Preliminary Results From a Phase I Dose Escalation Trial of Ruxolitinib and the PI3Kδ Inhibitor TGR-1202 in Myelofibrosis

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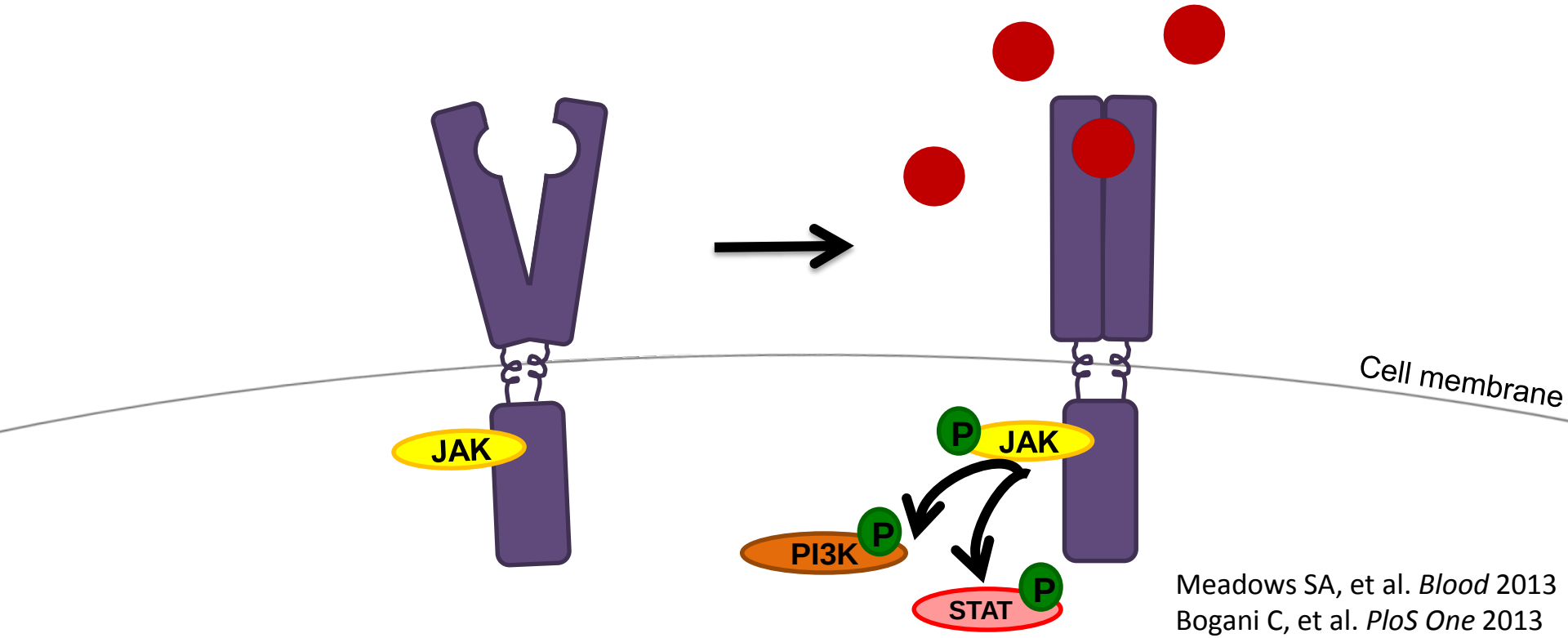
Background

- The JAK1/2 inhibitor ruxolitinib improves symptoms, reduces spleen size, and improves overall survival in Intermediate-2/High risk myelofibrosis.
- Response is variable, but few patients achieve complete remission.
- Loss of response remains a major problem.

Verstovsek S, et al. *NEJM* 2012
Harrison CN, et al. *NEJM* 2012
Harrison CN, et al. *Leukemia* 2016

PI3 Kinase and Myelofibrosis

- PI3Kδ is overexpressed in MF patient samples, independent of ruxolitinib pre-exposure.
- Inhibition of PI3K/AKT signaling reduced proliferation and clonogenic potential of hematopoietic progenitors of MF patients.



Meadows SA, et al. *Blood* 2013
Bogani C, et al. *PloS One* 2013

TGR-1202 is a potent PI3Kδ Inhibitor

- Highly selective for PI3Kδ isoform

Fold-selectivity				
Isoform	PI3Kα	PI3Kβ	PI3Kγ	PI3Kδ
TGR-1202	>1000	>50	>48	1
[1]Idelalisib	>300	>200	>40	1
[2]IPI-145	>640	>34	>11	1

TGR-1202 is a potent PI3Kδ Inhibitor

- Highly selective for PI3Kδ isoform
- Led to apoptosis in leukemia and lymphoma cell lines
- Was well-tolerated, with a toxicity profile distinct from that of ruxolitinib and other PI3Kδ inhibitors

Definite, Probable, or Possibly Related AEs (N=22)

Adverse Event, n	Grade 1 & 2 (>5% of patients)	Grade ≥ 3 (all events)
Diarrhea	4	-
Neutropenia	-	1
Rash	-	1
Thrombocytopenia	-	1

Savona MR, et al. *Blood* 2013

Hypothesis

Addition of TGR-1202 to ruxolitinib could *resensitize* or *augment* the response of MF patients with suboptimal response to single-agent ruxolitinib.

Phase I Study Design

- Two escalation stages based on a 3+3 (Up and Down) design:

  – Stage I: Any stable dose of ruxolitinib + escalating dose of TGR-1202

  – Stage II: Escalating doses of ruxolitinib + maximum tolerated dose of TGR-1202

Study Objectives

- **Primary Objectives:**
  - To evaluate safety of TGR-1202 in combination with ruxolitinib
  - To evaluate pharmacokinetics of TGR-1202 administered with ruxolitinib

- **Secondary Objectives:**
  - To evaluate efficacy of the drug combination
    - Marrow response
    - Hematologic parameters
    - Symptom burden

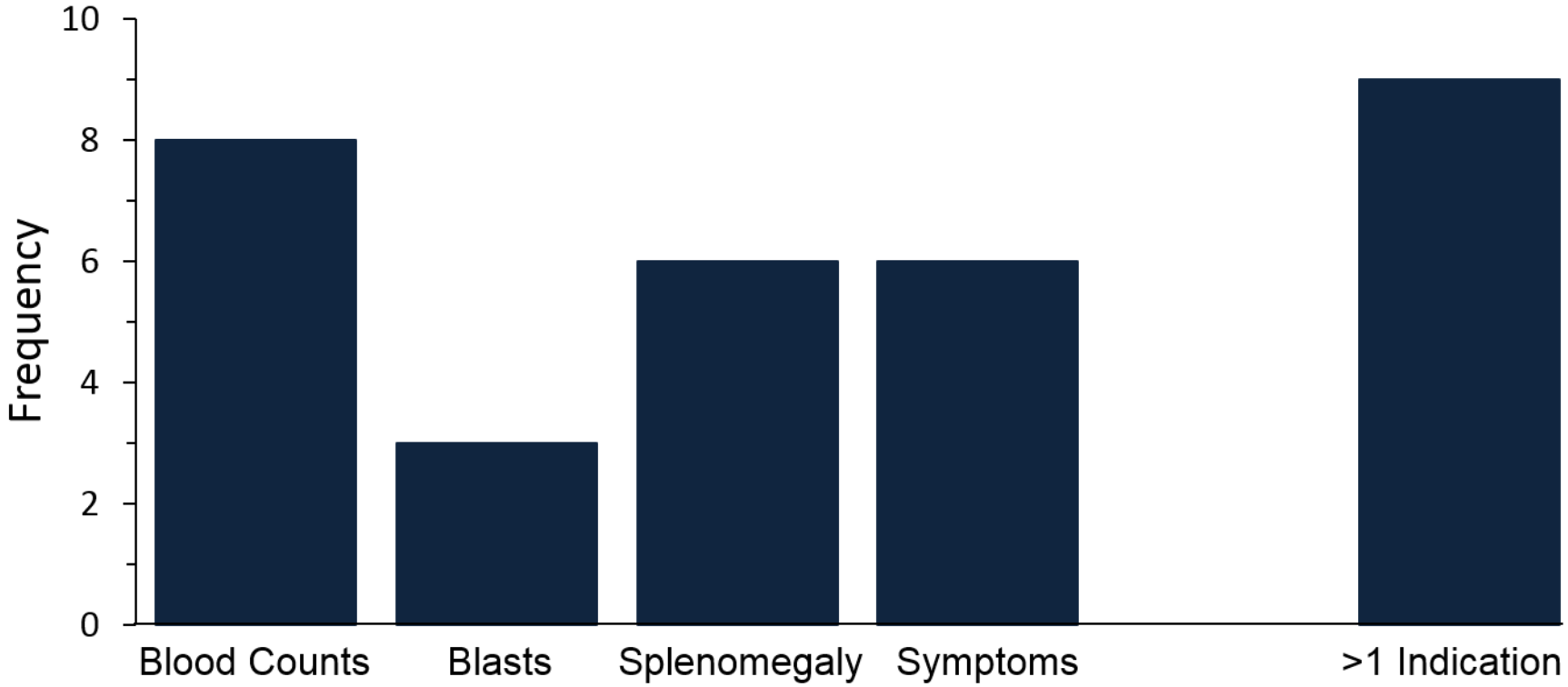
Study population

- Adult patients with PPV-MF, PET-MF, or PMF
- ≥ Grade 1 marrow fibrosis
- Intermediate -1 risk or higher disease by the DIPSS
- Lost, suboptimal or no response to a stable dose of ruxolitinib for at least 8 weeks
- No prior PI3K or mTOR inhibition
- ECOG PS 0-2
- Adequate organ function
- Life expectancy ≥ 6 months

Patient Characteristics

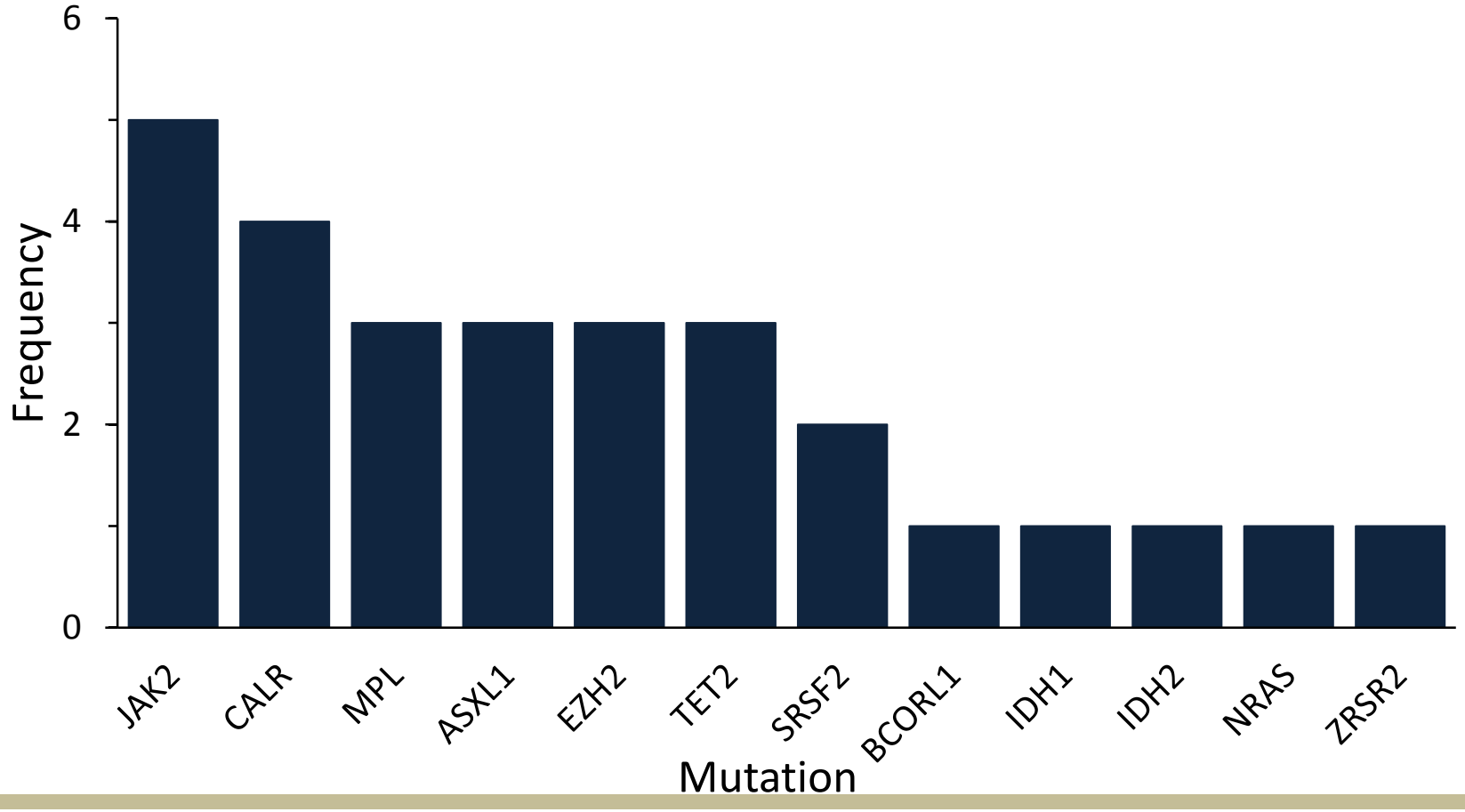
Baseline Characteristics	N=12 (range)
Median Age	66.5 (52-81)
Male	8
MF Subtype	
Primary MF	5
PET MF	4
PPV MF	3
DIPSS Plus	
Int-1	4
Int-2	6
High	2
Median Plt x10^{-9}/L	252 (108-1139)
Median Hgb g/dL	10.0 (8.5-12.9)
Median ANC x10^{-9}/L	5.3 (1.8-10.4)
Leukoerythroblastosis	9
Splenomegaly	7
JAK2 ^{V617F}	5
CALR	4
MPL	3

Patient Characteristics



Baseline Mutation Status

- Next Generation Sequencing of 37 genes commonly mutated in myeloid disease



Baseline Mutation Status

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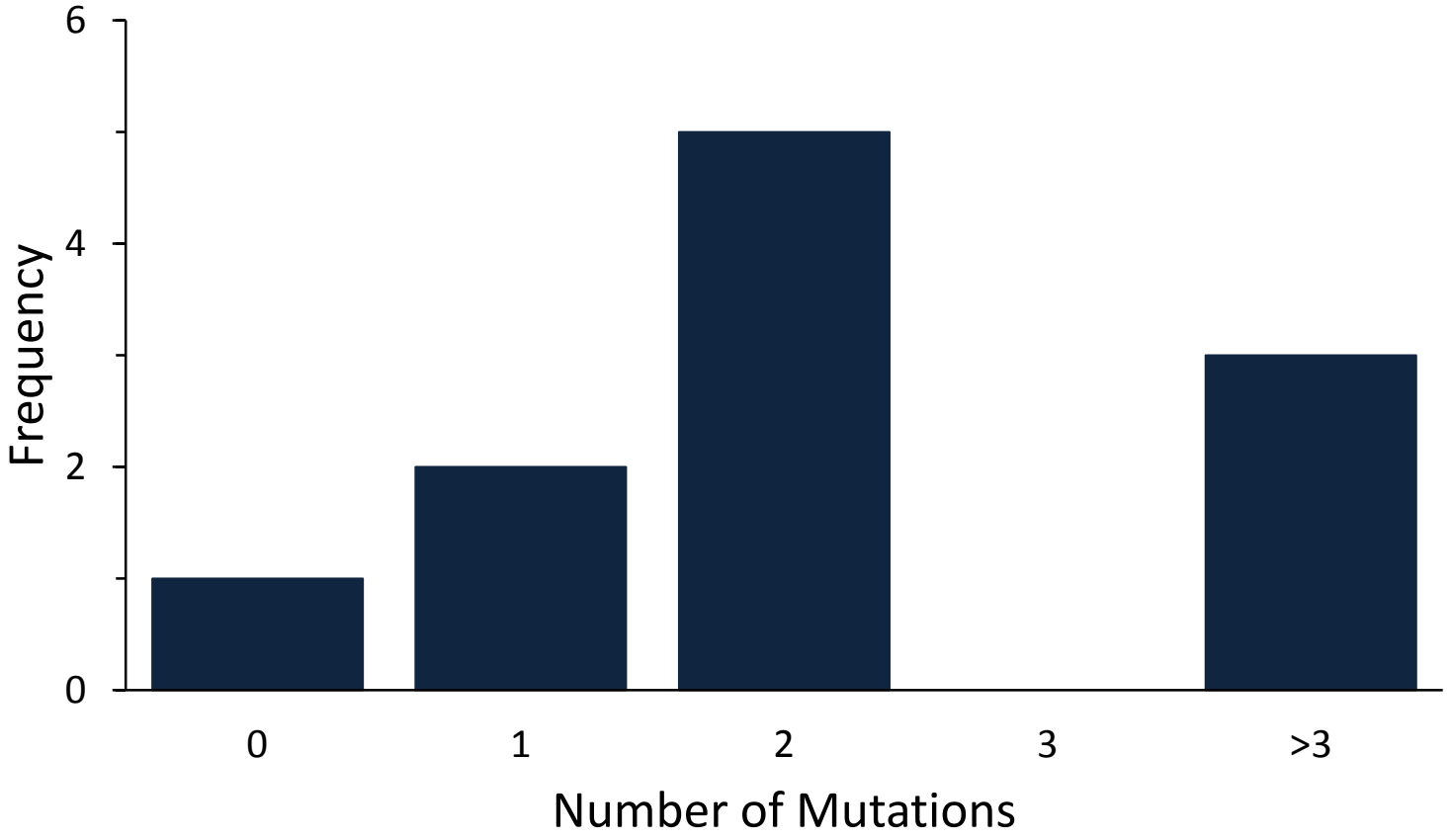
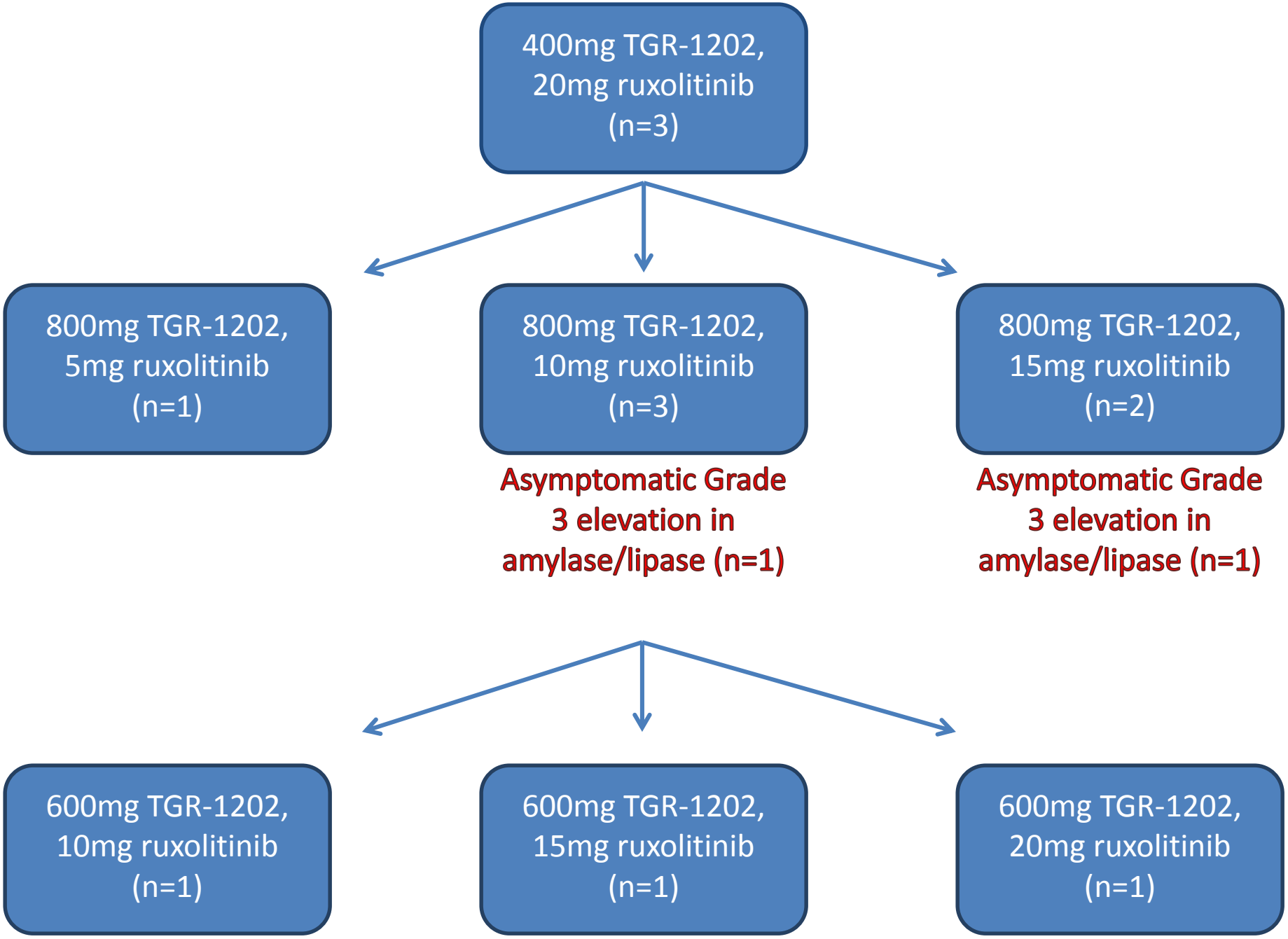



400mg TGR-1202, 20mg ruxolitinib (n=3)
800mg TGR-1202, 5mg ruxolitinib (n=1)
800mg TGR-1202, 10mg ruxolitinib (n=3)
800mg TGR-1202, 15mg ruxolitinib (n=2)
Asymptomatic Grade 3 elevation in amylase/lipase (n=1)
Asymptomatic Grade 3 elevation in amylase/lipase (n=1)
600mg TGR-1202, 10mg ruxolitinib (n=1)
600mg TGR-1202, 15mg ruxolitinib (n=1)
600mg TGR-1202, 20mg ruxolitinib (n=1)

Adverse Events (any cause)

Event	n (%)	Grade 1	Grade 2	Grade 3	Grade 4
Anemia*		1 (8.3%)	7 (58.3%)		
Thrombocytopenia		3 (25%)			
Neutropenia		1 (8.3%)	1 (8.3%)	1 (8.3%)	
Leukocytosis				1 (8.3%)	
AST/ALT elevation		5 (41.7%)			
Amylase/lipase elevation		1 (8.3%)		2 (16.7%)	
Neck pain				1 (8.3%)	
Mucositis				1 (8.3%)	
Diarrhea*				2 (16.7%)	
Dyspnea*				1 (8.3%)	
Pneumonia*			1 (8.3%)		1 (8.3%)
Sepsis*					1 (8.3%)

*Unrelated events in one patient

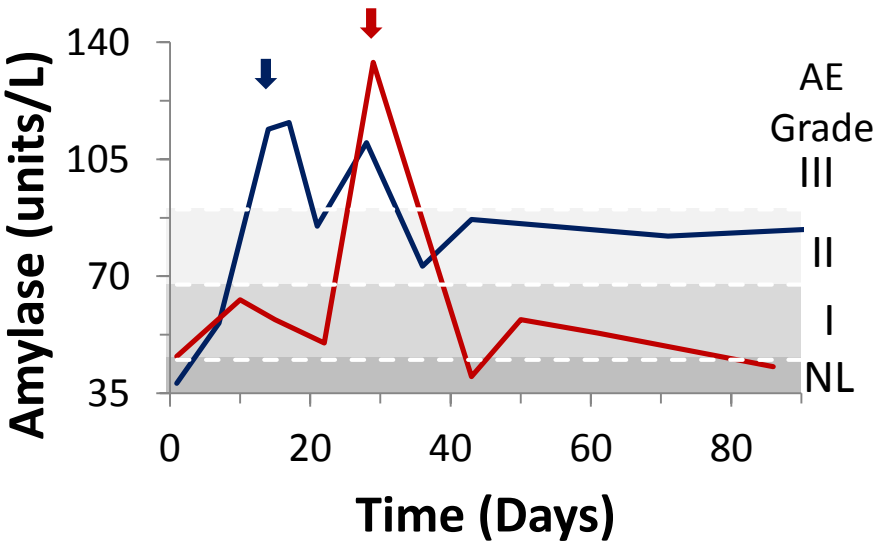
Adverse Events (any cause)

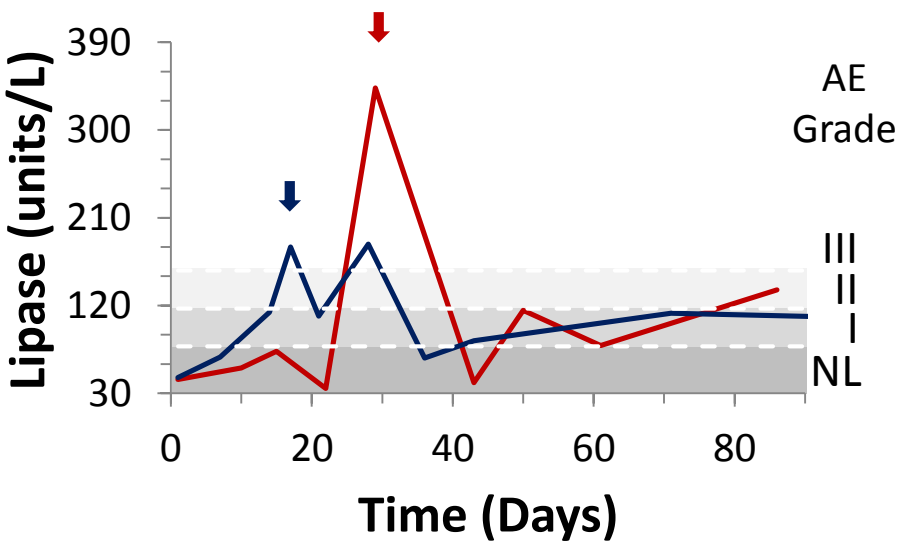
At least possibly related to TGR-1202

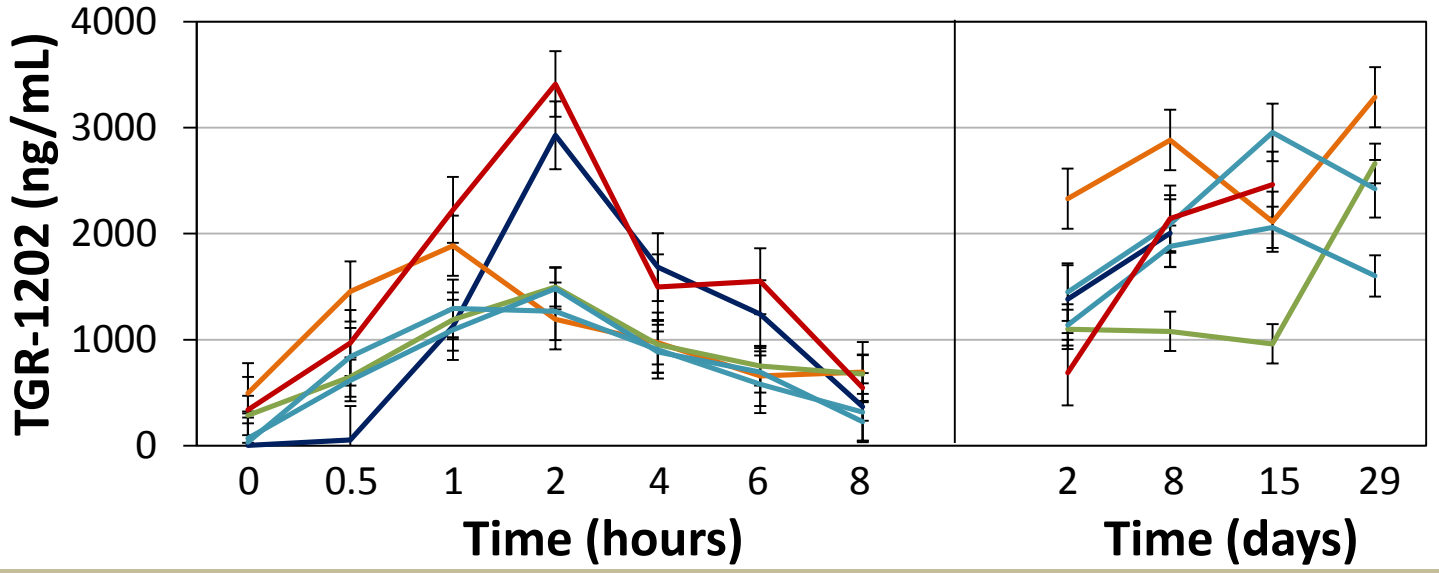
Event	n (%)	Grade 1	Grade 2	Grade 3	Grade 4
Anemia*			2 (16.7%)		
Thrombocytopenia		3 (25%)			
Neutropenia			1 (8.3%)		
Leukocytosis					
AST/ALT elevation		2 (16.7%)			
Amylase/lipase elevation		1 (8.3%)		2 (16.7%)	
Neck pain					
Mucositis					
Diarrhea*				1 (8.3%)	
Dyspnea*					
Pneumonia*					
Sepsis*					

*Unrelated events in one patient

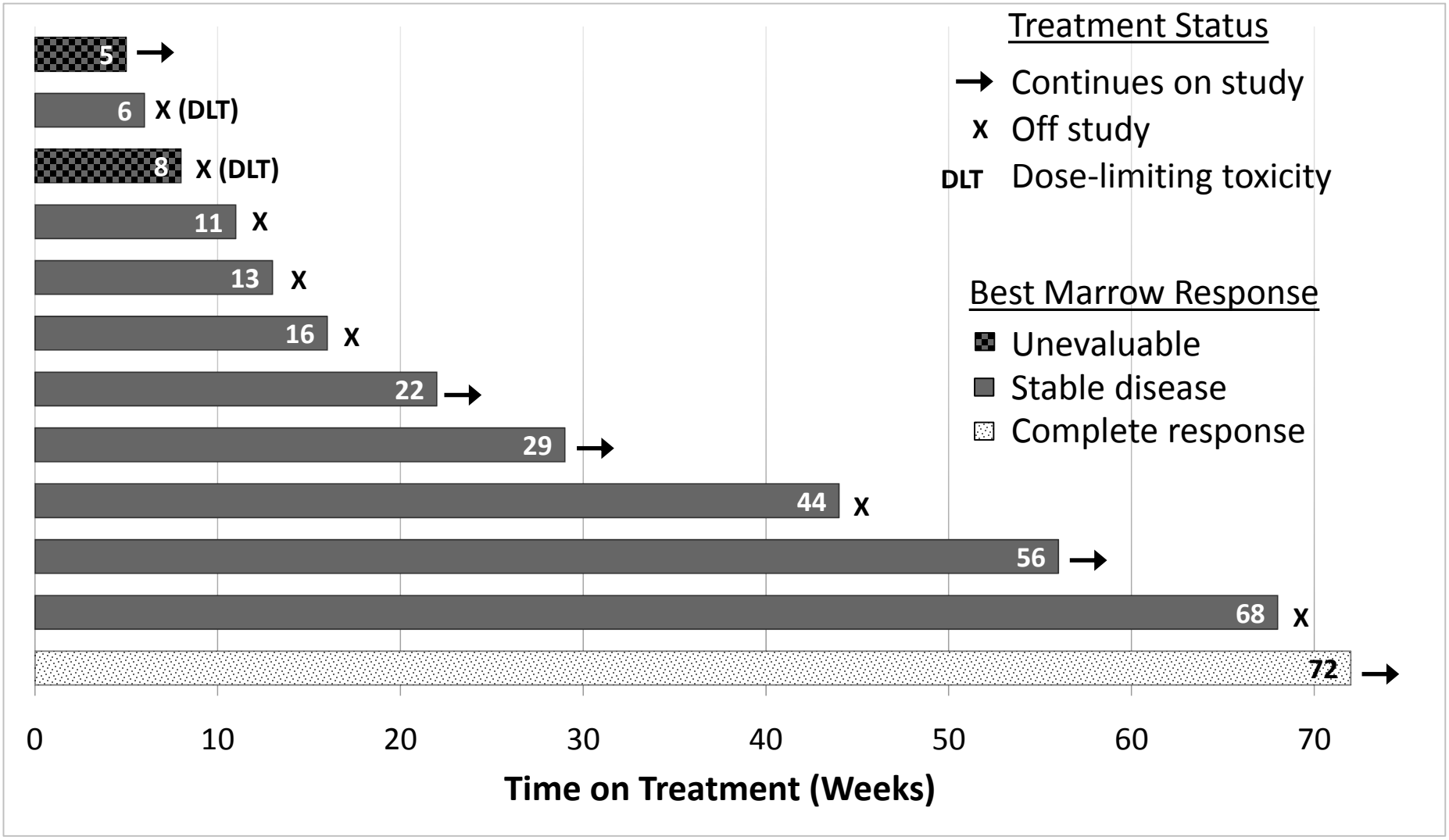
Safety/Pharmacokinetics



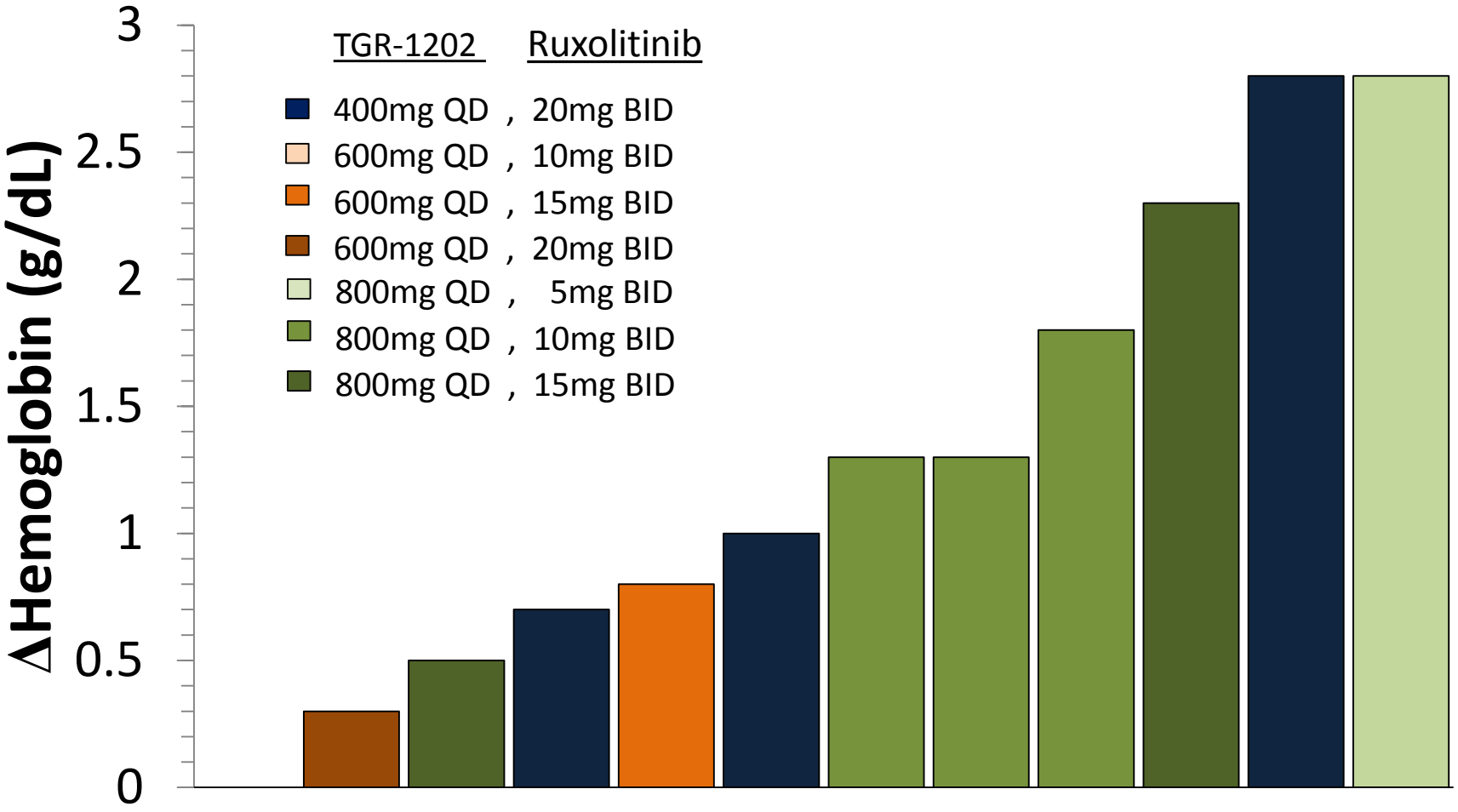




Treatment Outcomes

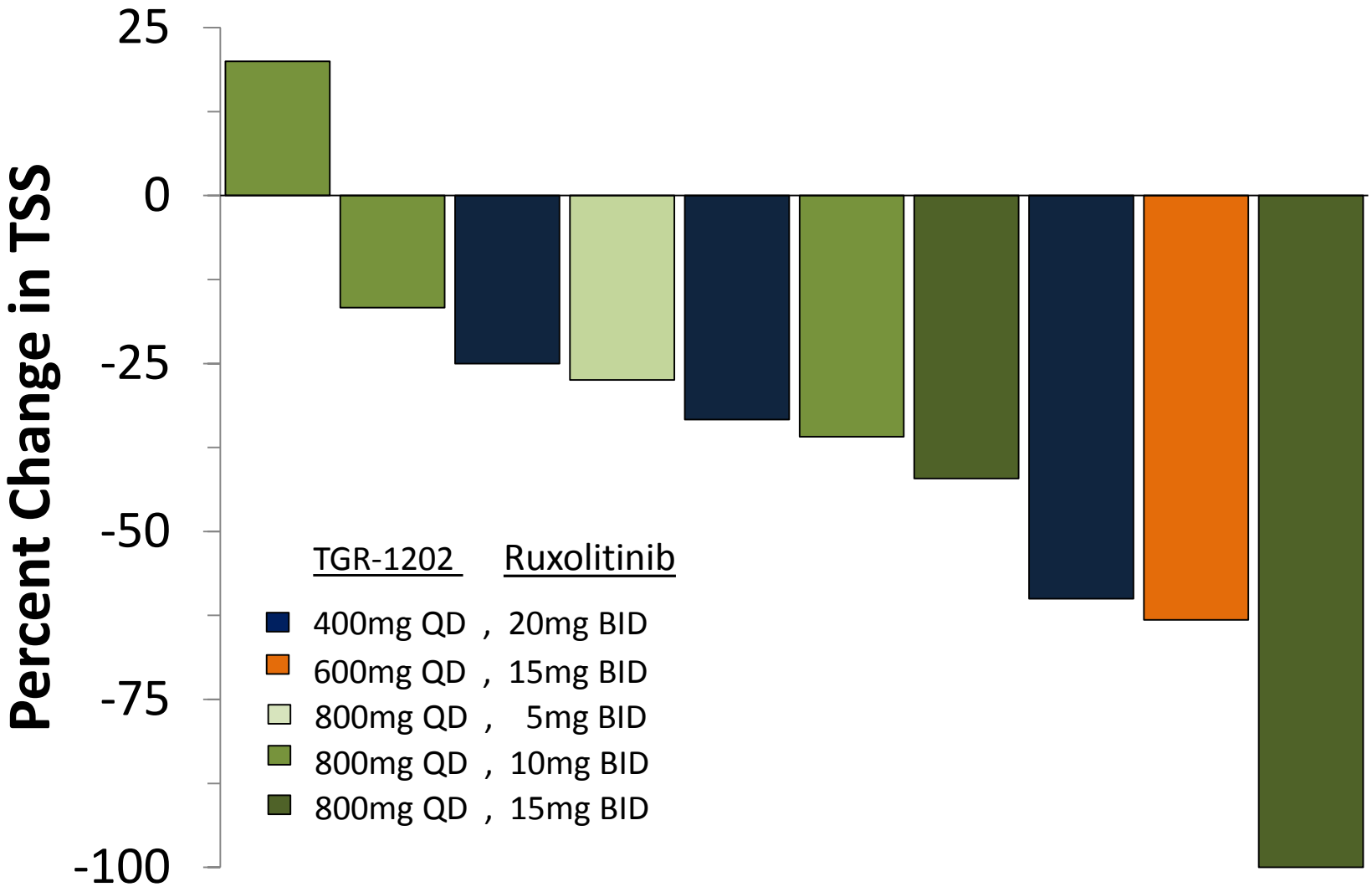


Best Hemoglobin Response



Baseline platelet >375 x 10^9/L

Symptom Reduction



Conclusions

- TGR-1202 + ruxolitinib was well-tolerated.
- Ruxolitinib does not alter absorption or metabolism of TGR-1202.
- Maximum tolerated dose of TGR-1202 was 600 mg by mouth daily.
- 83% of study participants experienced clinical benefit (hematologic improvement, reduced spleen size and/or improvement in symptoms).
- Further exploration of the drug combination in myelofibrosis is warranted.

Ongoing Research

- Stage 2 of the Dose Escalation Study of TGR-1202 + Ruxolitinib in Myelofibrosis
- Does combination therapy reduce pro-inflammatory cytokine production in a predictable and meaningful way?
- Does treatment reduce mutation burden in the bone marrow? Is there clonal evolution?
- Do intracellular signaling patterns correlate with disease response?

Acknowledgements

- Savona lab
  Michael Savona
  Andrew Sochacki
- Vanderbilt CTSR
- Division of Hematology/ Oncology

The patients and their families

- Collaborators
  Dan Ayers
  Lynne Berry
  Laura Michaelis
  Ruben Mesa
- Funding
  TG Therapeutics

VANDERBILT-INGRAM CANCER CENTER

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