Resurrecting response to ruxolitinib: A Phase I study of ruxolitinib and umbralisib (TGR-1202) in ruxolitinib-experienced myelofibrosis

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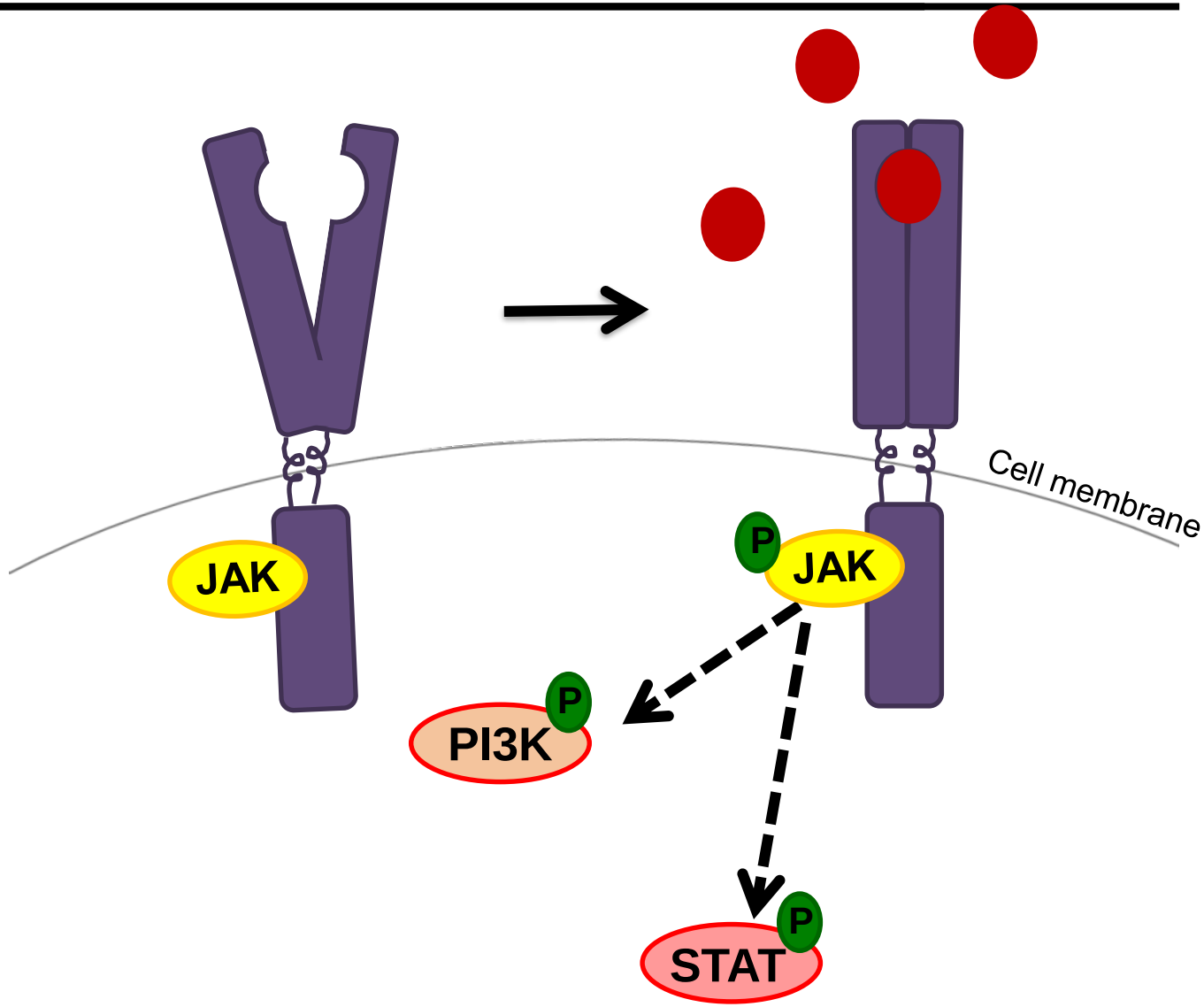
Background

- The JAK1/2 inhibitor ruxolitinib improves symptoms, reduces spleen size, and improves overall survival in Intermediate-2/High risk myelofibrosis.
- Depth of response is variable.
- Loss of response to ruxolitinib poses a clinical challenge
  - Alternative therapies are currently limited
  - OS after failure of ruxolitinib response is poor.
- New *adjunct* therapies may resurrect or amplify inhibition of JAK-STAT signaling, and/or improve outcomes in myelofibrosis.

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

PI3Kδ is overexpressed in myelofibrosis

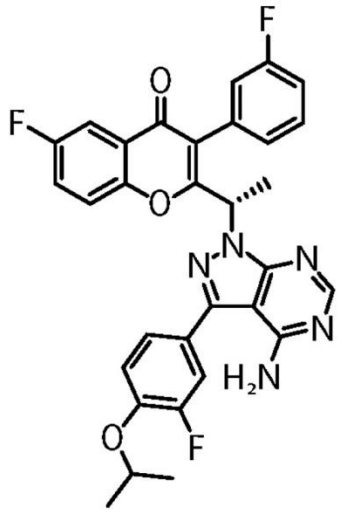
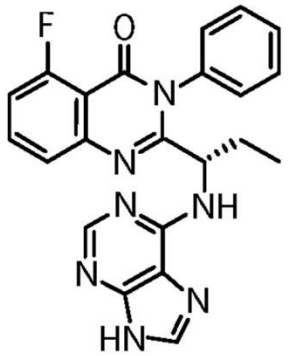
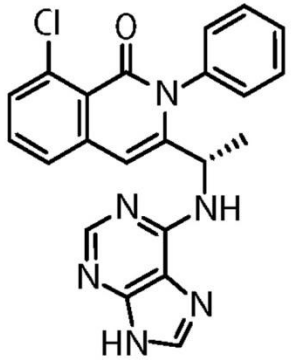
- PI3Kδ is overexpressed in PMF patient samples irrespective of prior exposure to ruxolitinib.
- Inhibition of PI3K/AKT signaling reduces proliferation and clonogenic potential of hematopoietic progenitors of PMF patients.



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

Umbralisib (TGR-1202) is highly selective for PI3Kδ

- Chemically distinct from other inhibitors in its class.
- More selective than other PI3K inhibitors for the delta isoform.
- Led to apoptosis in AML and ALL cell lines and patient-derived AML, ALL, and CLL cells

	Umbralisib	Idelalisib	Duvelisib
			
Isoform	K_d (nM)		
PI3Kα	>10 000	600	40
PI3Kβ	>10 000	19	0·89
PI3Kγ	1400	9·1	0·21
PI3Kδ	6·2	1·2	0·047

Friedman DR, et al. *Blood* 2012
Vakkalanka S, et al. *Blood* 2012
Burris HA, et al. *Lancet Oncology* 2018

Single-agent umbralisib is well-tolerated

Adverse Event	Umbralisib	Idelalisib		Duvelisib	Ruxolitinib
	n = 90 CLL	n=125 NHL	n=110 CLL*	n=210 LEUK/LYMPH	n=155 MF
Anemia	9%	2%	5%	19%	45%
Neutropenia	13%	27%	42%	32%	7%
Thrombocytopenia	6%	6%	10%	14%	13%
Hepatotoxicity	3-6%	13%	5-9%	19%	
Colitis	2%	3%	11%	6%	
Diarrhea	3%	13%		11%	1.9%
Pneumonitis		2%	4%	4%	
Dyspnea	4%	3%	2%	11%	1.3%

* in combination with rituximab

- Toxicity profile is distinct from other PI3Kδ inhibitors and ruxolitinib
- Most common side effects were diarrhea, fatigue, and nausea/vomiting.
  - Majority of diarrhea was Gr 1 and resolved without intervention
  - Two cases of colitis in patients receiving dose that exceeds the RP2D (800 mg daily)

Burris HA, et al. *Lancet Oncology* 2018
Gopal AK, et al. *NEJM* 2014
Furman RR, et al. *NEJM* 2014
Flinn IW, et al. *Blood* 2018
Verstovsek S, et al. *NEJM* 2012

Hypothesis

Addition of umbralisib to ruxolitinib could *augment* or *re-sensitize* response for patients with *suboptimal or lost response* to single-agent ruxolitinib.

Study design and patient populations

Ruxolitinib-experienced Myelofibrosis (MF)

- PMF, post-PV MF or post-ET MF
- Grade ≥1 fibrosis
- Lost, suboptimal or no response on a stable dose of ruxolitinib for ≥ 8 weeks

ESCALATION STAGE 1
Ruxolitinib-experienced MF

Stable ruxolitinib + Escalating umbralisib

ESCALATION STAGE 2
Ruxolitinib-experienced MF

Escalating ruxolitinib + Umbralisib MTD from ES1

EXPANSION COHORT 1
Ruxolitinib-experienced MF

EXPANSION COHORT 2
Treatment-naïve MF

EXPANSION COHORT 3
Polycythemia vera

EXPANSION COHORT 4
CMML

EXPANSION COHORT 5
Other MDS/MPNs

Stable ruxolitinib (cleared ES2) + Umbralisib MTD from ES1

Patient characteristics

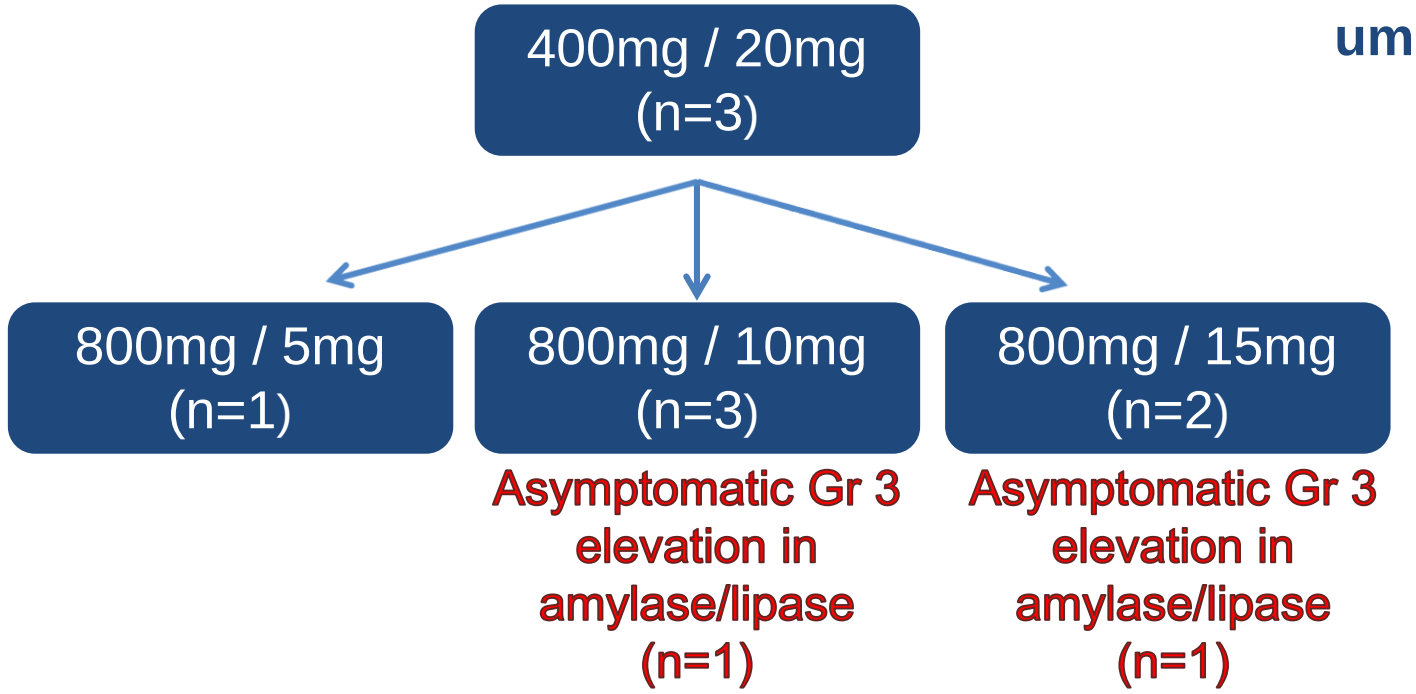
Baseline Characteristic	n = 23 (range)
Median Age	67 (49-83)
Male	14
Diagnosis	
Primary MF	7
PET MF	10
PPV MF	6
ECOG PS	
0	9
1	12
2	2
DIPSS Plus	
Low (Score 0)	0
Int-1 (Score 1-2)	8
Int-2 (Score 3-4)	8
High (Score 5-6)	7

Baseline Characteristic	N = 23(range)
Median Plt x10^{-9}/L	197 (34-1420)
Median Hgb g/dL	9.5 (8.5-13.9)
Median ANC x10^{-9}/L	6.7 (2.1-57.1)
Splenomegaly	14
<5cm below LCM	7
5-10 cm below LCM	4
>10 cm below LCM	3
Driver Mutation Status	
JAK2 ^{V617F}	10
CALR	7*
MPL	4*
Triple-negative	3

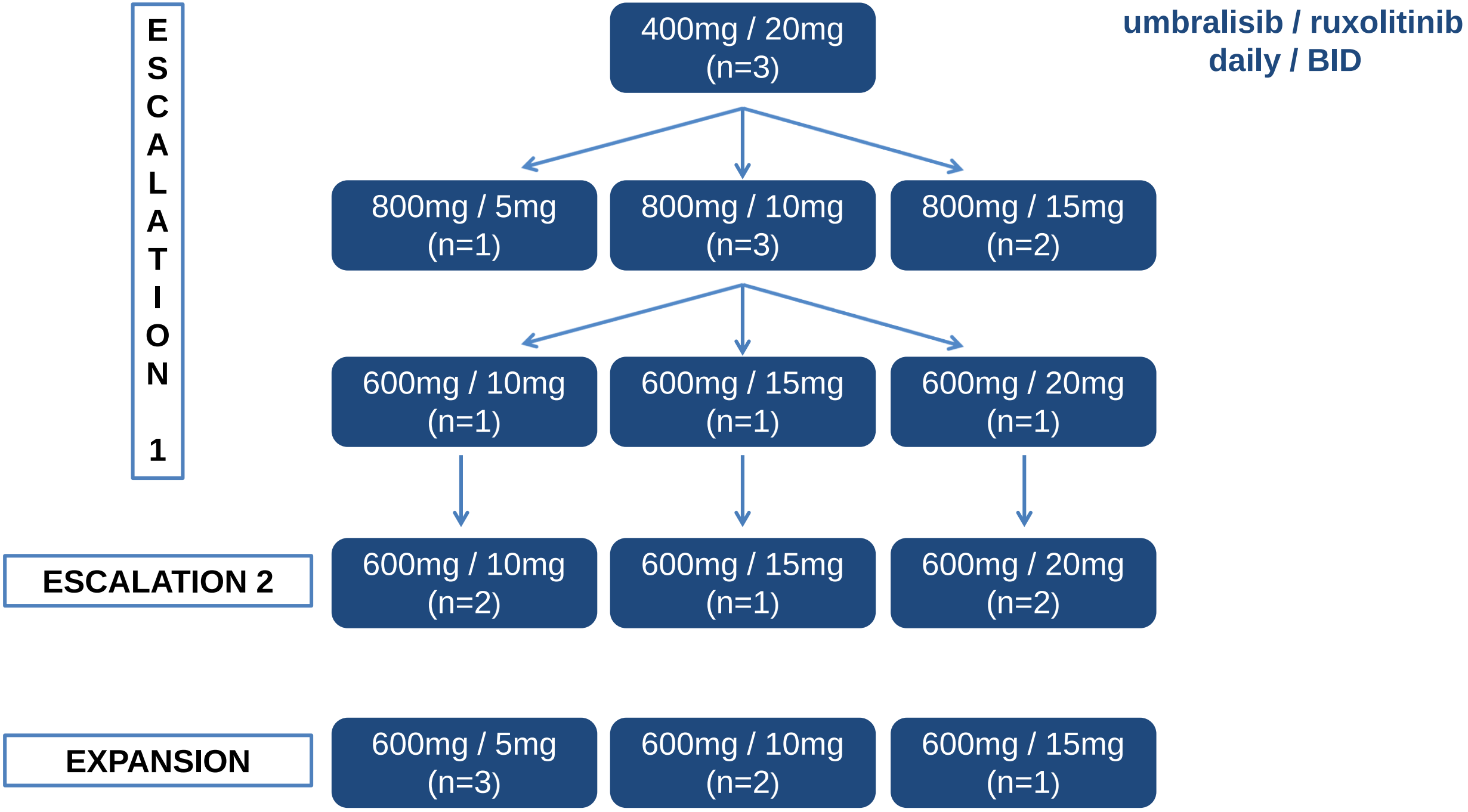
*co-occurring CALR & MPL mut in 1 patient

Safety

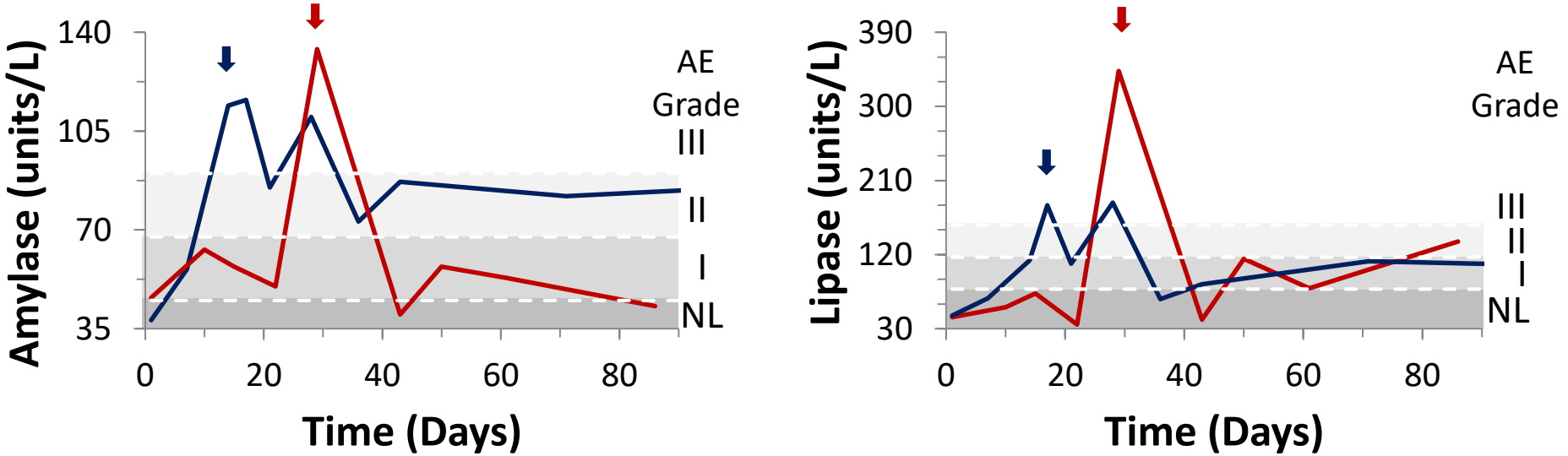
ESCALATION 1

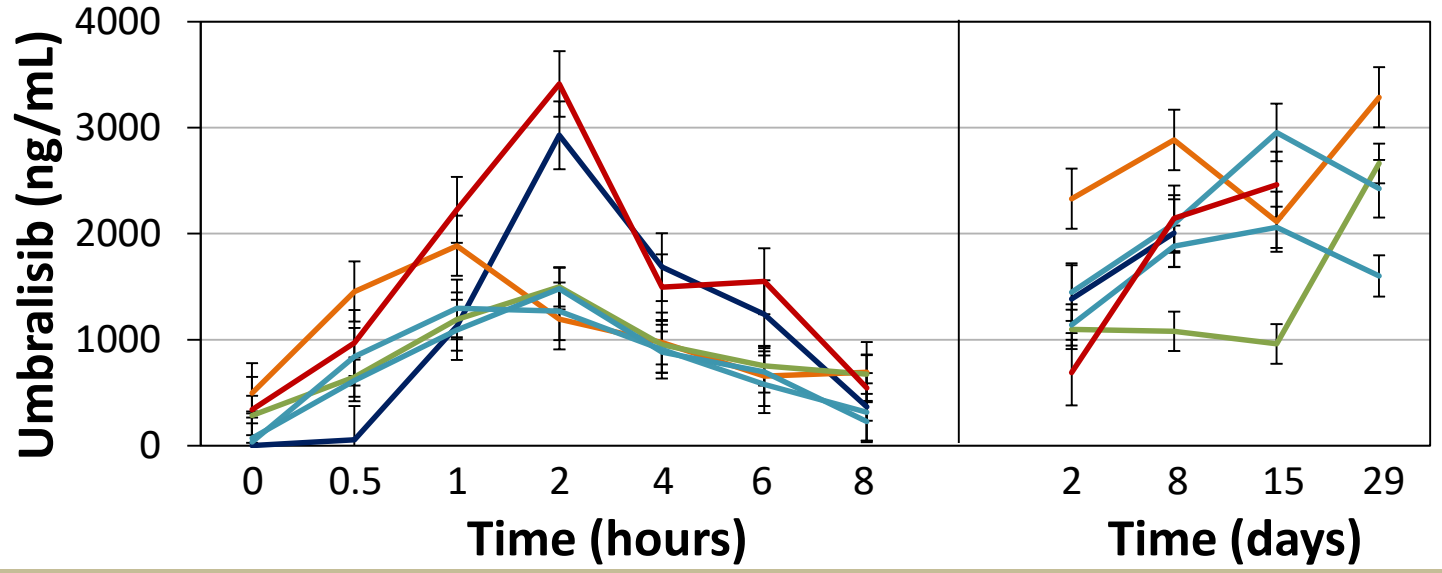


umbralisib / ruxolitinib daily / BID


umbralisib / ruxolitinib
daily / BID
ESCALATION 1
400mg / 20mg (n=3)
800mg / 5mg (n=1)
800mg / 10mg (n=3)
800mg / 15mg (n=2)
600mg / 10mg (n=1)
600mg / 15mg (n=1)
600mg / 20mg (n=1)
ESCALATION 2
600mg / 10mg (n=2)
600mg / 15mg (n=1)
600mg / 20mg (n=2)
EXPANSION
600mg / 5mg (n=3)
600mg / 10mg (n=2)
600mg / 15mg (n=1)

Dose limiting toxicity investigation





Adverse events (all cause)

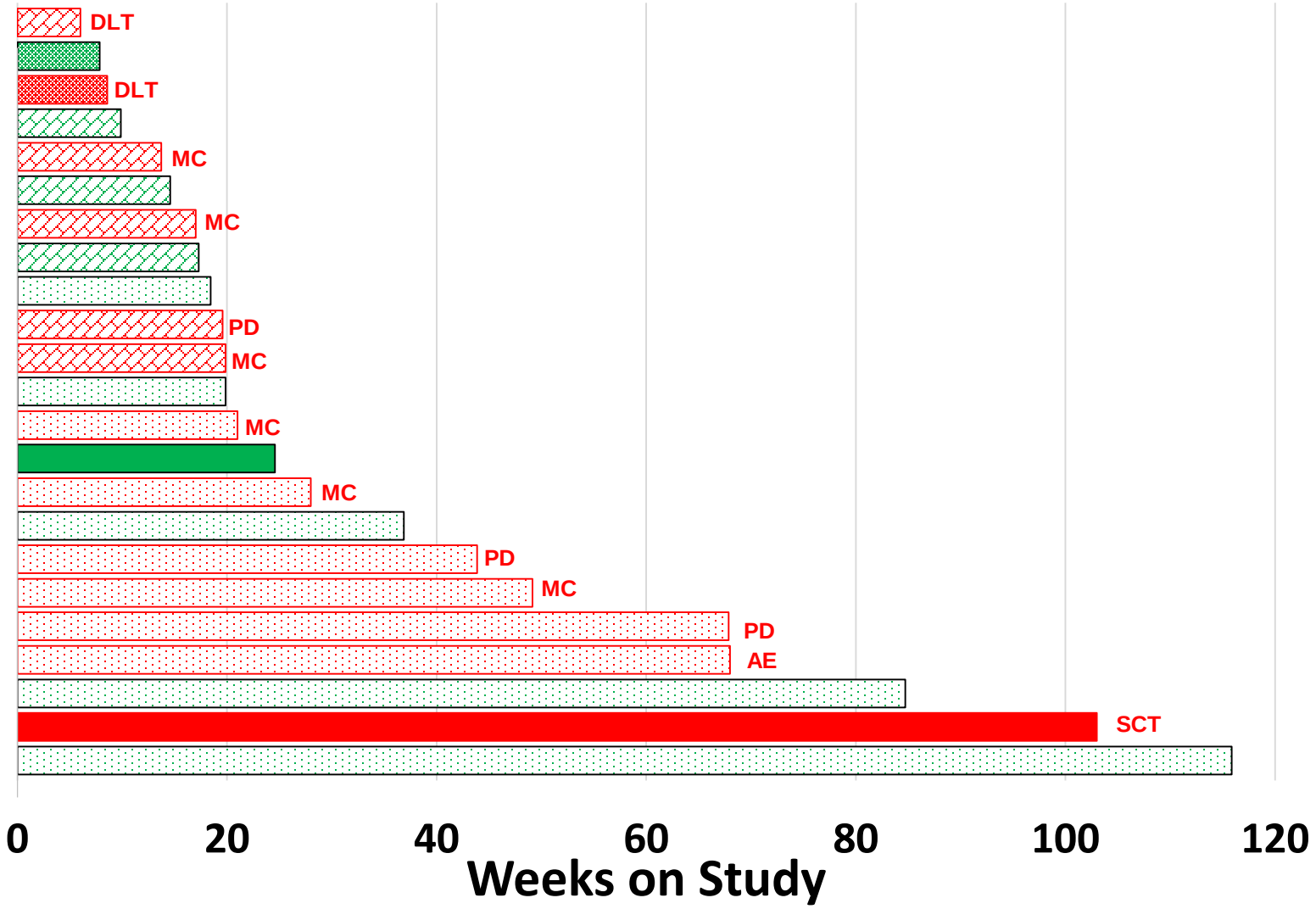
- Seventeen subjects experienced at least one adverse event (AE).
- Thirteen subjects collectively experienced 17 AEs Grade ≥ 3.

Most Common (>5%) AEs and all AEs of Special Interest

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)
Anemia	1 (4%)	6 (26%)	3 (13%)	-
Neutrophil decreased	-	-	2 (9%)	-
Platelet count decreased	3 (13%)	2 (9%)	-	-
AST increased	6 (26%)	-	-	-
ALT increased	3 (13%)	-	-	-
Amylase increased	1 (4%)	-	2 (9%)	-
Lipase increased	1 (4%)	-	2 (9%)	-
Diarrhea	-	-	2 (9%)	-
Colitis	-	-	1 (4%)	-
Dyspnea	-	-	1 (4%)	-
Upper respiratory infection	-	2 (9%)	-	-
Pneumonia	1 (4%)	2 (9%)	1 (4%)	-
Other infections	-	4 (17%)	2 (9%)	-
Sepsis	-	-	-	1 (4%)

Efficacy

IWG-MRT & ELN responses to umbralisib + ruxolitinib



Best IWG-MRT & ELN Response*

- Not Assessed
- Stable Disease
- Clinical Benefit
- Complete Remission

Status

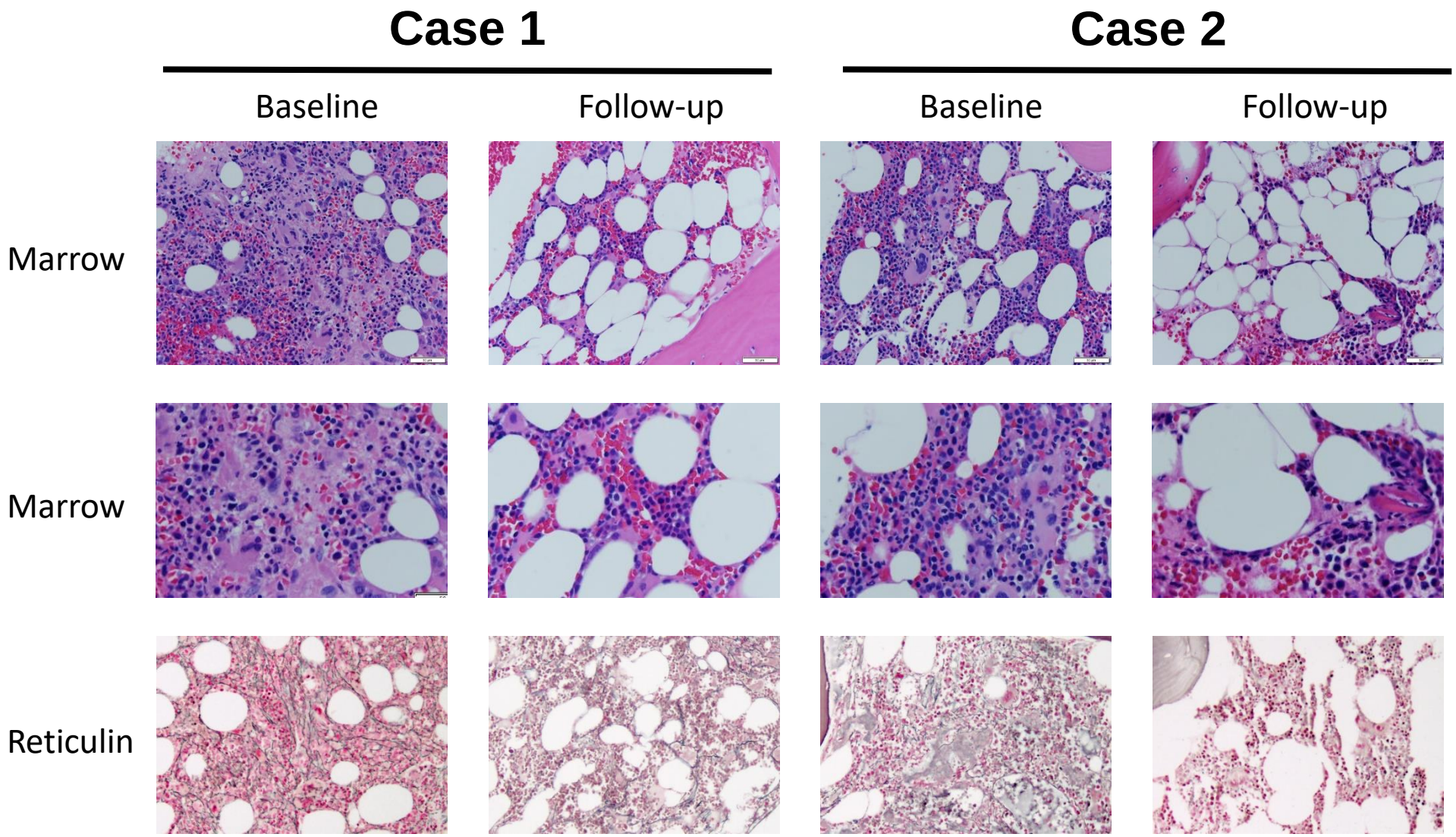
- Off-study
- Continues on Treatment

Off Study Reason

- DLT Dose-limiting Toxicity (n=2)
- AE Adverse Event (n=1)
- PD Progressive Disease (n=3)
- MC Physician or Patient Decision (n=6)
- SCT Transplant (n=1)

* Tefferi A, et al. *Blood* 2013

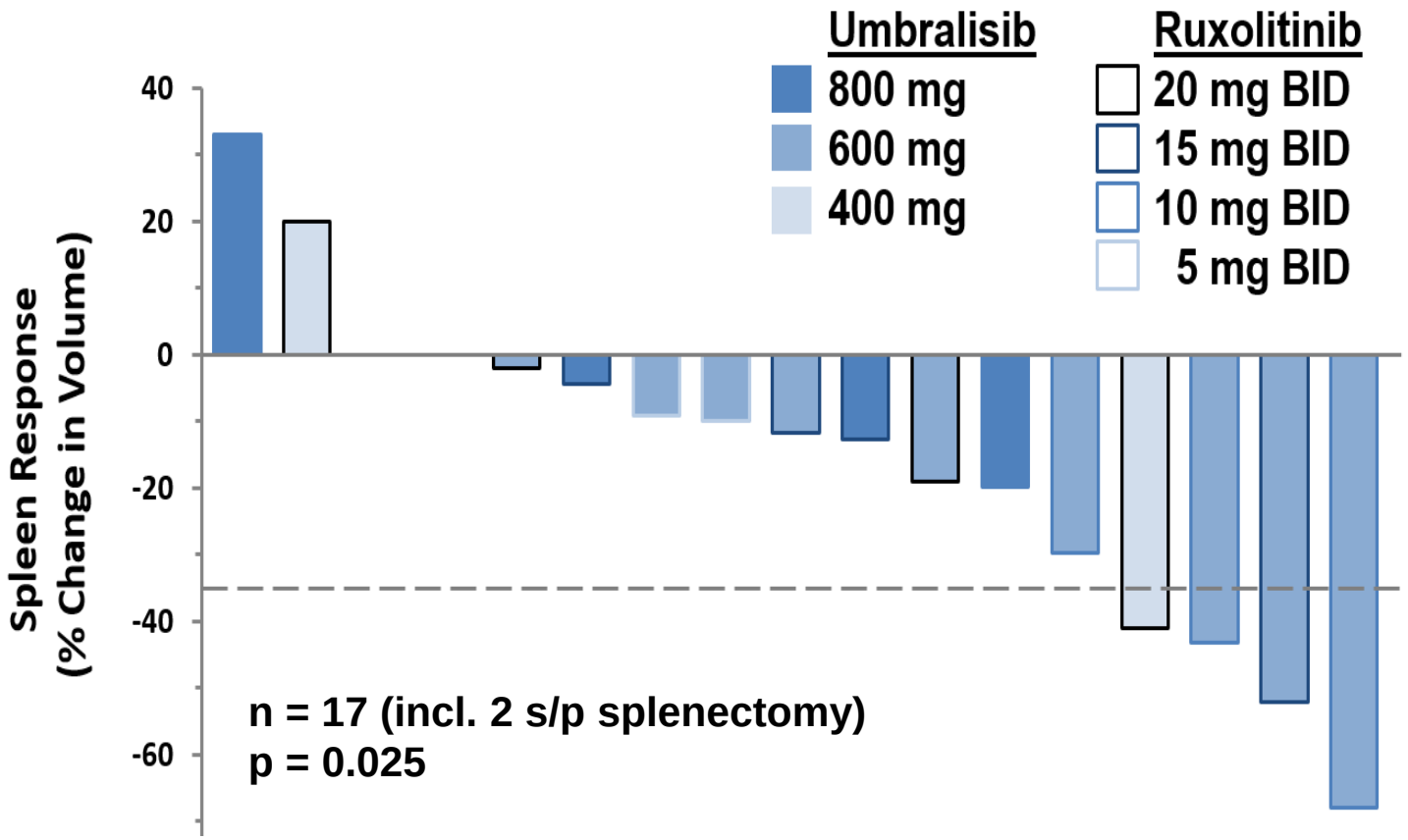
Two subjects achieved complete remission

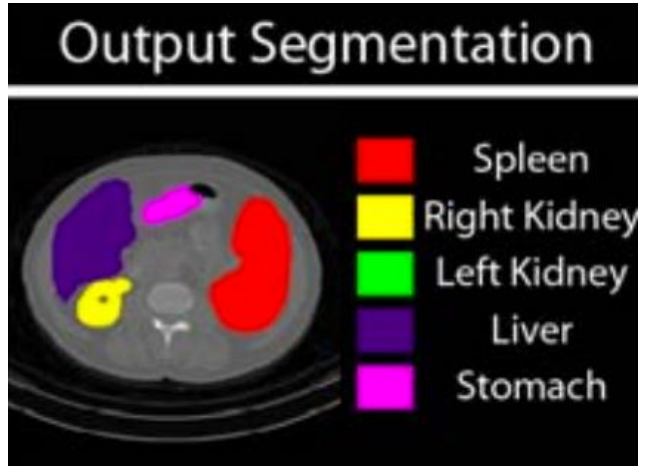


Complete remission case comparison

	Case 1	Case 2
Diagnosis	Post-ET MF	Post-PV MF
EHA Fibrosis Score	MF-2	MF-1
DIPSS Risk	Intermediate-1	Intermediate-1
Driver Mutation	MPL 515W	JAK2 V617F
Stable dose of ruxolitinib	20 mg BID	15 mg BID
Measures of insufficient response	Thrombocytosis, leuko-erythroblastosis, persistent MF-related symptoms	New MF-related symptoms, rising LDH, thrombocytosis
Umbralisib dose	400 mg QD	600 mg QD
First notation of CR	Cycle 15	Cycle 5
Outcome	Remained on study 2y → MRD HSCT and NED ~1yr	Remains on study, currently cycle 12

Umbralisib augments rux to reduce spleen volume

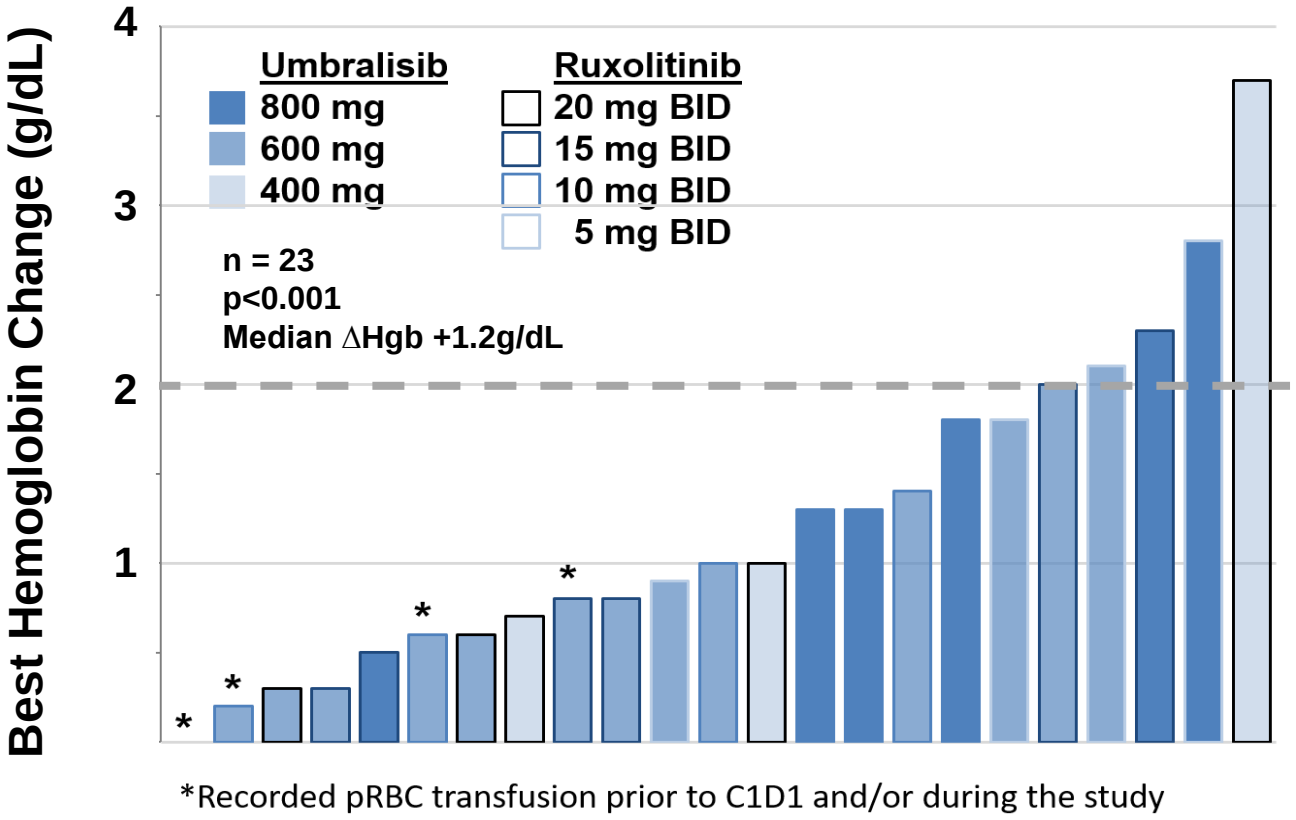


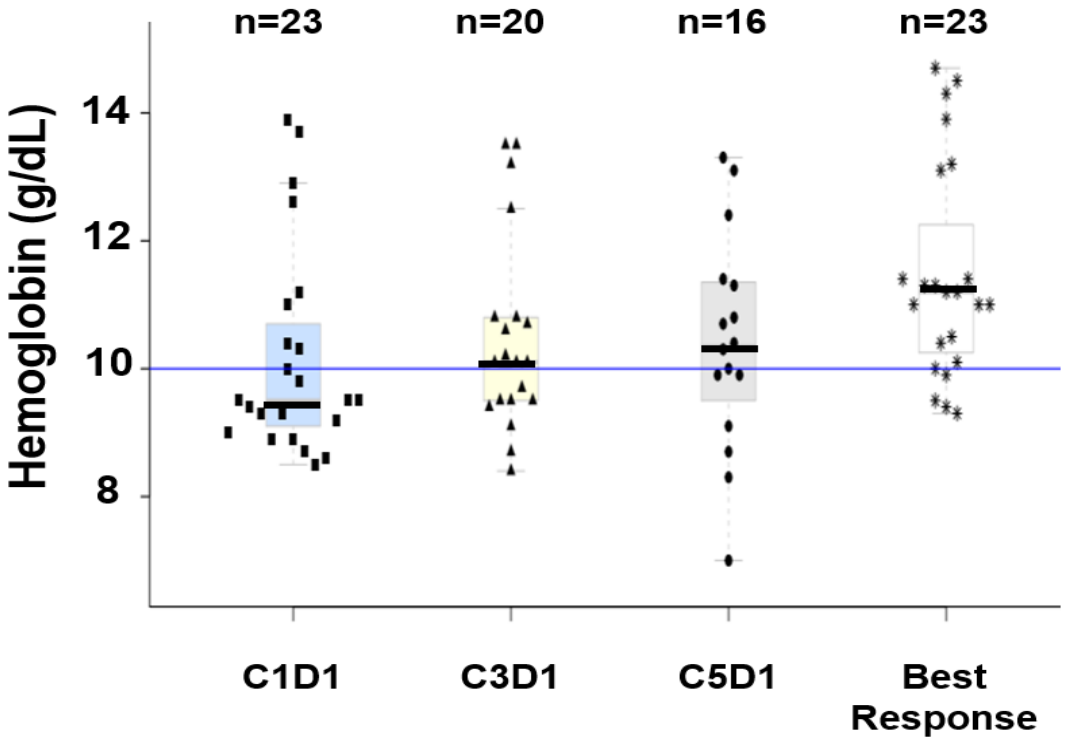


- Spleen volume determined from CT images using synthetic segmentation network
- Median decrease in spleen volume by 13% (mean 18%)
  - Largest absolute reductions in spleen size with baseline spleen volumes >1000 cm^3

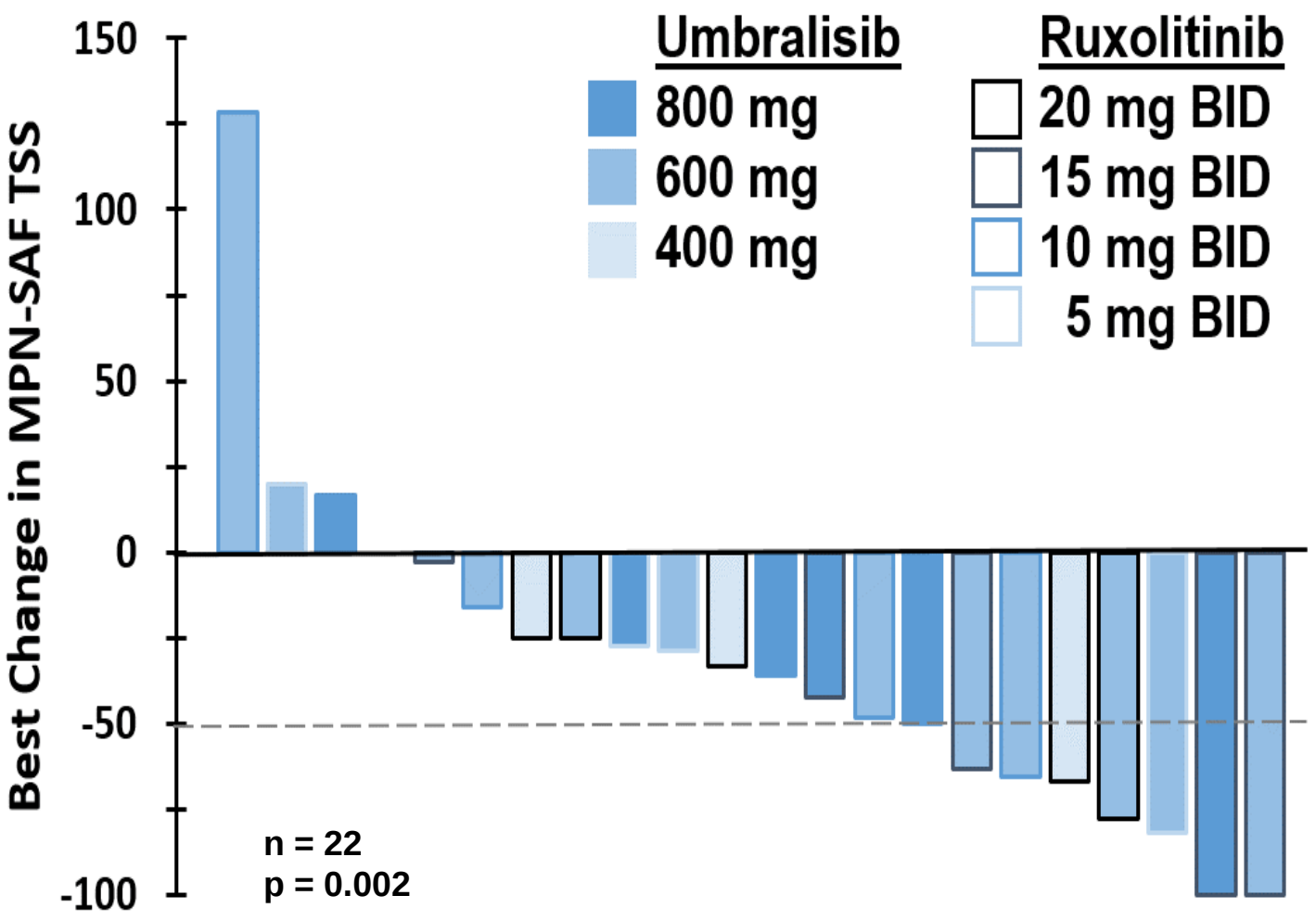
Umbralisib led to increase in hemoglobin levels

- Five subjects achieved >2 g/dL increase in hemoglobin
  - Median time to >2 g/dL was 141 days (range 36-197 days)
  - Response was sustained beyond 100 days in 3/5 subjects





Umbralisib improved MF-related symptoms



- Majority of subjects had improvement in MF-related symptoms after addition of umbralisib to ruxolitinib
- Seven subjects achieved IWG-MRT and ELN Symptom Response criterion (50% reduction)
- Median response was 35% reduction in MPN-SAF total symptom score

Conclusions

- Umbralisib + ruxolitinib was well-tolerated
  - Dose-limiting toxicities of asymptomatic amylase/lipase elevations of unclear clinical consequence
  - AST/ALT elevations were mild and transient.
  - Only one event of colitis (in pt with known mesenteric ischemia) and no pneumonitis
- Increases in hemoglobin, improvements in spleen size, and reduction in symptoms meeting IWG-MRT criteria for clinical improvement were seen in 13 (57%) ruxolitinib-experienced myelofibrosis patients.
- Importantly, 2 patients (9%) achieved a durable complete remission after progressing on ruxolitinib.
- **The addition of umbralisib to ruxolitinib can augment or resurrect a response in myelofibrosis patients who had suboptimal or lost response to ruxolitinib alone.**
- Further exploration of this combination in a randomized study is warranted.

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