MPN-100

High Rate of Disease Progression in Patients With Low-Risk Myelofibrosis (MF) Enrolled in the Prospective Myelofibrosis and Essential Thrombocythemia Observational Study (MOST)

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Introduction

- Myelofibrosis (MF) is characterized by megakaryocyte atypia, clonal mutations, and bone marrow fibrosis[1]
- Patients with MF are stratified for risk of disease progression using prognostic scoring systems based on disease phenotype[2]
- Prospective data regarding disease progression in patients with low-risk MF are limited, as this patient population is typically excluded from interventional clinical trials and previous studies are largely of retrospective design
- The **M**yelofibrosis and Essential Thrombocythemia **O**bservational **St**udy (MOST) is a prospective observational study that collected data from patients with low-risk and intermediate (INT)-1–risk (by age alone) MF

Objective

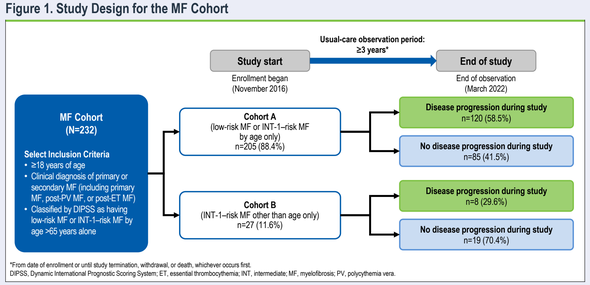
- This analysis evaluates disease progression in patients with MF enrolled in MOST

Methods

Study Design

- MOST (NCT02953704) is a prospective observational study that enrolled patients with MF or essential thrombocythemia at clinical practices throughout the United States (**Figure 1**)
- Physician-reported data were collected during usual-care visits over a planned 36-month observation period, as previously described[3]
- Patients enrolled with MF were low risk or INT-1 risk (by age >65 years alone), defined by Dynamic International Prognostic Scoring System (DIPSS)[2] criteria
- Criteria for enrollment into MOST were confirmed locally and centrally; key eligibility criteria are shown in **Figure 1**
- Disease progression on study was defined as the acquisition of ≥1 of the progression criteria outlined in **Table 1**

Figure 1. Study Design for the MF Cohort



*From date of enrollment or until study termination, withdrawal, or death, whichever occurs first.
DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; INT, intermediate; MF, myelofibrosis; PV, polycythemia vera.

Table 1. Criteria for Disease Progression on Study*

Laboratory-Defined Criteria	• Hemoglobin <10 g/dL • Platelets <100×10⁹/L • Blasts >1% • White blood cell count >25×10⁹/L • Leukemic transformation (blasts >20%)
Physician-Reported Criteria	• Presence of constitutional symptoms (weight loss, fever, or sweats) • New or worsening splenomegaly • >1 red blood cell transfusion during study • Leukemic transformation (physician-reported) • Death due to disease progression

A patient was determined to have disease progression if they had ≥1 documentation of progression criteria during the study period.
*The definition of disease progression used in this study has not been validated across other studies.

Results

Patient Disposition

- All 232 patients with MF enrolled in MOST were included in this analysis
- Of the 232 patients, 205 met study inclusion criteria upon central review and were included in this analysis as cohort A (**Figure 1**)
  - The remaining 27 patients were enrolled despite having ≥1 DIPSS risk factor (other than age >65 years) and were analyzed separately as cohort B

Disease Progression

- In cohort A, 120 patients (58.5%) had disease progression during the study (**Table 2**)
  - Of the 29 patients who met ≥3 progression criteria, 15 met 3 criteria, 7 met 4 criteria, 4 met 5 criteria, 2 met 6 criteria, and 1 met 8 criteria
  - The most common progression criteria met were hemoglobin <10 g/dL (47.5%) and platelets <100×10⁹/L (31.7%)
  - 12 patients (10.0%) died due to disease progression and 6 (5%) had leukemic transformation (**Figure 2**)
- In cohort B, at the time of enrollment (n=27) (**Table 3**):
  - The most frequent criteria met were hemoglobin <10 g/dL (51.9%), followed by white blood cell count >25×10⁹/L (29.6%)
  - 8 patients (29.6%) in cohort B had disease progression during the study (**Table 4**)

Table 2. Progression Criteria Met During Study (Cohort A; N=205)

	Number of Progression Criteria Met in Study			
Variable	1 (n=64)	2 (n=27)	≥3 (n=29)	≥1 (n=120)
Hemoglobin <10 g/dL	19 (29.7)	17 (63.0)	21 (72.4)	57 (47.5)
Platelets <100×10⁹/L	12 (18.8)	7 (25.9)	19 (65.5)	38 (31.7)
Presence of constitutional symptoms (weight loss, fever, or sweats)	13 (20.3)	7 (25.9)	17 (58.6)	37 (30.8)
New or worsening splenomegaly	13 (20.3)	5 (18.5)	16 (55.2)	34 (28.3)
Blasts >1%	4 (6.3)	5 (18.5)	11 (37.9)	20 (16.7)
White blood cell count >25×10⁹/L	2 (3.1)	6 (22.2)	11 (37.9)	19 (15.8)
Death due to disease progression	1 (1.6)	3 (11.1)	8 (27.6)	12 (10.0)
Received >1 red blood cell transfusion during study	0	3 (11.1)	5 (17.2)	8 (6.7)
Leukemic transformation	0	1 (3.7)	5 (17.2)	6 (5.0)

Table 3. Summary of Progression Criteria Met at Enrollment (Cohort B)

Variable	Cohort B (N=27)
Met 1 criterion, n (%)	25 (92.6)
Hemoglobin <10 g/dL	13 (48.1)
White blood cell count >25×10⁹/L	7 (25.9)
Constitutional symptoms	4 (14.8)
Blasts >1%	1 (3.7)
Met 2 criteria, n (%)	1 (3.7)
Hemoglobin <10 g/dL and constitutional symptoms	1 (3.7)
Met 3 criteria, n (%)	1 (3.7)
White blood cell count >25×10⁹/L, blasts >1%, and constitutional symptoms	1 (3.7)

Table 4. Progression Criteria Met During Study (Cohort B)

Criterion, n (%)	≥1 Progression Criterion Met During Study (n=8)
Hemoglobin <10 g/dL	5 (62.5)
Platelets <100×10⁹/L	5 (62.5)
Presence of constitutional symptoms (weight loss, fever, or sweats)	3 (37.5)
New or worsening splenomegaly	3 (37.5)
Leukemic transformation	2 (25.0)
Blasts >1%	1 (12.5)
Received >1 red blood cell transfusion during study	1 (12.5)
White blood cell count >25×10⁹/L	0
Death due to disease progression	0

Clinical Characteristics

- In cohort A, for patients with vs without progression during the study (**Table 5**):
  - A significantly larger percentage were aged >65 vs ≤65 years at diagnosis (53.3% vs 35.3%; *P*=0.0384)
  - The duration from diagnosis to enrollment was not significantly different (median: 1.9 vs 1.4 years; *P*=0.9997)
- Median (range) time from diagnosis to enrollment for patients in cohort B was 1.9 (0-31) years
- Median (range) duration of enrollment for patients in cohort A with and without disease progression on study was 4.5 (3.5-5.7) years and 4.3 (3.5-5.6) years, respectively
- For cohort B, median (range) duration of enrollment was 4.3 (3.6-5.4) years
- The percentage of patients in cohort A receiving MF-directed therapy at enrollment was similar for those with vs without progression (59.2% vs 61.2%)
  - For patients with vs without progression, a significantly higher percentage were receiving ruxolitinib (33.3% vs 14.1%; *P*=0.0078), and a nonsignificantly lower percentage were receiving hydroxyurea (22.5% vs 36.5%; *P*=0.0913)

Table 5. Enrollment Demographics and Clinical Characteristics in Patients With and Without Progression

	Cohort A			Cohort B
Variable	Total (N=205)	No Progression Criteria Met During Study (n=85)	≥1 Progression Criterion Met During Study (n=120)	Total (N=27)
Age at diagnosis, median (range), years	64.6 (21-88)	62.9 (35-86)	65.9 (21-88)	66.3 (32-84)
>65 years, n (%)	94 (45.9)	30 (35.3)	64 (53.3)*	16 (59.3)
≤65 years, n (%)	111 (54.1)	55 (64.7)	56 (46.7)	11 (40.7)
Age at enrollment, median (range), years	68.0 (35-88)	66.0 (35-88)	70.5 (35-88)	68.0 (45-87)
Male, n (%)	102 (49.8)	45 (52.9)	57 (47.5)	14 (51.9)
Race, n (%)				
White	178 (87.3)	71 (83.5)	107 (89.9)	21 (77.8)
Black	13 (6.4)	7 (8.2)	6 (5.0)	1 (3.7)
Other†	13 (6.4)	7 (8.2)	6 (5.0)	5 (18.5)
Time from MF diagnosis to enrollment, median (range), years	1.8 (0-38)	1.4 (0-24)	1.9 (0-38)	1.9 (0-31)
MF-directed therapy at enrollment, n (%)	123 (60.0)	52 (61.2)	71 (59.2)	18 (66.7)
Hydroxyurea	58 (28.3)	31 (36.5)	27 (22.5)	7 (25.9)
Ruxolitinib	52 (25.4)	12 (14.1)	40 (33.3)*	10 (37.0)
Other‡	19 (9.3)	10 (11.8)	9 (7.5)	2 (7.4)
Enrollment duration, median (range), years	4.4 (3.5-5.7)	4.3 (3.5-5.6)	4.5 (3.5-5.7)	4.3 (3.6-5.4)

*P<0.05 vs patients without progression. †Other includes Asian, American Indian/Alaskan Native, and other. ‡Other treatments include anagrelide and interferon.
MF, myelofibrosis.

Mutation Testing

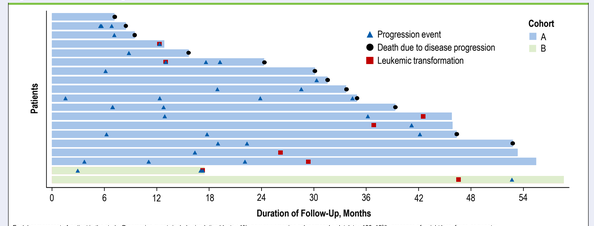
- Among all enrolled patients, 186 were evaluated for ≥1 known driver mutation (**Table 6**)

Table 6. Mutation Status at Enrollment

	Cohort A			Cohort B
Mutation	Total (N=205)	No Progression Criteria Met (n=85)	≥1 Progression Criterion Met (n=120)	Total (N=27)
JAK2 positive, n/N*	108/158	42/65	66/93	15/17
CALR positive, n/N*	33/44	17/23	16/21	1/3
MPL positive, n/N*	5/31	4/21	1/10	0
Triple negative, n/N†	3/16	2/10	1/6	0
Unknown, n‡	51	25	26	3

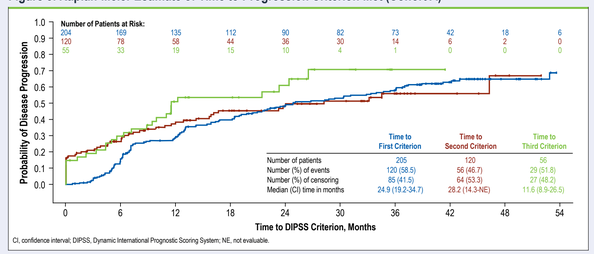
A patient may have >1 positive mutation.
*Numerator = patients positive for mutation; denominator = patients tested for mutation. †Numerator = patients negative for all 3 mutations; denominator = patients tested for all 3 mutations.
‡Unknown refers to patients with ≥1 mutation test done (*JAK2*, *CALR*, or *MPL*) who did not test positive for a mutation or negative for all 3 mutations.
CALR, calreticulin; *MPL*, myeloproliferative leukemia virus oncogene; *JAK*, Janus kinase.

Figure 2. Time to Progression in Patients With Leukemic Transformation or Death



Each bar represents 1 patient in the study. Progression events include circulating blasts >1%; new or worsening splenomegaly; platelets >100×10⁹/L; presence of weight loss, fever, or sweats; received >1 red blood cell transfusion during study; and white blood cell count >25×10⁹/L.

Figure 3. Kaplan-Meier Estimate of Time to Progression Criterion Met (Cohort A)



CI, confidence interval; DIPSS, Dynamic International Prognostic Scoring System; NE, not evaluable.

Duration of Time to Meeting Progression Criteria

- In cohort A, median (95% confidence interval) durations of time to meeting first, second, and third progression criteria were 24.9 (19.2-34.7), 28.2 (14.3-not evaluable), and 11.6 (8.9-26.5) months, respectively (**Figure 3**)

Conclusions

- **Over 4 years of follow-up, 58.5% of patients with low-risk or INT-1–risk (by age alone) MF had evidence of disease progression**
- **In patients with lower-risk MF, median time to meeting first and second disease progression criteria was approximately 2 years for each, decreasing to approximately 1 year for the third criterion**
  - **This observation indicates an increasing rate of progression over the course of the study**
- **These data provide real-world insight into the characteristics and rates of disease progression in patients with lower-risk MF**

Disclosures

Grunwald: Consulting fees – *AbbVie, Agios/Servier, Amgen, Astellas Pharma, Blueprint Medicines, Bristol Myers Squibb, Cardinal Health, CTI BioPharma/Sobi, Daiichi Sankyo, Gamida Cell, Genentech, Gilead Sciences, GlaxoSmithKline/Sierra Oncology, Incyte Corporation, Invitae, Jazz Pharmaceuticals, Novartis, Ono Pharmaceutical, Pfizer, Pharmacosmos, Premier Pharma, Stemline Therapeutics*; Research support – *Incyte Corporation, Janssen*; Stock ownership – *Medtronic*.

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