634.MYELOPROLIFERATIVE SYNDROMES: CLINICAL | NOVEMBER 5, 2020

The Final Analysis of Expand: A Phase 1b, Open-Label, Dose-Finding Study of Ruxolitinib (RUX) in Patients (pts) with Myelofibrosis (MF) and Low Platelet (PLT) Count (50 × 10^9/L to < 100 × 10^9/L) at Baseline

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BACKGROUND

RUX, a potent oral JAK1/JAK2 inhibitor, has shown superiority over standard therapies in MF. RUX was approved for the treatment of MF on the basis of the phase 3 COMFORT trials, in which RUX led to sustained improvements in splenomegaly and symptom burden as well as longer survival compared with placebo (COMFORT-I) and best available therapy (COMFORT-II).

The starting dose (prescribing information) is based on PLT count: > 200 × 10^9/L, 20 mg bid; 100-200 × 10^9/L, 15 mg bid. Due to limited data available at the time, the recommended starting dose in pts with PLT counts of 50 to < 100 × 10^9/L was determined to be 5 mg bid. However, findings from COMFORT-I and Study 258 (phase 2 study of RUX in pts with MF with low PLT count) demonstrated that final titrated doses of ≥ 10 mg bid were safe and resulted in larger improvements in spleen volume and MF-related symptoms compared with titrated doses of ≤ 5 mg bid.

The EXPAND study established a maximum safe starting dose (MSSD) in pts with low baseline PLT count (50 to < 100 × 10^9/L) and evaluated the safety and tolerability of RUX in this population. The 24-wk (Vannucchi AM, et al. ASH 2015 #2817) and 48-wk (Vannucchi AM, et al. *Haematologica*. 2019) analyses determined the MSSD to be 10 mg bid for pts with baseline PLT count of 50 to < 100 × 10^9/L. We present the final results from the study, confirming 10 mg bid as a safe starting dose for pts with low PLT count.

METHODS

EXPAND is a phase 1b, dose-finding study (NCT01317875) in pts with MF and baseline PLT count of 50 to < 100 × 10^9/L (Stratum [S] 1, 75 to < 100 × 10^9/L; S2, 50 to < 75 × 10^9/L). The study had a core period (up to wk 24) consisting of 2 phases (dose escalation and safety expansion) followed by an extension period (up to 3 years total). The primary objective was determination of the MSSD for both strata; safety and efficacy were secondary objectives.

RESULTS

Of 69 enrolled pts, 38 received RUX at the MSSD of 10 mg bid (S1, n = 20; S2, n = 18) and are the focus of this analysis. Baseline characteristics were indicative of advanced disease in both strata. Overall, 50% of pts in S1 and 83% of pts in S2 discontinued study treatment. Primary reasons for discontinuation were progressive disease (15%), adverse events (AEs; 10%), and other (10%) in S1 and AEs (33%), death (17%), and physician decision (17%) in S2.

Median (range) duration of exposure was 155 (4-210) wk in S1 and 83 (4-161) wk in S2; 17/20 pts (85%) in S1 and 11/18 (61%) in S2 received RUX for ≥ 48 wk. AEs were consistent with the known safety profile of RUX (*Table*). The most common AEs were thrombocytopenia (S1, 50%; S2, 78%) and anemia (S1, 55%; S2, 44%); other common (> 30% all grade) AEs included diarrhea, ecchymosis, PLT decrease, and pyrexia (each 30%) in S1, and cough (33%) in S2. A total of 85% of pts in S1 and 89% in S2 had grade ≥ 3 AEs; thrombocytopenia (S1, 40%; S2, 78%) and anemia (25%; 17%) were most common.

Overall, 20% and 50% of pts in S1 and S2 had AEs leading to study drug discontinuation, most commonly thrombocytopenia (S1, 5%; S2, 20%); other AEs led to discontinuation in 1 pt each. On-treatment deaths included 1 cardiac arrest (S1), 1 AML (S1), 1 multiorgan failure (S2), and 1 sepsis (S2). The death due to cardiac arrest was assessed as related to study drug; the others were unrelated.

Overall, 40% (6/15) and 38% (3/8) of evaluable pts in S1 and S2 achieved a spleen response (≥ 50% reduction in spleen length from baseline) at wk 24; 33% (5/15) and 30% (3/10) of evaluable pts in S1

and S2 achieved a spleen response at wk 48; 55% (11/20) and 67% (12/18) of pts achieved a response at any time. A symptom response (≥ 50% reduction in MF-SAF TSS from baseline to wk 24) was achieved by 31% (4/13) of evaluable pts in S1 and 40% (4/10) in S2; at wk 24, there was a mean (SD) decrease (improvement) in total daily score from baseline by 7.7 (9.7) in S1 and 3.9 (11.4) in S2.

There was no significant difference in the PK of RUX among pts with low PLT counts in this study compared with that in pts with PLT ≥ 100 × 10^9/L.

CONCLUSIONS

A starting dose of RUX 10 mg bid was manageable in this previously unstudied MF pt population with low PLT counts (50 to < 75 × 10^9/L and 75 to < 100 × 10^9/L). AEs were consistent with the known safety profile of RUX, with no new or unexpected adverse findings. This was supported by the PK/PD results as well. RUX treatment at a starting dose of 10 mg bid provided the benefit of spleen length reductions and clinical symptom improvements. EXPAND results confirm that a starting dose of RUX 10 mg bid is suitable for pts with MF and low PLT counts.

Table. Most Frequent AEs (≥ 20%) Regardless of Study Drug Relationship in Patients Who Received the MSSD (10 mg bid)

	Stratum 1 (n = 20)		Stratum 2 (n = 18)	
Patients, n (%)	All Grades	Grade ≥ 3	All Grades	Grade ≥ 3
Any AE	20 (100.0)	17 (85.0)	18 (100)	16 (88.9)
Thrombocytopenia	10 (50.0)	8 (40.0)	14 (77.8)	14 (77.8)
Anemia	11 (55.0)	5 (25.0)	8 (44.4)	3 (16.7)
Diarrhea	6 (30.0)	1 (5.0)	5 (27.8)	0
Ecchymosis	6 (30.0)	0	2 (11.1)	0
Platelet count decreased	6 (30.0)	5 (25.0)	1 (5.6)	1 (5.6)
Pyrexia	6 (30.0)	0	4 (22.2)	1 (5.6)
Epistaxis	5 (25.0)	0	0	0
Abdominal pain	5 (25.0)	0	4 (22.2)	0
Nasopharyngitis	4 (20.0)	0	5 (27.8)	0
Back pain	4 (20.0)	0	3 (16.7)	0
Blood bilirubin increased	4 (20.0)	2 (10.0)	1 (5.6)	0
Fatigue	4 (20.0)	4 (20.0)	3 (16.7)	0
Hemoglobin decreased	4 (20.0)	0	0	0
White blood cell count decreased	5 (25.0)	2 (10.0)	1 (5.6)	0
Cough	2 (10.0)	0	6 (33.3)	0
Asthenia	3 (15.0)	1 (5.0)	5 (27.8)	2 (11.1)
Hypocalcemia	2 (10.0)	0	5 (27.8)	0
Headache	1 (5.0)	0	4 (22.2)	0
Hypertension	1 (5.0)	1 (5.0)	4 (22.2)	0
Nausea	1 (5.0)	0	4 (22.2)	0

Disclosures

Kiladjian:*AbbVie:* Membership on an entity's Board of Directors or advisory committees; *AOP Orphan:* Membership on an entity's Board of Directors or advisory committees; *Bristol Myers Squibb:* Membership on an entity's Board of Directors or advisory committees; *Novartis:* Membership on an

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OffLabel Disclosure:

sLabel dose in this patient population is 5 mg bid starting dose. EXPAND presents data for a 10 mg bid starting dose.