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Disease Progression and Leukemic Transformation in Patients With Lower-Risk Myelofibrosis: An Analysis From the Myelofibrosis and Essential Thrombocythemia Observational Study (MOST)

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Introduction

- Progressive disease (PD) in myelofibrosis (MF) is associated with increased bone marrow fibrosis, worsening anemia, and an increase in circulating blasts[1]
- Leukemic transformation (LT) is a rare but fatal complication in patients with MF with an incidence of approximately 8-23%[2-5] and a median survival of 3.6 months[6]
- Real-world data regarding PD and LT in lower-risk MF are limited

Objectives

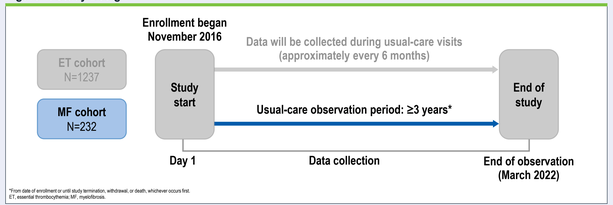
- This analysis from the **M**yelofibrosis and Essential Thrombocythemia **O**bservational **ST**udy (MOST; NCT02953704) describes the incidence of PD, including LT, in patients with low-risk and intermediate-1 (INT-1)–risk (by age >65 years alone) MF, and compares the baseline characteristics of patients with vs without physician-reported PD during the study

Methods

Study Design

- MOST is a longitudinal, noninterventional, prospective, observational study in patients with clinical diagnoses of specific risk categories of essential thrombocythemia or MF enrolled at clinical practices throughout the United States **(Figure 1)**
- Key eligibility criteria are shown in **Table 1**; key assessments and statistical analyses methods are shown in **Table 2**

Figure 1. Study Design



*From date of enrollment or until study termination, withdrawal, or death, whichever occurs first.
ET, essential thrombocythemia; MF, myelofibrosis.

Table 1. Key Patient Eligibility Criteria

Inclusion Criteria	• ≥18 years of age • Clinical diagnosis of primary or secondary MF (including primary MF, post-PV MF, or post-ET MF) • Classified by DIPSS[7] as having: – Low-risk MF ***OR*** INT-1–risk MF by >65 years of age alone • Followed for ≥3 years
Exclusion Criteria	• Participation in an active, blinded study or Incyte-funded investigational/interventional drug trial • Life expectancy ≤6 months • Diagnosis of secondary acute myeloid leukemia, myelodysplastic syndrome, chronic myelogenous leukemia, or secondary thrombocytosis

DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; INT-1, intermediate-1; MF, myelofibrosis; PV, polycythemia vera.

Table 2. Key Study Assessments and Statistical Analyses

Assessments	• Data from patient records and physician-reported baseline data (demographics, signs and symptoms, and treatment) were collected as previously characterized[8] during usual-care visits over a planned observation period of 36 months • Physician-reported PD: A patient was considered as having PD if the treating physician reported PD for any reason, and/or LT, and/or death due to disease progression
Statistical Analyses	• Descriptive statistics were used to summarize: – Baseline demographics, disease characteristics, and treatments – Incidence of LT and death by any cause • Statistical comparison between PD and non-PD groups was calculated using the Fisher exact test

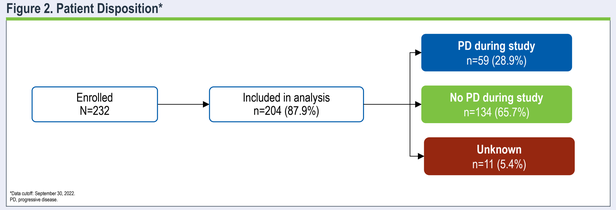
LT, leukemic transformation; PD, progresive disease.

Results

Patient Disposition

- Of 232 patients with MF enrolled in MOST, 204 were included in this analysis **(Figure 2)**
  - Median (range) time from MF diagnosis to enrollment was 1.8 (0-38) years
  - Median (range) duration of enrollment was 4.4 (3.5-5.6) years
- During the study
  - 59 (28.9%) had physician-reported PD
  - 15 (7.4%) had LT
  - 30 (14.7%) died due to any cause
- Twenty-eight patients were not included in the analysis due to having a prognostic factor for INT-1 risk other than age >65 years

Figure 2. Patient Disposition*



*Data cutoff: September 30, 2022.
PD, progressive disease.

Baseline Demographics

- Compared with patients with no PD during the study, patients who had PD were older (median age, 70.0 vs 66.5 years), less likely to be employed (20.3% vs 44.4%) at enrollment, and more likely to be unable to work (16.9% vs 2.3%) **(Table 3)**
- Patients who had PD during the study were more likely to have INT-1–risk (by age >65 years alone) MF than low-risk MF
- A larger percentage of Black patients (6/14, 42.9%) had PD during the study compared with White patients (49/179, 27.4%)

Table 3. Baseline Demographics

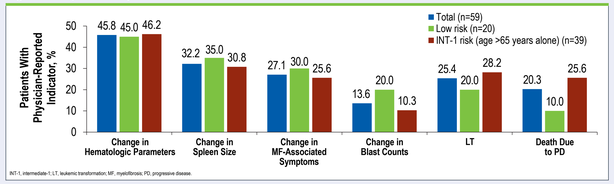
Characteristic	Total (N=204)	PD During Study (N=59)	No PD During Study (N=134)	Unknown (N=11)
DIPSS at enrollment, n (%)				
Low risk	84 (41.2)	20 (33.9)	62 (46.3)	2 (18.2)
INT-1 risk by age >65 years alone	120 (58.8)	39 (66.1)	72 (53.7)	9 (81.8)
Age at enrollment, median (range), y	68.0 (35-88)	70.0 (35-88)	66.5 (35-88)	76.0 (53-85)
Men, n (%)	102 (50.0)	31 (52.5)	65 (48.5)	6 (54.5)
Race, n (%)				
White	179 (87.7)	49 (83.1)	120 (89.6)	10 (90.9)
Black	14 (6.9)	6 (10.2)	7 (5.2)	1 (9.1)
Other*	11 (5.4)	4 (6.8)	7 (5.2)	0
Current employment status, n (%)†	203 (99.5)	59 (100.0)	133 (99.3)	11 (100.0)
Employed (full- or part-time)	74 (36.5)	12 (20.3)	59 (44.4)	3 (27.3)
Retired	102 (50.2)	35 (59.3)	61 (45.9)	6 (54.5)
Unable to work‡	14 (6.9)	10 (16.9)	3 (2.3)	1 (9.1)
Other§	13 (6.4)	2 (3.4)	10 (7.5)	1 (9.1)
Smoking status, n (%)	202 (99.0)	59 (100.0)	133 (99.3)	10 (90.9)
Current	16 (7.9)	6 (10.2)	8 (6.0)	2 (20.0)
Former	85 (42.1)	19 (32.2)	61 (45.9)	5 (50.0)
Never	101 (50.0)	34 (57.6)	64 (48.1)	3 (30.0)
BM biopsy/aspiration at diagnosis, n/N (%)	188/204 (92.2)	58/59 (98.3)	123/134 (91.8)	7/11 (63.6)
Mutation testing at diagnosis, n/N (%)	165/202 (81.7)	46/57 (80.7)	111/134 (82.8)	8/11 (72.7)

*Other includes Asian, American Indian/Alaskan Native, and other. †P<0.0003 for employment indicates employment status is significantly different between patients with PD vs no PD during the study. ‡Unable to work includes due to MF and due to other reasons. §Other employment status includes homemaker, student, other, and unknown.
BM, bone marrow; DIPSS, Dynamic International Prognostic Scoring System; INT-1, intermediate-1; MF, myelofibrosis; PD, progressive disease.

Physician-Reported Indicators of PD by MF Risk Category

- Among the 59 patients with physician-reported PD, 15 (25.4%) had LT, 12 (20.3%) died due to disease progression, and 4 (6.8%) died due to other causes
- Physician-reported indicators of disease progression by MF risk category are shown in **Figure 3**; the percentages of patients with:
  - Change in hematologic parameters, spleen size, and MF-associated symptoms were similar between the low-risk and INT-1–risk groups
  - Change in blast counts was higher in the low-risk group compared with the INT-1–risk group
  - LT and death due to disease progression were higher in the INT-1–risk group compared with the low-risk group

Figure 3. Physician-Reported Indicators of PD



INT-1, intermediate-1; LT, leukemic transformation; MF, myelofibrosis; PD, progressive disease.

Physician-Reported Signs and Symptoms

- The symptomatology of patients recorded at time of enrollment was not significantly different for patients with PD compared with patients with no PD during the study **(Table 4)**

Table 4. Physician-Reported Signs and Symptoms at Enrollment

Characteristic	Total (N=204)	PD During Study (N=59)	No PD During Study (N=134)	Unknown (N=11)
Patients with physician-reported symptoms at diagnosis, n/N (%)*	203/204 (99.5)	59/59 (100.0)	133/134 (99.3)	11/11 (100.0)
LDH above ULN	62 (30.5)	19 (32.2)	39 (29.3)	4 (36.4)
Leukocytosis (WBC count ≥11×10^9/L)	51 (25.1)	15 (25.4)	35 (26.3)	1 (9.1)
Palpable spleen	44 (21.7)	13 (22.0)	30 (22.6)	1 (9.1)
Anemia (Hb <10 g/dL)	28 (13.8)	9 (15.3)	15 (11.3)	4 (36.4)
Increasing splenomegaly	27 (13.3)	8 (13.6)	19 (14.3)	0
Leukoerythroblastosis†	13 (6.4)	2 (3.4)	10 (7.5)	1 (9.1)
Additional symptoms	78 (38.4)	26 (44.1)	46 (34.6)	6 (54.5)
Fatigue	64 (31.5)	20 (33.9)	41 (30.8)	3 (27.3)
Night sweats	13 (6.4)	4 (6.8)	9 (6.8)	0
Weight loss	13 (6.4)	6 (10.2)	5 (3.8)	2 (18.2)
Fever	5 (2.5)	3 (5.1)	1 (0.8)	1 (9.1)
Other	28 (13.8)	10 (16.9)	15 (11.3)	3 (27.3)

*Patients with available symptom data. †Shown on peripheral blood smear.
Hb, hemoglobin; LDH, lactate dehydrogenase; PD, progressive disease; ULN, upper limit of normal; WBC, white blood cell.

MF-Directed Therapy at Enrollment

- More than half of patients with and without PD during the study were receiving MF-directed monotherapy at enrollment **(Table 5)**
  - Six patients (PD, n=3; without PD, n=3) received >1 MF-directed therapy
- The most common monotherapies received by patients at enrollment were hydroxyurea (44.4%) and ruxolitinib (41.9%)
  - Fewer patients on monotherapy with vs without PD were receiving hydroxyurea at enrollment (25.7% vs 51.4%)
  - More patients on monotherapy with vs without PD were receiving ruxolitinib at enrollment (62.9% vs 32.4%)

Table 5. MF-Directed Therapy at Enrollment*

Characteristic	Total (N=204)	PD During Study (N=59)	No PD During Study (N=134)	Unknown (N=11)
MF-directed therapy at enrollment, n (%)	123 (60.3)	38 (64.4)	77 (57.5)	8 (72.7)
Monotherapy, n (%)	117 (57.4)	35 (59.3)	74 (55.2)	8 (72.7)
Hydroxyurea	52 (44.4)	9 (25.7)	38 (51.4)	5 (62.5)
Ruxolitinib	49 (41.9)	22 (62.9)	24 (32.4)	3 (37.5)
Interferon	12 (10.3)	4 (11.4)	8 (10.8)	0
Anagrelide	4 (3.4)	0	4 (5.4)	0
>1 MF-directed therapy at enrollment, n (%)	6 (2.9)	3 (5.1)	3 (2.2)	0
Hydroxyurea + ruxolitinib	3 (50.0)	2 (66.7)	1 (33.3)	0
Hydroxyurea + interferon	2 (33.3)	1 (33.3)	1 (33.3)	0
Interferon + ruxolitinib	1 (16.7)	0	1 (33.3)	0

*All therapies listed were those recorded at enrollment and may differ from what the patient was taking at the time of progression.
MF, myelofibrosis; PD, progressive disease.

Disease Characteristics at Enrollment by MF-Directed Monotherapy

- A larger percentage of patients receiving ruxolitinib at enrollment had risk factors for PD compared with patients receiving hydroxyurea **(Table 6)**
  - More had INT-1–risk (by age >65 years alone) MF at enrollment (65.3% vs 48.1%)
  - More had palpable spleens at enrollment (50.0% vs 28.2%)
  - Median durations from MF diagnosis to enrollment and from MF diagnosis to PD were longer for patients receiving ruxolitinib at enrollment (2.6 vs 1.1 years; 4.3 vs 3.0 years)

Table 6. Disease Characteristics at Enrollment by MF-Directed Monotherapy

Characteristic	Total Receiving Monotherapy at Enrollment (N=117)	Hydroxyurea (N=52)	Ruxolitinib (N=49)	Interferon (N=12)	Anagrelide (N=4)
DIPSS risk status, n (%)					
Low risk	48 (41.0)	27 (51.9)	17 (34.7)	3 (25.0)	1 (25.0)
INT-1 risk	69 (59.0)	25 (48.1)	32 (65.3)	9 (75.0)	3 (75.0)
Time from diagnosis to enrollment, median (range), y	2.2 (0-38)	1.1 (0-21)	2.6 (0-18)	4.5 (0-24)	3.2 (0-38)
Time from diagnosis to PD, median (range), y	4.1 (0-26)	3.0 (0-8)	4.3 (0-16)	4.2 (2-26)	—
Spleen palpability at enrollment, n (%)					
Total	87	39	32	12	4
Palpable	32 (36.8)	11 (28.2)	16 (50.0)	4 (33.3)	1 (25.0)
Nonpalpable	53 (60.9)	28 (71.8)	14 (43.8)	8 (66.7)	3 (75.0)
Indeterminate	2 (2.3)	0	2 (6.3)	0	0

DIPSS, Dynamic International Prognostic Scoring System; INT-1, intermediate-1; MF, myelofibrosis; PD, progresive disease.

Conclusions

- **This real-world analysis of data from 204 patients enrolled in MOST describes the disease evolution in patients with low-risk and INT-1–risk (by age >65 years alone) MF**
- **Of the 204 patients analyzed, 59 (28.9%) had physician-reported PD during the study, of whom 25.4% had LT and 20.3% died due to disease progression**
- **Compared with patients with no PD during the study, those with PD were older, less likely to be employed or able to work, and more likely to be Black**
- **Although a higher percentage of patients who had PD were receiving ruxolitinib compared with hydroxyurea at enrollment, patients receiving ruxolitinib were more likely to have risk factors for PD**
  - **Patients receiving ruxolitinib at enrollment were older and more likely to have splenomegaly compared with those receiving hydroxyurea**
  - **Time from diagnosis to enrollment was longer in patients receiving ruxolitinib compared with hydroxyurea**
  - **This suggests that ruxolitinib use is greater in patients at higher risk for PD**
- **Further longitudinal analyses from MOST will provide additional insight into risk factors for PD to facilitate improved disease management and outcomes for patients with lower-risk MF**

Disclosures

Komrokji: Consultancy – *AbbVie, Bristol Myers Squibb, Jazz Pharmaceuticals, Novartis, Servier;* Honoraria – *AbbVie, Bristol Myers Squibb, CTI BioPharma, Jazz Pharmaceuticals, PharmaEssentia, Servier;* Research funding – *Bristol Myers Squibb;* Speakers bureau – *AbbVie, Bristol Myers Squibb, CTI BioPharma, PharmaEssentia, Jazz Pharmaceuticals, Servier.* **Grunwald:** Consulting fees – *AbbVie, Agios/Servier, Amgen, Astellas Pharma, Blueprint Medicines, Bristol Myers Squibb, Cardinal Health, CTI BioPharma, Daiichi Sankyo, Gamida Cell, Genentech, Gilead Sciences, GSK/Sierra Oncology, Incyte Corporation, Invitae, Jazz Pharmaceuticals, Karius, Novartis, Ono Pharmaceutical, Pfizer, Pharmacosmos, Premier, Stemline Therapeutics;* Research support – *Incyte Corporation, Janssen;* Stock ownership – *Medtronic.* **Braunstein, Kalafut, Hamer-Maansson:** Employment and stock ownership – *Incyte Corporation.* **Mascarenhas:** Research funding – *Bristol Myers Squibb, Celgene, CTI BioPharma, Geron, Incyte Corporation, Janssen, Kartos Therapeutics, Merck, Novartis, PharmaEssentia, Roche;* Participated in consulting or advisory committees – *Bristol Myers Squibb, Celgene, Constellation Pharmaceuticals, CTI BioPharma, Galecto, Geron, GSK, Incyte Corporation, Karyopharm Therapeutics, Novartis, PharmaEssentia, Prelude Therapeutics.*

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