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Abstract #346

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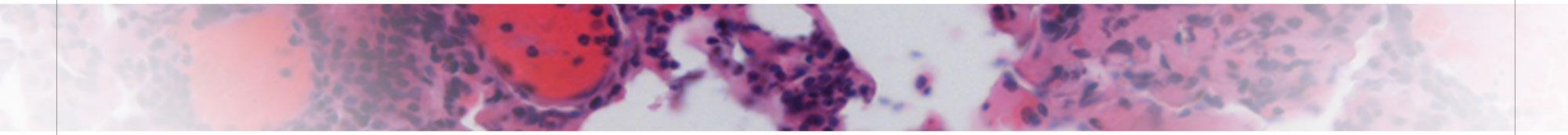

Potential Disease-Modifying Activity of Imetelstat Demonstrated By Reduction in Cytogenetically Abnormal Clones and Mutation Burden Leads to Clinical Benefits in Relapsed/Refractory Myelofibrosis Patients

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Disclosure

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- **Disclosure:**
  - Consultancy: Celgene/BMS, Incyte, Roche, PharmaEssentia, Constellation, Kartos, Prelude, Geron, Abbvie
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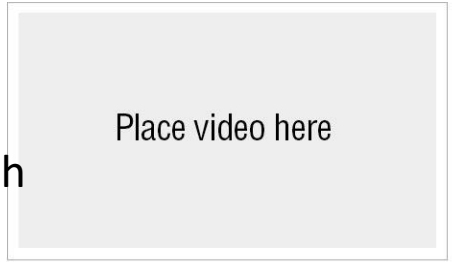
Background

- Myelofibrosis (MF) is a clonal stem cell disease characterized by bone marrow fibrosis and a heterogeneous disease phenotype with a variable degree of splenomegaly, cytopenias, and constitutional symptoms that significantly impact quality of life and survival.
- Both cytogenetic abnormalities and gene mutations in MF carry prognostic significance.
- Janus kinase (JAK) inhibition has contributed to relief from symptoms and splenomegaly. It is insufficient for long-term remission and does not significantly modify the natural course of the disease.[1,2]
- Development of novel agents for treatment of MF that effectively target the underlying malignant clones remains a significant area of unmet need.



[1]Verstovsek, et al. *J. Hematol. Oncol* 2017; [2]Harrison, et al. *Leukemia* 2016;

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

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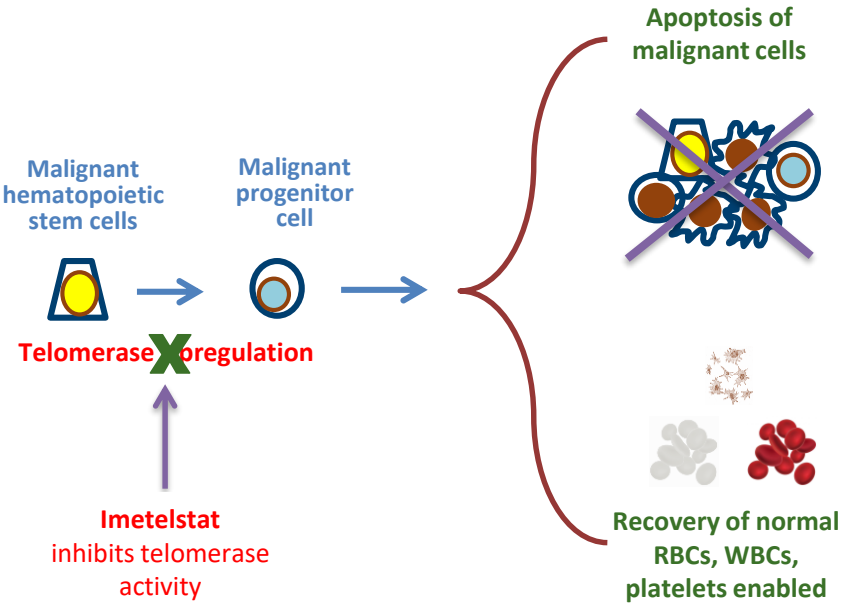
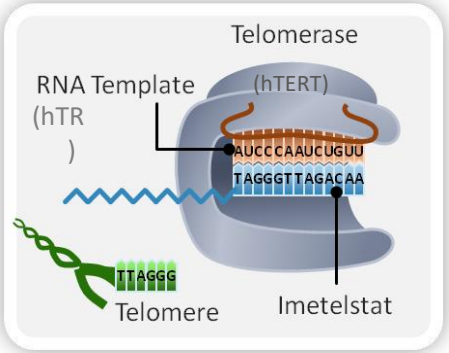


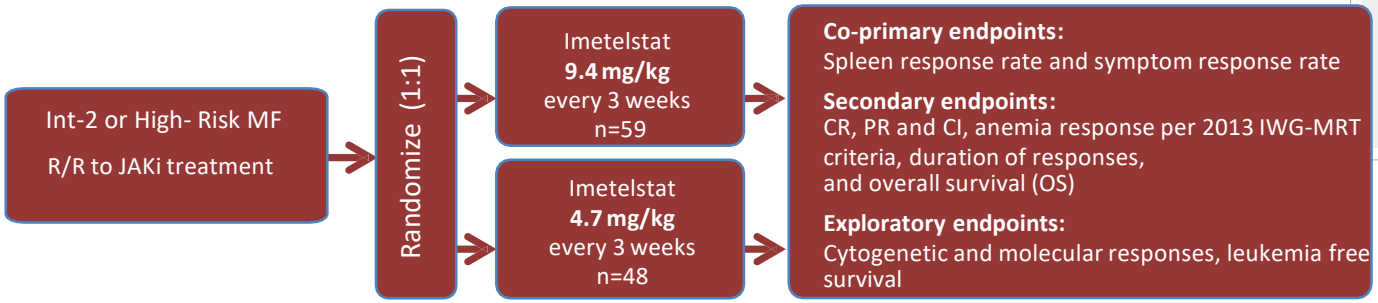
Imetelstat binds to RNA template, preventing maintenance of telomeres



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
- **Disease-modifying potential: selective killing** of malignant stem and progenitor cells enabling normal blood cell production

IMbark Phase 2 Trial: Study Design



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Patient Population:

- Patients with Intermediate-2 or High-risk MF (Int-2/High-risk) patients who have relapsed after or are refractory to prior treatment with a janus kinase (JAK) inhibitor
- 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

IMbark Phase 2 Trial Results: Dose-dependent Clinical Benefits from Imetelstat treatment

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Key efficacy findings suggest potential disease modifying activity of imetelstat

Clinical Benefits	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Median OS, months (95% CI)	**19.9 (17.1, 33.9)**	**28.1 (22.8, 31.6)**
Reduction in bone marrow fibrosis , n/N (%)	**4/20 (20.0%)**	**16/37(43.2%)**
≥ 25% Reduction in VAF of JAK2, CALR or MPL , n/N (%)	**1/18 (5.6%)**	**8/19 (42.1%)**
Symptom Response at week 24 (TSS reduction ≥50%), n (%)	3 (6.3%)	19 (32.2%)
Spleen Response at week 24 (SVR ≥35% by IRC), n (%)	0	6 (10.2%)
Median PFS, months (95% CI)	14.8 (8.3, 17.1)	20.7 (12.0, 23.2)
Clinical improvement, per IWG-MRT, n (%)	8 (16.7%)	15 (25.4%)
Transfusion independence of 12 weeks, n/N (%)	2/14 (14.3%)	3/12 (25.0%)

CALR = calreticulin gene, CI = confidence interval, JAK = Janus kinase, IWG-MRT = International Working Group – Myeloproliferative Neoplasms Research and Treatment, MPL = thrombopoietin receptor gene, OS = overall survival, PFS = progression free survival, SVR = spleen volume reduction, TSS = total symptom score, VAF = variant allele frequency

Mascarenhas et al. EHA 2020, EP1107
Mascarenhas et al. ASH 2020, Abstract #53

Potential Improvement in OS with Imetelstat Treatment

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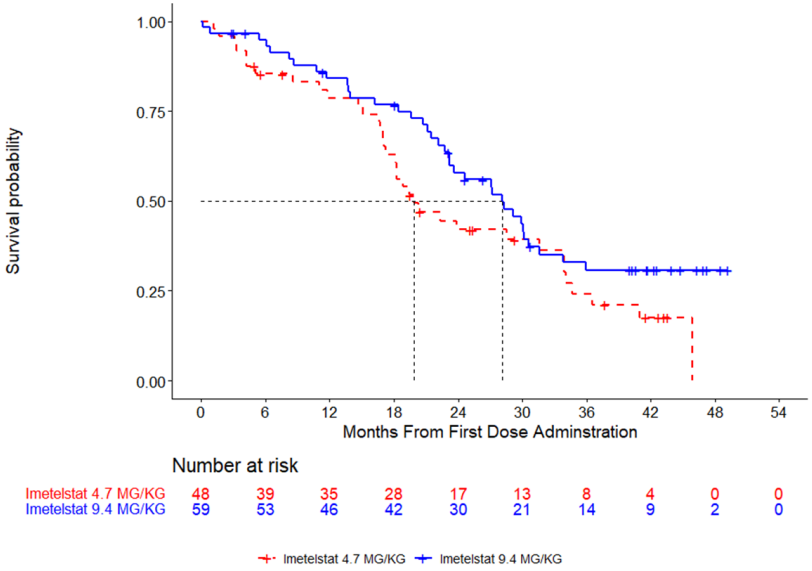
OS improvement with 9.4 mg/kg imetelstat treatment in MF R/R to JAK inhibitor



	4.7 mg/kg (N = 48)	9.4 mg/kg (N = 59)
Number of events, n (%)	35 (72.9%)	36 (61.0%)
Number censored, n (%)	13 (27.1%)	23 (39.0%)
Median Overall Survival (months) (95% CI)	19.9 (17.1, 33.9)	28.1 (22.8, 31.6)
12-months survival rate % (95% CI)	78.6 (63.9, 87.9)	84.0 (71.6, 91.4)
24-months survival rate % (95% CI)	42.0 (27.4, 56.0)	57.9 (43.6, 69.7)

Similar results were observed when sensitivity analyses accounted for confounding factors of subsequent therapies, including hematopoietic stem cell transplantation and dose escalation from 4.7 to 9.4 mg/kg.

Mascarenhas et al. EHA 2020, EP1107
Mascarenhas et al. ASH 2020, Abstract #53

Lower Risk of Death Significantly Correlates with Improved Bone Marrow Fibrosis in Patients Treated with Imetelstat

- **Dose related improvement in bone marrow fibrosis**
- **Patients with bone marrow fibrosis stable or improvement had lower risk of death than those who had worsening bone marrow fibrosis**

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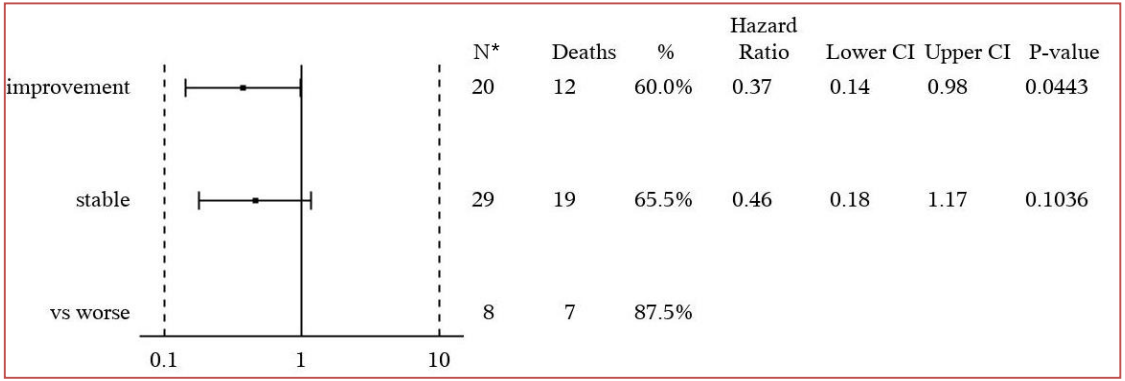
	4.7 mg/kg	9.4 mg/kg
Bone marrow fibrosis improvement, n/N (%)	4/20 (20.0%)	16/37(43.2%)



	N*	Deaths	%	Hazard Ratio	Lower CI	Upper CI	P-value
improvement	20	12	60.0%	0.37	0.14	0.98	0.0443
stable	29	19	65.5%	0.46	0.18	1.17	0.1036
vs worse	8	7	87.5%				

Mascarenhas et al. EHA 2020, EP1107
Mascarenhas et al. ASH 2020, Abstract #53

*N: 57 pts with baseline and at least one post-baseline bone marrow fibrosis assessment irrespective of dose
Bone marrow fibrosis was assessed by central pathology laboratory and graded by European Consensus method, including evaluation of reticulin and collagen changes.
Fibrosis improvement was defined as a decrease in fibrosis by ≥1 grade.

Enrichment for Triple Negative and High Molecular Risk Patients on the study

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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 (TN)[a]	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)
High Molecular Risk[b]	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] TN: No mutation detected in JAK2V617F, CALR and MPL genes, subpopulation associated with a higher incidence of leukemic transformation and shorter overall survival

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

Mascarenhas et al. Blood 2018;132:68.5.

Encouraging Clinical Benefits in TN MF Patients Treated with Imetelstat 9.4 mg/kg

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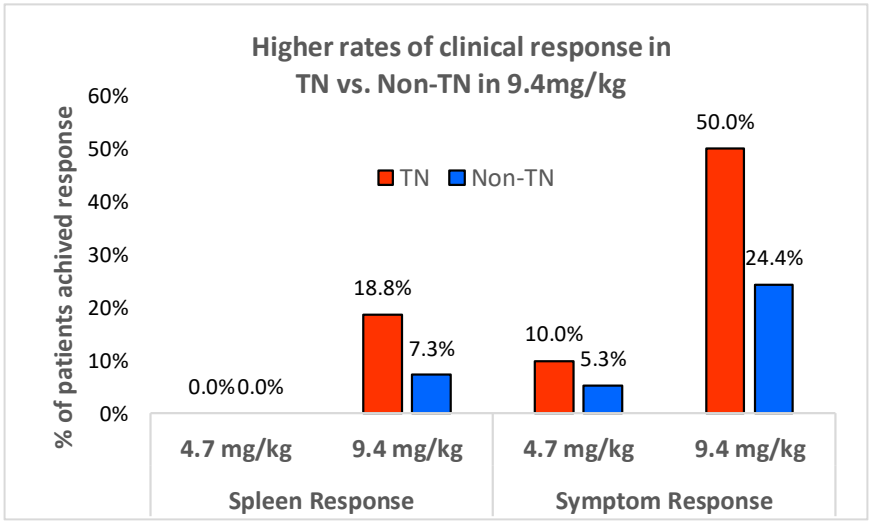
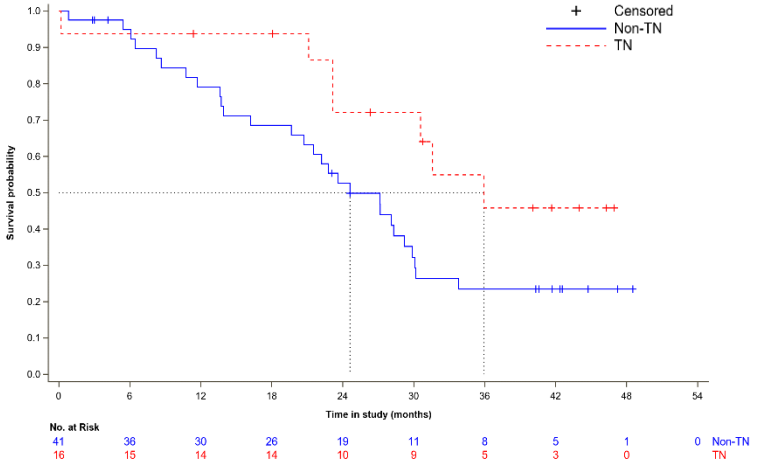
Higher spleen and symptom response rates in TN MF patients than non-TN MF patients



Spleen response: ≥35% spleen volume reduction at Week 24
Symptom response: ≥50% total symptom score reduction at Week 24

Prolonged OS in TN MF patients treated by 9.4 mg/kg imetelstat



	Percentage of Subjects Who Died	Median Survival (months) (95% CI)	HR (95% CI)	P-value (Log-rank)
TN	7 / 16 (43.8%)	35.9 (23.2, NE)	0.45 (0.19, 1.03)	0.05
Non-TN	28 / 41 (68.3%)	24.6 (19.6, 29.9)		

Kiladjian J, et al, EHA 2020, EP1101
Kiladjian J, et al, ASH 2020, Abstract 3084

Encouraging Clinical Benefits in HMR Patients Treated with 9.4 mg/kg of Imetelstat

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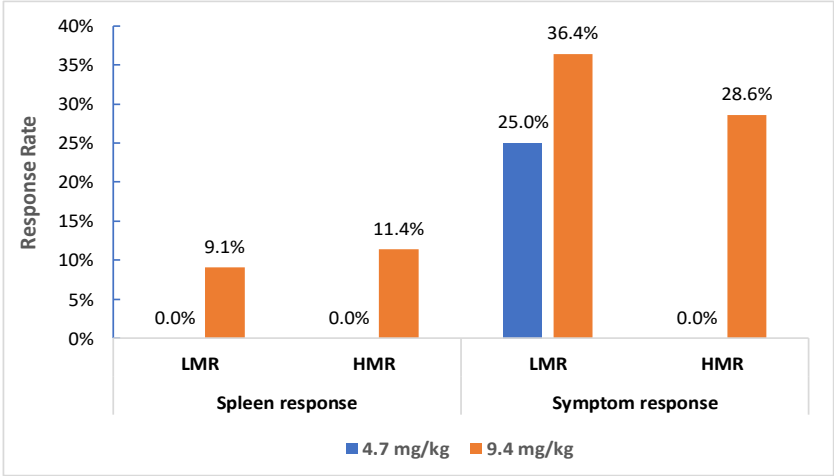
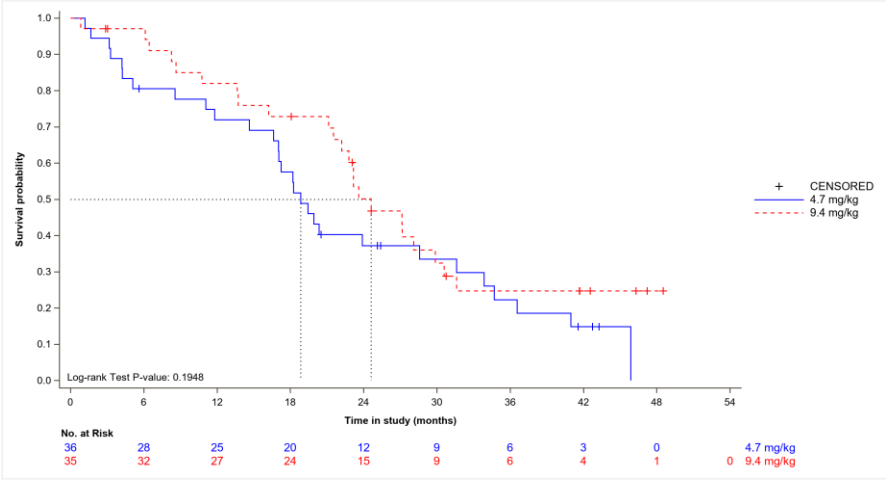
Treatment with 9.4 mg/kg imetelstat achieved higher rates of spleen and symptom responses observed in both LMR and HMR groups compared to 4.7 mg/kg



Improved survival by 9.4 mg/kg imetelstat treatment in HMR subgroup



Spleen response: ≥35% spleen volume reduction at Week 24
Symptom response: ≥50% total symptom score reduction at Week 24
HMR: high molecular risk; ie, 1 or more mutations in ASXL1, EZH2, SRSF2, IDH1, or IDH2.

Dose-dependent Complete Elimination of Mutation Burden with Imetelstat Treatment

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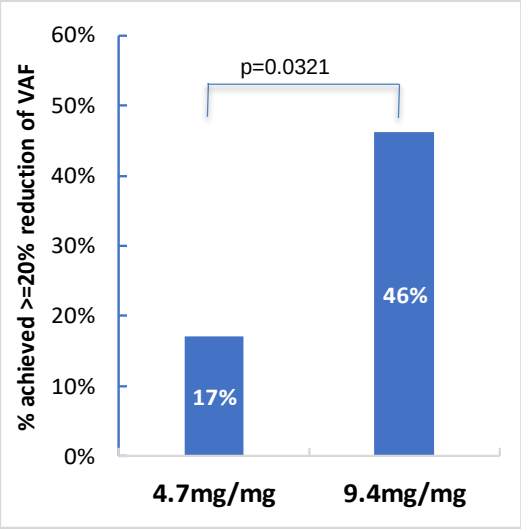
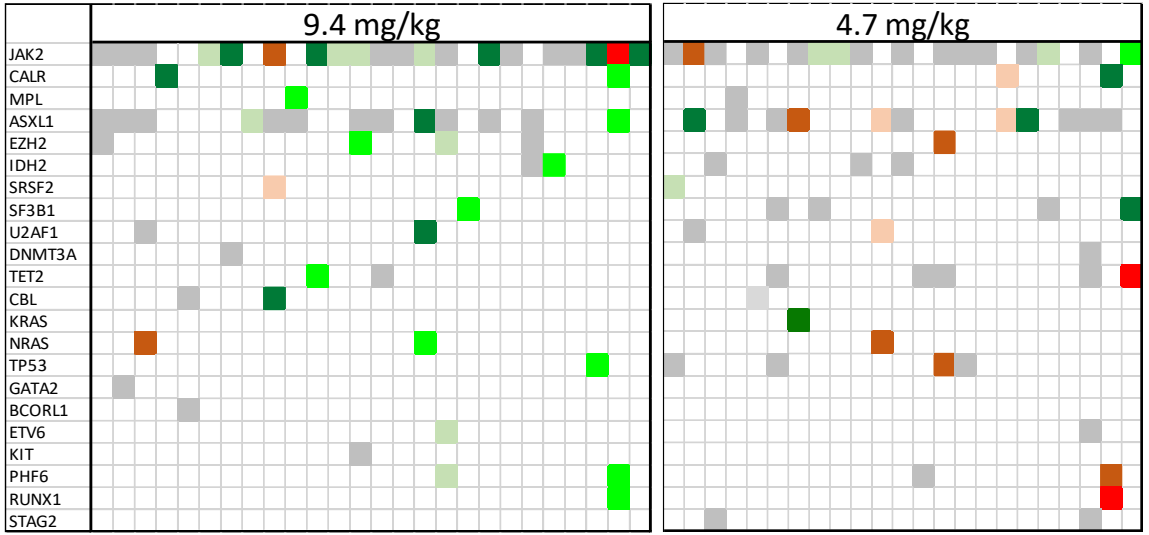
Significant dose-dependent ≥20% VAF reduction by imetelstat treatment



Imetelstat treatment had dose-dependent complete elimination of mutation burden in multiple genes, including driver- and non-driver genes



- Mutation status and variant allele frequency (VAF) were evaluated by next-generation sequencing (NGS) using Illumina TruSight Myeloid Sequencing Panel of 54-genes.
- Lower limit detection is 5% and 2% for well documented hotspots
- 49 pts had matched pre- and at least a post-imetelstat treatment NGS data

≥20% VAF Reduction Leads to Improved Clinical Benefits

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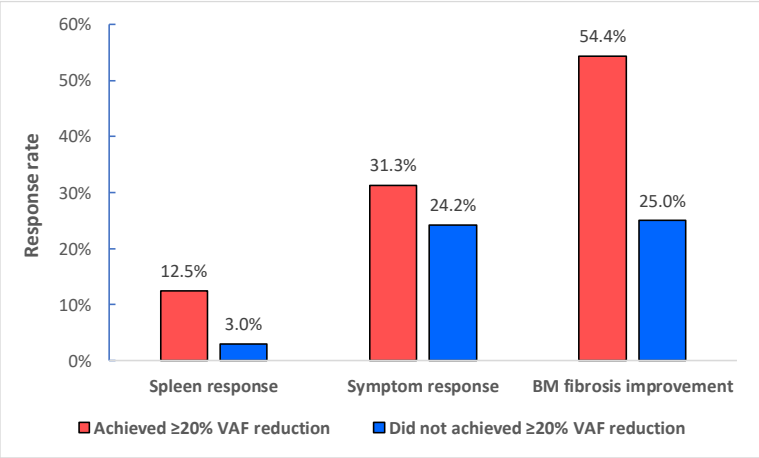
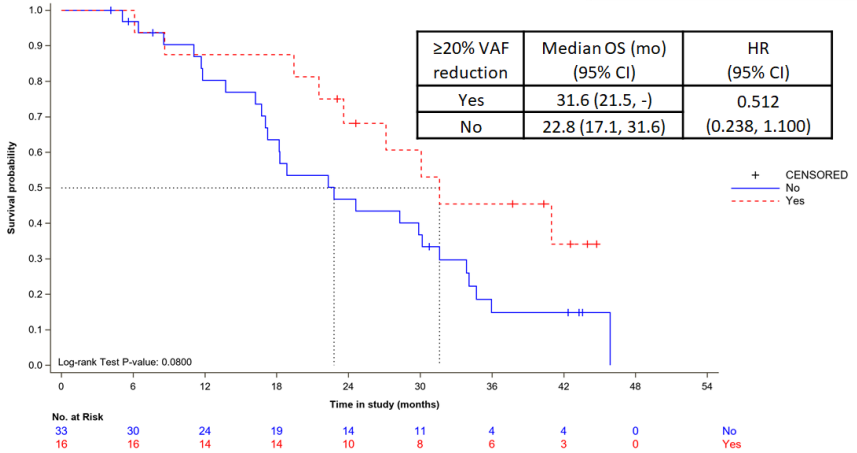
Higher rates of spleen response, symptom response and bone marrow fibrosis improvement in patients who achieved greater mutation VAF reduction



Longer median OS and higher survival rate in patients who achieved ≥ 20% VAF reduction



≥20% VAF reduction	Median OS (mo) (95% CI)	HR (95% CI)
Yes	31.6 (21.5, -)	0.512 (0.238, 1.100)
No	22.8 (17.1, 31.6)	

- Spleen response: ≥35% spleen volume reduction at Week 24
- Symptom response: ≥50% total symptom score reduction at Week 24
- Fibrosis improvement was defined as a decrease in fibrosis by ≥1 grade.

Survival rate	Mutation VAF Reduction >=20%	
	Yes	No
24-months (95% CI)	0.682 (0.395, 0.854)	0.468 (0.285, 0.632)
30-months (95% CI)	0.606 (0.321, 0.802)	0.368 (0.202, 0.535)
36-months (95% CI)	0.455 (0.196, 0.683)	0.149 (0.048, 0.302)
42-months (95% CI)	0.341 (0.103, 0.601)	0.149 (0.048, 0.302)

Symptom Response Across Different Cytogenetic Subsets

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- 83 (77.6%) patients had baseline cytogenetic results available
  - 38 (45.8%) with normal karyotype
  - 45 (54.2%) had an abnormal karyotype: 32 (71.1%) with sole abnormality and 13 (28.8%) >=2 abnormalities
- Symptom response (≥ 50% total symptom score at Week 24) was observed in patients treated with 9.4 mg/kg imetelstat regardless of cytogenetic subtypes including unfavorable profile

	All		4.7 mg/kg		9.4 mg/kg	
Cytogenetic profile	**N**	**TSS Responder**	**N**	**TSS Responder**	**N**	**TSS Responder**
Normal karyotype	38	9 (23.7%)	14	2 (14.3%)	24	7 (29.2%)
Abnormal karyotype	45	11 (24.4%)	24	3 (12.5%)	21	8 (38.0%)
Sole abnormality	32	6 (18.8%)	15	1 (6.7%)	17	5 (29.4%)
Sole 13q-	11	3 (27.3%)	5	0	6	3 (50%)
Sole 20q-	4	1 (25%)	1	0	3	1 (33.3%)
2 or complex	13	5 (38.5%)	9	2 (22.2%)	4	3 (75%)
Favorable	58	14 (24.1%)	23	3 (13.0%)	35	11 (31.4%)
Unfavorable/VHR	25	6 (24.0%)	15	2 (13.3%)	10	4 (40%)

Reduction of Cytogenetically Abnormal Clones with Imetelstat Treatment

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Among 24 patients who had cytogenetic abnormalities at baseline and matched post-treatment cytogenetic results available, 5 (20.8%) achieved ≥50% reduction in their cytogenetically abnormal clones, all had isolated deletion of 13q

Subject	Abnormal Karyotype	% of abnormal clones	
		At screening	Week 24 post-treatment
26	46, XX, del(13)(q12q22)	100%	30%
78	46, XX, del(13)(q12q14)	100%	10%
79	46, XX, del(13)(q12q14)	57%	7%
33*	46, XY, del(13)(q12q22)	65%	5%
104	46, XY, del(13)(q12q14)	40%	20%

*At week 48, the abnormal clones became 0%.

Conclusions

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- Spleen and symptom responses were observed across different molecularly defined subtypes regardless of the baseline mutational or cytogenetic profile, including those with poor prognostic subtypes such as TN, HMR or unfavorable cytogenetics.
- Significant dose-dependent reduction of mutation burden were observed, including complete elimination of mutations in MF driver- and non-driver genes.
- ≥20% VAF reduction correlated with improved clinical benefits, including higher rate of spleen and symptom responses, bone marrow fibrosis improvement and longer OS.
- A subset of patients achieved ≥50% reduction in cytogenetically abnormal clones at week 24 post-imetelstat treatment, all with del(13q) abnormality.
- Overall, imetelstat demonstrated disease-modifying activity by targeting malignant clones, improvement in bone marrow fibrosis and overall survival.
- Results from this phase 2 study demonstrated that imetelstat 9.4 mg/kg IV every 3 weeks is a promising agent for JAK inhibitor failure MF patients and will be tested in a phase 3 clinical trial (IMpactMF, NCT04576156) to be open for screening and enrollment in Q1-2021 with primary endpoint of OS.

Acknowledgements

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