New Directions in MPN Management

MPN Horizons – Belgrade 2016

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Disclosures

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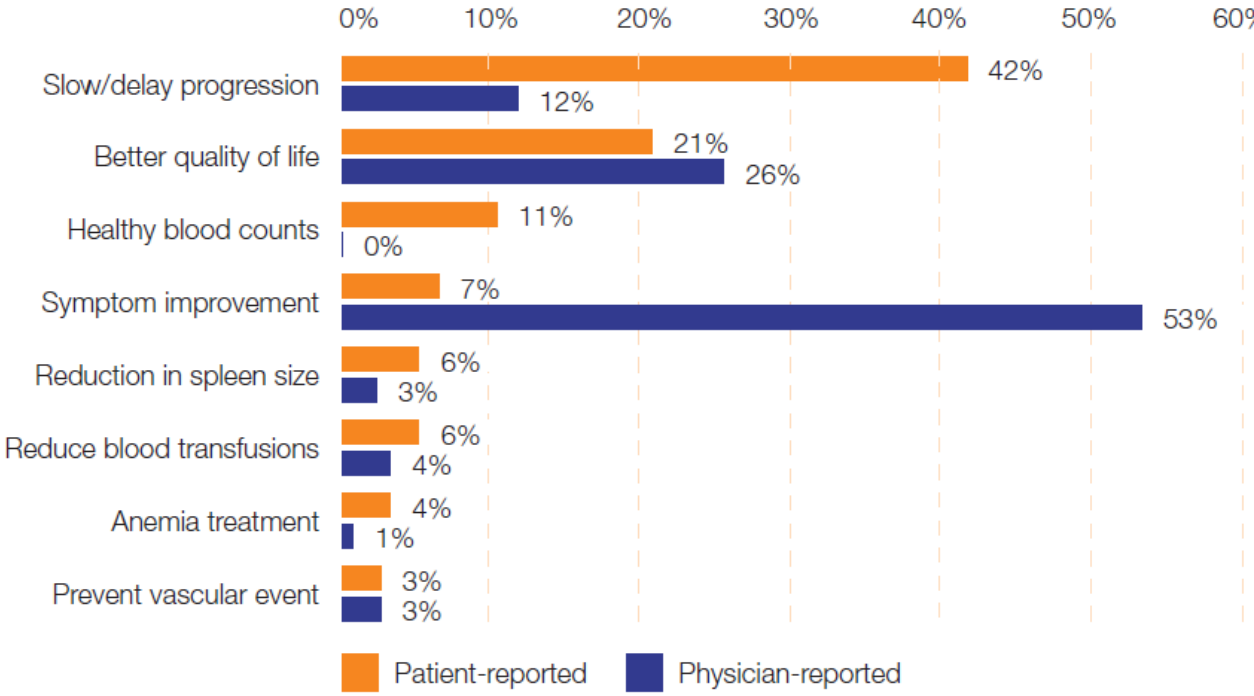
New Directions in MPN Management

- Target earlier disease and delay progression
- Understand and track disease burden
- Multi-disciplinary MPN care
- Expanding medical therapy – Immune Therapy
- Genetic Repair - CRISPR
- Non pharmacologic options in addition to medical therapy

MF Patient vs physician-reported most important goal for therapy



PV Top 5:
- Slow/delay progression (25%, 6%)
- Prevention of vascular/thrombotic events (24%, 43%)
- Healthy blood counts (18%, 2%)
- Better QOL (12%, 11%)
- Symptom improvement (9%, 20%)

ET Top 5:
- Prevention of thrombotic event (35%, 57%)
- Slow/delay progression (21%, 4%)
- Healthy blood counts (17%, 4%)
- Better QOL (14%, 18%)
- Symptom improvement (9%, 14%)

Figure 55. Question 32: Other than a cure for diagnosis, what is your most important treatment goal for therapy? (n = 207)
Question 36: Other than a cure for this diagnosis, what is your most important treatment goal for therapy? (n = 156)

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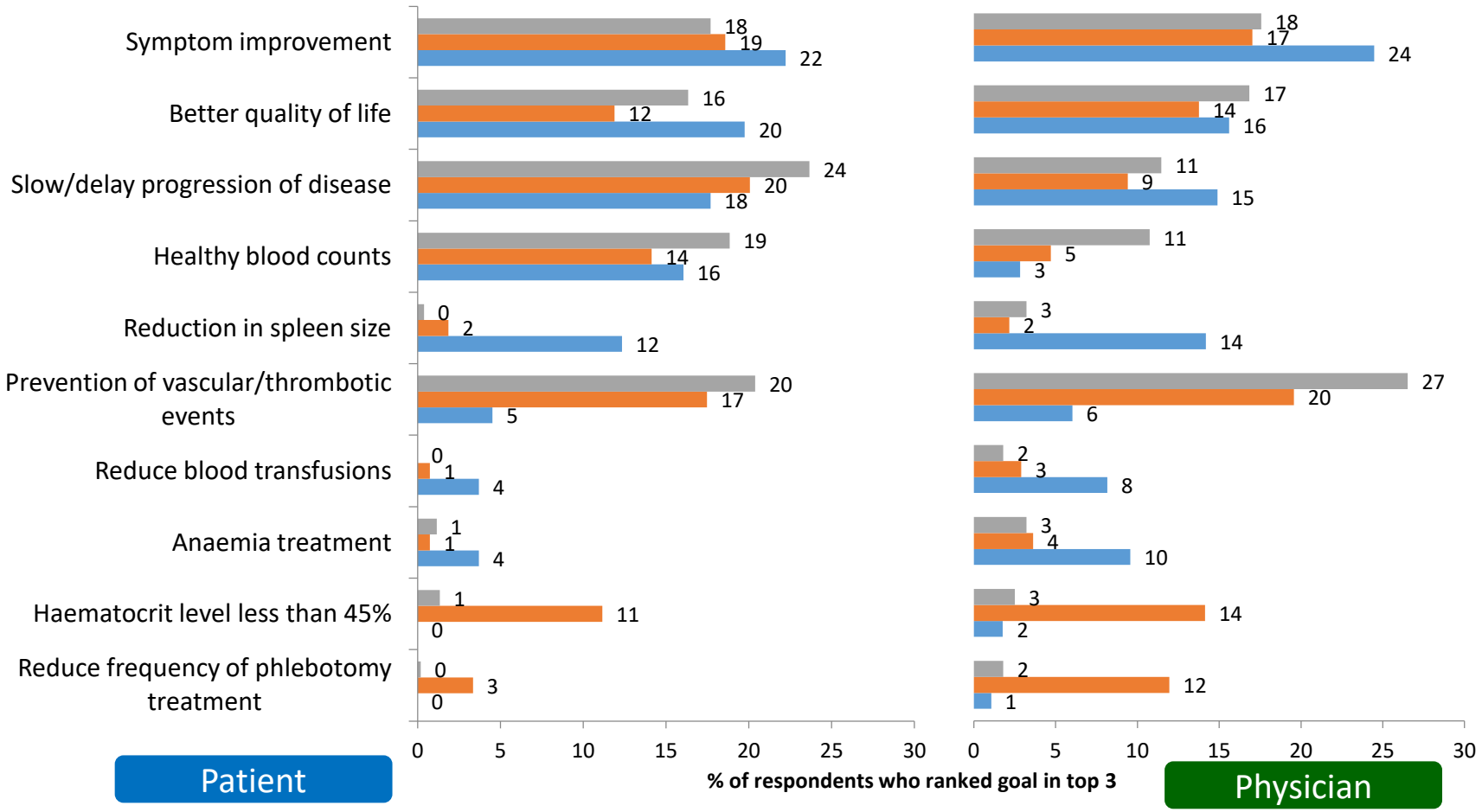
USA MPN Landmark Study: Mesa et. al. Cancer 2016

Treatment goals - Patients vs. Physicians view *(Q36 + Q31)*

ET and PV patients wish to slow disease progression whilst physicians are more concerned about thrombotic events. In all diseases both Patients & Physicians look for symptom improvements

MF
PV
ET

What is your most important treatment goal for your condition?

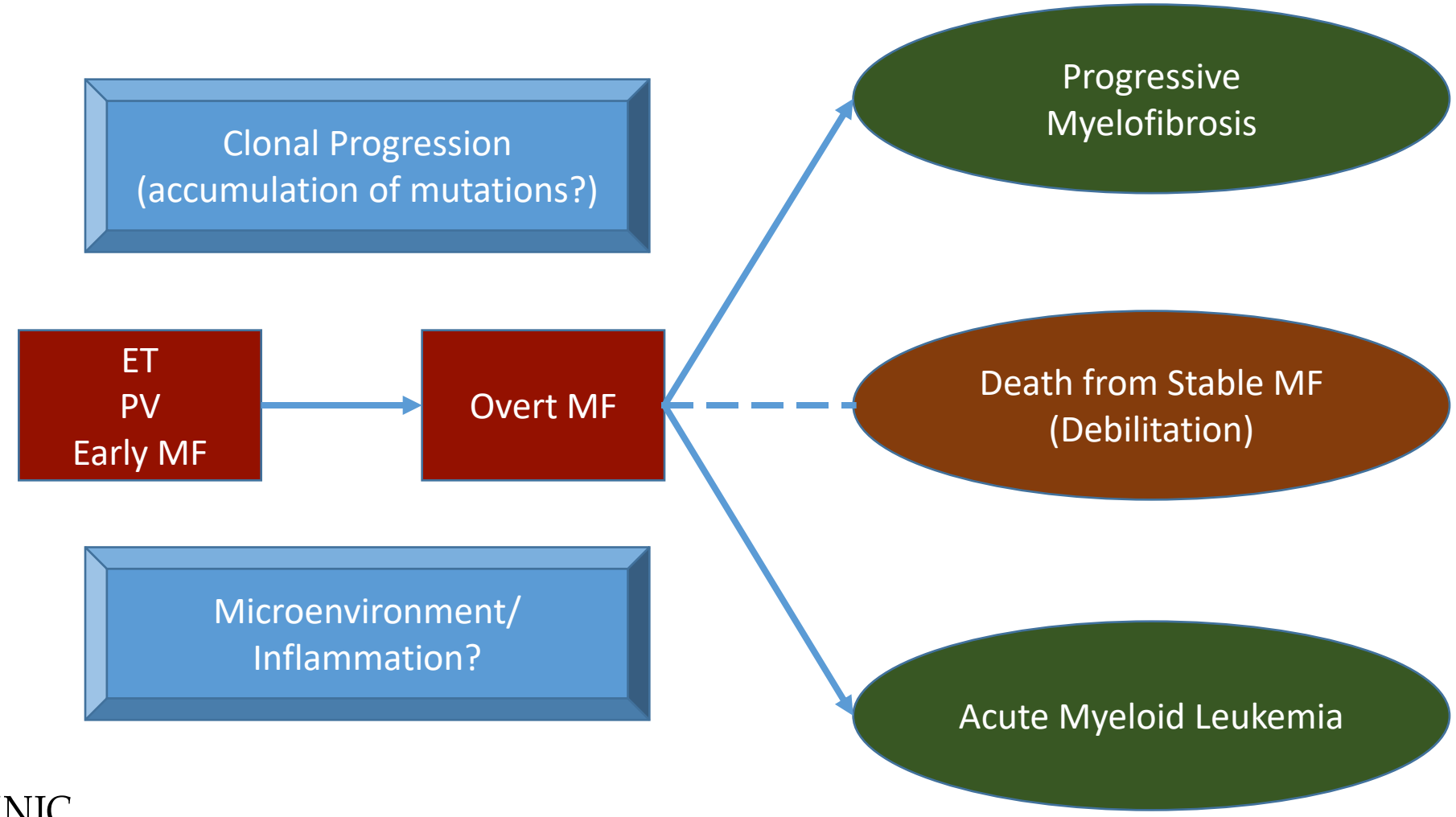


n: MF = 81, PV = 90, ET = 174

n: MF = 94, PV = 92, ET = 93

International MPN Landmark Study – Harrison et. al. ASH 2016

Why do MPNs Progress?



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Pegylated IFNs Alpha

1. **PEG-Intron** PEG-IFN-α-2b
   PEG size is 12K
   PEG → >14 positional isomers
   Dose **every week**
2. **PEGASYS** PEG-IFN-α-2a
   PEG size is 40K
   PEG → > 8 positional isomers
   Dose **every week**
3. **Ropeginterferon alfa 2b** PEG-IFN-α-2b
   PEG size is 40K
   PEG single-site-specific conjugation → *predominant single* positional form
   Dose **every 2-4 weeks**

MPD – RC 112
PEG INF vs HU
(Front Line)
High Risk ET/PV
NCT01258856

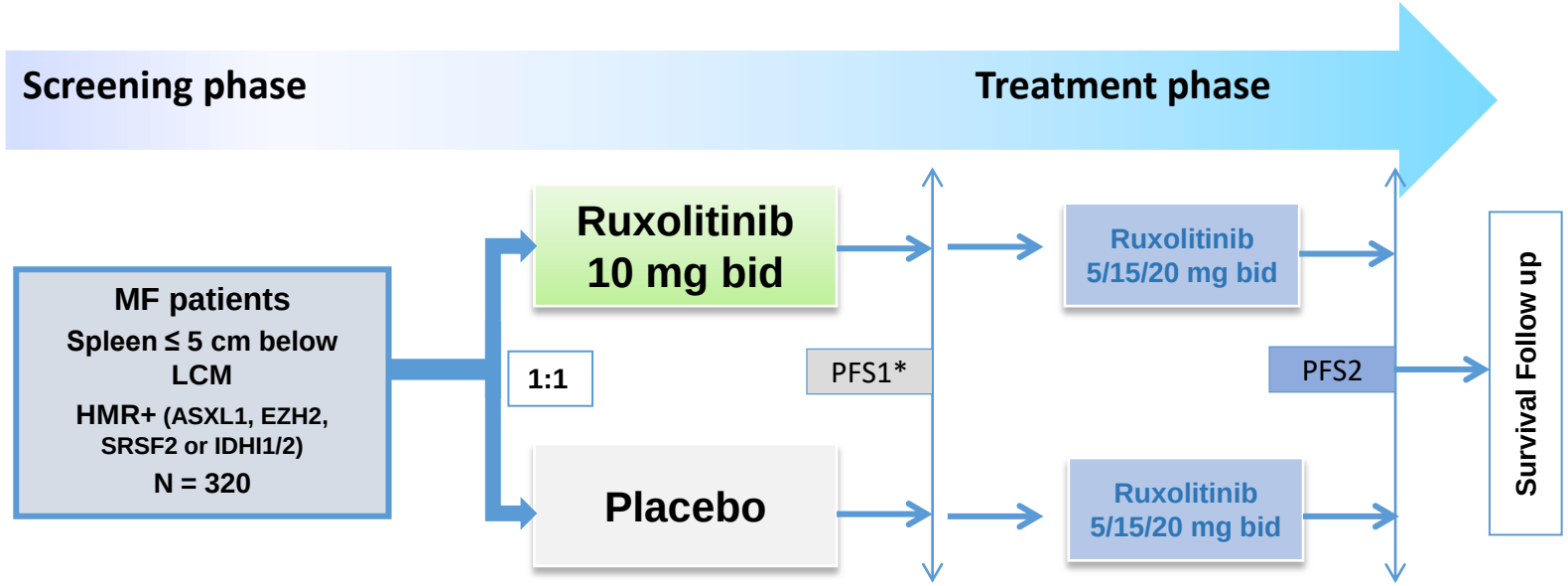
PROUD - PV
AOP2014/P1101 vs HU
(Front Line)
High Risk PV
NCT01949805

INF in Early Myelofibrosis

P1101/AOP2014
In Treating Patients with Early Myelofibrosis
NCT02370329
Now Accruing – Mayo Clinic

Peg IFN-A2b in Early PMF
NCT01758588

Trial design – RETHINK Rux vs placebo (MF DIPSS LR/ HMR+)



Inclusion population:

- Hb > 10 g/dl; transfusion independent
- ANC > 1, WBC < 15000
- Blast < 1%
- Platelets > 75000
- MPN10 ≤15 (individual items ≤ 3)

Primary endpoint:

- PFS-1 (90 events)

Secondary endpoints

- PFS-2, safety &tolerability, QOL, OS

* If progression is achieved by spleen or symptoms

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Passamonti et. al. ASCO 2016

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MPN SYMPTOMS

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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

MYELOPROLIFERATIVE NEOPLASM SYMPTOM ASSESSMENT FORM TOTAL SYMPTOM SCORE (MPN-SAF TSS-10 ITEMS)

(Recommended for monitoring symptoms during the course of treatment)

Circle the one number that describes how, during the past week how much difficulty you have had with each of the following symptoms

Filling up quickly when you eat (early satiety)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration-compared to prior to my MPD	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Numbness/Tingling (in my hands and feet)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching (pruritus)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone pain (diffuse not joint pain or arthritis)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever (>100 F)	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Daily)
Unintentional weight loss last 6 months	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

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MF Patient vs. physician-reported symptom assessment

PATIENT

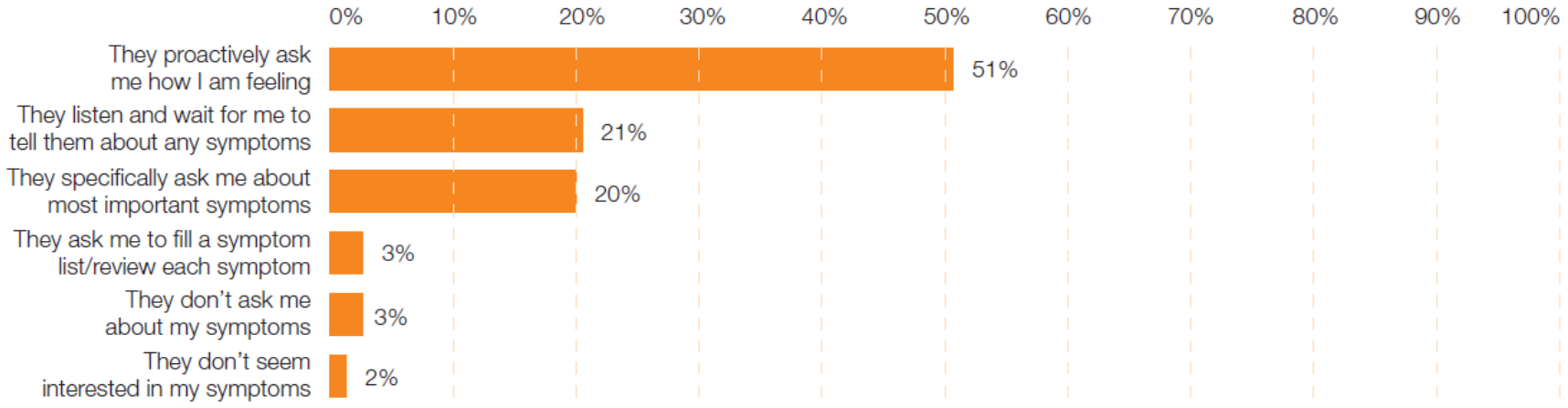
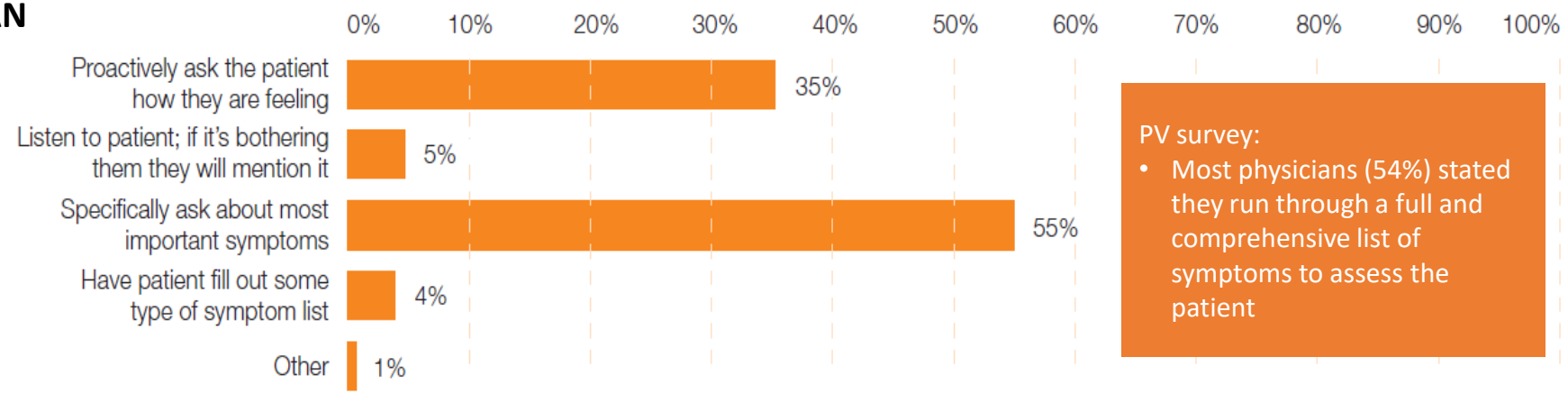


Figure 47. Question 41: How does the doctor you see most often for your diagnosis, assess any symptoms you may be experiencing? (n = 207)

PHYSICIAN



PV survey:

- Most physicians (54%) stated they run through a full and comprehensive list of symptoms to assess the patient

Figure 48. Question 27: During an average patient visit, how do you assess patient's symptoms? (n = 156)

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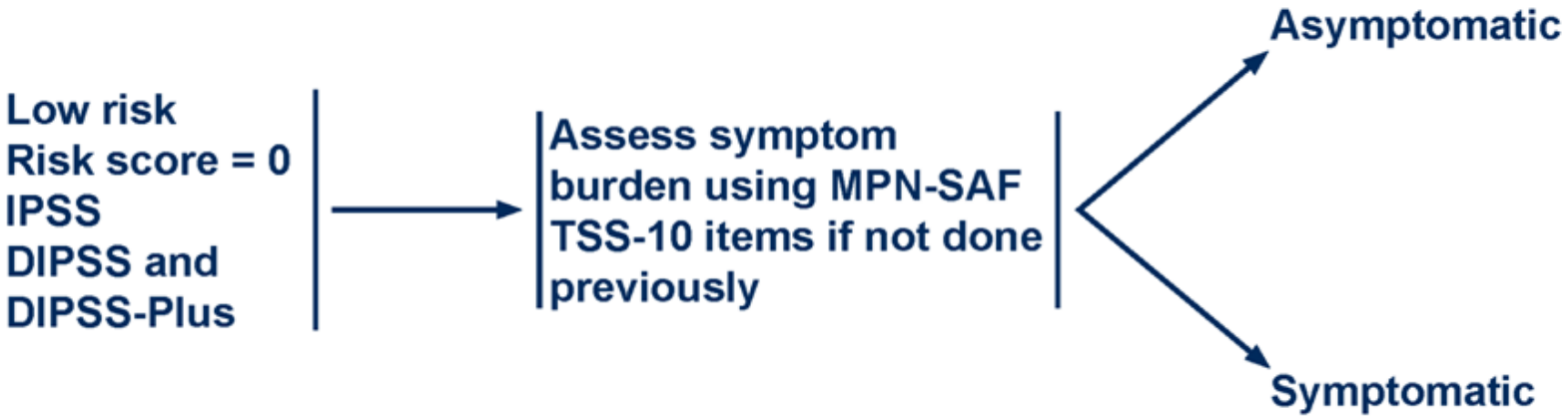
USA MPN Landmark Study: Mesa et. al. Cancer 2016

TREATMENT FOR LOW-RISK MYELOFIBROSIS



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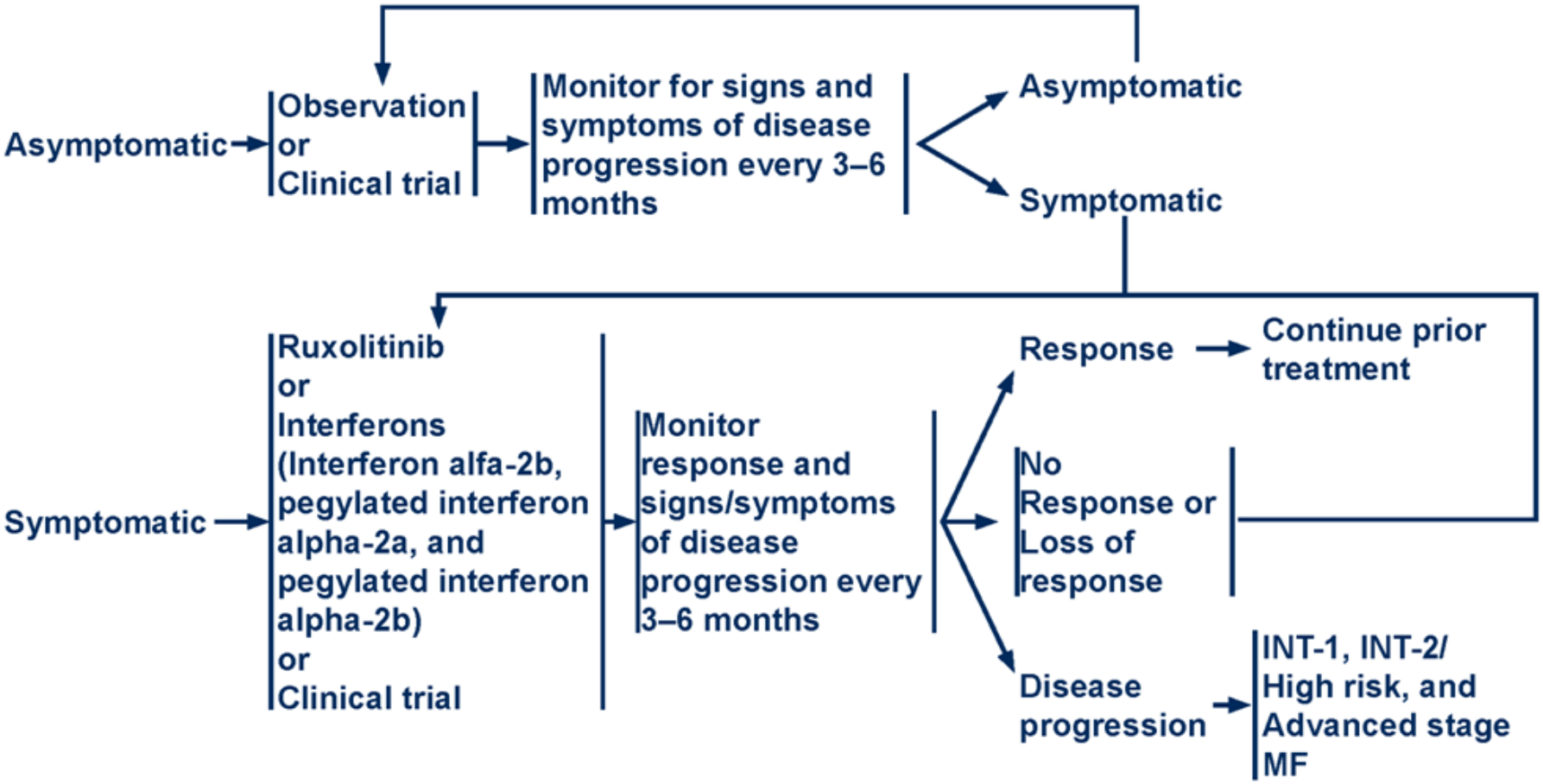
TREATMENT FOR LOW-RISK MYELOFIBROSIS



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What is "Symptomatic" in MF, enough to consider Rx?

Analysis of 425 MF with MPN-10, DIPSS Risk, Spleen Size

Table 1: Ordinal logistic regression models of DIPSS risk score (N=420) by symptoms in JAK2-naïve myelofibrosis patients.

Model	DIPSS Risk AIC
TSS >20	936.657*
Worst single symptom score >5	935.281*
Worst single symptom score >6	942.198
Worst single symptom score >7	942.684
TSS >20 & single score >5	938.510
TSS >20 & single score >6	943.335
TSS >20 & single score >7	944.867

*Optimal models based on lowest AIC.

Single Item

>5 (out of 10)

TSS

>20 (out of 100)

Scherber et. al. ASH 2016

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Meeting Threshold – Higher WBC, Blasts, Lower Platelets (even < DIPSS Cutoffs)

What is "Symptomatic" in ET or PV in HU Failure, enough to consider Rx?

Analysis of 838 PV/ 867 ET with Disease Features

Single Item

>5 (out of 10)

TSS

>20 (out of 100)

Meeting Threshold
-Prior Vascular Events
-Lower Hb (even without anemia)
-Higher WBC
? Different molecular features

Scherber et. al. ASH 2016

MPN Patient Burden- Disease Impact

2014 Landmark Study

Mesa et. al.
BMC Cancer
2016;16:167

ANY MPN Patient
- Survey online
- MPN Forum
- MPN Advocacy
- MPN Research Foundation
- CMPD Ed Foundation

Register/ Online Consent

Online Survey
- Demographics
- MPN History
- MPN-SAF (MPN10)
- Impact on QoL
- Impact on Employment
- Impact on ADLs

Patients
- 813 MPN Patients
  - MF (207)/ PV (380), ET (226)
  - INT/ High Risk
    - MF (94%)
    - PV (78%)
    - ET (74%)

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Employment change due to MPNs

Among those who employed full-time or part-time at diagnosis	MF (N=63)	PV (N=135)	ET (N=84)	Total (N=282)
Have you ever left a job due to disease? [Q7]	30 (47.6)	43 (31.9)	18 (21.4)	91 (32.3)
Have you ever taken early retirement due to disease? [Q22]	17 (27.0)	26 (19.3)	10 (11.9)	53 (18.8)
Have you ever gone on medical disability leave? [Q29]	26 (41.3)	35 (25.9)	13 (15.5)	74 (26.2)
Have you ever changed from full to part time employment? [Q40]	7 (11.1)	21 (15.6)	12 (14.3)	40 (14.2)
Have you ever had any other reductions in your hours? [Q47]	17 (27.0)	32 (23.7)	19 (22.6)	68 (24.1)
Were you ever reassigned to or did you take another job at a lower salary? [Q56]	6 (9.5)	16 (11.9)	5 (6.0)	27 (9.6)

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Impact of Living with MPN Survey Trial: Yu et. al. ASH 2016

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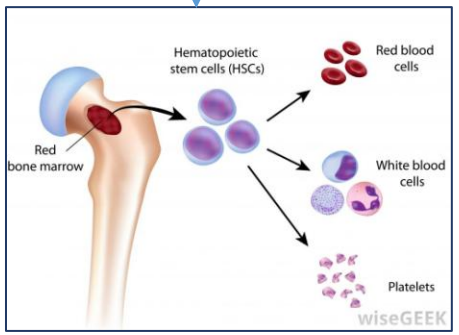
What do symptoms tell us about MPN Biology?

MPN Symptoms



?

Mood Disorders
Anxiety over Uncertainty

Cytokine Driven Symptoms
Spleen/ Inflammation

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MPN "Fatigue" Project 2014

Scherber *Cancer* in Press

Collaborative Internet Based Trial with MPN Forum

ANY MPN Patient
- Survey online
- MPN Forum
- MPN Advocacy
- MPN Research Foundation
- CMPD Ed Foundation

Register/ Online Consent

Online 70 Item Survey
- Demographics
- MPN History
- MPN-SAF (MPN10)
- Brief fatigue inventory (BFI)
- Profile of mood states (POMS-Short)
- Patient Health Questionnaire (PHQ-2)
- Mental Health Inventory (MHI-5)

Patients

1788 MPN patients/ 1676 Eval.

ET 33%, PV 39%, MF 25%

68% Female, median age 59. MPN10 Score average 28.4 (range 0-83)

Psych Comorbidity

23% high likelihood of depression (≥ 3 on PHQ-2)

Prior diagnosis depression (32%), anxiety (29%), stress (26%), grief (15%)

22% on therapy for mood disorder in last 6 months

MPN Correlation

Higher BFI, MPN-SAF, MPN10 scores all correlated with increased depressive symptoms ($p<0.0001$)

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Item	PHQ ≥3 (high likelihood of depression)	PHQ <3 (low likelihood of depression)
MPN-SAF items and scoring		
MPN-TSS (MPN-10, mean score)*	41.1 (16.7)	24.7 (15.9)
Brief Fatigue Inventory (BFI)*	6.3 (1.7)	3.8 (2.3)
Worst Fatigue (last 24-hours)*	7.8 (1.9)	5.8 (2.7)
Early Satiety*	4.1 (3.1)	2.5 (2.8)
Abdominal pain*	2.8 (3.1)	1.4 (2.2)
Abdominal discomfort*	3.6 (3.1)	2.1 (2.5)
Inactivity*	5.6 (2.6)	2.8 (2.7)
Headache*	3.8 (3.3)	2.2 (2.7)
Concentration difficulties*	6.1 (2.6)	3.4 (2.9)
Dizziness*	4.2 (3.3)	2.3 (2.6)
Numbness*	3.8 (3.3)	2.7 (3.0)
Insomnia*	5.4 (3.3)	3.7 (3.0)
Sad mood*	6.2 (2.3)	2.4 (2.4)
Sexual difficulties*	6.2 (3.4)	3.7 (3.4)
Cough*	2.9 (3.1)	1.5 (2.4)
Night sweats*	4.0 (3.5)	2.4 (2.9)
Pruritus*	3.8 (3.5)	2.5 (2.9)
Bone Pain*	3.9 (3.6)	2.2 (2.9)
Fever*	0.7 (1.8)	0.2 (1.1)
Weight loss*	1.5 (2.7)	0.8 (2.0)
Overall quality of life (QOL)*	5.8 (2.1)	3.1 (2.2)
Mental Health Inventory Score*	16.5 (4.3)	23.3 (3.9)
POMS-B Subscales		
Tension-anxiety*	11.5 (4.0)	16.2 (3.2)
Vigor-activity*	3.3 (3.0)	6.8 (4.4)
Fatigue-inertia*	5.3 (3.9)	11.2 (5.1)
Depression-dejection*	10.6 (4.4)	17.0 (3.1)
Confusion-bewilderment*	11.2 (4.0)	15.2 (3.0)
Anger-hostility*	12.6 (4.6)	16.7 (3.3)
POMS-B total score*	54.6 (16.0)	83.2 (16.0)

Mood and MPNs
1788 MPN Patients

- MPN-SAF
- PHQ3, POMS-B
- *MPN10 and every Symptom higher with Depression*
- *Depression not linked to MF, PV or ET risk scores*

Scherber et. al. ASH 2016

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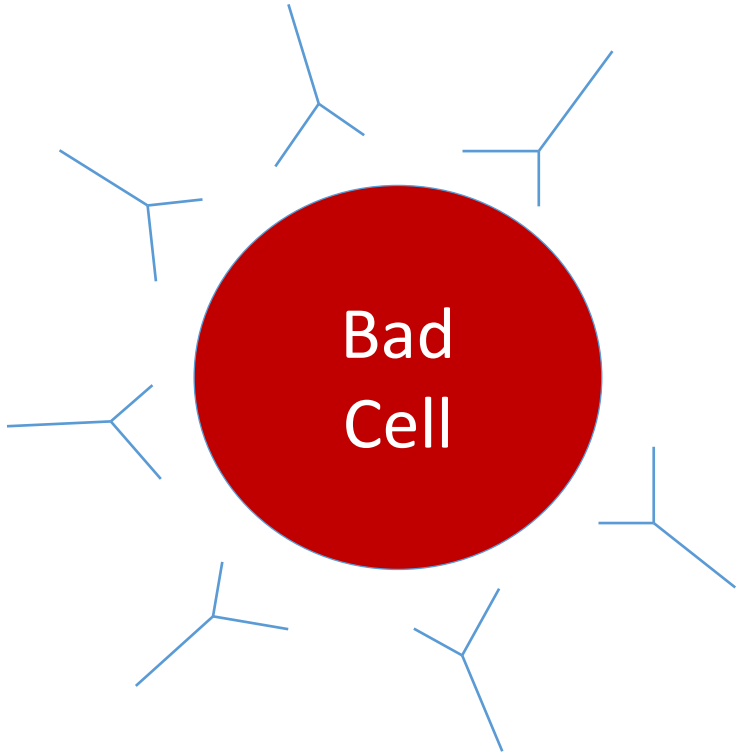
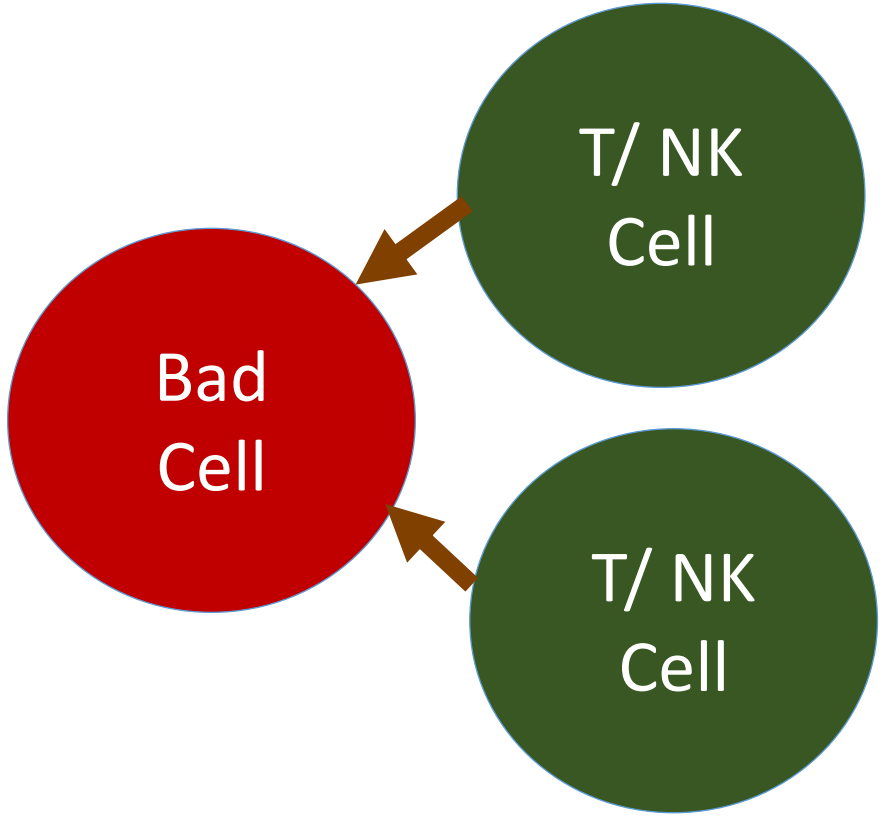
Using your immune system to treat your disease

Humoral – B Cell Immunity



Cellular – T Cell Immunity



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Using your immune system to treat your disease

Humoral – B Cell Immunity
" – Mabs"

- Rituximab
- Bexxar
- Zevalin
- Blinatumomab
- Ofatumumab
- Daratumumab
- Pembrolizumab
- PRM151

Cellular – T Cell Immunity

- CART (Chimeric Antigen Receptor) T Cell Therapy
- Allogeneic Stem Cell Transplant

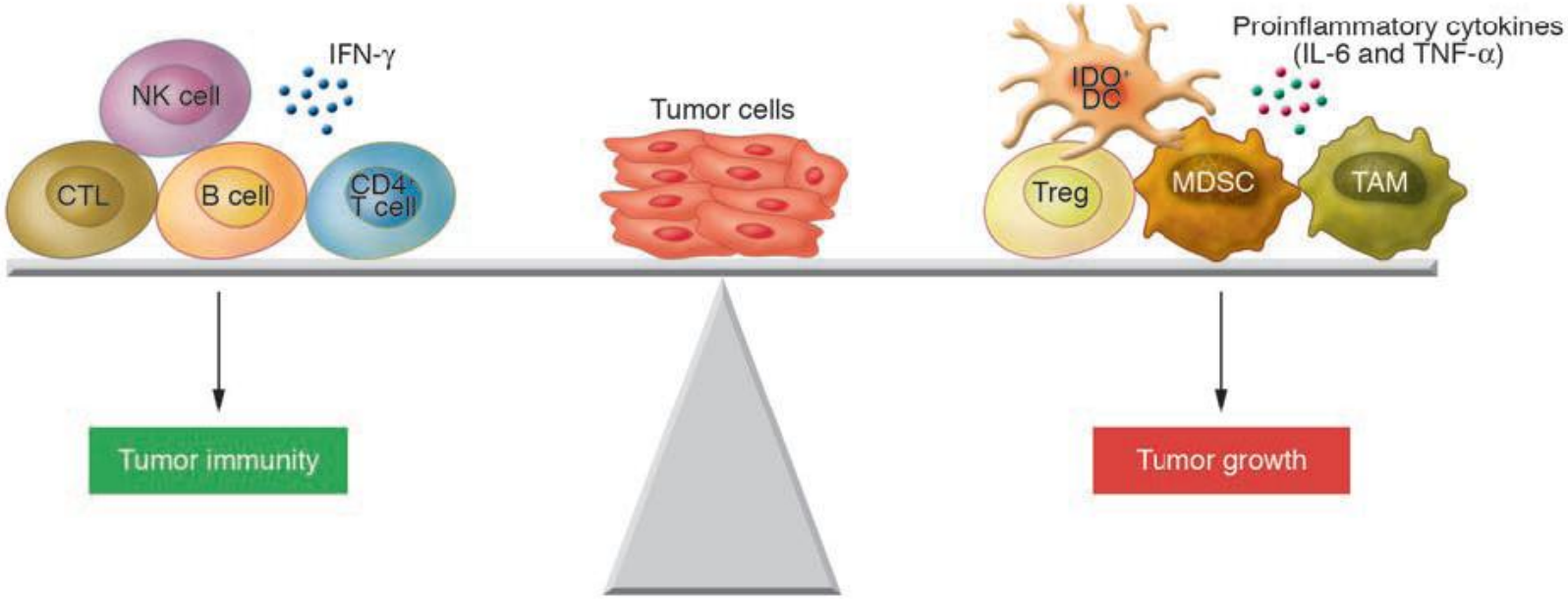
Using the immune system to fight cancer rests on **THREE** assumptions

1. Tumor cells express antigens that differentiate them from normal cells
2. The immune system can recognize and respond to these antigens
3. The response must be sufficient to lessen or reverse tumor growth

The basic idea is to stimulate the body's own immune response, so it will act to destroy a tumor

Immune cells influence tumor development and progression

- The balance between tumor-promoting and tumor-suppressing immune responses and the difference between them ultimately determine whether a cancer escapes immune recognition mechanisms.



Clin. Invest. (2007)

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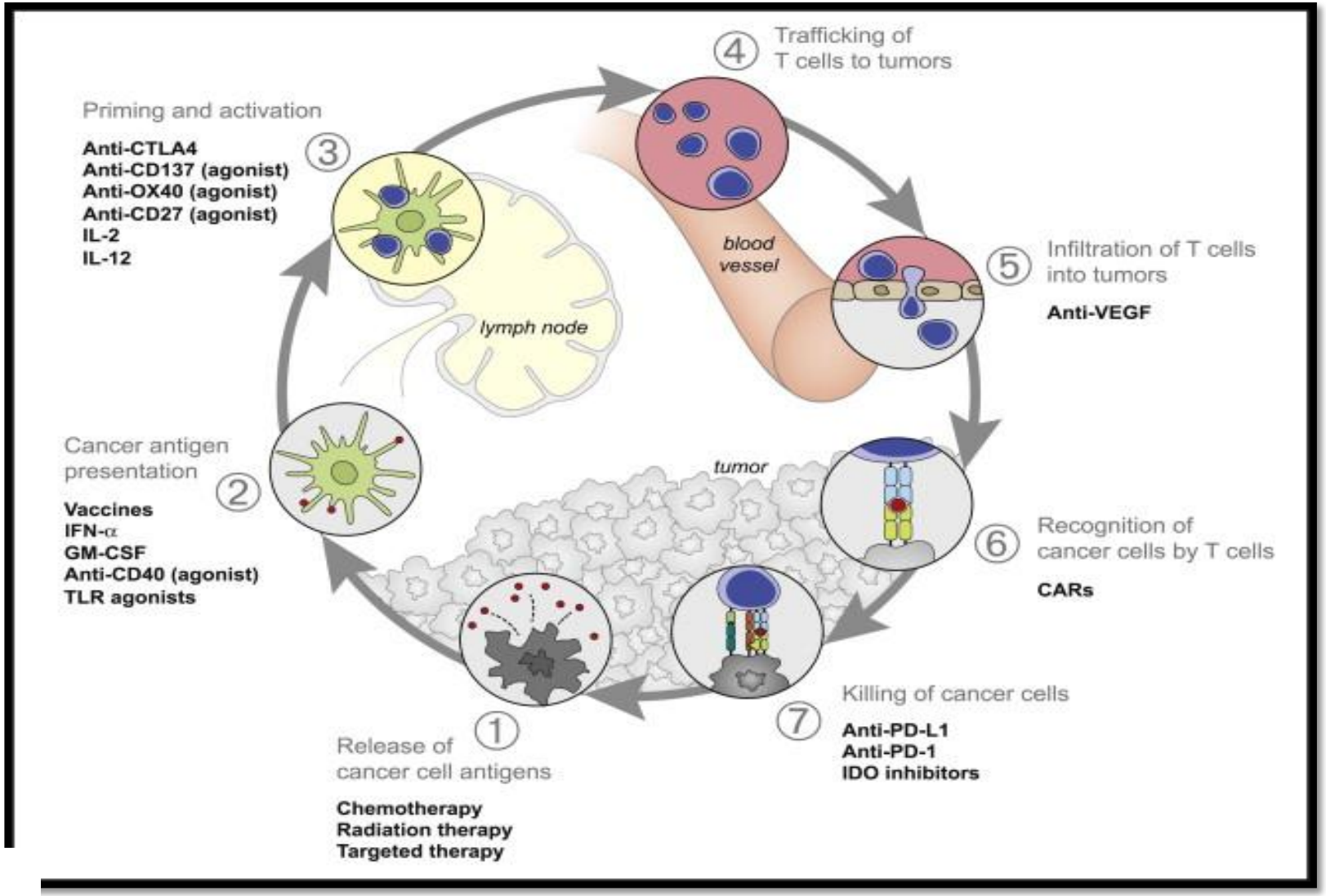
Cancer-Immunity Cycle : Targeting Opportunities



Chen and Mellman . Immunity 2013

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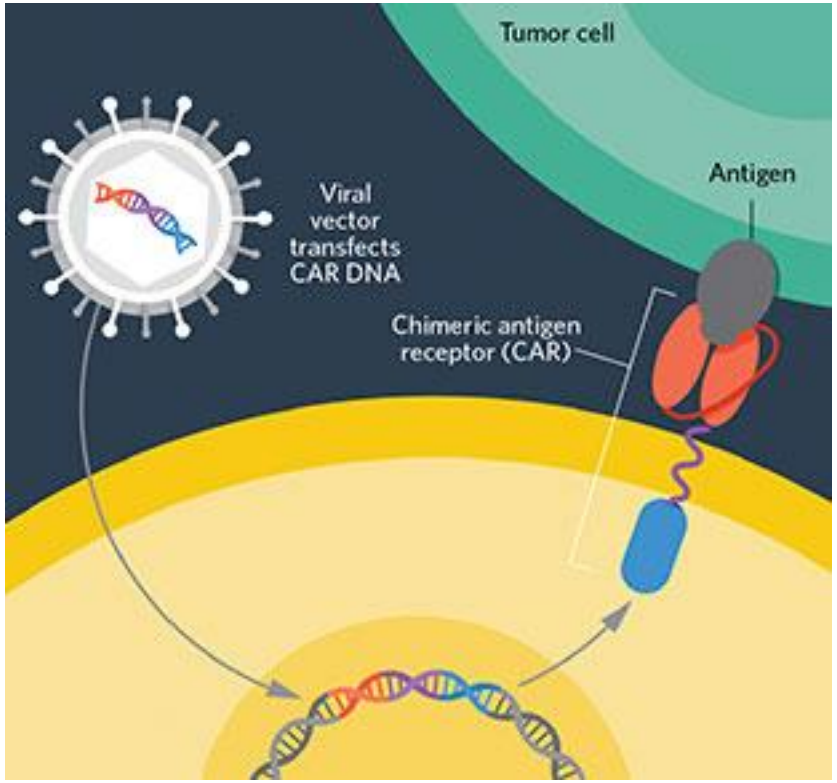
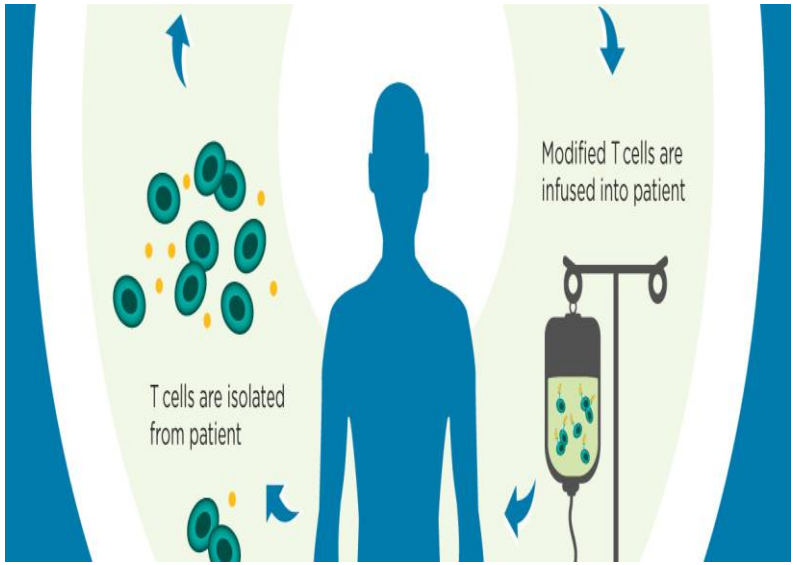
Chimeric Antigen Receptor (CAR) T cells



BUILDING A BETTER T-CELL:

- Modifying T cells to express chimeric antigen receptors (CARs) that recognize cancer-specific antigens,
- Prime the cells to recognize and kill tumor cells that would otherwise escape immune detection.

The process involves extracting a patient's T cells, transfecting them with a gene for a CAR, then reinfusing the transfected cells into the patient.



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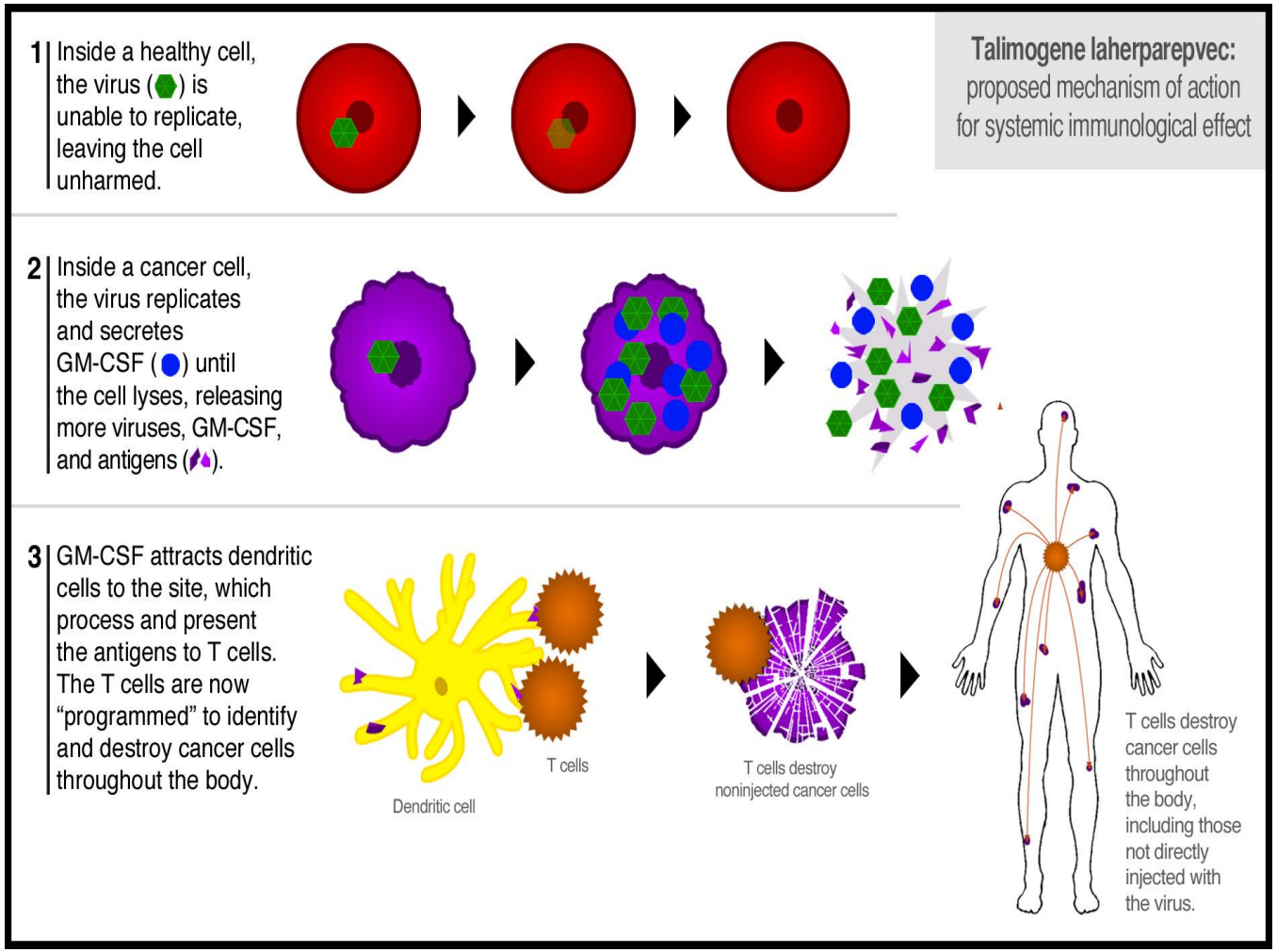

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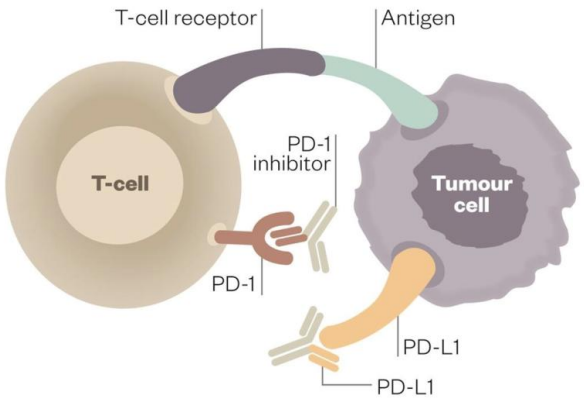
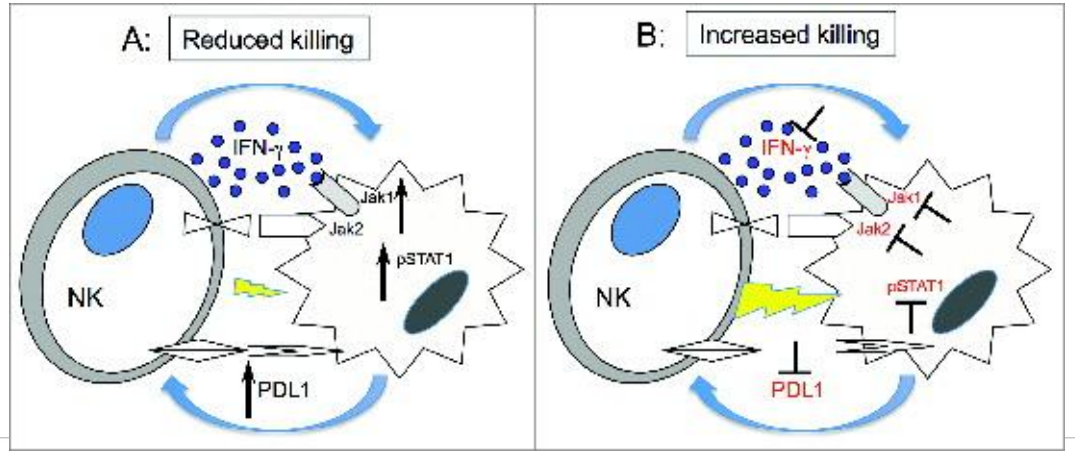
Immunotherapy in MPN

- New era of immunotherapy in oncology with checkpoint inhibition
- Role of PD-1 inhibition starting to be elucidated in myeloid malignancies
- Rationale for immunotherapy in MPN- allogeneic transplantation, IMIDs

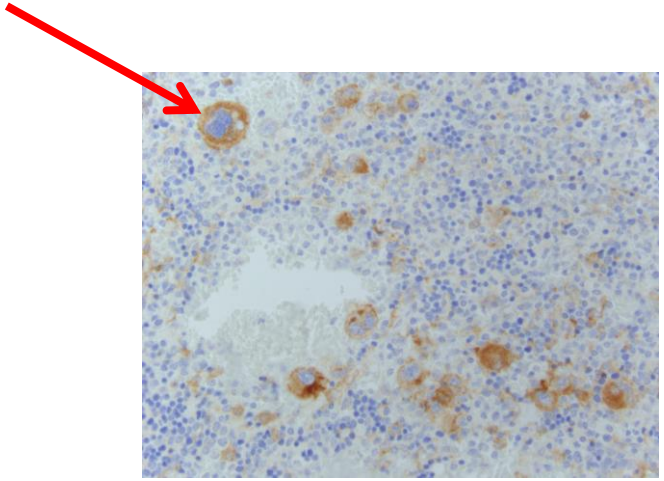




Yang *et al* Leukemia 2014:28:1280-8
Riley *et al* Eur J Haematol 2014
Tefferi *et al* J Clin Oncol 2009;27:45639
Pharmaceutical Journal, Nov. 2014.
Belluci *et al* OncoImmunology, 2015

Pre-Clinical Work

- Where we were-
  - Megakaryocytes in splenectomy samples express PD-L1

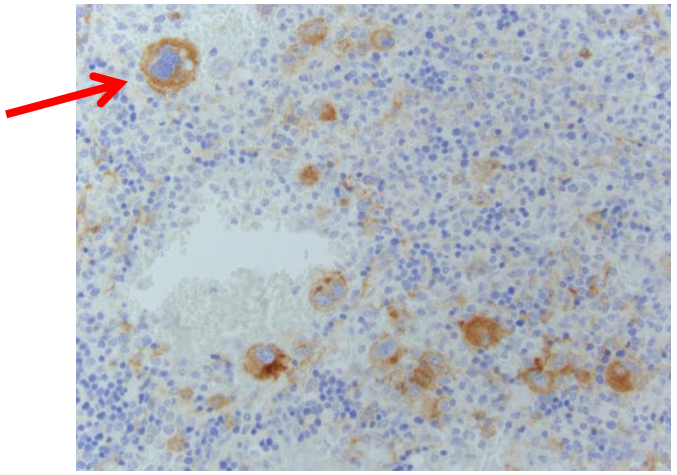


- Moving forward is not easy
  - Staining for PD-1/L1 is not that straight forward…
  - Tested 20 myelofibrosis samples and 3 controls at MGH
  - Found? Nothing!
  - ?issues with antibodies

Belluci *et al* OncoImmunology, 2015

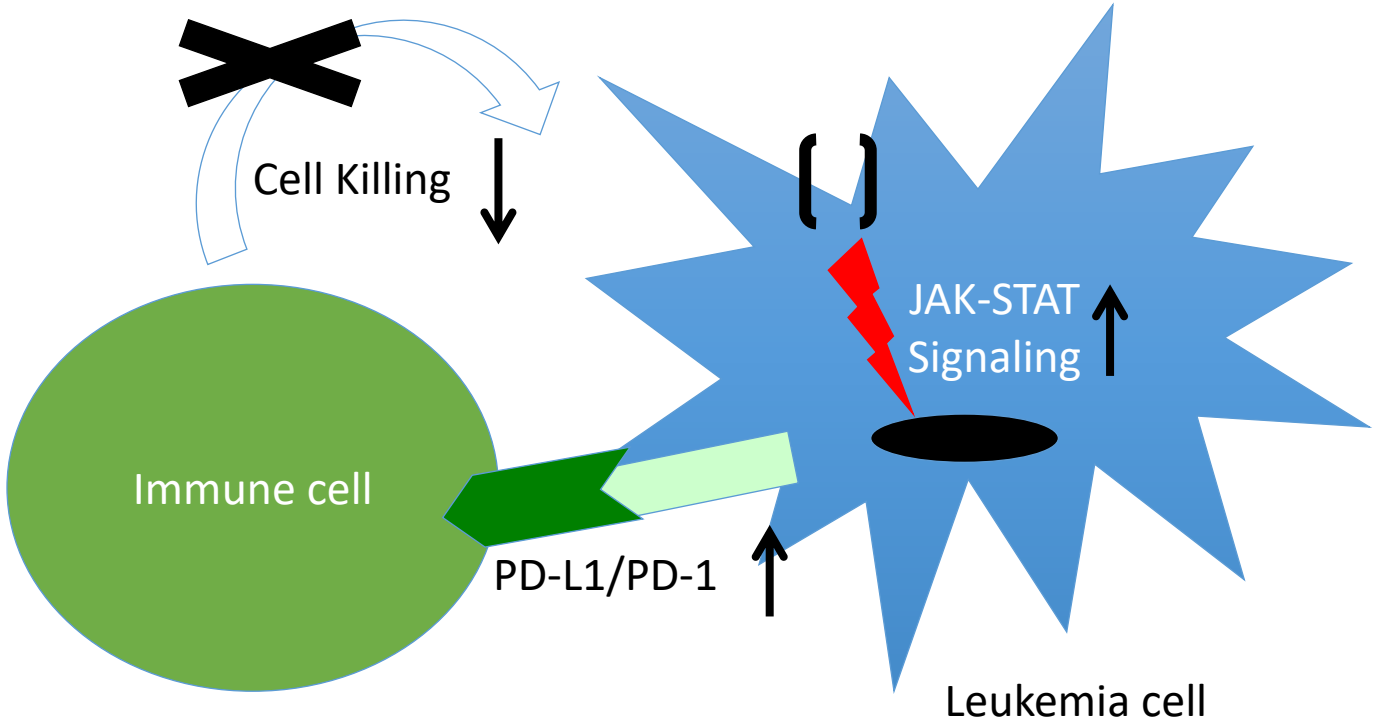
PD-L1 expression in Spleens

- 26 splenectomy samples in advanced MF patients, 19 were JAK2V617F positive
- PD-L1 is expressed in megakaryocytes in 75% of patients, novel finding
- PD-L1 aberrantly expressed in a variety of solid tumors



PD-L1 staining in megakaryocytes

Where we are

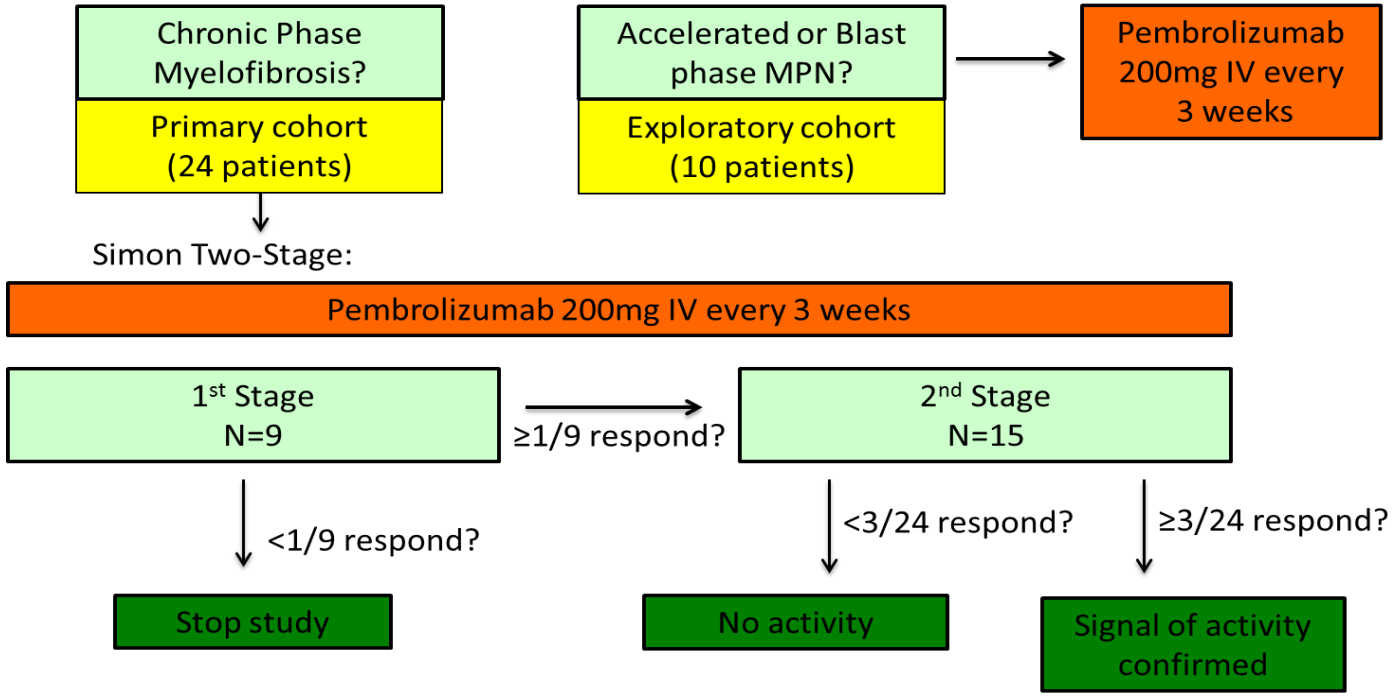


- Leukemia cell lines exposed to interferon express PD-L1 and avoid cell killing by T cells and NK cells
- JAK-STAT is at the center of MPN pathophysiology

Belluci *et al* OncoImmunology, 2015

Clinical Trial- Pembrolizumab in Myelofibrosis

- Phase II, open label study at MGH and MSSM



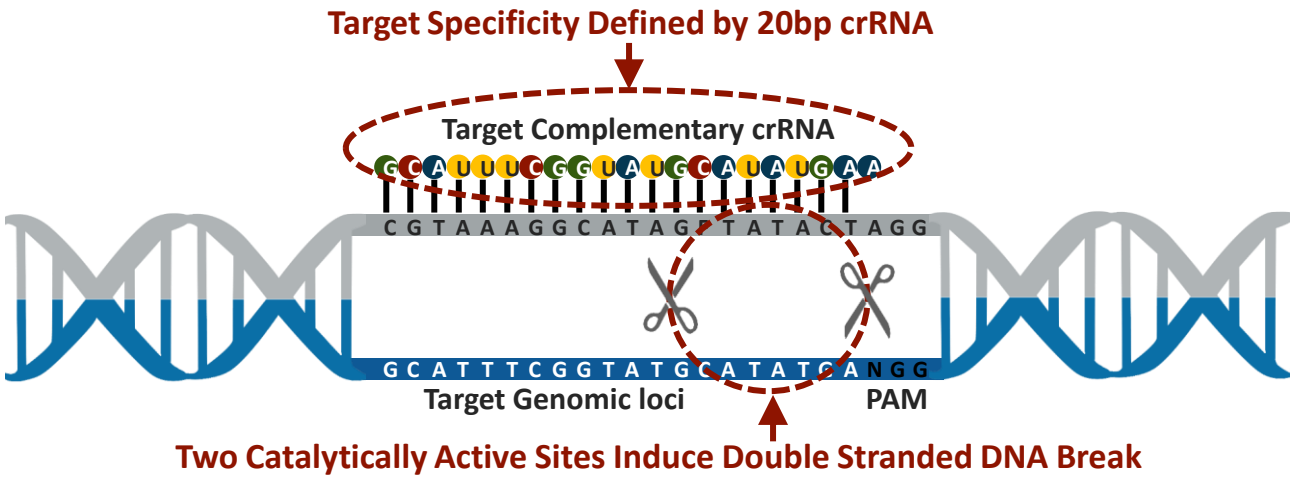
- Protocol *almost* approved by Merck, plan to open later this year

New Directions in MPN Management

- Target earlier disease and delay progression
- Understand and track disease burden
- Multi-disciplinary MPN care
- Expanding medical therapy – Immune Therapy
- Genetic Repair - CRISPR
- Non pharmacologic options in addition to medical therapy

CRISPR: Gene Therapy Finally Coming to MPNs?

- Clustered Regularly Interspaced Short Palindromic Repeat
  - Bacterial immune response system leveraged for genome editing
  - Cas9 DNA nuclease
  - GuideRNA = CrisprRNA (crRNA) + tracrRNA



MPN forum Magazine. CRISPR/Cas9: Gene Editing with Precision. www.mpnforum.com/cascade

CRISPR and MPNs: Collaborations – Advocacy by Patient Groups/ Foundations and Scientists

- Patient groups have been at vanguard encouraging CRISPR scientists to explore MPNs as a target genetic disease
- Clinical trials first in HIV, now in hemophilia B
- CRISPR Editing of JAK2-V617F in vitro in patient samples[a]

MPN RESEARCH FOUNDATION
CHANGE YOUR PROGNOSIS

a. Smith C, et al. *Mol Ther*. 2015;23:570-577.

New Directions in MPN Management

- Target earlier disease and delay progression
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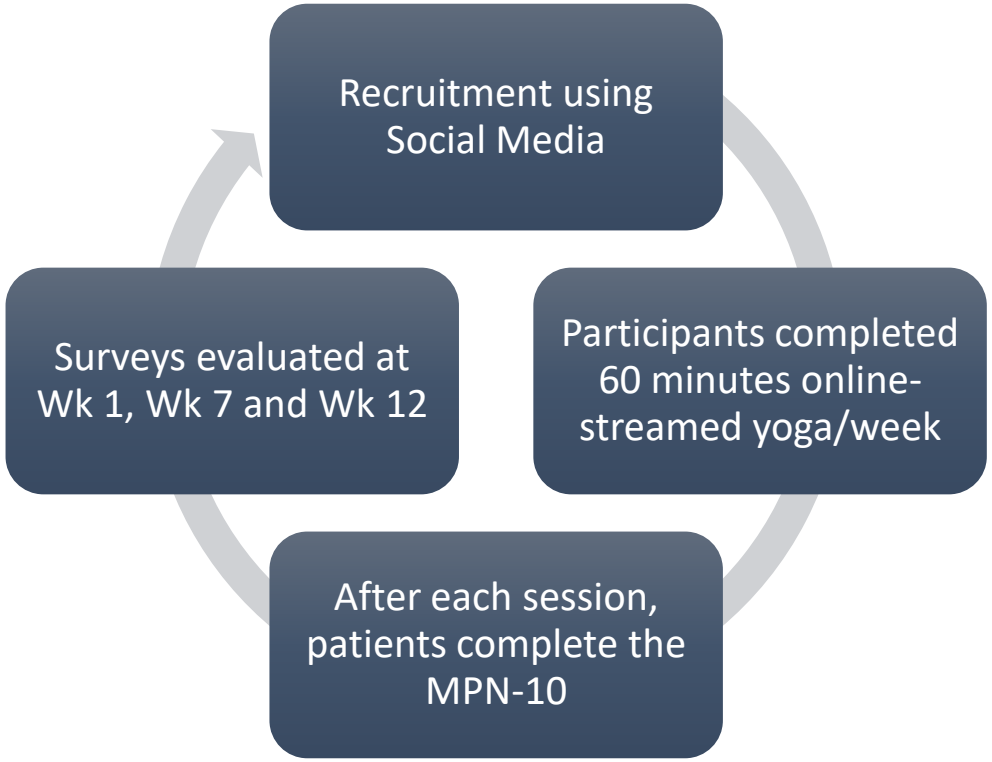
The MPN Yoga Study - Feasibility 1

METHODS



RESULTS

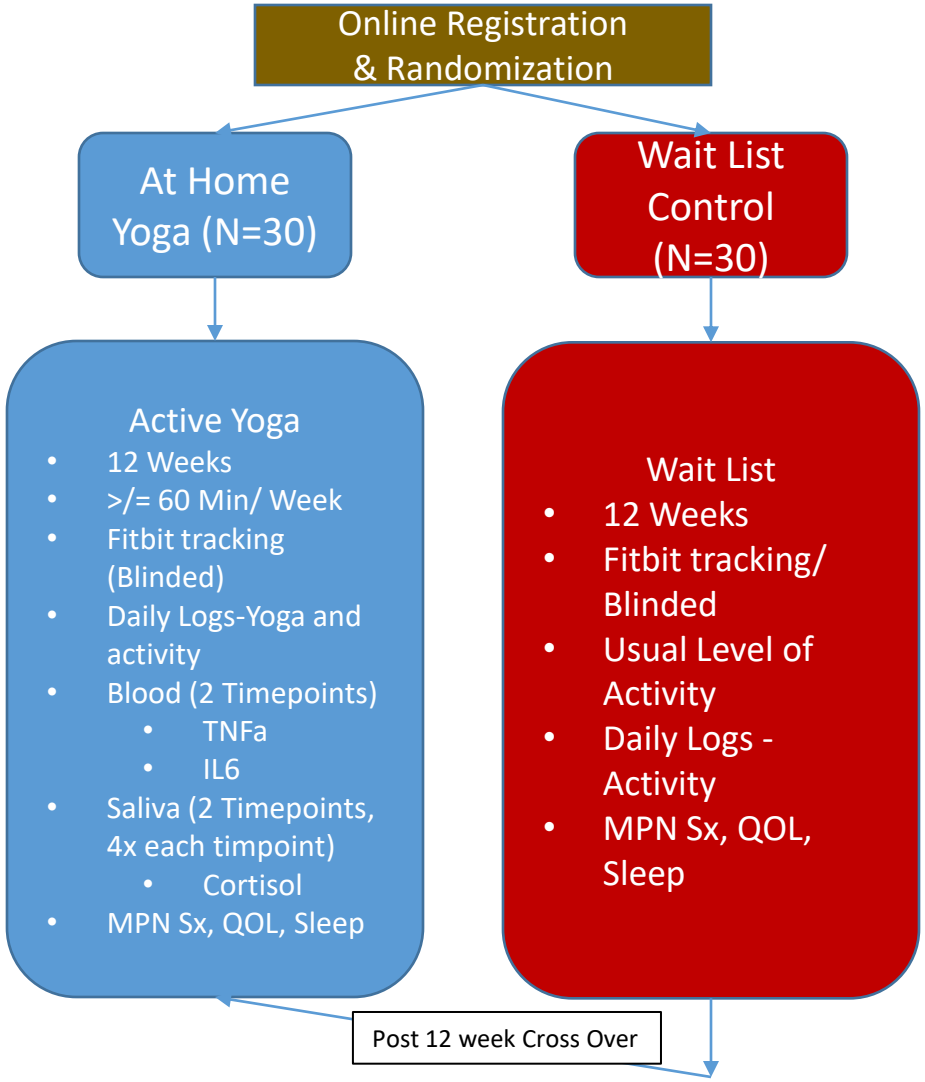
- **38 MPN Patients participated**
  - **PV (38%)**
  - **ET (37%)**
  - **MF (20%)**
- **43% of participants completed >60min/wk**
- **Baseline MPN TSS: 34.6**

- ***68% were satisfied (32%) or very satisfied (36%) w/ online yoga***
- ***Improved MPN-10 by 4.77 points, p0.004***
- ***Improved fatigue, anxiety, depression, sleep (all p=0.05)***

MPN Yoga II - Pilot

Key Eligibility

- MPN Patient
- Not Depressed
- PS<3
- Not already doing yoga or Mindfullness
- <150 Min of weekly exercise



MPN Yoga Team:

Arizona State University:
Jennifer Huberty PhD
Linda Larkey, PhD
Ryan Eckert, B.S.

Mayo Clinic Arizona
R. Mesa, MD
Amylou Dueck, PhD
K. Gowin, MD

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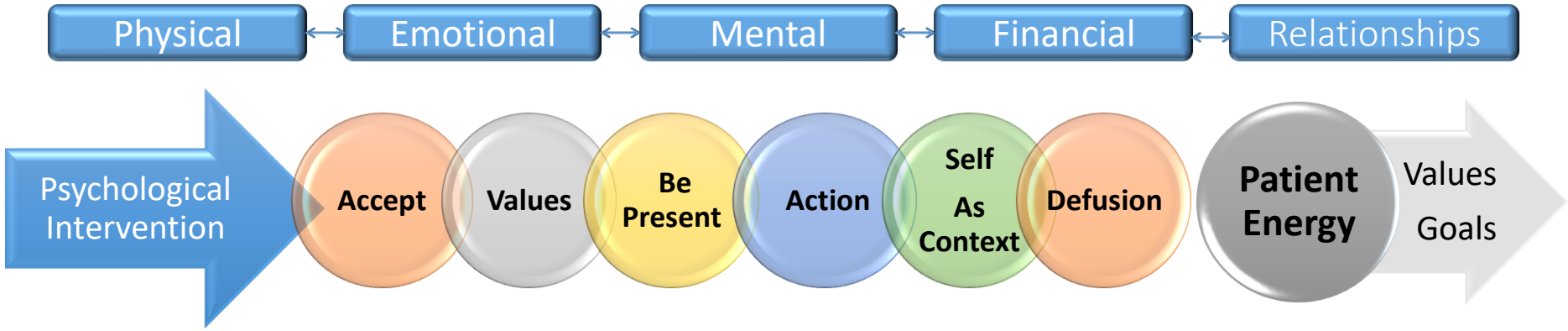
Acceptance and Commitment Therapy for MPNs -The Opportunity-



ACT in Chronic Conditions

Chronic Pain	Fibromyalgia	Chronic Fatigue
↓ anxiety	↑ mental QOL	↓ insomnia
↓pain,	↓ anxiety	↓ anxiety
↓pain disability	↓ depression	↓ fatigue
↑ QOL		

ACT In Cancer

Breast Cancer	CNS Tumors
Completed Cancer Treatment	Completed Cancer Treatment
↓ Depressive	↑ QOL
↓ Anxiety	↑ QOL brain tumor specific

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Padrnos, Geda, Stonnington & Mesa: Mayo Clinic

ACT Therapy Plan

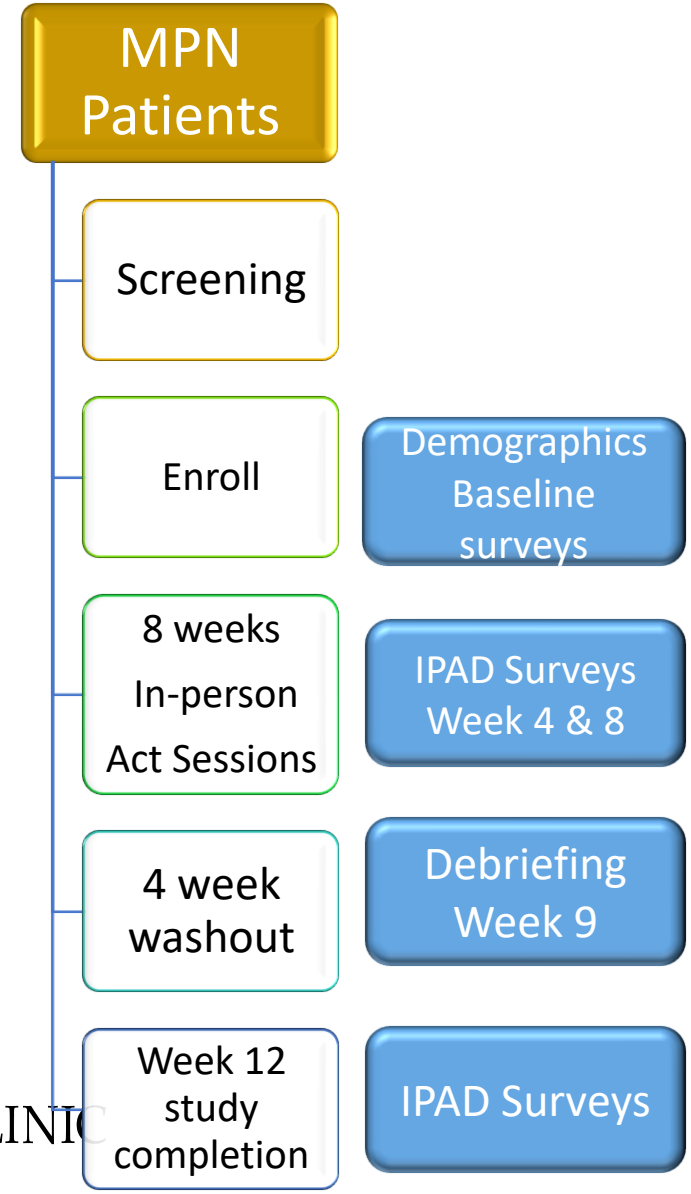
8 Weekly Therapy Topics

Introduction	• Information of symptom burden
Acceptance	• Of thoughts and emotions
Defusion	• Decrease attachment to negative thoughts
Being Present	• Improves sense of action, not reaction
Self as Context	• Facilitates defusion and acceptance
Values	• Chosen and purposeful
Committed Action	• Achievable goals
Conclusion	• Encourage continued use of topics

MAYO CLINIC
Cancer Center

Padrnos, Geda, Stonnington & Mesa: Mayo Clinic

AIM 1: Evaluate Feasibility



Population & Accrual

- MPN diagnosis
- At local institution
- Able to travel weekly sessions
- English speaking
- Exclusion: severe depression/anxiety

Assessment for Feasibility

- Trial Enrollment: 2 patients per month
- Reasons for Ineligibility
- Reasons for non-enrollment
- Therapy Attendance Rate
- Survey Completion
- Ease of Completion

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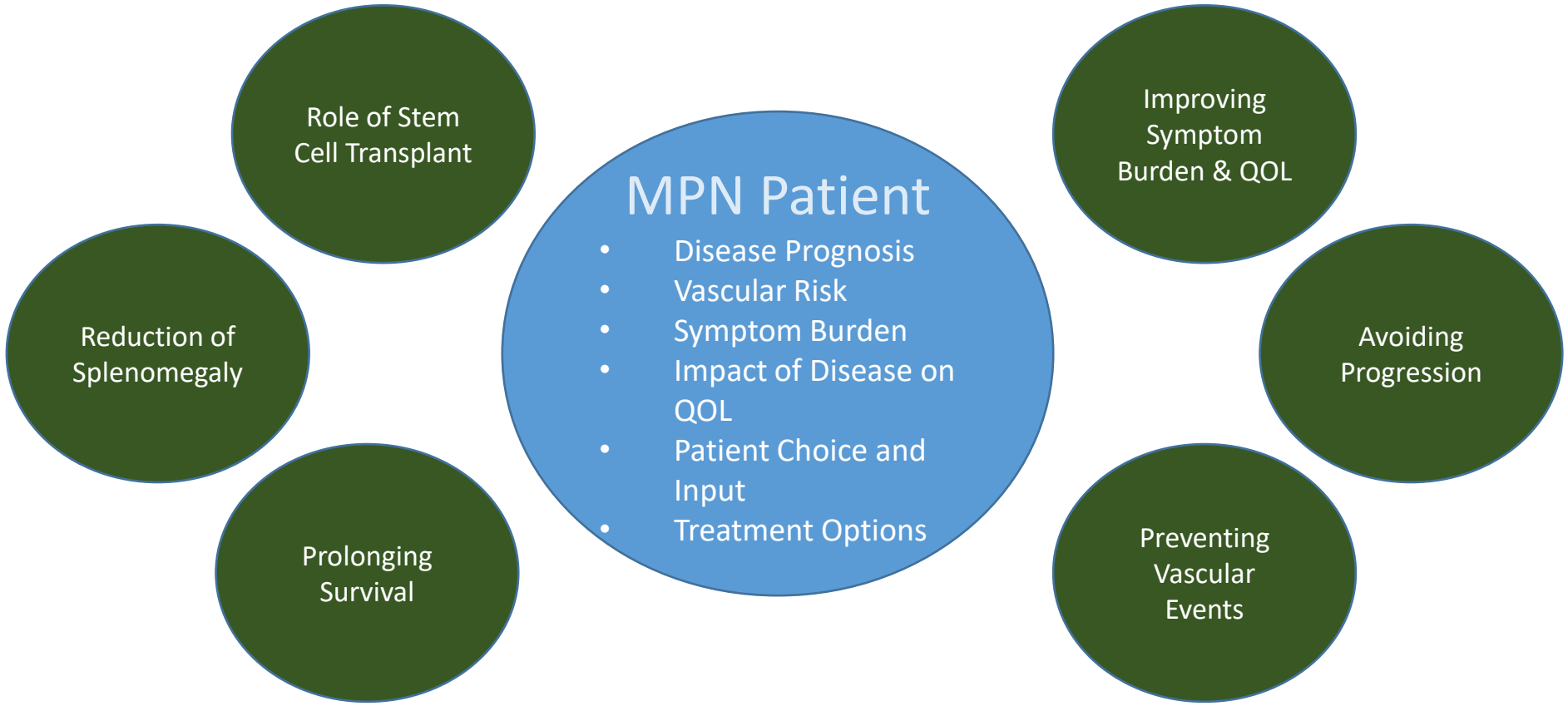
AIM 2: Does ACT improve HrQOL in MPNS?

OBJECTIVE	OUTCOMES	MEASUREMENTS	ITEMS
Primary	Quality of Life	• PROMIS Global Health	10
General Health	Chronic illness impact	• PROMIS 29	29
	Stress	• Perceived Stress Scale	4
MPN Symptoms	MPN specific symptoms	• MPN-SAF	24
	Fatigue	• Brief Fatigue Inventory	3
ACT Therapy	Acceptance and Avoidance	• Acceptance and Action Questionnaire	7

Putting It All Together – MPNs and QOL



The Itch

I have an itch you cannot know,
not the least hint will ever show
No bump no rash no insect bite
provides a clue as to my plight
My clothes, a shower, the air I breathe
make my skin prickle and seethe
Constant reminders it provides
of the disease my body hides
Maddening tears the burning brings,
no scratch, no pills can stop the stings
Life is good,
it could be much worse
I can live with my itchy curse
I walk the dog to pass the time,
take deep breaths and clear my mind
Pruritus is a small price
for my wonderful blessed life

Paul Nudelman
Poet & PV Patient

Gurnee, IL, USA

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