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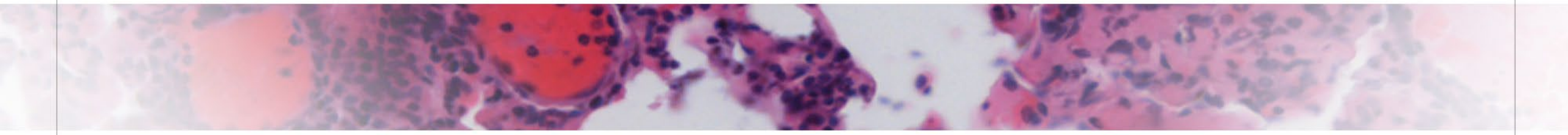
Abstract #459



Imetelstat Achieved Prolonged, Continuous Transfusion Independence in Patients With Heavily Transfused Non-Del(5q) Lower-Risk Myelodysplastic Syndromes Relapsed/Refractory to Erythropoiesis Stimulating Agents Within the IMerge Phase 2 Study

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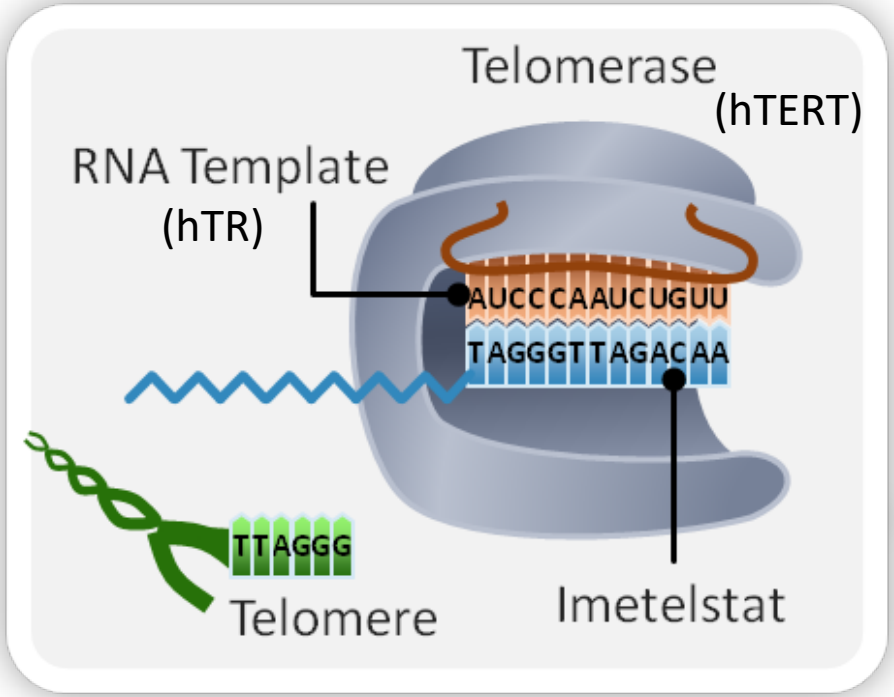
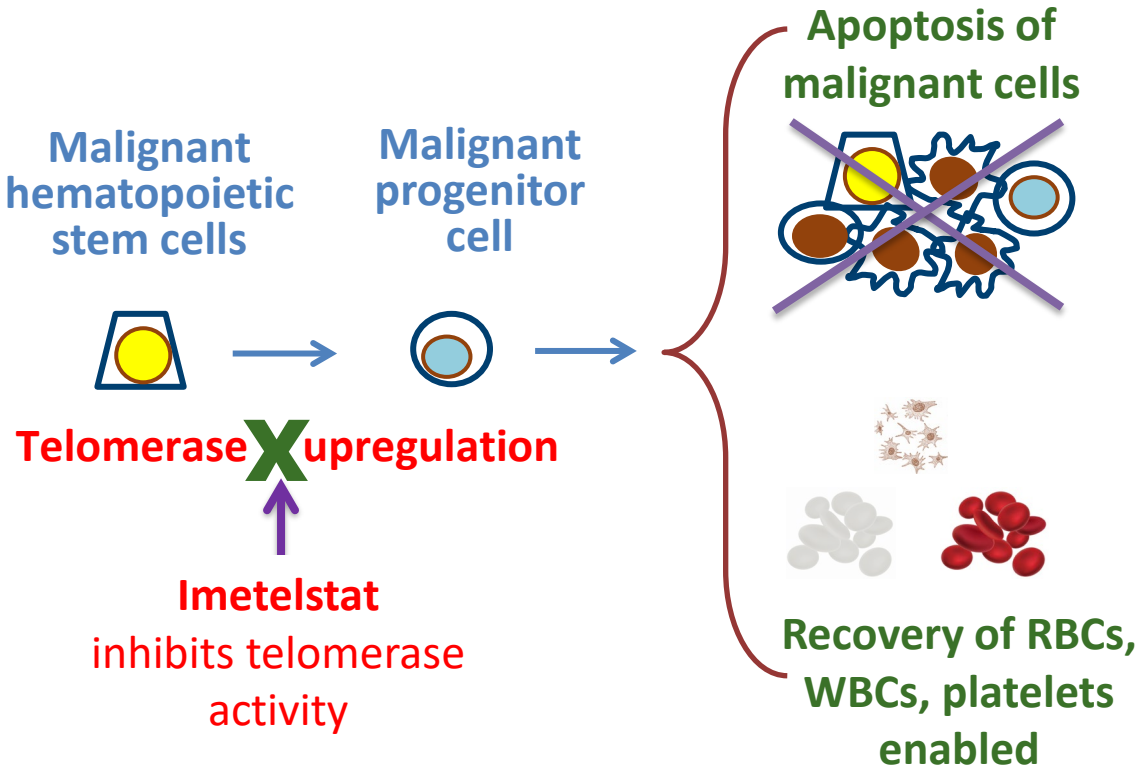
Imetelstat: First-in-Class Telomerase Inhibitor

- Imetelstat is a direct and competitive inhibitor of telomerase activity[1,2]



- Imetelstat has disease-modifying potential to selectively kill malignant stem and progenitor cells, enabling recovery of blood cell production[3,4]



hTERT, human telomerase reverse transcriptase; hTR, catalytic component; RBC, red blood cell; WBC, white blood cell.

1. Asai A, et al. *Cancer Res.* 2003;63(14):3931-3939; 2. Herbert BS, et al. *Oncogene.* 2005;24(33):5262-5268; 3. Mosoyan G, et al. *Leukemia.* 2017;31(11):2458-2467; 4. Wang X at al. *Blood Adv.* 2018;25;2(18):2378-2388.

IMerge (MDS3001; NCT02598661) Phase 2/3 Study Design

Part 1[1,2]
Phase 2, single-arm, open-label
Overall N=57

Target population of non-del(5q)/len/HMA-naive
N=38
Enrollment Complete

Imetelstat
7.5 mg/kg IV q4w

Part 2
Phase 3, randomized, double-blind, placebo-controlled
N=170
Enrollment complete; Top line results early Jan 2023

Stratification: transfusion burden (≤6 vs >6 units); IPSS risk group (low vs intermediate-1)

- **Patients with LR-MDS**[1,2]
  - IPSS low or intermediate-1
  - Relapsed/refractory to ESA or sEPO >500 mU/mL
  - Transfusion dependent: ≥4 units RBC/8 weeks over the 16-week prestudy period
  - Non-del5(q), len/HMA-naive
- **Primary endpoint**: ≥8-week RBC TI
- **Key secondary endpoints**: safety, ≥24-week TI rate, HI-E, OS, PFS, and time to progression to AML

Treatment continues until disease progression, unacceptable toxicity, or withdrawal of consent
Pre-medication: diphenhydramine, hydrocortisone 100-200mg (or equivalent)
Supportive care: transfusions, myeloid growth factors per local guidelines

AML, acute myeloid leukemia; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agent; IPSS, International Prognostic Scoring System; IV, intravenous; len, lenalidomide; LR, lower-risk; MDS, myelodysplastic syndromes; OS, overall survival; PFS, progression-free survival; q4w, every 4 weeks; RBC, red blood cell; sEPO, serum erythropoietin; TI, transfusion independence.

1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 3113.

Meaningful and Durable TI With Imetelstat Treatment

- Of 57 patients treated in the phase 2 study, 38 patients were non-del(5q) and lenalidomide/HMA naive (target patient population)[1,2]
  - Longer duration of TI was seen in the target population (median, 88 weeks) vs all 57 treated patients (median, 65 weeks)

Efficacy parameters	Target population N=38[2]
8-week TI, n (%)	16 (42)
Median duration of TI, weeks (95% CI)[a]	88.0 (23.1-140.9)
24-week TI, n (%)	12 (32)
TI ≥1 year, n (%)	**11 (29)**

- **The analysis in this presentation describes the characteristics and clinical benefits of the 11 patients within the target patient population who had continuous TI for ≥1 year while on imetelstat after 57 months of follow-up**
- The 29% of patients who achieved sustained TI ≥1 year[2] represent:
  - 69% of the ≥8-week TI responders
  - 92% of the ≥24-week TI responders
  - 37% (10 of 27) of MDS-RS+ patients treated

[a]Based on the Kaplan Meier method. HMA, hypomethylating agent; MDS, myelodysplastic syndromes; RS+, ring sideroblast-positive; TI, transfusion independence.

1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. 2. Platzbecker U, et al. Presented at: ASH Annual Meeting 2020; Abstract 658.

Baseline Characteristics of ≥1-Year TI Imetelstat-Treated Patients Compared to the Overall Target Population

Baseline characteristic	Patients with TI ≥1 year (n=11)	Target population (N=38)
≥2 years since initial diagnosis, n (%)	10 (90.9)	28 (73.7)
IPSS category, n (%)		
Low	5 (45.5)	24 (63.2)
Intermediate-1 risk	6 (54.5)	14 (36.8)
MDS-RS+, n (%)	10 (90.9)	27 (71.1)
Normal karyotype, n (%)	7 (63.6)	28 (73.7)[a]
Mutations at baseline, n (%)		
SF3B1	11 (100)	27 (71.1)[b]
Other	4 (36.4)	13 (34.2)[b]
Prior ESA, n (%)	11 (100)	34 (89.5)
Prior luspatercept, n (%)	2 (18.2)	6 (15.8)
Median prior RBC transfusion burden (over 8 weeks) prior to study treatment, units (range)	6.0 (4-14)	8.0 (4-14)

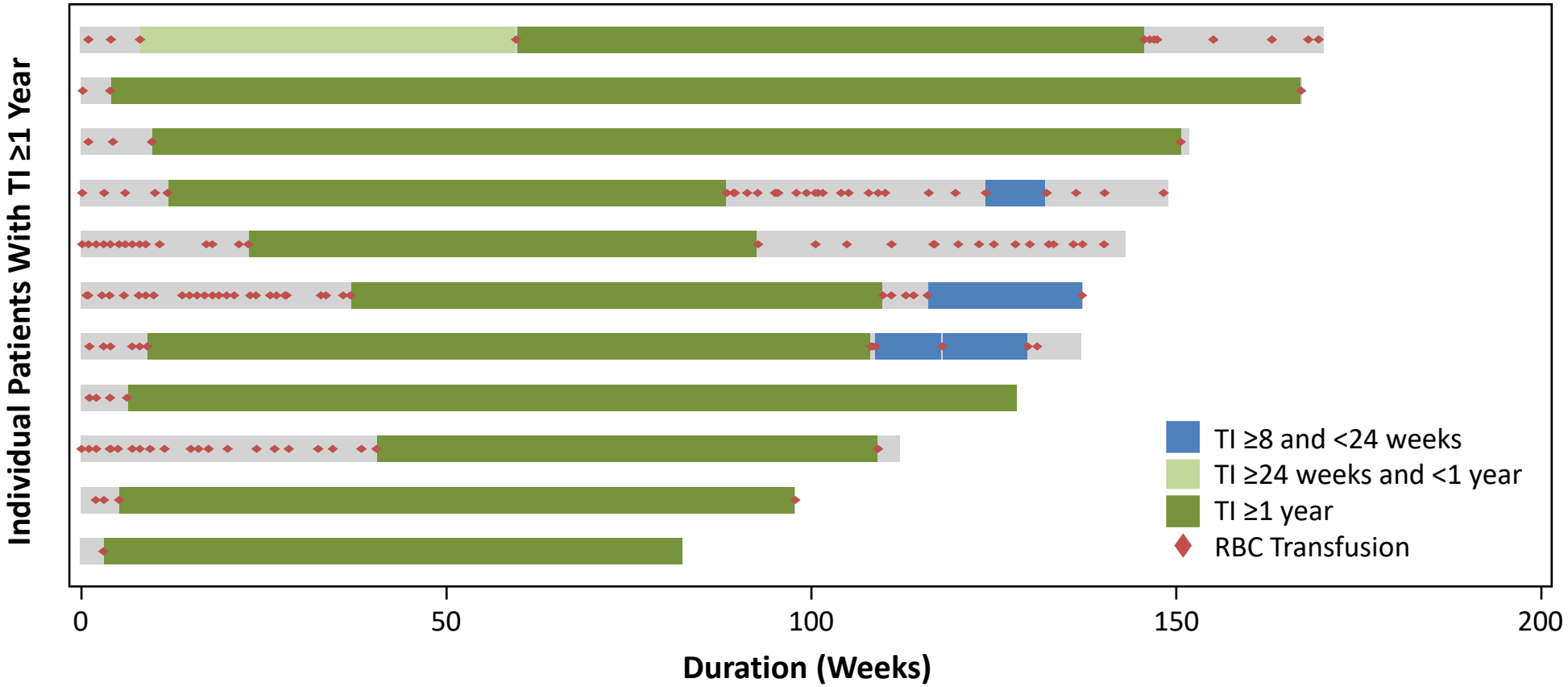
[a]Thirty-four patients had karyotyping results. [b]Baseline mutation samples were collected in 31 patients, 28 out of 31 (90.3%) had a mutation detected. ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System; MDS, myelodysplastic syndromes; RBC, red blood cell; RS+, ring sideroblast-positive; TI, transfusion independence.

Disposition and Treatment Exposure for Imetelstat-Treated Patients With TI ≥1 Year

	Patients with TI ≥1 year (n=11)
Median time on study,[a] months (range)	57.3 (19.0-57.8)
Median treatment duration, weeks (range)	126.1 (70.1-168.1)
Median treatment cycles, n (range)	27.0 (18-40)
Median relative dose intensity,[b] % (range)	98.9 (85.5-102.4)

Data cutoff: October 13, 2022.
[a]Defined as the interval between study day 1 and the date of death (censored) or last day on the trial; based on the Kaplan-Meier method. [b]Defined as the total actual dose/total planned dose.
TI, transfusion independence.

LR-MDS Patients Treated With Imetelstat Achieved Sustained, Continuous TI ≥1 Year



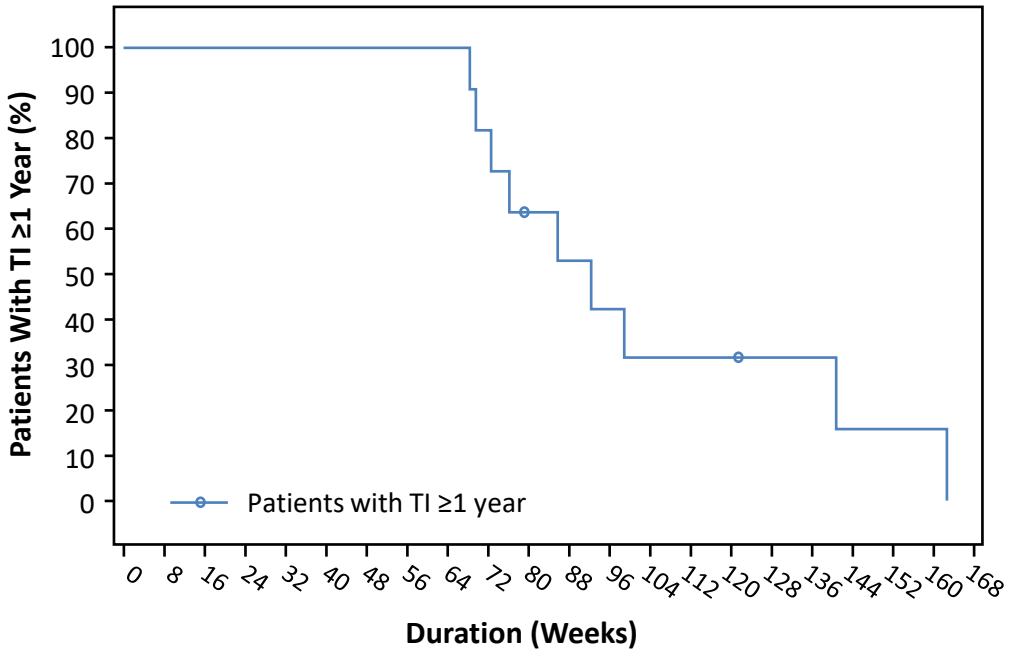
- Median onset of 8-week TI was 9.29 weeks (range, 3.3-40.7)

Data cutoff: October 13, 2022.
LR, lower-risk; MDS, myelodysplastic syndromes; RBC, red blood cell; TI, transfusion independence.

Durable TI Accompanied by Substantial Increase in Hgb in TI ≥1-Year Responders

Median TI duration: 92.4 weeks[a]
(95% CI, 69.57-140.86)

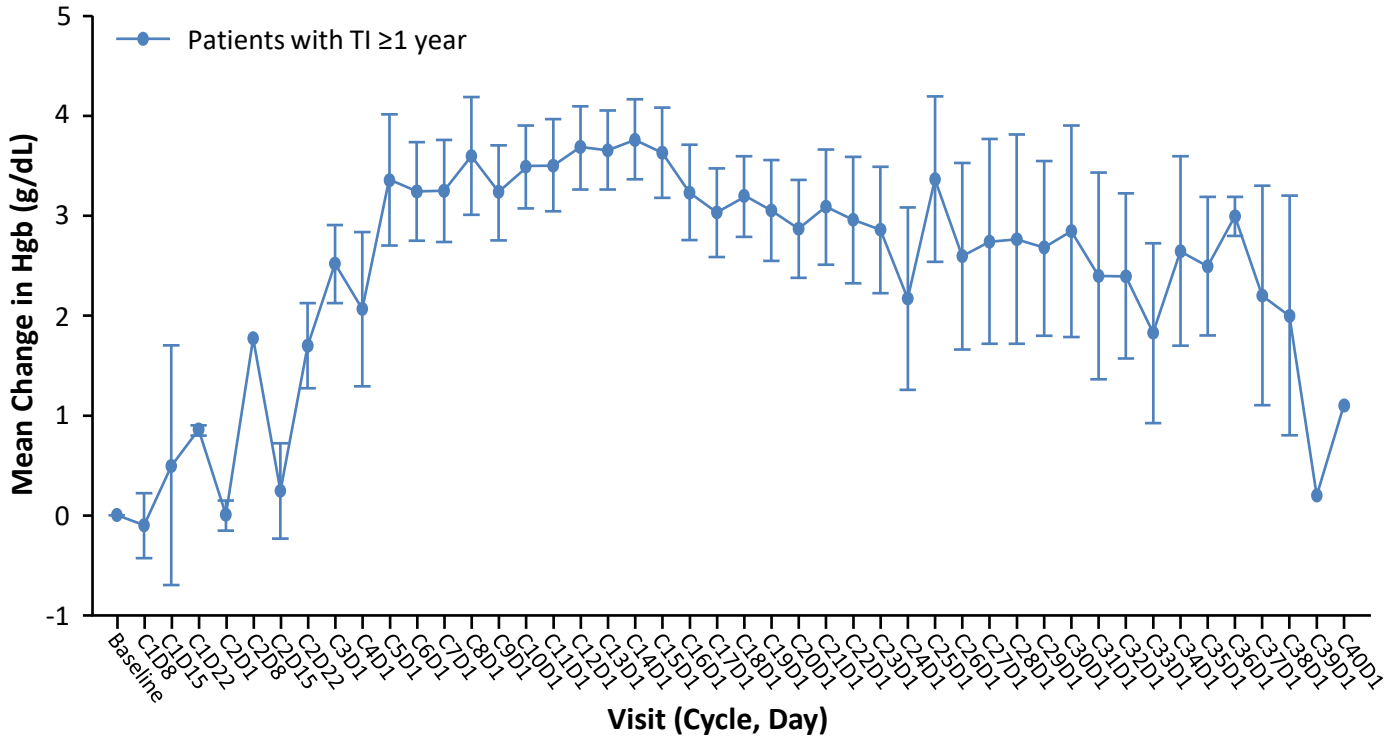
Duration of TI[a]



Patients at Risk

n	11	11	11	11	11	11	11	11	11	9	6	5	4	3	3	3	2	2	1	1	1	0		

Mean Change in Hgb[b]



Patients at Risk

n	11	4	2	2	3	1	3	4	6	9	9	10	10	10	11	10	10	11	11	11	11	11	11	11

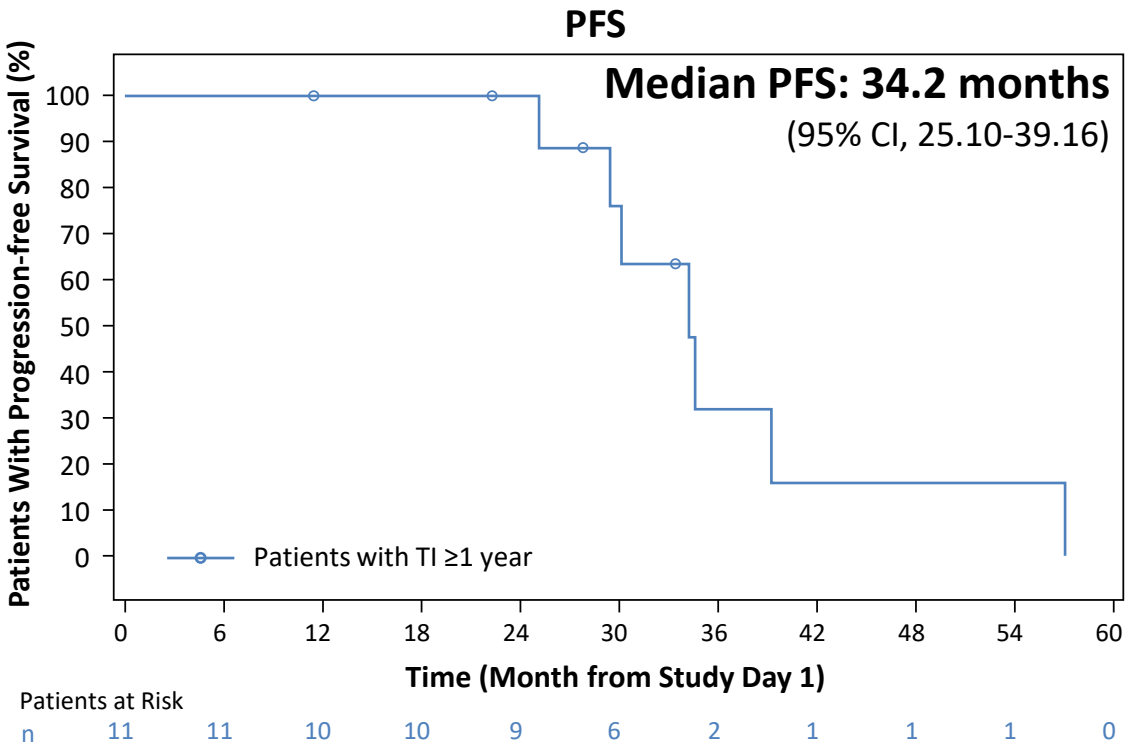
n	9	10	9	9	9	8	6	6	5	5	4	4	4	4	4	2	2	2	2	2	1	1		

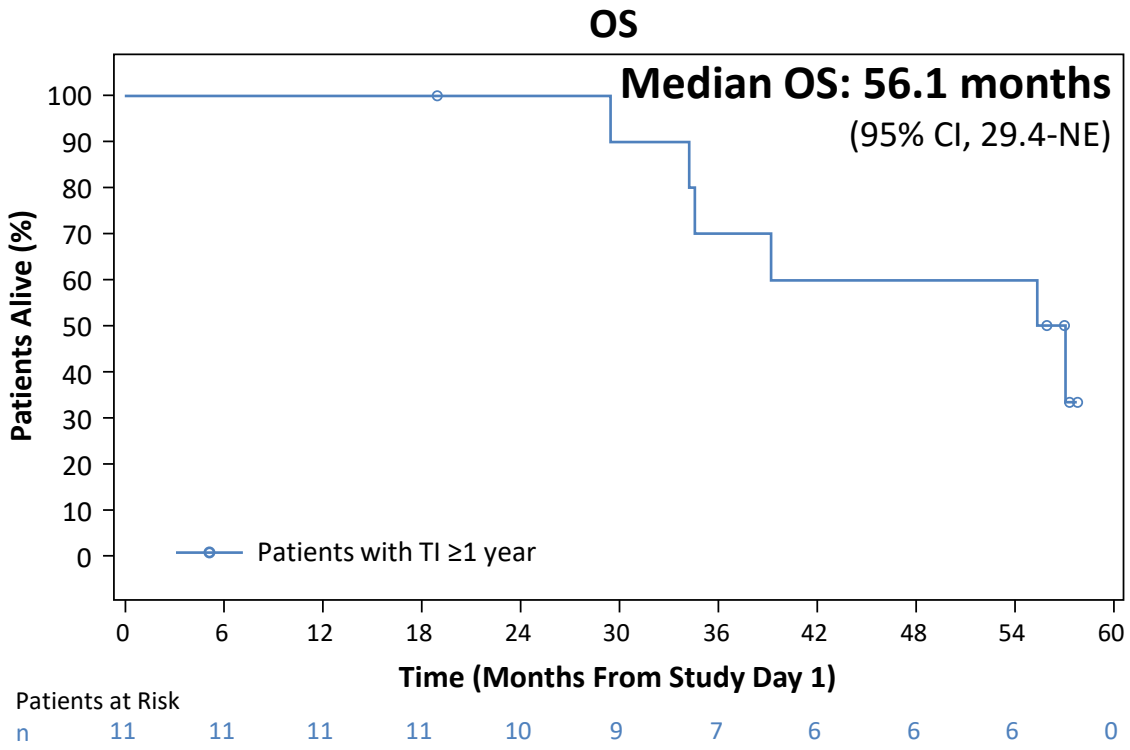
Data cutoff: October 13, 2022.

[a]Based on the Kaplan Meier method. [b]The mean changes from the minimum hgb of the values in the 8 weeks prior to the first dose date are shown and values that within 14 days of RBC transfusions were excluded. This plot does not include the values from unscheduled visits.

Hgb, hemoglobin; RBC, red blood cell; TI, transfusion independence.

Robust PFS and Survival of Imetelstat-Treated Patients With TI ≥1 Year





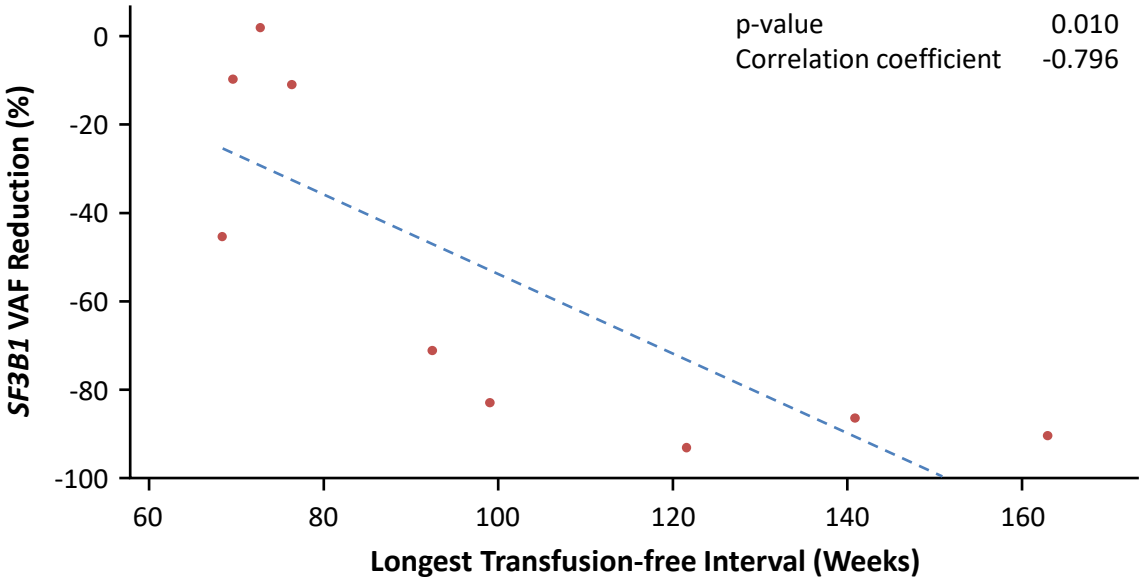
- After a median follow-up of 57 months, no progressions to AML were observed among the ≥1-year TI responders

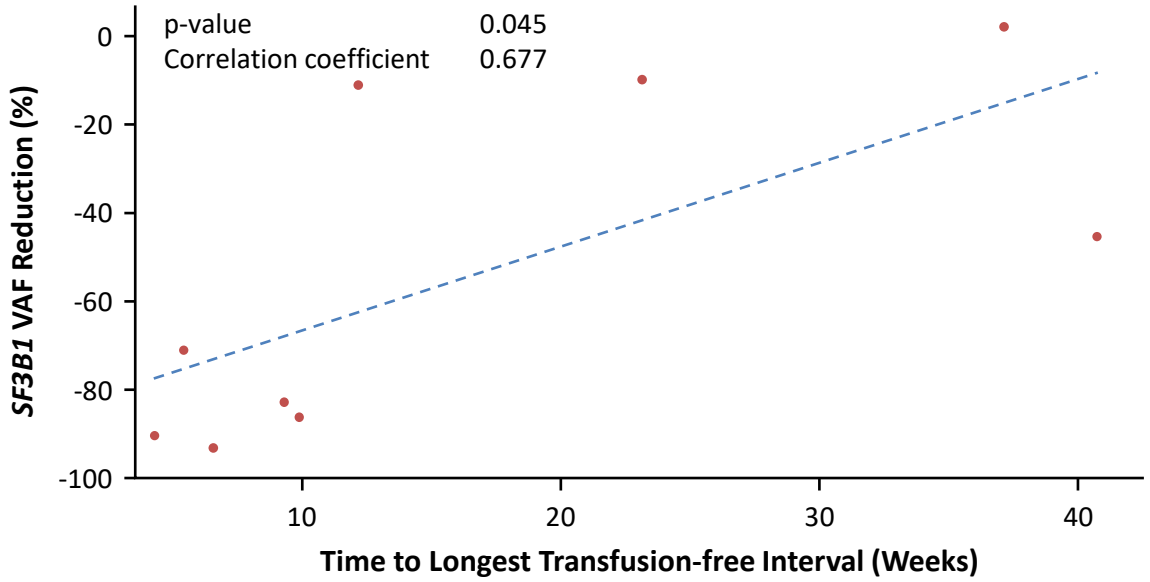
Parameter	Patients with TI ≥1 year (n=11)	Others (n=27)	Target population (N=38)
Median PFS, months (95% CI)	34.2 (25.1, 39.2)	25.5 (11.5, 44.2)	34.2 (25.1, 41.4)
Median OS, months (95% CI)	56.1 (29.4, NE)	47.1 (38.1, NE)	55.2 (38.1, 67.1)

Data cutoff: October 13, 2022.
Based on the Kaplan-Meier method.
AML, acute myeloid leukemia; NE, not evaluable; OS, overall survival; PFS, progression-free survival; TI, transfusion independence.

Reduction in *SF3B1* VAF in Imetelstat-Treated Patients With TI ≥1 Year Correlated With Longer TI Duration

- Of the 11 patients with TI duration ≥1 year, 9 had pre- and post-treatment mutation data available
  - 8 (89%) demonstrated a reduction in *SF3B1* VAF
  - 5 (56%) achieved ≥50% VAF reduction
- Reduction in VAF correlated with longer TI duration (median, >20 months) and shorter time to onset of TI (median, <10 weeks)





Data cutoff: October 13, 2022.
TI, transfusion independence; VAF, variant allele frequency.

Updated Phase 2 Safety Profile in Imetelstat-Treated Patients Similar to Previous Reports[1,2]

- Overall safety was consistent between the TI ≥1-year group and the target patient population
- The most frequent adverse events were reversible thrombocytopenia and neutropenia

Grade 3/4 Cytopenias n (%)	>1 year TI N=11	Target population N=38
Thrombocytopenia	7 (63.6)	23 (60.5)
Neutropenia	6 (54.5)	21 (55.3)
Anemia	2 (18.2)	8 (21.2)
Leukopenia	2 (18.2)	7 (18.4)

  - >97% of grade 3/4 thrombocytopenia and neutropenia within the >1 year TI population resolved to grade 2 or lower within 4 weeks (consistent with target population)
  - Events were manageable with dose holds (n= 10/11) and reduction (n=7/11) as specified in the protocol with limited clinical consequences
  - Imetelstat-related cytopenias are on-target effects based on the selective reduction of malignant cells through telomerase inhibition[2]

Data cutoff: October 13, 2022.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TI, transfusion independence.
1. Steensma DP, et al. *J Clin Oncol.* 2021;39(1):48-56. ; 2. Mascarenhas J, et al. Presented at: EHA Annual Meeting 2021; Abstract EP0116.

Conclusions

- Imetelstat demonstrated ≥1 year sustained, continuous TI in 29% of patients with transfusion dependent, non-del(5q) LR-MDS relapsed/refractory to ESAs and lenalidomide/HMA naive
  - Attainment of 24-week TI was indicative of the likelihood to achieve TI ≥1 year
- Strong evidence of disease-modifying activity for imetelstat mechanism of action:
  - Durable TI with median duration of TI of 92.4 weeks and robust increase in Hgb by ≥3 g/dL
  - Notable survival post-ESA (median OS, 56 months)
  - Meaningful reduction in mutational burden that correlated with longer TI and shorter time to onset of TI
- Safety findings were consistent with those of the overall target population and previous reports
- Enrollment is complete for the phase 3 part of IMerge, a randomized (2:1), double-blind, placebo-controlled trial to compare efficacy of imetelstat versus placebo in transfusion dependent, ESA-relapsed/refractory, non-del(5q), lenalidomide/HMA-naive LR-MDS
  - Results from the primary analysis are expected in early January 2023

ESA, erythropoiesis-stimulating agent; Hgb, hemoglobin; HMA, hypomethylating agent; LR, lower risk; MDS, myelodysplastic syndromes; OS, overall survival; TI, transfusion independence.

Acknowledgments

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- IMerge (MDS3001): https://www.geron.com/patients/imerge-study
- ClinicalTrials.gov Identifier: NCT02598661; email mds3001-info@geron.com