EUROPEAN HEMATOLOGY ASSOCIATION

EHA25 VIRTUAL

Abstract Code: S183

TREATMENT WITH IMETELSTAT PROVIDES DURABLE TRANSFUSION INDEPENDENCE (TI) IN HEAVILY TRANSFUSED NON-DEL(5Q) LOWER RISK MDS (LR-MDS) RELAPSED/REFRACTORY (R/R) TO ERYTHROPOIESIS STIMULATING AGENTS (ESAs)

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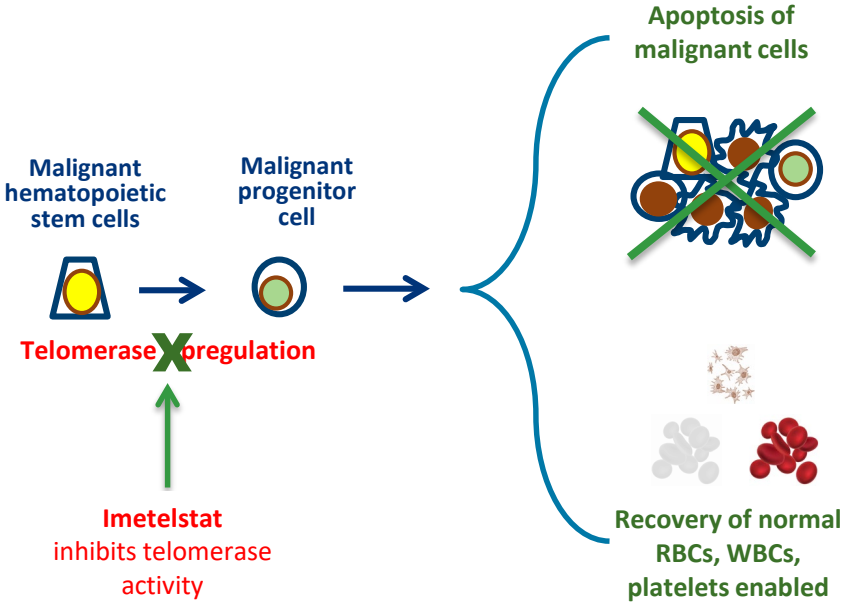
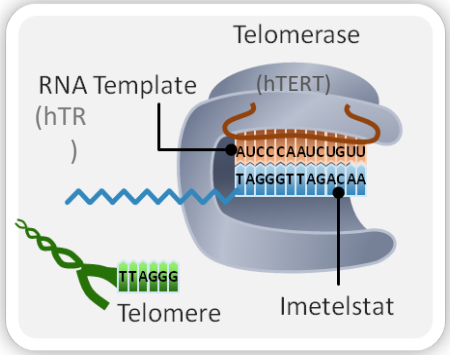
Program Section: Novel treatments for MDS I

Imetelstat: First-in-Class Telomerase Inhibitor with Disease-Modifying Potential



Imetelstat binds to RNA template, preventing maintenance of telomeres

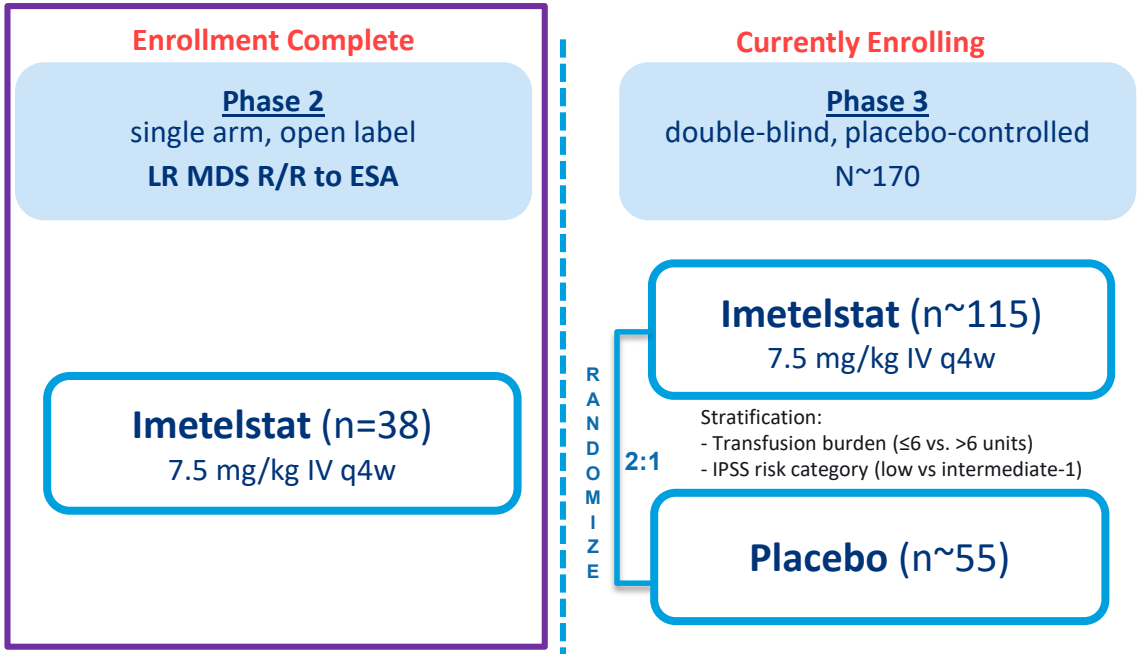


Mechanism of Action

- **Potent competitive inhibitor of telomerase activity**
- **Structure:** Proprietary 13-mer thio-phosphoramidate (NPS) oligonucleotide, with covalently-bound lipid tail to increase cell permeability/tissue distribution
- **Disease-modifying potential: selective killing** of malignant stem and progenitor cells enabling normal blood cell production

Phase 2/3 Study Design

IMerge
63935937MDS3001



- **LR MDS patients:**
  - Non-del(5q), IPSS Low or Int-1
  - Relapsed/Refractory to ESA or EPO >500 mU/ml; HMA/Len naïve
  - 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**

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agents; IPSS, International Prognostic Scoring System; Len, lenalidomide; LR, low risk; RBC, red blood cell; R/R, relapsed/refractory

Treatment Exposure

- 38 patients with non-del(5q) LR MDS R/R to ESA
- Clinical cutoff for analyses: 4 Feb 2020

Parameters	N = 38
Median follow-up, months (range)	24.0 (5.6 – 45.5)
Median treatment duration, months (range)	8.5 (0.02 – 38.7)
Median treatment cycles (range)	9 (1 – 40)
Median dose intensity*, %	100

*Median dose intensity of the assigned dose

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)**
4-5 units / 8 weeks at baseline, n (%)	6 (16)
≥ 6 units / 8 weeks at baseline, n (%)	**32 (84)**
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; ESA, erythropoiesis-stimulating agent; IPSS, International Prognostic Scoring System; sEPO, serum erythropoietin; RA, refractory anemia; RAEB1, refractory anemia with excess blasts; RARS, refractory anemia with ringed sideroblasts; RBC, red blood cell; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; WHO, World Health Organization

Patient Disposition

Parameters	N = 38 n (%)
Ongoing on treatment	9 (24)
Discontinued study treatment	29 (76)
Lack of Efficacy	12 (32)
Adverse Event	8 (21)
Progressive Disease	4 (10)
Withdrawal by Patient	2 (5)
Death	1 (3)
Physician Decision	1 (3)
Disease Relapse	1 (3)
Ongoing study participation *	27 (71)
Terminated study participation	11 (29)
Death	8 (21)
Withdrawal by Patient	3 (8)

* Median follow up time: 24 months (5.6 - 45.5)

Meaningful and Durable Transfusion Independence (TI) with Imetelstat Treatment

Parameters	N = 38
8-week TI, n (%)	**16 (42)**
Time to onset of 8-week TI, weeks, median (range)	8.3 (0.1-40.7)
Duration of TI, weeks, median (95% CI)[a]	**88.0 (23.1 – 140.9*)**
Cumulative duration of TI ≥ 8 weeks[b], median (95% CI)[a]	92.3 (42.9, 140.9)
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	12 (32)
24-week TI, n (%)	**12 (32)**
Hb rise ≥ 3.0 g/dL during TI[c], n (%)	11 (29)
1-year TI, n (%)	**11 (29)**

[a] Kaplan Meier method; [b] Cumulative Duration of TI ≥ 8 weeks is defined as the sum of all periods of TI ≥ 8 weeks during the treatment; [c] Maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb / 8 weeks).
CI, confidence interval; Hb, hemoglobin

***Longest TI > 2.7 years**

Hematologic Improvement and IWG Response with Imetelstat Treatment

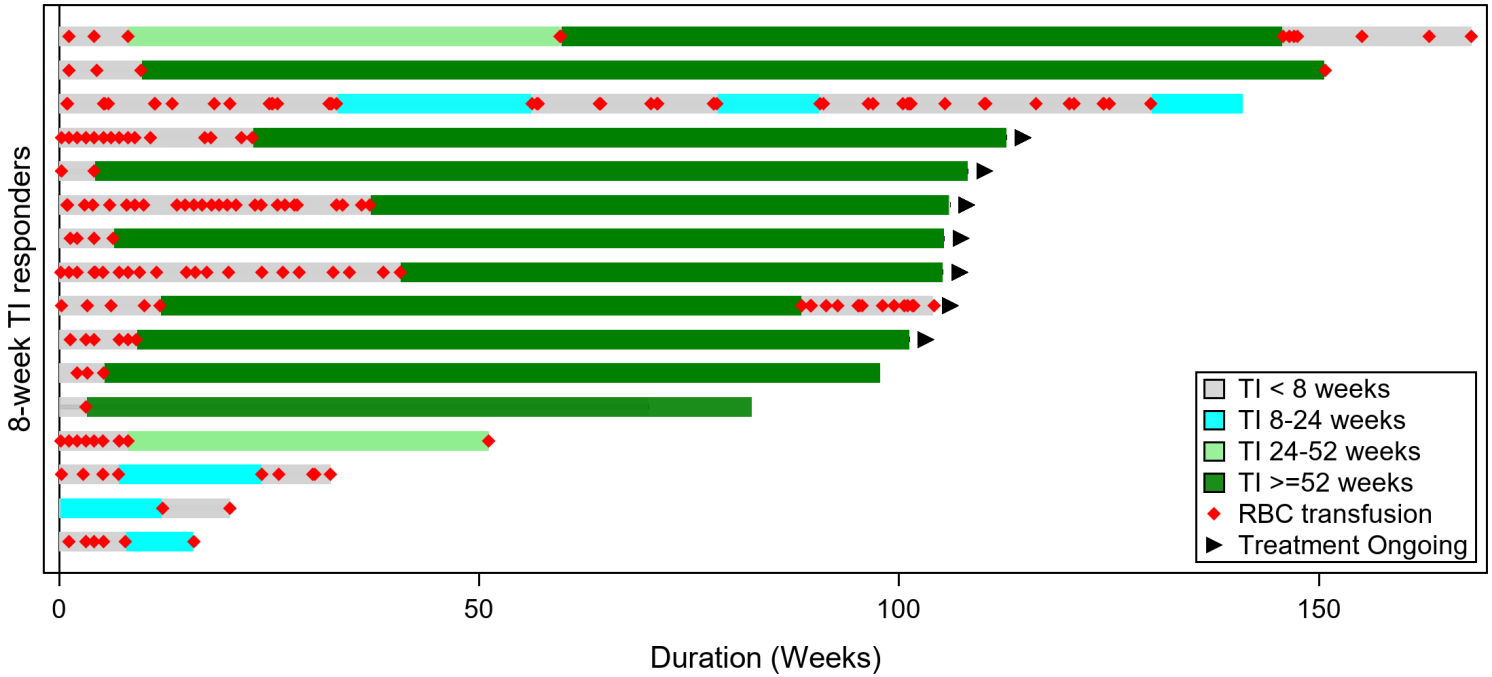
Parameters	N = 38
HI-E per IWG 2006, n (%)	**26 (68)**
≥1.5 g/dL increase in Hb lasting ≥ 8 weeks[a], n (%)	13 (34)
Transfusion reduction by ≥ 4 units/8 weeks, n (%)	26 (68)
Duration of HI-E, weeks, median (95% CI)[b]	**92.7 (37.1, 149.4)**
Major and Minor Response per IWG 2018	
Major response: 16-week TI, n (%)	**14 (37)**
Minor response: ≥ 50% transfusion reduction/16 weeks, n (%)	21 (55)
CR + marrow CR, n (%)	9 (24)
CR, n (%)	4 (11)
marrow CR, n (%)	5 (13)

[a] All patients also achieved 8 week TI

[b] Kaplan Meier method

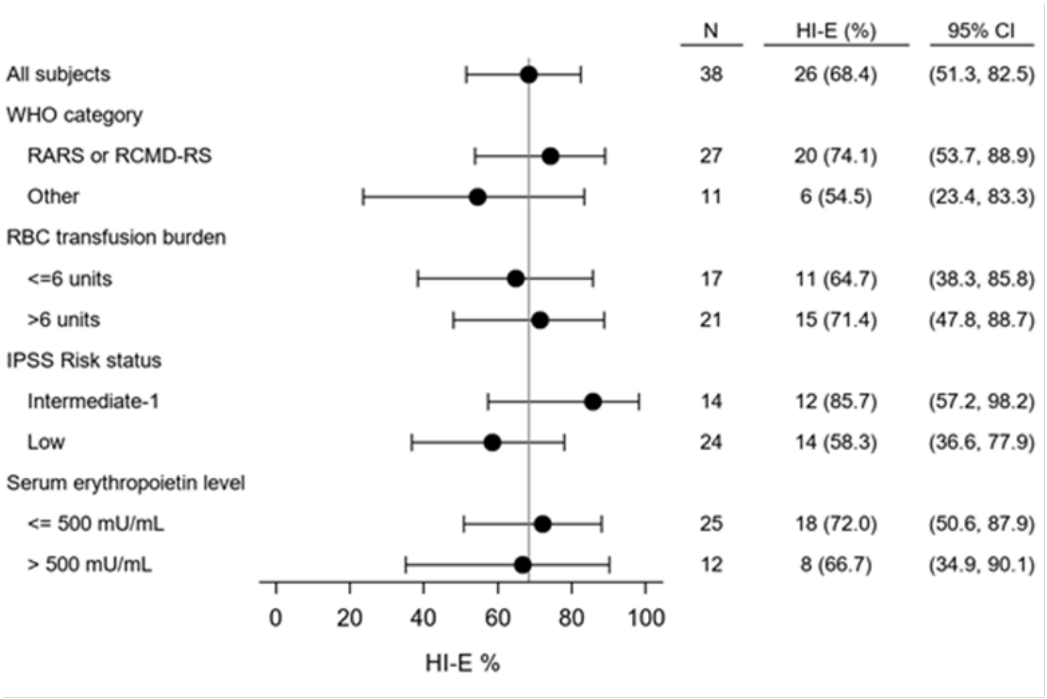
CI, confidence interval; CR, complete remission; Hb, hemoglobin; HI-E, hematologic improvement-erythroid; IWG 2006, International Working Group Response Criteria 2006; TI, Transfusion Independence

Potential Disease-Modifying Activity with Imetelstat Treatment: Durable TI and Substantial Increase in Hb



- **29% of the patients transfusion-free for at least one year**
- **Longest transfusion-free period 2.7 years**
- **75% of TI responders had the maximum Hb rise of ≥ 3g/dL from pretreatment level**
  (pretreatment level defined as mean Hb / 8 weeks)

Clinical Benefit Observed Across Different Patient Subgroups



All 8-week TIs (16 patients, 42%) are also HI-E responders in this study

Similar HI-E responses across different patient subgroups

- **RS Subgroups:**
  RS+ (RARS/RCMD- RS) vs. RS- (Other)
- **Baseline transfusion burden:**
  High (4-6 units) vs. Very High (>6 units)
- **Serum EPO level:**
  ≤ 500 mU/mL vs. > 500 mU/mL

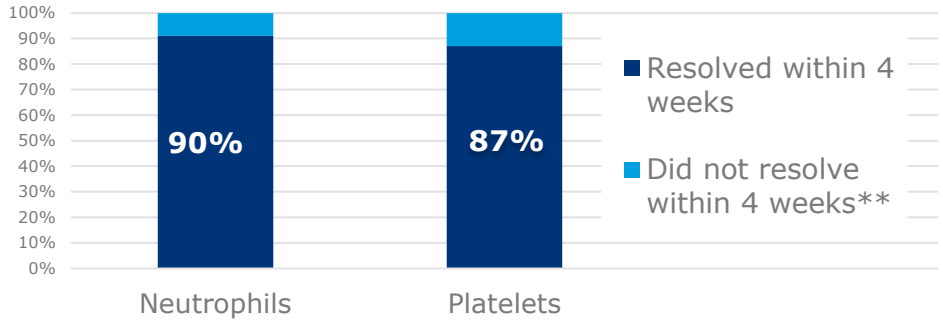
Reversible Grade 3/4 Cytopenias without Significant Clinical Consequences

Frequency of Hematologic AEs

AE	All Grades N=38 n (%)	Grade 3/4 N=38 n (%)
Thrombocytopenia	25 (66)	23 (61)
Neutropenia	22 (58)	21 (55)
Anemia	11 (29)	8 (21)

- 2/38 pts (5%) had febrile neutropenia (Gr3)
- 3/38 pts (8%) had Grade 3/4 bleeding

Reversibility of Grade 3/4 Cytopenias*



* Resolve to Grade 2 or lower by laboratory assessment
** Resolved ≥4 weeks or ongoing by cutoff date

Most Frequently Reported Non-Hematologic AEs: no new clinically significant events

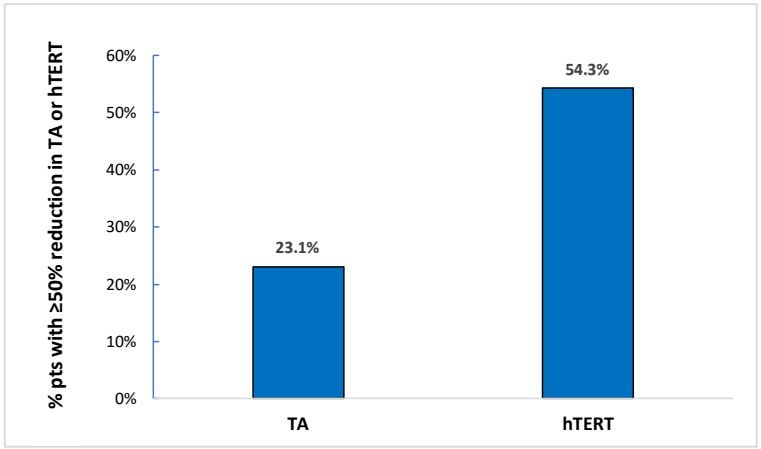
TEAE	All Grades N=38 n (%)	Grade 3/4 N=38 n (%)
Back pain	9 (24)	2 (5)
Pyrexia	8 (21)	0
Diarrhea	7 (18)	0
Nasopharyngitis	7 (18)	0
ALT increased	7 (18)	2 (5)*
AST increased	6 (16)	3 (8)*
Bronchitis	6 (16)	3 (8)
Asthenia	6 (16)	1 (3)
Headache	6 (16)	1 (3)
Urinary tract infection	6 (16)	1 (3)
Constipation	6 (16)	0
Edema peripheral	6 (16)	0
Fatigue	6 (16)	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase

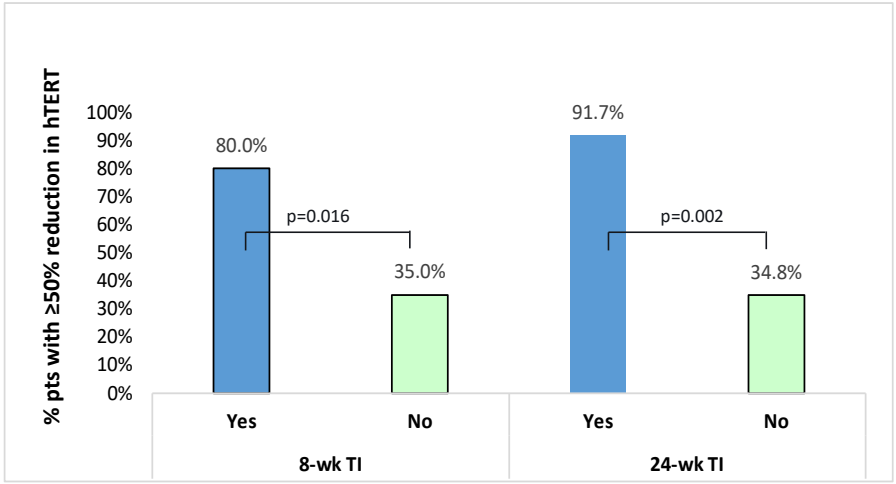
*Grade ≥3 AST and ALT were reversible

On-Target Activity of Imetelstat Correlates with Transfusion Independence

On-Target* activity demonstrated by reduction in Telomerase Activity (TA) and hTERT expression



Reduction in hTERT expression correlates with 8- and 24-weeks TI



*Optimal target activity/PD effect defined as ≥ 50% reduction in TA or hTERT expression based on pre-clinical PK/PD/efficacy experiments

Potential Disease-Modifying Activity with Imetelstat Treatment: Reduction of Malignant Clones Associated with Treatment Response

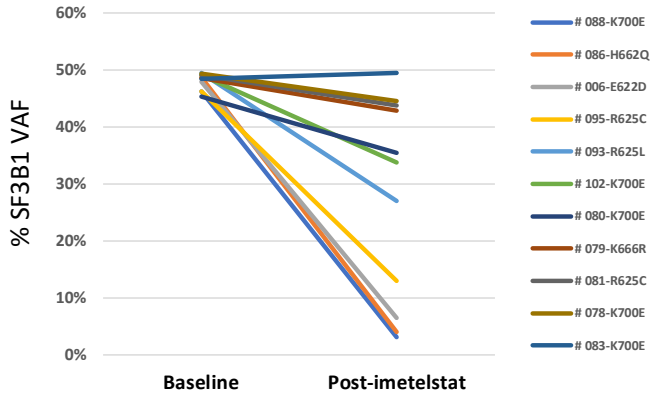
11 patients had SF3B1 mutations detected at baseline and had paired post-treatment mutation data available:

A. 10/11 had reduction (ranging 10-93%) in SF3B1 variant allele frequency (VAF)

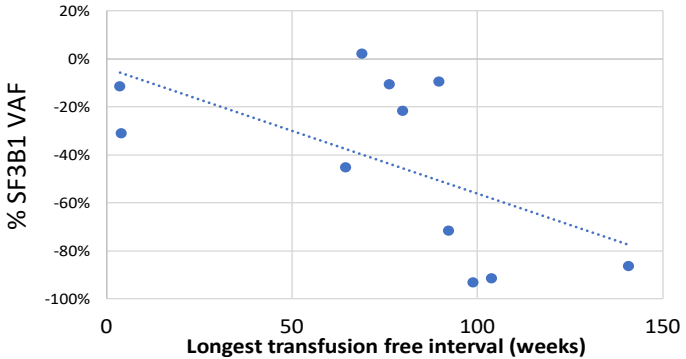
B. The greater reduction of SF3B1 VAF, the longer TI duration patients maintained

C. Significant correlation between greater reduction of SF3B1 VAF and shorter onset time to achieve the longest TI interval (Pearson correlation coefficient r=0.646, p=0.032)

A. Reduction of SF3B1 VAF with Imetelstat treatment



B. Reduction of SF3B1 VAF vs the longest TI duration



C. Reduction of SF3B1 VAF vs time to the longest TI

Patient ID	The longest TI interval (weeks)	Time to the longest TI interval start (weeks)	% SF3B1 VAF reduction
200088*	98.9	6.6	-93.3%
200086*	104	4.3	-91.8%
200006	140.9	9.9	-86.4%
200095	92.4	5.4	-71.9%
200093*	64.6	40.7	-45.5%
200102*	4	32.9	-31.2%
200080	79.9	44.1	-21.9%
200079	3.6	20.7	-11.6%
200081*	76.3	12.1	-10.9%
200078*	89.7	23.1	-9.8%
200083*	68.9	37.1	2.0%

*Remain on treatment as of 4 Feb 2020

Imetelstat in LR MDS Key Conclusions

- **Imetelstat treatment shows meaningful and durable transfusion independence:**
  - **High rates of TI and HI-E:** 42% 8-week TI rate and 68% HI-E rate
  - **Durable TI and HI-E:** Median duration of TI is 20 months and median duration of HI-E is 21 months
  - **TI across multiple patient subtypes**: RS+ and RS-, high and very high transfusion burden
- **Potential disease-modifying activity:**
  - 29% of patients transfusion free for ≥1 year
  - 75% of TI responders had hemoglobin rise of ≥ 3g/dL from pretreatment level
  - Reduction in SF3B1 mutation correlated with shorter onset time to achieve TI
- **No new safety signal** identified; reversable cytopenias were most frequent AEs, without significant clinical consequences
- **Phase 3 trial ongoing:** double-blind, placebo-controlled, 2:1 randomization

Phase 2/3 Study Design

IMerge
63935937MDS3001

Enrollment Complete

Phase 2
single arm, open label
LR MDS R/R to ESA

Imetelstat (n=38)
7.5 mg/kg IV q4w

Currently Enrolling

Phase 3
double-blind, placebo-controlled
N~170

RANDOMIZE 2:1

Imetelstat (n~115)
7.5 mg/kg IV q4w

Stratification:
- Transfusion burden (≤6 vs. >6 units)
- IPSS risk category (low vs intermediate-1)

Placebo (n~55)

- **Key Elements Same as Phase 2:**
  - Dose and schedule
  - Primary/secondary endpoints
  - Patient population as n=38
  - Continuity of most of the clinical sites
- **Current Status/Progress:**
  - First patient dosed in October 2019
  - Currently enrolling

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