	**14 (24%)**
Mean (SD), days	**13.5** (14.43)	**49.8** (94.94)
Median (min, max), days	**6.0** (1, 52)	**25.5** (1, 370)

Joint RBC and Platelet Transfusion Independence Rates Similar to Primary and Secondary RBC TI Endpoints



Grade 3 or 4 Neutropenia and Thrombocytopenia Events Per Patient is Low

Lab value	Imetelstat N = 118	Placebo N = 59
Patients with events of Grade 3/4 neutropenia	**84 (71%)**	**4 (7%)**
Number of events		
Mean (SD)	2.3 (2.94)	0.1 (0.34)
Median (range)	1.0 (0-14)	0 (0-2)
Patients with events of Grade 3/4 thrombocytopenia	**77 (65%)**	**5 (9%)**
Number of events		
Mean (SD)	1.7 (2.35)	0.1 (0.42)
Median (range)	1.0 (0-12)	0 (0-2)

Thrombocytopenia and Neutropenia Occur Early

	Imetelstat N = 118			Placebo N = 59		
	n	Neutropenia	Thrombocytopenia	n	Neutropenia	Thrombocytopenia
Grade 3 or 4		71%	65%		7%	8%
Cycle 1 – 3	118	65%	48%	59	3%	2%
Cycle 4 – 6	103	35%	29%	53	4%	4%
Cycle 7 – 9	76	26%	26%	41	0	2%
Cycle 10 – 12	53	21%	17%	24	0	4%

- 65% of Grade 3/G4 neutropenia and ~ 48% of thrombocytopenia by lab occurred within cycles 1-3

***By laboratory assessment**

Dose Reductions During TI Did Not Result in Loss of Response