MPN-099

Characteristics of Patients With Myelofibrosis and Essential Thrombocythemia Who Harbor a Calreticulin (*CALR*) Gene Mutation: Subanalysis of the MOST Study

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Introduction

- The prospective **M**yelofibrosis and Essential Thrombocythemia **O**bservational **St**udy (MOST) collected data from patients with essential thrombocythemia (ET) and myelofibrosis (MF)
- ET and MF are chronic myeloproliferative neoplasms (MPNs) that can cause splenomegaly (SPM), cytopenias, and thrombotic complications, and have the potential to transform into acute leukemia
  - Mutations in Janus kinase 2 (*JAK2*) or calreticulin (*CALR*) genes are known to drive the disease phenotype in ET and MF[1,2]
- Patients with *CALR* mutations are considered to have lower-risk disease than those with *JAK2* mutations[3]; however, prospective data on clinical characteristics and disease progression are limited

Objective

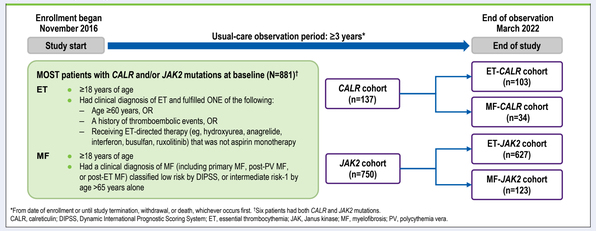
- To compare the disease characteristics, treatment patterns, and disease progression in patients with MF or ET enrolled in MOST who had *CALR* mutations vs those with *JAK2* mutations

Methods

Study Design

- MOST (NCT02953704) was a prospective, longitudinal, observational study of patients with low-risk MF and high-risk ET **(Figure 1)**
- Eligible patients were aged ≥18 years with a reported *CALR* or *JAK2* mutation at enrollment, based on pre-enrollment mutation testing, and a clinical diagnosis of either MF or ET
- Patients were enrolled at multiple sites within the United States; data were collected at enrollment and at usual-care visits over a period of ≥36 months
- Physician-reported data relating to disease and clinical characteristics were collected and have been previously reported[1,2,4]

Figure 1. Study Design and Patient Disposition



*From date of enrollment or until study termination, withdrawal, or death, whichever occurs first. †Six patients had both *CALR* and *JAK2* mutations.
CALR, calreticulin; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; JAK, Janus kinase; MF, myelofibrosis; PV, polycythemia vera.

Definitions of ET and MF Progression

- ET progression was defined as transformation to MF; MF progression was defined as worsening of objective clinical and laboratory assessments of disease **(Table 1)**
- Disease progression criteria defined for use in this analysis have not been validated in other studies

Table 1. Progression Criteria*

ET	**Progression from ET to MF was defined as meeting any of the following criteria during the study period:** • Bone marrow biopsy with fibrosis grade ≥2 or pathologic diagnosis of MF • Death owing to MF/MDS/AML • Circulating blasts >1% and new/worsening splenomegaly • New/worsening splenomegaly and ≥2 of: WBC count >11×10⁹/L, hemoglobin <10 g/dL, and platelets <100×10⁹/L
MF	**Progression from MF was defined as meeting any of the following criteria during the study period:** • Laboratory-defined criteria: – Hemoglobin <10 g/dL – Platelets <100×10⁹/L – Blasts >1% – WBC 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 – Leukemic transformation (physician-reported) – Death due to disease progression

*The definition of disease progression used in this study has not been validated across other studies. AML, acute myeloid leukemia; ET, essential thrombocythemia; MDS, myelodysplastic syndrome; MF, myelofibrosis; WBC, white blood cell.

- Patients lacking data on reported mutation status were excluded from this analysis
- Statistical significance of differences between patients with *CALR* and *JAK2* mutations were analyzed using *P* values calculated by chi-square test for categorical variables, and Student's *t* test for continuous variables

Results

Patient Characteristics

- Of 1469 patients enrolled in MOST (November 29, 2016, to March 29, 2019), 881 (MF, n=156; ET, n=725) had reported *CALR* or *JAK2* mutations and were included in this analysis
- Median (range) follow-up time was 56.0 (42-70) months
- In total, 137 patients (15.6%) had *CALR* mutations (*CALR* cohort) and 750 (85.1%) had *JAK2* mutations (*JAK2* cohort) **(Table 2)**
  - Of 156 patients with MF, 34 (21.8%) had a *CALR* mutation (MF-*CALR* cohort) and 123 (78.8%) had a *JAK2* mutation (MF-*JAK2* cohort) **(Table 3)**
  - Of 725 patients with ET, 103 (14.2%) had a *CALR* mutation (ET-*CALR* cohort) and 627 (86.5%) had a *JAK2* mutation (ET-*JAK2* cohort) **(Table 4)**
- The *CALR* cohort was younger than the *JAK2* cohort at enrollment and at diagnosis

Table 2. Characteristics of Total Study Population by Mutation Status

Characteristic	*CALR* Cohort (n=137)	*JAK2* Cohort (n=750)	*P* Value	Total* (N=881)
Age at enrollment, median (range), years	63.0 (24-89)	70.0 (26-93)	<0.001	69.0 (24-93)
>65 years, n (%)	56 (40.9)	488 (65.1)	<0.001	541 (61.4)
Female, n (%)	76 (55.5)	486 (64.8)	0.037	557 (63.2)
Race, n (%)				
White	118 (87.4)	657 (88.5)	0.181	769 (88.3)
Black	10 (7.4)	53 (7.1)		63 (7.2)
Other	7 (5.2)	32 (4.3)		39 (4.4)
Missing	2	8		10
Age at diagnosis, median (range), years	59.3 (21-87)	66.3 (22-93)	<0.001	65.2 (21-93)
>65 years, n (%)	45 (32.8)	404 (53.9)	<0.001	446 (50.6)
Time from diagnosis to enrollment, median (range), years	1.9 (0-38)	2.8 (0-32)	0.721	2.6 (0-38)
Disease duration, median (range), years	6.5 (4-42)	7.4 (4-36)	0.863	7.2 (4-42)
Duration of enrollment, median (range), months	52.8 (43-68)	56.6 (42-70)	<0.001	56.0 (42-70)

Significant values (*P*<0.05) are shown in blue. *Six patients reported positive for both *CALR* and *JAK2* mutations. Percentages are calculated using nonmissing totals as denominator. CALR, calreticulin; JAK, Janus kinase.

Table 3. Characteristics of Patients With MF

Characteristic	MF-*CALR* Cohort (n=34)	MF-*JAK2* Cohort (n=123)	*P* Value	Total* (N=156)
Age at enrollment, median (range), years	64.0 (35-80)	68.0 (46-88)	0.004	67.5 (35-88)
>65 years, n (%)	14 (41.2)	76 (61.8)	0.096	89 (57.1)
Female, n (%)	15 (44.1)	67 (54.5)	0.285	81 (51.9)
Age at diagnosis, median (range), years	59.5 (21-78)	65.9 (41-88)	0.001	64.6 (21-88)
>65 years, n (%)	11 (32.4)	64 (52.0)	0.012	74 (47.4)
Time from diagnosis to enrollment, median (range), years	1.0 (0-38)	1.1 (0-19)	0.184	1.1 (0-38)
Disease duration, median (range), years	5.6 (4-42)	5.9 (4-24)	0.258	5.8 (4-42)
Duration of enrollment, median (range), months	50.5 (43-62)	53.1 (42-68)	0.091	52.8 (42-68)
Disease burden at enrollment†				
MPN-SAF TSS, mean (SD)	16.2 (14.0)	17.4 (15.4)	0.7538	17.1 (15.1)
MPN-SAF TSS >25, n (%)	4 (11.8)	22 (17.9)	0.3954	26 (16.6)
Splenomegaly, n/N (%)‡	6/31 (19.4)	38/95 (40.0)	0.0668	44/126 (34.9)
WBC >10×10⁹/L, n (%)	12 (35.3)	40 (32.5)	0.7610	52 (33.1)
Platelets >400×10⁹/L, n (%)	18 (52.9)	41 (33.3)	0.0367	59 (37.6)

Significant values (*P*<0.05) are shown in blue. *One patient with MF reported positive for both *CALR* and *JAK2* mutations. †History of TEs was not collected for patients with MF. ‡Two patients (2.1%) with MF and *JAK2* mutations had indeterminate palpable spleen at enrollment. CALR, calreticulin; JAK, Janus kinase; MF, myelofibrosis; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; SD, standard deviation; TE, thromboembolic event; WBC, white blood cell.

Table 4. Characteristics of Patients With ET

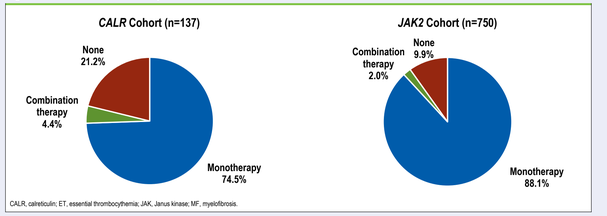
Characteristic	ET-*CALR* Cohort (n=103)	ET-*JAK2* Cohort (n=627)	*P* Value	Total* (N=725)
Age at enrollment, median (range), years	63.0 (24-89)	70.0 (26-93)	<0.001	69.0 (24-93)
>65 years, n (%)	42 (40.8)	412 (65.7)	<0.001	452 (62.3)
Female, n (%)	61 (59.2)	419 (66.8)	0.132	476 (65.7)
Age at diagnosis, median (range), years	58.9 (22-87)	66.3 (22-93)	<0.001	65.5 (22-93)
>65 years, n (%)	34 (33.0)	340 (54.2)	<0.001	372 (51.3)
Time from diagnosis to enrollment, median (range), years	2.3 (0-18)	3.1 (0-32)	0.998	3.0 (0-32)
Disease duration, median (range), years	6.7 (4-23)	7.8 (4-36)	0.666	7.7 (4-36)
History of TEs	12 (11.7)	171 (27.3)	0.001	183 (25.2)
Duration of enrollment, median (range), months	53.9 (44-68)	57.4 (45-70)	<0.001	56.7 (44-70)
Disease burden at enrollment				
MPN-SAF TSS, mean (SD)	14.8 (14.4)	16.3 (15.1)	0.4711	16.1 (15.0)
MPN-SAF TSS >25, n (%)	12 (11.7)	97 (15.5)	0.3134	109 (14.9)
Splenomegaly, n/N (%)†	6/78 (7.7)	37/487 (7.6)	0.3443	43/565 (7.6)
WBC >10×10⁹/L, n (%)	6 (5.8)	106 (16.9)	0.0038	112 (15.3)
Platelets >400×10⁹/L, n (%)	55 (53.4)	344 (54.9)	0.7817	399 (54.7)

Significant values (*P*<0.05) are shown in blue. *Five patients with ET reported positive for both *CALR* and *JAK2* mutations. †Thirteen patients (2.7%) with ET and *JAK2* mutations had indeterminate palpable spleen at enrollment. CALR, calreticulin; ET, essential thrombocythemia; JAK, Janus kinase; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score; SD, standard deviation; TE, thromboembolic event; WBC, white blood cell.

Treatment at Enrollment

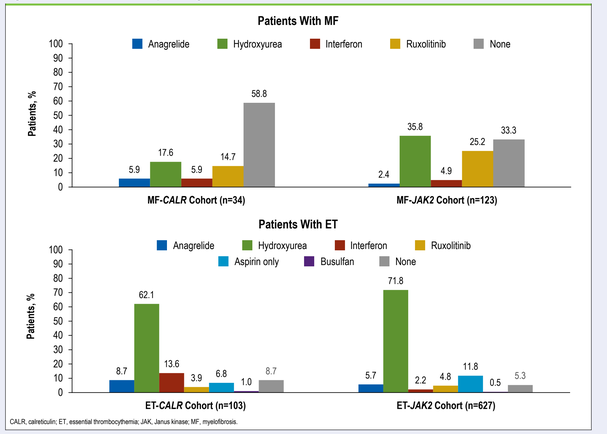
- Most patients in the *CALR* and *JAK2* cohorts (78.8% and 90.1%, respectively; *P*=0.0001) were receiving MPN-directed therapy at enrollment **(Figure 2)**
  - Overall, hydroxyurea was the most common monotherapy received by patients in both the *CALR* and *JAK2* cohorts (51.1% and 65.9%, respectively)
- More than half of the patients (58.8%) in the MF-*CALR* cohort vs 33.3% of patients in the MF-*JAK2* cohort had no record of receiving any MPN-directed therapy at enrollment **(Figure 3)**

Figure 2. MF-/ET-Directed Therapies Received at Enrollment



CALR, calreticulin; ET, essential thrombocythemia; JAK, Janus kinase; MF, myelofibrosis.

Figure 3. MF-/ET-Directed Therapeutic Agents Received at Enrollment



CALR, calreticulin; ET, essential thrombocythemia; JAK, Janus kinase; MF, myelofibrosis.

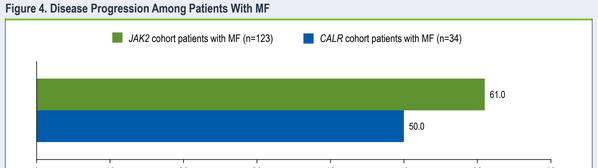
Disease Burden at Enrollment

- For the *CALR* vs *JAK2* cohorts, the percentages of patients with white blood cell count >10×10⁹/L (13.1% vs 19.5%), platelet count >400×10⁹/L (53.3% vs 51.3%), SPM (11.0% vs 12.9%), and Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS) >25 (11.7% vs 15.9%) were similar
- 19.4% and 40.0% of patients in the MF-*CALR* and MF-*JAK2* cohorts, respectively, had SPM
- 53.4% of patients in the ET-*CALR* cohort had platelet count >400×10⁹/L, despite 91.3% receiving ET-directed therapies at enrollment
- Despite high rates of treatment at enrollment, mean MPN-SAF TSS remained unchanged during the study for *CALR*- and *JAK2*-positive patients; mean (standard deviation) values were 15.1 (14.3) and 16.5 (15.2) at baseline, and 15.4 (16.3) and 14.7 (14.7) at 36 months, respectively

Disease Complications and Progression

- Thrombotic and hemorrhagic events during the study period were infrequent in both the *CALR* and *JAK2* cohorts (2.2% vs 4.0% and 0.7% vs 2.5%, respectively)
- MF progression rates were comparable among patients in the MF-*CALR* and MF-*JAK2* cohorts (50.0% vs 61.0%; *P*=0.2501) **(Figure 4)**
- ET to MF progression rates were similar in the ET-*CALR* vs ET-*JAK2* cohorts (1.9% vs 4.6%; *P*=0.2107)
- Leukemic transformation (LT) occurred in a total of 48 of 881 patients (5.4%)
  - Among the MF-*CALR* and MF-*JAK2* cohorts, LT occurred in no patients vs 7 patients (5.7%), respectively
  - Among the ET-*CALR* and ET-*JAK2* cohorts, LT occurred in 6 patients (5.8%) vs 36 patients (5.7%), respectively
- Deaths due to disease progression occurred in 7 patients (5.7%) in the MF-*JAK2* cohort and 11 patients (1.8%) in the ET-*JAK2* cohort; no patients with *CALR* mutations died due to disease progression during the study period

Figure 4. Disease Progression Among Patients With MF



CALR, calreticulin; JAK, Janus kinase; MF, myelofibrosis.

Conclusions

- **This analysis compares the 881 patients with reported *CALR* and/or *JAK2* mutations enrolled in MOST**
- **Symptom burden was similar among patients with *CALR* and *JAK2* mutations, and between patients with MF-*CALR* vs MF-*JAK2*, and ET-*CALR* vs ET-*JAK2* mutations**
- **Despite almost 80% of patients with *CALR* mutations receiving MPN-directed therapy, blood counts were elevated at enrollment and symptoms were unchanged during the study**
- **Half of patients with MF-*CALR* mutations experienced disease progression during the study and nearly 60% were not receiving MF-directed therapy at enrollment, suggesting an unmet need in this patient population**
- **This analysis is limited by a lack of reported mutation status in many patients enrolled in MOST**
- **Additional analyses, including use of biospecimens to determine driver mutation status, may provide insight into optimal management of patients with *CALR* mutations**

Disclosures

Oh: Consulting fees – *AbbVie, Bristol Myers Squibb, Cogent Biosciences, Constellation Pharmaceuticals/MorphoSys, CTI BioPharma, Geron, Incyte Corporation, Morphic Therapeutic, Protagonist Therapeutics, Sierra Oncology/GlaxoSmithKline.*

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