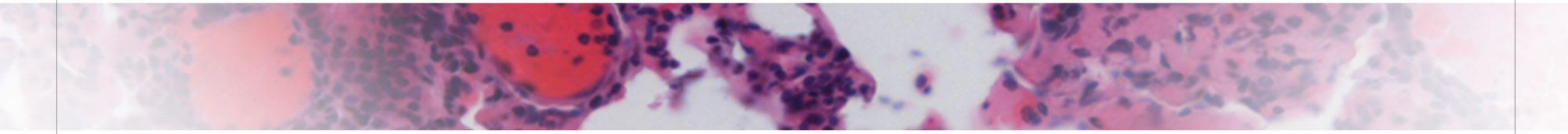
American Society of Hematology
Helping hematologists conquer blood diseases worldwide



Phase I/II Study of TP-3654, a Selective Oral PIM1 Kinase Inhibitor, in Patients with Myelofibrosis Previously Treated with or Ineligible for JAK Inhibitor Therapy

Firas El Chaer MD[1], James McCloskey MD[2], Lindsay AM Rein, MD[3], Randy A Brown MD[4], Steven D Green MD[5], Jeffrey J Pu MD PhD[6], Shuichi Shirane MD PhD[7], Kazuya Shimoda MD PhD[8], Michiko Ichii MD PhD[9], Junichiro Yuda MD PhD[10], Joseph Scandura MD PhD[11], Sujan Kabir MD[12], Jason M Foulks PhD[13], Jian Mei PharmD[12], Huyuan Yang PhD[12], Mark Wade PhD[12], Carl Stapinski[12], Claudia Lebedinsky MD[12] , and Raajit K Rampal MD PhD[14]

[1]University of Virginia Health System, VA; [2]The John Theurer Cancer Center at Hackensack Meridian Health, NJ; [3]Duke University Medical Center, NC; [4]Shands HealthCare &University of Florida, FL; [5]Roswell Park Comprehensive Cancer Center, NY; [6]University of Arizona Cancer Center, AZ; [7]Juntendo University School of Medicine, Tokyo, Japan; [8]University of Miyazaki, Miyazaki, Japan; [9]Osaka University Graduate School of Medicine, Suita City, Japan; [10]National Cancer Center Hospital East, Kashiwa, Japan; [11]Richard T. Silver, Weill Cornell Medicine, NY; [12]Sumitomo Pharma Oncology, Inc., MA; [13]Sumitomo Pharma Oncology, Inc., UT; [14]Memorial Sloan Kettering Cancer Center, NY

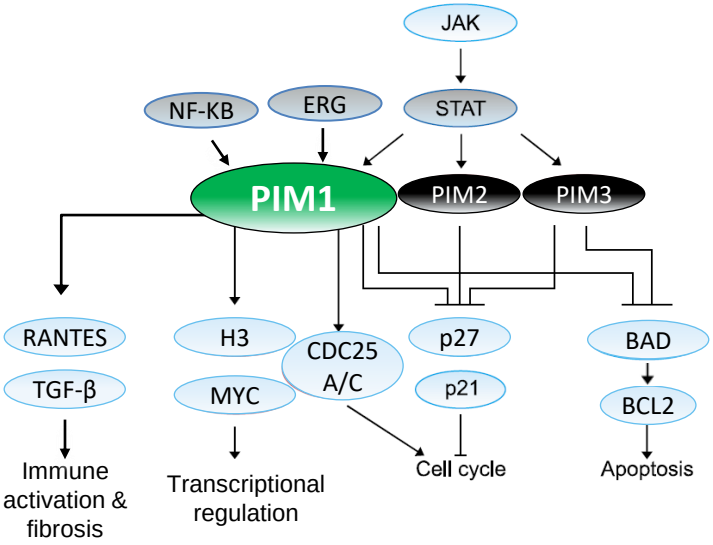
Myelofibrosis: Background & Evolving Treatment Landscape

- JAK inhibitors, current standard of care treatment, are limited by thrombocytopenia, anemia, and lack of disease modifying effects[1]
  - Most patients have either inadequate response, or eventually lose response to JAK inhibitors
  - Patients with cytopenia or who have progressed from JAK inhibitors have poor prognosis
  - Anemia and thrombocytopenia are common and prevents JAK inhibitor dose optimization
- Novel therapies with unique MOA are needed for MF patients who have progressed from JAK inhibitors and/or have cytopenia
- Evolving treatment landscape includes doublet combination regimen; however, are challenged by overlapping toxicities including cytopenia[2]
- An ideal combination partner should have disease modifying effects and minimal cytopenia, in addition to spleen reduction and symptoms improvement

1. Verstovsek et al. *J Hematol Oncol.* 2017
2. Assi et al. Curr Opin Hematol. 2017

Background: PIM1 Kinase Signaling

- PIM1 is a proto-oncogene regulated in part through the Janus kinase (JAK)/signal transducers and activators of transcription (STAT) pathway[3]
- PIM1 kinase also has an essential role in cytokine-induced signal transduction by controlling transcription factors[3]
- Upregulation of PIM1 kinase leads to increased cytokines relevant to immune activation and fibrosis including RANTES and TGF-β[3]



Adapted from Zhang et al 2018.

3. Tursynbay et al. *Biomed Rep*. 2016

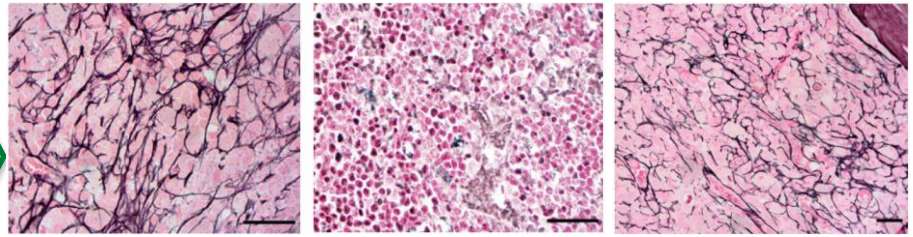
PIM1 Kinase: A Novel Target in MF

- PIM1 expression was shown to be significantly increased in MF patients' bone marrow and PBMC samples[4]

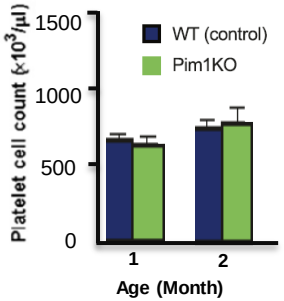
- PIM1 knockout was shown to prevent myelofibrosis progression, but PIM2 knockout has no effect in MF mouse models[4]

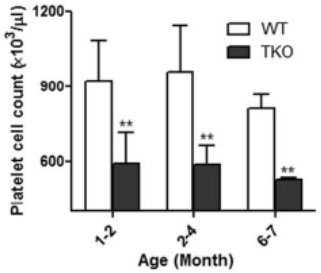
- PIM1 knockout was shown not to cause platelet count decrease, while pan-PIM knockout resulted in thrombocytopenia in mice[5]

MPL^{W515L} Mouse Model Bone Marrow (Reticulin Stain)



PIM WT | PIM1KO | PIM2KO



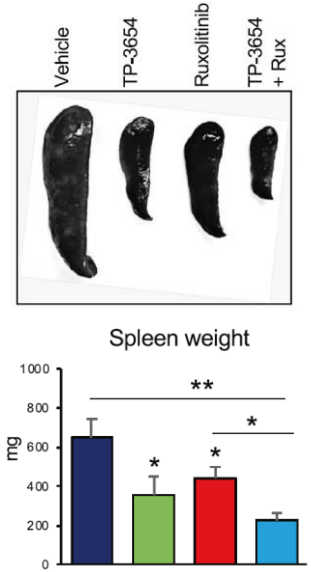


- Novel therapies which **selectively** inhibit PIM1 kinase may provide disease-modifying benefits for MF patients while avoiding cytopenia adverse effects

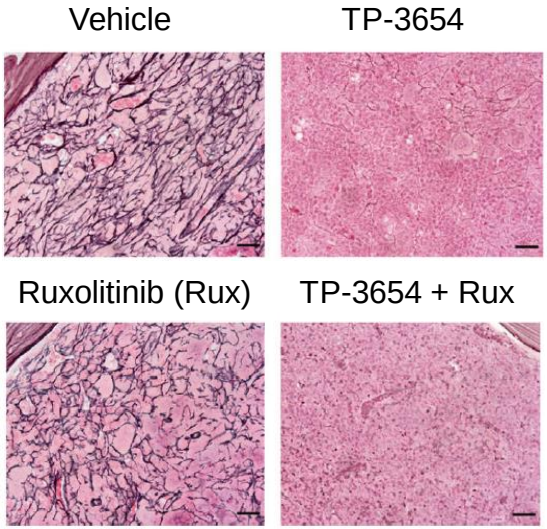
4. Dutta et al. Leukemia 2021 5. An et al. JH&O, 2013

TP-3654: An Oral Selective PIM1 Inhibitor in Murine MPL^{W515L} MF Model

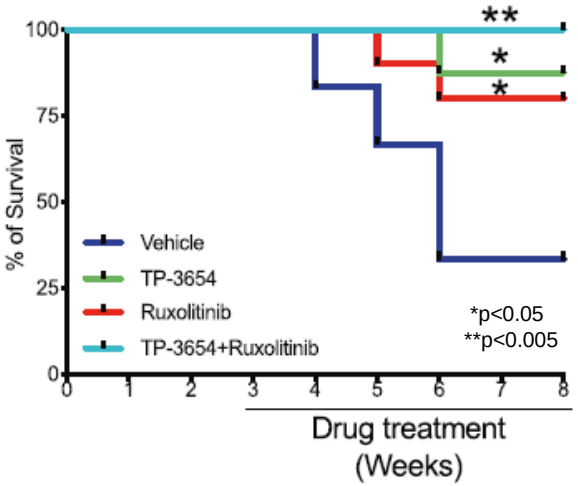
✓ Spleen Size Reduction



✓ Bone Marrow Fibrosis Reduction



✓ Overall Survival Increase



- Similar TP-3654 activity was observed in murine JAK2^{V617F} MF model[4]

4. Dutta et al. Leukemia 2021

TP-3654 Phase I/II Study Design in MF

- **Primary, Post-PV, Post-ET MF**
- **Relapsed, refractory, intolerant, or ineligible for treatment with JAK inhibitors**

Phase 1 Monotherapy Dose Escalation
480 mg QD - 1440 mg BID

Bayesian Dose Escalation

→ **MTD/ RP2D** →

Phase 2 Dose Expansion

Key Eligibility

- DIPSS Intermediate- 1, 2, or high-risk
- **Platelet count ≥ 25 x 10^9/L**
- ECOG ≤ 2
- Splenomegaly (volume of ≥ 450 cm^3)
- At least 2 symptoms by MF-SAF v4.0

Endpoints

- **Primary:**
  - Safety and tolerability
- **Secondary**
  - Spleen volume reduction
  - Total symptoms score reduction (MF-SAF v4.0)
  - Overall survival
  - Bone marrow fibrosis change
  - Pharmacokinetics

TP-3654 Phase 1: Baseline Characteristics

Patient Characteristics, n=9	
Age, median (range)	71 years (61 - 77)
Spleen length, median (range)	12 cm (0 - 25)
Spleen volume, median (range)	2231 cm^3 (857 - 4407)
Total Symptoms Score (MF-SAF v4.0), median (range)	18 (4 - 62)
Platelet count, median (range) ≥ 100 x 10^9/L < 100 x 10^9/L	120 x10^9/L (68 - 237) 6 (66%) 3 (33%)
Hemoglobin, median (range) ≥ 10 g/dL < 10 g/dL	10.1 g/dL (5.9 - 13.7) 5 (56%) 4 (44%)
Transfusion dependent	2 (22%)

Disease Characteristics, n=9		
Myelofibrosis subtypes	Primary Post-PV Post-ET	4 (44%) 4 (44%) 1 (11%)
DIPSS Risk Group	Int-1 Int-2 High	3 (33%) 4 (44%) 2 (22%)
Driver Mutations	JAK2V617F CALR	7 (78%) 2 (22%)
Prior Treatment n(%), median duration (range)		
	Ruxolitinib Fedratinib	9 (100%), 33 weeks (10 - 268) 2 (22%), 36 weeks (36 - 49)
Response to JAK Inhibitors		
	Primary refractory Loss of response Intolerant	3 (33%) 4 (44%) 2 (22%)

Preliminary data as of 11-OCT-2022

TP-3654: Dose Escalation and Safety

Cohort	Number of Patients	DLT
480mg QD	1	None
720mg QD	2	None
360mg BID	1	None
480mg BID	4	None
720mg BID	1 / ongoing	None

- No DLT or related serious AE.
- The most common AEs are Grade 1 diarrhea, nausea, and vomiting, and transient resolving within 1-2 weeks.
- Transient Grade 3 anemia and thrombocytopenia were observed in 1 patient.
- No dose reduction or discontinuation due to AE.

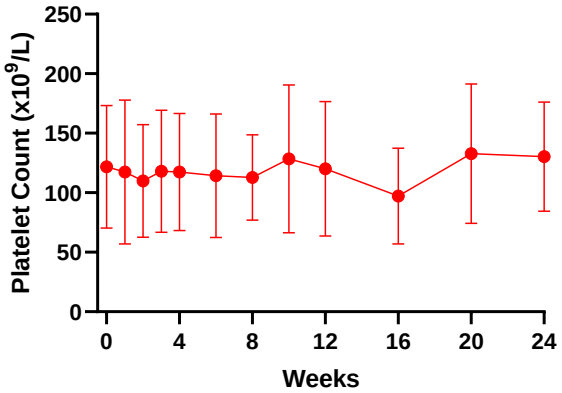
*G3 Bilirubin and G3 Anemia from a patient with baseline G2 bilirubin and transfusion-dependent.

TEAE (≥2 patients) n = 9	Grade 1/2	Grade 3
Non-hematological		
Diarrhea	7 (78%)	0
Nausea	5 (56%)	0
Vomiting	4 (44%)	1 (11%)
Abdominal distension	2 (22%)	0
Abdominal pain	1 (11%)	1 (11%)
UTI	2 (22%)	0
Bilirubin Increased	1 (11%)	1 (11%)*
Muscle spasms	2 (22%)	0
Insomnia	2 (22%)	0
Fatigue	2 (22%)	0
Dyspnea	2 (22%)	0
Hematological		
Platelet count decreased	2 (22%)	1 (11%)
Anemia	1 (11%)	1 (11%)*
Leukocytosis	1 (11%)	1 (11%)

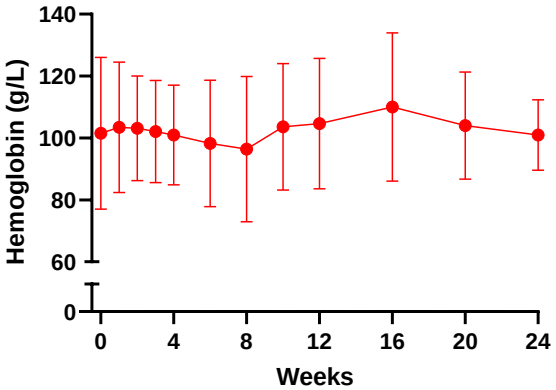
Preliminary data as of 11-OCT-2022

TP-3654: Stable Lab Values in the Dose Escalation with No Worsening of Blood Counts

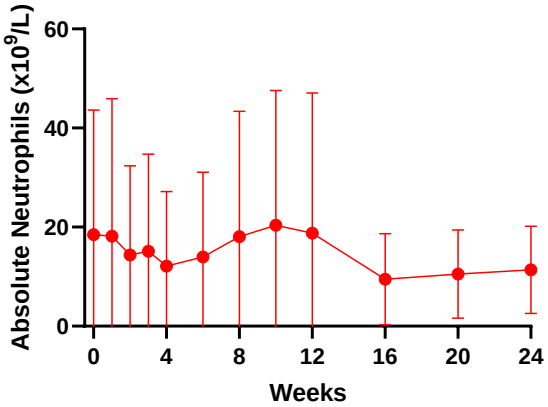
Platelet Count During Treatment*



Hemoglobin During Treatment*



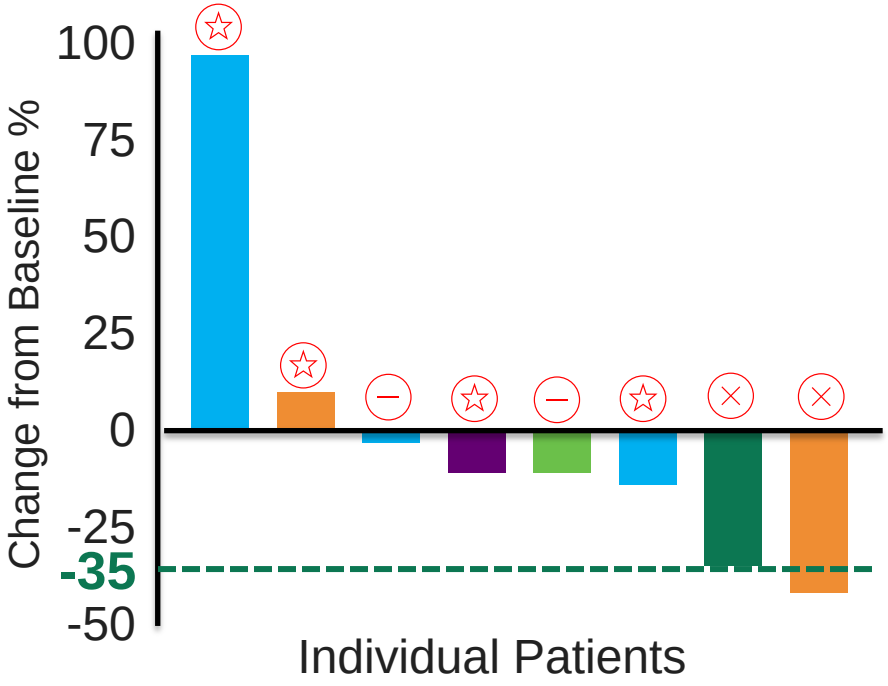
Neutrophil During Treatment*



*N=9; Mean ± SD

Preliminary data as of 11-OCT-2022

TP-3654: Best Spleen Volume Response in Dose Escalation



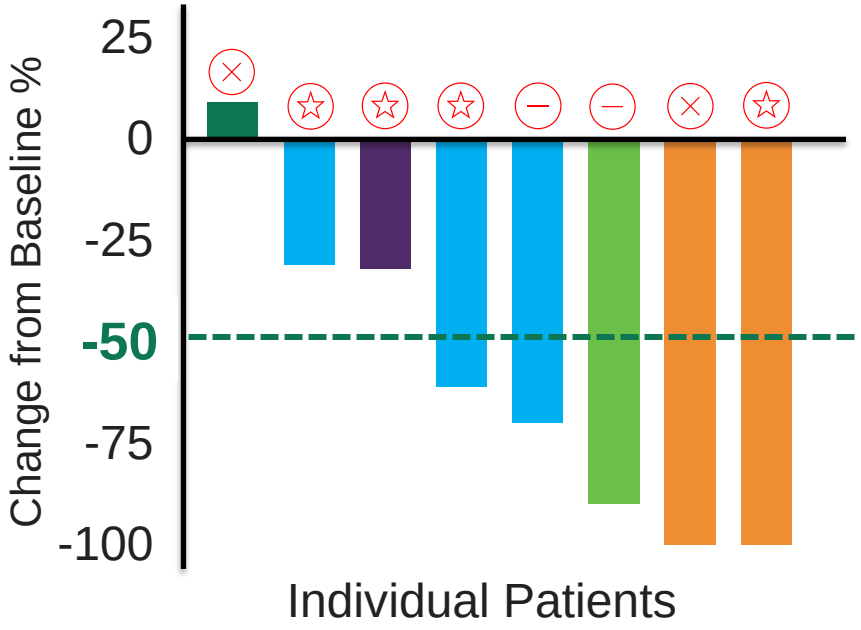
- 8 evaluable patients on treatment ≥ 12 weeks
- Baseline spleen volume median 2535 cm^3 (1189 to 4407)
- 6 of 8 have SVR
  - Median -11%
  - 5 of 8 patients have ≥ 10% SVR
  - 2 of 8 patients have ≥ 35% SVR

Dose 480mg QD | 720mg QD | 360mg BID | 480mg BID | 720mg BID

Response to JAK Inhibitor: ⊗ = Primary Refractory | ☆ = Loss of Response | — = Intolerant

Preliminary data as of 11-OCT-2022

TP-3654: Best Symptoms Response in Dose Escalation



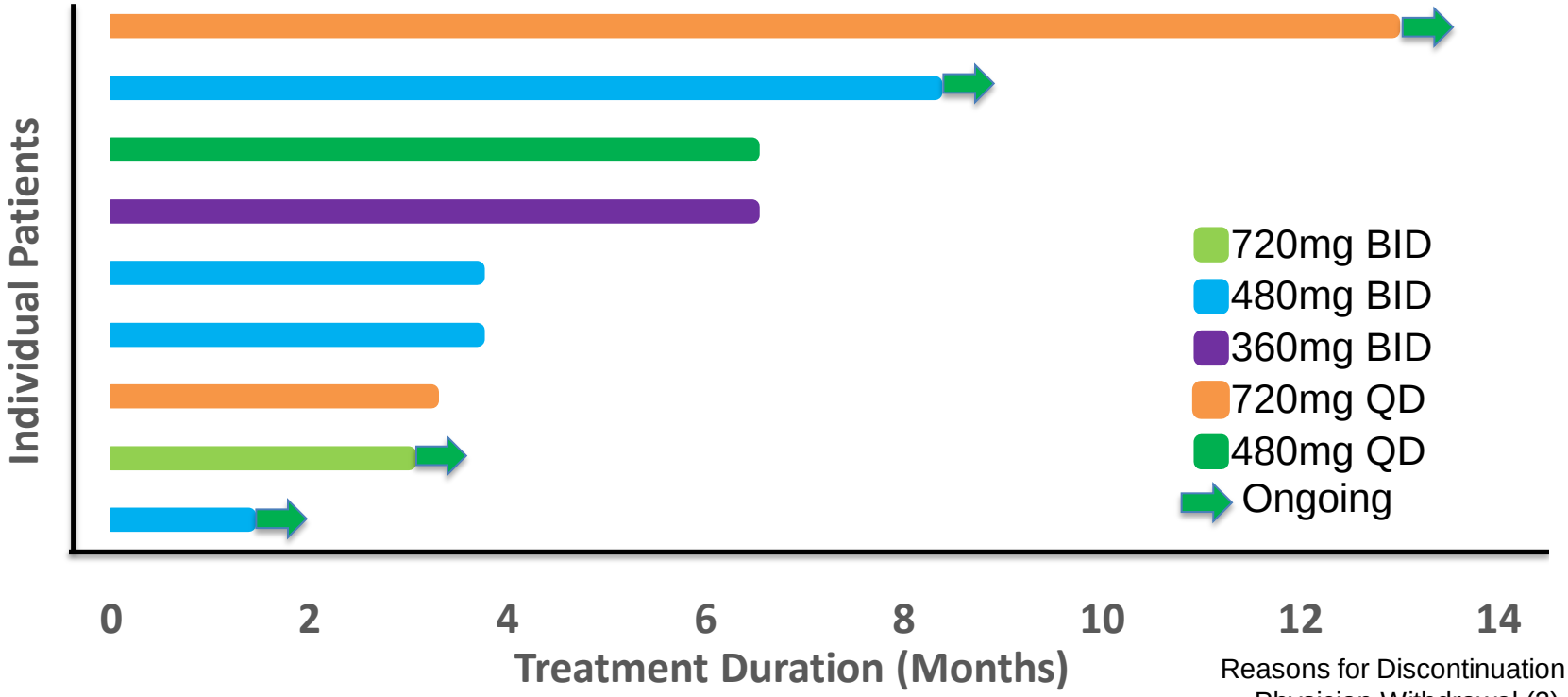
- MF-SAF v4.0 (Max TSS 70): Baseline symptom burden median 21 (4 to 62)
- 8 evaluable patients on treatment ≥ 12 weeks
- 7 of 8 have TSS reduction
  - Median -66%
  - 5 of 8 patients have ≥ 50% TSS reduction

Dose 480mg QD | 720mg QD | 360mg BID | 480mg BID | 720mg BID

Response to JAK Inhibitor: ⊗ = Primary Refractory ☆ = Loss of Response — = Intolerant

Preliminary data as of 11-OCT-2022

TP-3654: Duration of Treatment



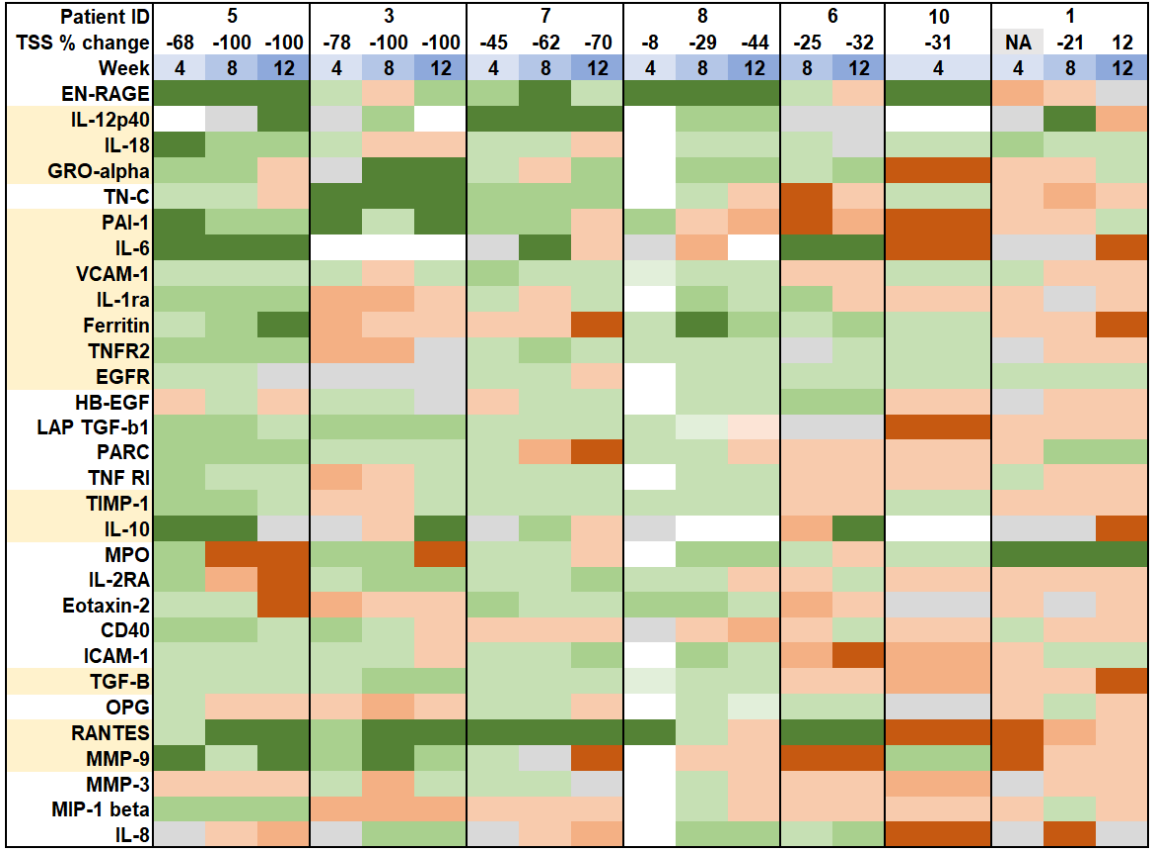
- No discontinuation due to AE

Reasons for Discontinuation
- Physician Withdrawal (2)
- Progression (2)
- Patient Withdrawal (1)

Preliminary data as of 11-OCT-2022

TP-3654: PIM1 Inhibition Leads to Early Reduction in Cytokines

- Cytokine reduction observed as early as Week 4 from initial dose cohorts
- Cytokine reduction generally correlate with TSS reduction
- 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 change relative to baseline

Reduction	> 0 - 25%	>25 - 50%	> 50%
Increase	> 0 - 25%	>25 - 50%	> 50%
No change			

Preliminary data as of 11-OCT-2022

Conclusions: TP-3654 an Oral Selective PIM1 Inhibitor for MF

- PIM1, a novel 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 RANTES and TGF-B
- PIM1 kinase inhibition leads to reduced bone marrow fibrosis, splenomegaly, and improved overall survival in MF **mouse models** with minimal effect on platelet count.
- **TP-3654 is an oral selective PIM1 kinase inhibitor**
  - **Dose escalation is ongoing and TP-3654 appears to be well tolerated, no DLT to date, and the most common AE are Grade 1 GI toxicities that resolved in 1-2 weeks**
  - **Preliminary signs of clinical activity include spleen volume reduction, symptom improvement, and broad cytokine reduction**
- Enrollment is ongoing as monotherapy and current data support the development of TP-3654 as potential partner combination with JAK inhibitors given preliminary activity signals observed and the lack of cytopenia