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S212 A RANDOMIZED DOUBLE-BLIND PHASE 3 STUDY OF JAKTINIB VERSUS HYDROXYUREA IN PATIENTS WITH INTERMEDIATE-2 OR HIGH RISK MYELOFIBROSIS

Topic: Clinical advances in myelofibrosis

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Background:

Ruxolitinib and hydroxyurea are recommended by Chinese myelofibrosis guideline for splenomegaly. There is an unmet need for new treatments. Jaktinib, a novel JAK and AVCR1 inhibitor, showed promising activity on splenomegaly, anemia, and myelofibrosis symptoms in a phase 2 study (NCT03886415).

Aims:

This randomized double-blind phase 3 study was aimed to assess the efficacy and safety of jaktinib compared to hydroxyurea in patients with intermediate-2 or high risk myelofibrosis.

Methods:

Patients aged ≥18 with primary, post-polycythemia vera or post-essential thrombocythemia myelofibrosis, dynamic international prognostic scoring system (DIPSS) Int-2 or high risk, and no prior or ≤10 days' treatment with a JAK inhibitor were enrolled and randomly assigned (2:1) to receive jaktinib 100 mg bid plus hydroxyurea placebo or hydroxyurea 0.5 g bid plus jaktinib placebo, stratified by DIPSS risk status (Int-2 or high risk). One interim analysis was pre-specified to be conducted when the 70 patients completed the 24-week treatment or met the criteria for the treatment termination before week 24. The primary endpoint was the proportion of patients with a spleen volume reduction of ≥35% from baseline (SVR35) at week 24, measured by MRI/CT images and assessed by Independent Review Committee. Secondary endpoints included the best spleen response rate (defined as achieving SVR35 at any time), the proportion of patients with a ≥50% reduction in Total Symptom Score (TSS50), improvement of anemia, safety, etc.

Results:

This interim analysis (data cut-off: April 8, 2022) included 47 patients receiving jaktinib and 23 receiving hydroxyurea. 66.0% (jaktinib) and 69.6% (hydroxyurea) had a baseline hemoglobin <100 g/L. 59.6% (jaktinib) and 69.6% (hydroxyurea) were JAK2V617F positive. Patient baseline characteristics were well balanced between the two arms (Table 1).

The SVR35 rates at week 24 were 72.3% for jaktinib *vs.* 17.4% for hydroxyurea ($p \leq 0.0001$). Jaktinib showed a consistent spleen response benefit over hydroxyurea across all subgroups analyzed (Figure 1). The best spleen response rates were 80.9% of jaktinib-treat patients *vs.* 26.1% of hydroxyurea-treated patients ($p \leq 0.0001$). The median maximum percentage change from baseline in spleen volume were -46.59% *vs.* -18.50%.

The TSS50 rates at week 24 were 63.8% for jaktinib *vs.* 43.5% for hydroxyurea ($p=0.1163$). 5 of 7 jaktinib-treated and two of 5 hydroxyurea-treated patients who required red blood cell transfusion at baseline achieved a ≥50% decrease in red blood cell transfusion by week 24. One of four jaktinib-treated and 0 of three hydroxyurea-treated patients who were transfusion-dependent at baseline changed to transfusion-independent. In transfusion-independent patients with baseline hemoglobin ≤100 g/L, 39.3% for jaktinib and 15.4% for hydroxyurea had a ≥20 g/L hemoglobin increase.

The most common grade ≥3 hematological treatment-emergent adverse events (TEAEs) were anemia (25.5% [jaktinib] *vs.* 43.5% [hydroxyurea]), thrombocytopenia (17.0% *vs.* 39.1%), leukopenia (2.1% *vs.* 21.7%), neutropenia (2.1% *vs.* 21.7%) and decreased lymphocyte count (2.1% *vs.* 13.0%). Most common non-hematological TEAEs were upper respiratory tract infection (21.3% *vs.* 21.7%), elevated bilirubin (12.8% *vs.* 26.1%), fever (12.8% *vs.* 21.7%) and diarrhea (10.6% *vs.* 21.7%), predominantly of grade 1 or 2. TEAEs leading to treatment discontinuation occurred in 8.5% of jaktinib and 17.4% of hydroxyurea.

Table 1. Demographics and Baseline Characteristics

Variables	Jaktinib (n=47)	Hydroxyurea (n=23)
Age (year)	63.0 (46, 76)	62.0 (42, 74)
Gender		
Male	18 (38.3%)	9 (39.1%)
Female	29 (61.7%)	14 (60.9%)
Myelofibrosis subtype		
PMF	33 (70.2%)	17 (73.9%)
Post–PV MF	6 (12.8%)	3 (13.0%)
Post–ET MF	8 (17.0%)	3 (13.0%)
Myelofibrosis grading		
MF-0	0	2 (8.7%)
MF-1	1 (2.1%)	0
MF-2	18 (38.3%)	11 (47.8%)
MF-3	28 (59.6%)	10 (43.5%)
DIPSS risk status		
Int-2	42 (89.4%)	20 (87.0%)
High	5 (10.6%)	3 (13.0%)
Spleen volume per IRC (cm^3)	1389.7 (433.6, 5070.5)	1249.1 (579.6, 3011.4)
MPN-SAF TSS	24.0 (0, 63)	20.0 (6, 66)
JAK2 V617F–positive	28 (59.6%)	16 (69.6%)
White blood cell count (10^9/L)	13.2 (1.5, 74.2)	20.3 (2.2, 101.9)
Hemoglobin (g/dL)	92.0 (50.0, 166.0)	91.0 (46.0, 181.0)
Platelet count (10^9/L)	239.0 (78.0, 1601.0)	293.0 (102.0, 2056.0)

Note: Data are median (range) or n (%).
Abbreviations: DIPSS, Dynamic International Prognostic Scoring System; PMF, primary myelofibrosis; Post–ET MF: post-essential thrombocythemia myelofibrosis; Post–PV MF: post-polycythemia vera myelofibrosis; TSS, total symptom score.

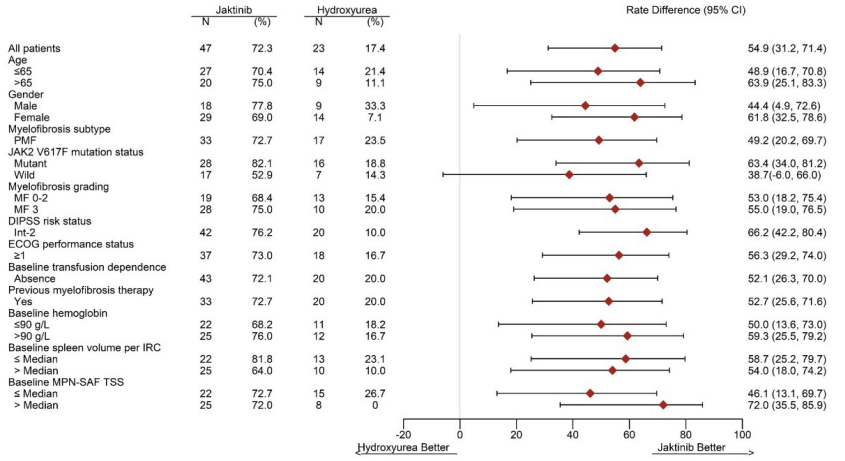

Figure 1. Subgroup Analysis of SVR35 Rates at Week 24

Forest-plots for SVR35 rates at Week 24 by subgroup were analyzed for the baseline demographic and disease characteristics using the study interim datasets. Any subgroup with less than 21 patients was not analyzed and shown because the estimation was not meaningful.

Summary/Conclusion:

Jaktinib demonstrated significant clinical benefits over hydroxyurea in myelofibrosis patients for spleen response with improved symptom response and less cytopenias. Jaktinib may be a new treatment option for myelofibrosis patients, especially for those with anemia.