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ORAL ABSTRACTS

634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL AND EPIDEMIOLOGICAL

A Phase 2 Study of Fedratinib in Patients with MDS/MPN and Chronic Neutrophilic Leukemia

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Introduction

MDS/MPNs are clinically and molecularly complex diseases that exhibit proliferative symptoms and aggressive clinical courses. Evaluation of mutational patterns and gene expression profiles suggest these diseases should be viewed as a spectrum rather than distinct disease entities. Treatment options are limited and poorly defined as patients (pts) are often excluded from clinical trials.

The JAK1/JAK2 inhibitor, ruxolitinib, has shown clinical benefit in pts with MDS/MPN and pts harboring *CSF3R* mutations. The experience of JAK2 inhibitors in myelofibrosis (MF) has shown that non-JAK2 kinase targets of JAK inhibitors may result in unique profiles of clinical benefit.

Fedratinib is a JAK2 inhibitor approved for higher-risk MF. Compared to ruxolitinib, it has a broader kinase inhibition profile which may convey enhanced efficacy in high-risk, molecularly complex disease. Fedratinib potently inhibits FLT3 and BRD4 and potently suppresses c-Myc expression which may have biologic relevance in MDS/MPN.

Study Design

This is a phase 2, multi-institutional, investigator-initiated clinical trial (NCT05177211) assessing the efficacy of fedratinib in pts with atypical chronic myeloid leukemia (aCML), chronic neutrophilic leukemia (CNL), MDS/MPN-unclassifiable (MDS/MPN-U), and MDS/MPN-ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) per 2016 WHO classification.

Inclusion criteria included splenomegaly ($\geq$ 5 cm below left costal margin or $\geq$ 450 cc) and/or significant disease-related symptoms (MPN TSS $\geq$ 10). Pts with a platelet count $< 35 \times 10^9$/L or peripheral/marrow blasts $> 10\%$ were excluded. There was no exclusion based on prior treatment.

The primary endpoint of this ongoing study is overall response rate defined as complete or partial response or clinical benefit at 24 weeks per proposed MDS/MPN IWG response criteria. C-Myc (a potential biomarker for response) was stained in the bone marrow collected at baseline and week 24. C-Myc expression product was scored by multiplying % positive cells by intensity (0 = none, 1 = mild, 2 = moderate, 3 = marked).

Fedratinib was given at a dose of 400 mg daily. Planned enrollment is 25 pts with an interim analysis completed after 9 pts are evaluable for efficacy.

Results

At time of data cut-off, 10 pts have been enrolled with a median follow-up of 5 months. Eight pts remain on treatment. Baseline demographics, genetic makeup, and treatment history are shown in table 1. Enrolled pts include 1 with aCML, 4 with CNL, 4 with MDS/MPN-RS-T, and 1 with MDS/MPN-U. Three or more mutations were present in 7 (70%) pts.

Three of 5 (60%) evaluable pts responded at week 24. This included 3 (75%) symptom responses and 1 (20%) spleen response (1 pt with both). Six pts have completed 12 weeks of treatment with 1 spleen response and 2 symptoms responses (Figure 1). Among 6 pts with baseline splenomegaly who received 12 weeks of treatment, spleen volume decreased in 5 (83%) by an

average of -23% (+5% to -71%). Among 5 pts with significant baseline symptom burden who received 12 weeks of treatment, 4 (80%) experienced an improvement in symptom burden by an average of -43% (range 0% to -76%). One pt who discontinued treatment prior to week 8 for reasons unrelated to disease or treatment was considered a spleen and symptom non-responder despite experiencing a 48% symptom improvement at week 4.

At baseline, C-Myc expression was demonstrated by IHC staining in a median of 10% of cells (5-15%). Average baseline c-Myc expression product (% positive cells * staining intensity) was 26.5 (range 10-37.5). In pts with paired samples (n = 4), c-Myc expression product decreased in all cases by an average of 51% (25%-85%), p = 0.02.

Ten pts were evaluable for safety. The most common AEs occurring in >2 pts were anemia, platelet count decrease, diarrhea, nausea, muscle cramp, and constipation. Grade ≥3 AEs were anemia (40%) and neutropenia (10%). There were no grade ≥ 3 non-hematologic AEs. Two pts discontinued study treatment: one due to disease progression after initial response and one due to pt decision unrelated to disease or treatment.

Conclusion:

Fedratinib demonstrates promising clinical efficacy in MDS/MPN and CNL pts with proliferative features. The safety profile is consistent with prior experience. Fedratinib's unique kinase inhibition profile may provide a mechanism for enhanced effectiveness in this pt population. Updated results will be presented at the meeting.

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Table 1. Baseline characteristics of first 10 patients enrolled

Characteristic	Enrolled patients (n = 10)
Age, years	71.5 (39.9-84.7)
Time from diagnosis, mo	12.9
Sex	
Female	3 (30)
Male	7 (70)
Diagnosis	
CNL	4 (40)
aCML	1 (10)
MDS/MPN-U	1 (10)
MDS/MPN-RS-T	4 (40)
Prior Therapy	
Hydroxyurea	4 (40)
Ruxolitinib	2 (20)
Lenalidomide	1 (10)
Luspatercept	1 (10)
Hypomethylating agent	1 (10)
Splenomegaly	9 (90)
Spleen volume by US, cc	1648 (308-4478)
MPN-SAF TSS	34 (1-53)
WBC, x 10^9/L	21.89 (2.15-139.69)
ANC, x 10^9/L	17.65 (1.12-125.72)
Hemoglobin, g/dL	9.2 (7.7-12.1)
Platelets x 10^9/L	289.5 (79-664)
Mutations	
CSF3R T618I	4 (40)
JAK2 V617F	4 (40)
SETBP1	4 (40)
ASXL1	6 (60)
SRSF2	4 (40)
SF3B1	3 (30)
RAS-pathway	3 (30)
U2AF1	2 (20)
≥ 3 mutations	7 (70)
Abnormal cytogenetics	3 (30)

Note: Data presented as median (range) or no (%)

Figure 1. Change in total symptom score and spleen volume from baseline to 12 weeks in patients who have completed 12 weeks of therapy.

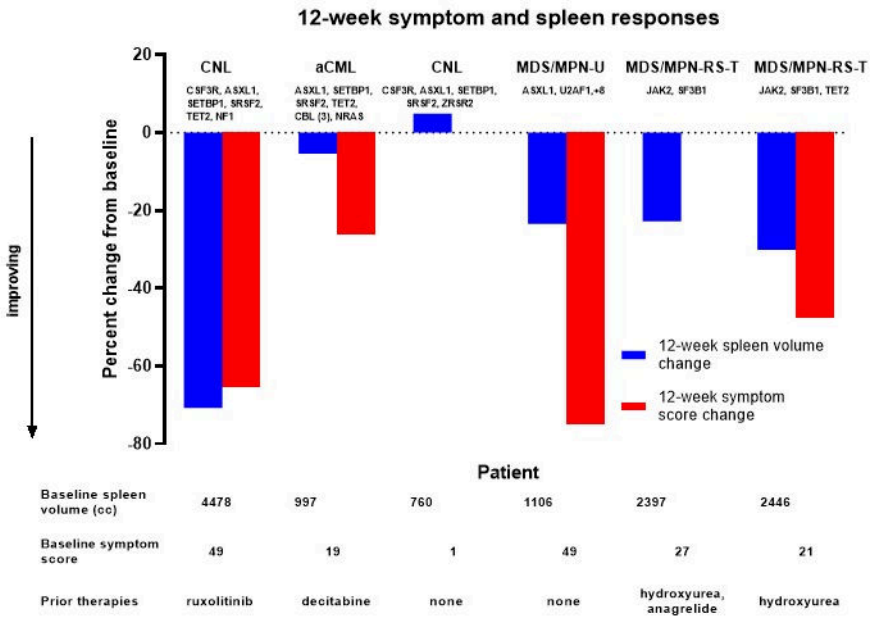

Figure 1