Myeloproliferative Disorders Update

January 26th 2024, 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

Table 3. Criteria for polycythemia vera (PV)

Diagnosis requires the presence of both major criteria and one minor criterion or the presence of the first major criterion together with two minor criteria:

Major criteria

1. Hemoglobin > 18.5 g/dL in men, 16.5 g/dL in women or other evidence of increased red cell volume*
2. Presence of *JAK2* V617F or other functionally similar mutation such as *JAK2* exon 12 mutation

Minor criteria

1. Bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. Serum erythropoietin level below the reference range for normal
3. Endogenous erythroid colony formation in vitro

*Hemoglobin or hematocrit > 99th percentile of method-specific reference range for age, sex, altitude of residence

or hemoglobin > 17 g/dL in men, 15 g/dL in women if associated with a documented and sustained increase of at least 2 g/dL from a person's baseline value that cannot be attributed to correction of iron deficiency

or elevated red cell mass > 25% above mean normal predicted value.

ET Diagnosis

Table 1. WHO Diagnostic Criteria for Essential Thrombocythemia and Prefibrotic or Early-Stage Myelofibrosis.*

Essential Thrombocythemia	Prefibrotic or Early-Stage Myelofibrosis
Diagnosis requires all major criteria or the first three major criteria plus a minor criterion.	Diagnosis requires all major criteria and at least one minor criterion.
Major criteria	
Platelet count ≥450,000 per cubic millimeter Bone marrow biopsy showing proliferation mainly of the megakaryocytic lineage, with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no substantial increase or left shift in neutrophil granulopoiesis or erythropoiesis; in rare instances, minor (grade 1) increase in reticulin fibers Criteria for *BCR-ABL1*–positive chronic myeloid leukemia, polycythemia vera, primary myelofibrosis, or other myeloid neoplasm not met *JAK2* V617F, *CALR*, or *MPL* mutation	Megakaryocytic proliferation and atypia, without reticulin fibrosis >grade 1, accompanied by increased, age-adjusted bone marrow cellularity, granulocytic proliferation, and in many cases decreased erythropoiesis Criteria for *BCR-ABL1*-positive chronic myeloid leukemia, polycythemia vera, essential thrombocythemia, myelodysplastic syndrome, or other myeloid neoplasm not met *JAK2* V617F, *CALR*, or *MPL* mutation or presence of another clonal marker or of minor reactive reticulin fibrosis in bone marrow†
Minor criteria	
Presence of clonal marker or of evidence of reactive thrombocytosis	Anemia not attributed to a coexisting condition Leukocytosis (≥11,000 cells per cubic millimeter) Palpable splenomegaly Lactate dehydrogenase level above upper limit of normal of institutional reference range

* Data are from Arber et al.[7]

† In the absence of any of the three major clonal mutations, a search for other mutations associated with myeloid neoplasms (e.g., *ASXL1, EZH2, TET2, IDH1, IDH12, SRSF2,* and *SF3B1* mutations) may be helpful in determining the clonal nature of the disease. Minor (grade 1) reticulin fibrosis caused by infection is noteworthy, as are autoimmune disorders or other chronic inflammatory conditions, hairy-cell leukemia or other lymphoid neoplasms, metastatic cancer, or toxic (i.e., chronic) myelopathies.

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]**

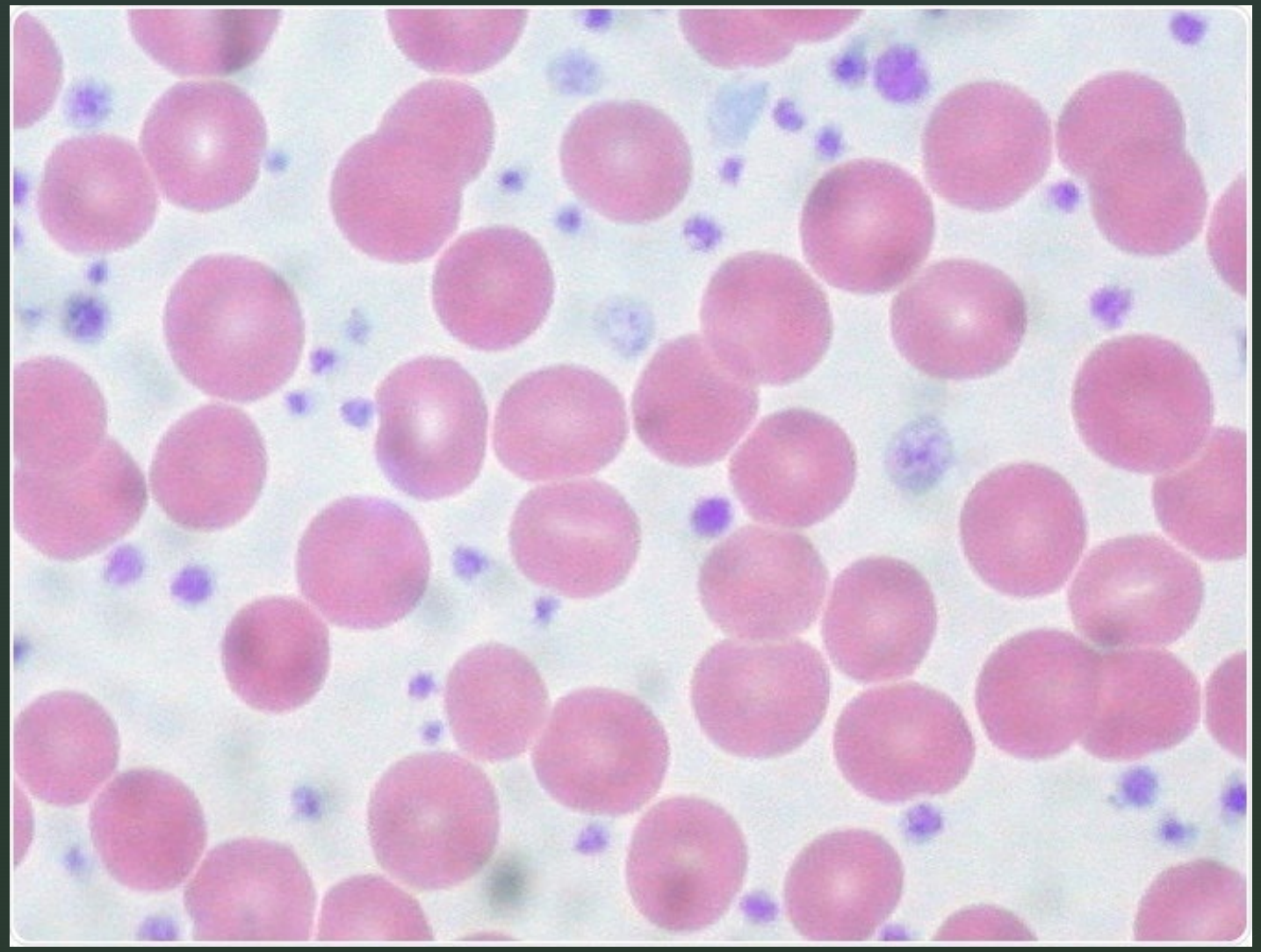
- **Minor criteria**
  - **Presence of at least one of the following, confirmed in 2 consecutive determinations:**
    - **Anemia not attributed to a comorbid condition**
    - **Leukocytosis ≥11 x 10^9/L**
    - **Palpable splenomegaly**
    - **LDH increased to above upper normal limit of institutional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



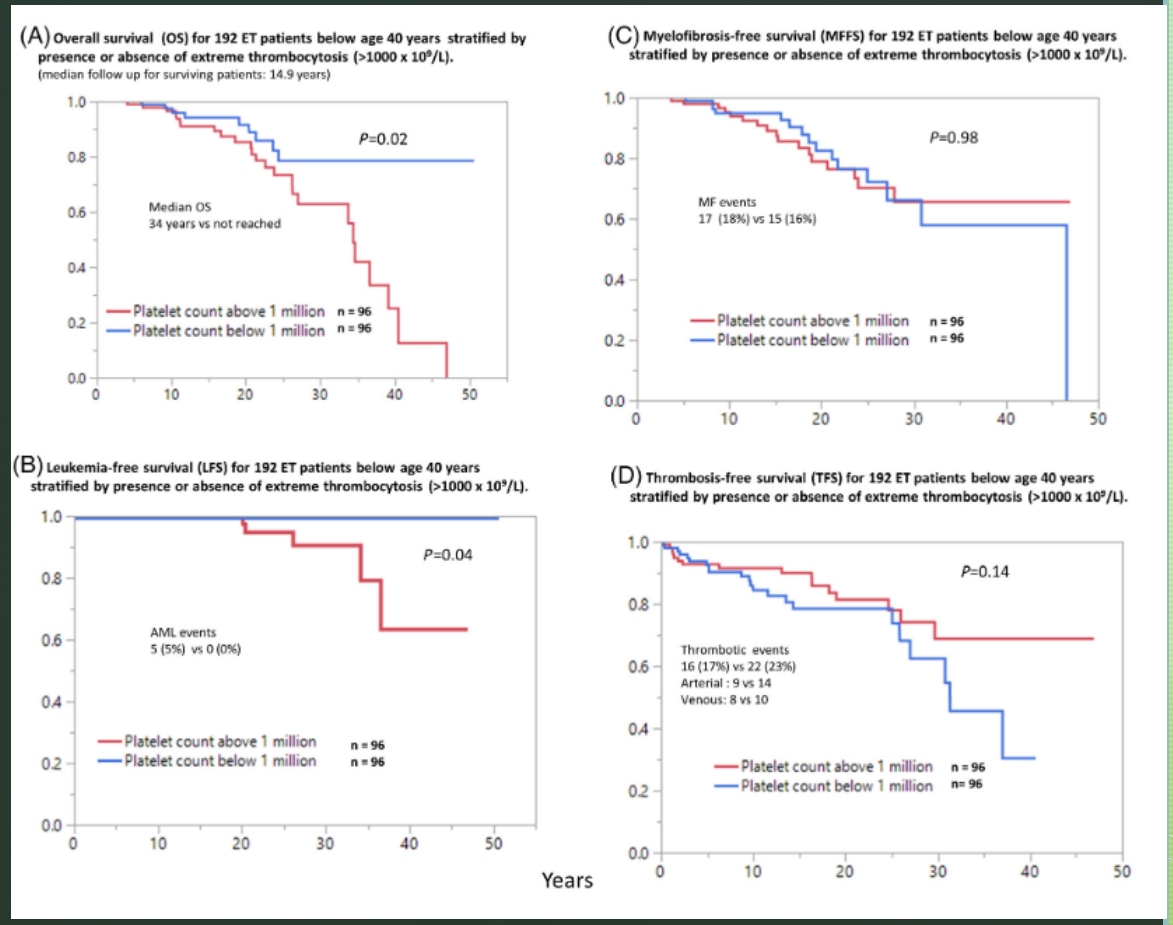
Essential Thrombocytosis

- 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]



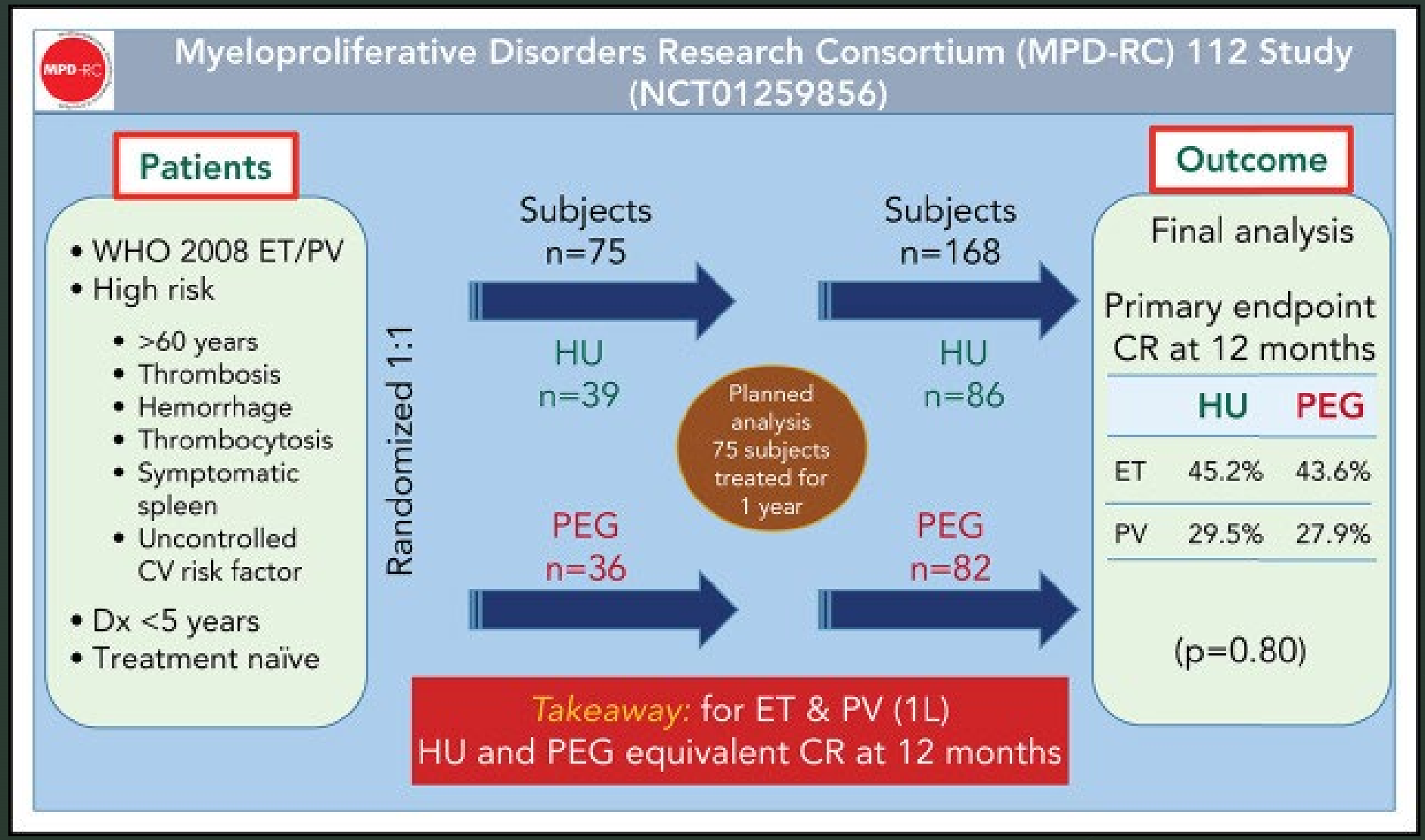
ET Treatment

- **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

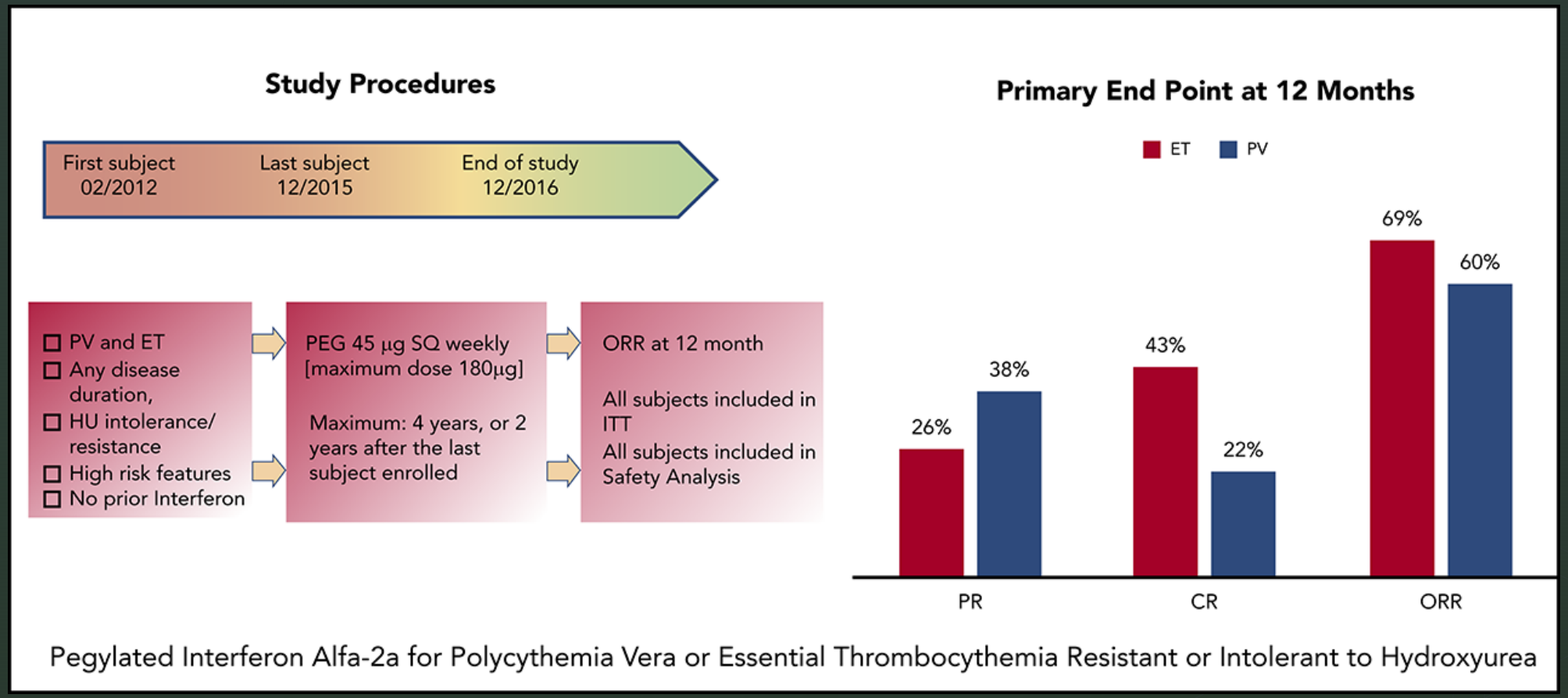
- Hydroxyurea is generally first line
- Anagrelide or Interferon can also be used
- Goal platelet count is often unclear
  - 400?
  - 450?
  - 600?

Front-line data:

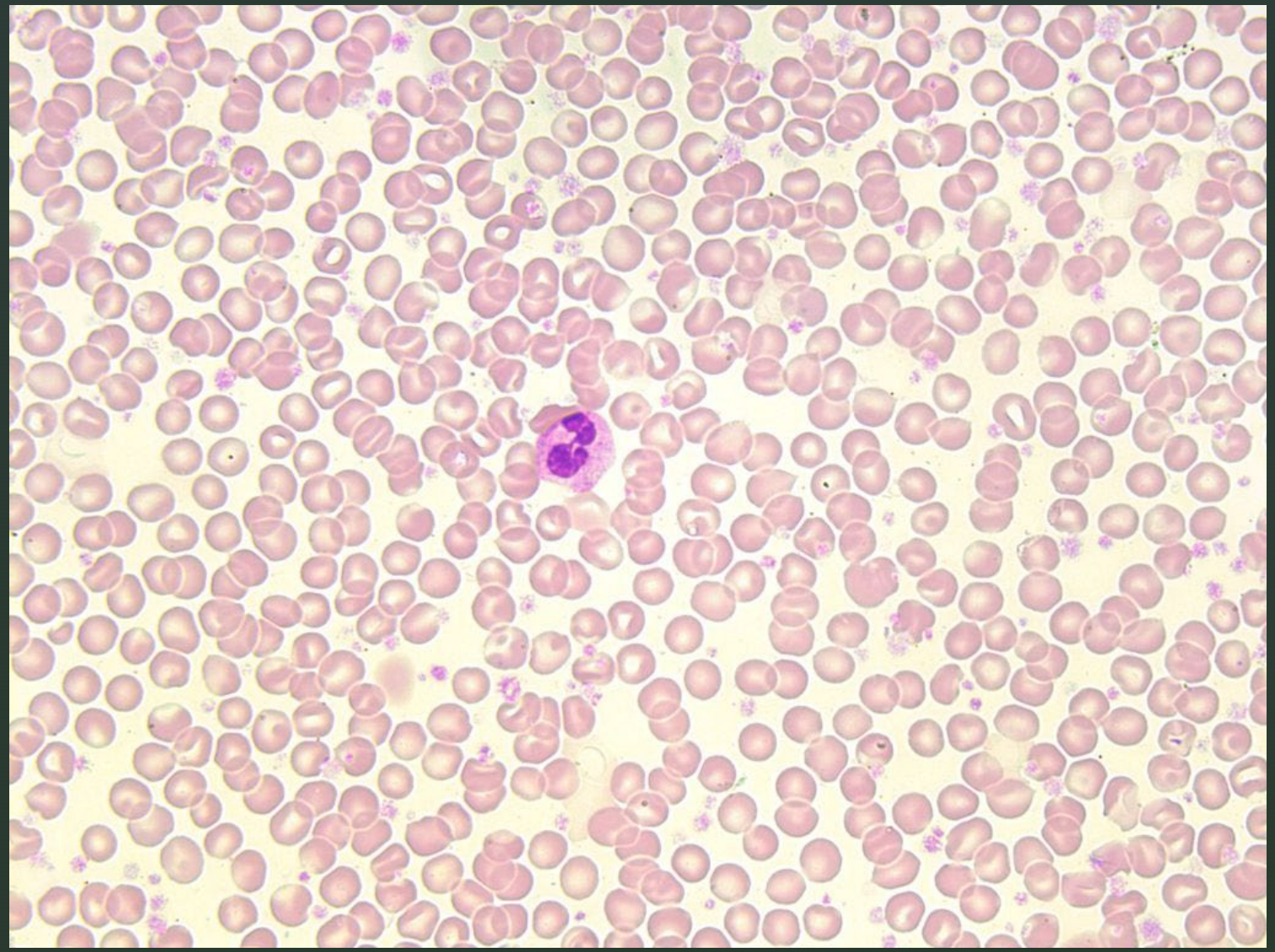


What's new in Cytoreduction

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



Polycythemia Vera



Polycythemia Vera

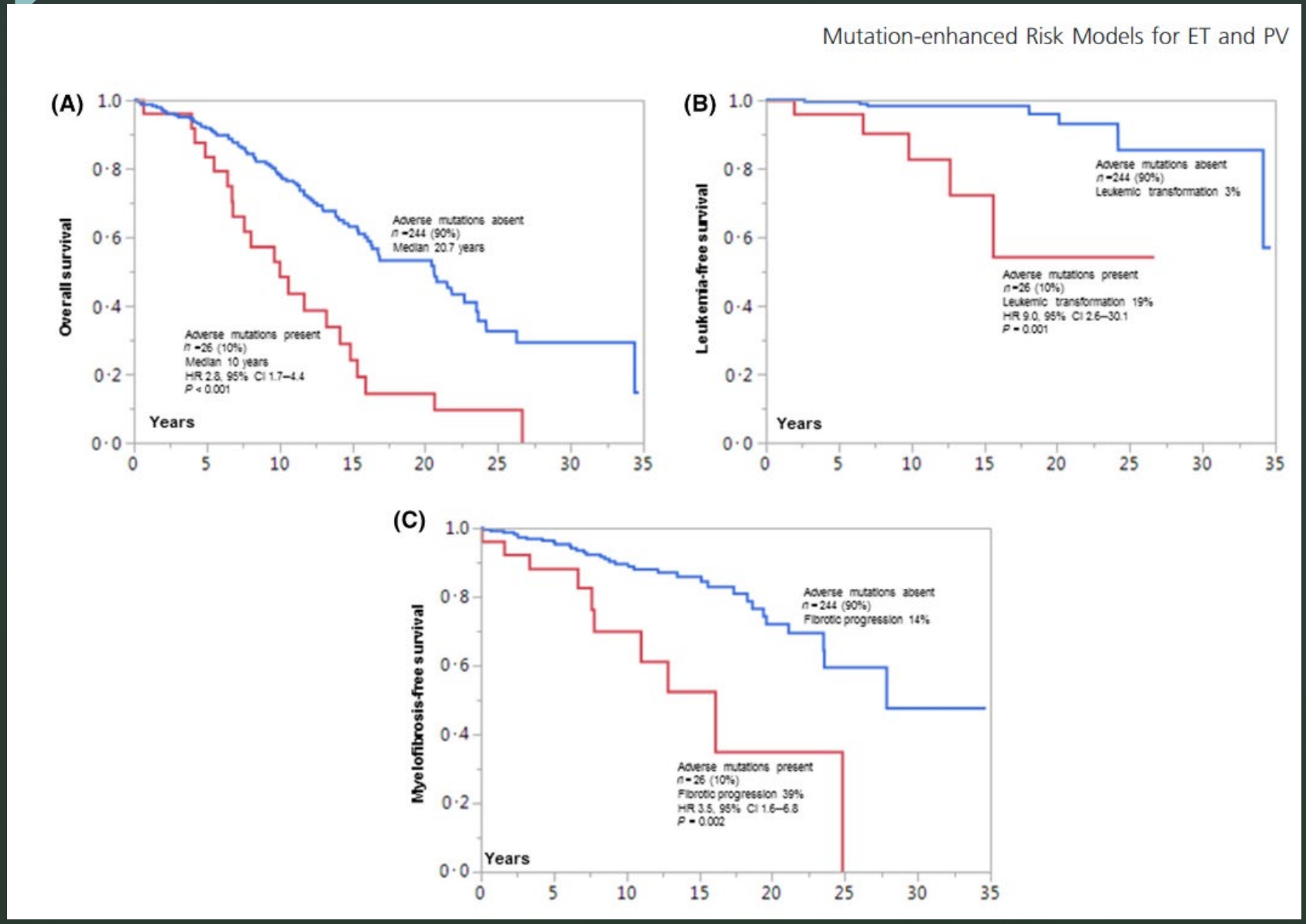
RISK STRATIFICATION FOR PATIENTS WITH PV[a]

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 or Interferon.
  - Can use both phlebotomy and cytoreduction in high risk or refractory patients
  - If unable to obtain response or intolerant to Hydrea IFN or Ruxolitinib may be used second line.

FDA Approves Besremi for Polycythemia Vera

November 13, 2021

Jamie Cesanek

Article

The Food and Drug Administration granted approval to Besremi for the treatment of adults with polycythemia vera.

The Food and Drug Administration (FDA) approved Besremi (ropeginterferon alfa-2b-njft) to treat adults with polycythemia vera, a rare type of blood cancer in which the bone marrow produces too many red blood cells due to a mutation in the stem cells.

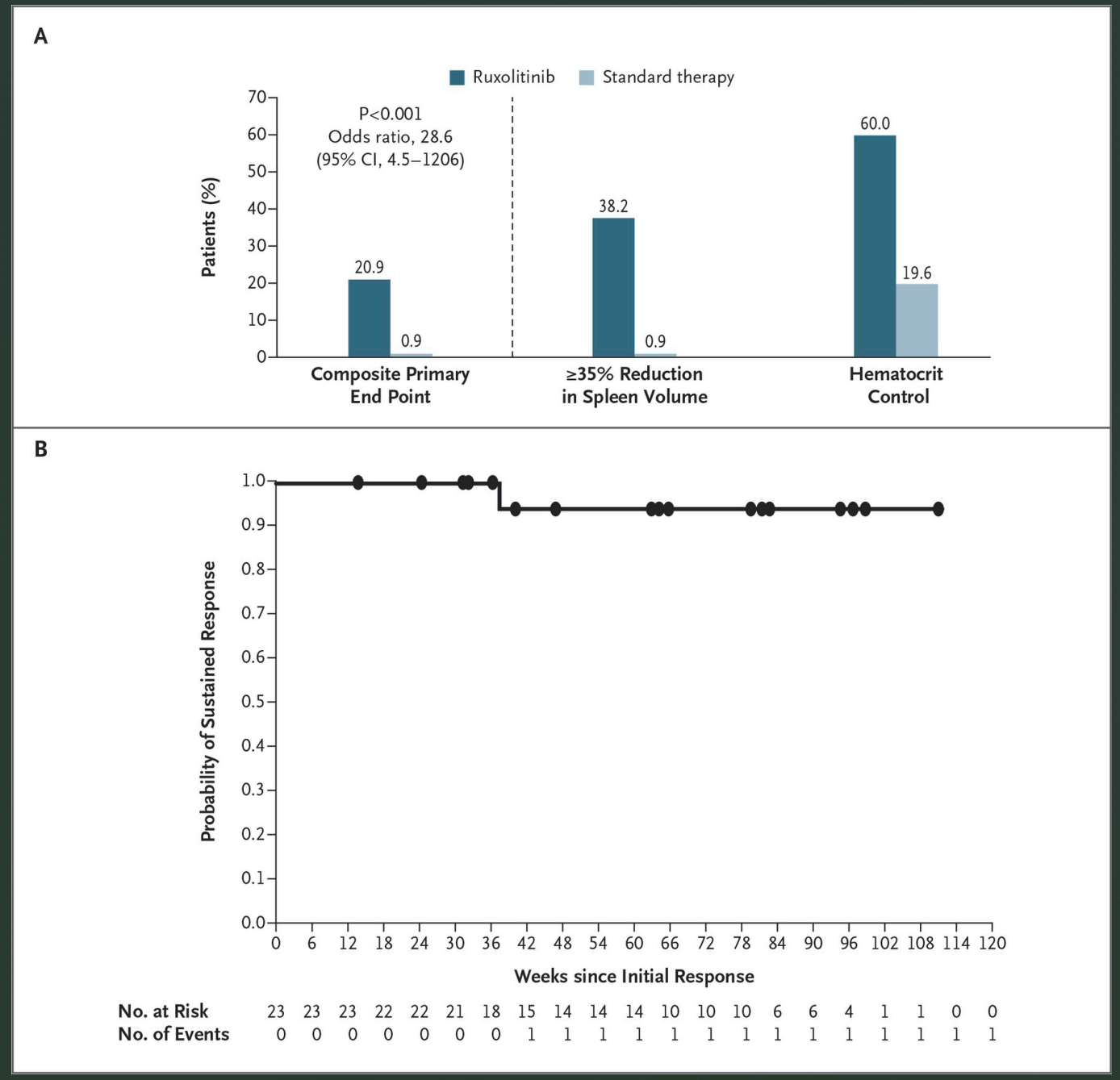
DEFINITION OF RESISTANCE/INTOLERANCE TO HYDROXYUREA[1]

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



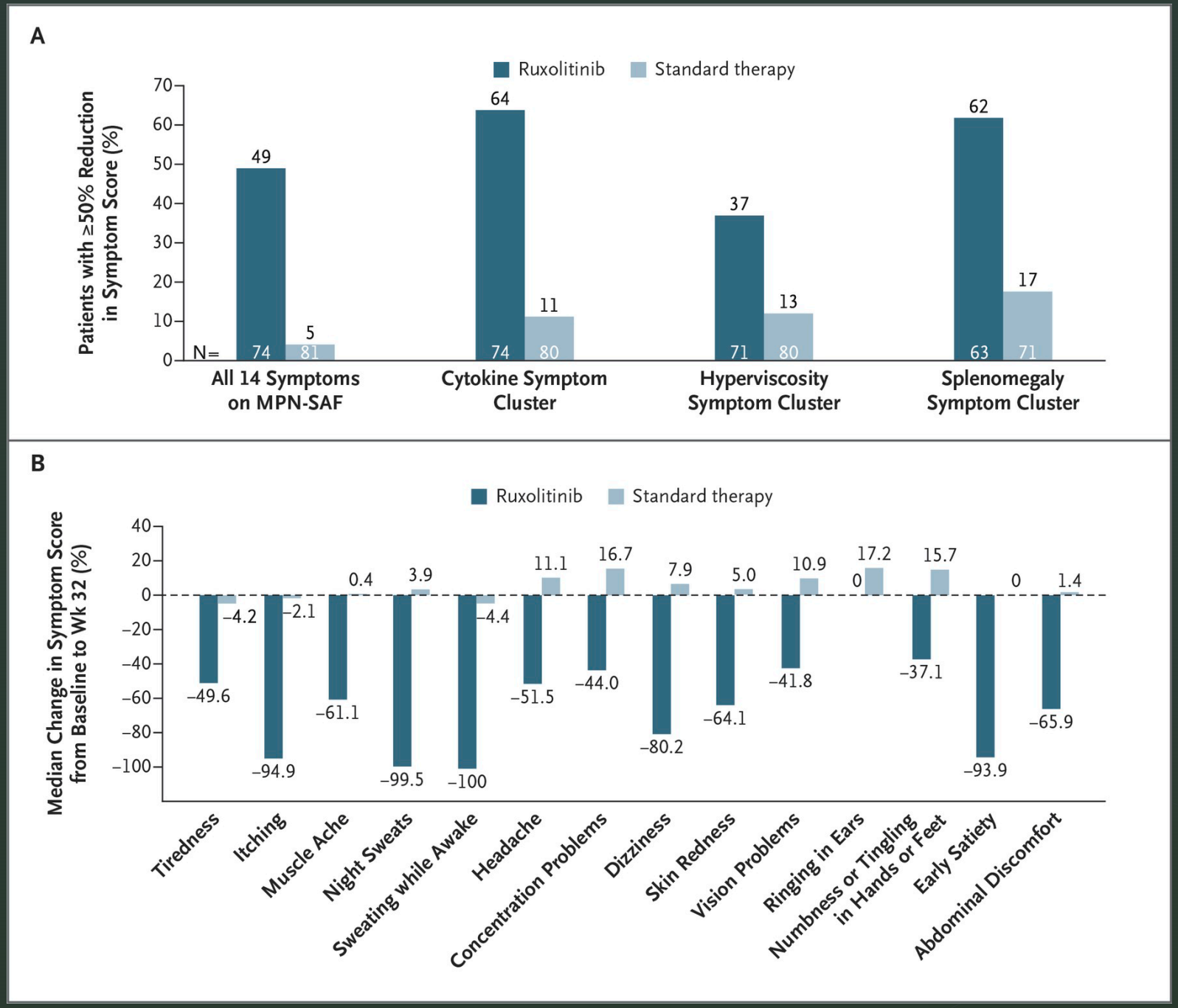

A
Ruxolitinib
Standard therapy
Patients with ≥50% Reduction in Symptom Score (%)
70
60
50
40
30
20
10
0
N=
74
81
74
80
71
80
63
71
49
5
64
11
37
13
62
17
All 14 Symptoms on MPN-SAF
Cytokine Symptom Cluster
Hyperviscosity Symptom Cluster
Splenomegaly Symptom Cluster
B
Ruxolitinib
Standard therapy
Median 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

Please refer us your PV patients for clinical trials:

Patient who meet the WHO criteria for JAK2 driven PV who have had recent phlebotomy.

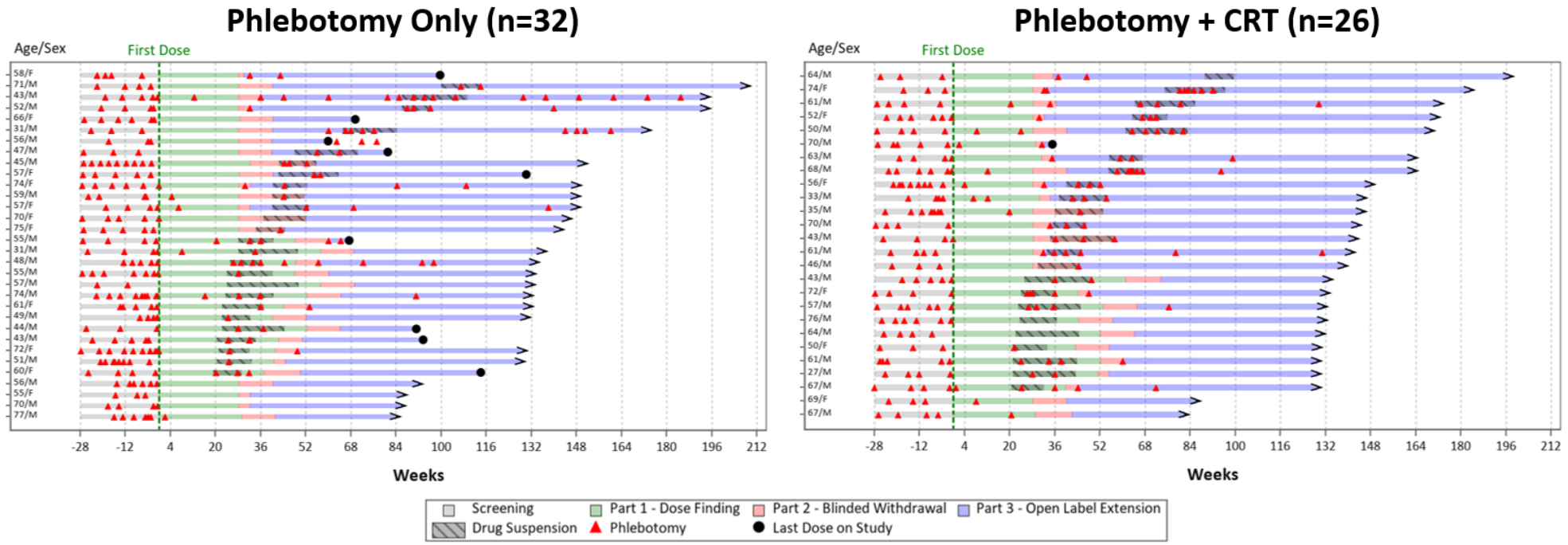
-Rustferitide

Patient with PV who are refractory to one prior therapy.

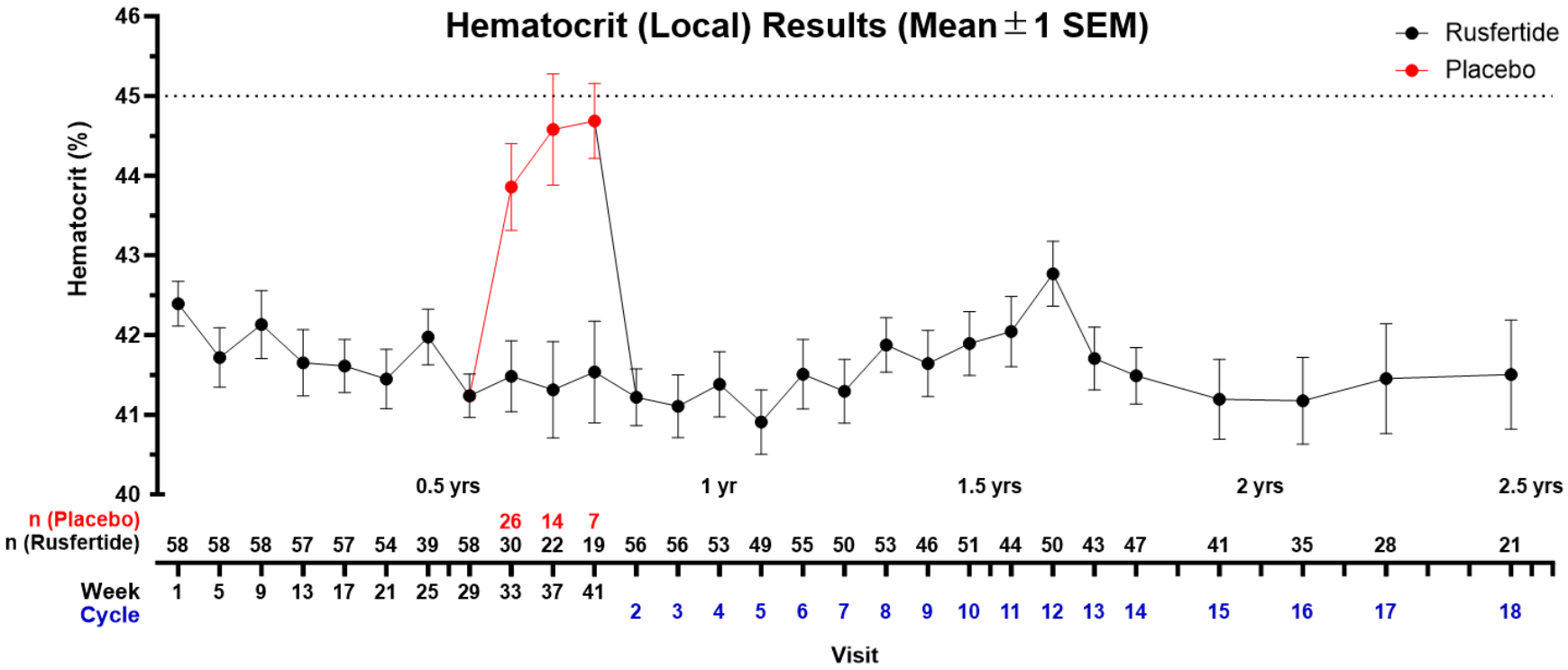
-Bromedemstat

Rusfertide Decreased the Frequency of Therapeutic Phlebotomy With or Without Concurrent Cytoreductive Therapy

- In patients who continued onto Part 3, 32 (55.2%) and 26 (44.8%) patients were treated with phlebotomy alone or phlebotomy with CRT, respectively
  - Of those patients receiving phlebotomy with CRT, 13 (22.4%) received hydroxyurea, 7 (12.1%) received interferon, 5 (8.6%) received a JAK inhibitor, and 1 patient (1.7%) received hydroxyurea and interferon

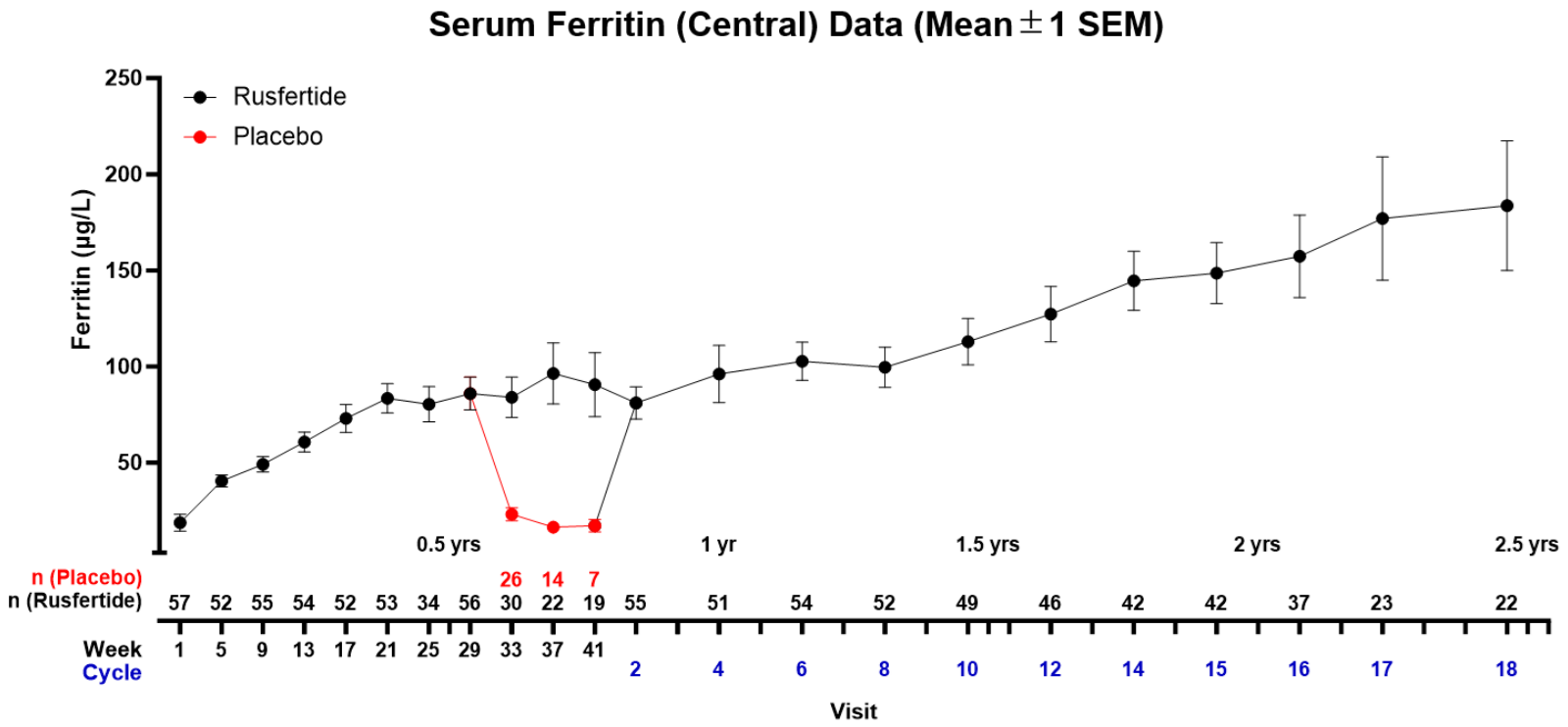


Rusfertide Provided Durable Control of Hematocrit Through 2.5 Years



- Rusfertide treatment resulted in consistent maintenance of hematocrit <45%

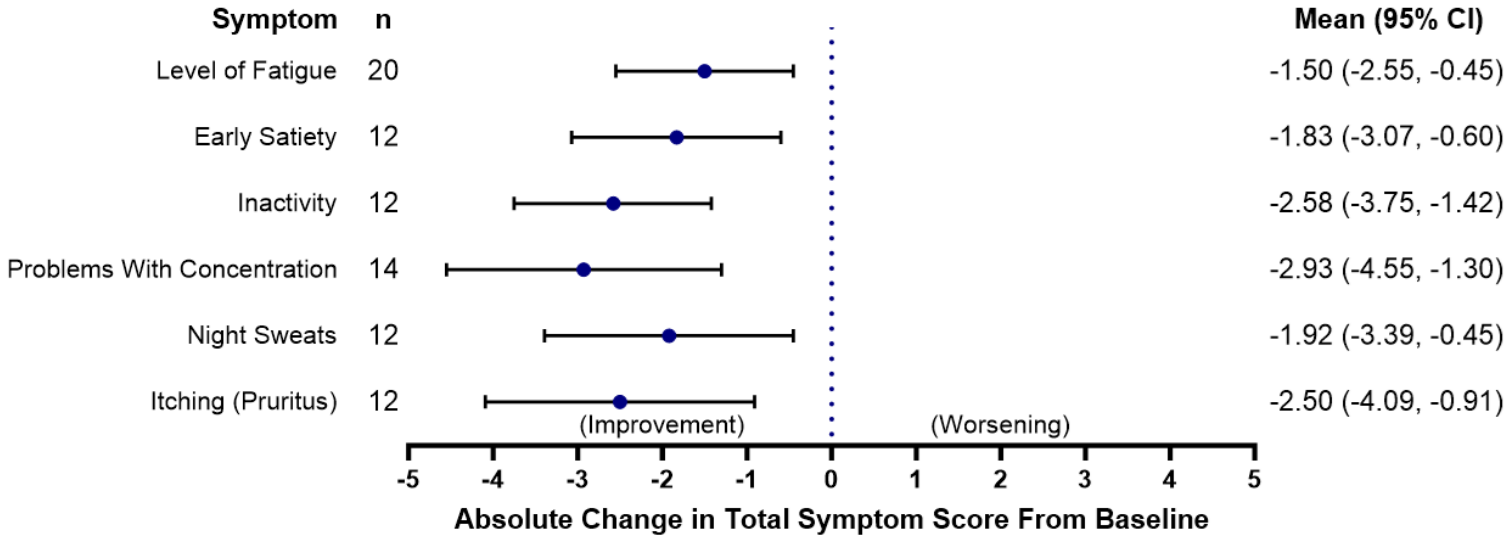
Rusfertide Resulted in Normalization of Serum Ferritin Levels Over 2.5 Years



- Prior to enrollment, iron-related parameters were consistent with systemic iron deficiency

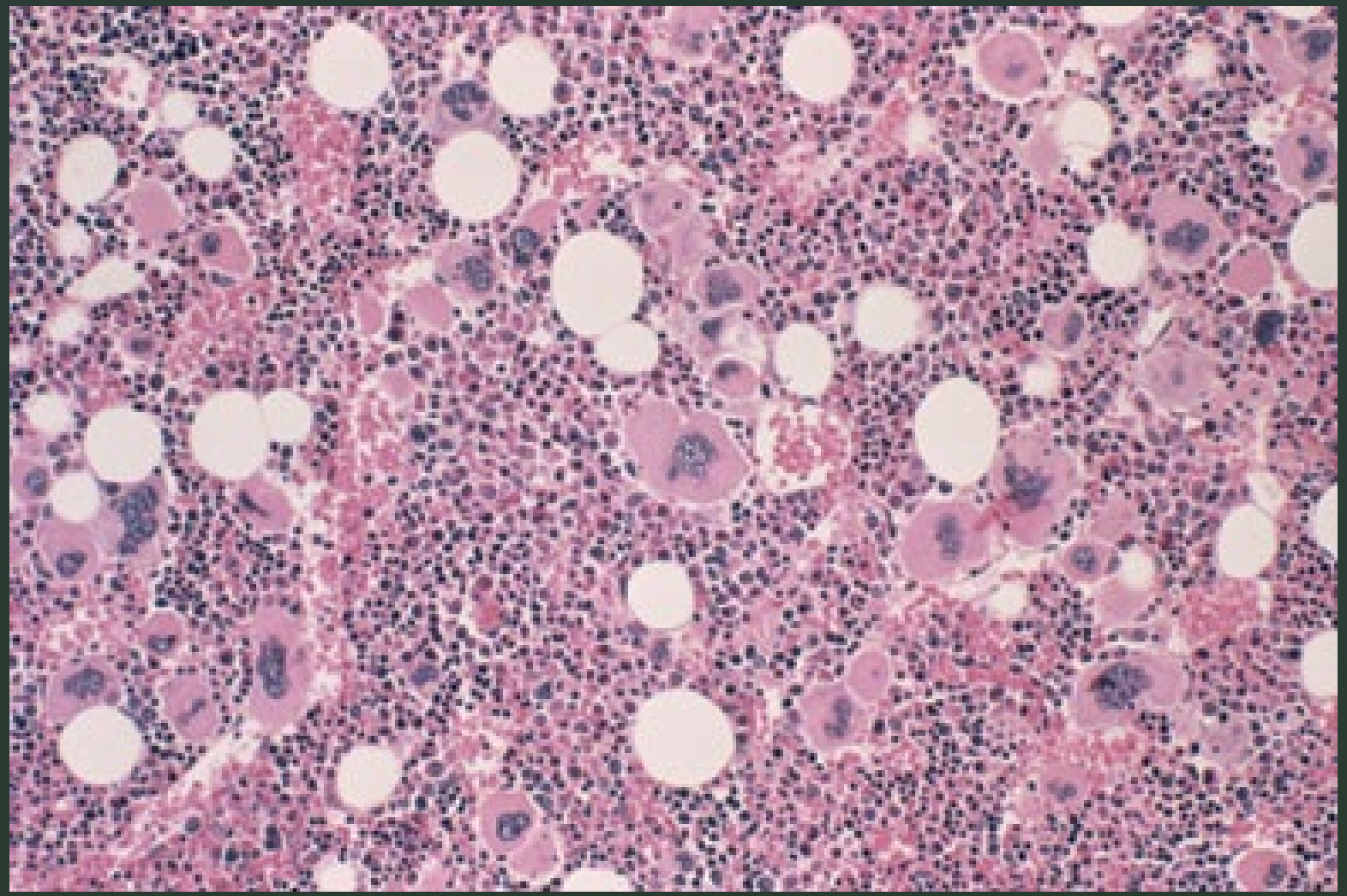
REVIVE Part 1: Rusfertide Improved Patient-Reported Outcomes

- In Part 1, PROs were assessed using the MPN-SAF TSS
  - Mean change from Baseline (Week 1) to Week 29 of ISSs from the MPN-SAF for patients with moderate (score, 4-6 out of 10) to severe symptoms (score, 7-10 out of 10) at Baseline
  - In patients with moderate or severe ISSs at Baseline (≥4 out of 10), rusfertide significantly decreased symptoms in fatigue, early satiety, night sweats, problems with concentration, inactivity, and itching



Error bars represent 95% CIs around the mean change from baseline. No multiplicity adjustments were made for analyses for all the supportive efficacy endpoints. Symptoms presented are limited to those with at least 10 patients.

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]

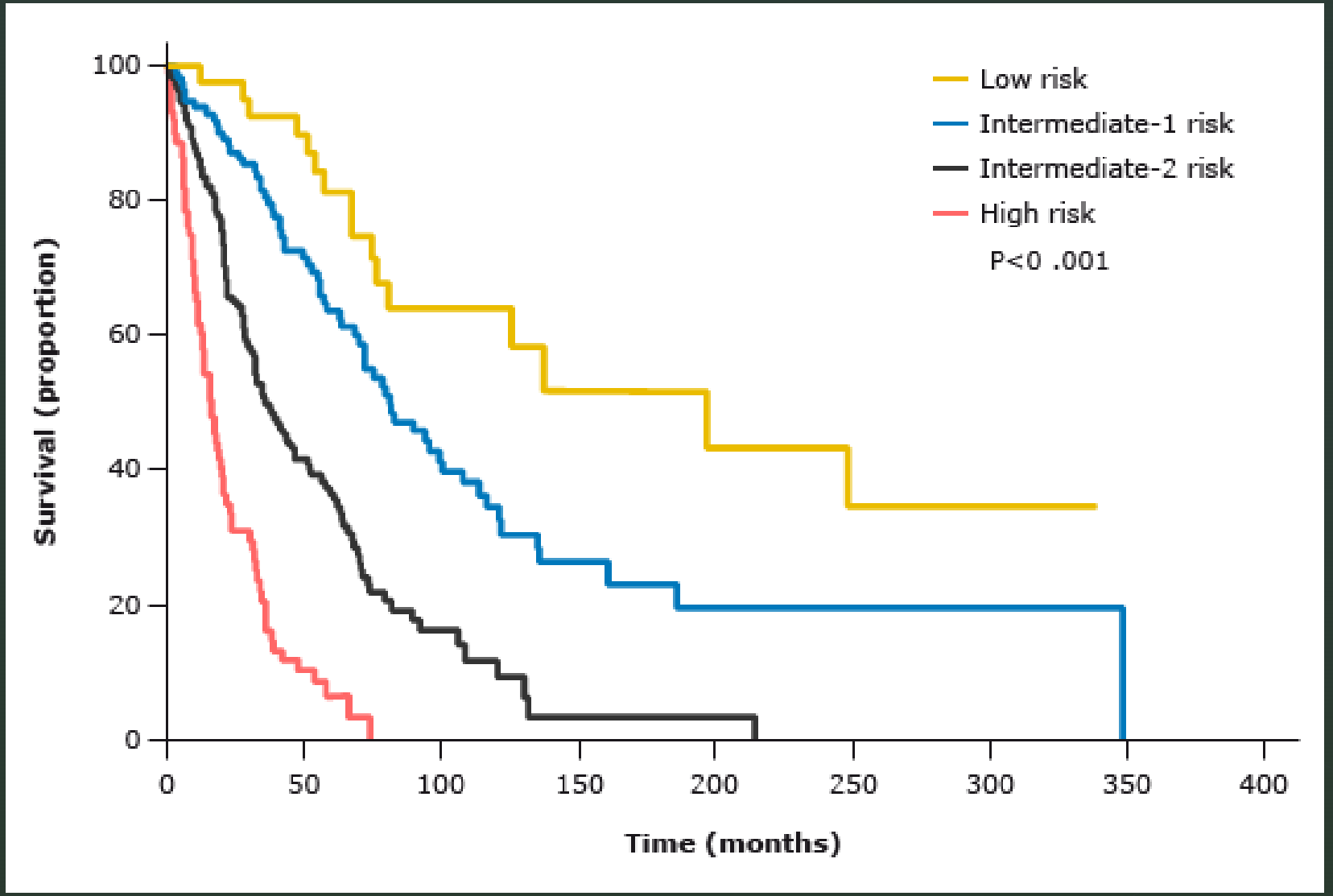
Prognostic Variable	Points
DIPSS low-risk	0
DIPSS intermediate-risk 1 (INT-1)	1
DIPSS intermediate-risk 2 (INT-2)	2
DIPSS high-risk	3
Platelets <100 x 10^9/L	1
Transfusion need	1
Unfavorable karyotype*	1

*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.

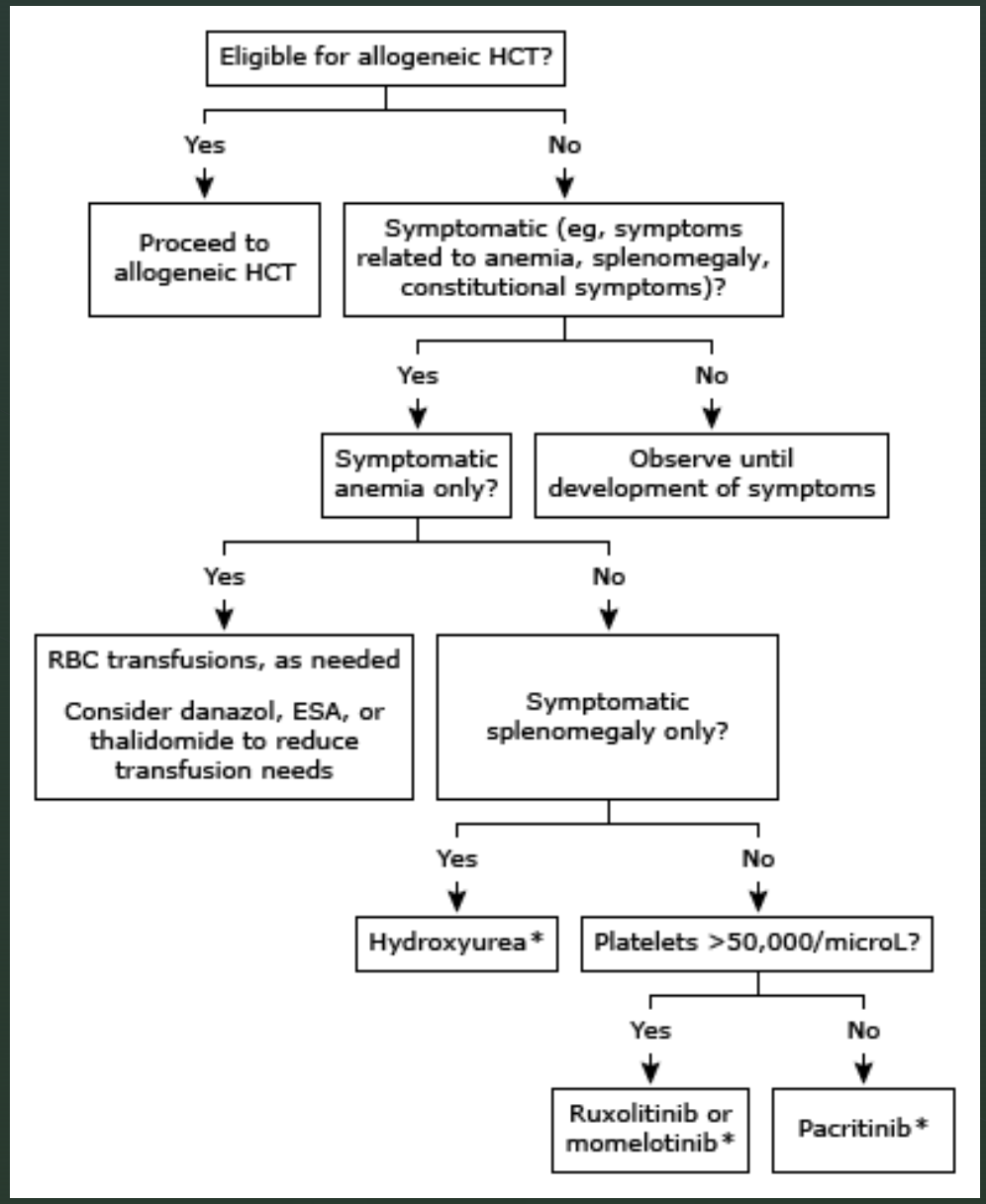
Risk Group	Points
Low	0
Intermediate-1 (INT-1)	1
Intermediate-2 (INT-2)	2 or 3
High	4 to 6

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

Prognosis

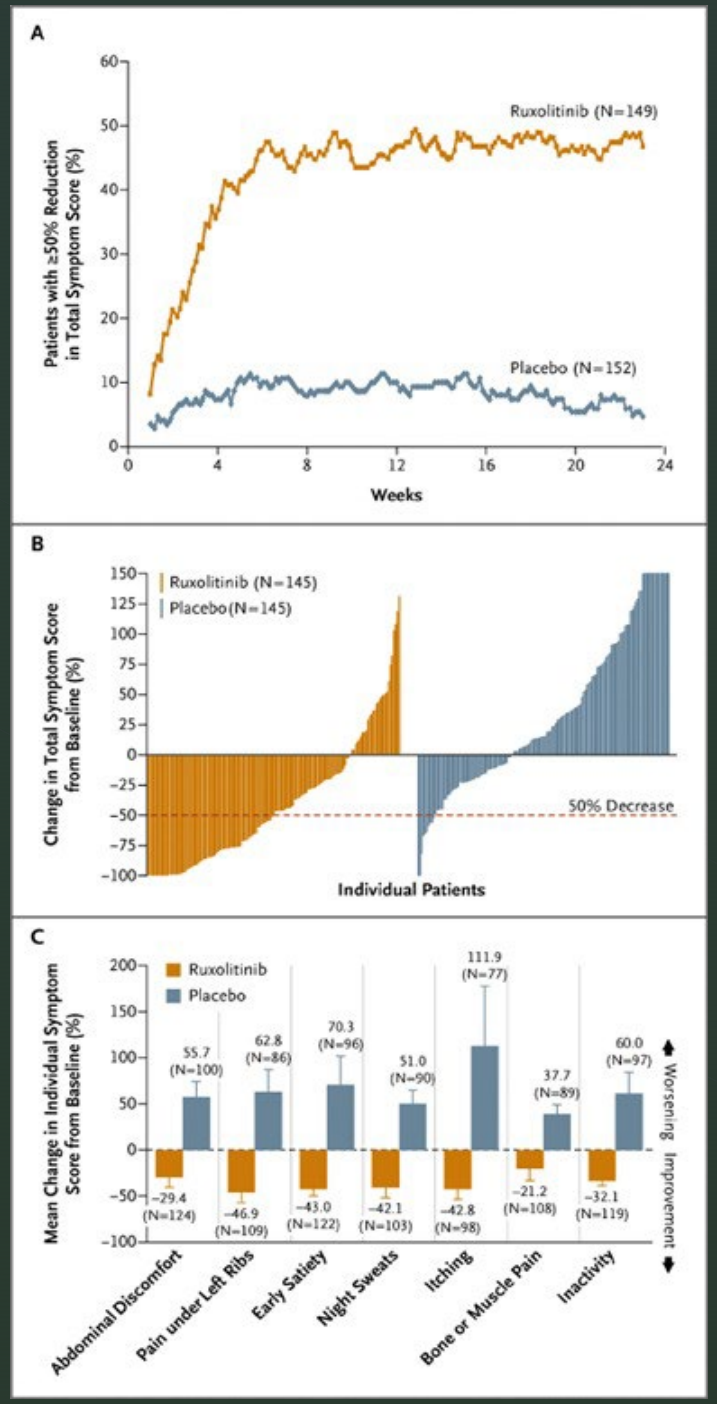

Low risk
Intermediate-1 risk
Intermediate-2 risk
High risk
P<0 .001
Survival (proportion)
100
80
60
40
20
0
0
50
100
150
200
250
300
350
400
Time (months)

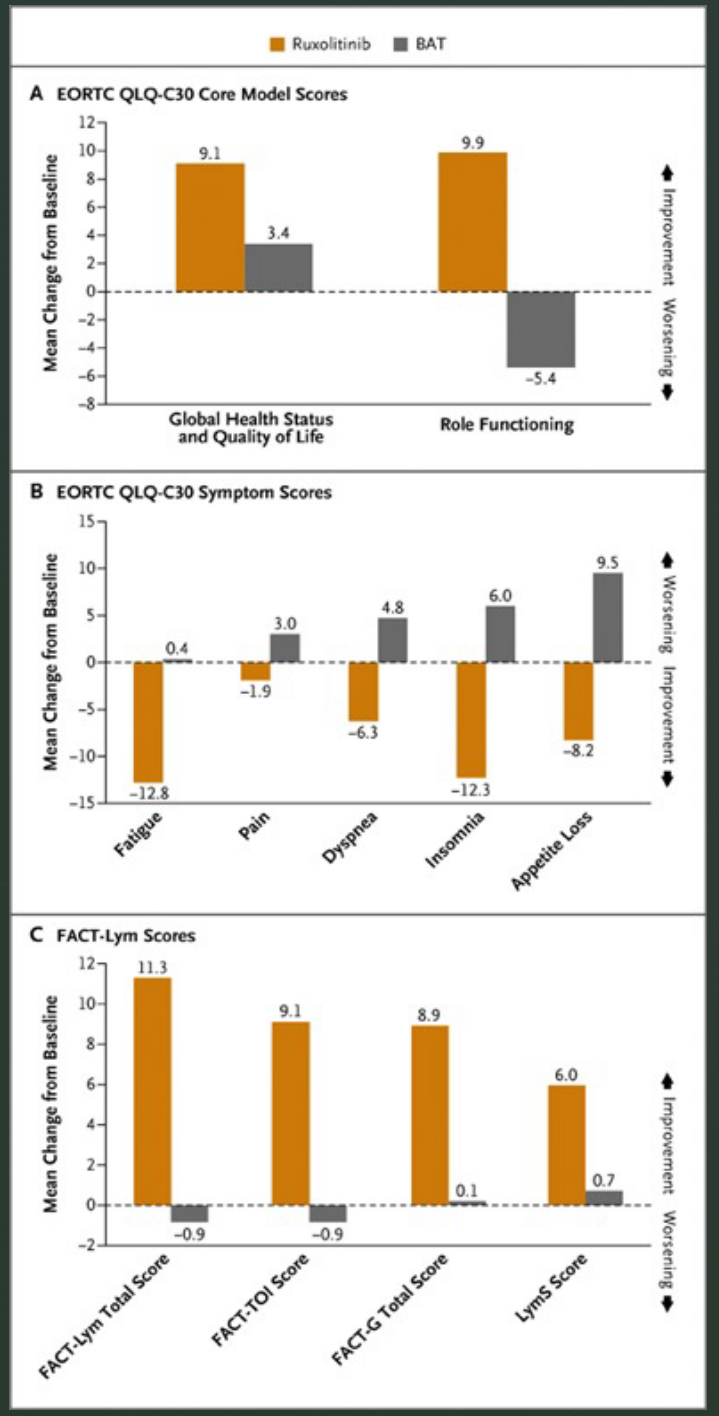
Treatment

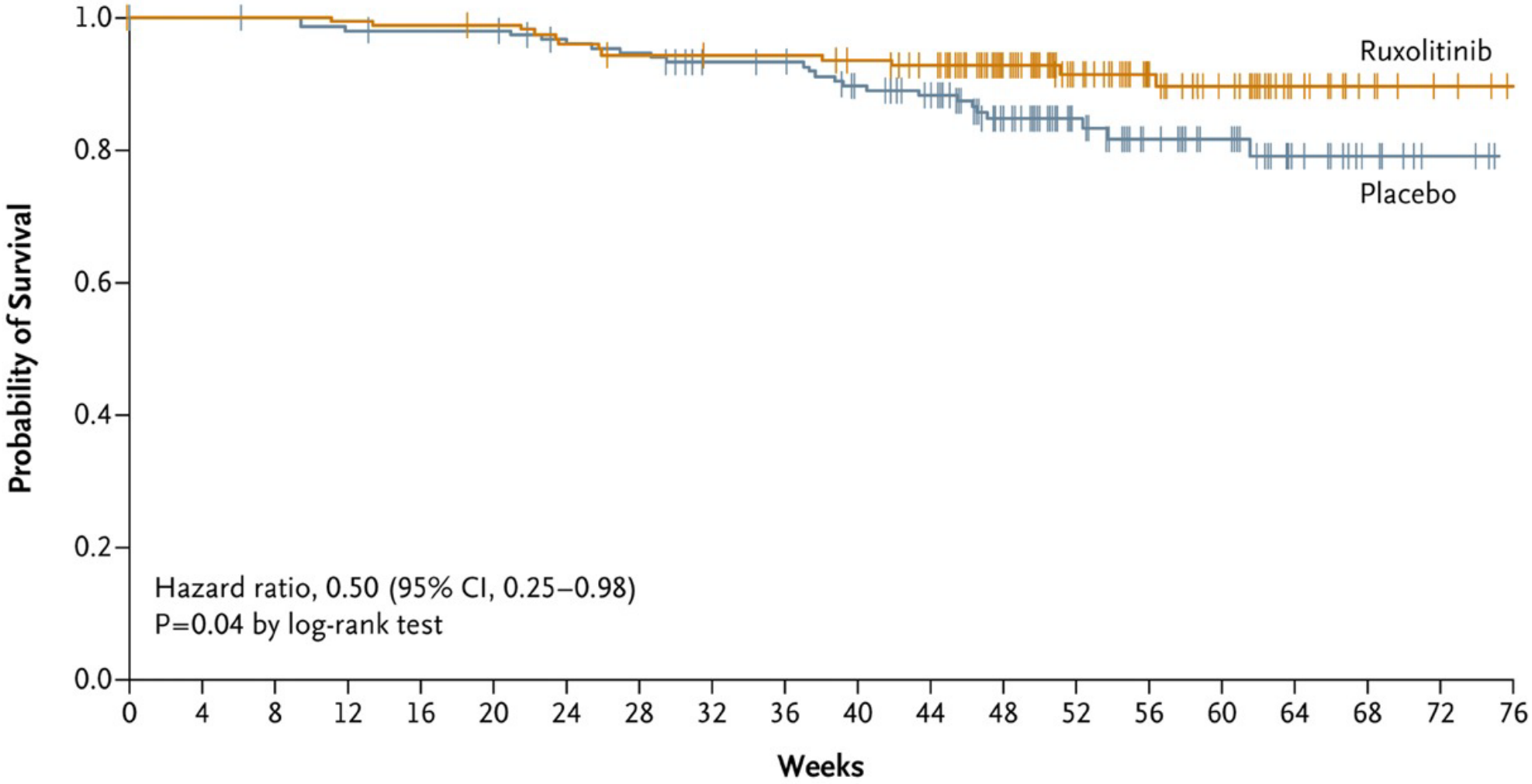

Eligible for allogeneic HCT?
Yes
No
Proceed to allogeneic HCT
Symptomatic (eg, symptoms related to anemia, splenomegaly, constitutional symptoms)?
Yes
No
Symptomatic anemia only?
Observe until development of symptoms
Yes
No
RBC transfusions, as needed
Consider danazol, ESA, or thalidomide to reduce transfusion needs
Symptomatic splenomegaly only?
Yes
No
Hydroxyurea*
Platelets >50,000/microL?
Yes
No
Ruxolitinib or momelotinib*
Pacritinib*

Drug name	FDA approved for MF	Indication	Unique toxicity	Trial outcomes
Ruxolitinib	Yes (2011)	intermediate or high-risk myelofibrosis	• Infections • Withdrawal syndrome	• Reduction in spleen volume and symptoms • **Survival**
Fedratinib	Yes (2019)	intermediate or high-risk myelofibrosis	• Rare cases of encephalopathy	• Reduction in spleen volume and symptoms
Pacritinib	Yes (2022)	intermediate or high-risk myelofibrosis **With platelet count <50**	• QT prolongation • Bleeding? • Clotting?	• Reduction in spleen volume and symptoms
Momelitinib	Yes (2023)	intermediate or high-risk myelofibrosis **With anemia**	• Infections	• Reduction in spleen volume and symptoms

Ruxolitinib



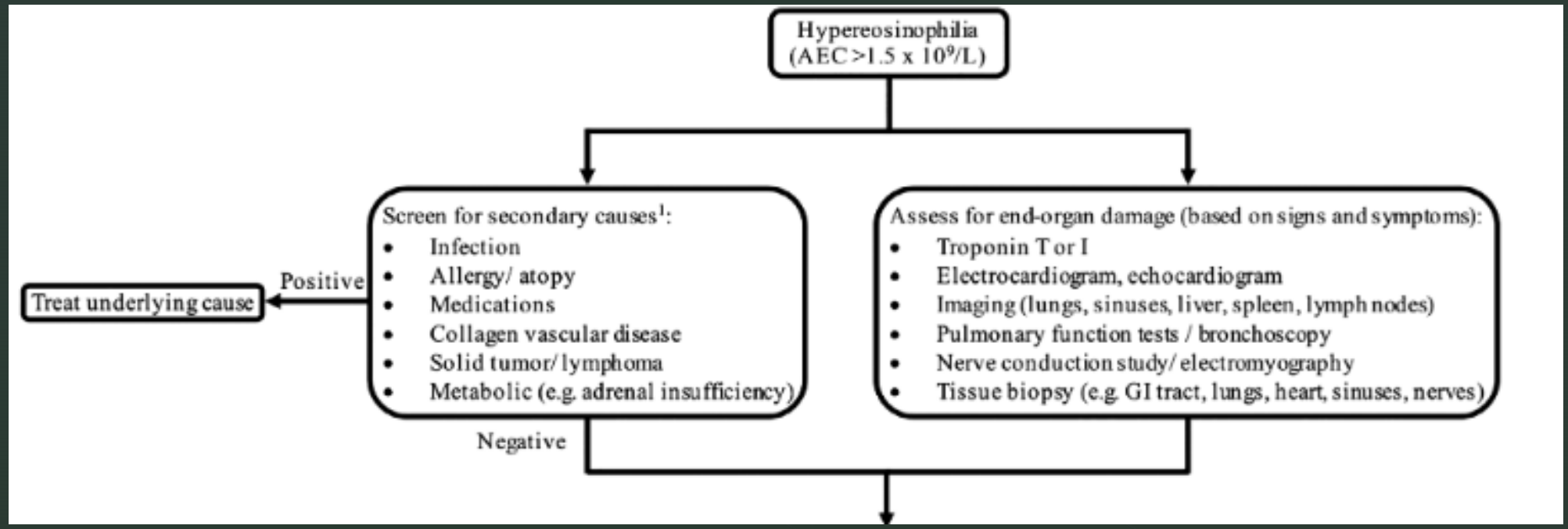


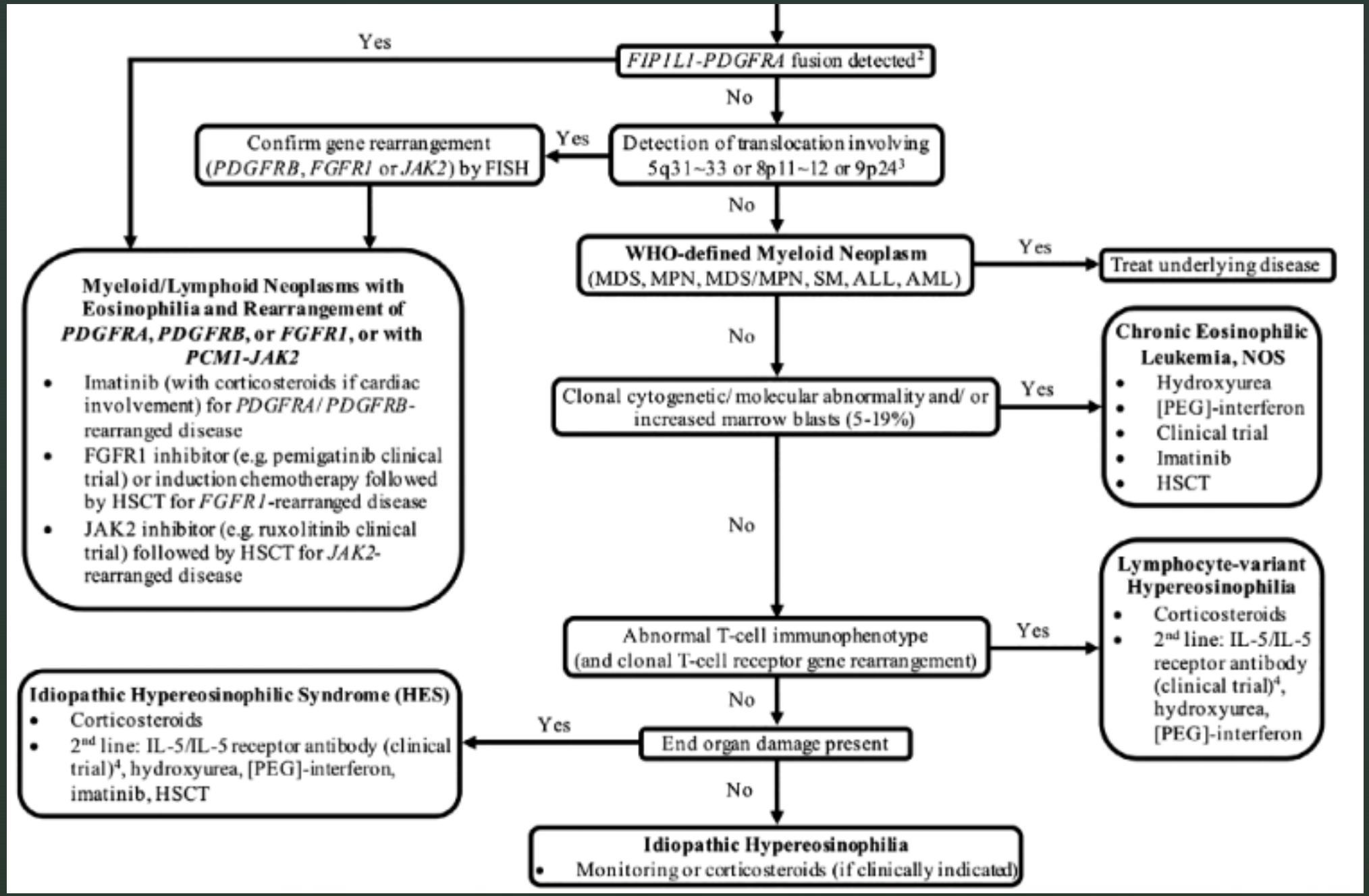


No. at Risk

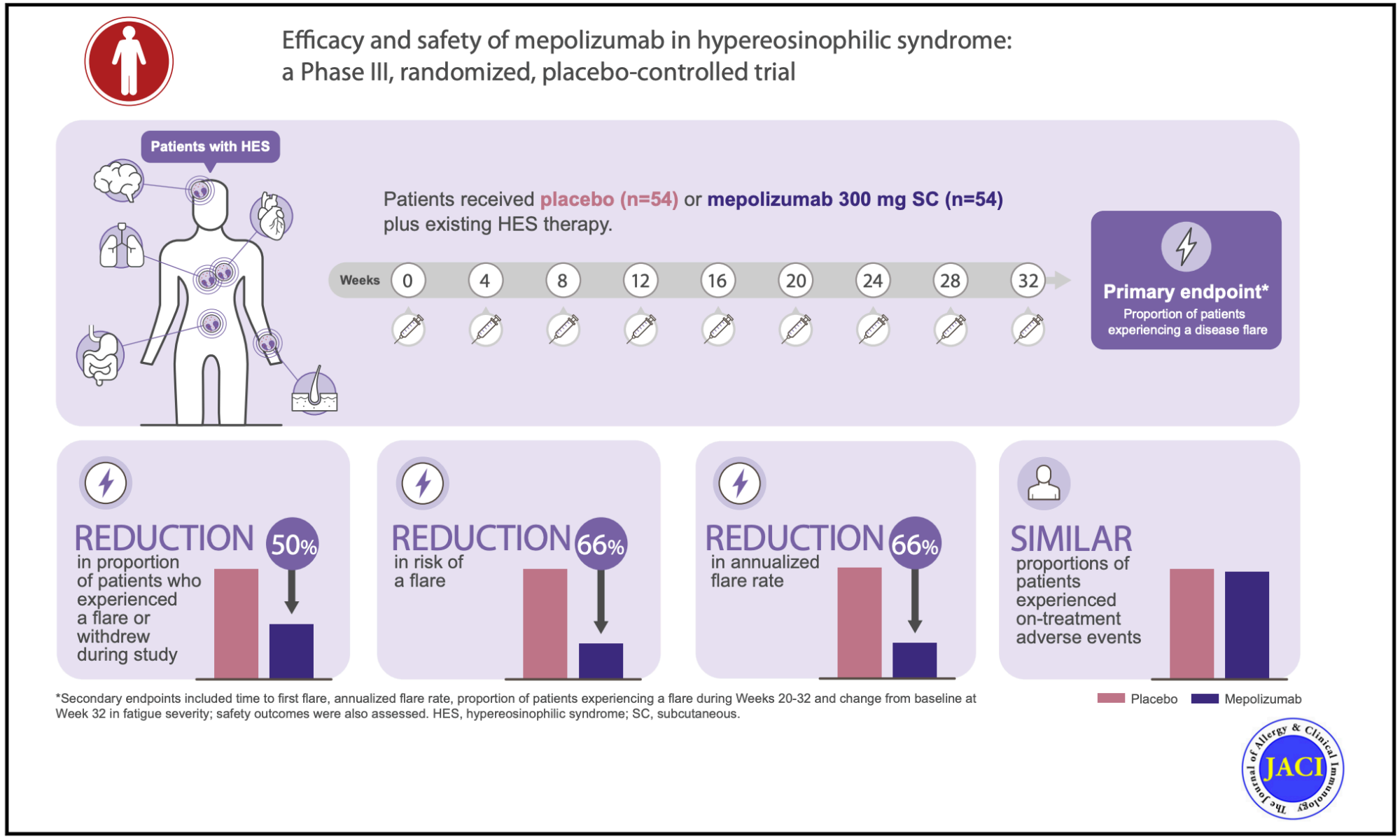
Ruxolitinib	155	155	155	154	153	152	148	144	143	143	140	134	102	68	52	37	18	8	3
Placebo	154	152	151	148	147	147	142	139	132	131	123	115	83	58	45	35	20	9	3

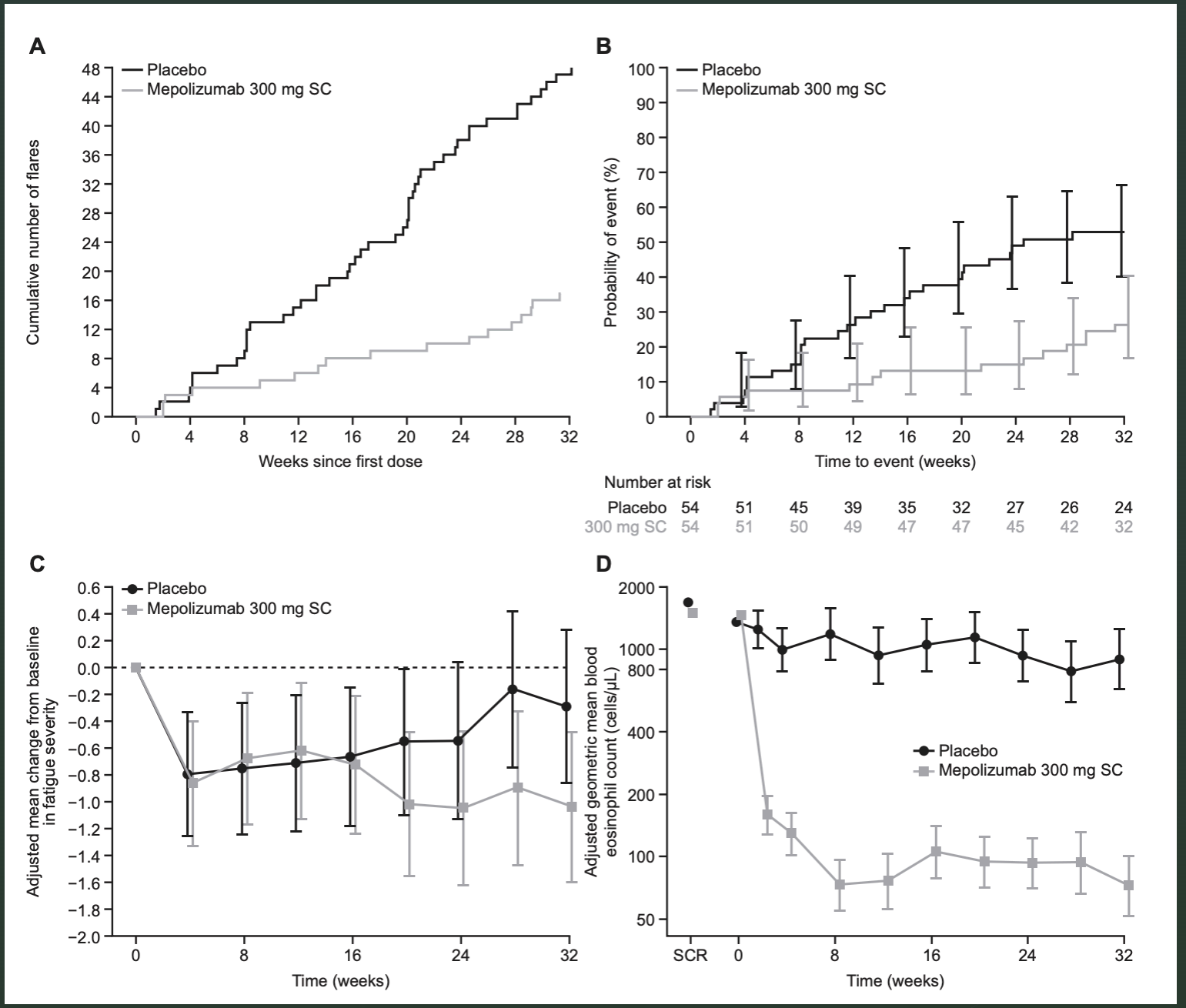
Hypereosinophilic syndrome




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




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: