



MAYO CLINIC  
Cancer Center



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Arizona, USA

## *What should you expect of your MPN Therapy?*

**Ruben A. Mesa, MD**

*Professor & Chairman, Division of Hematology & Medical Oncology  
Deputy Director, Mayo Clinic Cancer Center  
Mayo Clinic – Arizona, USA*

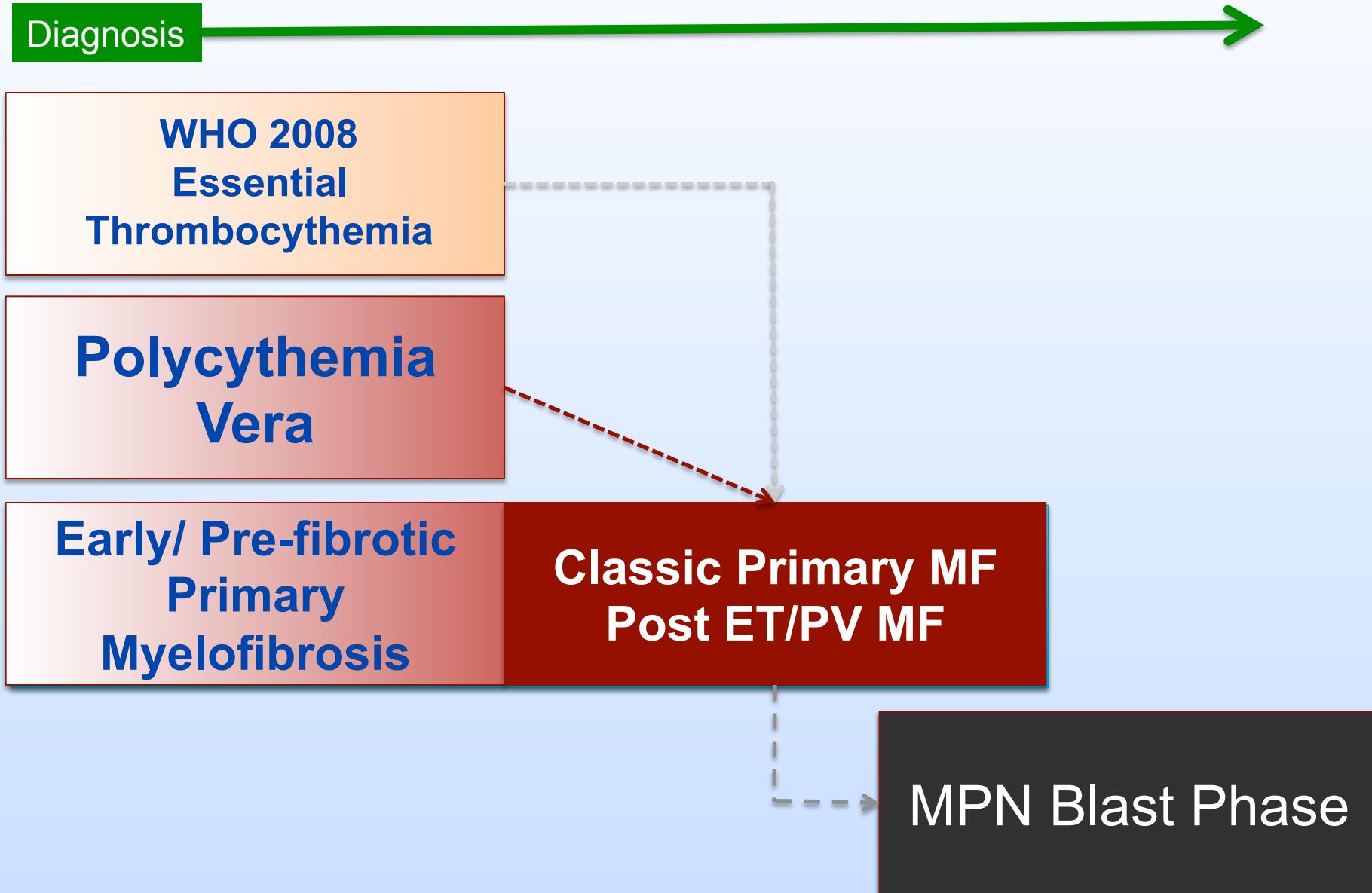
# What should you expect of your MPN Therapy?

## *Individualizing Therapy*

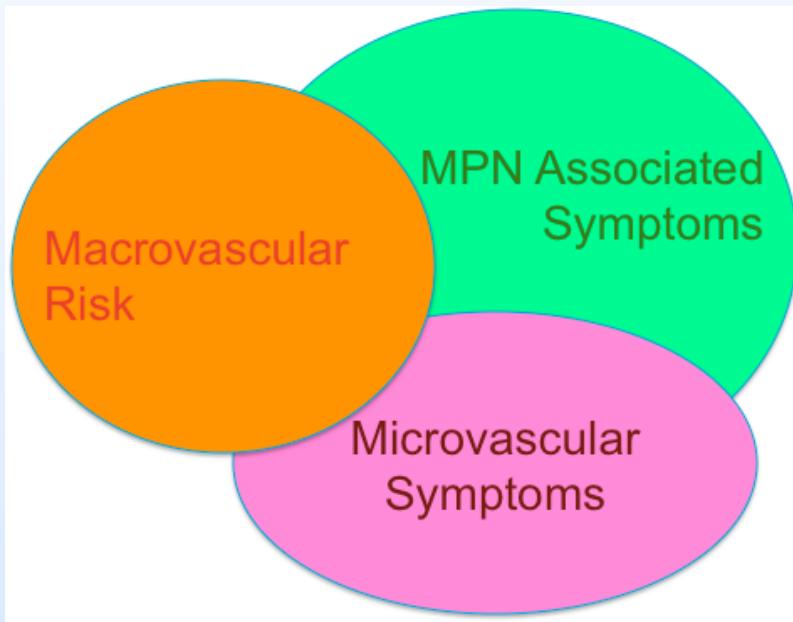
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- What is the spectrum of disease burden and risk in MPNs?
- What phenotypic clusters exist in MPN patients?
- How might we incorporate the assessment of disease burden and risk in choosing therapy for MPN patients?

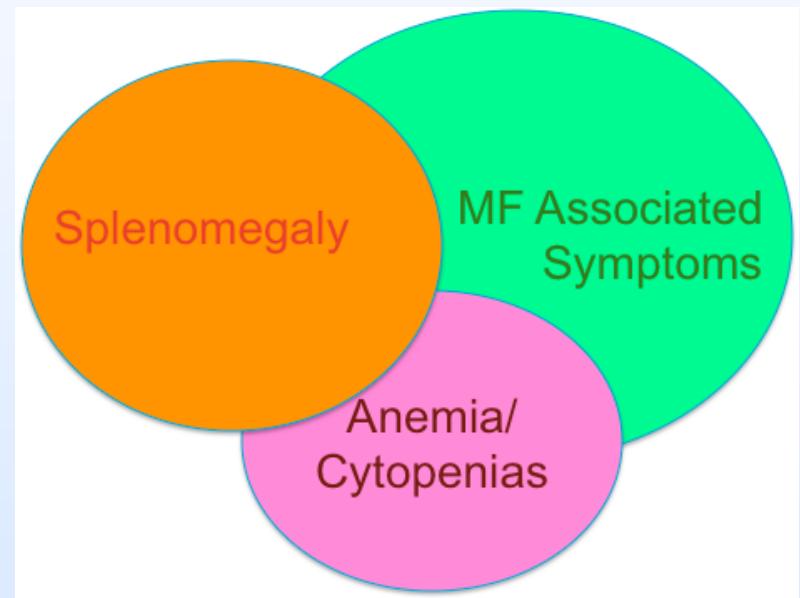
# The Natural History of MPNs



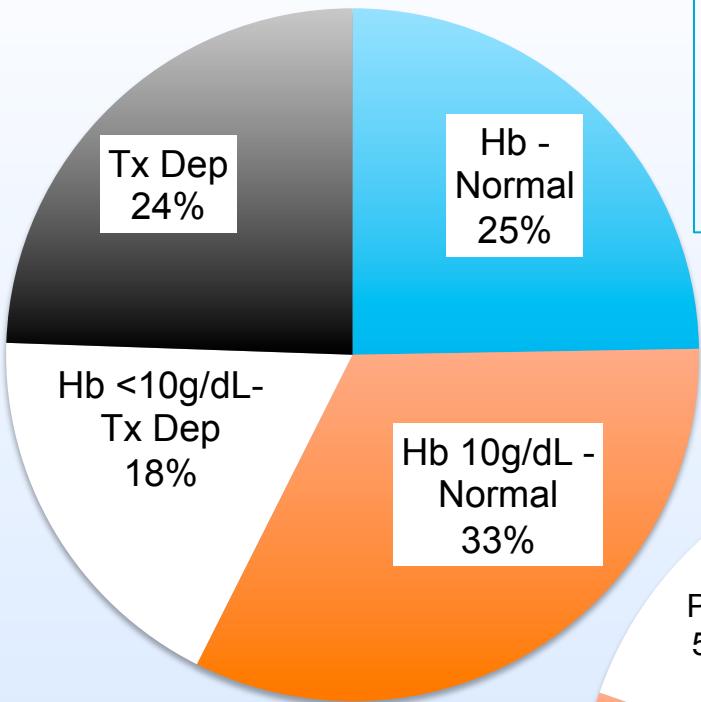
# Burden of ET/PV



# Burden of Myelofibrosis

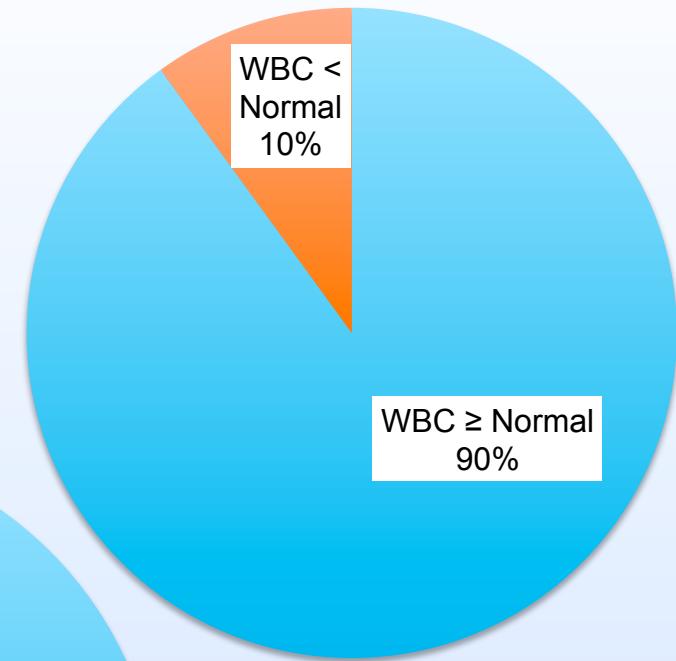
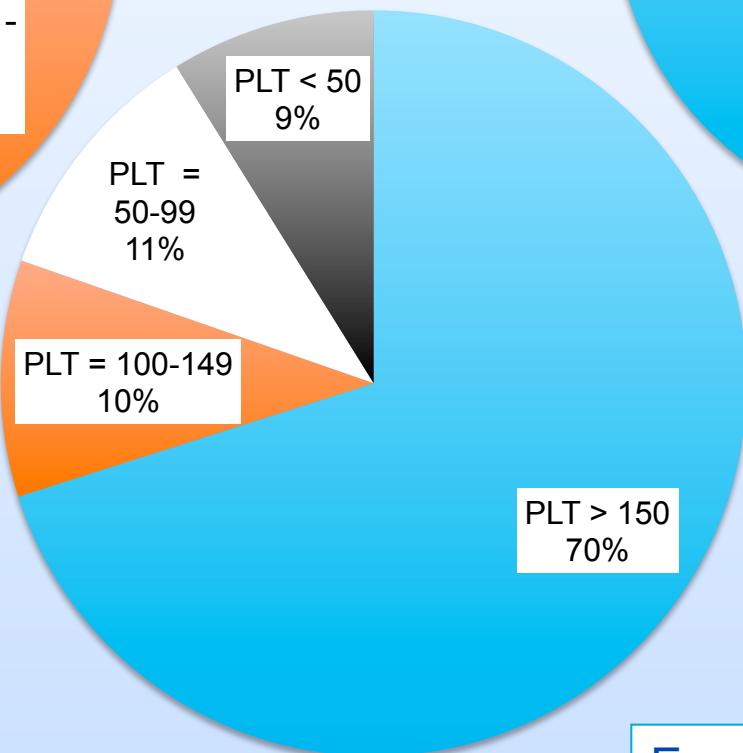


# Myelofibrosis and Cytopenias (N=364)



N.B.

- Varying times
- NL Hg
  - Men 13.5 g/dL
  - Women 12 g/dL



Emanuel et. al. JCO 2012

# Cytopenias and their impact MF

Anemia

- *Fatigue*
- *Dyspnea*
- *Organ Dysfunction*

>

Thrombocytopenia

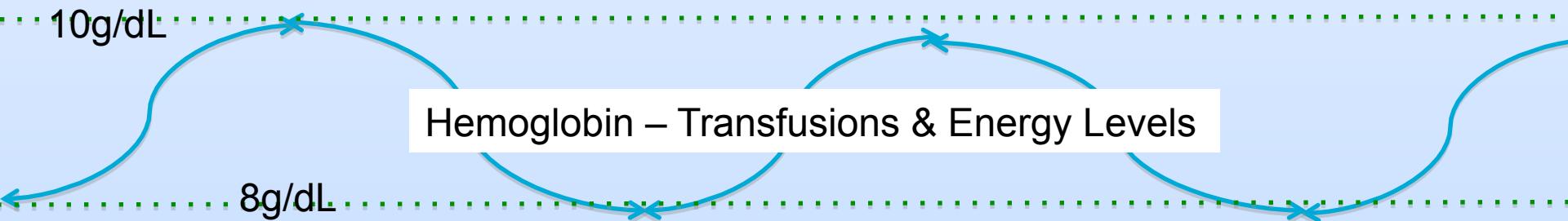
- *Hemorrhage*

>

Leukopenia

- *Infection*

Normal Energy Levels



# Myelofibrosis and Splenomegaly

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- 89% of MF with palpable splenomegaly (at diagnosis)  
Multi-institutional database of 1054 patients at time of diagnosis of PMF  
**(Cervantes et. al. Blood 2009)**
- 64% with palpable splenomegaly (By physician report)
- Median spleen size 7.4 cm BLCM  
International prospective MPN symptom study N=329  
MF patients  
**(Emanuel et. al. JCO 2012)**

# Why does splenomegaly in MF matter?

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1. Mechanical discomfort
2. Pain
3. Possible splenic infarction
4. Early satiety adding to cachexia
5. Splenic sequestration and exacerbation of cytopenias
6. May delay engraftment in setting of allogeneic stem cell transplant

# Burden of Vascular Events

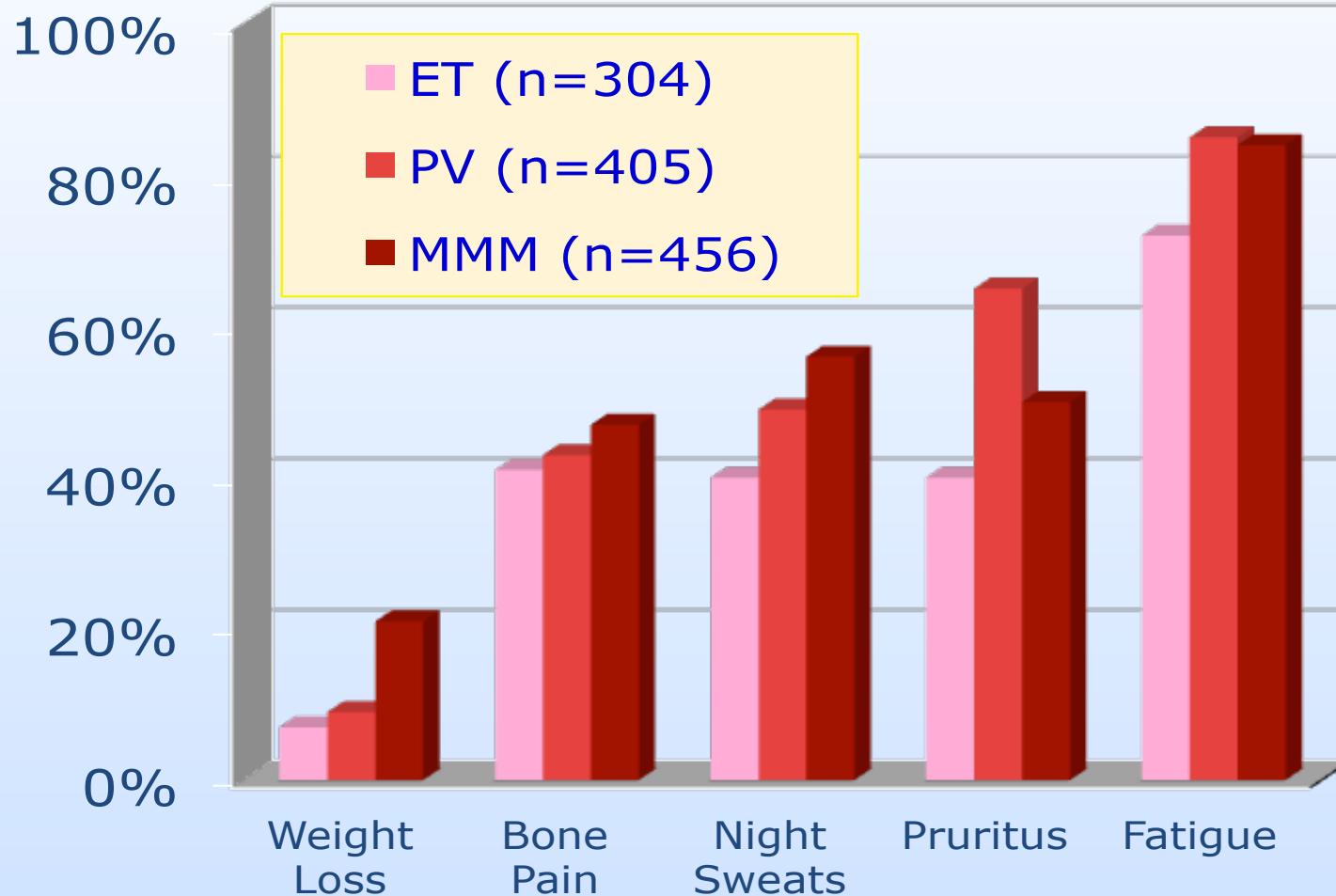
## *Retrospective Review of 707 patients with PMF*

<b>Patients with history of thrombotic events, no. (%)</b>	
AMI	13 (1.8)
Stroke-TIA	16 (2.3)
PAT	2 (0.3)
VTE	32 (4.5)
Splanchnic	4 (0.6)

Barbui et. al. Blood 2010;115:778-782

# Symptoms in 1179 MPN Patients

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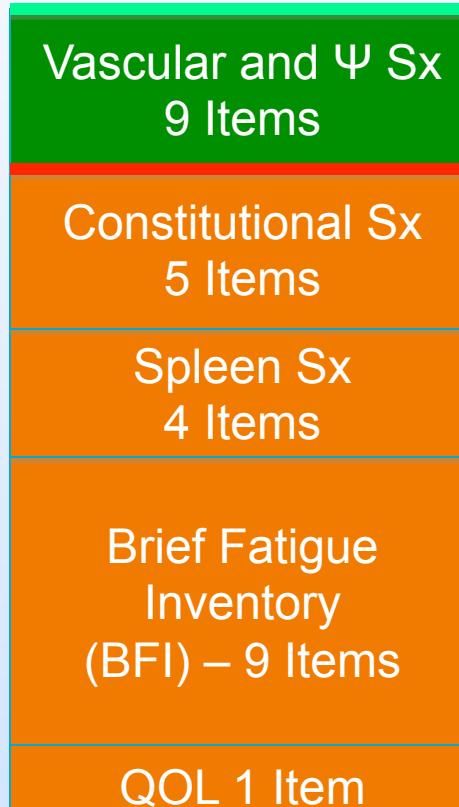


Woman Ironing  
1904

Guggenheim, New York, NY

Pablo Picasso (1881-1973)

# Evolution of MPN Symptom Assessment Tools



## MPN-SAF Languages

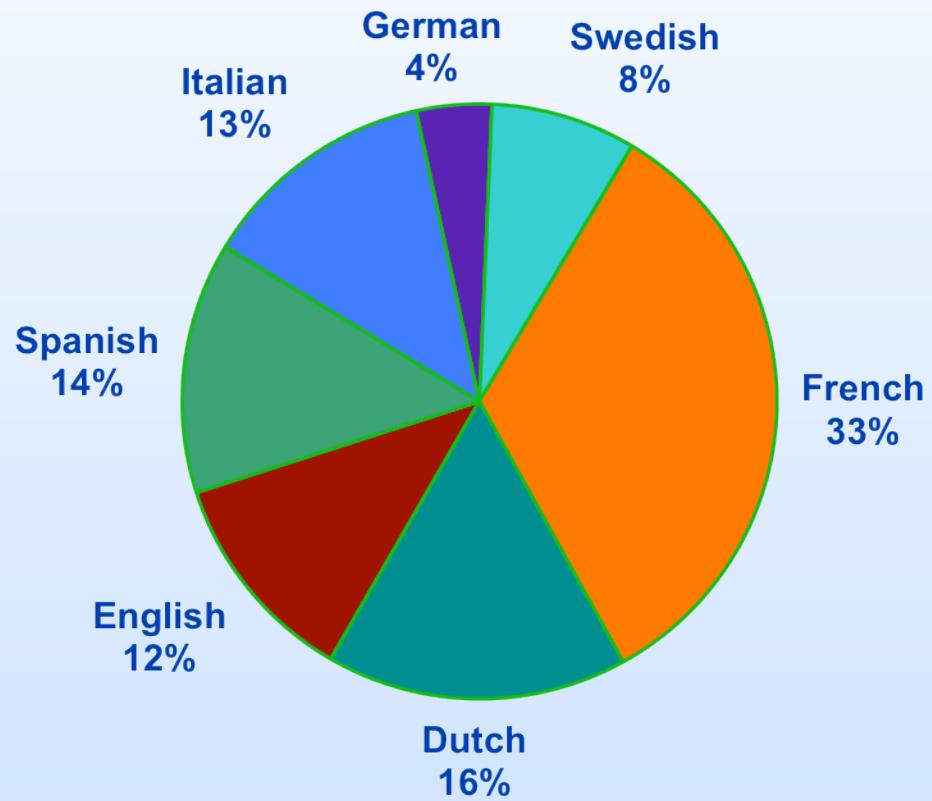
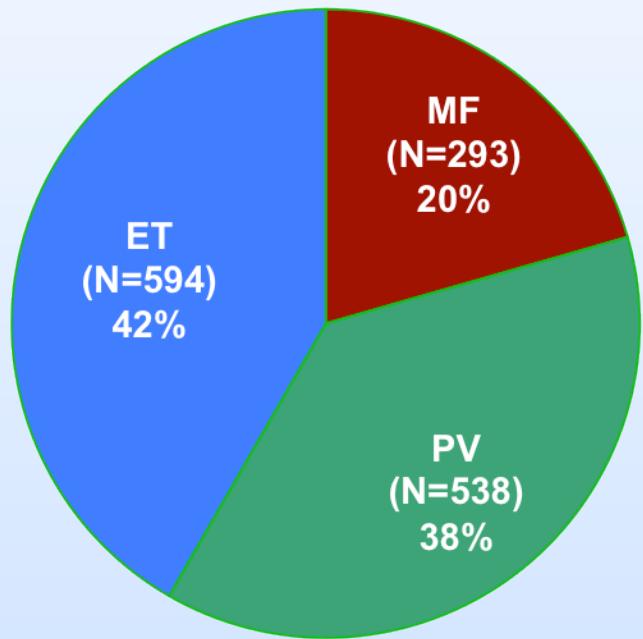
- English
- French
- German
- Spanish
- Dutch
- Swedish
- Italian
- Portuguese
- Mandarin
- Japanese
- Hebrew

MPN-SAF  
2011  
(27 items)  
*Blood 2011*

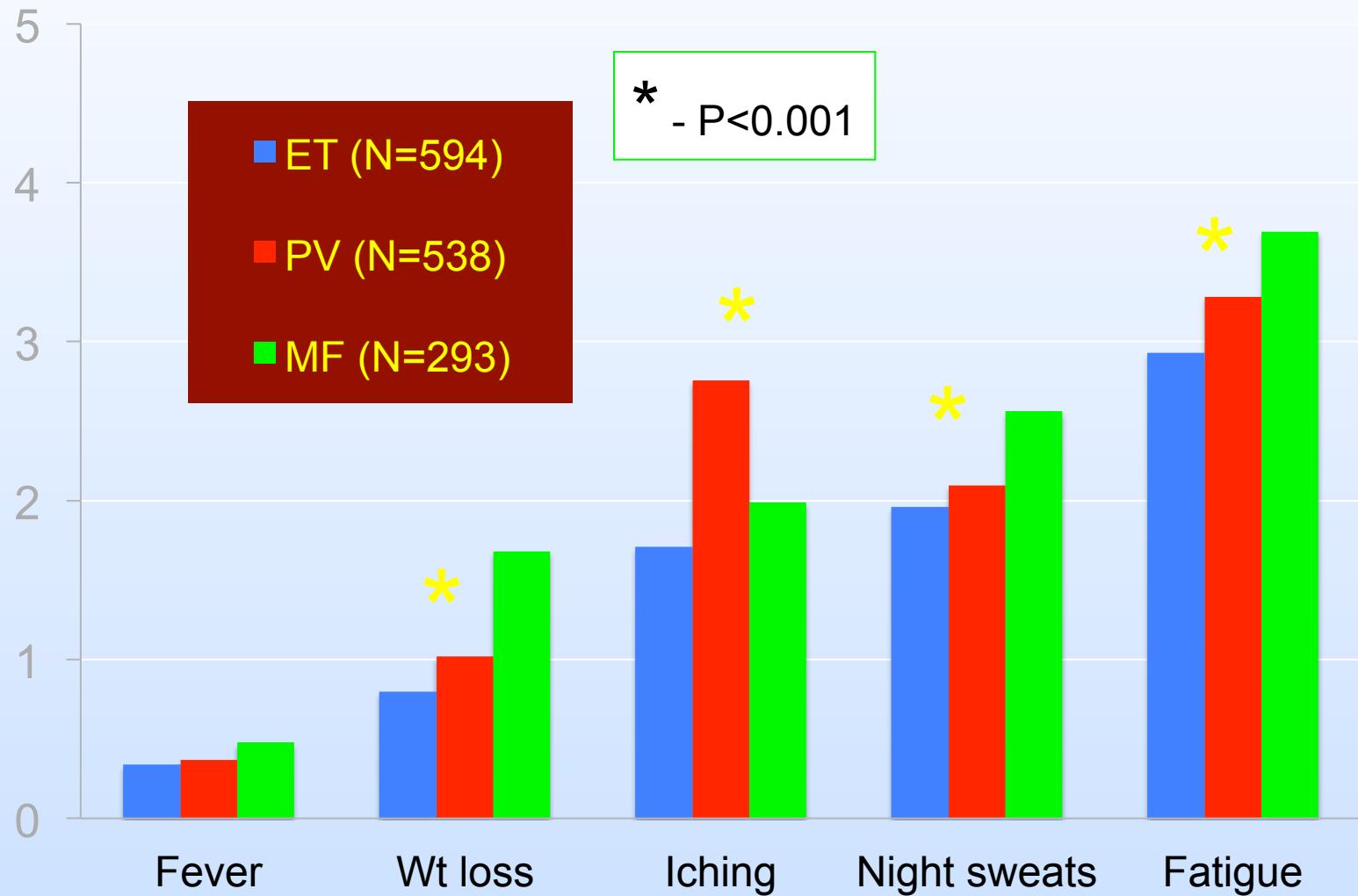
MPN-SAF TSS  
(10 items 2012)  
*JCO 2012*

# MPN-SAF (N=1433)

*Myeloproliferative Neoplasm Symptom Assessment Form*

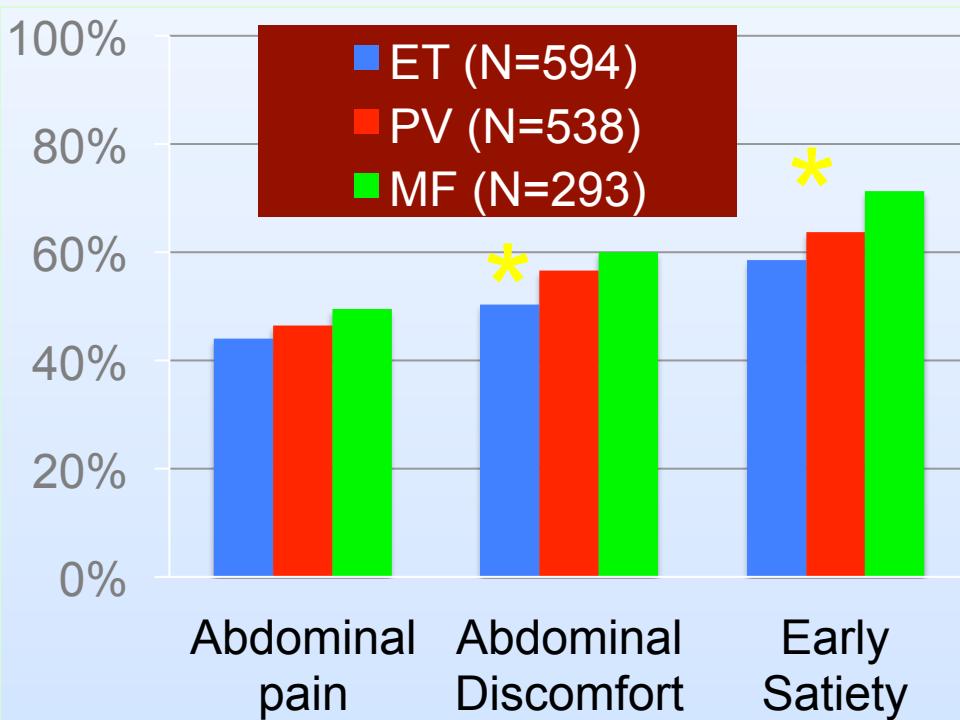


# Severity of “Constitutional” Symptoms in 1433 MPN Patients

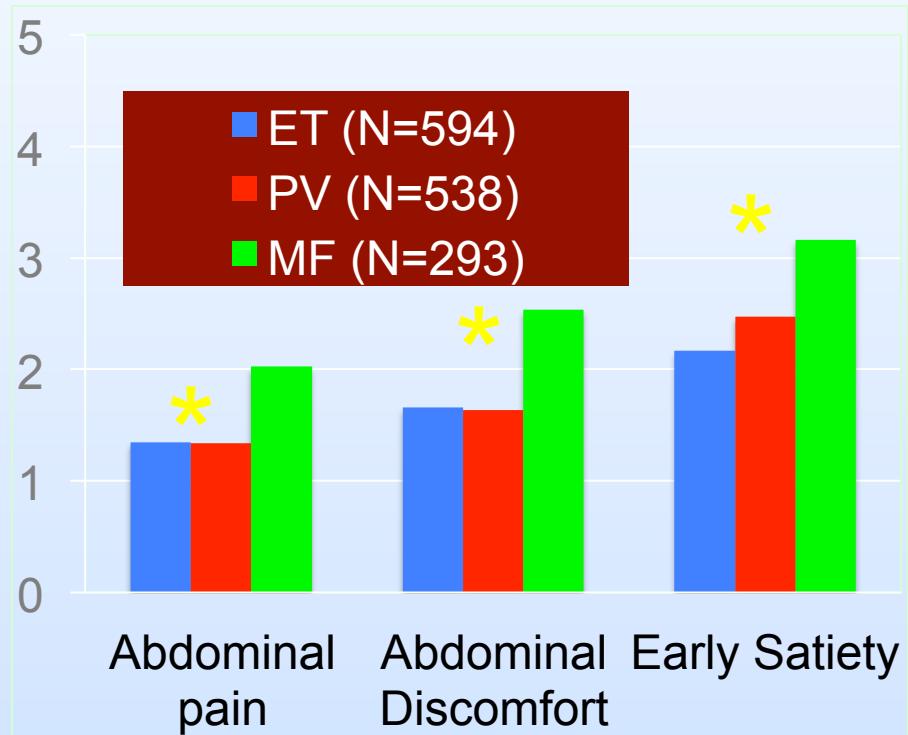


# Spleen Derived Symptoms in 1433 MPN Patients

## Prevalence

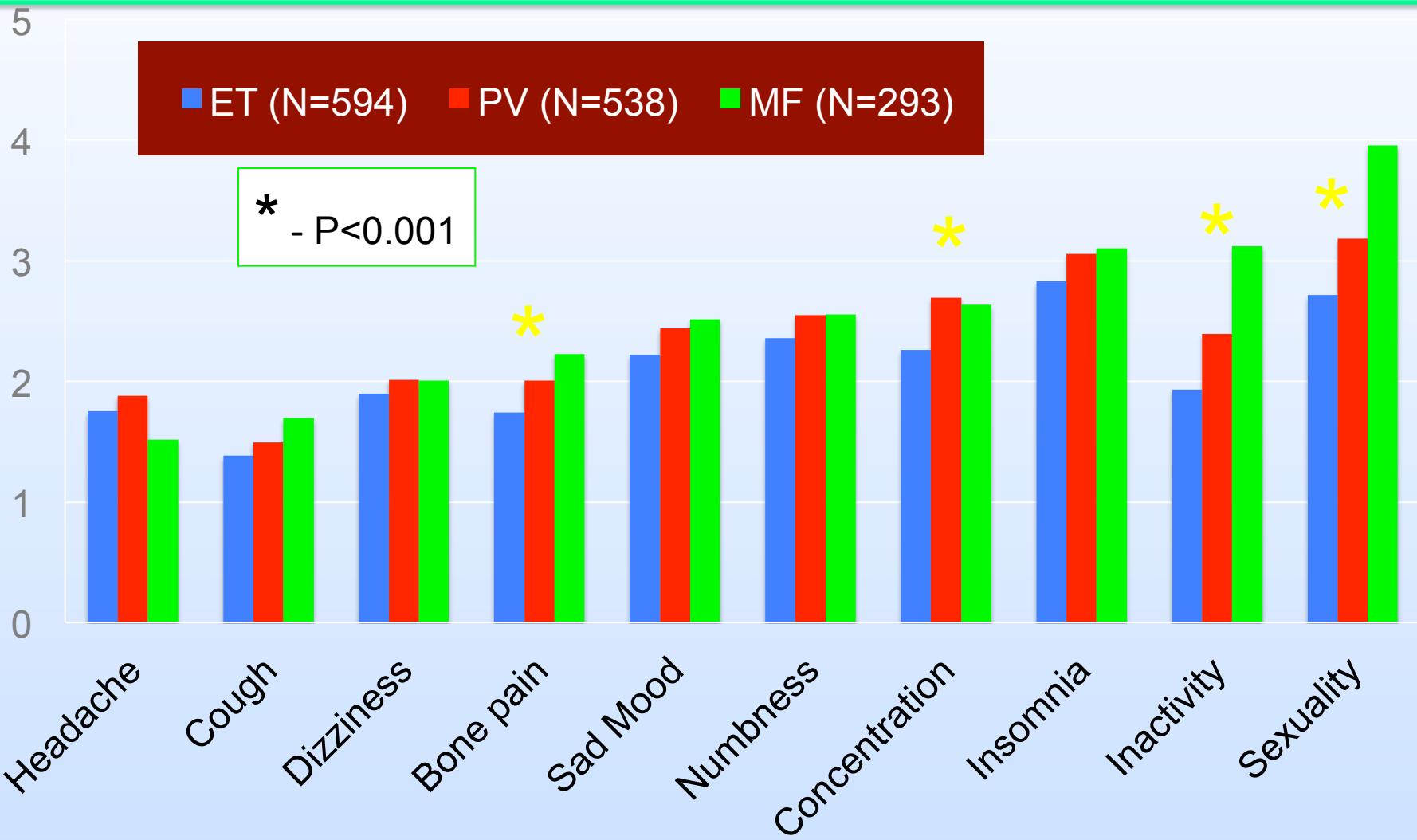


## Severity



\* - P<0.001

# Severity of “End Organ” Symptoms in 1433 MPN Patients



# EORTC QLQ-C30 Scores in MF and Other Hematologic Malignancies and Solid Tumors

EORTC QLQ-C30	Myelofibrosis COMFORT-I placebo arm (N=147*)	Myelofibrosis (N=96) <sup>1</sup>	CML (N=73) <sup>2</sup>	Myeloma (N=944) <sup>3</sup>	Breast (N=2782) <sup>3</sup>	Lung (N=3332) <sup>3</sup>	Recurrent/ metastatic cancers (N=4812) <sup>3</sup>
Global Health Status/QoL	52.9	59.9	70.2	55.7	61.8	56.6	56.3
Functional Subscales							
Physical Functioning	67.2	74.9	78.0	67.7	78.4	71.9	75.8
Role Functioning	63.2	68.8	78.1	60.1	70.9	61.5	60.7
Emotional Functioning	75.5	76.5	78.8	71.3	68.6	68.9	68.7
Cognitive Functioning	80.1	77.0	86.1	78.1	81.5	82.3	80.5
Social Functioning	66.1	74.9	84.3	63.2	77.0	71.3	70.5
Symptom Scales/Single Items							
Fatigue	54.1	41.0	29.8	48.7	33.3	41.1	41.8
Pain	29.9	22.6	10.1	47.1	28.7	29.7	33.7
Dyspnea	37.0	29.8	15.5	26	18.1	37.9	23.4
Insomnia	39.1	33.7	26.9	28.9	29.8	31.6	33.6
Appetite loss	33.3	15.1	13.7	23.2	18.5	28.1	28.2

→ = Worsening Direction



The Kiss

1907

Österreichische Galerie Belvedere  
Vienna

Gustav Klimt (1862-1918)

# Phenotypic Clusters in MPNs

## *Individualizing Therapy*

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- What is the spectrum of disease burden and risk in MPNs?
- What phenotypic clusters exist in MPN patients?
- How might we incorporate the assessment of disease burden and risk in choosing therapy for MPN patients?

# PV and ET

## *Symptom Burden - Methods*

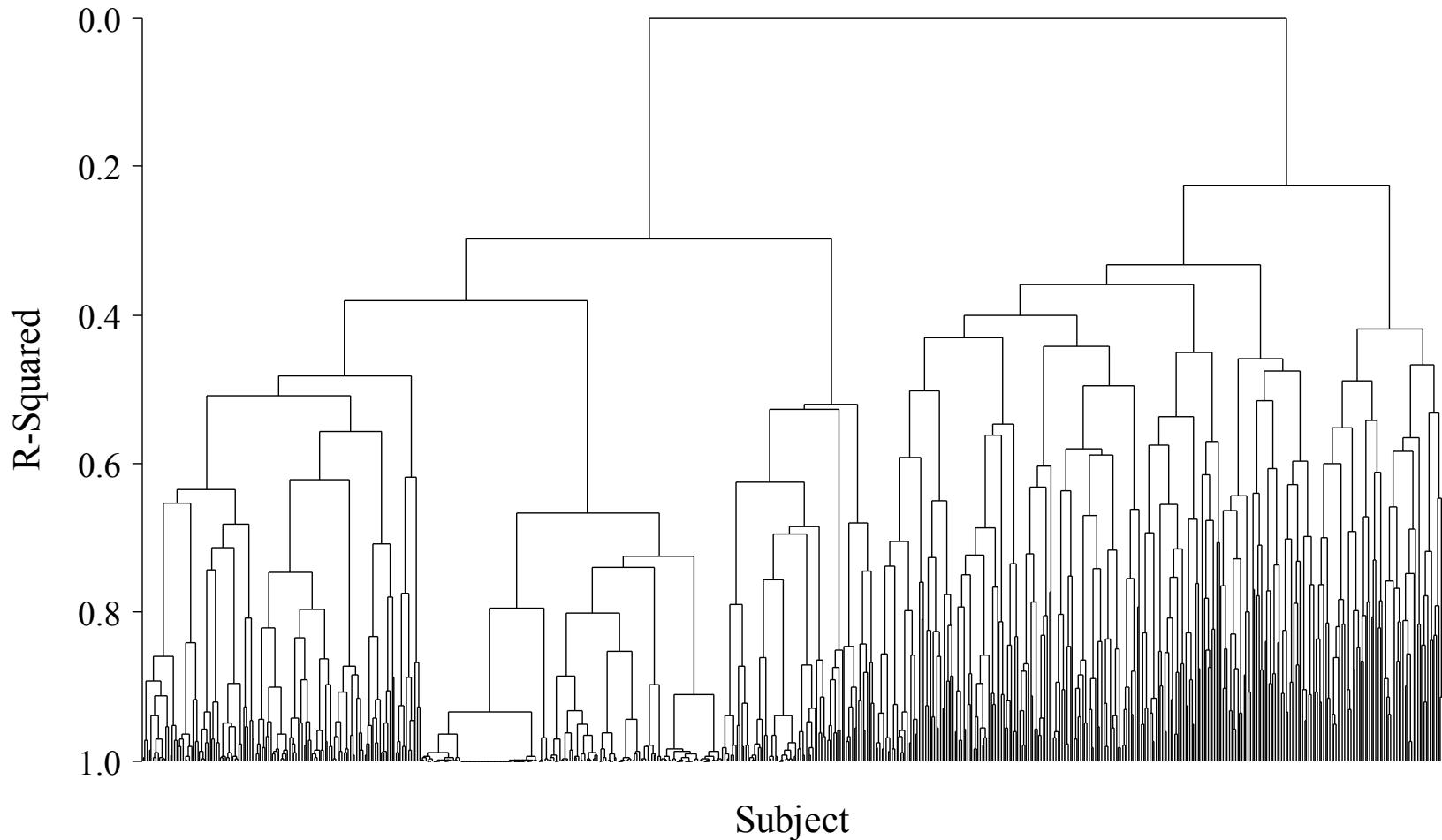
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- 1141 patients with PV (N=519) and ET (N=622) prospectively assessed in North America, South America, Europe, and Asia
  - English, Spanish, French, German, Dutch, Swedish, Italian, Chinese
- MPN-SAF, BFI, EORTC-QLQc30, Disease Features
- *Cluster development was based on consideration of r-squared in hierarchical clustering using Ward linkage. Final cluster assignment was based on the nonhierarchical k-means method. Comparisons across symptom clusters were based on ANOVA and chi-squared tests*

ET

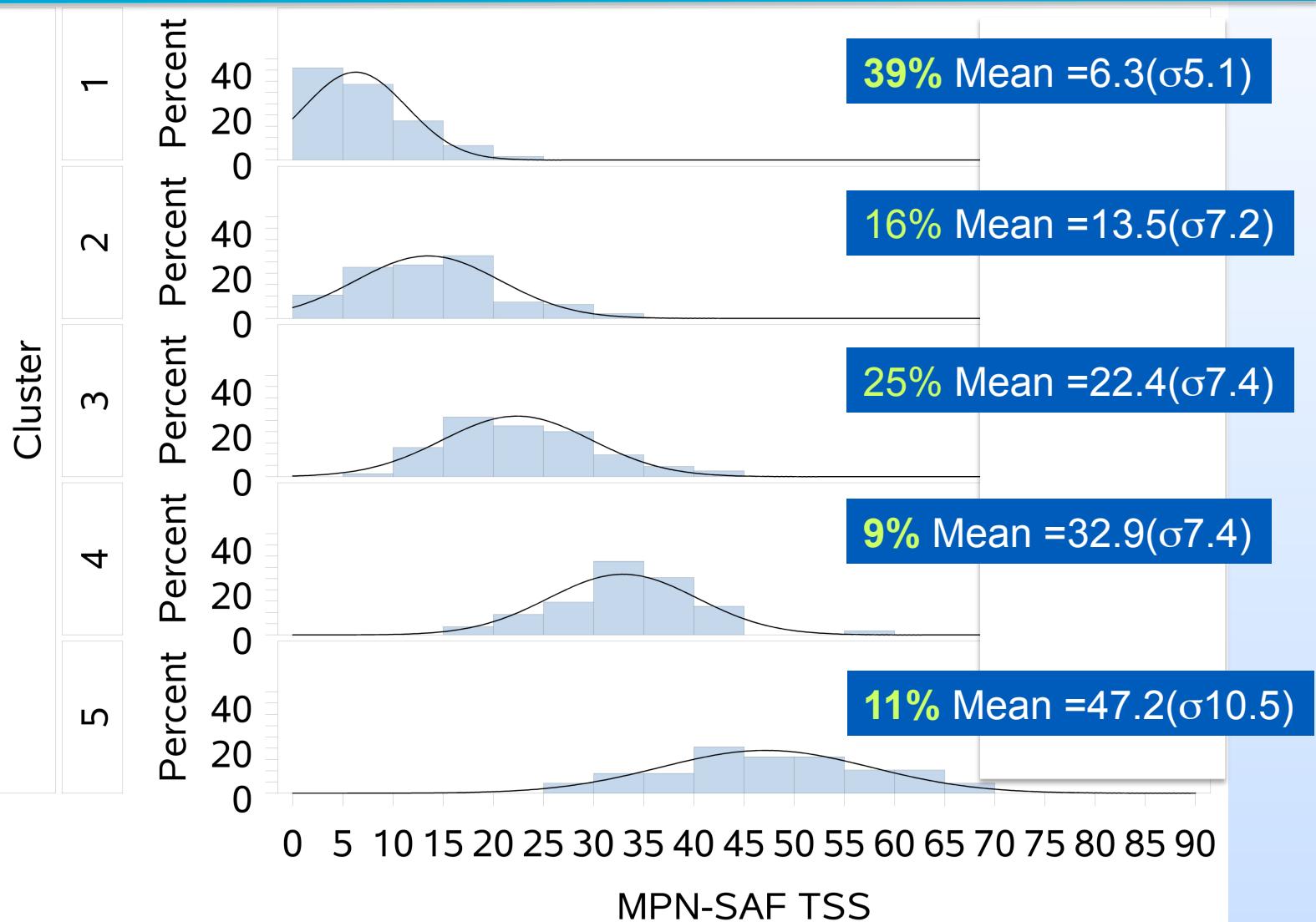
*Symptom Burden - Clusters*

## ET Cluster Analysis



# ET

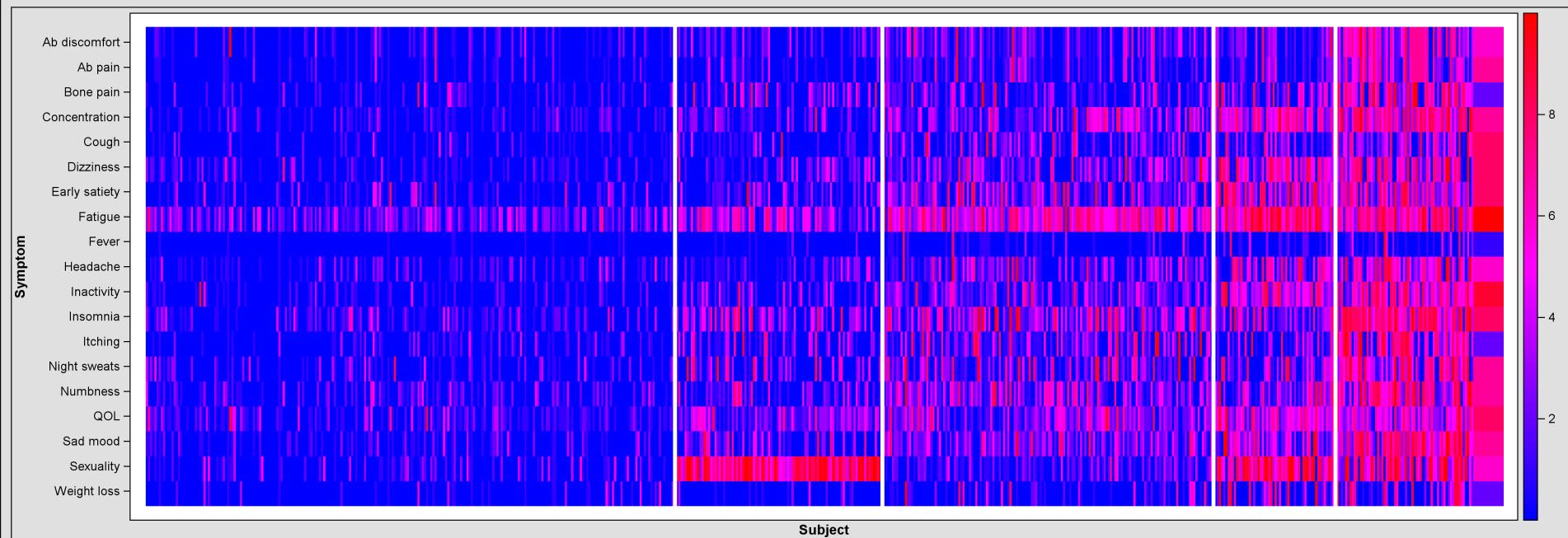
## Symptom Burden - Clusters



# ET Symptom Burden Clusters (N=622)

Difference in each symptom between clusters all  $p < 0.001$

Cluster 5 (N=68)



Cluster 1 (N=247)

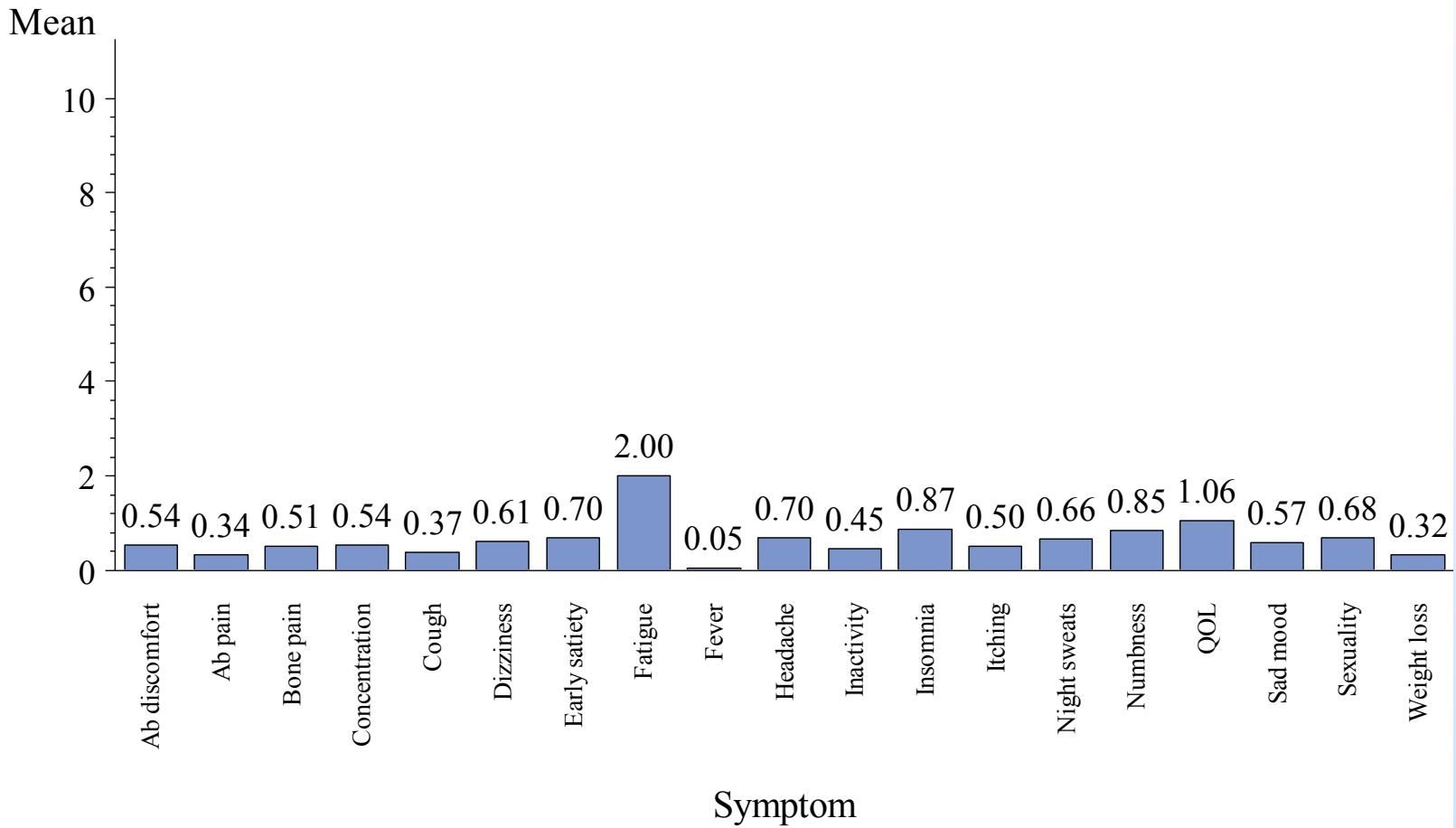
Cluster 2 (N=97)

Cluster 3 (N=155)

Cluster 4 (N=55)

# Cluster 1: Reduced Symptom Cluster (39%)

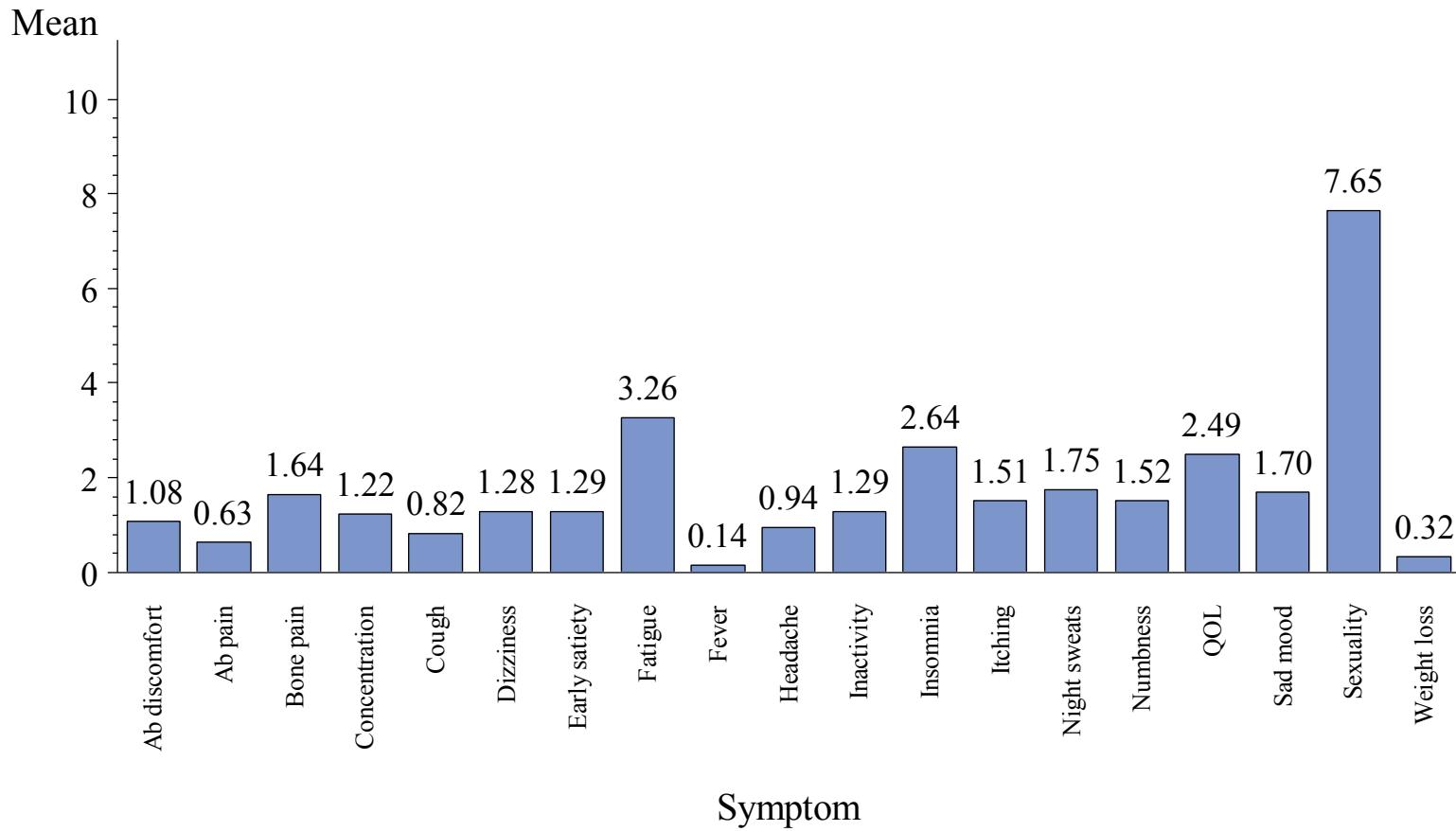
## Cluster 1



# Cluster 2: Fatigue Dominant Cluster

(16%)

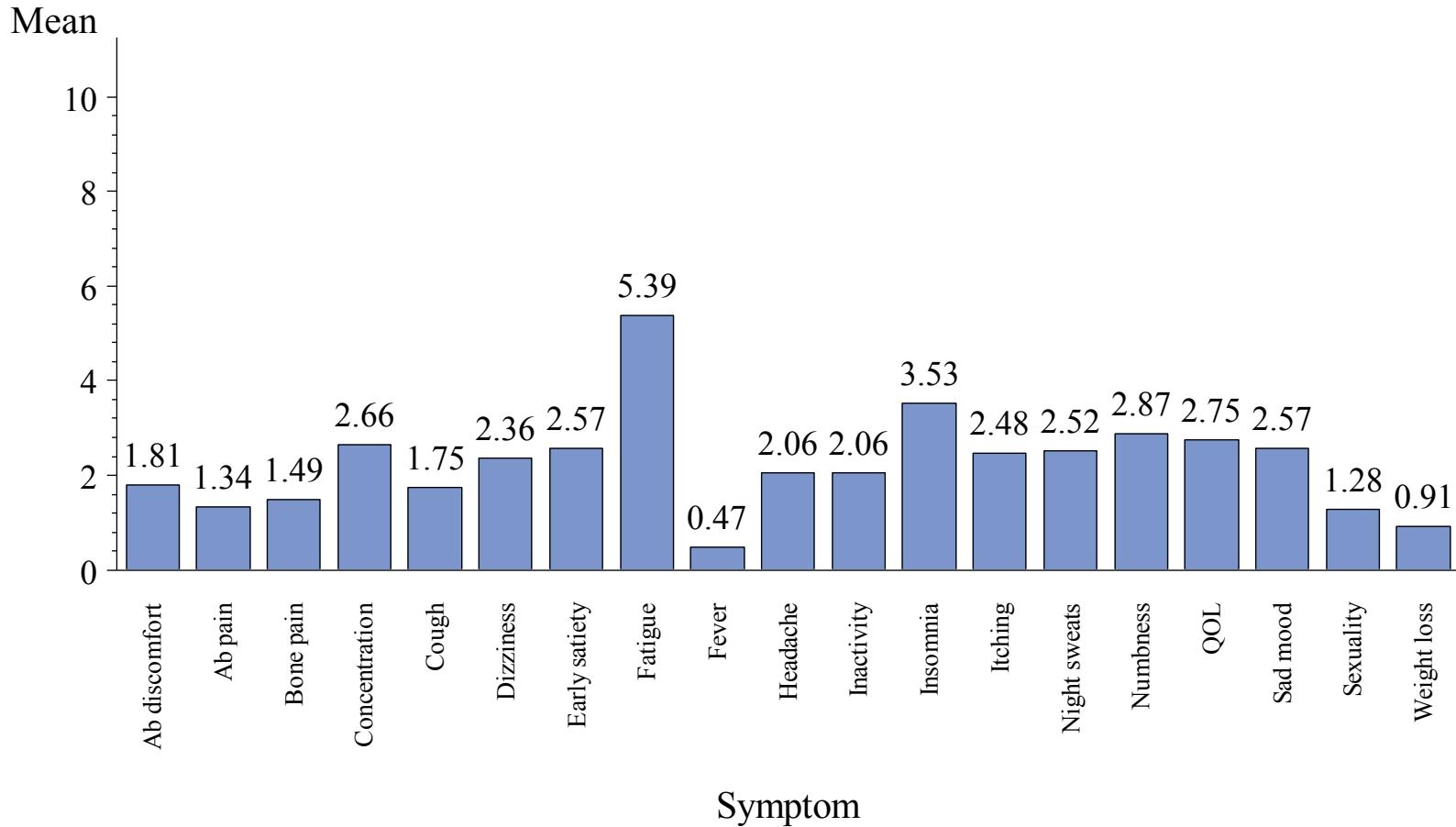
## Cluster 2



# Cluster 3: End Organ Complaints Cluster

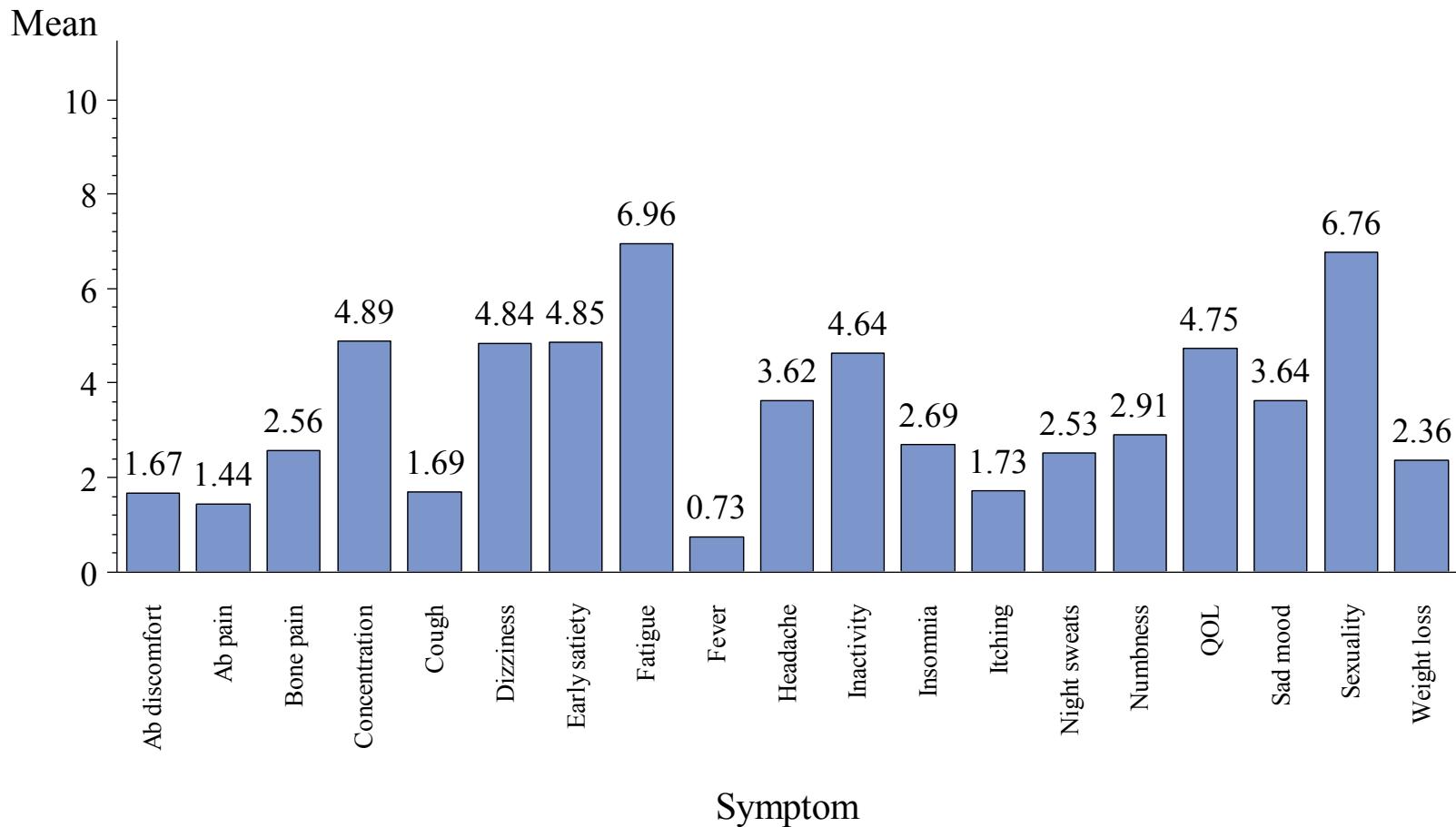
(25%)

## Cluster 3



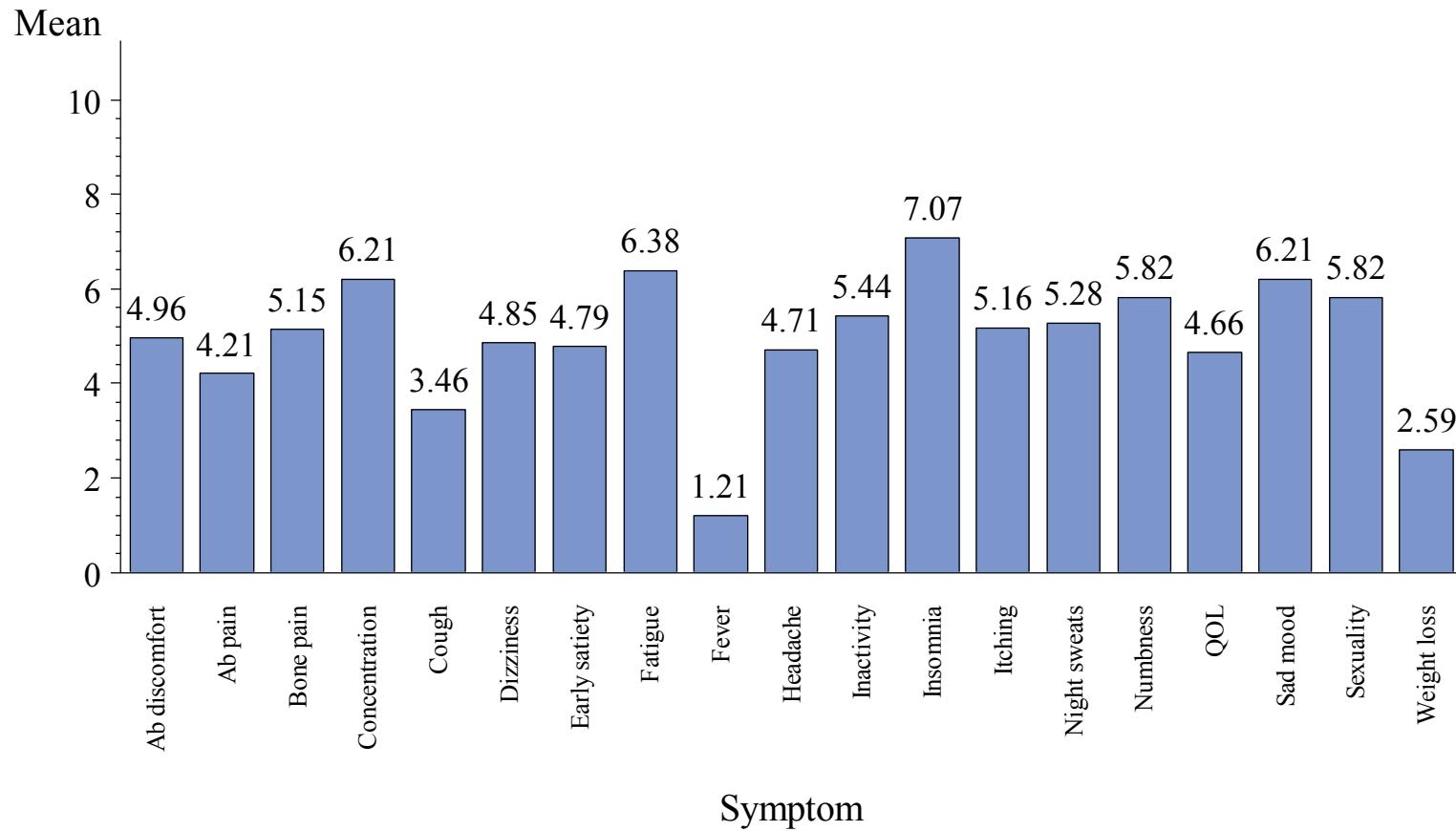
# Cluster 4: Cognitive Complaints Cluster (9%)

## Cluster 4



# Cluster 5: Highly Symptomatic Cluster (11%)

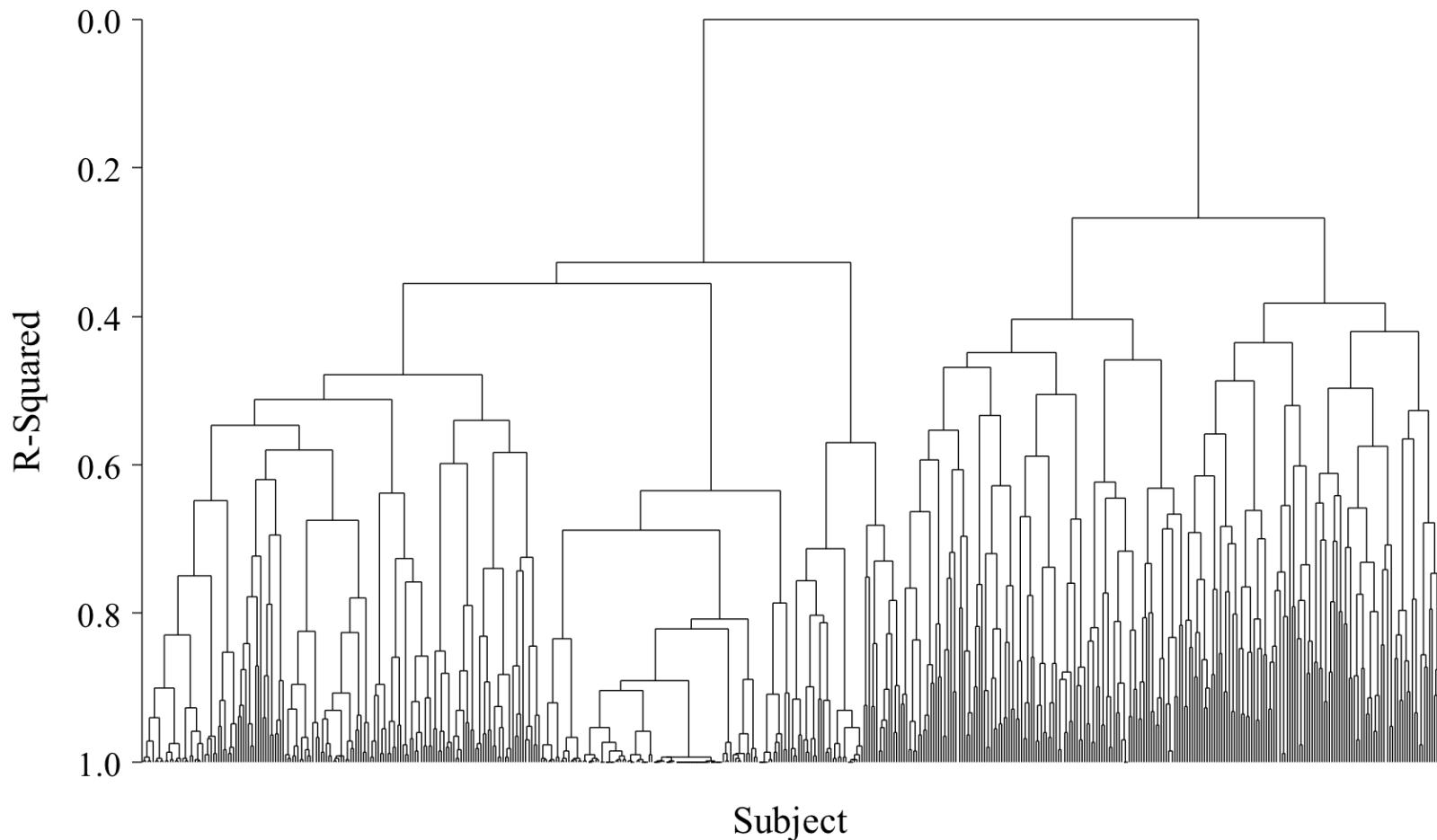
## Cluster 5



PV

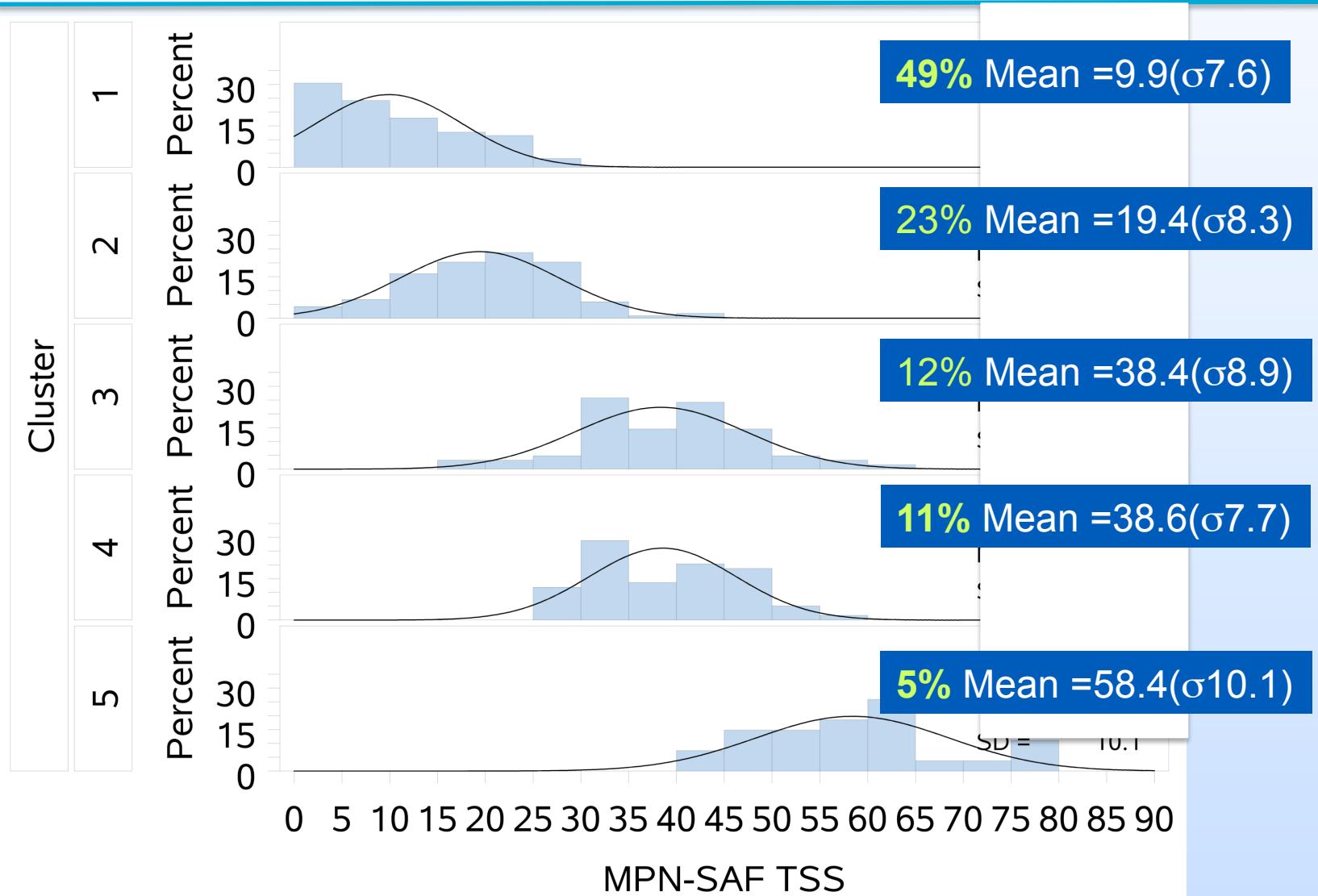
*Symptom Burden - Clusters*

## PV Cluster Analysis



PV

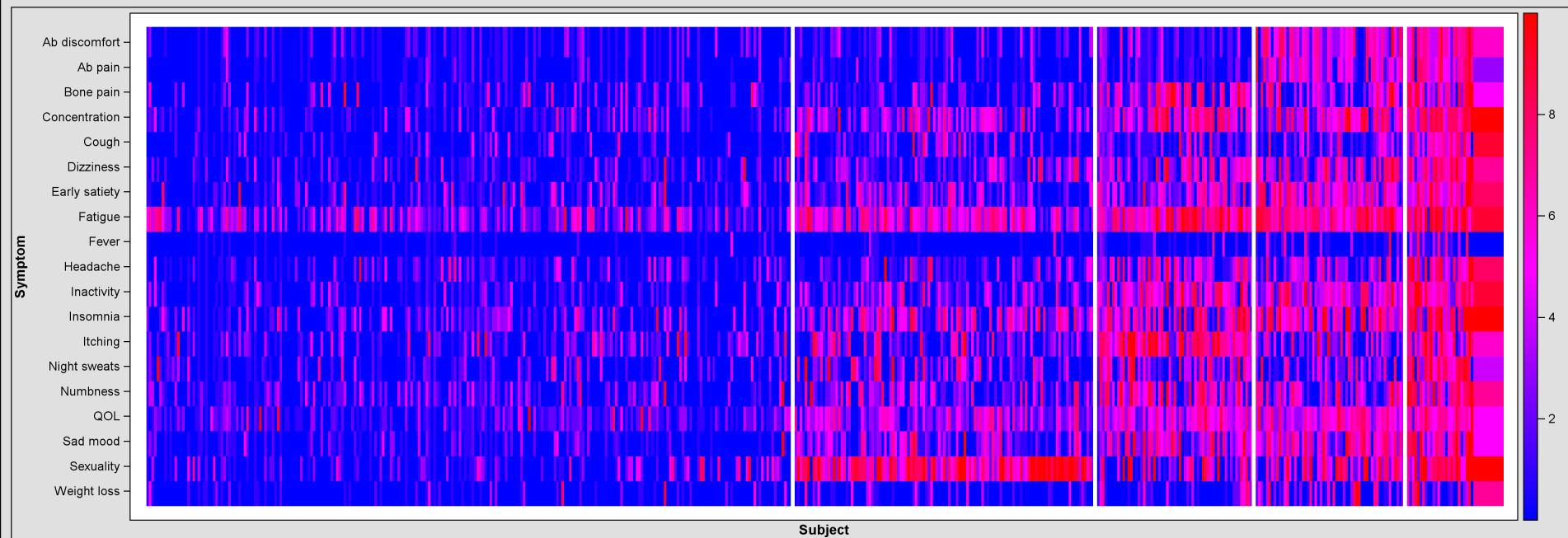
## Symptom Burden - Clusters



# PV Symptom Burden Clusters (N=519)

Difference in each symptom between clusters all  $p < 0.001$

Cluster 5 (N=27)



Cluster 1 (N=252)

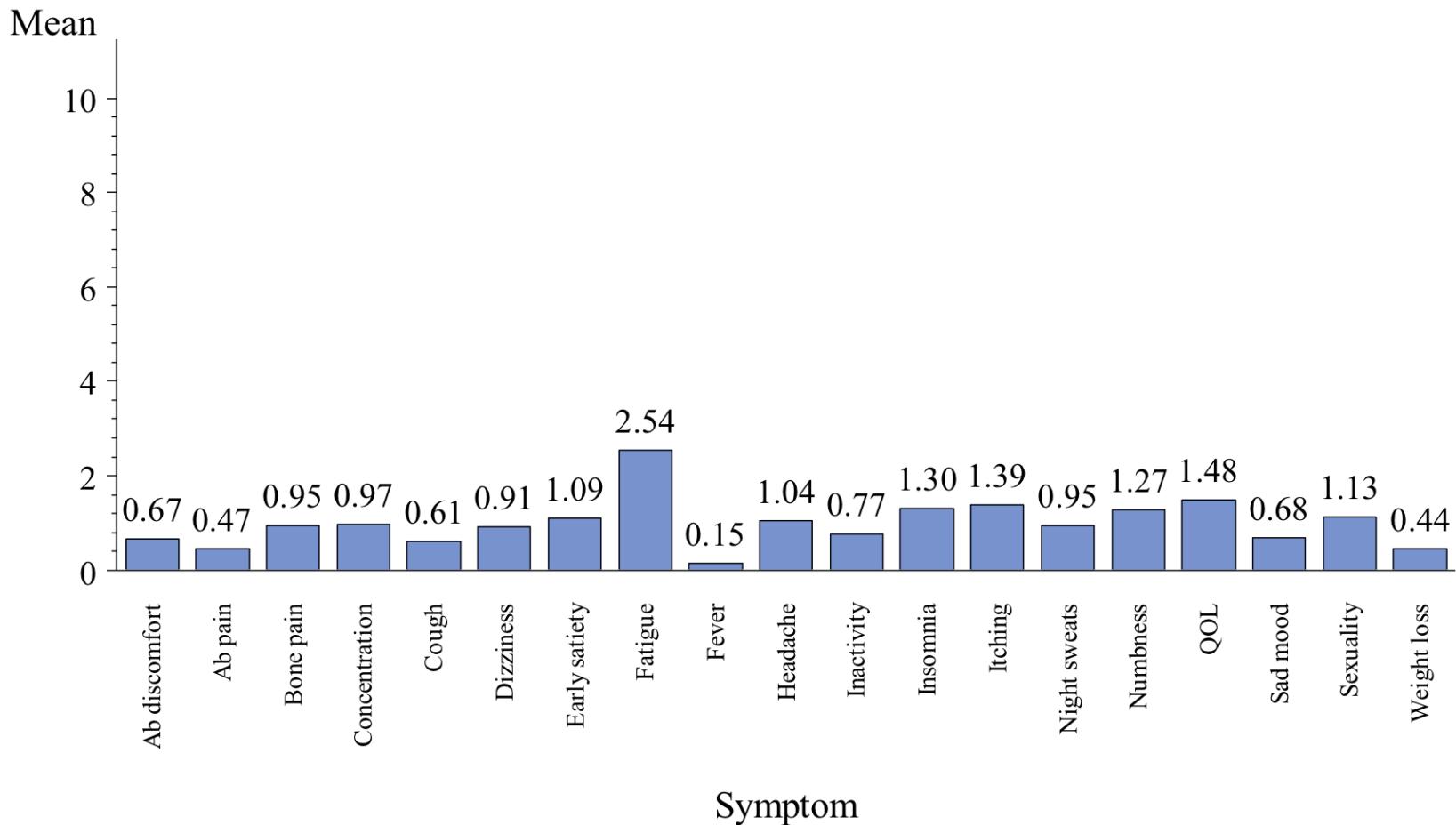
Cluster 2 (N=118)

Cluster 3 (N=62)

Cluster 4 (N=59)

# Cluster 1 PV: Reduced Symptom Cluster (49%)

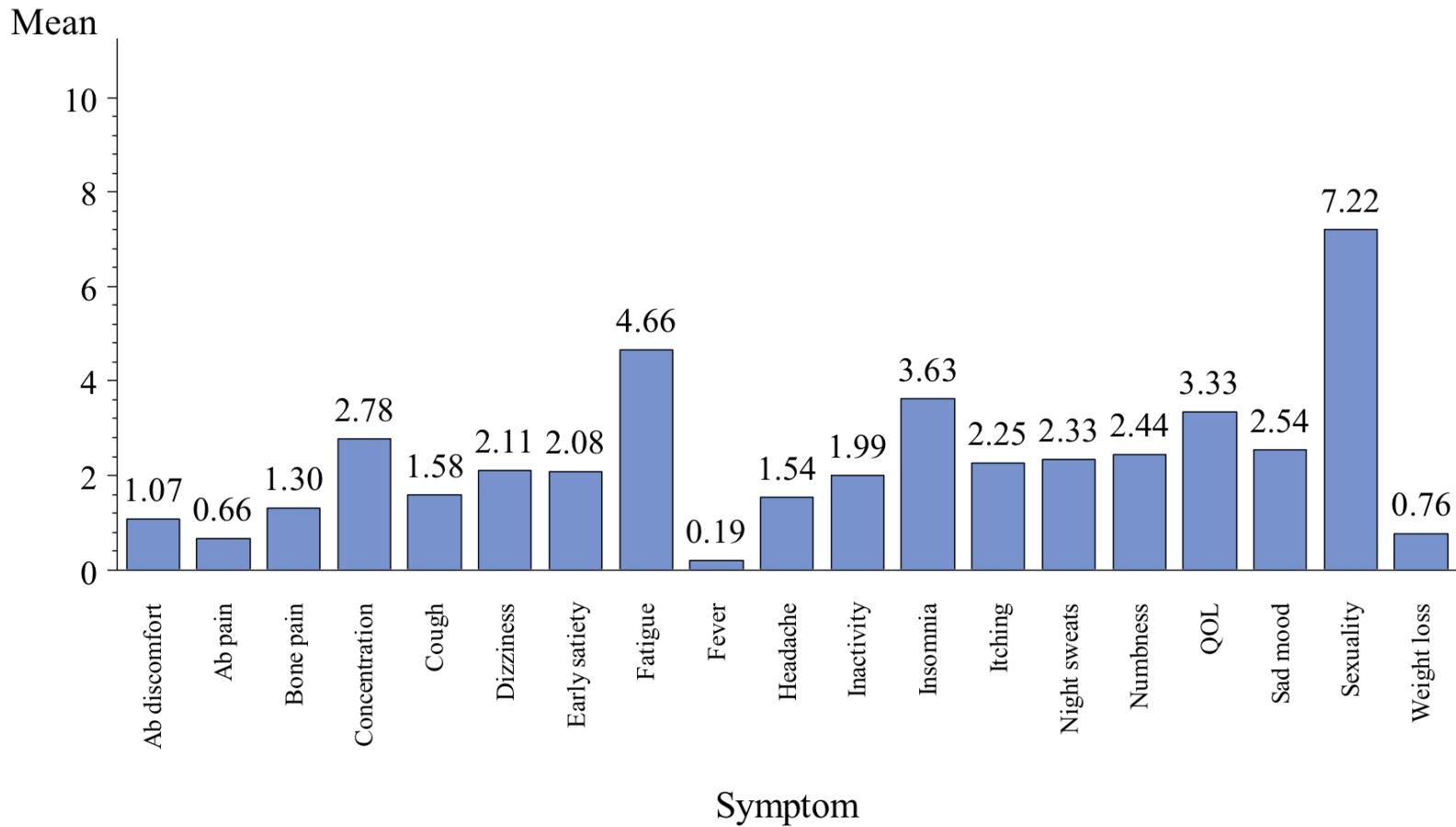
## Cluster 1



# Cluster 2: Fatigue Dominant Cluster

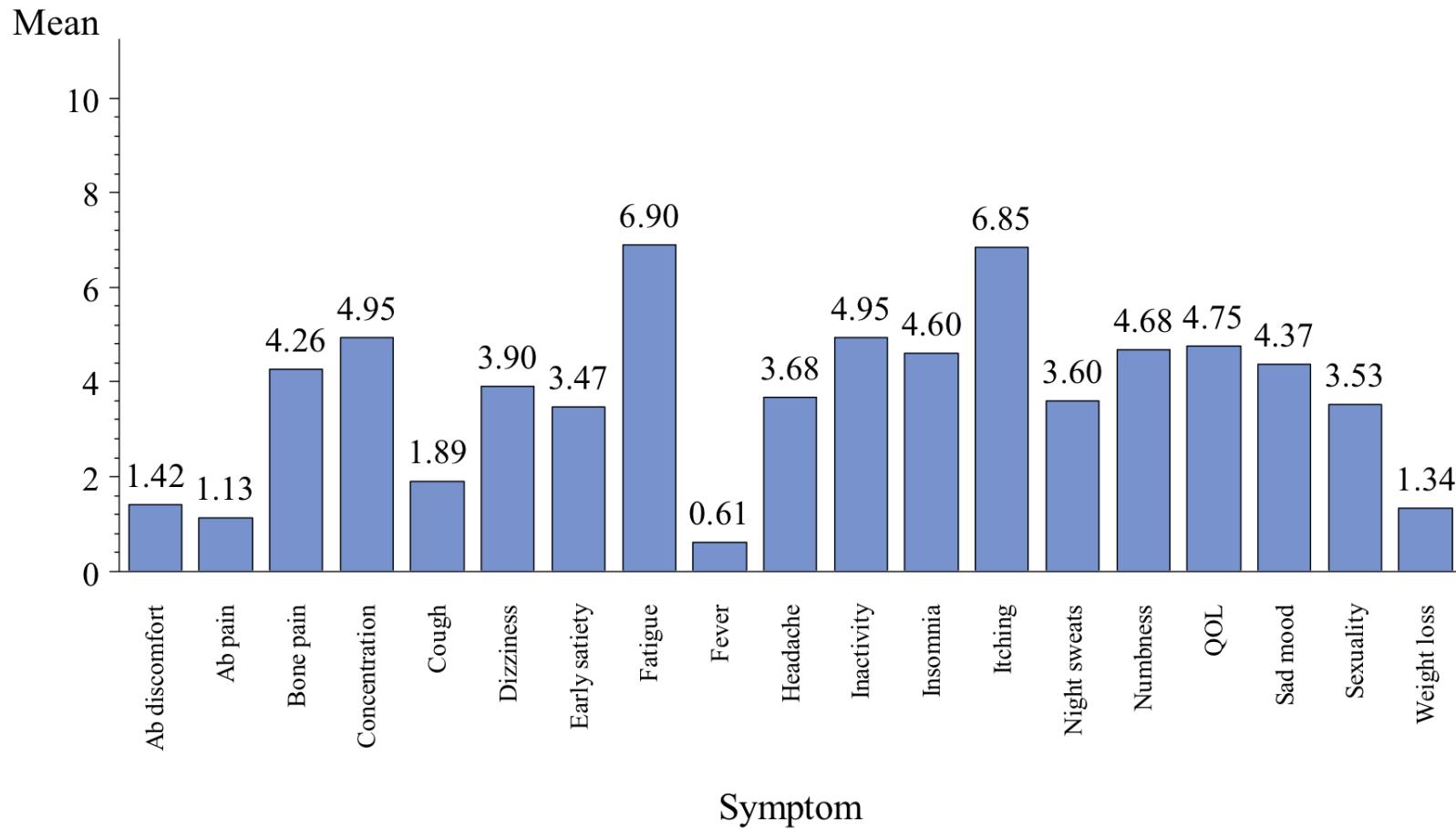
(23%)

## Cluster 2



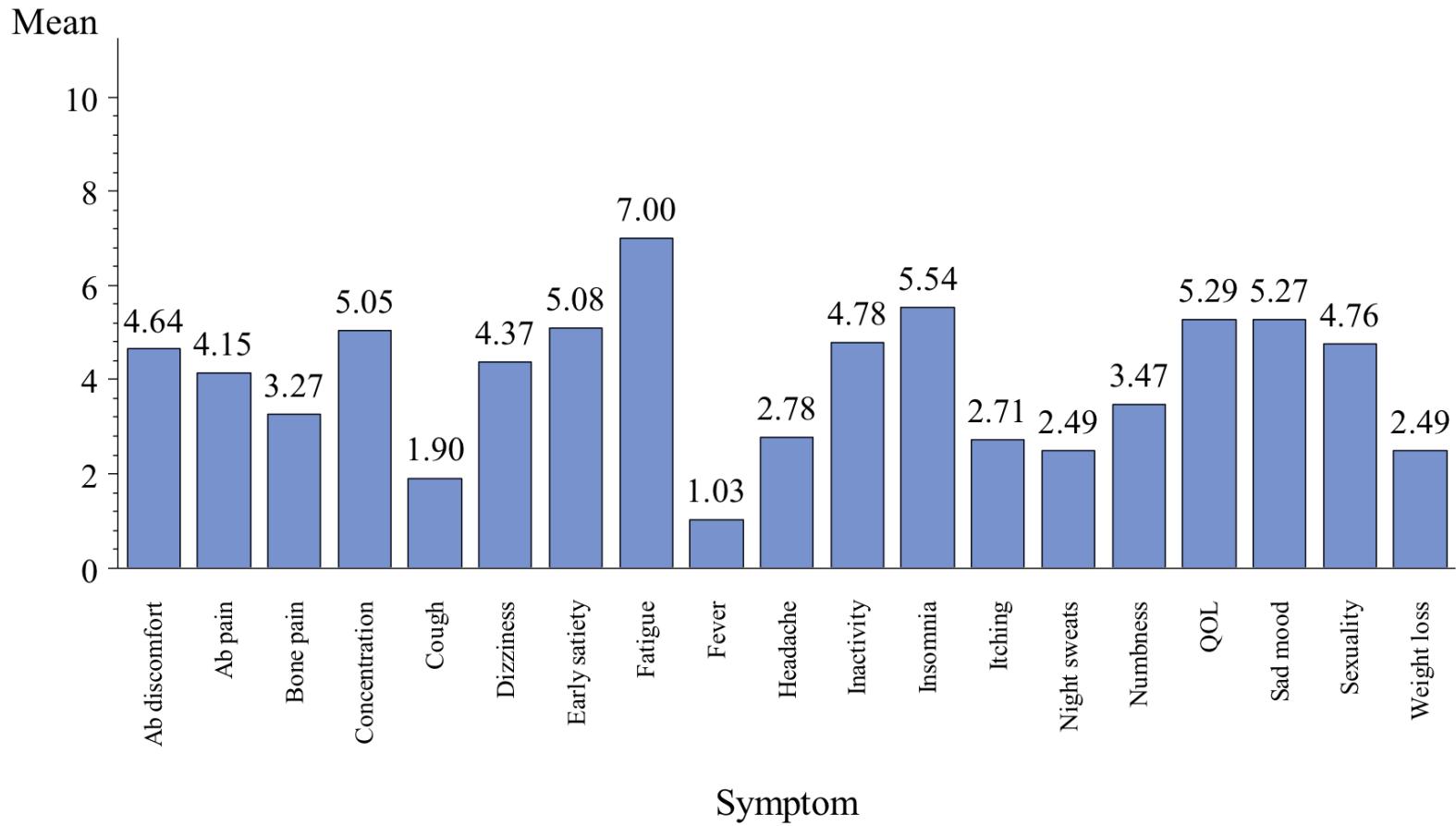
# Cluster 3: End Organ Complaints Cluster (12%)

## Cluster 3



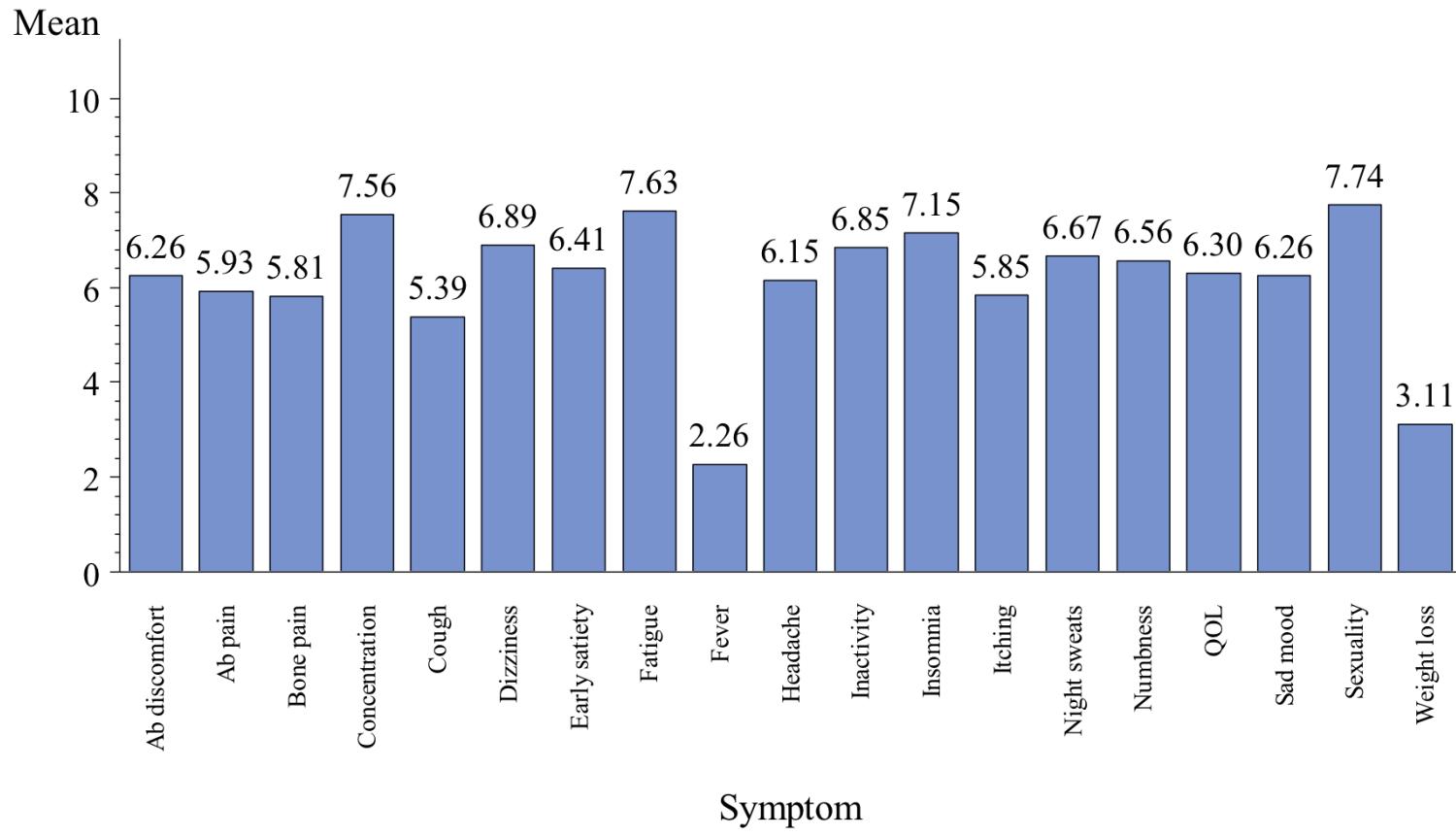
# Cluster 4: Cognitive Complaints Cluster (11%)

## Cluster 4



# Cluster 5: Highly Symptomatic Cluster *(5%)*

## Cluster 5





Death and Life  
1908

Leopold Museum  
Vienna

Gustav Klimt  
(1862-1918)

# Evolving MPN Prognostic Scales

	<b>IPSET (ET – 3 groups) <i>Survival</i> <i>Thrombosis Risk</i></b>	<b>PV Risk (4 groups) <i>Survival</i> <i>Leukemia Rates</i></b>	<b>DIPSS (PMF – 4 groups) <i>Survival</i></b>
Age	$\geq 60$ (2pts) vs. < 60	$\geq 70$ (3pts) 60-69 (2pts), <60	$\geq 65$ (1pt) vs. <65
Leukocytes	$\geq 11$ (1pt) vs. $< 11 \times 10^9/L$	$\geq 15$ (1 point) vs. $< 15 \times 10^9/L$	$>25$ (1pt) vs. $\leq 25 \times 10^9/L$
Hemoglobin			$<10$ (2 pts) vs. $\geq 10g/dL$
Constitutional Symptoms			Present <sup>#</sup> (1pt) vs. Absent
Blasts			$\geq 1\%$ (1pt) vs. <1%
Prior Thrombosis	Yes (1 point) vs. No		
Risk Group Point Cutoffs	0; 1-2; 3-4 pts.	0; 1-2; 3; 4 pts.	0; 1-2; 3-4; $\geq 4$ pts.

Passamonti  
Blood 2012

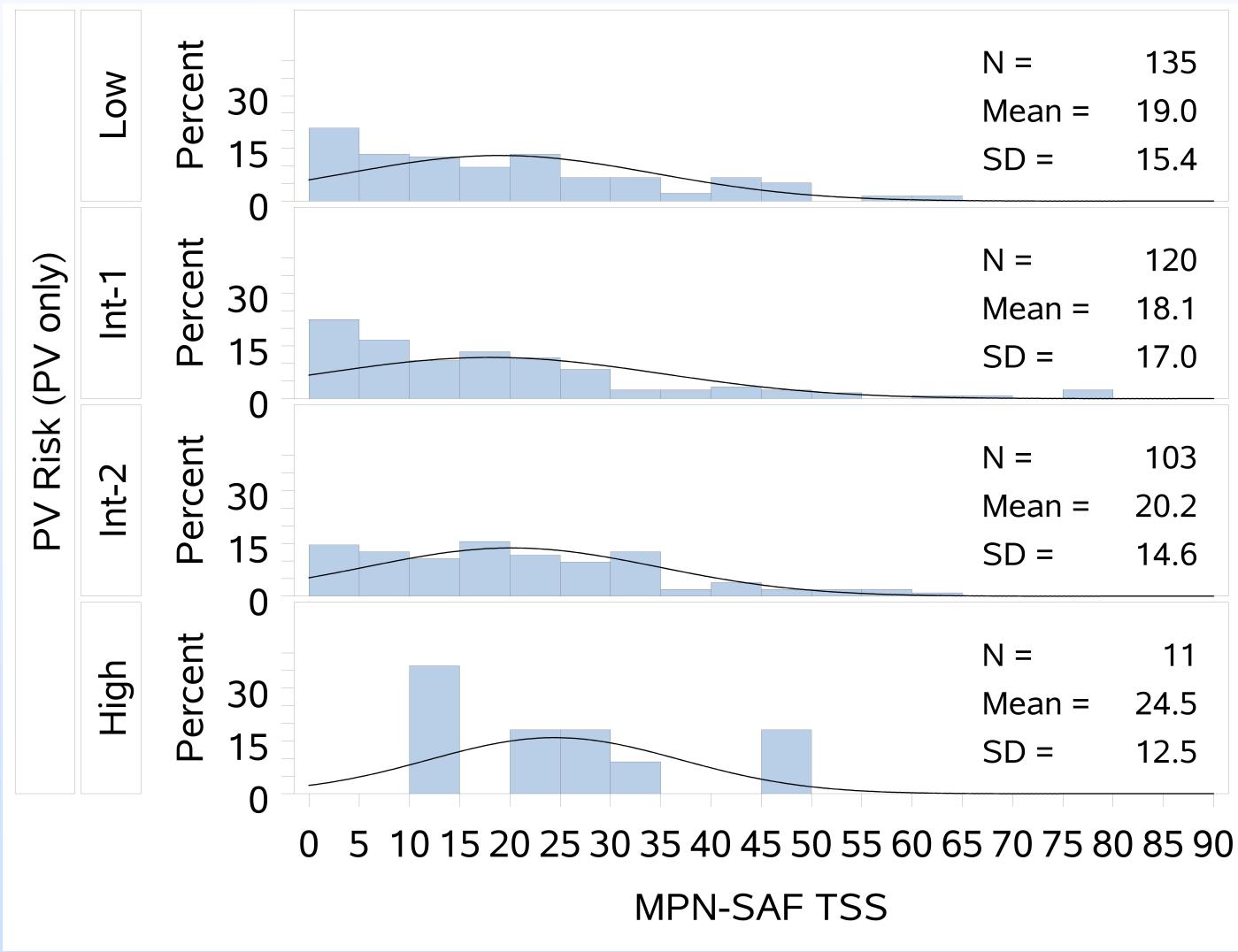
Tefferi  
ASH 2011

Passamonti  
Blood 2010

# = >10% Weight Loss over prior 6 months, Night Sweats, Unexplained Fever

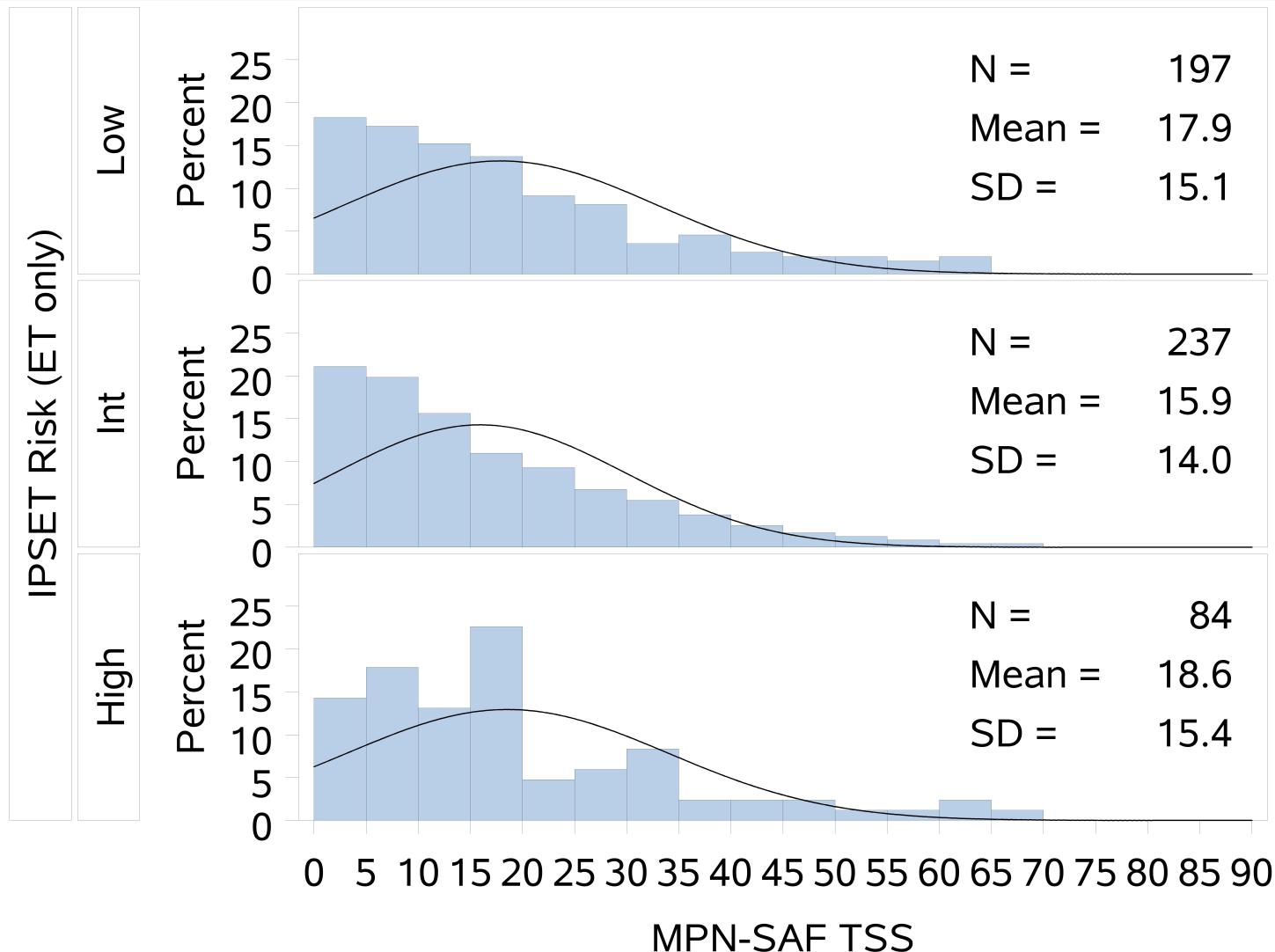
# PV Risk

## *Symptom Burden - Clusters*



# ET Risk

## Symptom Burden - Clusters



# Differences Between ET/PV Clusters (N=1141)

Age	P=0.07
<b>Gender (F&gt;M)</b>	<b>P&lt;0.001</b>
<b>ET vs. PV (PV &gt; ET)</b>	<b>P=0.01</b>
IPSET (ET)	P=0.24
<b>PV Risk</b>	<b>P=0.02</b>
<b>Language of MPN-SAF</b>	<b>P&lt;0.001</b>
<b>Anemia Present (&lt;11g/dL)</b>	<b>P&lt;0.001</b>
Leukopenia (<3.5 x 10(9)/L)	P=0.17
Thrombocytopenia (<150 x 10(9)/L)	P=0.62
<b>Spleen Size (cm BLCM)</b>	<b>P&lt;0.001</b>
Prior Thrombosis	P=0.84
<b>Erythrocytosis</b>	<b>P=0.03</b>
Extreme Thrombocytosis (>1000 x 10(9)/L)	P=0.92



# Self Portrait with Bandaged Ear

1889

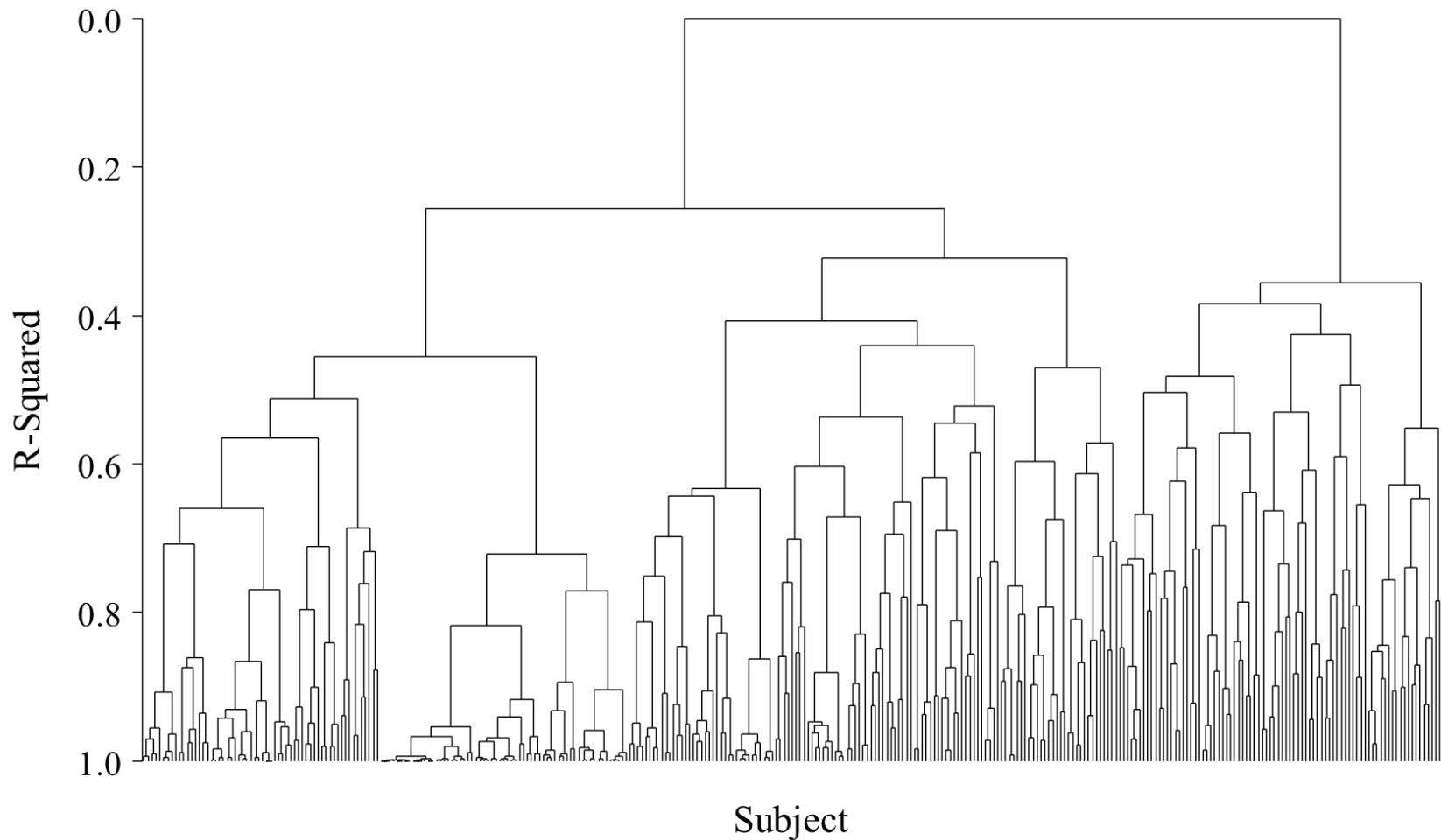
National Gallery - London

Vincent Van Gogh (1853-1890)

# Myelofibrosis (N=329)

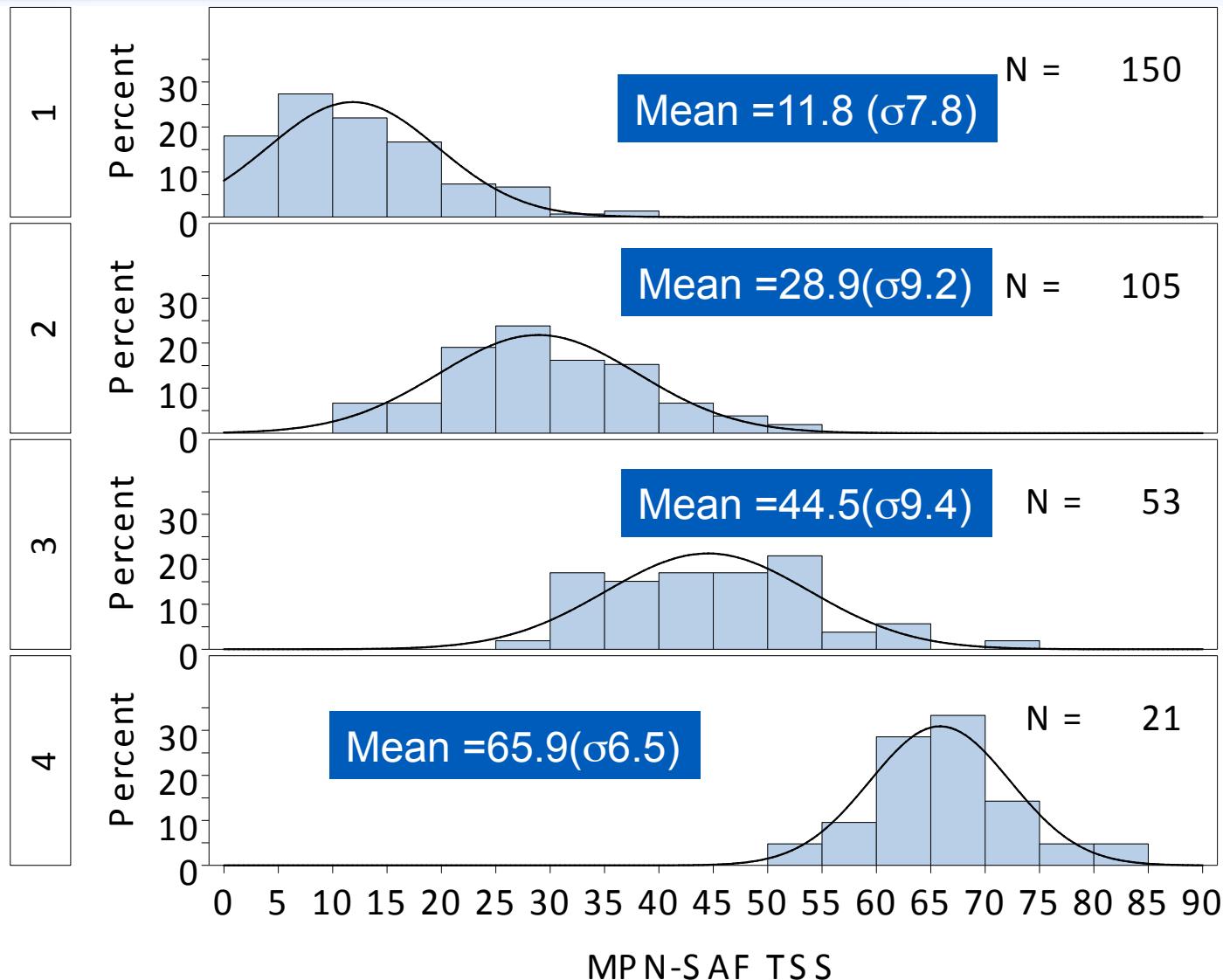
## *Symptom Burden - Clusters*

### MF Cluster Analysis



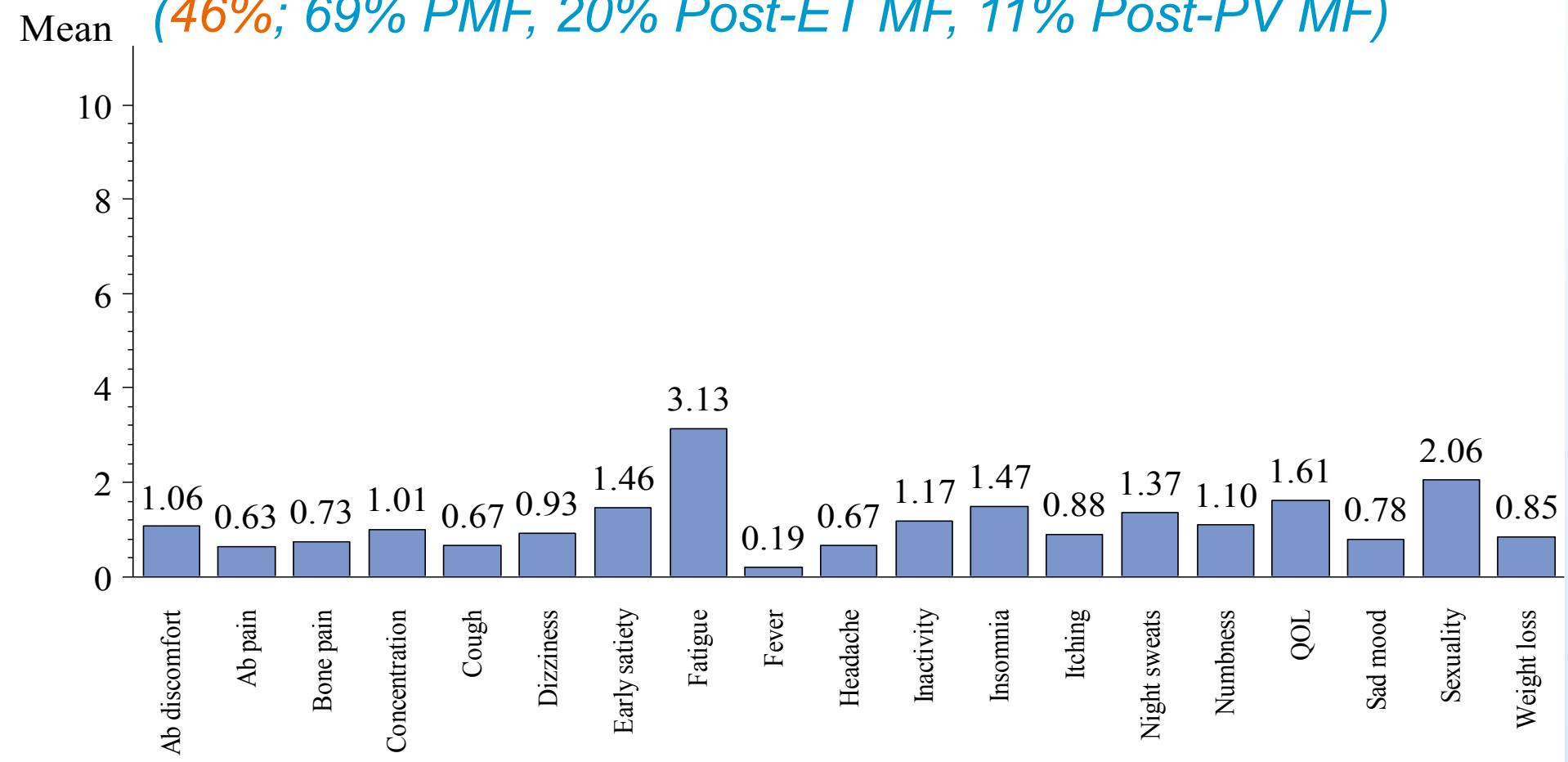
# Myelofibrosis

## Symptom Burden - Clusters



# Cluster 1: Fatigue Dominant – Few Lab Abnormalities

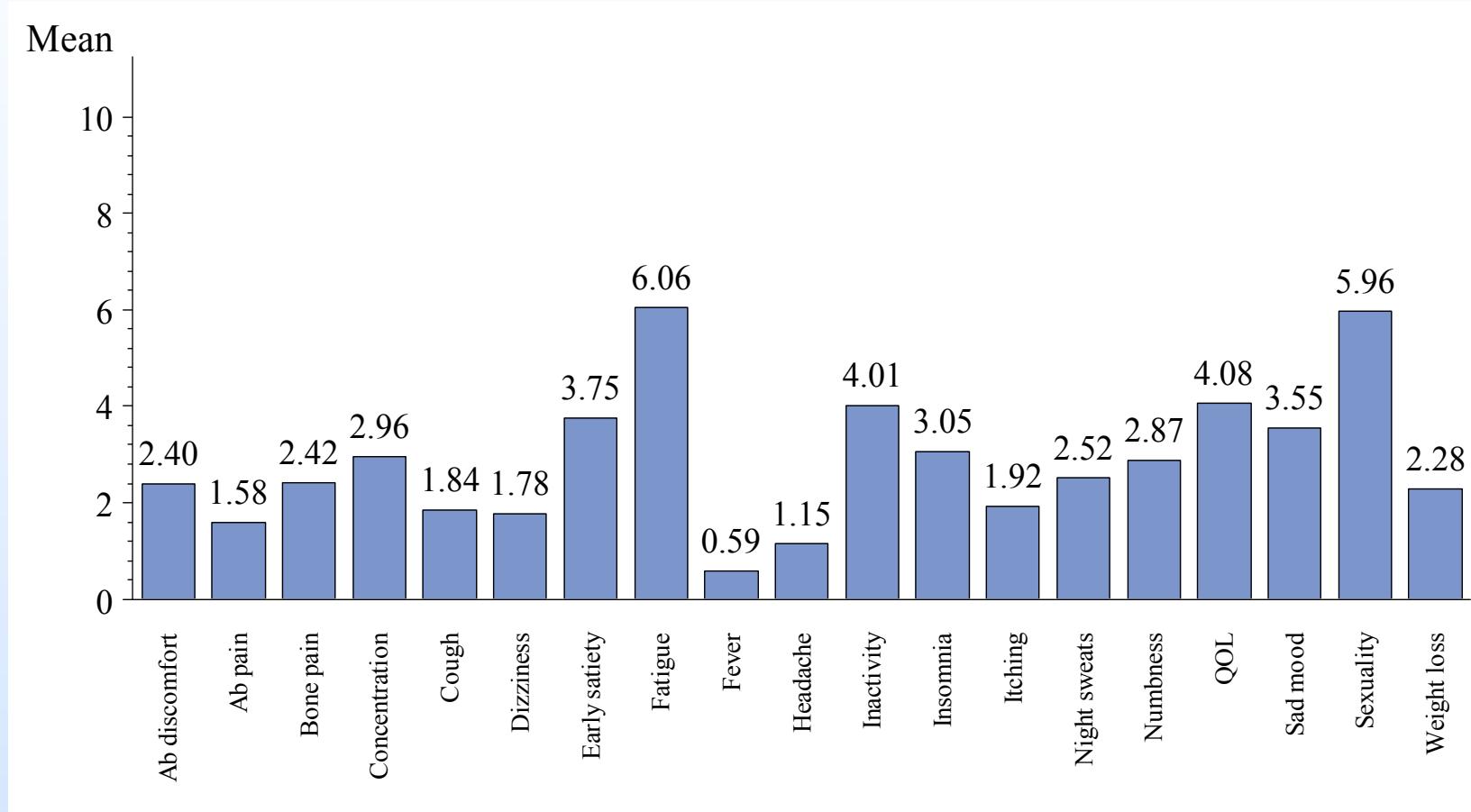
(46%; 69% PMF, 20% Post-ET MF, 11% Post-PV MF)



- Lowest rate of cytopenias (65% - Anemia 56%, thrombocytopenia 20%)
- Mean palpable spleen length = 6.0 cm

# Cluster 2: Cognitive Complaints & Splenomegaly

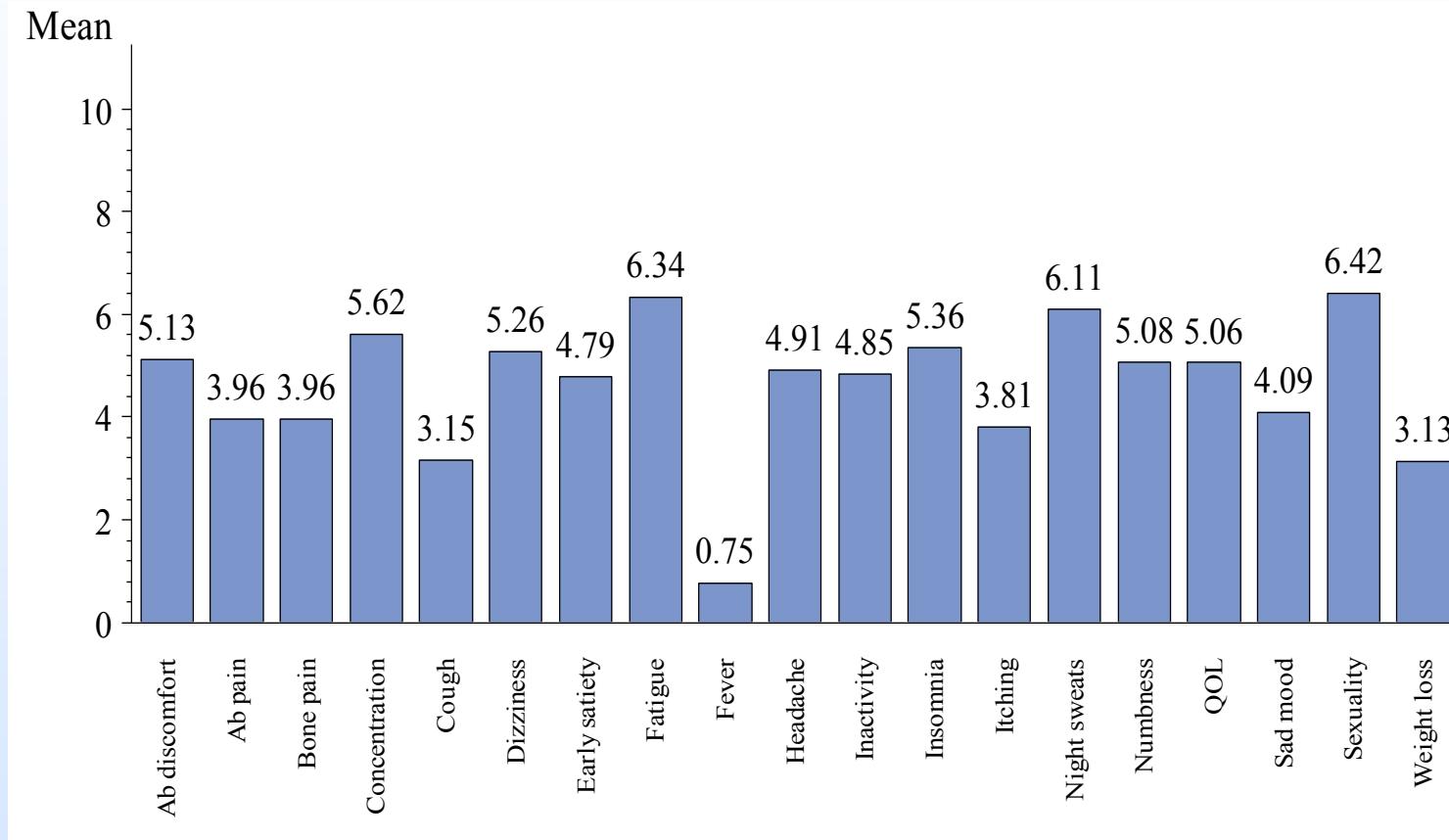
(32%; 65% PMF, 20% Post-ET MF, 15% Post-PV MF)



- Mean palpable spleen length = 8.7 cm

# Cluster 3: Nighttime and Cognitive Complaints

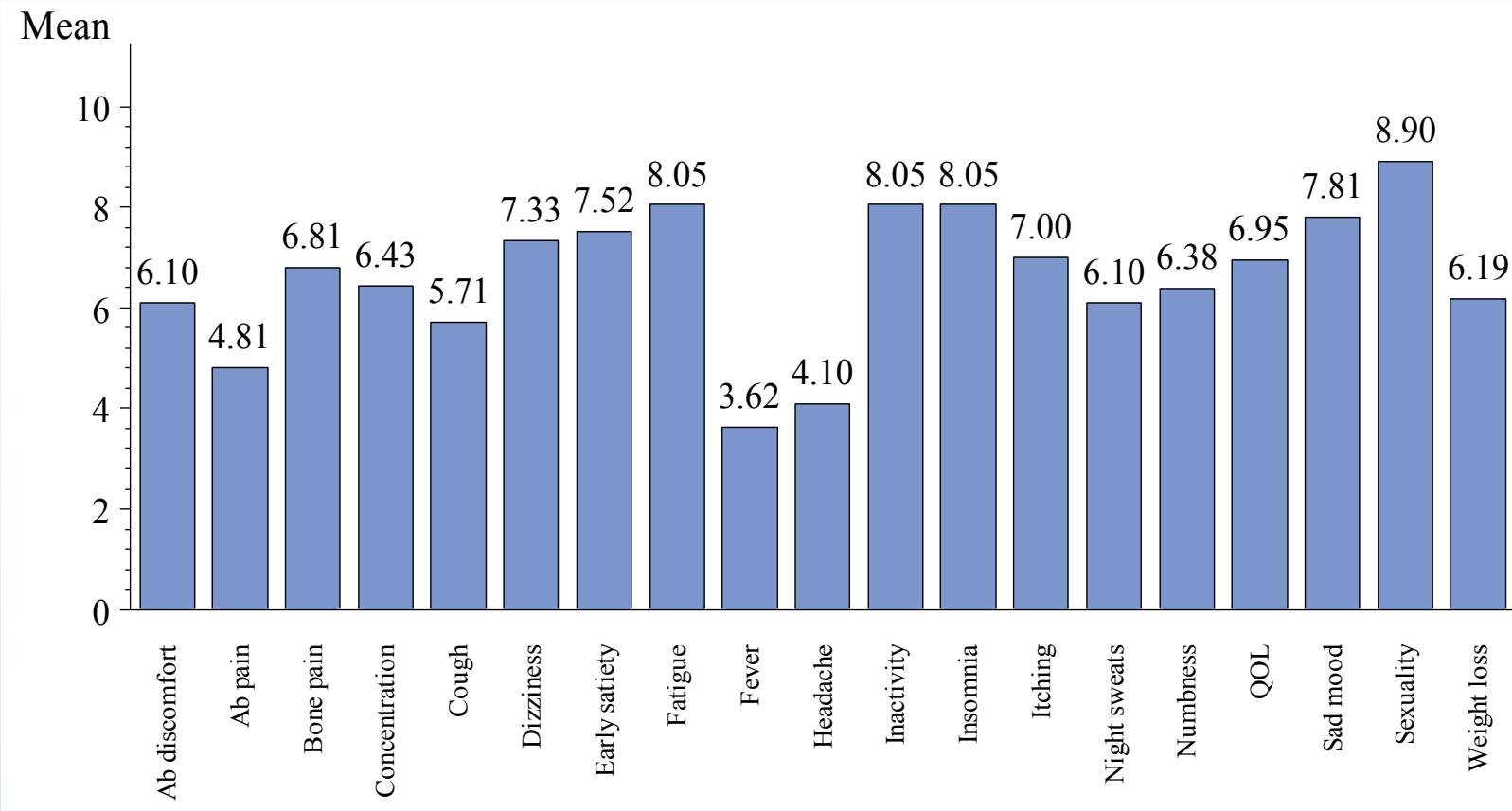
(16%; 64% PMF, 25% Post-ET MF, 15% Post-PV MF)



- Mean palpable spleen length = 7.0 cm

# Cluster 4: Severe Fatigue – Few End Organ Complaints

(6%; 81% PMF, 14% Post-ET MF, 5% Post-PV MF)

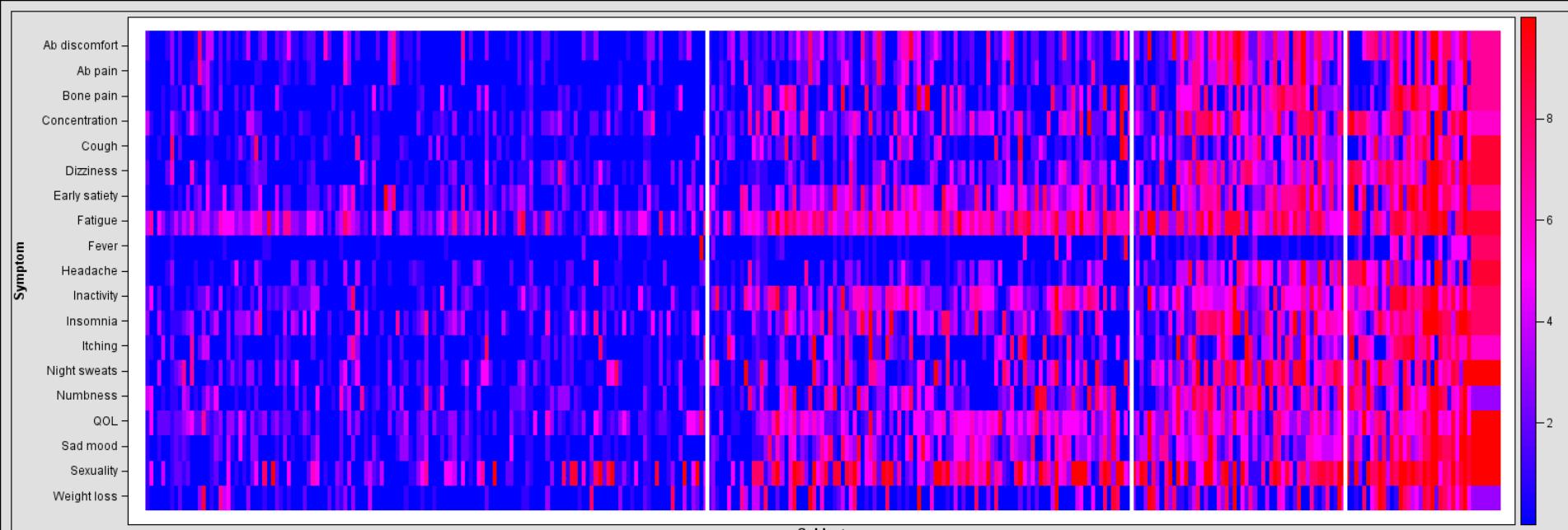


- Highest rate of cytopenias (77% - Anemia 41%, thrombocytopenia 71%)
- Highest rate of prior vascular events and transfusion dependence
- Mean palpable spleen length = 6.7 cm (no prior splenectomies)

# Myelofibrosis Symptom Burden Clusters (N=329)

Difference in each symptom between clusters all  $p < 0.001$

Cluster 4 (N=21)



Cluster 1 (N=150)

Cluster 2 (N=105)

Cluster 3 (N=53)

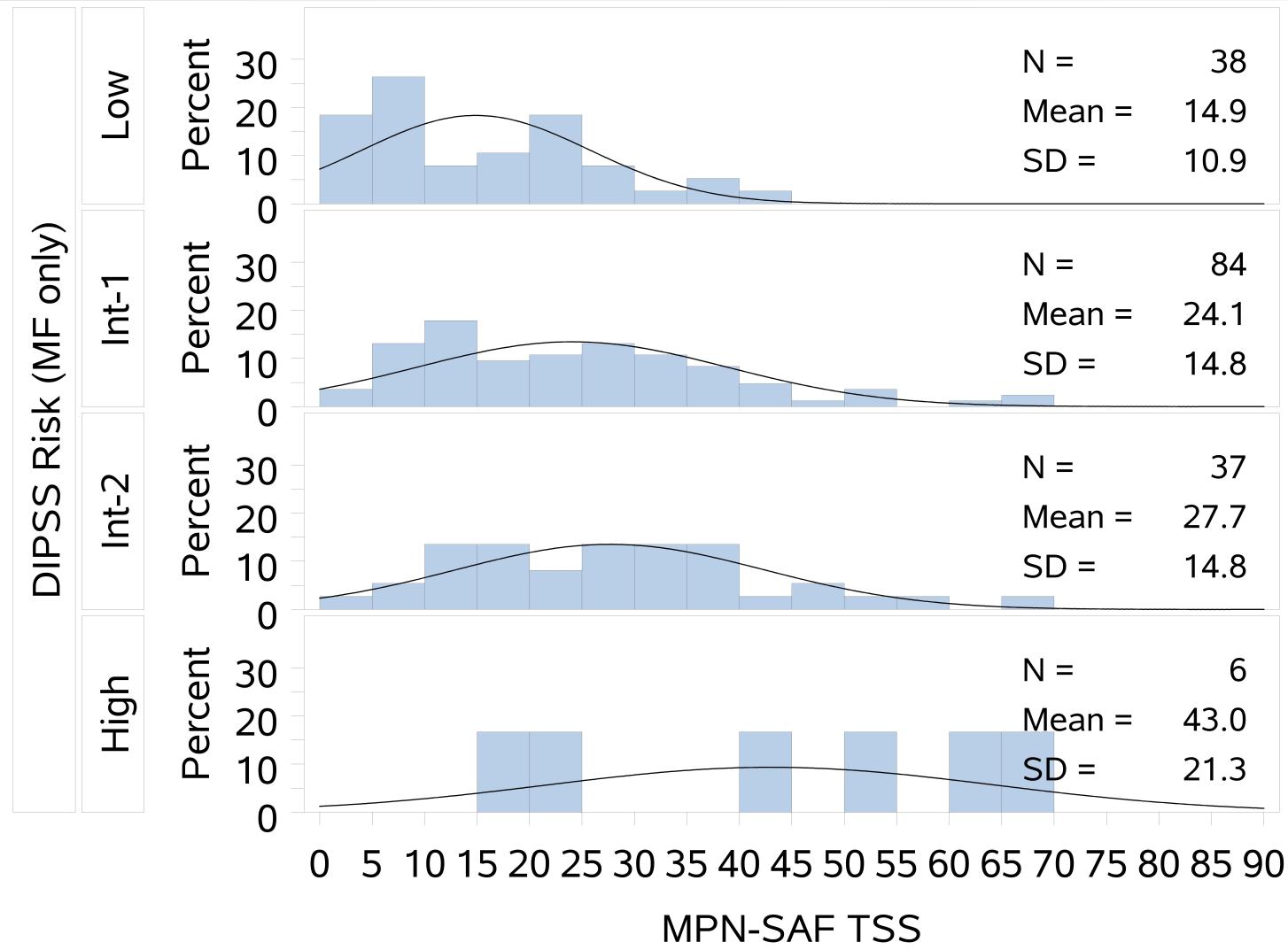
# Differences Between MF-SB Clusters (N=329)

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Age	P=0.78
Gender	P=0.20
Type of MF	P=0.71
<b>DIPSS Risk Category</b>	<b>P&lt;0.001</b>
Language of MPN-SAF	P=0.24
Anemia Present (<11g/dL)	P=0.48
<b>Leukopenia (&lt;3.5 x 10(9)/L)</b>	<b>P=0.009</b>
<b>Thrombocytopenia (&lt;150 x 10(9)/L)</b>	<b>P&lt;0.001</b>
<b>Spleen Size (cm BLCM)</b>	<b>P=0.03</b>
Prior Thrombosis	P=0.06

# MF

## Symptom Burden - Clusters





Insomnia #13  
2010

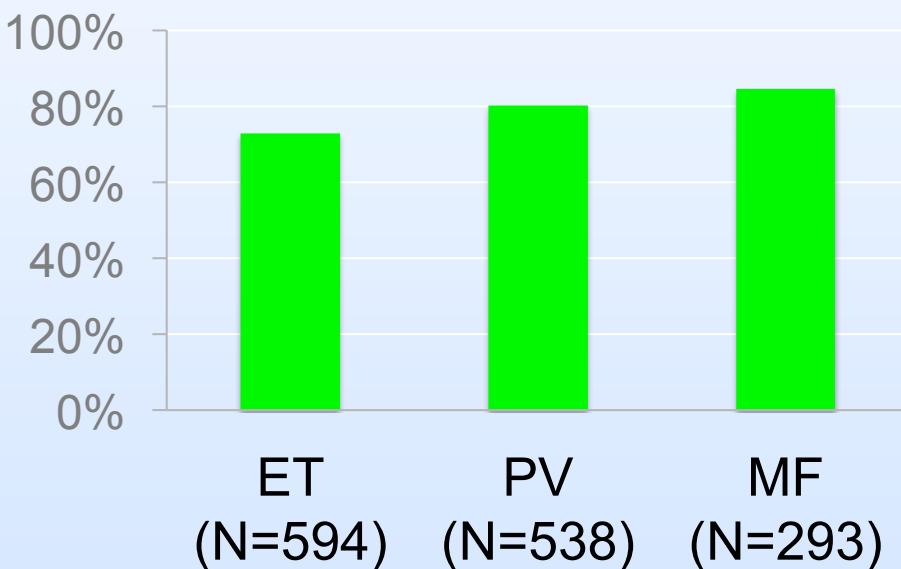
Private Collections

Kira Ayn Varszegi (1978 - )

# Decreased QOL in 1433 MPN Patients

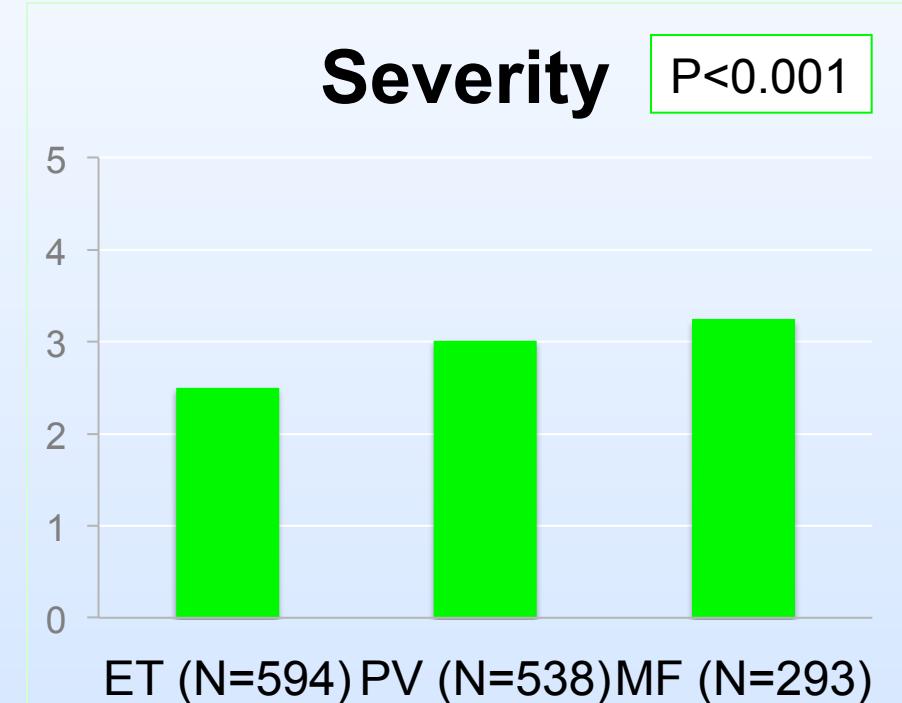
## Prevalence

P<0.001

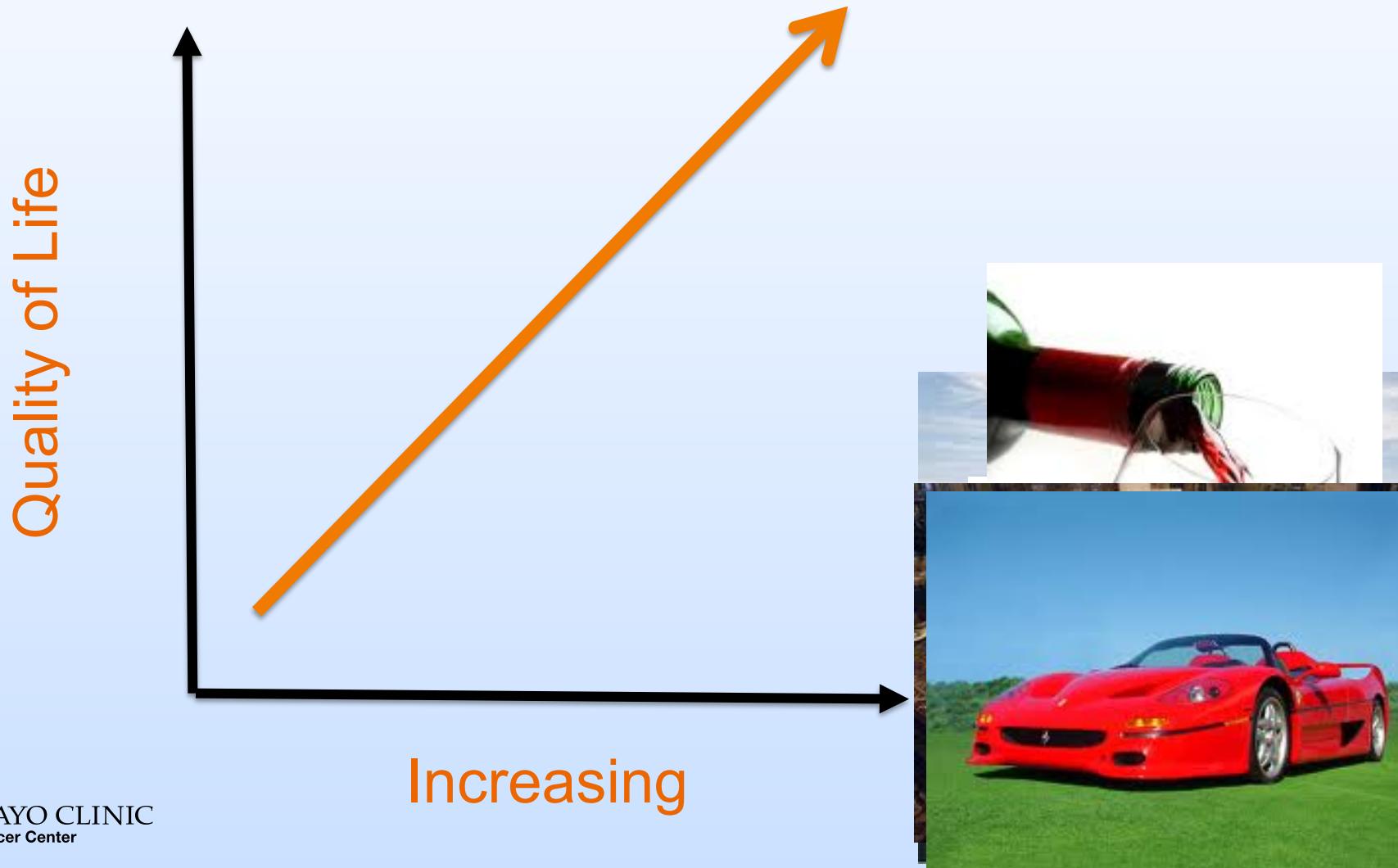


## Severity

P<0.001



# What is quality of life



# Definitions

## HRQOL in MPNs?

Σ

- MPN related symptoms
- Medication related toxicities
- Problems from prior MPN complications
- Stressors from having their MPN
  - Financial
  - Emotional
  - Intrapersonal
- Co-morbidities
- Hassle of medical care

# Phenotypic Clusters in MPNs

## *Individualizing Therapy*

---

- What is the spectrum of disease burden and risk in MPNs?
- What phenotypic clusters exist in MPN patients?
- How might we incorporate the assessment of disease burden and risk in choosing therapy for MPN patients?

# ENDPOINTS

Cure

Prolong Life

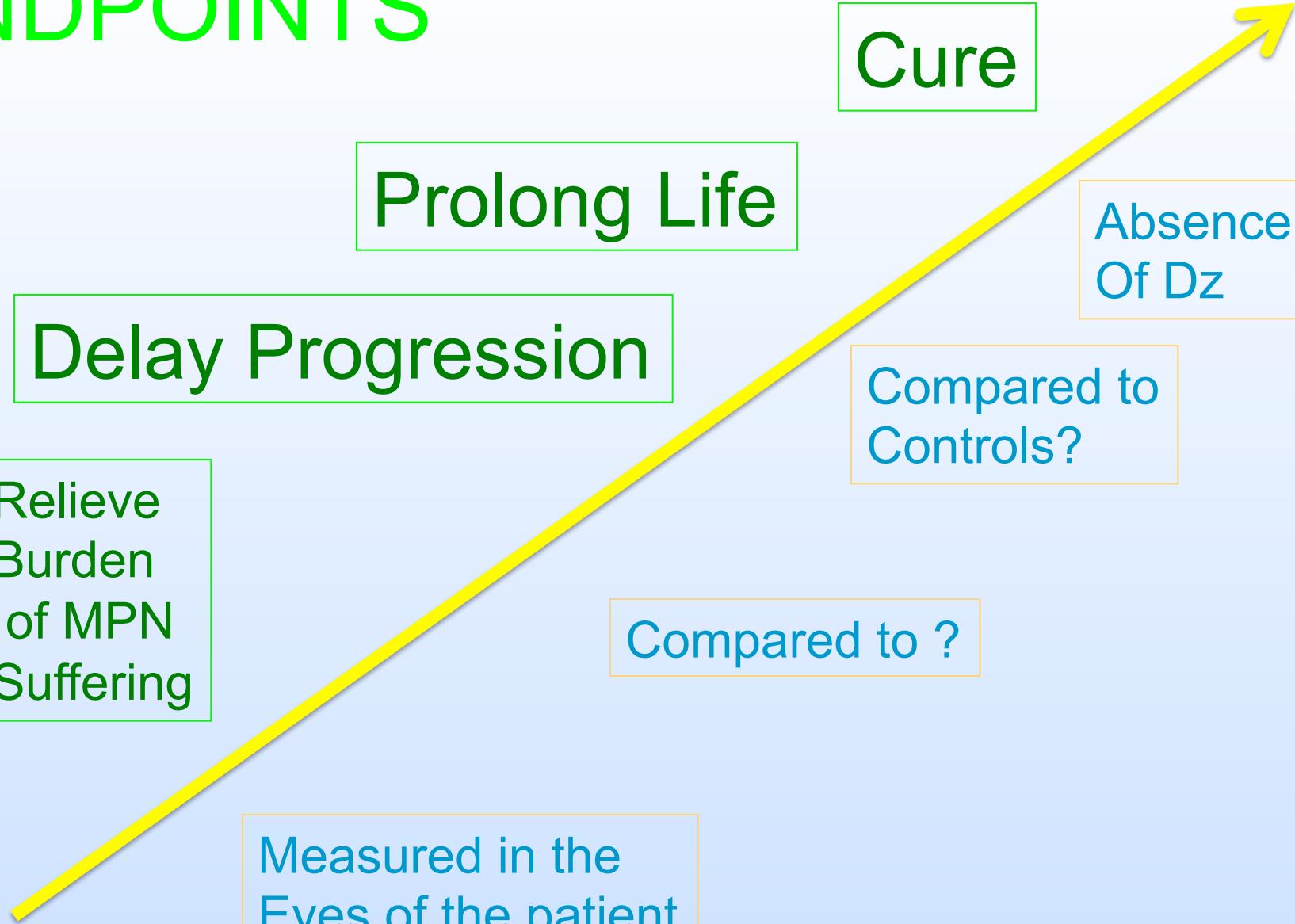
Delay Progression

Relieve  
Burden  
of MPN  
Suffering

Compared to  
Controls?

Compared to ?

Measured in the  
Eyes of the patient



## VALIDATION

# JAK2 Inhibitors in Clinical Use/ Development

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Ruxolitinib (FDA Approved)

SAR302503 (TG101348)

Pacritinib (SB1518)

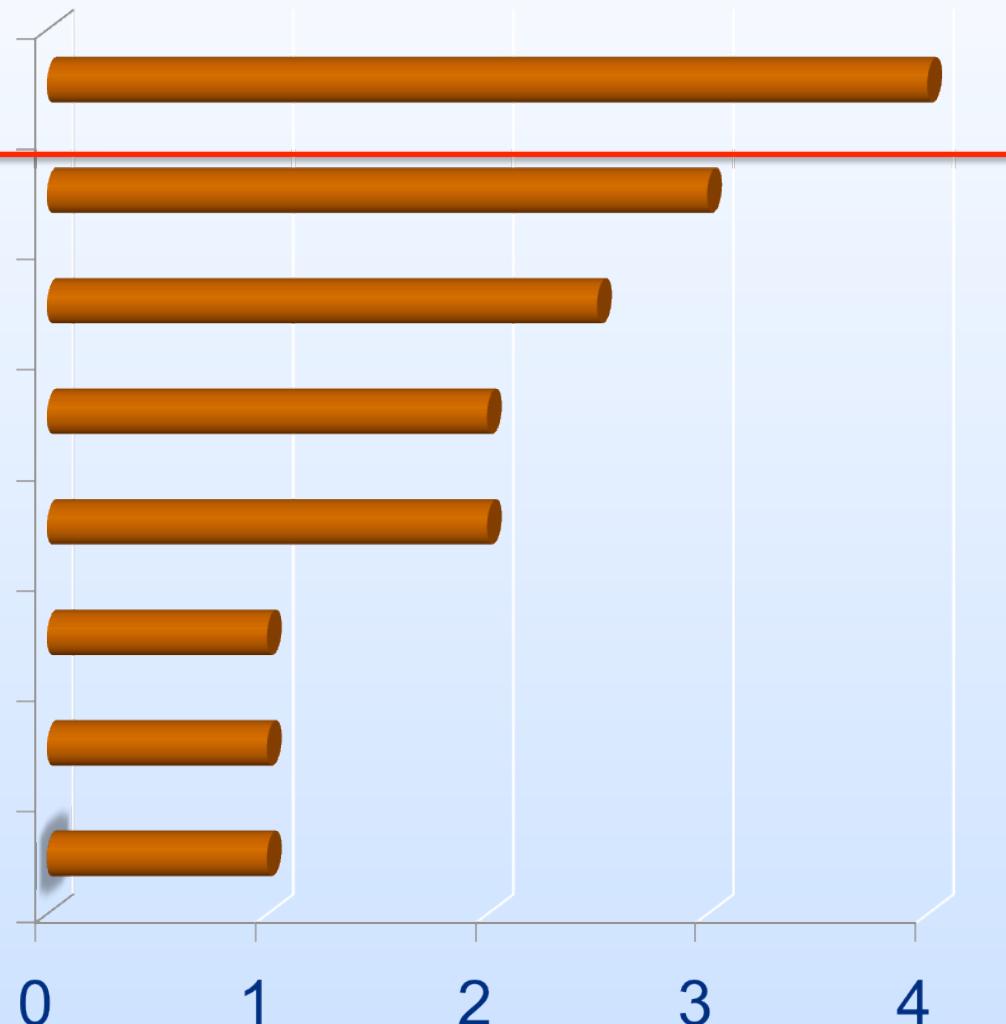
CEP701

CYT387

BMS-911543

LY2784544

NS018



Clinical Phase of Testing

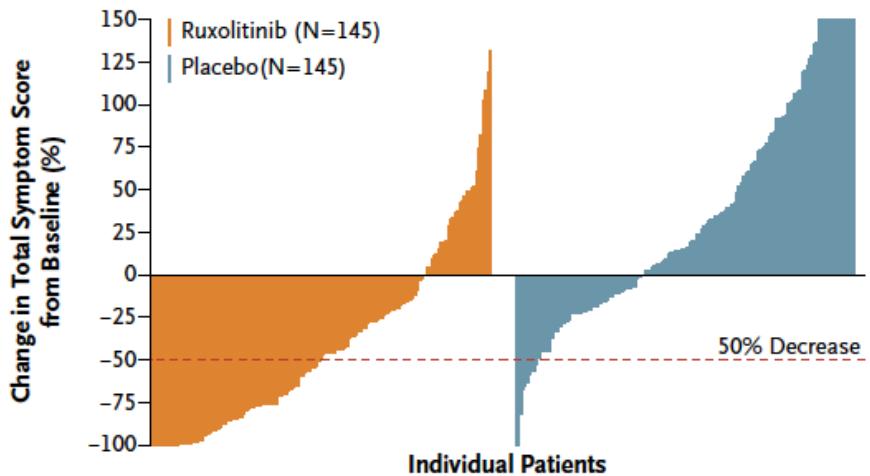
# Patient-Reported Outcome Assessments in Comfort 1

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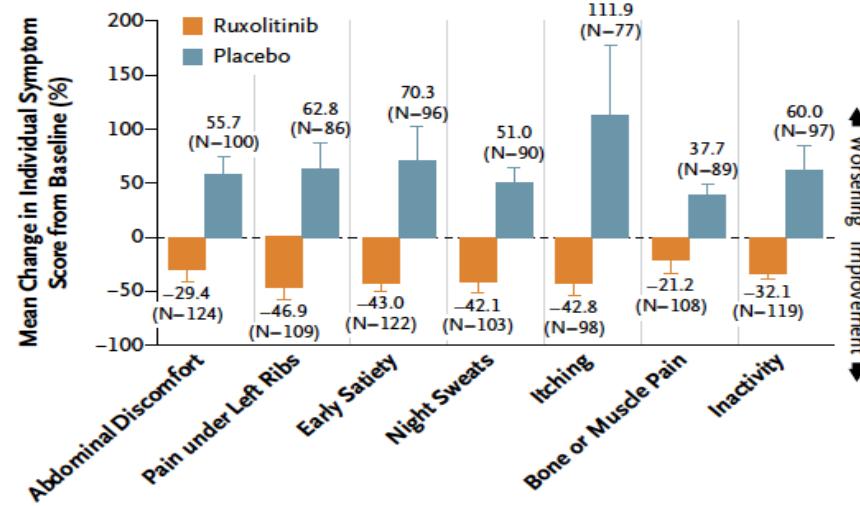
- **MFSAF v2.0 electronic diary**
  - Total Symptom Score = Sum of Scores for itching, night sweats, bone/muscle pain, abdominal discomfort, pain under the ribs on left, and early satiety
  - Individual symptom scores
- **Patient Global Assessment of Change (PGIC)**
  - Patient's overall impression of change on a scale from 1 (very much improved) to 7 (very much worse), with 4 representing no change
- **European Organization for Research and Treatment of Cancer Quality-of-Life 30 (EORTC-QLQ30) questionnaire**
- **Patient-Reported Outcomes Measurement System (PROMIS) fatigue scale**

# Ruxolitinib Phase III Trials (COMFORT I – *Symptom Response*)

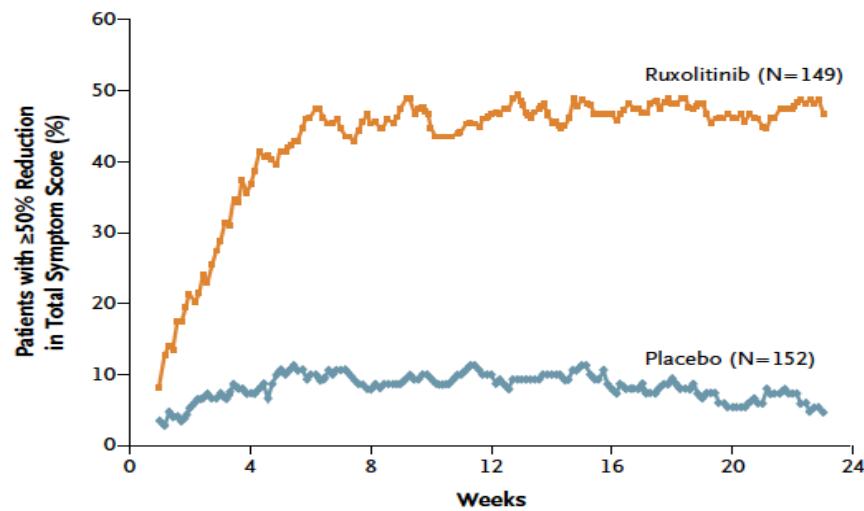
B



C

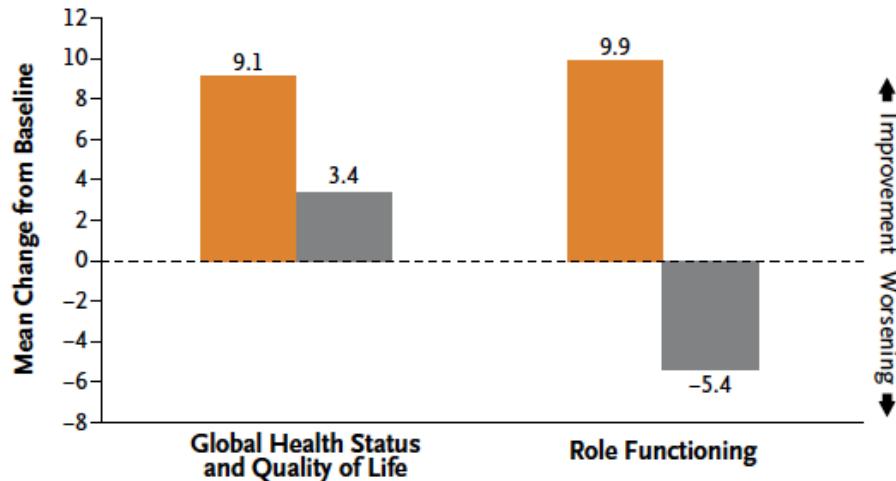


A

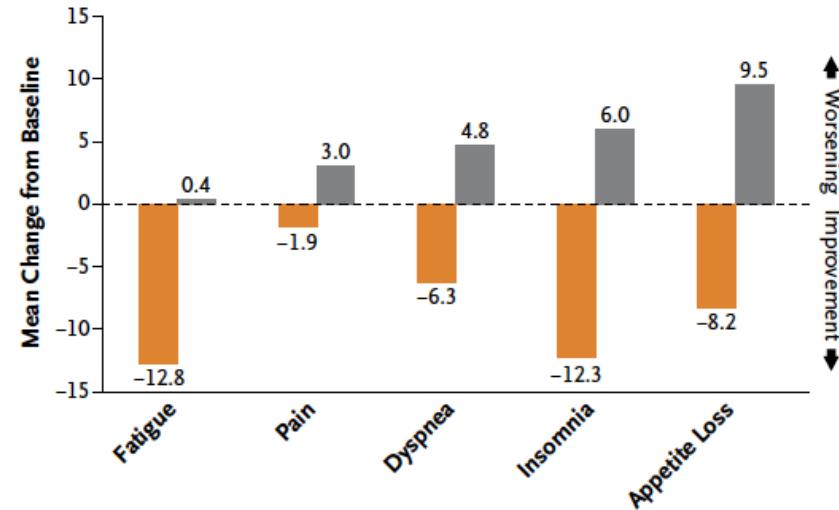


# Ruxolitinib Phase III Trials (COMFORT II – *Symptom Response*)

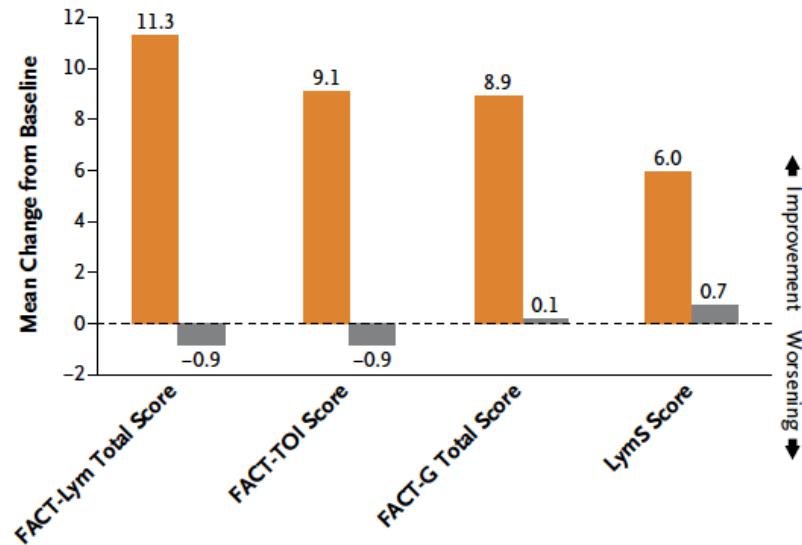
A EORTC QLQ-C30 Core Model Scores



B EORTC QLQ-C30 Symptom Scores

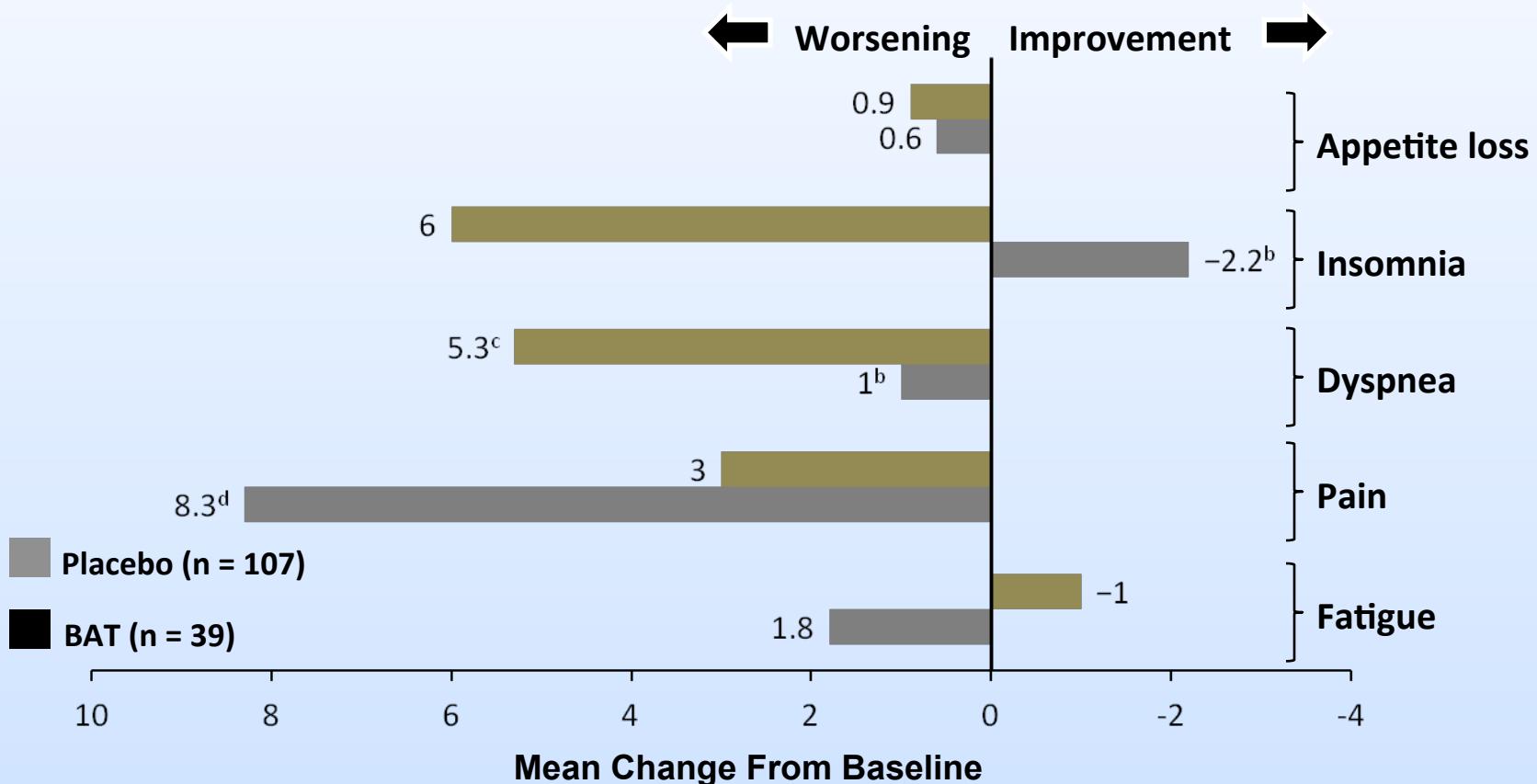


C FACT-Lym Scores



# COMFORT-I and COMFORT-II: Placebo vs BAT

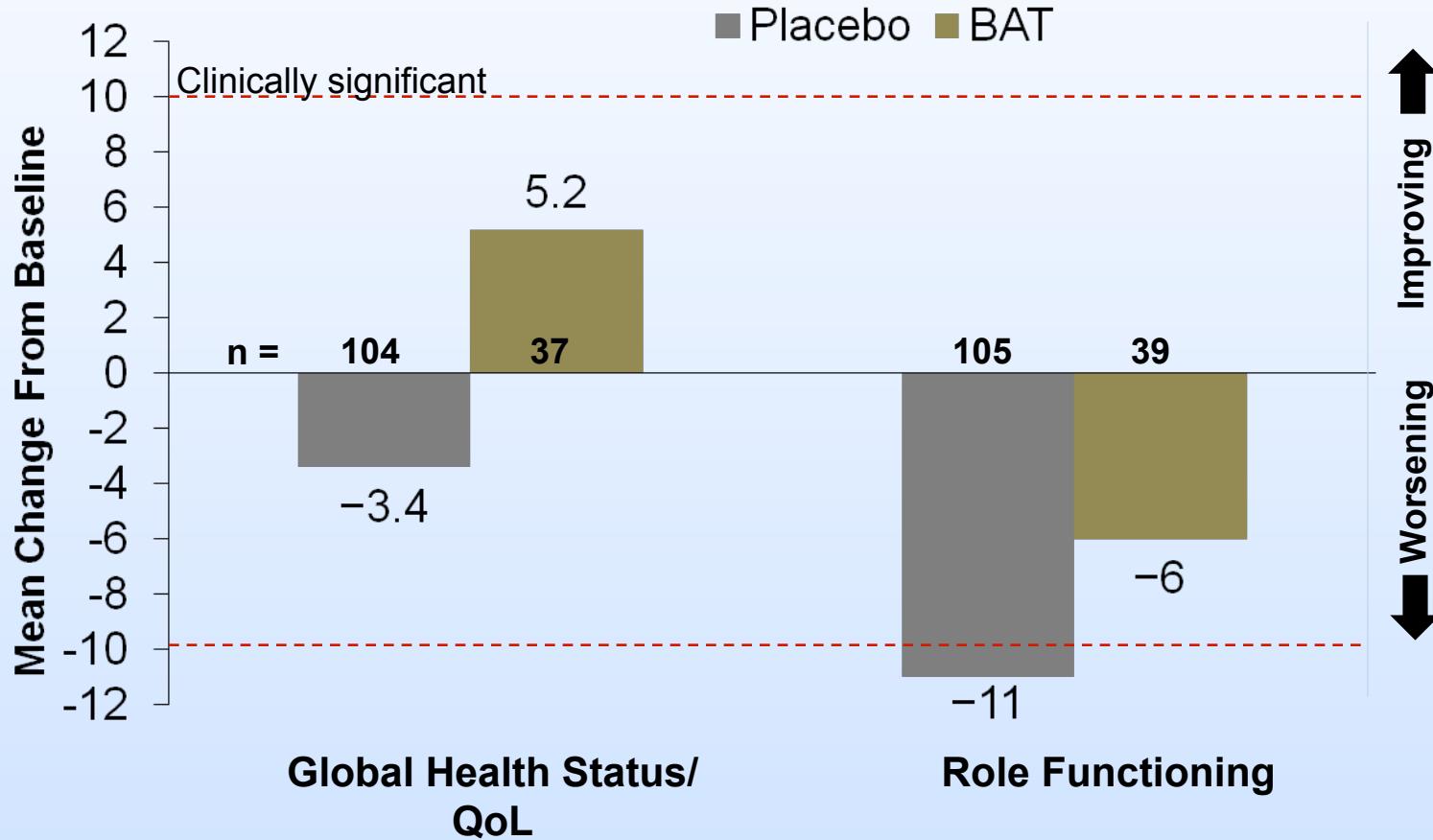
## Mean Change From Baseline in EORTC QLQ-C30 Symptom Scores at Week 24<sup>a</sup>



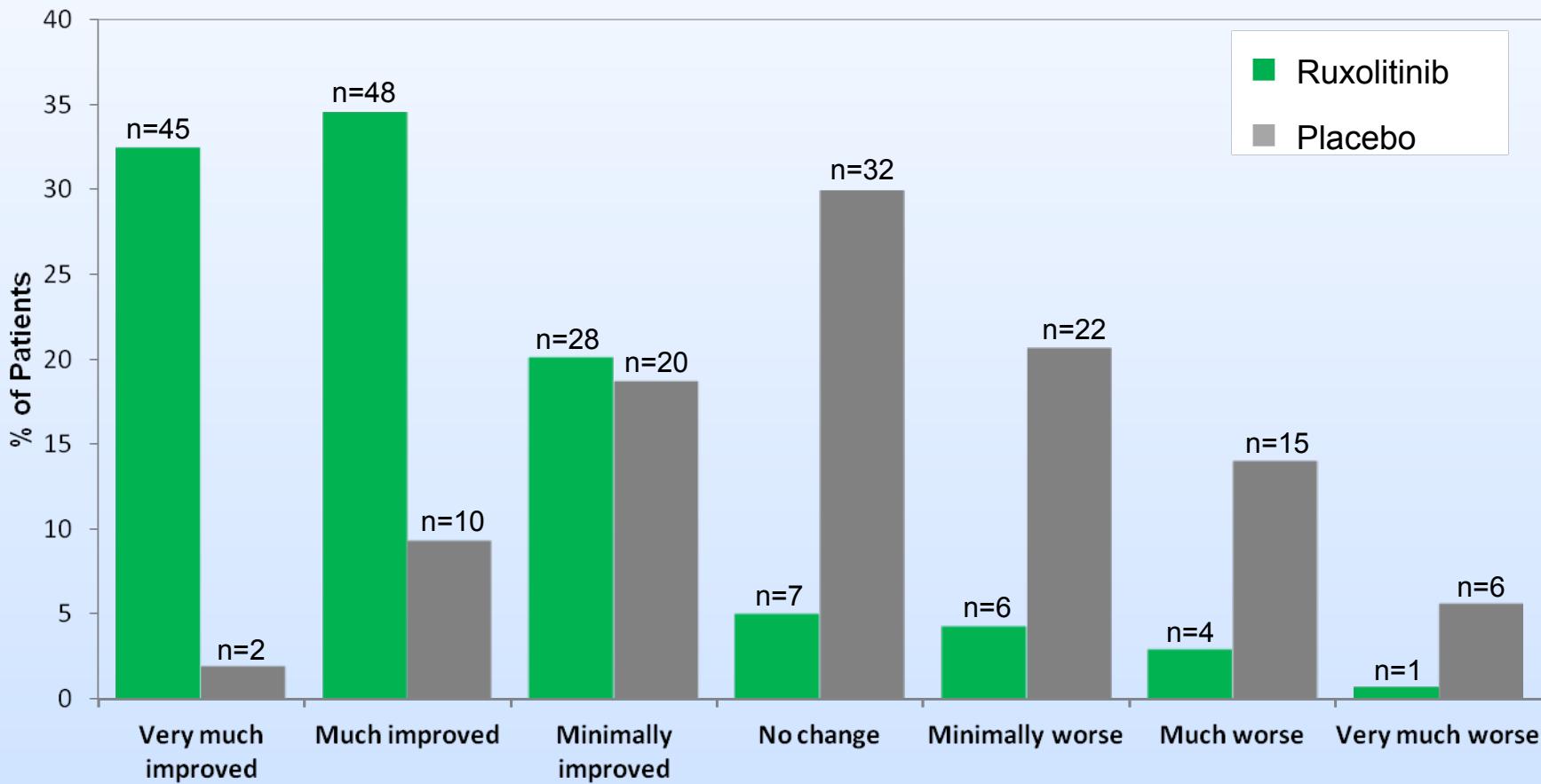
<sup>a</sup> For patients with measurements at both baseline and week 24.

# COMFORT-I and COMFORT-II: Placebo vs BAT

## Mean Change From Baseline in EORTC QLQ-C30 Scores at Week 24



# COMFORT-I: Patient Global Impression of Change at Week 24



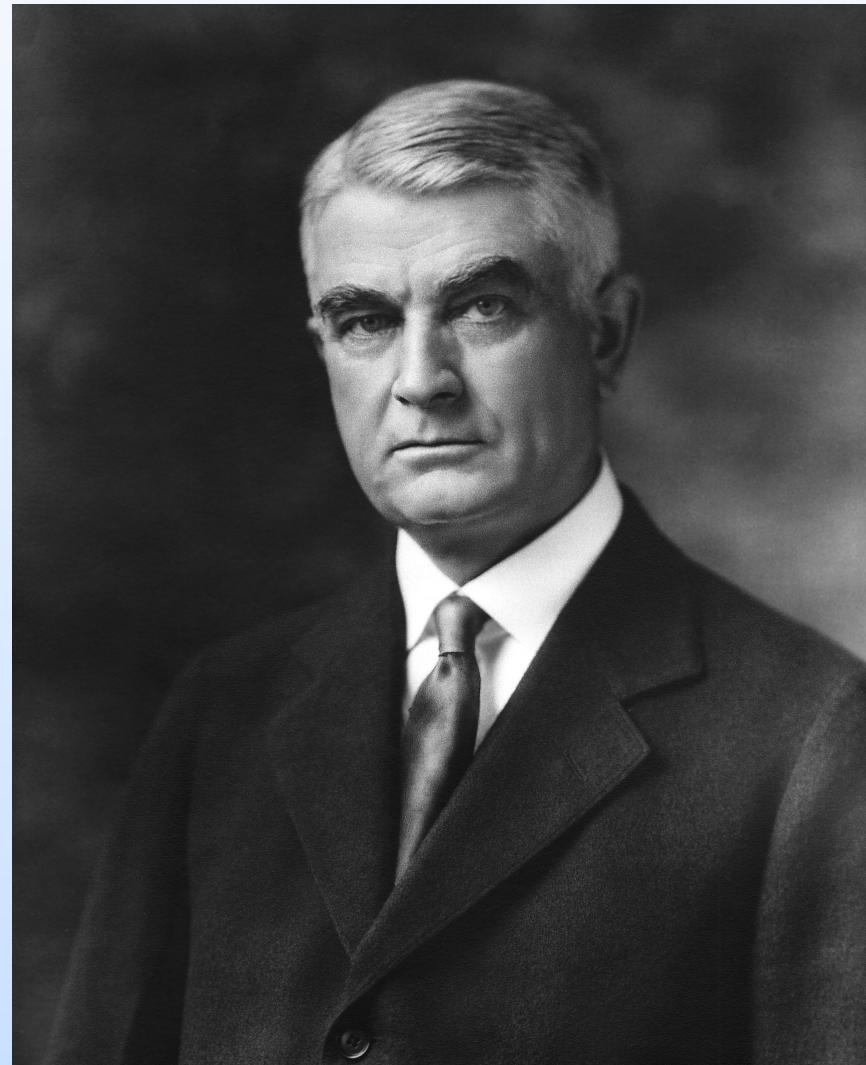


The Little Deer  
1946

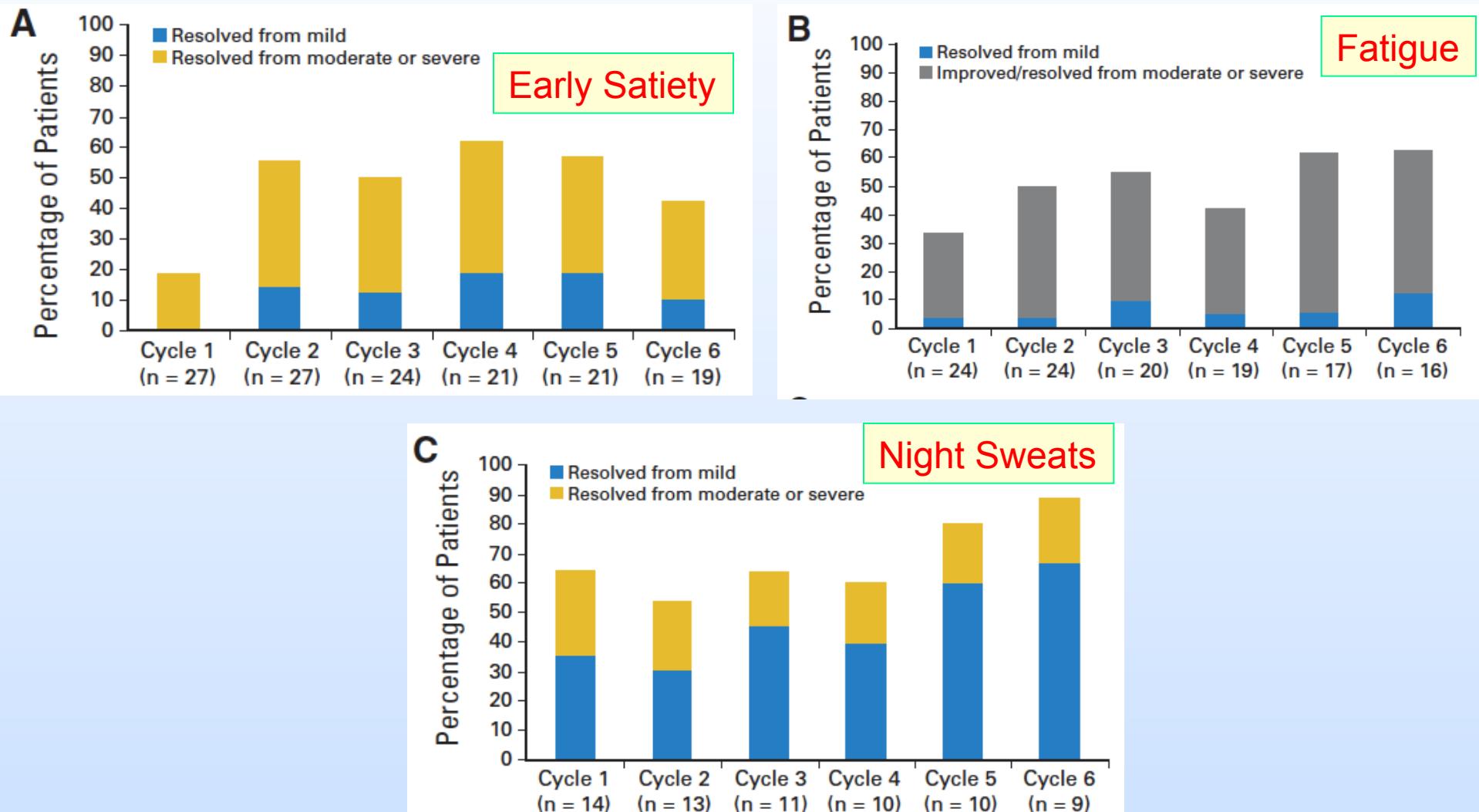
Collection of Carolyn Farb – Houston, Tx

Frida Kahlo (1907-1954)

- “The spleen is an organ of contradiction and mystery: in health of relatively unimportant function, in disease a menace of grave import.”  
- *Dr. Will Mayo*

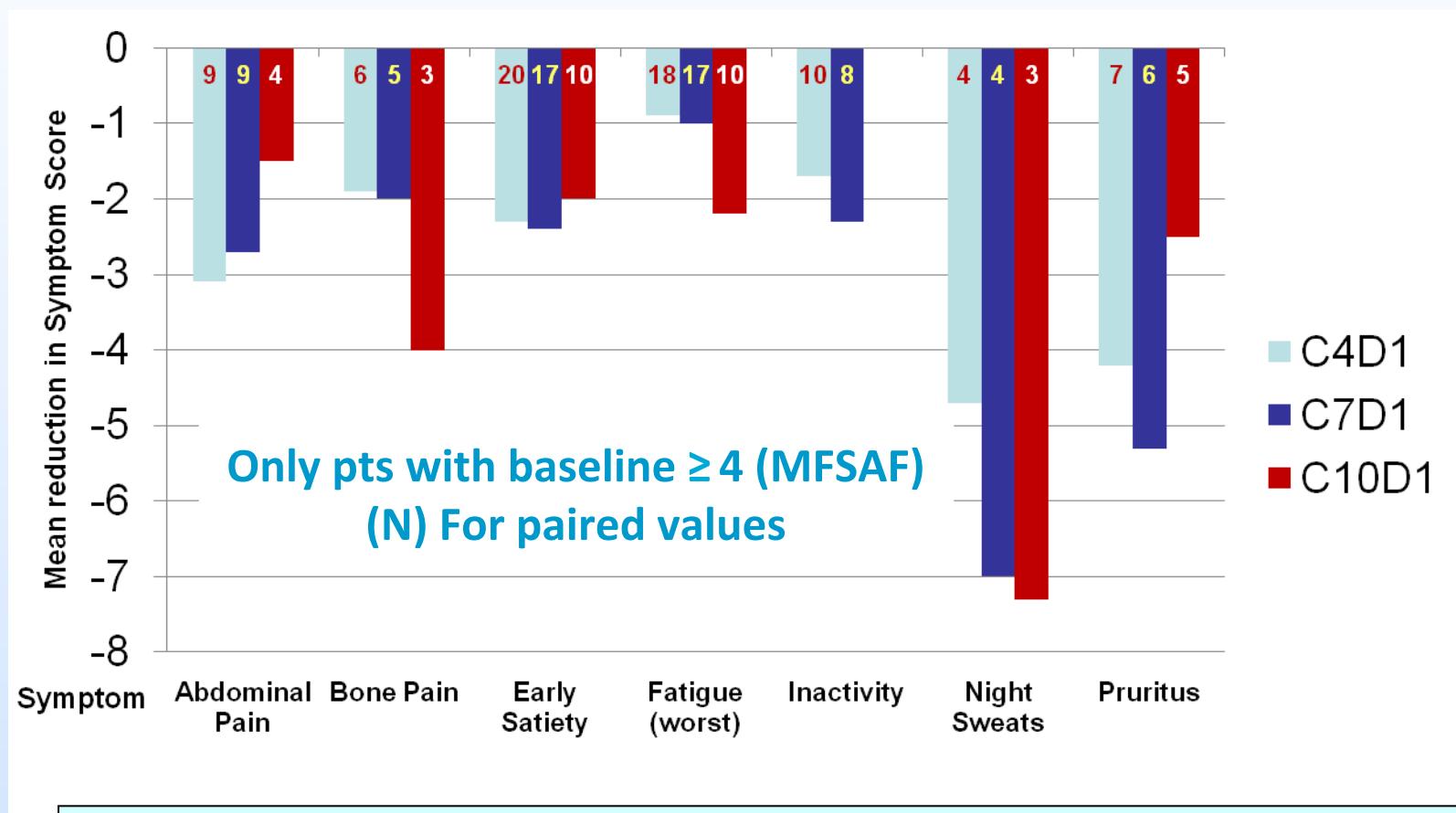


# Symptom Responses to TG101348 (SAR302503)



# > 9 Months Sustained Improvement in MF-related Symptoms

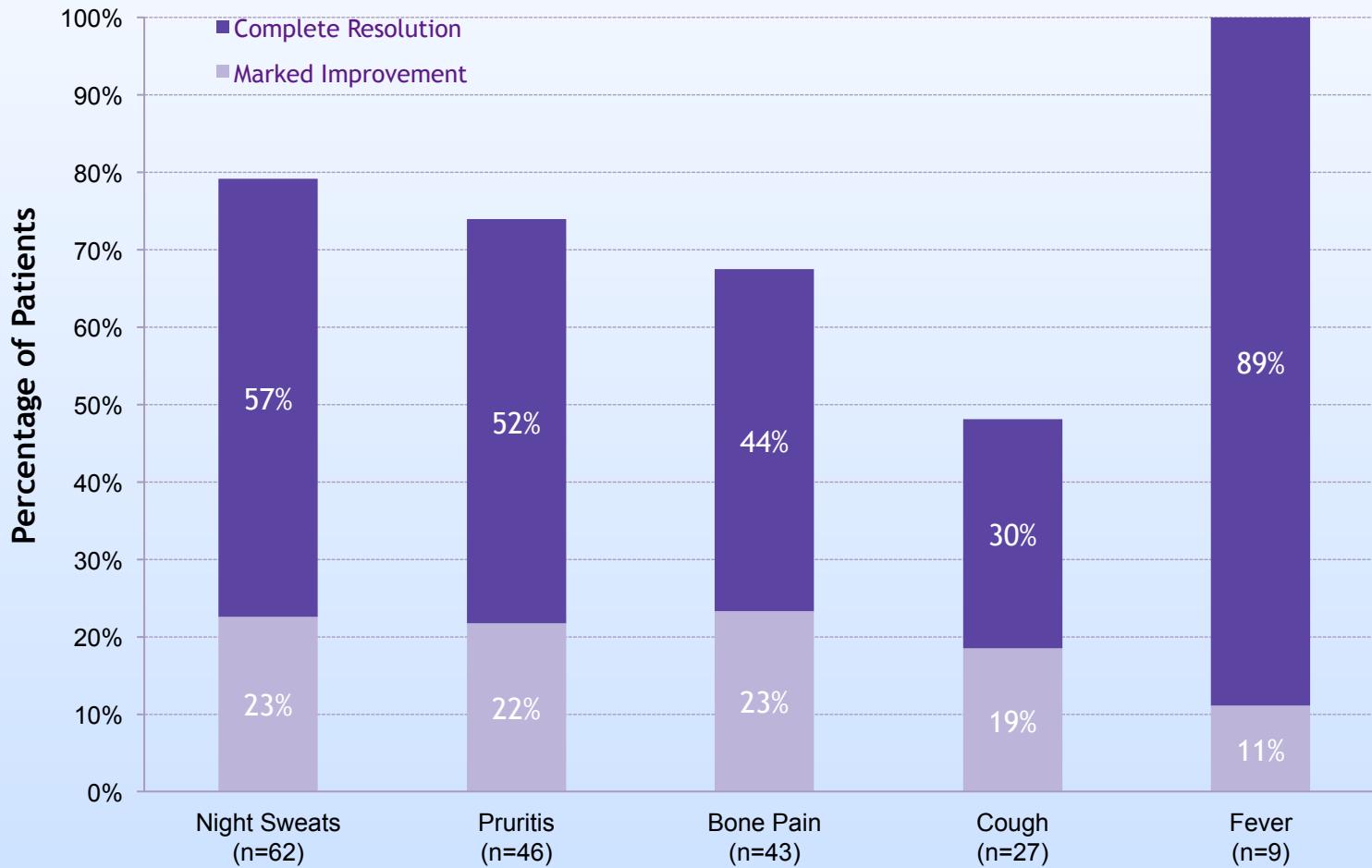
## Pacritinib: SB 1518



*Durable improvement in most symptom scores was observed*

# Constitutional Symptoms Response at Six Months

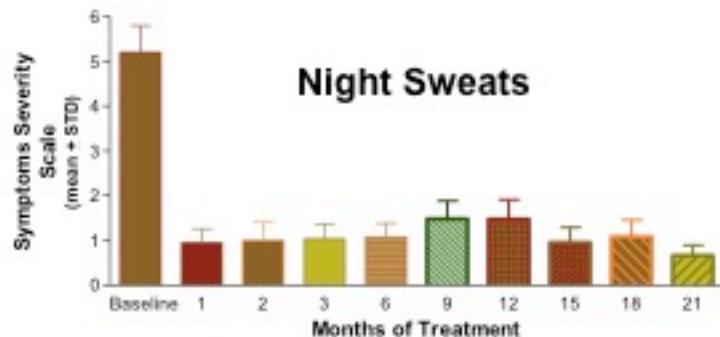
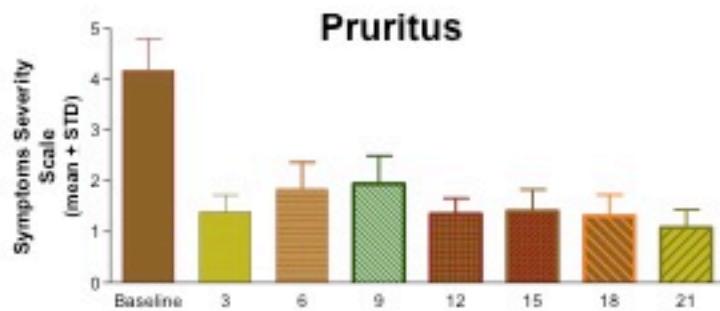
## CYT 387



# PV Results: Symptoms

## Mean Symptom Severity Scores

Ruxolitinib in Phase II PV trial



- Rapid improvements in patient reported symptom scores observed

- Responses have been durable in the majority of responding patients through the last follow-up visit

*High and ? Int Risk = Cytoreduction*

*All Risk = ASA*

**ET**

**PV**

*No Known Therapy  
? JAK2 Inhibitors*

*Short Term*

**Thrombosis  
& Bleeding**

*Long Term*

**Post ET/PV MF  
& MPN Blast Phase**

# Management of PV/ET in 2012

- ALL Patients
  - *Maintain HCT <45% Men, 42% Women (PV)*
  - *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*

# JAK1 & 2 Inhibitors in MPNs – Efficacy Summary

Yes

No

Occasional

Not Reported Yet

	Myelofibrosis				Polycythemia Vera			Essential Thrombocythemia		
	Spleen	Const. Sympt.	Anemia	Survival	↓ Counts	Const. Sympt.	↓ Vasc Events	↓ Counts	Const. Sympt.	↓ Vasc Events
Ruxolitinib - <i>Approved</i>	P III	P III	P III	P III	P II	P II	P II	P II	P II	P II
SAR302503 – <i>P III Ongoing (MF)</i>	P II	P II	P II							
Pacritinib- <i>P III Ongoing (MF)</i>	P II	P II	P II							
CYT387	P II	P II	P II							
LY2784544	P I	P I								
NS-018										
BMS-911543										
CEP701	P II	P II			P II		P II	P II		P II

# JAK1 & 2 Inhibitors in MPNs – Toxicity Summary

	Hematological Toxicities			Gastrointestinal Toxicities				Neurological Toxicities		
	Anemia	↓ ANC	↓ PLT	Nausea	Diarrhea	↑ LFTs	↑ Lipase	Headache	Dizzy	NeuroP/Parathia
Ruxolitinib - Approved	45%	7%	13%		2%				0.6%	
SAR302503 – PIII Ongoing (MF)	30%			9%	10%	20%	10%			
Pacritinib- PIII Ongoing (MF)				6%		9%	6%			
CYT387 PII Ongoing (MF)				10%			2%	20%	1%	

Toxicity Color – Represents All Grades ( Grade ¾ Toxicity - Percentage in Table Above)



Ruxolitinib: Verstovsek et. al. PHIII Trial (Comfort 1) NEJM 2012  
 SAR302503: Talpaz et. al. PHII ASH 2012  
 Pacritinib: Komrokji et. al. PH II ASH 2011  
 CYT387: Pardanani et. al. PH II ASH 2012

# JAK1 & 2 Inhibitors in MPNs – Efficacy Summary

Yes

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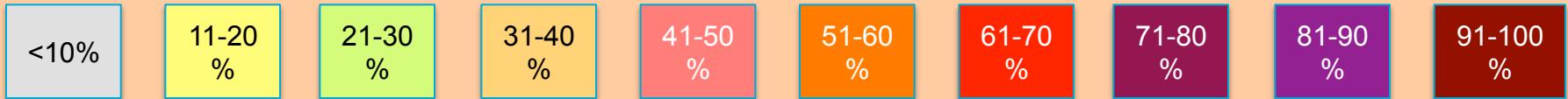
Not Reported Yet

	Myelofibrosis				Polycythemia Vera			Essential Thrombocythemia		
	Spleen	Const. Sympt.	Anemia	Survival	↓ Counts	Const. Sympt.	↓ Vasc Events	↓ Counts	Const. Sympt.	↓ Vasc Events
Ruxolitinib - <i>Approved</i>	P III	P III	P III	P III	P II	P II	P II	P II	P II	P II
SAR302503 – <i>P III Ongoing (MF)</i>	P II	P II	P II							
Pacritinib- <i>P III Ongoing (MF)</i>	P II	P II	P II							
CYT387	P II	P II	P II							
LY2784544	P I	P I								
NS-018										
BMS-911543										
CEP701	P II	P II			P II		P II	P II		P II

# JAK1 & 2 Inhibitors in MPNs – Toxicity Summary

	Hematological Toxicities			Gastrointestinal Toxicities				Neurological Toxicities		
	Anemia	↓ ANC	↓ PLT	Nausea	Diarrhea	↑ LFTs	↑ Lipase	Headache	Dizzy	NeuroP/Parathia
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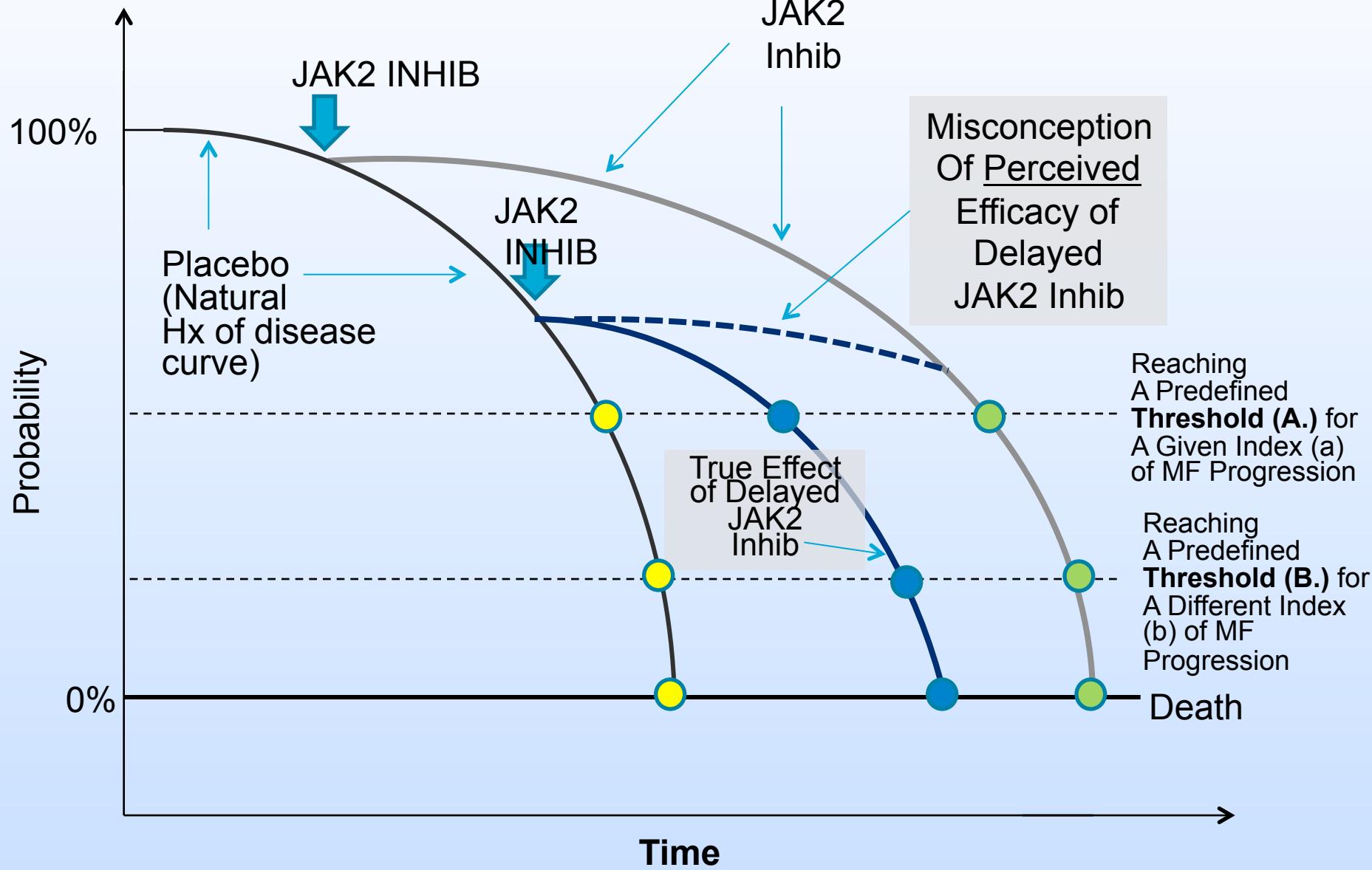
# JAK2 Inhibition in MF

## *Unanswered Questions*

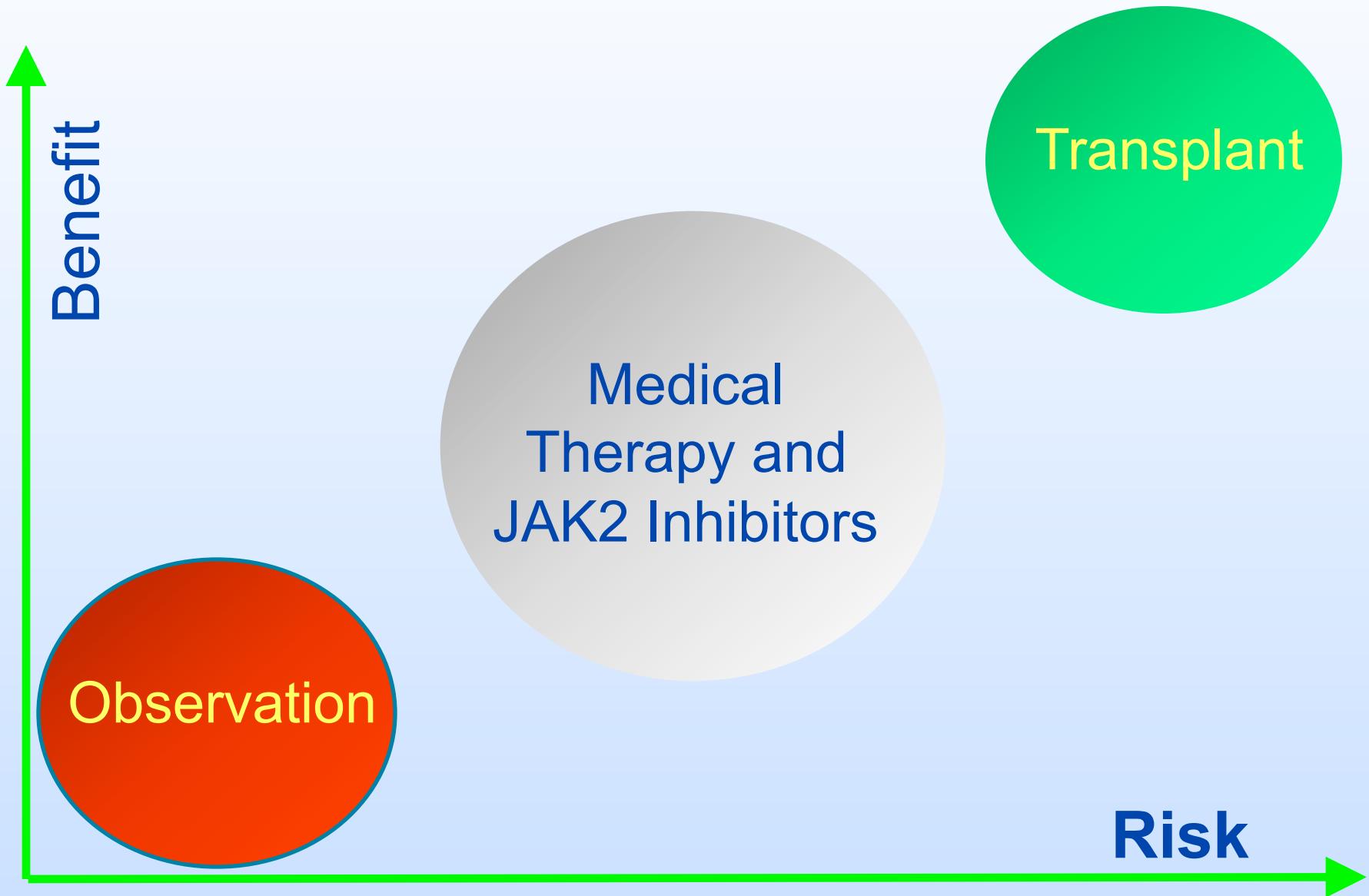
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- If you inhibit JAK2 in PV does it prevent Post PV MF?
  - If you inhibit JAK2 in WHO ET does it prevent Post ET MF?
  - What is benefit of JAK2 inhibition in Symptomatic Low Risk and Int 1 MF?
- 
- JAK2 Inhibition as part of Allo SCT Strategy?
  - JAK2 Inhibition as part of MPN-BP Strategy?

## **Freedom from MF “Progression” or Death)**



# Therapy Choices - MF



# Medications for MF prior to JAK2 Inhibitors

## Medicines for MF Anemia

- *Androgens*
- *EPO*
- *Thalidomide*

## Medicines for MF Spleen

- *Hydroxyurea*
- *Busulfan*
- *2-CDA*
- *Splenectomy*
- *Splenic Radiation*

## Medicines for Anemia & Spleen

- *Lenalidomide*

## Medicines for MF Symptoms

- *None*

# Selected Ongoing MPN Clinical Trials 2013

## MF – MonoRx

- *Ruxolitinib (alt doses)*
- *SAR302503*
- *Pacritinib*
- *CYT387*
- *NS018*
- *LY2784544*
- *BMS 911543*
  
- *INCB39110*
- *GRN163 (Imetelstat)*
- *Pomalidomide*

## MF – ComboRx

- *Ruxolitinib plus*
  - *Panobinostat*
  - *Allo SCT*
  - *IMID (Len or POM)*
  - *Danazol*
  - *IPI926 (HH)*
  - *GS-6624 (LOXL2 ab)*
  - *RAD001*
  - *Decitabine (MPN-BP)*
  - *5 AZA*

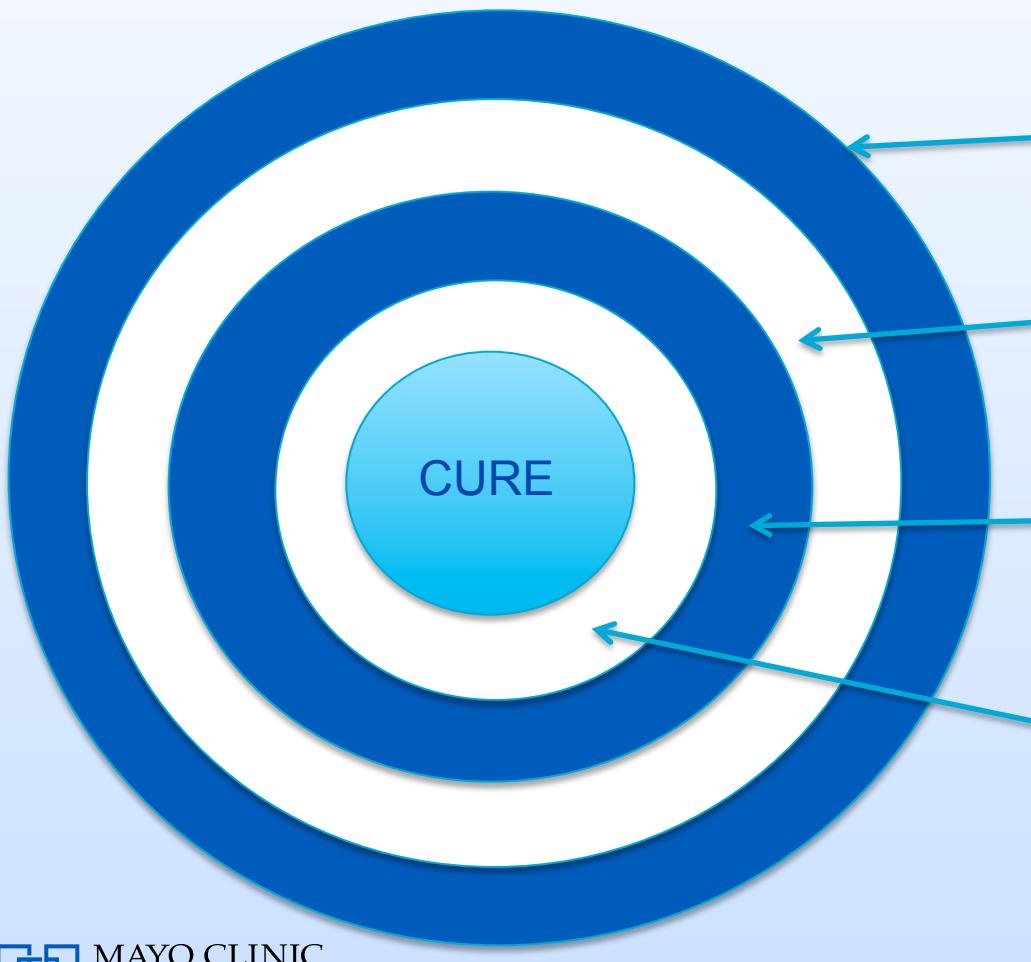
## PV

- *Ruxolitinib*
- *PegINFa2a*
- *SAR302503*

## ET

- *PegINFa2a*
- *Imetelstat*
- *SAR302503*

# Individualizing MPN Therapy



Patient Goals & Input

Improving Symptom Burden  
/HR QOL

“Balancing” Spleen/  
Cytoses/ Cytopenias

Extending Life

# MPN-QOL International Study Group

[www.mpn-qol.org](http://www.mpn-qol.org)

- MEASURE Trial
  - Serial assessment of MPN symptoms and QOL in all currently available therapies
- SYMPTOM Trial
  - Serial assessment of the BMT experience in MPN symptoms (and BMT/GVHD symptoms) and QOL

# Conclusions

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1. Symptomatic Burden in MPNs is a real issue across the spectrum of disease
2. Distinct symptom clusters exist for ET/PV vs. MF
3. Improvement in MPN Symptom Burden is an appropriate and achievable goal from MPN therapy
4. Individualizing therapy for MPN patients is needed given heterogeneous nature of the diseases and spectrum of medical therapy efficacy

# Acknowledgements

- Mayo Clinic
  - Amylou Dueck, PhD
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- France
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  - Francesco Passamonti, MD
  - Giovanni Barosi, MD
  - Alessandro Rambaldi, MD
  - Maria Ferarri, MD
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  - Bjorn Andreasson, MD
  - Jan Samuelsson, MD
  - Gunnar Birgegard, MD
- Denmark
  - Hans Hasselbalch, MD
- Germany
  - Heike Pahl, PhD
  - Martin Grisshammer, MD



Joy  
2009

Weatherburn Gallery, Naples, FL, USA

Diane Leonard (1958 - )