Imetelstat Treatment Leads to Durable Transfusion Independence in RBC Transfusion-Dependent, Non-Del(5q) Lower Risk MDS Relapsed/Refractory to Erythropoiesis-Stimulating Agent Who Are Lenalidomide and HMA Naive

David P. Steensma, MD[1], Uwe Platzbecker, MD[2], Koen Van Eygen, MD[3], Azra Raza, MD[4], Valeria Santini, MD[5], Ulrich Germing, MD, PhD[6], Patricia Font, MD[7], Irina Samarina, MD[8], Maria Díez-Campelo, MD, PhD[9], Sylvain Thepot, MD[10], Edo Vellenga, MD[11], Mrinal M. Patnaik, MD, MBBS[12], Jun Ho Jang, MD, PhD[13], Jacqueline Bussolari, PhD[14], Laurie Sherman, BSN[14], Libo Sun, PhD[14], Helen Varsos, MS, RPh[14], Esther Rose, MD[14] and Pierre Fenaux, MD, PhD[15]

[1]Dana-Farber Cancer Institute (US), [2]University Hospital Carl Gustav Carus, Dresden (DE), [3]Algemeen Ziekenhuis Groeninge, Kortrijk (BE), [4]Columbia University Medical Center (US), [5]MDS Unit, AOU Careggi-University of Florence (IT), [6]Heinrich-Heine-Universität, Düsseldorf (DE), [7]Hospital General Universitario Gregorio Marañon, Madrid (ES), [8]Emergency Hospital of Dzerzhinsk, Nizhny Novgorod (RU), [9]The University Hospital of Salamanca (ES), [10]CHU Angers (FR), [11]University Medical Center Groningen (NE), [12]Mayo Clinic, Rochester (US), [13]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul (KO), [14]Janssen Research & Development, LLC (US), [15]Hôpital Saint-Louis, Université Paris (FR)

Funded by Janssen Research & Development and Geron Corporation

Abstract #463

Steensma *et al*. ASH 2018 Oral Presentation

Background: Myelodysplastic Syndromes (MDS) and Imetelstat

- Patients with TD LR-MDS that has relapsed or is refractory to ESA therapy have limited treatment options
- Higher telomerase activity, expression of hTERT and shorter telomeres predict for shorter overall survival in lower risk MDS
- Imetelstat is a first-in-class telomerase inhibitor that targets cells with short telomere lengths and active telomerase and has clinical activity in myeloid malignancies[1-3]
  - FDA granted Fast-Track designation for LR-MDS (Oct 2017)
- IMerge is an ongoing global phase 2/3 study of imetelstat in RBC TD patients with LR-MDS (IPSS Low or Int-1)[4]

ESA, erythropoiesis-stimulating agent; hTERT, human telomerase reverse transcriptase; IPSS, International Prognostic Scoring System; Int-1, Intermediate-1; LR, lower risk; RBC, red blood cell; TD, transfusion dependent.

1. Baerlocher GM, et al. N Engl J Med 2015;373:920-928
2. Tefferi A, et al. N Engl J Med 2015;373:908-919
3. Tefferi A, et al. Blood Cancer J 2016;6:e405
4. Fenaux P, et al. HemaSphere 2018;2(S1):S1557 [oral presentation]

Background: IMerge/NCT02598661 (Part 1) Study Design[1]

Patients with MDS

- IPSS Low or Int-1
- Relapsed / refractory to ESA or ineligible for ESA
- Transfusion dependent (≥ 4u RBC/8 weeks)
- ANC ≥ 1.5 x 10^9/L
- Platelets ≥ 75 x 10^9/L

single arm

open label

Imetelstat Treatment

7.5 mg/kg IV q4w
(2-hr infusion)

1º Endpoint: 8-Week RBC TI
2º Endpoints: 24-Week RBC TI / Time to TI / TI duration / TR (HI-E: Transfusion Reduction by ≥ 4 RBC units over 8 weeks) / MDS response per IWG / Overall survival / Incidence of AML / Safety
Exploratory: telomerase activity / hTERT / telomere length / genetic mutations

Pre-medication: diphenhydramine, hydrocortisone 100-200 mg (or equivalent)

Supportive care: RBC transfusions, myeloid growth factors per local guidelines

AML, acute myeloid leukemia; ANC, absolute neutrophil count; HI-E, hematologic improvement-erythroid; IWG, International Working Group; TI, transfusion independence; TR, transfusion reduction.

1. Fenaux P, et al. HemaSphere 2018;2(S1):S1557 [oral presentation]

Background: Key Efficacy and Safety Outcomes from IMerge (Part 1)[1]

Parameters	All Treated (N=32)	Lenalidomide and HMA naïve and Non-del (5q) (n=13)
Rate of 8-week TI, n (%)	11 (34)	7 (54)
Rate of 24-week TI, n (%)	5 (16)	4 (31)
Rate of transfusion reduction (HI-E), n (%)	19 (59)	9 (69)
Most common adverse events, n (%)		
Neutropenia	23 (72)	7 (54)
Grade 3 / 4	8 (25) / 13 (41)	2 (15) / 5 (38)
Thrombocytopenia	18 (56)	8 (62)
Grade 3 / 4	10 (31) / 8 (25)	5 (38) / 3 (23)

Most grade ≥ 3 cytopenias were reversible in < 4 weeks

HI-E, hematologic improvement-erythroid; HMA, hypomethylating agents; TI, transfusion independence.

[1]Fenaux P, et al. HemaSphere 2018;2(S1):S1557 [oral presentation]

IMerge: Patients and Treatment Exposure

- An additional 25 lenalidomide and HMA naïve patients without del(5q) were enrolled
- Here we report updated results for 38 patients

	Median Follow-up
Initial 13 lenalidomide and HMA naïve patients without del(5q)	29.1 mo
25 patients meeting the same criteria	8.7 mo

- Clinical Cutoff: 26-Oct-2018
- Median number of treatment cycles: 8.0 (range: 1–34) cycles
  - Mean dose intensity was 6.9 mg/kg/cycle

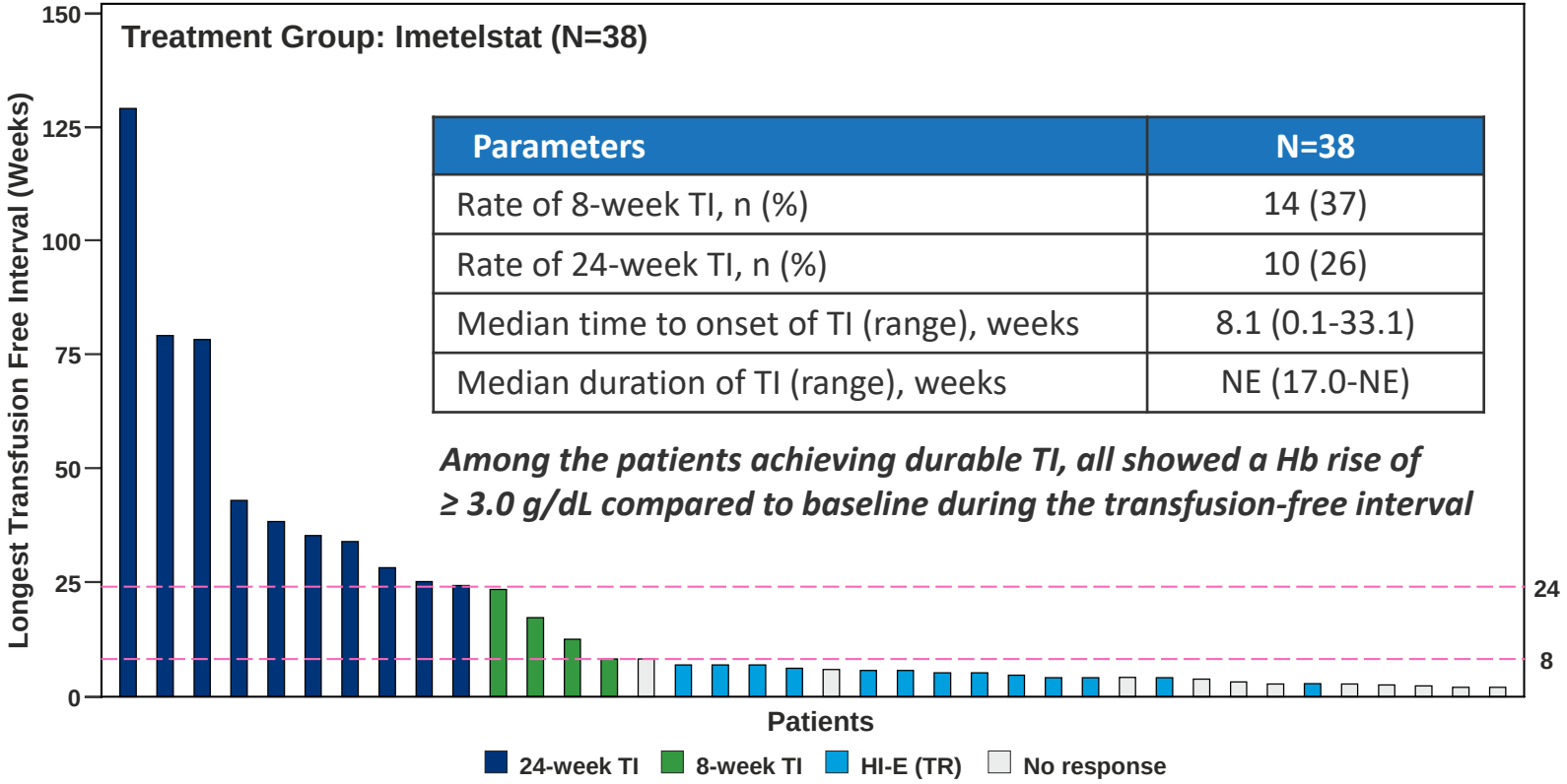
IMerge: Baseline Characteristics

Parameters	N=38
Median age (range), years	71.5 (46-83)
Male, n (%)	25 (66)
ECOG PS 0-1, n (%)	34 (89)
IPSS risk, n (%) Low Intermediate-1	 24 (63) 14 (37)
Baseline median (range) RBC transfusion burden, units/8 weeks	8 (4–14)
WHO 2001 category, n (%) RARS or RCMD-RS All others	 27 (71) 11 (29)
Prior ESA use, n (%)	34 (89)
sEPO > 500 mU/mL, n (%)	12[a] (32)

[a]Of the 37 patients with sEPO levels reported.

Steensma *et al*. ASH 2018 Oral Presentation

IMerge: Longest Transfusion-Free Interval



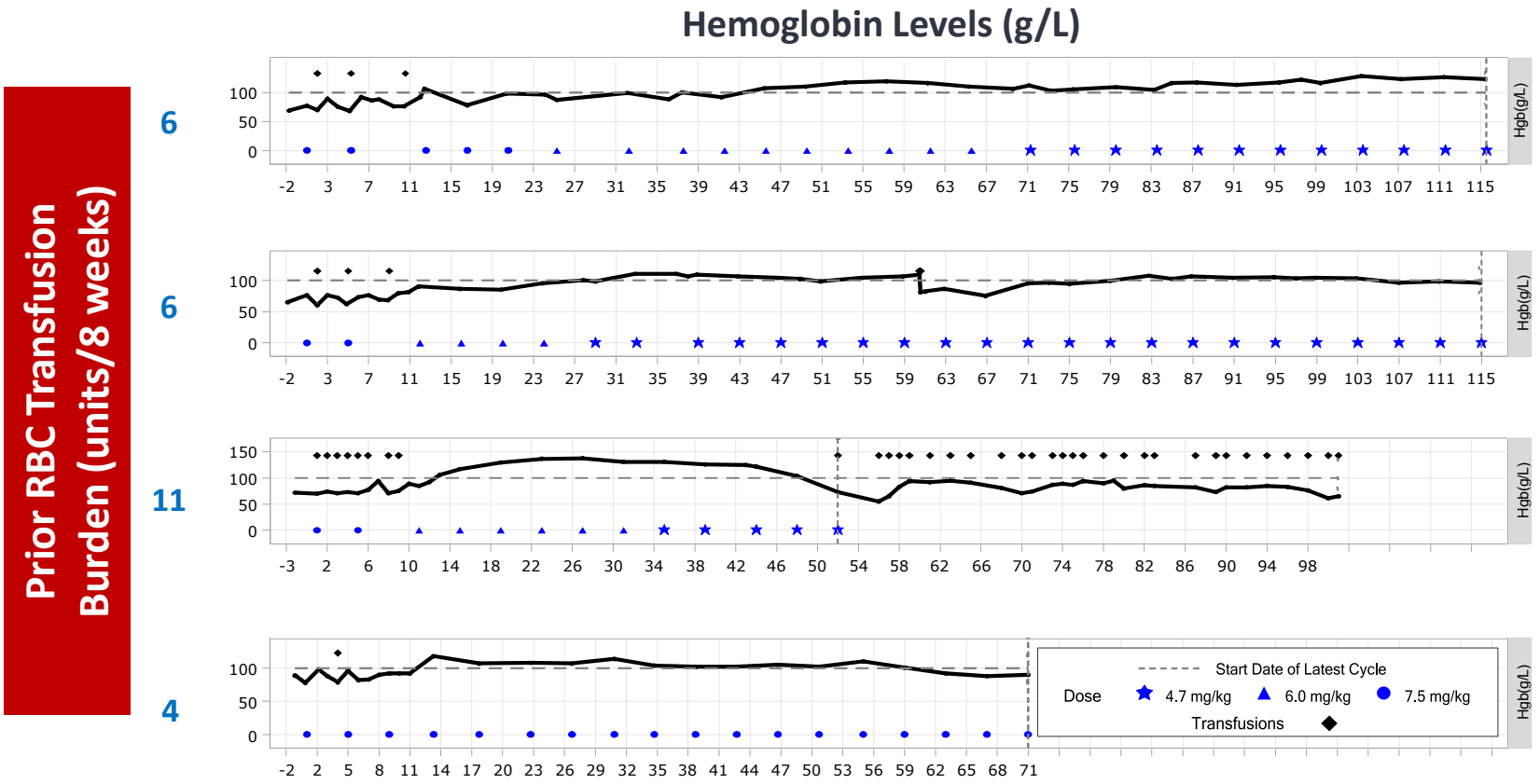
Parameters	N=38
Rate of 8-week TI, n (%)	14 (37)
Rate of 24-week TI, n (%)	10 (26)
Median time to onset of TI (range), weeks	8.1 (0.1-33.1)
Median duration of TI (range), weeks	NE (17.0-NE)

Among the patients achieving durable TI, all showed a Hb rise of ≥ 3.0 g/dL compared to baseline during the transfusion-free interval

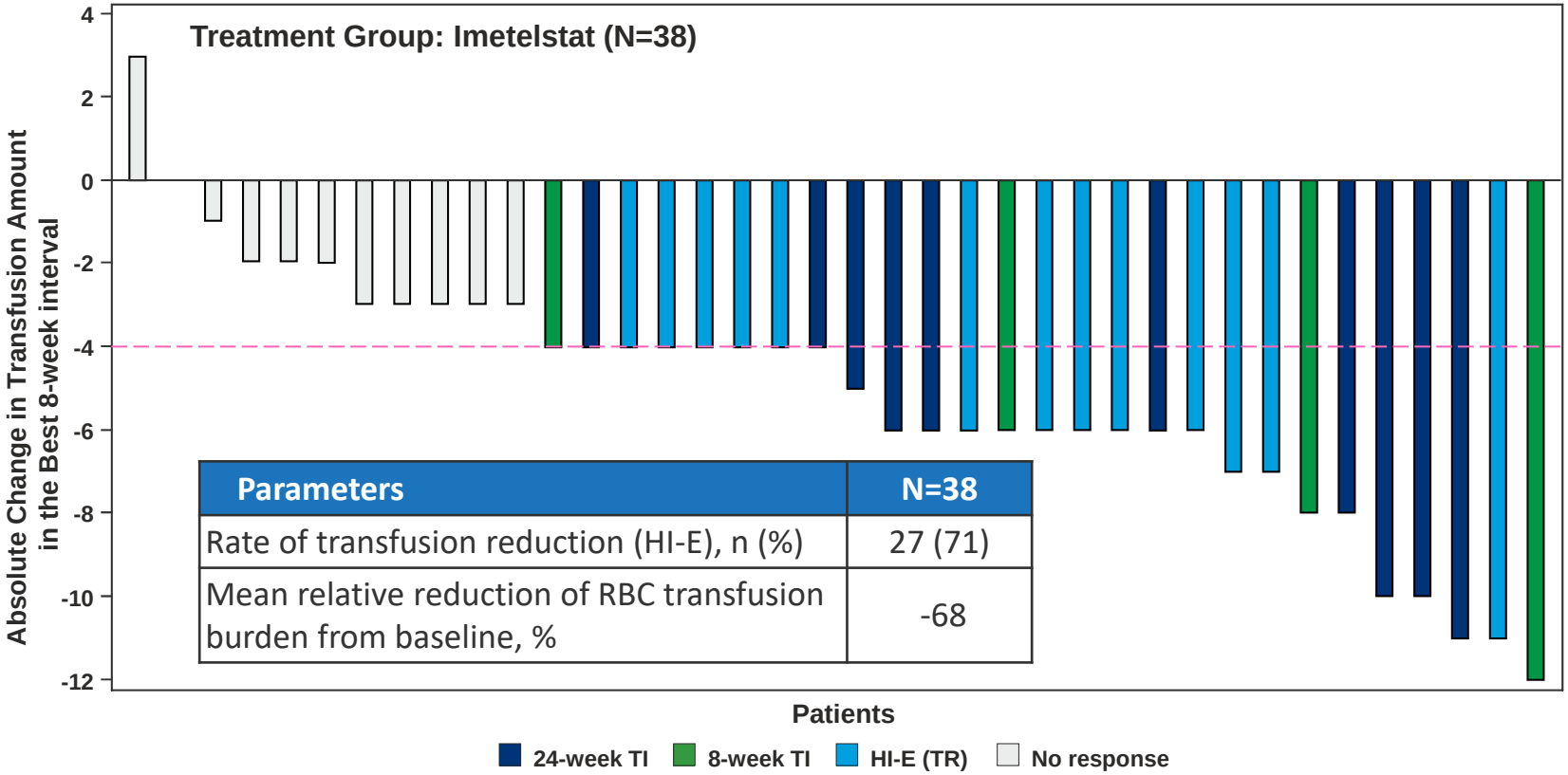
Hb, hemoglobin; HI-E, hematologic improvement-erythroid; TI, transfusion independence; TR, transfusion reduction.

Steensma *et al*. ASH 2018 Oral Presentation

IMerge: Hemoglobin and Imetelstat Dosing Among Patients with Durable TI



IMerge: Absolute Change in Transfusion Amount in the Best 8-Week Interval



Parameters	N=38
Rate of transfusion reduction (HI-E), n (%)	27 (71)
Mean relative reduction of RBC transfusion burden from baseline, %	-68

HI-E, hematologic improvement-erythroid; RBC, red blood cell; TI, transfusion independence; TR, transfusion reduction.

Steensma *et al*. ASH 2018 Oral Presentation

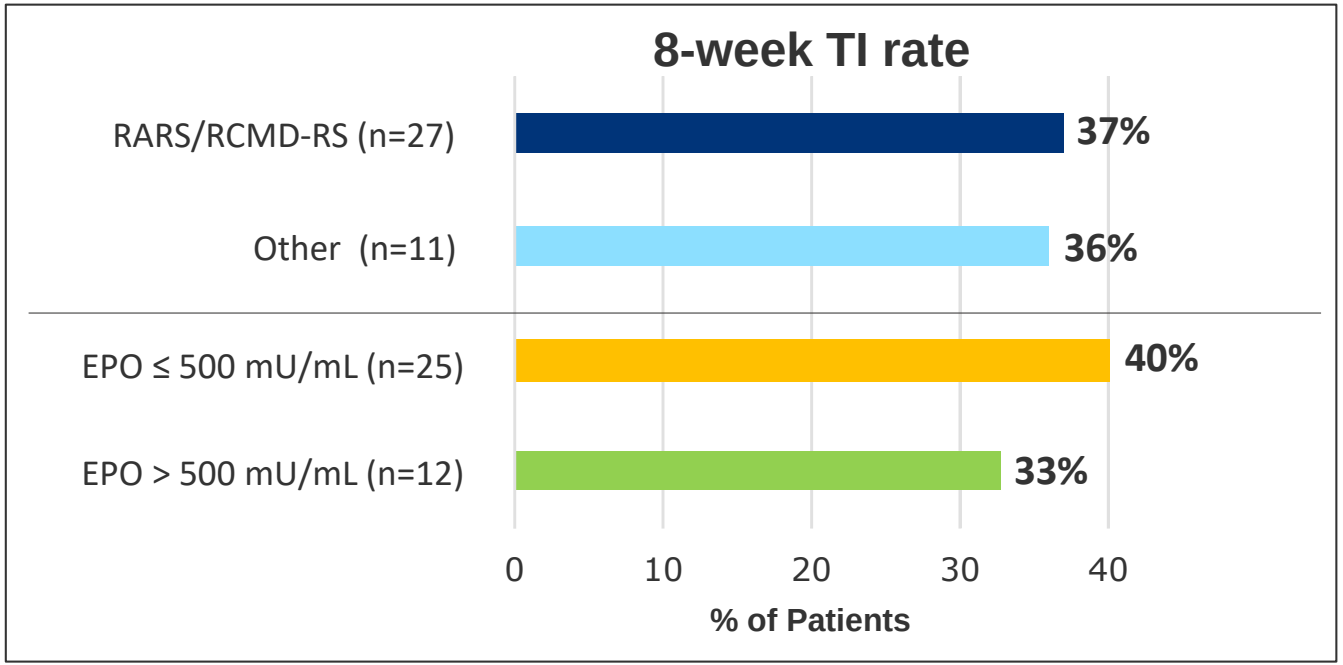
IMerge: Key Efficacy Outcomes

Parameters	N=38
Rate of 8-week TI, n (%)	14 (37)
Rate of 24-week TI, n (%)	10 (26)
Median time to onset of TI (range), weeks	8.1 (0.1-33.1)
Median duration of TI (range), weeks	NE (17.0-NE)
Rate of transfusion reduction (HI-E), n (%)	27 (71)
Mean relative reduction of RBC transfusion burden from baseline, %	-68
CR + marrow CR + PR (per IWG), n (%)	8 (21)

CR, complete remission; HI-E, hematologic improvement-erythroid; IWG, International Working Group; NE, not estimable; PR, partial remission; RBC, red blood cell; TI, transfusion independence.

Steensma *et al*. ASH 2018 Oral Presentation

IMerge: Efficacy Results in EPO and RS Subgroups

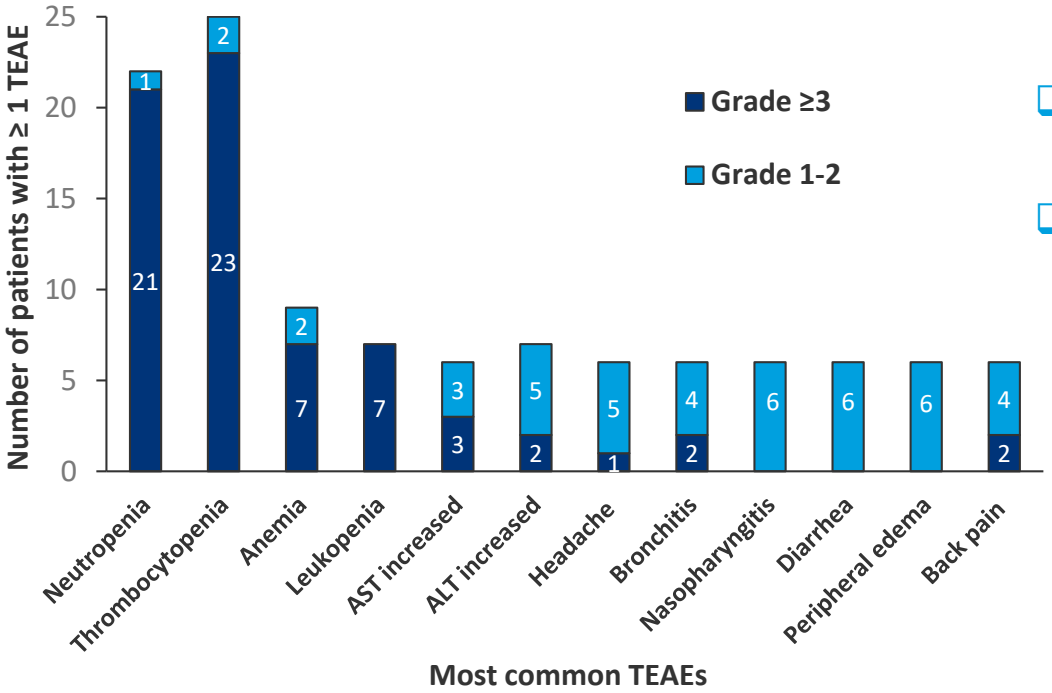


Similar efficacy was observed across these subgroups

EPO, erythropoietin; RARS, refractory anemia with ringed sideroblasts; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RS, ring sideroblast; TI, transfusion independence.

Steensma *et al*. ASH 2018 Oral Presentation

IMerge: Most Common Treatment-Emergent Adverse Events



- 19 patients (50%) had dose reductions and 26 patients (68%) had cycle delays
- Reversible grade 3 LFT elevations were observed in 3 (8%) patients on study
  - Independent Hepatic Review Committee considered these not drug-related

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test; TEAE, treatment-emergent adverse event.

Steensma *et al*. ASH 2018 Oral Presentation

IMerge: Occurrence/Reversibility of Grade 3/4 Cytopenias

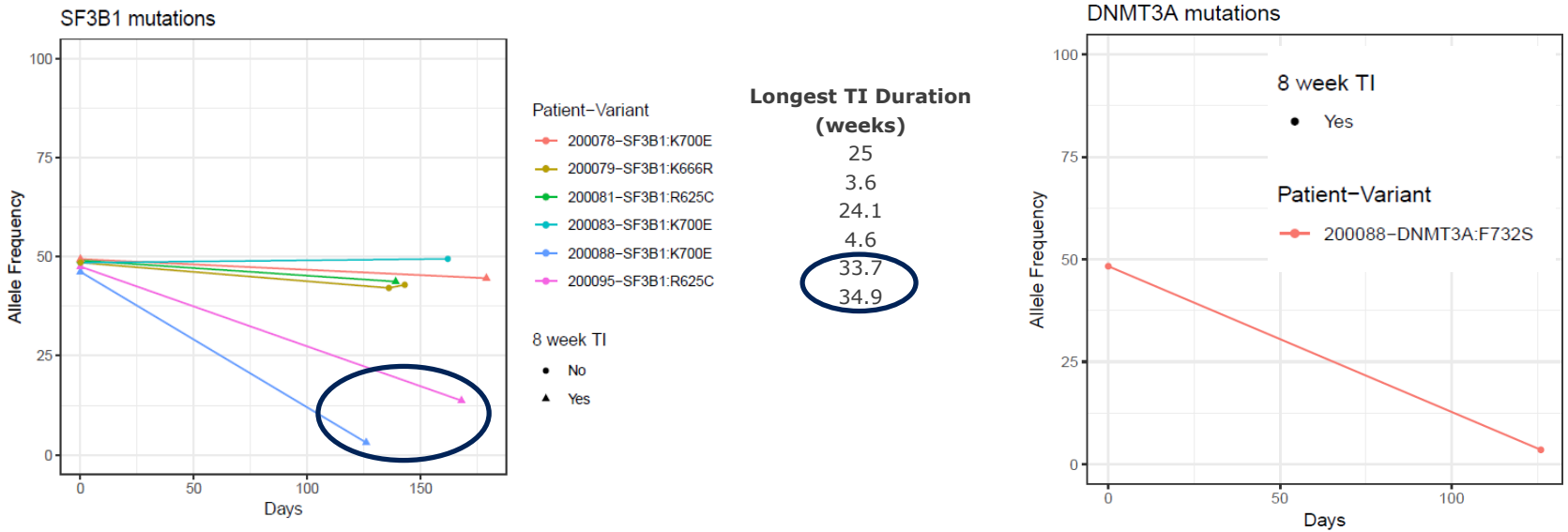
	All events, n (%) of patients (N=38)	Recovered in < 4 weeks, n (%) of patients with an event
Neutrophils, n (%)		
Grade 3	10 (26)	8 (80)
Grade 4	12 (32)	12 (100)
Platelets, n (%)		
Grade 3	14 (37)	13 (93)
Grade 4	10 (26)	9 (90)

- 2 patients had febrile neutropenia
- 12 patients received G-CSF for neutropenia
- 7 patients received platelet transfusions
- 3 patients with Grade 1 bleeding events

Steensma *et al*. ASH 2018 Oral Presentation

IMerge: Change in Mutation Variant Frequency

- 6 patients had SF3B1 mutations at baseline, with reduction of variant frequency observed in patients 200088 and 200095, both of whom had durable TI
- Patient 200088 also had reduction in DNMT3A mutation, and substantial reduction in bone marrow ringed sideroblasts (75% to 3%)



TI, transfusion independence.

Conclusions: Overall Efficacy and Safety

- In this cohort of 38 non-del(5q) LR-MDS patients with a high RBC transfusion burden who were ESA relapsed/refractory and naïve to lenalidomide/HMA, single-agent imetelstat yielded:
  - 8-week TI rate of 37%
  - 24-week TI rate of 26%
  - 24-week TI responses were accompanied by Hb rise of ≥ 3.0 g/dL
  - Median duration of TI was not reached
  - HI-E rate of 71%
- Side effects were limited, mainly cytopenias that were predictable, manageable and reversible

Conclusions: Overall Efficacy and Safety *(con't)*

- Similar efficacy was seen in EPO high/low and RS+/RS- subgroups, supporting broad clinical activity
- Reductions in mutation burden and RS noted among responding patients, suggesting potential disease modification
- These results support the planned Phase 3 study, expected to start mid-2019

Acknowledgements

The authors thank all the patients for their participation in this study and acknowledge the collaboration and commitment of all investigators and their staff

Mazure, Dominiek
Meers, Stef
Breems, Dimitri

Kim, Inho
Lee, Je-hwan

Klein, Saskia
Langemeijer, Saskia
van de Loosdrecht, Arjan

Oliva, Esther

Gourin, Marie-Pierre
Gyan, Emmanuel
Legros, Laurence
Thepot, Sylvain

Pristupa, Alexander
Samoilova, Olga
Udovitsa, Dmitry

De Paz, Raquel
Esteve, Jordi
Valcarcel, David
Xicoy, Blanca

Boccia, Ralph
Erba, Harry / DiStasi, Antonio
Grunwald, Michael
Jacoby, Megan
Miller, Carole
Schiller, Gary
Silverman, Lewis
Stevens, Don