

JADPRO Clinical Case Series

Cytopenias, Including Transfusion-Dependent Anemia, in Myelofibrosis

SUPPORTED BY

GSK

PRESENTER



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Pre-Test Questions & Case Polling Results

Prior to this educational activity, how confident are you about your ability to effectively reduce treatment burden in patients with myelofibrosis and anemia?

- a. Extremely
- b. Somewhat
- c. Not at all

Prior to this educational activity, how confident are you about your ability to effectively conducting pre-treatment regimens and managing adverse events associated with the newly approved agent momelotinib?

- a. Extremely
- b. Somewhat
- c. Not at all

Case 1 Polling Question Results

For patients with myelofibrosis who have relapsed status post-allogeneic transplant, which care team members are involved in discussing treatment decisions in a tumor board or patient rounds environment?

- a. Transplant team **11%**
- b. Malignant hematology team **32%**
- c. Blood bank clinical team **0%**
- d. All of the above **58%**

Case 2 Polling Question Results

When discussing a new treatment with patients with MF and their caregivers, what data from clinical research do you most frequently cite? (select all that apply)

- a. Data regarding reduction improvements in MF-associated symptoms (MFSAF TSS) **20%**
- b. Anemia measures **17%**
- c. Spleen measures **13%**
- d. Common side effects of therapy **21%****
- e. Alternative treatment options **14%**
- f. Relevant survival data (overall survival, progression-free survival, etc.) **15%**

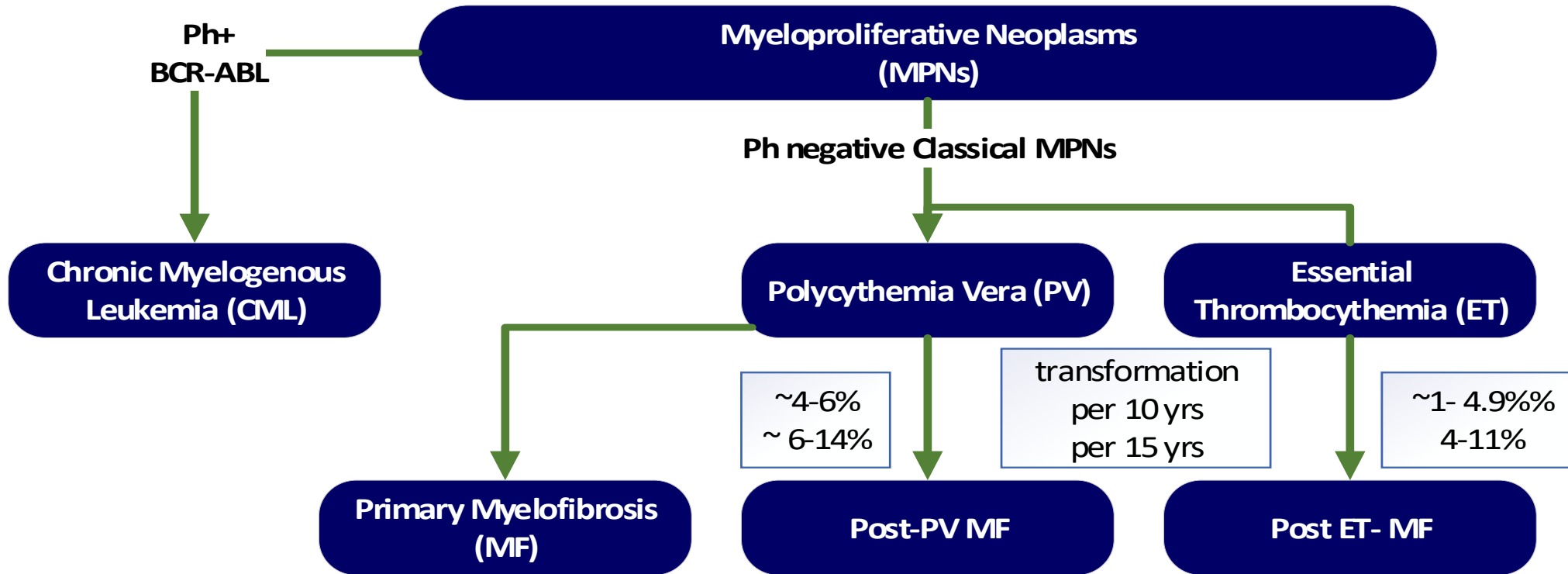
Case 3 Polling Question Results

If a patient develops a Grade 1 laboratory abnormality on therapy, at what interval do you recheck labs?

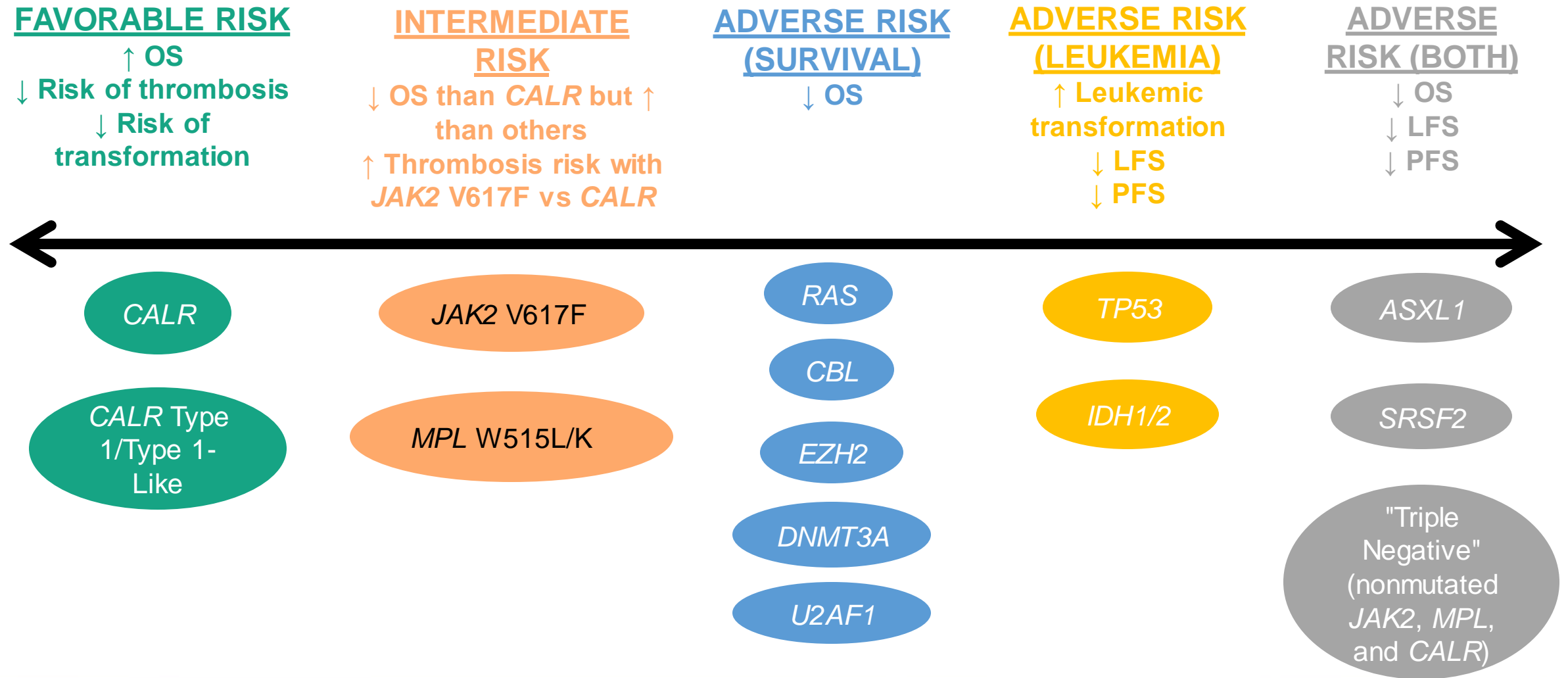
- a. Less than 1 week **6%**
- b. 1 week 56%**
- c. 2 weeks **22%**
- d. 1 month **16%**

Myelofibrosis Disease State

Myeloproliferative Neoplasms (MPNs)



Prognostic Significance of Genetic Mutations in MF



Symptom Burden in MF

Wide Range of Constitutional Symptoms



Yoon J, et al. *Expert Rev Hematol.* 2021;14:607-619. Verstovsek S, et al. *Leukemia.* 2016;30:1413-1415. Cervantes F, et al. *Expert Rev Hematol.* 2016;9:489-496.

Courtesy of Medscape Oncology with permission

JADPRO Clinical Case Series

Assessing Symptom Burden in MPNs

Myeloproliferative Neoplasm Symptom Assessment Form Total Symptom Score (MPN-SAF TSS)

- 10-symptom assessment scale for MPNs
- Each symptom is rated on a 0 to 10 scale from absent (0) to worst imaginable (10)
- Total possible score: 100

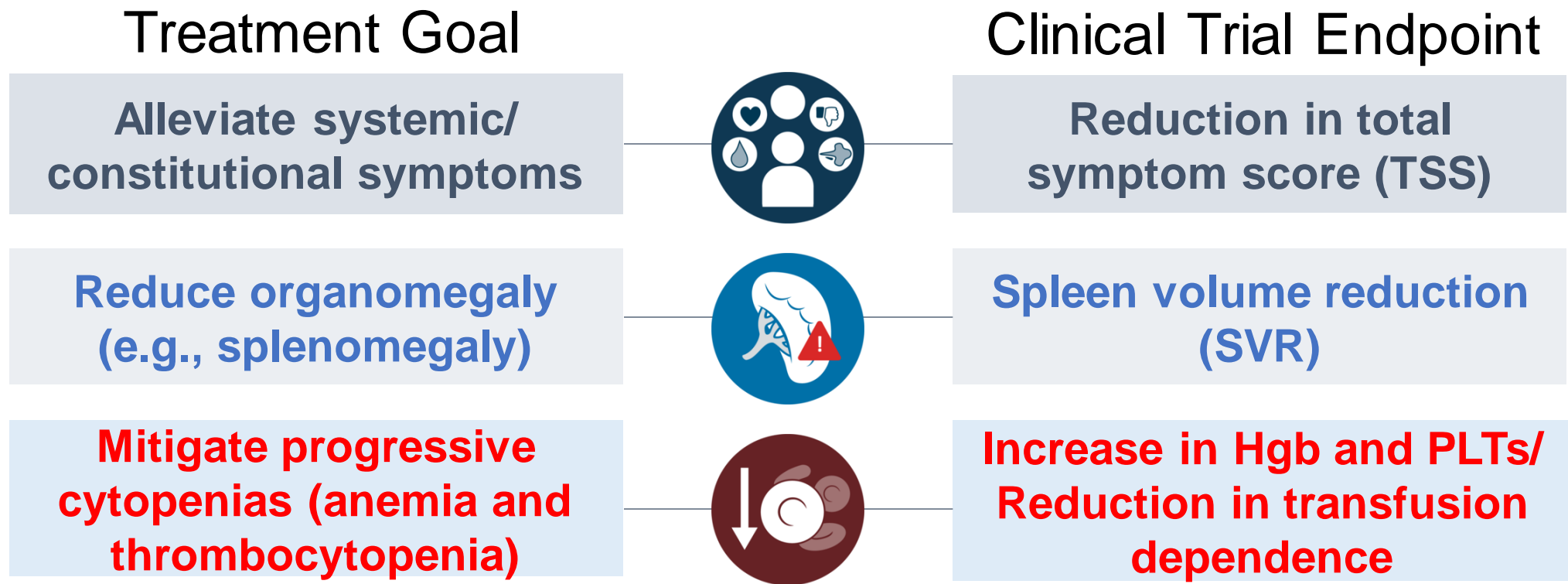
Symptom	1 to 10 (0 if absent) ranking 1 is most favorable and 10 least favorable
Please rate your fatigue (weariness, tiredness) by circling the one number that best describes your WORST level of fatigue during past 24 hours	(No Fatigue) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

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)

Primary Treatment Goals in MF

The practical treatment goals for patients with MF are unusually well aligned with the endpoints commonly used in clinical trials for new MF therapies.



Which of the following physiologic processes contributing to anemia in patients with myelofibrosis can be targeted simultaneously with disease modifying treatment to reduce transfusion burden?

- a. Reduction of bone marrow blasts to < 20% and Inhibition of the JAK-STAT pathway
- b. Inhibition of ACVR1 and the JAK-STAT Pathway
- c. Inhibition of the JAK-STAT pathway and endoscopic cauterization of esophageal varices
- d. Unsure

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- c. Inhibition of the JAK-STAT pathway and endoscopic cauterization of esophageal varices
- d. Unsure

Anemia in Patients with Myelofibrosis

42-Year-Old Man Diagnosed With Primary MF in 2022 (Case 3)

- Presented with anemia (hemoglobin: 6.8 g/dL), splenomegaly (28 cm), white blood cell count: 26 K/mm³
- BMBX: Very-high-risk primary myelofibrosis (mutational enhanced MIPSS70 v2 score of 13)
- The patient received a transfusion of one unit of packed red blood cells.
- Upon completing the transfusion, he developed shaking chills, chest pain, shortness of breath, severe back pain, hypoxia (O₂ sat 82% on room air), and a fever of 39°C.
- He was transferred to the ICU for evaluation of transfusion associated circulatory overload (TACO).

Preferred Risk Stratification Tool for Primary MF: MIPSS70+ Version 2.0

Mutation and Karyotype-Enhanced IPSS for Patients with Primary MF (MIPSS-70+ V2.0)	
Prognostic Variable	Points
Severe anemia (Hgb < 8 g/dL women, < 9 g/dL men)	2
Moderate anemia (Hgb 8–9.9 g/dL women, 9–10.9 g/dL men)	1
Circulating blasts ≥ 2%	1
Constitutional symptoms	2
Absence of <i>CALR</i> type 1 mutation	2
High molecular risk (HMR) mutations	2
≥ 2 HMR mutations	3
Unfavorable karyotype	3
Very-high-risk (VHR) karyotype	4

Risk Group	Points
Very low	0
Low	1 to 2
Intermediate	3 to 4
High	5 to 8
Very high	9

Online calculator for MIPSS-70+ Version 2.0 can be found at <http://www.mipss70score.it/>

Preferred Risk Stratification Tool for Secondary MF: MYSEC-PM

MF Secondary to PV and ET Prognostic Model (MYSEC-PM)

Prognostic Variable	Points
Age at diagnosis	0.15 per patient year of age (71 × 0.15 = 10.65)
Hgb < 11 g/dL	2
Circulating blasts ≥ 3%	2
Absence of <i>CALR</i> type 1 mutation	2
Platelet count < 150 × 10 ⁹ /L	1
Constitutional symptoms	1

Risk Group	Points
Low	< 11
Intermediate-1	≥ 11
Intermediate-2	≥ 14 and < 16
High	≥ 16

Online calculator for MYSEC can be found at <http://mysec-pm.eu>

Anemia in Myelofibrosis

- Anemia and subsequent transfusion dependence in patients with MF is inevitable due to multiple factors:
 - Dysregulation of the JAK-STAT pathway
 - Hyperactivation of activin A receptor type 1 (ACVR1)
 - Treatment-related cytopenias
 - Comorbidities
 - Chronic blood loss from esophageal varices (hepatosplenomegaly)
- Upregulation of the JAK-STAT pathway results in chronic and progressive inflammation, progressive bone marrow fibrosis, and elevation of hepcidin
- Increased hepcidin production results in sequestration of iron, a reduction in erythropoietin production, and progressive anemia
- JAK inhibitors that do not inhibit ACVR1, do not restore iron homeostasis and effective erythropoiesis
- Transfusion dependence is associated with inferior outcomes and reduced quality of life

Risks Associated with Transfusion Dependence

Infectious	Immune Related	Non-Immune Related	Human Error
<p>Viral, bacterial, protozoan, or prior infections may be noted at variable times. Risk varies.</p>	<p>Acute:</p> <ul style="list-style-type: none"> • Acute hemolytic reaction • Febrile non-hemolytic reaction • Anaphylactic shock • Transfusion-related acute lung injury (TRALI) <p>Transfusion-associated dyspnea (TAD)</p> <p>Delayed:</p> <ul style="list-style-type: none"> • Delayed hemolytic reaction. • Transfusion associated graft-versus-host disease (TAGVHD) • Transfusion associated micro chimerism (increased risk in trauma) • Post transfusion purpura • Alloimmunization and HLA • Transfusion-related immunomodulation (TRIM) 	<p>Acute</p> <ul style="list-style-type: none"> • Transfusion-related circulatory overload (TACO) • Hypotension – Hypertension • Non-immunological hemolysis • Hypocalcemia, Hyperkalemia • Hypothermia <p>Delayed</p> <ul style="list-style-type: none"> • Transfusion-related iron overload 	<ul style="list-style-type: none"> • ABO incompatibility • Wrong name on tube • Wrong product transfused

Tailoring Treatment for Patient with Myelofibrosis and Anemia

Therapeutic Timeline for Myelofibrosis



- Ruxolitinib has been the only approved JAK inhibitor for treatment of higher-risk MF for more than a decade.
- Ruxolitinib failure or intolerance has been the underpinning of subsequent FDA approvals.
- Definitions of ruxolitinib failure have evolved.
- Limitations to continuous treatment (progression, intolerance), in particular cytopenias (anemia and thrombocytopenia), have introduced the concept of a tailored approach to treatment.

NCCN Guidelines

Recommended Treatments for MF by Risk Level

MIPSS Very Low

- Median OS: not reached all ages

MIPSS Low

- Median OS < 70 years: 16.4 years
- All ages: 10.3 years

MIPSS Intermediate

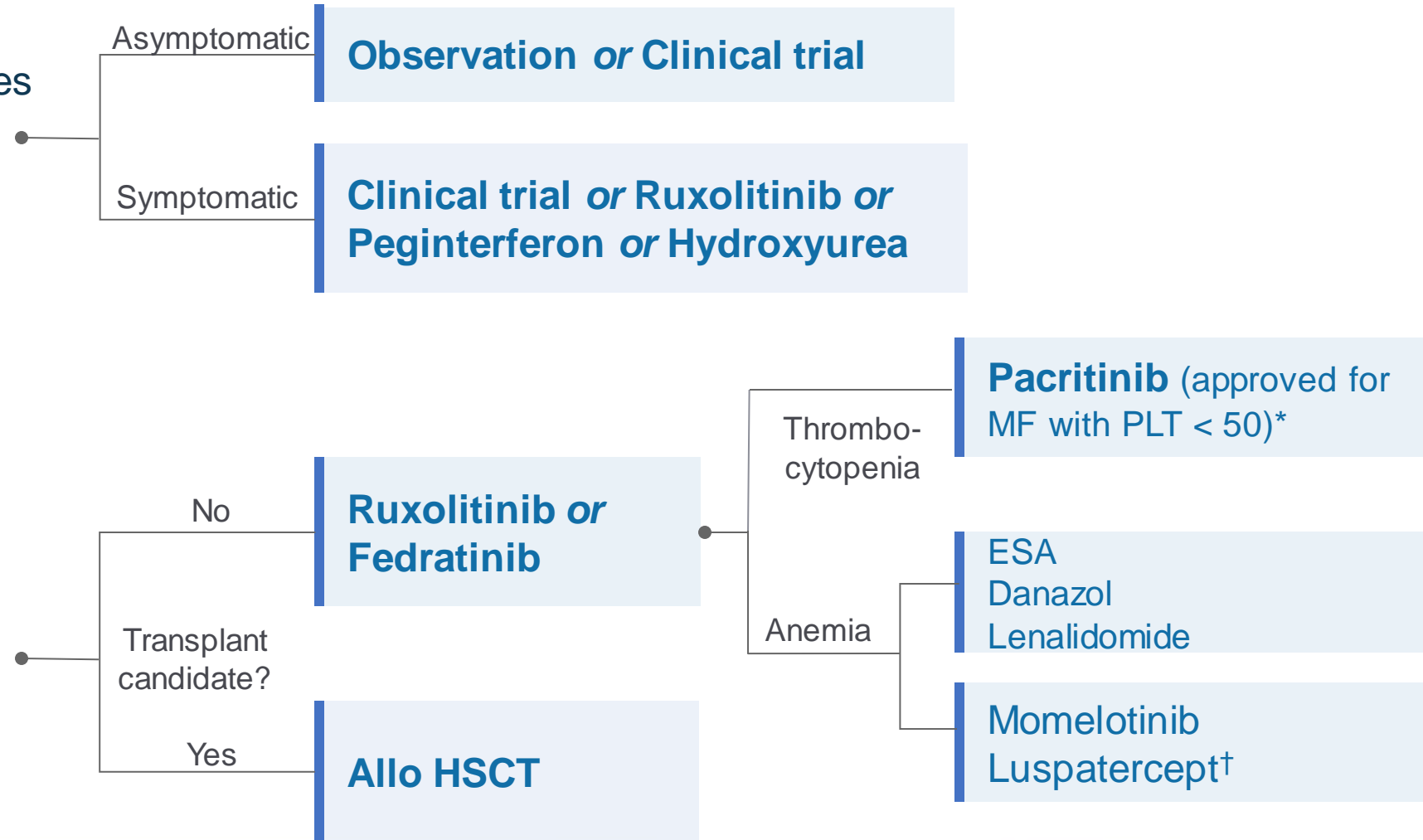
- Median OS: 7-8 years

MIPSS Very High

- Median OS: 1.8 years (all ages)

MIPSS High

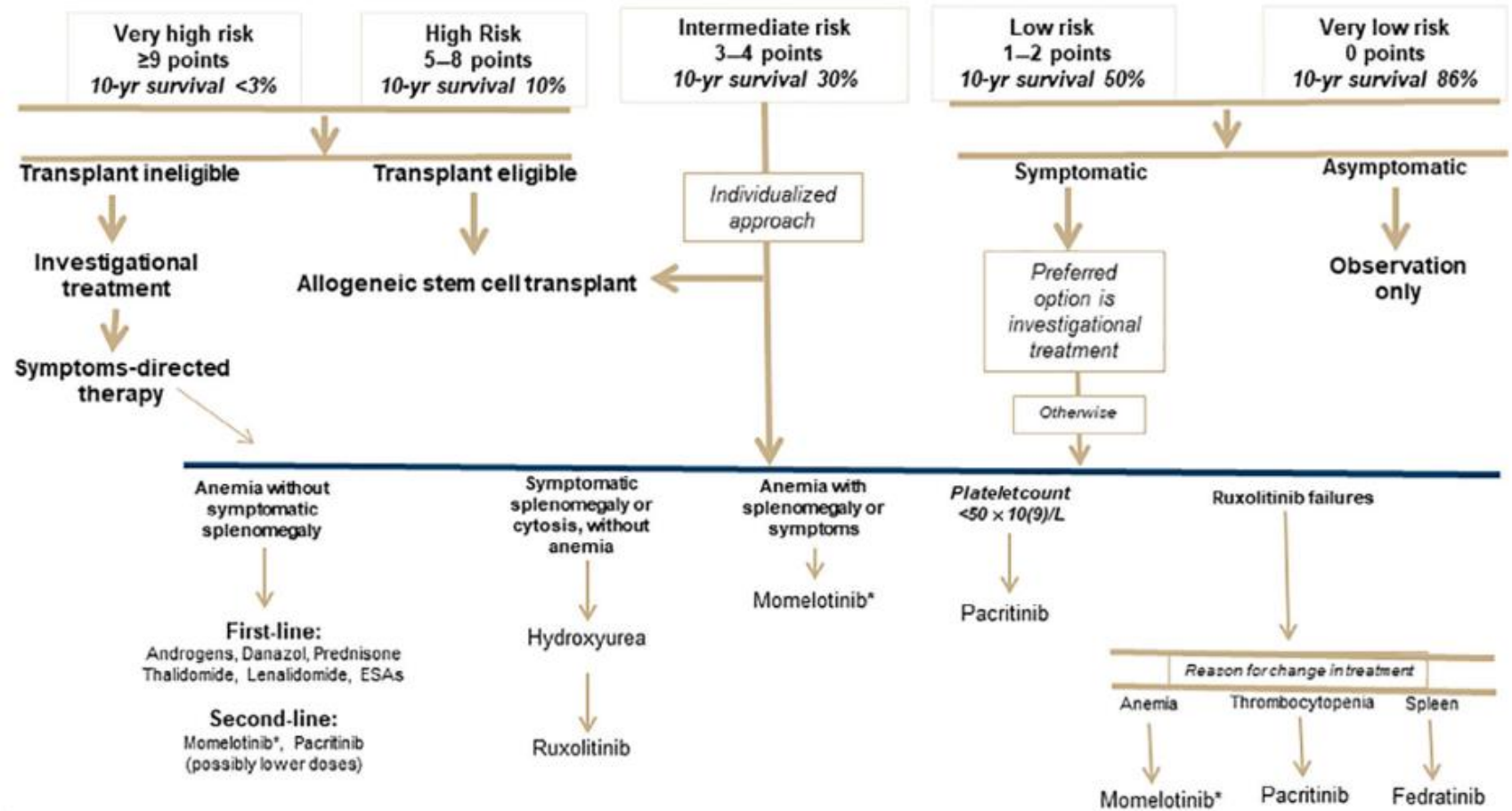
- Median OS < 70 years: 4.1 years, all ages: 3.5 years



*According to the NCCN, pacritinib can be considered for second-line treatment in patients with platelet counts $\geq 50 \times 10^9/L$ with 1 prior JAK inhibitor. † Not approved for this indication. NCCN Guidelines. Myeloproliferative neoplasms (V1.2023).

Risk-adapted Treatment Approach in Primary MF Using the Mutation and Karyotype Enhanced International Prognostic System, Version 2.0 (MIPPS v2)

Karyotype: Very high risk, 4 points; unfavorable, 3 points
Mutations: ≥ 2 high-risk mutations, 3 points; one high-risk mutation, 2 points
Type 1 CALR mutation: absent, 2 points
Clinical risk factors: Constitutional symptoms, 2 points; severe anemia, 2 points; moderate anemia, 1 point; $\geq 2\%$ circulating blasts, 1 point



42-Year-Old Man Diagnosed With primary MF in 2022 (Case 3 *continued*)

- During his initial consultation, the diagnosis of primary MF was explained as an incurable myeloid malignancy for which an allogeneic stem cell transplant provides the only potential cure.
- Patient does not want to proceed with an allogeneic stem cell transplant at this time due to limited financial resources and concerns about loss of employment.
- For this patient, using the algorithm, high-risk MF with anemia and splenomegaly with symptoms, the recommended treatment in lieu of or as a bridge to allogeneic stem cell transplant, would be momelotinib

84-Year-Old Woman With Post-PV MF and Secondary Anemia on Cytoreductive Therapy (Case 2)

- PV diagnosed at age 72 — managed with phlebotomy → hydroxyurea → ruxolitinib
- Progressive cytopenias and splenomegaly → bone marrow biopsy confirmed post-PV MF
- Not a candidate for allogeneic stem cell transplant (age)
- Restarted ruxolitinib
- Dose reduction and interruptions were required due to progressive anemia requiring transfusion, thrombocytopenia, and general intolerance.

84-Year-Old Woman With Post-PV MF and Secondary Anemia on Cytoreductive Therapy (Case 2 *continued*)

- The patient was enrolled in a clinical trial, MOMENTUM (SRA-MMB-301), a randomized, double-blind, phase 3 study to evaluate the activity of momelotinib versus danazol in symptomatic, anemic subjects with primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis who were previously treated with JAK inhibitor therapy (ClinicalTrials.gov: NCT04173494).

Momelotinib in MF

- **Novel JAK1, JAK2, and ACVR1 inhibitor**
- **FDA approval September 15, 2023**

SIMPLIFY-1^a

Phase 3 trial, MMB vs Rux (N = 432)

ELIGIBILITY

- MF **untreated** with JAK inhibitors

RESULTS

- SVR35: **noninferior to Rux** (27% vs 29%, $P = .011$)
- TSS50: **inferior to Rux** (28% vs 42%, $P = .98$)
- TI: **67%** (vs 49% for Rux, $P < .001$)

SIMPLIFY-2^b

Phase 3 trial, MMB vs BAT (N = 156)

ELIGIBILITY

- MF **pretreated** with Rux

RESULTS

- SVR35: **not superior to BAT** (7% vs 6%, $P = .89$)
- TSS50: **superior to BAT** (26% vs 6%, $P < .001$)
- TI: **43%** (vs 21% for BAT, $P = .0012$)

MOMENTUM^c

Phase 3 trial, MMB vs Dan (N = 195)

ELIGIBILITY

- MF **pretreated** with JAK inhibitors

RESULTS

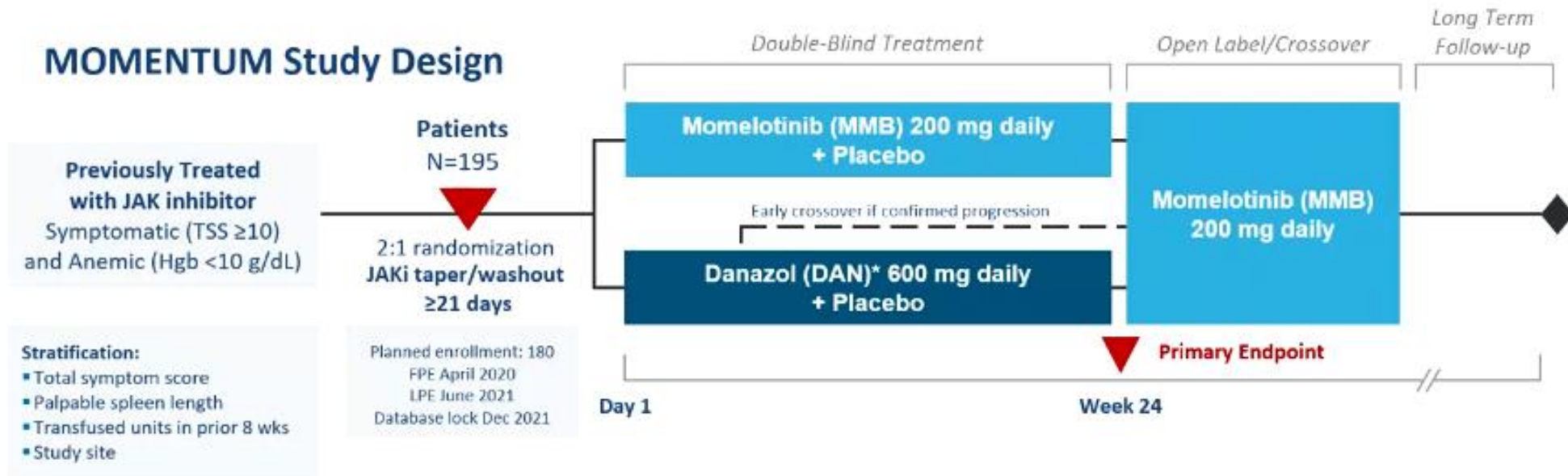
- SVR35: **23%** (vs 3% Dan, $P = .0006$)
- TSS50: **25%** (vs 9% Dan, $P = .0095$)
- TI: **31%** (vs 20% Dan, one-sided $P = .0064$)

BAT, best available therapy; Dan, danazol; MMB, momelotinib; Rux, ruxolitinib; TI, transfusion independence at Week 24.

a. Mesa RA, et al. J Clin Oncol. 2017;35:3844-3850. b. Harrison CN, et al. Lancet Haematol.

2018;5:e73-e81. c. Verstovsek S, et al. Lancet. 2023; 401:269-280.

MOMENTUM Assessed Momelotinib in Patients Previously Treated With Ruxolitinib Who Were Symptomatic and Anemic



Primary Endpoint

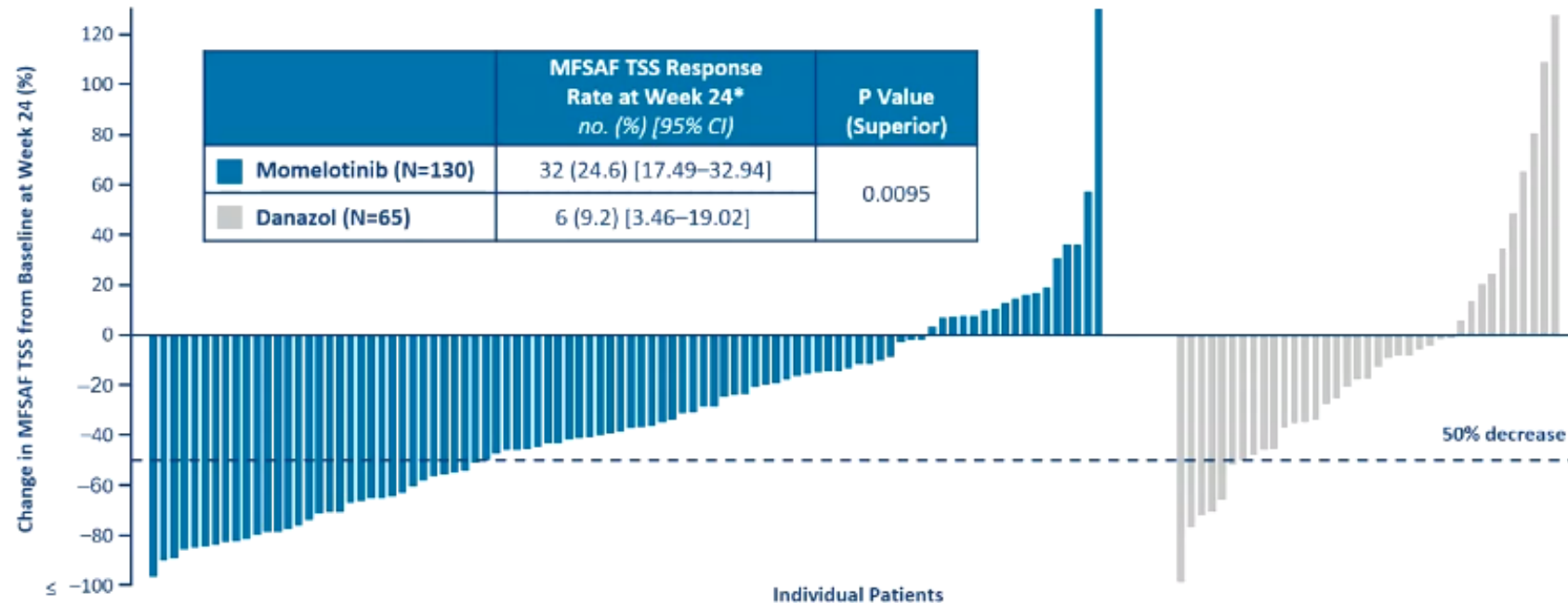
- Total symptom score (TSS) response rate at Week 24

Key Secondary Endpoints

- Transfusion independence (TI) rate at Week 24
- Splenic response rate (SRR) at Week 24

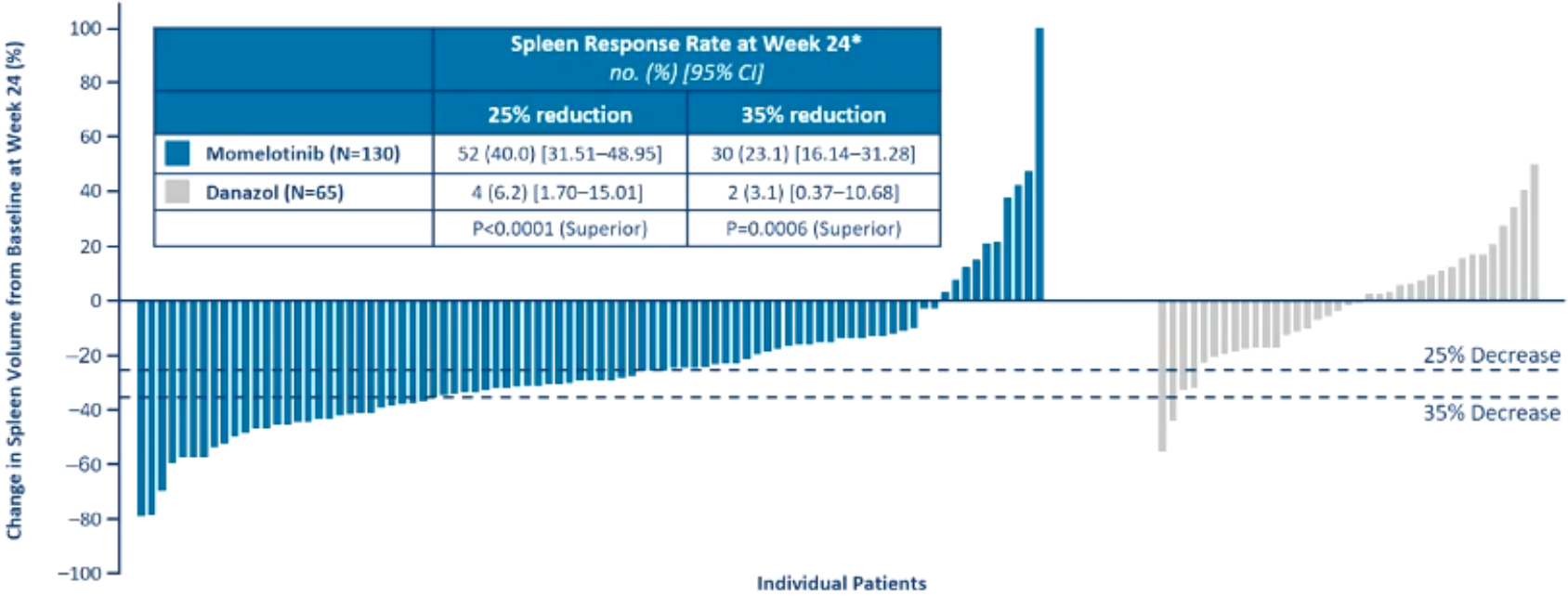
Momelotinib Superior to Danazol in Patients With Symptomatic MF With Anemia and Prior Ruxolitinib Treatment

MFSAF Total Symptom Score Response Rate* at W24



Momelotinib Superior to Danazol in Patients With Symptomatic MF With Anemia and Prior Ruxolitinib Treatment (continued)

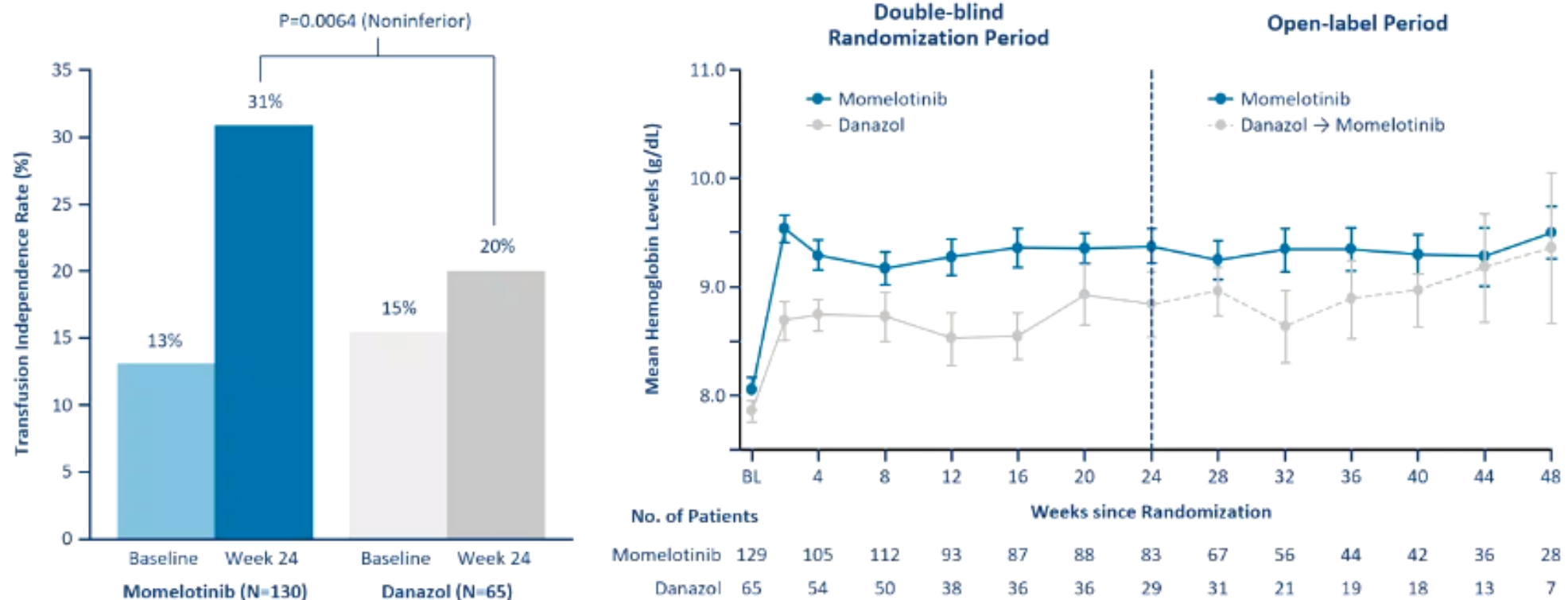
Spleen Response Rate* at Week 24



*Defined as the proportion of patients who have a reduction in spleen volume of ≥25% or ≥35% from baseline.

Momelotinib Better Than Danazol in Patients With Symptomatic MF With Anemia, Prior Ruxolitinib Treatment

Transfusion Independence* Rate at W24 and Mean Hemoglobin Over Time



*Defined as not requiring red blood cell transfusion in the terminal 12 weeks of the 24-week randomized period, with all hemoglobin levels during the 12-week interval of ≥ 8 g/dL.

70-Year-Old Woman With Post-ET MF With Relapse After ASCT (Case 1)

- Ms. P developed transfusion-dependent anemia (1 unit every 12-20 days, average Hgb 7.0 g/dL).
- Developed transfusion-related hemosiderosis (ferritin: 3,200 mg).
- A trial of danazol was initiated with no improvement in her transfusion burden.
- Ruxolitinib was restarted at a lower dose due to progressive fatigue, weight loss, and bone pain; however, Ms. P did not tolerate the lower dose and showed no improvement in her anemia.

70-Year-Old Woman With Post-ET MF With Relapse After ASCT (Case 1 *continued*)

- At this time, momelotinib, which had been under investigation in the MOMENTUM trial, received FDA approval for the treatment of patients with intermediate- or high-risk myelofibrosis with anemia regardless of prior therapy.
- Ms. P was initiated on momelotinib at a dose of 200 mg orally once daily, with or without food.
- Hepatitis B serologies were tested prior to starting therapy, due to known risk of reactivation of hepatitis B — her values were negative.
- She tolerated therapy well, with grade 1 thrombocytopenia. Her transfusion requirement decreased to 1 unit every 8 weeks.
- She continues to be monitored on therapy.

NCCN Guidelines: Management of MF-Associated Anemia

Rule out coexisting causes
(bleeding, iron, B12 or folate deficiency, hemolysis)

Treat coexisting causes and provide supportive care

- Replace iron, folate, and B12
- Treat hemolysis
- Provide RBC transfusions (leuko-reduced)

Serum EPO < 500 mU/mL

- ESAs
 - Darbepoetin alfa
 - Epoetin alfa
- Clinical trial

*No response or
loss of
response*

Serum EPO ≥ 500 mU/mL

Preferred Regimens:

- Clinical trial or momelotinib

Useful in certain circumstances:

- Danazol
- Lenalidomide ± prednisone
- Thalidomide ± prednisone
- Luspatercept

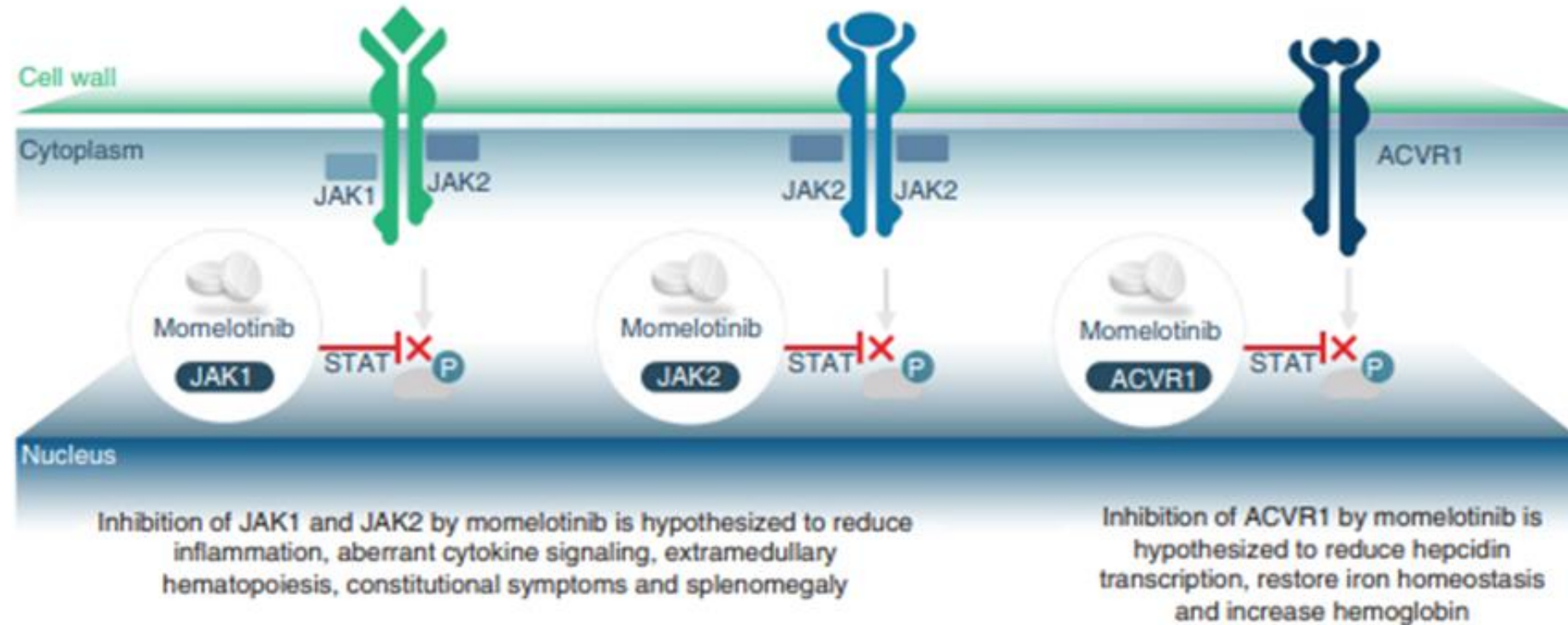
You are monitoring a patient receiving momelotinib 200 mg orally twice daily for post-PV myelofibrosis. You know that you will monitor closely for which of the following common adverse events?

- a. Diarrhea
- b. Nausea and Vomiting
- c. Acute kidney injury
- d. A&C
- e. Unsure

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- d. A&C
- e. Unsure

Momelotinib: Mechanism of Action



Momelotinib Dosing and Administration

- The recommended dosage of momelotinib is 200 mg orally once daily with or without food.
- How supplied: 100 mg, 150 mg, 200 mg tablets
- Pre-treatment testing
 - CBC, differential and platelet count
 - Liver enzymes
 - Hepatitis B serologies
 - If HBsAg and/or anti-HBc antibody is positive, consider consultation with a hepatologist
 - Patients with chronic HBV infection should have their chronic HBV infection treated and monitored according to clinical HBV guidelines
- Dose modifications
 - Severe hepatic impairment (Child-Pugh Class C): Reduce the starting dose to 150 mg orally once daily.
 - Dose modifications are indicated for thrombocytopenia and neutropenia

84-Year-Old With Post-PV MF and Secondary Anemia on Cytoreductive Therapy (Case 2 *continued*)

- One week after beginning therapy, the patient reported new-onset diarrhea, with 3 loose stools per day.
- Given that her symptoms were Grade 1, she was continued on therapy, and the diarrhea was managed with Imodium and a low-residue diet.
- The diarrhea improved, with only intermittent mild episodes after 1 month on therapy.
- After 3 months of momelotinib therapy, her platelet count remains above 90,000 and her hemoglobin has remained above 8.9 g/dL.

Long-Term Safety and Survival Profile of Mometotinib

- Integrated analysis of 3 randomized trials
- 725 patients with myelofibrosis receiving momelotinib
- Most common nonhematologic adverse event occurring in $\geq 20\%$ of patients:
 - Diarrhea (any grade, 27% and grade ≥ 3 , 3%).
- Hematologic adverse events (any grade):
 - Thrombocytopenia (25%)
 - Anemia (23%)
 - Neutropenia (7%)
- The most common reason for momelotinib discontinuation was thrombocytopenia (4% discontinuation rate).

42-Year-Old Man Diagnosed With Primary MF in 2022 (Case 3 *continued*)

- Mr. W was started on momelotinib 200 mg orally daily.
- He tolerated therapy well, and his symptoms of abdominal pain and bloating improved as his spleen size decreased.
- He developed a Grade 1 elevation in AST/ALT, which was monitored without intervention or change in dose.
- After 24 weeks on therapy, his Hgb increased to 8.2 g/dL.
- Mr. W presented to clinic for a regular follow-up visit, noting a new non-painful swelling in his right lower extremity.
- The AP ordered a right leg ultrasound, which was positive for an occlusive thrombus in the right popliteal vein.
- CT of the chest did not show pulmonary emboli.
- Mr. W was started on a direct oral anticoagulant (DOAC) with resolution of the swelling and pain.
- His treatment with momelotinib continued.

Adverse Event Profile for Mometotinib

AEs During 24-Week Randomized Treatment	Mometotinib (N = 130)		Danazol (N = 65)	
	% of patients			
Grade ≥ 3 adverse events	53.8		64.6	
Serious adverse events	34.6		40.0	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Nonhematologic (preferred term)				
Diarrhea	22.3	0	9.2	1.5
Nausea	16.2	2.3	9.2	3.1
Blood creatinine increased	7.7	0.8	15.4	3.1
Asthenia	13.1	0.8	9.2	1.5
Dyspnea	7.7	2.3	13.8	1.5
Peripheral edema	7.7	1.5	13.8	0
Acute kidney injury	4.6	3.1	12.3	9.2
Fatigue	6.2	0.8	10.8	3.1
Pruritus	10.8	1.5	10.8	0
Weight decreased	10.8	0	6.2	0
Hematologic abnormalities				
Anemia	99.2	60.8	100	75.4
Thrombocytopenia	76.2	27.7	61.5	26.2
Neutropenia	29.2	12.3	26.2	9.2

Warnings and Precautions: Mometotinib

- Risk of infection
- Thrombocytopenia and neutropenia
- Hepatotoxicity
- Thrombosis
- Major adverse cardiovascular events
- Malignancies

Which of the following pre-treatment tests are recommended prior to initiating treatment with momelotinib?

- a. Cytomegalovirus titers
- b. Echocardiogram
- c. Hepatitis B serologies
- d. A&C
- e. Unsure

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Clinical Pearls

- Evolving treatment options with novel mechanisms of action that limit treatment-related anemia provide promise for patients with transfusion-dependent anemia.
- Patients with polycythemia vera (PV) or essential thrombocythemia (ET) who develop progressive cytopenias, including anemia, should be evaluated for secondary myelofibrosis.
- In patients not eligible for allogeneic stem cell transplantation, selecting a clinical trial or a disease-modifying treatment that limits treatment-related anemia is ideal.
- Concurrent supportive care is recommended for all patients.

Clinical Pearls

- Progressive anemia and transfusion-dependent anemia are inevitable in most patients with myelofibrosis.
- Transfusion of red blood cells carries significant risks, both acute and chronic.
- Monitoring for this risk is essential in patients that are transfusion dependent.
- Disease-modifying treatments tailored to the individual patients based on risk category and symptom profile is recommended.

Q & A

Please type your questions for Sandra Kurtin
into the **question box**.

Thank You