Mielofibrosi

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Disclosures

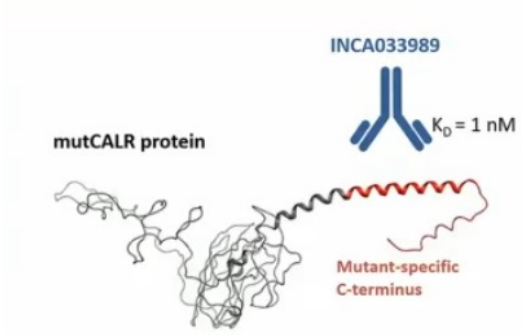
- F Passamonti received honoraria for lectures and advisory boards from Novartis, Bristol-Myers Squibb/ Celgene, Sierra Oncology, Abbvie, Janssen, Roche, AOP Orphan, Karyiopharma, Kyowa Kirin and MEI, GSK.

Molecular predictors of RUX response/loss of response

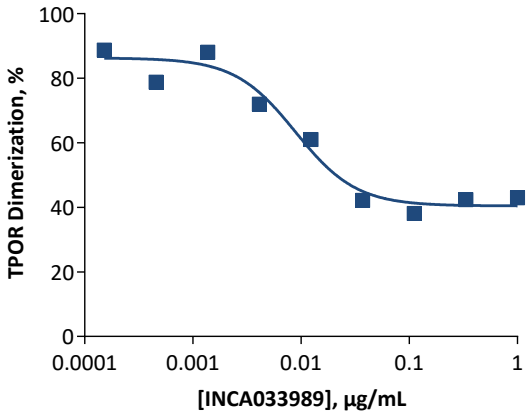
- *Bad baseline molecular predictors (171 patients with MF)*
  - HMR status
  - >1 *RAS* pathway mutated gene (*CBL, NRAS, KRAS, PTPN11*)
  - Isolated *CBL* and *U2AF1*

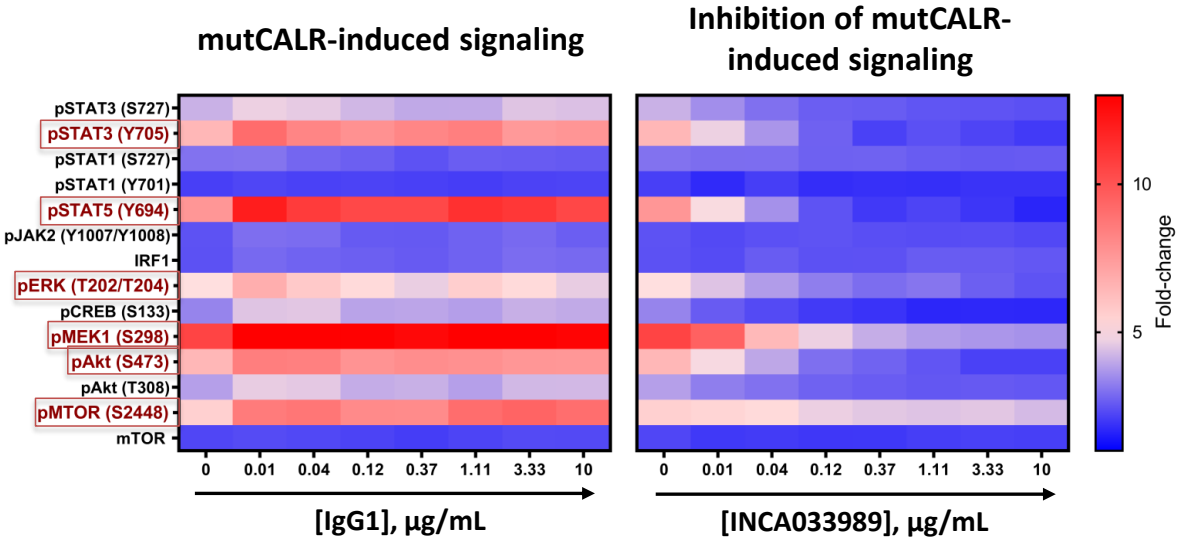
Guglielmelli et al ASH 2022 abs 342

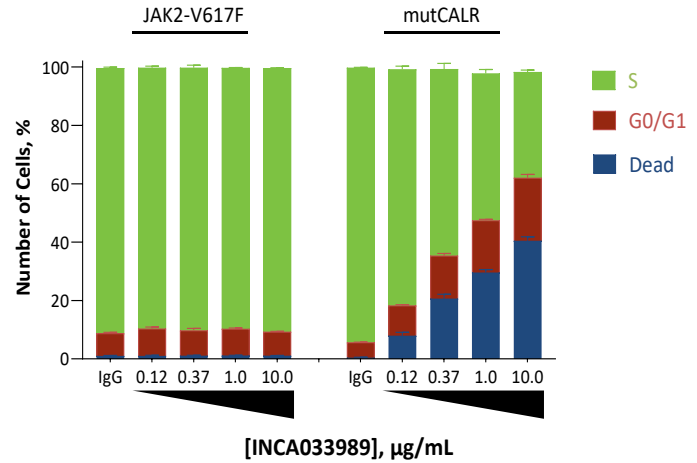
INCA033989: a monoclonal antibody that selectively antagonizes mutant CALR function



- INC989 reverts mutCALR-induced TPO dimerization
- INC989 inhibits mutCALR-induced oncogenic signaling
- INC989 selectively inhibits cell proliferation and induces death of mutCALR+ cells







- INC989 targets disease-initiating (stem) cells

Reis et al, ASH 2022. Plenary

- JAKi update

Fedratinib: FREEDOM study design

Screening

Key inclusion criteria

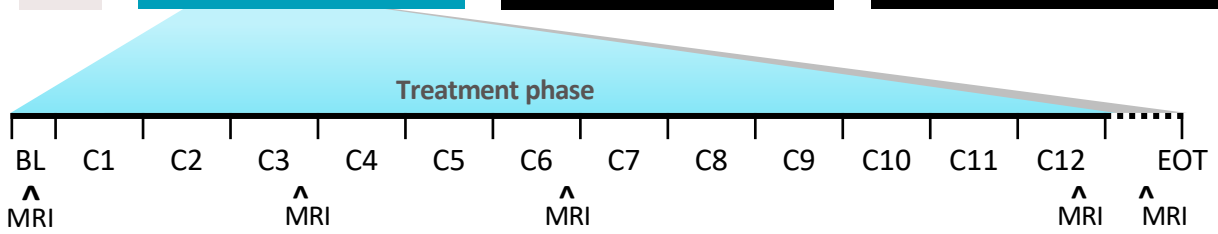
- Age ≥ 18 years
- WHO[2]-defined primary, post-PV, or post-ET MF
- DIPSS[3] intermediate-1, intermediate-2, or high-risk MF
- ECOG PS score 0–2
- Splenomegaly ≥ 450 cm³ (MRI) or palpable spleen ≥ 5 cm below LCM
- Prior ruxolitinib treatment for ≥ 3 months, or for ≥ 28 days with development of RBC TD (≥ 2 units/month for 2 months) or grade ≥ 3 thrombocytopenia, anemia, hematoma, or hemorrhage
- Platelet count ≥ 50 × 10^9/L
- ANC ≥ 1.0 × 10^9/L
- Peripheral blasts < 5%
- Normal thiamine level

Enrollment N ≈ 110

Treatment phase
Fedratinib 400 mg QD
Continuous 28-day treatment cycles

Treat until
- Lack of efficacy
- Intolerance
- Disease progression
- Withdrawal of consent

EOT/follow-up
- Patients followed for AEs (30 days) and survival (12 months) after treatment discontinuation



Primary endpoint
- Spleen RR: proportion of patients with ≥ 35% SVR from BL at EOC6

Key secondary endpoints
- Safety
- Duration of spleen response
- Spleen size reduction
- Symptom RR and duration
- Risk-mitigation strategies for GI AEs, neurotoxicity, and WE

Exploratory endpoints
- Survival
- Patient-reported outcomes
- Biomarkers of fedratinib efficacy and biochemical activity

AE mitigation strategies:
- Prophylactic/symptomatic use of anti-emetic/vomiting and anti-diarrheal Tx
- Administration of fedratinib with food
- Fedratinib dosing modifications
- Thiamine supplementation

- 38 patients were enrolled and treated (enrollment stopped early for Covid-19)
- At database cutoff (Nov2021), median treatment duration was 38 (2–124) weeks
- 13 patients had ongoing FEDR; 25 patients had discontinued FEDR

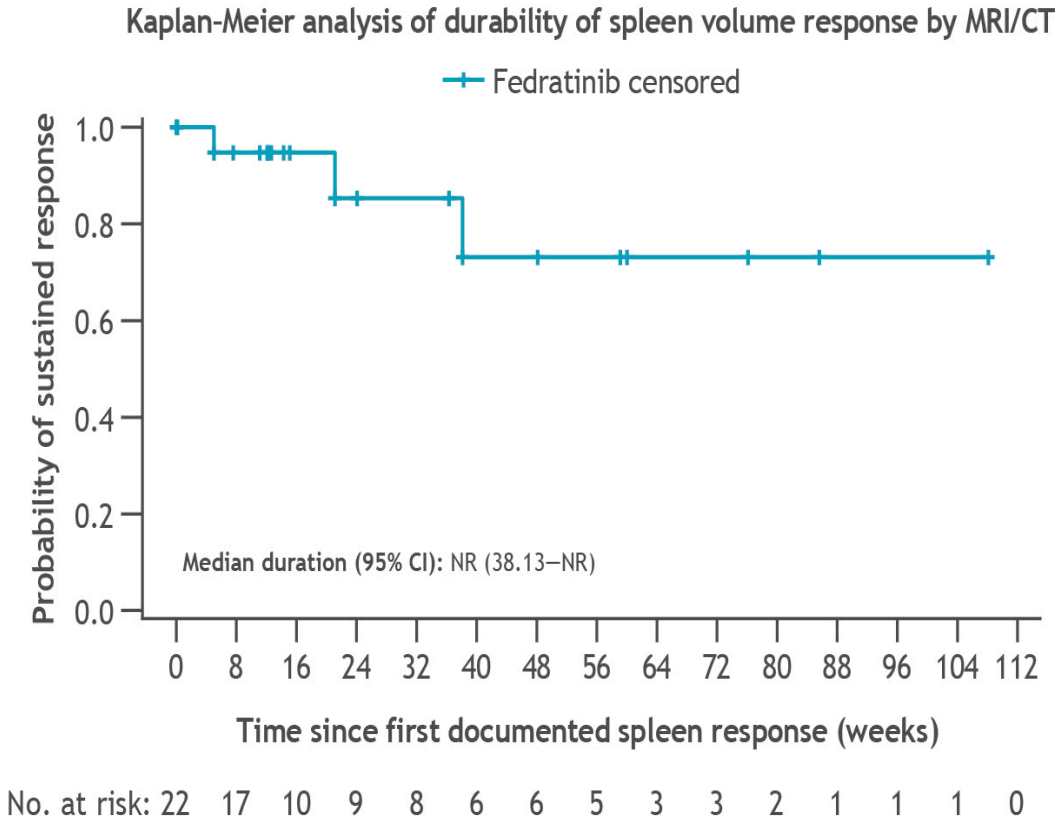
Gupta et al, ASH 2022, abs 1711

FEDR efficacy on spleen volume/size, and symptoms (N=38)

Response parameter	N*
SVR35 at EOC6 (n = 35)	9 (25.7)
Sensitivity analysis of SVRR (n = 35)	
≥ 35% SVR EOC6 (with LOCF)	13 (37.1)
Best overall response SVR35 anytime	22 (62.9)
≥ 25% SVR EOC6 (with LOCF)	24 (68.6)
Best overall response SVR25 anytime	30 (85.7)
SRR by palpation at EOC6 (n = 37)	6 (16.2)
Anytime	25 (68)
Symptom response (n = 36)	
≥ 50% reduction in TSS at EOC6	16 (44.4)
≥ 50% reduction in TSS at EOC3	21 (58.3)

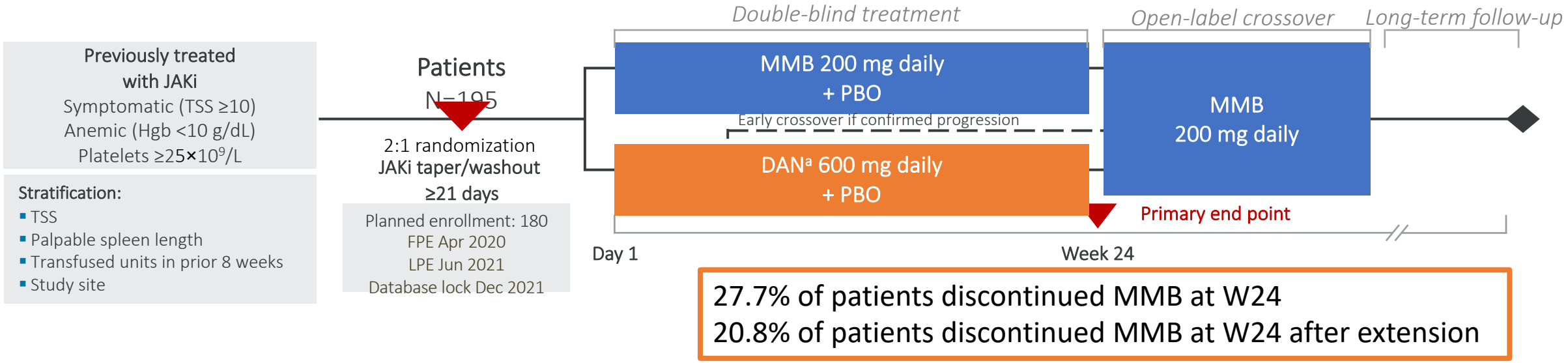
*LOCF: last observation carried forward; * % of evaluable*

- Of SVR35 responders, 19/22 (86.4%) maintained a durable response at data cutoff



Gupta et al, ASH 2022, abs 1711

Momelotinib: MOMENTUM study design (MMB *vs.* Danazole in symptomatic, anemic, JAKi-experienced patients)



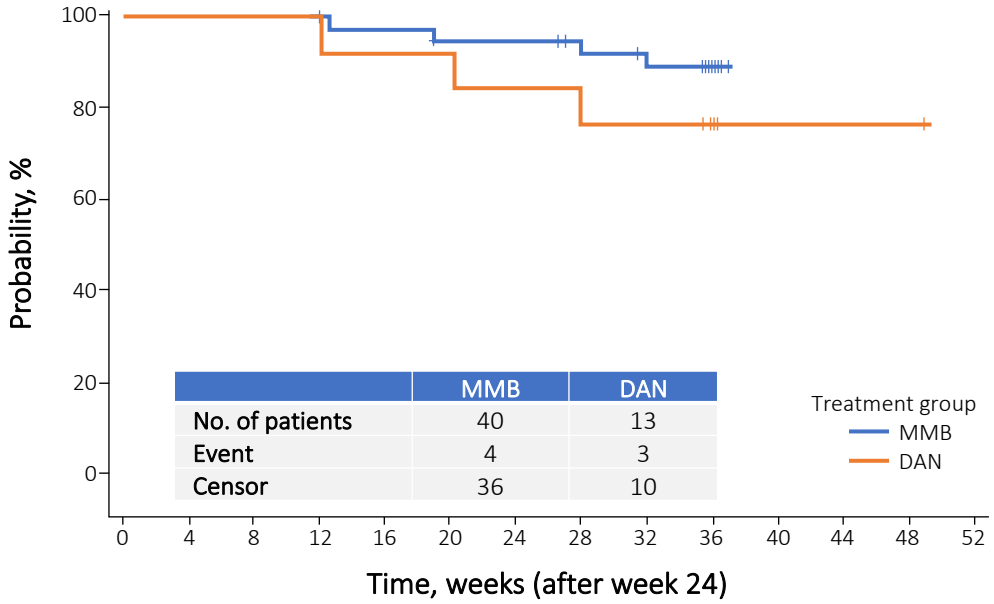
MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met

	MFSAF TSS[b] response rate (primary end point)	TI response[c] rate	SRR[d] (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P=.0095 (superior)	1-sided *P*=.0064 (noninferior)	*P*=.0006 (superior)

Gerds et al, ASH 2022, abs 627

MMB showed sustained W24 TI responses

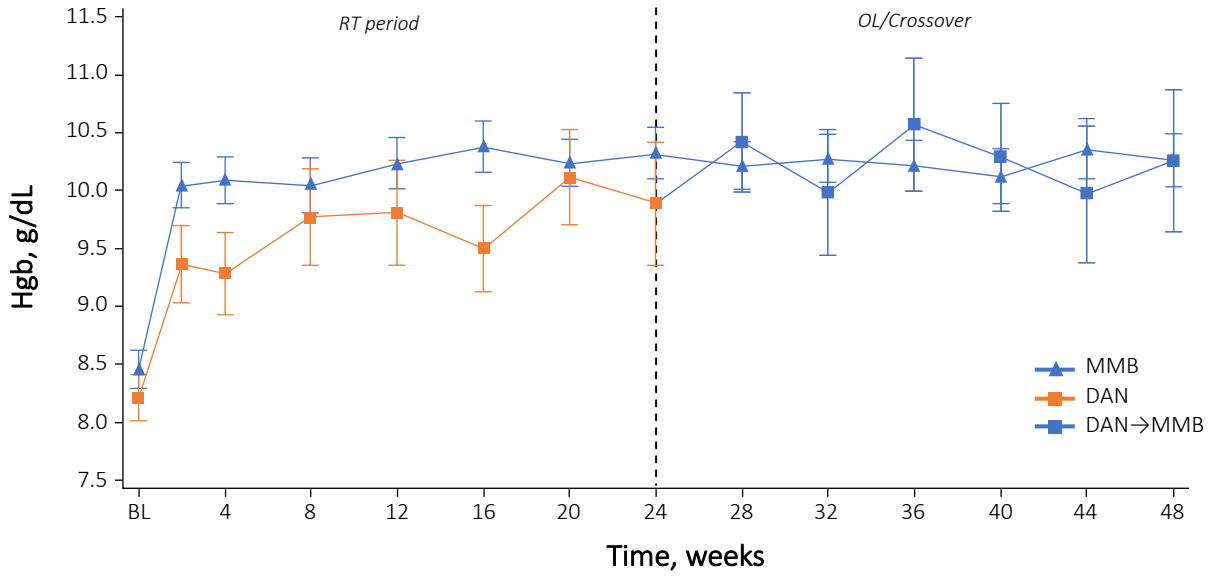
TI Duration of Response in ITT Population



	MMB	DAN
No. of patients	40	13
Event	4	3
Censor	36	10

MMB (n)	40	40	40	40	38	36	36	34	32	23	0	1	1	0
DAN (n)	13	13	13	13	12	12	11	11	10	9	1			

Mean Hgb Over Time in TI Responders



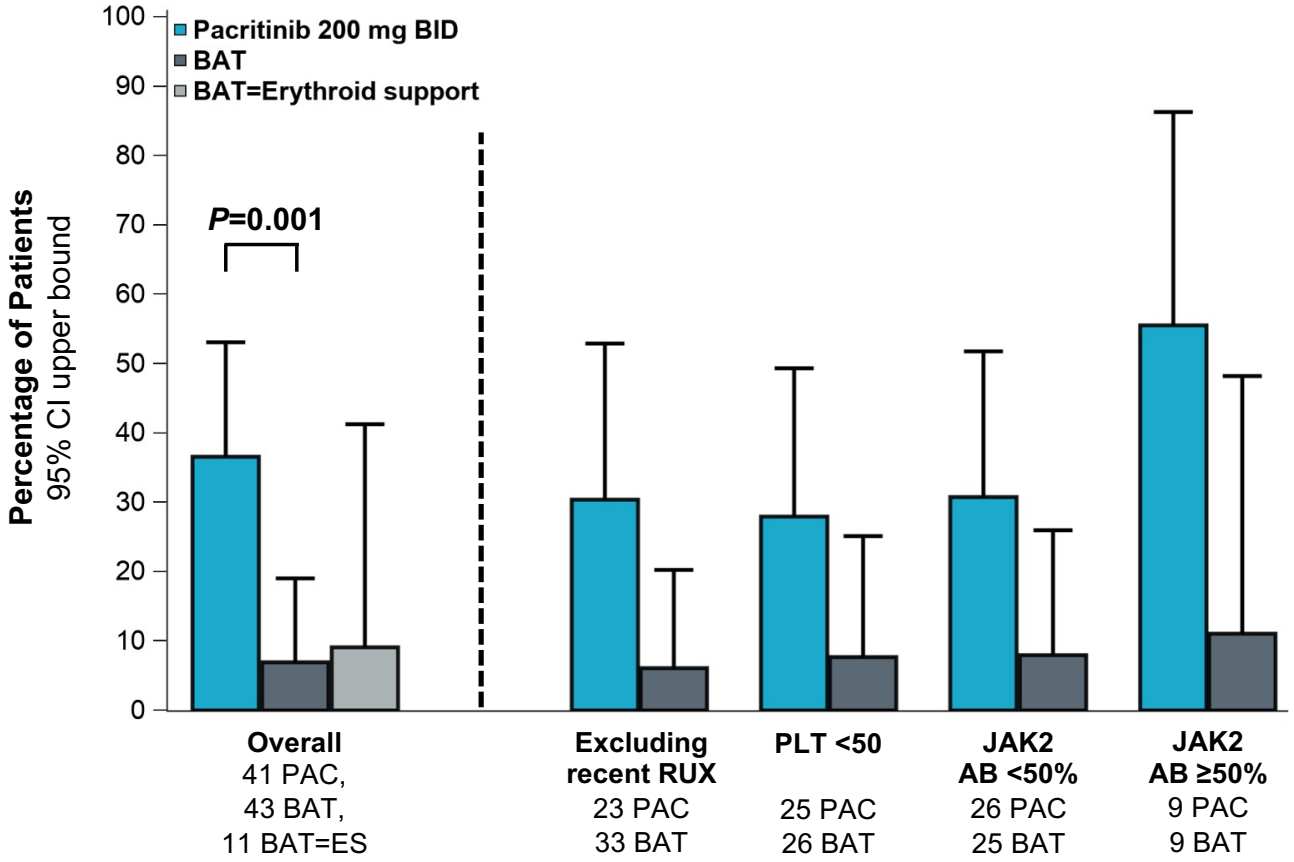
MMB (n)	39	34	32	33	35	36	34	36	37	33	33	34	33
DAN (n)	13	11	12	11	11	12	10	11	11	7	10	9	10

- Week 24 TI response was 31% in the MMB group and 20% in the DAN group
  - Consecutive 12-week TI-R[b] was 44.6% in the MMB group and 29.2% in the DAN group (Poster #3028)
- Week 24 TI response was maintained in 36 of 40 (90%) MMB→MMB and 10 of 13 (77%) DAN→MMB pts

Gerds et al, ASH 2022, abs 627

TI-responses of PAC in the PERSIST-2

PERSIST-2 (PAC vs. BAT in JAKi exposed, PLT<100x10^9/L)



TI conversion rate (no RBC transfusion over 12W)

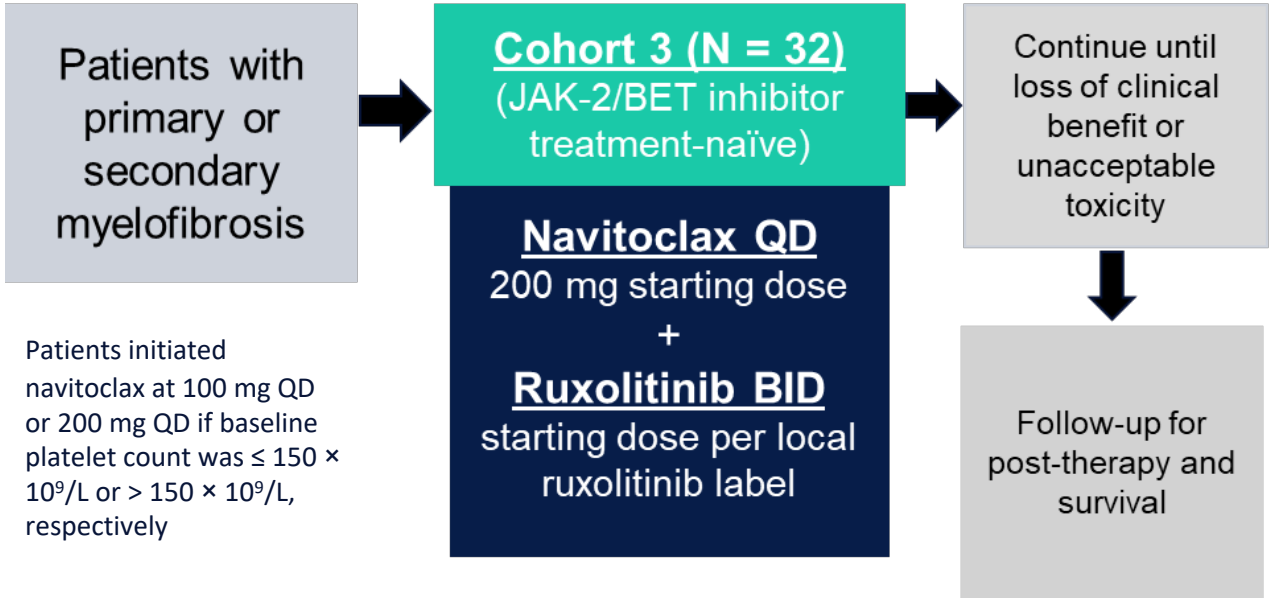
Pacritinib N=41	BAT N=43	*P*-value
37%	7%	0.001

Oh et al. ASH 2022. abs 628

- JAKi-naive setting

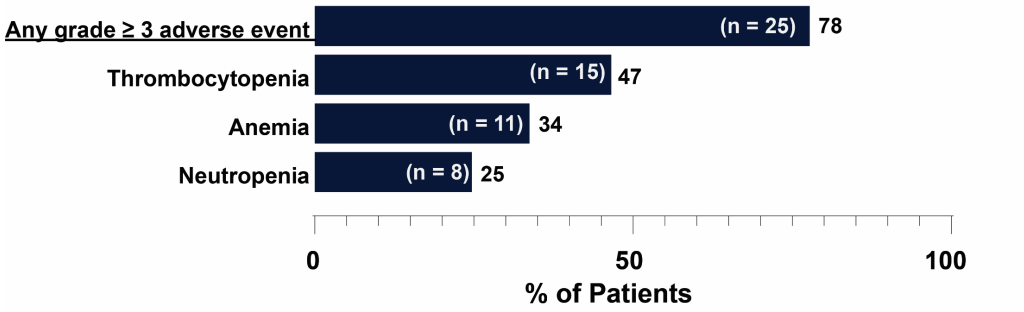
Navitoclax & RUX in 32 JAKi-naïve patients (arm 3, ph. 2 REFINE)

Phase II REFINE Study Design (NCT03222609)

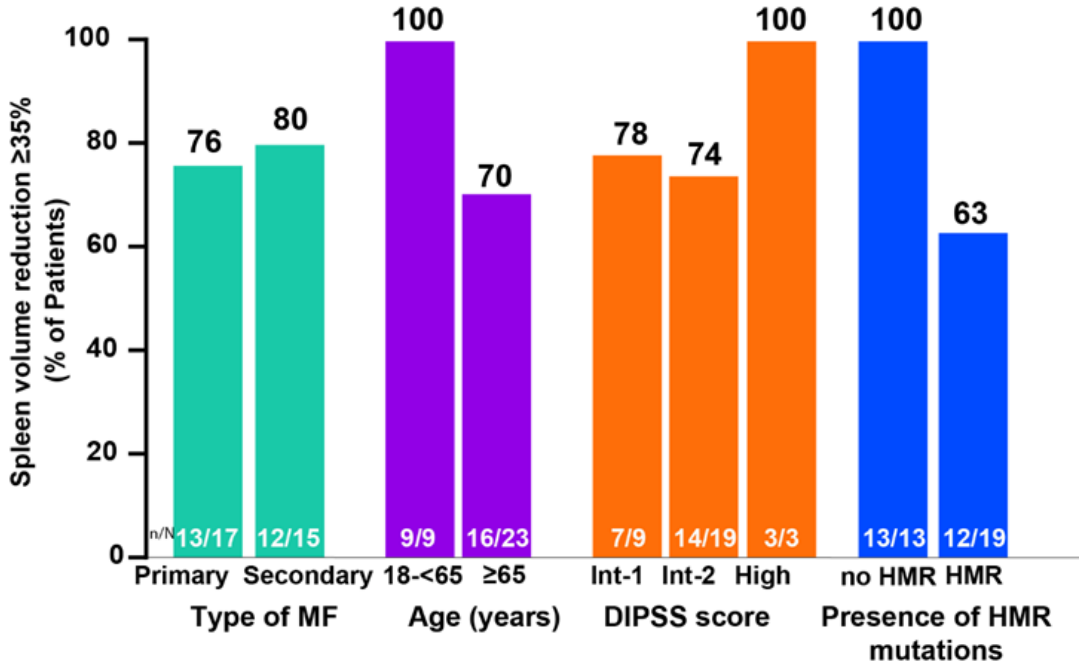


Patients initiated navitoclax at 100 mg QD or 200 mg QD if baseline platelet count was ≤ 150 × 10^9/L or > 150 × 10^9/L, respectively

The safety was manageable

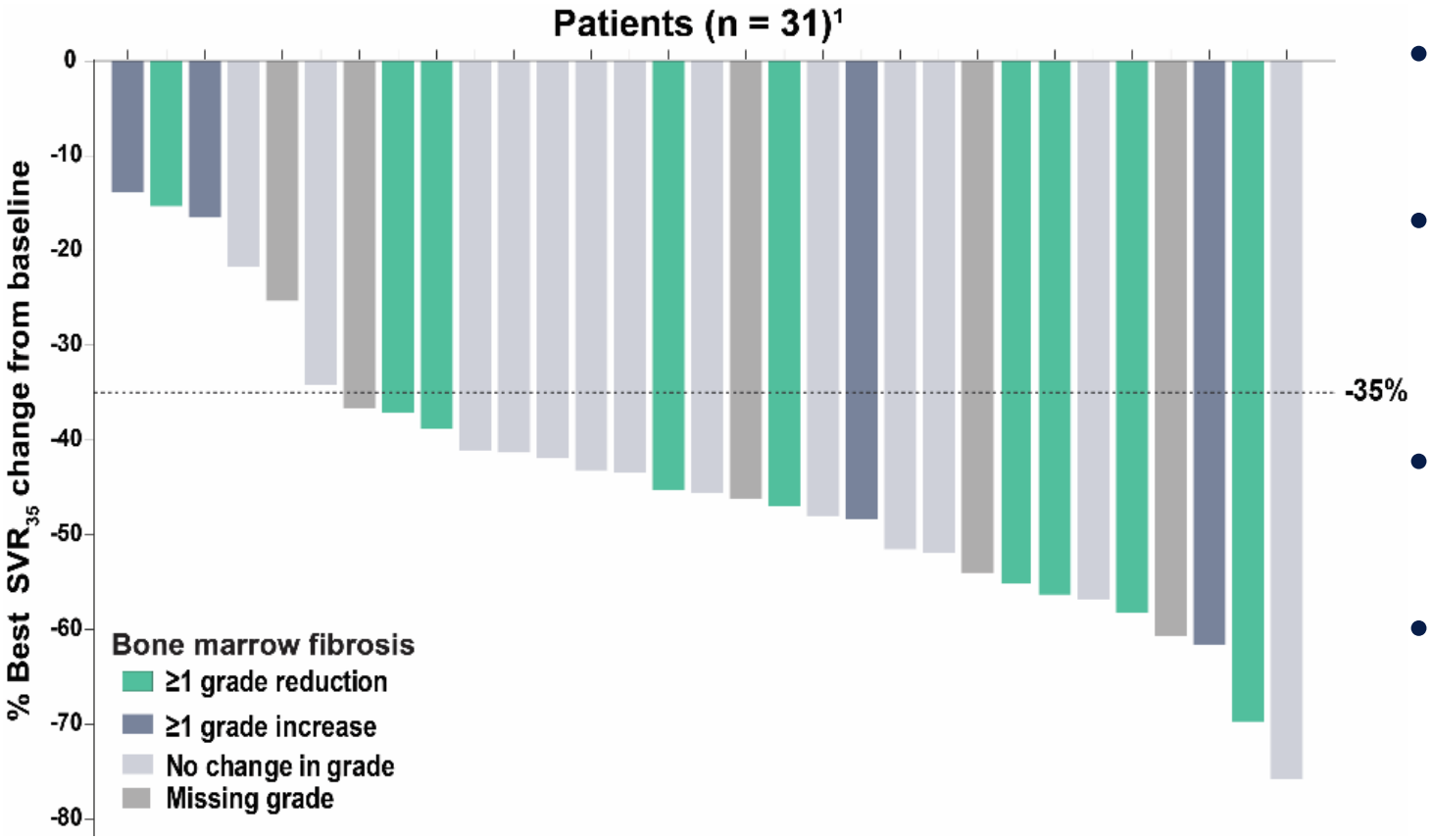


SVR35 at anytime during study treatment



Passamonti et al, ASH 2022, abs 237

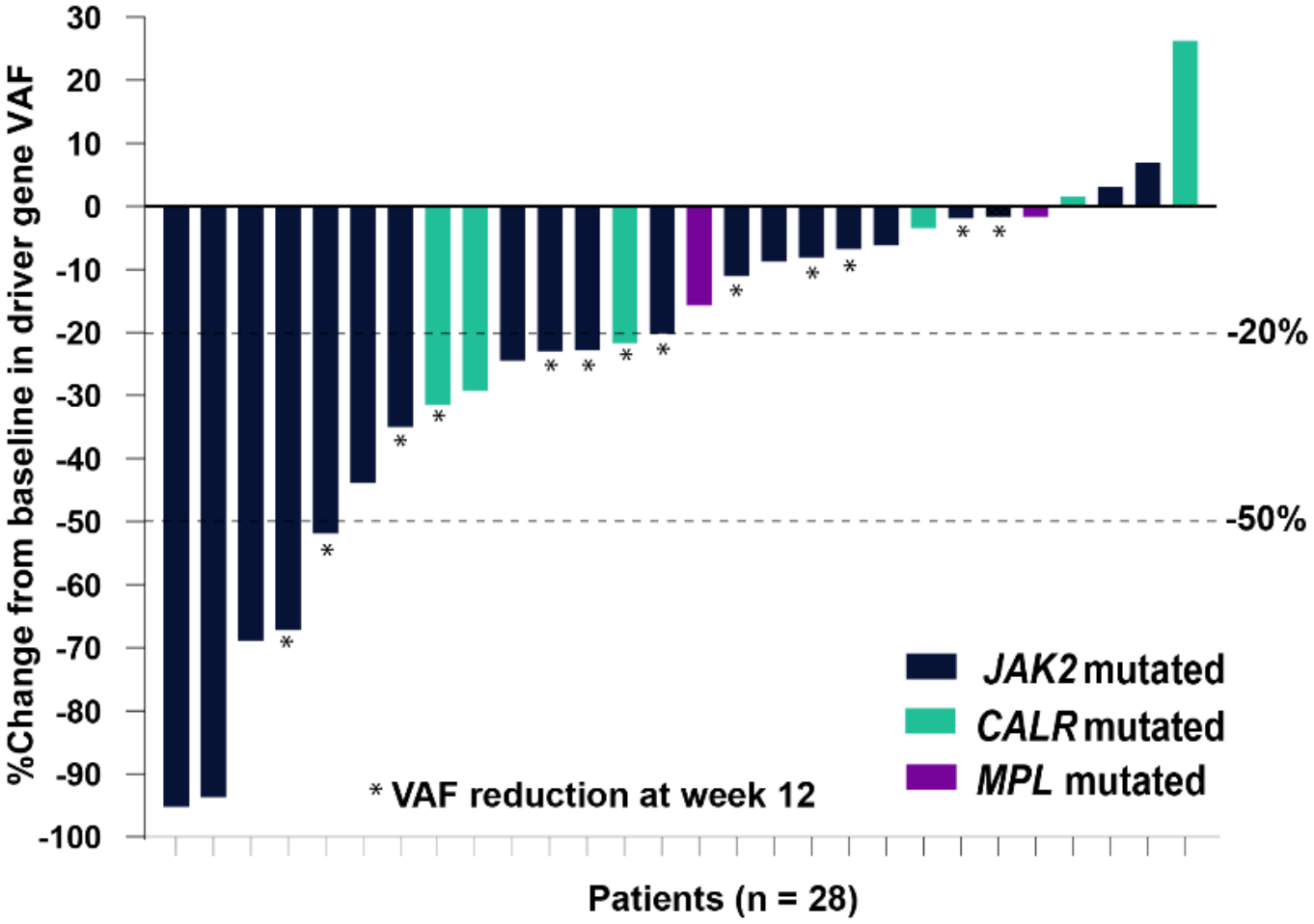
Navitoclax+RUX in JAKi naïve patients: efficacy on bone marrow fibrosis



- 9/32 (28%) patients achieved ≥ G1 reduction in BMF
- Complete resolution of BMF was observed in 2/9 (22%) patients (baseline BMF G2, G3)
- Median time to BMF reduction was 12.3 weeks
- 8/25 (32%) patients with SVR35 also achieved ≥ G1 reduction in BMF

Passamonti et al, ASH 2022, abs 237

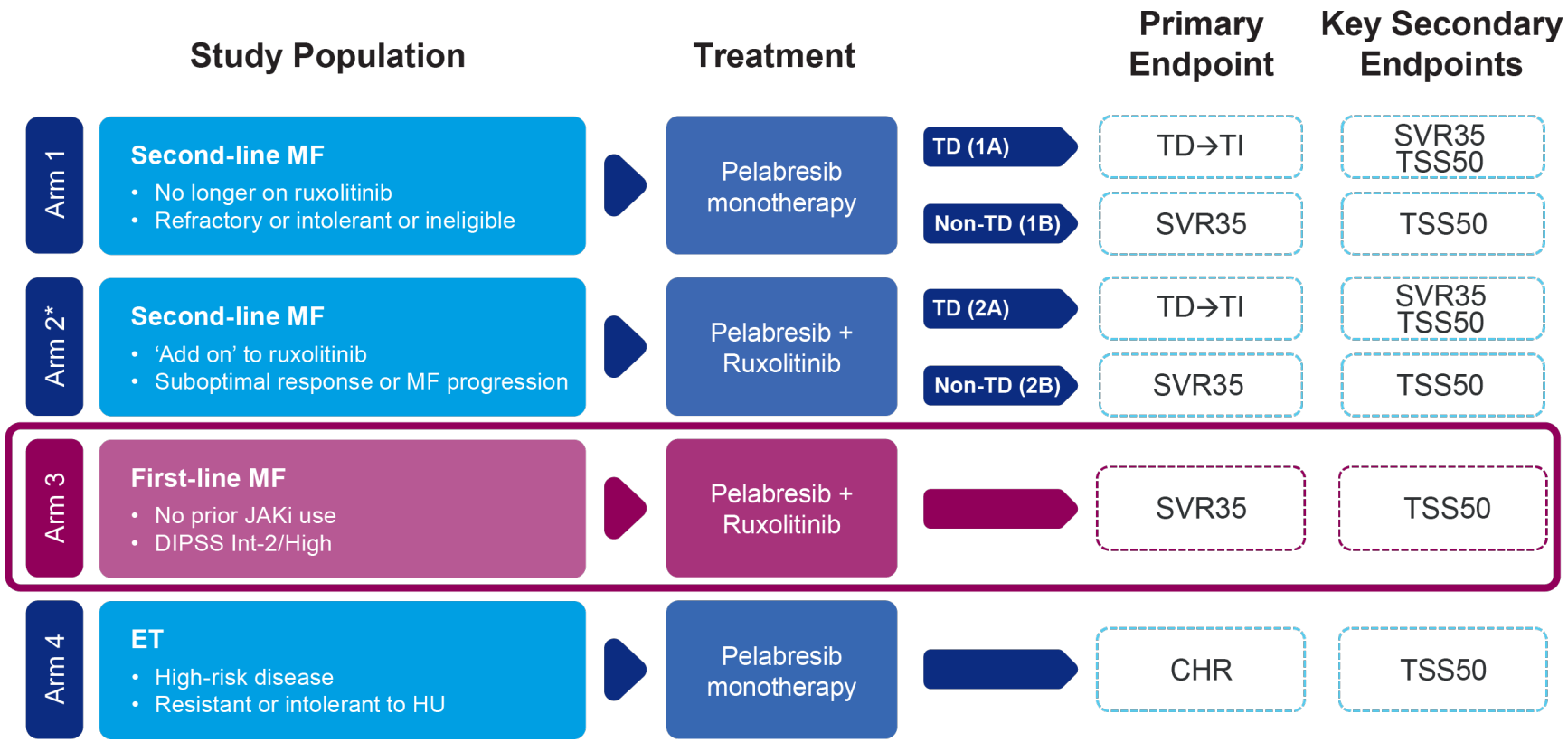
Navitoclax+RUX in JAKi naïve patients: efficacy on *JAK2mut* VAF



- Molecular responses were observed as early as week 12
- 11/22 (50%) patients had ≥ 20% reduction in VAF for *JAK2V617F*
- No differences in ≥20% VAF reductions from baseline to week 12 or 24 between those with or without HMR mutations (47% *vs.* 54%)

Passamonti et al, ASH 2022, abs 237

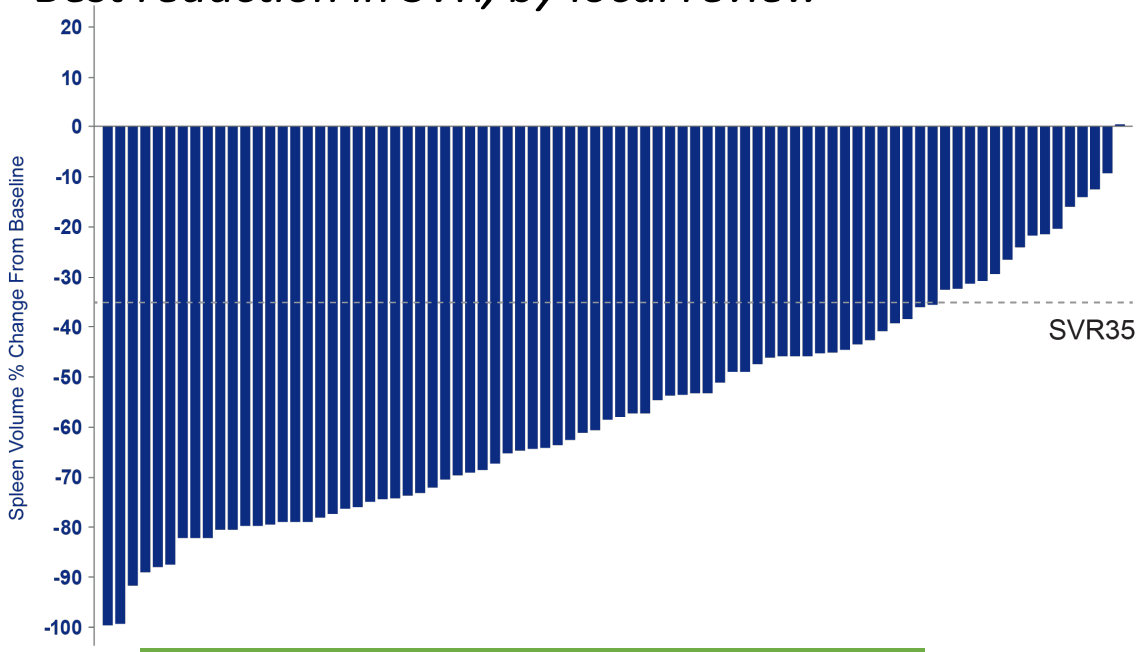
Pelabresib & RUX in 84 JAKi-naïve MF patients (MANIFEST, A3)



Mascarenhas J, et al. ASH 2022. Abstract 238

Pela & RUX effect on spleen/symptoms in JAKi-naïve MF (MANIFEST, A3)

Best reduction in SVR, by local review

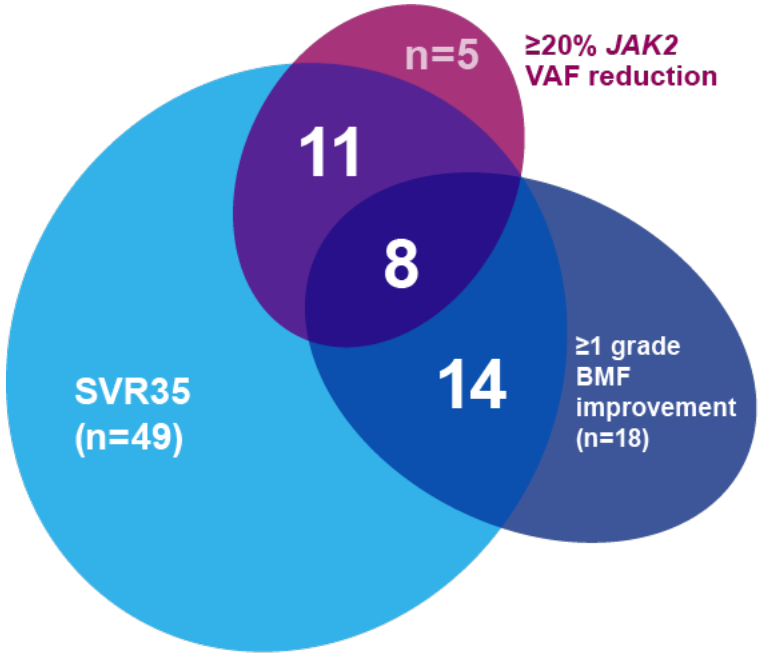


	N=84
SVR35 at Wk 24	68% (57/84)
SVR35 at any time	80% (67/84)
TSS50 at Week 24	56% (46/82)
TSS50 at any time	83% (68/82)

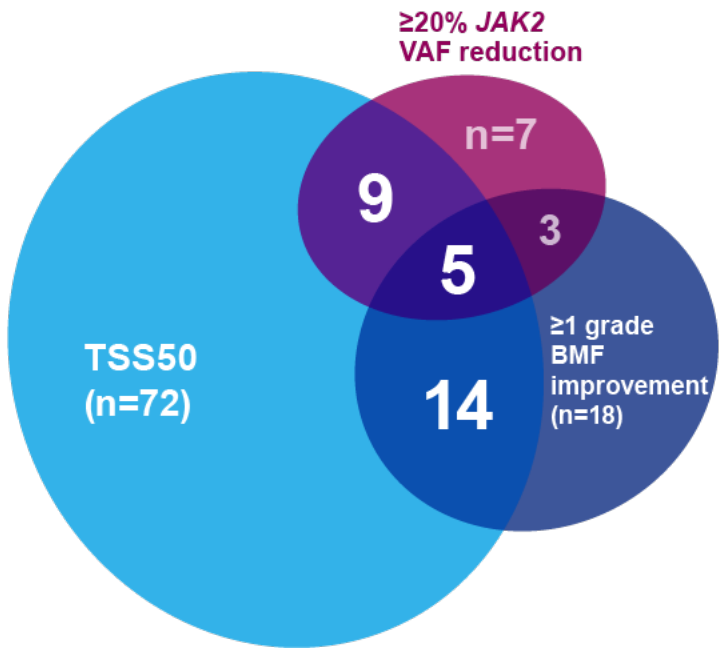
SV mean percentage change over time

N=84	
Median time to SVR35 response	12 wks (10–51)
Median follow-up for SVR35 resp	84 wks (66–90)
Response maintained at data cutoff	70% (47/67)

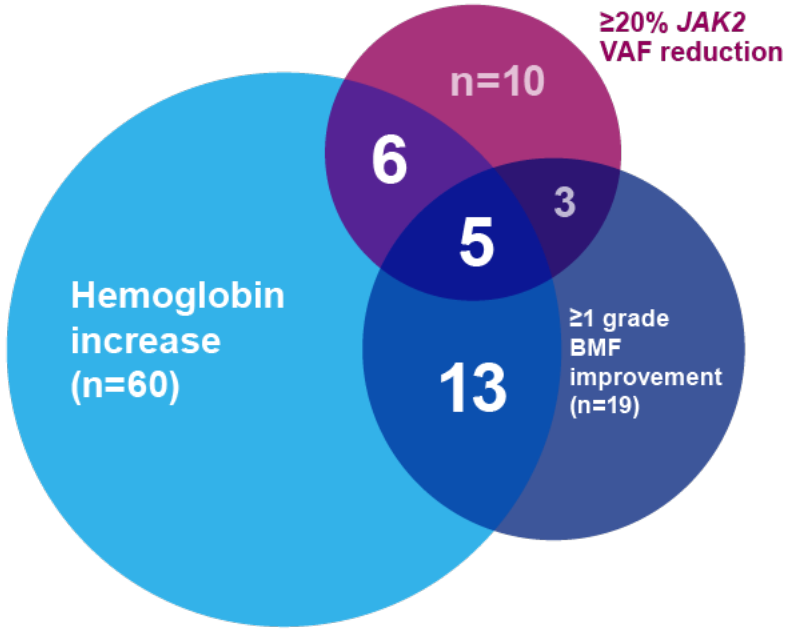
MANIFEST (all arms): Clinical responses associated with *JAK2 V617F* VAF reduction and ≥1 grade improvement in BMF at Week 24



33/82 (40%) of SVR35 responders had *JAK2 V617F* VAF reduction and/or BMF improvement



28/100 (28%) of TSS50 responders had *JAK2 V617F* VAF reduction and/or BMF improvement

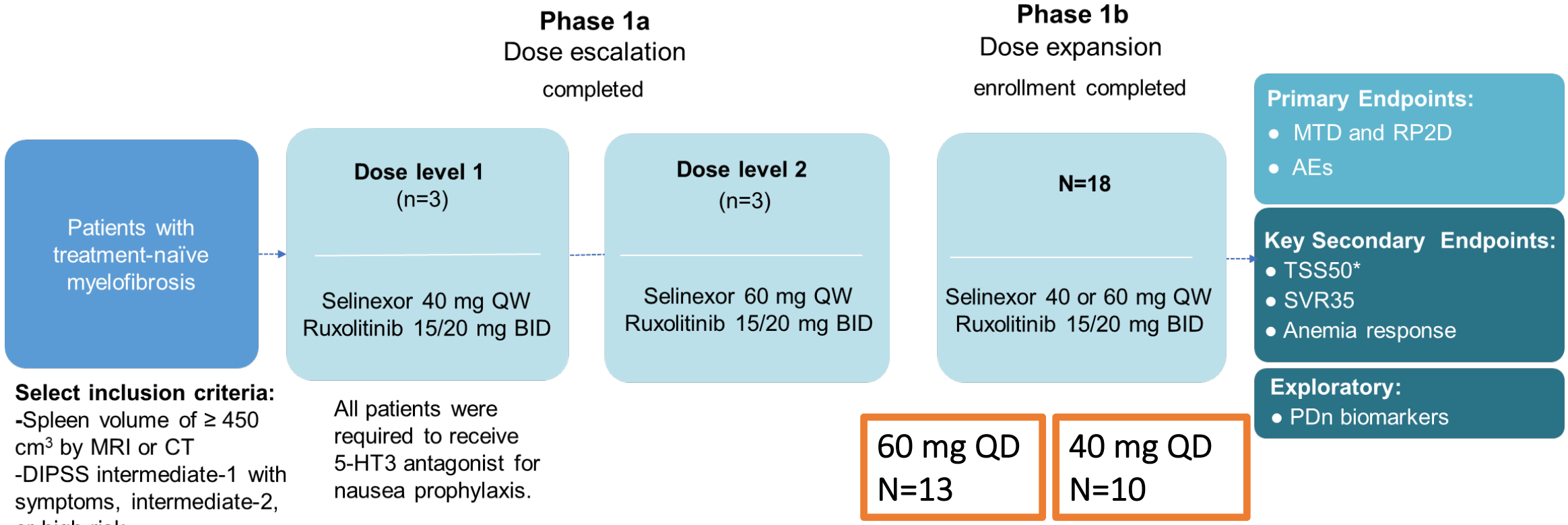


24/84 (29%) patients with hemoglobin improvement had *JAK2 V617F* VAF reduction and/or BMF improvement

All patients who had clinical responses, *JAK2 V617F* VAF reduction and BMF improvement at Week 24 were JAKi treatment naïve (Arm 3)

Scandura J, et al. ASH 2022. Abstract 630

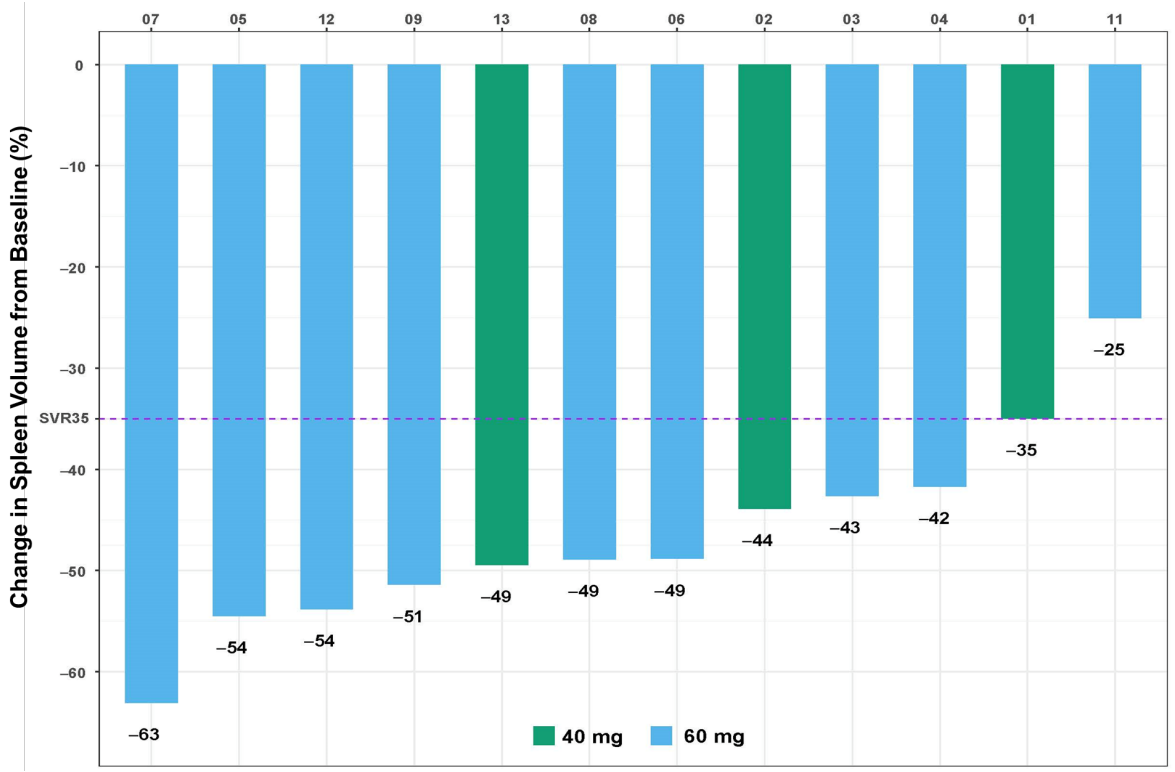
Selinexor & RUX in 24 JAKi-naïve MF patients (phase 1/b trial)



Ali et al. ASH 2022, abstract

Selinexor & RUX effect on spleen and symptoms in 24 JAKi-naïve MF patients (phase 1/b trial)

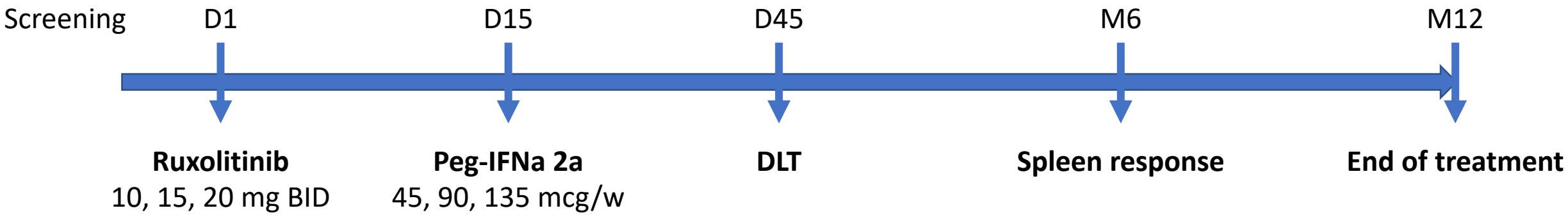
Time point	Endpoint	Efficacy Evaluable** n (%)
Week 24	SVR35	11/12 (92)
	TSS50*	4/6 (67)



- The most common TEAE was nausea with 50% of the events grade 1; only 1 grade 3 nausea was observed
- 2 G4 thrombocytopenia (60 mg dose level), not clinically relevant

Ali et al. ASH 2022, abstract

Pegylated Interferon alpha 2a & RUX (RUXOPEG phase 1-2 study)



	SRL at W24	SRL at 1Y
Phase 1	67% [41;87]	67% [41;87]
Phase 2	74% [49;91]	84% [60;97]
Total	**70% [53;84]**	**76% [59;88]**

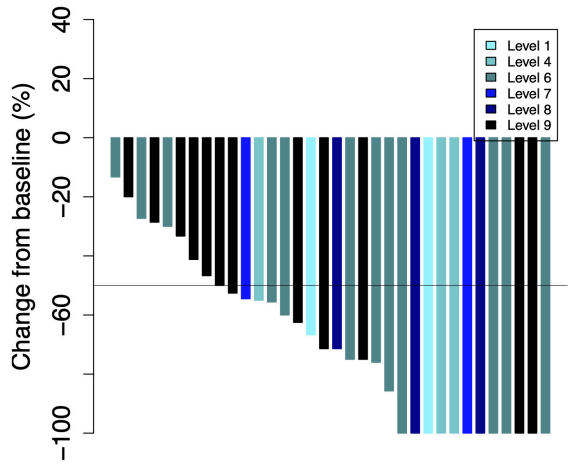


Figure 1 - Waterfall plot of percent change in spleen length at week 24 according to dose levels

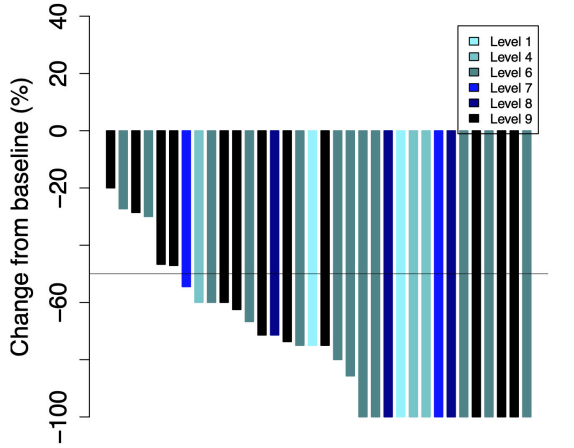
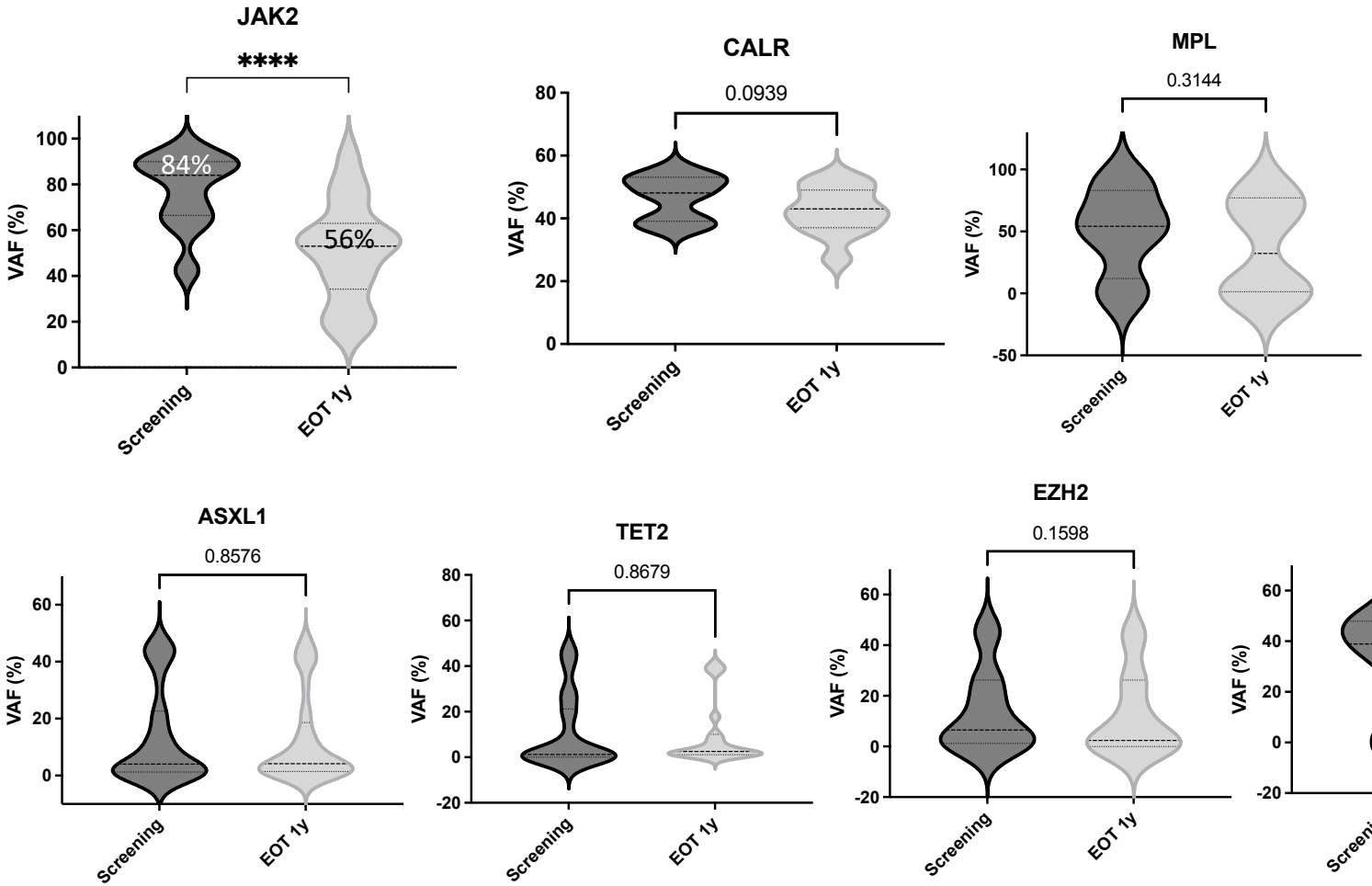


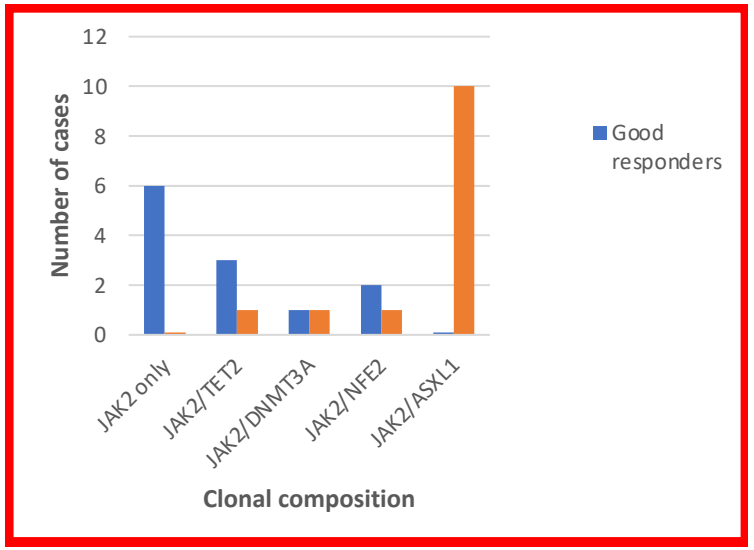
Figure 2 - Waterfall plot of percent change in spleen length at 12 months according to dose levels

Kiladjian et al ASH 2022, abs 235

RUXOPEG: molecular responses



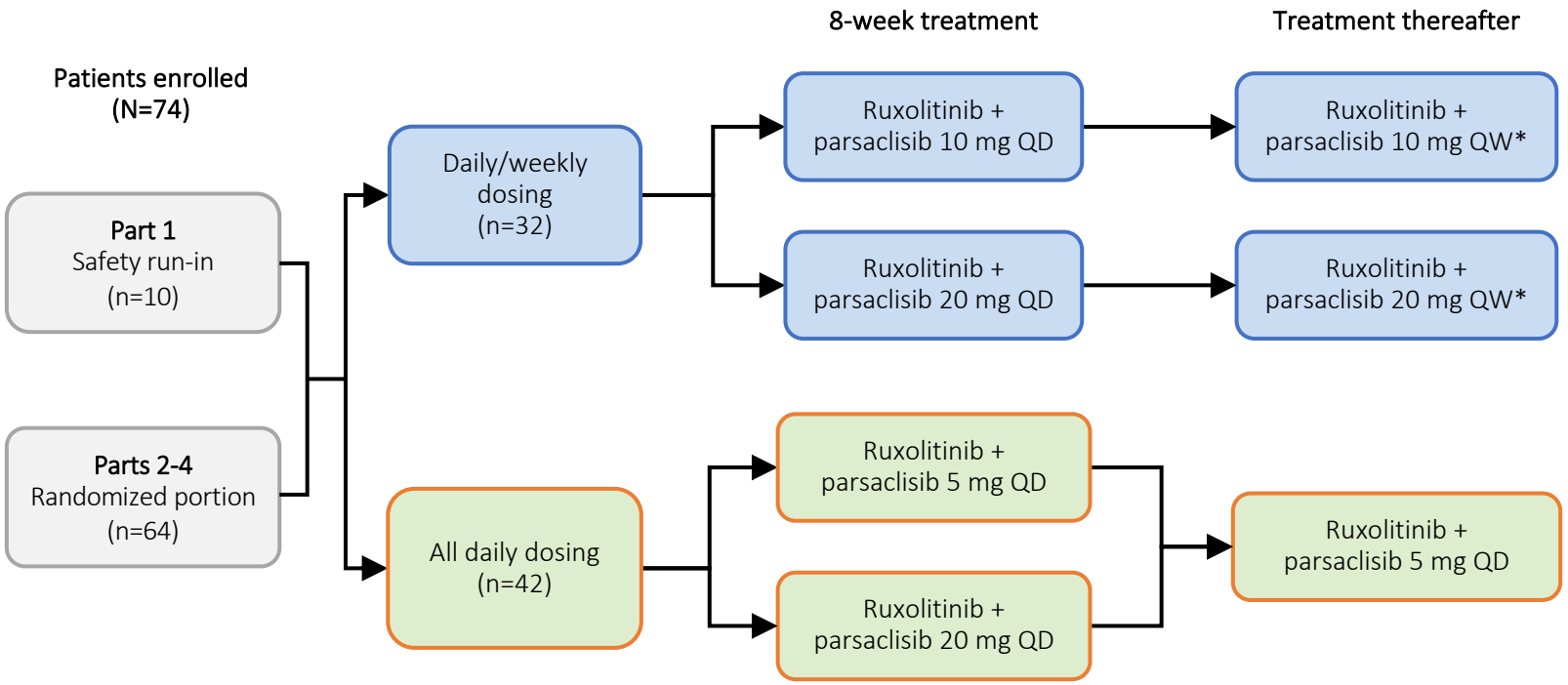
Molecular response per clonal architecture

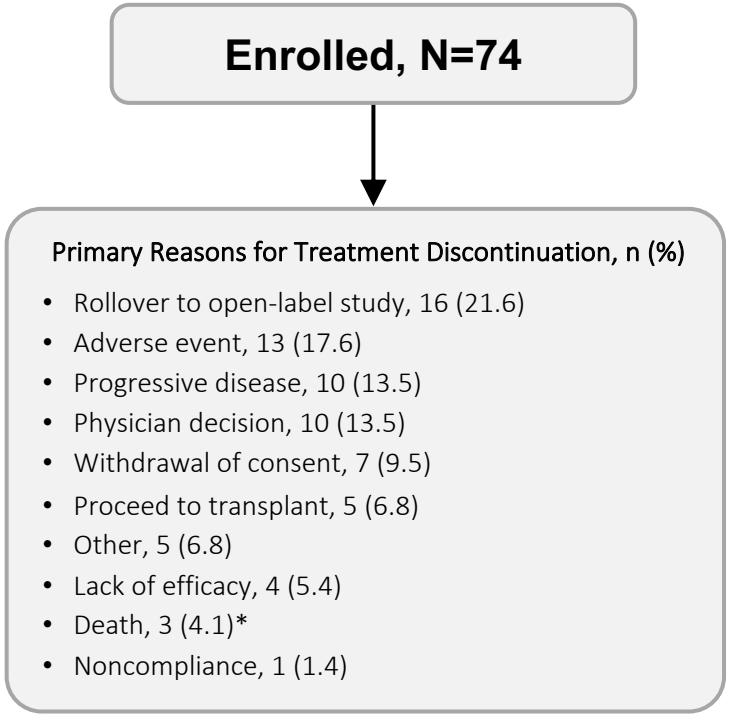


Kiladjian et al ASH 2022, abs 235

- RUX add-on setting

Parsaclisib (different dose schedules) & stable-dose RUX in pts treated for at least 6 mos of RUX with suboptimal response (spleen >10cm; spleen 5-10 +symptoms; PLT >50x10^9/L)

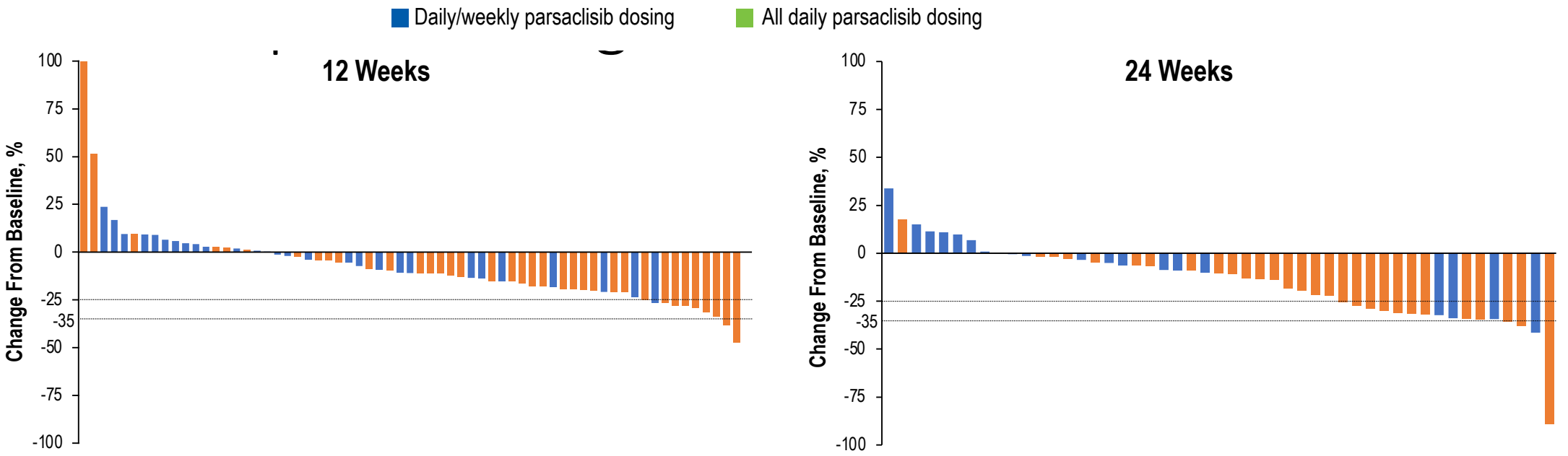




- Median (range) treatment duration was 48.1 (4.3-213.4) weeks
- 31 patients (41.9%) received study treatment for ≥1 year, and 10 patients (13.5%) for ≥2 years

Yacoub et al. ASH 2022, abs 236

Parsaclisib & RUX effect on SRR at 12 and 24 Weeks



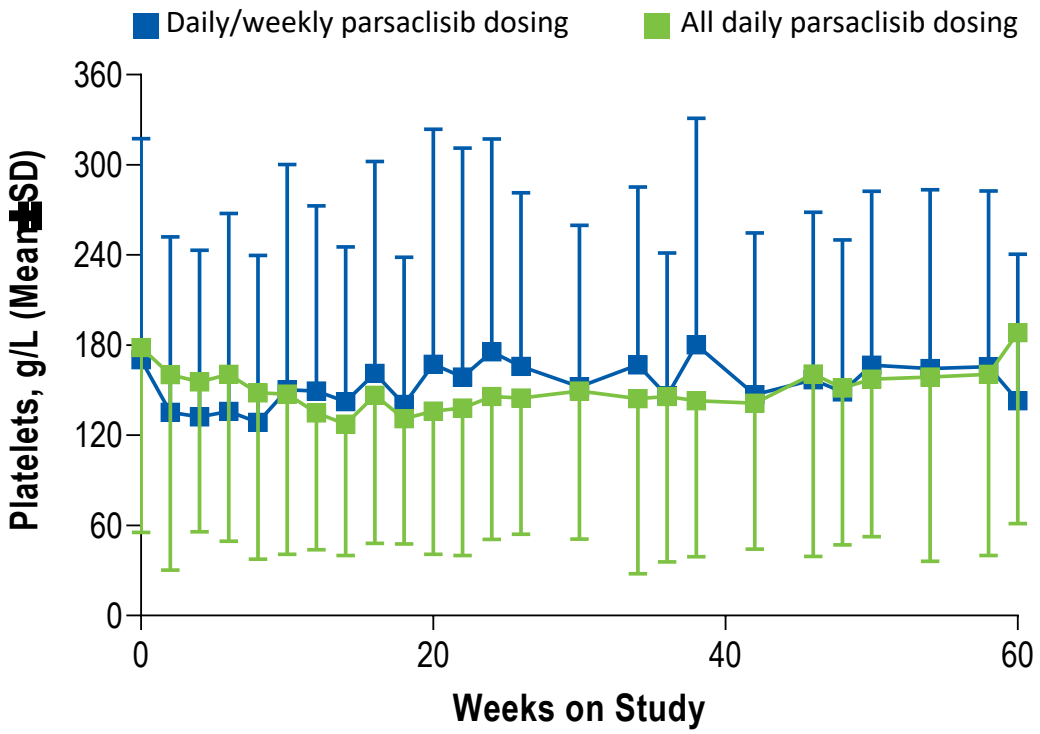
Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 12	n=32	n=42
≥10% reduction	9 (28.1)	25 (59.5)
≥25% reduction	1 (3.1)	9 (21.4)
≥35% reduction	0	2 (4.8)

Response Category, n (%)	Daily/Weekly Dosing	All Daily Dosing
Week 24	n=32	n=42
≥10% reduction	4 (12.5)	21 (50.0)
≥25% reduction	4 (12.5)	12 (28.6)
≥35% reduction	1 (3.1)	3 (7.1)

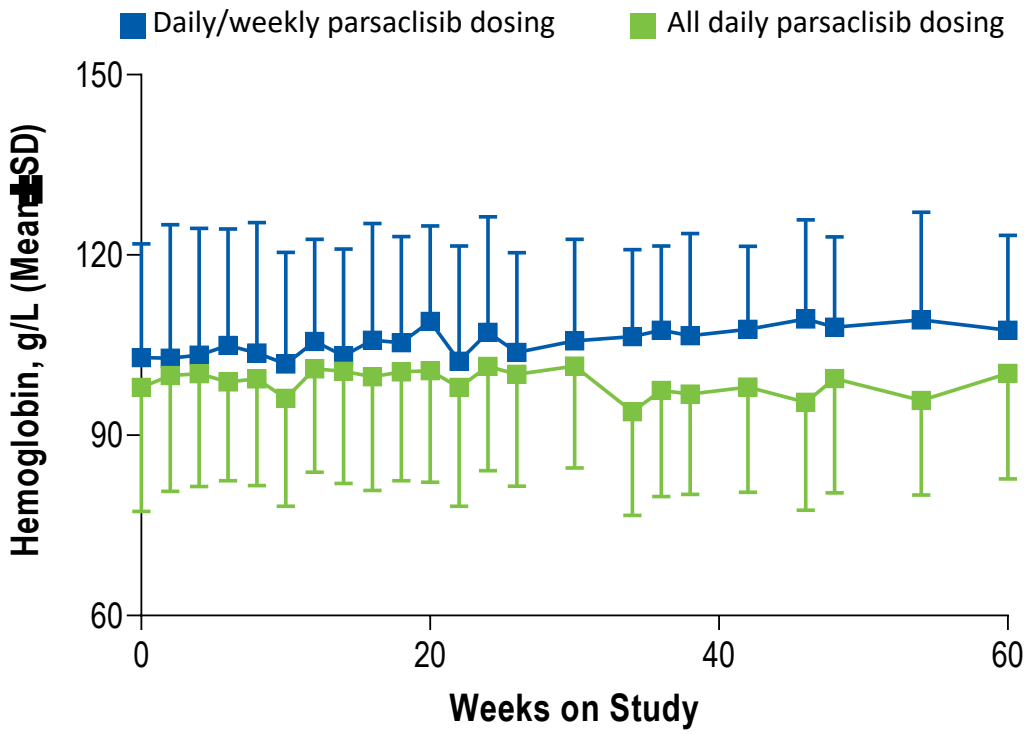
Yacoub et al. ASH 2022, abs 236

Parsaclisib & RUX effect on platelet and hemoglobin Levels

Platelet Levels



Hemoglobin Levels

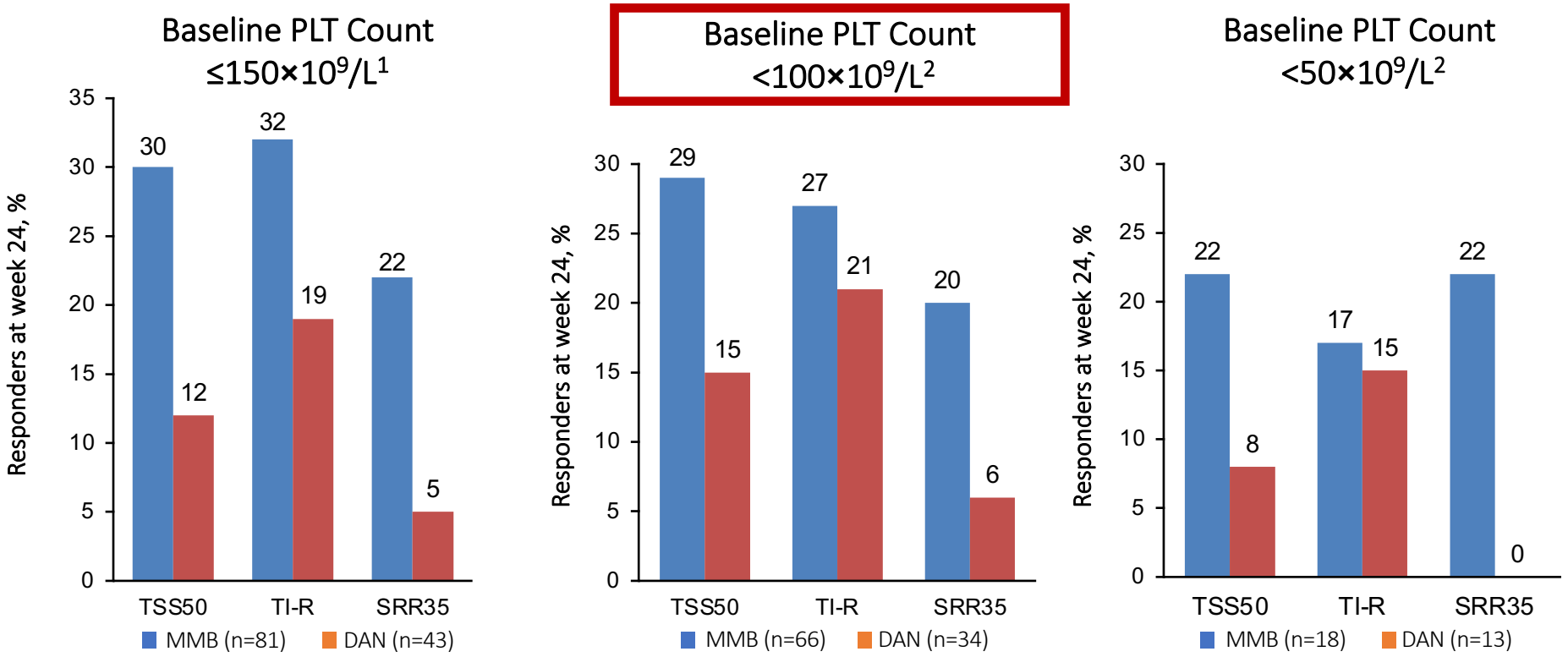


Yacoub et al. ASH 2022, abs 236

Conclusions

- FEDR confirmed safety
- PAC showed effect on anemia, mediated by ACVR1 inhibition
- MMB showed sustained transfusion-independence responses
- Navitoclax+RUX, Pelabresib+RUX showed potential disease modifying effect

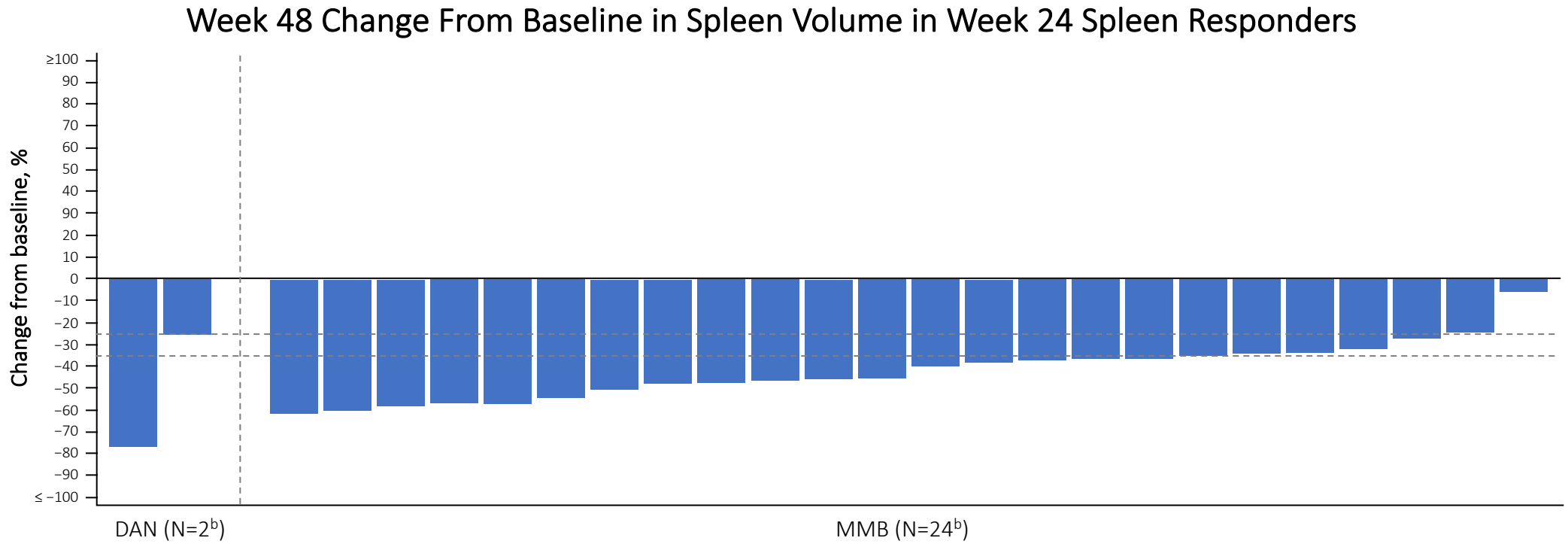
MMB efficacy (TSS, TI-R, SRR) in patients with low-PLT



- For baseline PLTs <100×10⁹/L, week 24 responses were also maintained during OL period:
  - TSS50 responders: 18 of 19 (95%) MMB→MMB and all DAN→MMB patients maintained TSS responses
  - TI-R responders: 16 of 18 (89%) MMB→MMB and 5 of 7 (71%) DAN→MMB patients maintained TI responses
  - SRR35 responders: all MMB→MMB and all DAN→MMB patients maintained splenic responses

Gerds et al, ASH 2022, abs 627

MMB showed sustained W24 spleen responses

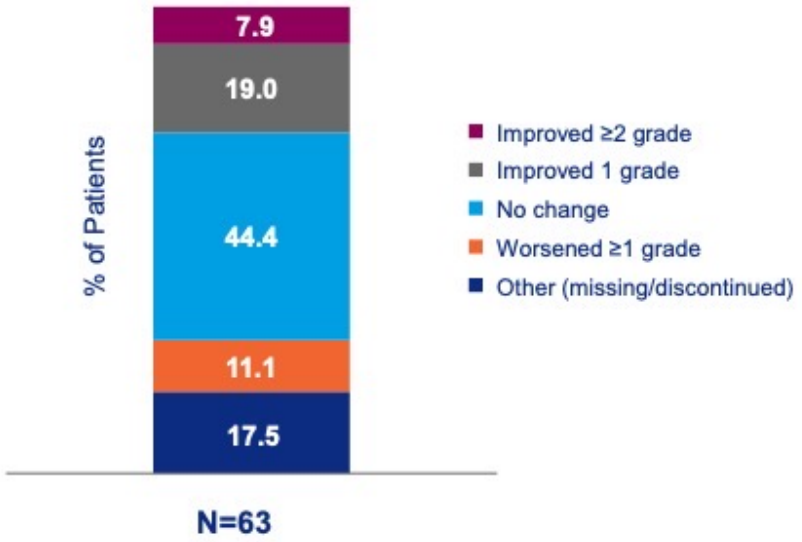


- Week 24 SRR35 response was 23% in the MMB group and 3% in the DAN group
- All SRR35 responders at week 24 maintained spleen volume below baseline (24 of 24 MMB→MMB and 2 of 2 DAN→MMB patients)

Gerds et al, ASH 2022, abs 627

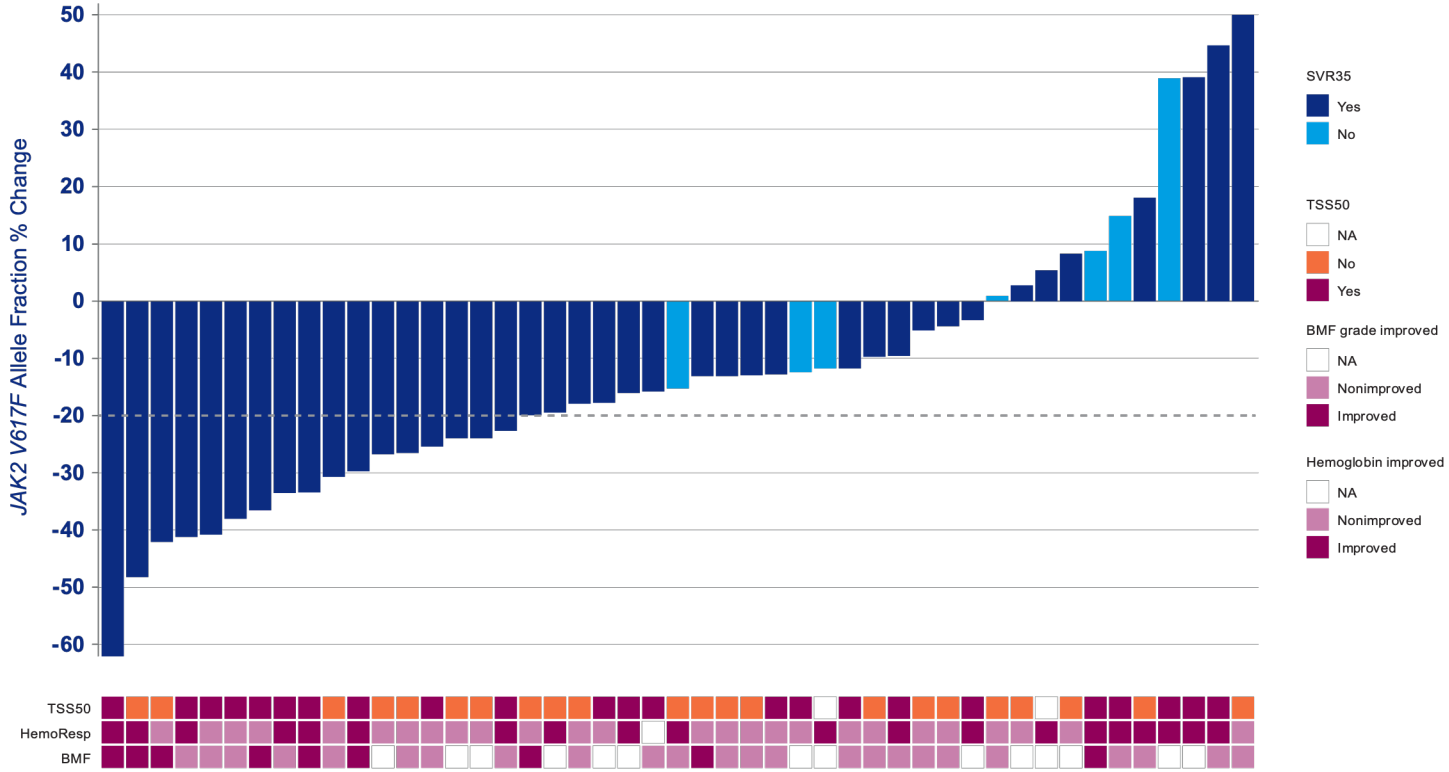
Pela & RUX effect on BMF and *JAK2* VAF in JAKi-naïve MF (MANIFEST, A3)

Change in BMF Grade at Week 24



- 27% showed ≥G1 improvement W24
  - This improvement was maintained in 59% (10/17) of patients at the next available assessment or longer
- 40% had ≥G1 improvement at any time

Change in JAK2 VAF at Week 24



- 38% reached ≥20% reduction in *JAK2 V617F* VAF

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