Intermediate-1 Myelofibrosis Management

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Prognostic Models for MF

Parameter[1]	Included in IPSS[2]	Included in DIPSS[3]	Included in DIPSS-Plus[4]
Age > 65 y	Yes (1 point)	Yes (1 point)	Yes[a]
Hgb < 10 g/dL	Yes (1 point)	Yes (2 points)	Yes[a]
WBC > 25×10^9/L	Yes (1 point)	Yes (1 point)	Yes[a]
PB blood blasts ≥ 1%	Yes (1 point)	Yes (1 point)	Yes[a]
Constitutional symptoms	Yes (1 point)	Yes (1 point)	Yes[a]
Unfavorable karyotype[b]	No	No	Yes (1 point)
RBC transfusion dependence[c]	No	No	Yes (1 point)
Platelet count < 100×10^9/L	No	No	Yes (1 point)
Can be used at any time point	No (only at diagnosis)	Yes	Yes

	Median Survival, Years		
Risk Group	IPSS[2]	DIPSS[3]	DIPSS-Plus[4]
Low	11.3	Not reached	15.4
Intermediate-1	7.9	14.2	6.5
Intermediate-2	4.0	4.0	2.9
High	2.3	1.5	1.3

Abbreviations: DIPSS, dynamic International Prognostic Scoring System; Hgb, hemoglobin; IPSS, International Prognostic Scoring System; PB, peripheral blood; RBC, red blood cell; WBC, white blood cell count.

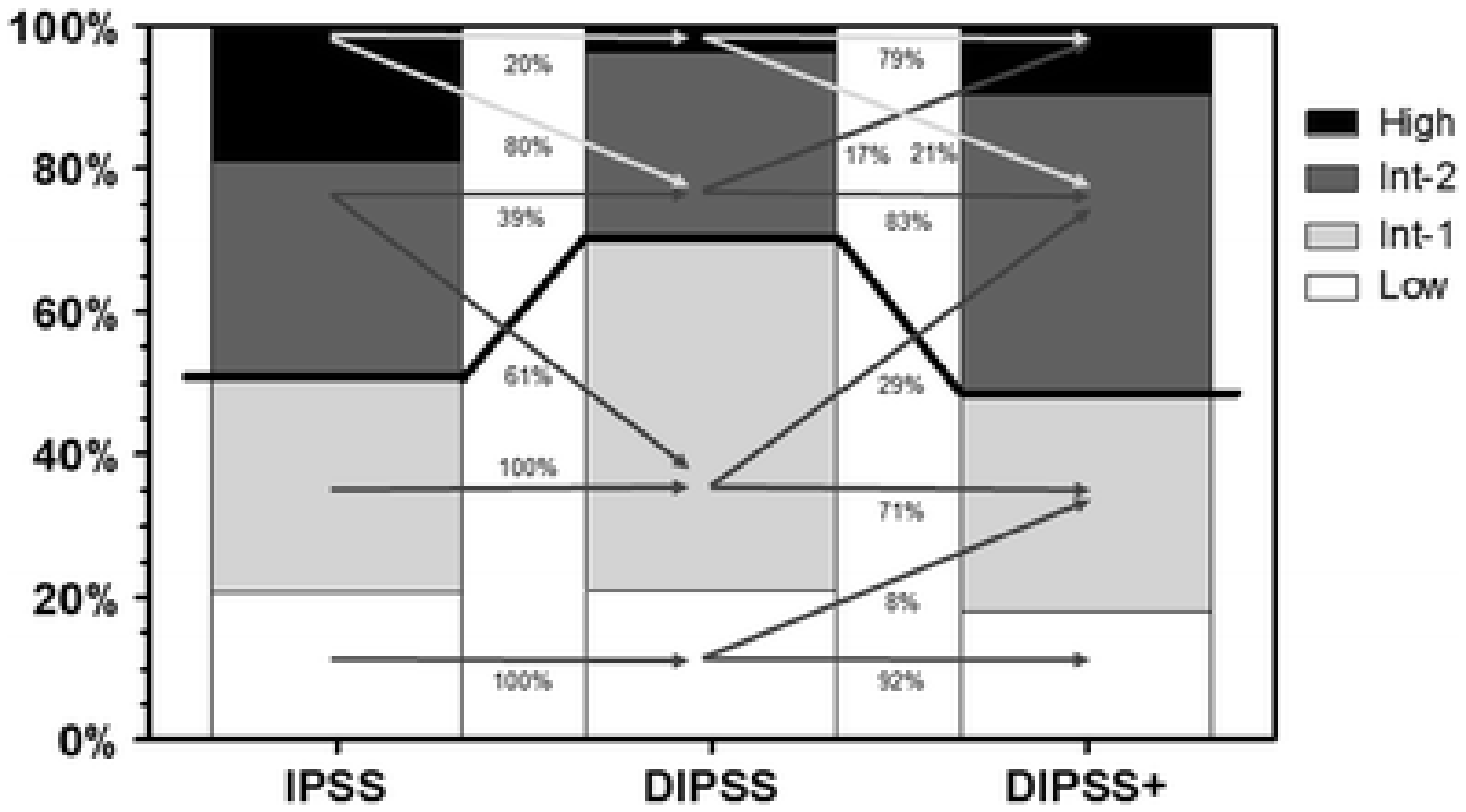
[a] Zero, 1, 2, and 3 points are assigned to DIPSS categories of low, intermediate-1, intermediate-2, and high risk, respectively; features are not weighted individually.

[b] Complex karyotype or a single or 2 abnormalities including + 8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), or 11q23 rearrangement.

[c] Presentation with symptomatic anemia necessitating RBC transfusion at time of referral, or a history of RBC transfusions for myelofibrosis-associated anemia, without regard to the number of RBC transfusions.

1. Bose P, Verstovsek S. *Cancer*. 2016;122:681-92; 2. Cervantes F, et al. *Blood*. 2009;113:2895-2901; 3. Passamonti F, et al. *Blood*. 2010;115:1703-1708; 4. Gangat N, et al. *J Clin Oncol*. 2011;29:392-397.

Distribution of myelofibrosis patients by the different prognostic models



Hernandez-Boluda ,Ann Hematol. 2018 May;97(5):813-820

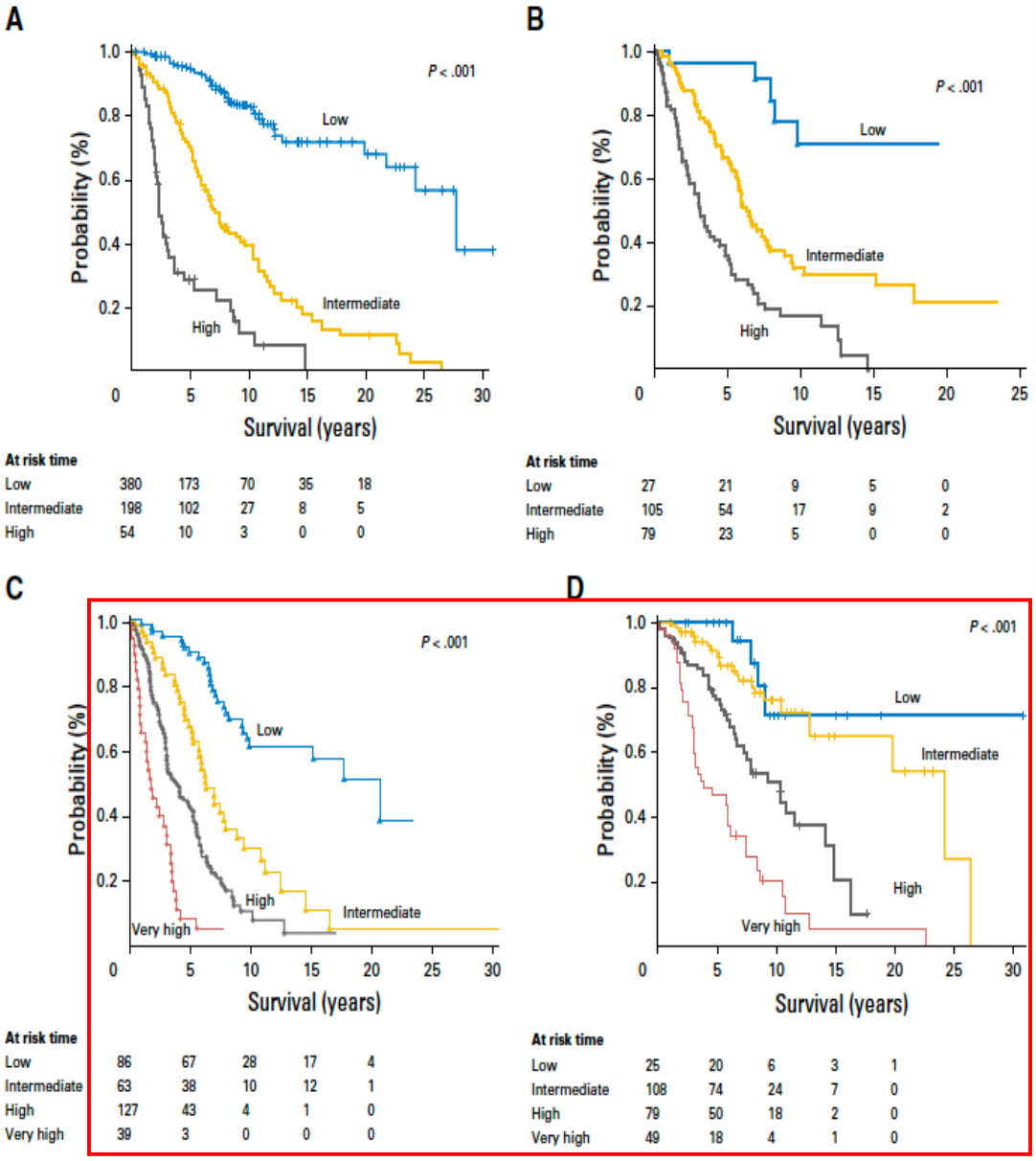
MIPSS70 and MIPSS70-plus*

http://mipss70score.it

Key Elements:

- Hb <10 g/dL*
- WBC >25 x 10^9/L
- PLT <100 x 10^9/L
- Blasts ≥2%*
- Fibrosis > grade 1
- Constitutional symptoms*
- Absence of type 1/-like *CALR* mutation*
- HMR mutations*
  - *ASXL1*
  - *EZH2*
  - *SRSF2*
  - *IDH1/2*
- 2 or more HMR*

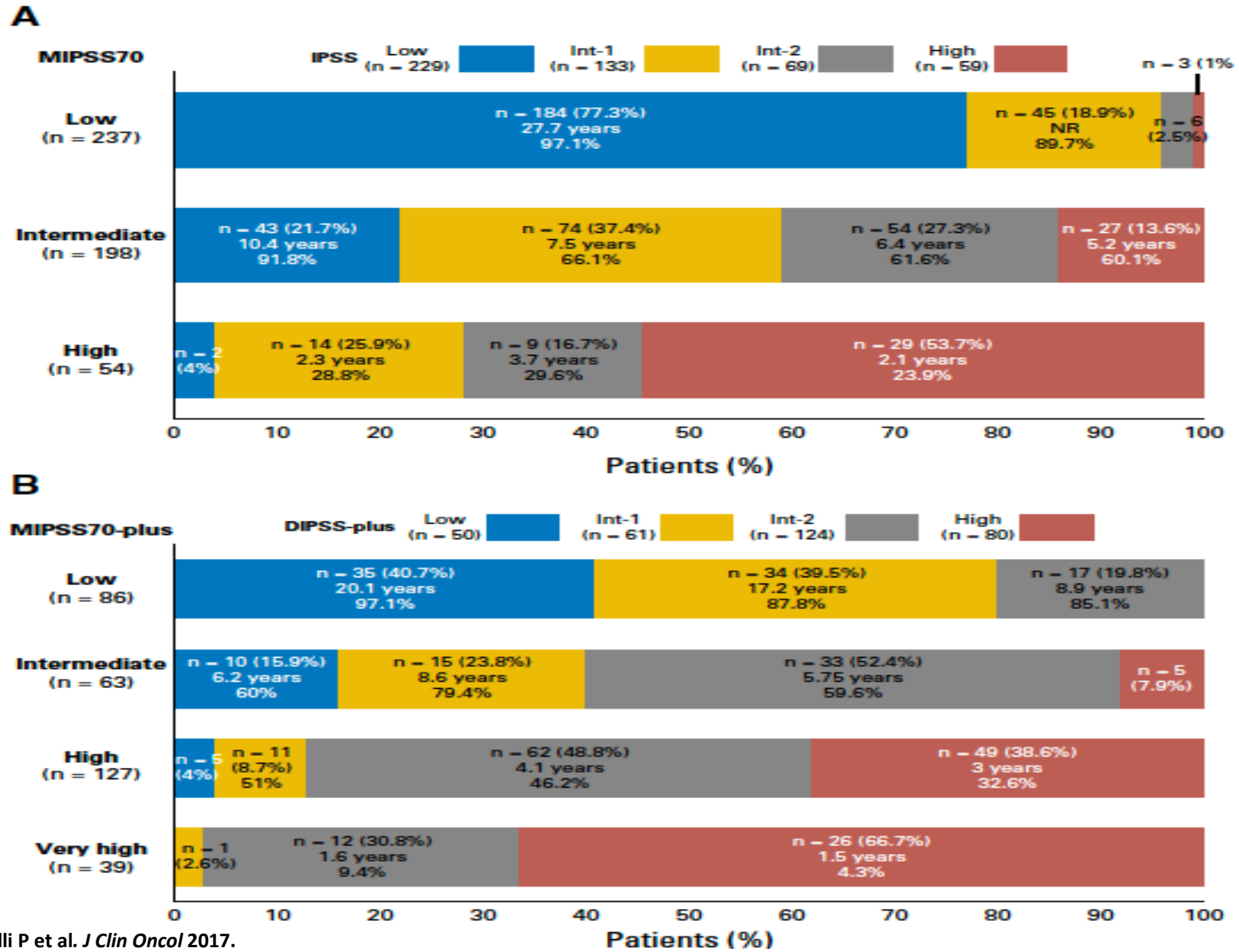
Unfavorable karyotype*



Guglielmelli P et al. *J Clin Oncol* 2017.

MIPSS70

http://mipss70score.it



Guglielmelli P et al. *J Clin Oncol* 2017.

The MYSEC-PM nomogram

https://mysec.shinyapps.io/prognostic_model/

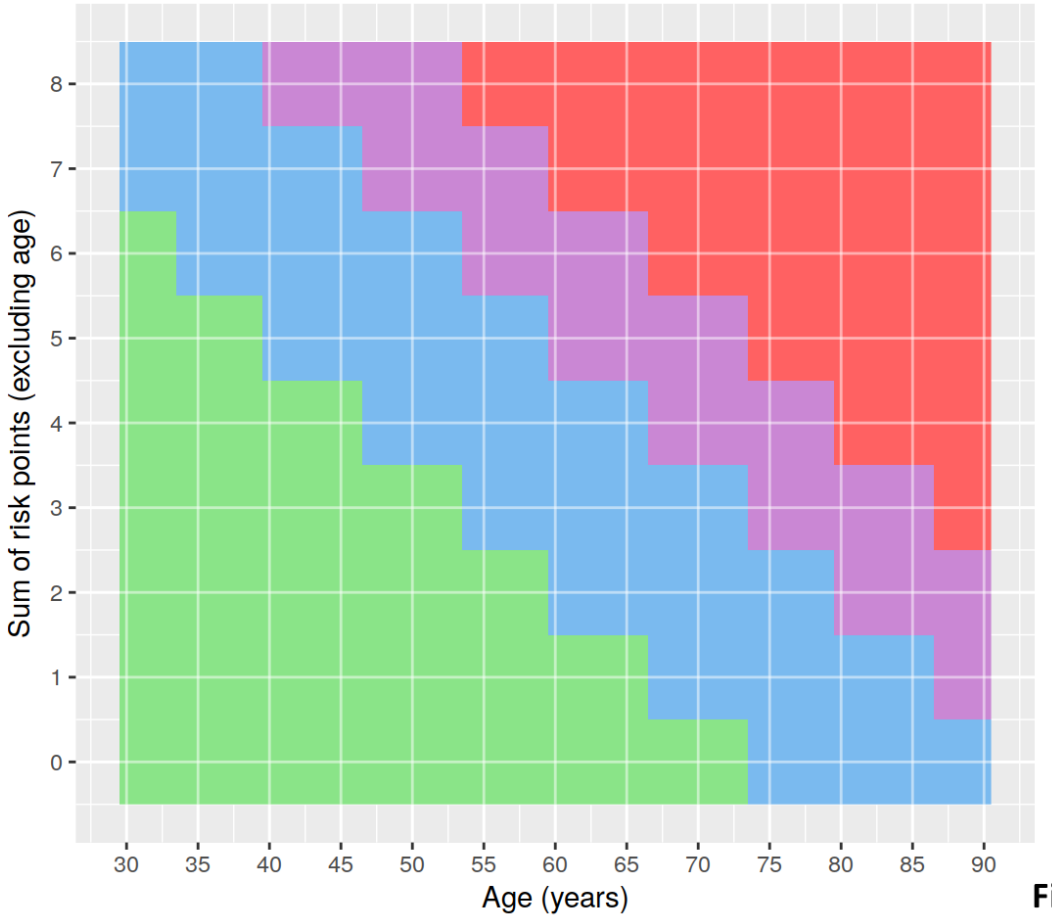


Figure 2B

Covariate	Points
Hgb <11 g/dl	2
Plts <150 x 10^9/L	1
PB blasts ≥3%	2
CALR-WT	2
Const sx	1

1) Put on the vertical axis the score value assigned for non-age prognostic variables
2) Put patient's age on horizontal axis
3) Locate the combination of non-age score and age
4) The color at the location indicates the final risk category

Passamonti F et al. *Leukemia* 2017.

DIPSS progression

Risk group	Time spent in group median, years (range)
Low-risk	4.9 (0 - 26.7)
Intermediate-1R	2.1 (0 - 18.7)
Intermediate-2R	1.7 (0 - 13.4)
High-risk	0.74 (0 - 13.7)

DIPSS, dynamic international prognostic scoring system; LR, low risk; Int-1R, intermediate-1 risk; Int-2R, intermediate-2 risk; HR, high risk

MPN10 (Total Symptom Score)

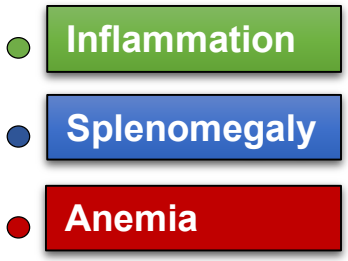
An easy tool to assess symptoms in MPNs

- Inflammation
- Splenomegaly
- Anemia

	Value	Prognostic variable
Fatigue	0	1 to 10 ranking (0 if absent; 1 most favorable; 10 least favorable)
Early satiety	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Abdominal discomfort	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Inactivity	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Problems with concentration	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Night sweats	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Itching	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Bone Pain	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Fever	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
Unintentional weight loss last 6 months	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)
MPN10 score	0	

MPN10 (Total Symptom Score)

An easy tool to assess symptoms in MPNs



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Unintentional weight loss last 6 months	0	(Absent) 0 1 2 3 4 5 6 7 8 9 10 (Worst Imaginable)

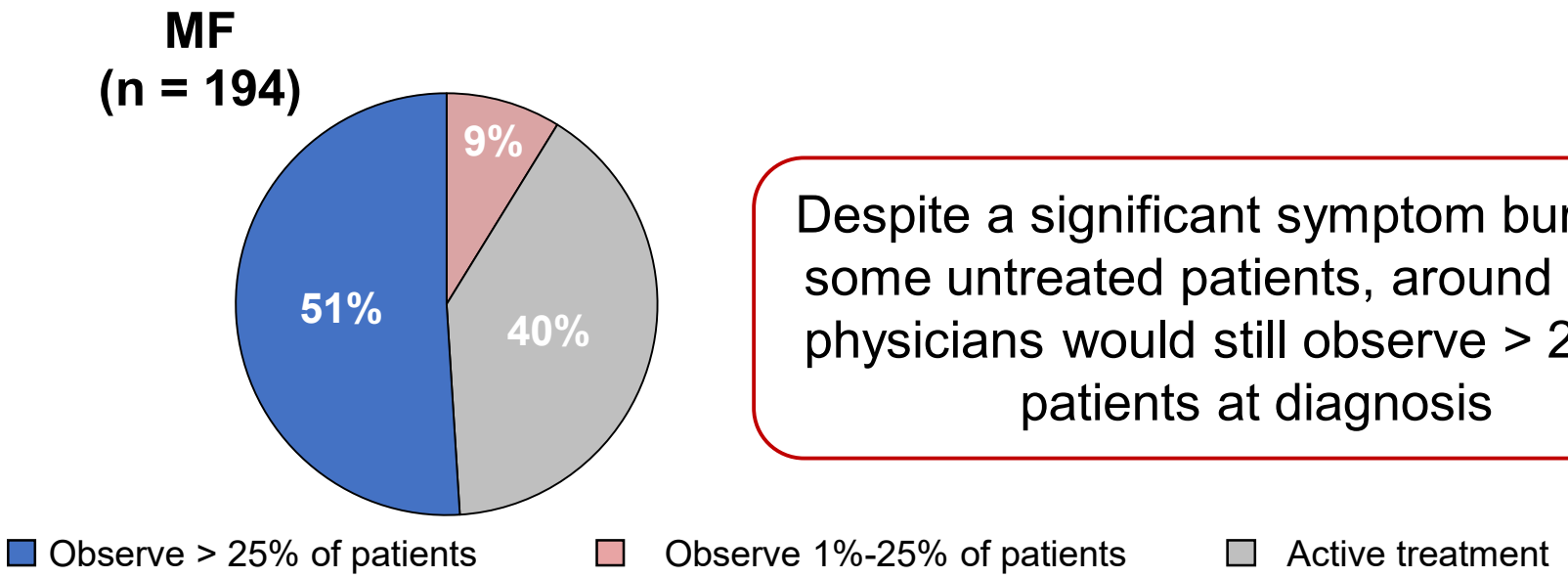
MPN10 is necessary for a standardized and quantitative assessment of MF-related symptoms

Scherber R et al, *Blood* 2011;118:401-408

MPN Patient Treatment—Watch and Wait

2016 International Landmark Study

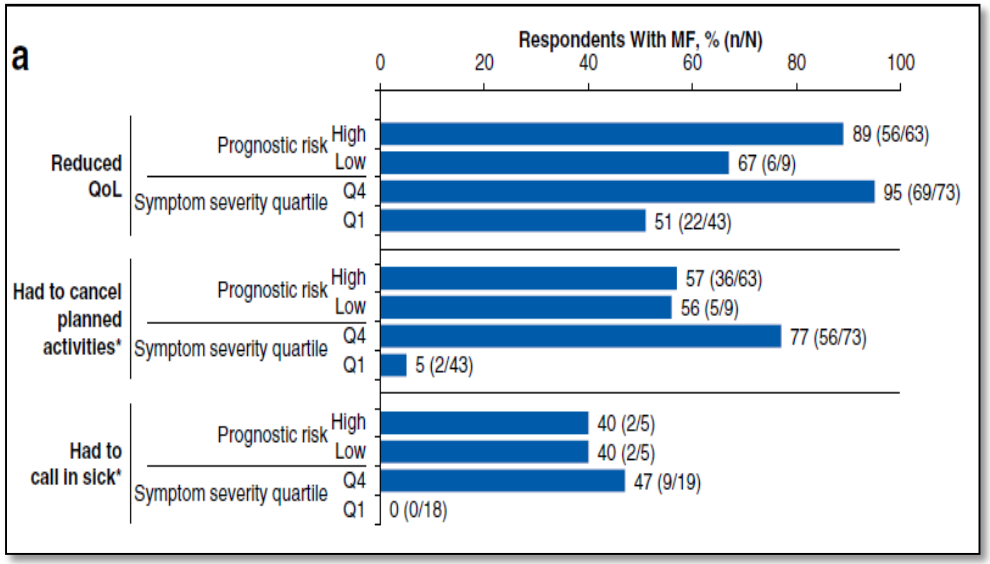
- 23% of patients managed with watch and wait had high to moderate symptom burden
- Only 36% reported not currently experiencing symptoms



Despite a significant symptom burden in some untreated patients, around half of physicians would still observe > 25% of patients at diagnosis

From Koschmieder S, et al. Congress of the European Hematology Association; June 22 - 25, 2017; Madrid, Spain [poster 706]. Reprinted with author's permission.

Early-Stage MF May Have a Significant Clinical Burden



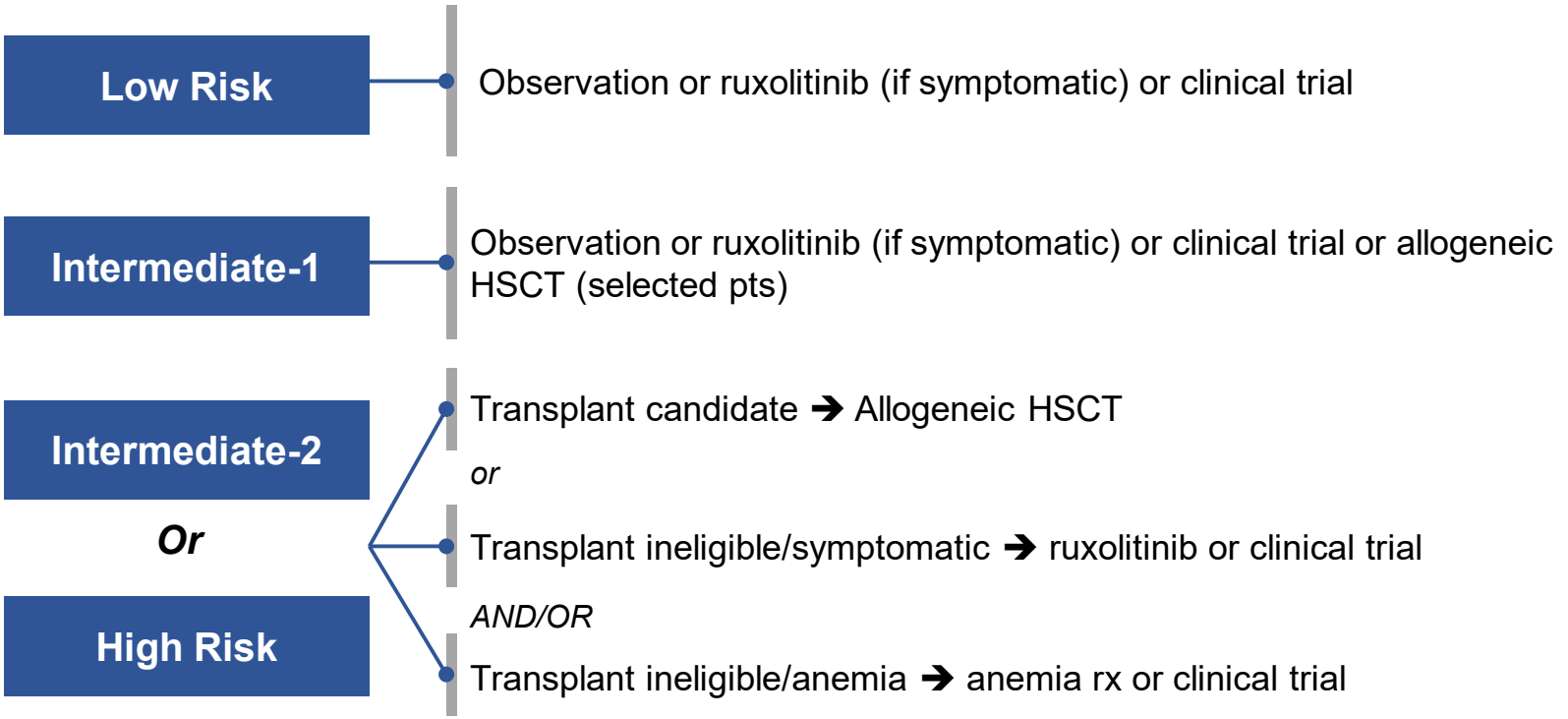
Reprinted from Mesa R, et al. BMC Cancer. 2016 Feb 27;16:167. Creative Commons Attribution 4.0 International License (https://creativecommons.org/licenses/by/4.0/).

- 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

- Increased TSS was also significantly associated with spleen size (> 10 cm: mean TSS, 25.2 vs 30.0, *P* = .02; > 15 cm: 25.5 vs 32.9, *P* = .004)
- A cutoff criteria of the worst single symptom being > 5/10 using the MPN10 and MPN ≥ 44/100 have been suggested for identifying patients who will most benefit from symptom-based treatment . Also, severe itching/fever/relevant weight loss may trigger treatment irrespectively of overall MPN10 score

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.

NCCN Guidelines 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

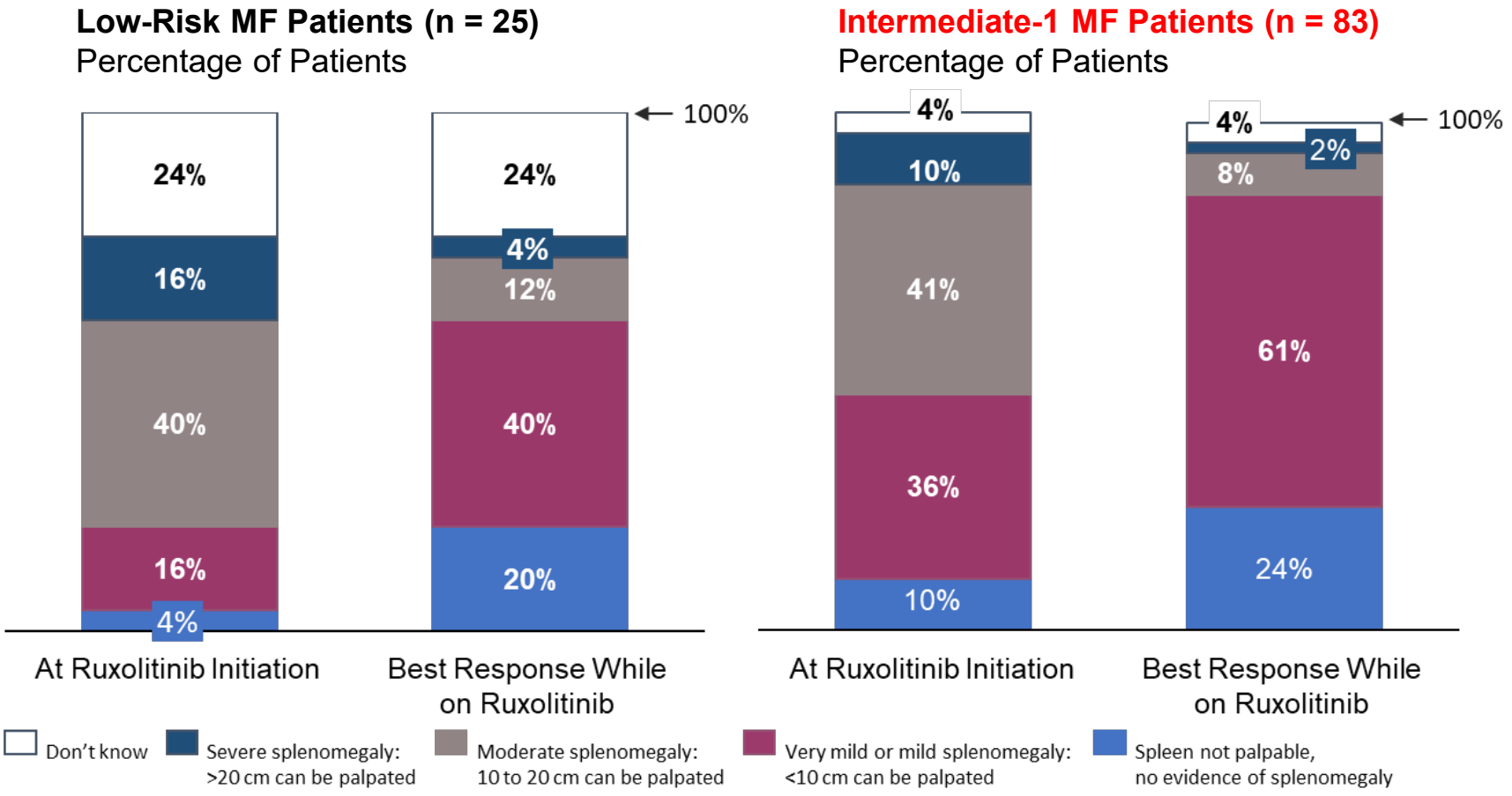
Adapted from National Comprehensive Cancer Network (NCCN). Myeloproliferative Neoplasms (Version 2.2017, https://www.nccn.org/professionals/physician_gls/pdf/mpn.pdf

HU for First-line MF Treatment

- Ruxolitinib is preferred medication for control of symptoms and splenomegaly
- Use of HU reserved for isolated cases of progressive leukocytosis or thrombocytosis

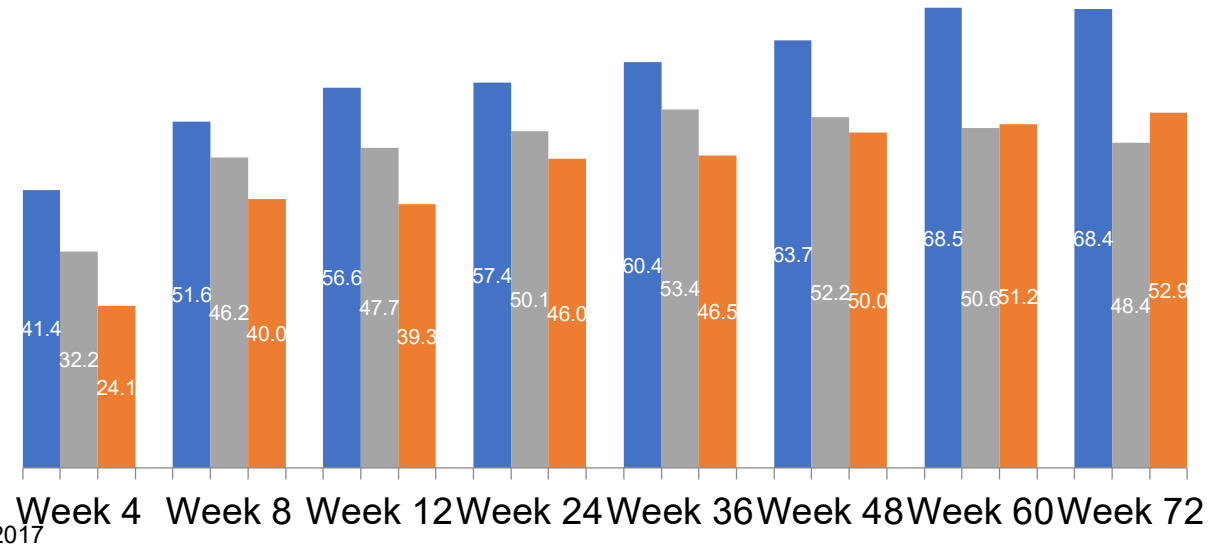
A Real-Life Retrospective US-based Study of Ruxolitinib in Lower Risk IPSS Patients

Spleen Size Distribution



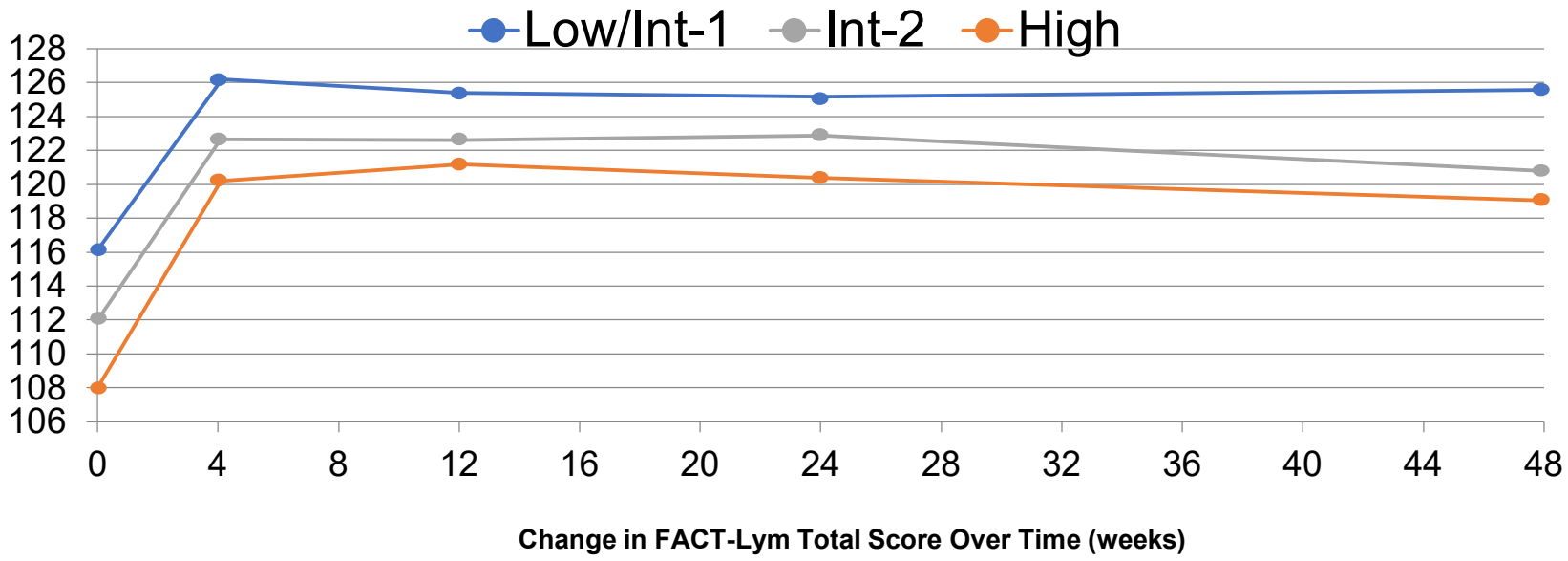
JUMP study: patients intermediate-1 risk benefit from ruxolitinib – spleen response

- phase IIIb expanded access study
- enrolled 2233 patients in 26 countries
- Allowed DIPSS low/Int-1/Int-2/high-risk MF
- Lower-risk patients received higher starting doses yet had lower rates of hematologic AEs



Passamonti et. al. EHA Poster 2017

JUMP study: patients intermediate-1 risk benefit from ruxolitinib – symptoms response



Passamonti et. al. EHA Poster 2017

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%

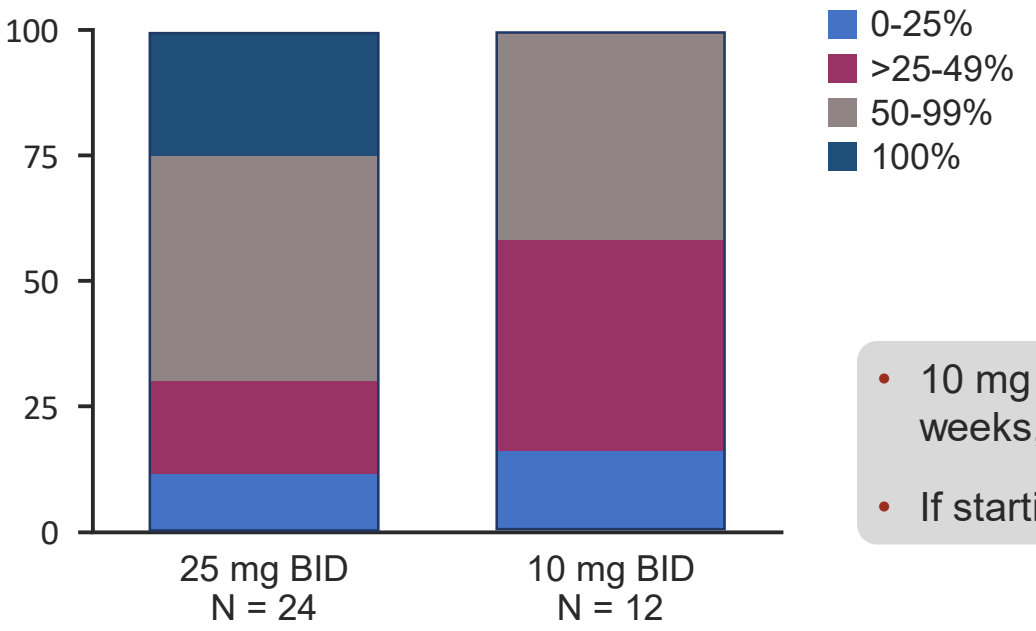
IPSS intermediate-1 patients may possibly achieve higher reponse rates and experience lower toxicities than patients with higher-risk disease

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.

Spleen Response Analysis Based on Starting Ruxolitinib Dose: Phase 1

Proportion of Subjects

% Reduction in Spleen or Liver



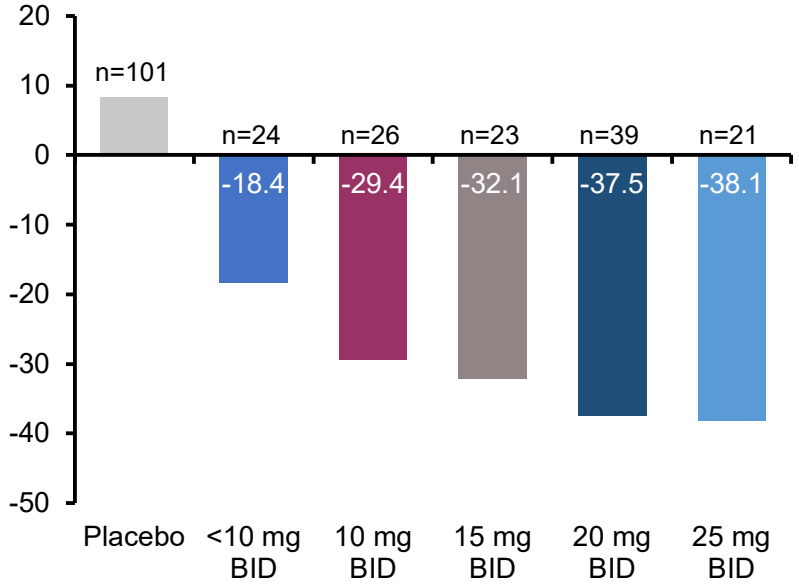
- 10 mg BID allowed to escalate dose after 12 weeks, not before, and had poor response!
- If starting with low dose, escalate fast!

Verstovsek S et al. *Blood* 2012;120(6):1202-1209

Ruxolitinib Efficacy by Titrated Dose: COMFORT-I

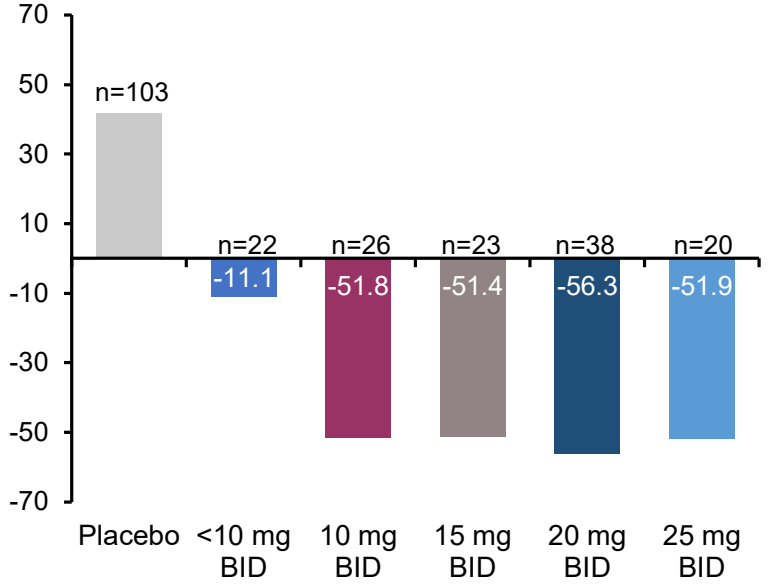
Spleen Volume

Week 24



Total Symptom Score

Week 24

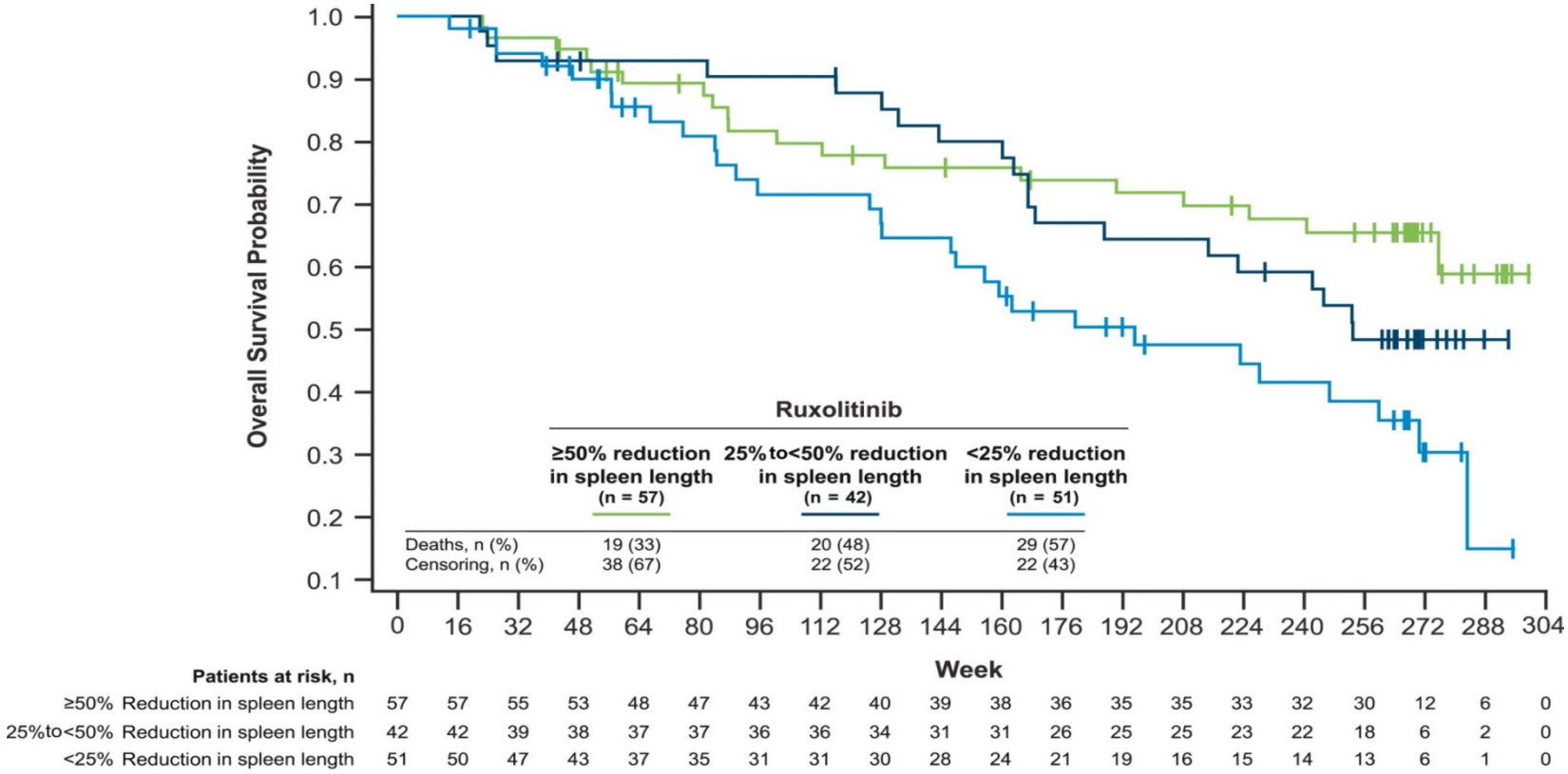


- Avoid starting with low dose!
- Start dosing per guidelines and modify based on platelets if needed
- Doses less than 10 mg BID are not effective long term

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

Overall Survival of Patients by Degree of Spleen Length Reduction on Ruxolitinib (COMFORT-I)

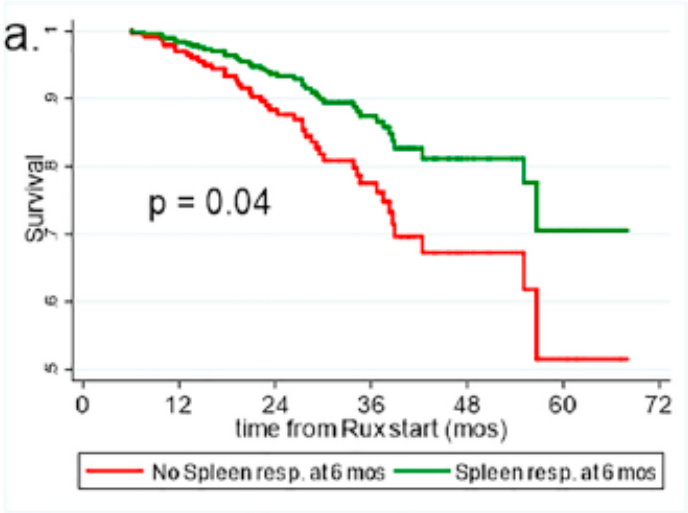
Overall survival probability



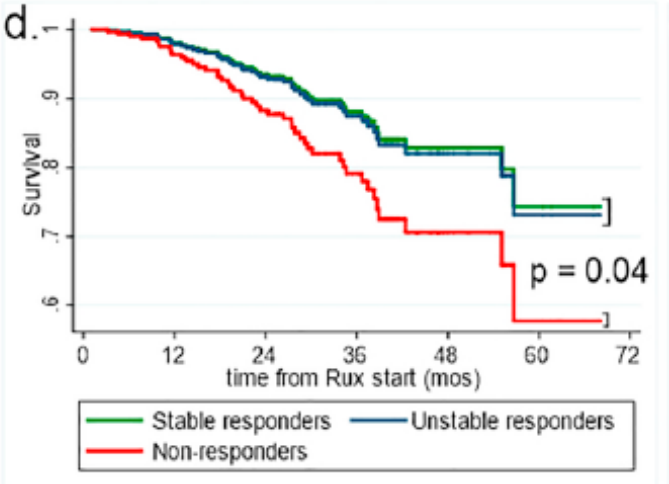
Spleen Response Affects Outcomes of Ruxolitinib-Treated Patients With MF

- Multicenter study (N = 284)[1]

OS by spleen response at 6 months



OS by durability of spleen response



Baseline factors associated with lower spleen response to RUX include High/Int-2 disease severity, spleen size >20 cm; high WBC; delay in RUX start after diagnosis, and titrated doses <10 mg BID.[2,3]

1. Palandri F, et al. *Leuk Res.* 2018;74:86-88; 2. Palandri F, et al. *Oncotarget.* 2017;8:79073-79086; 3. Menghrajani K, et al. *Leuk Lymphoma.* 2018; Sep 20:1-7 [E-pub ahead of print].

Rationale for Use of Ruxolitinib in Early MF Patients

A Retrospective Italian Study (N = 408)

1. The influence of disease stage on a quality of response
   - A more advanced disease and a delay in treatment start may reduce ruxolitinib efficacy
   - Spleen/symptoms responses are lower if
     - Time interval between MF diagnosis and ruxolitinib start > 2 years
     - Larger splenomegaly/higher TSS
     - Transfusion dependency/lower platelet count
     - Int-2/high IPSS risk
2. The influence of ruxolitinib dose
   - Early MF patients may tolerate a higher ruxolitinib dose
   - Patients starting with higher doses have a higher rate of spleen responses
   - The use of lower ruxolitinib doses may also result in reduced efficacy

Palandri F, et al. *Oncotarget.* 2017; 8:79073-79086.

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)
- Data comparing ruxolitinib vs other treatment options in lower risk patients are needed

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- 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

MPN, JAK inhibitors, and Lymphoma

- **Porpaczy et al BLOOD 2018**
  - **N= 626 with MPN; n=69 with MF receiving JAKi**
  - **B-cell lymphomas → 4 (5.8%) of 69 patients receiving JAKi compared with 2 (0.36%) of 557 with standard/other treatments (16-fold increased risk)**
  - **A similar 15-fold increase was observed in an independent cohort of 929 patients with MPN**
  - **The Lymphomas occurring during JAKi therapy were preceded by a preexisting B-cell clone in all 3 patients that were evaluated**

- **Pemmaraju et al BLOOD 2019**
  - **2,500 + MPN patients**

n=9 total had lymphoma ; n=6 after JAKi, n=3 without JAKi (p=value Not significant)

  - **No statistically significant difference in cases of lymphoma after JAKi vs no JAKi**

Porpaczy, et al BLOOD 2018; Pemmaraju et al BLOOD Feb 2019

THANK YOU

sverstov@mdanderson.org

Case Presentation 1

- A 58-year-old female is referred to you due to CBC abnormalities found on routine exam
- On physical exam she is found to have spleen of 9 cm, and no other significant physical exam findings but she also c/o significant fatigue, itching, night sweating, low grade fever, and some weight loss. PS is 1
- CBC shows: Hb 10.9, WBC: 18,000, with 8% metamyelocytes and 0% blasts, and platelets: 162,000
- LDH is 1780; erythropoietin is 35 (high)
- BM is compatible with MF, *JAK2* mutation positive

What is the Appropriate Next Step?

- Observation, with follow-up in one month
- Prednisone
- Interferon
- Thalidomide + prednisone
- Ruxolitinib
- Hydroxyurea
- Erythropoietin injections
- Other (combo?)

Follow-Up

- You prescribe ruxolitinib at the dose of 15 mg twice a day, as per guidelines
- You follow up with patient in 3 weeks and see her again in another 4 weeks, at which time patient reports feeling much better, without any symptoms, eating more and having no side effects
- Spleen is 2 cm by exam
- CBC shows Hb 8.9 g/dl, platelet count of 97,000 and a WBC of 11,200

What Would You Recommend at This Time?

- Add erythropoietin
- No change in therapy
- Thalidomide + prednisone
- Ruxolitinib at 10 mg twice a day
- Ruxolitinib at 5 mg twice a day
- Hydroxyurea
- Add danazol
- immediate transplant, or other…

Follow-Up

- You decided not to change therapy and continue to see patient monthly, and after 3 additional months patient still reports feeling great, has gained 6 pounds, and has no side effects
- Spleen is not palpable
- Hb is 9.8 g/dl, platelet count 95,000 and a WBC of 11,600

Case 2:

- A 68 year old female presents with c/o of abdominal discomfort to local doctor who referred patient to you because of enlarged spleen and abnormal CBC

Characteristic	Finding
Current laboratory values	▪ Hgb 9.9 g/dL ▪ WBC: 18 x 10^9/L with no blasts ▪ Platelets: 122 x 10^9/L ▪ LDH 1780 ▪ Erythropoietin 35 (high) ▪ BM is compatible with MF
Physical examination and interview	▪ Spleen of 15 cm ▪ She c/o abdominal fullness and early satiety, and no other symptoms

What is appropriate next step?

- Observation, with follow up in one month
- Prednisone
- Peg-IFNα2a
- Thalidomide + prednisone
- Ruxolitinib
- Hydroxyurea
- Erythropoietin injections
- Other

Follow up

- You prescribe ruxolitinib 15 mg twice a day due to low platelets
- You follow up with patient in 2 weeks and see her again in 1 week at which time patient reports feeling better, eating more and have no side effects; spleen is 2 cm
- CBC shows Hgb 8.2 gm/dL, platelet count of 68,000 and a WBC of 11,200

What would you recommend at this time?

- Erythropoietin
- No change in therapy
- Thalidomide + prednisone
- Ruxolitinib at 10 mg twice a day
- Ruxolitinib at 5 mg twice a day
- Hydroxyurea
- Allotransplant
- Other (combinations, cladribine,…)

Follow up

- You decided to decrease the dose of ruxolitinib to 5 mg twice a day due to rapid decrease of platelets. After another month of therapy you see the patient in a follow up: patient reports feeling better than before ruxolitinib but now again has some fatigue
- You feel that spleen has regrown to 5 cm
- Hgb is 8.9 gm/dL, platelet count 97,000 and a WBC of 16,600

What would you recommend at this time?

- Erythropoietin
- No change in therapy
- Peg-IFNα2a
- Thalidomide + prednisone
- Ruxolitinib at 10 mg twice a day
- Hydroxyurea
- Allotransplant
- Ruxolitinib at 15 mg twice a day

Follow up – Case #2

- You have increased ruxolitinib to 10 mg twice a day
- Her hemoglobin is now 8.8 gm/dL, platelet count 77,000 and a WBC of 14,600
- Patient feels great and spleen is barely palpable

Case 1:

- A 56-yr-old man living with established *MPL* mutation-positive primary myelofibrosis. Patients regular doctor is about to retire

Characteristic	Finding
Past treatments	▪ Prednisone and thalidomide, for anemia (transfused PRBC every 4 months), currently no therapy
Current laboratory values	▪ Hgb is 8.9 gm/dl ▪ Platelets: 189 x 10^9/L ▪ WBC 19 x 10^9/L with 2% blasts
Physical examination and interview	▪ Liver is enlarged 4 cm by palpation and spleen to 12 cm ▪ Patient is skinny but only c/o fatigue and occasional SOB

What would you choose as the best therapy for this man?

- Hydroxyurea
- Peg-IFNα2a
- Allotransplant
- Ruxolitinib
- Clinical trial
- Lenalidomide + prednisone
- Observation
- Best supportive care/hospice

Follow up

- Assume you asked for transplant consult but donor is not available
- Ruxolitinib started 15 mg twice a day
- Over 3 months patient gained 6 kg and that his fatigue resolved; he feels “better then ever”
- He needed 4 blood transfusions during these 3 months
- Spleen and liver markedly reduced in size

What would you choose as the best next step in therapy for this man?

- No change
- Peg-IFNα2a
- Clinical trial with different JAK2 inhibitor
- Add androgens
- Lenalidomide + prednisone
- Decrease ruxolitinib dose to 10 mg BID
- Other

Follow up – Case 1

- You select to add danazol
- Over next 6 months patient gained another 4 kg, and goes to gym regularly
- His PRBC transfusion decreased to 1 every 3 months
- Spleen and liver became non palpable