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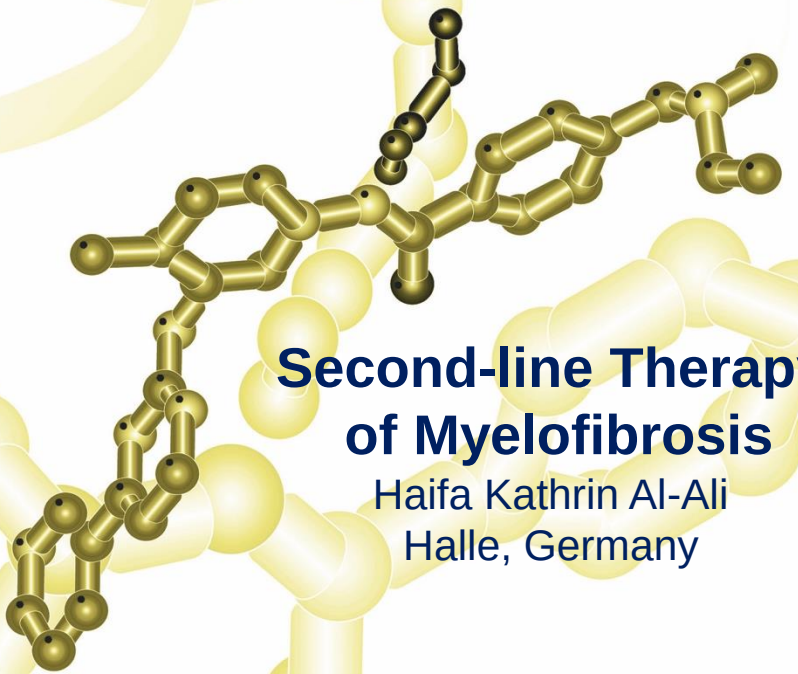

Second-line Therapy of Myelofibrosis

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New Drugs in Hematology

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Disclosures of Al-Ali, Haifa Kathrin

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS	yes	no	yes	no	no	yes	
Incyte	yes	no	no	no	no	no	
Novartis	yes	no	yes	no	no	yes	
AbbVie	no	no	yes	no	no	yes	
AOP Pharma	no	no	yes	no	no	yes	
Blueprint	no	no	no	no	no	yes	
GSK	no	no	yes	no	no	yes	
Alexion	no	no	no	no	no	no	Travel grant
Otsuka	no	no	yes	no	no	no	

Limitations with Ruxolitinib-Based Treatment in MF

Cytopenic MF

- Lower **peripheral blood counts and will frequently require transfusion support**
- More **likely primary MF**; **higher risk scores**, **advanced fibrosis**; **more blasts**
- More **frequent additional somatic mutations outside the JAK/STAT pathway**
- Lower ***JAK2* VAF**
- Fewer **therapeutic options**
- **A worse prognosis**

Marcellino BK, et al. *Lymphoma Myeloma Leuk.* 2020;20(7):415-421.

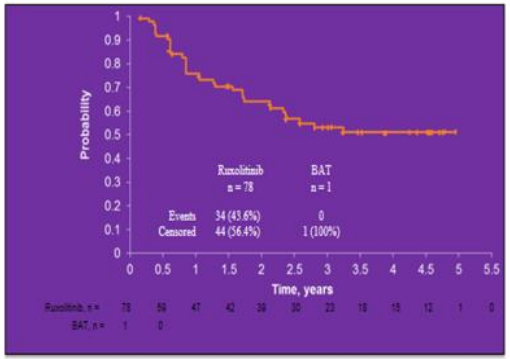
Ruxolitinib-Related Cytopenias

Clinical trial[a]	Incidence of anemia Grade 3/4, %	Incidence of thrombocytopenia Grade 3/4, %
Int-2- and High-risk patients		
COMFORT-I (n = 155)	45.0	13.0
COMFORT-II (n = 146)	42.0	8.0
Int-1-risk patients		
JUMP (n = 163)	24.5	11.0
ROBUST (n = 14)	N/A	N/A
Italian study (n = 70)	21.7	2.9

1. Verstovsek S, et al. *N Engl J Med.* 2012. **2.** Harrison C, et al. *N Engl J Med.* 2012. **3.** Al-Ali HK, et al. *Br J Haematol.* 2020. **4.** Al-Ali HK, et al. *Haematologica.* 2016. **5.** Mead AJ, et al. *Br J Haematol.* 2015. **6.** Palandri F, et al. *Hematol Oncol.* 2018. **7.** Harrison CN, et al. *Am J Hematol.* 2020. **8.** Gupta V, et al. *Leuk Lymphoma.* 2020.

Loss of response to Ruxolitinib

COMFORT II : Median duration of spleen response is 3,2 years



Harrison C, et al. Leukemia 2016;

Criteria for ruxolitinib failure used in the re-analysis of the JAKARTA-2, PAC203, and FREEDOM trials (adapted from Bose P., Verstovsek S. Hemasphere, 2020;4:E424)

Relapsed	Ruxolitinib for ≥3 months with spleen regrowth (defined as <10% SVR or <30% decrease in spleen size by palpation from baseline) following an initial response*
Refractory	Ruxolitinib for ≥3 months with <10% SVR or <30% decrease in spleen size by palpation from baseline
Intolerant	Ruxolitinib for ≥28 days complicated by development of RBC transfusion requirement (≥2 units/month for two consecutive months); or grade ≥3 thrombocytopenia, anemia, hematoma/hemorrhage or other, non-hematologic adverse events while on ruxolitinib

*Response is defined as ≥35% reduction in spleen volume from baseline or ≥50% reduction in spleen size for baseline sizes >10cm below LCM, a non-palpable spleen for baseline spleen sizes between 5cm and 10cm below LCM, or not eligible spleen response for baseline spleen <5cm below LCM (Harrison CN. et al. Am J Hematol, 2020;95:594-603).
LCM, left costal margin; RBC, red blood cell; SVR, spleen volume reduction.

Claire N. Harrison, et al. ASH 2023, #2355

Where to Go from Here? (allogeneic SCT excluded!)

Secondline JAKi

- Fedratinib (approved by EMA and available)
- Momelotinib (approved by EMA and soon to become available)
- Pacritinib (only FDA approved but not by EMA)

Combination Therapy

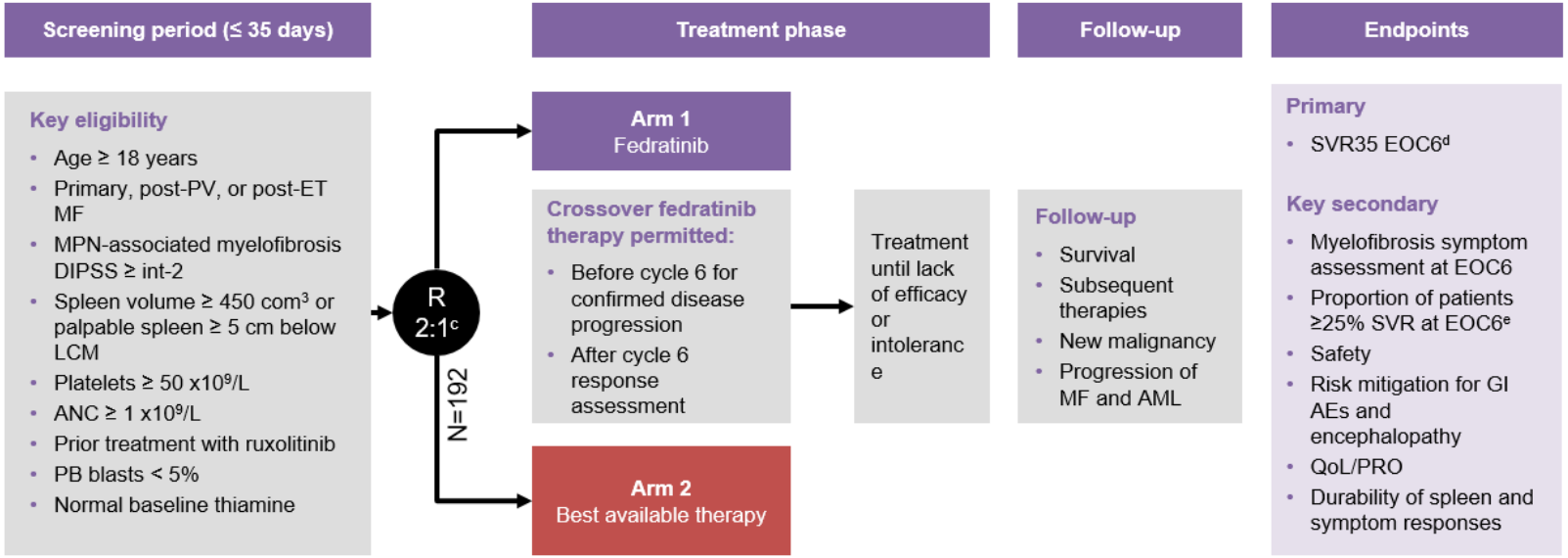
- JAKi + BETi
- JAKi + Selinexor
- JAKi + X + Y

Non-JAKi Therapy

- Imetelstat
- PIM1 Kinase-i

Secondline JAKi - Fedratinib

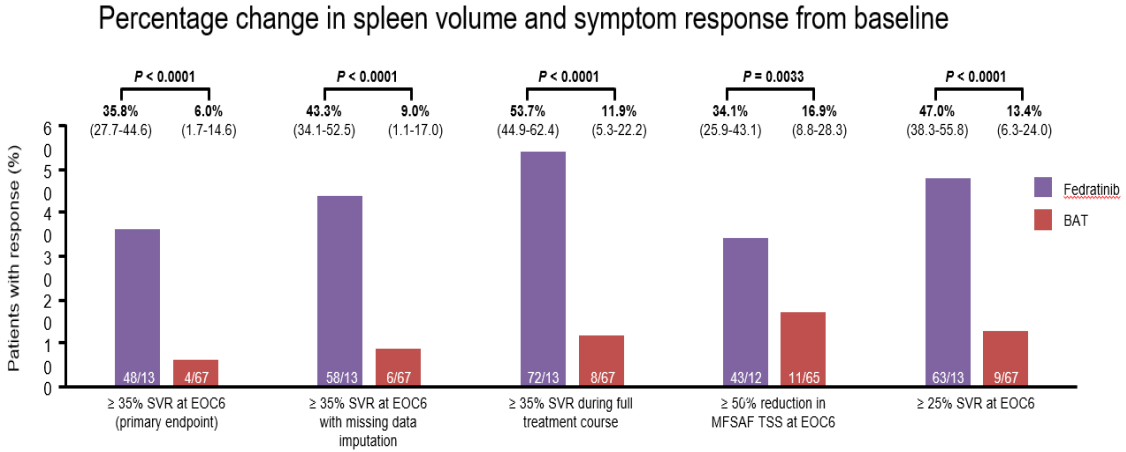
Efficacy and Safety of Fedratinib in Patients with MF Previously Treated with Ruxolitinib: Results from the Phase 3 Randomized FREEDOM2 Study



Claire N. Harrison, et al. ASH 2023, #3204

Secondline JAKi - Fedratinib

Efficacy and Safety of Fedratinib in Patients with MF Previously Treated with Ruxolitinib: Results from the Phase 3 Randomized FREEDOM2 Study



Adverse events during the first 6 cycles in > 5% of patients

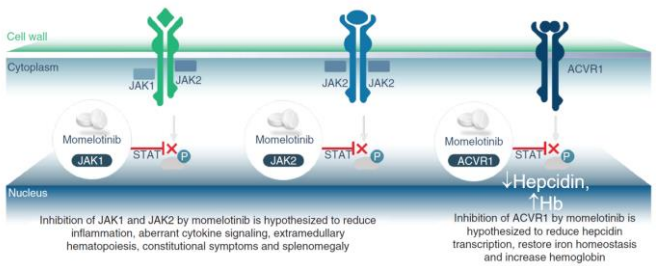
System organ class	Grade 3/4	
Preferred term	Fedratinib (n=134)	BAT (n=67)
Patients with ≥1 TRAE related to study drug	52 (38.8)	8 (11.9)
Gastrointestinal disorders	5 (3.7)	0
Diarrhea	1 (0.7)	0
Nausea	1 (0.7)	0
Vomiting	0	0
Constipation	0	0
Blood and lymphatic system disorders	26 (19.4)	8 (11.9)
Thrombocytopenia	16 (11.9)	2 (3.0)
Anemia	12 (9.0)	6 (9.0)
Investigations	7 (5.2)	0
Alanine aminotransferase increased	4 (3.0)	0
Vitamin B1 decreased	0	0
Renal and urinary disorders	13 (9.7)	0
Metabolism and nutrition disorders	8 (6.0)	0
General disorders and administration siteconditions	4 (3.0)	0
Skin and subcutaneous tissue disorders	0	0
Musculoskeletal and connective tissue disorders	0	0
Nervous system disorders	0	0

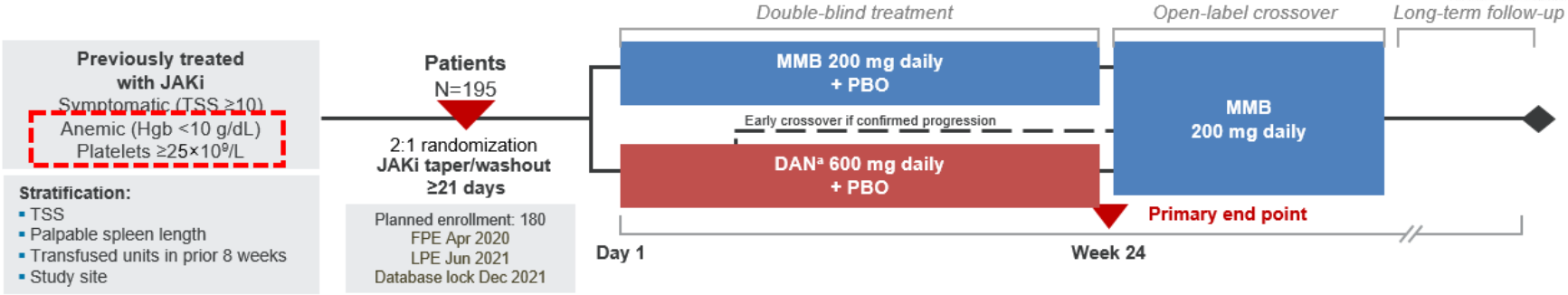
Claire N. Harrison, et al. ASH 2023, #3204

Secondline JAKi - Momelotinib

Results from the Momentum of Momelotinib (MMB) Versus Danazol (DAN) in Symptomatic and Anemic MF Patients Previously Treated with a JAKi

Verstovsek et al Front Oncol 2021





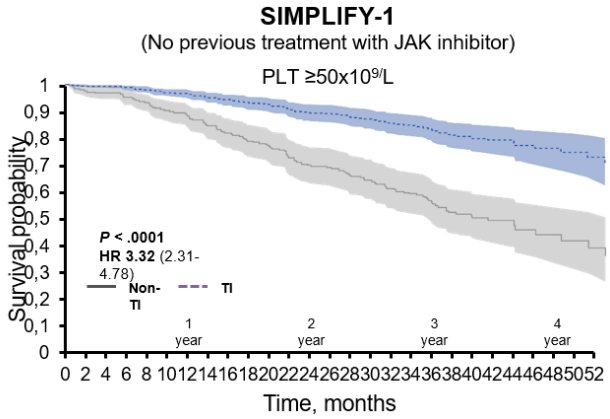
MOMENTUM Topline Results at Week 24: All Primary and Key Secondary End Points Met[1,2]

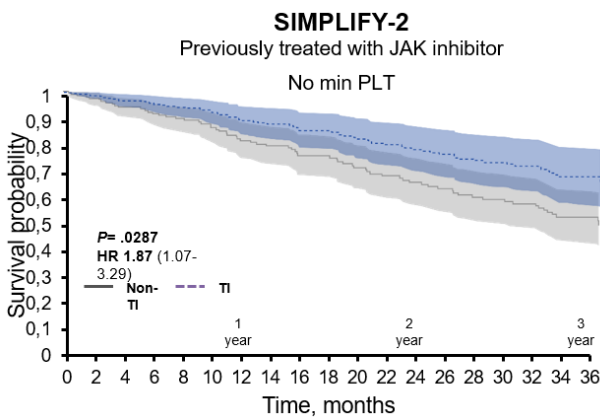
	MFSAF TSS response rate (primary end point)	TI response rate	SRR[d] (35% reduction)
MMB (N=130)	32 (24.6%)	40 (30.8%)	30 (23.1%)
DAN (N=65)	6 (9.2%)	13 (20.0%)	2 (3.1%)
	P=.0095 (superior)	1-sided *P*=.0064 (noninferior)	*P*=.0006 (superior)

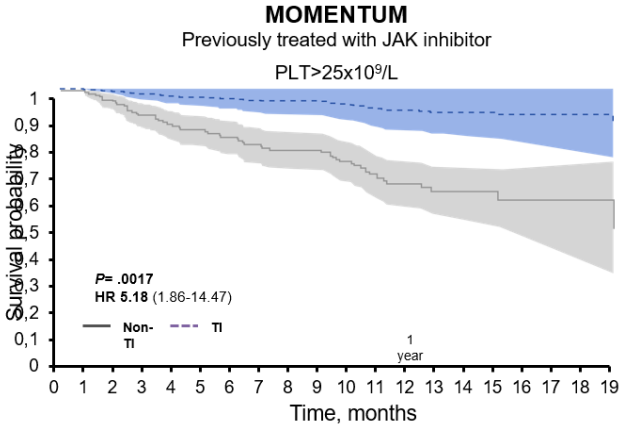
Verstovsek S, et al. Lancet. 2023.

Secondline JAKi - Momelotinib

RBC Transfusion Independence Is an Independent Predictor of Survival: A Post Hoc Time-Dependent Analysis of the Phase 3 Simplify-1, Simplify-2, and Momentum Trials







Vikas Gupta, et al. ASH 2023, #3188

Secondline JAKi - Pacritinib

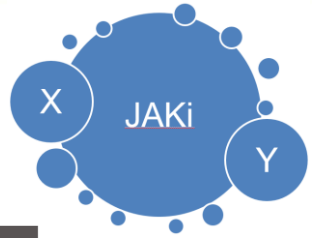
- Pacritinib has demonstrated clinical benefit at the recommended dose of 200 mg BID in patients with cytopenias in the Phase 2 dose-finding PAC203 and Phase 3 PERSIST-2 studies

- Patients with baseline platelets < 50 x 10^9/L treated with pacritinib 200 mg BID in PERSIST-2 and PAC203 or BAT in PERSIST-2 were included in a retrospective analysis

Baseline characteristics (pacritinib 200 mg BID)	**N = 71**
Median platelet count, 10^9/L	30
Platelet transfusion dependent, n (%)	13 (18)
Prior JAKi, n (%)	45 (63)
Some AEs (all grades)	**N (%)**
Thrombocytopenia	23 (32)
Any grade bleeding	49 (58)
Grade ≥ 3 bleeding	11 (16)
Grade ≥ 3 cardiac AE	6 (9)

Mascarenhas J, et al. Blood. 2021;138:3640.

Combination Therapy



BMS-986158, a potent BET inhibitor, in combination with Rux or Fedratinib in patients with Int- or high-risk MF: updated results from a phase 1/2 study

Inclusion criteria
- Primary or secondary MF
- ECOG PS ≤ 2
- DIPSS risk score of
  - Intermediate-1 with symptoms
  - Intermediate-2
  - High risk

Dose-escalation phase

Part 1A: 1L MF (RUX-naïve)
BMS-986158 2.0, 3.0, or 3.75 mg QD 5 days on/2 days off + RUX 15 mg BID

Part 1B: 2L MF (RUX-exposed)
BMS-986158 0.5, 0.75, 1.0, or 1.25 mg QD 5 days on/2 days off + FED 400 mg QD

Dose-expansion phase

Part 2A1: 1L MF combination
BMS-986158 2.0 or 3.0 mg + RUX 10 mg BID

Part 2A2: 1L MF combination
BMS-986158 2.0 mg + RUX previously tolerated dose

Part 2B1: 2L MF combination
BMS-986158 RP2D + FED 400 mg QD

Part 2B2: 2L MF monotherapy[c]
BMS-986158 RP2D

Objectives of dose-escalation phase
- **Primary:** Safety and tolerability, MTD and/or RP2D
- **Key secondary:** Preliminary efficacy based on SVR
- **Key exploratory:** Assessment of pharmacodynamic markers (*JAK2*^{V617F} VAF, BMF)

2L MF
BMS-986158 + FED

1.25 mg
n = 4

DLTs (n = 3):[b]
- G4 thrombocytopenia (n = 2)
- G3 diarrhea (n = 1)
- G3 hyperbilirubinemia (n = 1)

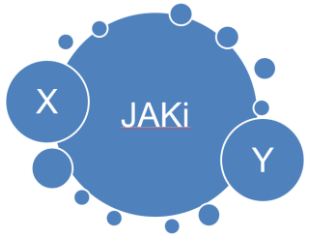
1 mg
n = 18

0.75 mg
n = 8

0.5 mg
n = 2

David Lavie et al. ASH 2023, #623

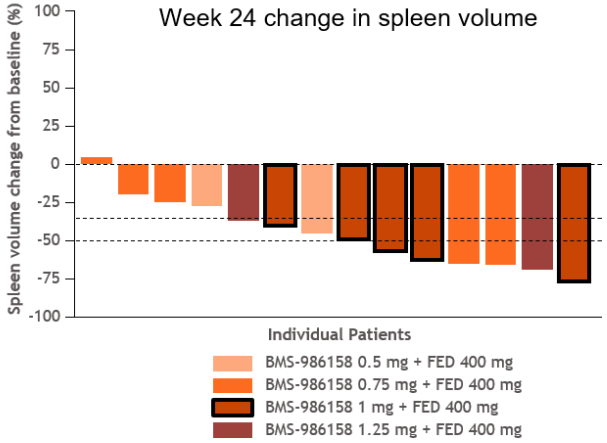
Combination Therapy



BMS-986158, a potent BET inhibitor, in combination with Rux or Fedratinib in patients with Int- or high-risk MF: updated results from a phase 1/2 study

TRAEs	2L MF, Part 1B BMS-986158 + FED (n = 32)							
	0.5 mg (n = 2)		0.75 mg (n = 8)		1.0 mg (n = 18)		1.25 mg (n = 4)	
	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4	Any grade	Grade 3/4
Patients with ≥ 1 TRAE, n (%)	2 (100)	1 (50)	6 (75)	3 (38)	13 (72)	6 (33)	4 (100)	4 (100)
Diarrhea	0	0	3 (38)	0	11 (61)	0	4 (100)	1 (25)
Thrombocytopenia	1 (50)	0	3 (38)	2 (25)	6 (33)	4 (22)	4 (100)	4 (100)
Anemia	1 (50)	1 (50)	4 (50)	2 (25)	5 (28)	4 (22)	3 (75)	3 (75)
Nausea	1 (50)	0	2 (25)	0	4 (22)	0	2 (50)	0
Vomiting	1 (50)	0	2 (25)	0	3 (17)	0	0	0
Dysgeusia	0	0	0	0	5 (28)	0	0	0
Dry mouth	0	0	0	0	2 (11)	0	2 (50)	0

- No grade 5 TRAEs
- Three serious TRAEs: grade 2 anemia (1.25 mg), grade 4 thrombocytopenia (1.25 mg), and grade 3 viral gastroenteritis (0.75 mg)
- Two TRAEs led to treatment discontinuation: grade 4 thrombocytopenia (1.25 mg) and grade 3 hyperbilirubinemia (1.25 mg)

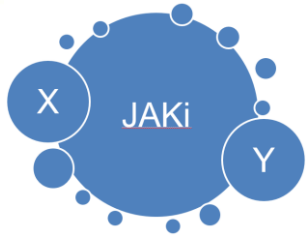


SVR35, BMS-986158 1 mg + FED 400 mg

12 weeks	24 weeks
9/11 (82%)	**5/5 (100%)**

David Lavie et al. ASH 2023, #623

Combination Therapy



The Efficacy and Safety of Selinexor in Combination with Rux in Rux-Treated MF Patients: the Interim Analysis of a Prospective, Open-Label, Multicenter, Parallel-Cohort, Phase 2 Study

Key inclusion criteria:

- Diagnosed MF patients, including PMF or Post-ET MF or Post-PV MF
- Enlarged spleen or systemic constitutional symptoms
- No stem cell transplant program within 6 months

→ SEL (40/60 mg QW) + RUX (5 - 20 mg bid, dosage per investigator judgement) →

Primary endpoint:

- Spleen response

Secondary endpoints:

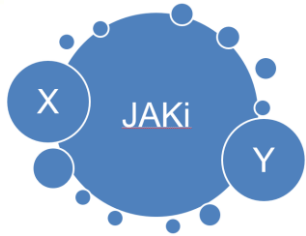
- Anemia response
- Symptom response
- Safety

Exploratory endpoints:

- Duration of response
- 2-year PFS rate
- 2-year OS rate

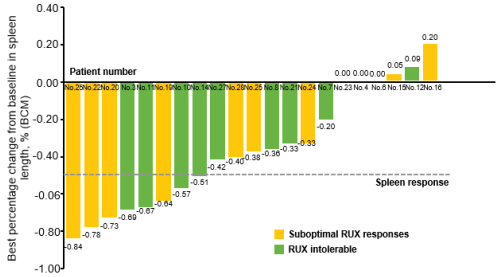
Minghui Duan et al. ASH 2023, #4578

Combination Therapy



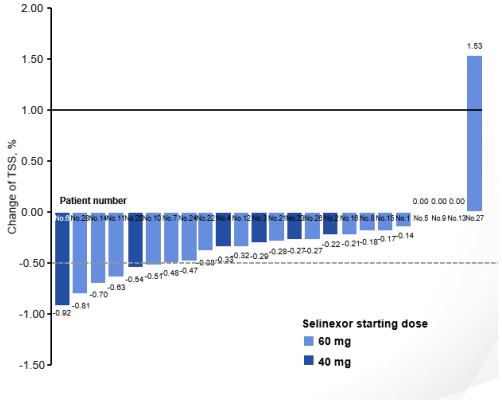
The Efficacy and Safety of Selinexor in Combination with Rux in Rux-Treated MF Patients: the Interim Analysis of a Prospective, Open-Label, Multicenter, Parallel-Cohort, Phase 2 Study

Change in spleen length



Cohort	Evaluable patients, n	Spleen reduction, n (%)	Spleen response, n (%)
RUX intolerable (n=16)	11	8 (72.73)	4 (36.36)
Suboptimal RUX responses (n=12)	10	7 (70.00)	4 (40.00)
Total (n=28)	21	15 (71.42)	8 (38.09)

Change in TSS



Safety and reasons for discontinuation

The most common TEAEs
- Nausea 14 (50.00%)
- Vomiting 9 (32.14%)
- Decreased appetite 8 (28.57%)
- Anemia 7 (25.00%)

The most frequent TEAEs ≥ grade 3
- Anemia 3 (10.71%)
- Thrombocytopenia 2 (7.14%)

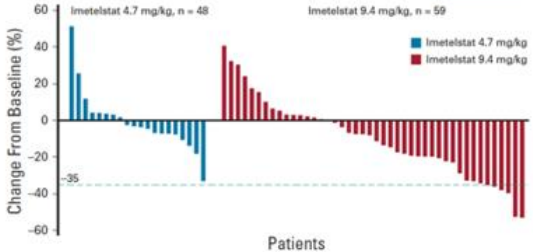
Treatment discontinuation
- Death in 4 patients (3 from covid-19, 1 sepsis)
- Participation in clinical trial (2 patients)
- Unsatisfactory response (2 patients)
- Transplantation (1 patient)
- Toxicity (2 patients)
- Economic burden (1 patient)
- Lost to follow-up (3 patients)

Minghui Duan et al. ASH 2023, #4578

Non-JAKi Therapy - Imetelstat

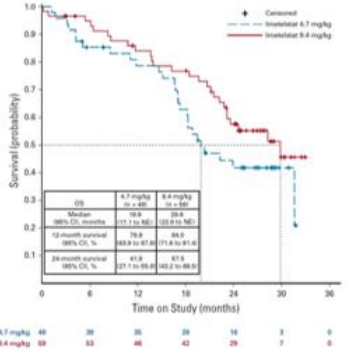
Imetelstat in relapsed or refractory myelofibrosis

A. Waterfall plot of maximum percent change in SVR at Week 24 in patients with MF treated with imetelstat



Spleen Response	4.7 mg/kg (n = 48)	9.4 mg/kg (n = 59)
≥ 10% SVR at week 24, No. (%)	4 (8.3)	22 (37.3)
≥ 20% SVR at week 24, No. (%)	1 (2.1)	13 (22)
≥ 35% SVR at week 24, No. (%)	0	6 (10.2)

B. Kaplan-Meier ITT analysis of OS. All patients on study by random assignment arm



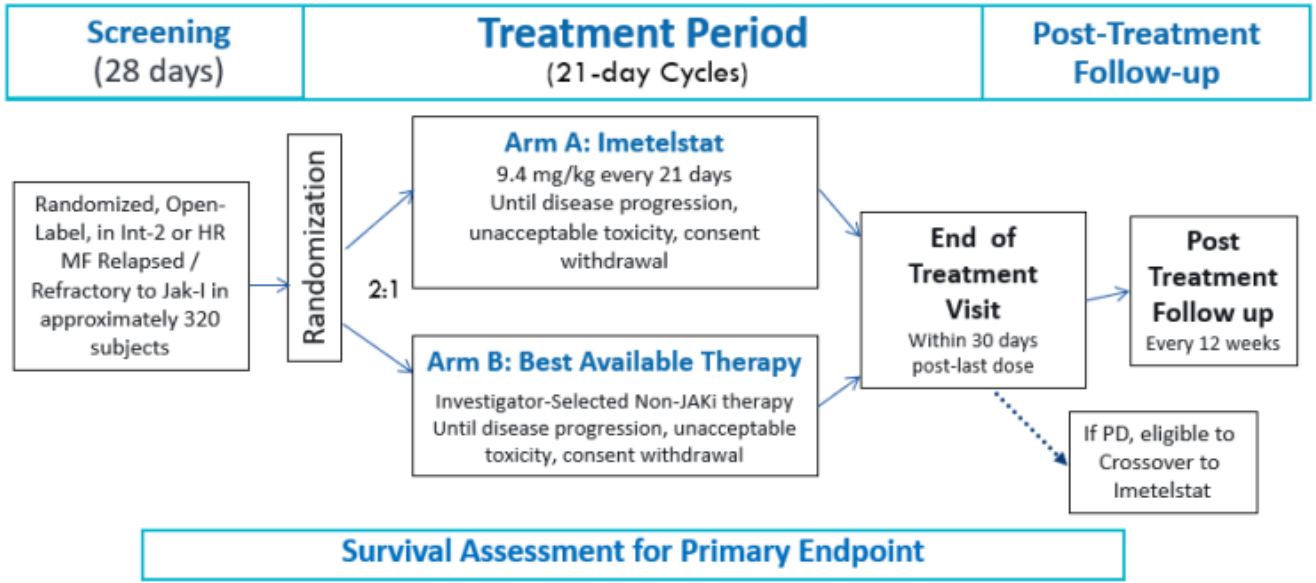
- The most common grade 3 or 4 treatment-emergent AEs were hematologic and included anemia (4.7 mg/kg: 31%; 9.4 mg/kg: 39%), thrombocytopenia (4.7 mg/kg: 23%; 9.4 mg/kg: 41%), and neutropenia (4.7 mg/kg: 10%; 9.4 mg/kg: 32%)
  - Most cytopenias were manageable and resolved within 4 weeks
- The most common grade ≥ 3 nonhematologic treatment-emergent AEs with 9.4 mg/kg were asthenia (10%) and fatigue (7%) and with 4.7 mg/kg were dyspnea (13%), asthenia (6%), and fatigue (6%)

Mascarenhas J, et al. J Clin Oncol. 2021

Non-JAKi Therapy - Imetelstat

A Randomized Open-Label, Phase 3 Study to Evaluate Imetelstat (GRN163L) Versus BAT in Patients with Int.-2 or High-risk MF Relapse / Refractory to JAKi

Protocol GRN163LMYF3001



Non-JAKi Therapy – PIM1 Kinase-i

Phase 1/2 Study of TP-3654: Preliminary Data Showed Clinical Activity and Cytokine Reductions in Patients with Relapsed/Refractory MF

Key eligibility

- DIPSS Intermediate-1, 2, or high-risk
- **Platelet count ≥ 25 x 10^9/L**
- No restriction on hemoglobin
- ECOG performance status ≤ 2
- Splenomegaly (≥ 450 cm^3 by MRI/CT)
- At least 2 symptoms by MF-SAF v4.0

Phase 1 monotherapy dose escalation
480 mg QD – 1440 mg BID
Bayesian dose escalation

→ **MTD / RP2D** → **Phase 2 dose expansion**

Study population

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

Endpoints

Primary:

- Safety and tolerability

Secondary:

- Spleen volume reduction (SVR)
- Total symptoms score (TTS) reduction
- Overall survival
- Bone marrow fibrosis change
- Pharmamacokinetics

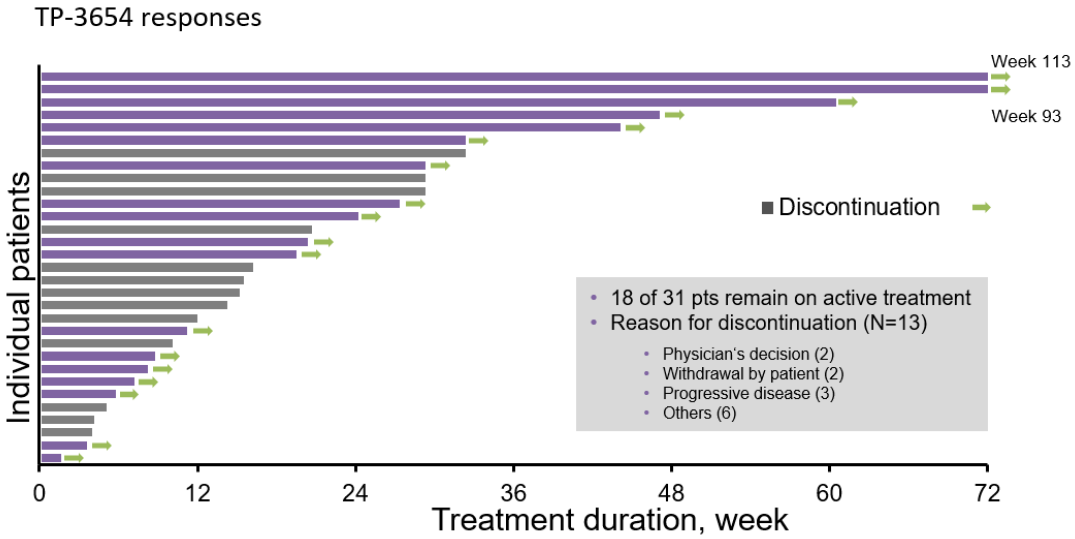
Patient disposition (N=31)

Cohort	Number of patients	DLT
480 mg QD	1	None
720 mg QD	2	None
360 mg BID	5	None
480 mg BID	13	None
720 mg BID	10	None

Lindsay A.M. Rein et al. ASH 2023, #626

Non-JAKi Therapy – PIM1 Kinase-i

Phase 1/2 Study of TP-3654: Preliminary Data Showed Clinical Activity and Cytokine Reductions in Patients with Relapsed/Refractory MF



Treatment emergent adverse events

AE preferred term (n=31)	Grade ≥3
Non-hematological (n, %)	
Diarrhea	2 (6.5%)
Nausea	0 (0.0)
Vomiting	0 (0.0)
Abdominal pain	1 (3.2%)
Fatigue	0 (0.0)
Blood bilirubin increased[a]	2 (6.5%)
Decreased appetite	1 (3.2%)
Abdominal distension	0 (0.0)
Hyperhidrosis	0 (0.0)
Dyspnoea	0 (0.0)
Hematological (n, %)	
Platelet count decreased[b]	5 (16.1%)
Anemia	3 (9.7%)

Lindsay A.M. Rein et al. ASH 2023, #626

Thank you

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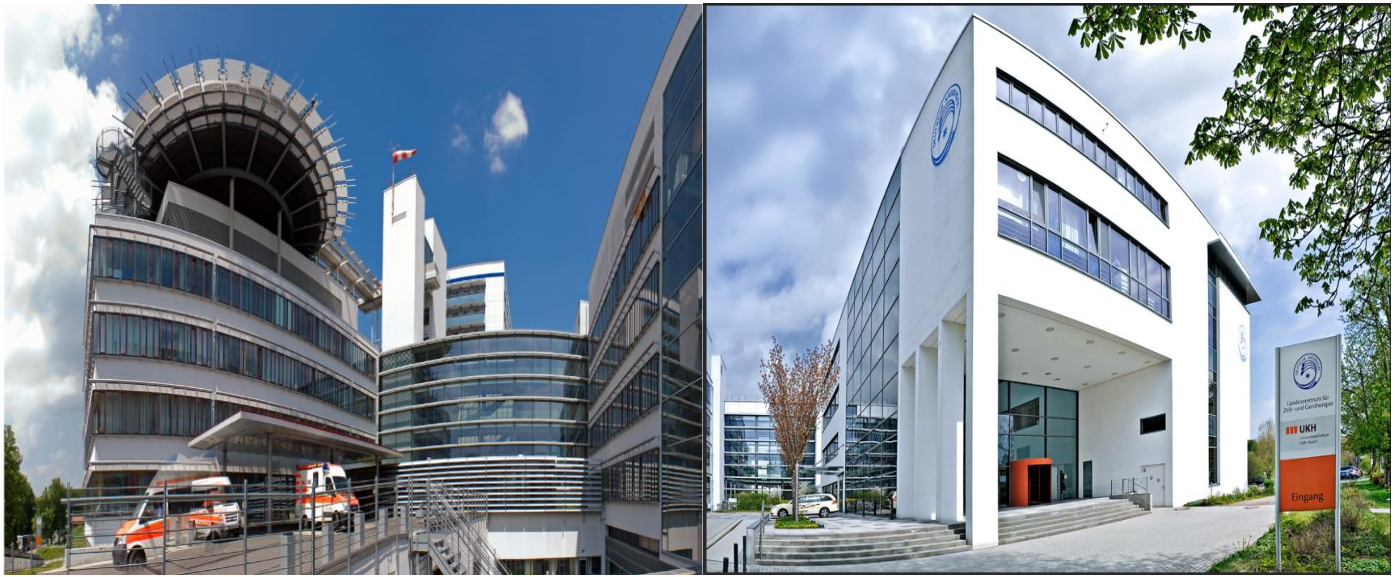


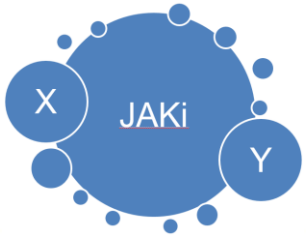
KKH Krukenberg Krebszentrum Halle
DKG Zertifiziertes Onkologisches Zentrum
Martin-Luther-Universität Halle-Wittenberg
UKH Universitätsklinikum Halle (Saale)

Secondline JAKi

- Fedratinib (approved by EMA and available)
- Momelotinib (approved by EMA and soon to become available)
- Pacritinib (only FDA approved but not by EMA)

Combination Therapy

- JAKi + BETi
- JAKi + Selinexor



Non-JAKi Therapy

- Imetelstat
- PIM1 Kinase-i