Post-San Diego 2023
Mielofibrosi

Francesco Passamonti
Chair of Hematology, University of Milano Statale
Division of Hematology, Fondazione I.R.C.C.S.
Ospedale Maggiore Policlinico of Milano

UNIVERSITÀ DEGLI STUDI
DI MILANO

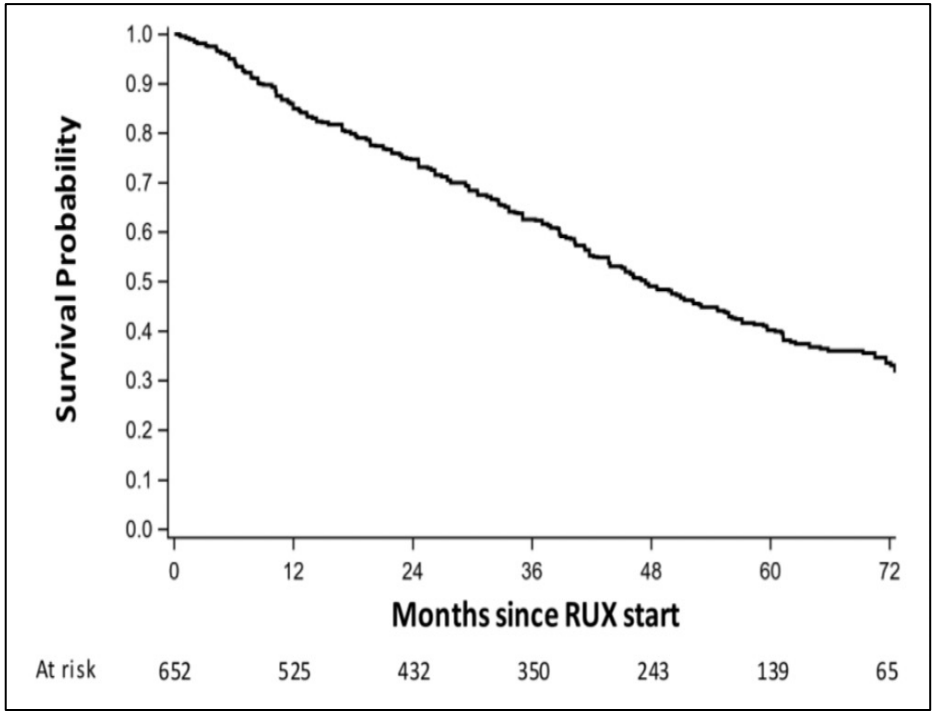
Fondazione IRCCS Ca' Granda
Ospedale Maggiore Policlinico

Sistema Socio Sanitario
Regione Lombardia

Disclosures

- F Passamonti received honoraria for lectures and for advisory boards from Novartis, GSK, Bristol-Myers Squibb, Sierra Oncology, Abbvie, MSK, Janssen, Roche, AOP Orphan, Karyiopharm, Kyowa Kirin and MEI, Sumitomo

An Italian population-based study on OS in 652 higher risks MF patients receiving ruxolitinib

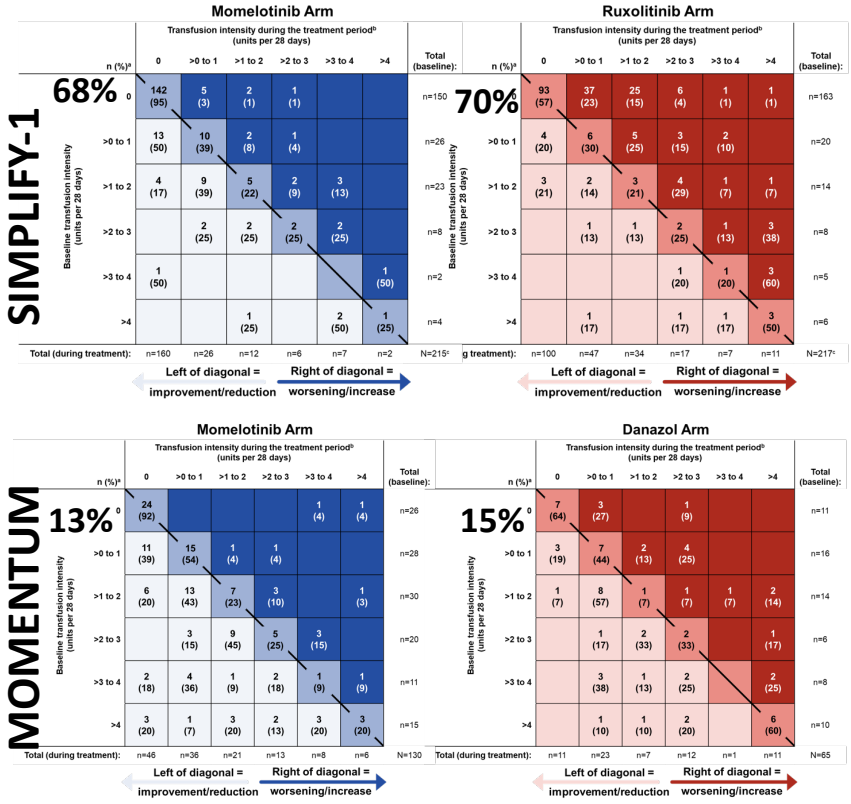


- Minimum follow-up: 3.5Y
- The 1-, 3- and 6-years OS rates were 85%, 63% and 34%, respectively
- Factors independently associated with mortality were male gender, older age classes, high MCS score and less than 20 mg BID as RUX initial dose

Mora et al. ASH 2023 Abs 4572

Momelotinib: changes in RBC transfusion requirements and prognostic relavance

Change in RBC needs intensity



Treatment-agnostic prognostic factors for OS

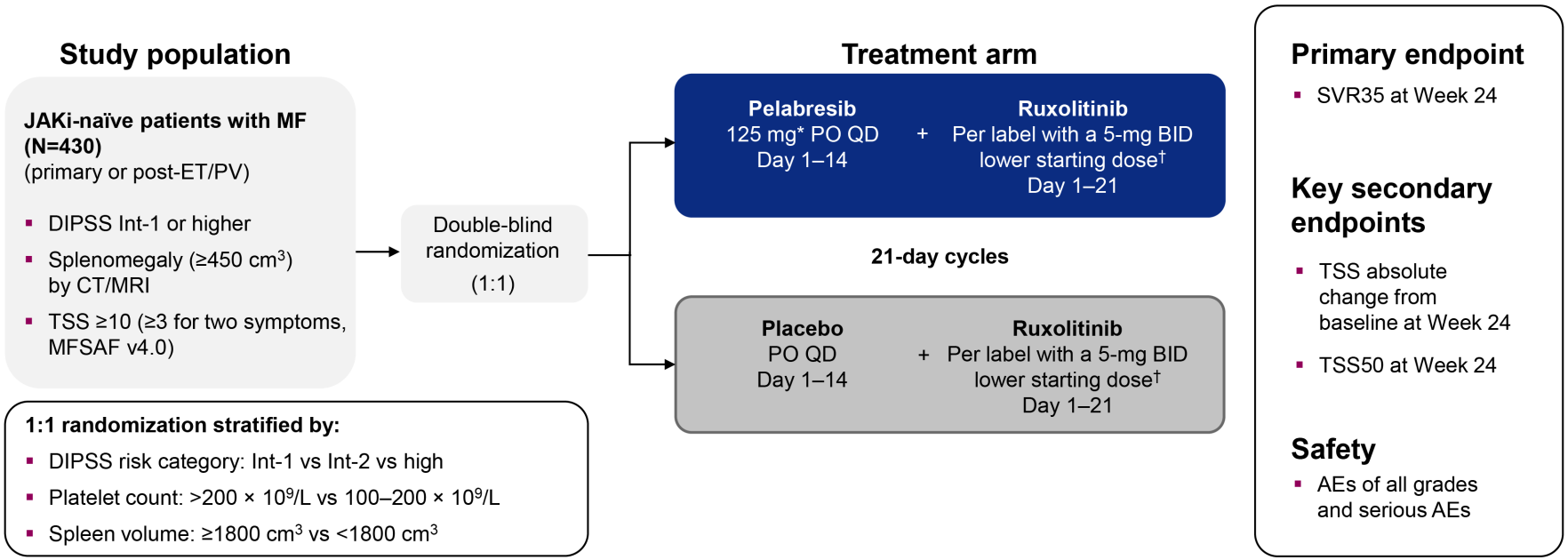
Covariate, reference vs comparator	HR (95% CI)[a]	*P* value[b]
MOMENTUM		
RBC transfusion status, TI[c] vs non-TI	5.18 (1.86-14.47)	.0017
SIMPLIFY-1		
RBC transfusion status, TI[c] vs non-TI	3.32 (2.31-4.78)	<.0001
BL age, <65[c] vs ≥65 years	2.40 (1.59-3.64)	<.0001
BL PLT count, ≥100[c] vs <100×10^9/L	1.97 (1.17-3.32)	.0109
BL spleen volume, < median[c] vs ≥ median	1.81 (1.25-2.62)	.0015
SIMPLIFY-2[d]		
RBC transfusion status, TI[c] vs non-TI	1.87 (1.07-3.29)	.0287
BL age, <65[c] vs ≥65 years	2.71 (1.44-5.09)	.0020
BL spleen volume, < median[c] vs ≥ median	2.55 (1.55-4.20)	.0002
BL DIPSS, intermediate-1[c] vs high risk	2.97 (1.27-6.91)	.0118
BL DIPSS, intermediate-2[c] vs high risk	2.66 (1.47-4.82)	.0013

RBC TI: time dependent covariate assessed every 4W, absence of RBC transfusion and no Hb level of <8 g/dL in the prior 12 weeks

Mesa R, et al. ASH 2023. Poster 3182. Gupta V, et al. ASH 2023. Poster 3188.

JAKi-naive MF

Pelabresib (BETi) + ruxolitinib in JAKi-naïve MF: the MANIFEST-2 random, double-blind, phase 3 study



The starting dose for pelabresib was 125 mg QD and protocol-defined dose modifications based on AEs and treatment response allowed a dose range between 50 mg and 175 mg QD

†Ruxolitinib was started at 10 mg BID (baseline platelet count 100–200 × 10⁹/L) or 15 mg BID (baseline platelet count >200 × 10⁹/L) with a mandatory dose increase by 5 mg BID after one cycle and a maximum dose of 25 mg BID per label.

Median follow-up: 11 months

27% discontinued study treatment

Rampal R, et al. ASH 2023. Oral 628.

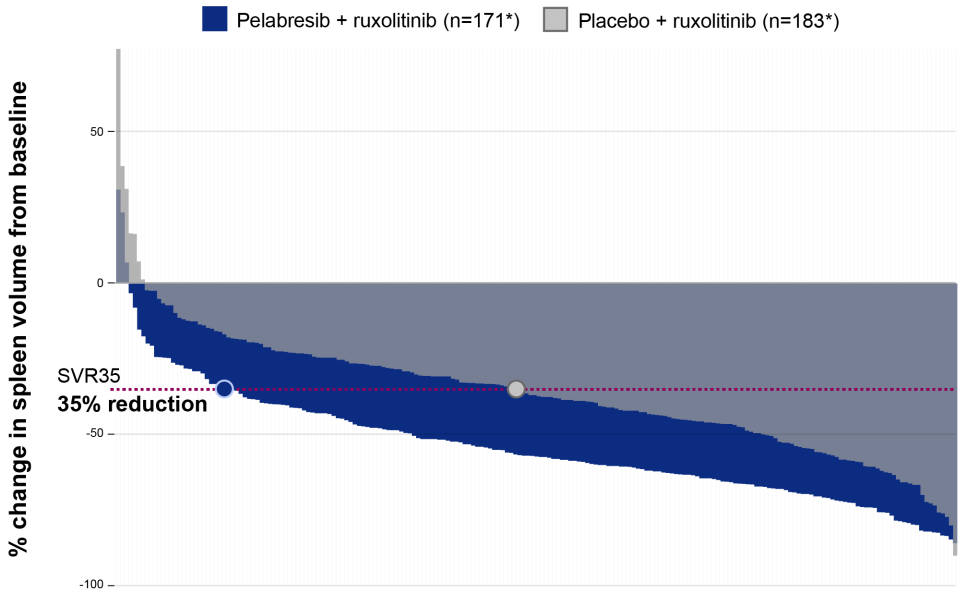
MANIFEST-2: Baseline disease characteristics

Characteristic		Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
Age — years	Median (min, max)	66 (19, 84)	66 (26, 88)
Sex — n (%)	Female / male	85 (39.7) / 129 (60.3)	94 (43.5) / 122 (56.5)
Race — n (%)	White / Asian / Black American Indian or Alaska Native Not reported / Unknown	160 (74.8) / 35 (16.4) / 2 (0.9) 1 (0.5) 15 (7.0) / 1 (0.5)	163 (75.5) / 42 (19.4) / 0 0 11 (5.1) / 0
Myelofibrosis subtype — n (%)	Primary myelofibrosis Post-polycythemia vera myelofibrosis Post-essential thrombocytopenia myelofibrosis	107 (50) 45 (21) 62 (29)	110 (50.9) 53 (24.5) 53 (24.5)
Dynamic International Prognostic Scoring System — n (%)	Intermediate-1 Intermediate-2 High-risk	128 (59.8) 75 (35) 11 (5.1)	127 (58.8) 74 (34.3) 15 (6.9)
Mutations — n (%)*	*JAK2* V617F *CALR* *MPL* Triple negative High-molecular risk mutations Missing	125 (67.2) 45 (24.2) 11 (5.9) 8 (4.3) 72 (38.7) 28 (13.1)	122 (64.6) 50 (26.5) 13 (6.9) 5 (2.6) 88 (46.6) 27 (12.5)
Hemoglobin — g/dL	Median (range) ≤10 — n (%)	10.9 (5.8–18.0) 70 (32.7)	11.0 (6.7–17.9) 76 (35.2)
Platelets — × 10^9/L	Median (min, max) >200 × 10^9/L — n (%)	285 (99, 1303) 154 (72)	287 (66, 1084) 157 (72.7)
Peripheral blasts	Mean (SD)	0.8 (1.18)†	0.8 (1.25)‡
RBC transfusions — patient n (%)	Requiring RBC transfusion at baseline	35 (16)	25 (12)
ECOG performance status — n (%)	0 1 ≥2 Missing	107 (50) 97 (45.3) 10 (4.7) 0	109 (50.5) 95 (44.0) 10 (4.6) 2 (0.9)
Spleen volume (central read)§	Median spleen volume (range) — cc	1308.89 (200.24–7117.03)	1382.97 (277.87–5540.45)
Total symptom score¶	Median total symptom score (range)	26.6 (7.3–66.4)	24.7 (9.0–68.4)

Rampal R, et al. ASH 2023. Oral 628.

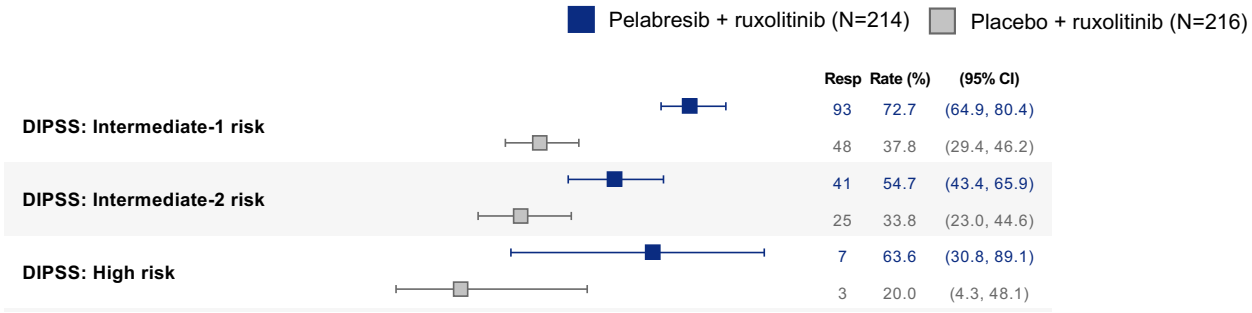
PELA+RUX combo double SVR35 at Week 24

Significantly greater response in patients treated with pelabresib + ruxolitinib vs placebo + ruxolitinib



ITT population

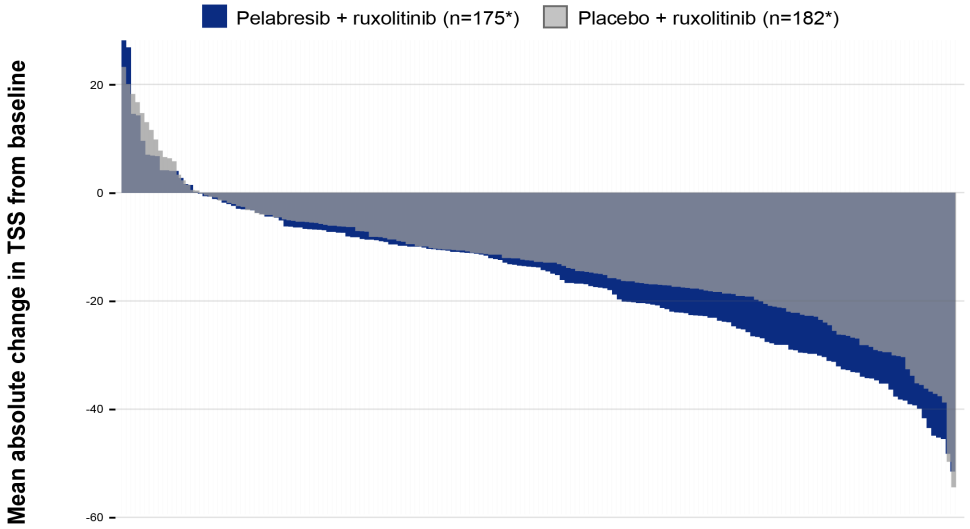
	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	p-value
SVR35 at Week 24	65.9%	35.2%	
Difference† (95% CI)	30.4 (21.6, 39.3)		<0.001
Mean % change in spleen volume at Week 24‡	-50.6 (n=171)	-30.6 (n=183)	
95% CI	-53.2, -48	-33.7, -27.5	



Rampal R, et al. ASH 2023. Oral 628.

PELA+RUX combo do not significantly improve TSS

TSS change from baseline to Week 24

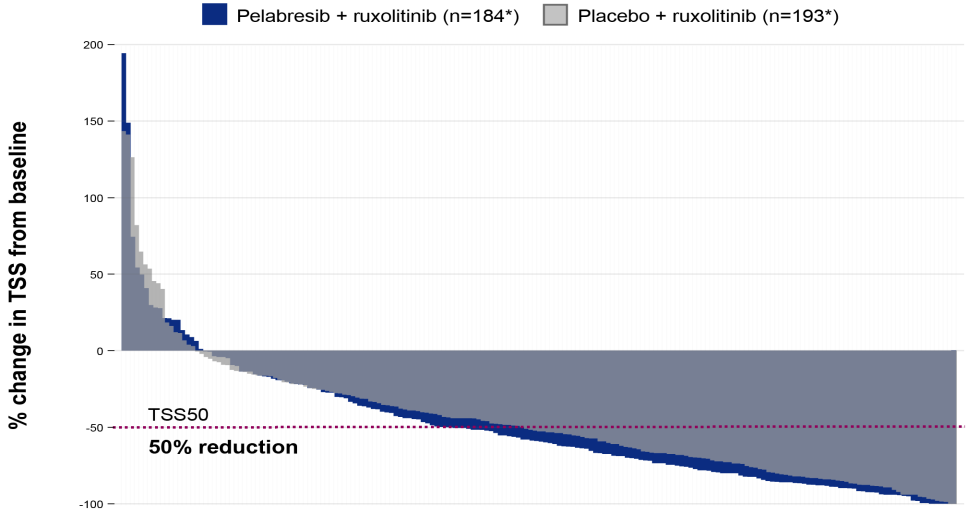


ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	p-value
TSS change† from baseline at Week 24	-15.99	-14.05	
Mean difference‡ (95% CI)	-1.94 (-3.92, 0.04)		0.0545

- **Absolute change in TSS is a continuous endpoint** that estimates magnitude of symptom burden reduction with enhanced precision

TSS50 at Week 24

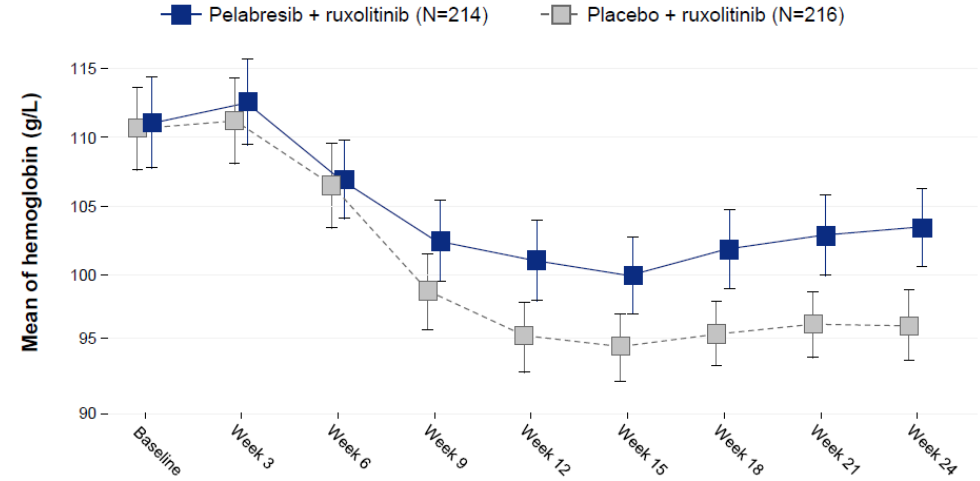


ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)	p-value
TSS50 at Week 24	52.3%	46.3%	
Difference† (95% CI)	6.0 (-3.5, 15.5)		0.216

Rampal R, et al. ASH 2023. Oral 628.

PELA+RUX combo: effect of hemoglobin



Number of patients

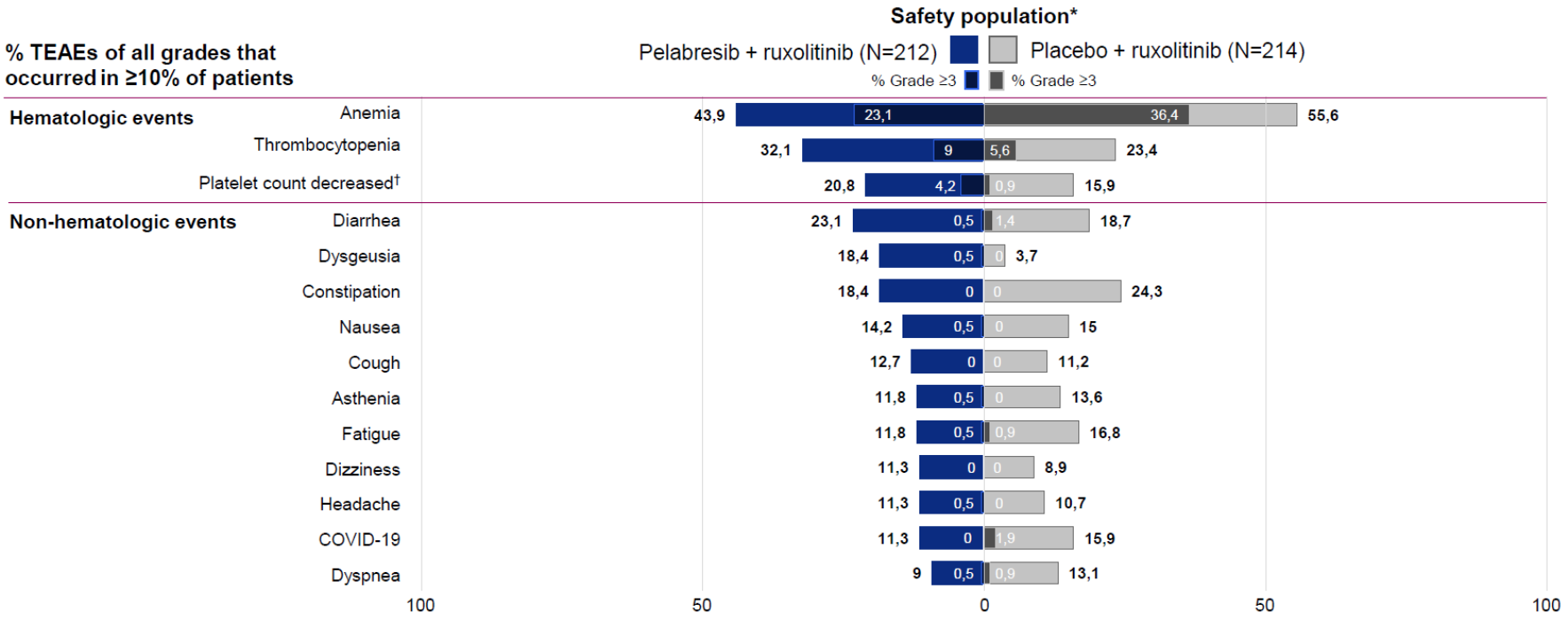
Pelabresib + ruxolitinib	212	204	209	199	193	189	186	185	184
Placebo + ruxolitinib	214	206	211	209	207	205	204	199	196

ITT population

	Pelabresib + ruxolitinib (N=214)	Placebo + ruxolitinib (N=216)
Hemoglobin response* ≥1.5 g/dL mean increase (95% CI)	9.3% (5.45, 13.25)	5.6% (2.50, 8.61)
Patients requiring RBC transfusion during screening, n (%)	35 (16.4)	25 (11.6)
Patients requiring RBC transfusion during first 24 weeks of study treatment, n (%)	66 (30.8)	89 (41.2)

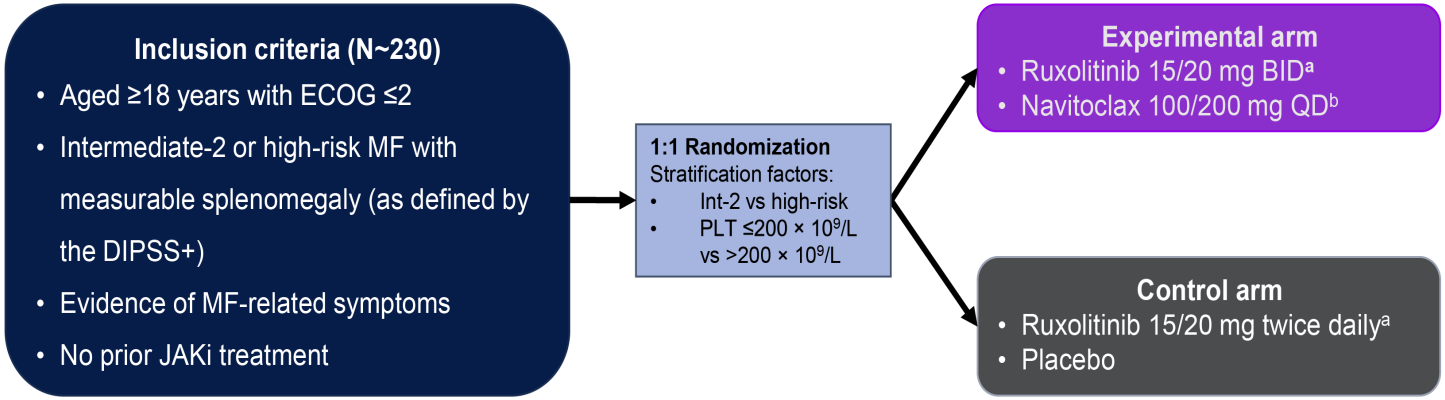
Rampal R, et al. ASH 2023. Oral 628.

PELA+RUX adverse events



Rampal R, et al. ASH 2023. Oral 628.

Navitoclax (BCL2/BCLXLi) + ruxolitinib in JAKi-naïve MF: the TRANSFORM-1 random, 2-blind, P3 study



Endpoints

- Primary endpoint: SVR_{35W24} (assessed for superiority) as measured by MRI or CT scan, per IWG criteria
- Secondary endpoints:
  - Change in TSS[c] from baseline at Week 24 as measured by MFSAF v4.0
  - SVR_{35} at any time
  - Duration of SVR_{35}
  - Anemia response per IWG criteria
- Safety endpoints: AEs

Median follow-up: 15 months

33% discontinued study treatment

Pemmaraju N. et al. ASH 2023. Oral 620

TRANFORM-1: Baseline disease characteristics

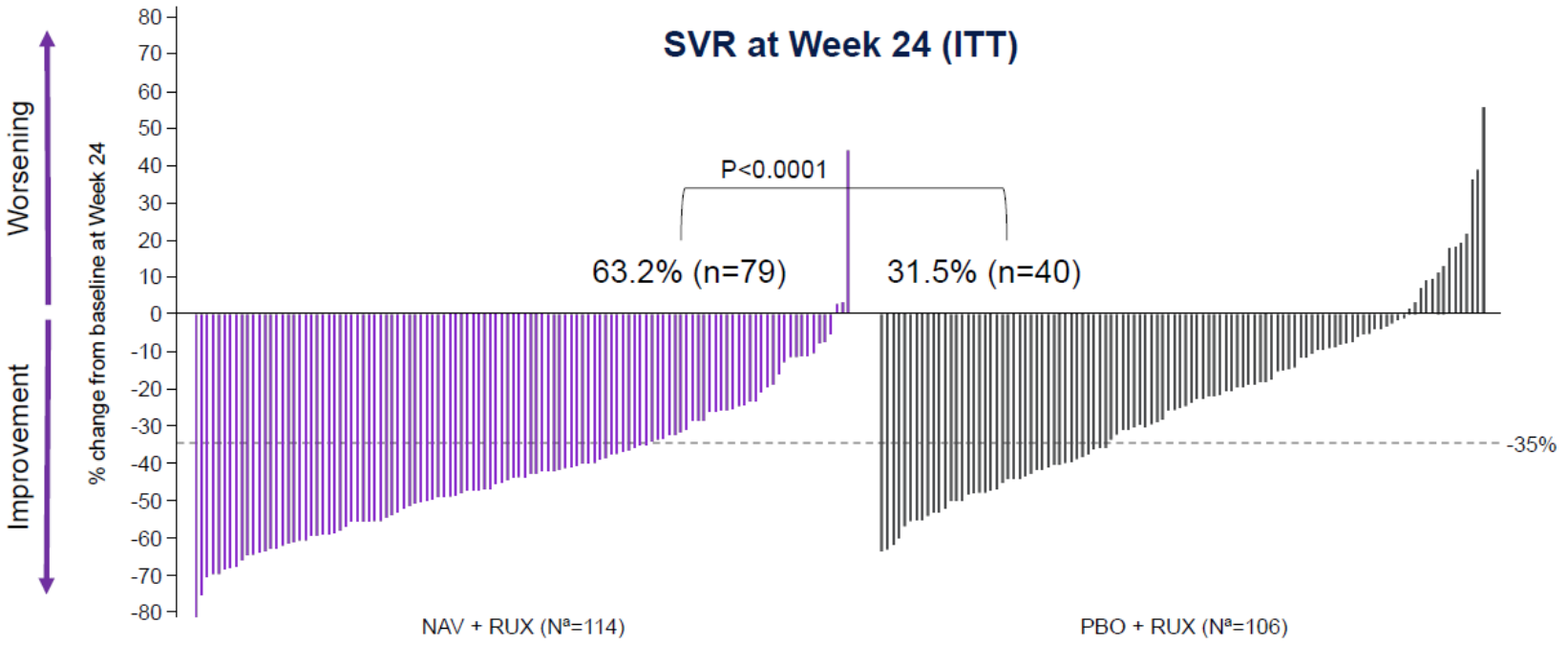
	NAV + RUX (N=125)	PBO + RUX (N=127)
Age, median (range), years	70 (42–87)	69 (37–85)
Sex, male	63 (50)	81 (64)
Time from last MF diagnosis to study entry, median (range), months	8 (0.3–181.6)	6 (0.3–198.8)
Type of MF		
Primary	63 (50)	72 (57)
Post-PV-MF or Post-ET-MF	62 (50)	55 (43)
Number of prior lines of therapy, median (range)	1 (1–3)	1 (1–4)
Spleen volume, median (range), cm^3	1441 (419–8020)	1639 (219–5664)
TSS score, median (range)	21 (0.1–60.6)	24 (6.7–61.6)
Transfusion dependent at BL	5 (4)	4 (3)
Calculated DIPSS+ risk at study entry[a]		
Intermediate-1	8 (6)	5 (4)
Intermediate-2	104 (83)	110 (87)
High	13 (10)	12 (9)
Driver mutations		
JAK2 V617F	81 (65)	79 (62)
CALR	22 (18)	26 (20)
MPL W515	14 (11)	10 (8)
HMR mutations, n/N (%)	57/120 (48)	50/117 (43)

- Median (range) follow-up was 14.9 (0.0–29.5) months

Pemmaraju N. et al. ASH 2023. Oral 620

NAVI+RUX combo double SVR35 at Week 24

- A significantly higher number of patients achieved SVR_{35W24} in NAV + RUX arm compared with PBO + RUX [79 (63.2%) vs 40 (31.5%); P<0.0001]

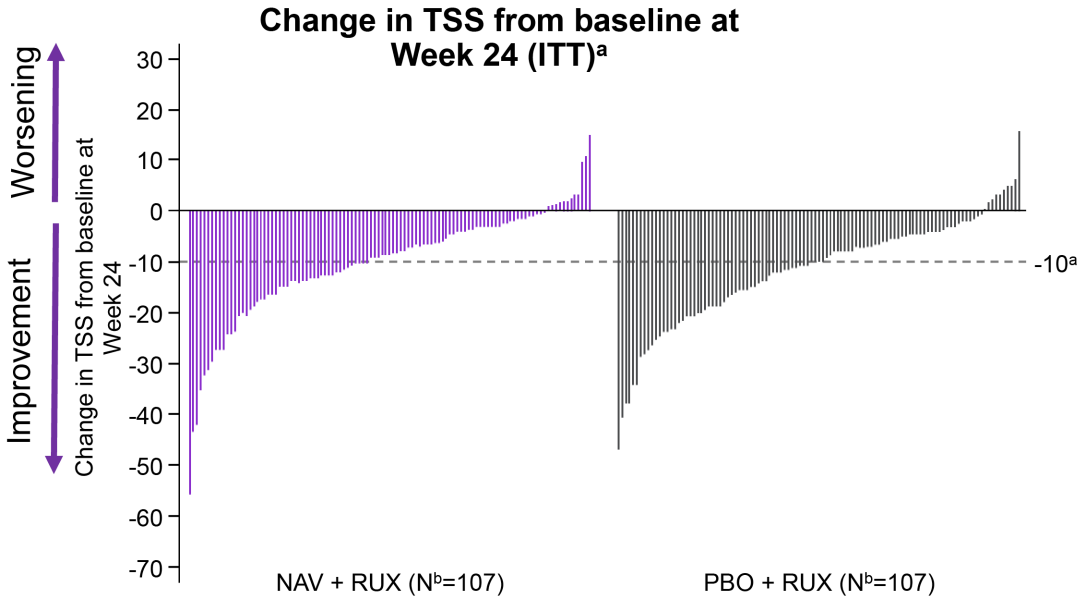


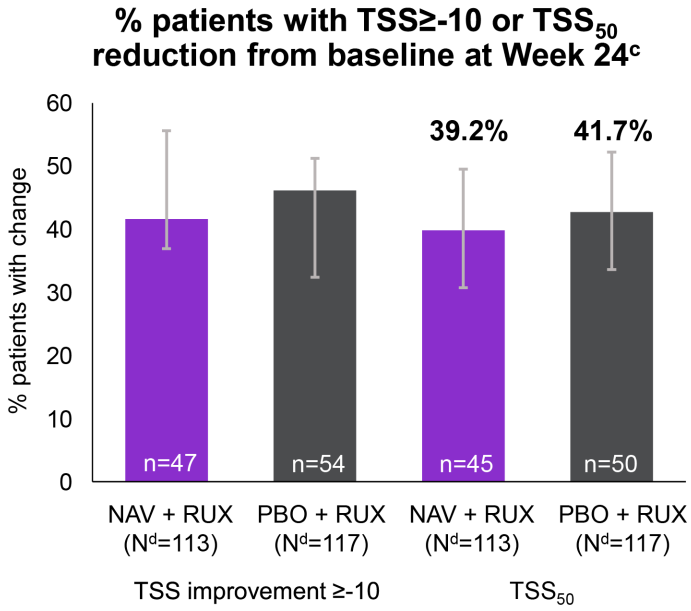
SVR_{35} at any time on-study; n (%)	96 (76.8)	53 (41.7)	**34.6 (23.6–45.6); P<0.0001***
Time to first SVR_{35} response; median (range) weeks	12.3 (10.1–48.3)	12.4 (11.3–72.3)	
Subjects who lost SVR_{35} response; n/N (%)	18/96 (18.8)	14/53 (26.4)	
12-month duration of SVR_{35} rate; % (95% CI)	76.7 (64.7, 85.0)	76.9 (59.8, 87.4)	

Pemmaraju N. et al. ASH 2023. Oral 620.

NAVI+RUX combo do not significantly improve TSS

- At Week 24, the mean change in TSS from baseline was -9.7 (95% CI: -11.8, -7.6) with NAV + RUX compared with -11.1 (95% CI: -13.2, -9.1) with PBO + RUX arm in ITT population (P=0.2852)





Pemmaraju N. et al. ASH 2023. Oral 620

NAVI+RUX adverse events

	NAV + RUX (N=124)[a] N (%)		PBO + RUX (N=125)[a] N (%)	
Any AE	124 (100)		121 (97)	
Any AE grade ≥3	105 (85)		87 (70)	
Most common AEs (>30% patients receiving NAV)	**Any grade**	**Grade ≥3**	**Any grade**	**Grade ≥3**
Thrombocytopenia	112 (90)	63 (51)	62 (50)	19 (15)
Anemia	74 (60)	57 (46)	61 (49)	49 (39)
Neutropenia	56 (45)	47 (38)	7 (6)	5 (4)
Diarrhea	42 (34)	6 (5)	17 (14)	0
Bleeding/hemorrhagic events	30 (24)	2 (2)	27 (22)	7 (6)
COVID-19	26 (21)	1 (1)	23 (18)	7 (6)
Contusion	13 (10)	0	7 (6)	0
Abdominal pain	11 (9)	1 (1)	8 (6)	1 (1)
Abdominal pain upper	9 (7)	1 (1)	10 (8)	1 (1)
Bone pain	9 (7)	0	6 (5)	0
Any serious AE	32 (26)		40 (32)	
AEs leading to dose reduction				
Navitoclax/placebo	101 (81)		39 (31)	
Ruxolitinib	112 (90)		76 (61)	
AE leading to dose interruption				
Navitoclax/placebo	87 (70)		44 (35)	
Ruxolitinib	78 (63)		41 (33)	
All deaths	13 (10)		13 (10)	
Deaths ≤30 days following last dose of study drug	6 (5)		5 (4)	

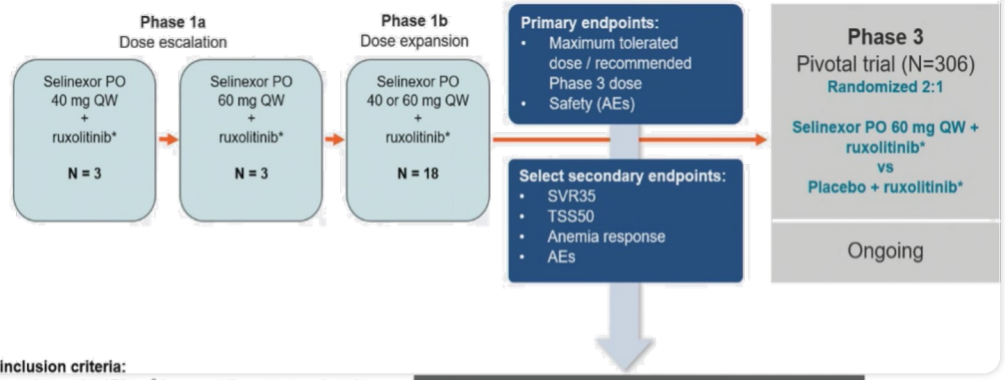
- Most commons AEs were thrombocytopenia, anemia, neutropenia, and diarrhea
- Most common serious AEs reported were
  - COVID-19 pneumonia and pneumonia in 3 patients each with NAV + RUX and 2 each with PBO + RUX
- Dose reductions and interruptions were mostly due to thrombocytopenia, none were due to bleeding

Pemmaraju N. et al. ASH 2023. Oral 620.

Selinexor + RUX in JAKi-naïve patients with MF, open label phase 1 XPORT-MF-034

Study design

Phase 1 of XPORT-MF-034 was an open-label study evaluating the safety and efficacy of selinexor 40mg and 60mg once-weekly plus ruxolitinib in patients with JAKi-naïve MF



Select inclusion criteria:

- Spleen volume of ≥ 450 cm^3 by magnetic resonance imaging or computed tomography
- Dynamic International Prognostic Scoring System (DIPSS) intermediate-1 and symptomatic, intermediate-2, or high risk
- Eastern Cooperative Oncology Group 0–2
- Platelet count ≥ 100×10^9/L

DIPSS risk, n (%)	
Intermediate-1	3 (21.4)
Intermediate-2	8 (57.1)
High risk	3 (21.4)
HMR†	5 (35.7)

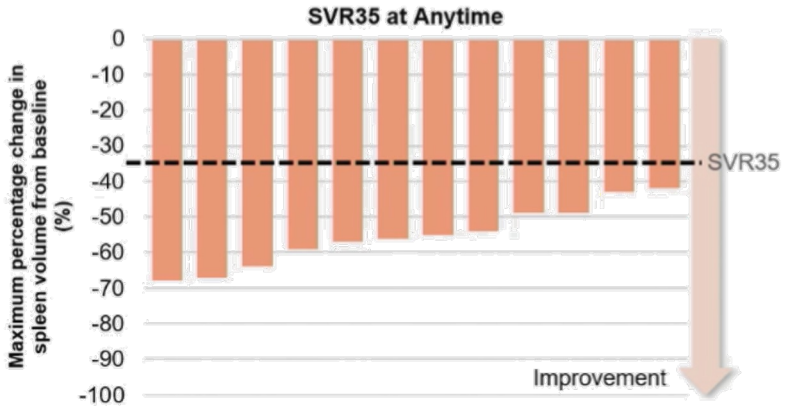
Safety Results

TEAEs	SEL 60 mg QW + RUX (N=14)
Any grade (≥30% overall), n (%)	
Nausea	11 (78.6)
Anemia	9 (64.3)
Thrombocytopenia	9 (64.3)
Fatigue	8 (57.1)
Constipation	7 (50.0)
Vomiting	7 (50.0)
Dyspnea	5 (35.7)
Headache	5 (35.7)
Hyponatremia	5 (35.7)
Leukopenia	5 (35.7)
Neutropenia	5 (35.7)
Grade 3+ (>5%), n (%)	
Anemia	6 (42.9)
Thrombocytopenia	4 (28.6)
Back pain	2 (14.3)
Neutropenia	1 (7.1)
Atrial fibrillation	1 (7.1)
Leukopenia	1 (7.1)
TRAEs leading to treatment discontinuations, n (%)	
Thrombocytopenia, Grade 3	1 (7.1)
Peripheral neuropathy, Grade 3	1 (7.1)

Tantravahi S, et al. ASH 2023. Oral 622.

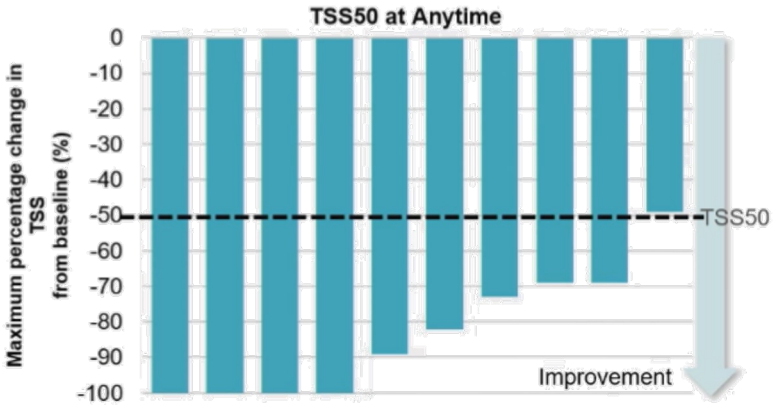
Selinexor+RUX in JAKi-naïve patients with MF: XPORT-MF-034

		SVR35
Population	Timepoint	Selinexor 60 mg QW + ruxolitinib n (%)
Efficacy evaluable	Week 12	10/12† (83)
	Week 24	**11/12 (92)**
Intent-to-treat	Week 12	10/14 (71)
	Week 24	**11/14 (79)**



All patients in the efficacy evaluable population treated with selinexor 60 mg QW achieved SVR[35] at any time

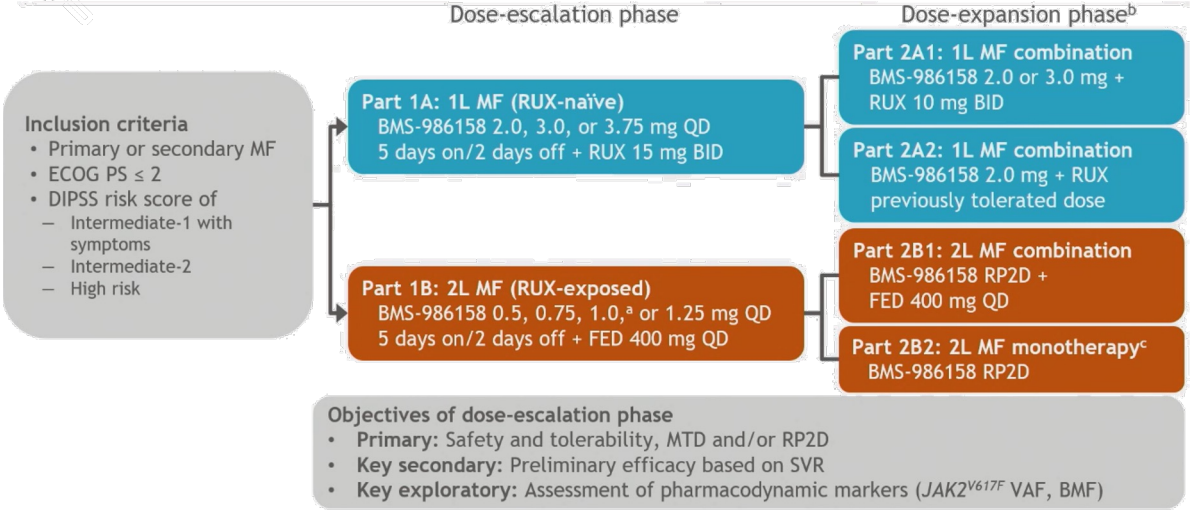
		TSS50
Population	Timepoint	Selinexor 60 mg QW + ruxolitinib n (%)
Efficacy evaluable	Week 12	8/10‡ (80)
	Week 24	**7/9§ (78)**
Intent-to-treat	Week 12	8/12 (67)
	Week 24	**7/12 (58)**



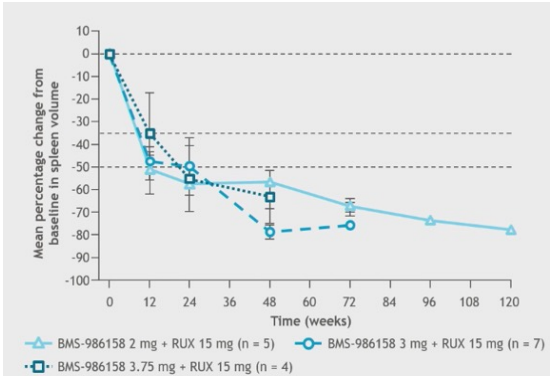
90% of patients in the efficacy evaluable population treated with selinexor 60 mg QW achieved TSS50 at any time

Tantravahi S, et al. ASH 2023. Oral 622.

BMS-986158, BETi, + RUX (JAKi-naïve) or + FEDR (RUX-exposed) in int- or high-risk MF

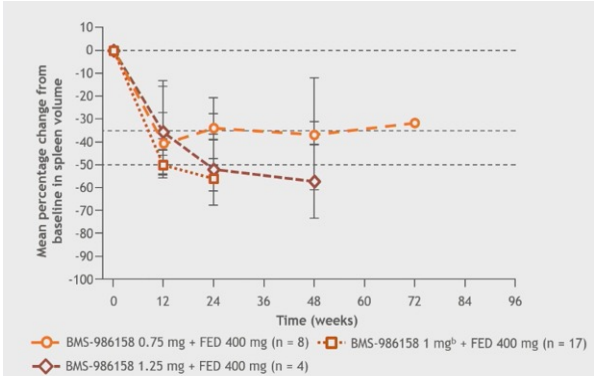


1L MF: Spleen volume reduction
BMS-986158 + ruxolitinib



100% of patients treated with 2 mg BMS-986158 and 75% treated with 3 mg achieved SVR[35] by 24 weeks

2L MF: Spleen volume reduction
BMS-986158 + fedratinib



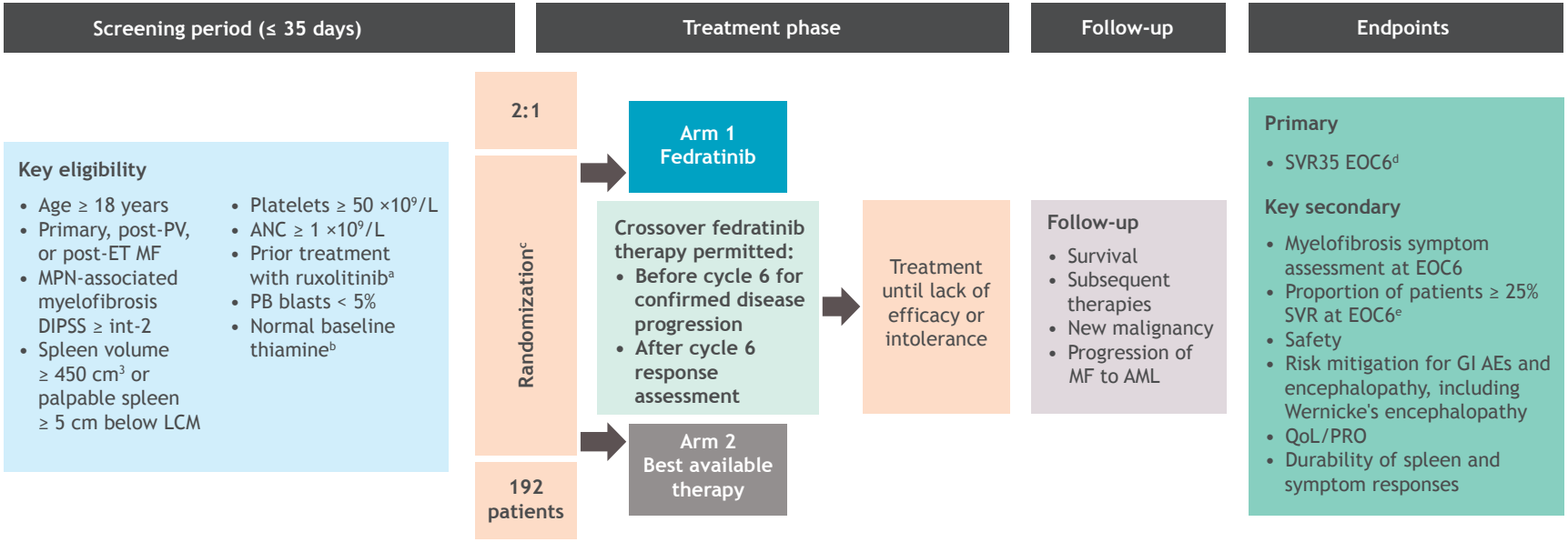
100% of patients treated with 1 mg BMS-986158 achieved SVR[35] by 24 weeks

Hematological toxicity as main adverse event

Lavie D, et al. Presented at ASH 2023. Oral 623.

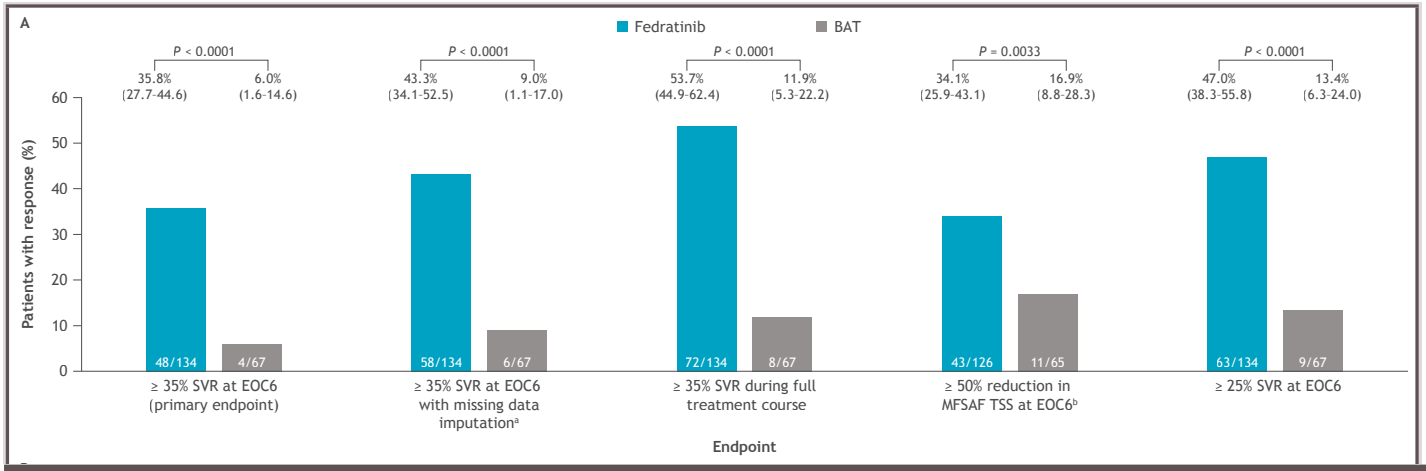
JAKi-exposed MF

Fedratinib in patients with MF previously treated with RUX: phase 3 randomized FREEDOM2 study

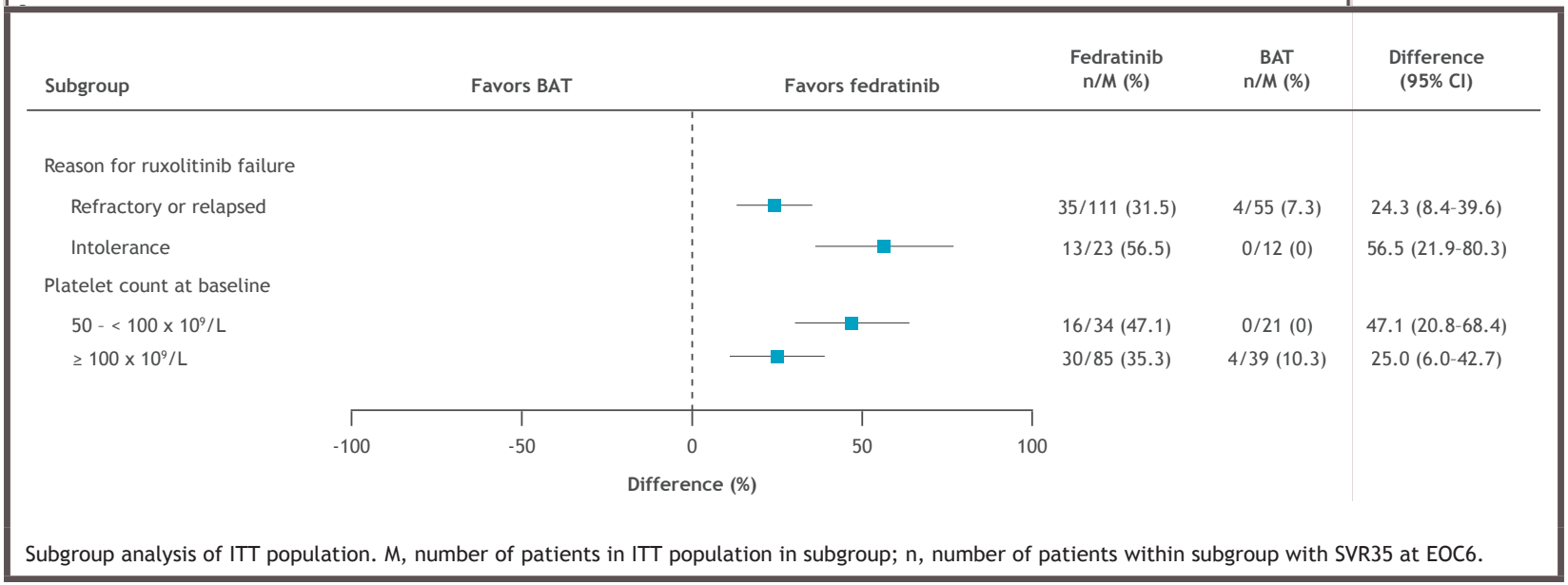


Harrison et al. ASH 2023 Abs 3204

FEDR achieved SVR35 at EOC6 in 35.8% of patients vs. 6.0% with BAT



BAT:
78% RUX
28% RBC transf.
20% HU



Subgroup analysis of ITT population. M, number of patients in ITT population in subgroup; n, number of patients within subgroup with SVR35 at EOC6.

Harrison et al. ASH 2023 Abs 3204

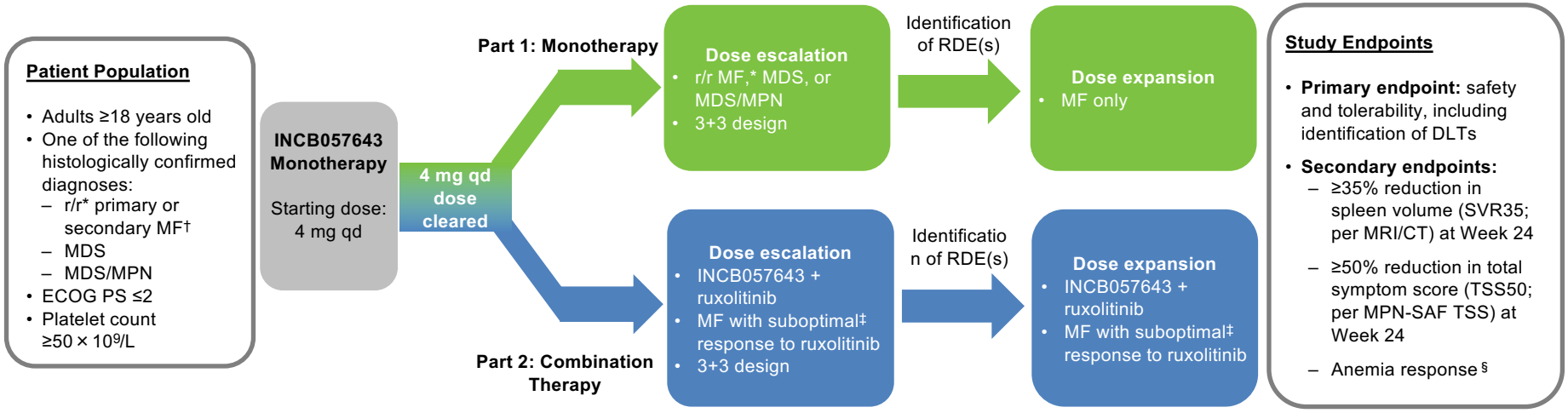
FEDR adverse events in the Freedom-2 study

System organ class Preferred term	Any grade		Grade 3/4	
	Fedratinib (n = 134)	BAT (n = 67)	Fedratinib (n = 134)	BAT (n = 67)
Patients with ≥ 1 TRAE related to study drug	109 (81.3)	23 (34.3)	52 (38.8)	8 (11.9)
Gastrointestinal disorders	80 (59.7)	6 (9.0)	5 (3.7)	0
Diarrhea	51 (38.1)	0	1 (0.7)	0
Nausea	43 (32.1)	1 (1.5)	1 (0.7)	0
Vomiting	18 (13.4)	1 (1.5)	0	0
Constipation	12 (9.0)	3 (4.5)	0	0
Blood and lymphatic system disorders	33 (24.6)	12 (17.9)	26 (19.4)	8 (11.9)
Thrombocytopenia	22 (16.4)	3 (4.5)	16 (11.9)	2 (3.0)
Anemia	18 (13.4)	9 (13.4)	12 (9.0)	6 (9.0)
Investigations	26 (19.4)	0	7 (5.2)	0
Alanine aminotransferase increased	10 (7.5)	0	4 (3.0)	0
Vitamin B1 decreased	9 (6.7)	0	0	0
Renal and urinary disorders	17 (12.7)	0	13 (9.7)	0
Metabolism and nutrition disorders	14 (10.4)	4 (6.0)	8 (6.0)	0
General disorders and administration site conditions	11 (8.2)	4 (6.0)	4 (3.0)	0
Skin and subcutaneous tissue disorders	11 (8.2)	2 (3.0)	0	0
Musculoskeletal and connective tissue disorders	9 (6.7)	3 (4.5)	0	0
Nervous system disorders	9 (6.7)	0	0	0

Harrison et al. ASH 2023 Abs 3204

INCB057643 (LIMBER-103), BET-i, in R/R MF (P1)

- The initial INCB057643 dose was 4 mg qd with dose escalation up to 12 mg qd; all doses were administered continuously in 28-day cycles

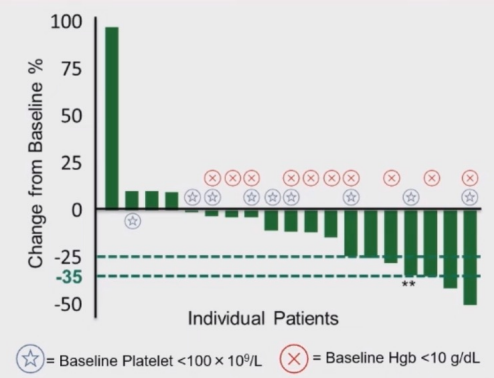


- INCB057643 monotherapy or in combination with RUX was well tolerated
- Improvements in spleen size and symptom burden were observed in patients receiving INCB057643 ≥8-mg (mono) and INCB057643 4- and 6-mg (combo)
- 6 mg and 10 mg INCB057643 were identified as monotherapy doses for expansion; Dose escalation is ongoing in the combination therapy group

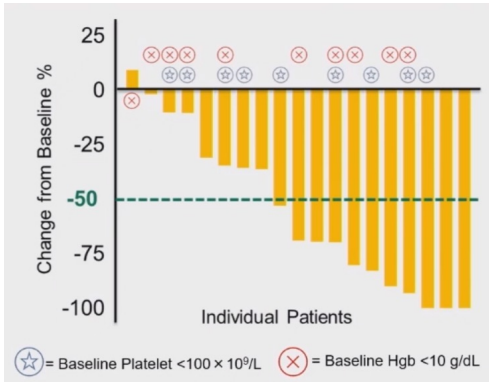
Watts et al. ASH 2023 abs 750

TP-3654, PIM1i, in R/R MF

Best change in spleen volume at any time

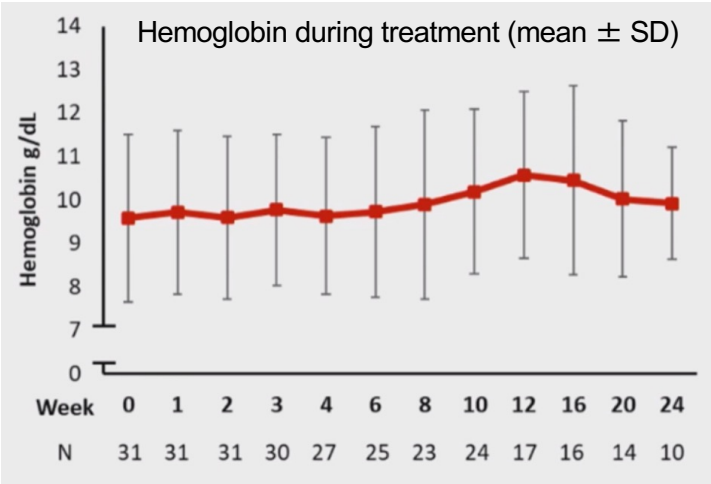


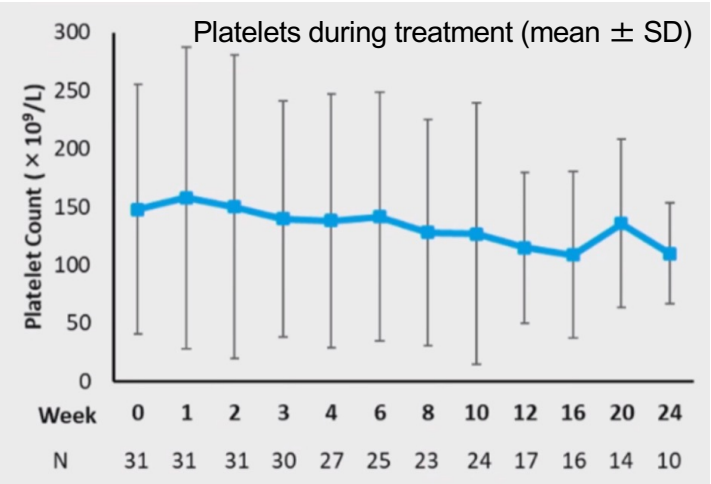
Best change in symptoms at any time



SVR[35] was achieved by 20% of patients; SVR[25] by 30% of patients, and SVR[10] by 55% of patients

TSS50 was achieved by 55% of patients





Rein L, et al. Presented at ASH 2023. Oral 626.

Anemia in MF

Zilurgisertib, an ALK2/ACVR1 inhibitor

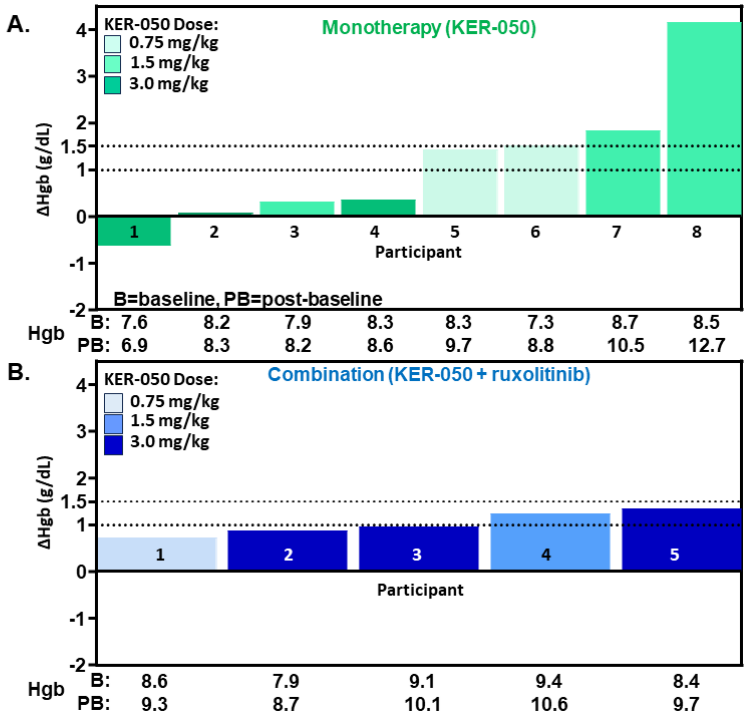
- ***Monotherapy Population (Resistant, refractory, lost response to or intolerant/ineligible for JAKi)***
  - Among the 7 NTD patients who completed 24 weeks of treatment, anemia improvement (Hb increase ≥1.5 g/dL from BL) was observed in 2 patients
  - None of the 6 TD patients who completed 24 weeks of treatment achieved transfusion independence
- ***Combo population (add on RUX , if anemia)***
  - Among the 10 NTD patients who completed 24 weeks of treatment, anemia improvement (Hb increase ≥1.5 g/dL from BL) was observed in 2 patients
  - The one TD patient who completed 24 weeks of treatment did not achieve transfusion independence

Mohan et al. ASH 2024.Abs 624

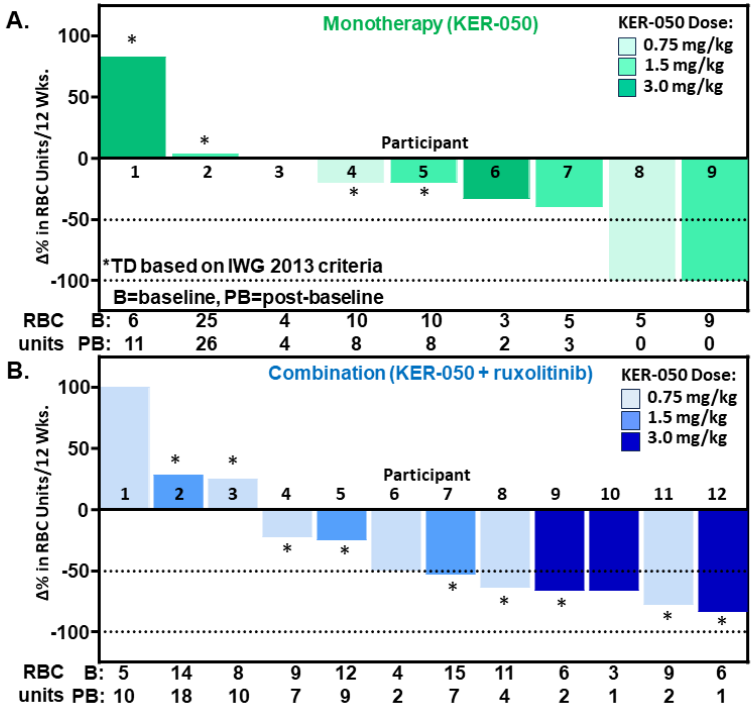
KER-050 and KER-050+RUX in MF patients with anemia, an ongoing Phase 2 RESTORE study

- KER-050 is an investigational, modified activin receptor type IIA ligand trap designed to inhibit activin A and other select TGF-β superfamily ligands, activin B and GDFs 8 and 11

Maximum Change in Hgb: NTD Participants



Reductions in Transfusion Burden



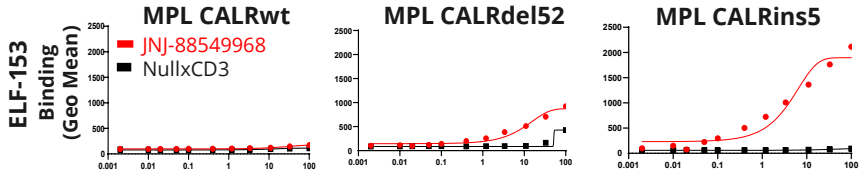
Harrison et al. ASH 2023 Abs 3185

Potential target therapies

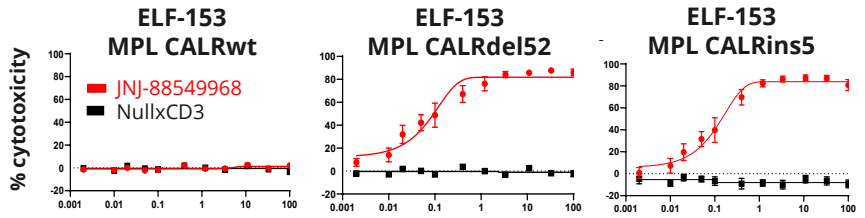
JNJ-88549968, a Novel, First-in-Class CALRmut x CD3 T-cell Redirecting Antibody

- CALRmut is detected on the surface of CALRmut MPN cells
- No substantial changes in CALRmut patient T cell functionality

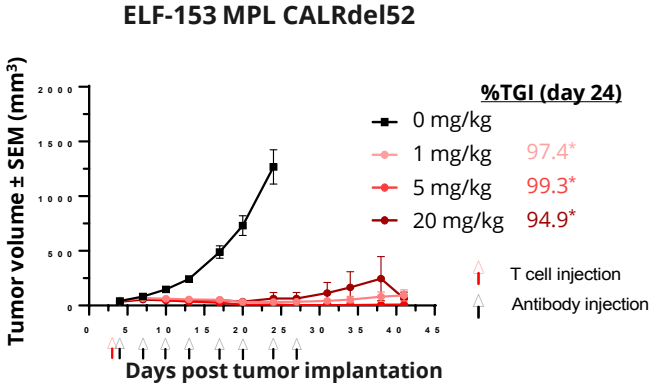
JNJ-88549968 selectively binds to CALRmut expressing cells



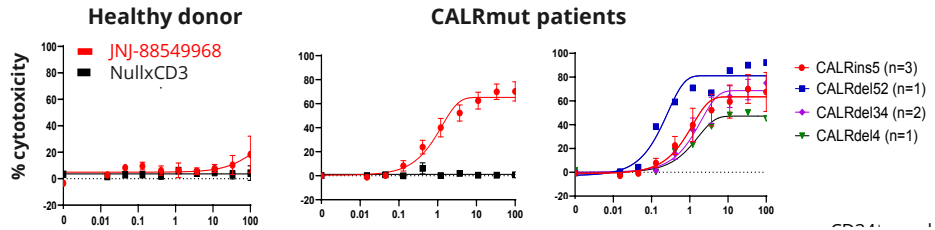
JNJ-88549968 mediates CALRmut selective cytotoxicity



JNJ-88549968 mediates anti-tumor activity *in vivo*



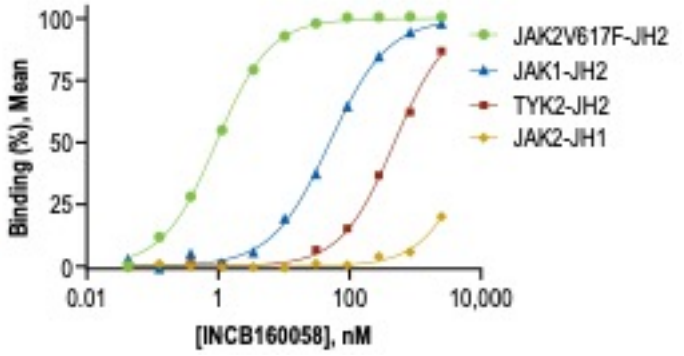
JNJ-88549968 mediates cytotoxicity of CALRmut patient-derived CD34⁺ cells in autologous setting



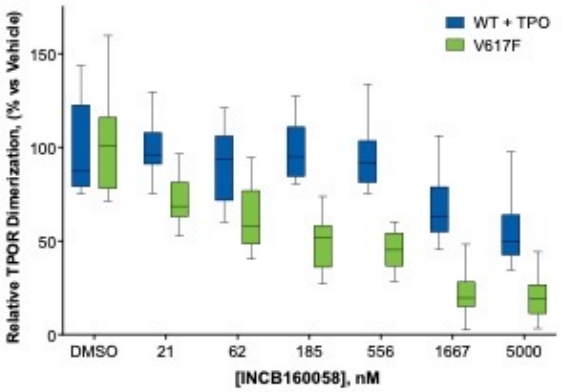
Kuchnio et al. ASH 2023. Abs 1777

INCB160058, a selective pseudokinase (JH2)-binding inhibitor of JAK2V617F

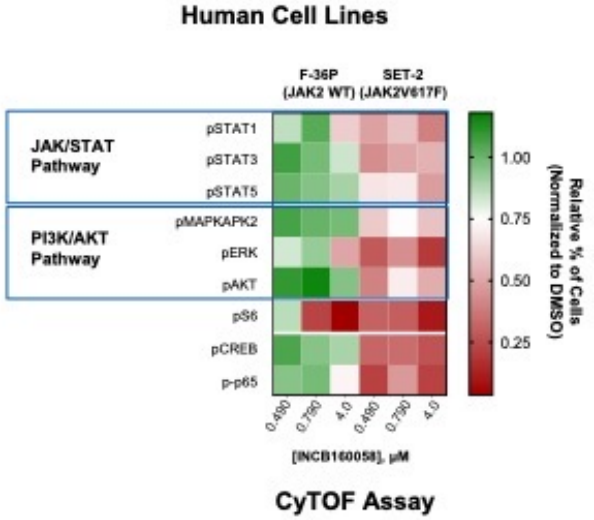
INCB058 is a selective pseudokinase (JH2)-binding Inhibitor of JAK2V617F



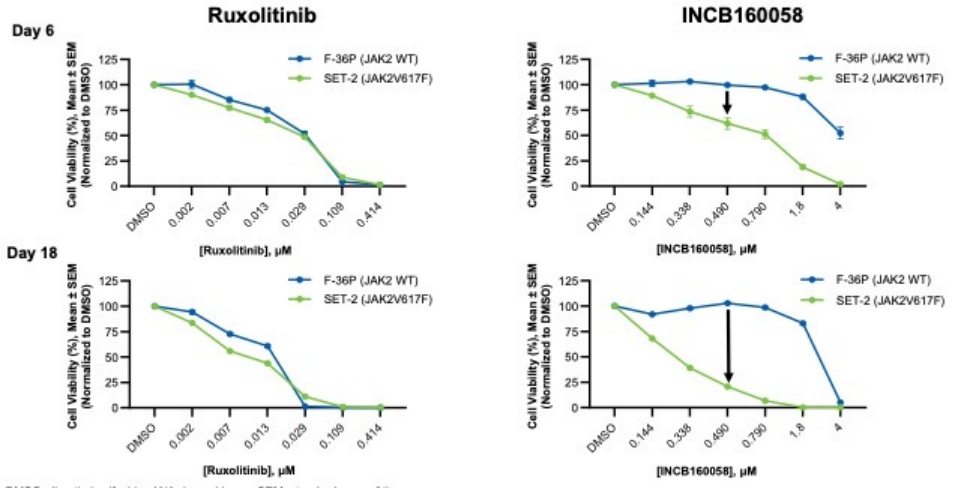
Inhibition of V617F-driven TPOR Dimerization



Inhibition of JAK2V617F signaling



Selective growth inhibition of V617F-expressing cells



Stubbs et al. ASH 2023. Abs 860

Conclusions

- Combination therapies in 1L, as pelabresib plus ruxolitinib (MANIFEST-2, mostly int-1) or navitoclax plus ruxolitinib (TRANSFORM-1, mostly int-2) provided evidence of efficacy doubling SVR35 at W32 *vs.* ruxolitinib single agent, leaving unaffected symptomatology control of ruxolitinib
- Selinexor plus ruxolitinib in 1L setting is under investigation
- Fedratinib definitively represents the 2L treatment of MF with a 54% rate of SVR35 during treatment course
- Bet-inhibitors (BMS-986158, INCB057643), PIM inhibitor and anemia-oriented molecules (zilurgisertib and KER-050) are under investigation
- Immunotherapies for $CALR^{mut}$ and JH2 inhibition for $JAK2^{mut}$ have interesting preclinical profiles