# 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].
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.

1. O'Sullivan, J.M. and C.N. Harrison, *Myelofibrosis: clinicopathologic features, prognosis, and management.* Clin Adv Hematol Oncol, 2018. 16(2): p. 121-131.
2. Vainchenker, W., et al., *JAK inhibitors for the treatment of myeloproliferative neoplasms and other disorders.* F1000Res, 2018. 7: p. 82.

## AIMS

The co-primary objectives of the study are 1) identifying a safe and tolerable recommended Phase II dose 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.

## METHODS

- 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 60 patients will be recruited across three rux dose groups: low-dose (5-20 mg daily), mid-dose (25-45 mg daily), and high-dose (≥50 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.

## CONTACT INFORMATION

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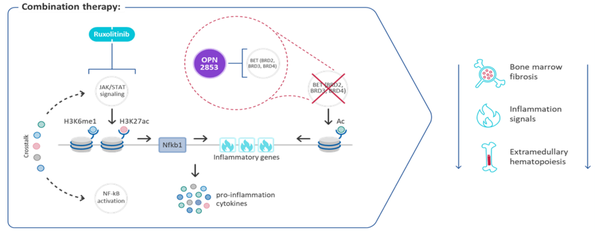
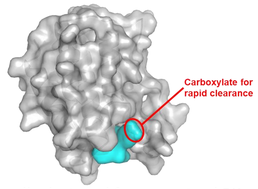
## BACKGROUND

### OPN-2853 Mechanism of Action



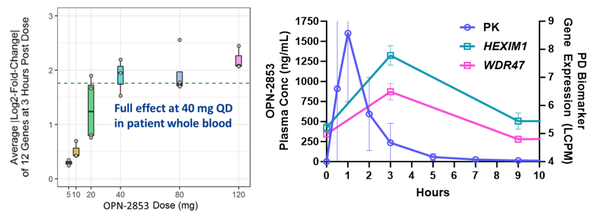

- OPN-2853 is a potent, orally active small molecule inhibitor of BET family proteins
- OPN-2853 binds to the BRD domains of BET proteins with nanomolar $K_d$
- OPN-2853 significantly downregulates malignancy signatures (*Myc, Myc* targets) and BET inhibitor responsive genes (*HEXIM1, WDR47*)
- Combined treatment of rux and OPN-2853 effectively reduces disease burden in preclinical models of MF

### Co-crystal Structure of OPN-2853 and BRD4




- OPN-2853 is rationally designed for an optimal PK profile, with the carboxylate group enabling rapid clearance while the core scaffold maintains potency and selectivity

### OPN-2853 Exhibits Prolonged PD Effects




- A high Cmax and short half-life mitigate toxicity, enabling continuous daily dosing and effective target engagement
- Prolonged PD effects underlie the efficacy of OPN-2853

## ACKNOWLEDGEMENTS

This trial is funded by CRUK. An unrestricted educational grant was provided to support the trial by Opna Bio. OPN-2853 was provided free of charge by Opna Bio.

## RESULTS

### Baseline Characteristics

- 16 patients have been evaluated; 6 were on low-dose ruxolitinib, 8 on mid-dose and 2 on high-dose.*

| Characteristic | Overall (N=16) |
|---|---|
| Age at Registration (years) | 71 (66, 74) |
| Time from diagnosis (years) | 3.8 (2.3, 7.0) |
| Sex | |
| Female : Male | 7 (44%) : 9 (56%) |
| Disease Type | |
| Primary : Secondary | 9 (56%) : 7 (44%) |
| Secondary Myelofibrosis Type | |
| PET-MF : PPV-MF | 4 (57%) : 3 (43%) |
| Fibrosis Grade | |
| MF-2 : MF-3 | 2 (18%) : 9 (82%) |
| Transfusion Status | |
| Transfusion dependent | 5 (31%) |
| Transfusion independent | 11 (69%) |
| Spleen Size (cm) | |
| Palpable | 9 (6, 13) |
| Ultrasound, Width | 9 (8, 12) |
| Ultrasound, Length | 21 (16, 23) |
| Hemoglobin (g/L) | 102 (92, 114) |
| Platelets ($10^9$/L) | 128 (93, 186) |
| White Blood Cell Count ($10^9$/L) | 9 (6, 12) |
| Neutrophils ($10^9$/L) | 5 (4, 10) |
| Lymphocytes ($10^9$/L) | 1.20 (0.65, 1.98) |
| Blasts (%) | 2 (0, 4) |

*The data cut off was February 2024

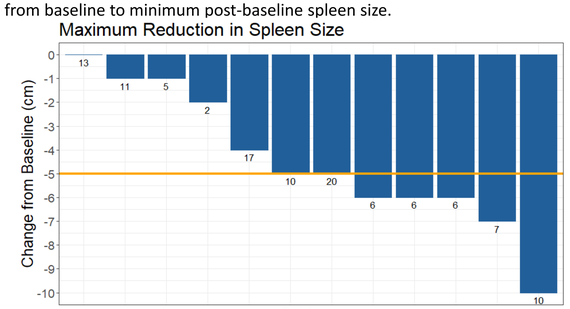
### Adverse Events

| Any Grade AE | # of patients (N=16) |
|---|---|
| Hematological AEs | |
| Platelet count decreased or thrombocytopenia | 7 (43.8%) |
| Anemia | 4 (25%) |
| Febrile neutropenia | 1 (6.2%) |
| Non-hematological AEs | |
| Diarrhea | 11 (68.8%) |
| Nausea | 7 (43.8%) |
| Abdominal pain | 5 (31.2%) |
| Fatigue | 5 (31.2%) |
| Other | 16 (100%) |
| Bleeding related AEs | |
| Epistaxis | 2 (12.5%) |
| Hematuria | 1 (6.2%) |
| Oral hemorrhage | 1 (6.2%) |

- Platelet count reduction (n=5, 31%) and anemia (n=2, 12.5%) were the most common grade 3 or above adverse events.

### Spleen Length Reduction

- In 12 evaluable patients, the median (range) spleen size is reduced by 5 (0, 10) cm calculated as the change from baseline to minimum post-baseline spleen size.




*Numbers on the bar indicate patients' spleen size at baseline.

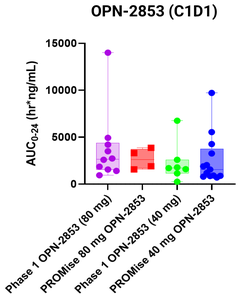
### Serious Adverse Events

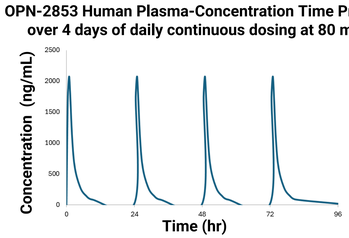
| SAE | # of events (N=7) |
|---|---|
| OPN-2853 Relatedness | |
| Related | 2 (28.6%) |
| Unrelated | 4 (57.1%) |
| Unknown | 1 (14.3%) |
| Grade | |
| Grade <3 | 3 (42.9%) |
| Grade 3 | 3 (42.9%) |
| Grade 4 | 1 (14.3%) |

*The data cut off was February 2024

- Seven serious adverse events were reported in 3 patients.
- Two dose-limiting toxicities (Grade 3 thrombocytopenia and elevated liver transaminases) were observed in the 40 mg OPN-2853 cohort.
- There has been 1 reported disease related death
- No patient experienced an SAE of transformation to leukemia.

### Pharmacokinetics




- The distinct PK profile of OPN-2853 allows for continuous daily dosing that results in a pulsatile effect where the drug is onboard to inhibit the target effectively and systemically cleared rapidly to avoid toxicities.

## CONCLUSIONS

The ongoing PROMise study (EudraCT 2019-000916-27) combines a daily dose of OPN-2853 with standard of care ruxolitinib to test the hypothesis that a continuous daily dosing regimen of oral agents will improve disease burden. To-date the dose combinations tested have been well tolerated, and the majority of patients have completed 8 cycles of combination treatment. Encouraging levels of spleen reduction have been observed in the context of a well-tolerated agent and the study continues to recruit patients.