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Abstract #3084

Imetelstat Treatment Results In Clinical Benefits, Including Improved Overall Survival, in Patients With Higher-Risk Triple-Negative Myelofibrosis Relapsed/Refractory To Janus Kinase Inhibitors (JAKi)

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Disclosure

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Background

- Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm. JAK2, MPL, or CALR mutations are considered "driver mutations" and directly contribute to the myeloproliferative phenotype through convergent activation of intracellular JAK-STAT signaling, which led to the development of JAK inhibitors (JAKi).[1]
- MF patients (pts) negative for JAK2, CALR and MPL mutations are termed Triple Negative (TN), a subpopulation associated with a higher incidence of leukemic transformation and shorter overall survival (OS) ~2.5-3 years from diagnosis compared to pts carrying a mutation in JAK2, CALR or MPL gene.[2, 3]
- Allogeneic hematopoietic stem cell transplantation (alloHSCT) is the only potentially curative treatment for MF, but TN MF pts also have worse prognosis and non-relapse mortality vs. non-TN pts after alloHSCT.[4]
- New agents with novel mechanisms of action beyond JAKi are needed to treat TN MF pts. Imetelstat is a telomerase inhibitor that selectively targets malignant cells with continuously upregulated telomerase, inducing their apoptosis and thereby enabling potential recovery of normal hematopoiesis.[5] Imetelstat is currently in clinical development for hematologic malignancies.
- IMbark (MYF2001; NCT02426086) was a 2-dose (9.4 mg/kg or 4.7 mg/kg, IV every 3 weeks), randomized, single-blinded, phase 2 study of imetelstat that enrolled intermediate-2/high-risk MF pts, including TN, who were relapsed/refractory (R/R) to prior JAKi treatment. 32% symptom response rate and median OS of 29.9 mo were reported in the overall population on the 9.4 mg/kg arm, with acceptable safety.[6]

1. Mascarenhas J et al. Curr Med Chem. 2012;19:4399-413.
2. Rumi et al. Blood 2014; 124:1062-9.
3. Tefferi et al. Leukemia 2014;28:1472-7
4. Panagiota et al. Leukemia 2014;28:1552-5
5. Wang X et al, Blood Adv. 2018;2:2378-88.
6. Mascarenhas J et al, Blood. 2018;132:685.

Objectives and Methods

Objectives:

To evaluate triple negative (TN) patients enrolled in the IMbark study for spleen response [spleen volume reduction (SVR) ≥35%] and symptom response [total symptom score (TSS) reduction ≥50%] at Week 24, fibrosis improvement and OS to determine if this molecularly defined subset, associated with poor prognosis, benefits from imetelstat treatment.

Methods

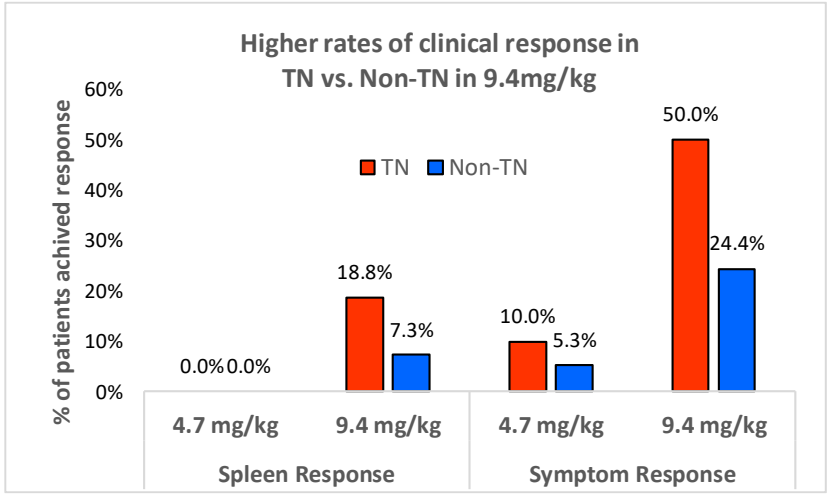
- Blood samples collected at baseline were analyzed for:
  - Driver mutations on JAK2, CALR or MPL by next-generation sequencing (NGS) using Illumina TruSight Myeloid Sequencing Panel of 54-genes with lower limit detection is 5% and 2% for well documented hotspots
  - Human telomerase reverse transcriptase (hTERT) level by Taqman RT-PCR assay;
  - Telomere length (TL) by quantitative fluorescence in situ hybridization technology.
- 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 decrease in fibrosis by ≥1 grade per central review.
- OS was defined as the interval between the date of randomization on this study and death, with a clinical cut off date April 21, 2020.
- All correlative analyses performed were not pre-specified and are exploratory.

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

Enrichment of Triple Negative, a poor prognostic subgroup of patients in the study

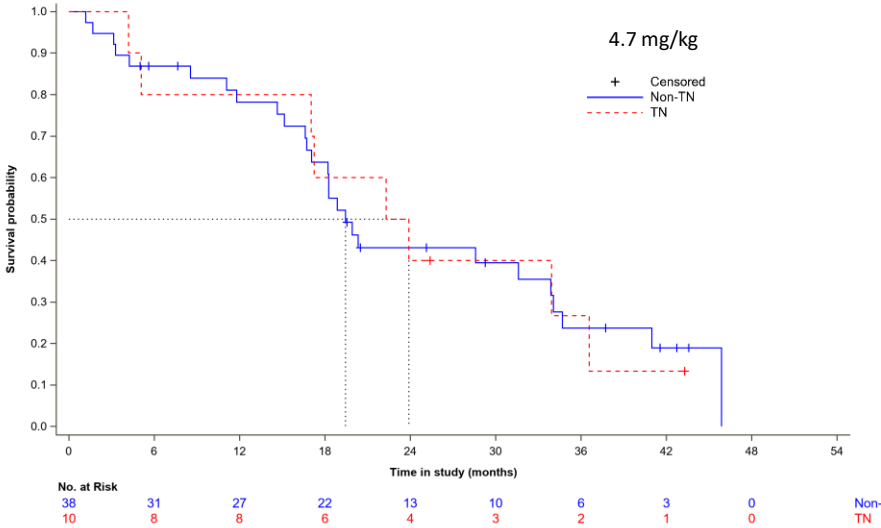
Molecular Subtype	4.7 MG/KG, N=48	9.4 MG/KG, N=57	Total N=105
JAK2 V617F	32 (66.7%)	32 (56.1%)	64 (61%)
CALR	2 (4.2%)	7 (12.3%)	9 (8.5%)
MPL	4 (8.3%)	2 (3.5%)	6 (5.7%)
TN	10 (20.8%)	16 (28.1%)	26 (24.8%)

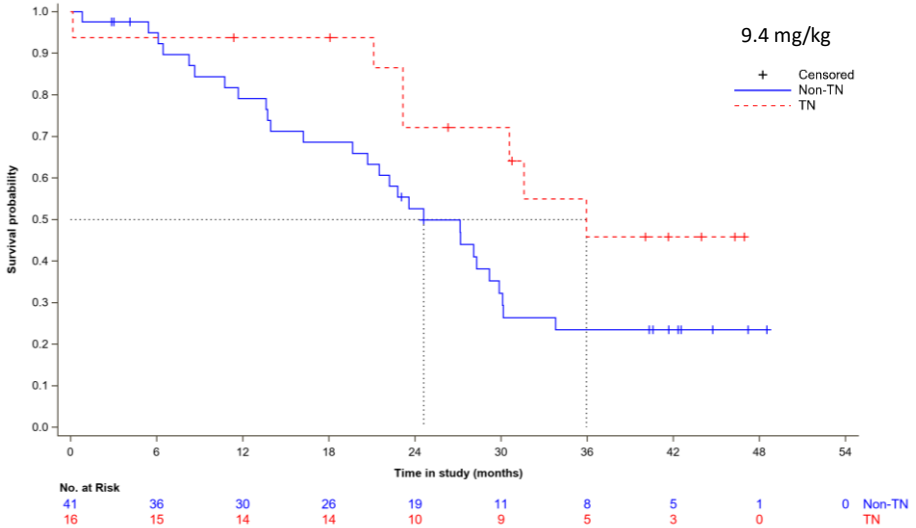
Higher spleen and symptom response rates in TN MF patients than non-TN MF patients



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 with 9.4 mg/kg Imetelstat

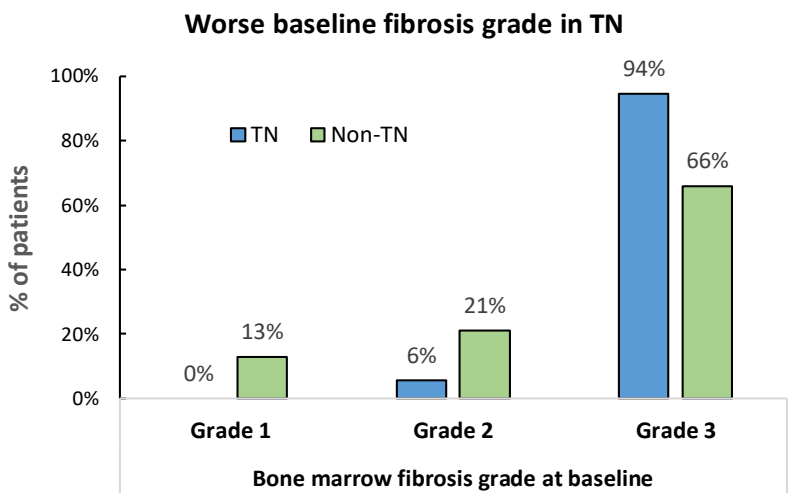


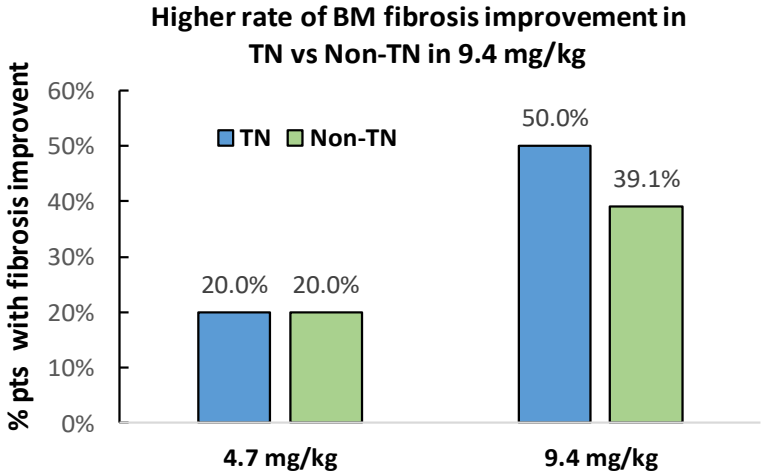


Imetelstat Dose (mg/kg)	TN vs Non-TN	Percentage of Subjects Who Died	Median Survival (months) (95% CI)	HR (95% CI)	P-value (Log-rank)
4.7	TN	8 / 10 (80.0%)	23.1 (4.2, 36.6)	1.01 (0.46, 2.23)	0.98
	Non-TN	27 / 38 (71.1%)	19.4 (16.7, 33.9)		
9.4	TN	7 / 16 (43.8%)	35.9 (23.2, NE)	0.45 (0.19, 1.03)	0.05
	Non-TN	28 / 41 (68.3%)	24.6 (19.6, 29.9)		

Higher Rate of Bone Marrow Fibrosis Improvement in TN MF Patients Treated with 9.4mg/kg Imetelstat

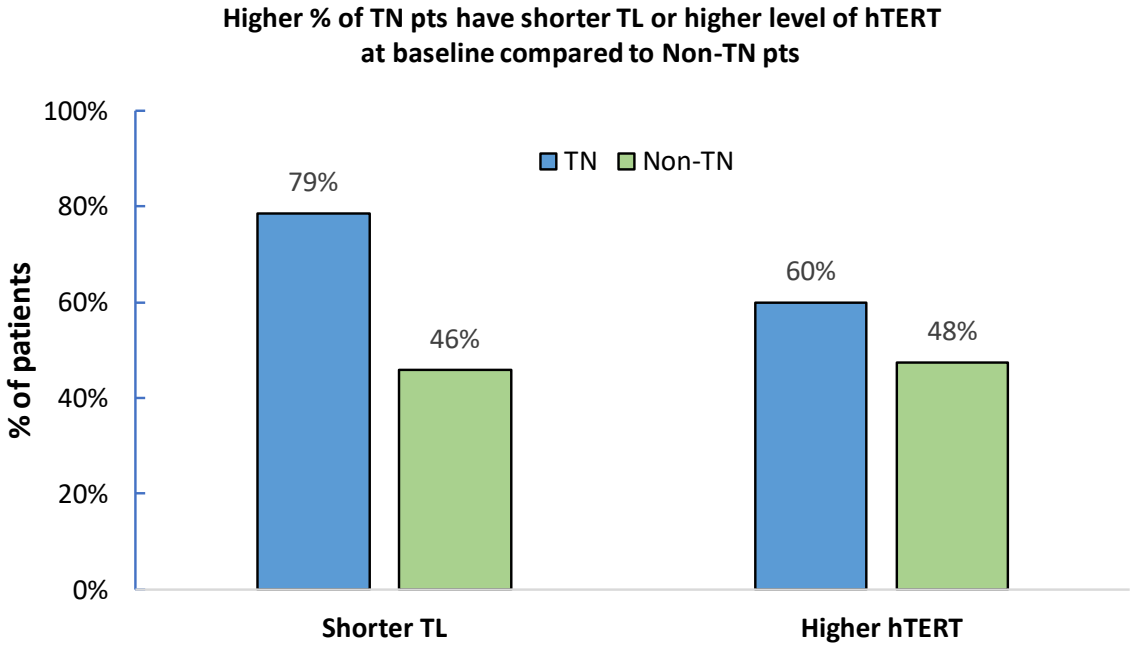
Bone marrow fibrosis improvement in TN MF patients treated with 9.4 mg/kg imetelstat despite that majority of the TN patients had Grade 3 fibrosis at study entry





- For all pts enrolled on the study 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.

TN MF Patients Trend to Have Shorter Telomeres and Higher Level of hTERT, Representing a Population Suited for Treatment with Imetelstat



Shorter TL (telomere length) was defined by ≤ median baseline TL value of patients enrolled in this study
Higher hTERT (human telomerase reverse transcriptase) was defined by ≤ median baseline hTERT value of patients enrolled in this study

Conclusions

TN MF patients R/R to JAKi treated with 9.4 mg/kg imetelstat had better clinical outcomes and prolonged OS compared to non-TN pts, suggesting that imetelstat may improve the poor outcomes expected for TN patients.

- There were 20.8% TN patients in the 4.7 arm and 28.1% in the 9.4 arm, for a total of 24.8% TN patients on the study.
- With 9.4 mg/kg imetelstat treatment, clinical response rates were higher in TN vs non-TN pts: spleen response rate was 18.8% in TN vs 7.3% in non-TN; and symptom response was 50.0% in TN vs 24.4% in non-TN pts.
- Imetelstat treatment with 9.4 mg/kg resulted in significantly longer median OS of 35.9 mo for TN pts (95% CI: 23.2, NE) vs 24.6 mo for non-TN pts (95% CI: 19.6, 29.9) with HR=0.45 (95%CI: 0.19, 1.03, p=0.05).
- Majority (94%) of the TN patients enrolled on the study had Grade 3 fibrosis at study entry. Higher rate of bone marrow fibrosis improvement was noted in the TN (50%) vs non-TN (39.1%) patients, although not reach statistical significance due to small sample size.
- TN patients enrolled on the study trend to have short telomere length and high hTERT expression level at baseline, representing a suitable target population for imetelstat, a telomerase inhibitor.
- These data warrant further investigation of imetelstat in a targeted clinical trial in TN MF pts who have poor outcomes.