Imetelstat Is Effective Treatment for Patients with Intermediate-2 or High-Risk Myelofibrosis Who Have Relapsed on or Are Refractory to Janus Kinase Inhibitor Therapy: Results of a Phase 2 Randomized Study of Two Dose Levels

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Abstract #685

Background

- Imetelstat, a 13-mer oligonucleotide that specifically targets the RNA template of human telomerase, is a potent competitive inhibitor of telomerase enzymatic activity[1,2]
- Clinical activity and an acceptable safety profile were reported in a 33-patient pilot study in intermediate-2 (int-2) or high-risk myelofibrosis (MF)
  - 48% of patients had been previously treated with a Janus Kinase inhibitor (JAKi)[3]
- Currently, JAKi is the only approved therapy for MF, with failure leading to poor outcomes
- Here, we report the results of a phase 2 clinical study of imetelstat at two dose levels in patients with MF who have relapsed after or are refractory to JAKi therapy (MYF2001, NCT02426086)

[1]Asai, et al. *Cancer Res* 2003;63:3931-3939. [2]Herbert, et al. *Oncogene* 2005;24:5262-5268. [3]Tefferi, et al. *N Engl J Med* 2015;373:908-919.

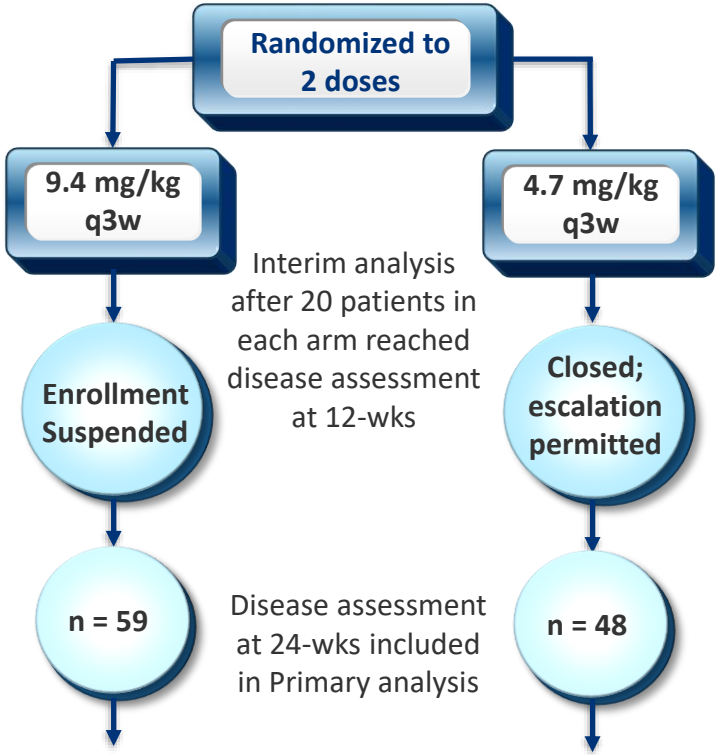
Patient Population

- Int-2/high-risk MF per DIPSS criteria
- Relapsed or refractory to JAKi defined as documented progressive disease during or after JAKi:
  - Patients must have worsening of splenomegaly-related abdominal pain at any time after the start of JAKi therapy **and** EITHER:
    - No reduction in spleen volume or size after 12 weeks of JAKi therapy, **OR**
    - Worsening splenomegaly* at any time after the start of JAKi therapy documented by:
      - ✓ Increase in spleen volume from nadir by 25% measured by MRI or CT, **or**
      - ✓ Increase in spleen size by palpation
- Active symptoms of MF
- Baseline measurable splenomegaly (palpable spleen ≥ 5 cm below LCM or ≥ 450 cm^3 by MRI)

* Adapted from IWG-MRT response criteria definition of progressive disease.

Study Design

- Co-primary endpoints at Week 24
  - **Spleen response rate**: proportion of patients achieving ≥ 35% reduction in spleen volume by MRI at 24 weeks
  - **Symptom response rate**: proportion of patients achieving ≥ 50% reduction in total symptom score per modified MFSAF v2.0 at 24 weeks
- Key secondary endpoints: safety, overall survival (OS), treatment response, and pharmacokinetic and pharmacodynamic relationships
- Stratification
  - Spleen size ≥ 15 cm (yes/no)
  - Platelets 75K – 150K vs ≥ 150K



Treatment Exposure

- 107 patients were enrolled at 55 institutions
- Clinical cutoffs for analyses:
  - April 26, 2018 – Primary analysis of efficacy and safety, with a median follow-up of 22.6 (0.2-27.4) months
  - October 22, 2018 – Overall survival, with a median follow-up of 27.4 (0.2-33.0) months
- Median treatment duration: 26.9 (0.1-118.1) weeks
  - Median duration on treatment was 33.3 weeks on the 9.4 mg/kg arm and 23.9 weeks on the 4.7 mg/kg arm
  - The 4.7 mg/kg arm had been closed early, influencing duration of treatment

Baseline Demographics and Disease Characteristics

	4.7 mg/kg (n = 48)	9.4 mg/kg (n = 59)	Total (N = 107)
Median age (range), years	68.5 (44, 84)	67 (31, 86)	68.0 (31, 86)
Male, n (%)	32 (67)	35 (59)	67 (63)
Myelofibrosis subtype, n (%)			
Primary	27 (56)	36 (61)	63 (59)
Post-ET	9 (19)	10 (17)	19 (18)
Post-PV	12 (25)	13 (22)	25 (23)
DIPSS risk status, n (%)			
Intermediate-1 risk	1[a] (2)	0	1 (1)
Intermediate-2 risk	28 (58)	34 (58)	62 (58)
High Risk	19 (40)	25 (42)	44 (41)
Spleen length (palpation) – Median (range), cm	18 (4, 35)	18 (3, 32)	18 (3, 35)
≥ 15cm, n (%)	31 (65)	35 (59)	66 (62)
Spleen volume (MRI) – Median, IRC (range), cm^3	3353 (726, 7243)	2998 (890, 7607)	3167 (726, 7607)
Total Symptom Score – Median (range)	22 (7, 58)	24 (3, 57)	23 (3, 58)
RBC transfusion dependent[b], n (%)	14 (29)	12 (20)	26 (24)
Platelet count – Median (range), $x10^9/L$	153 (74, 1097)	146 (65, 798)	147 (65, 1097)
Time since initial diagnosis – Median (range), months	49 (2, 227)	43 (7, 201)	44 (2, 227)
Time since last JAKi Tx – Median (range), months	1.4 (1, 31)	1.7 (1, 38)	1.7 (1, 38)
Duration of prior JAKi Tx – Median (range), months	22 (3, 90)	25 (1, 73)	23 (1, 90)

[a] Indicated in eCRF comments, but does not appear in statistical output. This is a protocol deviation.

[b] Received 6 units PRBC in 12 weeks prior to enrollment.

Patients Disposition

n (%)	4.7 mg/kg (n = 48)	9.4 mg/kg (n = 59)	Total (N = 107)
Discontinued study treatment	47 (98)	53 (90)	100 (93)
Adverse Event [a]	12 (25)	15 (25)	27 (25)
Death	0	1 (2)	1 (1)
Lack of Efficacy	7 (15)	10 (17)	17 (16)
Physician Decision	7 (15)	4 (7)	11 (10)
Protocol Violation	1 (2)	1 (2)	2 (2)
Withdrawal by Patient / Refused Study Treatment	12 (25)	11 (19)	23 (21)
Progressive Disease	8 (17)	9 (15)	17 (16)
Other	0	2 (3)	2 (2)
Ongoing study participation	17 (35)	33 (56)	50 (47)
Terminated study participation	31 (65)	26 (44)	57 (53)
Death	24 (50)	21 (36)	45 (42)
Lost to Follow-up	1 (2)	0	1 (1)
Withdrawal by Patient	6 (13)	5 (8)	11 (10)

[a] Discontinuations from study treatment due to fatal adverse events occurred in 4 patients on 4.7 mg/kg and 3 patients on 9.4 mg/kg. The patient who discontinued treatment due to death had a primary reason for death recorded as progressive disease (adverse event not reported).

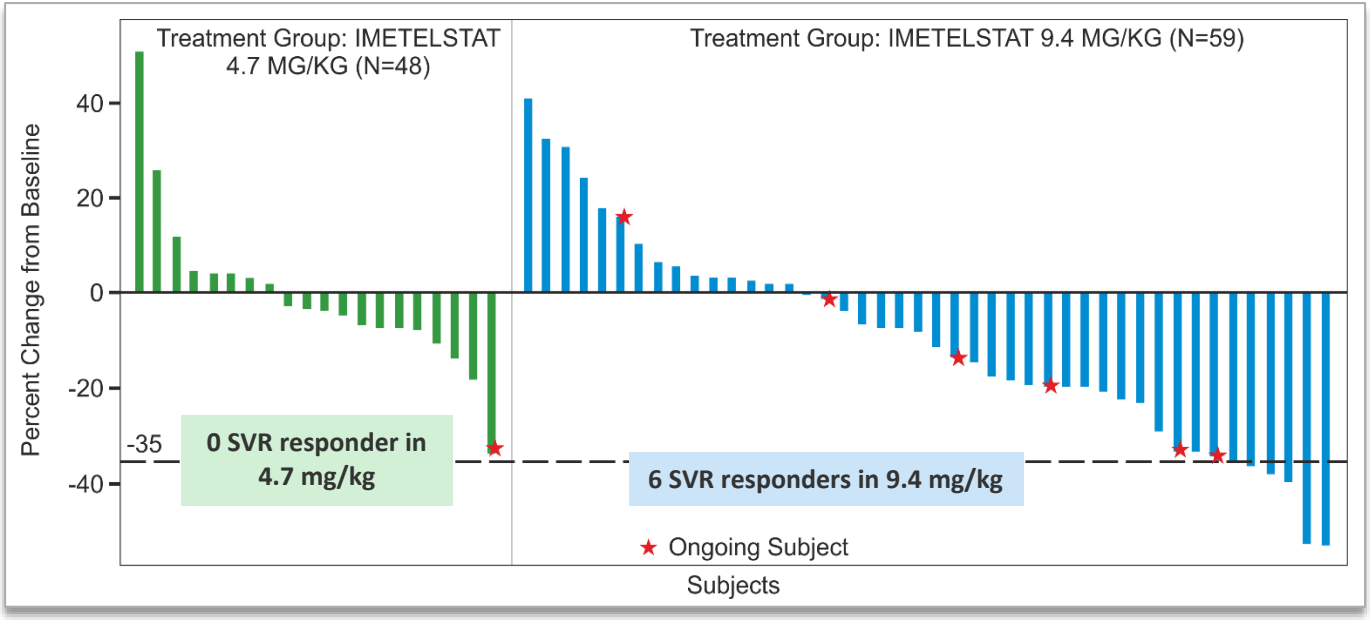
Baseline Mutation Summary on Selected Genes

n (%)	4.7 mg/kg	9.4 mg/kg	Total
Biomarker population, n	48	57	105
With ≥ 1 mutation	48 (100)	55 (96.5)	103 (98)
≥ 3 mutations	40 (83)	38 (67)	78 (74)
Triple Negative	10 (21)	16 (28)	26 (25)
JAK2 V617F	32 (67)	32 (56)	64 (61)
CALR	2 (4)	7 (12)	9 (9)
MPL	4 (8)	2 (4)	6 (6)
HMR[a]	36 (75)	35 (61)	71 (68)
ASXL1	24 (50)	25 (44)	49 (47)
EZH2	10 (21)	18 (32)	28 (27)
SRSF2	5 (10)	2 (4)	7 (7)
IDH1	2 (4)	2 (4)	4 (4)
IDH2	4 (8)	5 (9)	9 (9)

[a]HMR, high molecular risk; ie, 1 or more mutations in ASXL1, EZH2, SRSF2, IDH1, or IDH2.

SVR Per IRC at Week 24

- 6 (10%) patients in the 9.4 mg/kg arm had ≥ 35% SVR at Week 24
- 23 (37%) patients in the 9.4 mg/kg arm had ≥ 10% SVR at Week 24

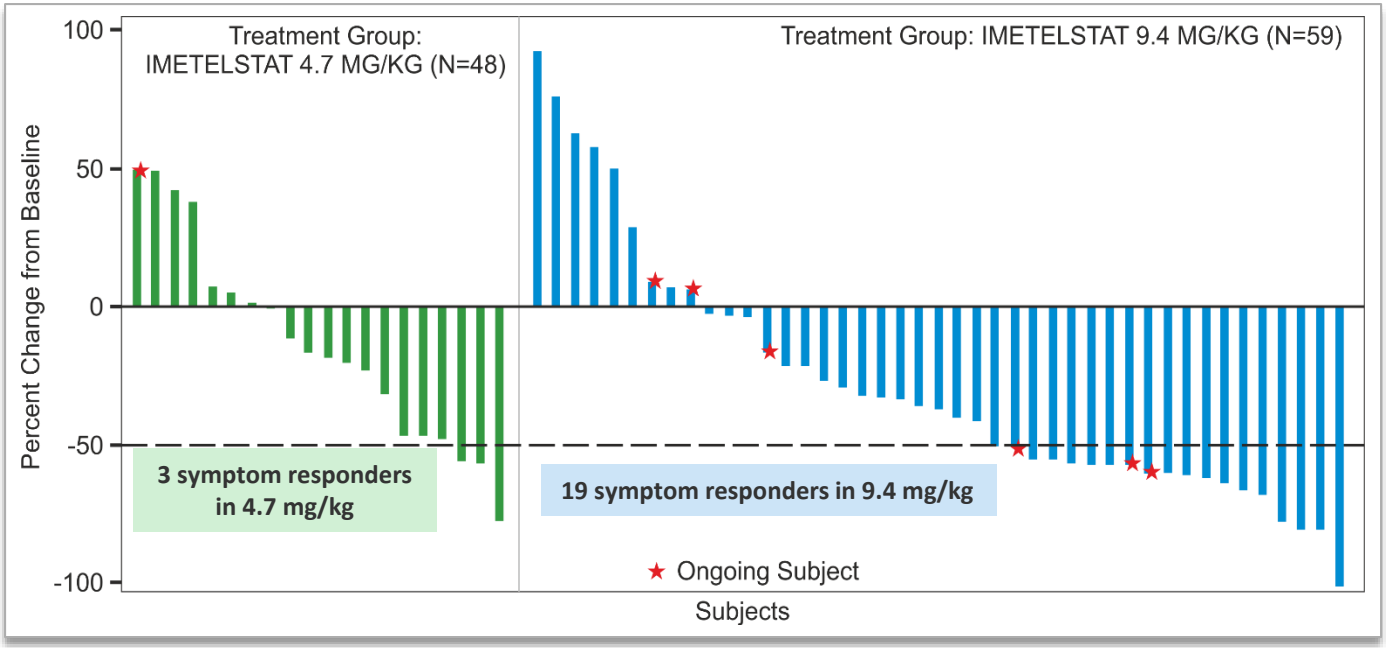


At time of cut-off, 20 patients in the 4.7 mg/kg and 44 patients in the 9.4 mg/kg had Week 24 MRI, however, ITT is used as denominator for percentages.

IRC, Independent Review Committee; SVR, spleen volume reduction.

Symptom Response based on TSS at Week 24

- **19 (32%) patients in the 9.4 mg/kg arm had ≥ 50% symptom response at Week 24**



At time of cut-off, 20 patients in the 4.7 mg/kg and 43 patients in the 9.4 mg/kg had Week 24 TSS e-diary entries, however, ITT is used as denominator for percentages.

TSS, total symptom score.

Change in Bone Marrow Fibrosis

Shift in Central Bone Marrow Fibrosis from Baseline to Best Fibrosis Grading		
n (%)	**4.7 mg/kg (n = 48)**	**9.4 mg/kg (n = 59)**
Completed baseline and post-baseline BM assessment, n	20	37
Improvement	4 (8)	15 (25)
Stable	15 (31)	15 (25)
Worsening	1 (2)	7 (12)

BM, bone marrow.

- 19 (18%) patients had an improvement in bone marrow fibrosis per central assessment

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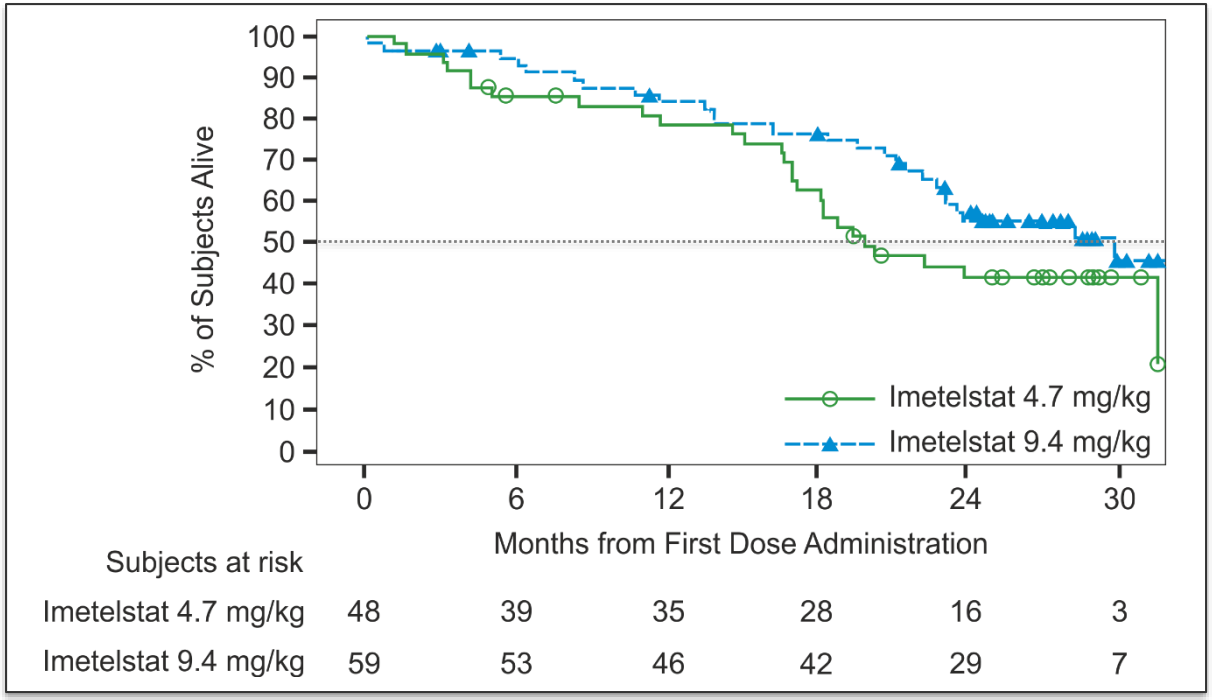
Overall Survival (ITT) for Imetelstat at Different Dose Levels



- **Median follow-up: 27.4 months**
- **Median survival:**
  - **19.9 months (95% CI, 17.1, NE) in 4.7 mg/kg**
  - **29.9 months (95% CI, 22.8, NE) in 9.4 mg/kg**

Multiple sensitivity analyses were performed (including data censoring at time of dose escalation, censoring at subsequent JAKi or stem cell transplant and excluding patients who were dose escalated or randomized after closure of the 4.7 mg/kg arm), all generating similar results

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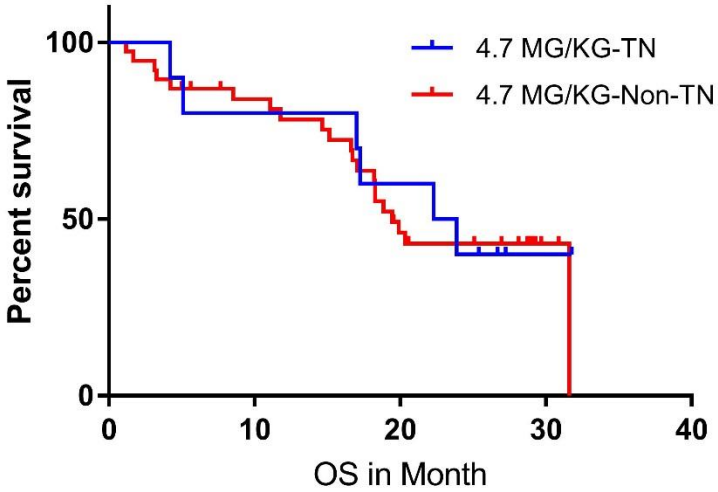
OS in Triple Negative Disease

In 9.4 mg/kg arm, lower death rate seen in Triple Negative (TN) group compared to Non-TN group

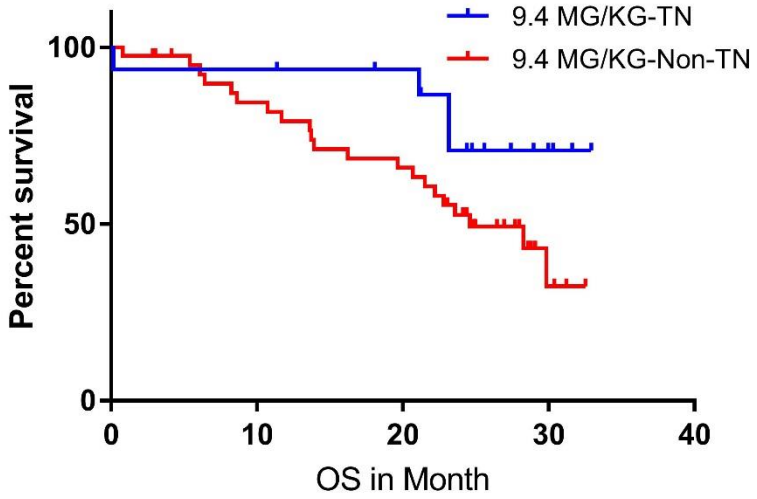
4.7 mg/kg	Death Rate	Median Survival (months)
TN	60%	23.1 (17.0, NE)
Non-TN	55%	19.4 (17.1, NE)



Patients at risk

TN	10	9	7	1
Non-TN	38	30	16	2

9.4 mg/kg	Death Rate	Median Survival (months)
TN	25%	NE (NE, NE)
Non-TN	51%	24.6 (20.7, NE)



Patients at risk

TN	16	16	14	3
Non-TN	41	33	20	4

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Most Frequent Hematologic* and Non-Hematologic AEs

	4.7 mg/kg (n = 48)		9.4 mg/kg (n = 59)	
n (%)	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Hematologic (≥ 10% in either arm)				
Thrombocytopenia	11 (23)	11 (23)	29 (49)	24 (41)
Anemia	15 (31)	15 (31)	26 (44)	23 (39)
Neutropenia	5 (10)	5 (10)	21 (36)	19 (32)
Leukopenia	3 (6)	3 (6)	8 (14)	8 (14)
Non-hematologic (≥ 20% in either arm)				
Nausea	15 (31)	1 (2)	20 (34)	2 (3)
Vomiting	10 (21)	1 (2)	8 (14)	1 (2)
Diarrhea	18 (38)	2 (4)	18 (31)	0
Fatigue	10 (21)	3 (6)	16 (27)	4 (7)
Cough	11 (23)	0	9 (15)	0
Dyspnea	9 (19)	6 (13)	14 (24)	3 (5)
Abdominal Pain	10 (21)	2 (4)	14 (24)	3 (5)
Asthenia	9 (19)	3 (6)	14 (24)	6 (10)
Pyrexia	8 (17)	1 (2)	13 (22)	3 (5)
Edema peripheral	13 (27)	0	11 (19)	0

*Treatment emergent, per reported AEs (not laboratory values). Frequency of reported Grade 3/4 hematologic AEs were consistent with cytopenias reported through lab values.

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Cytopenias and LFTs

- Most grade 3/4 cytopenias were reversible within 4 weeks
- Clinical consequences of cytopenias

n (%)	4.7 mg/kg (n = 48)	9.4 mg/kg (n = 59)
Grade 3 Febrile Neutropenia	1 (2)	1 (2)
Grade ≥ 3 Hemorrhagic events	2 (4)	3 (5)
Grade ≥ 3 Infections	10 (21)	6 (10)

- Grade 3/4 LFT elevations were observed in 7 patients on study
  - An independent Hepatic Review Committee reviewed all LFT and hepatic data
  - Imetelstat-related hepatic toxicities were not observed

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Conclusions

- Imetelstat at 9.4 mg/kg IV every 3 weeks has demonstrated clinical activity in int-2 or high-risk MF patients who are relapsed/refractory to JAKi, notably in observed median OS that approached 30 months
- Though no formal study has reported survival for patients who are truly relapsed/refractory to JAKi, median OS of patients who were previously treated with JAKi has been reported to be 12-14 months[1,2]
- The safety profile for imetelstat was considered acceptable for this poor-prognosis population
- Imetelstat at 9.4 mg/kg IV every 3 weeks is a promising agent for JAKi failure MF patients and warrants further testing in clinical trials

[1]Kuykendall, et al. *Ann Hematol* 2018;97:435-441.

[2]Newberry, et al. *Blood* 2017;130:1125-1131.

Acknowledgements

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