How I Treat Symptom Burden in MPNs

Ruben A. Mesa, MD
Executive Director, UT Health San Antonio Cancer Center
Mays Family Foundation Distinguished University Presidential Chair

Twitter: @mpdrc

Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center

Disclosures

- Consultant (Honoraria) over past 3 years
  - Novartis
  - Sierra Oncology
  - La Jolla Pharma
  - AOP

- Research Support
  - Incyte
  - Gilead
  - CTI
  - Celgene
  - Abbvie
  - Genentech

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

How I Treat Symptom Burden in MPNs

- The Burden of an MPN
- Lessons from the Landmark Studies
- The Biology of MPN Symptoms
- Including symptoms in treatment planning and management
- Future Options

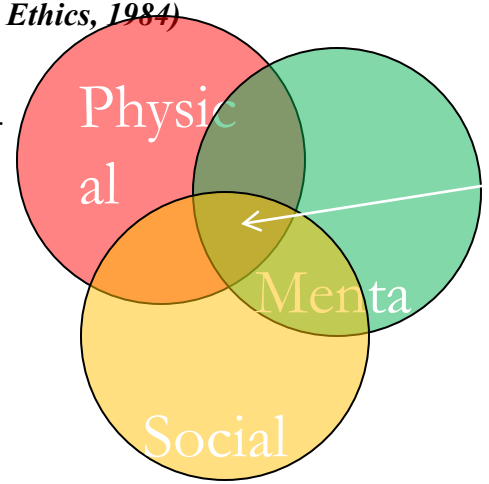
Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Quality of Life (QOL)

- Definitions
  - *"net consequence of life characteristics on a person's perception of their position in life, in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards, and concerns."* **(WHO, *Soc Sci Med* 1995)**

  - **Calman's Gap**: *"the gap between one's life expectations and actual life experiences….a good quality of life can be said to be present when the hopes of an individual are matched and fulfilled by experience."* ***(Calman, J Med Ethics, 1984)***

    <u>The narrower the gap the better.</u>



Symptoms vs QOL

- Quality of Life: Broad concept across all aspects of life
- HrQOL: Health related QoL (just limited to aspects of health to QoL). Includes symptoms but also much more (Hassle/ Expense)
- Symptoms: Discreet disease related signs which differ from the individuals perceived state of normalcy

Assessing MPN burden

WHO diagnosis does not tell whole story

Vascular events
- PV/ET > MF
- Counts matter
- Can be unrecognised

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

Cytopenias
- MF > ET/PV
- Anaemia
  - MF 75%
  - Tx dep 25%
- TPN 30%

Baseline health
Age/medicines
Comorbidities

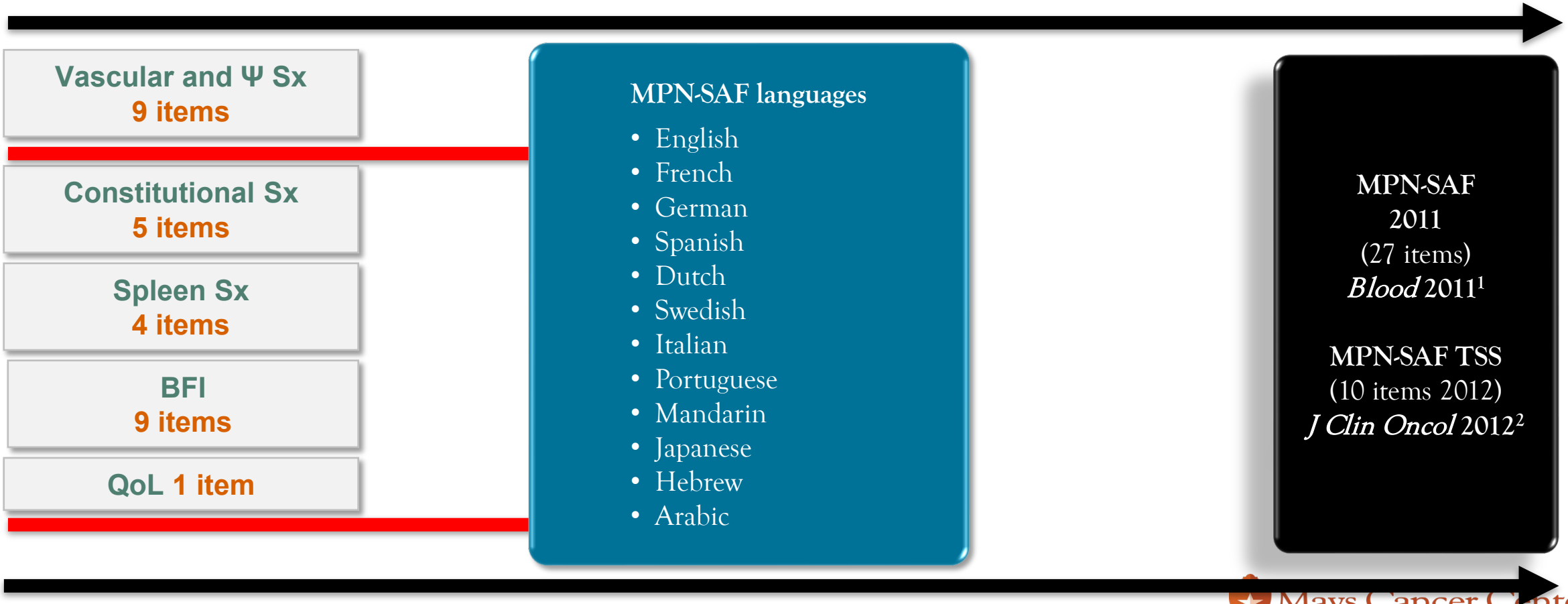
Splenomegaly
- MF > ET/PV
- Pain not always a function of size

MPN symptoms
- MF > PV > ET
- Multifactorial
- Some ET/PV > MF
- Cytoreductive Rx frequently not effective

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

AML, acute myeloid leukaemia; ET, essential thrombocythaemia; MDS, myelodysplastic syndrome; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythaemia vera; Rx, prescription; Tx, treatment; TPN, total parenteral nutrition; WHO, World Health Organization.
Personal opinion of Professor Mesa.

Evolution of MPN symptom assessment tools

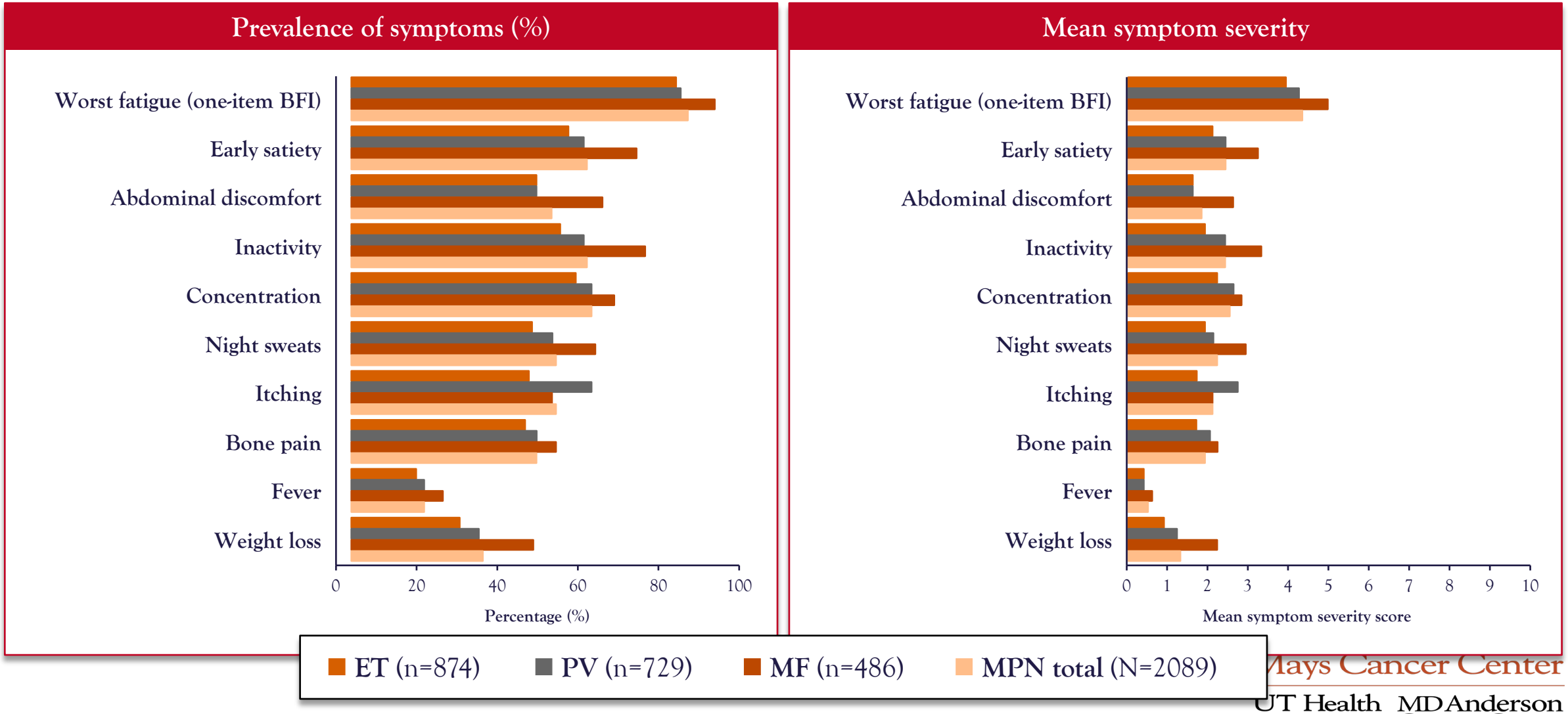


Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

BFI, Brief Fatigue Inventory; MF, myelofibrosis; MPN, myeloproliferative neoplasm; QoL, quality of life; SAF; symptom assessment form; Sx, symptoms; TSS, total symptom score.

1. Scherber R, et al. *Blood.* 2011;118:401–8; 2. Emanuel RM, et al. *J Clin Oncol.* 2012;30:4098–103.

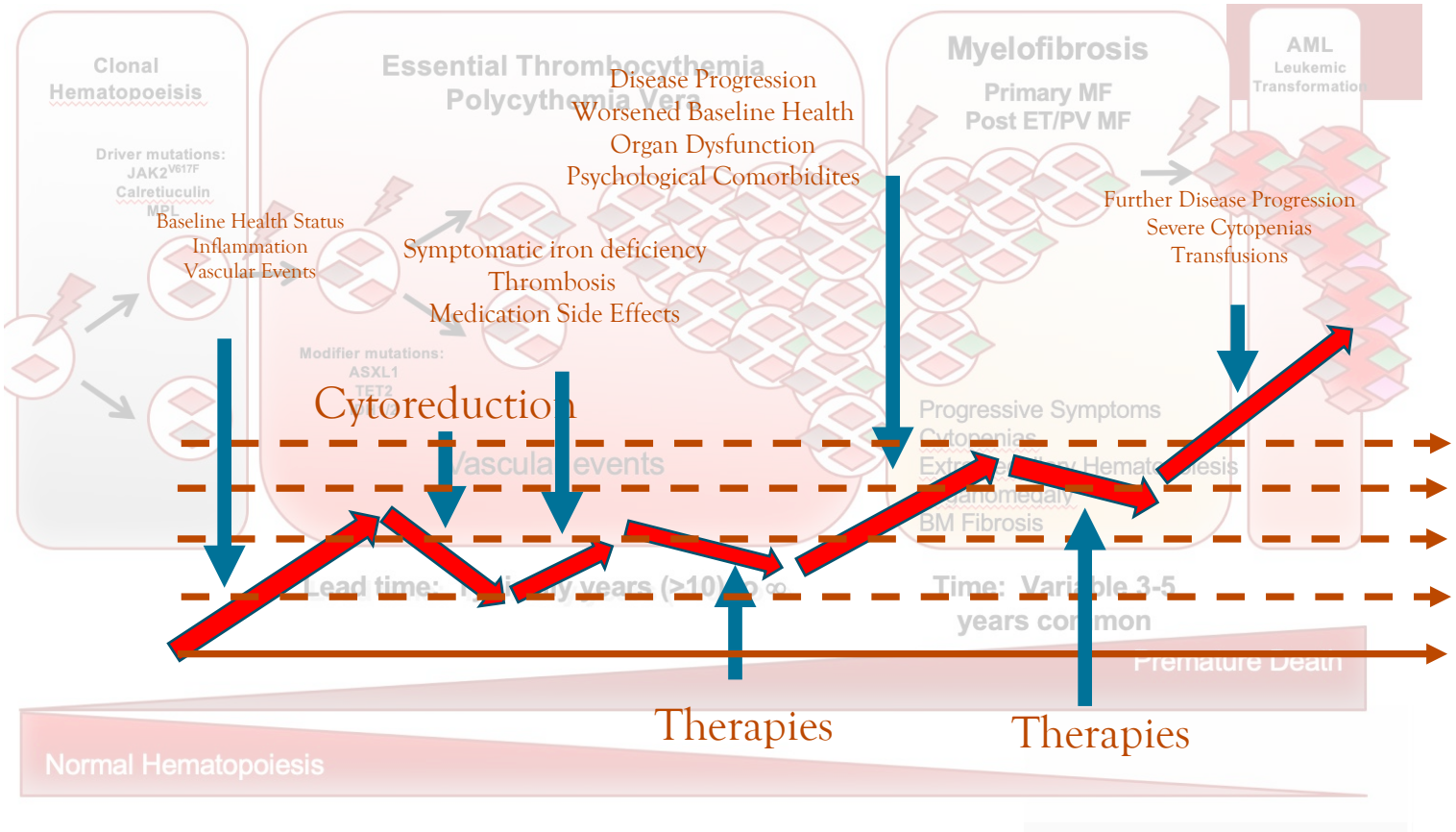
Classic signs and symptoms of MPNs



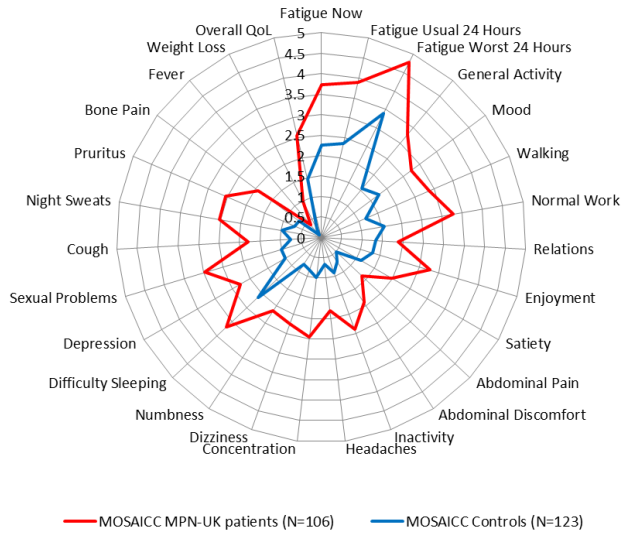
Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center

BFI, Brief Fatigue Inventory; ET, essential thrombocythaemia; MF, myelofibrosis; MPN, myeloproliferative neoplasm; PV, polycythaemia vera.
Geyer HL, et al. *Blood.* 2014;124:3529–37.

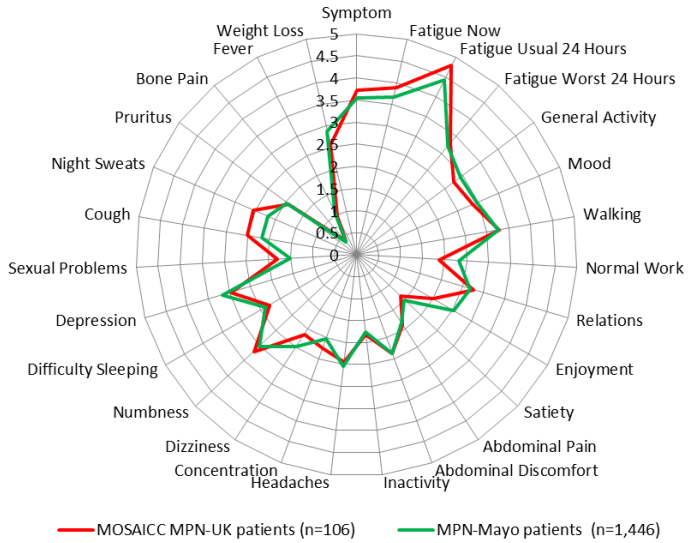
Symptoms Change During the Natural History of MPNs



MPN Symptoms



MPN-SAF scores MPN patients versus controls



MPN-SAF scores UK versus USA

Anderson et. al, 2016.

MPN Recent Phase III Trials

MPN Symptom Assessment

Disease	Drug	MPN Symptom Tool
MF	RUXO (COMFORT 1)	MF-SAF 2.0
MF	RUXO (COMFORT 2)	FACT-LYM
MF	Fedratinib (JAKARTA)	MF-SAF
MF	Pacritinib (PERSIST 1&2)	MPN-SAF
MF	Momelotinib (SIMLIFY 1&2)	MPN-SAF
MF	Pomalidomide (RESUME)	FACT-AN
MF	RUXO (RETHINK)	MPN-10
PV	Ruxo (RESPONSE)	MPN-SAF
PV	Ruxo (RELIEF)	MPN-SAF
PV	PEG INFa2a (MPD-RC 112)	MPN-SAF
ET	Ruxo (MAGIC)	MPN-SAF
ET	PEG INFa2a (MPD-RC 112)	MPN-SAF

How I Treat Symptom Burden in MPNs

- The Burden of an MPN
- Lessons from the Landmark Studies
- The Biology of MPN Symptoms
- Including symptoms in treatment planning and management
- Future Options

Myeloproliferative neoplasms (MPNs) have a significant impact on patients' overall health and productivity: the MPN Landmark survey.

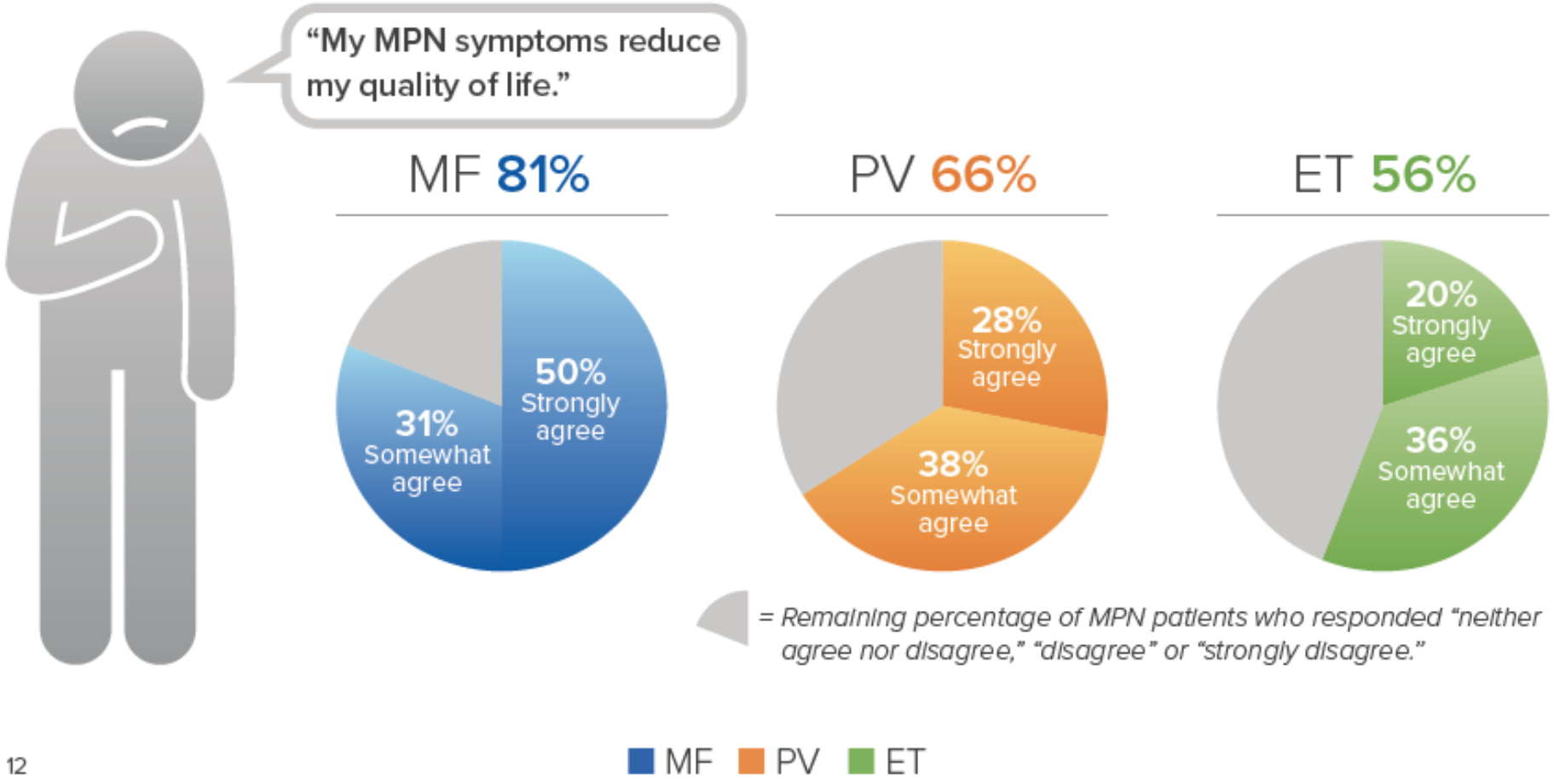
Ruben Mesa,[1,a] Carole B. Miller,[2] Maureen Thyne,[3] James Mangan,[4] Sara Goldberger,[5] Salman Fazal,[6] Xiaomei Ma,[7] Wendy Wilson,[8] Dilan C. Paranagama,[9] David G. Dubinski,[9] John Boyle,[10] John O. Mascarenhas[11]

[1]Mayo Clinic Cancer Center, Scottsdale, AZ; [2]St. Agnes Hospital, Baltimore, MD; [3]Weill Cornell Medical College, New York, NY; [4]University of Pennsylvania, Abramson Cancer Center, Philadelphia, PA; [5]Cancer Support Community, New York, NY; [6]Allegheny Health Network, Pittsburgh, PA; [7]Yale School of Public Health, New Haven, CT; [8]Fred Hutchinson Cancer Research Center, Seattle, WA; [9]Incyte Corporation, Wilmington, DE; [10]ICF International, Rockville, MD; [11]Icahn School of Medicine at Mount Sinai, New York, NY

[a] Corresponding author.

Mesa R, et al. *BMC Cancer*. 2016;16:167.

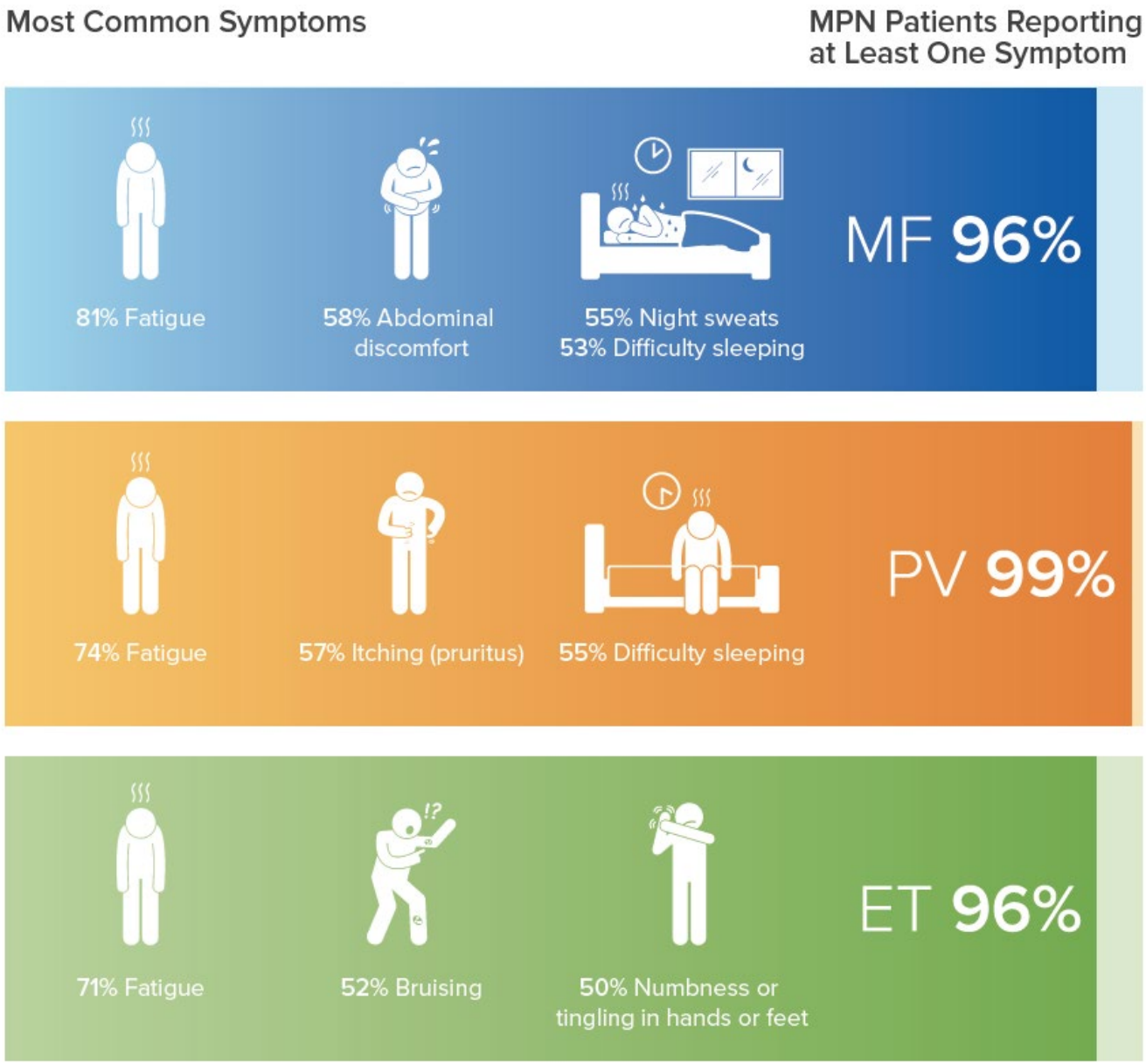
MPN Landmark Study - USA



Mesa et. al. BMC Cancer 2016

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

MPN Landmark Study - USA



Mesa et. al. BMC Cancer 2016

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

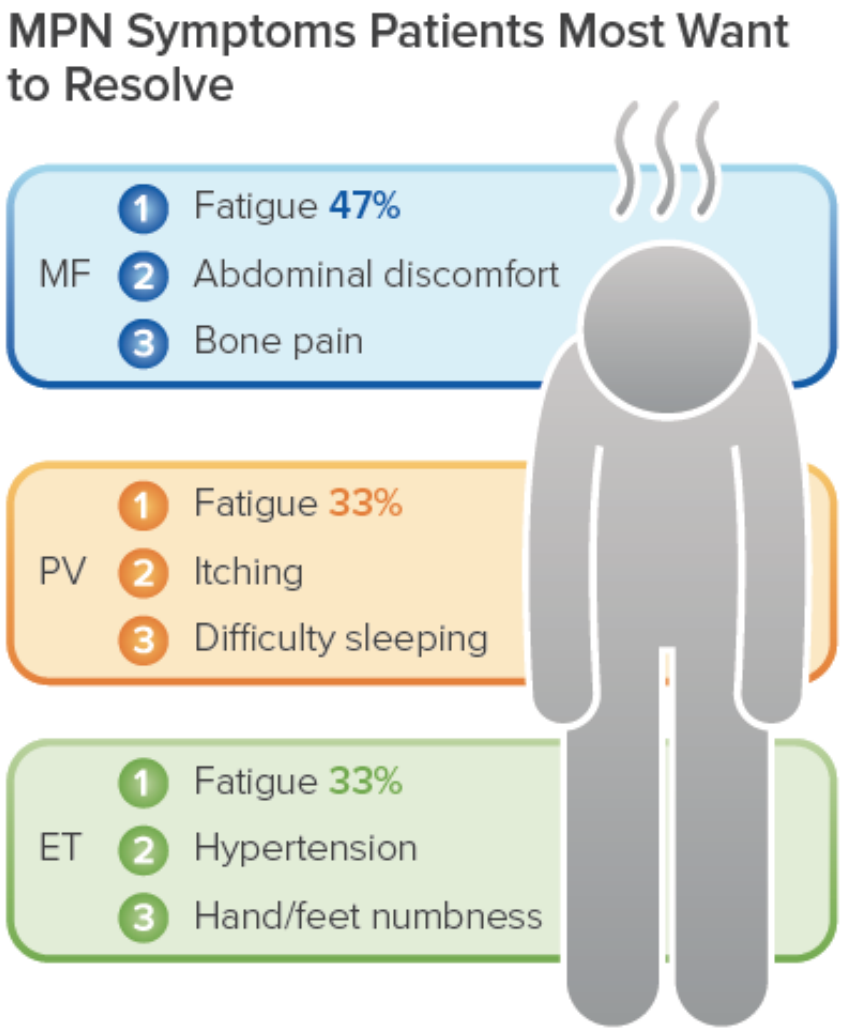
MPN Landmark Study - USA

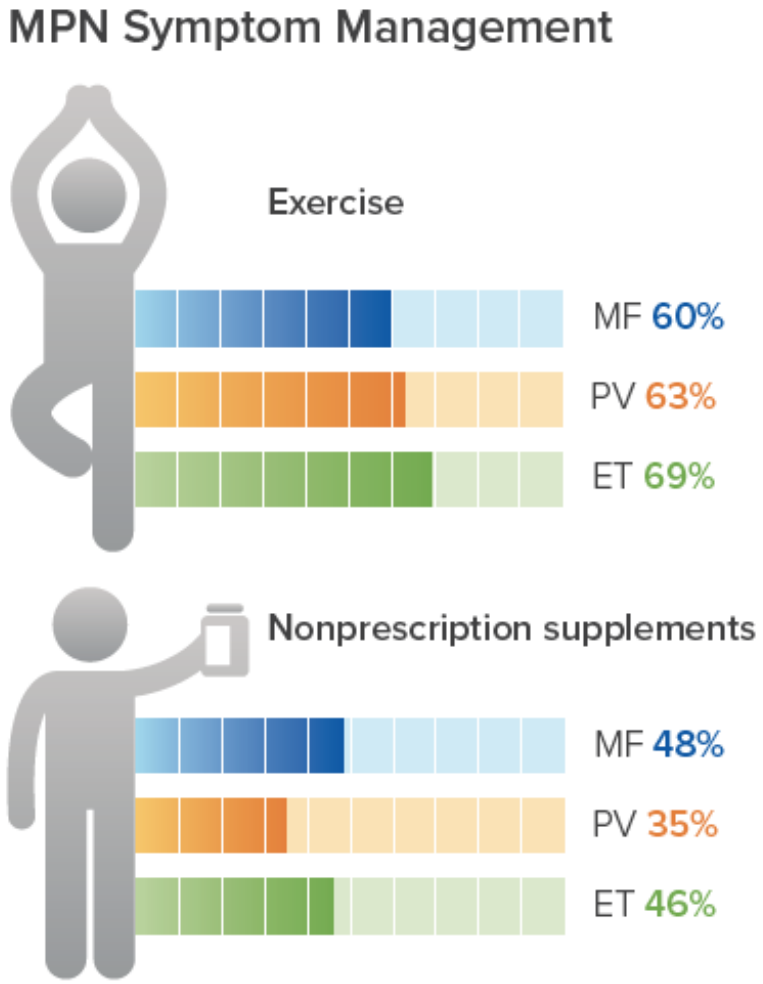
Most Severe Symptoms Reported by MPN Patients	MF	PV	ET
Fatigue	✓	✓	✓
Problems with sexual desire	✓	✓	✓
Inactivity	✓	✓	✓
Problems concentrating	✓	✓	
Difficulty sleeping	✓	✓	
Weakness			✓
Muscle aches			✓

Mesa et. al. BMC Cancer 2016

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

MPN Landmark Study - USA

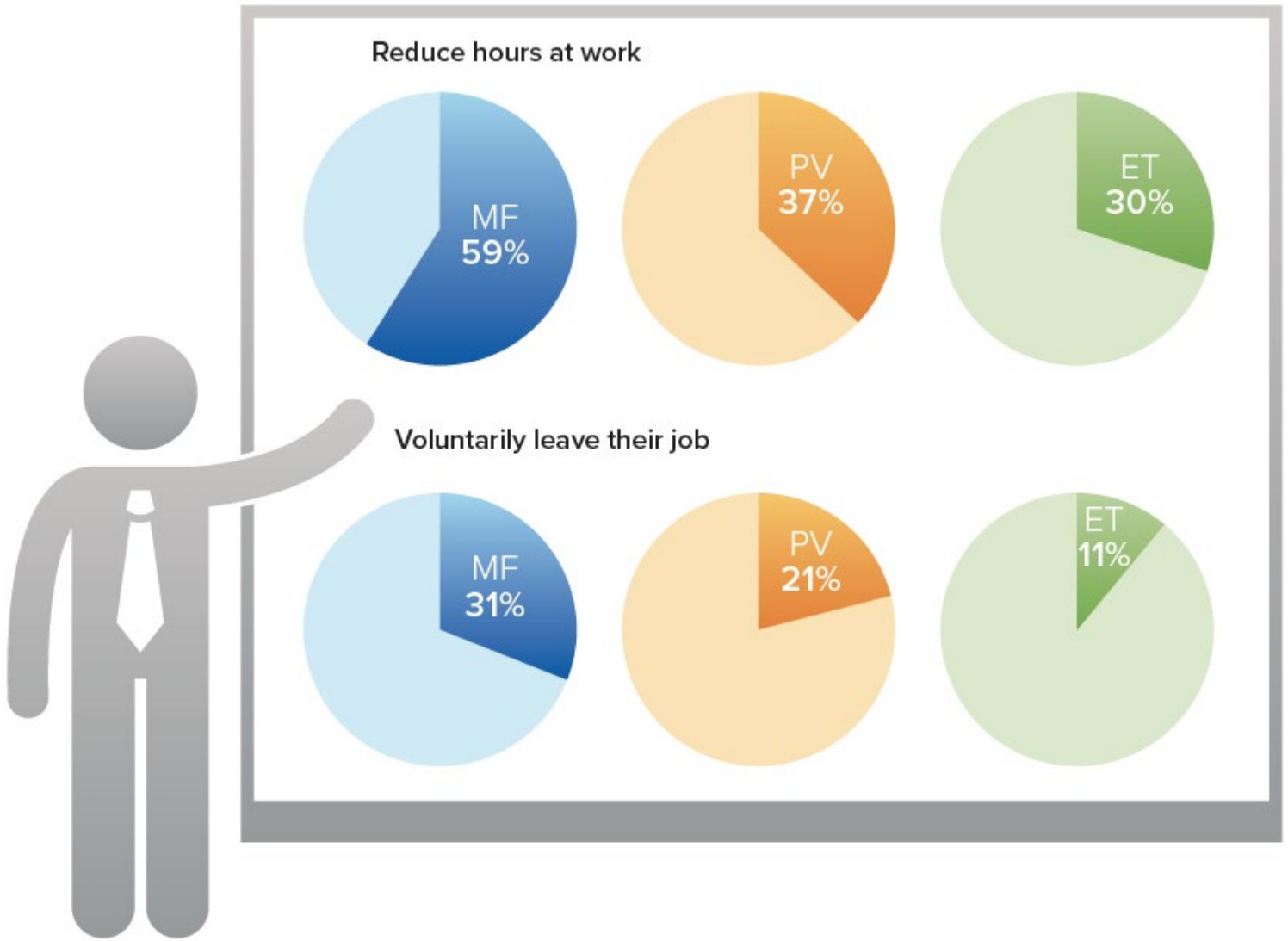




Mesa et. al. BMC Cancer 2016

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

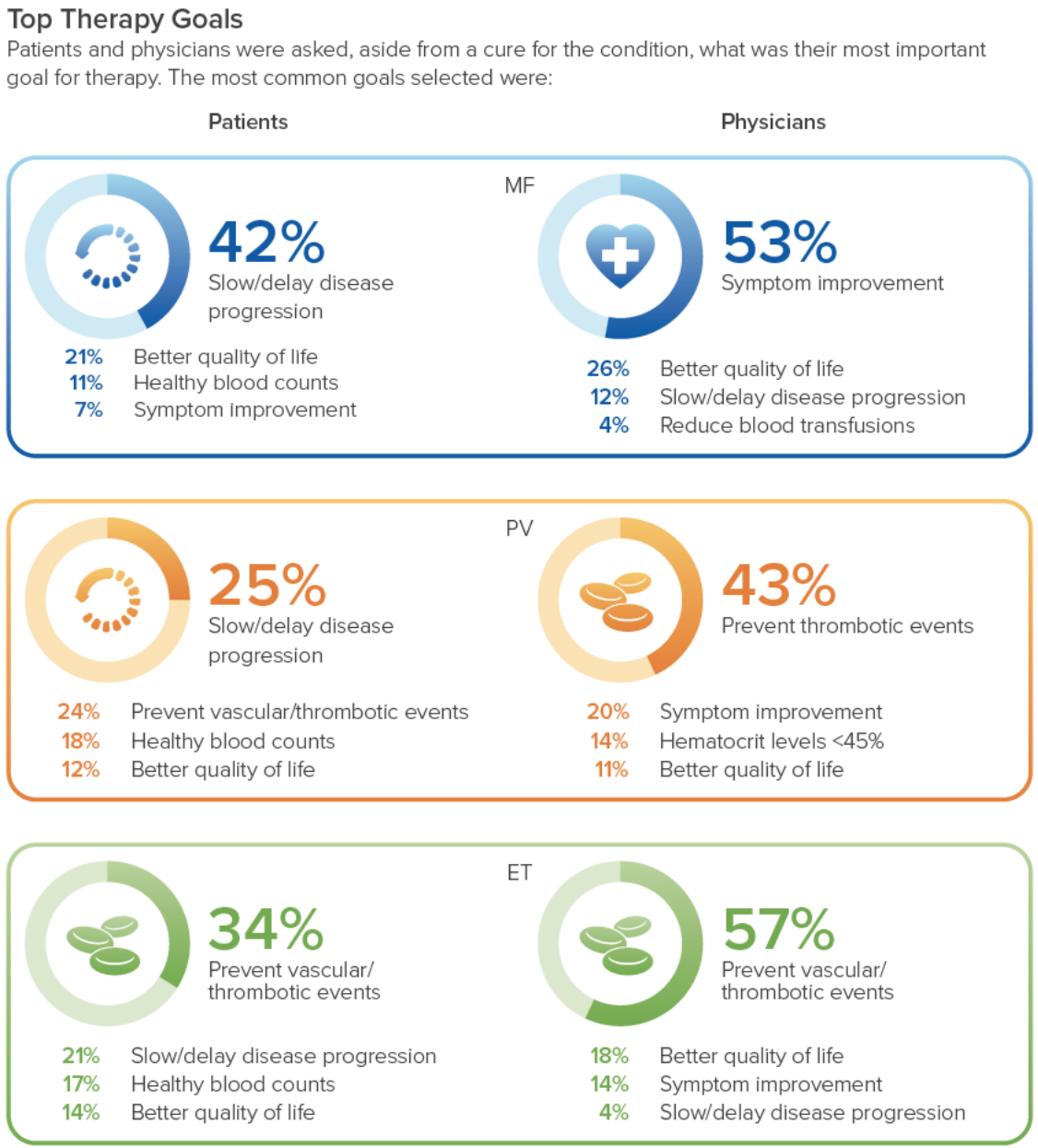
MPN Landmark Study - USA



Mesa et. al. BMC Cancer 2016

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

MPN Landmark Study - USA



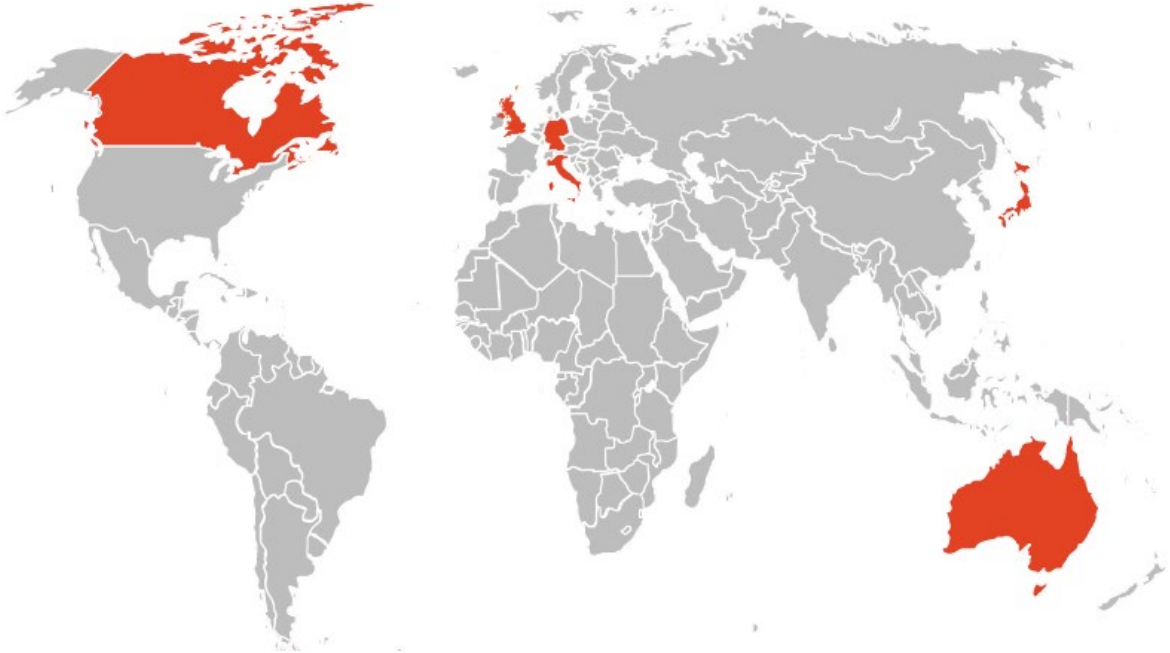
Mesa et. al. BMC Cancer 2016

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Aims and Methods

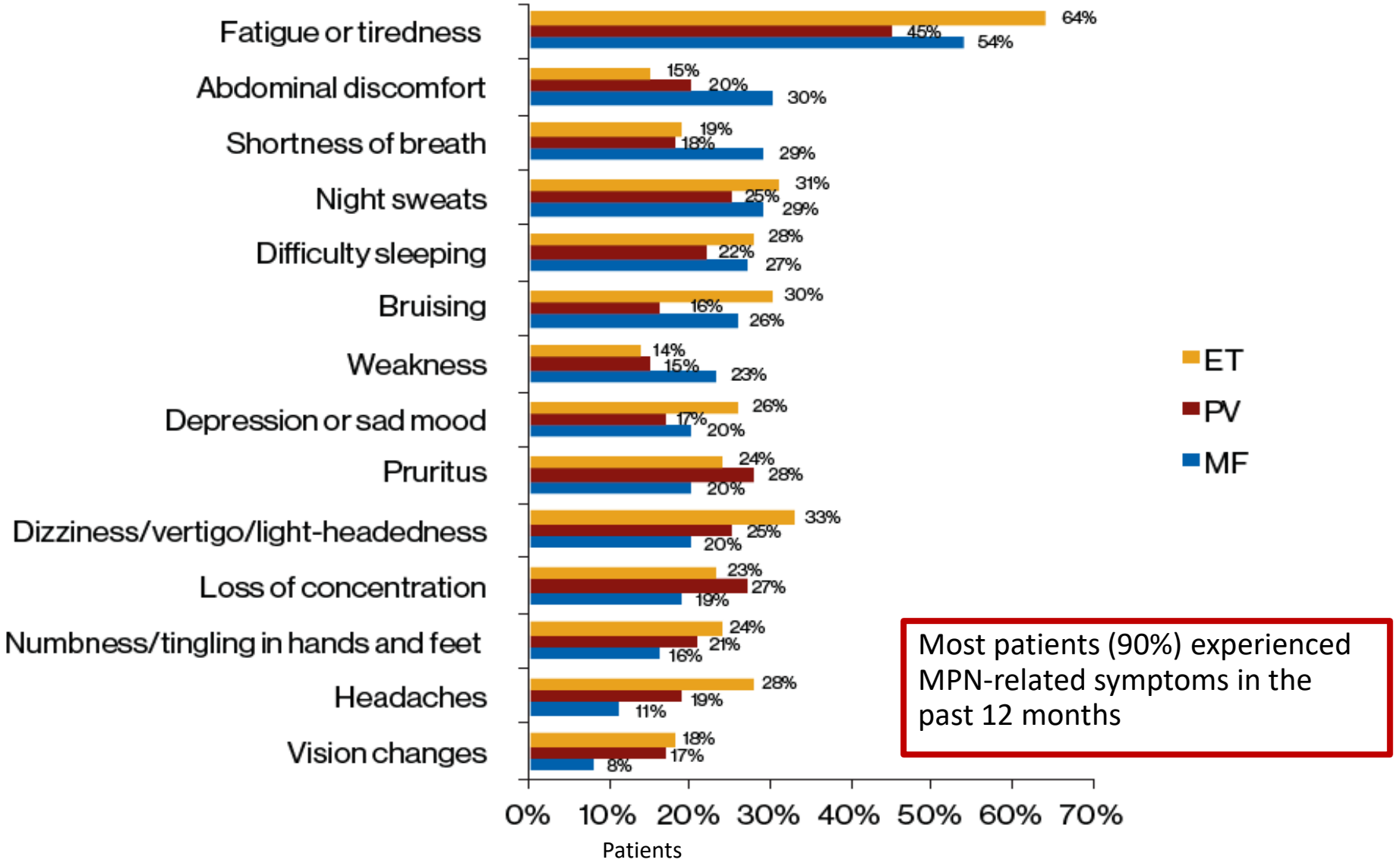
- To investigate the patient-reported MPN impact on symptom burden, QOL, daily functionality, and work/productivity in a global cohort of patients with MPNs
- Online survey of 63 questions (some with multiple parts); required approximately 25-30 minutes to complete
- Results presented relate to patient experience and resolution of symptoms, the emotional and physical impact of MPNs, and the work and activity impairment associated with MPNs
- 699 eligible patients (174 MF, 223 PV, 302 ET) completed the survey May-October 2016

UK (n = 286)
Germany (n = 149)
Italy (n = 106)
Japan (n = 84)
Canada (n = 64)
Australia (n = 10)



Harrison Ann Hematol 2017

Symptoms experienced by patients in past 12 months

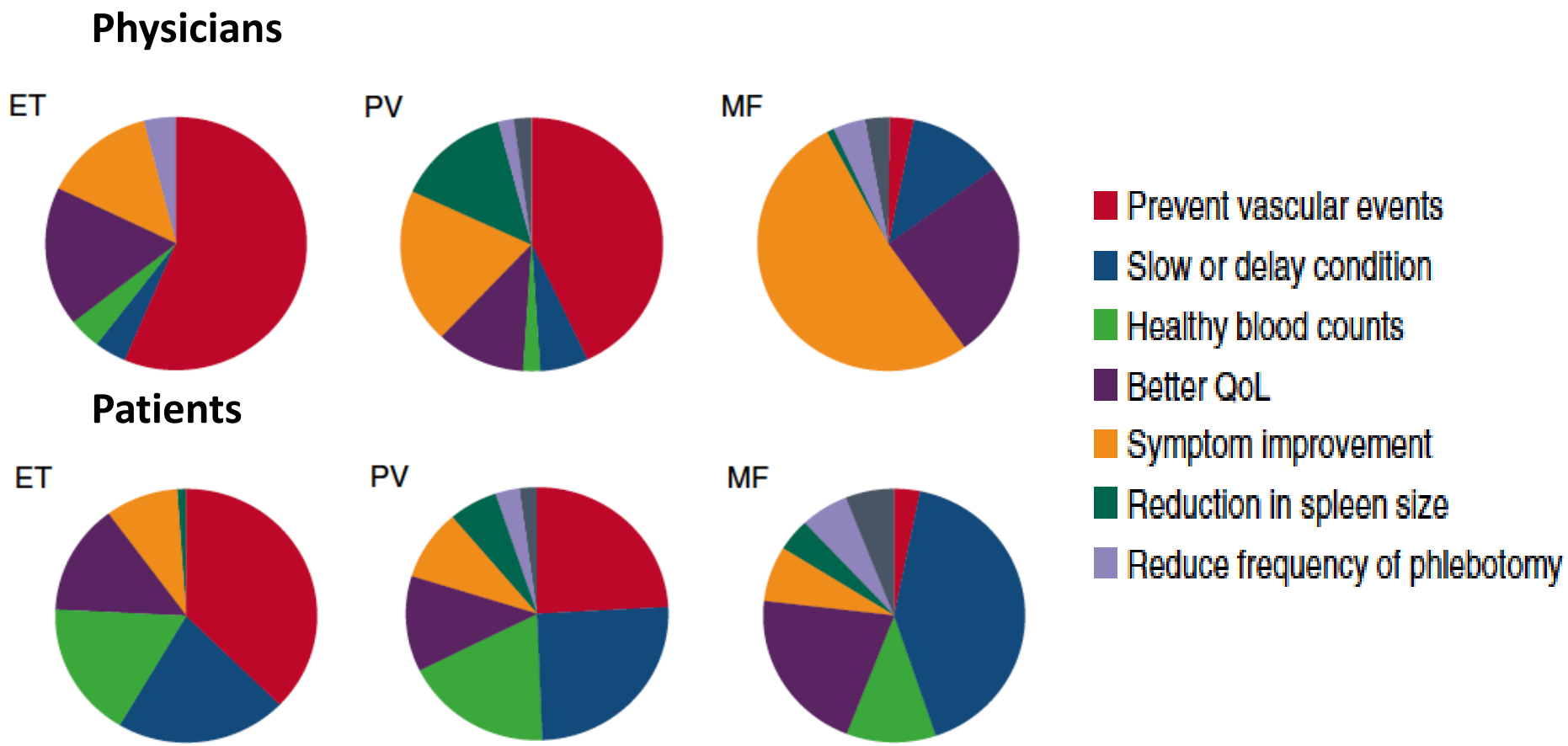


Most patients (90%) experienced MPN-related symptoms in the past 12 months

Top 10 symptoms for each disease are reported.

Harrison Ann Hematol 2017

Physician vs patient treatment goals



ET: Essential thrombocythaemia; MF: Myelofibrosis; PV: Polycythaemia vera; Qol: Quality of life.

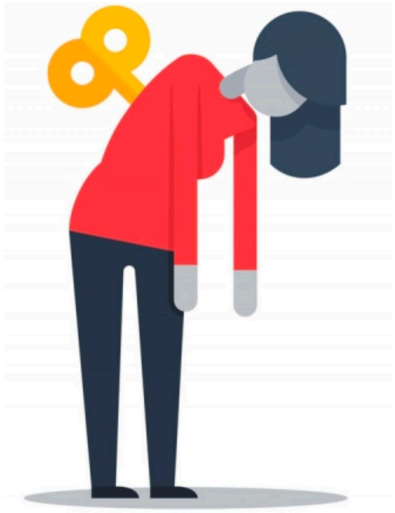
Mesa R, et al. Poster 4827. Presented at American Society of Hematology, San Francisco, USA, 6–9 December 2014.

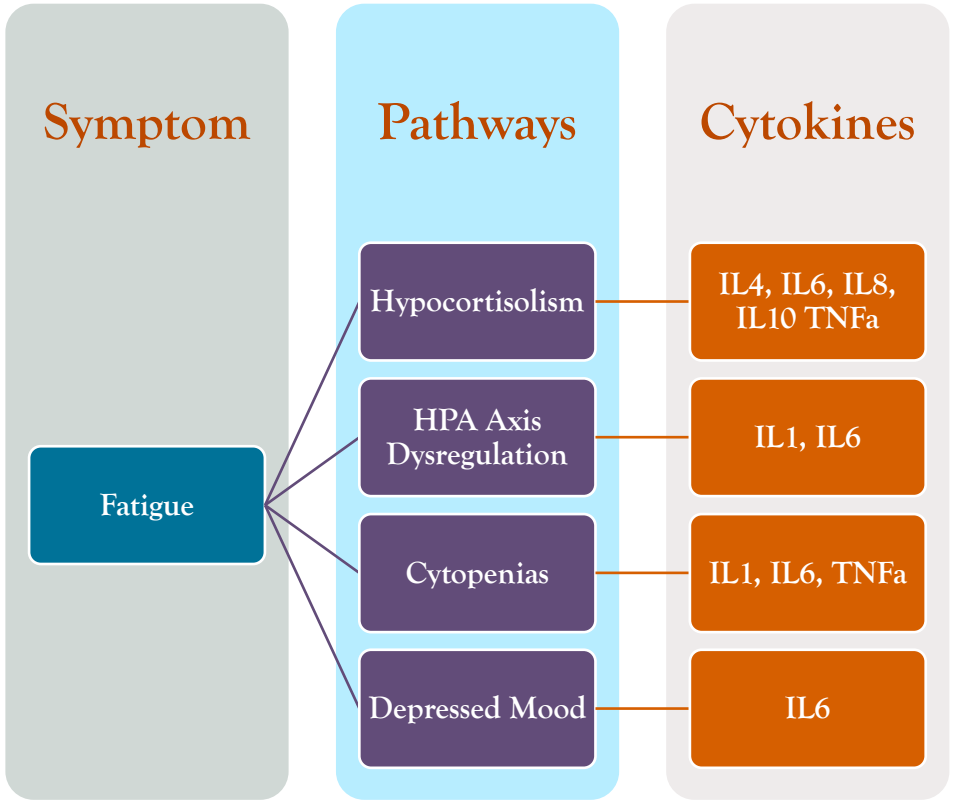
How I Treat Symptom Burden in MPNs

- The Burden of an MPN
- Lessons from the Landmark Studies
- The Biology of MPN Symptoms
- Including symptoms in treatment planning and management
- Future Options

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

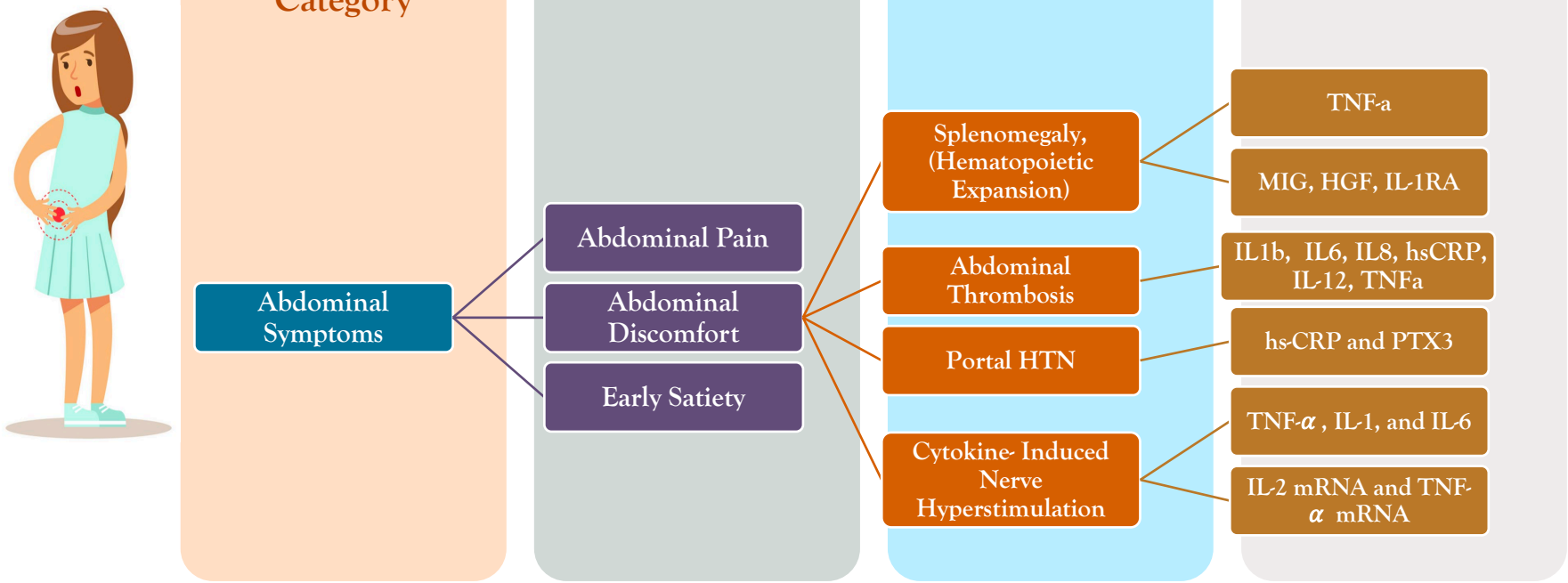
Fatigue



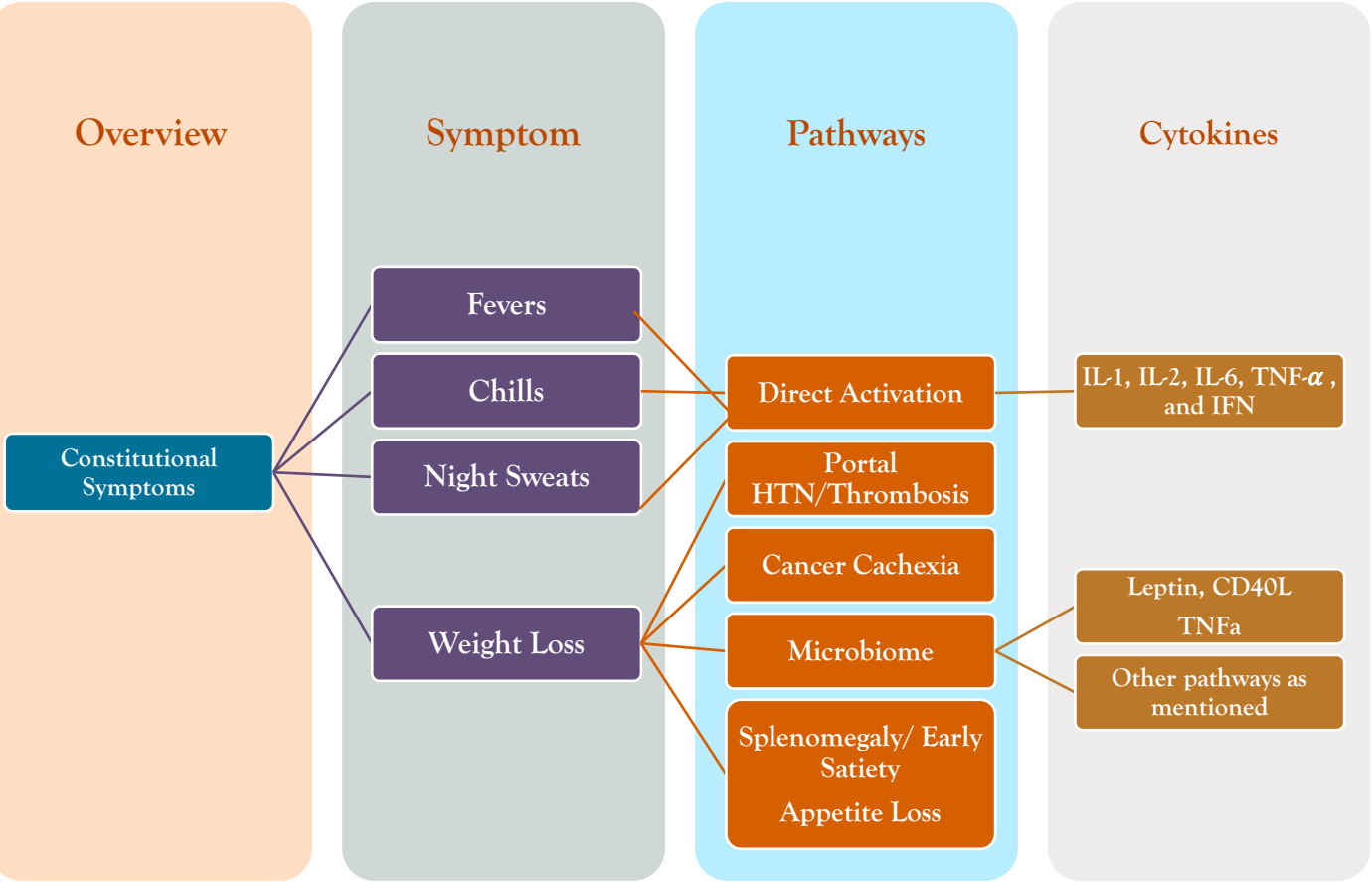


Cancer, vol. 92, no. 6, pp. 1684–1688, 2001.
Cancer, vol. 104, no. 4,pp. 788–793, 2005.
Brain, Behavior, and Immunity, vol. 21,no. 3, pp. 251–258, 2007.
Cancer, vol. 106, no. 4, pp. 751–758, 2006.
[American Journal ofPsychiatry, vol. 158, no. 8, pp. 1252–1257, 2001.

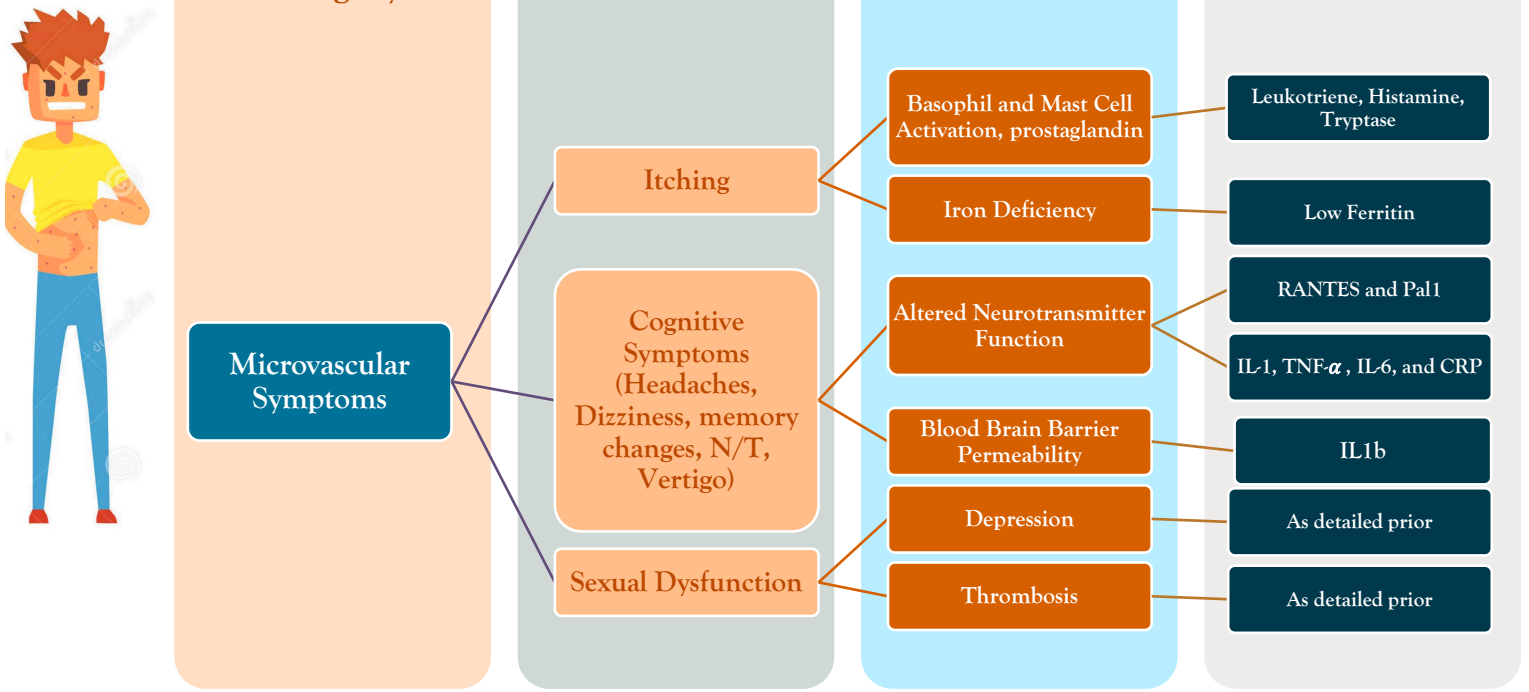
Abdominal Symptoms



Constitutional Symptoms



Microvascular Symptoms



How I Treat Symptom Burden in MPNs

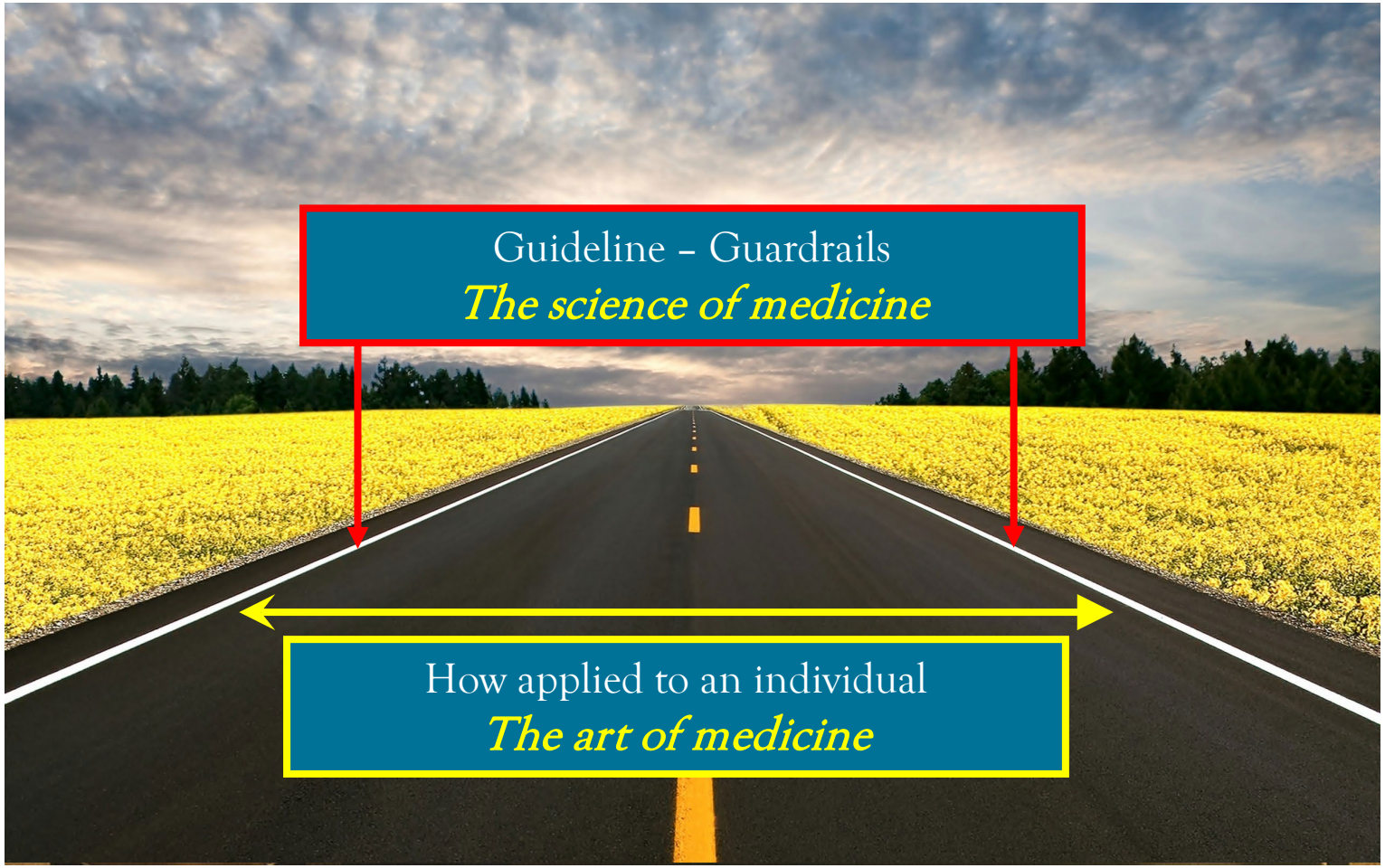
- The Burden of an MPN
- Lessons from the Landmark Studies
- The Biology of MPN Symptoms
- Including symptoms in treatment planning and management
- Future Options

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Treatment Goals

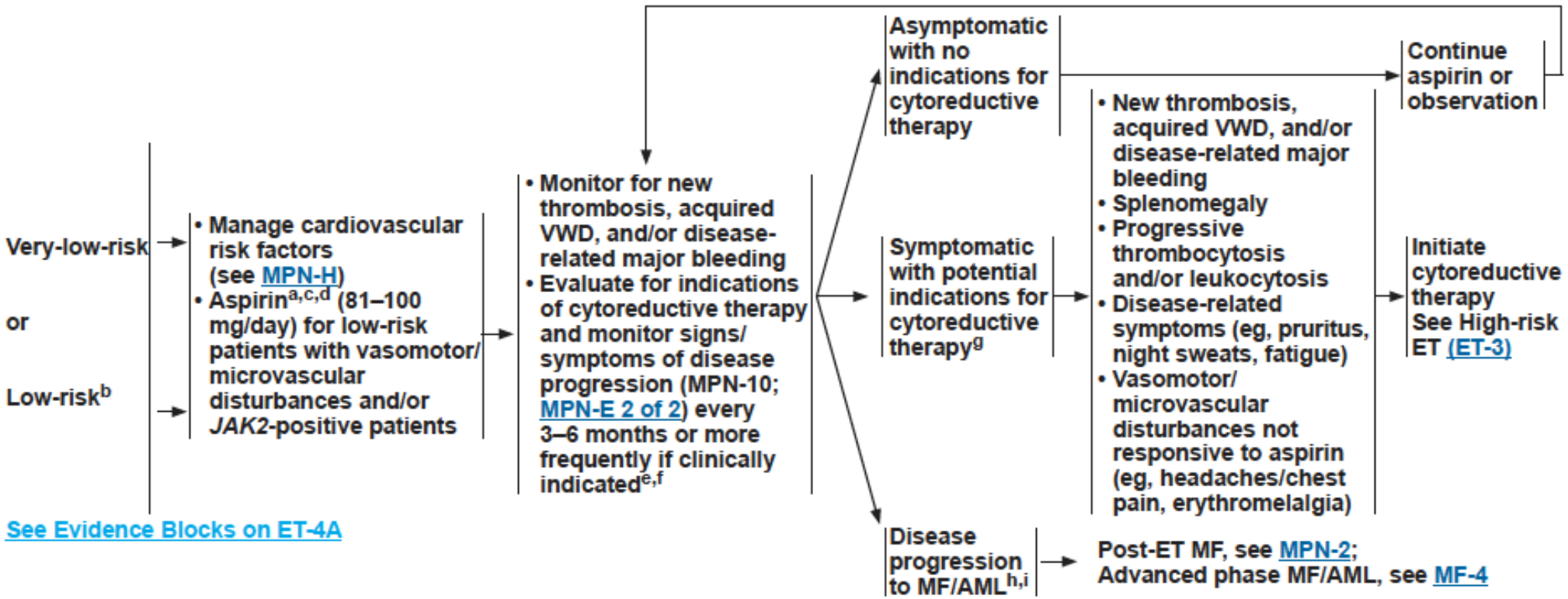
- Avoiding thrombosis and bleeding?
- Improving MPN associated symptoms?
- Increase activity?
- Decreasing splenomegaly?
- Improving anemia?
- Improving low platelets?
- Decreasing progression?
- Preventing progression?
- Live longer?

What is a treatment guideline?



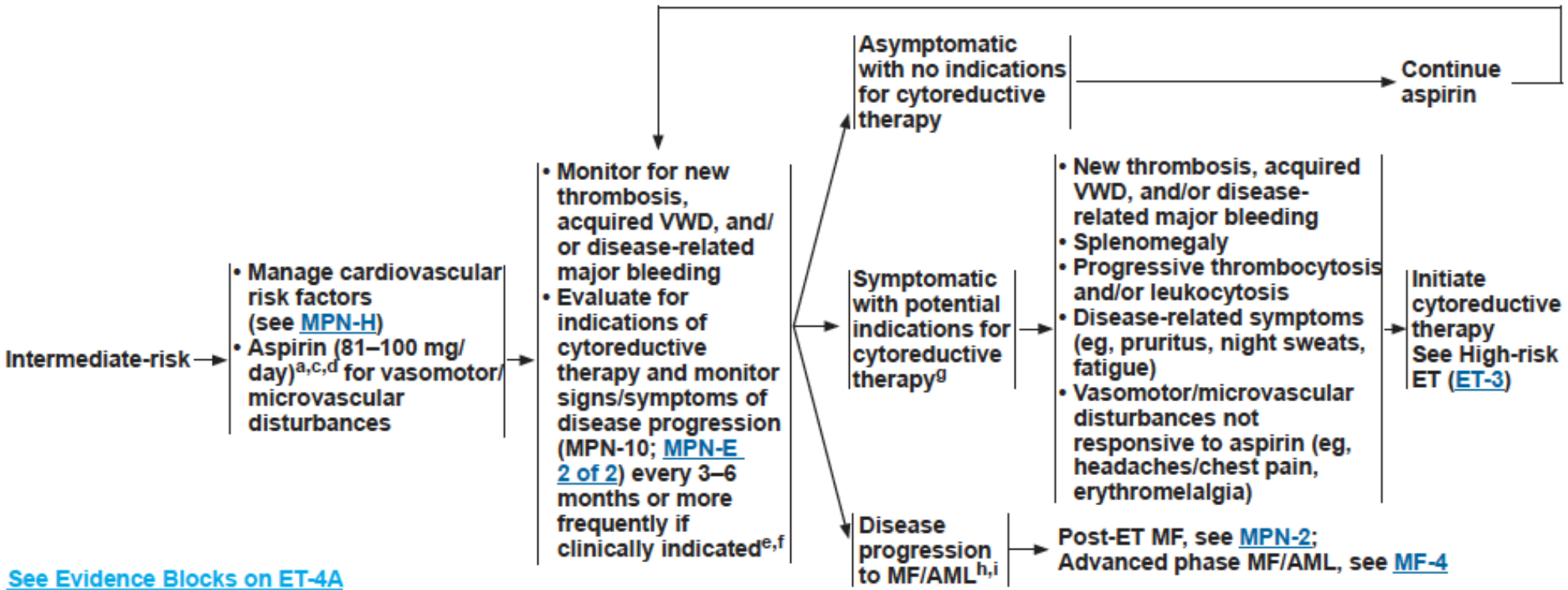
Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

TREATMENT FOR VERY-LOW-RISK OR LOW-RISK ESSENTIAL THROMBOCYTHEMIA[a]



See Evidence Blocks on ET-4A

TREATMENT FOR INTERMEDIATE-RISK ESSENTIAL THROMBOCYTHEMIA[a]



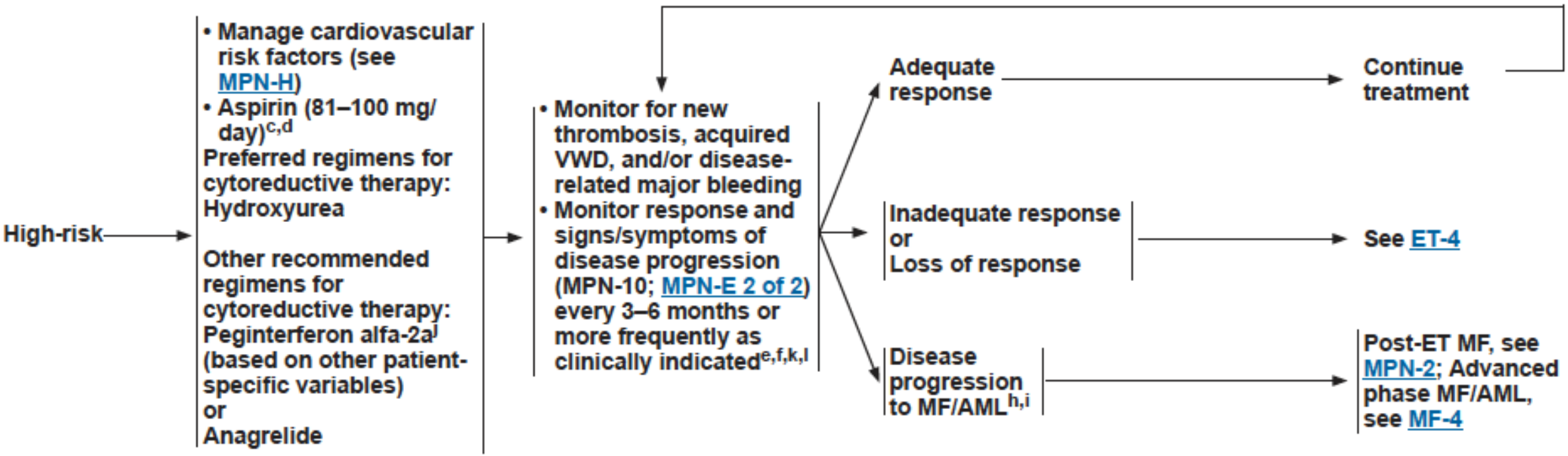
See Evidence Blocks on ET-4A

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Essential Thrombocythemia
NCCN Evidence Blocks™

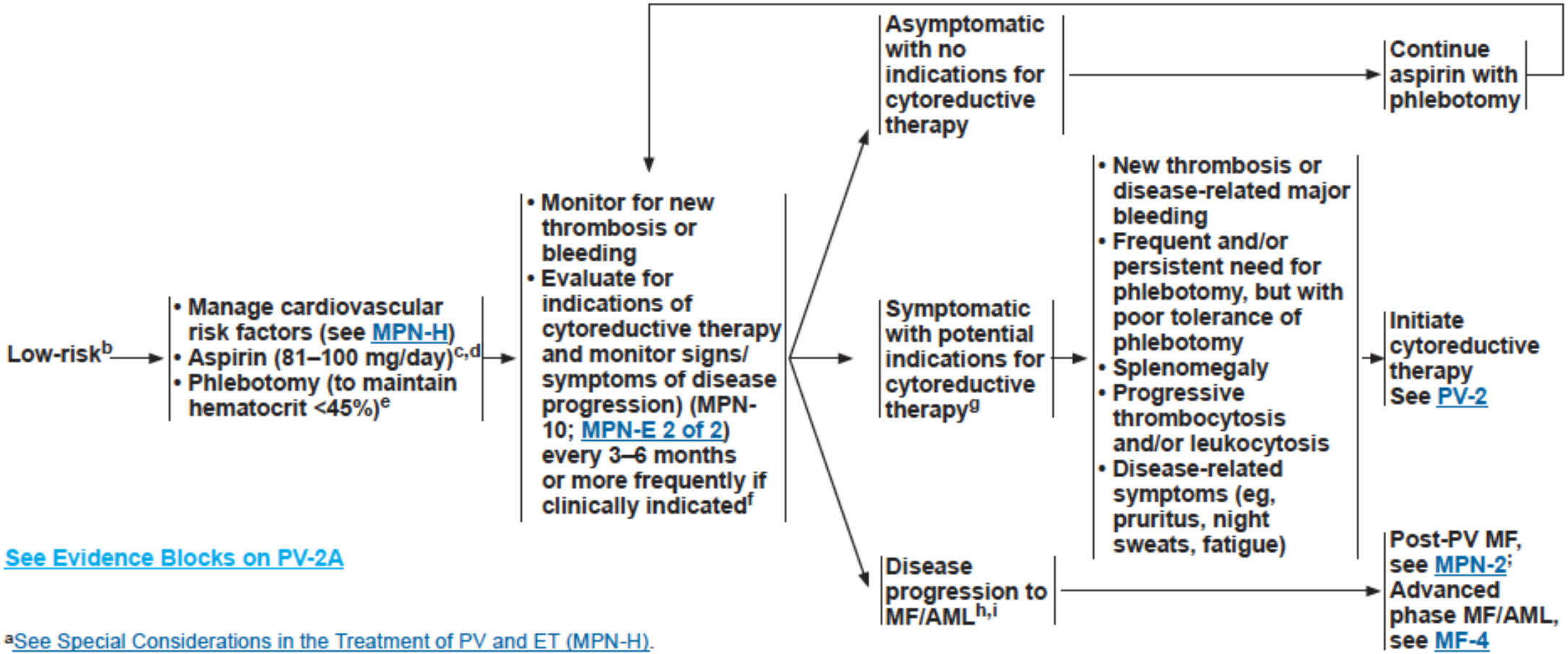
NCCN Guidelines Index
Table of Contents
Discussion

TREATMENT FOR HIGH-RISK ESSENTIAL THROMBOCYTHEMIA[a]



See Evidence Blocks on ET-4A

TREATMENT FOR LOW-RISK POLYCYTHEMIA VERA[a]



See Evidence Blocks on PV-2A

[a]See Special Considerations in the Treatment of PV and ET (MPN-H).

[b]Cytoreductive therapy is not recommended as initial treatment.

TREATMENT FOR HIGH-RISK POLYCYTHEMIA VERA[a]

High-risk

- Manage cardiovascular risk factors (see MPN-H)
- Aspirin (81–100 mg/day)[c,d]
- Phlebotomy (to maintain hematocrit <45%)[e]

Preferred regimens for cytoreductive therapy:
Hydroxyurea
or
Peginterferon alfa-2a[j]

See Evidence Blocks on PV-2A

- Monitor for new thrombosis or bleeding
- Monitor response and signs/symptoms of disease progression (MPN-10; MPN-E 2 of 2) every 3–6 months or more frequently as clinically indicated[f,k,l]

Adequate response → **Continue treatment**

Inadequate response or Loss of response

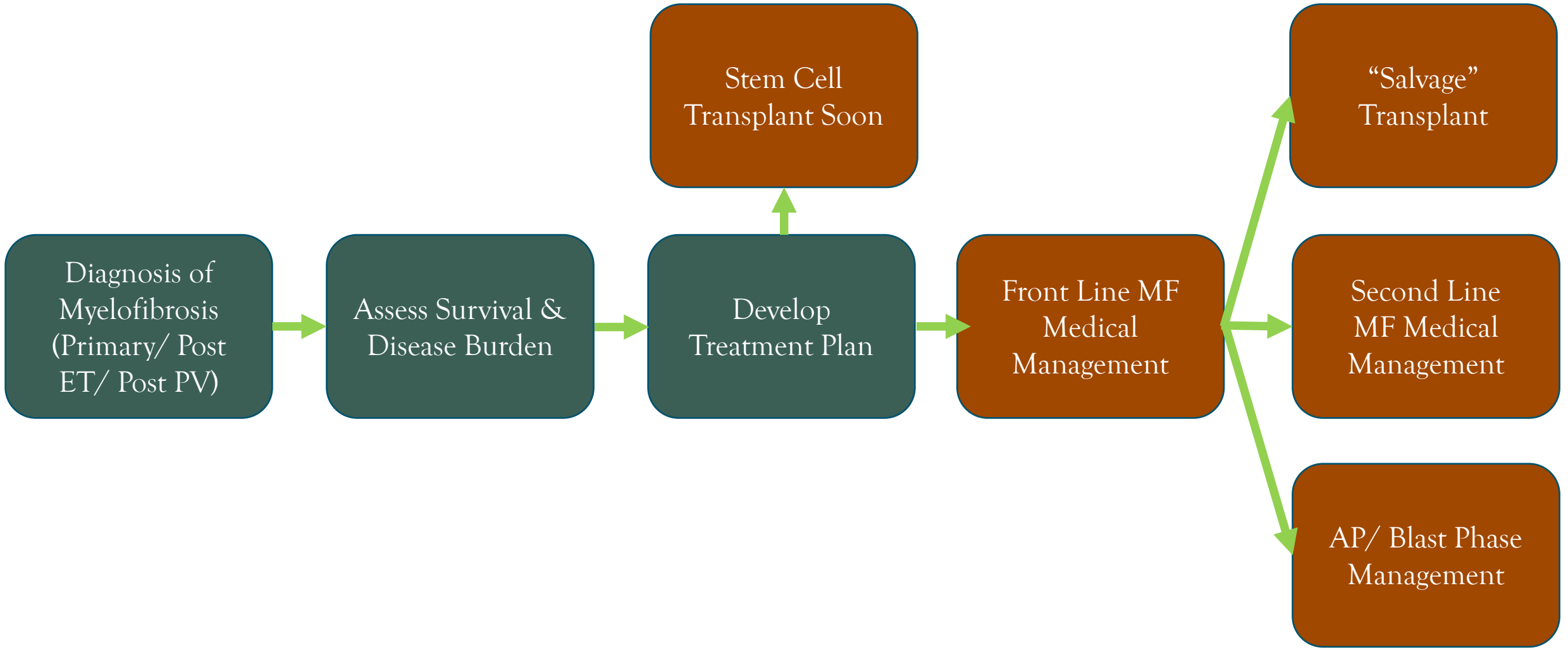
Potential indications for change of cytoreductive therapy:[g]
- Intolerance or resistance to hydroxyurea[m] or peginterferon alfa-2a
- New thrombosis or disease-related major bleeding
- Frequent and/or persistent need for phlebotomy, but with poor tolerance of phlebotomy
- Splenomegaly
- Progressive thrombocytosis and/or leukocytosis
- Disease-related symptoms (eg, pruritus, night sweats, fatigue)

Preferred regimens:
Clinical trial
or
Ruxolitinib[n]
or
Other recommended regimens:
Hydroxyurea if not previously used
or
Peginterferon alfa-2a[i] if not previously used
or
Useful in certain circumstances:
Busulfan (PO) (category 2B) (especially for older adults)[o]

Disease progression to MF/AML[h,i] → Post-PV MF, see MPN-2; Advanced phase MF/AML, see MF-4

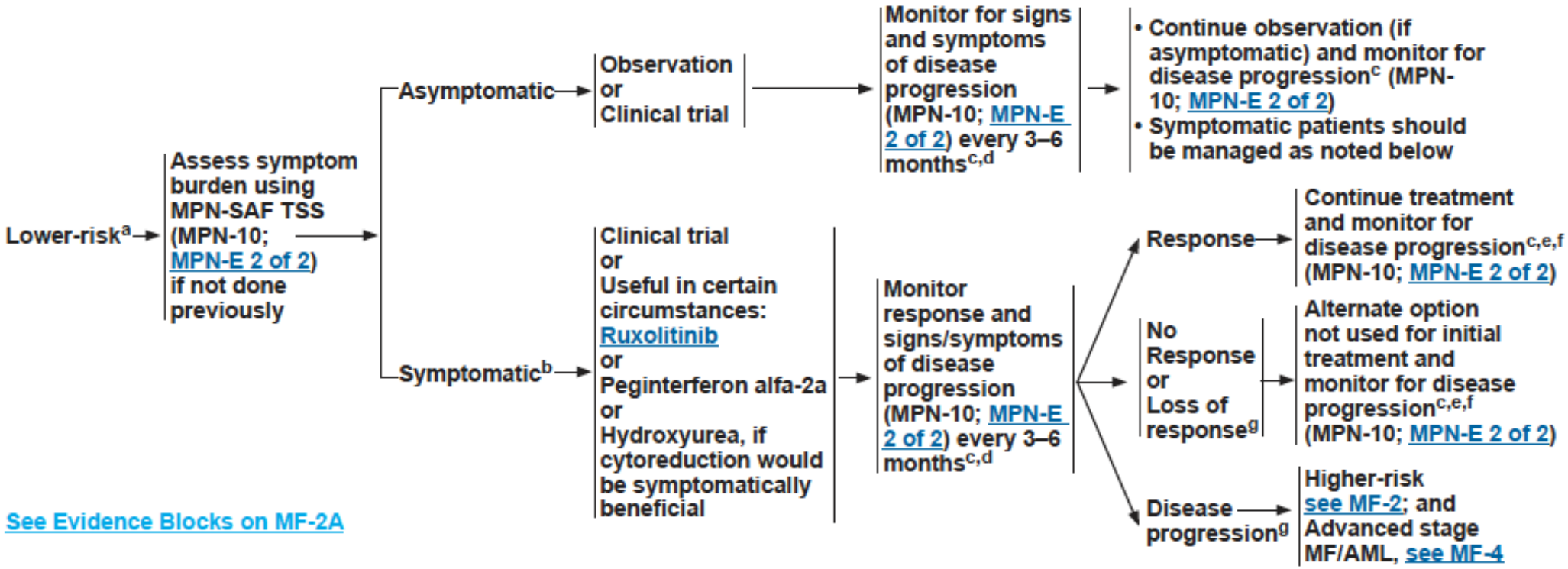
[a] See Special Considerations in the Treatment of PV and ET (MPN-H).
[c] Landolfi R, et al. N Engl J Med 2004;350:114-124.
[d] Aspirin twice daily may be considered for patients with refractory symptoms (Dillinger JG, et al.Thromb Res 2012;129:91-94; Pascale S, et al. Blood 2012;119:3595-3603).
[e] Hematocrit <45% is based on the data from the CYTO-PV Study (Marchioli R et al. N Engl J Med 2013;368:22-33). There may be situations in which a lower hematocrit cutoff may be appropriate

Management of Myelofibrosis 2021



Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

TREATMENT FOR LOWER-RISK MYELOFIBROSIS



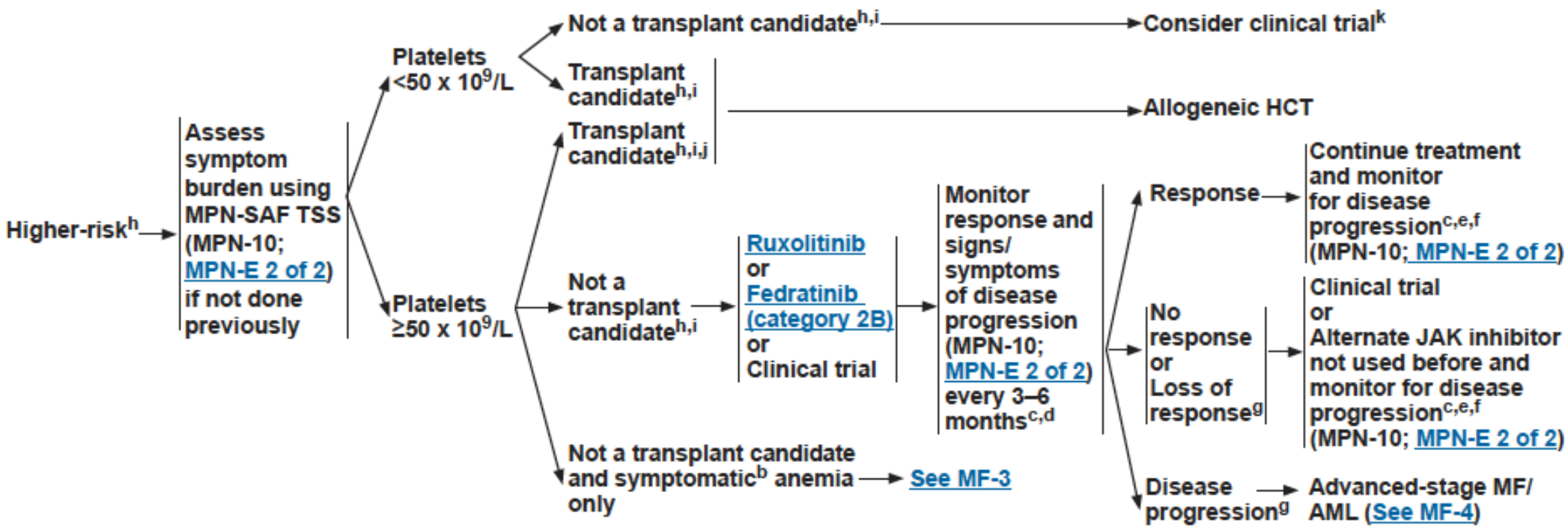
See Evidence Blocks on MF-2A

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2021
Myelofibrosis
NCCN Evidence Blocks™

NCCN Guidelines Index
Table of Contents
Discussion

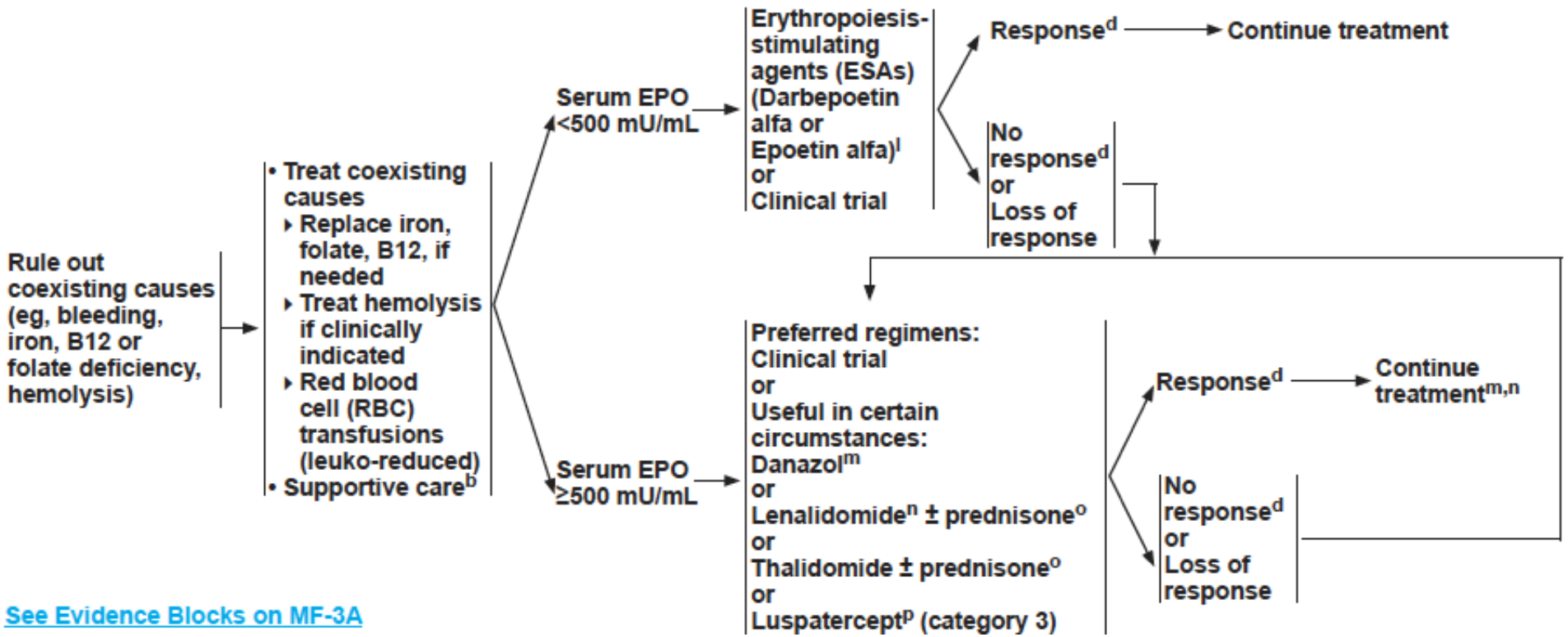
TREATMENT FOR HIGHER-RISK MYELOFIBROSIS



See Evidence Blocks on MF-2A

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

MANAGEMENT OF MF-ASSOCIATED ANEMIA[j]

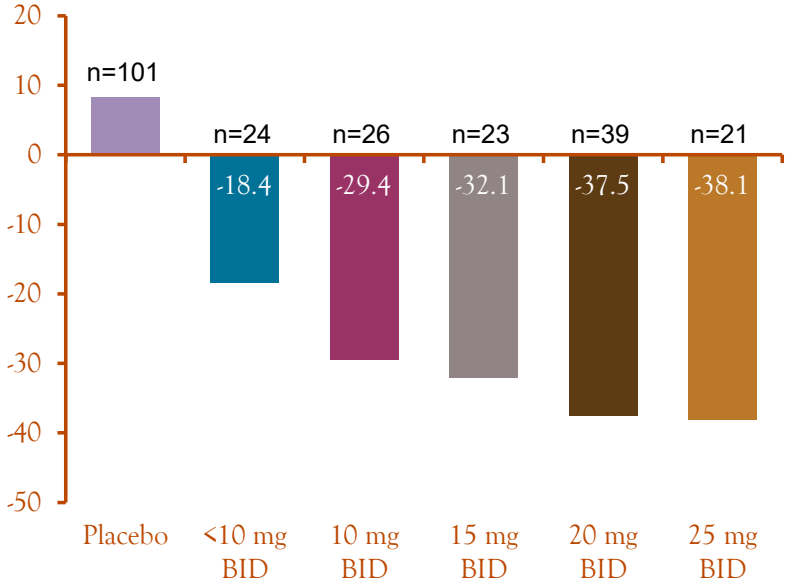


See Evidence Blocks on MF-3A

Ruxolitinib Efficacy by Titrated Dose: COMFORT-I

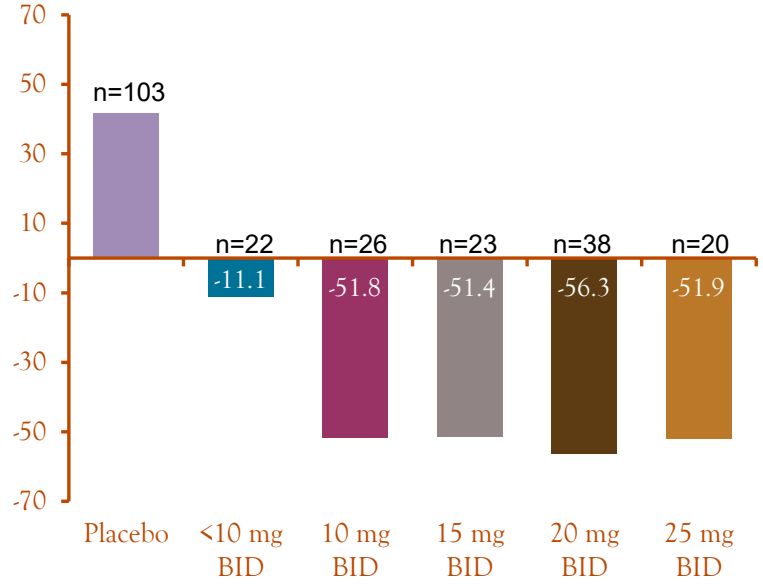
Spleen Volume

Week 24



Total Symptom Score

Week 24

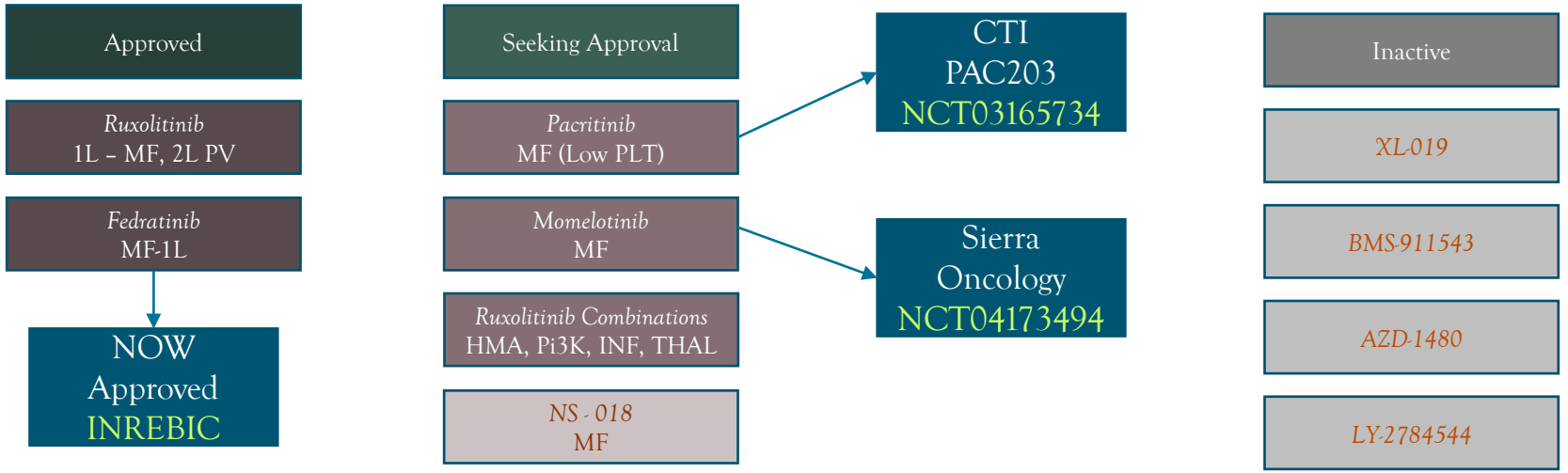


- Avoid starting with low dose!
- Start dosing per guidelines and modify based on platelets if needed
- Doses less than 10 mg BID are not effective long term

s Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Verstovsek S et al. *OncoTargets and Therapy*. 2014;7:13-21.

JAK Inhibitor Landscape 2021



Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

A selection of novel agents/targets being developed in MPN particularly MF

Cell-cycle Checkpoint

- P2 Imetelstat | Telomerase Inhibitor (*Geron*)
- P1 Alisertib | Aurora Kinase Inhibitor (*Takeda*)

Anti-fibrotic

- P2 PRM-151 | Pentraxin-2 (*Promedior*)

Receptor Ab / ADC

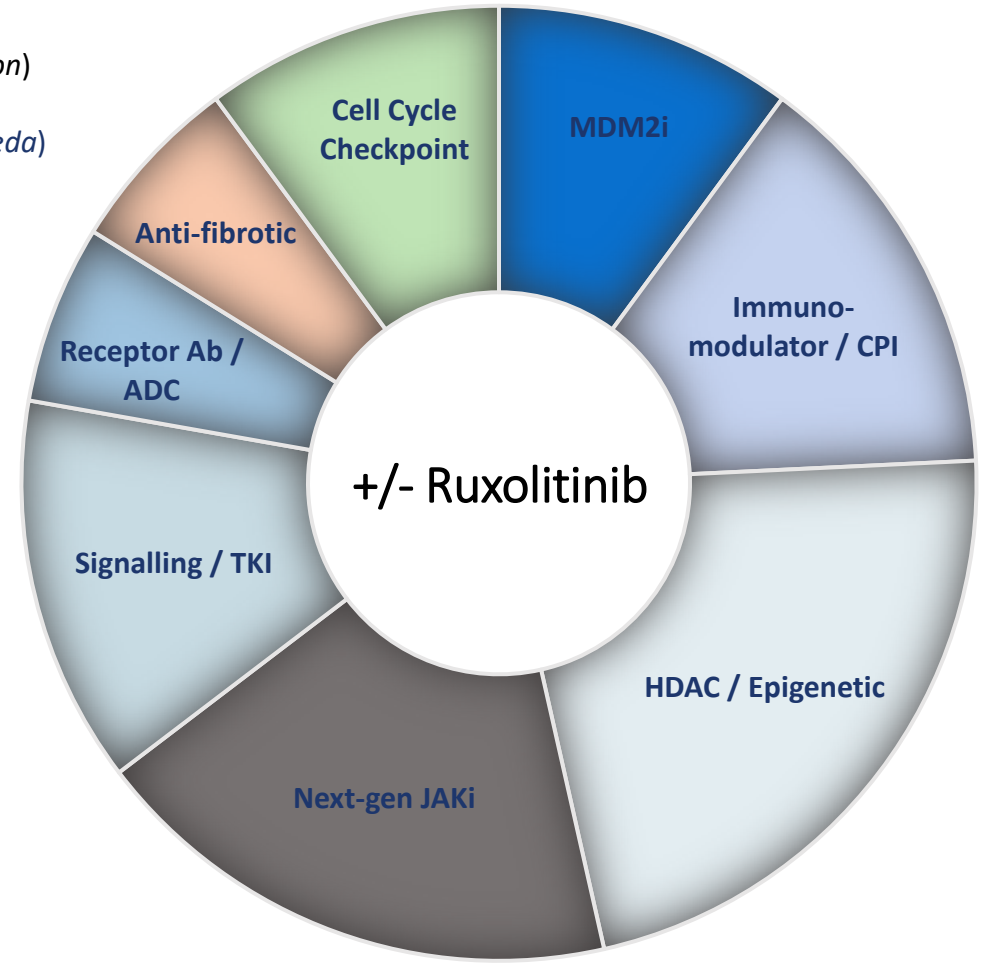
- P2 SL-401 | CD123-toxin (*Stemline*)

Signaling / TKI

- P2 Glasdegib | Hedgehog (*Pfizer*)
- P2 Sonidegib | Hedgehog (*Sun*)
- P2 INCB'465 | PI3Ki (*Incyte*)
- P2 LCL1 I SMAC/IAP (Novartis)

Next-gen JAKi

- P3 Fedratinib | JAK2 (*Celgene*)
- P3 Pacritinib | JAK2/FLT3 (*CTI Bio*)
- P3 Momelotinib | JAK2/1/ACVR1 (*Sierra*)
- P2 Itacitinib | JAK1 (*Incyte*)



Slide Courtesy of Prof Claire Harrison

Apoptosis/MDM2/BCL

- P1 KRT-232 (*Kartos Therapeutics*)
- P2 Idasanutlin / RG7388 (*Roche*)
- P1 Navitoclax | BCL2 inhibition (*Abbvie*)

Immuno-modulator / CPI

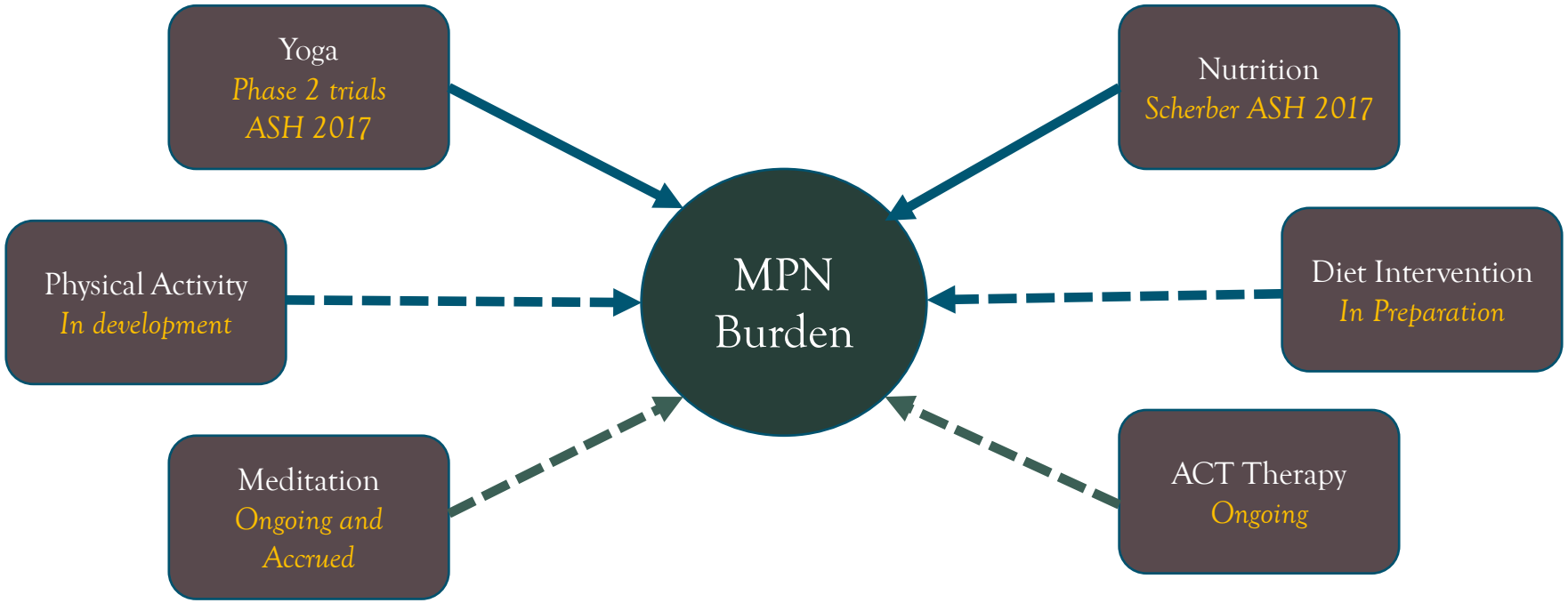
- P3 Pegasys | IFN-α2a (ESR/Roche)
- P3 Ropeg-IFN-α2b (*PharmaEssentia*)
- P2 Nivolumab / Pembrolizumab | PD-1 (*BMS / MRK*)

HDAC / Epigenetic

- P3 Azacytidine | HMA (*ESR/Celgene*)
- P3 Panobinostat | HDAC (*Novartis*)
- P2 Givinostat I HDAC (Italfama)
- P2 IMG-7289 | LSD1 (*Imago*)
- P1 CPI-0610 | BETi (*Constellation*)
- P1 PU-H71 | HSP90i (*Samus*)

PHASE OF DEVELOPMENT (IN MPN): P1 P2 P3

Non Pharmacological Approaches for MPN Burden Relief



Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

The SIMM Survey: Integrative Medicine

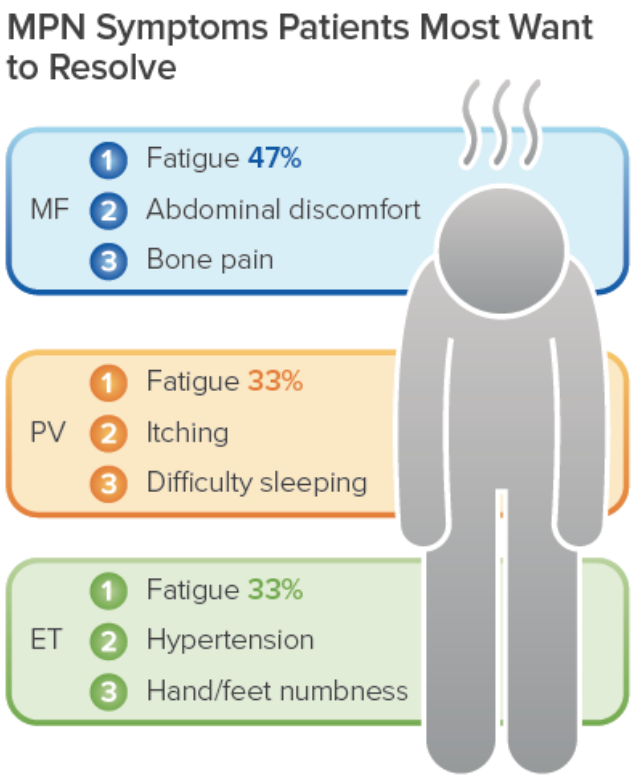
Intervention Comparisons for Symptom Burden, QOL, Depression, and Fatigue				
Overall N = 858	MPN-SAF TSS mean yes / no	QoL mean yes / no	PHQ-2 odds ratio (95%CI)	BFI mean yes / no
Aerobic Activity n=442	33.2 / 39.7 **	4.2 / 5.2 **	0.60 (0.42, 0.86) **	5.1 / 5.9 **
Massage n=244	40.5 / 35.3 **	5.0 / 4.6 *	1.05 (0.72, 1.55)	6.1 / 5.4 **
Yoga n=220	35.1 / 37.3	4.5 / 4.8	0.61 (0.39, 0.94) *	5.5 / 5.6
Nutrition n=216	35.5 / 37.3	4.6 / 4.8	1.09 (0.71, 1.67)	5.5 / 5.6
Strength training n=204	34.0 / 37.7 *	4.2 / 4.9 **	0.58 (0.37, 0.91) *	5.2 / 5.7 *
Acupuncture n=166	38.2 / 36.6	5.1 / 4.7	0.74 (0.47, 1.17)	5.9 / 5.5
Meditation n=163	35.4 / 37.3	4.7 / 4.8	0.62 (0.38, 1.01)	5.4 / 5.6
Breathing exercise n=158	39.5 / 36.4	5.1 / 4.7	1.47 (0.95, 2.28)	6.1 / 5.5 *
Chiropractic n=139	36.7 / 37.0	4.8 / 4.8	.75 (0.46, 1.21)	5.6 / 5.6
Support groups n=124	42.3 / 36.0 **	5.4 / 4.6 **	1.45 (0.91, 2.31)	6.2 / 5.5 **

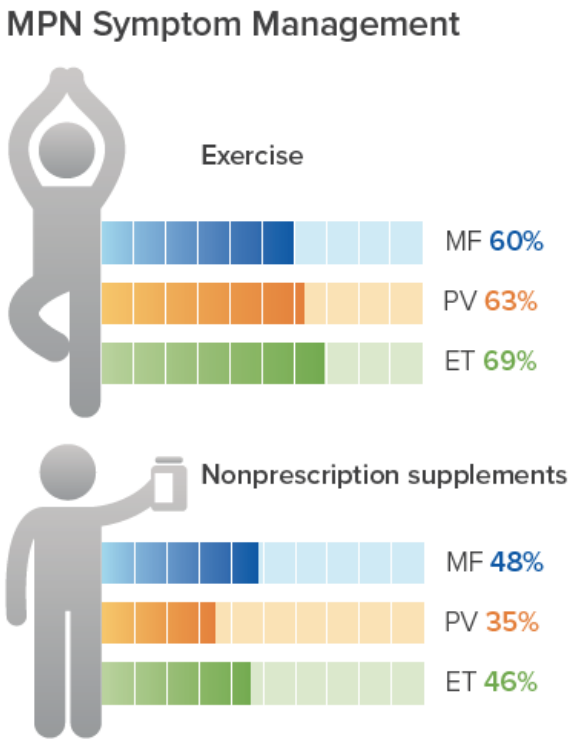
Results adjusted for alcohol consumption, smoking status, BMI, current dietary modification, and MPN

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Gowin et. al. EHA 2017., article in preparation.

MPN Landmark Study - USA





Mesa et. al. BMC Cancer 2016

Mays Cancer Center
UT Health San Antonio MD Anderson Cancer Center

Yoga In MPNs

Initial Investigation Efforts

MPN Patients Completing the Yoga Study (N=38)

12 Week Online Yoga Course

Yoga participation averaged 50.8 min/week.

Significant improvements in total symptom burden (effect size =-0.36, p=0.004)

- *Anxiety (ES=-0.67, p=0.002)*
- *Depression (ES=-0.41, p=0.049)*
- *Sleep (ES=-0.58, p<0.001)*
- *Fatigue (ES=-0.33, p=0.04)*

Patient Satisfaction:

- 68% of participants were either satisfied or very satisfied
- 75% felt that is was helpful for coping

Subsequent Investigation Efforts

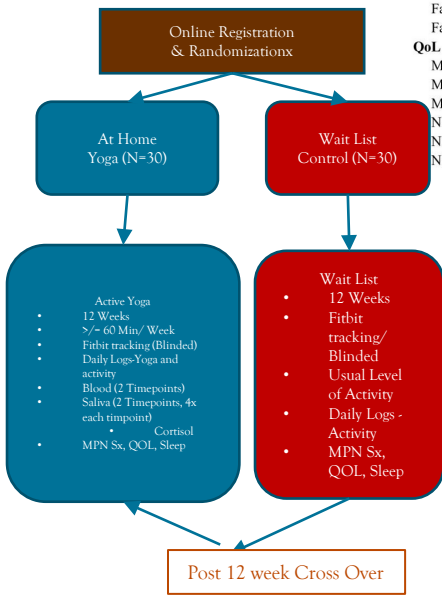


Table 2. Changes in Fatigue and QoL

	Yoga Group (n=27)	Control Group (n=21)		
	Mean (SD)	Mean (SD)	*d*	p[1]
Fatigue				
Fatigue baseline*	5.4±2.3	4.5±2.8	-	-
Fatigue wk 7*	4.6±2.4	3.5±2.3	0.47	0.36
Fatigue wk 12*	4.9±2.6	4.5±1.8	0.18	0.72
QoL				
MPN SAF QoL baseline**	6.2±1.7	6.9±2.0	-	-
MPN SAF QoL wk 7**	7.2±2.6	8.0±2.3	-0.33	0.4
MPN SAF QoL wk 12**	6.4±2.4	7.4±1.2	-0.53	0.2
NIH Global Health QoL baseline***	3.1±0.8	2.6±0.9	-	-
NIH Global Health QoL wk 7***	2.6±0.6	2.2±0.7	0.62	0.14
NIH Global Health QoL wk 12***	2.9±0.8	2.2±0.6	0.7	*0.03*

Cytokine analysis: Significant decrease in TNF-a from wk 0 to wk 12 (-1.3±1.5; p=0.005) but no significant differences in CBC or IL-6.

Huberty et. al. Blood 2016 128:5478

Cognitive Interventions in MPNs

CALM Study:

MPN Patients

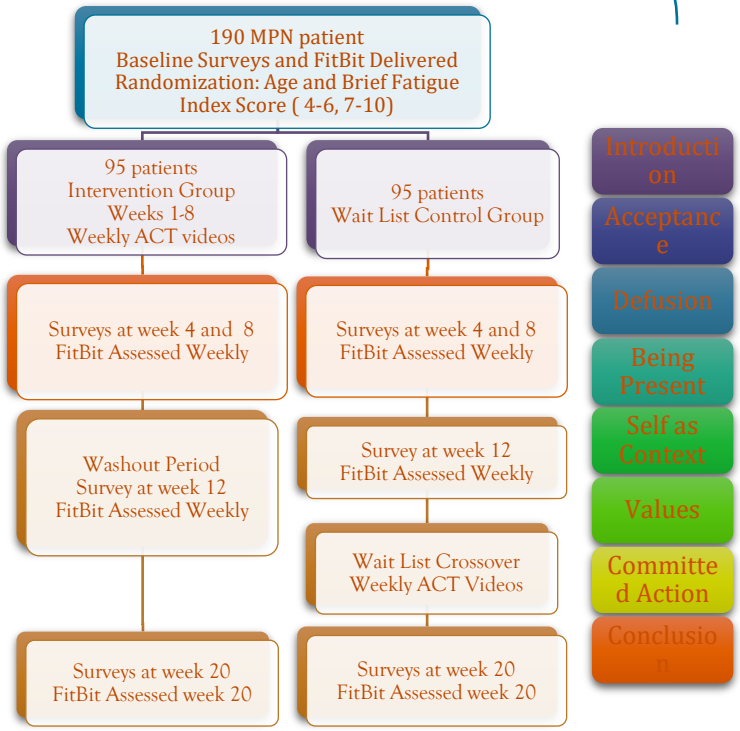
R

Usual Care Control
Asked to maintain usual routine for 4 weeks

***Calm* Meditation**
10 min/day of *Calm*
Week 1 – "7 Days of *Calm*"
Weeks 2-4 – "Daily *Calm*"

Outcomes:
- **Emotional distress (i.e., anxiety, depression),**
- **Sleep disturbance**
- **Inflammatory markers (IL-1, IL-6, IL-8, and TNF-a)**
- **MPN10 Score change**

MyACT Study:



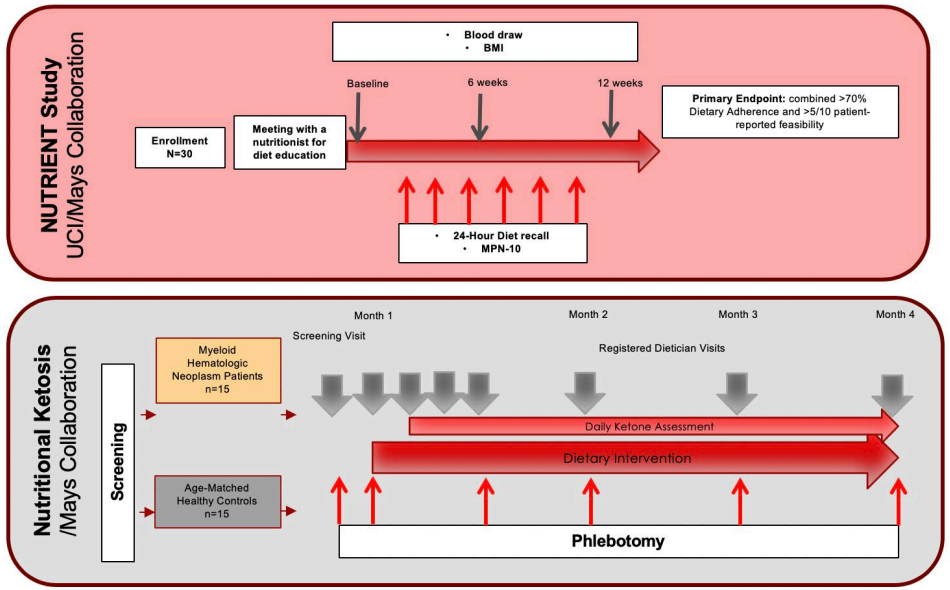
Nutrition in MPNs

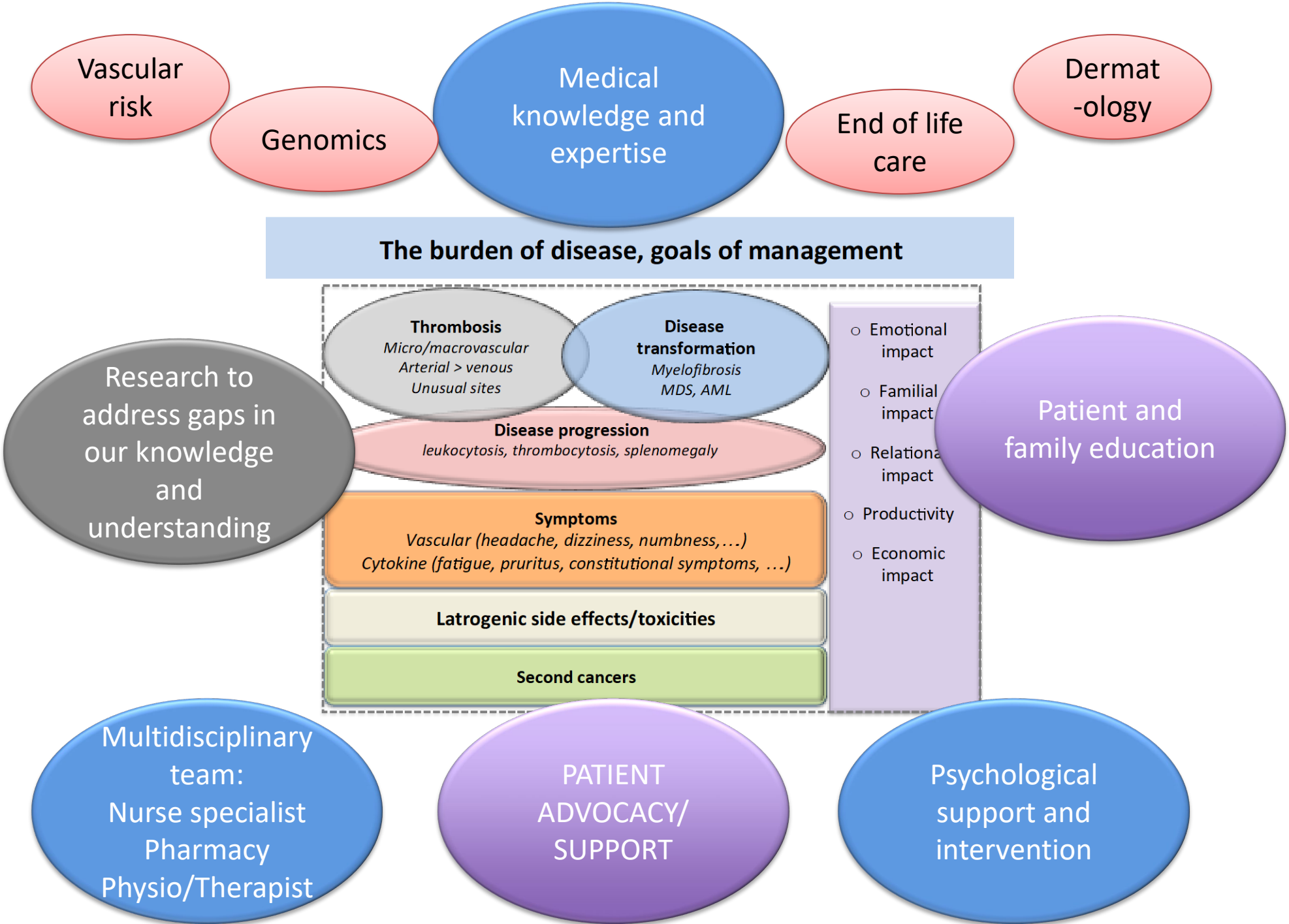
Initial Investigation Efforts

Correlative	Mean symptom burden (MPN-10)		P-value
Diet	**Not Following Diet**	**Following Diet**	**Pr >|t|**
Diabetic diet	3.33	4.67	<0.0001
Lactose Intolerant	3.35	3.87	0.0433
Food Intake (Dichotomous)	**Never**	**At Least Once Per Week**	**Pr >|t|**
Alcohol	3.62	3.11	<0.0001
Fast Food	3.24	3.59	0.0015
Fried Foods	3.22	3.46	0.0198
Rice	3.57	3.30	0.0452
Soda	3.22	3.72	<0.0001
Food Intake (Continuous)		**Pearson Correlation**	**P-value**
Alcohol	-	-0.139	<0.0001
Baked Goods	-	-0.070	0.0212
Dairy other than Cheese (milk, cream)	-	-0.069	0.0240
Fast Food	-	0.104	0.0007
Fried Foods	-	0.086	0.0051
Pasta	-	-0.072	0.0183
Pre-made Snack Foods	-	0.067	00296
Soda	-	0.121	<0.0001
Refined Sugars	-	0.075	0.0139
Tacos	-	0.068	0.0277

Foods associated with worsened symptom score in red, foods associated with improved score in green

Subsequent Investigation Efforts




Vascular risk
Genomics
Medical knowledge and expertise
End of life care
Dermat -ology
The burden of disease, goals of management
Thrombosis
Micro/macrovascular
Arterial > venous
Unusual sites
Disease transformation
Myelofibrosis
MDS, AML
Disease progression
leukocytosis, thrombocytosis, splenomegaly
Symptoms
Vascular (headache, dizziness, numbness,…)
Cytokine (fatigue, pruritus, constitutional symptoms, …)
Latrogenic side effects/toxicities
Second cancers
Emotional impact
Familial impact
Relationa impact
Productivity
Economic impact
Research to address gaps in our knowledge and understanding
Patient and family education
Multidisciplinary team:
Nurse specialist
Pharmacy
Physio/Therapist
PATIENT ADVOCACY/ SUPPORT
Psychological support and intervention


ASU
MAYO CLINIC
MPN QoL STUDY GROUP
Mays Cancer Center
UT Health San Antonio
MD Anderson Cancer Center