ASH 2023 Myelofibrosis Update

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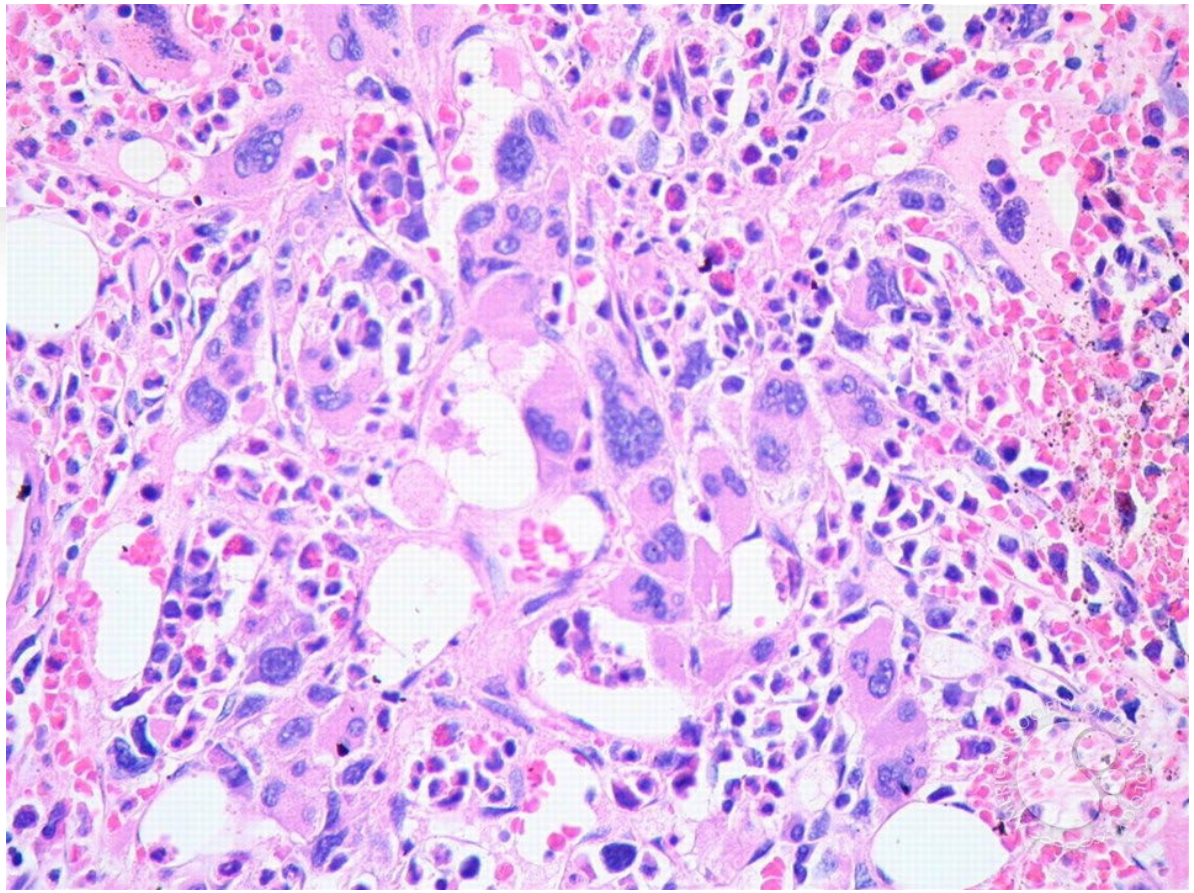
I have no relevant disclosures.

What is Myelofibrosis?

- Clonal myeloproliferative neoplasm (MPN) characterized by the proliferation of myeloid cells in the bone marrow (mostly megakaryocytes and granulocytes), which leads to reactive deposition of fibrous connective tissue and with extramedullary hematopoiesis
  - Ranges from pre-fibrotic / early stage to overt fibrotic stage
- Associated with elevated blood counts, cytopenias, constitutional symptoms, hepatomegaly, splenomegaly, thrombosis
- Typically impacts older patients (Age >60)
- Associated mutations: *JAK2* V617F (2005), *MPL* (2006), *CALR* (2013)



Courtesy of ASH Image Bank

https://seer.cancer.gov/seertools/hemelymph/51f6cf57e3e27c3994bd5381/#:~:text=Primary%20myelofibrosis%20(PMF)%20is%20a,connective%20tissue%20and%20with%20extramedullary

INTERNATIONAL CONSENSUS CLASSIFICATION (ICC) AND WHO DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS[1,a]

PMF, early/prefibrotic stage (pre-PMF)	PMF, overt fibrotic stage
Major criteria 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* bone marrow fibrosis grade <2, increased age-adjusted bone marrow cellularity, granulocytic proliferation, and (often) decreased erythropoiesis 2. *JAK2, CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive bone marrow reticulin fibrosis§ 3. Diagnostic criteria for *BCR::ABL1*-positive CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms are not met	**Major criteria** 1. Bone marrow biopsy showing megakaryocytic proliferation and atypia,* accompanied by reticulin and/or collagen fibrosis grades 2 or 3 2. *JAK2, CALR*, or *MPL* mutation† or presence of another clonal marker‡ or absence of reactive myelofibrosis§ 3. Diagnostic criteria for ET, PV, *BCR::ABL1*-positive CML, myelodysplastic syndrome, or other myeloid neoplasms‖ are not met
Minor criteria • Anemia not attributed to a comorbid condition • Leukocytosis ≥11 x 10^9/L • Palpable splenomegaly • LDH level above the above reference range	**Minor criteria** • Anemia not attributed to a comorbid condition • Leukocytosis ≥11 x 10^9/L • Palpable splenomegaly • LDH level above the above reference range • Leukoerythroblastosis
The diagnosis of pre-PMF or overt PMF requires all 3 major criteria and at least 1 minor criterion confirmed in 2 consecutive determinations	

* Morphology of megakaryocytes in pre-PMF and overt PMF usually demonstrates a higher degree of megakaryocytic atypia than in any other MPN subtype; distinctive features of megakaryocytes include small to giant megakaryocytes with a prevalence of severe maturation defects (cloud-like, hypolobulated, and hyperchromatic nuclei) and presence of abnormal large dense clusters (mostly >6 megakaryocytes lying strictly adjacent).

† It is recommended to use highly sensitive assays for *JAK2* V617F (sensitivity level <1%) and *CALR* and *MPL* (sensitivity level 1% to 3%); in negative cases, consider searching for noncanonical *JAK2* and *MPL* mutations.

‡ Assessed by cytogenetics or sensitive NGS techniques; detection of mutations associated with myeloid neoplasms (eg, *ASXL1, EZH2, IDH1, IDH2, SF3B1, SRSF2,* and *TET2* mutations) supports the clonal nature of the disease.

§ Minimal reticulin fibrosis (grade 1) secondary to infection, autoimmune disorder or other chronic inflammatory conditions, hairy cell leukemia or another lymphoid neoplasm, metastatic malignancy, or toxic (chronic) myelopathies.

‖ Monocytosis can be present at diagnosis or develop during the course of PMF; in these cases, a history of MPN excludes chronic myelomonocytic leukemia (CMML), whereas a higher variant allelic frequency for MPN-associated driver mutations is supporting the diagnosis of PMF with monocytosis rather than CMML.

[a] The WHO 2022 criteria are the same as the WHO 2017 criteria. Swerdlow SH, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon 2017; Khoury JD, et al. Leukemia 2022;36:1703-1719.

IWG-MRT DIAGNOSTIC CRITERIA FOR POST-POLYCYTHEMIA VERA AND POST-ESSENTIAL THROMBOCYTHEMIA MYELOFIBROSIS[1]

Criteria for Post-PV Myelofibrosis

Required criteria:

- **Documentation of a previous diagnosis of PV as defined by the WHO criteria[2]**
- **Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,5]**

Additional criteria (two are required):

- **Anemia[6] or sustained loss of requirement of either phlebotomy (in the absence of cytoreductive therapy) or cytoreductive treatment for erythrocytosis**
- **A leukoerythroblastic peripheral blood picture**
- **Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the left costal margin [LCM]) or the appearance of a newly palpable splenomegaly**
- **Development of ≥1 of three constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)**

Criteria for Post-ET Myelofibrosis

Required criteria:

- **Documentation of a previous diagnosis of ET as defined by the WHO criteria[2]**
- **Bone marrow fibrosis grade 2–3 (on 0–3 scale)[3] or grade 3–4 (on 0–4 scale)[4,5]**

Additional criteria (two are required):

- **Anemia[6] and ≥2 g/dL decrease from baseline hemoglobin level**
- **A leukoerythroblastic peripheral blood picture**
- **Increasing splenomegaly defined as either an increase in palpable splenomegaly of ≥5 cm (distance of the tip of the spleen from the LCM) or the appearance of a newly palpable splenomegaly**
- **Increased LDH (above reference level)**
- **Development of ≥1 of 3 constitutional symptoms: >10% weight loss in 6 months, night sweats, unexplained fever (>37.5°C)**

[1] Reproduced with permission from Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the international working group for myelofibrosis research and treatment. Leukemia 2008;22:437-438.
[2] Tefferi A, Thiele J, Orazi A, et al. Proposals and rationale for revision of the World Health Organization diagnostic criteria for polycythemia vera, essential thrombocythemia, and primary myelofibrosis: recommendations from an ad hoc international expert panel. Blood 2007;110:1092-1097.
[3] Thiele J, Kvasnicka HM, Facchetti F, et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. Haematologica 2005;90:1128-1132.
[4] Manoharan A, Horsley R, Pitney WR. The reticulin content of bone marrow in acute leukaemia in adults. Br J Haematol 1979;43:185-190.
[5] Grade 2–3 according to the European classification: diffuse, often coarse fiber network with no evidence of collagenization (negative trichrome stain) or diffuse, coarse fiber network with areas of collagenization (positive trichrome stain). Grade 3–4 according to the standard classification: diffuse and dense increase in reticulin with extensive intersections, occasionally with only focal bundles of collagen and/or focal osteosclerosis or diffuse and dense increase in reticulin with extensive intersections with coarse bundles of collagen, often associated with significant osteosclerosis.
[6] Below the reference range for appropriate age, sex, gender, and altitude considerations.

Side note

- Patients with any suspected myeloproliferative neoplasm (MPN) require a bone marrow biopsy!
- Why? Polycythemia Vera, Essential Thrombocytosis and Myelofibrosis are all treated differently – only a bone marrow can distinguish them
- Example: If a 70 y/o patient has an elevated platelet count without other CBC abnormalities in the presence of *JAK2* V617F detected in the peripheral blood, that alone is not sufficient to make the diagnosis of Essential Thrombocytosis
  - I always perform a bone marrow biopsy on outside referrals even if their disease has been stable for the past couple of years
- Long-term use of Hydroxyurea can impact morphologic findings on a bone marrow biopsy = perform the marrow sooner than later

FDA-approved JAK inhibitors

JAK Inhibitor	Ruxolitinib	Fedratinib	Pacritinib	Momelotinib
Mechanism of action	JAK1 and JAK2 inhibition	JAK2 (and FLT3) inhibition	JAK2, FLT3, CSF1R, IRAK1 inhibition	JAK1, JAK2, and ACVR1 inhibition
Adverse effects	Cytopenias, HSV reactivation, LFT's↑	Diarrhea, nausea, cytopenias, LFT's↑	Diarrhea, nausea, cytopenias, QTc prolongation	Cytopenias, diarrhea, nausea, infections, LFT's↑
Laboratory monitoring	Baseline CBC, then q2-4 weeks until stable dose	CBC, creatinine + BUN, B1, LFT's, amylase + lipase	CBC's, coags, and EKG's as needed	CBC's and LFT's periodically
Metabolism	CYP3A4 (major)	CYP3A4, CYP2C19, FMO3	CYP3A4 (major)	Multiple CYP enzymes (CYP3A4, CYP2C8, etc)
Unique concerns	Avoid abrupt discontinuation	Risk for Wernicke encephalopathy	Hemorrhage with PLT <50K, infection	Bacterial + viral infx; HBV increases

Abbreviated Treatment Guide for Myelofibrosis (MF)

- Can be a Primary Myelofibrosis or secondary (arising from PV or ET)
- Lower-risk: *MIPSS-70: ≤3, *MIPSS-70+ (Version 2.0): ≤3, DIPSS-Plus: ≤1, DIPSS: ≤2, MYSEC-PM: <14 (Post-PV or Post-ET)
  - If asymptomatic, can consider observation or clinical trial
  - Symptomatic: clinical trial vs Ruxolitinib, Peginterferon, Hydroxyurea, or Momelotinib (cat 2B)
- Higher-risk: *MIPSS-70: ≥4, *MIPSS-70+ (Version 2.0): ≥4, DIPSS-Plus: >1, DIPSS: >2, MYSEC-PM: ≥14 (Post-PV or Post-ET)
  - Consider platelet count (above or below 50K?) and **transplant eligibility**
  - Platelets <50: Transplant, otherwise clinical trial, Pacritinib, mor Momelotinib (cat 2B)
  - Platelets >50: Transplant, otherwise Ruxolitinib, Fedratinib, Momelotinib, or Pacritinib (cat 2B)
- Accelerated/blast phase MPN
  - 10-19% blasts and at least 20% blasts, respectively
  - Transplant-eligible: bridging therapy (HMA with JAK-i or Ven) followed by allogeneic HCT
  - Not transplant-eligible: HMA +/- JAK inhibitor, HMA + Venetoclax, or low-intensity chemo

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2023
Myeloproliferative Neoplasms

NCCN Guidelines Index
Table of Contents
Discussion

ASSESSMENT OF SYMPTOM BURDEN

- Assessment of symptoms (in provider's office) at baseline and monitoring symptom status (stable, improved, or worsening) during the course of treatment is recommended for all patients.
- Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS; MPN-10) is recommended for the assessment of symptom burden at baseline and monitoring symptom status during the course of treatment (MPN-F, 2 of 2).
- MPN-SAF TSS is assessed by the patients themselves. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0–100 scale).
- Symptom response requires ≥50% reduction in the MPN-SAF TSS. A symptom response <50% may be clinically meaningful and justify continued use of ruxolitinib.
- Changes in symptom status could be a sign of disease progression. Therefore, change in symptom status should prompt evaluation of treatment efficacy and/or disease status.

MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS; MPN-10)[1]

(Recommended for monitoring symptoms during the course of treatment)

Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Circle the one number that describes, during the past week, how much difficulty you have had with each of the following symptoms

Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration-compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

Relevant ASH 2023 Abstracts

620 Transform-1: A Randomized, Double-Blind, Placebo-Controlled, Multicenter, International Phase 3 Study of Navitoclax in Combination with Ruxolitinib Versus Ruxolitinib Plus Placebo in Patients with Untreated Myelofibrosis

Program: Oral and Poster Abstracts
Type: Oral
Session: 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Charting The Future Of MPN Therapies
Hematology Disease Topics & Pathways:
Research, clinical trials, adult, Clinical Research, Combination therapy, Chronic Myeloid Malignancies, Diseases, Therapies, Myeloid Malignancies, Study Population, Human

Sunday, December 10, 2023: 4:45 PM

Naveen Pemmaraju, MD[1], *Adam J Mead, MRCP, FRCPath, PhD*[2,3], *Tim CP Somervaille, PhD FRCP FRCPath*[4], *James K McCloskey, MD*[5], *Francesca Palandri, MD*[6*], *Steffen Koschmieder*[7,8], *David Lavie*[9*], *Brian Leber, MD*[10], *Su-Peng Yeh, MD*[11*], *Maria Teresa Gómez-Casares, MD, PhD*[12*], *Emanuele Ammatuna, MD, PhD*[13*], *Ho-Jin Shin, MD*[14*], *Keita Kirito, MD*[15], *Eric Jourdan, MD, PhD*[16*], *Timothy Devos, MD*[17,18*], *Hun S Chuah*[19*], *Atanas Radinoff*[20*], *Andrija Bogdanovic, Professor*[21,22*], *Rastislav Moskal, PharmD*[23*], *Qi Jiang*[23*], *Avijeet S Chopra*[23*], *Elektra Papadopoulos*[23*], *Jalaja Potluri*[24] *and Francesco Passamonti, MD*[25*]

628 Pelabresib in Combination with Ruxolitinib for Janus Kinase Inhibitor Treatment-Naïve Patients with Myelofibrosis: Results of the MANIFEST-2 Randomized, Double-Blind, Phase 3 Study

Program: Oral and Poster Abstracts
Type: Oral
Session: 634. Myeloproliferative Syndromes: Clinical and Epidemiological: Myelofibrosis: New Therapeutic Frontiers
Hematology Disease Topics & Pathways:
Research, Clinical Research, Combination therapy, drug development, Diseases, Therapies, Myeloid Malignancies, Study Population, Human

Sunday, December 10, 2023: 5:15 PM

Raajit K. Rampal, MD, PhD[1], *Sebastian Grosicki, MD, PhD*[2*], *Dominik Chraniuk*[3*], *Elisabetta Abruzzese, MD*[4], *Prithviraj Bose, MD*[5], *Aaron T. Gerds, MD, MS*[6], *Alessandro M. Vannucchi, MD*[7*], *Francesca Palandri, MD*[8*], *Sung-Eun Lee, MD*[9,10*], *Vikas Gupta, MD*[11], *Alessandro Lucchesi, MD*[12*], *Stephen T. Oh, MD, PhD*[13], *Andrew T. Kuykendall, MD*[14], *Andrea Patriarca, MD*[15*], *Alberto Alvarez-Larran, MD*[16*], *Ruben A. Mesa, MD*[17], *Jean-Jacques Kiladjian, MD, PhD*[18], *Moshe Talpaz, MD*[19], *Morgan Harris, PharmD*[20*], *Sarah-Katharina Kays, PhD*[21*], *Anna-Maria Jegg, PhD*[21*], *Qing Li, PhD*[22*], *Barbara Brown, PhD*[20*], *Claire N Harrison*[23] *and John Mascarenhas, MD*[24*]

Transform-1

- Phase 3, double-blind, placebo-controlled, multicenter, international study evaluating the safety and efficacy of Navitoclax plus Ruxolitinib (NAV+RUX) versus Placebo plus Ruxolitinib (PBO+RUX) in JAK2i-naïve adults with MF
- Navitoclax is an orally available inhibitor of antiapoptotic B-cell lymphoma 2 proteins (BCL-X, BCL-2, BCL-W)
  - Previously shown to have antitumor activity in the phase 2 REFINE trial

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https://ashpublications.org/blood/article/142/Supplement%201/620/502738/Transform-1-A-Randomized-Double-Blind-Placebo

Transform-1: Methods

- Included patients with intermediate-2 or high-risk MF with measurable splenomegaly, evidence of MF-related symptoms, no prior JAK2i therapy, and ECOG ≤2
- Randomized patients 1:1 to receive NAV or PBO plus RUX at labeled dose
  - NAV starting dose of 200 mg daily (PLT >150), or 100 mg escalated to 200 mg daily if tolerated after at least 7 days (PLT ≤150)
  - RUX dose also dependent on platelet count (for PLT ≤200 × 109/L vs >200)
- Primary endpoint: splenic volume reduction of ≥35% at Week 24 (SVR_{35W24})
- Secondary endpoints:
  - Change in total symptom score at Week 24 (TSSW24) based on MFSAF v4.0 (scale 0–70), duration of SVR35, anemia response (per IWG), reduction in marrow fibrosis, OS, LFS, reduction in PROMIS fatigue scale, improvement in functional status (EORTC QLQ-C30)

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https://ashpublications.org/blood/article/142/Supplement%201/620/502738/Transform-1-A-Randomized-Double-Blind-Placebo

Table 1. Baseline demographics and disease characteristics

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 myelofibrosis		
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)
Transfusion dependent at BL	5 (4)	4 (3)
Transfusion independent at BL	120 (96)	123 (97)
Hemoglobin (g/dL), median (range)	10 (4–18)	10 (6–18)
Platelet count (10^9/L), median (range)	289 (100–1278)	286 (94–1847)
150 × 10^9/L to ≤200 × 10^9/L	31 (25)	34 (27)
>200 × 10^9/L	94 (75)	93 (73)
WBC (10^9/L), median (range)	14 (2–95)	14 (2–117)
Risk group calculated by DIPSS+ at study entry		
Intermediate-1	8 (6)	5 (4)
Intermediate-2	104 (83)	110 (87)
High	13 (10)	12 (9)
HMR mutations, n/N (%)	57/120 (48)	50/117 (43)

Data are n (%) unless otherwise stated.

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https://ashpublications.org/blood/article/142/Supplement%201/620/502738/Transform-1-A-Randomized-Double-Blind-Placebo

Transform-1: Results

- 252 patients were enrolled at data cutoff with median (range) follow-up of 14.9 (0-29.5) months
  - 125 patients randomized to NAV+RUX, 127 randomized to PBO+RUX
- Majority were men (57%) with median (range) age of 69 (37-87)
- Primary endpoint was met, with 79 patients (63.2%) in NAV+RUX arm achieving SVR_{35W24} compared with 40 patients (31.5%) in the PBO + RUX arm (P<0.0001)
  - SVR_{35} at any time was achieved by 96 patients (77%) in NAV+RUX arm compared with 53 patients (42%) in PBO+RUX arm
- Median (range) time to first SVR_{35} response was 12.3 (10.1-48.3) weeks with NAV+RUX vs 12.4 (11.3-72.3) weeks for PBO+RUX arm
  - Fewer patients lost SVR35 in the combination arm vs control arm (18.8 vs 26.4%)
- Median duration of SVR_{35} was not reached (NR) in the NAV + RUX arm compared with 19.4 months (95% CI 16.8, NR) in the PBO + RUX arm

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https://ashpublications.org/blood/article/142/Supplement%201/620/502738/Transform-1-A-Randomized-Double-Blind-Placebo

Transform-1: Results (cont.)

- At week 24, 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 (P=0.2852)
- Grade ≥3 adverse events (AEs) were experienced by 85% of patients with NAV + RUX and 70% with PBO + RUX
  - Most common AEs (>30% of patients receiving NAV) were thrombocytopenia, anemia, diarrhea, neutropenia
  - Serious AEs experienced by 26% of patients in NAV+RUX arm vs 32% in PBO+RUX arm, specifically anemia, thrombocytopenia, neutropenia
- For NAV+RUX arm, AEs lead to NAV dose reduction in 101 (81%) of patients and NAV interruption in 87 (70%) of patients, mainly for thrombocytopenia (without clinical bleeding)

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Transform-1: Results (cont.)

- Of all enrolled patients, 83 (33%) discontinued treatment
  - Main reasons for NAV/PBO discontinuation were AE's (39% of all discontinuations) and physician decision (17% of discontinuations)
- In each arm, 13 (10%) patients died
  - 6 in NAV+RUX arm and 5 in PBO+RUX arm died within 30 days of final dose

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Transform-1: Adverse Effects

Table 2. Safety data

	NAV + RUX (N=124)	PBO + RUX (N=125)
Any AE	124 (100)	121 (97)
Any AE grade ≥3	105 (85)	87 (70)
Most common AEs (>30% patients receiving NAV)		
Thrombocytopenia, any grade [grade ≥3]	112 (90) [63 (51)]	62 (50) [19 (15)]
Anemia, any grade [grade ≥3]	74 (60) [57 (46)]	61 (49) [49 (39)]
Diarrhea, any grade [grade ≥3]	42 (34) [6 (5)]	17 (14) [0]
Neutropenia, any grade [grade ≥3]	56 (45) [47 (38)]	7 (6) [5 (4)]
Any serious AE	32 (26)	40 (32)
All deaths	13 (10)	13 (10)
Deaths <30 days following last dose of study drug	6 (5)	5 (4)

Data are n (%) unless otherwise stated.

AE, adverse event; BL, baseline; DIPSS, Dynamic International Prognostic Scoring System; HMR, high molecular risk (defined as mutations in *ASXL1, EZH2, SRSF2, IDH1/2,* or *U2AF1*); MF, myelofibrosis; NAV, navitoclax; PBO, placebo; Post-PV, post-polycythemia vera; Post-ET, post-essential thrombocythemia; RUX, ruxolitinib; WBC, white blood cell.

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Transform-1: Conclusion

- NAV+RUX combination led to an SVR_{35W24} rate significantly higher than that of PBO+RUX with durable responses
- Adverse effects (mainly anemia and thrombocytopenia) appear common but manageable with dose reductions

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MANIFEST-2

- Phase 3, randomized, double-blind, active-control, global study of Pelabresib (Pela) + Ruxolitinib (Rux) versus Placebo + Rux in JAKi treatment-naïve patients with primary MF, post-polycythemia vera MF or post-essential thrombocythemia MF
- Pelabresib is an investigational oral small-molecular drug designed to inhibit BET-mediated MF target gene modulation
- Aim: evaluate the efficacy and safety of Pela+Rux

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https://ashpublications.org/blood/article/142/Supplement%201/628/502728/Pelabresib-in-Combination-with-Ruxolitinib-for

MANIFEST-2: Methods

- Key eligibility criteria: DIPSS score of Int-1 or higher, PLT ≥100k, spleen volume ≥450 cm3 by CT or MRI, ≥2 symptoms with an average score ≥3 or a TSS of ≥10 using the MFSAF v4.0, peripheral blast count <5%, ECOG ≤2
- Patient randomization stratified by DIPSS risk category (Int-1 vs Int-2 vs High), PLT count (>200k vs 100-200k), and spleen volume (≥1800 cm3 vs <1800 cm3
- Double-blind treatment of Pela (125-175 mg daily) or placebo was administered for 14 consecutive days, followed by a 7-day break = 1 cycle of therapy
- Rux was administered twice daily based on platelet counts and spleen response for all 21 days of the cycle
  - Starting dose was 10 mg BID or 15 mg BID to, but patients were required to have dose escalation after cycle 1 if parameters were met
- Primary endpoint: SVR35 response at week 24 (SVR_{35W24})
- Secondary endpoints: TSS50 and change in TSS (baseline vs week 24).
- Additional endpoints: safety, pharmacokinetics, changes in bone marrow fibrosis, progression-free survival, overall survival, conversion from transfusion dependence to independence, rate of RBC transfusion for the first 24 wks

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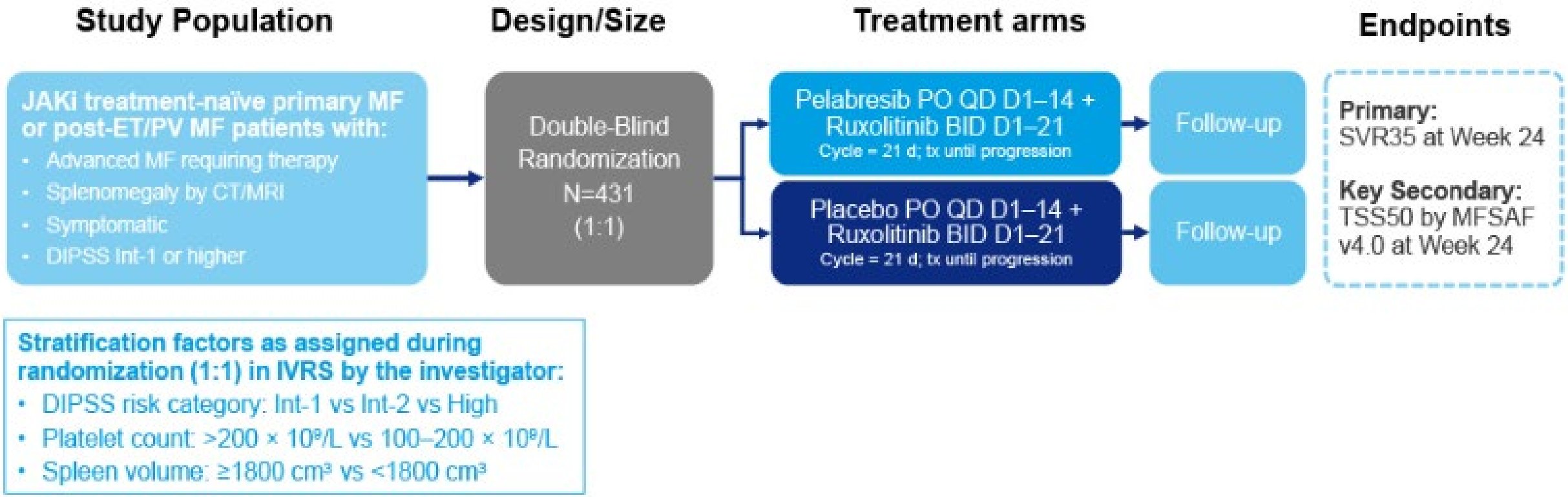
https://ashpublications.org/blood/article/142/Supplement%201/628/502728/Pelabresib-in-Combination-with-Ruxolitinib-for

Figure 1. MANIFEST-2 study schema



BID, twice daily; CT, computerized tomography; D, day; DIPSS, Dynamic International Prognostic Scoring System; ET, essential thrombocythemia; Int-1, Intermediate-1; Int-2, Intermediate-2; IVRS, Interactive Voice Response Systems; JAKi, Janus kinase inhibitor; MF, myelofibrosis; MFSAF, Myelofibrosis Symptom Assessment Form; MRI, magnetic resonance imaging; PO, by mouth; PV, polycythemia vera; QD, once daily; SVR35, ≥35% spleen volume reduction from baseline; TSS50, reduction in total symptom score of ≥50% from baseline; tx, treatment.

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https://ashpublications.org/blood/article/142/Supplement%201/628/502728/Pelabresib-in-Combination-with-Ruxolitinib-for

MANIFEST-2: Results

- Of the 591 patients screened at 138 sites, 430 patients from North America, Europe, Asia, Australia were randomized
- Enrollment opened in November 2020 – the first patient received initial treatment on 4/22/21 and the last patient received their first treatment on 3/2/2023
  - Data cutoff date was 8/31/23
- Majority of patients had DIPSS Int-1 or Int-2 (59.3% and 34.7%, respectively), had a platelet count above 200k (72.4%), and splenic volume <1800 cm^3
- Mean hemoglobin was 11 g/dL (5.8-18.0); 34% had a hemoglobin of 10 g/dL or lower
  - 16% of patients on Pelabresib required RBC transfusions at baseline vs 12% in Placebo+Rux arm
- Median platelet count >250k in each arm
- Median spleen volume was 1308 cc (Pela arm) vs 1382 cc (placebo arm)
- Median TSS was 26.6 (range, 7.3-66.4) and 24.7 (range, 9.0-68.4), respectively
- Median age across both arms was 66 years (range, 19-88); more than half were male (58.4%); majority were white (75.2%), half (50.5%) had primary myelofibrosis

Table 1. Numbers of patients randomized by stratification factor.

	Stratification Factor			
Strata no.	**DIPSS risk category**	**Platelet count**	**Spleen volume**	**N**
1	High	100–200 × 10^9/L	<1800 cm^3	9
2			≥1800 cm^3	3
3		>200 × 10^9/L	<1800 cm^3	14
4			≥1800 cm^3	4
5	Intermediate-1	100–200 × 10^9/L	<1800 cm^3	33
6			≥1800 cm^3	31
7		>200 × 10^9/L	<1800 cm^3	136
8			≥1800 cm^3	54
9	Intermediate-2	100–200 × 10^9/L	<1800 cm^3	35
10			≥1800 cm^3	19
11		>200 × 10^9/L	<1800 cm^3	59
12			≥1800 cm^3	34

DIPSS, Dynamic International Prognostic Scoring System.

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MANIFEST-2: Results (cont.)

- At median follow-up of 45.4 weeks, SVR35 response at week 24 was seen in 65.9% of patients in Pela+Rux arm (n=214) vs 35.2% of those in the Placebo+Rux arm (n=216)
  - 30.4 difference (95% CI, 21.6-39.3; P < .001) in the intention-to-treat (ITT) population = met primary endpoint
- Mean percentage change in spleen volume at week 24 was -50.6% (n=171; 95% CI, -53.2% to -48%) and -30.6% (n = 183; 95% CI, –33.7 to –27.5) with the Pela and placebo groups, respectively
- Absolute TSS improvement at week 24 for pelabresib/ruxolitinib as –15.99 compared with –14.05 with placebo/ruxolitinib, with a mean difference of –1.94 (95% CI, –3.92 to 0.04; P = .0545).
  - Response was higher among all the predefined subgroups for Pela+Rux
- TSS50 response: 52.3% for Pela+Rux arm vs 46.3% for Placebo+Rux; p=0.216
- Two-fold increase in patients achieving both SVR35 and TSS50 with Pela+Rux (40.2%) compared with Placebo+Rux arm (18.5%)

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MANIFEST-2: Results (cont.)

- At approximately 9 weeks, there was a separation in curves regarding Hgb response (approximately 1 g/dL difference)
  - For Pela+Rux arm, Hgb response at 1.5 g/L or greater mean increase was 9.3% compared with 5.6% with Placebo+Rux arm
  - 16.4% of Pela+Rux arm and 11.6% of Placebo+Rux arm required RBC transfusions at baseline -> 30.8% and 41.2% of patients, respectively, required RBC transfusions during the first 24 weeks of study therapy
- Reticulin fibrosis worsened by 1 grade or more in 16.3% of patients on Pela+Rux vs 28.3% of those on Placebo+Rux, while it improved by at least 1 grade in 38.5% and 24.2% of patients, respectively
- Inflammatory cytokines (NFkB, IL-6, IL-8, TNF alpha) were further reduced in Pela+Rux arm compared to Placebo+Rux arm

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MANIFEST-2: Results (cont.)

- Discontinued double-blind tx: Pela+Rux – 58 (27.1%); Placebo+Rux – 54 (25%)
  - Mainly for adverse events in Pela+Rux arm (10.7%) vs physician decision in control arm (9.3%)
- Any-grade and grade 3 or higher TEAEs occurred in 96.7% and 49.1% of pelabresib-treated patients compared with 97.2% and 57.5% of placebo-treated patients
  - Incidence of serious AEs was similar in both arms
- Anemia tended to be more severe in Placebo+Rux arm; thrombocytopenia and platelet count decrease rates were higher in Pela+Rux arm
- Diarrhea and dysgeusia were notable non-hematologic adverse events in Pela+Rux arm; dysgeusia tended to improve with Pela dose reduction
- TEAE dose reductions due to Pelabresib occurred in 32.5% of patients vs 29% for those on placebo; dose reductions with Ruxolitinib occurred in 47.6% and 41.5% of patients, respectively
- Pelabresib or placebo interruptions were reported in 32.1% and 22.9% of patients, respectively
- Ruxolitinib interruptions took place in 23.1% and 16.4% of those on pelabresib and placebo, respectively
- 2.4% deaths from TEAEs in Pela+Rux arm vs 2.8% deaths in Placebo arm

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MANIFEST-2: Results (cont.)

- Mean daily dose for Pelabresib: 106 mg
- Mean daily dose for Ruxolitinib in Pela+Rux arm: 29.3 mg
- Mean daily dose for Ruxolitinib in Placebo+Rux arm: 31.3 mg
- Median follow-up on study: 45.4 weeks
- Double-blind treatment was ongoing for 72% and 74.1% of patients, respectively

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MANIFEST-2: Conclusions

- Pelabresib + Ruxolitinib demonstrated a 35% or greater reduction in splenic volume (met primary endpoint)
- Pelabresib also trended toward reducing the absolute total symptom score and significantly improved TSS reduction by 50% (TSS50) at 24 weeks
- Doubled percentage of patients with dual SVR35/TSS50 response
- Pelabresib arm was associated improved hemoglobin response and fewer transfusions
- Pelabresib + Ruxolitinib reduced pro-inflammatory cytokines and lead to improvement of bone marrow fibrosis
- Safety profiles were comparable; fewer grade ≥ 3 adverse events in Pela+Rux arm

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Overall Conclusion

- Both trials demonstrate an improvement in splenic volume reduction when compared with Ruxolitinib monotherapy
- Ruxolitinib with or without additional therapy is associated with multiple adverse effects which need to be monitored closely
- Further investigation is needed for high-risk patients
- Transplant remains the best long-term option for high-risk patients (if eligible)

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THANK YOU

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