Myeloproliferative Disorders Update

January 20, 2023, Joseph Shatzel MD

Update Contents

- MPN workup
- Individual MPNs:
  - Essential Thrombocytosis
  - Polycythemia Vera
  - Myelofibrosis
- Hypereosinophilic syndrome (HES)

MPN Workup

- Patients presenting with unexplained thrombocytosis, polycythemia or marrow failure, especially in the setting of **unexplained thrombosis**.
- We prefer peripheral blood workup (OHSU has developed panels).
- Bone marrow can often be deferred in many patients if the molecular and phenotype is consistent

Table 16-4 Somatic mutations seen in patients with MPNs

Gene name	Mutation effect	PV (%)	ET (%)	MF (%)
JAK2 (V617F)	JAK/STAT signaling	95-97	50-60	50-60
JAK2 exon 12	JAK/STAT signaling	1-2	0	0
CALR	JAK/STAT signaling	0	25	30
MPL	JAK/STAT signaling	0	3-5	5-10

PV Diagnosis

2017 WHO DIAGNOSTIC CRITERIA FOR POLYCYTHEMIA VERA AND ESSENTIAL THROMBOCYTHEMIA[1]

Polycythemia Vera (PV)
(Diagnosis requires meeting either all 3 major criteria, or the first 2 major criteria and the minor criterion[2])

- **Major criteria**
  - **Hemoglobin >16.5 g/dL in men, >16.0 g/dL in women**
    OR
    Hematocrit >49% in men, >48% in women
    OR
    Increased red cell mass (RCM)[3]
  - **Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) including prominent erythroid, granulocytic, and megakaryocytic proliferation with pleomorphic, mature megakaryocytes (differences in size)**
  - **Presence of *JAK2* V617F or *JAK2* exon 12 mutation**

- **Minor criteria**
  - **Subnormal serum EPO level**

ET Diagnosis

Essential Thrombocythemia (ET)
(Diagnosis requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion)

- **Major criteria**
  - **Platelet count ≥450 x 10^9/L**
  - **Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei. No significant increase or left shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers**
  - **Not meeting WHO criteria for CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms**
  - **Presence of *JAK2, CALR,* or *MPL* mutation**

- **Minor criterion**
  - **Presence of a clonal marker or absence of evidence for reactive thrombocytosis**

2017 WHO DIAGNOSTIC CRITERIA FOR PRIMARY MYELOFIBROSIS[1]

WHO preMF Criteria
(Diagnosis of prePMF requires meeting all 3 major criteria, and at least 1 minor criterion)

- **Major criteria**
  - **Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1,[2] accompanied by increased age-adjusted BM cellularity, granulocytic proliferation, and often decreased erythropoiesis**
  - **Not meeting WHO criteria for *BCR-ABL1*+ CML, PV, ET, myelodysplastic syndromes, or other myeloid neoplasms**
  - **Presence of *JAK2, CALR,* or *MPL* mutation or in the absence of these mutations, presence of another clonal marker,[3] or absence of minor reactive BM reticulin fibrosis[4]**

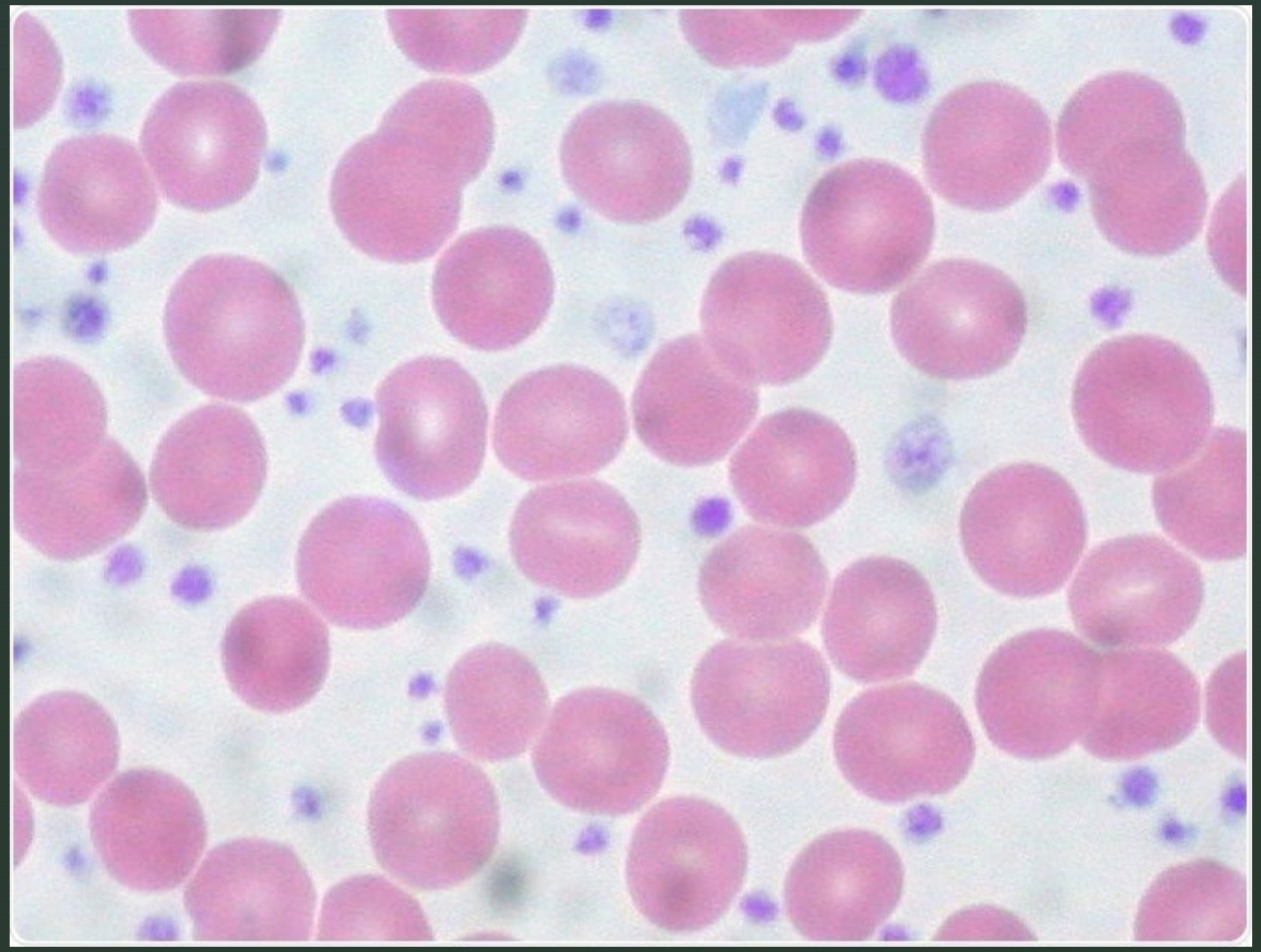
- **Minor criteria**
  - **Presence of at least one of the following, confirmed in 2 consecutive determinations:**
    - **Anemia not attributed to a comorbid condition**
    - **Leukocytosis ≥11 x 10^9/L**
    - **Palpable splenomegaly**
    - **LDH increased to above upper normal limit of institutional reference range**

WHO Overt PMF Criteria
(Diagnosis of overt PMF requires meeting all 3 major criteria, and at least 1 minor criterion)

- **Major criteria**
  - **Presence of megakaryocytic proliferation and atypia, accompanied by either reticulin and/or collagen fibrosis grades 2 or 3[2]**
  - **Not meeting WHO criteria for ET, PV, *BCR-ABL1*+ CML, myelodysplastic syndromes, or other myeloid neoplasms**
  - **Presence of *JAK2, CALR, or MPL* mutation or in the absence of these mutations, presence of another clonal marker,[3] or absence of reactive myelofibrosis[5]**

- **Minor criteria**
  - **Presence of at least one of the following, confirmed in 2 consecutive determinations:**
    - **Anemia not attributed to a comorbid condition**
    - **Leukocytosis ≥11 x 10^9/L**
    - **Palpable splenomegaly**
    - **LDH increased to above upper normal limit of institutional reference range**
    - **Leukoerythroblastosis**

Essential Thrombocytosis



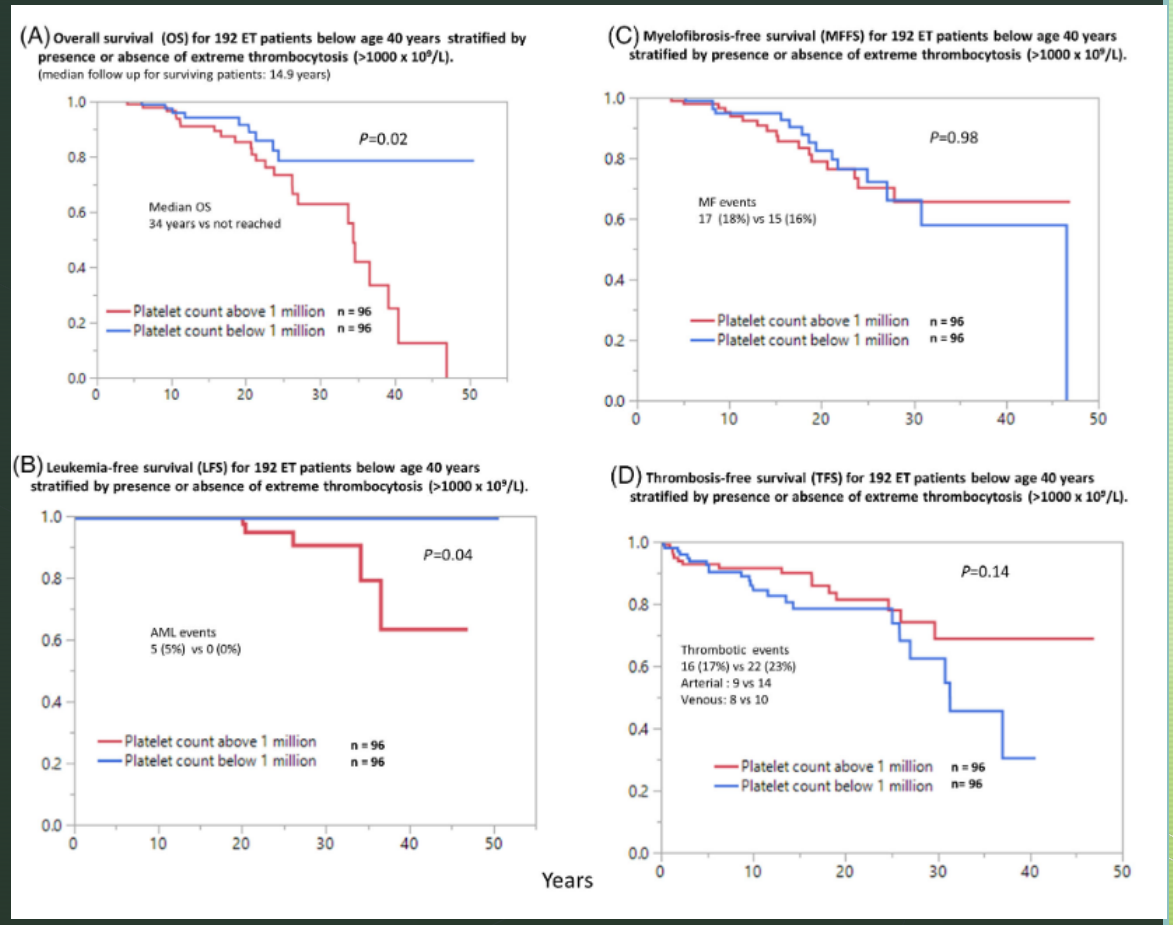
Essential Thrombocytosis

- Patients can generally enjoy a normal life span
- ET patients carry a low risk of thrombosis, and progression to MF and leukemia.
- “Young Platelet Millionaires still carry very good prognosis.

Am J Hematol. 2021 Apr 1;96(4):E93-E95. doi: 10.1002/ajh.26114. Epub 2021 Feb 18.

Young platelet millionaires with essential thrombocythemia

Naseema Gangat [1], Natasha Szuber [2], Tabinda Jawaid [1], Curtis A Hanson [3], Animesh Pardanani [1], Ayalew Tefferi [1]



ET Treatment

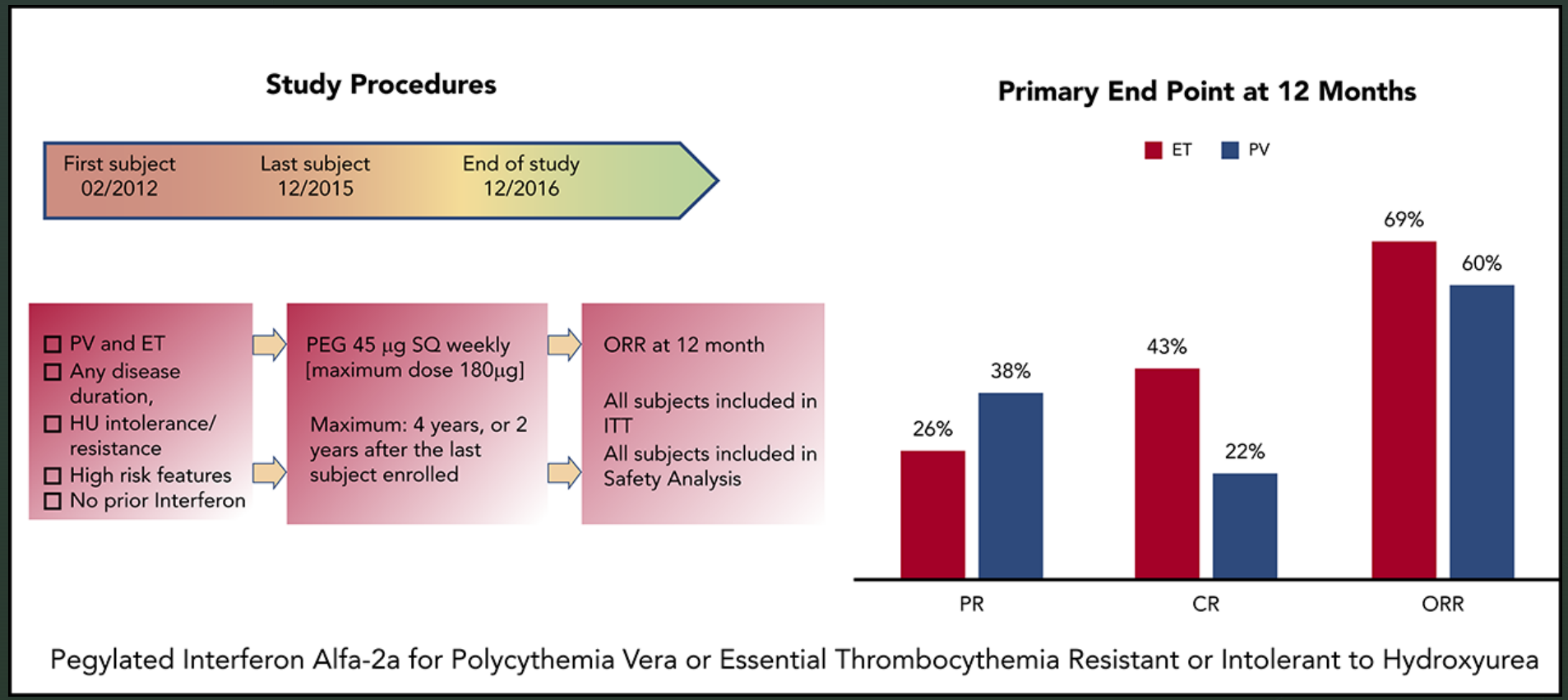
- **High-risk disease** – History of thrombosis at any age and/or age >60 with a *JAK2* V617F mutation — **RFR, Aspirin and Cytoreduction**
- **Intermediate-risk disease** – Age >60, no *JAK2* mutation detected, and no history of thrombosis — **RFR and Aspirin**
- **Low-risk disease** – Age ≤60 with *JAK2* mutation and no history of thrombosis — **RFR and Aspirin**
- **Very low-risk disease** – Age ≤60, no *JAK2* mutation detected, and no history of thrombosis — **RFR and Observation**

What is the cytoreduction goals

- Hydroxyurea is generally first line
- Anagrelide or Interferon can also be used
- Goal platelet count is often unclear
  - 400?
  - 450?
  - 600?

What's new in Cytoreduction

- **Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea**



Pegylated Interferon Alfa-2a for Polycythemia Vera or Essential Thrombocythemia Resistant or Intolerant to Hydroxyurea

Hydrea vs Interferon first line

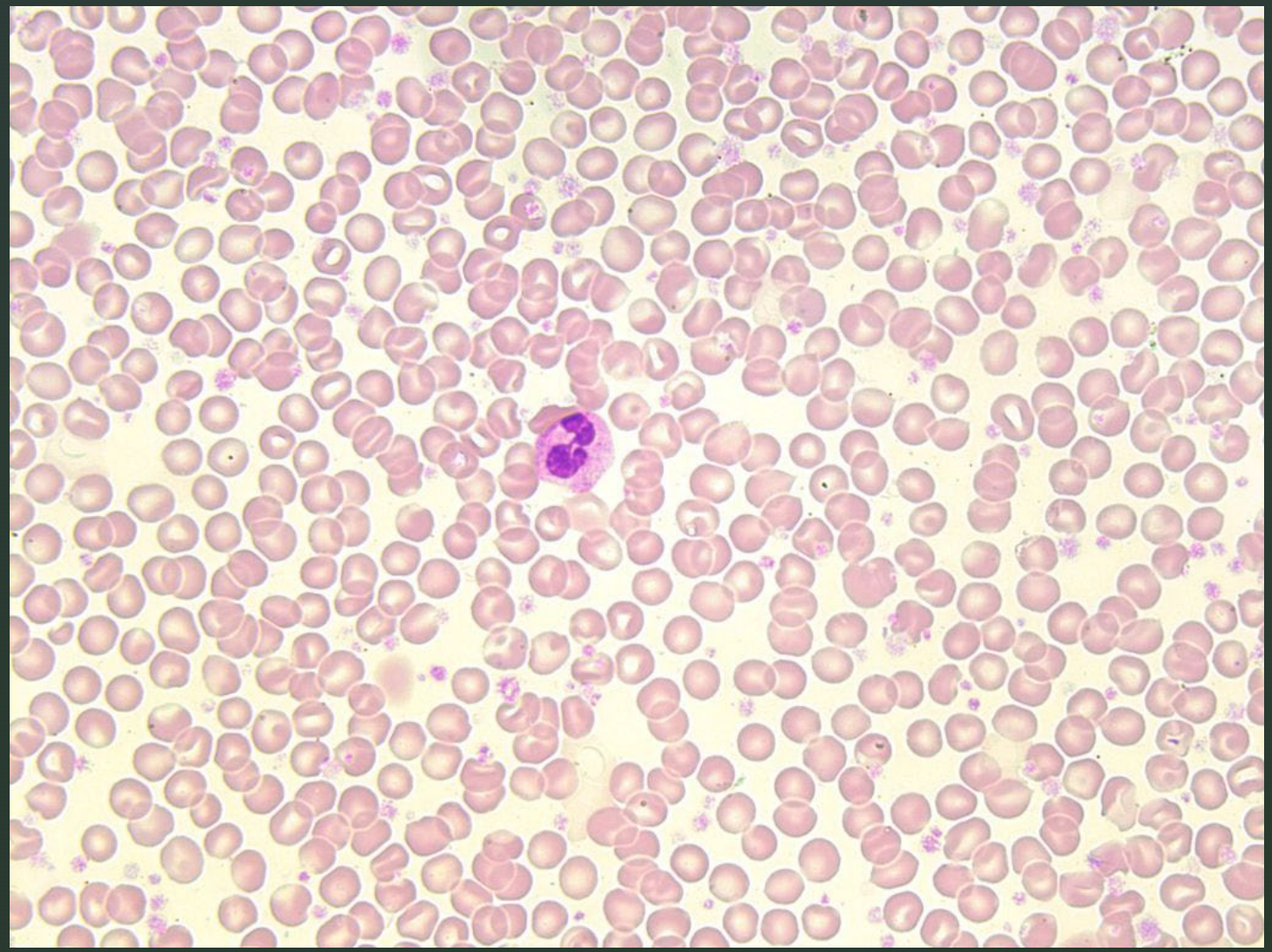
		HU (n=86)	PEG (n=82)	Difference in proportions for combined ET/PV, 95% CI (PEG – HU)	Rate Ratio (95% CI)
12 months	**Complete response** ET PV	**32 (37%)** 19 (45%) 13 (30%)	**29 (35%)** 17 (44%) 12 (28%)	-2% (-16 to 13)	0.95 (0.64, 1.42)
	Overall response ET PV	**60 (70%)** 30 (71%) 30 (68%)	**64 (78%)** 27 (69%) 37 (86%)	8% (-5 to 21)	1.12 (0.93, 1.34)
24 months		**(n=54)***	**(n=52)***		
	Complete response ET PV	**11 (20%)** 6 (25%) 5 (17%)	**15 (29%)** 9 (38%) 7 (25%)	9% (-9 to 26)	1.42 (0.72, 2.79)
	Overall response ET PV	**22 (41%)** 8 (33%) 14 (47%)	**31 (60%)** 14 (58%) 17 (61%)	19% (1 to 37)	1.46 (1.00, 2.16)
36 months		**(n=30)****	**(n=27)****		
	Complete response ET PV	**5 (17%)** 2 17%) 3 (17%)	**9 (33%)** 4 (40%) 5 (29%)	17% (-8 to 40)	2.0 (0.76, 5.23)
	Overall response ET PV	**14 (47%)** 4 (33%) 10 (56%)	**16 (59%)** 6 (60%) 10 (59%)	13% (-15 to 38)	1.27 (0.77, 2.08)

Overall response rate = complete + partial response

Table 3: Adverse events occurring in ≥ 10% in either arm (HU or PEG), regardless of attribution.

	HU (n=80)				PEG (n=82)			
Adverse Event	**Grade 1-2, n , %**		**Grade 3-4, n, %**		**Grade 1-2, n , %**		**Grade 3-4, n, %**	
Hematologic								
Leukopenia*	11	14			22	27		
Anemia	14	18			11	13	1	1
Thrombocytopenia	11	14	1	1	10	12		
Neutropenia	6	8	3	4	7	9	2	2
Lymphopenia	4	5	1	1	6	7	3	4
Non-hematologic								
Fatigue	34	43	2	3	40	49	6	7
Pain in extremity	14	18	2	3	16	20	1	1
Headache	12	15			18	22	3	4
Diarrhea	11	14	1	1	14	17		
Peripheral sensory neuropathy	7	9	3	4	16	20		
Nausea	12	15			13	16		
Flu like symptoms*	4	5			18	22	2	2
Cough	10	13			12	15		
Pruritus*	5	6			14	17	2	2
Abdominal pain	5	6	1	1	13	16		
Injection site reaction*					18	22		

Polycythemia Vera



Polycythemia Vera

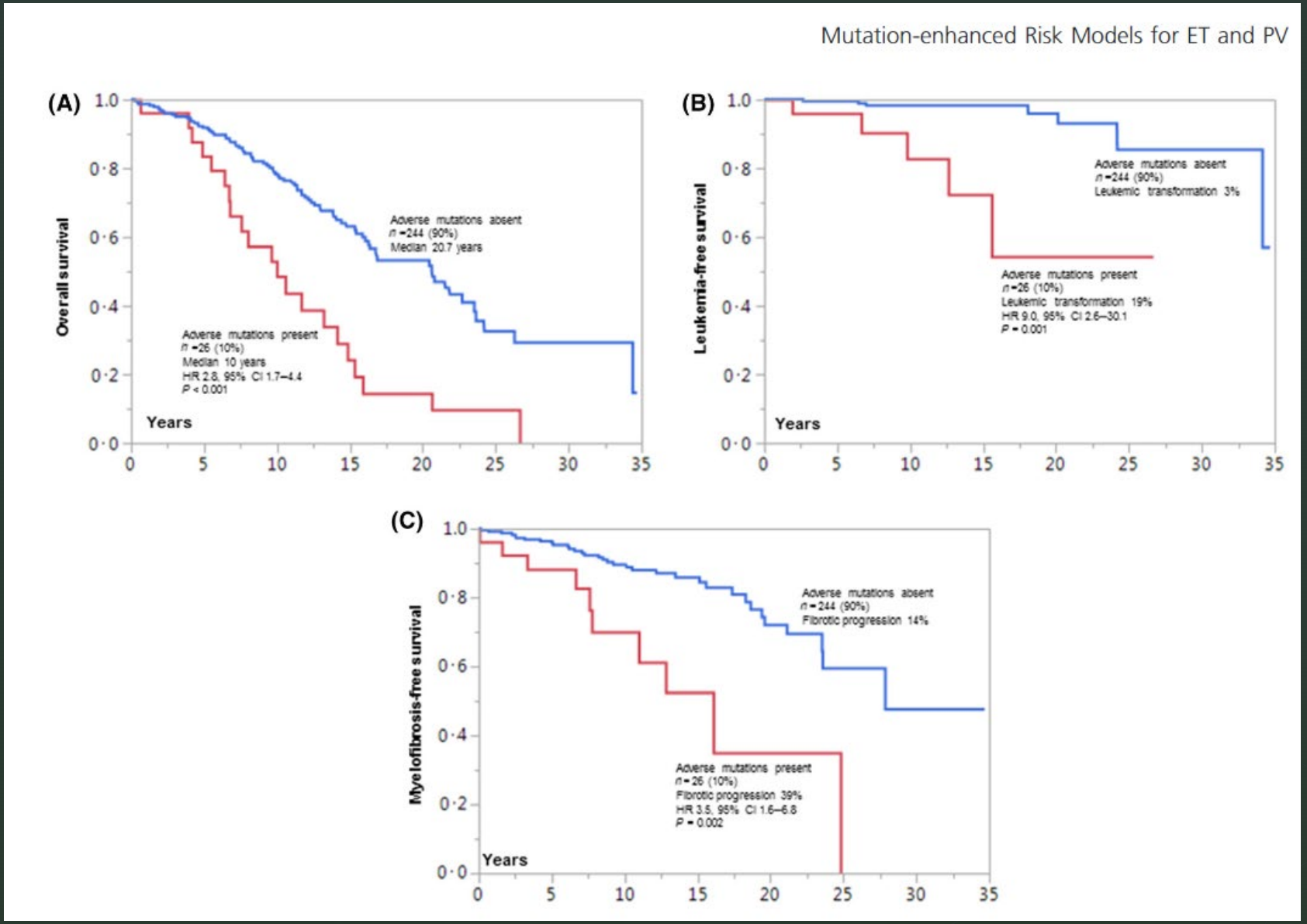
RISK STRATIFICATION FOR PATIENTS WITH PV[a]

MIPSS-PV

Prognostic Variable	Points
Thrombosis hisory	1
Leukocyte count ≥15x10^9/L	1
Age >67	2
Adverse mutations (*SRSF2*)	3

Risk Group	Points
Low	0–1
Intermediate	2–3
High	≥4

Prognosis


Mutation-enhanced Risk Models for ET and PV
(A)
Overall survival
1.0
0·8
0·6
0·4
0·2
0·0
Adverse mutations absent
n =244 (90%)
Median 20.7 years
Adverse mutations present
n =26 (10%)
Median 10 years
HR 2.8, 95% CI 1.7–4.4
P < 0.001
Years
0
5
10
15
20
25
30
35
(B)
Leukemia-free survival
Adverse mutations absent
n =244 (90%)
Leukemic transformation 3%
Adverse mutations present
n =26 (10%)
Leukemic transformation 19%
HR 9.0, 95% CI 2.6–30.1
P = 0.001
(C)
Myelofibrosis-free survival
Adverse mutations absent
n = 244 (90%)
Fibrotic progression 14%
Adverse mutations present
n = 26 (10%)
Fibrotic progression 39%
HR 3.5, 95% CI 1.6–6.8
P = 0.002

Treatment for PV

- **For all stages:**
  - Aspirin and RBC cytoreduction (to Hct <45) using phlebotomy or Hydrea.
  - Can use both phlebotomy and hydrea in high risk patients
  - If unable to obtain response or intolerant to hydrea IFN or ruxolitinib may be used second line.

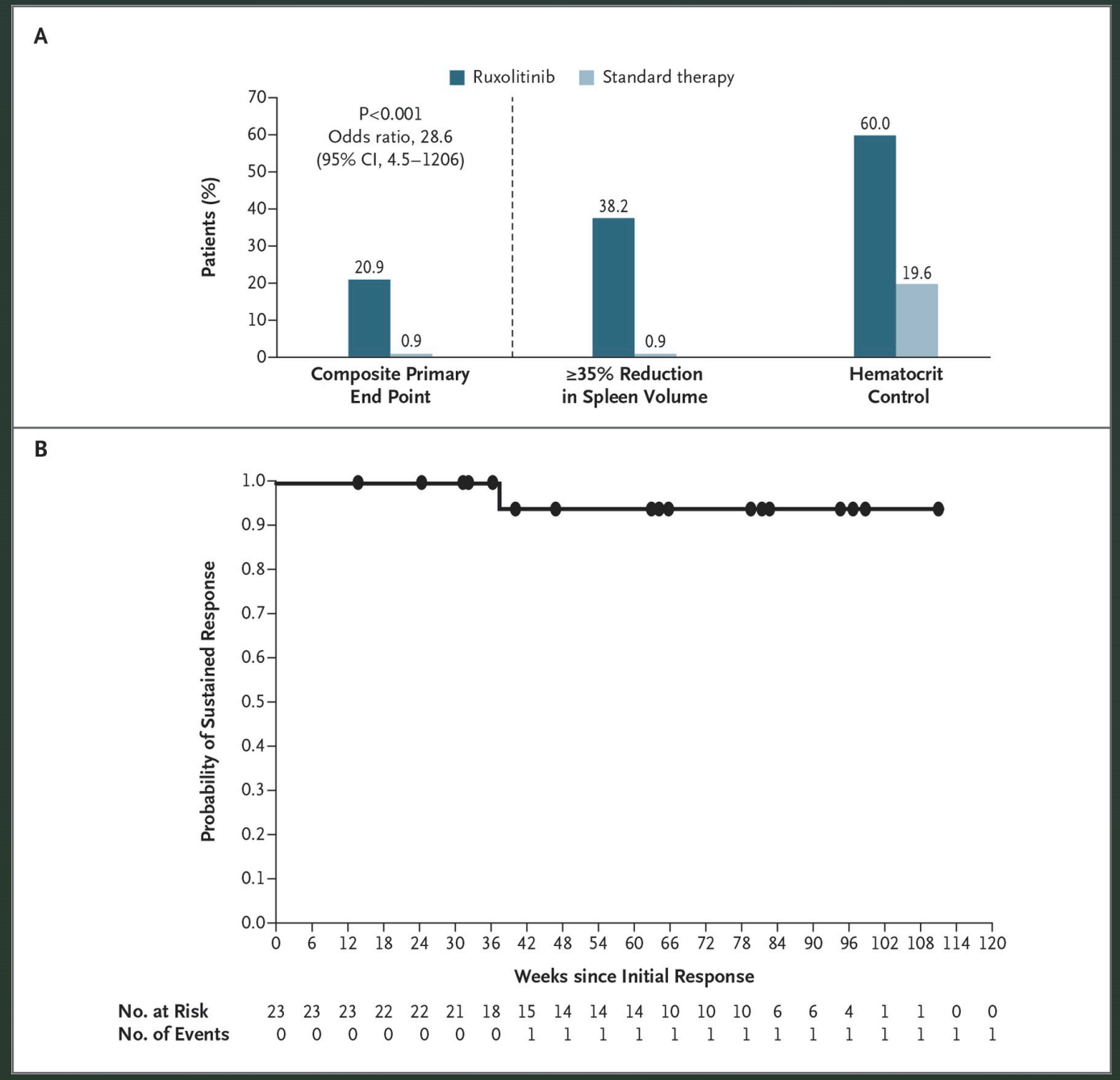
DEFINITION OF RESISTANCE/INTOLERANCE TO HYDROXYUREA[1]

Myeloproliferative Neoplasm	Definition of Resistance/Intolerance to Hydroxyurea
Polycythemia vera	1. Need for phlebotomy to keep hematocrit <45% after 3 months of at least 2 g/d of hydroxyurea, OR 2. Uncontrolled myeloproliferation (ie, platelet count >400 x 10^9/L AND WBC count >10 x 10^9/L) after 3 months of at least 2 g/d of hydroxyurea, OR 3. Failure to reduce massive* splenomegaly by >50% as measured by palpation OR failure to completely relieve symptoms related to splenomegaly after 3 months of at least 2 g/d of hydroxyurea, OR 4. Absolute neutrophil count <1.0 x 10^9/L OR platelet count <100 x 10^9/L OR hemoglobin <10 g/dL at the lowest dose of hydroxyurea required to achieve a complete or partial clinicohematologic response,† OR 5. Presence of leg ulcers or other unacceptable hydroxyurea-related nonhematologic toxicities, such as mucocutaneous manifestations, GI symptoms, pneumonitis, or fever at any dose of hydroxyurea
Essential thrombocythemia	1. Platelet count >600 x 10^9/L after 3 months of at least 2 g/d of hydroxyurea (2.5 g/d in patients with a body weight >80 kg), OR 2. Platelet count >400 x 10^9/L and WBC count <2.5 x 10^9/L at any dose of hydroxyurea, OR 3. Platelet count >400 x 10^9/L and hemoglobin <10 g/dL at any dose of hydroxyurea, OR 4. Presence of leg ulcers or other unacceptable mucocutaneous manifestations at any dose of hydroxyurea, OR 5. Hydroxyurea-related fever

*Organ extending by >10 cm from the costal margin.

†Complete response is defined as hematocrit less than 45% without phlebotomy, platelet count ≤400 x 10^9/L, WBC count ≤10 x 10^9/L, and no disease-related symptoms. Partial response is defined as hematocrit less than 45% without phlebotomy or response in three or more of other criteria.

Ruxolitinib



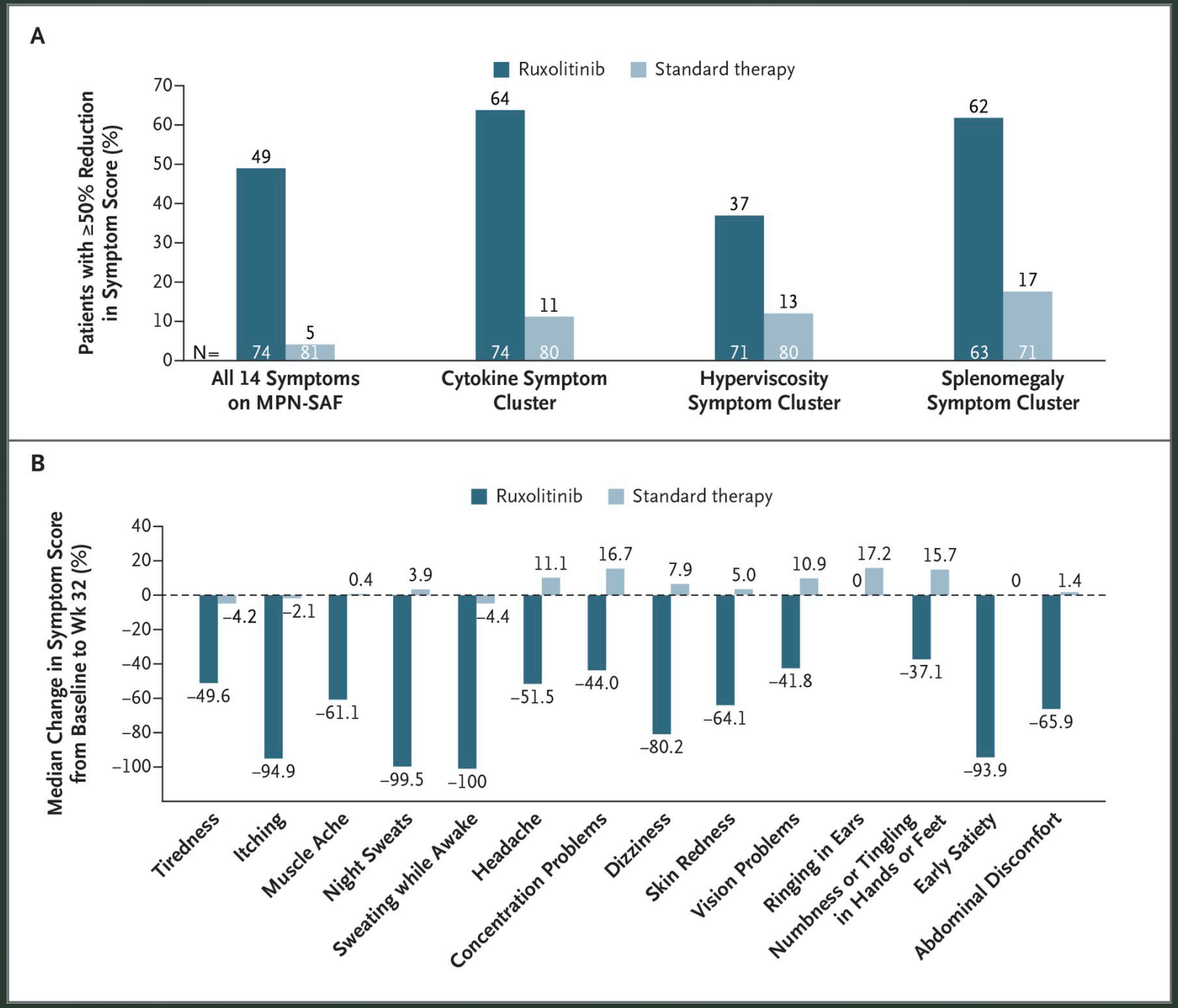
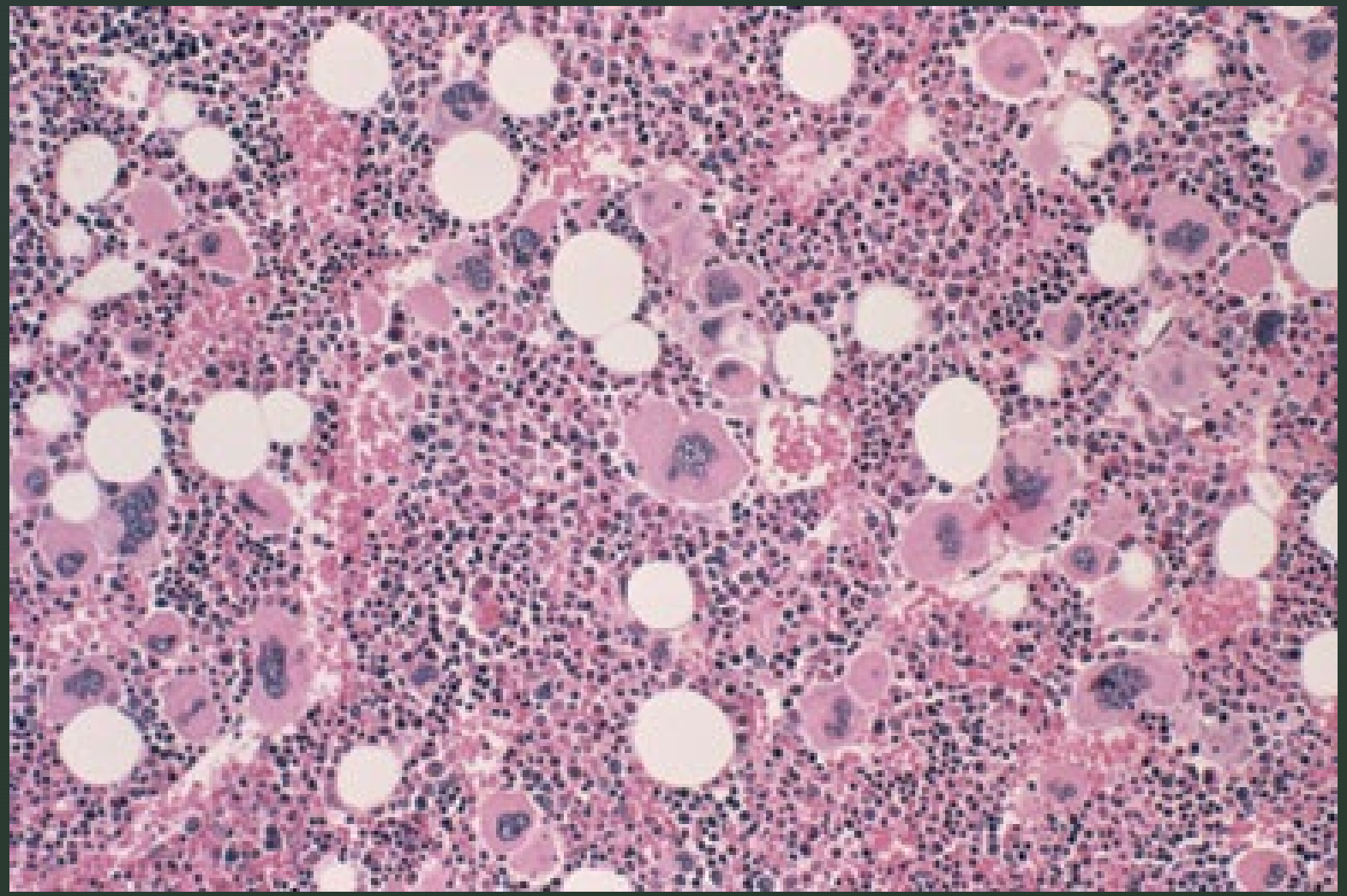

A
Ruxolitinib
Standard therapy
Patients with ≥50% Reduction in Symptom Score (%)
70
60
50
40
30
20
10
0
N=
74
81
74
80
71
80
63
71
49
5
64
11
37
13
62
17
All 14 Symptoms on MPN-SAF
Cytokine Symptom Cluster
Hyperviscosity Symptom Cluster
Splenomegaly Symptom Cluster
B
Ruxolitinib
Standard therapy
Median Change in Symptom Score from Baseline to Wk 32 (%)
40
20
0
−20
−40
−60
−80
−100
−49.6
−4.2
−94.9
−2.1
−61.1
0.4
−99.5
3.9
−100
−4.4
−51.5
11.1
−44.0
16.7
−80.2
7.9
−64.1
5.0
−41.8
10.9
0
17.2
−37.1
15.7
−93.9
0
−65.9
1.4
Tiredness
Itching
Muscle Ache
Night Sweats
Sweating while Awake
Headache
Concentration Problems
Dizziness
Skin Redness
Vision Problems
Ringing in Ears
Numbness or Tingling in Hands or Feet
Early Satiety
Abdominal Discomfort

Table 2. Adverse Events from Start of Study Drug to Week 32, Regardless of Whether They Were Related to the Study Drug.

Adverse Event	Ruxolitinib (N=110)			Standard Therapy (N=111)*		
	All Grades	Grade 3 or 4		All Grades	Grade 3 or 4	
	number of patients (percent)					
Nonhematologic†						
Headache	18 (16.4)	1 (0.9)		21 (18.9)	1 (0.9)	
Diarrhea	16 (14.5)	0		8 (7.2)	1 (0.9)	
Fatigue	16 (14.5)	0		17 (15.3)	3 (2.7)	
Pruritus	15 (13.6)	1 (0.9)		25 (22.5)	4 (3.6)	
Dizziness	13 (11.8)	0		11 (9.9)	0	
Muscle spasms	13 (11.8)	1 (0.9)		5 (4.5)	0	
Dyspnea	11 (10.0)	3 (2.7)		2 (1.8)	0	
Abdominal pain	10 (9.1)	1 (0.9)		13 (11.7)	0	
Asthenia	8 (7.3)	2 (1.8)		12 (10.8)	0	
	All Grades	Grade 3	Grade 4	All Grades	Grade 3	Grade 4
Hematologic‡						
Anemia	48 (43.6)	1 (0.9)	1 (0.9)	34 (30.6)	0	0
Thrombocytopenia	27 (24.5)	5 (4.5)	1 (0.9)	21 (18.9)	3 (2.7)	1 (0.9)
Lymphopenia	48 (43.6)	17 (15.5)	1 (0.9)	56 (50.5)	18 (16.2)	2 (1.8)
Leukopenia	10 (9.1)	1 (0.9)	0	14 (12.6)	2 (1.8)	0
Neutropenia	2 (1.8)	0	1 (0.9)	9 (8.1)	1 (0.9)	0

Myelofibrosis



RISK STRATIFICATION FOR PATIENTS WITH PMF

DYNAMIC INTERNATIONAL PROGNOSTIC SCORING SYSTEM (DIPSS)[1]

Prognostic Variable	Points		
	0	1	2
Age, y	≤65	>65	
White blood cell count, x10^9/L	≤25	>25	
Hemoglobin, g/dL	≥10		<10
Peripheral blood blast, %	<1	≥1	
Constitutional symptoms, Y/N	N	Y	

Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1 or 2
Intermediate-2 (INT-2)	3 or 4
High	5 or 6

Online calculator for DIPSS score can be found at https://qxmd.com/calculate/calculator_187/dipss-prognosis-in-myelofibrosis

DIPSS-PLUS[2]

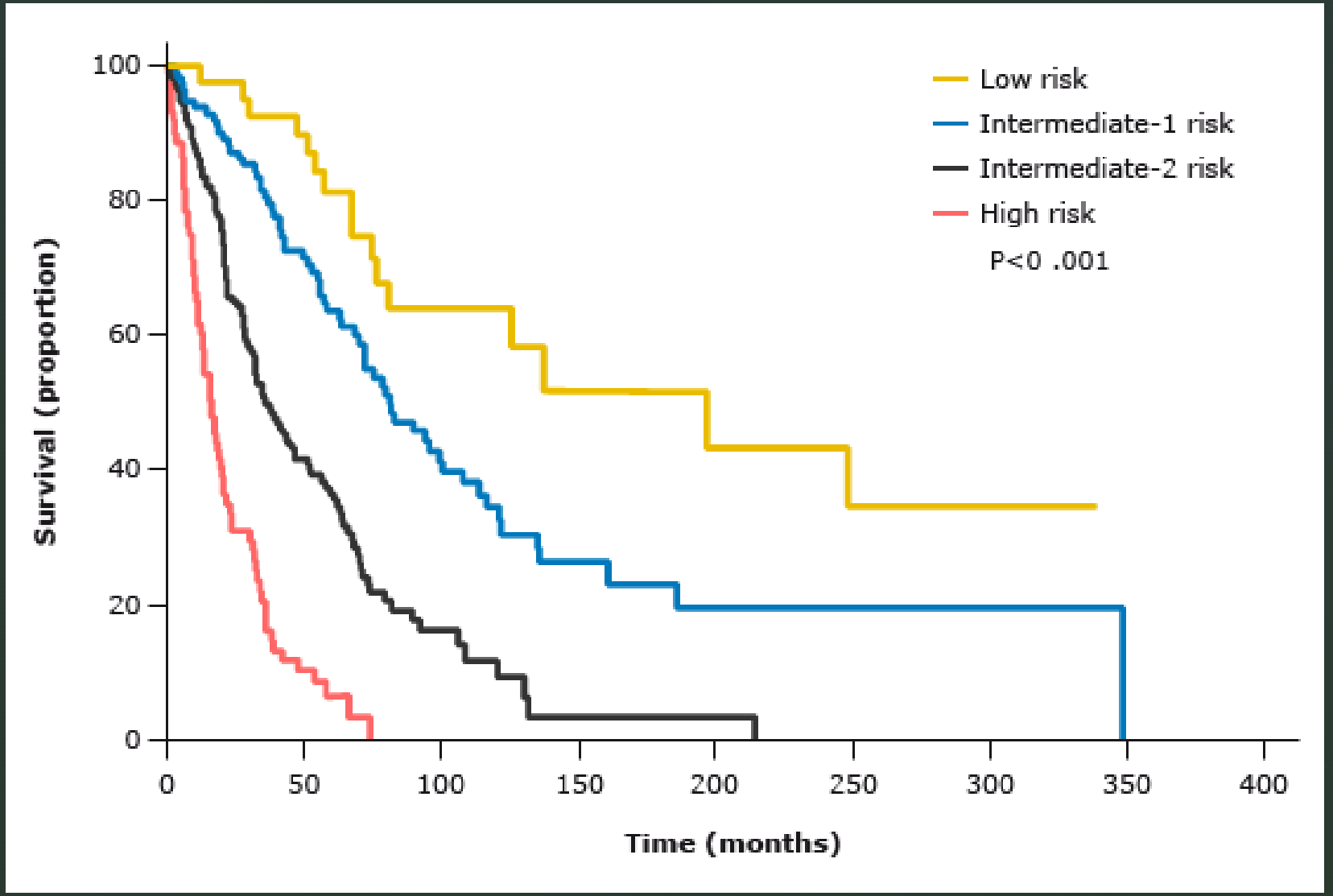
Prognostic Variable	Points
DIPSS low-risk	0
DIPSS intermediate-risk 1 (INT-1)	1
DIPSS intermediate-risk 2 (INT-2)	2
DIPSS high-risk	3
Platelets <100 x 10^9/L	1
Transfusion need	1
Unfavorable karyotype*	1

*Unfavorable karyotype: complex karyotype or sole or two abnormalities that include trisomy 8, 7/7q-, i(17q), 5/5q-, 12p-, inv(3), or 11q23 rearrangement.

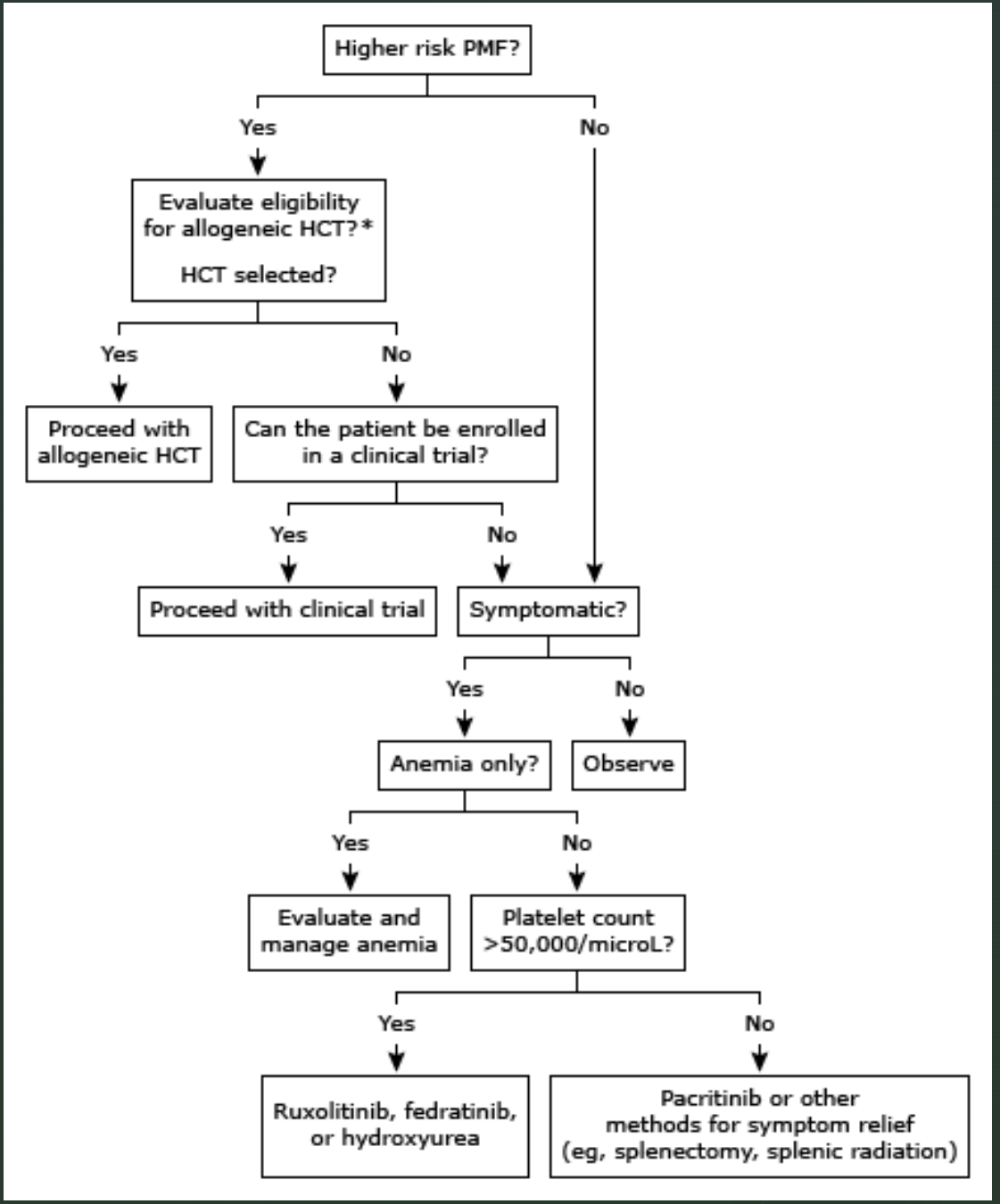
Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

Online calculator for DIPSS-PLUS score can be found at https://qxmd.com/calculate/calculator_315/dipss-plus-score-for-prognosis-in-myelofibrosis

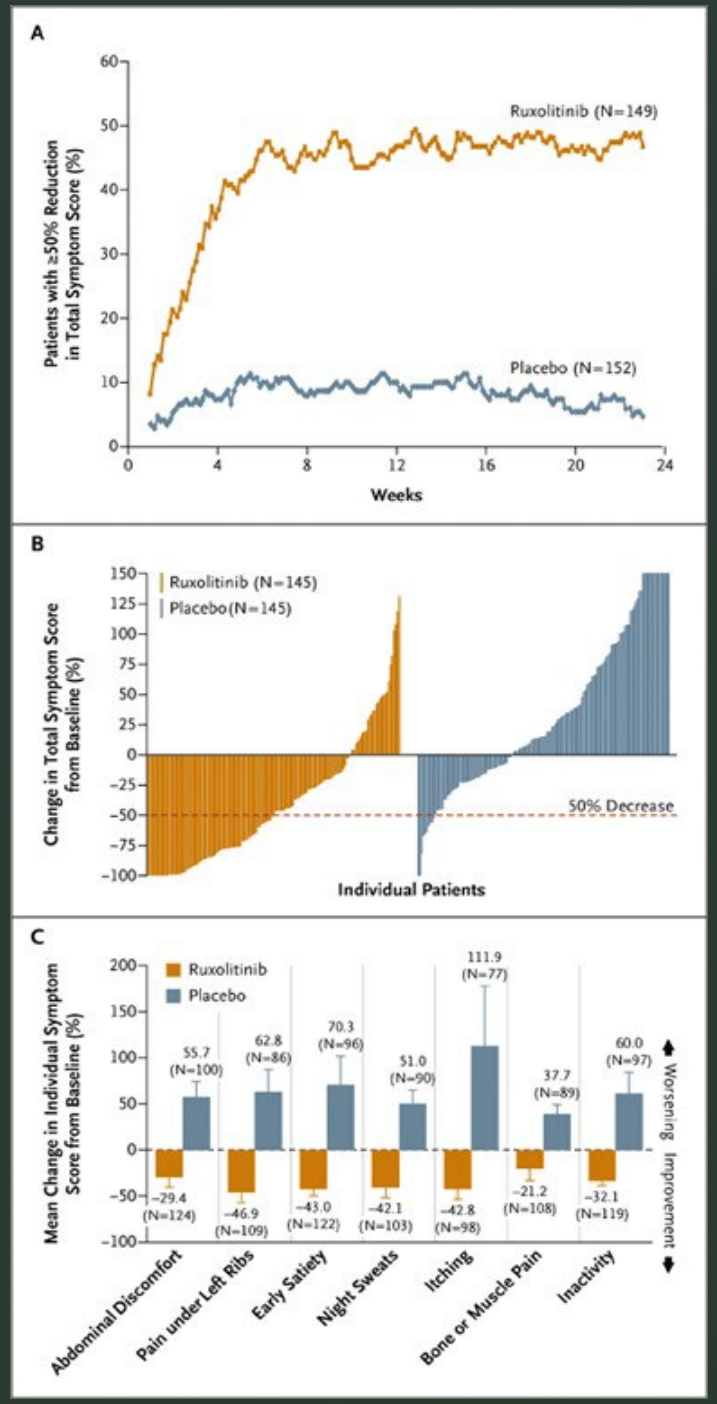
Prognosis

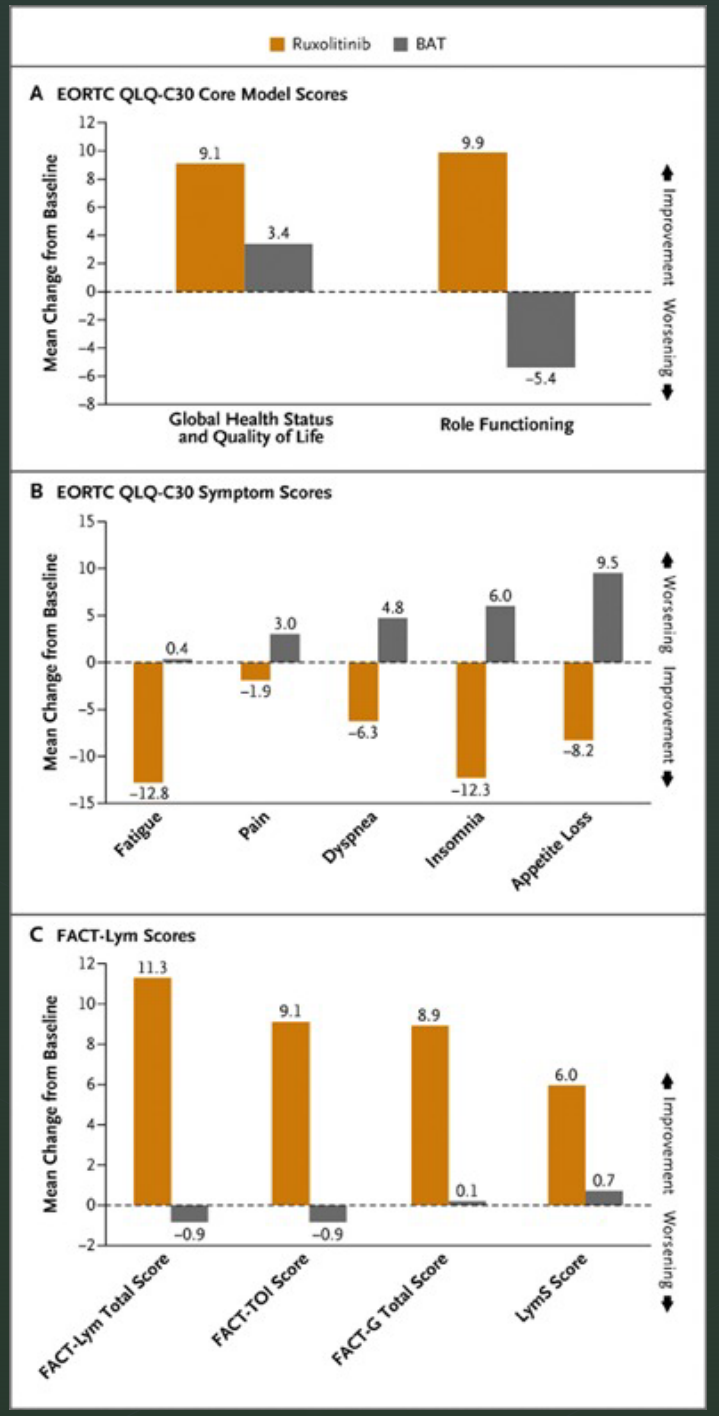

Low risk
Intermediate-1 risk
Intermediate-2 risk
High risk
P<0 .001
Survival (proportion)
100
80
60
40
20
0
0
50
100
150
200
250
300
350
400
Time (months)

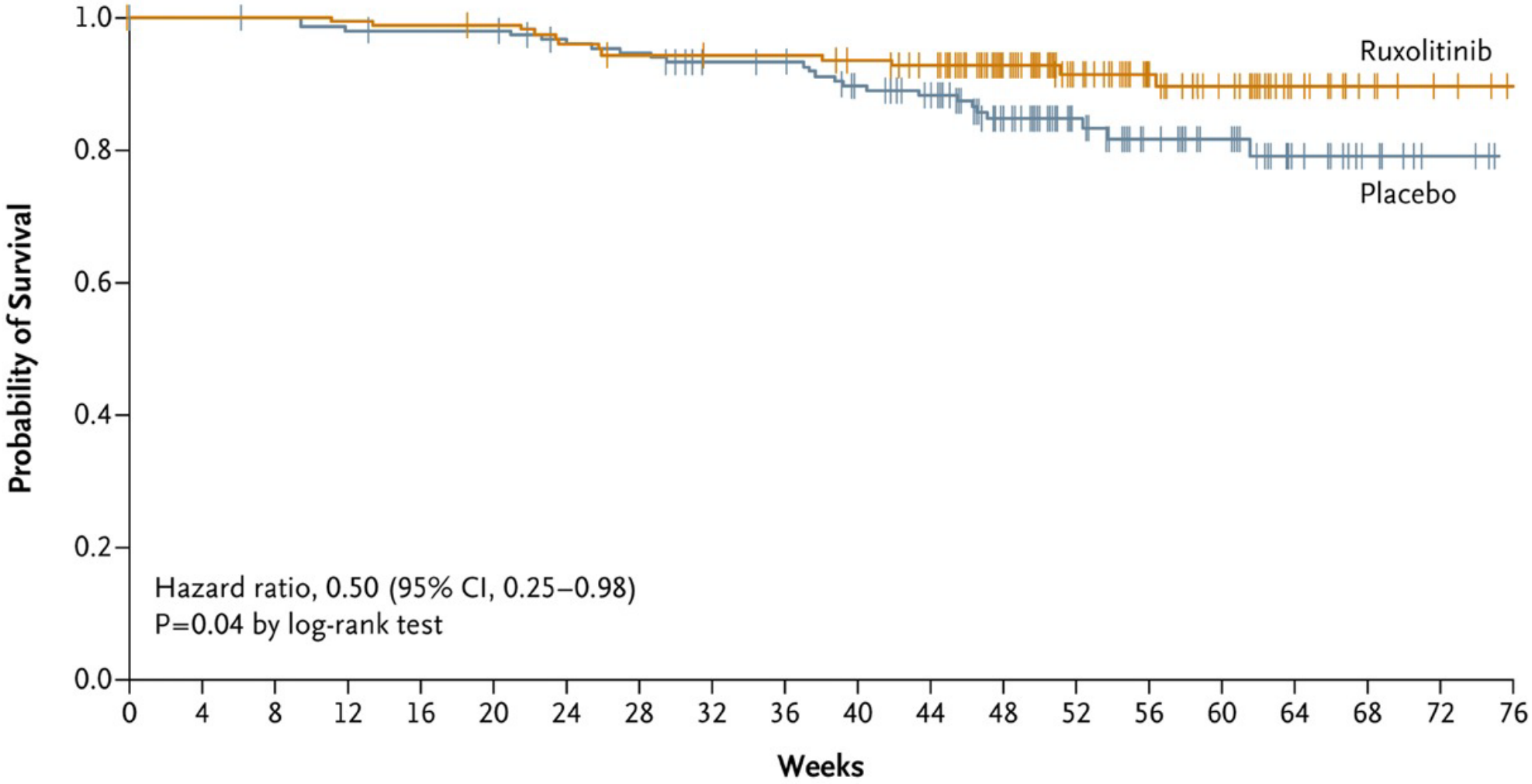
Treatment


Higher risk PMF?
Yes
No
Evaluate eligibility for allogeneic HCT?*
HCT selected?
Yes
No
Proceed with allogeneic HCT
Can the patient be enrolled in a clinical trial?
Yes
No
Proceed with clinical trial
Symptomatic?
Yes
No
Anemia only?
Observe
Yes
No
Evaluate and manage anemia
Platelet count >50,000/microL?
Yes
No
Ruxolitinib, fedratinib, or hydroxyurea
Pacritinib or other methods for symptom relief (eg, splenectomy, splenic radiation)

Ruxolitinib







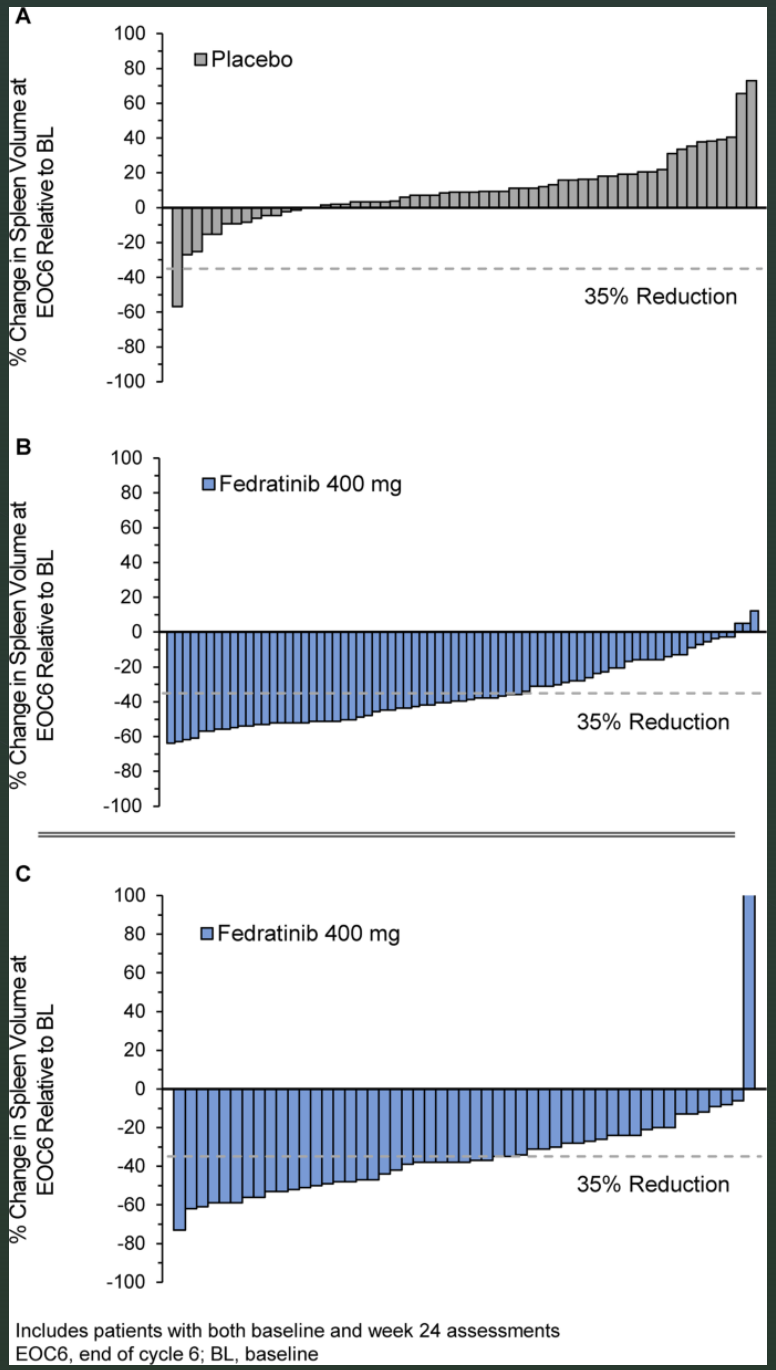
No. at Risk

Ruxolitinib	155	155	155	154	153	152	148	144	143	143	140	134	102	68	52	37	18	8	3
Placebo	154	152	151	148	147	147	142	139	132	131	123	115	83	58	45	35	20	9	3

Fedratinib in myelofibrosis

	JAKARTA1 (frontline)[23]	JAKARTA2 (second line)[24]
Design	Phase 3/randomized PB controlled	Single arm
Dosing/arms	Placebo FEDR 400 mg FEDR 500 mg	FEDR 400 mg
Inclusion	Disease: primary, post-ET/PV MF Risk: DIPSS INT-2, high risk Prior RX: JAK-inhibitor naive	Disease: primary, post-ET/PV MF Risk: DIPSS INT-1 (symptomatic), INT-2, high risk Prior RX: ruxolitinib intolerant/refractory
Primary end point	>35% SVR	>35% SVR
Key secondary end point	≥50% reduction in MFSAF-TSS	≥50% reduction in MFSAF-TSS
Enrollment	N = 289	N = 97
Initial published response rates		
Spleen volume response (>35% volume reduction)	FEDR 400 mg (36%) FEDR 500 mg (40%) Placebo (1%)	FEDR 400 mg (55% of 83 evaluable)
MFSAF-TSS (>50% reduction)	FEDR 400 mg (36%) FEDR 500 mg (34%) Placebo (7%)	FEDR 400 mg (26% of 90 evaluable)
Toxicity	Grade 1-2 GI toxicities Grade 3-4 cytopenias Suspected WE (more so in 500-mg arm) led to trial hold	Consistent with JAKARTA study toxicity ▪ Low-grade GI TOX ▪ Grade 3-4 anemia/thrombocytopenia

Fedratinib in myelofibrosis



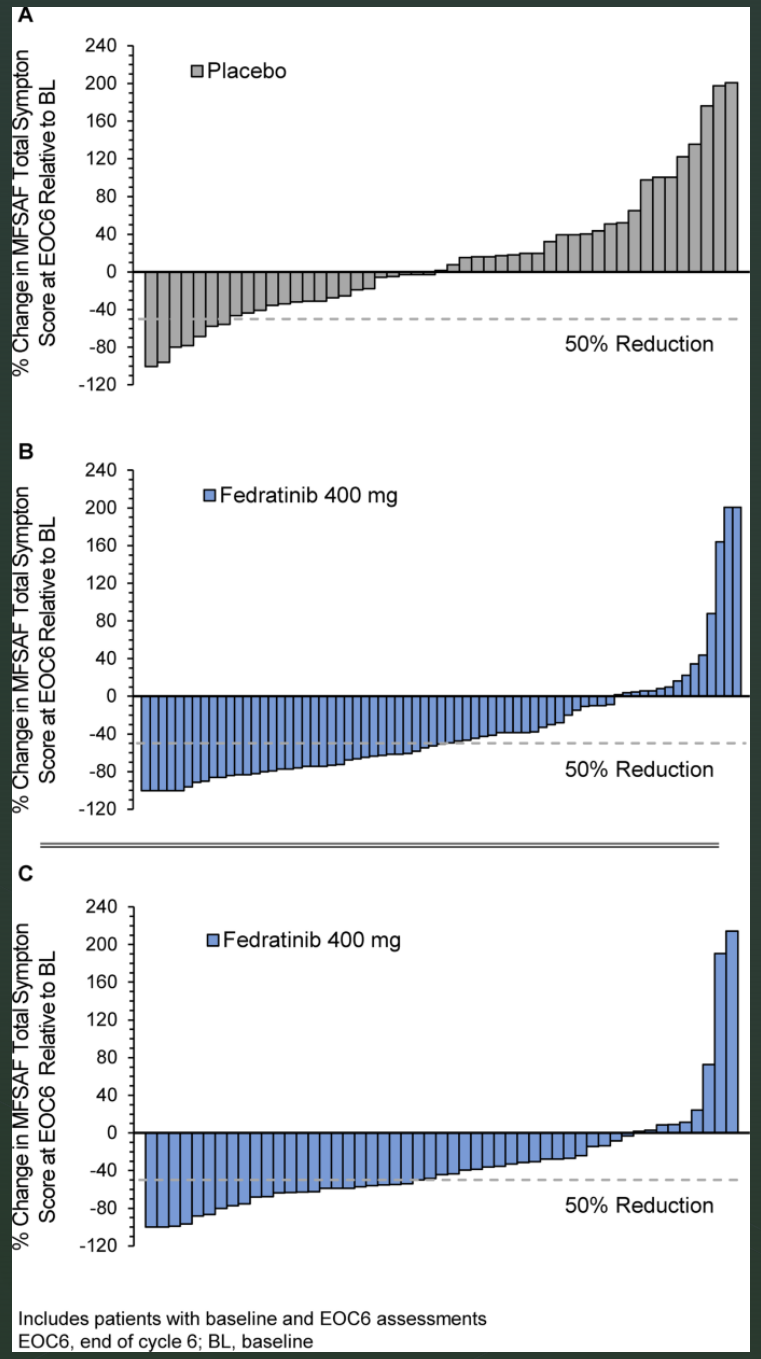
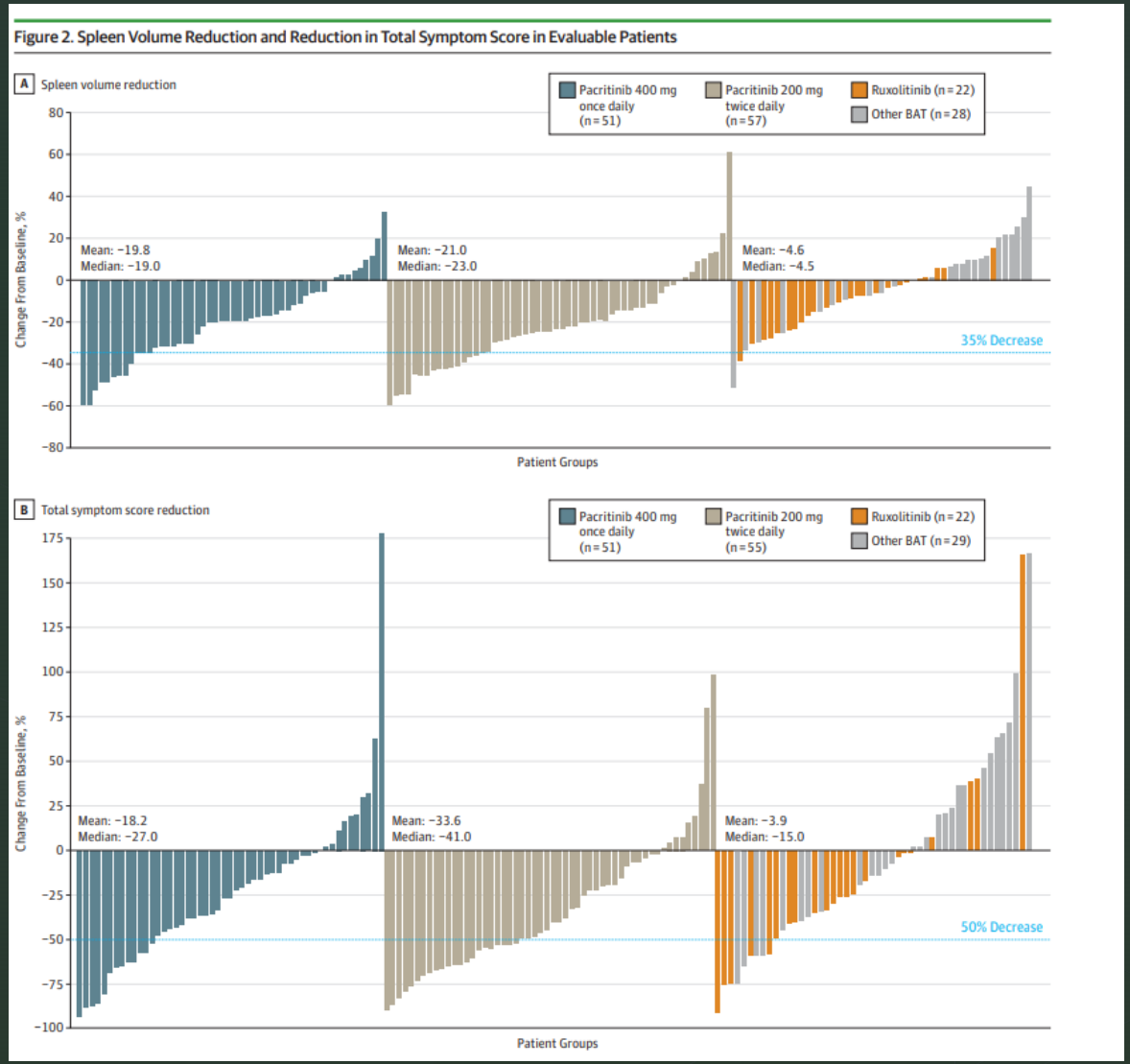


Table 2. Adverse Events Observed in at Least 10% of Patients in Any Treatment Group

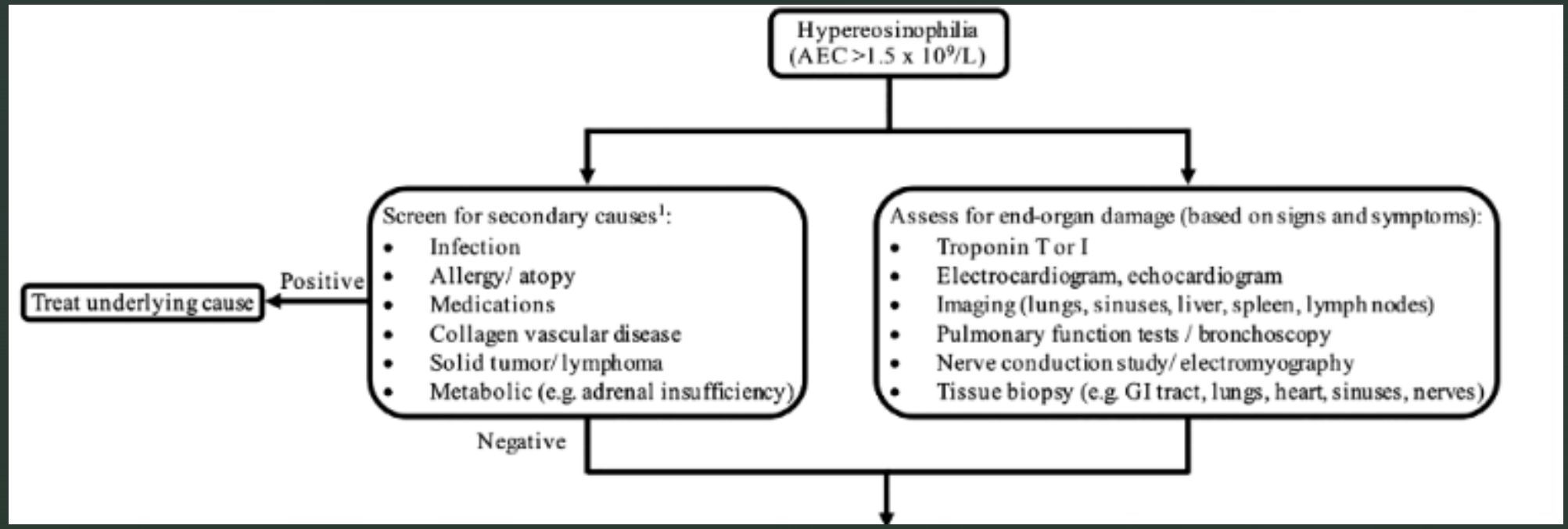
	Fedratinib 400 mg (n = 96)		Fedratinib 500 mg (n = 97)		Placebo (n = 95)	
Adverse Events, No. (%)	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Any TEAE	96 (100)	52 (54)	95 (98)	68 (70)	89 (94)	30 (32)
TEAE leading to treatment discontinuation to week 24	13 (14)	12 (13)	24 (25)	15 (16)	8 (8)	4 (4)
Serious TEAE	26 (27)	17 (18)	30 (31)	23 (24)	22 (23)	14 (15)
Nonhematologic[a]						
Diarrhea	63 (66)	5 (5)	54 (56)	5 (5)	15 (16)	0
Vomiting	40 (42)	3 (3)	53 (55)	9 (9)	5 (5)	0
Nausea	61 (64)	0	49 (51)	6 (6)	14 (15)	0
Constipation	10 (10)	2 (2)	17 (18)	0	7 (7)	0
Asthenia	9 (9)	2 (2)	15 (16)	4 (4)	6 (6)	1 (1)
Abdominal pain	14 (15)	0	12 (12)	1 (1)	15 (16)	1 (1)
Fatigue	15 (16)	6 (6)	10 (10)	5 (5)	9 (10)	0
Dyspnea	8 (8)	0	10 (10)	1 (1)	6 (6)	2 (2)
Weight decrease	4 (4)	0	10 (10)	0	5 (5)	0
Hematologic[a]						
Anemia	95 (99)	41 (43)	94 (98)	58 (60)	86 (91)	24 (25)
Thrombocytopenia	60 (63)	16 (17)	55 (57)	26 (27)	48 (51)	9 (9)
Lymphopenia	54 (57)	20 (21)	63 (66)	26 (27)	50 (54)	19 (21)
Leukopenia	45 (47)	6 (6)	51 (53)	15 (16)	18 (19)	3 (3)
Neutropenia	27 (28)	8 (8)	42 (44)	17 (18)	14 (15)	4 (4)
Infections and infestations[b]	40 (42)	2 (2)	38 (39)	12 (12)	26 (27)	4 (4)
Laboratory parameter elevation						
Alanine transaminase	51 (53)	3 (3)	44 (46)	3 (3)	16 (17)	0
Aspartate transaminase	58 (60)	2 (2)	46 (48)	2 (2)	27 (29)	1 (1)
Hyperbilirubinemia	30 (31)	2 (2)	27 (28)	1 (1)	38 (40)	2 (2)
Creatinine	52 (54)	3 (3)	60 (63)	0	28 (30)	1 (1)
Amylase	25 (26)	2 (2)	22 (23)	3 (3)	7 (7)	0
Lipase	43 (45)	12 (13)	34 (36)	9 (9)	6 (6)	2 (2)

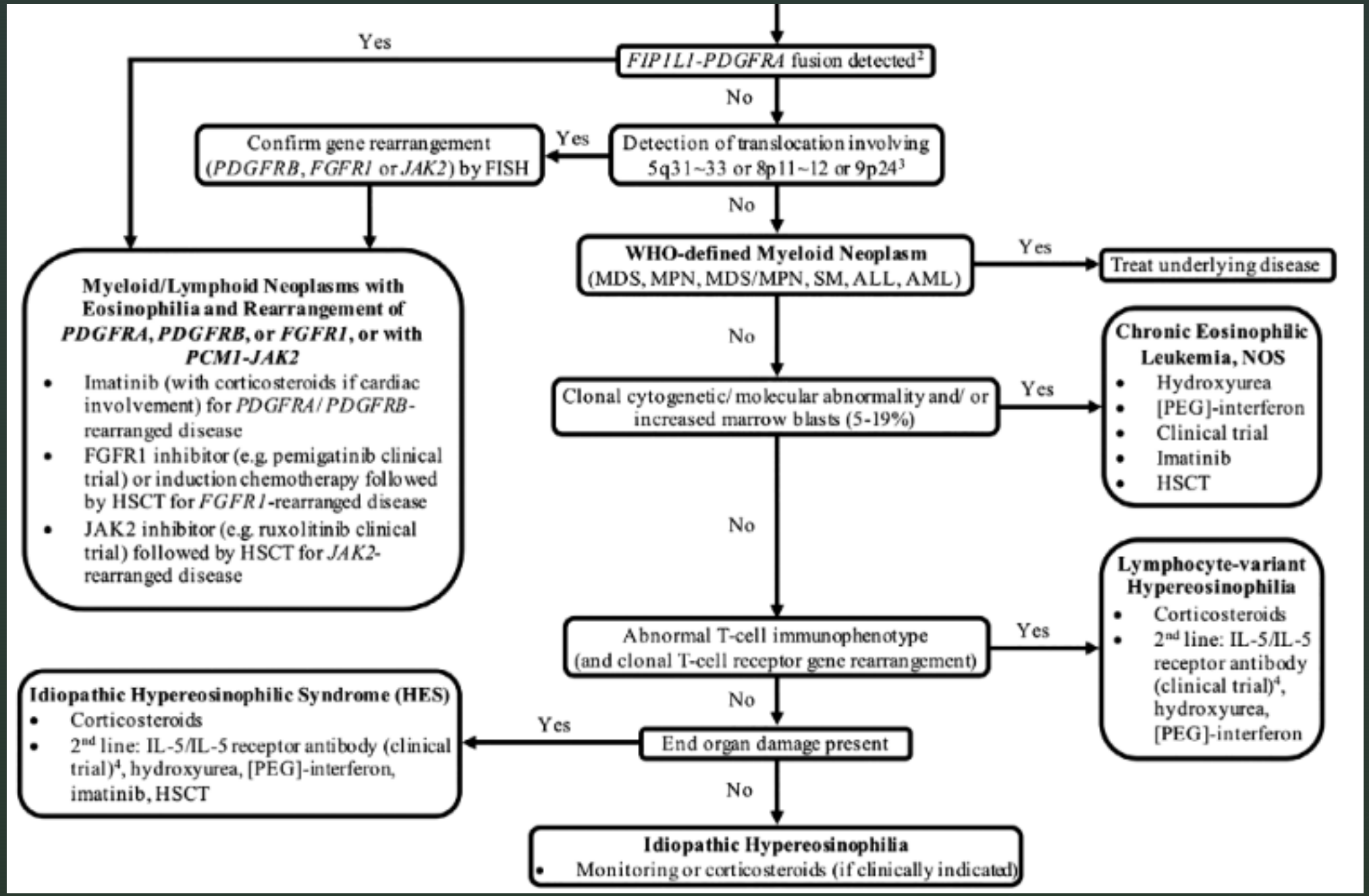
Pacritinib

- Indicated for the treatment of adults with intermediate or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis with a platelet count below 50 × 109 /L (1).

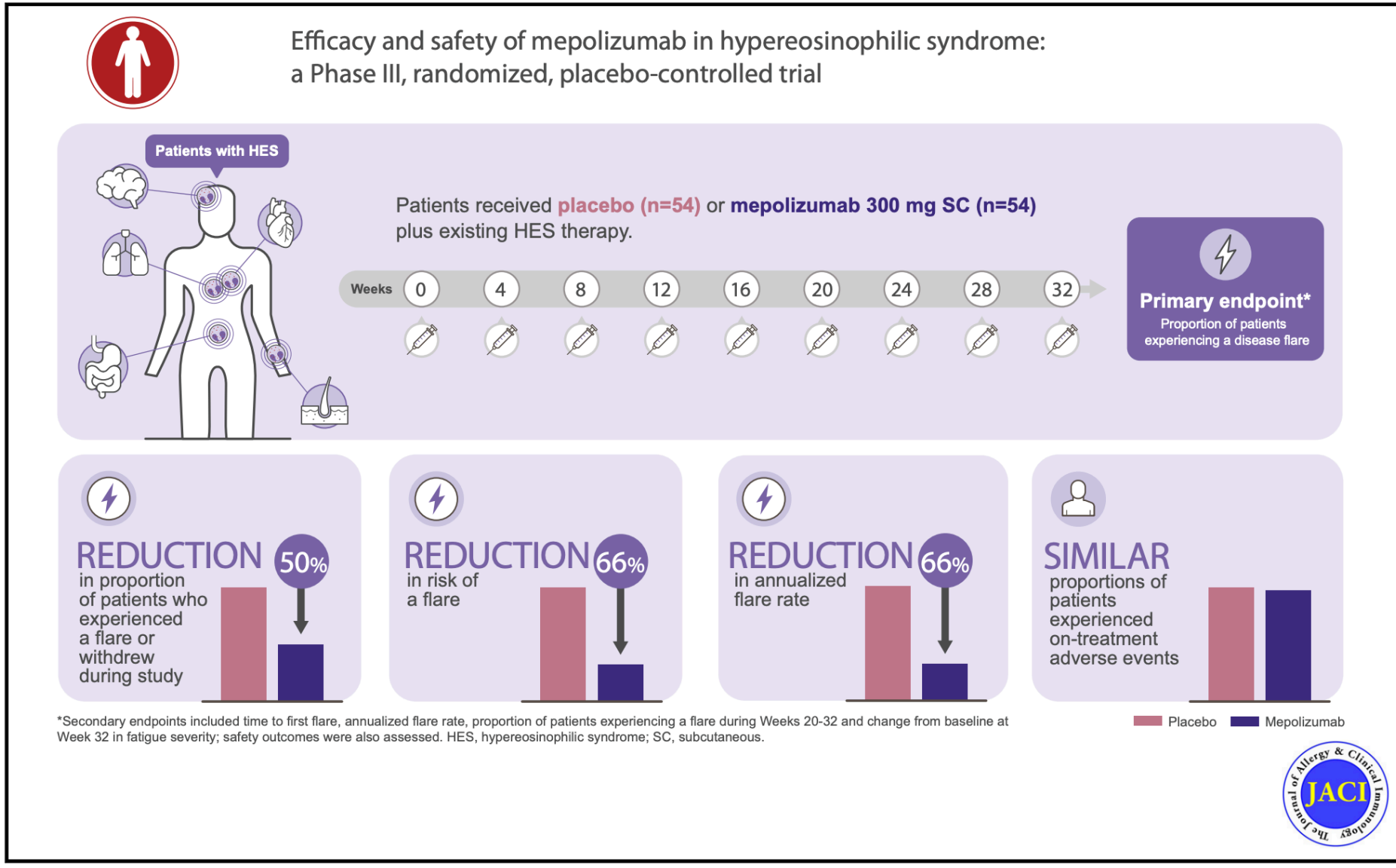


Hypereosinophilic syndrome

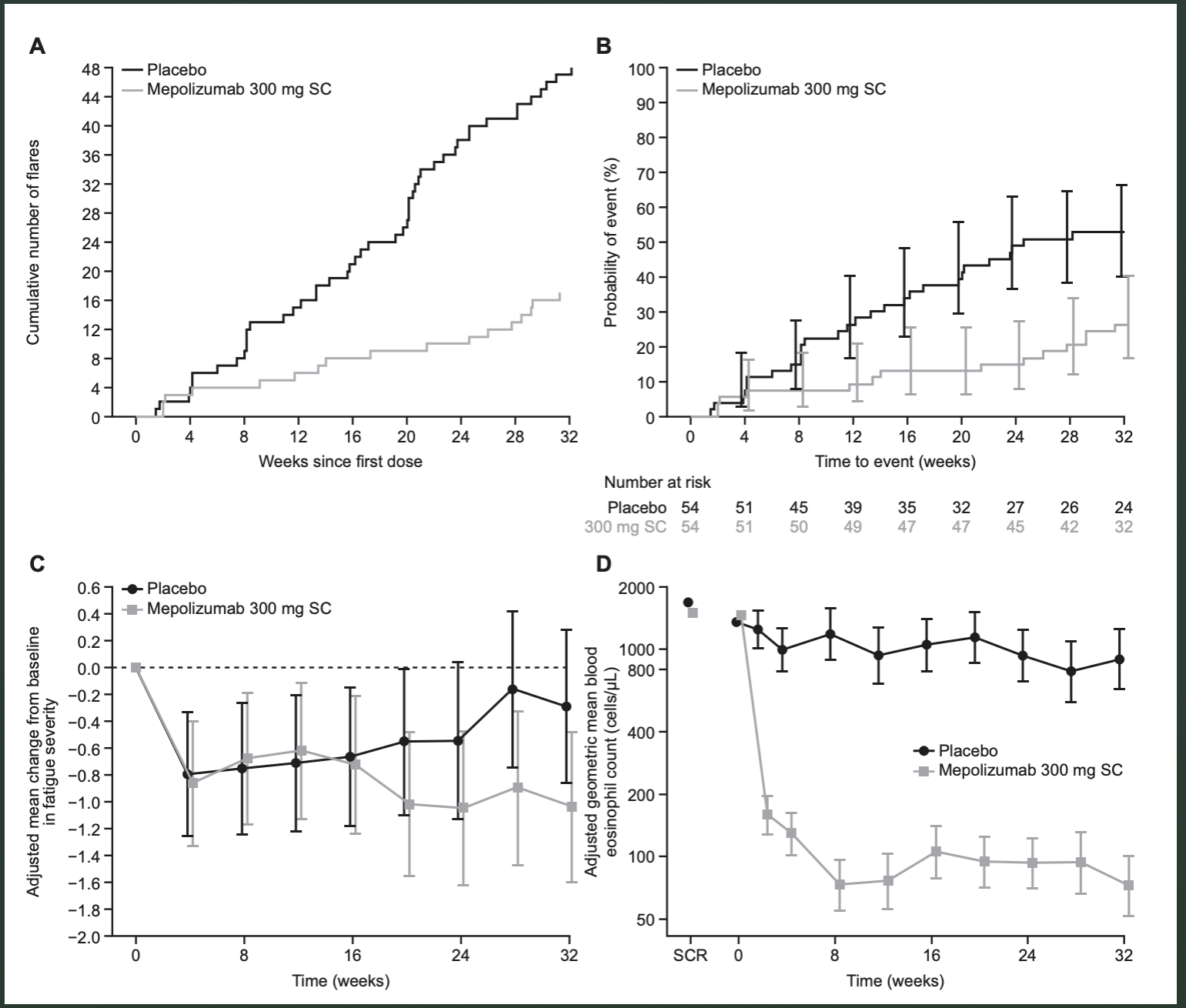



FIP1L1-PDGFRA fusion detected[2]
Yes
No
Detection of translocation involving 5q31~33 or 8p11~12 or 9p24[3]
Yes
Confirm gene rearrangement (*PDGFRB*, *FGFR1* or *JAK2*) by FISH
No
WHO-defined Myeloid Neoplasm (MDS, MPN, MDS/MPN, SM, ALL, AML)
Yes
Treat underlying disease
No
Clonal cytogenetic/ molecular abnormality and/ or increased marrow blasts (5-19%)
Yes
Chronic Eosinophilic Leukemia, NOS
• Hydroxyurea
• [PEG]-interferon
• Clinical trial
• Imatinib
• HSCT
No
Abnormal T-cell immunophenotype (and clonal T-cell receptor gene rearrangement)
Yes
Lymphocyte-variant Hypereosinophilia
• Corticosteroids
• 2nd line: IL-5/IL-5 receptor antibody (clinical trial)[4], hydroxyurea, [PEG]-interferon
No
End organ damage present
Yes
Idiopathic Hypereosinophilic Syndrome (HES)
• Corticosteroids
• 2nd line: IL-5/IL-5 receptor antibody (clinical trial)[4], hydroxyurea, [PEG]-interferon, imatinib, HSCT
No
Idiopathic Hypereosinophilia
• Monitoring or corticosteroids (if clinically indicated)
Myeloid/Lymphoid Neoplasms with Eosinophilia and Rearrangement of *PDGFRA*, *PDGFRB*, or *FGFR1*, or with *PCM1-JAK2*
• Imatinib (with corticosteroids if cardiac involvement) for *PDGFRA*/ *PDGFRB*-rearranged disease
• FGFR1 inhibitor (e.g. pemigatinib clinical trial) or induction chemotherapy followed by HSCT for *FGFR1*-rearranged disease
• JAK2 inhibitor (e.g. ruxolitinib clinical trial) followed by HSCT for *JAK2*-rearranged disease

GRAPHICAL ABSTRACT



*Secondary endpoints included time to first flare, annualized flare rate, proportion of patients experiencing a flare during Weeks 20-32 and change from baseline at Week 32 in fatigue severity; safety outcomes were also assessed. HES, hypereosinophilic syndrome; SC, subcutaneous.


A
Placebo
Mepolizumab 300 mg SC
Cumulative number of flares
Weeks since first dose
B
Placebo
Mepolizumab 300 mg SC
Probability of event (%)
Time to event (weeks)
Number at risk
Placebo 54 51 45 39 35 32 27 26 24
300 mg SC 54 51 50 49 47 47 45 42 32
C
Placebo
Mepolizumab 300 mg SC
Adjusted mean change from baseline in fatigue severity
Time (weeks)
D
Placebo
Mepolizumab 300 mg SC
Adjusted geometric mean blood eosinophil count (cells/µL)
SCR
Time (weeks)

Questions: