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FAVORABLE OVERALL SURVIVAL WITH IMETELSTAT TREATMENT CORRELATES WITH OTHER CLINICAL BENEFITS IN INTERMEDIATE 2 OR HIGH RISK MYELOFIBROSIS RELAPSED/REFRACTORY TO JANUS KINASE INHIBITOR

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INTRODUCTION

- Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm.
- Patients who are relapsed after or refractory to (R/R) therapy with Janus kinase inhibitors (JAKi) have dismal overall survival (OS) of 13-16 months.[1, 2]
- Imetelstat, a 13-mer oligonucleotide that specifically targets the RNA template of human telomerase, is a potent competitive inhibitor of telomerase enzymatic activity.
- Imetelstat selectively targets malignant cells with continuously upregulated telomerase, inducing their apoptosis and thereby enabling potential recovery of normal hematopoiesis.
- Treatment with imetelstat has demonstrated dose-related clinical benefit, specifically in terms of symptom response and improvement in OS in IMbark, a phase 2 study in MF patients R/R to a JAKi.[3]
- The improvement in OS for patients treated with 9.4mg/kg imetelstat was further supported by analyses of IMbark patients with closely matched real world controls.[4]

OBJECTIVES

- To evaluate the association between OS and spleen volume reduction (SVR) at Week 24, total symptom score (TSS) reduction at Week 24, and fibrosis improvement.
- To explore the prognostic pretreatment baseline characteristic factors on OS.

METHODS

- IMbark (MYF2001; NCT02426086) was a randomized, single-blinded, phase 2 study of imetelstat in R/R int-2/high-risk MF patients, that evaluated two doses of imetelstat: 9.4 mg/kg and 4.7 mg/kg IV every 3 weeks.
- Primary endpoints were spleen response (SVR ≥35%) and symptom response (TSS reduction ≥50%) rate at Week 24.
- OS was a key secondary endpoint. OS analysis was performed based on database lock in April 2020. All 107 enrolled patients (n=59 in 9.4 mg/kg arm, n=48 in 4.7 mg/kg arm) were included in ITT analysis. Median follow-up was 41.7 months (range 0.2, 49.2). All correlation analyses were done irrespective of treatment dose (e.g. patients who had fibrosis improvement were pooled together irrespective of treatment arm).
- Bone marrow fibrosis was assessed by central pathology laboratory, and included evaluation of reticulin and collagen changes. Fibrosis improvement was defined as a decrease in fibrosis by ≥1 grade.

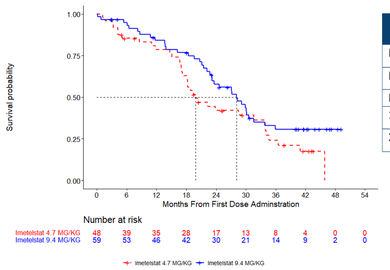
RESULTS

Table 1. Dose related clinical benefits from treatment with 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)
Symptoms 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%)
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%)

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

Figure 1. OS improvement with 9.4 mg/kg imetelstat treatment in MF R/R to JAKi



	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 stem cell transplantation and dose escalation from 4.7 mg/kg to 9.4 mg/kg.

Figure 2. Patients with bone marrow fibrosis improvement had a significantly longer OS than those who had worsening bone marrow fibrosis

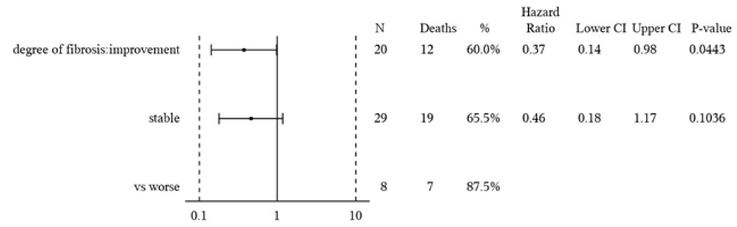


Figure 3. Patients who achieved symptom response at Week 24 demonstrated a trend of longer OS compared to those who did not achieve symptom response

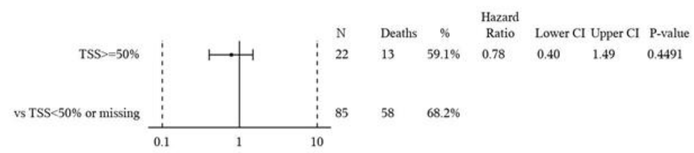
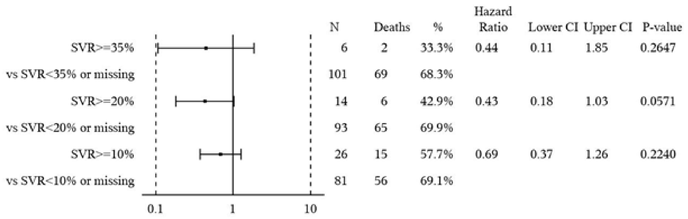
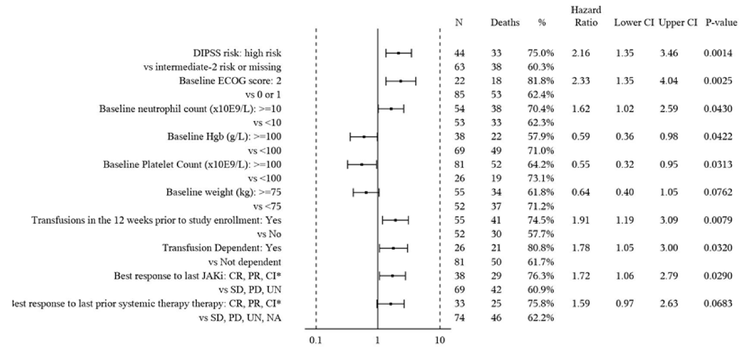


Figure 4. Patients who achieved SVR (≥35%, ≥20%, ≥10%) at Week 24 showed a trend of longer OS compared to those who did not achieve SVR



- Hazard ratios (HR) and p-values are based on Cox regression models with Imetelstat treatment cohort and bone marrow degree of fibrosis, or SVR reduction, or TSS reduction as factors.
- N: Number of patients in each (reference or non-reference) category.
- Deaths: Number of deaths in each category.

Figure 5. Prognostic disease characteristics for overall survival irrespective of treatment dose



Hazard ratios (HR) and p-values are based on Cox regression models with Imetelstat treatment cohort and demographic or baseline characteristic as factors.
CI* = Clinical Improvement

CONCLUSIONS

Imetelstat showed dose-related improvement in OS in patients who are R/R to JAKi. The survival benefit observed with imetelstat was supported by the trend of correlation with other clinical benefits.

- With a median follow-up of 41.7 months, the median OS was 28.1 months for the 9.4 mg/kg arm (95% CI: 22.8, 31.6) and 19.9 months for the 4.7 mg/kg arm (95% CI: 17.1, 33.9).
- Among 57 patients across both treatment arms that had matching bone marrow samples, 20 patients (35%) had ≥1 degree of bone marrow fibrosis improvement while on study and had a significant longer OS than those who had worsening bone marrow fibrosis (HR=0.37, 95% CI 0.14-0.98 p=0.04). A similar trend was seen in 29 patients (51%) with stable vs. worsening fibrosis (HR=0.46, 95% CI 0.18-1.17).
- Patients who achieved symptom and spleen response at week 24 showed trend of longer OS compared to patients who did not achieve response.
- Pretreatment DIPSS high risk, ECOG performance status, transfusion dependency, response to last JAKi, higher baseline neutrophils, lower baseline Hb and platelet values correlated with increased risk of death.

These data warrant a Phase 3 study of imetelstat in patients with myelofibrosis to confirm the OS benefit observed.

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CONTACT INFORMATION

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