THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Making Cancer History®

Managing Myelofibrosis in 2019

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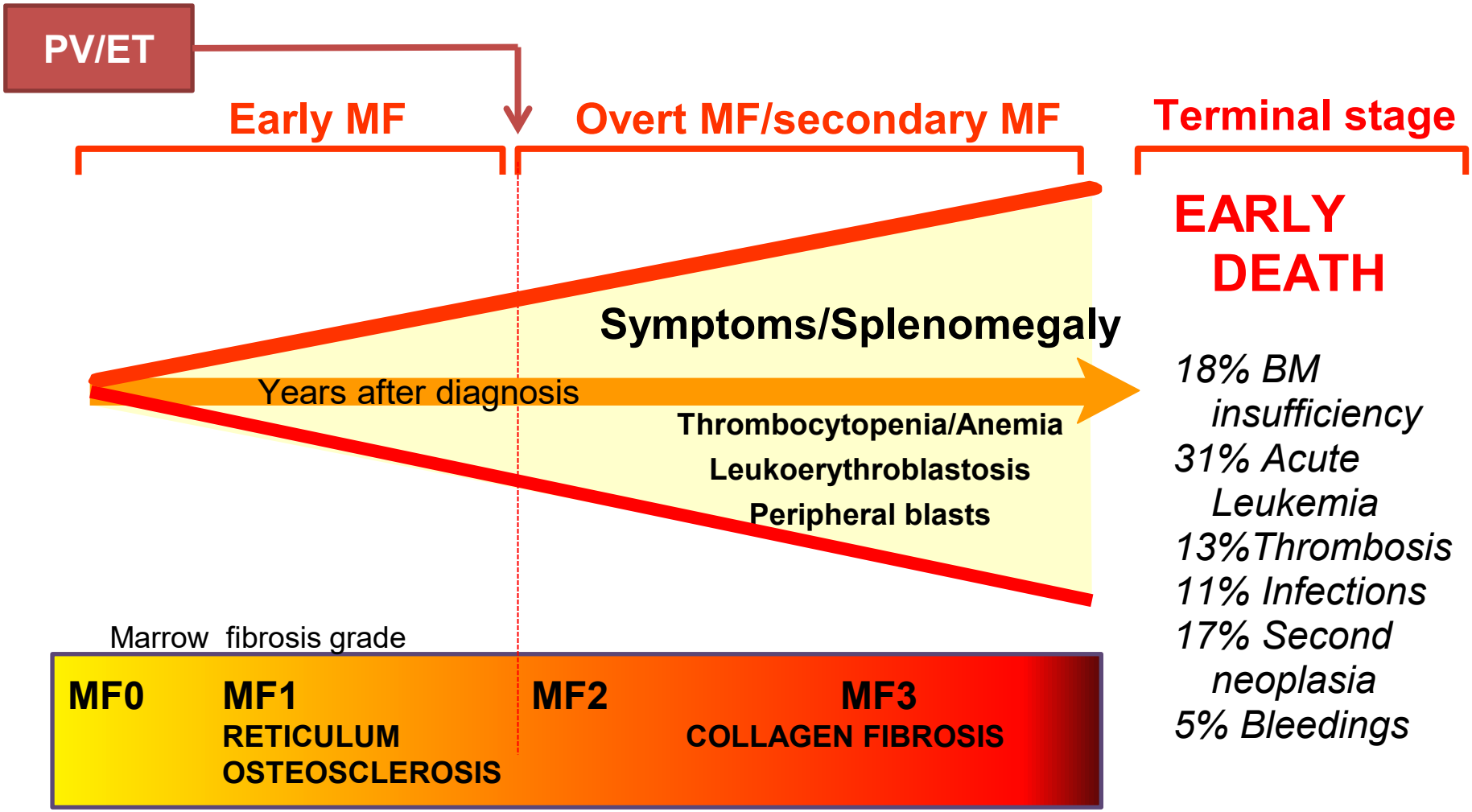
Evolution of Myelofibrosis



Barbui T, et al. J Clin Oncol. 2011 Feb 20;29(6):761-70. Caramazza D, et al. Leukemia. 2011 Jan;25(1):82-8.Tefferi A, et al. Leukemia. 2012 Jun;26(6):1439-41. Passamonti F, et al. Blood. 2010 Oct 14;116(15):2857-8. Cervantes F. Blood. 2009 Mar 26;113(13):2895-901. Arber et al. Blood. 2016; 127(20):2391-405.. Thiele J, et al. *Haematologica.* 2005;90:1128-1132; Thiele J, Kvasnicka HM, et al. *Ann Hematol*. 2006;85(4):226-232, Vener C, et al. *Blood.* 2008

WHO Diagnostic Criteria: Prefibrotic MF vs Overt MF

Primary MF Diagnosis

Requirement for diagnosis

- All 3 major criteria AND ≥ 1 minor criteria

Major criteria

1. Megakaryocytic proliferation and atypia, **without reticulin fibrosis > grade 1 (prefibrotic PMF)** or **with reticulin and/or collagen fibrosis grade 2/3 (overt fibrotic PMF)**
2. *JAK2*, *CALR*, or *MPL* mutation, presence of other clonal markers* OR absence of reactive MF
3. Not meeting WHO criteria for other myeloid malignancies

Minor criteria

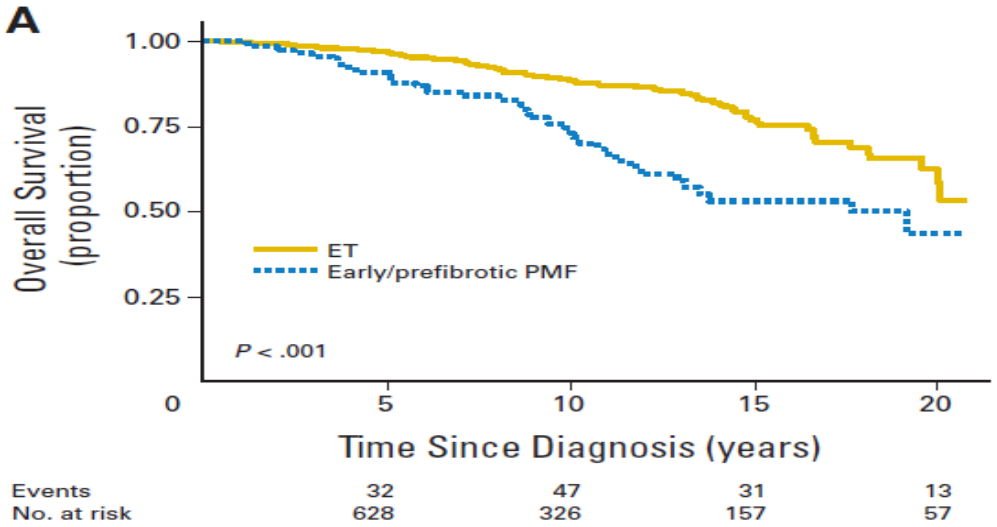
1. Anemia not attributed to a comorbid condition
2. Leukocytosis ≥ 11 × 10^9/L
3. Palpable splenomegaly
4. LDH increased above ULN
5. **Leukoerythroblastosis (overt fibrotic PMF)**

* eg, *ASXL1*, *EZH2*, *TET2*, *IDH1/IDH2*, *SRSF2*, *SF3B1*.

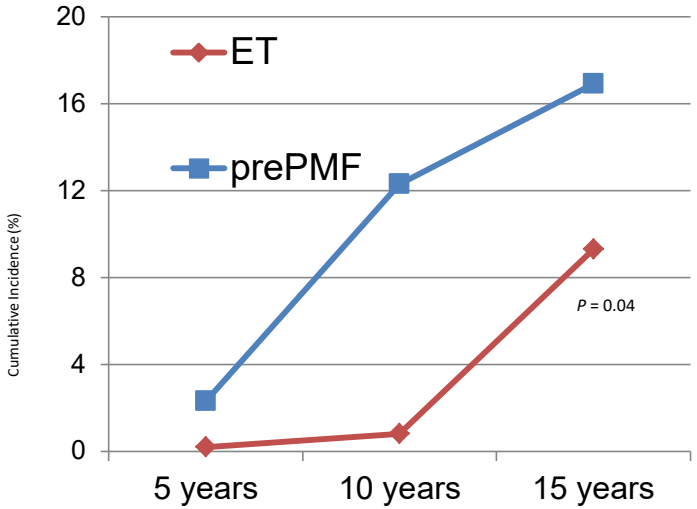
Arber DA, et al. *Blood*. 2016;127:2391-2405.

Disease Progression - ET vs. prePMF

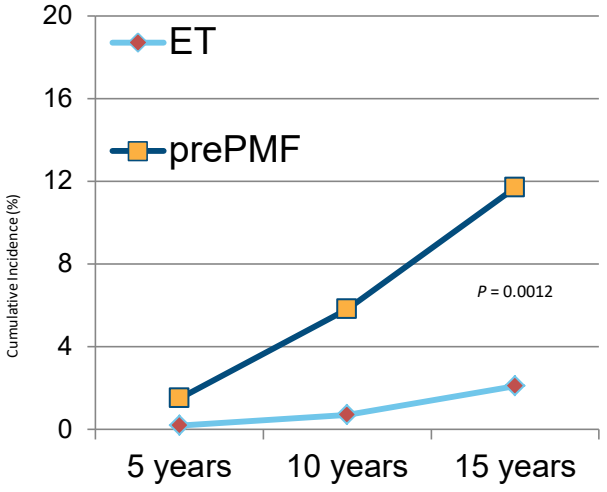
International Study on 1,104 Patients



Transformation to overt MF

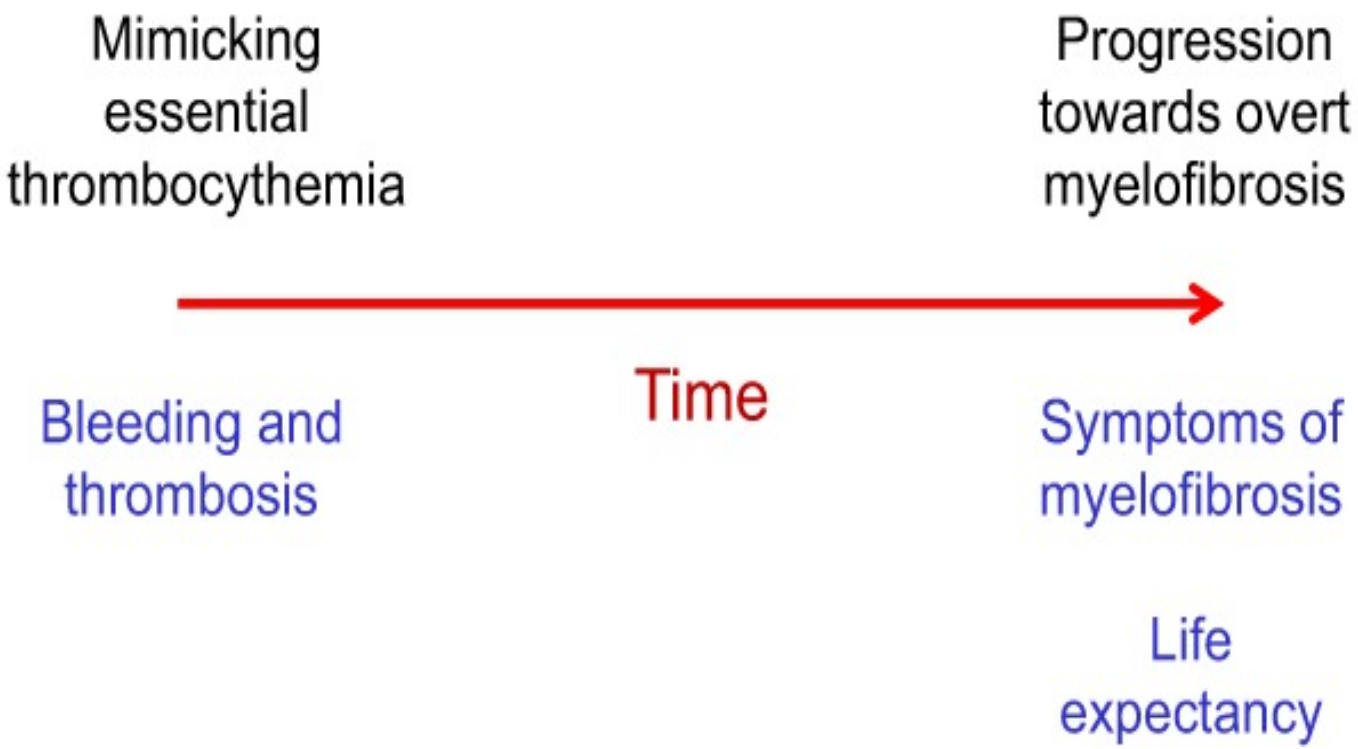


Risk of leukemic transformation



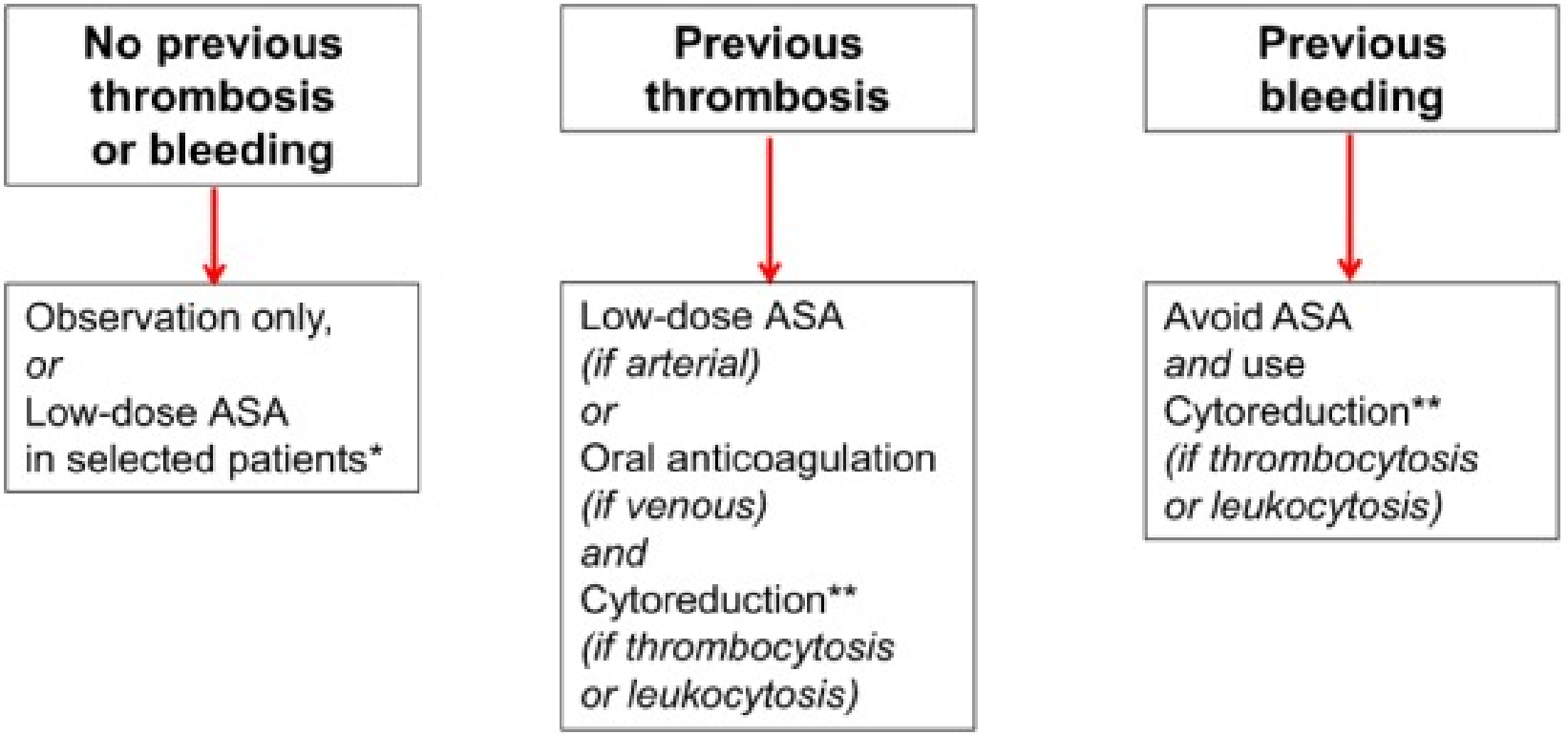
Barbui T, et al. *J Clin Oncol.* 2011;29:3179-3184.

The heterogeneous clinical spectrum of prefibrotic myelofibrosis



Finazzi Blood Cancer J 2018; 8:104

Treatment algorithm in prefibrotic myelofibrosis for the thrombotic and bleeding risk



* *Age > 60 yrs., or CV risk factors, or JAK2V617F mutation, or leukocytosis or microvascular symptoms and low bleeding risk*

** *Hydroxyurea as first choice, rIFNα in HU resistant or intolerant patients*

Finazzi Blood Cancer J 2018; 8:104

Diagnosing PPV- or PET-MF

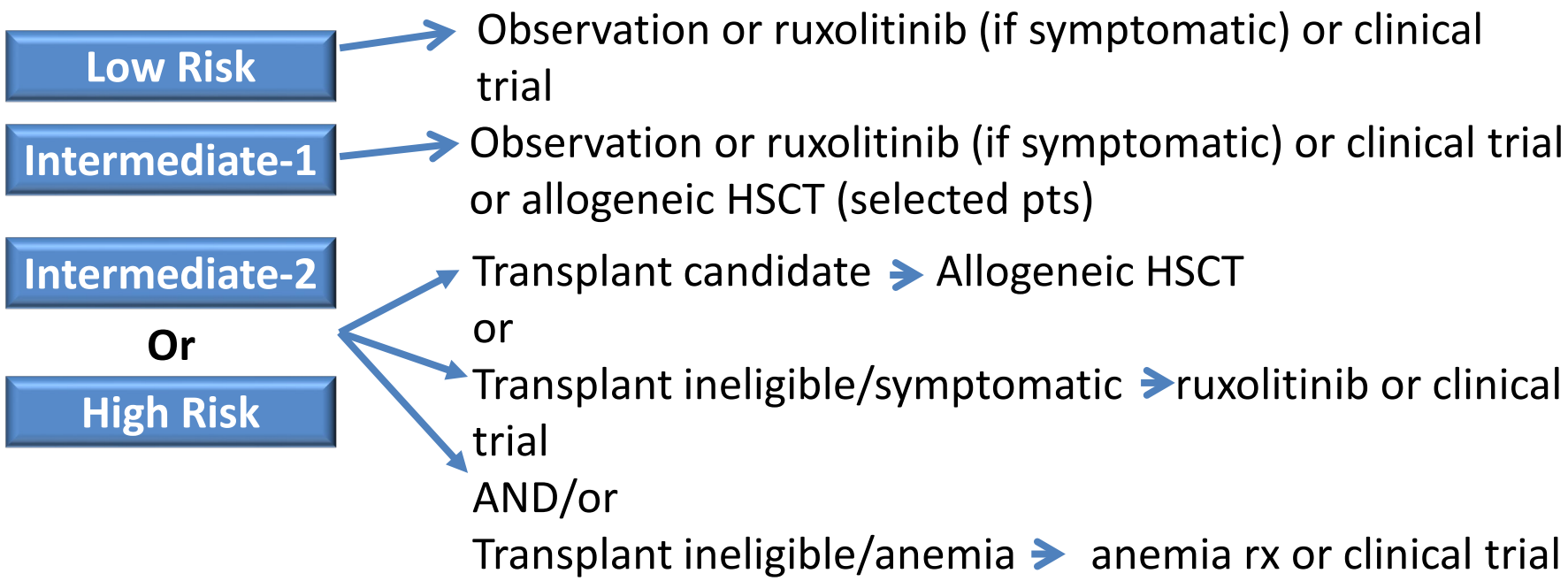
PV 10% transformation rate per 10 years[2]	ET <4% transformation rate per 10 years[2]
Post-PV or Post-ET Myelofibrosis[1]	
IWG Diagnostic Criteria for Post-PV Myelofibrosis	IWG Diagnostic Criteria for Post-PV Myelofibrosis
REQUIRED CRITERIA	
Documentation of previous diagnosis of PV or ET as defined by WHO criteria	
Grade 2 or 3 bone marrow fibrosis (0-3 scale) or grade 3 or 4 bone marrow fibrosis (0-4 scale)	
Additional Criteria (2 Required)	**Additional Criteria (2 Required)**
Anemia or sustained loss of need for either phlebotomy or cytoreductive therapy	Anemia and a decrease of ≥2 mg/mL from baseline hemoglobin level
Leukoerythroblastosis	Leukoerythroblastosis
≥5 cm increase in palpable splenomegaly or new splenomegaly	≥5 cm increase in palpable splenomegaly or new splenomegaly
Development of ≥1 of 3 constitutional symptoms[3]	Increased serum LDH level
	Development of ≥1 of 3 constitutional symptoms[3]

ET = essential thrombocythemia; IWG – International Working Group; LDH = lactate dehydrogenase; PET-MF – post-essential thrombocythemia myelofibrosis; PPV-MF = post-polycythemia vera myelofibrosis; PV = polycythemia vera; WHO = World Health Organization.

[3]Constitutional symptoms include > 10% weight loss in 6 months, night sweats and unexplained fever (>37.5°C).

1. Barosi G et al. *Leukemia.* 2008;22:437-438; 2. Tefferi A. *Am J Hematol.* 2008;83:491-497

NCCN Guideline for Treatment of MF: Based on Risk and Symptoms/Signs



Low risk = 0 on IPSS, DIPSS-Plus, or DIPSS
INT-1 risk = IPSS = 1, DIPSS-Plus = 1, DIPSS = 1 or 2
INT-2 risk = IPSS = 2, DIPSS-Plus =2 or 3, DIPSS = 3 or 4
High risk = IPSS = 3, DIPSS-Plus = 4 to 6, DIPSS = 5 or 6

Adapted from National Comprehensive Cancer Network (NCCN). Myeloproliferative Neoplasms (Version 2.2017, https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf.

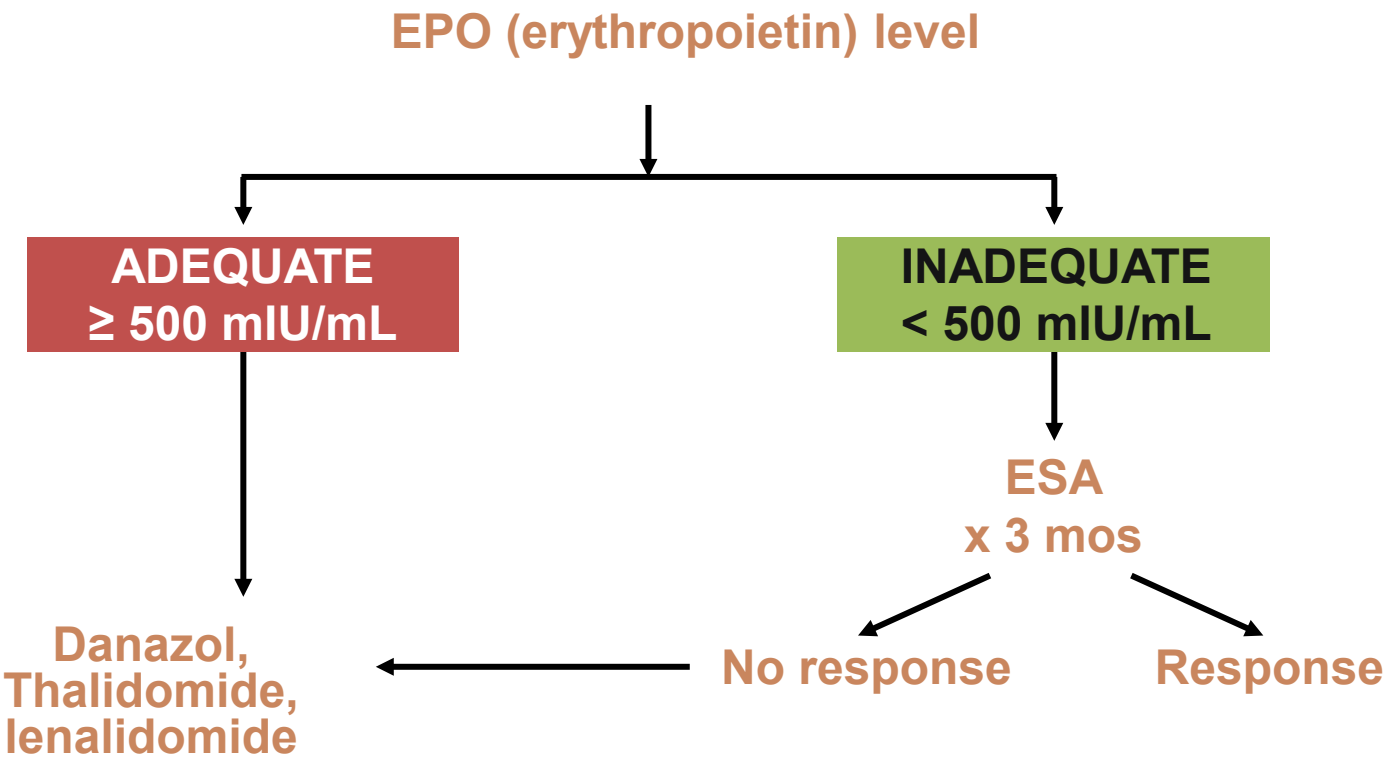
IFN for First-Line MF Treatment: Consideration in Early Hyperproliferative Stage

Impact of Use	
Early	• Blood count control • Address splenomegaly, when modest • Reduction in thrombosis risk
Late	• Anticlonal activity • Potential for regression of histologic changes and delayed transformation?

- Consider IFN use in selected pts
  - With preserved performance status and limited comorbidities
  - Who are earlier in disease course
  - When splenomegaly modest
  - Without additional non-*JAK2* mutations (?)
- Limitations:
  - Potential for short-term negative impact on QoL
  - Tolerable in the long term?

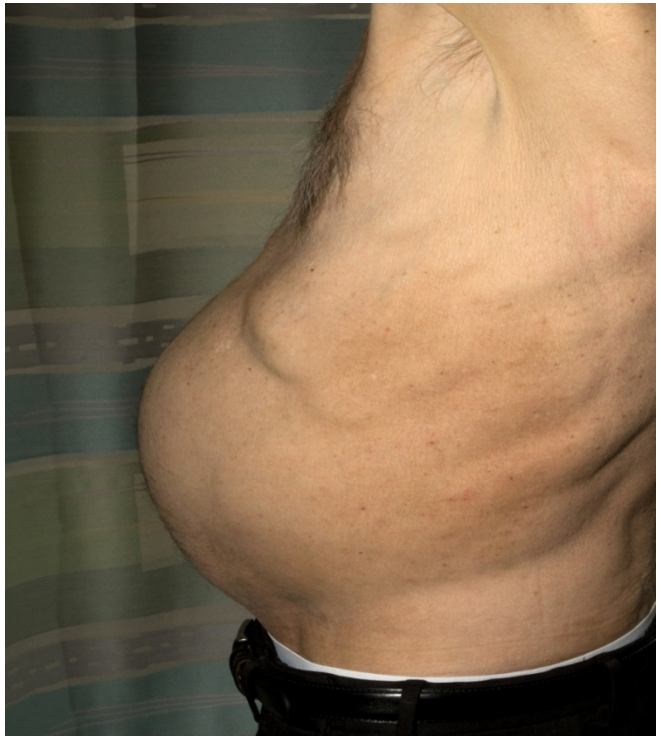
Foucar CE, et al. *Curr Hematol Malig Rep*. 2017.

Aproach to the Treatment of Anemia in MF

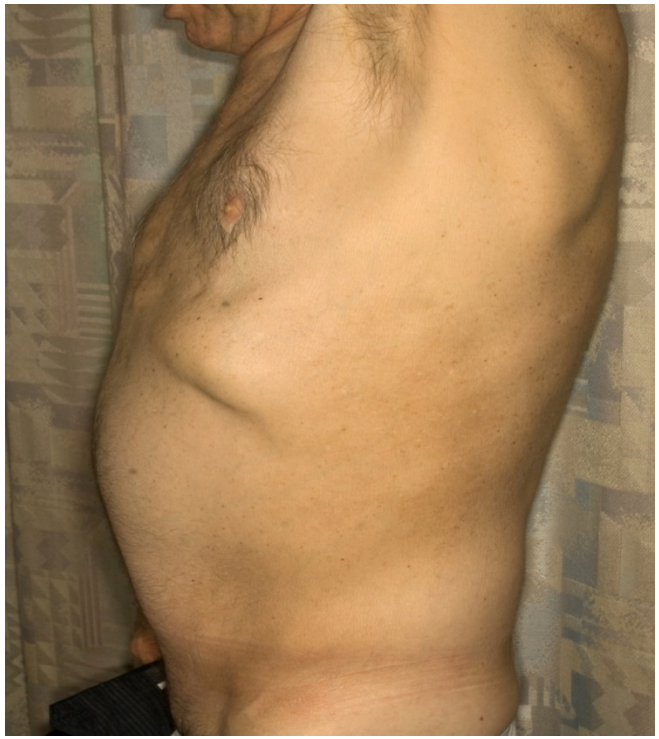


NCCN guidelines, 2017

MF: What does ruxolitinib do?



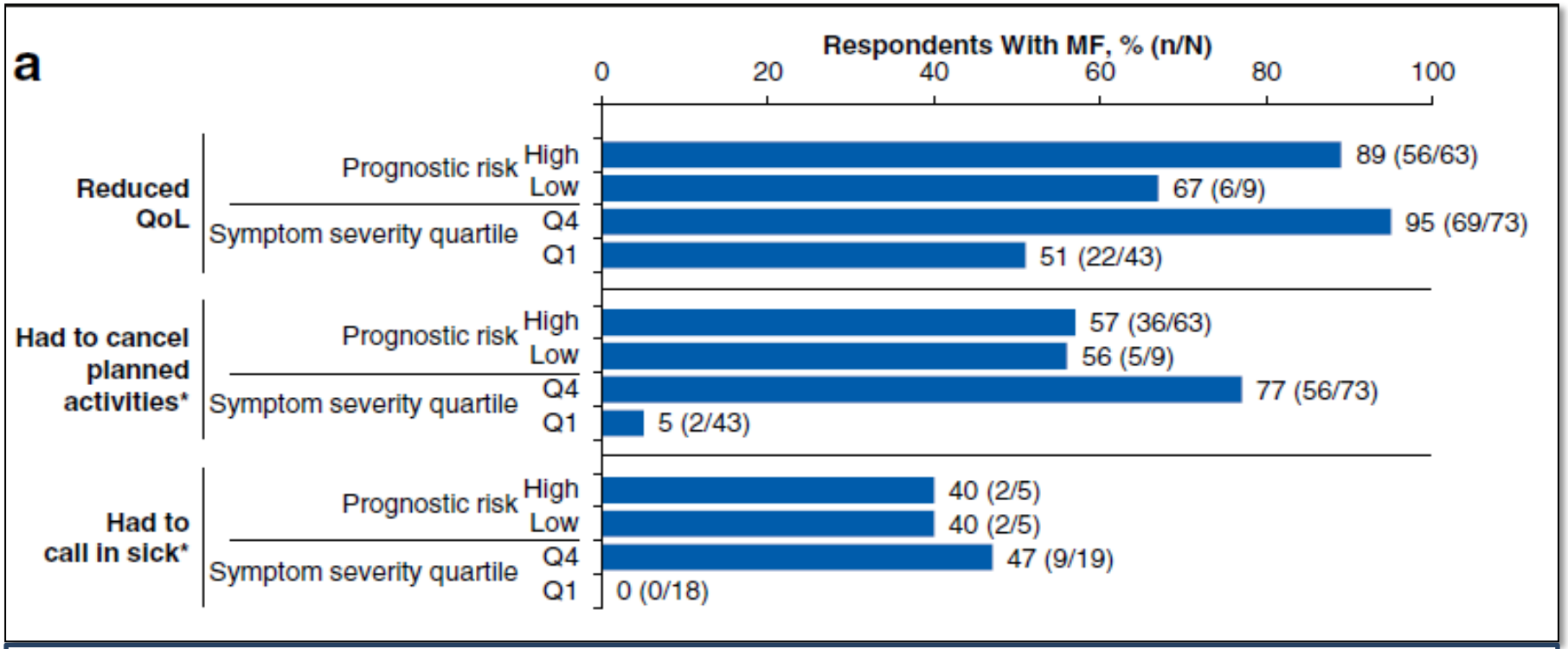
Patient Pre-Ruxolitinib Therapy



After 2 Months of Therapy

It is good for spleen and symptoms

Early-Stage MF May Have a Significant Clinical Burden



- DIPSS low-risk MF patients are moderately to highly symptomatic in 44% of the cases
- The reduction of quality of life and social/working activity is similar in low and high risk categories

Harrison C, et al. *Ann Hematol*. 2017:5; Mesa RA, et al. *BMC Cancer*. 2016:27;16:167; Scherber R, et al. *Blood* 2011;118:401-408; Scherber R, et al. EHA 2016 [abstract 2250]; Marchetti M, et al. *Leukemia*. 2016;1-7.

Ruxolitinib in IPSS-1 Patients
Higher response rate and lower toxicities

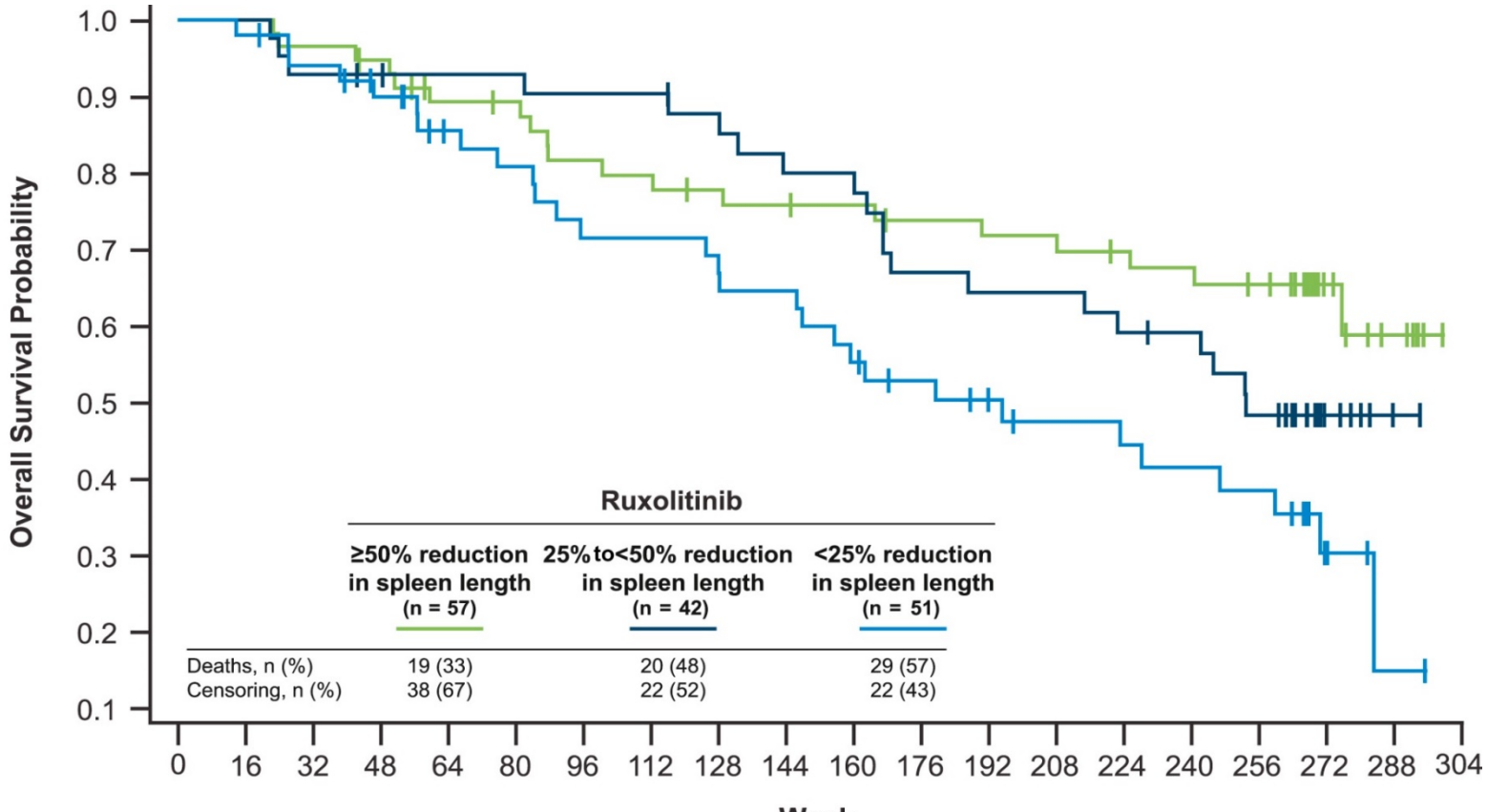
	Clinical Trial	Spleen Response at Week 24	Incidence of Anemia G3/G4	Incidence of Thrombocytopenia G3/G4	Incidence of Infections	Discontinuation rate
Intermediate-2 and high risk patients	COMFORT-I (n = 155)[1]	41.9%	45%	13%	≈ 50%	21%[6]
	COMFORT-II (n = 146)[2]	32%	42%	8%	≈ 50%	38%
Intermediate-1 risk patients	JUMP INTM-1 (n = 163)[3]	56.9%	24.5%	11%	40%	19.6%
	ROBUST trial (n = 14)[4]	50%	NA	NA	NA	NA
	Italian study (n = 70)[5]	54.7%	21.7%	2.9%	17.1%	17.1%

IPSS intermediate-1 patients may possibly achieve higher reponse rates and experience lower toxicities than patients with higher-risk disease

1. Verstovsek S, et al. *N Engl J Med.* 2012;366(9):799-807. 2. Harrison C, et al. *N Engl J Med*. 2012;366(9):787-98.
3. Al-Ali HK, et al. *Haematologica*. 2016;101(9):1065-73. 4. Mead AJ, et al. *Br J Haematol.* 2015;170(1):29-39.
5. Palandri F, et al. *Hematol Oncol*. 2017 [Epub ahead of print]. 6. Verstovsek, et al. *Haematologica.* 2015;100(4):479-488.

4/2008

Overall survival of patients by degree of spleen length reduction on ruxolitinib

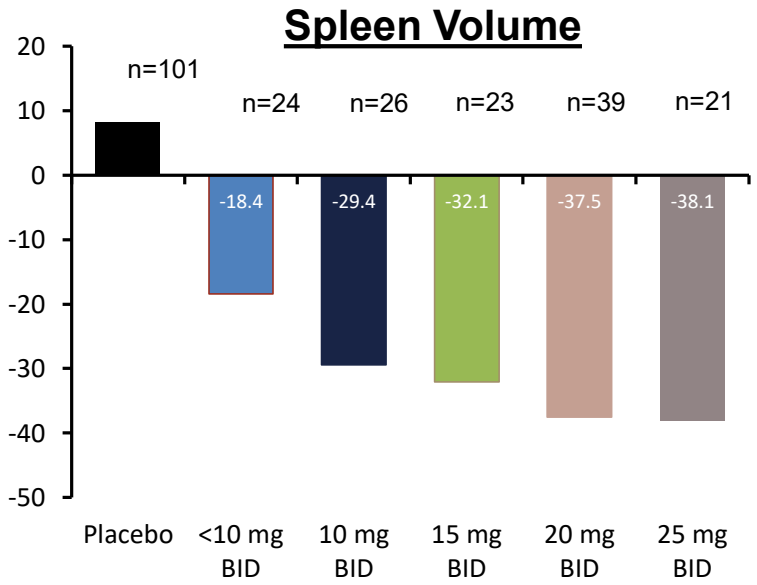


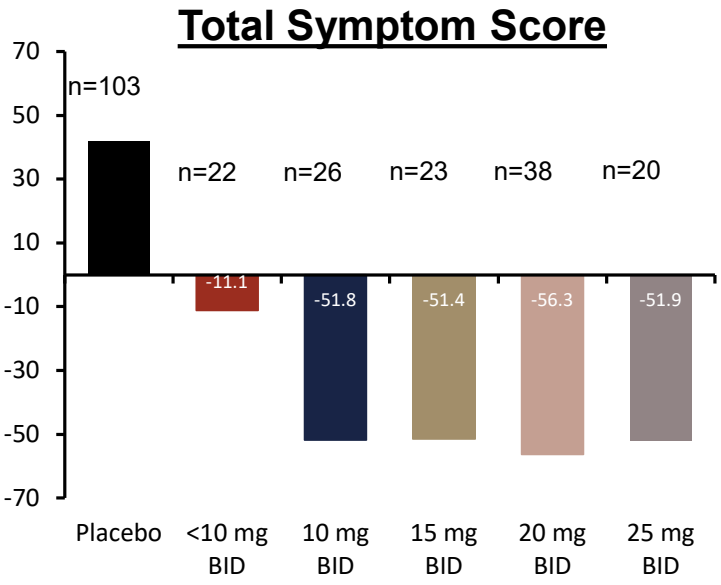
Patients at risk, n																				
≥50% Reduction in spleen length	57	57	55	53	48	47	43	42	40	39	38	36	35	35	33	32	30	12	6	0
25%to<50% Reduction in spleen length	42	42	39	38	37	37	36	36	34	31	31	26	25	25	23	22	18	6	2	0
<25% Reduction in spleen length	51	50	47	43	37	35	31	31	30	28	24	21	19	16	15	14	13	6	1	0

COMFORT-1 study; Miller CB, at al. Clin Lymphoma Myeloma Leuk. 2017 Aug;17(8):479-487.

Ruxolitinib Efficacy by Titrated Dose

Week 24





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

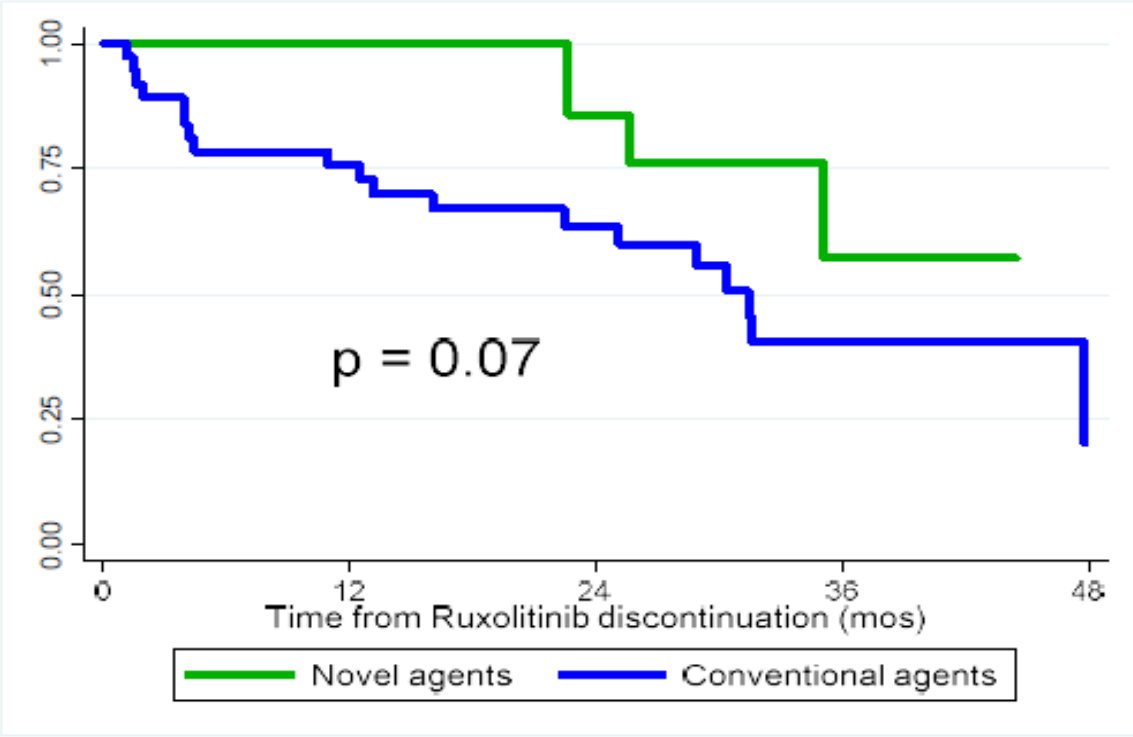
COMFORT-1 study; Verstovsek S et al. OncoTargets and Therapy 2014;7:13-21

Summary on Ruxolitinib in MF

- Indicated for splenomegaly or MF-related symptoms (regardless of a risk of dying)
- Early stage MF patients may achieve better therapeutic results with respect to IPSS intermediate-2/high-risk patients
- Also, toxicity (myelosuppression) could be lower due to better global health status and better bone marrow reserve (better CBC)

- Anemia is NOT contraindication; starting dose based on platelet number
- Avoid 'prophylactic underdosing' - maintain **maximum tolerated dose** to achieve larger reductions in splenomegaly **early** during treatment
- Development of anemia DOES NOT affect benefits of JAK2 inhibitor
  - Manage anemia as alternative to early dose reductions
- Avoid abrupt interruption of ruxolitinib in patients responding well
- Monitor for skin cancer
- Be aware of rare possibility of opportunistic infections

Outcome of patients with MF after ruxolitinib

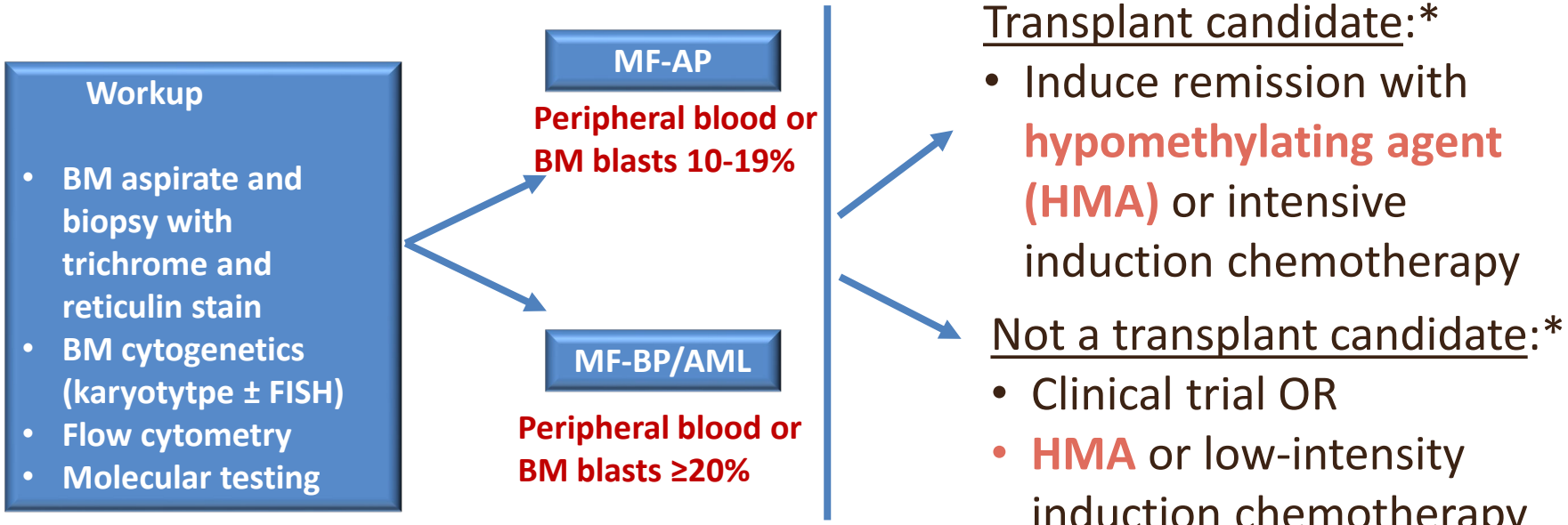


Overall survival according to the type of medical treatment after ruxolitinib discontinuation (N=171)

In chronic phase patients, survival probability may be improved by the use of medical therapies that are still in the experimental phase

Palandri; abstract 4277; ASH 2018

NCCN Guideline for Treatment of MF-AP or MF-BP/AML



***Consider ruxolitinib to control splenomegaly and systemic symptoms**
HMA: azacitidine and decitabine

MF-AP: myelofibrosis in accelerated phase; MF-BP/AML – myelofibrosis in blast phase or transformation to AML
Adapted from National Comprehensive Cancer Network (NCCN). Myeloproliferative Neoplasms (Version 2.2017, https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf. Accessed July 25, 2017

THANK YOU

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