TELOMERASE ACTIVITY, TELOMERE LENGTH AND hTERT EXPRESSION CORRELATE WITH CLINICAL OUTCOMES IN HIGHER-RISK MYELOFIBROSIS (MF) RELAPSED/REFRACTORY (R/R) TO JANUS KINASE INHIBITOR TREATED WITH IMETELSTAT

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INTRODUCTION

- Imetelstat is a potent, first-in-class competitive inhibitor of telomerase enzymatic activity.[1] Imetelstat selectively targets malignant cells with continuously upregulated telomerase, inducing their apoptosis and thereby enabling potential recovery of normal hematopoiesis.[2] It is currently in clinical development for hematologic malignancies.
- IMbark (MYF2001; NCT02426086) was a randomized, single-blind phase 2 study to evaluate the activity of 2 dose levels of imetelstat (9.4 mg/kg or 4.7 mg/kg, IV every 3 weeks) in intermediate-2/high-risk myelofibrosis (MF) relapsed/refractory (R/R) to prior Janus kinase inhibitor (JAKi) treatment. Dose-dependent clinical benefits, including symptom response and improvement in overall survival (OS) and an acceptable safety profile for 9.4 mg/kg dose were reported.[3, 4]
- Nonclinical studies demonstrated that imetelstat reduces telomerase activity (TA), human telomerase reverse transcriptase (hTERT) expression level, and JAK2V617$^+$ hematopoietic progenitor cells in MF patient samples, indicative of mechanism based on-target activity.[2, 5]
- Short telomere length (TL), high levels of TA and high expression of hTERT correlated with higher risk, disease progression and shorter OS in patients with myeloid malignancies.[6, 7, 8]
- Cells with short TL, high levels of TA and hTERT represent best target for treatment with telomerase inhibitor.

OBJECTIVES

- Evaluate on-target pharmacodynamic (PD) effect of imetelstat and relationship to dose and exposure levels in MF patients (pts).
- Assess the correlation of the optimal PD effect with symptom or spleen response and OS (clinical cut off date April 21, 2020).
- Explore the association between baseline telomere length and hTERT expression level and clinical benefits.
- Evaluate the change in allele burden of driver mutation, such as JAK2, CALR, MPL, by imetelstat treatment to assess disease-modifying activity.

METHODS

- Blood samples were collected to test for: 1) TA by quantitative telomeric repeat amplification protocol technology; 2) hTERT level by Taqman RT-PCR assay; 3) TL by high-throughput quantitative fluorescence in situ hybridization technology; 4)Mutations and variant allele frequency (VAF) by next-generation sequencing.
- Optimal PD effect of imetelstat was defined as ≥50% reduction in TA or hTERT from baseline as it correlated with antitumor activity in preclinical PK/PD/efficacy studies.
- Imetelstat plasma concentration was determined by a fully validated analysis method, the high exposure was defined by C1-AUC0-24hr or Cmax value >Mean value.

RESULTS

Figure 1. Dose-dependent PD Effect
Significantly higher % of pts in 9.4mg/kg arm achieved optimal PD effect

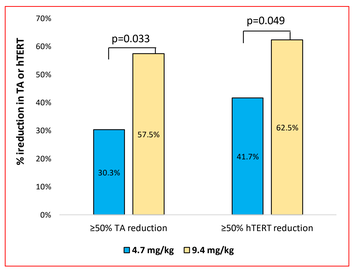


Figure 2. Exposure-dependent PD effect
Significantly higher % pts with high imetelstat exposure achieved ≥50% hTERT reduction

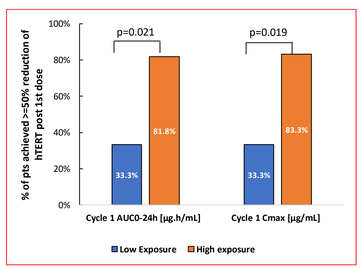
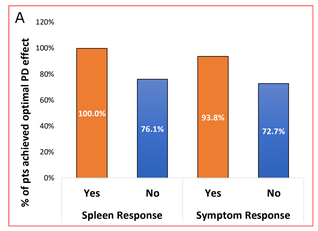


Figure 3. Optimal PD effect correlated with clinical responses and longer OS

A. Higher % of pts achieved optimal PD effect in responders [spleen response (SVR ≥35%) or symptom response (TSS reduction ≥50%)] at week 24 than in non-responders
B. Pts who achieved optimal PD effect had better OS



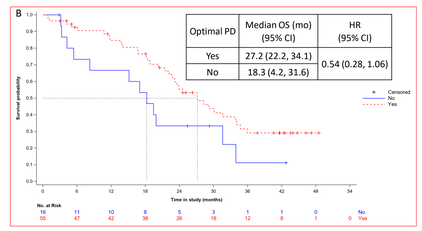


Figure 4. Imetelstat has disease-modifying activity by targeting malignant clones
Imetelstat resulted in dose-dependent reduction in VAF of JAK2V617F, CALR and MPL mutations

	4.7 mg/kg	9.4 mg/kg
JAK2	N=15	N=16
>=25% Decrease	0 (0%)	5 (31.3%)
CALR	N=2	N=2
>=25% Decrease	1 (50%)	2 (100%)
MPL	N=1	N=1
>=25% Decrease	0 (0%)	1 (100%)
Any of 3 genes	N= 18	N=19
>=25% Decrease	1 (5.6%)	**8 (42.1%)**

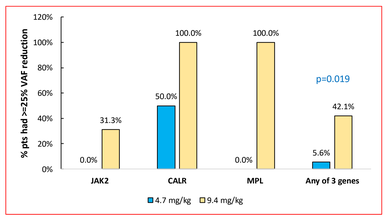
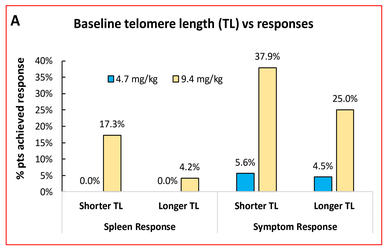


Figure 5. Patients with short telomere length (TL) or higher hTERT expression achieved higher rate of spleen and symptom response when treated with 9.4 mg/kg imetelstat

A. Pts with short baseline TL (<=median) had higher rate of responses in 9.4 mg/kg arm
B. Pts with high baseline hTERT level (>median) had higher rate of responses in 9.4 mg/kg arm



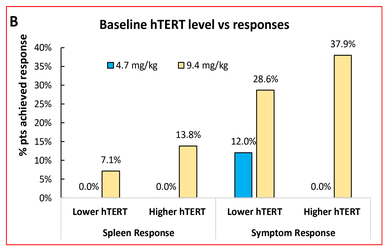
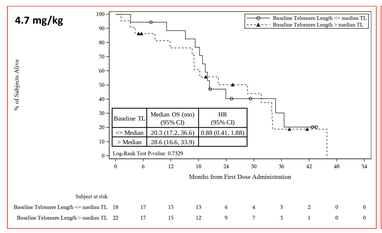
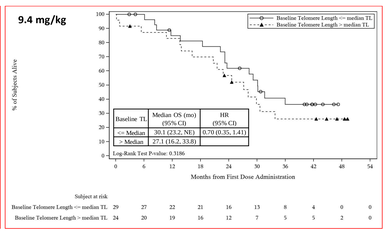


Figure 6. Pts with shorter baseline TL had better OS compared to pts with longer TL when treated with 9.4 mg/kg imetelstat





CONCLUSION(S)

- Imetelstat achieved dose- and exposure-dependent reduction of telomerase activity and hTERT expression level, demonstrating on-target mechanism of action.
- Achieving optimal PD effect (≥50% reduction of telomerase activity or hTERT level) in patients treated with imetelstat is correlated with clinical responses and longer OS. This validates the pre-clinical PD findings.
- Significant, dose-dependent, reduction in VAF of JAK2, CALR and MPL mutations were observed, indicating that imetelstat has disease-modifying activity by targeting the underlying MF malignant clones.
- Treatment with 9.4mg/kg imetelstat improved clinical outcomes in patients with short telomeres or high hTERT expression level at baseline. The results are consistent with telomere biology in cancer cells and provide evidence for on-target mechanism of action of imetelstat through telomerase inhibition.
- This is the first clinical report to systematically evaluate the mechanism of action based PD effect of imetelstat, and its relationship to exposure and clinical benefits.

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