MPN-052

Ruxolitinib Treatment in Patients With Polycythemia Vera Reduces *JAK2* Allele Burden and Improves Hematocrit Control and Symptom Burden

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Introduction

- Polycythemia vera (PV) is a myeloproliferative neoplasm characterized by elevated hematocrit, excessive red blood cell production, and presence of Janus kinase 2 (*JAK2*) activating mutations[1,2]
- Patients with PV often experience burdensome symptoms,[3,4] most commonly fatigue, concentration problems, itching, night sweats, and splenomegaly-related symptoms (eg, early satiety, abdominal discomfort)[5]
- Ruxolitinib is a potent and selective JAK1/JAK2 inhibitor approved for treatment of PV in adults who have had an inadequate response to or are intolerant of hydroxyurea[6]
- In the RESPONSE trials, ruxolitinib was superior to best available therapy (BAT) at providing hematocrit control and complete hematologic response, as well as in improving PV-related symptoms[7,8]

Objective

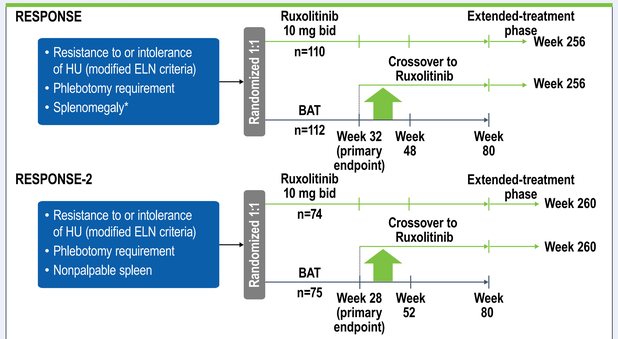
- To assess the efficacy of ruxolitinib in adults with PV who were resistant to or intolerant of hydroxyurea in a pooled analysis of RESPONSE and RESPONSE-2 data

Methods

Study Design and Patients

- RESPONSE and RESPONSE-2 were randomized, controlled, open-label, multicenter phase 3 trials
- The trials had similar design with the main difference being that in RESPONSE, patients were required to have splenomegaly to be enrolled, whereas patients enrolled in RESPONSE-2 did not have splenomegaly (**Figure 1**)

Figure 1. Study Design



BAT, best available therapy; bid, twice daily; CT, computed tomography; ELN, European LeukemiaNet; HU, hydroxyurea; MRI, magnetic resonance imaging.
* Palpable splenomegaly confirmed by MRI/CT to be ≥450 cm^3 in volume (ie, 2 to 3 times the upper limit of normal); patients with body habitus precluding spleen palpation must have had a spleen volume ≥450 cm^3 by MRI/CT.

Assessments in This Pooled Analysis

- Hematocrit control was defined as hematocrit <45% that was maintained since Week 16 with ≤1 phlebotomy occurring post-randomization and before Week 4
- Symptom control using the Myeloproliferative Neoplasm Symptom Assessment Form total symptom score (MPN-SAF TSS)[5] was assessed at the common time points of Weeks 16 and 30

Statistical Analyses

- Response rate 95% CIs were calculated using the Clopper-Pearson exact method
- Odds ratio (OR) and 95% CI for comparisons of the percentage of patients achieving ≥50% reduction from baseline in MPN-SAF TSS were calculated by the Mantel-Haenszel method

Results

Patients

Table 1. Patient Demographics and Baseline Characteristics

Variable	Ruxolitinib (n=184)	Best Available Therapy (n=187)	Total (N=371)
Age, median (range), y	62.0 (26–90)	62.0 (33–87)	62.0 (26–90)
≥60 y, n (%)	76 (41.3)	69 (36.9)	145 (39.1)
<60 y, n (%)	108 (58.7)	118 (63.1)	226 (60.9)
Male, n (%)	105 (57.1)	127 (67.9)	232 (62.5)
Race, n (%)			
White	165 (89.7)	162 (86.6)	327 (88.1)
Black	1 (0.5)	0	1 (0.3)
Asian	15 (8.2)	21 (11.2)	36 (9.7)
Other	3 (1.6)	4 (2.1)	7 (1.9)
MPN-SAF TSS, mean (SD)	10.3 (15.1)	8.7 (12.7)	–
Hct, mean (SD), g/L*	43.3 (2.0)	43.4 (2.0)	43.3 (2.0)
*JAK2*V617F allele burden, mean (SD), %†	66.1 (25.8)	69.8 (25.5)	67.9 (25.7)

Hct, hematocrit; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score.
* Ruxolitinib, n=183; best available therapy, n=186; total, n=369. † Ruxolitinib, n=181; best available therapy, n=180; total, n=361.

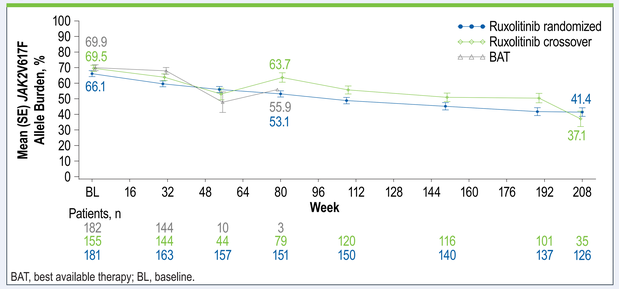
JAK2V617F Allele Burden

- Partial molecular response (PMR; ≥50% reduction in allele burden) was achieved by 68 patients (38.9%) in the ruxolitinib randomized group and 53 (35.3%) in the crossover group
  - Median (range) time to PMR was 112 (28–261) weeks in the ruxolitinib randomized group and 130 (24–234) weeks in the crossover group
- Among patients randomized to ruxolitinib, the mean *JAK2*V617F allele burden decreased from 66.1% to 41.4% at 4 years (**Figure 2**)
  - The best change from baseline through Week 208 was a decrease of ≥25% in 57.1% and ≥50% decrease in 38.9% of patients randomized to ruxolitinib (**Figure 3**)
- Among patients in the ruxolitinib crossover group, the mean *JAK2*V617F allele burden decreased from 69.5% to 37.1% at 4 years, with a best decrease of ≥25% and ≥50% in 48.7% and 35.3% of patients, respectively
- 38 patients (20.7%) in the ruxolitinib randomized group, 14 (9.0%) in the crossover group, and 7 (3.7%) in the BAT group achieved a best *JAK2*V617F allele burden <10%; 4 (2.2%), 0, and 0, respectively, achieved a best *JAK2*V617F allele burden <1%
- Analysis of the BAT group is limited by small patient numbers after Week 32, as most patients crossed over to ruxolitinib, with a best decrease of ≥25% and ≥50% in 7.2% and 2.6% of patients, respectively

Hematocrit Control

- Hematocrit control at Week 28 was higher with ruxolitinib (62.0%; 95% CI: 54.5%, 69.0%) than with BAT (18.2%; 95% CI: 12.9%, 24.5%; *P*<0.0001; **Figure 4**)
- Durable hematocrit control was maintained to Week 80 by 47.3% (95% CI: 39.9%, 54.8%) of patients randomized to ruxolitinib (nearly all patients in the BAT arm crossed over to ruxolitinib)

Figure 2. *JAK2*V617F Allele Burden



BAT, best available therapy; BL, baseline.

Figure 3. Best Change in *JAK2*V617F Allele Burden From Baseline

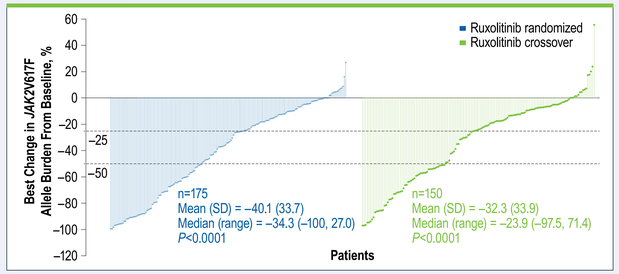
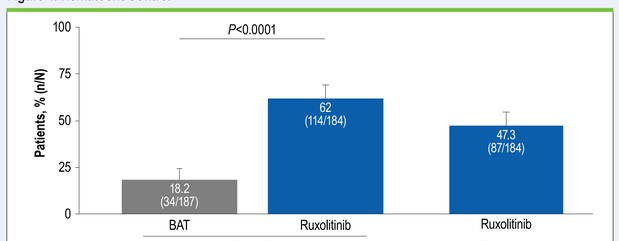


Figure 4. Hematocrit Control

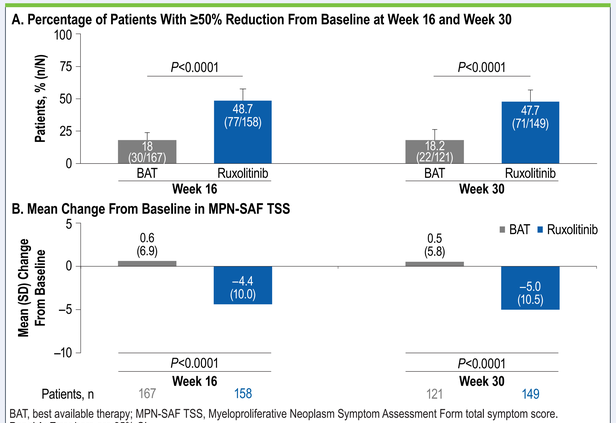


BAT, best available therapy.
Error bars are 95% CI.

Symptom Response

- The percentage of patients achieving ≥50% reduction from baseline in MPN-SAF TSS at Weeks 16 and 30 was higher for ruxolitinib vs BAT (**Figure 5A**)
- Mean change from baseline in MPN-SAF TSS was greater for ruxolitinib vs BAT (**Figure 5B**)

Figure 5. Symptom Response



BAT, best available therapy; MPN-SAF TSS, Myeloproliferative Neoplasm Symptom Assessment Form total symptom score.
Panel A: Error bars are 95% CI.
Panel B: Week 30 includes Week 32 of RESPONSE and Week 28 of RESPONSE-2.

Conclusions

- **Reductions in *JAK2*V617F allele burden were consistently observed through Week 208 in patients treated with ruxolitinib, including those who crossed over from BAT, comparable with results from the MAJIC-PV study[9]**
- **39% of patients in the ruxolitinib randomized group achieved PMR (≥50% reduction in *JAK2*V617F allele burden)**
- **Patients with PV treated with ruxolitinib achieved durable hematocrit control through Week 80 and had better symptom control through Week 30 compared with BAT**
- **These results provide further evidence of the benefit of ruxolitinib in patients with PV with or without splenomegaly**

Disclosures

CNH received honoraria from BMS, Novartis, CTI, GSK, AOP, Galecto, AbbVie, and MorphoSys; served on the speakers bureau for BMS, Novartis, CTI, GSK, AOP, Galecto, AbbVie, and MorphoSys; and received research funding from Novartis. J-JK acted as a consultant and received honoraria from Novartis, BMS, GSK, AOP Health, AbbVie, Incyte, and PharmaEssentia. FPal acted as a consultant and received honoraria from Novartis, BMS Celgene, GSK, Amgen, AbbVie, Karyopharm, AOP, Sierra Oncology, and CTI. JEH-M and EB are employees and shareholders of Incyte. FPas received honoraria from AbbVie and Janssen.

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