Interim Analysis of PROMise, a Clinical Study Combining the BET Inhibitor OPN-2853 with Ruxolitinib in Patients with Advanced Myelofibrosis Experiencing an Inadequate Response to Ruxolitinib

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INTRODUCTION

- Myelofibrosis (MF) is a chronic myeloproliferative neoplasm causing progressive splenomegaly, cytopenias, systemic symptoms and mortality[1].
- OPN-2853 is a potent, orally active small molecule BET inhibitor with a short half-life enabling once-daily continuous dosing with rapid clearance to limit toxicity. Through suppression of BRD4/NF-κB–driven inflammation, OPN-2853 offers mechanistic synergy with JAK inhibition to reduce splenomegaly and marrow fibrosis, justifying its evaluation with ruxolitinib in MF.
- Ruxolitinib (rux), a JAK 1/2 inhibitor, is an approved treatment for MF which effectively controls disease related symptoms and splenomegaly in some patients[2]. However, disease control is often inadequate, and disease progression eventually occurs in most patients.
- In mouse models of MF, the effects of rux are complemented by epigenetic inhibitors targeting bromodomain and extra-terminal motif (BET) proteins and combinations of BET and JAK inhibitors have shown promising initial clinical results.

AIM

The co-primary objectives of the study are

1) Identifying a safe and tolerable recommended Phase II dose (RP2D) of OPN-2853 in combination with ruxolitinib and
2) Assessing the efficacy of this combination in reducing spleen size in patients with high or intermediate-2 risk MF who are not adequately responding to ruxolitinib alone.

METHOD

- PROMise is a Phase I, multicentre, dose finding trial evaluating three dose levels of OPN-2853 given orally once daily: 20mg, 40 mg and 80 mg.
- A maximum of 40 patients will be recruited across two rux dose groups: low-dose (5-20 mg daily), or mid/high dose (≥25 mg daily).
- Patients must be ≥ 16 years, have been on rux for at least 24 weeks, with a stable dose for at least 4 weeks and have persistent splenomegaly extending at least 5 cm below the costal margin.
- The RP2D is determined using the continual reassessment method (CRM) in each rux dose group.

RESULTS

These results represent preliminary findings and analyses are ongoing.

Baseline Characteristics

Characteristic	Overall (N=29)
Age at Registration (years)	70 (65, 74)
Time from diagnosis (years)	4.0 (2.4, 7.9)
Sex: Female : Male	14 (48%) : 15 (52%)
Disease Type: Primary : Secondary	14 (48%): 15 (52%)
Secondary Myelofibrosis Type	
PET-MF : PPV-MF	8 (53%) : 7 (47%)
Fibrosis Grade: MF-2 : MF-3	3 (13%) : 18 (78%)
Transfusion Status	
Transfusion dependent	7 (24%)
Transfusion independent	22 (76%)
Spleen Size (cm)	
Palpable	8.5 (6.0, 13.8)
Ultrasound, Width	9 (8, 12)
Ultrasound, Length	20 (17, 23)
Hemoglobin (g/L)	106 (95, 126)
Platelets (10^9/L)	148 (104, 209)
White Blood Cell Count (10^9/L)	12 (7, 36)
Neutrophils (10^9/L)	10 (4, 23)
Peripheral Blasts (%)	2 (0, 4)

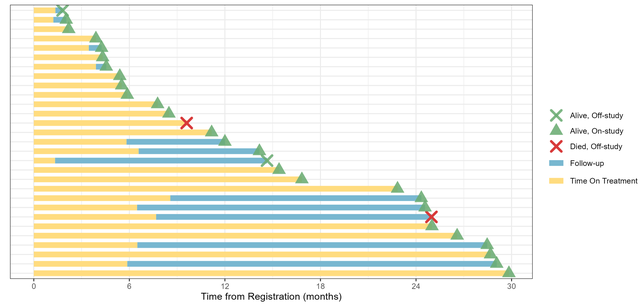
*Continuous data are presented as median (IQR). Categorical data are presented as n(%).

RP2D

- 29 patients received 40 mg (n=14) or 80 mg (n=15) OPN-2853 plus ruxolitinib (21 mid/high; 8 low); 24 have been assessed by the TSC.
- As of the last dose decision (March 2025), the current dose level is 80 mg once daily for both the low dose and mid/high dose group.
- 2 patients experienced dose-limiting toxicities (DLTs) (Grade 3 thrombocytopenia and elevated liver transaminases) were observed in the 40 mg OPN-2853 cohort. No DLTs occurred in 15 patients treated in 80 mg OPN-2853 cohort.
- Dose transition pathways (DTP) indicate 80mg as the RP2D in mid/high dose rux patients and that the dose recommendation will remain at 80mg for low dose rux patients unless 2/2 have a DLT in the current cohort.

Treatment Durations

- Median time on treatment was 6.5 months. 7/29 patients have been on treatment over 1 year. 4/29 patients have been on treatment over 2 years.
- Median time on follow-up was 12 months.



Safety

- Platelet count decreased (n=6, 20.7%) and anemia (n=2, 6.9%) were the most common grade 3 or above adverse events.

Any Grade AE	# of patients (N=29)	
	Grade ≥ 3	Total
Hematological AEs		
Platelet count decreased	6 (20.7%)	10 (34.5%)
Anemia	2 (6.9%)	5 (17.2%)
Febrile neutropenia	-	1 (3.4%)
Non-hematological AEs		
Diarrhea	-	18 (62.1%)
Nausea	-	14 (48.3%)
Fatigue	1 (3.4%)	11 (37.9%)
Bleeding related AEs		
Hemorrhage	-	6 (20.7%)
Epistaxis	-	5 (17.2%)
Hematuria	-	1 (3.4%)

- 19 serious adverse events (SAEs) were reported in 9 patients. 3 (15.8%) SAEs were possibly related to OPN-2853; 9 (47.4%) were Grade 3 and 1 (5.3%) was Grade 4.
- There have been 2 reported disease related deaths.
- 0 patients experienced an SAE of transformation to leukemia.

Myelofibrosis Grade

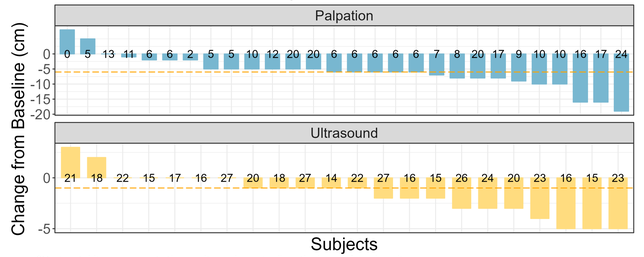
Baseline MF Grade	Best post-baseline MF Grade	
	MF-2	MF-3
MF-2	3	1
MF-3	4	6

- Of the 14 patients with non-missing baseline and post-baseline MF grades, 4 (28.6%) patients had a best improvement of at least 1-grade.

Spleen Size Reduction

- In 28 and 22 patients with evaluable palpation and ultrasound spleen data, the median (IQR) palpation spleen size was reduced by 6 (4.3, 8) cm calculated as the change from baseline to minimum post-baseline spleen size. The ultrasound spleen length was reduced by 1 (0,3) cm.

Maximum Reduction in Spleen Size

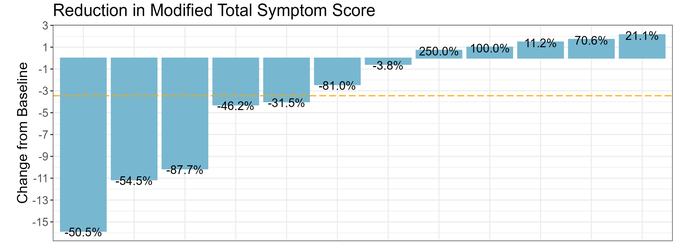


*Horizontal line represents the median spleen size/length change from baseline.
*Numbers on the bar indicate patients' spleen size/length at baseline.

Quality of Life

- In 12 patients with evaluable MFSAF data at Cycle 8, most of the symptoms improved after treatment. Symptoms are rated from 0 (absent) to 10 (worst imaginable severity).
- 4 patients have a 50% or greater reduction in the modified TSS.

Reduction in Modified Total Symptom Score



*Horizontal line represents the mean mTSS change from baseline. *Numbers on the bar indicate patients' percent change from baseline.

CONCLUSIONS

Overall, continuous dosing of OPN-2853 was well-tolerated, allowing prolonged treatment. Encouraging levels of spleen length reduction and a manageable safety profile have been observed with combination OPN-2853 & rux treatment. Clinical activity was also supported by symptom improvement. Notably, no patients experienced leukemic progression.

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