FIRST-IN-CLASS JAK/ROCK INHIBITOR ROVADICITINIB IN MYELOPROLIFERATIVE NEOPLASMS: A SINGLE ARM, MULTICENTER, OPEN-LABEL, PHASE I /IB STUDY

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INTRODUCTION

- JAK-STAT pathway is a central pathogenic component in myelofibrosis (MF). [1] Ruxolitinib is the only one approved JAK inhibitor (JAKi) to treat MF in China.[2,3] Therefore, there is a unmet medical needs for patients with MF in China.
- Rovadicitinib (TQ05105) is a first-in-class, oral, small molecule JAK/ROCK inhibitor which inhibits cell proliferation, induces cell apoptosis and decreases inflammatory cytokines by affecting the JAK-STAT signaling pathway in preclinical studies. [4]
- Meanwhile, Rovadicitinib has shown that is a therapeutically promising novel strategy with a favorable safety profile for glucocorticoid-refractory or -dependent cGVHD. [5,6]
- Here we report the primary results of the phaseI/Ib study of rovadicitinib in Myeloproliferative Neoplasms (MPN) patients (NCT04339400).

STUDY DESIGN

Inclusion criteria

- Aged ≥18 years;
- MF: PMF、Post-PV MF、 Post-ET MF, DIPSS Int-1 or higher risk of MF;
- Navie or resistant / intolerant to hydroxyurea and/or interferon therapy of PV or ET;
- Patients with MF must have palpable splenomegaly (≥5 cm below the left costal margin), Platelet count ≥100 x 10^9/L, Hemoglobin > 80 g/L;
- ……

Phase I Dose-escalation*

* a modified "3 + 3" design was used in phase I

N=1 5 mg qd → N=3+3 5 mg bid → N=3+3 10 mg bid → N=3+3 15 mg bid → N=3+3 20 mg bid

qd, once a day; bid, twice a day.

Phase Ib Dose-expansion

Rovadicitinib RP2D

(4 weeks/cycle)

Primary Endpoint

- Phase I: the maximum tolerated dose (MTD) /recommended phase 2 dose (RP2D)
- Phase Ib: the proportion of patients whose reduction of at least 35% in spleen volume (SVR35) at week 24 compared with baseline

Secondary Endpoint

- The proportion of patients whose Total Symptom Score decreased ≥ 50% (TSS50) at week 24
- The best spleen response rate and the symptom response
- Safety

RESULTS

Between November 20, 2018, and September 22, 2022, 102 patients were assessed for eligibility across two cohorts, 79 were enrolled and treated with rovadicitinib including, 15 patients in phase I and 64 in phase Ib.

As of March 17, 2023 data cut, 43 patients were still ongoing treatment.

Table 1. Patient characteristics

Characteristics	Rovadicitinib (N=79)
Age, median (range), years	59 (23, 81)
Male, n (%)	50 (63.29)
Myelofibrosis subtype	
PMF	55 (69.62)
Post-PV MF	5 (6.33)
Post-ET MF	4 (5.06)
PV	5 (6.33)
ET	10 (12.66)
DIPSS risk status (N=64)	
Int-1	46 (71.88)
Int-2	17 (26.56)
High	1 (1.56)
Myelofibrosis grading	
MF-0	7 (8.97)
MF-1	13 (16.67)
MF-2	26 (33.33)
MF-3	32 (41.03)
missing	1 (1.27)
Gene mutation status	
JAK2 V617F	60 (75.95)
CALR	10 (12.66)
MPL	4 (5.06)
missing	5 (6.33)
Spleen volume (cm^3)	1907.58 (247.12, 6156.13)
MPN-SAF TSS	16 (0, 53)
White blood cell count (10^9/L)	13.05 (4.06, 66.19)
Hemoglobin (g/L)	120 (76, 211)
Platelet count (10^9/L)	357 (113, 1108)
Previous treatments	
JAK inhibitor	9 (11.54)
Hydroxyurea	42 (53.16)
Interferon	17 (21.52)

PMF, primary myelofibrosis; PV, polycythemia vera; ET, essential thrombocythemia; DIPSS, dynamic international prognostic scoring system; TSS, total symptom score.

RP2D

- The dose-limiting toxicities (DLTs) were experienced by two patients at 20 mg bid (one patient experienced grade 3 platelet count decrease with bleeding, one patient experienced grade 4 platelet count decrease).
- 0/3 patient achieved SVR35 at 5mg bid dose level, 1/4 patient achieved SVR35 at 10mg bid, and 3/3 patients achieved SVR35 at 15mg bid.
- Rovadicitinib plasma peak concentrations and areas under the concentration versus time curve (AUC) increased proportionally with dose. Terminal half-life was 1~2 h. No accumulation trend was noted.
- Given the safety profile, pharmacokinetics and shrinking spleen, 15 mg bid was identified as MTD and RP2D.

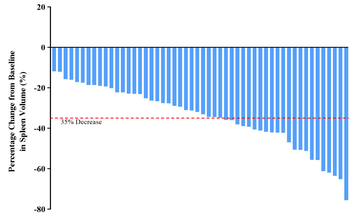

Figure 1. Spleen volume reduction at 24 weeks

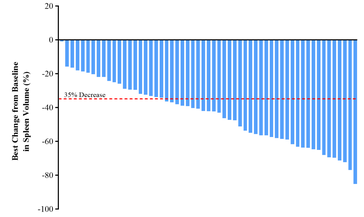

Figure 2. Best Reduction in Spleen Volume at Any Time

Efficacy

- In phase Ib, 58 patients were included spleen volume set, 56 patients were included TSS set.
- The proportion of patients who had SVR35 was 37.93% (22/58) at week 24 and 39.66% (23/58) at week 48, respectively.63.79% (37/58) patients achieved SVR35 during the study period. The mean duration of splenic response was approximately 16 months.
- The proportion of patients who had TSS50 was 71.43% (40/56) at week 24 and 48.21% (27/56) at week 48, respectively.87.5% (49/56) patients achieved TSS50 during the study period.

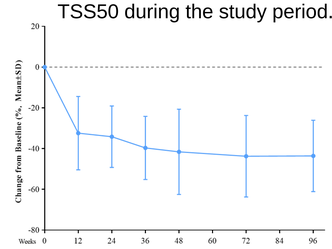

Figure 3. Spleen Volume Mean Percentage Change Over Time

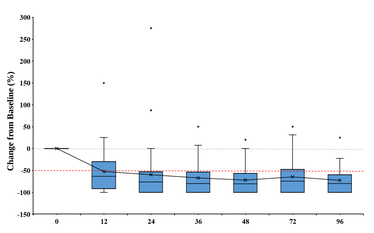

Figure 4. Change in Total Symptom Score Over Time

Table 2. Treatment-emergent adverse events (TEAEs)

	Rovadicitinib (N=79)
Any grade TEAEs, n (%)	**78 (98.73)**
Grade ≥3 TEAE	39 (49.37)
Serious TEAE	29 (36.71)
TEAE leading to dose reduction	27 (34.18)
TEAE leading to dose interruption	25 (31.65)
TEAE leading to treatment discontinuation	12 (15.19)

Table 3. Most commonTEAEs (≥10%)

Most common TEAE (occurring in ≥10%) n (%)		Any Grades	Grade ≥3
Hematologic	Anemia	40 (50.63)	13 (16.46)
	Platelet count decreases	35 (44.30)	14 (17.72)
Nonhematologic	Hyperuricemia	26 (32.91)	2 (2.53)
	Upper respiratory infection	19 (24.05)	1 (1.27)
	AST increased	17 (21.52)	0
	ALT increased	15 (18.99)	0
	Dizziness	15 (18.99)	0
	Blood bilirubin increased	14 (17.72)	0
	Hypertriglyceridemia	13 (16.46)	0
	COVID-19	13 (16.46)	0
	Diarrhea	13 (16.46)	1 (1.27)
	Blood creatinine increased	12 (15.19)	0
	Blood fibrinogen decreased	10 (12.66)	1 (1.27)
	Proteinuria	10 (12.66)	0
	Blood urea increased	9 (11.39)	0
	Headache	9 (11.39)	0
	Blood conjugated bilirubin increased	8 (10.13)	0
	Premature supraventricular contraction	8 (10.13)	0

Safety

- Regardless of rovadicitinib relationship, Anemia, platelet count decreases were most common TEAEs, but mostly low grade.
- There was only one death, due to disease progression and not related to rovadicitinib.

CONCLUSIONS

- **Rovadicitinib (15mg bid) was generally safe, well-tolerated and showed meaningful clinical activity in patients with MF, especially with palpable splenomegaly.**
- **Rovadicitinib may be a new treatment option for myelofibrosis patients.**
- **Furthermore, a randomized double-blind phase II study is ongoing, aiming to assess the efficacy and safety of rovadicitinib compared to hydroxyurea in patients with inte-2 or high risk myelofibrosis in China (NCT05020652).**

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