PRELIMINARY DATA FROM THE PHASE 1/2 STUDY OF TP-3654, AN INVESTIGATIONAL SELECTIVE PIM1 KINASE INHIBITOR, SHOWED CYTOKINE REDUCTION AND CLINICAL RESPONSES IN RELAPSED/REFRACTORY MYELOFIBROSIS

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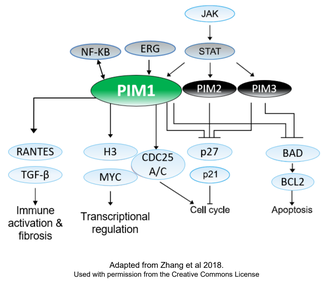
Introduction

- JAK inhibitors are the standard of care treatment for myelofibrosis (MF); however, they are limited by cytopenias due to disease and treatment[1]
- JAK inhibitors lack disease modifying effects[1]
- Therapies with unique mechanisms of action are needed for patients whose disease has progressed, or are unable to tolerate JAK inhibitors

Inhibition of PIM1 in Myelofibrosis

- Proviral integration site of moloney murine leukemia virus kinases 1 (PIM1) is a proto-oncogene regulated in part through JAK/STAT, NF-Kappa B, and ERG pathways[2]
- PIM1 kinase expression was significantly increased in bone marrow and PBMC samples from patients with MF[3]
- In preclinical MF mouse models: (i) PIM1 knockout prevented MF progression, but PIM2 knockout showed no effect, and (ii) PIM1 knockout does not cause platelet count decrease[3]



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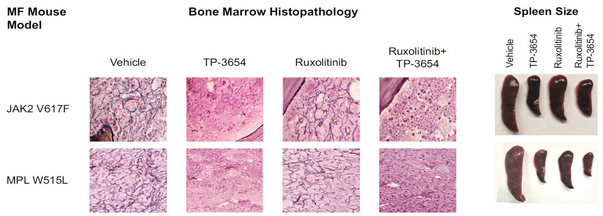
TP-3654 Showed Reduction in Spleen Size and Bone Marrow Fibrosis in Myelofibrosis Mouse Models



- In preclinical studies in MPL^{W515L} and JAK2^{V617F} MF mouse models, TP-3654 alone or in combination with ruxolitinib treatment leads to reduction of spleen size and reversion of bone marrow fibrosis vs ruxolitinib alone[3]

Study Design

Ongoing global phase 1/2 study

Study Population

- Primary, Post-PV, Post-ET MF
- Relapsed, refractory, intolerant, or ineligible for JAK inhibitors
- DIPSS Intermediate or high-risk
- Platelet count ≥ 25 x 10^9/L
- ECOG ≤ 2
- Spleen volume ≥ 450 cm^3
- ≥2 symptoms by MF-SAF v4.0

Treatment

Phase 1
Dose Escalation
Guided by the **BLRM**
480 mg QD - 1440 mg BID

Phase 2
Dose Expansion
Recommend Dose

Endpoints

- **Primary:**
  - Safety and tolerability
- **Secondary**
  - Spleen volume reduction
  - Total symptoms score reduction
  - Overall survival
  - Bone marrow fibrosis change
  - Pharmacokinetics

- Please refer to ClinicalTrials.gov (NCT04176198) for further information

Results

Patient Demographics and Baseline Characteristics*

Patient Characteristics, n=15		
Age, median (range)		69 years (61 - 77)
Spleen length, median (range)		12 cm (0 - 25)
Spleen volume, median (range)		1935.5 cm^3 (857 - 4408)
Total Symptoms Score (MF-SAF v4.0) median (range)		19 (4 - 62)
Platelet count, median (range)		129 x10^9/L (64- 520)
Hemoglobin, median (range)		9.7 g/dL (5.9 - 13.7)
Transfusion dependent		5 (33%)
Myelofibrosis subtypes (n, %)	Primary Post-PV Post-ET	8 (53%) 6 (40%) 1 (7%)
DIPSS Risk Group (n, %)	Int-1 Int-2 High	4 (27%) 8 (53%) 3 (20%)
Driver Mutations	JAK2V617F CALR	12 (80%) 3 (20%)
Prior Treatment n(%), median duration (range)		
	Ruxolitinib Fedratinib	15 (100%), 7.6 months (2.3 – 73) 2 (13%), 9.8 months (8.3 – 11)
Response to JAK Inhibitors (n, %)		
	Primary refractory Loss of response Intolerant	4 (27%) 7 (47%) 4 (27%)

Patient Disposition and Safety Summary*

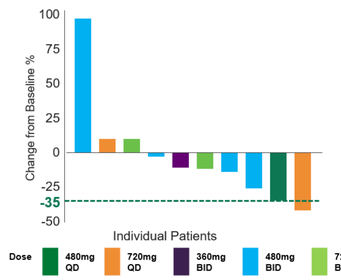
Dose Regimen	Enrolled Patients (n)	DLT Observed
480 mg QD	1	No
720 mg QD	2	No
360 mg BID	1	No
480 mg BID	7	No
720 mg BID	4	No

- No dose limiting toxicities (DLT) was observed.
- Maximum tolerated dose (MTD) not yet reached, enrollment is ongoing

TEAE in ≥20% Patients All Causality (n = 15)	Grade 1-2 (n, %)	Grade 3 (n, %)	Grade 4 (n, %)
Non-hematological			
Diarrhoea	11 (73.3)	1 (6.7)	0 (0.0)
Nausea	9 (60.0)	0 (0.0)	0 (0.0)
Vomiting	5 (33.3)	1 (6.7)	0 (0.0)
Abdominal pain	4 (26.7)	1 (6.7)	0 (0.0)
Fatigue	5 (33.3)	0 (0.0)	0 (0.0)
Decreased appetite	3 (20.0)	1 (6.7)	0 (0.0)
Abdominal distension	3 (20.0)	0 (0.0)	0 (0.0)
Blood bilirubin increased	2 (13.3)	1 (6.7)	0 (0.0)
Dyspnoea	3 (20.0)	0 (0.0)	0 (0.0)
Pruritus	3 (20.0)	0 (0.0)	0 (0.0)
Hematological			
Anaemia	2 (13.3)	1 (6.7)	0 (0.0)
Platelet count decreased	2 (13.3)	1 (6.7)	0 (0.0)

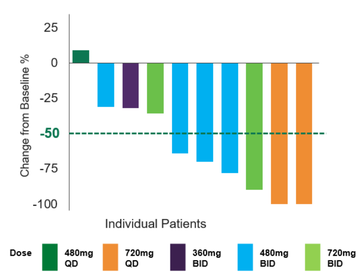
- The most common adverse events (AE) are Grade 1 and 2 diarrhea, nausea, and vomiting. Nausea and vomiting are transient and are manageable with supportive care.

Best Reduction in Spleen Volume*



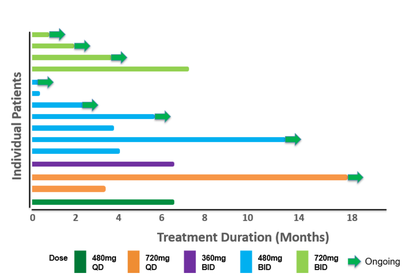
- 10 evaluable patient on treatment ≥ 12 weeks
- Median spleen volume reduction: -14%
- 2 of 10 patients have ≥ 35% SVR

Best Reduction in Symptoms*



- 10 evaluable patients on treatment ≥ 12 weeks
- Median total symptom score (TSS) reduction: -70%
- 6 of 10 patients have ≥ 50% TSS reduction

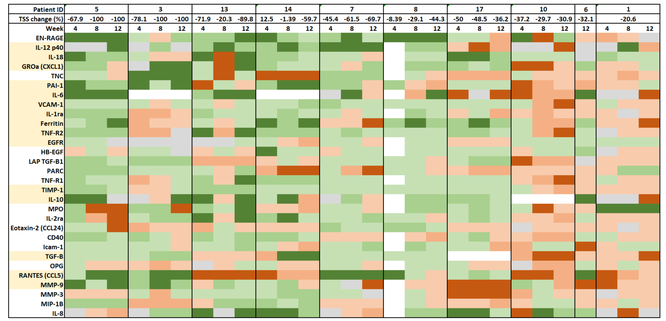
TP-3654 Treatment Duration*



- 8 of 15 patients are ongoing on treatment
- Median treatment duration is 16 weeks
- Reasons for treatment discontinuation include disease progression (7%), patient withdrawal, (7%), physician decision (13%), and other (20%)

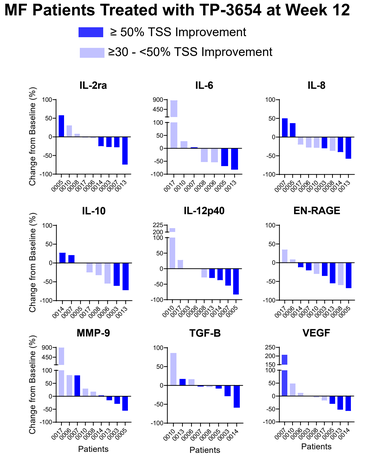
Changes in Inflammatory Cytokines*

TP-3654 Treatment Leads to Early Reduction in Cytokines



Cytokines highlighted in Yellow are associated with MF

Cytokine Reduction and TSS Improvement in MF Patients Treated with TP-3654 at Week 12



- Broad cytokine reduction observed as early as Week 4 from initial dose cohorts
- Cytokines associated with MF (IL-6, IL-10, IL-12, IL-18, TGF-b, EGFR, Ferritin, GRO-a, IL-1RA, MMP-9, PAI-1, RANTES, TIMP-1, TNFR-2, VCAM-1) show reduction after treatment
- Cytokine reduction generally correlate with TSS reduction (week 12 presented on the right)
- Bone marrow fibrosis reduction from grade 3 to 2 was seen in one patient who also achieved spleen and symptoms responses and showed reductions in MF associated cytokines: IL6 (68%), IL12p40 (83%), MMP9 (56%), and EN-RAGE (68%), and is on active treatment for more than 18 months.

Conclusions

- PIM1, a potential therapeutic target in MF, is a proto-oncogene regulated in part through the JAK / STAT, ERG and NF-kB pathways and modulates multiple downstream signaling pathways including induction of cytokines[2]
- TP-3654 is an oral investigational selective PIM1 kinase inhibitor
- TP-3654 appears to be well tolerated, no DLT to date, and the most common AE are Grade 1 and 2 GI toxicities
- Preliminary signs of early clinical activity include spleen volume reduction, symptom improvement, and broad cytokine reduction
- Enrollment is ongoing as TP-3654 monotherapy and emerging data support the development of TP-3654 as potential combination with JAK inhibitors

1. Verstovsek et al. *J Hematol Oncol.* 2017 2. Tursynbay et al. *Biomed Rep*. 2016 3. Dutta et al. Leukemia 2021

*Preliminary data as of 09 February 2023

European Hematology Association (EHA) 2023 Congress, June 8 – 15, Frankfurt, Germany

Thank you to the patients, caregivers, study investigators, and research staff. This study was supported by Sumitomo Pharma Oncology, Inc.