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)

EUROPEAN HEMATOLOGY ASSOCIATION

EP1101

J. Kiladjian[1], J. Mascarenhas[2], R. Komrokji[3], M. Cavo[4], B. Martino[5], D. Niederwieser[6], A. Reiter[7], B. Scott[8], M. Baer[9], R. Hoffman[10], O. Odenike[11], J. Bussolari[12], E. Zhu[12], E. Rose[12], L. Sherman[13], S. Dougherty[13], F. Feller[13], L. Sun[13], Y. Wan[13], A. Rizo[13], F. Huang[13], and A. Vannucchi[14]

[1]Hôpital Saint-Louis, Université Paris (FR), [2]Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai; MPN-RC (US), [3]H Lee Moffitt Cancer Center (US), [4]"Seràgnoli" Institute of Hematology, University of Bologna (IT), [5]Grande Ospedale Metropolitano-G.O.M. Bianchi-Melacrino-Morelli (IT), [6]University Hospital Leipzig (DE), [7]University Hospital Mannheim (DE), [8]Fred Hutchinson Cancer Research Center (US), [9]University of Maryland Greenebaum Comprehensive Cancer Center (US), [10]Tisch Cancer Institute, Mount Sinai School of Medicine (US), [11]University of Chicago (US), [12]Janssen Research & Development, LLC (US), [13]Geron Corporation (US), [14]AOU Careggi, University of Florence (IT)

INTRODUCTION

- Myelofibrosis (MF) is a serious and life-threatening myeloproliferative neoplasm. JAK2, MPL, and 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]

OBJECTIVE

To evaluate TN pts 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;
  - 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. 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.

RESULTS

Table 1. Baseline frequency of JAK2, CALR, MPL mutation and TN for patients with samples available for analysis

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%)

Figure 1. Higher rates of spleen response (SVR≥35%) and symptom response (TSS reduction ≥50) in TN MF pts treated with 9.4 mg/kg imetelstat

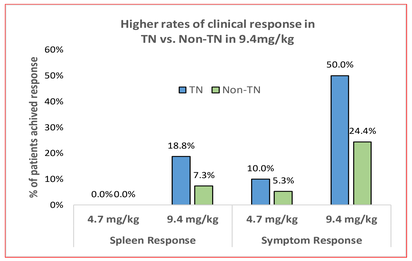
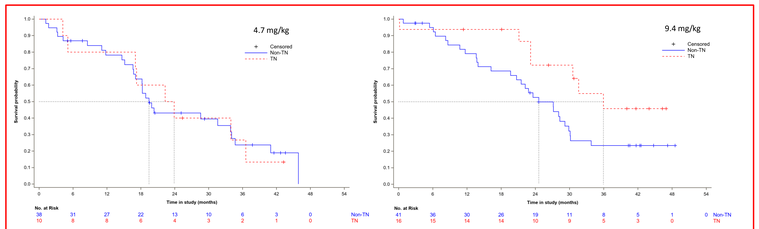
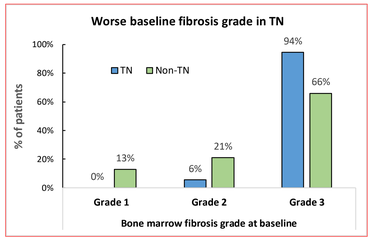


Figure 2. OS improvement in TN MF treated with 9.4 mg/kg imetelstat



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)		

Figure 3. Bone marrow fibrosis improvement in TN MF treated with 9.4 mg/kg imetelstat despite TN had higher percentage with worse fibrosis grade (Grade 3) at study entry



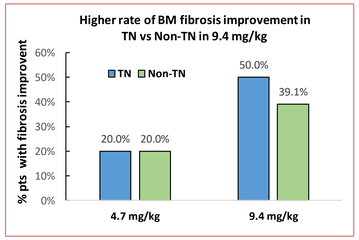
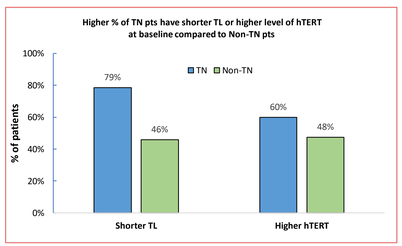


Figure 4. TN pts enrolled in 9.4 mg/kg arm had shorter telomeres and higher level of hTERT expression at baseline, representing a population suited for treatment with imetelstat



CONCLUSIONS

Overall, TN MF pts 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 pts.

- 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 at 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 (92%) of the TN patients enrolled on the study had Gr3 fibrosis. Higher rate of bone marrow fibrosis improvement was noted in the TN (50%) vs non-TN (39.1%) patients.
- TN pts enrolled on the study had 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.

ACKNOWLEDGEMENTS

The authors thank all the patients for their participation in this study and acknowledge the collaboration and commitment of all investigators and their staff.

REFERENCES

1. Mascarenhas J et al. Biology and clinical management of myeloproliferative neoplasms and development of the JAK inhibitor ruxolitinib. Curr Med Chem. 2012;19:4399-413.
2. Rumi et al. Clinical effect of driver mutations of JAK2, CALR, or MPL in primary myelofibrosis. Blood 2014; 124:1062-9.
3. Tefferi et al. CALR vs JAK2 vs MPL-mutated or triple-negative myelofibrosis: clinical, cytogenetic and molecular comparisons. Leukemia 2014;28:1472-7
4. Panagiota et al. Prognostic effect of calreticulin mutations in patients with myelofibrosis after allogeneic hematopoietic stem cell transplantation. Leukemia 2014;28:1552-5
5. Wang X et al, Imetelstat, a telomerase inhibitor, is capable of depleting myelofibrosis stem and progenitor cells. Blood Adv. 2018;2:2378-88.
6. Mascarenhas J et al, 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. Blood. 2018;132:685.

CONTACT INFORMATION

- Dr. Jean-Jacques Kiladjian: jean-jacques.kiladjian@aphp.fr
- Geron Corporation: info@geron.com