4567 PRELIMINARY RESULTS OF PATIENTS WITH MYELOFIBROSIS FROM A PHASE I TRIAL OF JAB-8263, A POTENT BET INHIBITOR

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INTRODUCTION

- Bromodomain and extra-terminal (BET) proteins play roles in epigenetic regulation in critical genes involved in inflammation and various oncogenic processes[1].
- JAB-8263 is a highly potent, orally available, small molecule BET inhibitor that is being evaluated as monotherapy in patients with solid tumors and hematological malignancies (NCT04686682).

METHOD

In the dose escalation portion of phase 1/2a trial, patients with intermediate-/high risk MF received JAB-8263 at doses ranging from 0.125 mg once daily (QD) to 0.4 mg QD.

Key inclusion criteria:

- Age ≥18 years
- Confirmed primary MF, post-polycythemia vera MF or post-essential thrombocythemia MF
- ECOG Performance Status ≤ 2
- Spleen volume ≥ 450 cm^3
- Dynamic International Prognostic score (DIPSS) ≥ intermediate-1

Primary Endpoints:

- Determination of maximum tolerated dose (MTD)/ recommended Phase 2 dose (RP2D)of JAB-8263

Key Secondary Endpoints:

- ≥35% reduction from baseline in SVR (SVR35), as measured by MRI or CT, at week 24
- Total Symptom Score (TSS) response, defined as a ≥50% decrease from baseline in TSS (TSS50), as measured by the MFSAF, at week 24

RESULTS

Patient Characteristics

As of Oct 17, 2024, 16 patients with intermediate-/high-risk MF have been enrolled across 4 dose levels of JAB-8263 (Table 1 and Table 2).

As of Oct 17, 2024, 11 patients are on active treatment. The median exposure of JAB-8263 is 7.9 months (Figure 1).

Table 1. Patient Demographics

	0.125mg QD (N=1)	0.20mg QD (N=4)	0.30mg QD (N=6)	0.40mg QD (N=5)	Total (N=16)
Age, median (range), y	56 (56)	61.5 (36-66)	65.5 (46-69)	59 (47-66)	62 (36-69)
Female, n (%)	1 (100%)	2 (50.0%)	2 (33.3%)	4 (80.0%)	9 (56.3%)
Race, n (%)					
Asian	1 (100%)	4 (100%)	6 (100%)	5 (100%)	16 (100%)
ECOG PS (%)					
0	0	1 (25.0%)	2 (33.3%)	2 (40.0%)	5 (31.3%)
1	1 (100%)	2 (50.0%)	4 (66.7%)	3 (60.0%)	10 (62.5%)
2	0	1 (25.0%)	0	0	1 (6.3%)

ECOG PS: Eastern Cooperative Oncology Group Performance Status

Table 2. Baseline Disease Characteristics

	0.125mg QD (N=1)	0.20mg QD (N=4)	0.30mg QD (N=6)	0.40mg QD (N=5)	Total (N=16)
MF subtype, n (%)					
PMF	1 (100%)	3 (75.0%)	5 (83.3%)	2 (40.0%)	11 (68.8%)
Post PV MF	0	0	1 (16.7%)	2 (40.0%)	3 (18.8%)
Post ET MF	0	1 (25.0%)	0	1 (20.0%)	2 (12.5%)
Prior JAK inhibitor treatment, n (%)	0	0	4 (66.7%)	4 (80.0%)	8 (50.0%)
JAK2 Mutation, n (%)	1 (100%)	4 (100%)	5 (83.3%)	5 (100%)	15 (93.8%)
Median Time Since Initial Diagnosis (range), months	0.9 (0.9)	3.0 (0.9-51.8)	17.8 (8.8-76.6)	26.7 (8.7-30.1)	13.5 (0.9-76.6)
DIPSS, n (%)					
Intermediate 1	1 (100%)	4 (100%)	2 (33.3%)	4 (80.0%)	11 (68.8%)
Intermediate 2	0	0	3 (50.0%)	1 (20.0%)	4 (25.0%)
High risk	0	0	1 (16.7%)	0	1 (6.3%)
Spleen volume, median (range), cm^3	582.7	1568.1 (453-1959)	2252.1 (789-6142)	1532 (926-3454)	1553.8 (453-6142)
TSS, median (range)	34	7.5 (2-17)	8.5 (5-19)	12 (6-38)	9.5 (2-38)

PMF: Primary myelofibrosis; Post PV MF: Post-polycythemia vera myelofibrosis; Post ET MF: Post-essential thrombocythemia myelofibrosis.

Figure 1. Duration of JAB-8263 Treatment

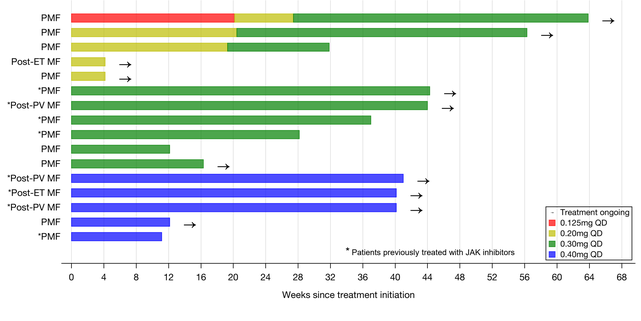

Table 3. Safety Summary

	0.125mg QD (N=1)	0.20mg QD (N=4)	0.30mg QD (N=6)	0.40mg QD (N=5)	Total (N=16)
Any TEAE	1 (100%)	3 (75.0%)	6 (100%)	5 (100%)	15 (93.8%)
≥ Grade 3 TEAE	0	0	2 (33.3%)	4 (80.0%)	6 (37.5%)
Serious TEAE	0	0	1 (16.7%)	3 (60.0%)	4 (25.0%)
Any TRAE	1 (100%)	2 (50.0%)	6 (100%)	5 (100%)	14 (87.5%)
≥ Grade 3 TRAE	0	0	2 (33.3%)	3 (60.0%)	5 (31.3%)
Serious TRAE	0	0	0.00	3 (60.0%)	3 (18.8%)
TRAE Leading to JAB-8263 Interruption	0	0	4 (66.7%)	3 (60.0%)	7 (43.8%)
TRAE Leading to JAB-8263 Reduction	0	0	1 (16.7%)	3 (60.0%)	4 (25.0%)
TRAE Leading to JAB-8263 Discontinuation	0	0	0	1 (20.0%)	1 (6.3%)
DLT	0	0	0	1	1

TEAE: Treatment Emergent Adverse Event:; TRAE: Treatment-Related Adverse Event; DLT: dose-limiting toxicity.

Table 4. Summary of Most Common JAB-8263-Related TEAE

Most Common TRAE, n(%)	0.125mg QD (N=1)	0.20mg QD (N=4)	0.30mg QD (N=6)	0.40mg QD (N=5)	Total (N=16)
Blood bilirubin increased	0	0	3 (50.0%)	5 (100%)	8 (50.0%)
Thrombocytopenia	0	0	3 (50.0%)	3 (60.0%)	6 (37.5%)
ALT increased	1 (100%)	1 (25.0%)	0	4 (80.0%)	6 (37.5%)
AST increased	1 (100%)	0	0	4 (80.0%)	5 (31.3%)
Diarrhea	1 (100%)	0	1 (16.7%)	2 (40.0%)	4 (25.0%)
Anemia	0	0	2 (33.3%)	2 (40.0%)	4 (25.0%)
Blood fibrinogen decreased	0	0	1 (16.7%)	3 (60.0%)	4 (25.0%)

ALT: alanine aminotransferase; AST: aspartate aminotransaminase.

Safety

- One patient was discontinued from the treatment due to JAB-8263-related adverse events and no treatment-related fatal events occurred in the study.
- One DLT (Grade 3 ALT increase and AST increase) occurred in a patient at the 0.4mg dose level.
- Grade 3 or high TRAEs were thrombocytopenia (18.8%), anemia (12.5%), ALT increase (6.3%), AST increase (6.3%) and blood fibrinogen decrease (6.3%).

Efficacy

As of Oct 17, 2024, 13 patients have undergone at least one post-treatment radiological efficacy assessment.

- All patients showed a mean SVR -19.95% (range: -39.4% to 3.6%) at week 24 and -26.16% (56.6% to -11.0%) at best response.
- Two patients achieved ≥35% SVR and an SVR of -34.9% was seen in one patient.
- Six of ten (60%) patients experienced a ≥50% reduction in TSS (TSS50) at week 24.
- The best response of SVR in 2 of 8 patients (JAK inhibitors treated) were -41.2% and 34.9%, respectively.
- At week 24, 3 of 6 (50%) patients (JAK inhibitors treated) achieved TSS50.

Figure 2. Spleen Volume Response from Baseline

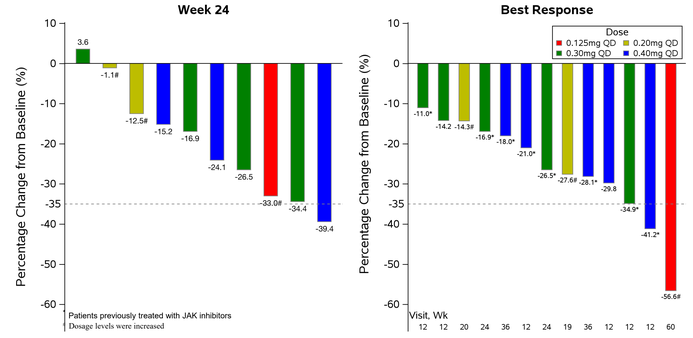

Figure 3. Symptom Improvement from Baseline

CONCLUSIONS

- JAB-8263 at 0.125mg QD-0.3mg QD was well tolerated. One DLT occurred in 0.4mg QD. RP2D was 0.3mg QD.
- Hematological and gastrointestinal AEs are mild with JAB-8263 continuous dosing comparing to other BET inhibitors.
- The preliminary efficacy data in MF for JAB-8263 monotherapy is promising. Most patients showed spleen reduction and TSS reduction.
- The monotherapy expansion is ongoing.

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REFERENCES

Loven J, Hoke HA, Lin CY, et al. Selective inhibition of tumor oncogenes by disruption of super-enhancers. Cell. 2013,153: 320-334