Mielofibrosis en 2015

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Mielofibrosis en 2015

- Diagnosis of MF
- Burden and Risk of Disease
- Establishing goals of care
- Therapy of MPNs
  - Anti-coagulation
  - Cytoreduction
  - JAK inhibition
  - Stem Cell Transplant
- Case Examples

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2008 WHO Diagnostic Criteria for PMF[5]

Diagnosis requires meeting all 3 major criteria and 2 minor criteria

Major Criteria

1. Presence of megakaryocyte proliferation and atypia,[a] usually accompanied by either reticulin or collagen fibrosis; or in the absence of significant reticulin fibrosis, the megakaryocyte changes must be accompanied by an increased bone marrow cellularity characterized by granulocytic proliferation and often decreased erythropoiesis (ie, prefibrotic cellular-phase disease)
2. Not meeting WHO criteria for PV,[b] BCR-ABL1+ CML,[c] MDS[d] or other myeloid neoplasms
3. Demonstration of JAK2V617F or other clonal marker (eg, MPLW515L/K); or in the absence of a clonal marker, no evidence that the bone marrow fibrosis is secondary to infection, autoimmune disorder or other chronic inflammatory condition; hairy cell leukemia or other lymphoid neoplasm; metastatic malignancy; or toxic (chronic) myelopathies[e]

Minor Criteria[f]

1. Leukoerythroblastosis
2. Increase in serum lactate dehydrogenase level
3. Anemia
4. Palpable splenomegaly

2008 IWG-MRT diagnostic criteria for post-PV MF and post-ET MF

Diagnostic criteria for post-PV MF	Diagnostic criteria for post-ET MF
REQUIRED CRITERIA	
1. Documentation of a previous diagnosis of ET or PV as defined by the WHO criteria	
2. Bone marrow fibrosis grade 2/3 (on a 0-3 scale) or grade 3/4 (on a 0-4 scale)	
ADDITIONAL CRITERIA (2 are required)	**ADDITIONAL CRITERIA (2 are required)**
1. Anemia[b] or sustained loss of requirement for either phlebotomy (in the absence of cytoreductive therapy) or for cytoreductive treatment for erythrocytosis	1. Anemia and a ≥ 2 mg/mL decrease from baseline hemoglobin level
	2. A leukoerythroblastic peripheral blood picture
2. A leukoerythroblastic peripheral blood picture	3. Increasing splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of newly palpable splenomegaly
3. Increasing splenomegaly of ≥ 5 cm (distance of the tip of the spleen from the left costal margin) or the appearance of a newly palpable splenomegaly	4. Increased lactate dehydrogenase (above reference level)
4. Development of ≥ 1 of 3 constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)	5. Development of ≥ 1 of 3 constitutional symptoms: > 10% weight loss in 6 months, night sweats, unexplained fever (> 37.5°C)

Barosi G, et al. *Leukemia*. 2008;22:437-438.

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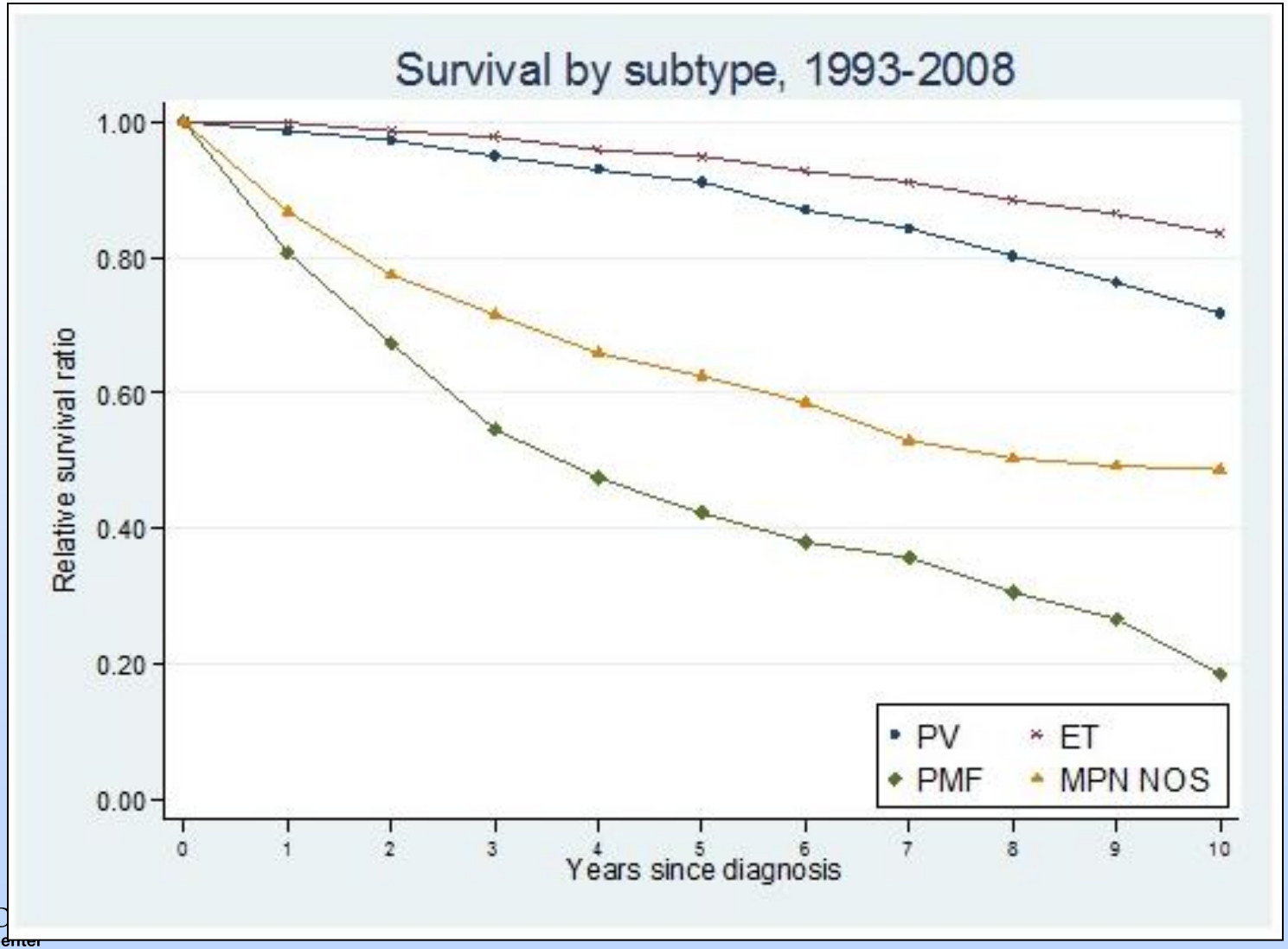
Patterns of Survival and Causes of Death In 9,384 Patients with Myeloproliferative Neoplasms Diagnosed In Sweden Between 1973 and 2008



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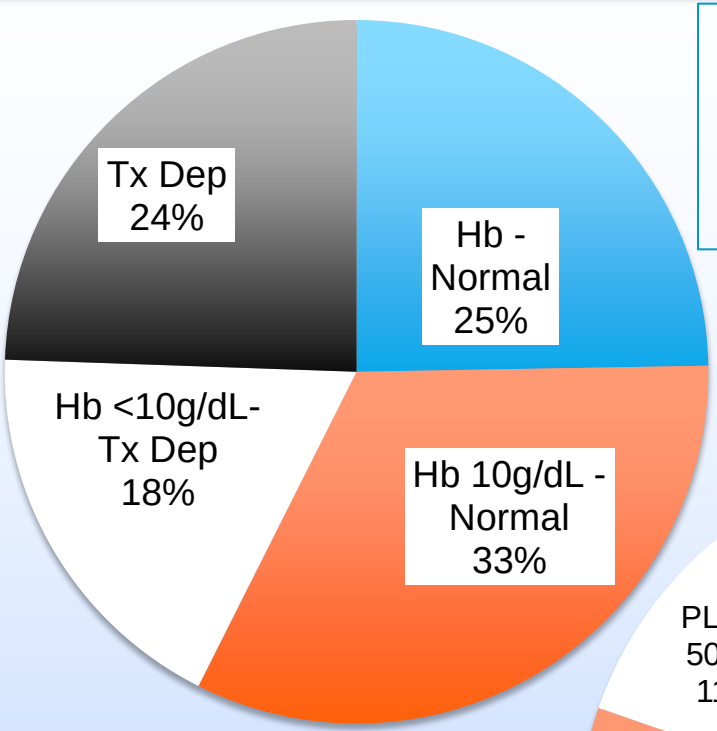
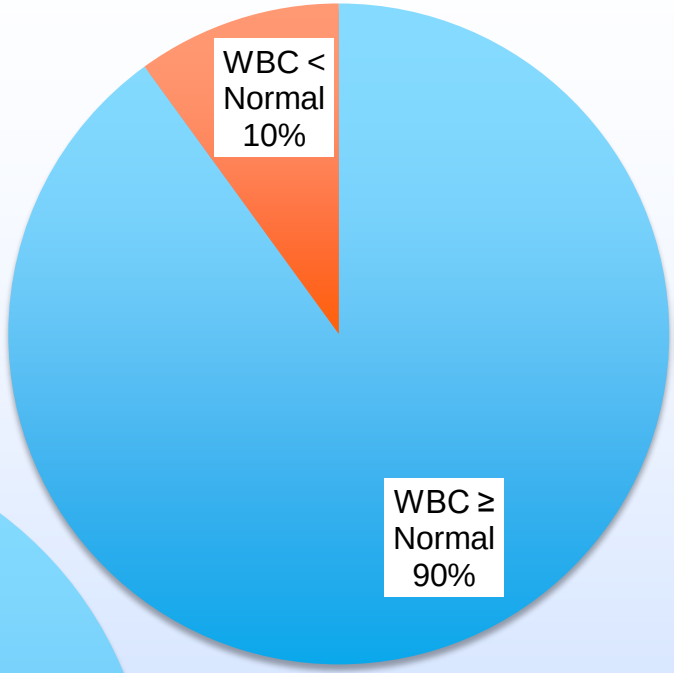
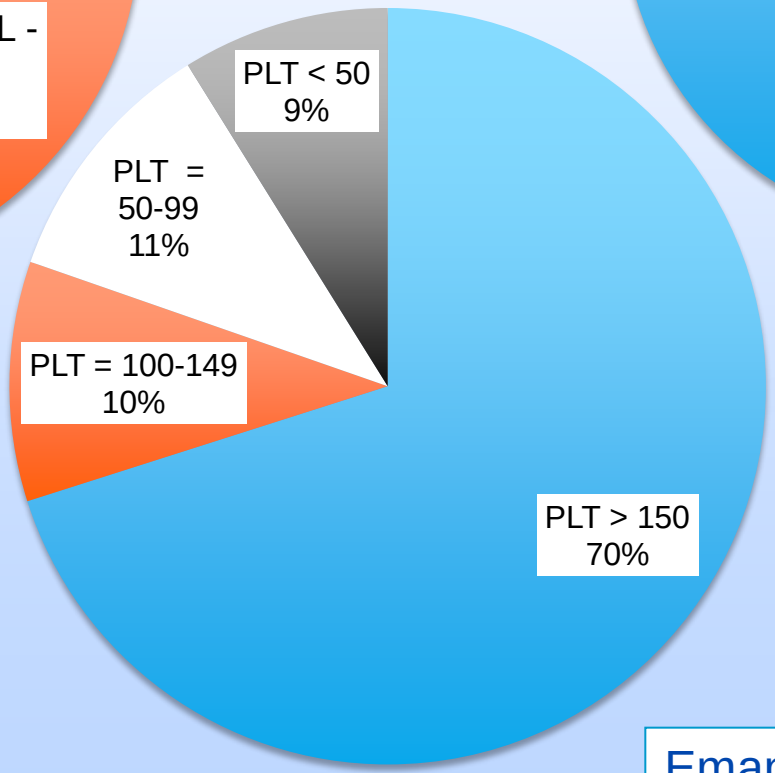
Hultcrantz et al Blood 2010 (a3071)

Myelofibrosis and Cytopenias (N=364)



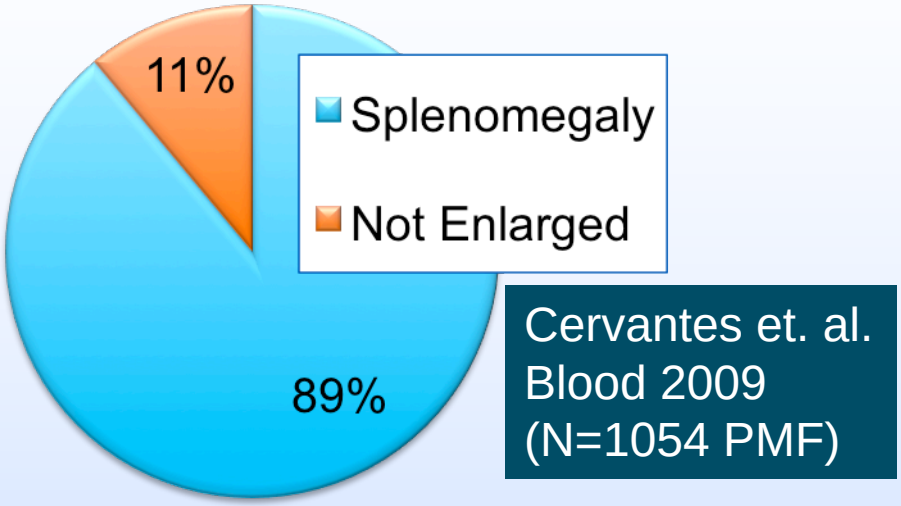
N.B.
- Varying times
- NL Hg
  - Men 13.5 g/dL
  - Women 12 g/dL



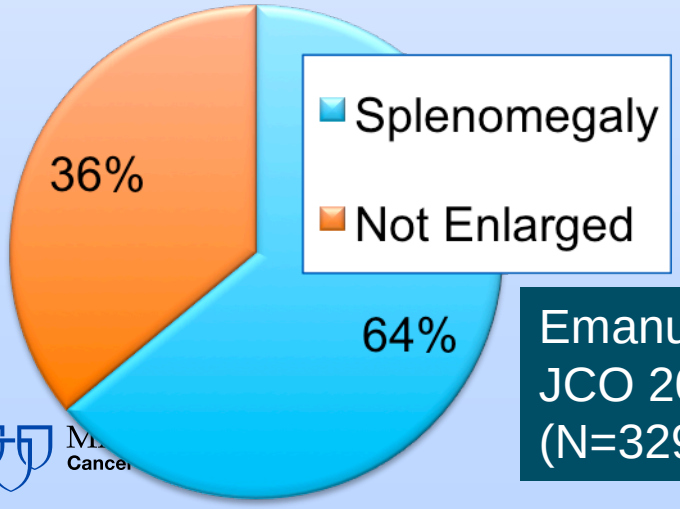


Emanuel et. al. JCO 2012

Myelofibrosis and Splenomegaly



Cervantes et. al.
Blood 2009
(N=1054 PMF)

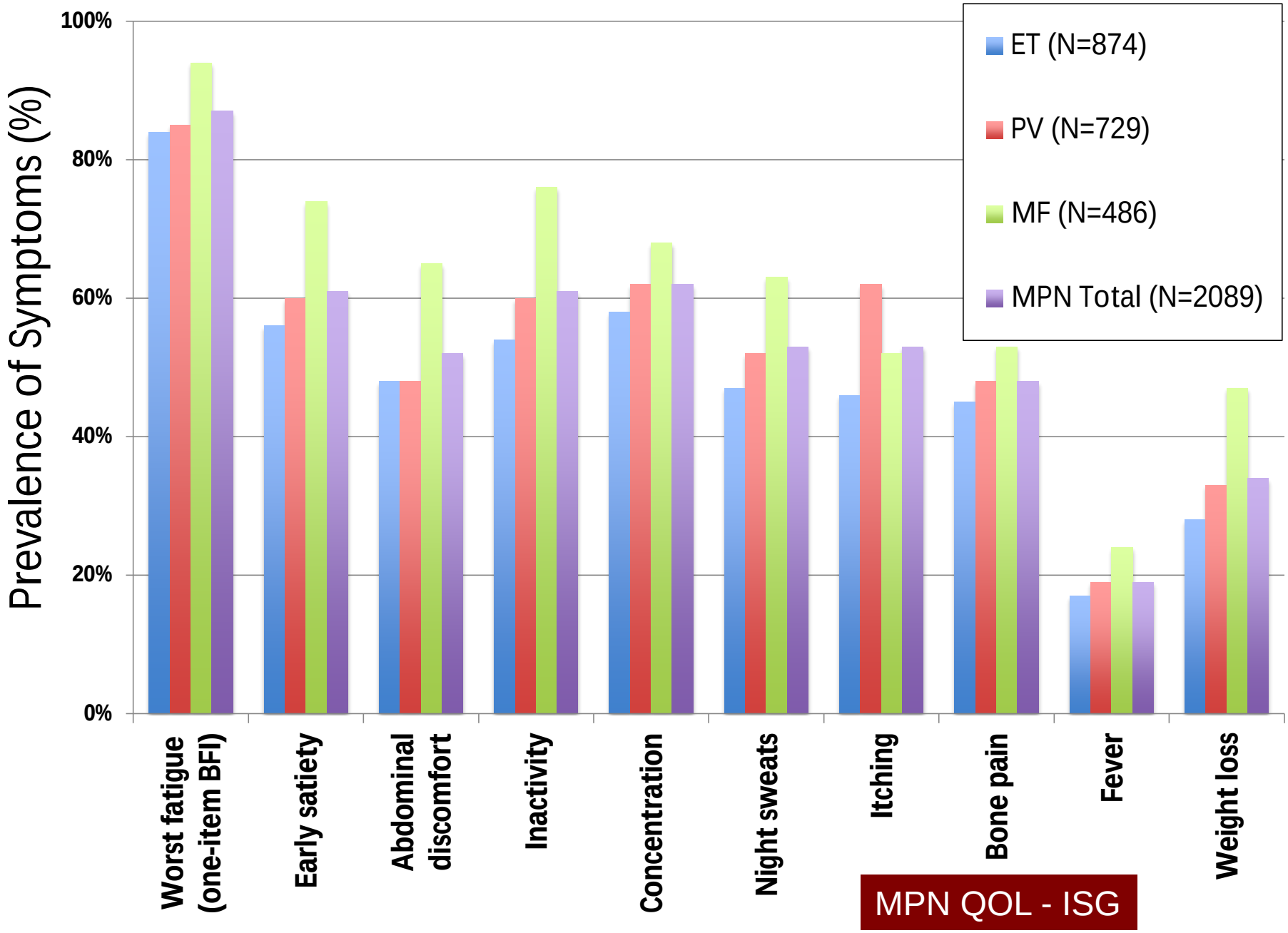


Emanuel et. al.
JCO 2012
(N=329 MF)

Why does Splenomegaly Matter in MF?

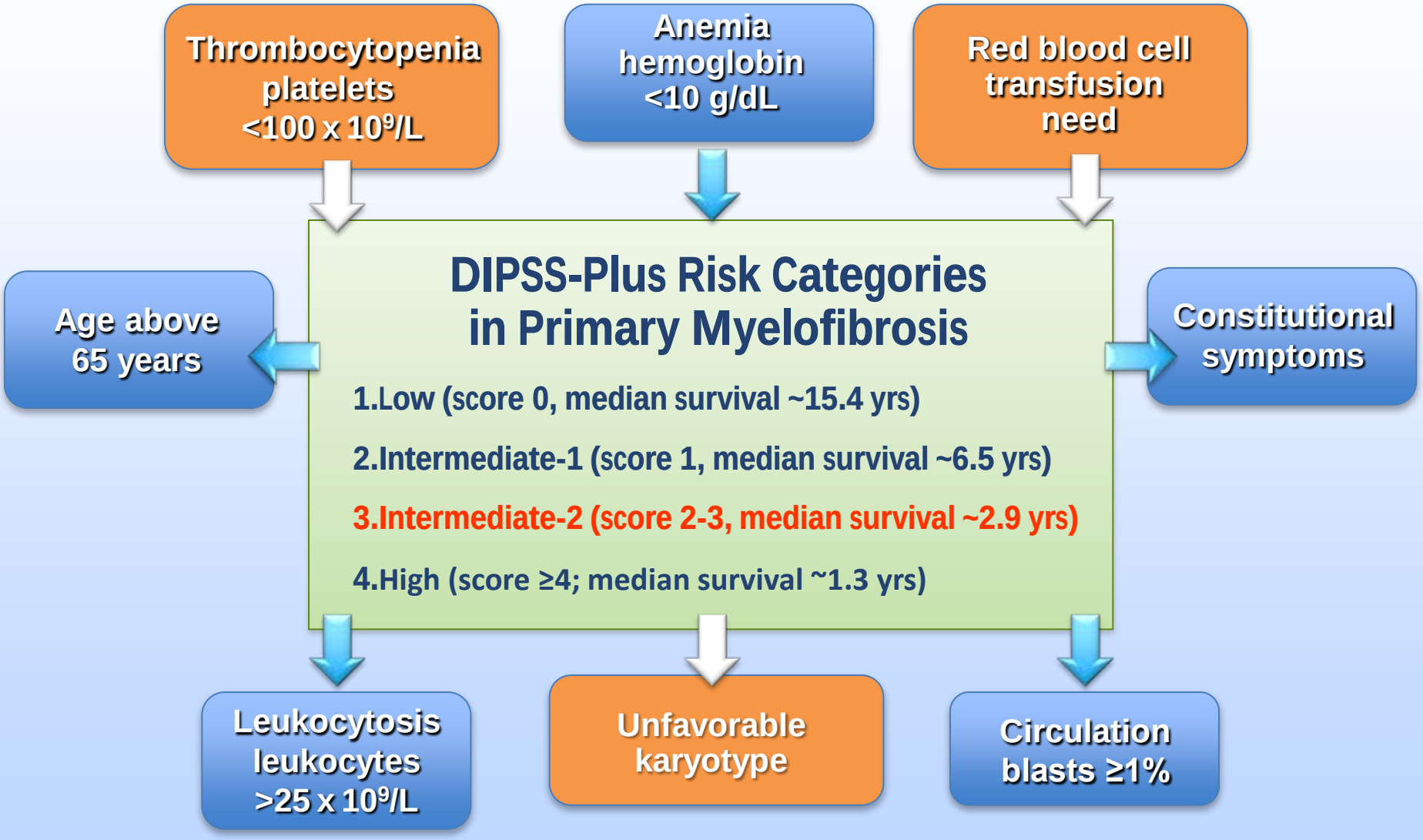
- Mechanical discomfort
- Pain
- Possible splenic infarction
- Early satiety adding to cachexia
- Splenic sequestration and exacerbation of cytopenias
- May delay engraftment in setting of allogeneic stem cell transplant

Symptoms from 2089 MPN Patients Using the MPN-SAF TSS (MPN10)



MPN QOL - ISG

DIPSS-PLUS



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Abbreviations: DIPSS-Plus, A Refined Dynamic International Prognostic Scoring System (DIPSS) for Primary Myelofibrosis.
Gangat N, et al. *J Clin Oncol*. 2011;29:392-397.

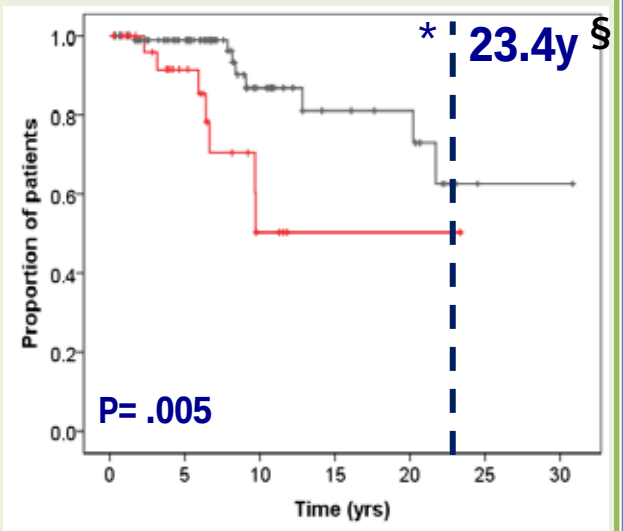
MIPSS: Molecular International Prognostic Score System

MULTIVARIATE ANALYSIS			Weighted value
Variables	HR (95% CI)	P	
Age >60yrs	3.8 (2.60-5.51)	<0.0001	1.5
Hb <100g/L	1.4 (1.01-1.99)	0.04	0.5
Constitutional Symptoms	1.5 .(1.13-2.16)	0.007	0.5
PLT <200x10^9/L	2.5 (1.77-3.42)	<0.0001	1.0
Triple Negativity	3.9 (2.20-6.80)	<0.0001	1.5
JAK2/MPL mutation	1.8 (1.11-2.90)	0.016	0.5
ASXL1 mutation	1.4 (1.06-1.99)	0.02	0.5
SRSF2 mutation	1.7 (1.08-2.58)	0.02	0.5

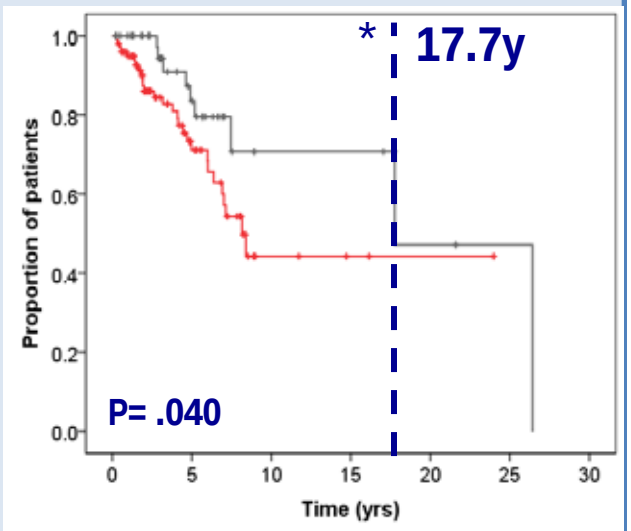
Vannucchi et. al. ASH 2014

MIPSS Permits to Refine Prognostic Stratification Within the IPSS Categories

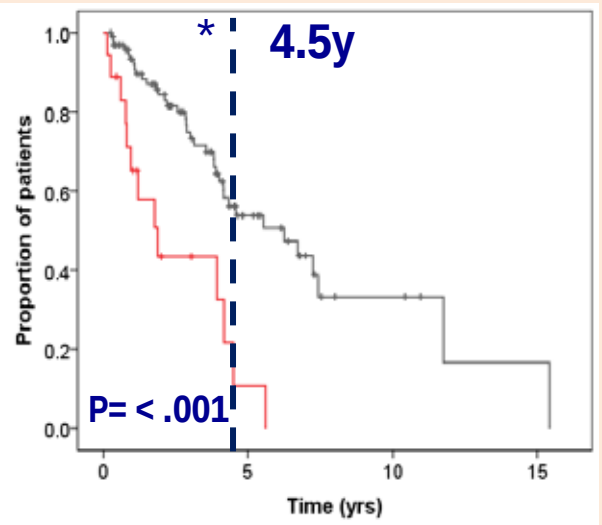
IPSS - LOW



IPSS - INT-1



IPSS - INT-2



Low 24.9y §	≤ Int-1 17.7y	≤ Int-2 6.2y
> Low 15.3y §	> Int-1 8.1y	> Int-2 1.9y

§Estimated

*, IPSS Median Survival – – – – –

MIPSS

Vannucchi et. al. ASH 2014

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Response Criteria for MPNs 2014 (All ≥ 12 Weeks)

ET/PV – ELN (Barosi et. al. *Blood 2013*) MF – IWG-MRT (Tefferi et. al. *Blood 2013*)

	Complete Remission	Partial Remission	Clinical Improvement	Other
ET	• Resolve ET Signs • ≥ 10 pt. MPN10 ê • Near normal counts • No Prog. or Vascular • BM rem & ≤Gr 1 MF	• Resolve ET Signs • ≥ 10 pt. MPN10 ê • Near normal counts • No Prog. or Vascular		Peripheral Blood Granulocytes • CR – Eradicated mutation • PR - ≥50% ê, *≥ 20% baseline*
PV	• Resolve PV Signs • ≥ 10 pt. MPN10 ê • Near normal counts • No Prog. or Vascular • BM rem & ≤Gr 1 MF	• Resolve PV Signs • ≥ 10 pt. MPN10 ê • Near normal counts • No Prog. or Vascular		Peripheral Blood Granulocytes • CR – Eradicated mutation • PR - ≥50% ê, *≥ 20% baseline*

MF	• Resolve MF Signs
	• Resolve MF sympts
	• Near normal counts
	• BM rem & ≤Gr 1 MF
		Like MF CR but
		• Hb (between 85 and 100 g/L)
		• PLT (between 50-100 x 10(9)/L)
			• Anemia (2g/dl or T.I.)
			• Spleen (Based on BL)
			• Symptoms (≥ 50% ê)
				• Molecular (ET/PV Criteria)
				• Cytogenetic
				  • CR – Normal
				  • PR - ≥ 50% ê

N.B. ET/PV – Progression is MF/MDS/ or AML
MF – Progression based on spleen growth or AML

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Management of MPNs – JAK Inhibitors

- Diagnosis of MPNs
- Burden and Risk of Disease
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Medications for MF Pre-JAK2 Inhibition

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*

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IMiDs in MF: Summary of Clinical Data

	Hb	PLT	SPLN	REFERENCE
THAL	29%	38%	41%	Barosi 2002
THAL-PRED	62%	75%	19%	Mesa 2002
LEN	22%	50%	33%	Tefferi 2006
LEN-PRED	19%	?	9%	Mesa 2010
LEN-PRED	30%	?	42%	Quintas-Cardama 2009
POM (0.5mg/day)	>50%	?	<25%	Mesa 2010
POM+/-PRED	30–40%	40%	<10%	Tefferi 2008

Stem Cell Transplant Use in Myelofibrosis

Baseline Assumptions/ Caveats

- **SCT *almost* exclusively for MF/ MPN-BP**
- **In MF evolving risk/benefit analysis for use**

Question 2

Pre Transplant Therapy?

- JAK Inhibition?
- Cytoreduction?
- Iron chelation?

"Problematic" MF & SCT Eligible

Allo SCT

Question 1

Timing?

- Urgent
- Delayed
- Never

Question 3

Post Transplant Therapy?

- JAK Inhibition?
- Interferon?
- other?

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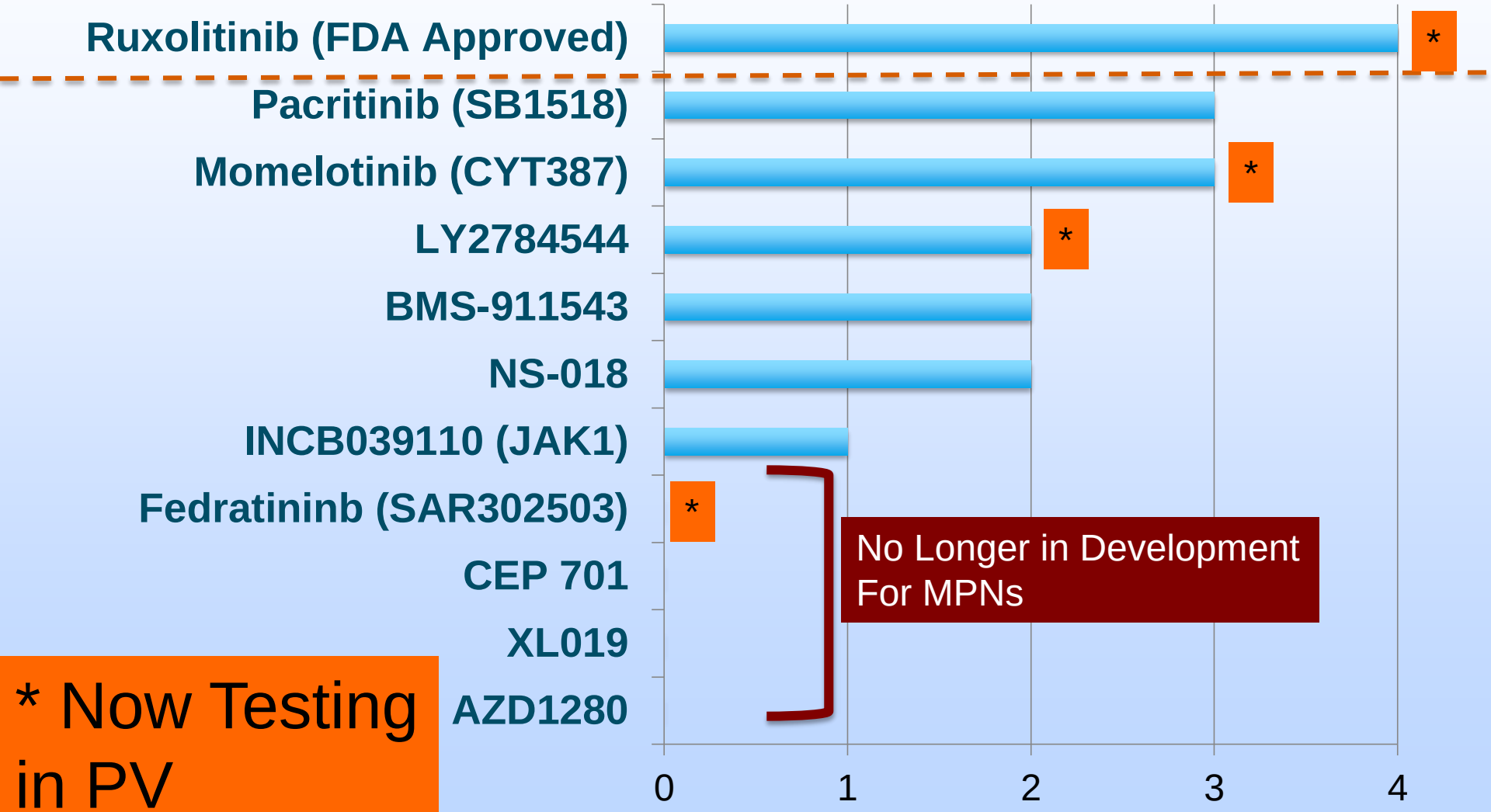
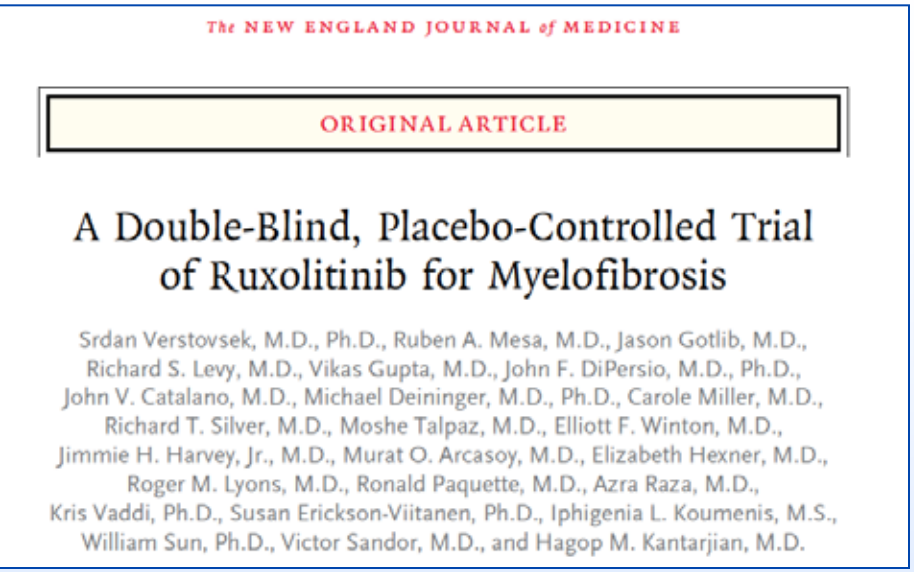
JAK Inhibitors and Status of Development
Myelofibrosis as lead indications



* Now Testing in PV

Ruxolitinib Phase III Trials (COMFORT I & II)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis

Srdan Verstovsek, M.D., Ph.D., Ruben A. Mesa, M.D., Jason Gotlib, M.D., Richard S. Levy, M.D., Vikas Gupta, M.D., John F. DiPersio, M.D., Ph.D., John V. Catalano, M.D., Michael Deininger, M.D., Ph.D., Carole Miller, M.D., Richard T. Silver, M.D., Moshe Talpaz, M.D., Elliott F. Winton, M.D., Jimmie H. Harvey, Jr., M.D., Murat O. Arcasoy, M.D., Elizabeth Hexner, M.D., Roger M. Lyons, M.D., Ronald Paquette, M.D., Azra Raza, M.D., Kris Vaddi, Ph.D., Susan Erickson-Viitanen, Ph.D., Iphigenia L. Koumenis, M.S., William Sun, Ph.D., Victor Sandor, M.D., and Hagop M. Kantarjian, M.D.

March 1, 2012

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 1, 2012 VOL. 366 NO. 9

JAK Inhibition with Ruxolitinib versus Best Available Therapy for Myelofibrosis

Claire Harrison, D.M., Jean-Jacques Kiladjian, M.D., Ph.D., Haifa Kathrin Al-Ali, M.D., Heinz Gisslinger, M.D., Roger Waltzman, M.D., M.B.A., Viktoriya Stalbovskaya, Ph.D., Mari McQuitty, R.N., M.P.H., Deborah S. Hunter, Ph.D., Richard Levy, M.D., Laurent Knoops, M.D., Ph.D., Francisco Cervantes, M.D., Ph.D., Alessandro M. Vannucchi, M.D., Tiziano Barbui, M.D., and Giovanni Barosi, M.D.

Patients with MF (N = 309) → Randomized 1:1 → **INC424 (oral) 15 mg BID or 20 mg BID**; **Placebo (oral) BID**

Patients with MF (N = 219) → Randomized 2:1 → **INC424 (oral) 15 mg BID or 20 mg BID**; **Best available therapy**

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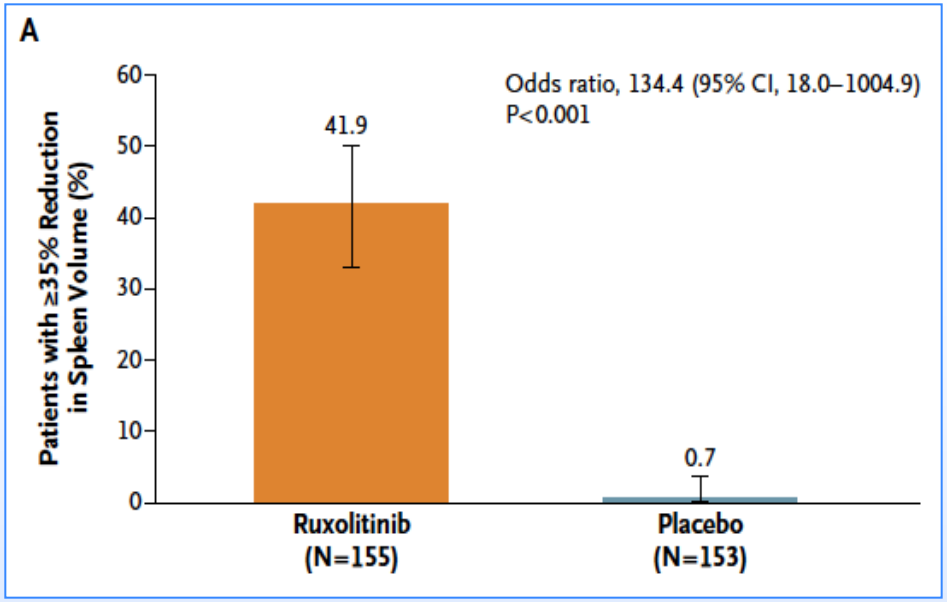
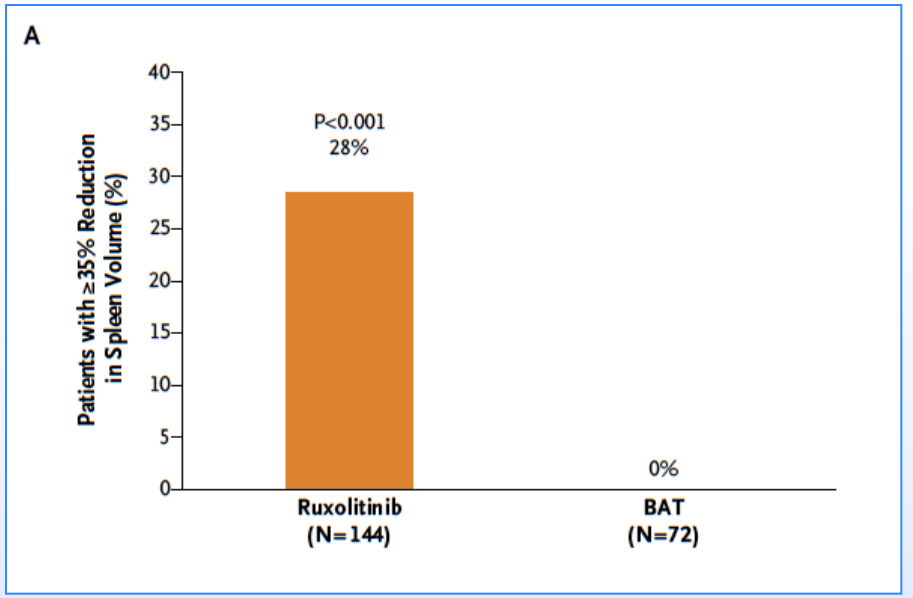
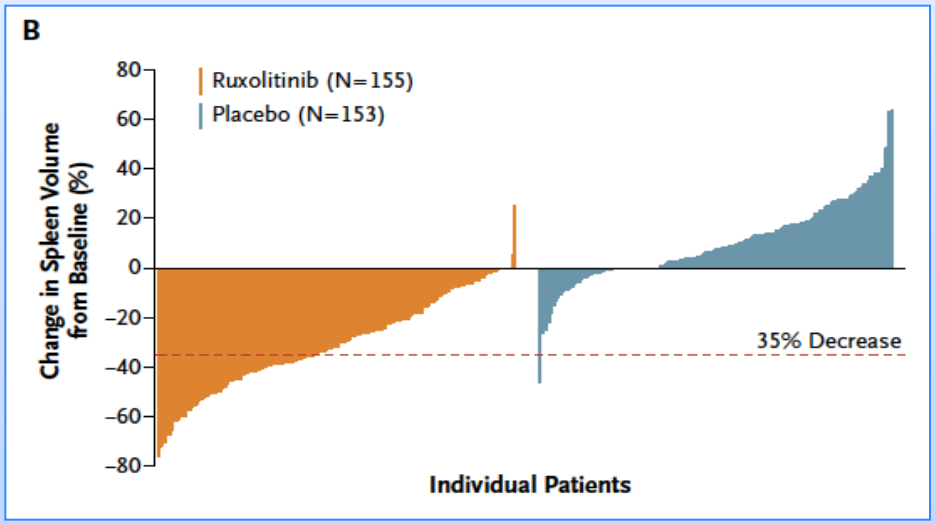
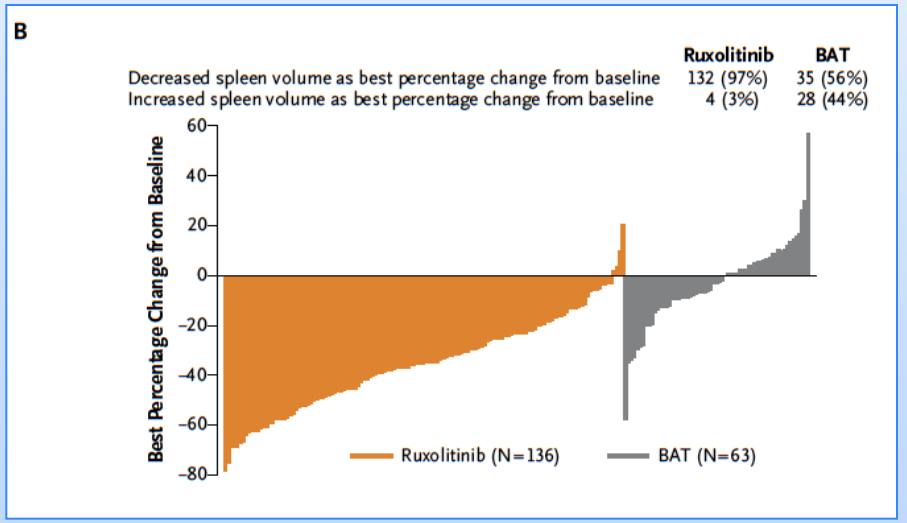
Verstovsek, Mesa, Gotlib et. al. NEJM 2012;366(9):799-807
Harrison, Kiladjian, Kathrin et.al. NEJM 2012;366(9):787-798

Ruxolitinib Phase III Trials (COMFORT I & II – *Spleen Response*)









COMFORT 1

COMFORT 2

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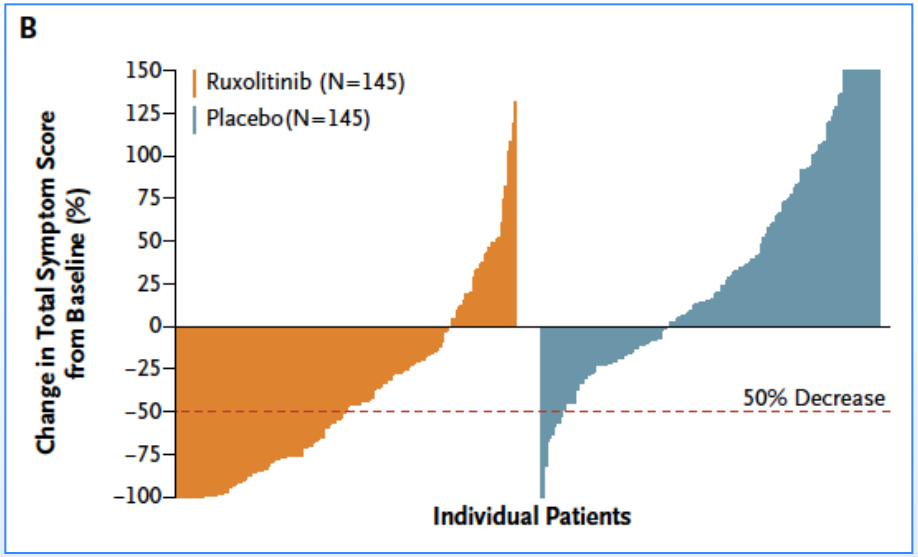
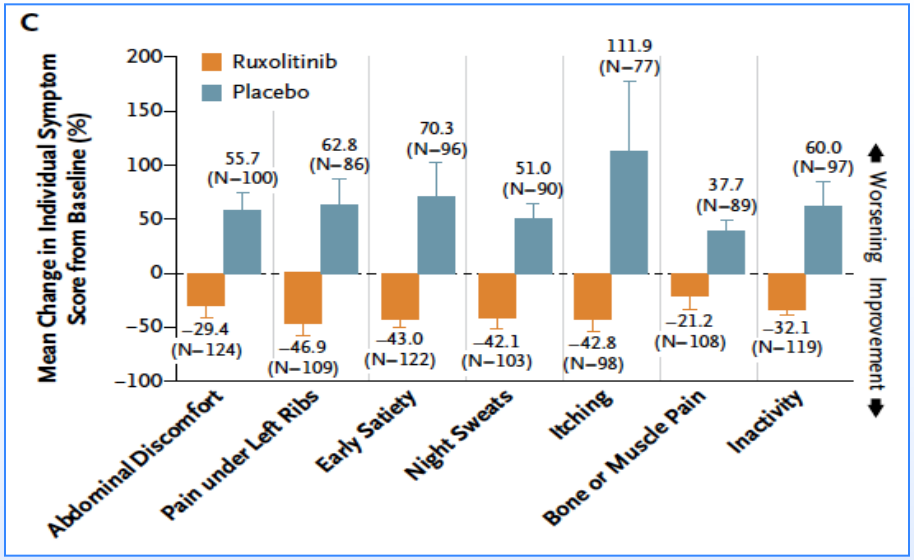
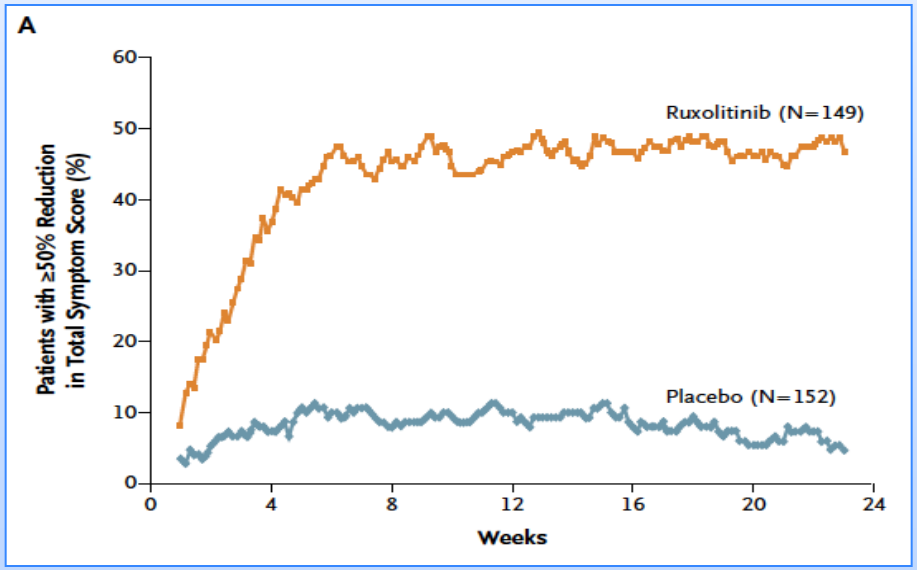
Verstovsek, Mesa, Gotlib et. al. NEJM 2012;366(9):799-807
Harrison, Kiladjian, Kathrin et.al. NEJM 2012;366(9):787-798

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







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Verstovsek, Mesa, Gotlib et. al. NEJM 2012;366(9):799-807

Ruxolitinib Phase III Trials (COMFORT I – *Survival Data*)

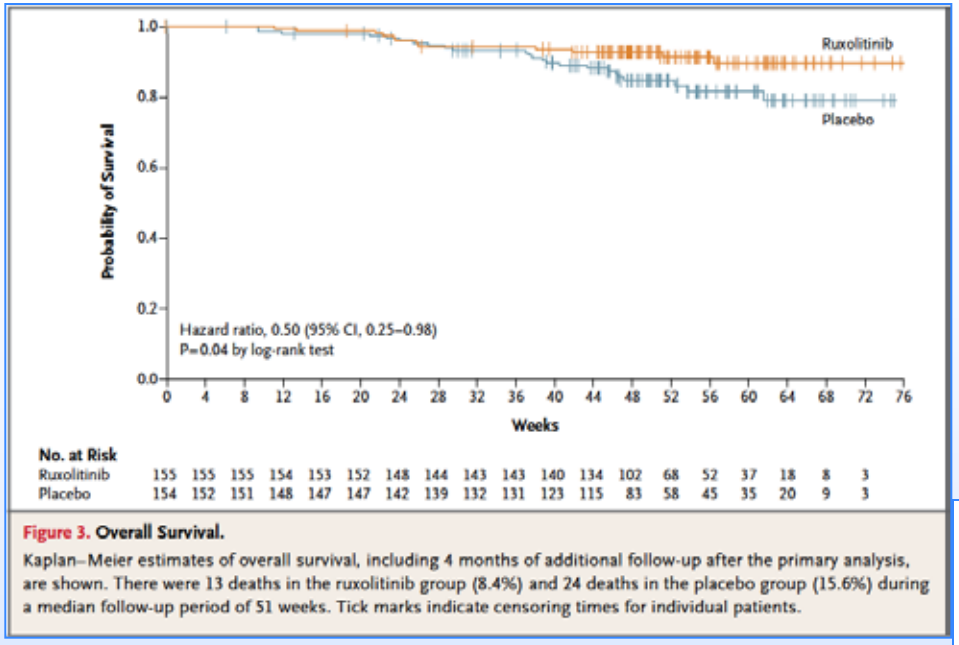
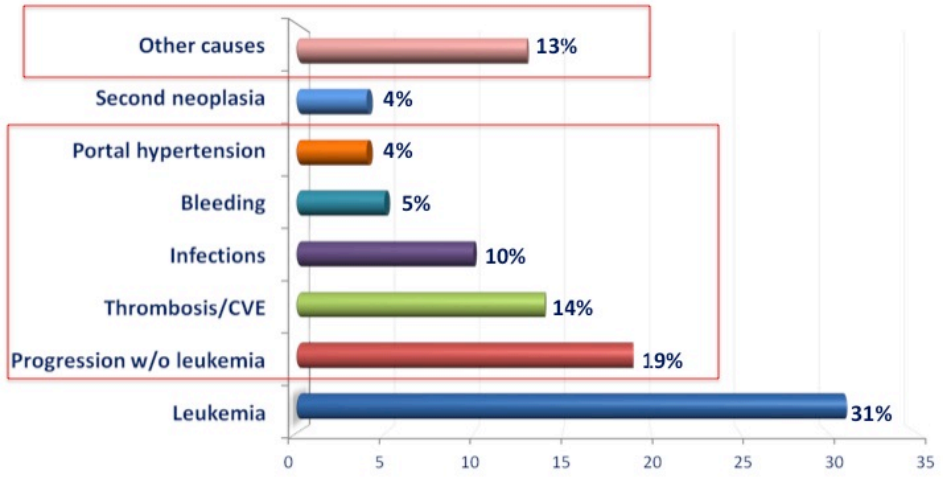


Figure 3. Overall Survival.

Kaplan–Meier estimates of overall survival, including 4 months of additional follow-up after the primary analysis, are shown. There were 13 deaths in the ruxolitinib group (8.4%) and 24 deaths in the placebo group (15.6%) during a median follow-up period of 51 weeks. Tick marks indicate censoring times for individual patients.

Causes of Death in PMF



Cervantes F *et al.*, Blood 2009;113:2895-901

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Verstovsek, Mesa, Gotlib et. al. NEJM 2012;366(9):799-807

Patient Disposition – 3 Year FU Comfort I

	Ruxolitinib (n = 155)	Placebo	
		Placebo (n = 151)	Placebo à Ruxolitinib (n=111)
Median exposure, weeks	145	37	105
Still on treatment, n (%)	77 (49.7)	0	57 (51.4)
Crossed over, n (%)		111 (73.5)	
Discontinued, n (%)	78 (50.3)	40 (26.5)	54 (48.6)
Primary reasons for discontinuation, n (%)*			
Death	15 (19.2)	7 (17.5)	11 (20.4)
Adverse event	15 (19.2)	9 (22.5)	8 (14.8)
Consent withdrawn	12 (15.4)	7 (17.5)	11 (20.4)
Disease progression	18 (23.1)	13 (32.5)	15 (27.8)

- All patients originally randomized to placebo crossed over or discontinued within 3 months of the primary analysis
- Median time to crossover: 41.1 weeks

ASH 2013

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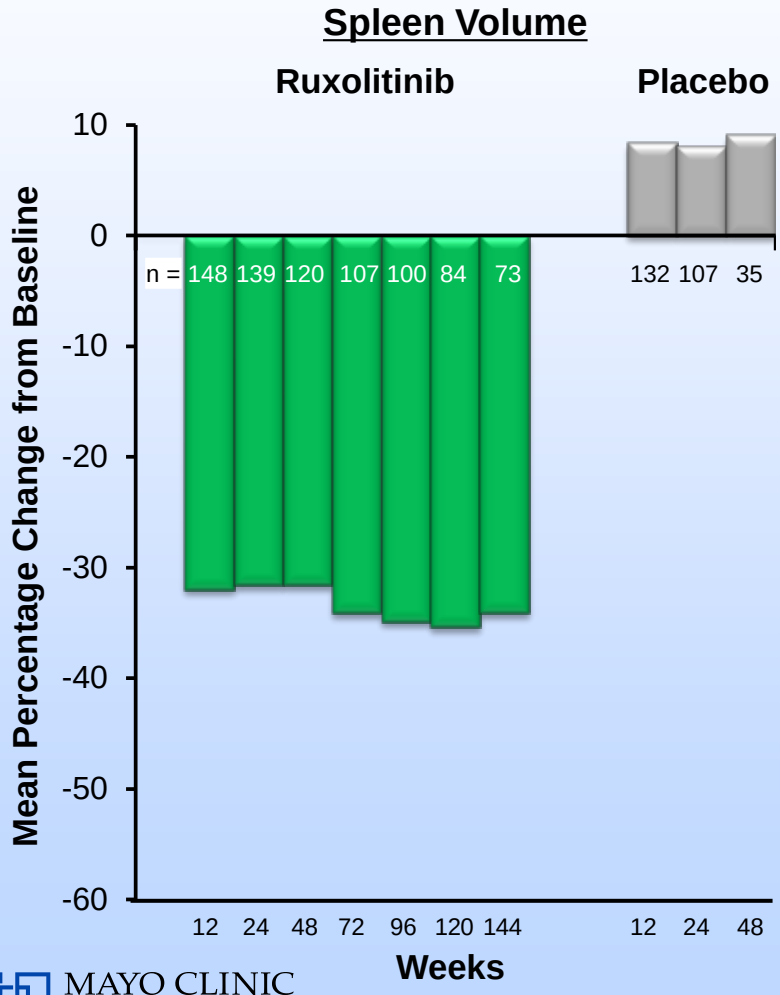
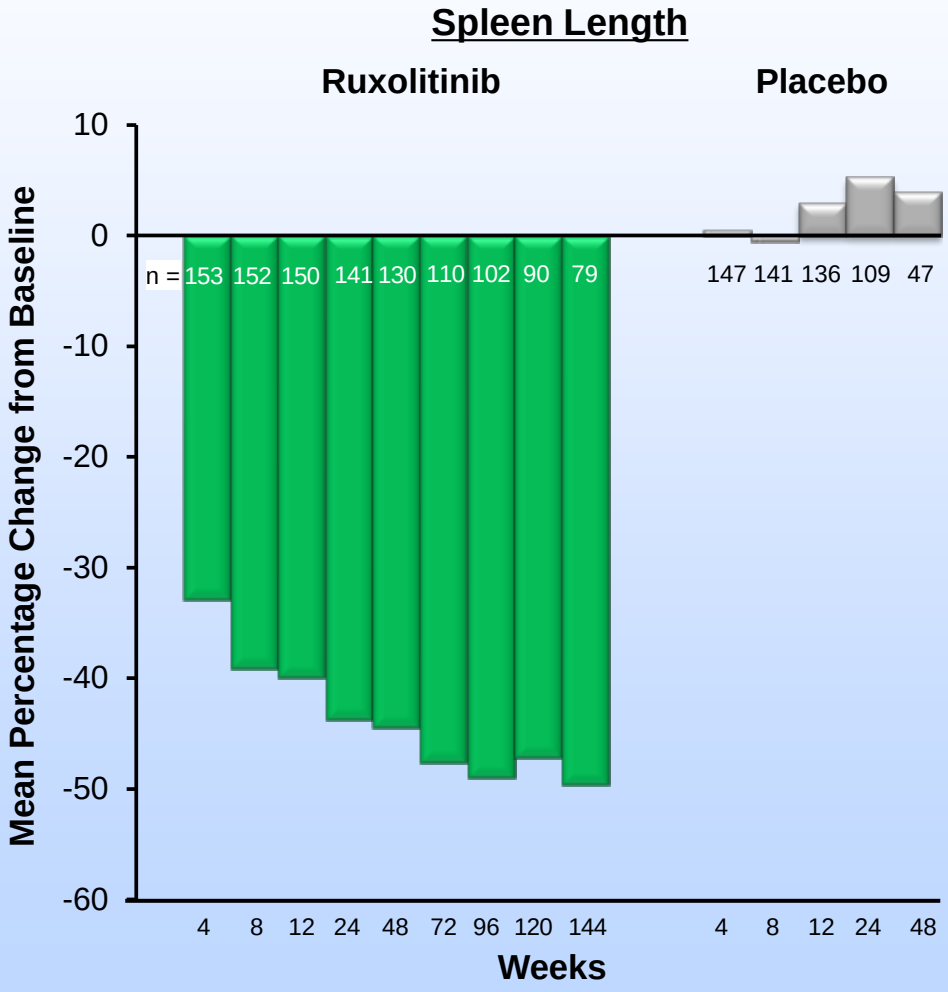
Percentage Change in Spleen Size

- Mean reductions in spleen volume and palpable spleen length with ruxolitinib were stable over time





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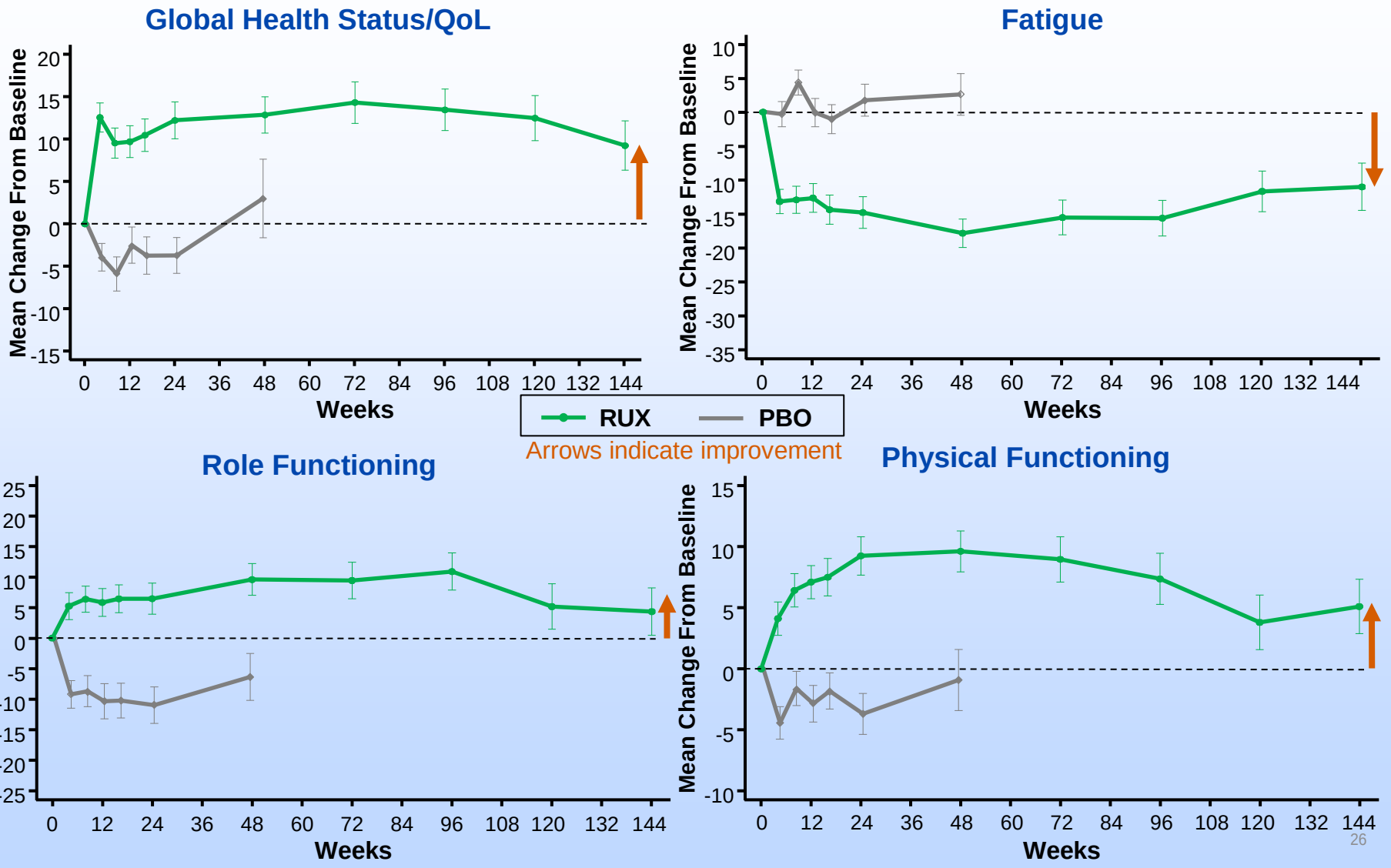
Improvements in EORTC QLQ-C30 Over Time



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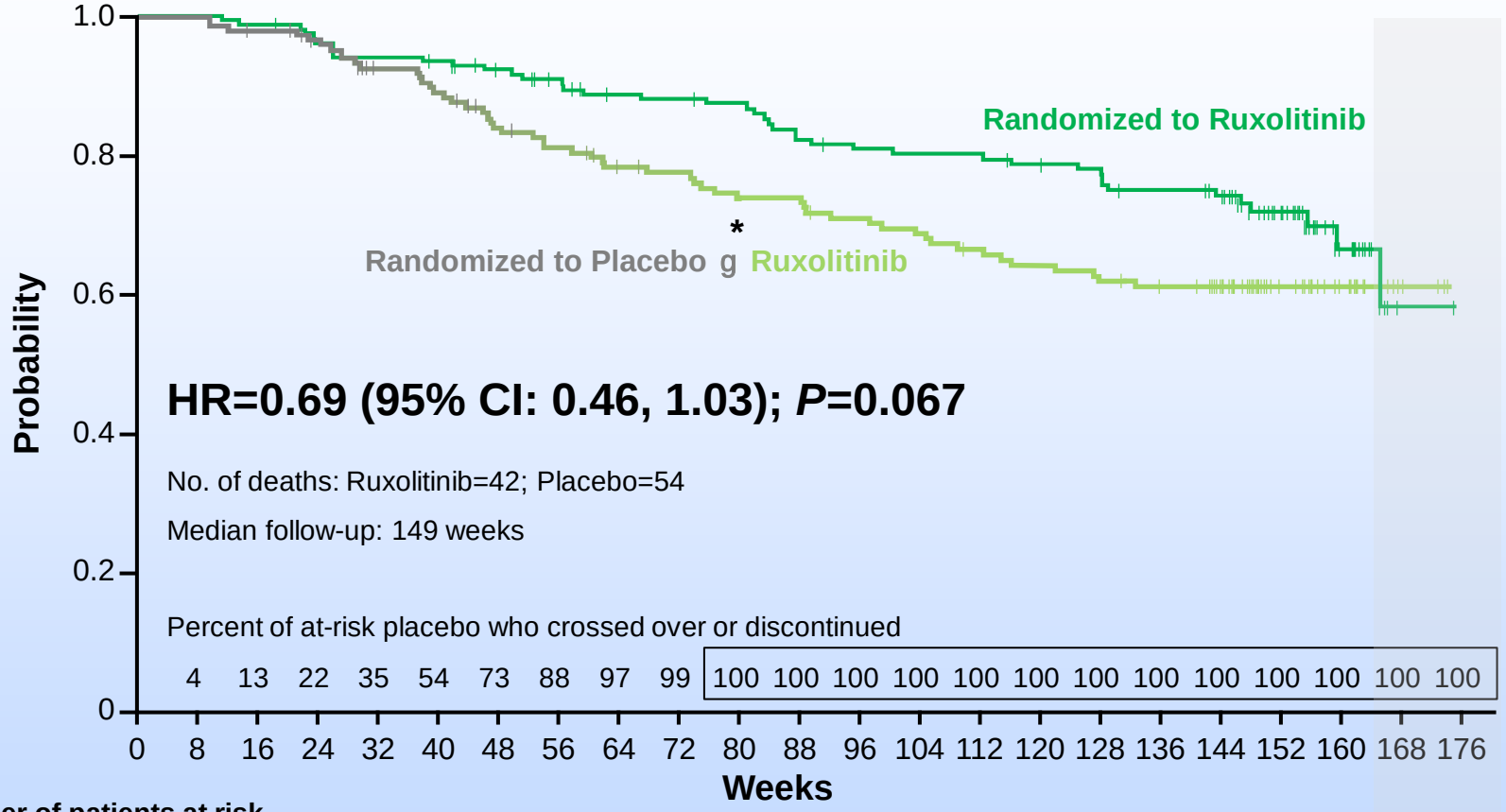
Overall Survival

ASH 2013

- Overall survival favored patients originally randomized to ruxolitinib compared with patients originally randomized to placebo



Number of patients at risk

Ruxolitinib	155	155	153	148	145	143	137	131	125	124	122	115	112	111	111	108	106	101	84	45	19	1	0
Placebo	154	153	149	144	134	129	119	114	107	105	100	100	95	92	88	85	82	79	68	38	28	8	0

*By week 80, all patients originally randomized to placebo discontinued or crossed over to ruxolitinib therapy

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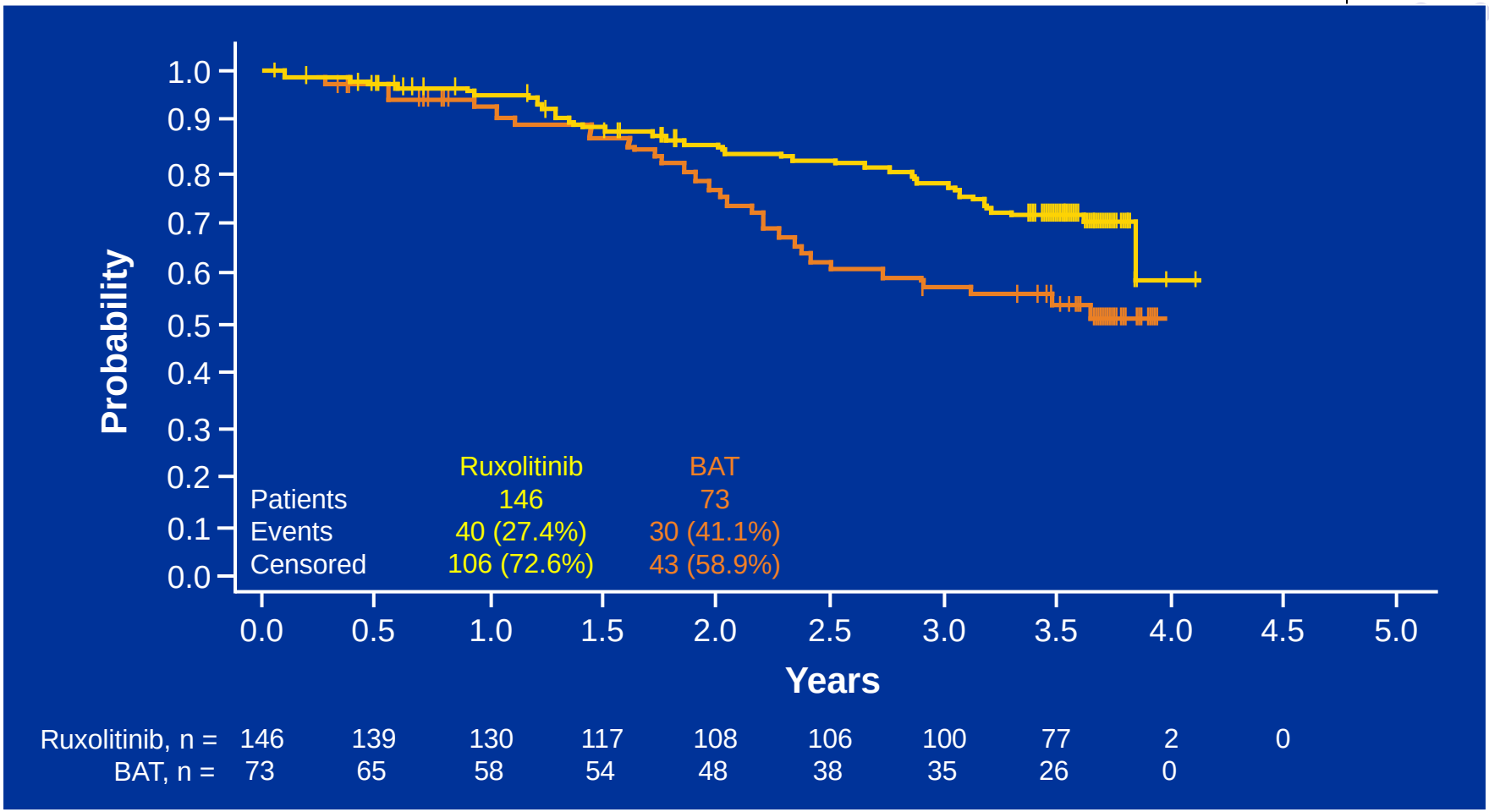
COMFORT-II Overall Survival after 3.5 years (EHA 2014)



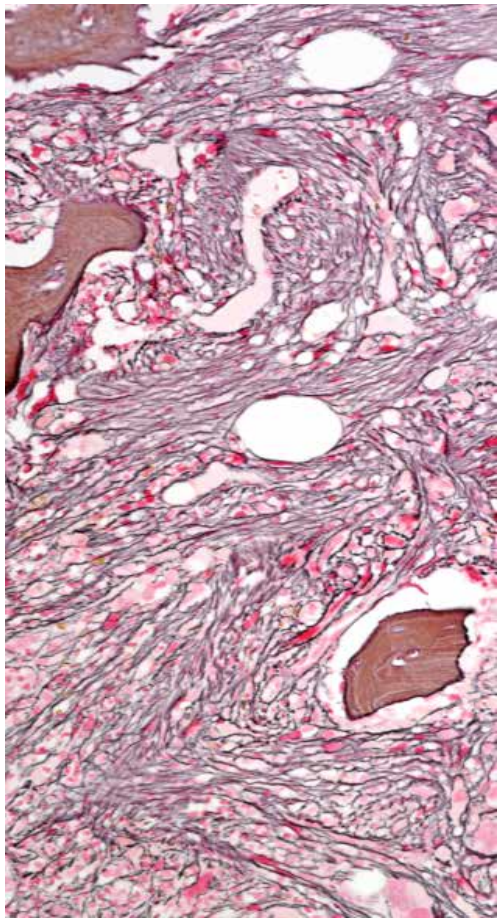
HR = 0.58; 95% CI, 0.36-0.93; log-rank test *P* = .022.
P value for log rank test is provided for descriptive purposes and was not adjusted for multiple comparisons.

Harrison C, et al. *Haematologica.* 2014;99(suppl1): P403.

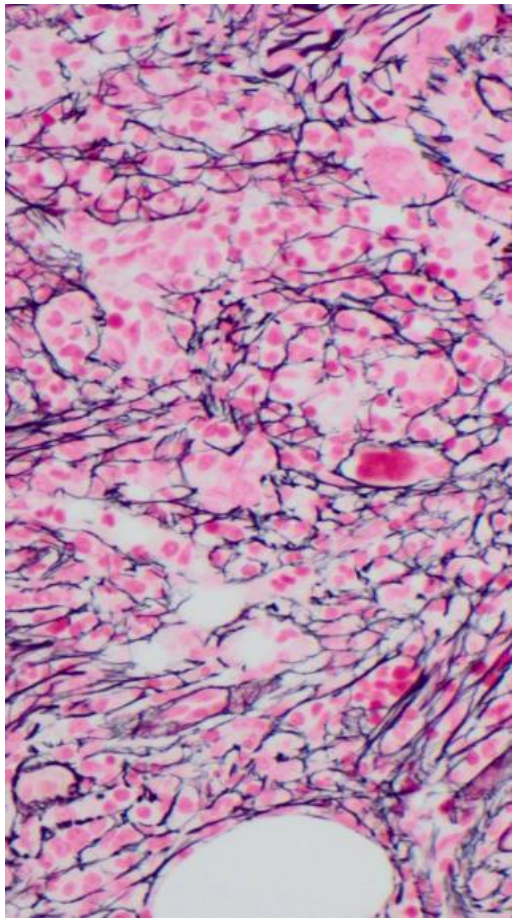
BM Morphology in a Ruxolitinib-Treated Patient: A Case Demonstrating Improvement on Ruxolitinib

ASH 2013

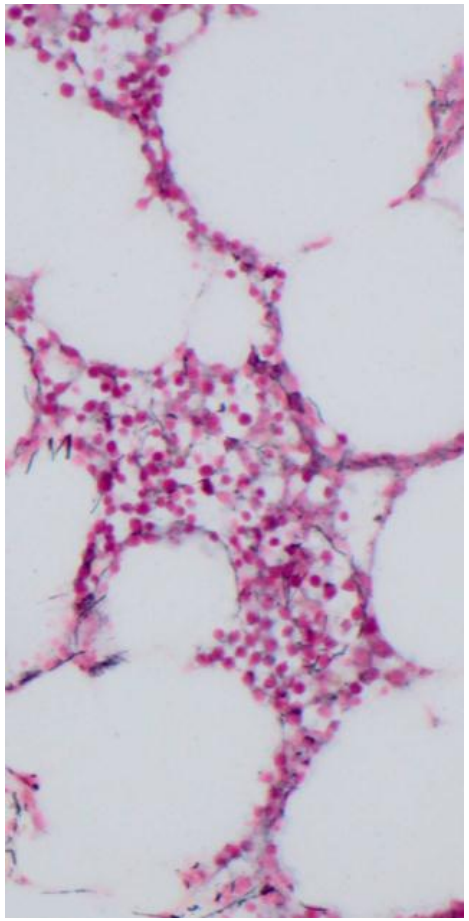
Baseline Biopsy
Grade 3



24 Mo
Post Ruxolitinib
Grade 2



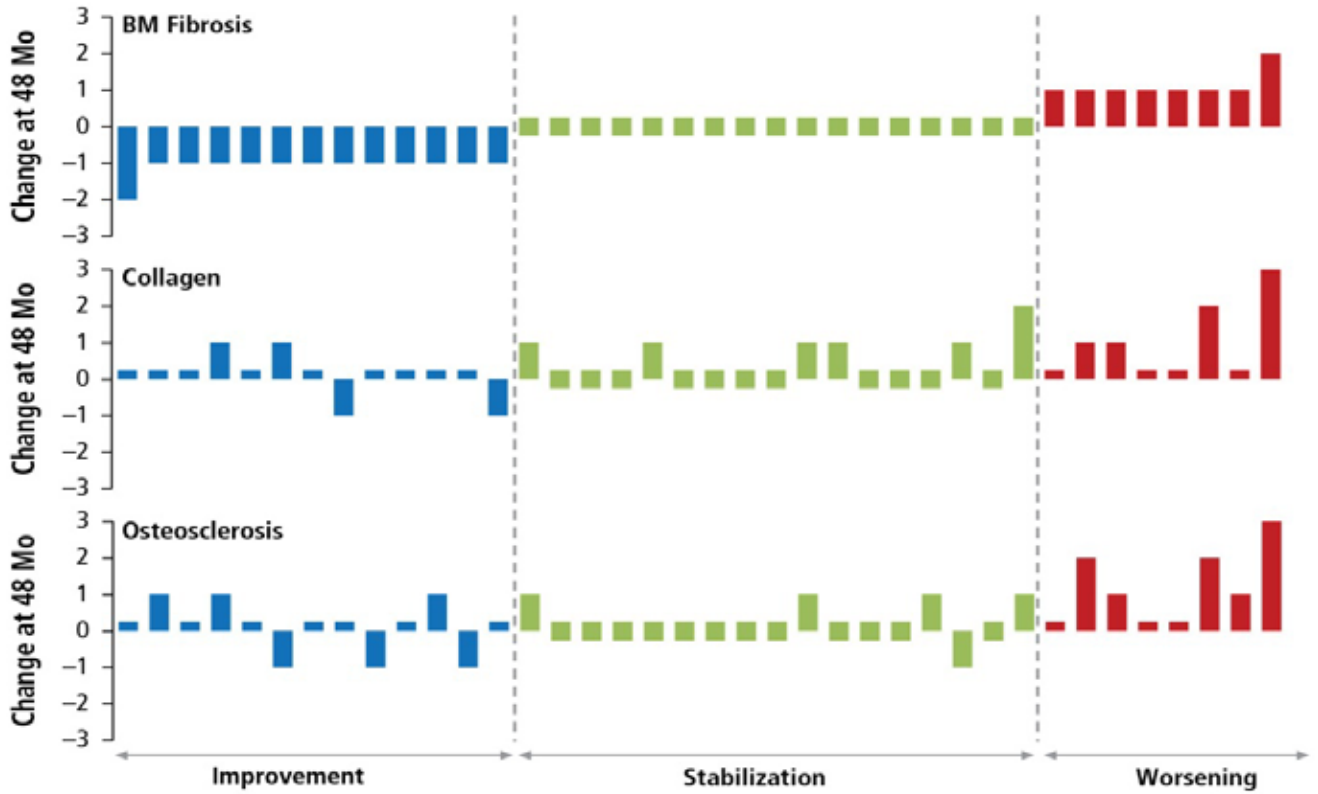
48 Mo
Post Ruxolitinib
Grade 0



Kvasnicka HM, et al. ASCO. 2013 (abstr 7030).

Permission to use images from Kvasnicka, HM

Dynamics of BM Changes Following Ruxolitinib Treatment at 48 Mo



ASH 2013

Kvasnicka, et al. ASH 2013. Abstract 4055.

Management of MPNs – JAK Inhibitors

- Diagnosis of MPNs
- Burden and Risk of Disease
- Establishing goals of care
- Therapy of MPNs
  - Anti-coagulation
  - Cytoreduction
  - JAK inhibition
  - Stem Cell Transplant
- Case Examples

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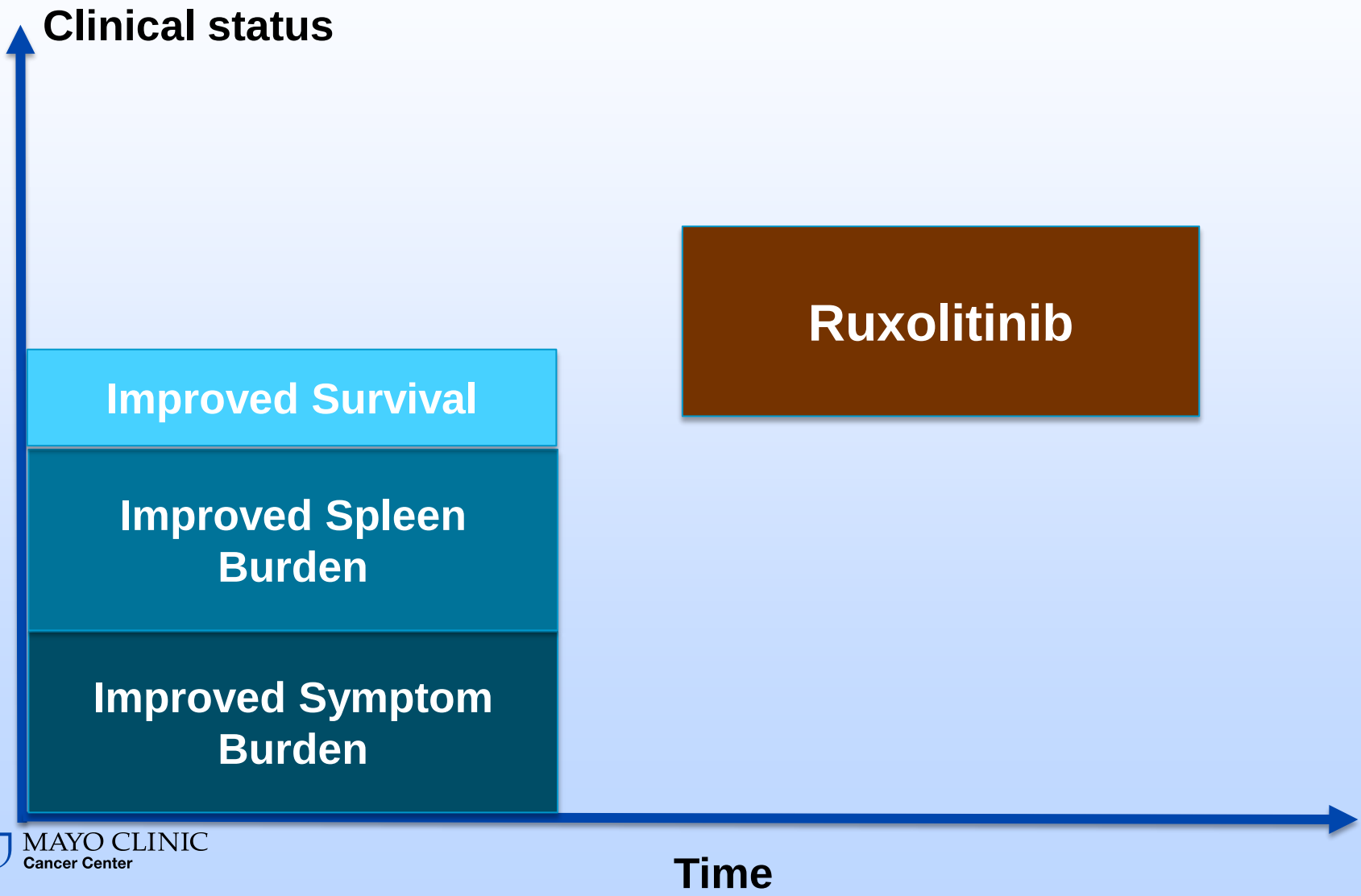
MPNs – Cumulative Benefits

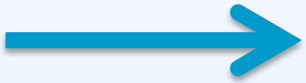


Case 1 – Intermediate 1 Myelofibrosis

- 63 year old gentleman had PV for 12 years. Progressive fatigue, cachexia, loss of need for phlebotomy.
  - MPN 10 (40 out of 100)
  - Spleen 10cm BLCM
  - Hb 11.8 g/dL
  - WBC = 18 x 10(9)/L
  - Platelets 240 x 10(9)/L
  - Peripheral Smear = 2% Myelocytes
- Bone Marrow
  - 3+ reticulin fibrosis. Karyotype 20q-
- Diagnosis of Post PV Myelofibrosis

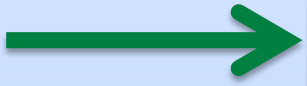
Case 1 – Intermediate 1 Myelofibrosis

DIPSS Risks	Present
Age >65 years	
Symptoms	X
Hemoglobin <10g/dL	
Leukocytes >25 x 10(9)/L	
Blasts >1% in Blood	



Intermediate 1 Risk Myelofibrosis

MF Patient Burden	Present
Symptoms (MPN 10 – Score 40)	X
Splenomegaly	X
Anemia	
Movement towards AML	



Begins Ruxolitinib 20 mg – Twice Daily

Monitor:

- Blood Counts
- Spleen Size
- MPN 10

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Case 1 – Intermediate 1 Myelofibrosis (Follow-Up)

- 4 Months later
  - (IWG-MRT Response Spleen and Symptoms)

  - Spleen originally10cm BLCM – NOW 2cm BLCM
  - Hb original 11.8 g/dL – NOW 10.4 g/dL
  - WBC original 18 x 10(9)/L – NOW 13.4 x 10(9)/L
  - Platelets Original 240 x 10(9)/L – Now 135 x 10(9)/L

  - MPN 10 – Original 40 (out of 100) – Now 14

Case 2 – Intermediate 2 Myelofibrosis

- 72 year old gentleman found to have primary myelofibrosis on workup of fatigue.
  - MPN 10 (56 out of 100)
  - Spleen (not palpable)
  - Hb 10.2 g/dL
  - WBC = 14 x 10(9)/L
  - Platelets 180 x 10(9)/L
  - Peripheral Smear = 2% Metamyelocytes
- Bone Marrow
  - 2+ Reticulin fibrosis. Karyotype +8
- Diagnosis of Primary Myelofibrosis

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Case 2 – Intermediate 2 Myelofibrosis

DIPSS Risks	Present
Age >65 years	X
Symptoms	X
Hemoglobin <10g/dL	
Leukocytes >25 x 10(9)/L	
Blasts >1% in Blood	

Intermediate 2 Risk Myelofibrosis

MF Patient Burden	Present
Symptoms (MPN 10 – Score 56)	X
Splenomegaly	
Anemia	
Movement towards AML	

Begins Ruxolitinib 15 mg – Twice Daily

Monitor:

- Blood Counts
- *Spleen Size*
- MPN 10

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Case 2 – Intermediate 2 Myelofibrosis (Follow-Up)

2 Months later

- (IWG-MRT Symptoms)
- Spleen remains not palpable
- Hb original 10.2 g/dL – NOW 8.2 g/dL (+Transfusion)
- WBC original 14 x 10(9)/L – NOW 10 x 10(9)/L
- Platelets Original 240 x 10(9)/L – Now 110 x 10(9)/L
- MPN 10 – Original 56 (out of 100) – Now 20

Ruxolitinib dose decreased to 10mg twice daily

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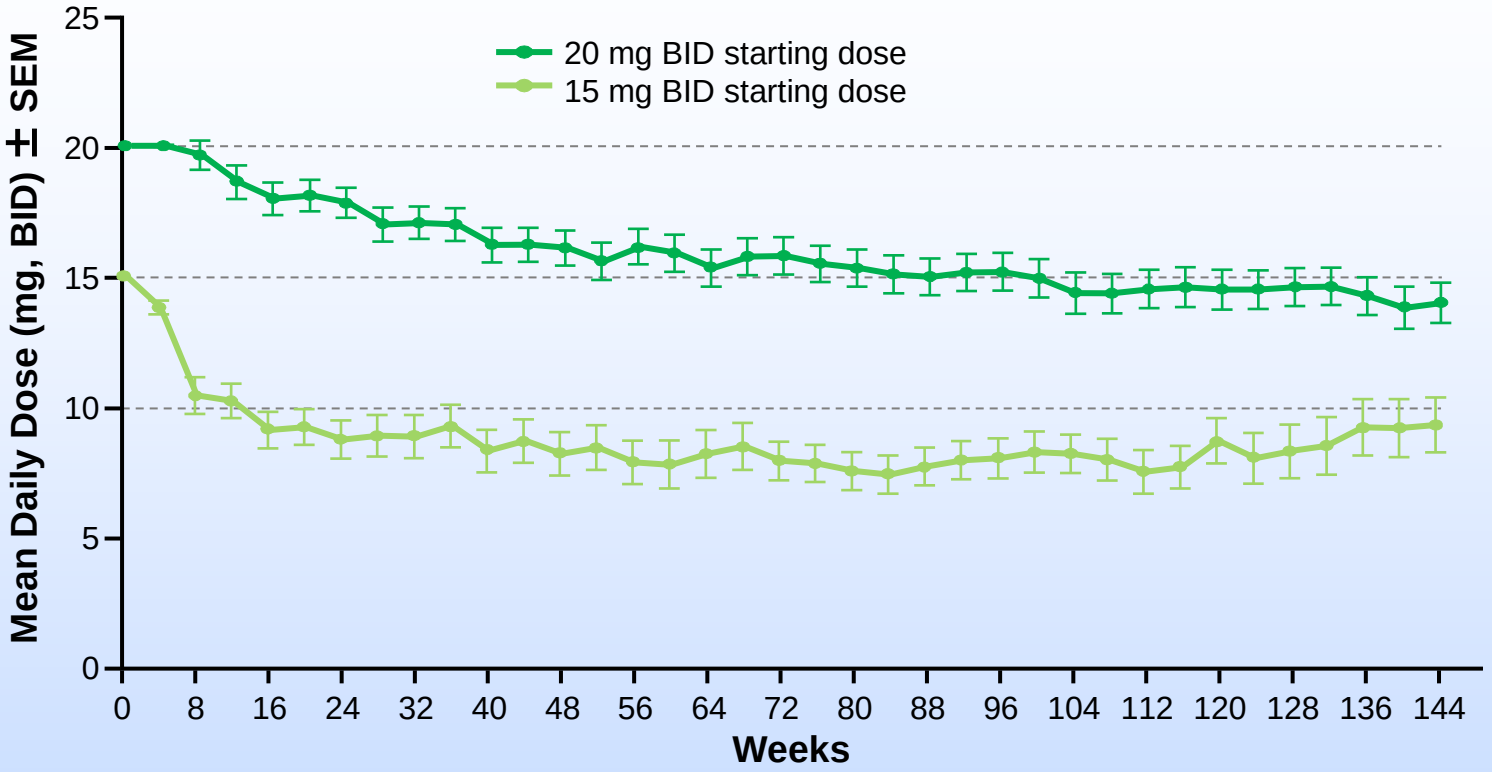
Mean Daily Dose of Ruxolitinib Over Time

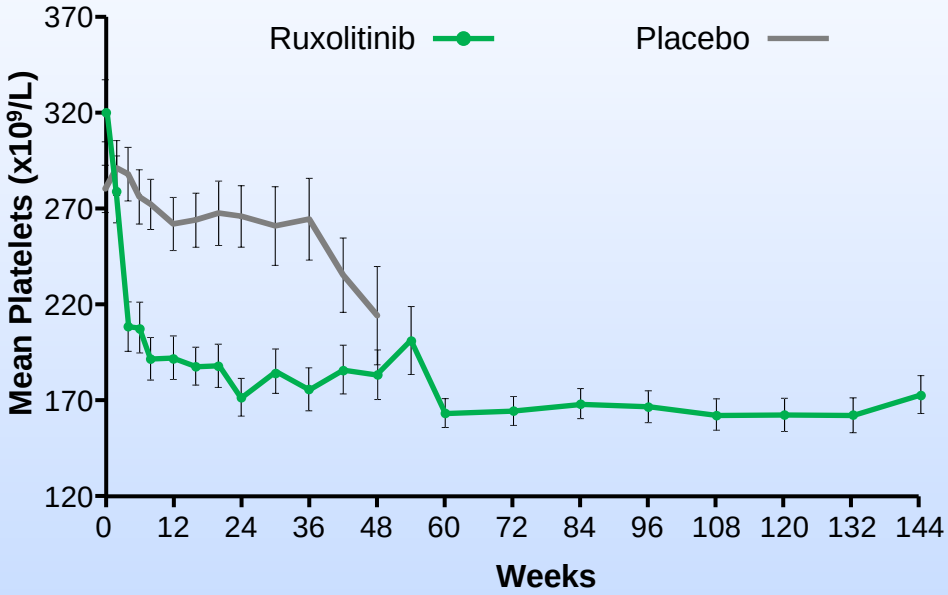


Number of patients							
20 mg BID	100	98	93	77	73	69	62
15 mg BID	55	49	35	33	30	26	20

- Approximately 70% of patients had dose adjustments during the first 12 weeks of therapy
- By week 24, patients originally randomized to RUX 15 mg BID and 20 mg BID were titrated to a mean dose of ~10 mg BID and 15-20 mg BID, respectively

Mean Platelet Count and Hemoglobin Level Over Time

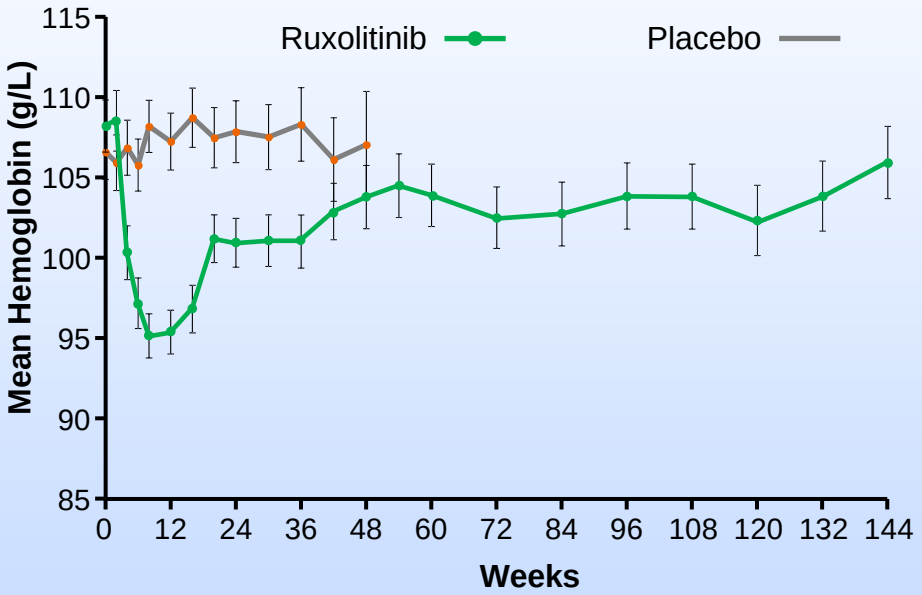
Platelet Count



Number of patients

RUX	155	144	143	136	124	112	110	107	104	100	94	88	79
PBO	151	128	112	82	37								

Hemoglobin



Number of patients

	155	145	143	136	124	113	110	107	104	100	94	88	79
	151	132	113	83	37								

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Verstovsek S, Mesa R *et al. Blood* 2013;122:Abs 396.

Case 2 – Intermediate 2 Myelofibrosis (Follow-Up)

- 6 Months after beginning therapy
  - (IWG-MRT Symptoms Response)
  - Spleen remains not palpable
  - Hb original 10.2 g/dL – NOW 9.6 g/dL
  - WBC original 14 x 10(9)/L – NOW 9 x 10(9)/L
  - Platelets Original 240 x 10(9)/L – Now 125 x 10(9)/L
  - MPN 10 – Original 56 (out of 100) – Now 10

- ***Ruxolitinib dose remains 10mg twice daily***

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Case 3 – High Risk Myelofibrosis

- 66 year old gentleman, ET for 20 years, now found to have Post ET Myelofibrosis on workup of fatigue. (No eligible transplant donor)
  - MPN 10 (63 out of 100)
  - Spleen 17cm BLCM
  - Hb 7.6 g/dL (+ transfusion)
  - WBC = 28 x 10(9)/L
  - Platelets 90 x 10(9)/L
  - Peripheral Smear = 4% Blasts
- Bone Marrow
  - 3+ Reticulin fibrosis. Karyotype Complex
- Diagnosis of Primary Myelofibrosis

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Proposed Algorithm of Therapy of MPN-MF in 2014

N.B.
Consider Rx for Prevention of Vascular Events in Appropriate Patients (Aspirin & Cytoreduction)

Symptom Quartiles by MPN 10
Q1:TSS <8 ***Q3:TSS 18-31***
Q2:TSS 8-17 ***Q4:TSS ≥32***

Diagnosis of MPN-MF (Primary, Post ET or Post PV Myelofibrosis)

Calculate DIPSS MF Score & Assess MPN Symptoms (MPN 10)

JAK2 Inhibitors
- Ruxolitinib (Jakifi/Jakivi)

(Approved for MF)
- Clinical Trial JAK2 Inhib

Anemia Rx
- Clinical Trials
- IMID/ Androgens/ EPO
- Splenectomy

Low Risk
Med S = 185m
Symptom Q1-Q2

Observation Vs. INF (Trial)

Low Risk
Med S <185m
Symptom Q3-Q4

Possible Role Of JAK2 Inhib (Trial) or INF (Trial)

Intermediate to High Risk
Med S = 16m (H), 35m (Int 2), 78 (Int 1)
Assess role and timing of ALLO SCT (Donor, Risk, Candidate)
ALLO – Urgent, Delayed, Never

Urgent ALLO

Proceed to ALLO (Possible JAK2 Inhib Prior) (Trial)

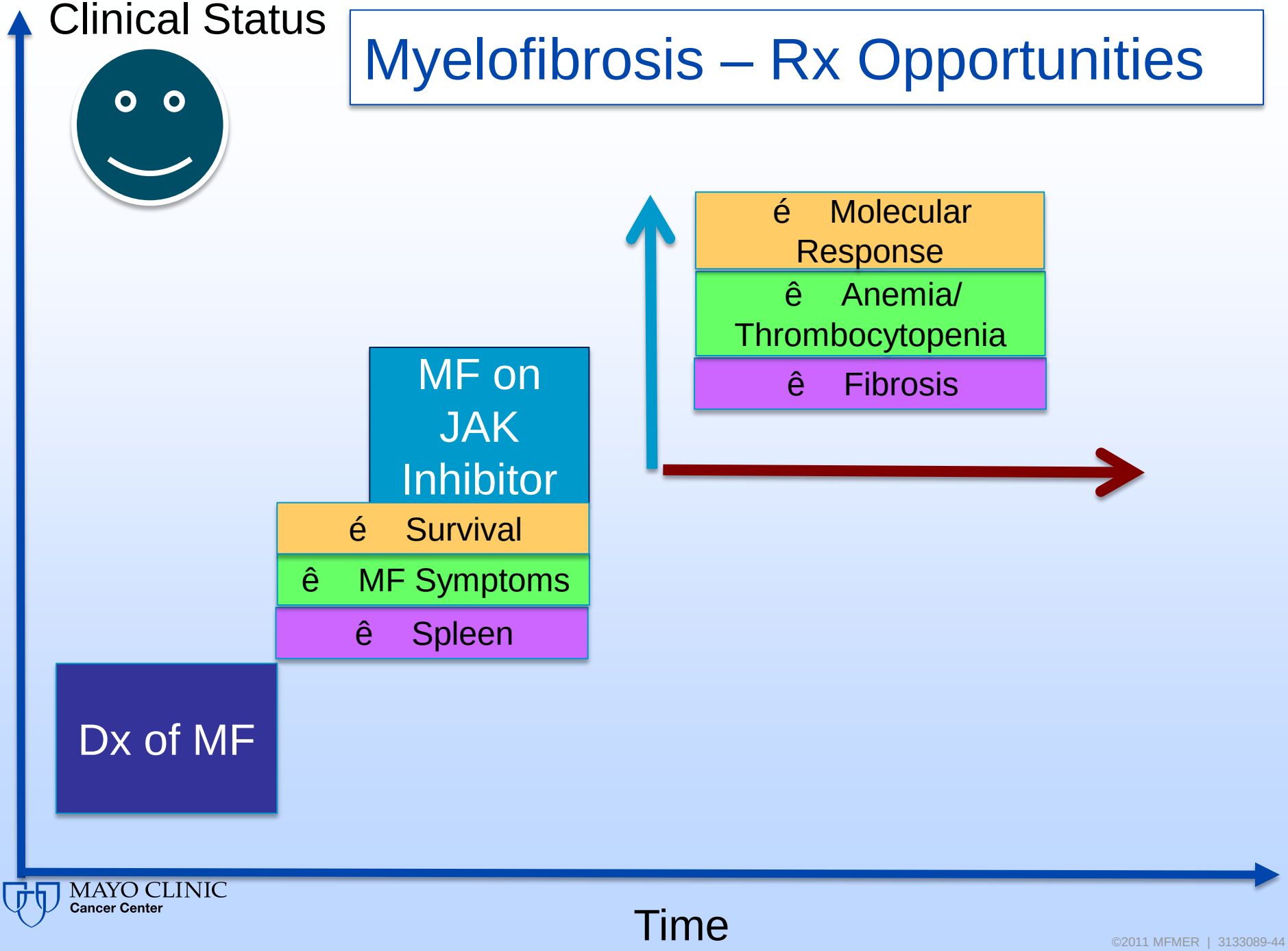
Delayed/Never ALLO

JAK2 Inhibitor*
*Unless anemia/ cytopenias main problem

JAK2 Single Agent Failure Refractory Cytopenias

Clinical Trials
- Ruxo Combination
- Non Ruxo JAK2
- New Targets

Myelofibrosis – Rx Opportunities



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LANDSCAPE MPN Clinical Trials 2015

ET/PV

- PEG INF vs HU MPD-RC 112 NCT01258856
- PEG INF (2nd Line) NCT01259817
- P1101 vs HU (PV) AOP NCT01949805
- Ruxolitinib (PV) Response 1,2 Relief Trials
- Momelotinib NCT01998828
- Givinostat (HDAC) NCT0190432

Single Agent MF

- Pacritinib v BAT (PERSIST1-PH III) NCT01773187
- Pacritinib v. BAT (PERSIST2- PH III) NCT02055781
- Momelotinib v. Rux (PH III) NCT01969838
- Momelotinib vs. BAT (PH III) NCT012101268
- NS-018 (PH II) NCT01423851
- Imetelstat
- PF04449913 (Smo) NCT02226172

Combination MF Rux Plus -

- Lenalidomide NCT013575140
- Pomalidomide NCT01644110
- Danazol NCT01732445
- Azacitidine NCT01787487
- Decitibine NCT02076191
- PRM-151 NCT01981850
- Panobinostat NCT01693601 NCT01433445
- BKM 120 (Pi3K) NCT01730248
- LDE 225 (HH) NCT01787552

Mielofibrosis 2015
Conclusions

- Myelofibrosis and MPNs impact patients with risk of symptom burden, vascular events, splenomegaly and risk of mortality
- Assessing disease burden and risk is key for treatment plan and goals in MPNs
- JAK inhibition, with ruxolitinib, has demonstrated improved symptom burden, spleen size, fibrosis, and survival in myelofibrosis
- Patience, and management of dosing of ruxolitinib in myelofibrosis important for dealing with anemia


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