Treatment with Imetelstat Provides Durable Transfusion Independence in Heavily Transfused Non-Del(5q) Lower Risk MDS Relapsed/Refractory to Erythropoiesis-Stimulating Agents

Pierre Fenaux[1], David P. Steensma[2] , Koen Van Eygen[3] , Azra Raza[4], Valeria Santini[5], Ulrich Germing[6], Patricia Font[7], Maria Diez-Campelo[8] , Sylvain Thepot[9] , Edo Vellenga[10], Mrinal M. Patnaik[11], Jun Ho Jang[12], Laurie Sherman[13], Libo Sun[14], Helen Varsos[14], Aleksandra Rizo[13], Ying Wan[13], Fei Huang[13], Jacqueline Bussolari[14], Esther Rose[14], Uwe Platzbecker [15]

[1]Hôpital Saint-Louis, Université Paris Diderot, Paris, France, [2]Dana-Farber Cancer Institute, Boston, United States, [3]Algemeen Ziekenhuis Groeninge, Kortrijk, Belgium, [4]Columbia University Medical Center, New York, United States, [5] MOS Unit, AOU Careggi-University of Florence, Florence, Italy, [6]Klinik für Hämatologie, Onkologie and Klinische Immunologie, Universitätsklinik Düsseldorf, Heinrich-Heine-Universität, Düsseldorf, Germany, [7]Department of Hematology, Hospital General Universitario Gregorio Marañon, Madrid, [8]Hematology Department, The University Hospital of Salamanca, Salamanca, Spain, [9]CHU Angers, Angers, France, [10]Department of Hematology, University Medical Center Groningen, Groningen, Netherlands, [11]Division of Hematology, Mayo Clinic, Department of Internal Medicine, Rochester, MN, United States, [12]Department of Hematology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, Republic Of, [13]Geron Corporation, Menlo Park, CA, United States, [14]Janssen Research & Development, LLC, Raritan, NJ, [15]Department of Hematology and Cell Therapy, University Clinic Leipzig, Leipzig, Germany

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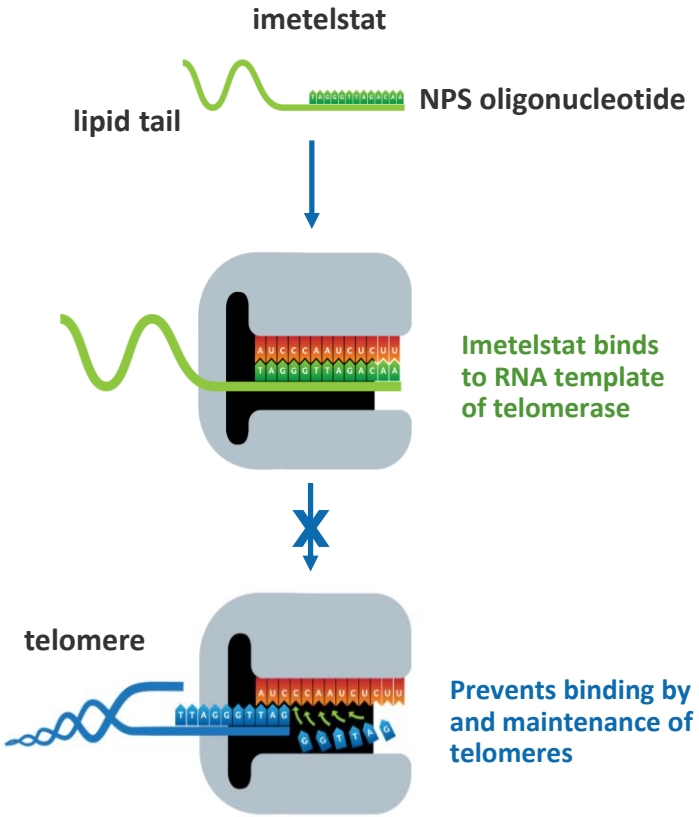
Background: Myelodysplastic Syndromes (MDS) and Imetelstat



- Patients with TD LR-MDS (low or intermediate 1 by IPSS) that has relapsed or is refractory to ESA therapy have limited treatment options
- Higher telomerase activity, expression of human telomerase reverse transcriptase (hTERT) and shorter telomeres predict for shorter overall survival in lower risk MDS[1]
- 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[2-4]
  - 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 with a primary endpoint of 8-week TI

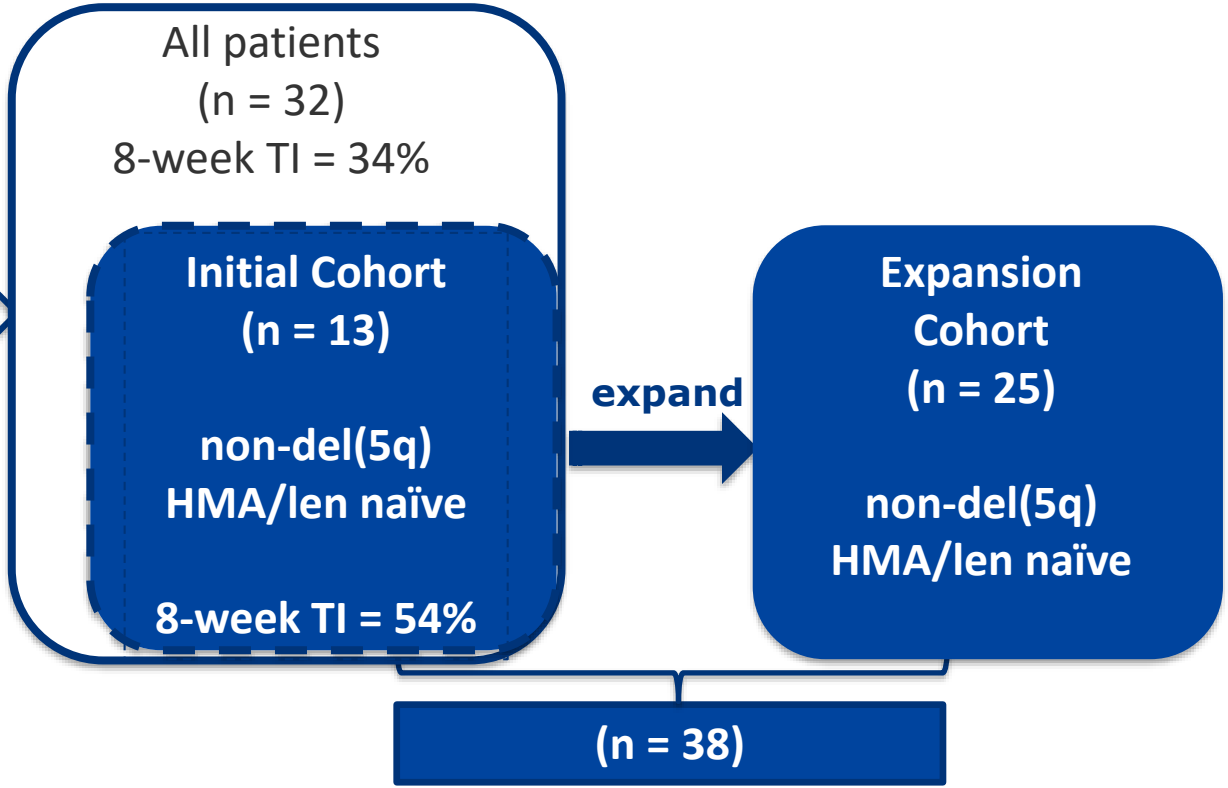
ESA, erythropoiesis-stimulating agent; hTERT, human telomerase reverse transcriptase; IPSS, International Prognostic Scoring System; Int-1, Intermediate-1; LR, lower risk; RBC, red blood cell; TD, transfusion dependent; TI, transfusion independence.

1- Gurkan E, et al Leuk Res 2005; 29:1131-9; 2- Baerlocher GM, et al. N Engl J Med 2015;373:920-928, 3-Tefferi A, et al. N Engl J Med 2015;373:908-919, 4- Tefferi A, et al. Blood Cancer J 2016;6:e405

IMerge Phase 2/3 Study: Phase 2 Portion

MDS patients:

- IPSS Low or Int-1
- Relapsed/Refractory to ESA or EPO >500 mU/ml
- Transfusion dependent: ≥ 4 units RBC/8 weeks over 16 week pre-study period



Primary Endpoint: 8-week RBC Transfusion Independence (TI)

Key Secondary Endpoints: 24-week RBC TI/Duration of TI/HI-E

HMA, hypomethylating agent; len, lenalidomide

Treatment Exposure

- **Data from 38** patients with non-del(5q) HMA/len naïve transfusion dependent lower risk MDS is presented
- Data Cutoff Date: 30 April 2019

Parameters	n = 38
Median Follow-up, months (range) Initial cohort (n=13) Expansion cohort (n=25)	15.7 (5.6 – 37.5) 33.7 (5.6 – 37.5) 14.3 (10.9 – 16.5)
Median treatment duration, months (range)	8.5 (0.02 – 37.5)
Median treatment cycles (range)	9 (1 – 39)
Median dose intensity, %	95.2

Patient Treatment Disposition

Parameters	n = 38 (n, %)
Ongoing on Treatment	12 (32)
Discontinued from Treatment	26 (68)
Reason: Lack of Efficacy	12 (32)
Adverse Event (AE)	8 (21)
Withdrawal by Subject	2 (5)
Progressive Disease	2 (5)
Relapse	1 (3)
Physician Decision	1 (3)

Baseline Patient Characteristics

Parameters	n = 38
Age, years, median (range)	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)
RBC transfusion burden, units / 8 weeks, median (range)	8 (4 – 14)
>4 units / 8 weeks at baseline, n (%)	35 (92)
WHO 2001 category, n (%) RARS or RCMD-RS RA, RCMD or RAEB-1	 27 (71) 11 (29)
Prior ESA use, n (%)	34 (89)
sEPO > 500 mU/mL, n (%)	12 (32) (from 37 patients with baseline sEPO levels)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; sEPO, serum erythropoietin; RA, refractory anemia; RAEB1, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; WHO, World Health Organization

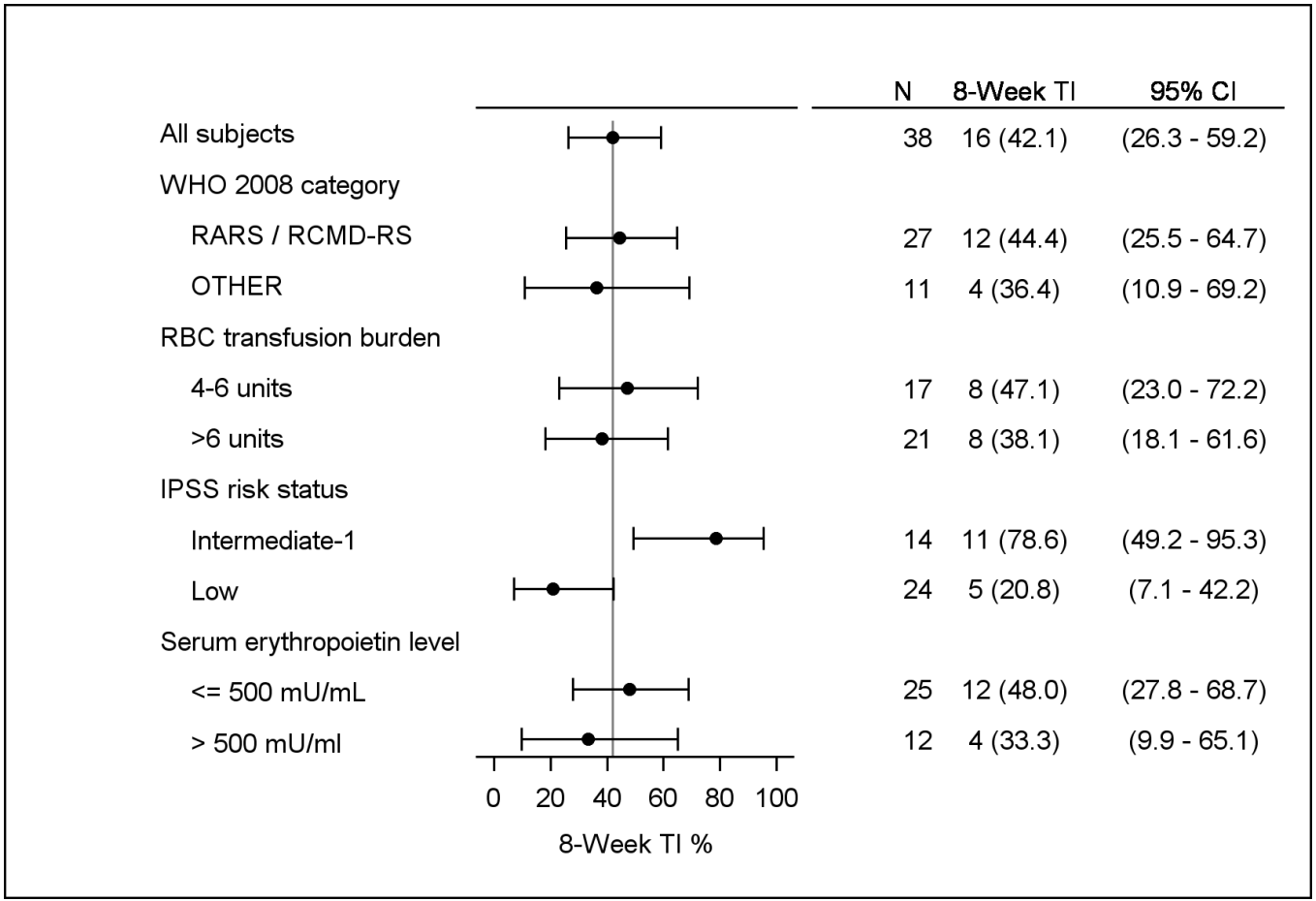
Meaningful and Durable Transfusion Independence with Imetelstat Treatment

Parameters	n = 38
8-week TI, n (%) Time to onset, weeks, median (range) Duration of TI[a], weeks, median (range)	16 (42) 8.3 (0.1 – 40.7) 85.9 (8.0 – 140.9)
24-week TI, n (%)	11 (29)
HI-E per IWG 2006, n (%) ≥1.5 g/dL increase in Hgb lasting ≥ 8 weeks Transfusion reduction by ≥ 4 units/8 weeks	26 (68) 12 (32) 26 (68)
CR + marrow CR + PR (per IWG 2006, central path review), n (%) CR marrow CR PR	9 (24) 5 (13) 4 (10) 0

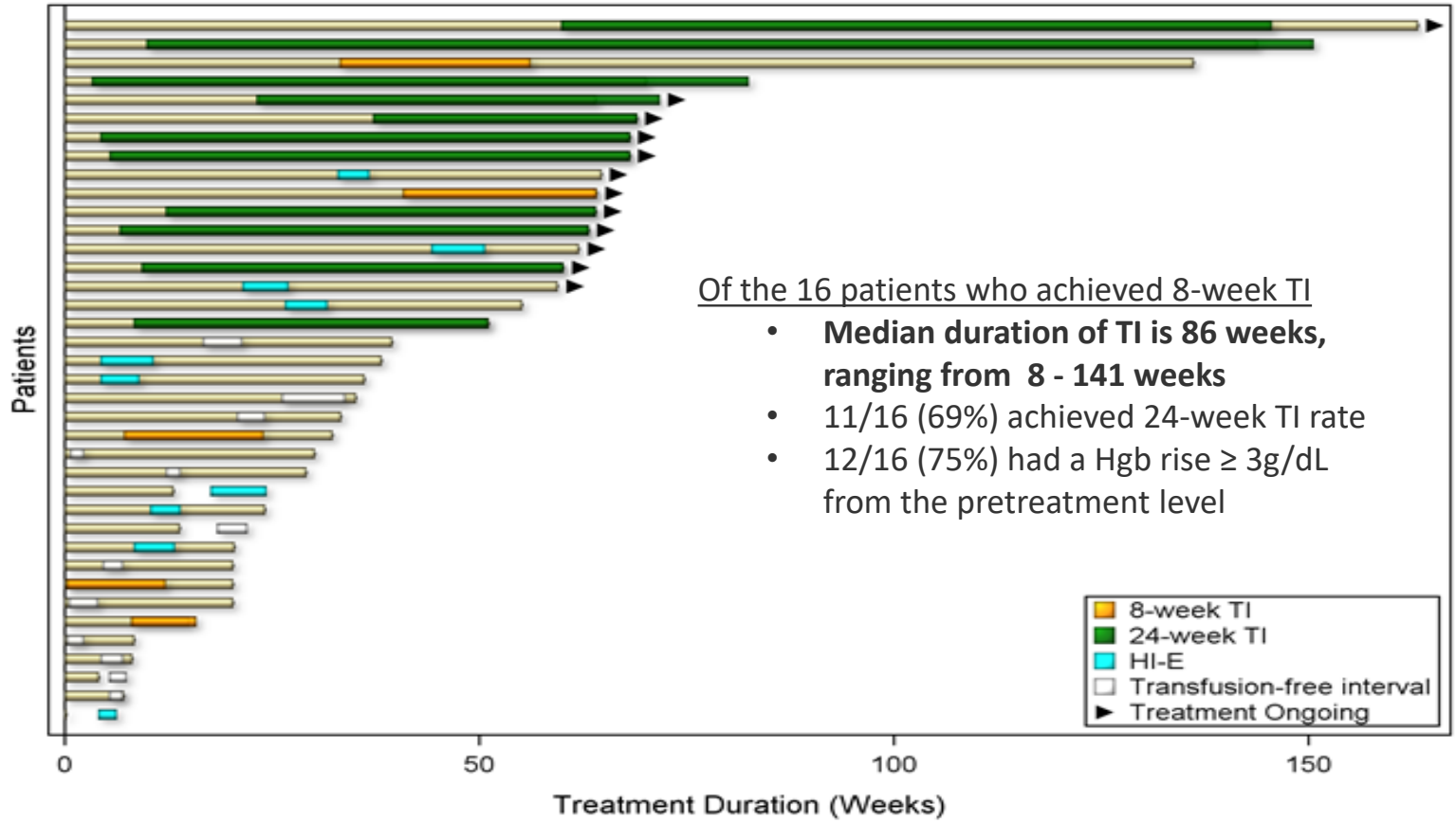
[a]Kaplan Meier method

CR, complete remission; IWG, International Working Group, PR, partial remission.

8-week TI Observed Across Different Subgroups



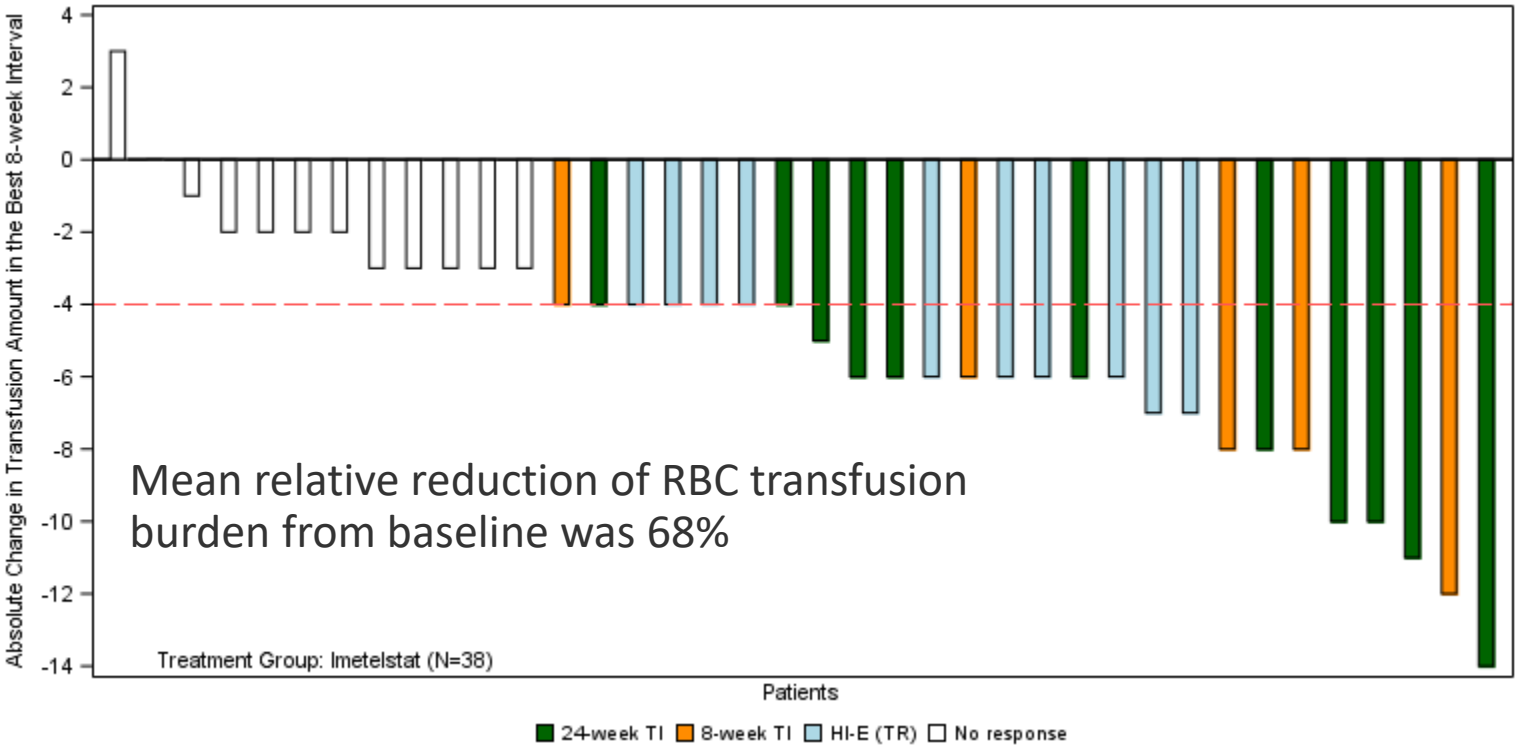
Durable Transfusion Independence with Imetelstat Treatment (median follow up 15.7 months; median treatment duration 8.5 months)



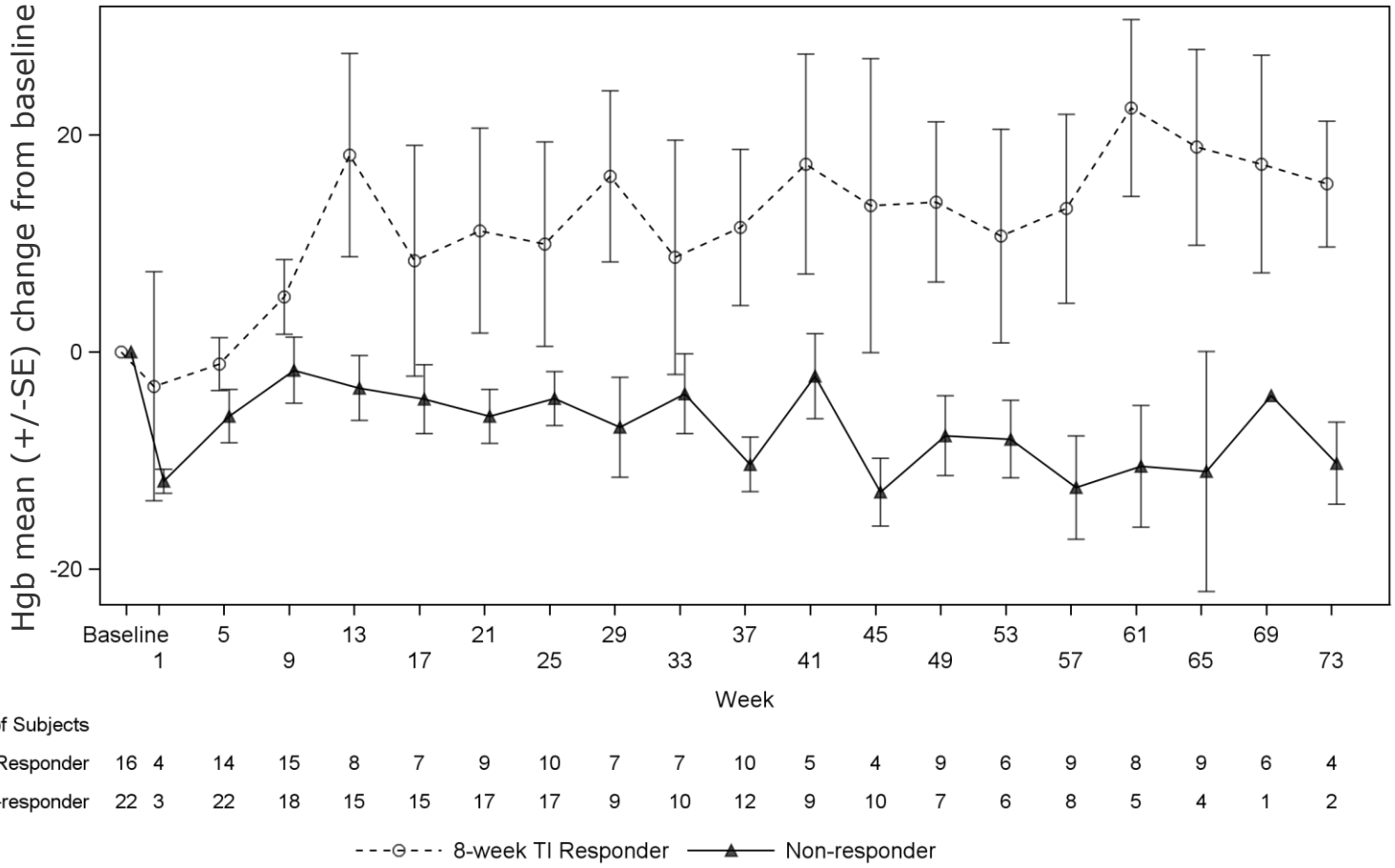
Of the 16 patients who achieved 8-week TI

- **Median duration of TI is 86 weeks, ranging from 8 - 141 weeks**
- 11/16 (69%) achieved 24-week TI rate
- 12/16 (75%) had a Hgb rise ≥ 3g/dL from the pretreatment level

Reductions in Transfusion Burden in Majority of Patients



Sustained Improvement in Hgb with Imetelstat Treatment



Activity in Patients with Intermediate or Poor Cytogenetic Risk

Among 34 patients with baseline cytogenetic data available:

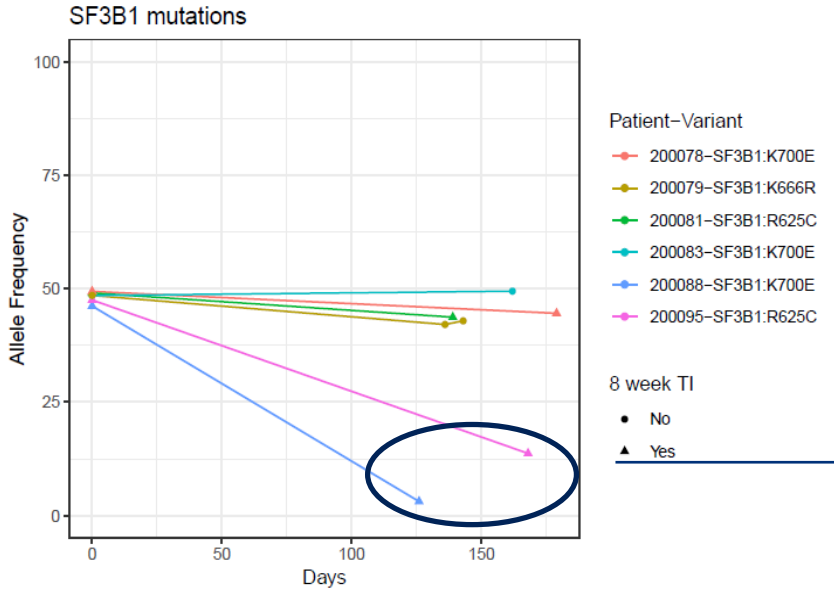
- 6/34 (18%) had intermediate or poor cytogenetic risk
  - 5/6 (83%) achieved 8-week TI and all had a ringed-sideroblast WHO subtype
  - 3/3 with trisomy 8 achieved 8-week TI and 2/3 achieved 24-week TI
  - 4/6 remain on treatment
- 2/3 patients with available post-treatment cytogenetic data achieved partial cytogenetic response

Subject	Karyotype	~24 wks post-imetelstat	~48 wks post-imetelstat	8-wk TI	WHO Classification
200083*	47,XX,+8 [9] (45%)	47,XX,+8 [1] (5%)		X	RCMD-RS
200088*	47,XY,+8 [20] (100%)	47,XY,+8 [5] (25%)	47,XX,+8 [1] (5%)	X	RCMD-RS
200061	47,XX,+8 [20] (100%)			X	RARS
200040	46,XY,DEL(7)(Q22) [5] (25%)			X	RCMD-RS
200093*	46,XX,Dup/Tri/Qtp(9)(P13P24) [20] (100%)	46,XX,Dup/Tri/Qtp(9)(P13P24) [19] (95%)	46,XX,Dup/Tri/Qtp(9)(P13P24) [19] (95%)	X	RCMD-RS
200102*	46,XY,T(3;3)(Q21;Q26.2) (100%)				RA

*remain on treatment

Potential Impact on the Malignant Clone with Imetelstat Treatment

2/6 patients with baseline SF3B1 mutations had reduction in variant allele frequency and maintained TI lasting over a year



SF3B1 mutated Patient ID	TI duration in SF3B1 patients (weeks)
200078*	48.7
200079	3.6
200081*	52
200083*	32
200088*	56.7
200095*	62.9

Confirmed partial cytogenetic response (from 100% to 5% abnormal karyotype)

*remain on treatment

No New Safety Signals Identified

Hematologic AEs

TEAE	All Grades N=38 (n, %)	≥Grade 3 N=38 (n, %)
Thrombocytopenia	25 (66)	23 (61)
Neutropenia	22 (58)	21 (55)
Anemia	10 (26)	8 (21)

Non-hematologic AEs

TEAE	All Grades N=38 (n, %)	≥Grade 3 N=38 (n, %)
Back pain[a]	7 (18)	0
ALT increased	7 (18)	2 (5)
AST increased	6 (16)	3 (8)
Bronchitis	6 (16)	3 (8)
Other AEs[b]	6 (16)	0
Headache	6 (16)	1 (3)

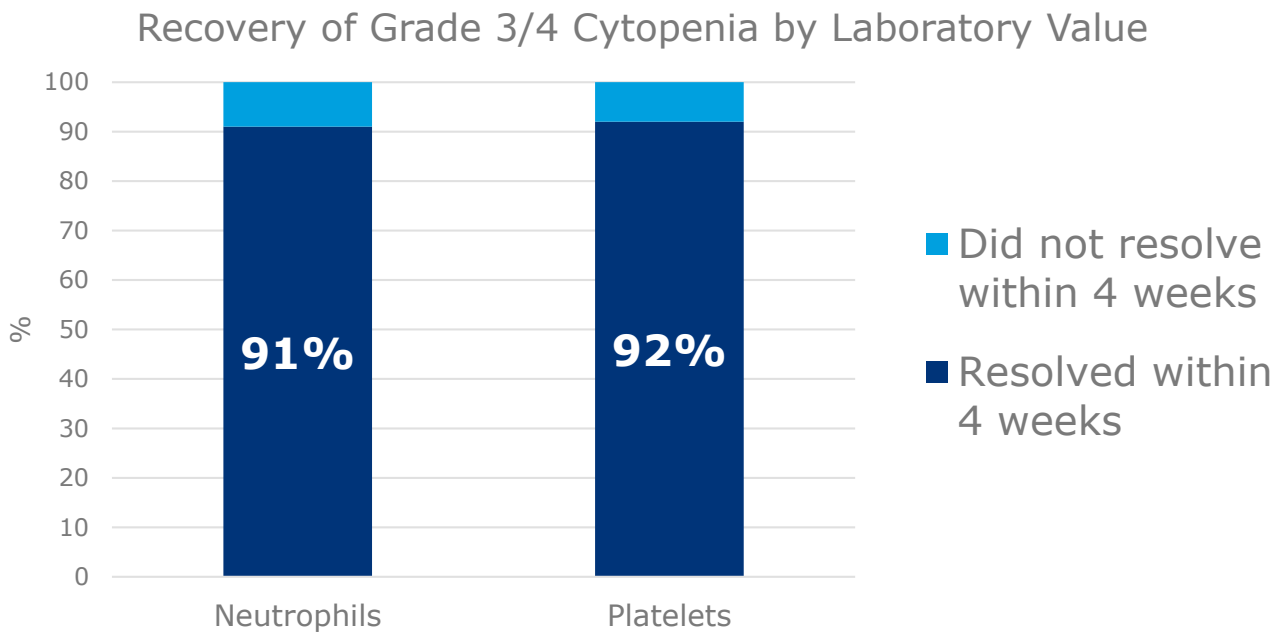
- Grade 3 LFT elevations were reversible

[a] In 3/7 (43%) patients back pain was an AE associated with infusion related reaction

[b] nasopharyngitis, diarrhea, constipation, edema peripheral and asthenia

ALT, alanine aminotransferase; AST, aspartate aminotransferase; LFT, liver function test

Reversible Grade 3/4 Cytopenias without Significant Clinical Consequences



- 2/38 patients (5%) had febrile neutropenia
- 4/38 patients (10%) had bleeding events, 2/38 (5%) were Grade 3/4

On Target Activity Demonstrated by Reduction in Telomerase Activity and hTERT Expression

Biomarker	TA	hTERT
Matched baseline / post baseline data available	12/38	35/38
Reduction from baseline	6/12 (50%)	26/35 (74%)

8- and 24-week TI correlate with a reduction in hTERT expression

hTERT expression	8-wk TI	No 8- wk TI	24- wk TI	No 24- wk TI
Matched baseline / post baseline data available	15/16	20/22	11/11	24/27
≥50% reduction from baseline*	73%	35%	82%	38%

* In preclinical xenograft models, a 50% reduction in hTERT expression is the threshold correlated with anti-tumor activity

Conclusions

- Imetelstat treatment shows meaningful and durable transfusion independence in heavily transfusion dependent non-del(5q) and HMA/len naïve lower risk MDS patients
  - 8-week TI rate 42%
  - 24-week TI rate 29%
  - Median TI duration approximately 20 months
  - HI-E rate 68%

Conclusions

- Transfusion independence observed across different clinical subgroups, including patients with int/poor cytogenetic risk
- Biomarker data suggest potential effect on the malignant clone and disease modification
- No new safety signal was identified; reversable cytopenias were most frequent AEs, without significant clinical consequences
- ***These results support initiation of the Phase 3 double-blind, placebo-controlled (2:1) portion of the study, expected to open this summer***

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