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Abstract #658

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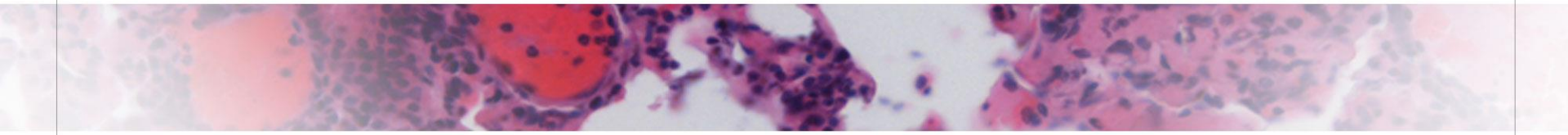

Treatment With Imetelstat Provides Durable Transfusion Independence (TI) in Heavily Transfused Non-Del(5q) Lower Risk MDS (LR-MDS) Relapsed/Refractory (R/R) to Erythropoiesis Stimulating Agents (ESAs)

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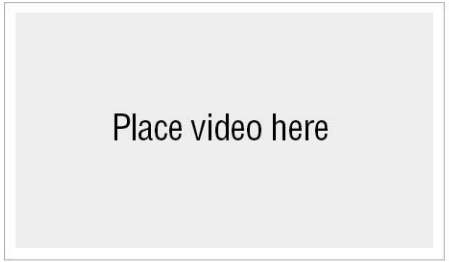
Disclosure



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- **Disclosure:**
  - Honoraria and research grant from BMS, Amgen, Novartis, Jazz
  - Honoraria from Geron

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

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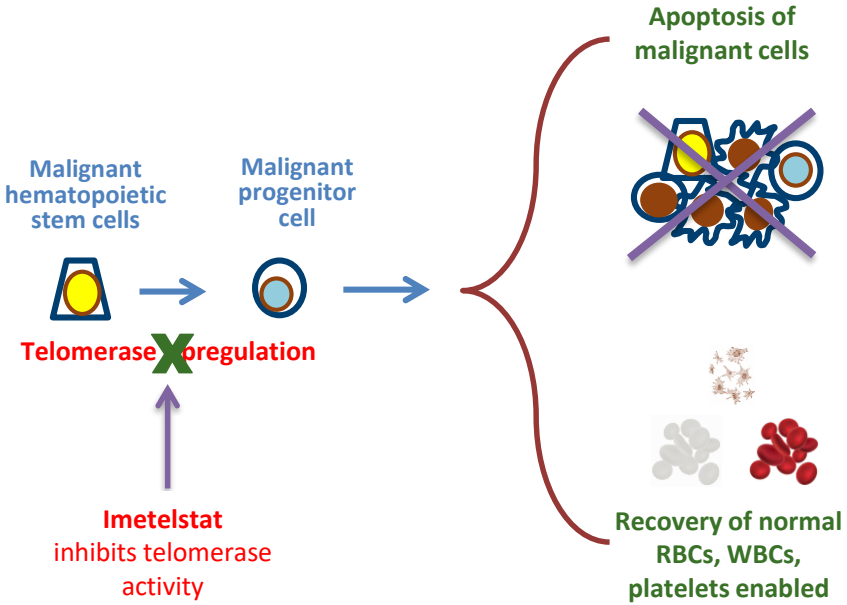

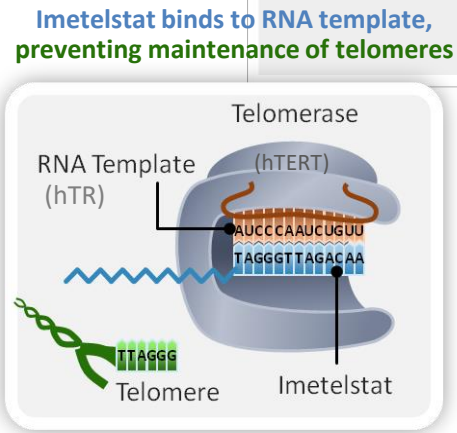

Mechanism of Action

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

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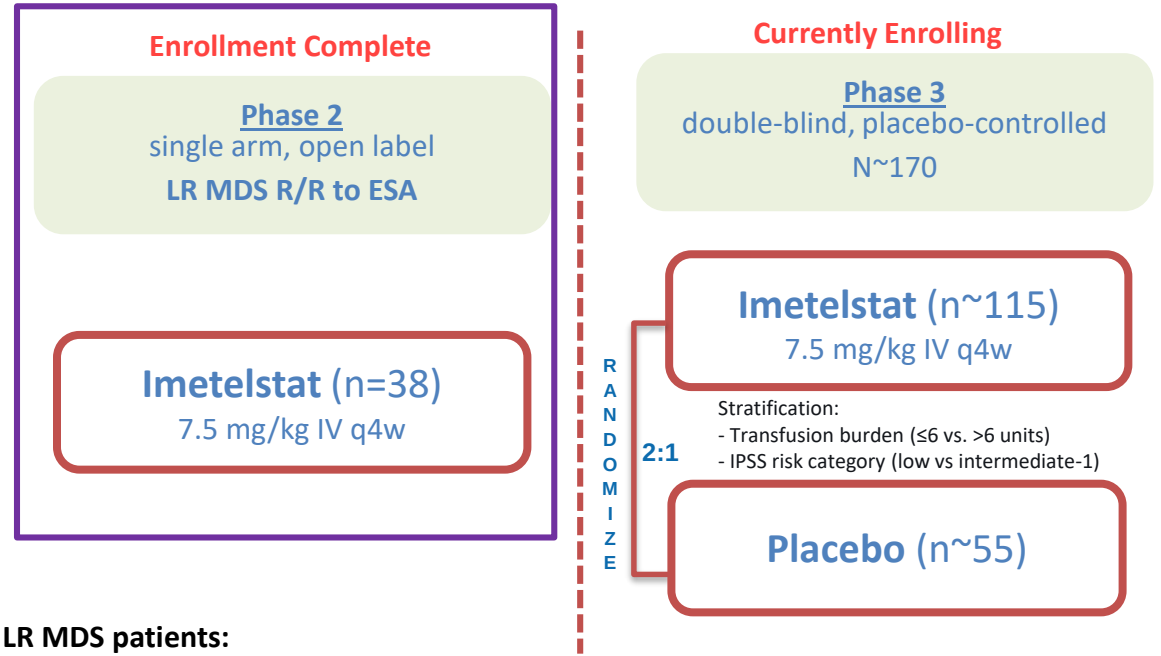
Phase 2/3 Study Design



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Results from Phase 2 recently published online ahead of print: 2020 Oct 27;JCO2001895

- **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

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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

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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

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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

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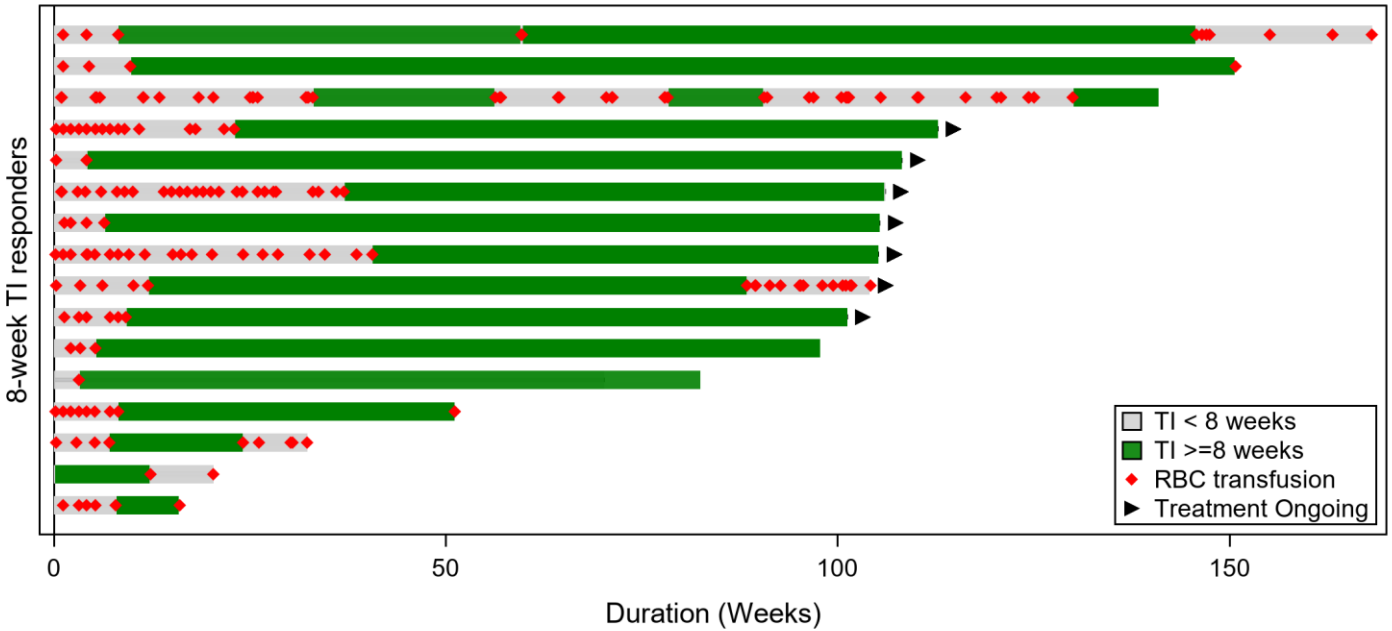

- **29% of the patients transfusion-free for at least one year**
- **Longest transfusion-free period 2.7 years**
- **75% of TI responders had the maximum Hb rise of ≥ 3g/dL from pretreatment level (pretreatment level defined as mean Hb / 8 weeks)**

Clinical Benefit Observed Across Different Patient Subgroups

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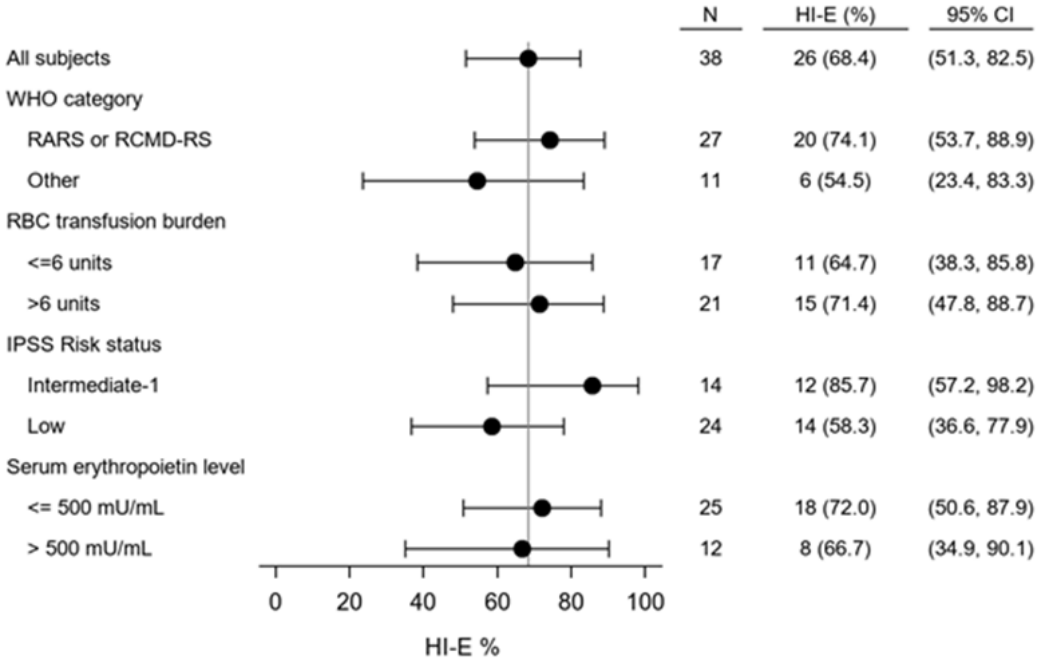
Similar HI-E response across different patient subgroups



- **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

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

Reversible Grade 3/4 Cytopenias without Significant Clinical Consequences

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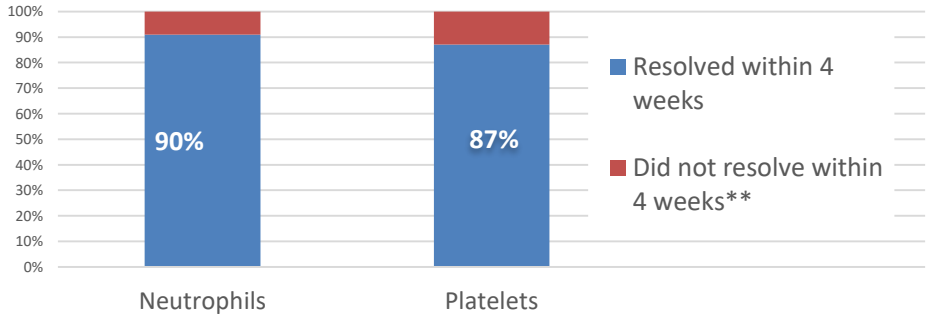
Frequency of Hematologic AEs

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

Dose modifications help with reversibility

Most Frequently Reported Non-Hematologic AEs: No New Clinically Significant Events

TEAE	All Grades, N=38 n (%)	Grade ¾, 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

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On-Target Activity of Imetelstat Correlates with Transfusion Independence

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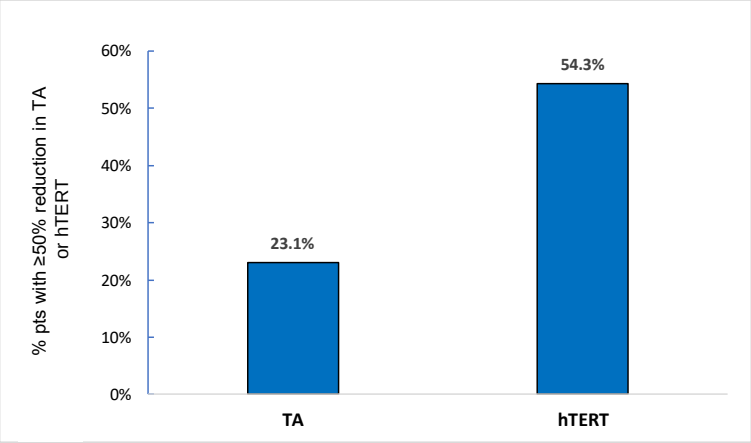
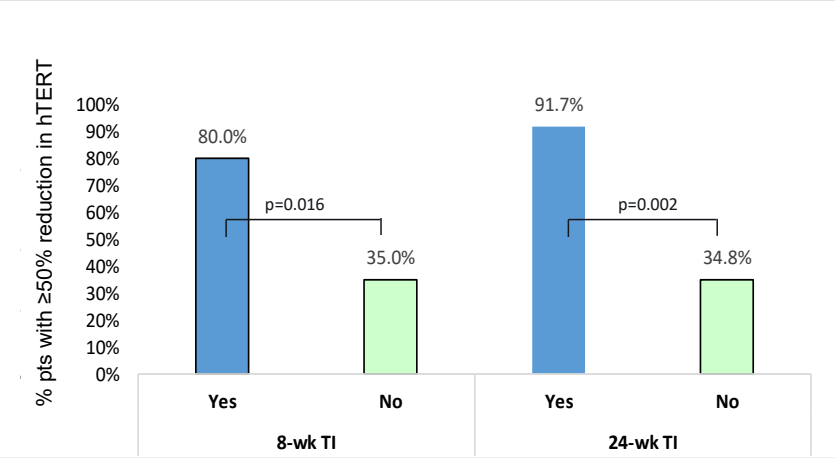
On-Target* activity demonstrated by reduction in Telomerase Activity (TA) and hTERT expression



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



*Optimal on-target activity/PD effect defined as ≥ 50% reduction in TA or hTERT expression based on pre-clinical PK/PD/efficacy experiments
TA: assayed in PBMC by quantitative telomeric repeat amplification protocol technology
hTERT: measured in peripheral blood by Taqman RT-PCR assay

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

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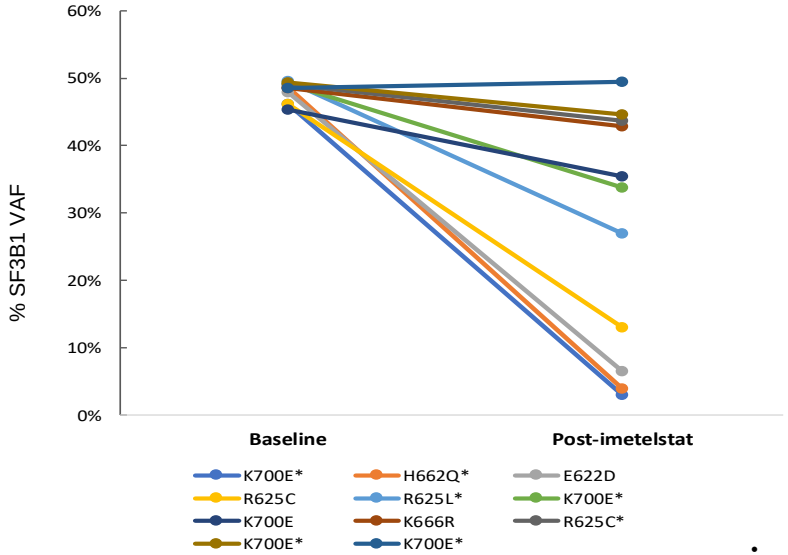
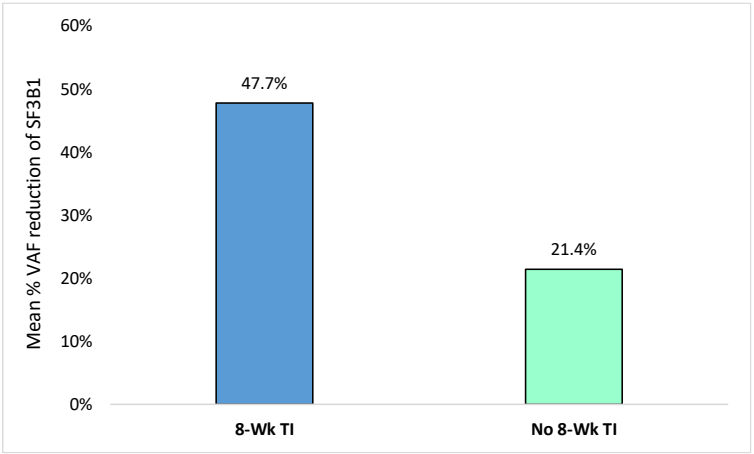
Imetelstat had SF3B1 VAF reduction regardless of mutation hotspots



* Remain on treatment as of 4 Feb 2020

8-wk TI responders had more reduction of SF3B1 VAF compared to 8-wk TI non-responders



- 11 patients had SF3B1 mutations detected at baseline and had paired post-treatment mutation data available
- 9 of 11 patients achieved 8-Wk TI
- Mutation status and variant allele frequency (VAF) were evaluated by next-generation sequencing (NGS)
- Lower limit detection is 5% and for well documented hotspots is 2%

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

- The greater reduction of SF3B1 VAF, the longer TI duration patients maintained.
- The greater reduction of SF3B1 VAF and the shorter onset time to achieve the longest TI interval.

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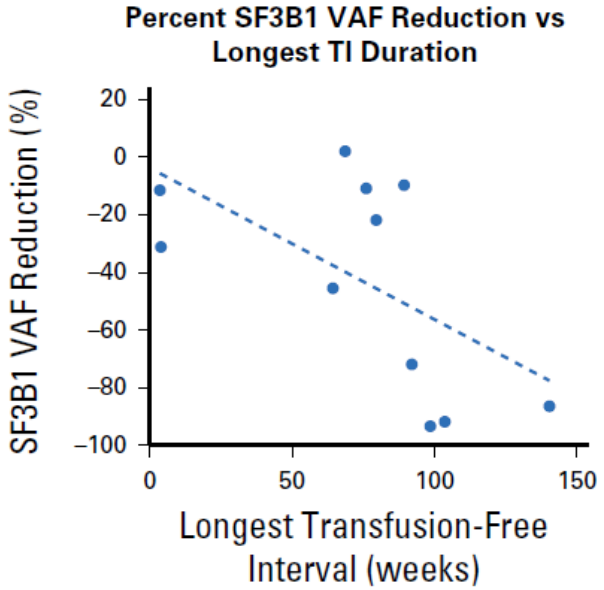

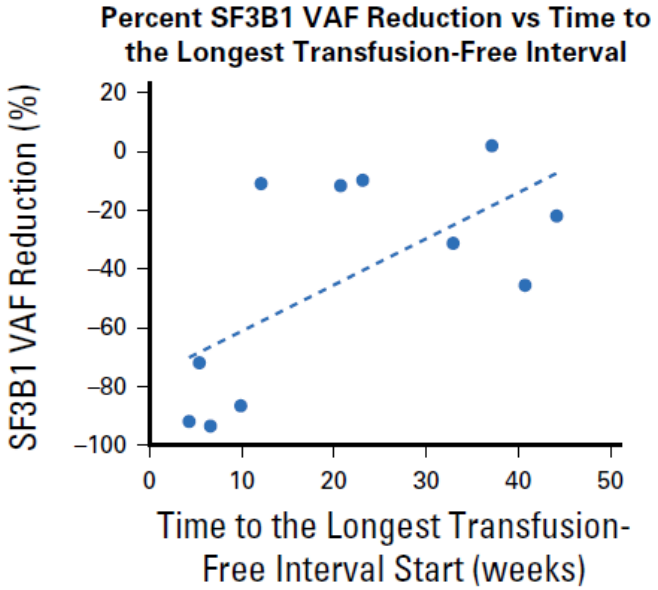

Imetelstat in LR MDS Key Conclusions

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- **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 currently enrolling:** double-blind, placebo-controlled, 2:1 randomization

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Phase 2/3 Study Design

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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

Placebo (n~55)

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

- **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**

- **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 of Phase 3:**
  - First patient dosed in October 2019
  - Currently enrolling

EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; HI-E, hematologic improvement-erythroid; HMA, hypomethylating agents; IPSS, International Prognostic Scoring System; RBC, red blood cell; Len, lenalidomide.

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