PV : Management

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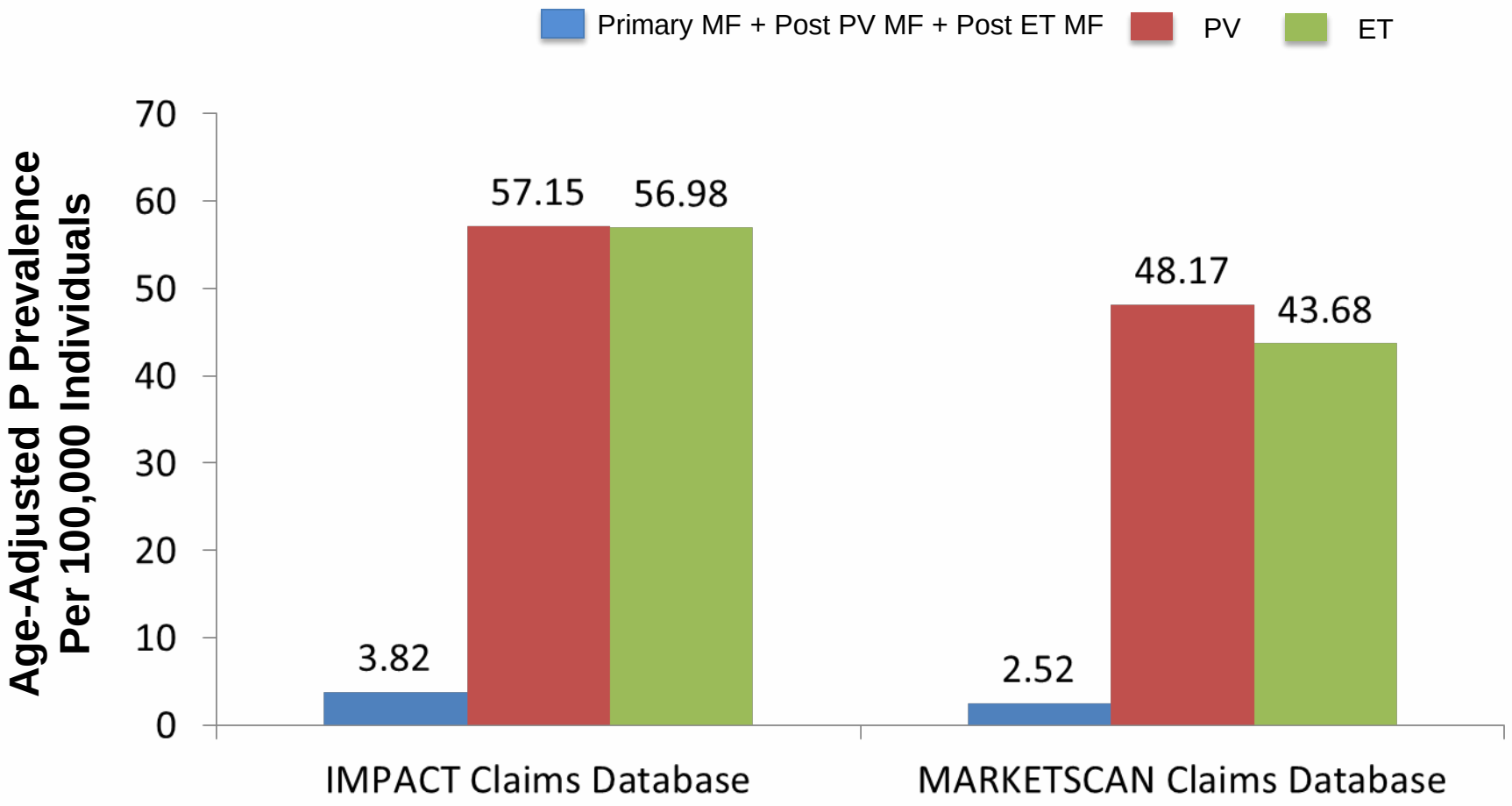
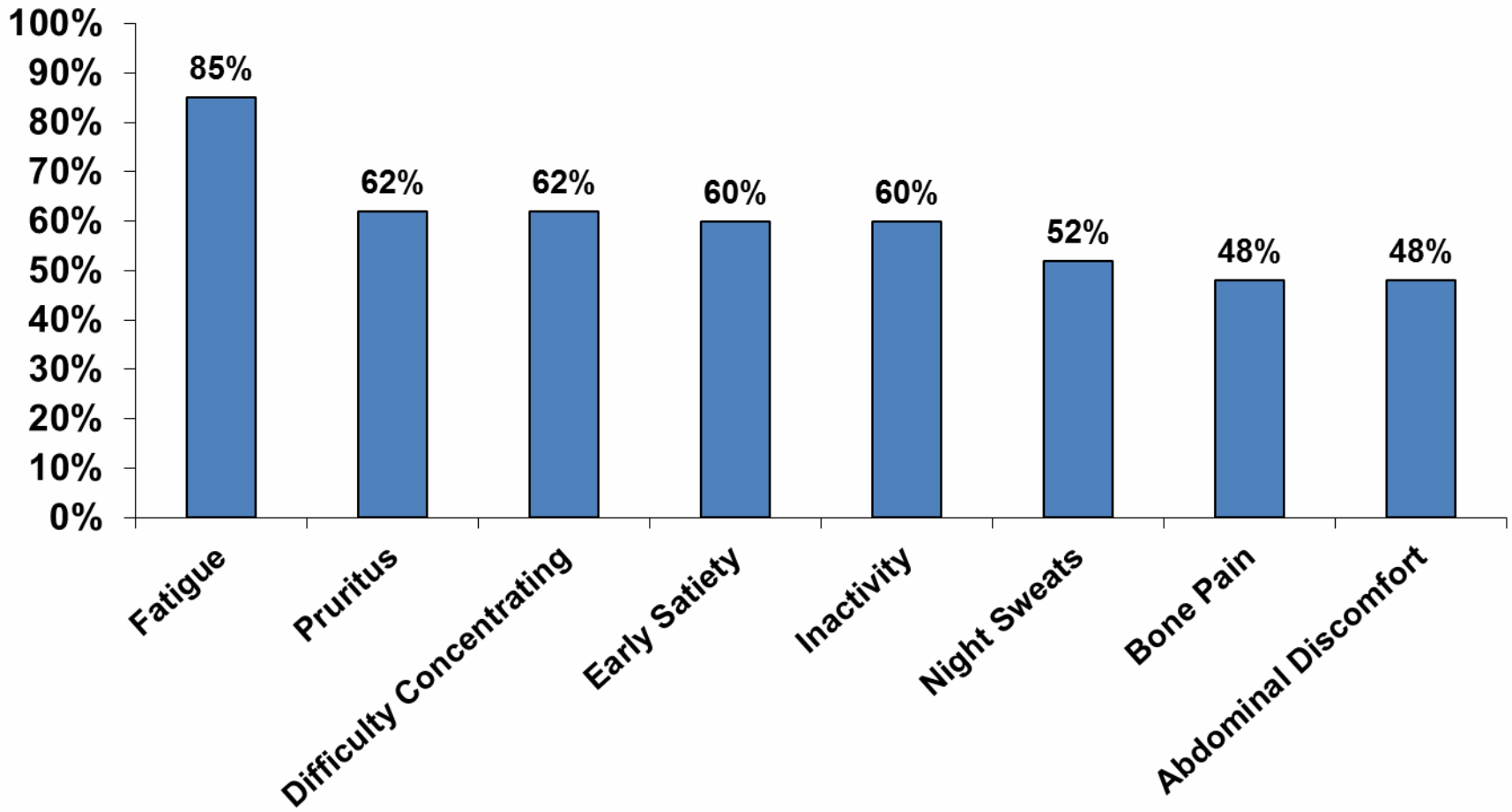
PREVALENCE OF MPNs PER 100,000 INDIVIDUALS



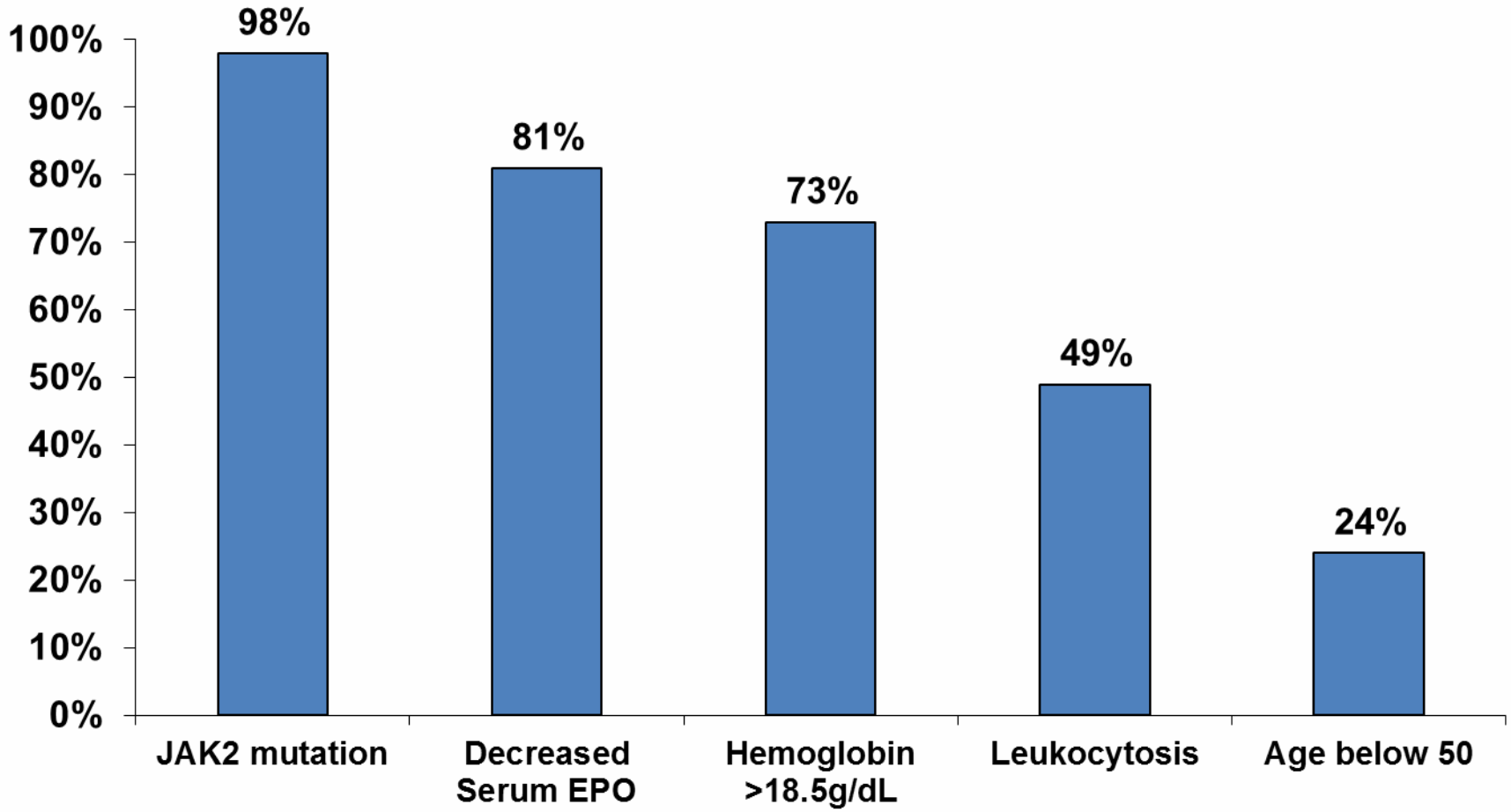
Mehta J. *Leuk Lymphoma*. **2014;55(3):595-600**

WHAT DOES A PV PATIENT LOOK LIKE? PRESENTING SIGNS AND SYMPTOMS



Geyer H. *Hematology Am Soc Hematol Educ Program*. 2014;2014(1):277-286.

WHAT DOES A PV PATIENT LOOK LIKE? CLINICAL FINDINGS



Tefferi A. *Leukemia*. 2013;27(9):1874-81.

Thrombotic Complications in PV

- Microvascular complications
- Microvascular complications are caused by thrombosis in small blood vessels[1]
  - These are sometimes referred to as microcirculatory disturbances[1]
- Macrovascular complications
- Macrovascular complications are caused by thrombosis in large arteries or veins[2]
- These are serious complications, often referred to as major thrombotic events[2]
- Major thrombotic events are the main cause of mortality, accounting for 45% of deaths in patients with PV[3]
  - Other major causes of death include solid tumors (19.5%) and hematologic transformations (13.0%)[3]

Microvascular complications

Erythromelalgia

Headache

Dizziness

Visual disturbances

Paresthesia

Transient ischemic attack

Macrovascular complications

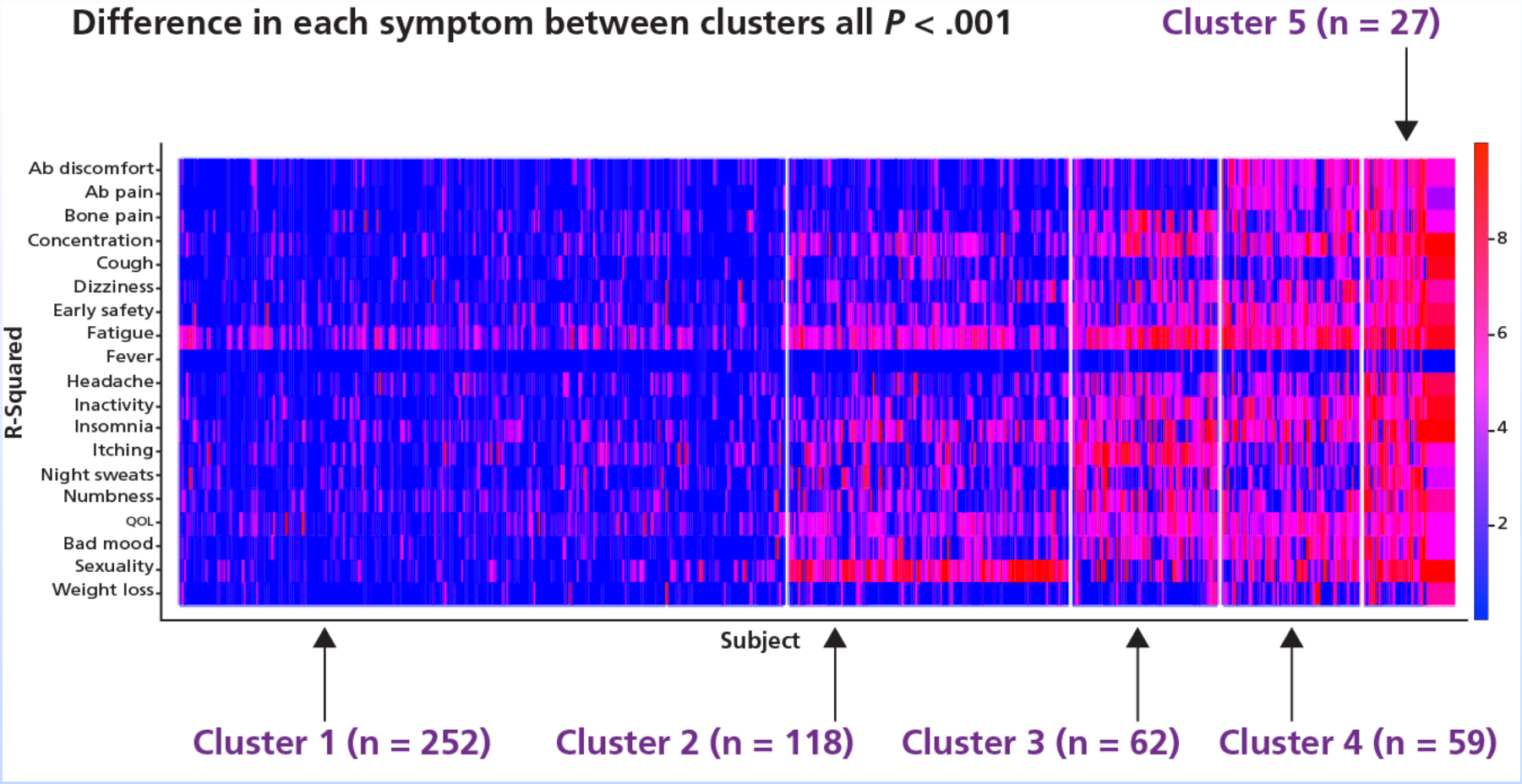
Arterial thrombotic events

- Myocardial infarction
- Unstable angina
- Stroke
- Peripheral arterial occlusion

Venous thrombotic events

- Deep vein thrombosis
- Pulmonary embolism
- Intra-abdominal vein thrombosis
- Cerebral vein thrombosis

PV Symptom Burden: Cluster Analysis



Emmanuel RM, et al. ASH 2012. Abstract 1726.

Assessing MPN Burden
WHO Diagnosis Does Not Tell Whole Story

Vascular Events
- PV/ET > MF
- Counts matter
- Can be unrecognized

Cytopenias
- MF> ET/PV
- Anemia
  - MF 75%
  - TX Dep 25%
- TPN 30%

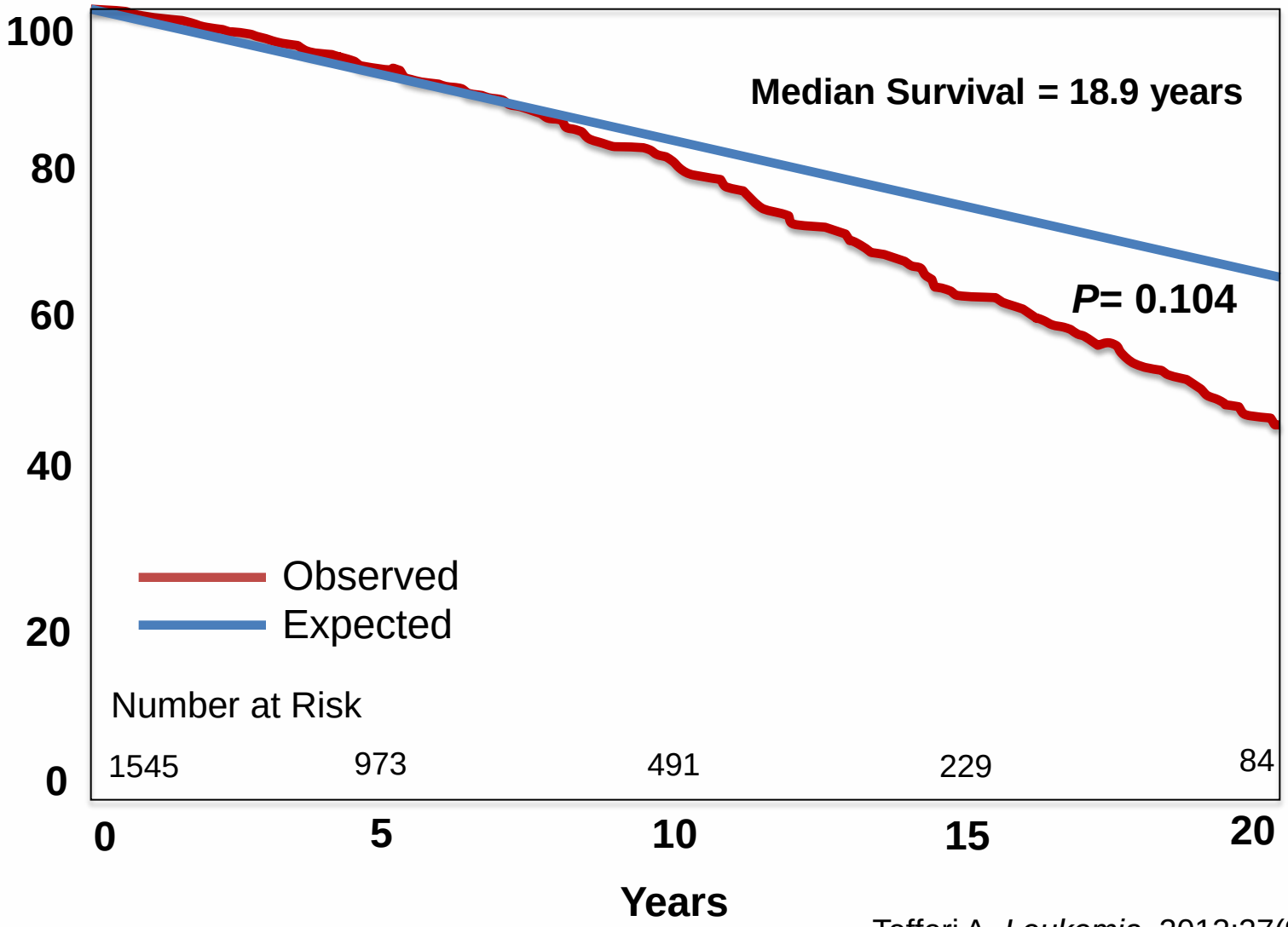
Baseline Health
AGE/ Medicines
Comorbidities

Progression
- PV/ET to MF
- PV/ET to AML
- MF to AML
- ? 2nd MDS

Splenomegaly
- MF> ET/PV
- Pain not always a function of size

MPN Symptoms
- MF>PV>ET
- Multifactorial
- Some ET/PV > MF
- Cytoreductive rx frequently not effective

OVERALL SURVIVAL AFTER DIAGNOSIS



Tefferi A. *Leukemia*. 2013;27(9):1874-81.

WHO CRITERIA 2008: POLYCYTHEMIA VERA

Major

- ü Absolute erythrocytosis (>18.5 g/dL in men; >16.5 g/dL in women)
- ü *JAK2* V617F mutation or similar (*JAK2* exon 12)

Minor

- ü Subnormal EPO level (<4 mU/mL)
- ü Bone marrow trilineage proliferation
- ü Endogenous erythroid colony growth

***2 major and 1 minor, or 1 major and 2 minor required for diagnosis**

Thiele J. *Curr Hematol Malig Rep*. 2009;4(1):33-40.

"MASKED" PV (mPV)

397 patients with PV marrow morphology

- "Masked" (n=140) vs. overt PV (n=257)
  - *mPV typically male, with history of arterial thrombosis, and ↑platelets*
  - *Similar vascular risk, but ↑rate of MF/AML, and ↓survival vs. overt PV*

- mPV distinguished from ET by Hgb >16/16.5, and Hct 48/49% in M/F

- Plasma volume increase can mask PV, typically in cases of abdominal venous thrombosis with splenomegaly

One of Osler's patients, Oxford 1916

***Masked PV=Hgb values below WHO threshold**

Lamy T. *Am J Med*. 1997; 102(1):14-20; Spivak J. *N Eng J Med*. 2006; 355(7):737; Barbui T. *Am J Hematol*. 2014;89(1):52-4.

PROPOSED REVISIONS TO THE DIAGNOSTIC CRITERIA

- **Major criteria:**

  ü Hgb >16.5 g/dl (Hct >49%) in men; >16 g/dl (>48%) in women

  ü BM trilineage myeloproliferation with pleomorphic megakaryocytes

  ü Presence of *JAK2* mutation

- **Minor criteria:**

  ü Subnormal Epo level

Diagnosis would require all 3 major criteria or 2 major and 1 minor criteria

Tefferi A. *Leukemia.* 2014;28(7):1407-13.

Management of PV-ET

- ALL PV Patients
  - *Maintain HCT <45% Men, 42% Women*
  - *Low Dose ASA*
  - *Aggressive control of CV risk factors*

- Cytoreduction
  - *High Risk or*
  - *Intol to Phlebotomy, Increasing Spleen, Severe Sx*
    Plt >1500 x 10(9)/L, or prog WBC
  - Medications
    - *Hydroxyurea or Interferon alpha as Front line (or second)*
    - *Busulfan, pipobroman, P-32 as second line*

Barbui T, et. al. LeukemiNET Consensus Guidelines. JCO 2011;29:761-770

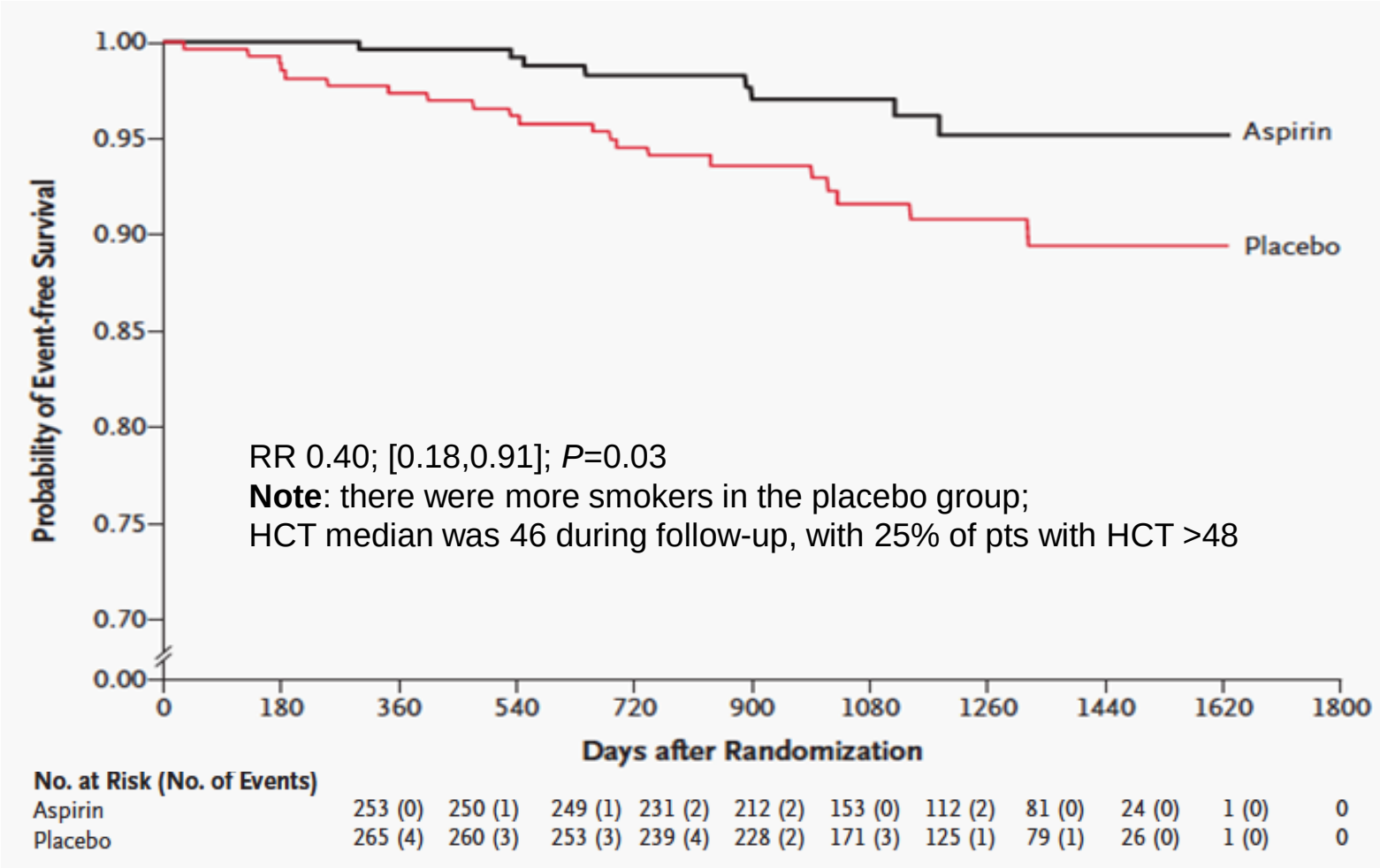
LOW-DOSE ASPIRIN IN PV: ECLAP STUDY

- Hypothesis: There is increased synthesis of platelet thromboxane in PV that can be suppressed by aspirin 100 mg daily
- 528 patients: 253 aspirin 100 mg daily, 265 placebo
- Inclusion Criteria:
  - No clear indication for, or contraindication to, aspirin
  - No significant comorbidities
- Primary endpoints:
  - Cumulative rates of nonfatal MI, stroke, or death from CV disease +/- PE or major venous thrombosis

Landolfi R. *N Engl J Med.* 2004;350(2):114-124.

ECLAP RESULTS

Probability of survival free of MI, stroke, death from CV disease, PE, or DVT



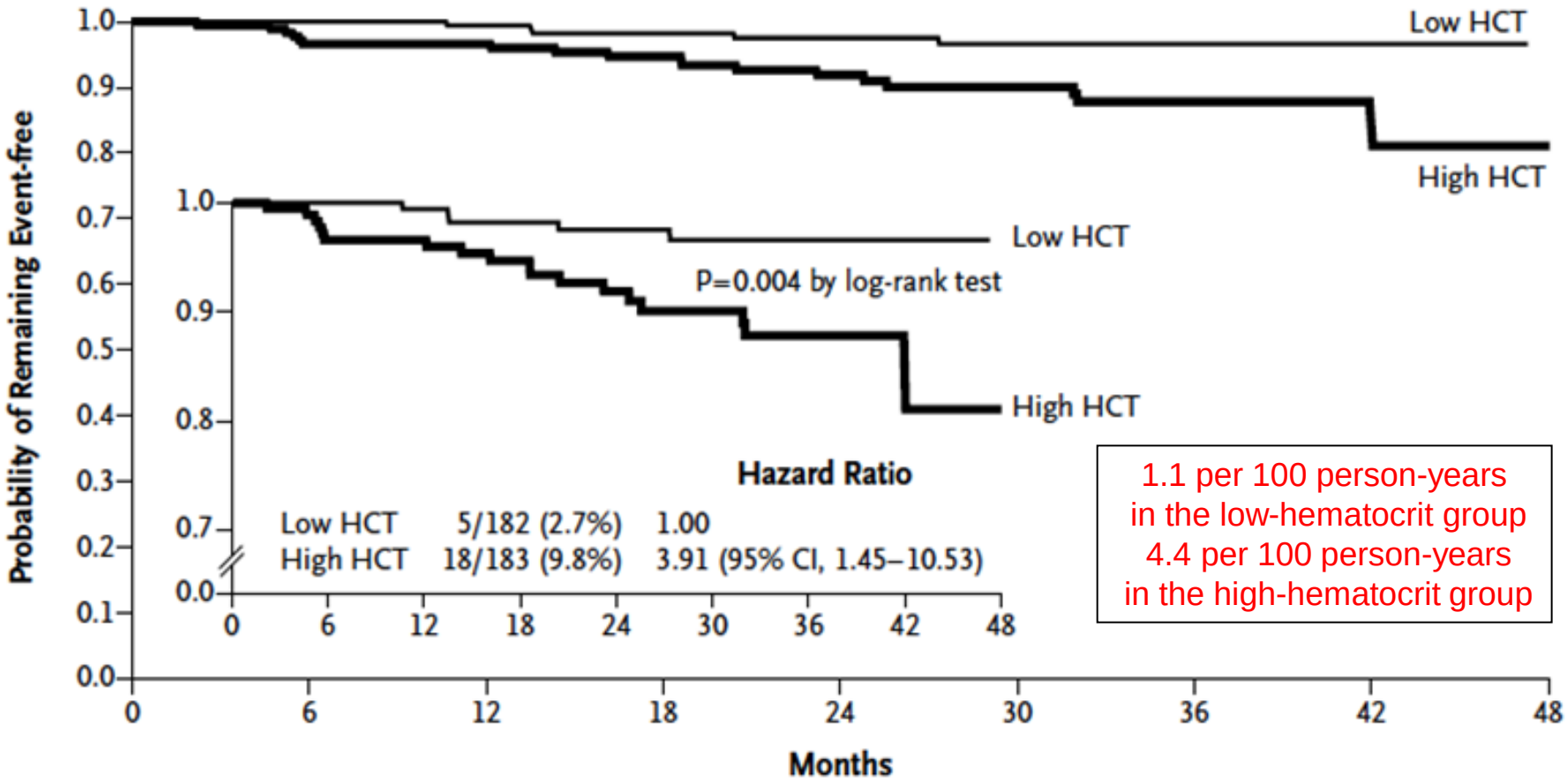
Landolfi R. *N Engl J Med.* 2004;350(2):114-124.

CYTO-PV STUDY TARGETS

- Two study arms
  - o More intensive Tx (target hct = <45%)
  - o Less intensive Tx (target hct = 45 to 50%)
- Primary end point: Time until death from CV complications or major thrombotic events
- Planned target was 1,000 patients, but slow enrollment and competing trials prevented completion

Marchioli R. *N Engl J Med.* 2013;368(1):22-33.

CV EVENTS AND INTENSITY OF TREATMENT



1.1 per 100 person-years
in the low-hematocrit group
4.4 per 100 person-years
in the high-hematocrit group

No. at Risk

Low HCT	182 (0)	177 (1)	168 (2)	154 (1)	129 (1)	95 (0)	62 (0)	18 (0)	0
High HCT	183 (6)	168 (0)	160 (3)	143 (4)	110 (2)	92 (2)	54 (1)	12 (0)	1

Marchioli R. *N Engl J Med.* 2013;368(1):22-33.

TREATMENT-RELATED RISK FACTORS FOR TRANSFORMATION TO AML AND MDS

Treatment	Odds Ratio	95% CI
None	1.0	Reference
Radioactive phosphorus (P^{32})	1.5	0.8 to 2.8
Alkylating agent only	0.9	0.4 to 2.1
HU only	1.2	0.6 to 2.4
Mixed treatment (2 or 3)	2.9	1.4 to 5.9

Bjorkholm M. *J Clin Oncol.* 2011;29(17):2410-5.

RISK OF TRANSFORMATION TO AML/MDS RELATIVE TO CUMULATIVE DOSE

Treatment	Odds Ratio	95% CI
HU, g		
1-499	1.5	0.6 to 2.4
500-999	1.4	0.6 to 3.4
≥1,000	1.3	0.5 to 3.3
Radioactive phosphorus (P^{32}), MBq		
1-499	1.5	0.6 to 3.3
500-999	1.1	0.5 to 2.2
≥1,000	4.6	2.1 to 9.,8
Alkylating agents, g		
1-499	1.1	0.5 to 2.3
500-999	1.7	0.6 to 5.0
≥1,000	3.4	1.1 to 10.6

Bjorkholm M. *J Clin Oncol.* 2011;29(17):2410-5.

RESPONSE CRITERIA FOR PV (≥12 WEEKS)

Complete Remission	Partial Remission	Molecular Response
• Resolution of PV signs • ≥10 pt. ê MPN TSS • Near normal counts • No progressive disease or vascular event • Bone marrow remission & ≤Gr 1 reticulin fibrosis	• Resolution of PV signs • ≥10 pt. ê MPN TSS • Near normal counts • No progressive disease or vascular event	Peripheral blood granulocytes •CR – Eradicated mutation •PR - ≥50% ê allele burden, *≥20% allele burden at baseline*

Progressive Disease = Post- PV MF, MDS, or AML

Barosi G. *Blood*. 2013:121(23):4778-4781.

Myeloproliferative Disorders Research Consortium Trial
Polycythemia Vera and Essential Thrombocythemia

MPD-RC 112 (NCT01259856 – clinicaltrials.gov)

Randomized Trial of *Pegylated* Interferon Alfa-2a versus Hydroxyurea Therapy in the Treatment of High Risk Polycythemia Vera (PV) and High Risk Essential Thrombocythemia (ET)

Registered & Randomized
High Risk ET and PV
(< 3 Months Prior Hydroxyurea)

PEG INF Alfa-2a

- Target dose 90 mcg/week
- Weekly Dosing
- ≥2 years of therapy in responders

HYDROXYUREA

- Titrated Dosing to Response
- Daily Dosing
- MPD-RC 111 in HYDROXYUREA Failures

ENDPOINTS

Primary: Complete response by ELN Criteria

Secondary: Partial response rate by ELN criteria, JAK2-V617F Allele Burden, Vascular Events, MPN Symptoms, Tolerability, Progression

Key Eligibility Criteria

- High risk PV or ET within 3 years from diagnosis
- No prior cytoreductive treatment (interferon or pegasys) other than hydroxyurea for up to 3 months (prior phlebotomy, aspirin, and/or anagrelide allowed)
- Age of 18 or older with relatively normal kidney and liver function
- No other serious medical problems

Questions contact MPD-RC (www.mpd-rc.org)
John Mascarenhas, MD john.mascarenhas@mssm.edu Phone: 1 (212) 241-6756

WHAT DOES INTOLERANCE/RESISTANCE TO HYDROXYUREA IN PV MEAN?

RESISTANCE

1. Need for phlebotomy (HCT<45%)
2. PLT >400 x 10^9/L **and** WBC >10 x 10^9/L
3. Failure to reduce spleen by > 50%
4. No reduction of spleen symptoms

Please Note

1. After > 3 Months
2. At maximum tolerated dose or 2 g/day

INTOLERANCE

1. Cytopenias (any)
   - ANC <1.0 x 10^9/L
   - Hemoglobin <100 g/l
   - Platelets <100 x 10^9/L
2. Leg ulcers
3. GI toxicity
4. Fever
5. Mucocutaneous manifestations
6. Skin cancers

Please Note

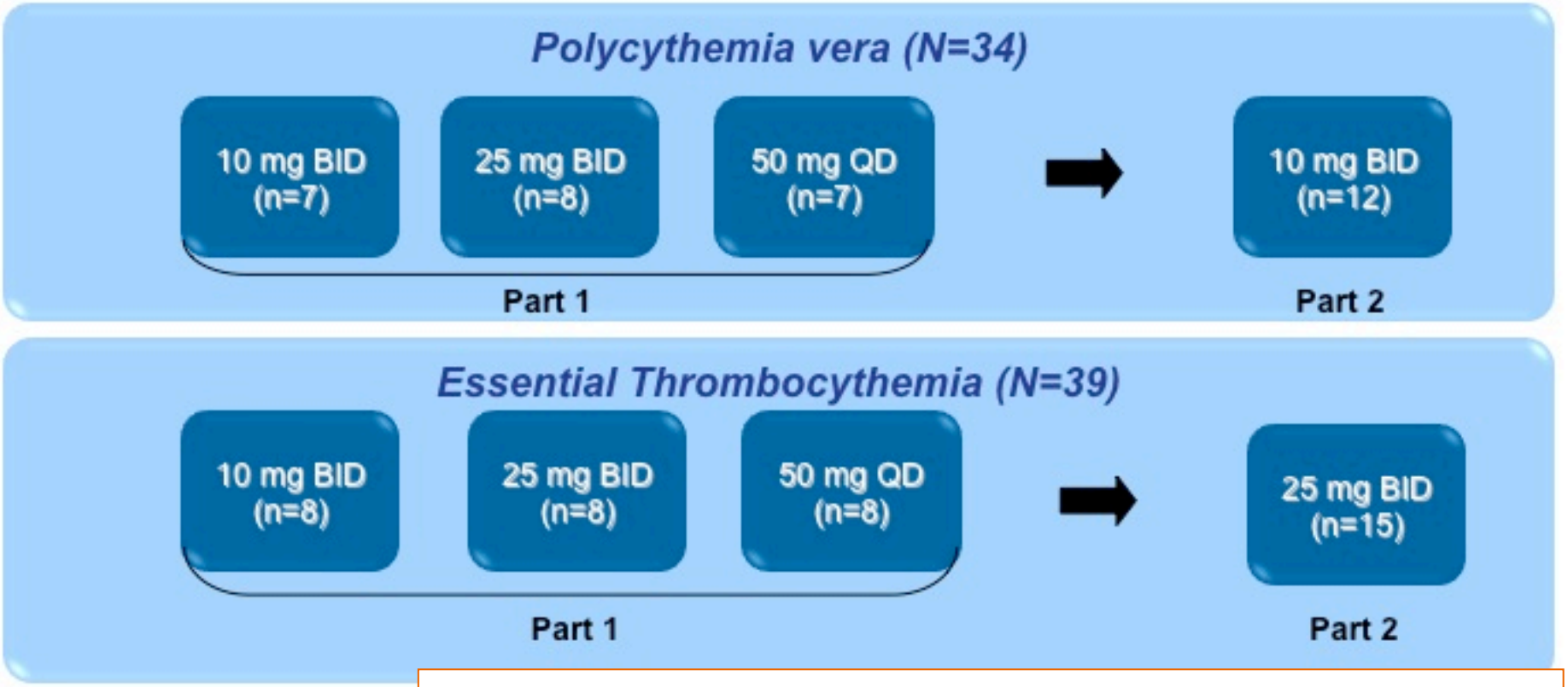
At lowest dose to achieve either a PR or CR

Barosi G et. al. *Br J Haematol*. 2009;148:961-3.

Phase II Study of INCB 18424 in Patients with Advanced ET and PV

Eligibility Criteria:

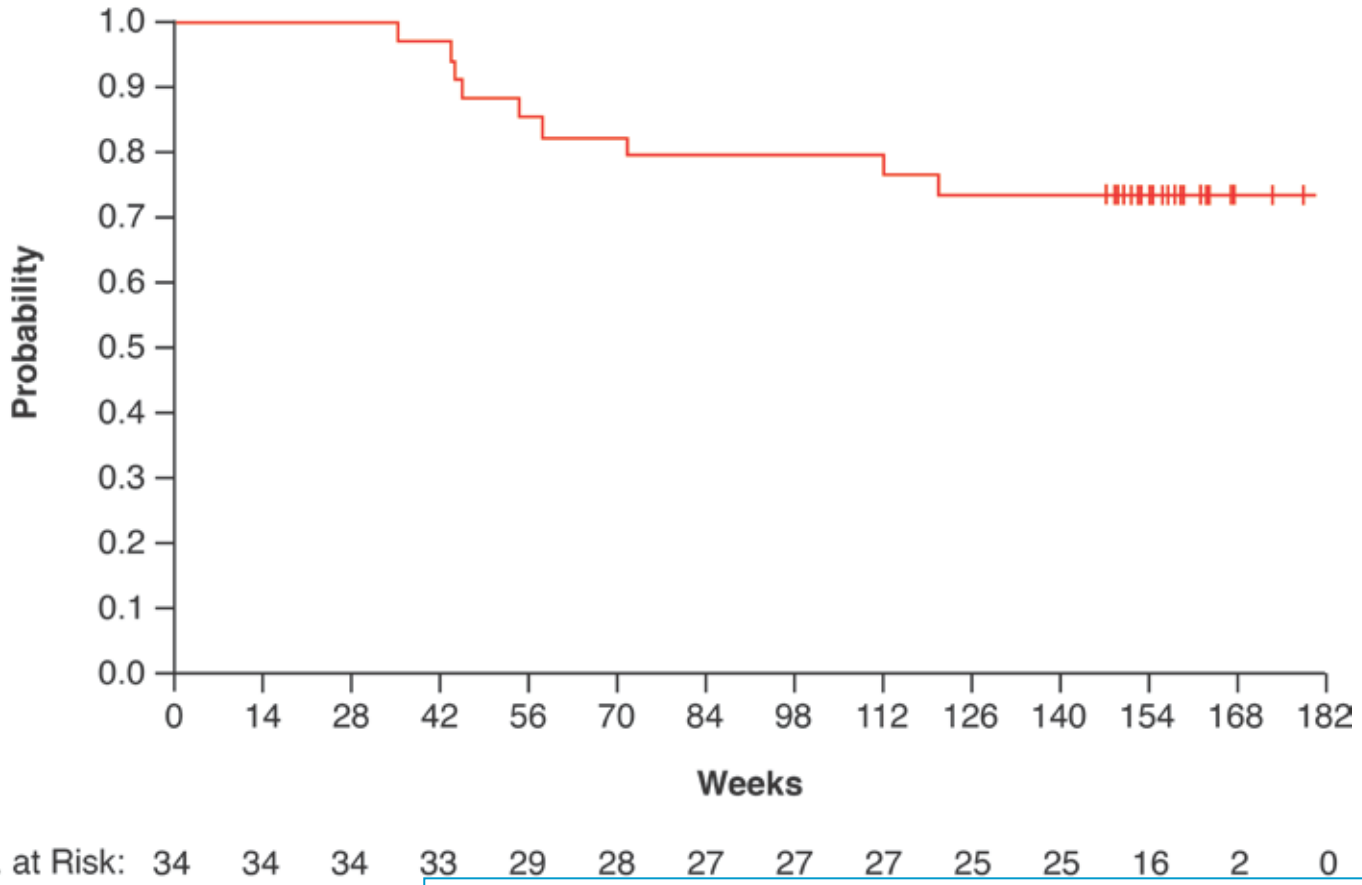
- Refractory or intolerant to hydroxyurea (HU) or HU contraindicated
- PV: Hct > 45% OR phlebotomy 2 times in last 6 months, with at least one phlebotomy in last 3 months
- ET: Platelets > 650 x 10^9/L unless on therapy



Verstovsek S, et. al. Blood (ASH) 2010;116: Abstract 313

Time to First Phlebotomy (n=1) or Discontinuation (n=8)

- 74% (25/34) remained on study and phlebotomy-free for at least 144 weeks



MAYO CLINIC Cancer Center

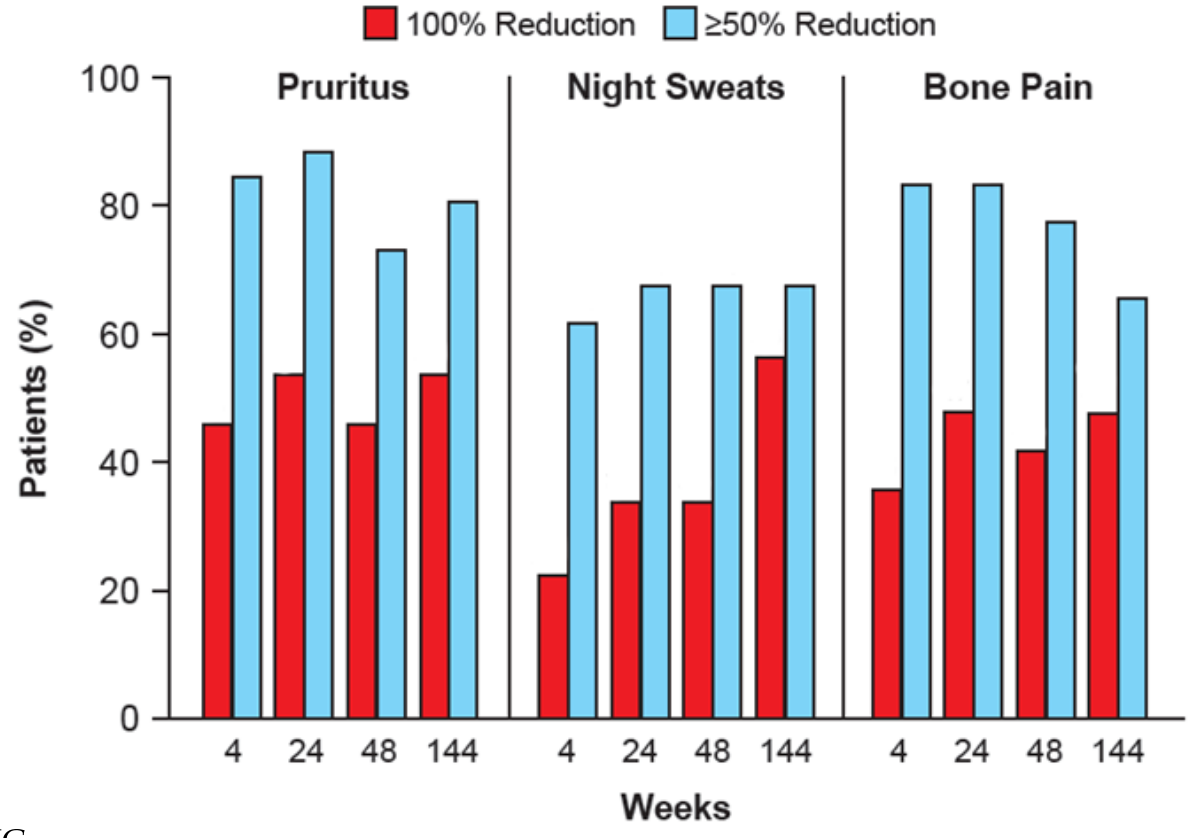
Verstovsek S et. al. Blood (ASH) 2012;120:abstr 804

NOTE: Analysis does not include phlebotomies that occurred in the first 4 weeks of treatment.

Reduction in PV-Associated Symptoms

Verstovsek S et. al. Blood (ASH) 2012;120:abstr 804

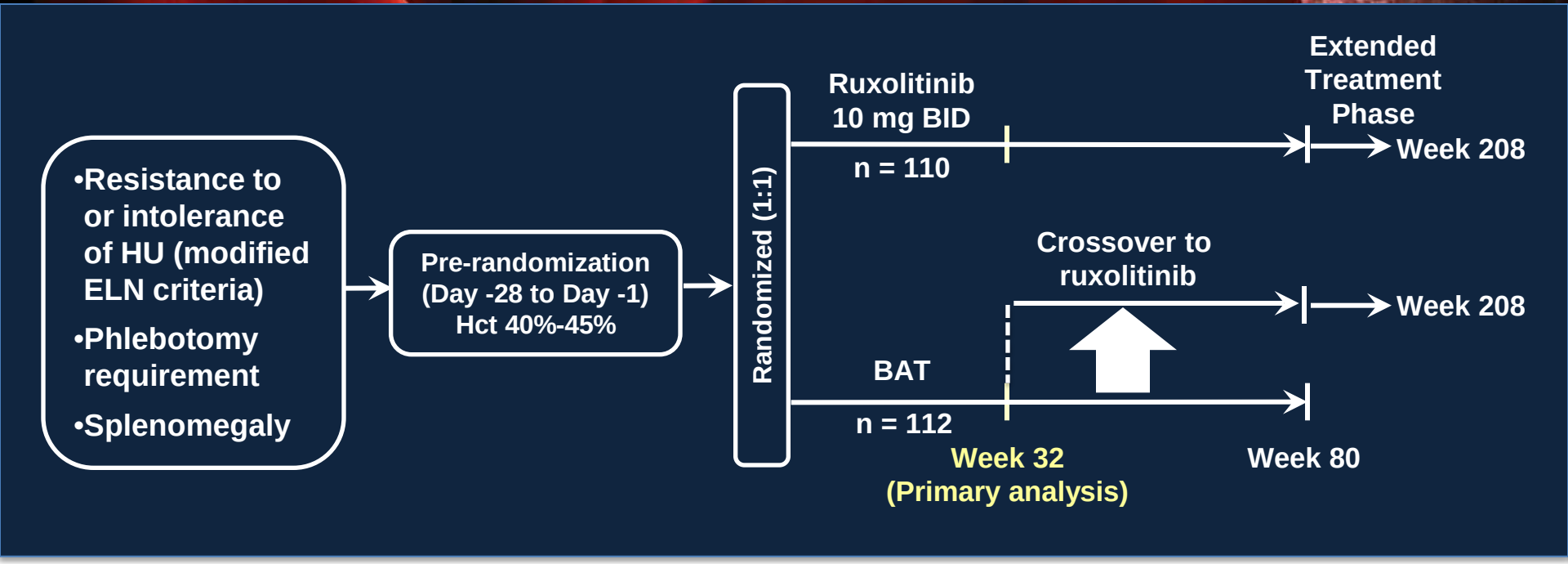
- Clinically meaningful improvements in pruritus, night sweats, and bone pain observed within 4 weeks of initiating therapy and sustained through Week 144



MAYO CLINIC
Cancer Center

ITT analysis: Patients who discontinued are counted as not having response for all study visits that they would have completed up to the date of analysis.

RUXOLITINIB (SINGLE AGENT) IN PV



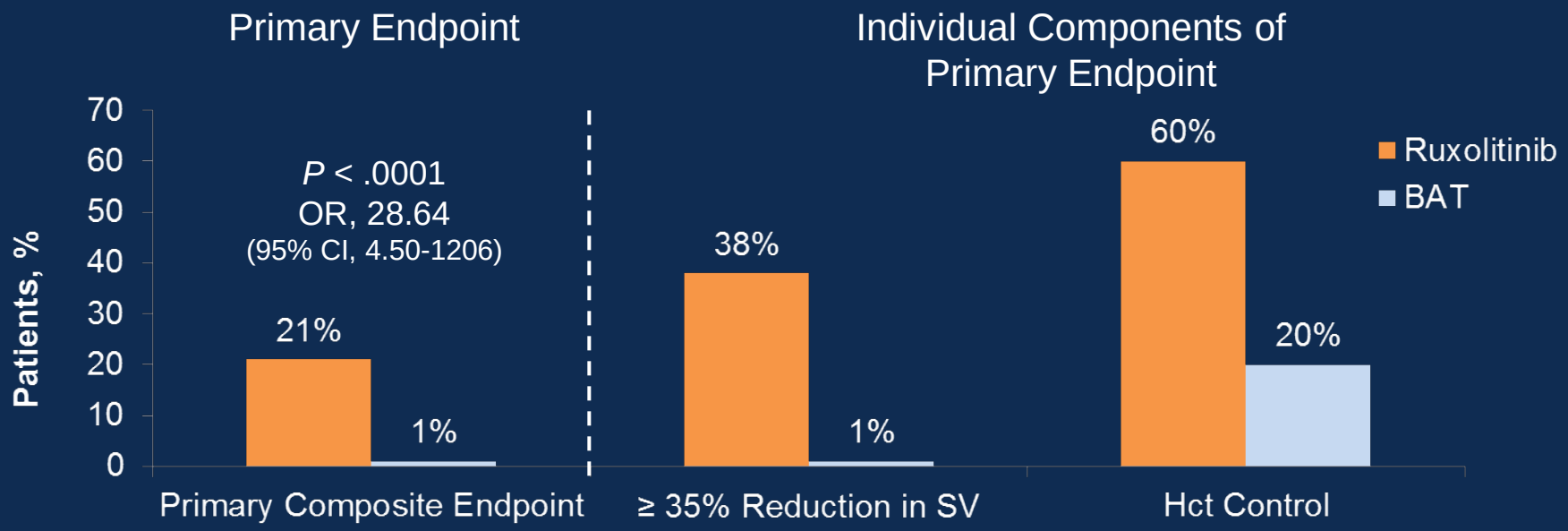
Compared to BAT, results showed that ruxolitinib led to:

1. Superior control of hematocrit
2. Superior reduction in splenomegaly
3. Superior reduction in PV-related symptoms
4. Trend for less thrombotic events

Vannucchi et al. EHA 2014. Abstract LB-2436.

Primary Response at Week 32

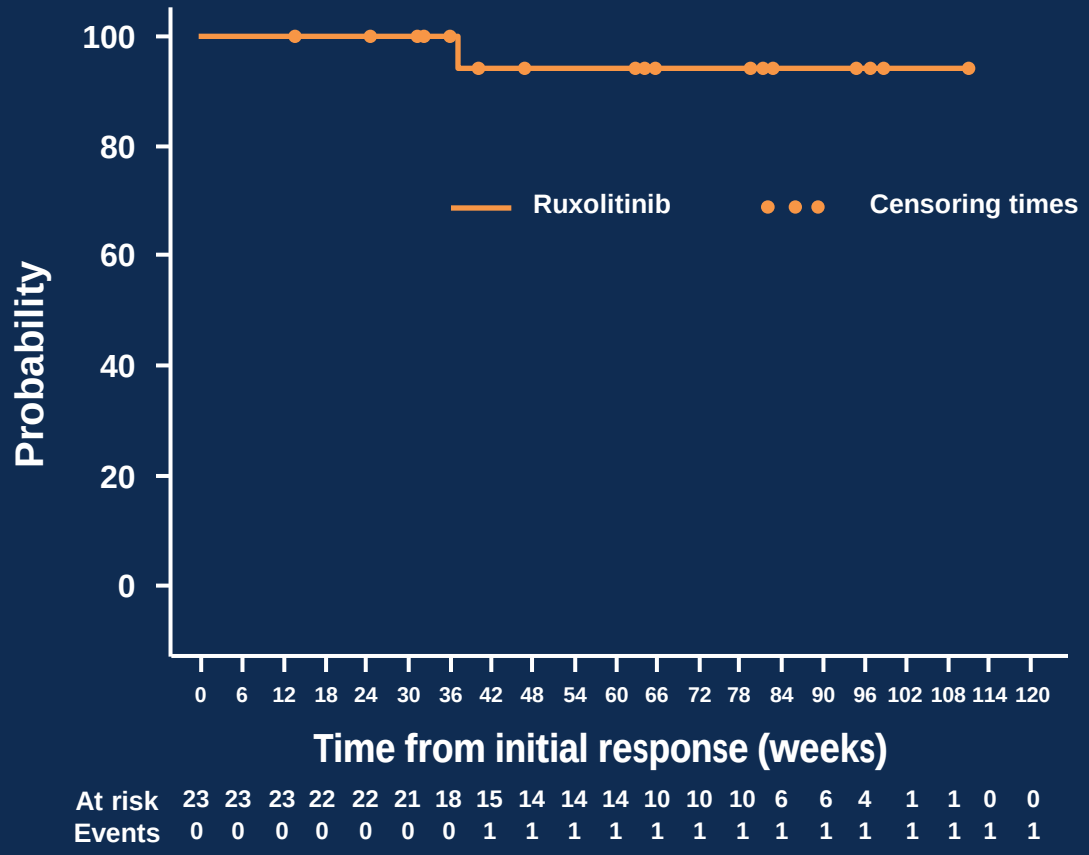
- 77% of patients randomized to ruxolitinib met at least 1 component of the primary endpoint



- To achieve Hct control, patients could not be eligible for phlebotomy based on protocol-defined Hct levels[a]
  - Phlebotomy eligibility defined as Hct > 45% and ≥ 3% higher than baseline or a Hct > 48%
- Patients with missing data or assessments outside of protocol-defined time windows were considered non-responders
- 91% of patients (21/23) who achieved the primary endpoint had durable responses at week 48

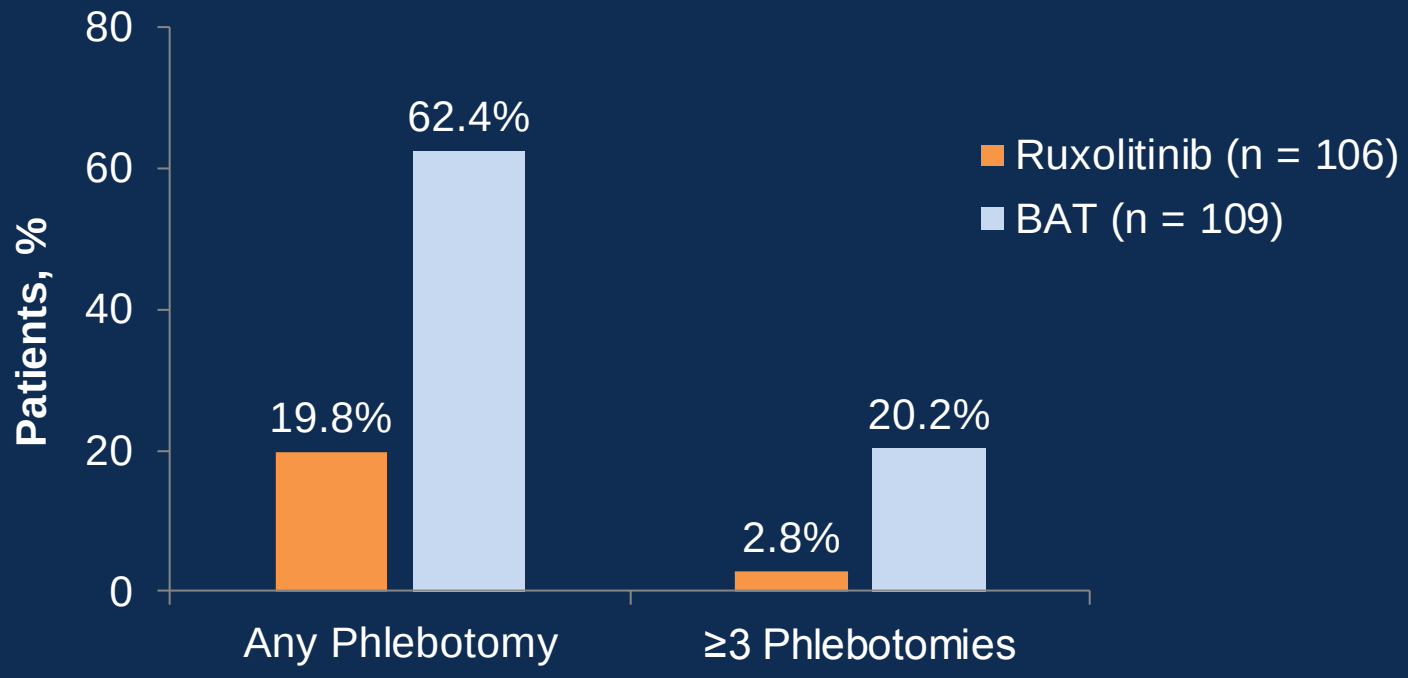
SV, spleen volume.

Duration of Primary Response



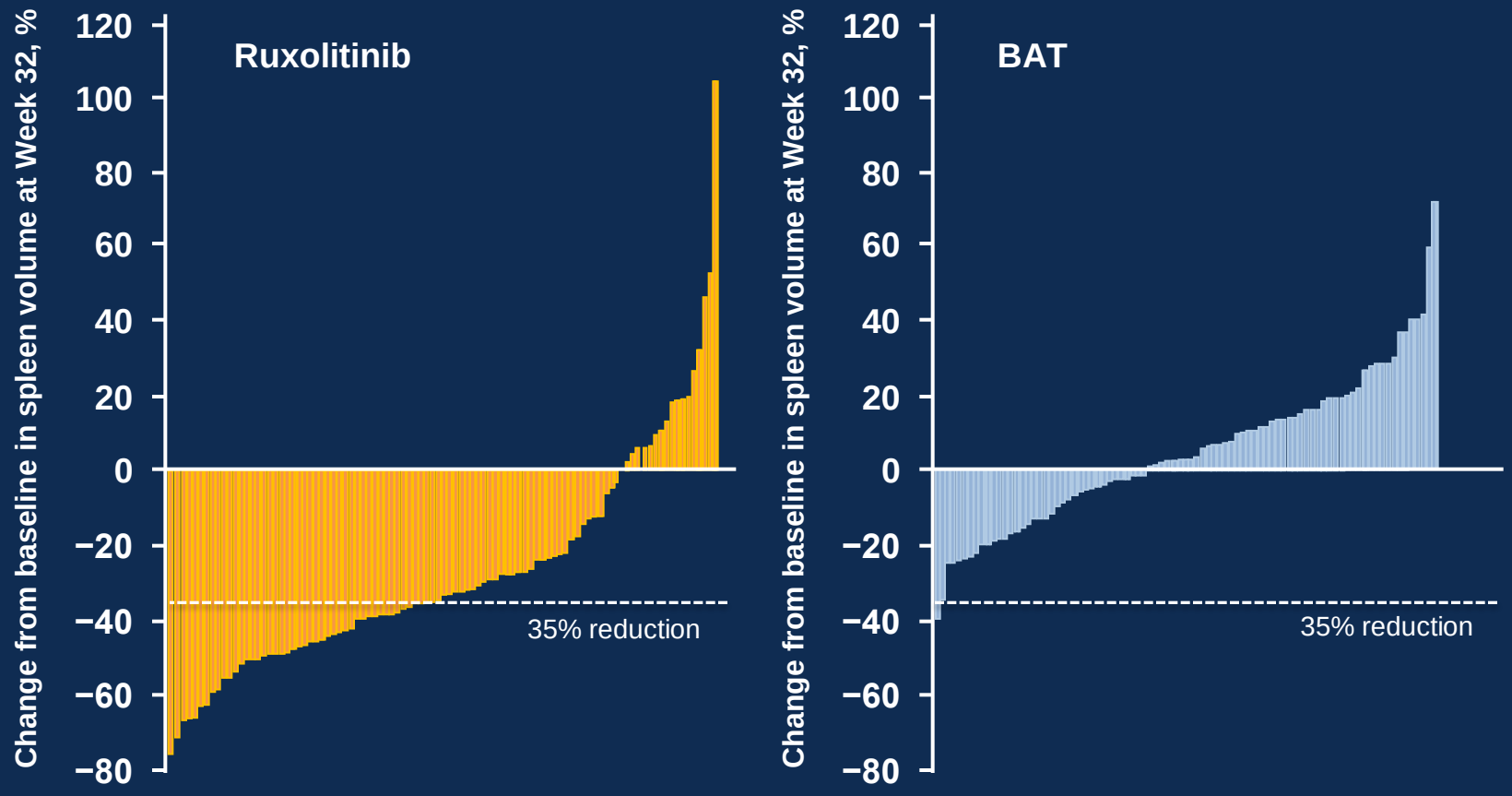
- At data cutoff, only 1 patient lost primary response 37.1 weeks after start of that response
- The probability of maintaining a primary response for ≥ 48 weeks was 94%

Rate of Phlebotomy Procedure

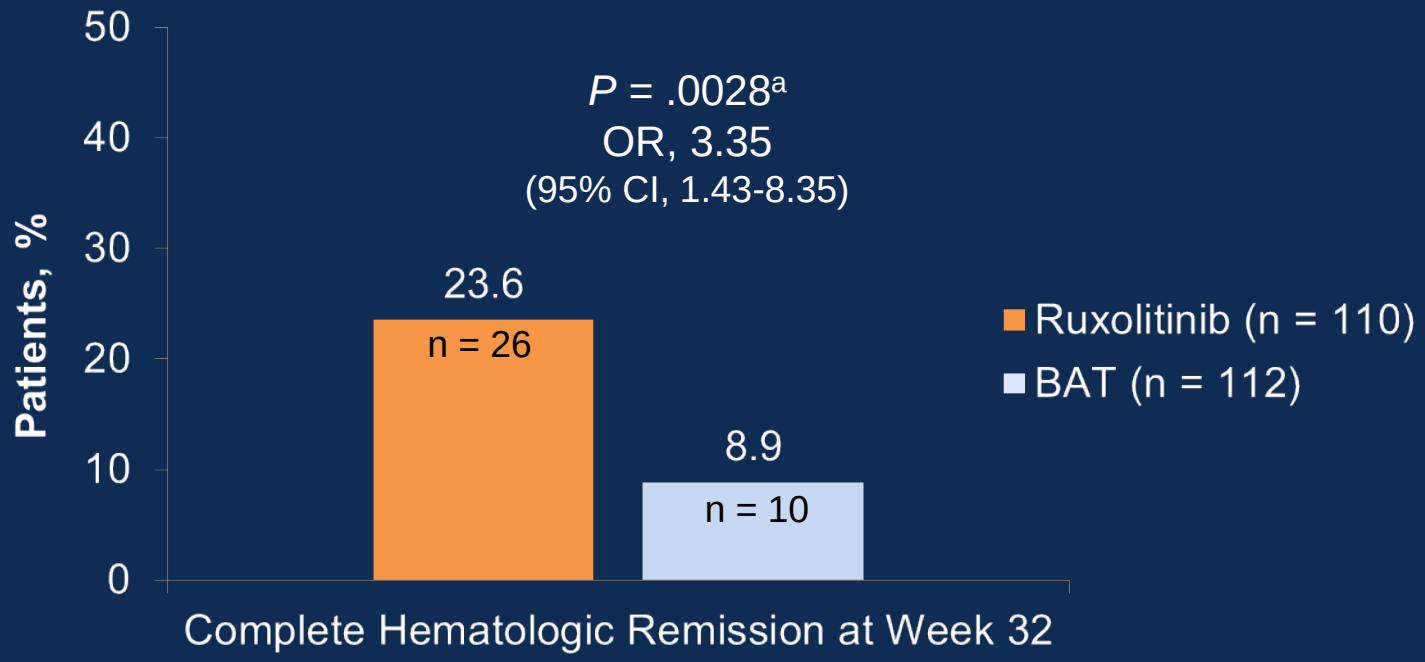


- The phlebotomy rate between week 8 and 32 was > 3 times higher in the BAT arm compared with the ruxolitinib arm
- Only 2.8% of patients in the ruxolitinib group versus 20.2% in the BAT group required 3 or more phlebotomies during this time

Percentage Change in Spleen Volume at Week 32



Complete Hematologic Remission at Week 32



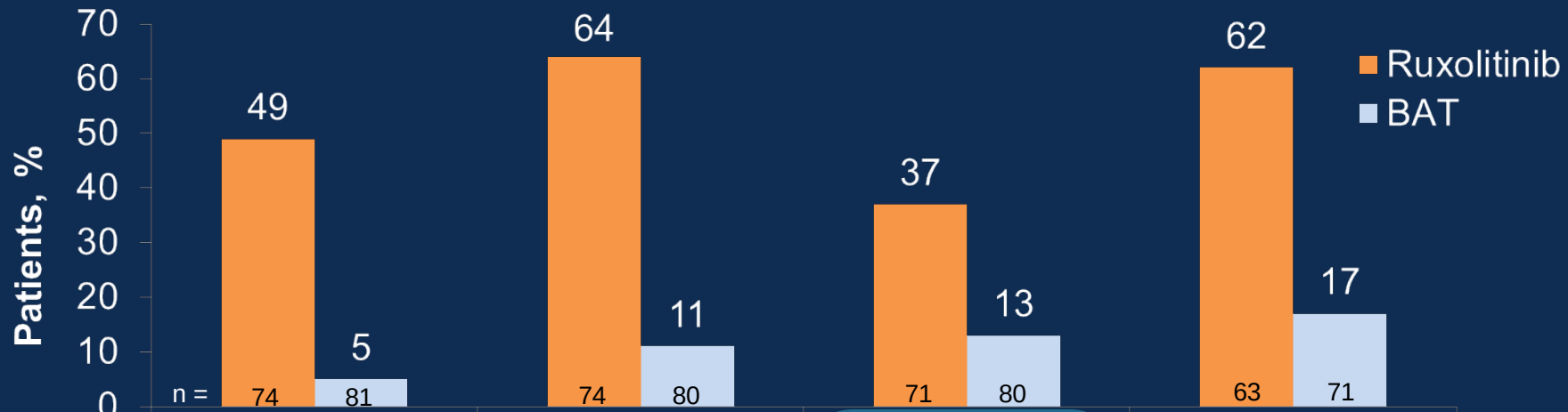
- 88.5% (23/26) of patients who achieved CHR had a durable response at Week 48

[a] P-value, odds ratio and 95% CI were calculated using stratified exact Cochran-Mantel-Haenszel test by adjusting for the WBC/PLT status (abnormal vs normal) at baseline. WBC/PLT status was defined as abnormal if WBC count was > 15 × 10^9/L, and/or PLT count > 600 × 10^9/L.

CHR is defined as Hct Control, PLT count ≤ 400 × 10^9/L, and WBC count ≤ 10 × 10^9/L.

Improvement in Symptoms (Week 32)

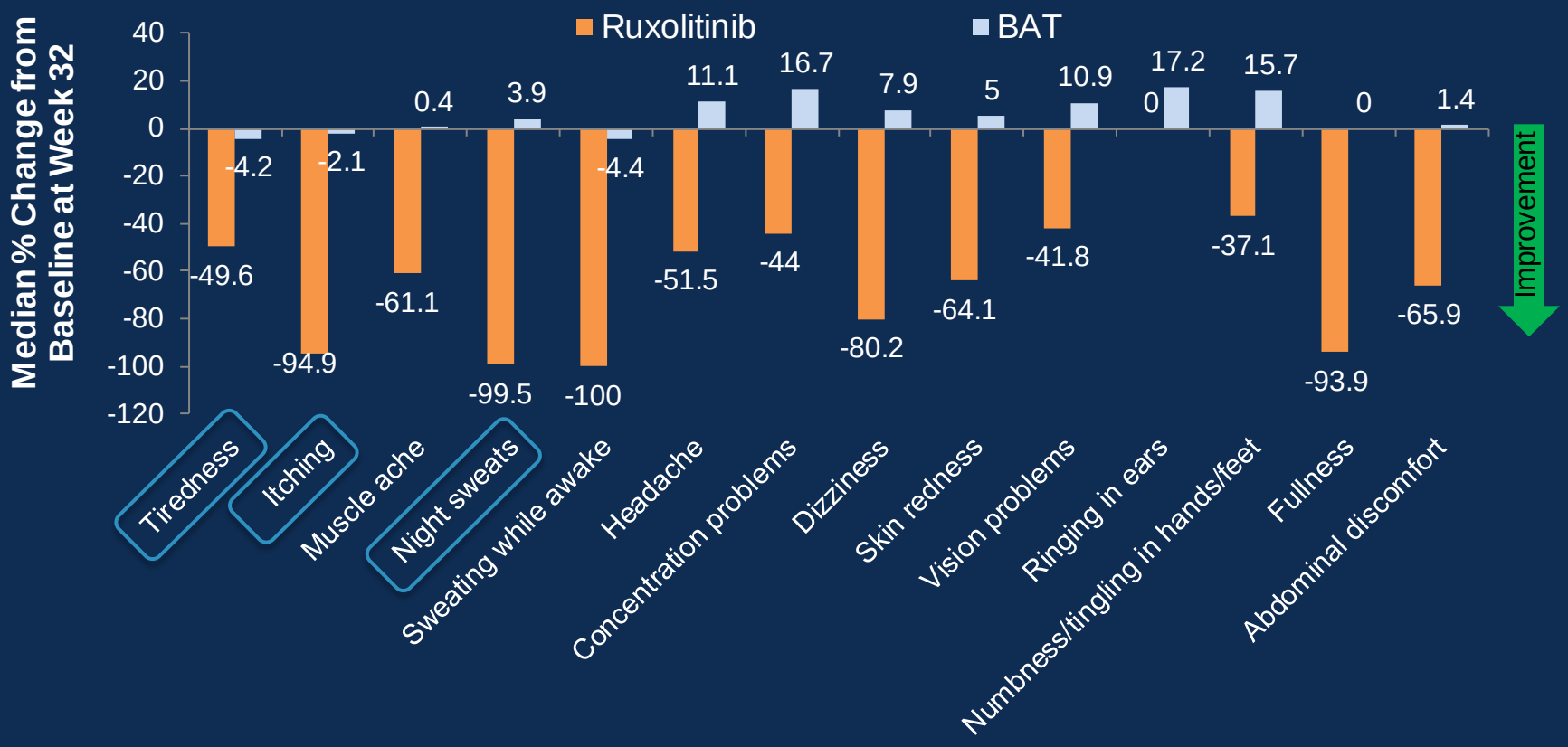
Percentage of Patients with a ≥ 50% Improvement in MPN-SAF Symptom Score at Week 32[a]



[a] In patients with scores at both baseline and week 32.
MPN-SAF, Myeloproliferative Neoplasm Symptom Assessment Form.

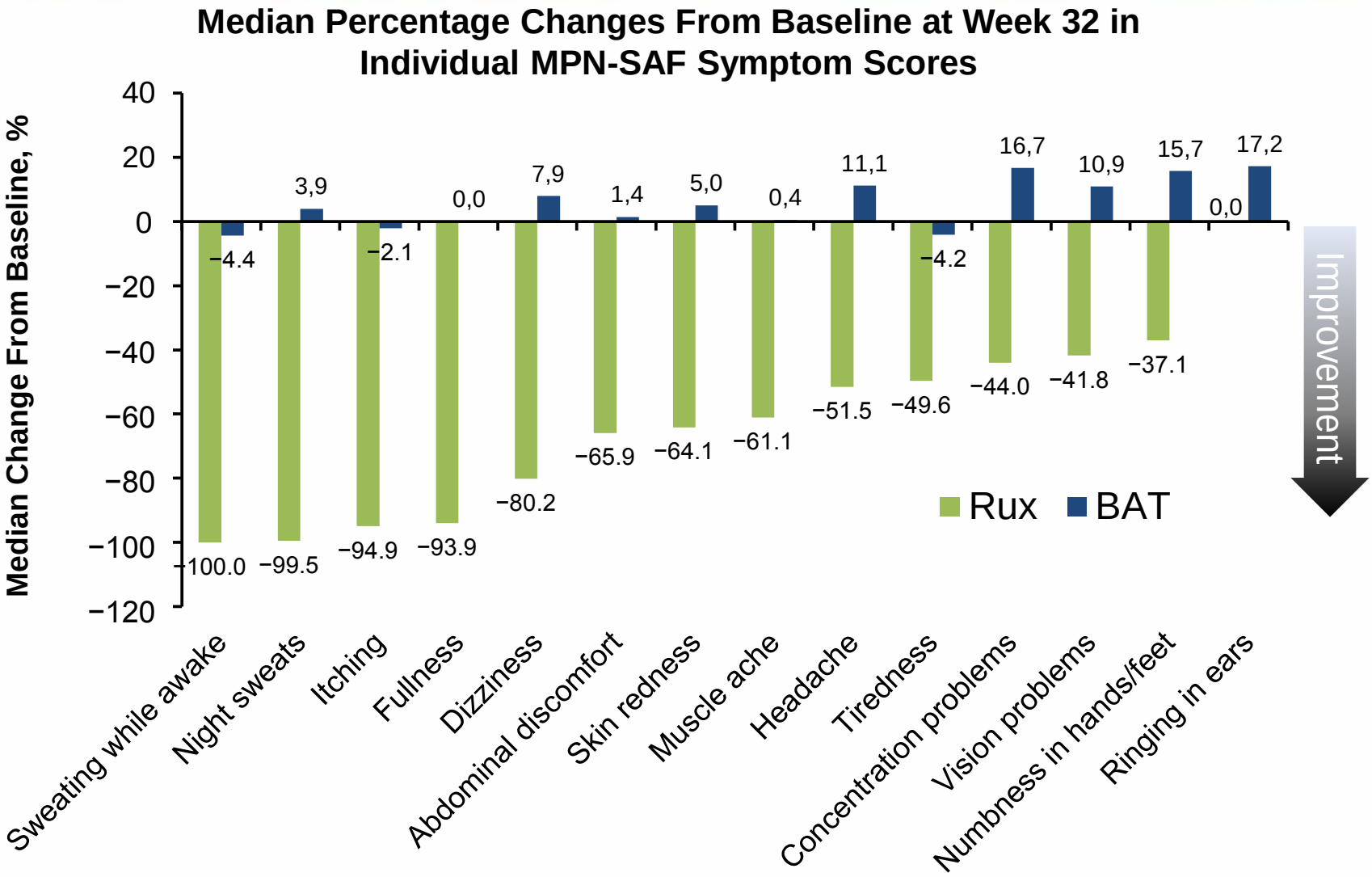
Improvement in Individual Symptoms

Median Percentage Changes From Baseline at Week 32 in Individual Symptom Scores (MPN-SAF)



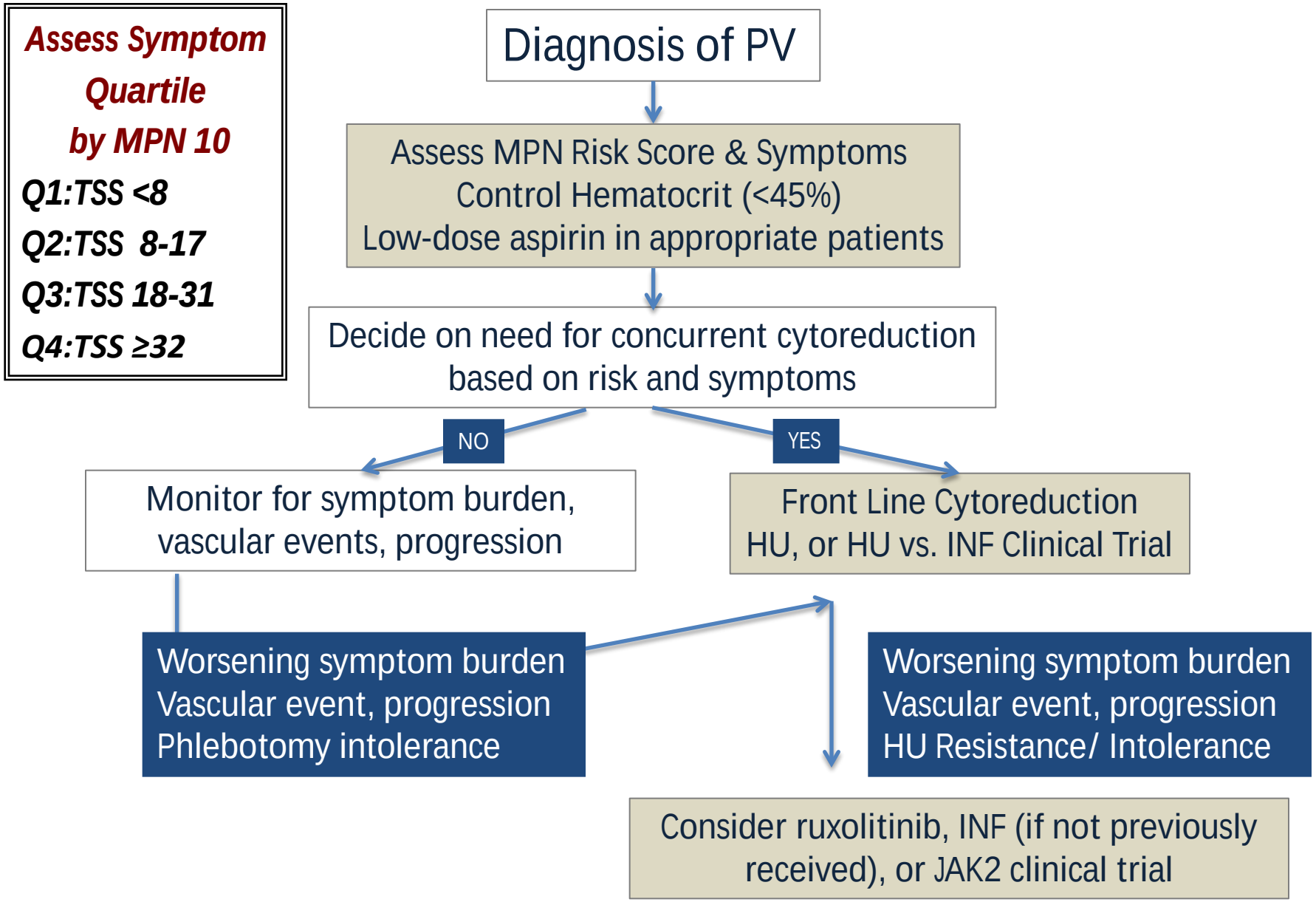
Patients with assessments at baseline and Week 32, with baseline value >0.

RESPONSE TRIAL: CHANGE IN PV SYMPTOMS



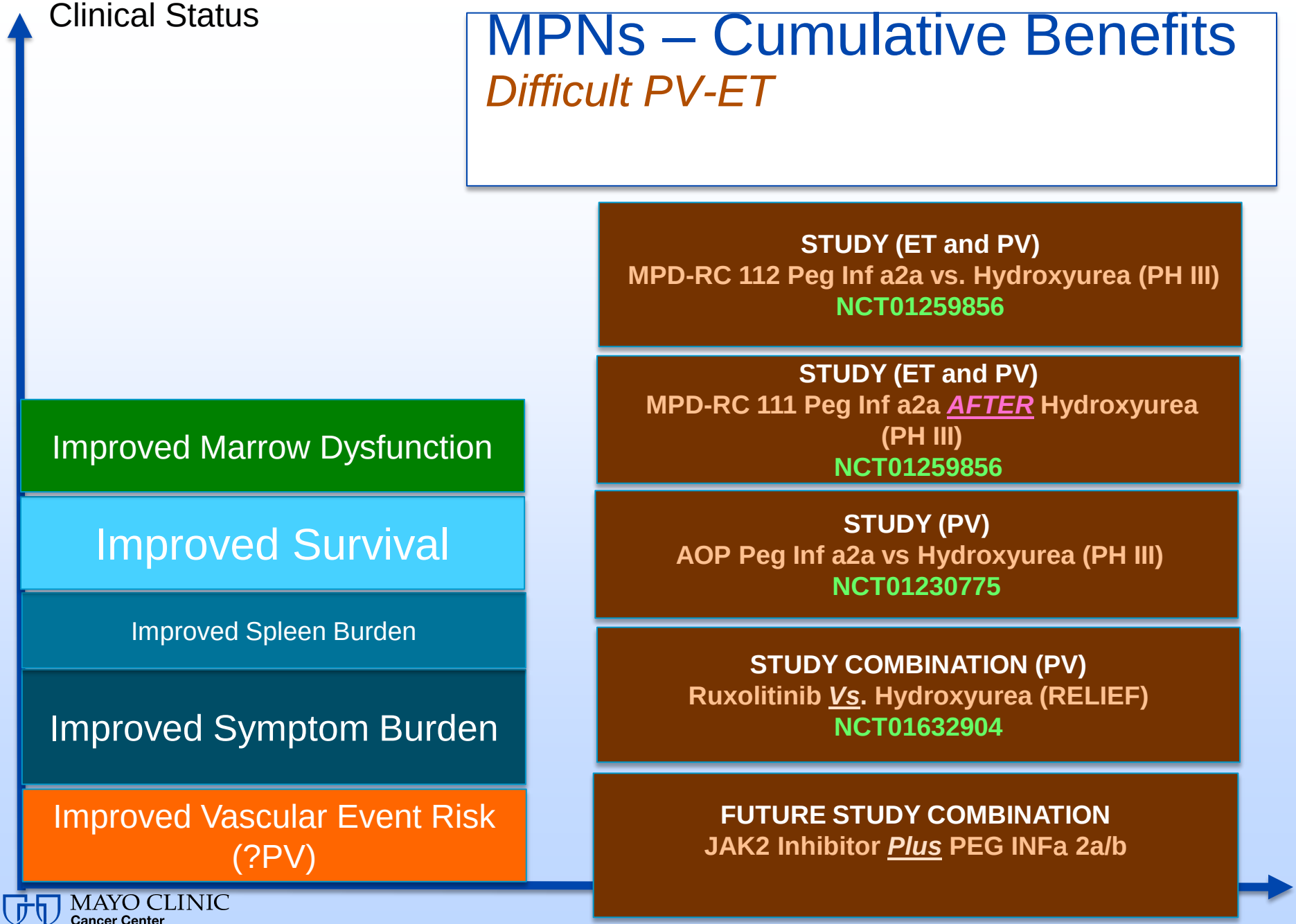
Mesa R. ASH 2014. Abstract 709.

POSSIBLE ALGORITHM OF THERAPY OF PV IN 2015



MPNs – Cumulative Benefits

Difficult PV-ET



PV IN 2015

- PV is a heterogeneous disease impacting risk of vascular events, symptom burden and variable risk of progression
- Therapy of PV begins with hematocrit control, and anti-platelet therapy
- Front line cytoreduction is currently hydroxyurea or interferon
- Ruxolitinib in “problematic” PV, after HU, has been helpful for control of symptoms, splenomegaly, control of erythrocytosis, and likely decreased vascular events