2nd edition

Unmet challenges in high risk hematological malignancies: from benchside to clinical practice

Turin, September 13-14, 2021

Starhotels Majestic

Scientific board:
Marco Ladetto (Alessandria)
Umberto Vitolo (Candiolo-TO)

How I treat high risk myeloproliferative neoplasms

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Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
BMS-Celgene						X	
Novartis						X	
Janssen						X	

Clinical risk stratification for myelofibrosis

Variable	IPSS	DIPSS	DIPSS-plus
Age > 65 years	✓	✓	✓
Constitutional symptoms	✓	✓	✓
Hb < 10 g/dL	✓	✓[a]	✓[a]
Leukocyte count > 25 × 10^9/L	✓	✓	✓
Circulating blasts ≥ 1%	✓	✓	✓
Platelet count < 100 × 10^9/L			✓
RBC transfusion need			✓
Unfavorable karyotype +8, −7/7q−, i(17q), inv(3), −5/5q−, 12p−, 11q23 rear.			✓

[a] accounts for 2 adverse points.

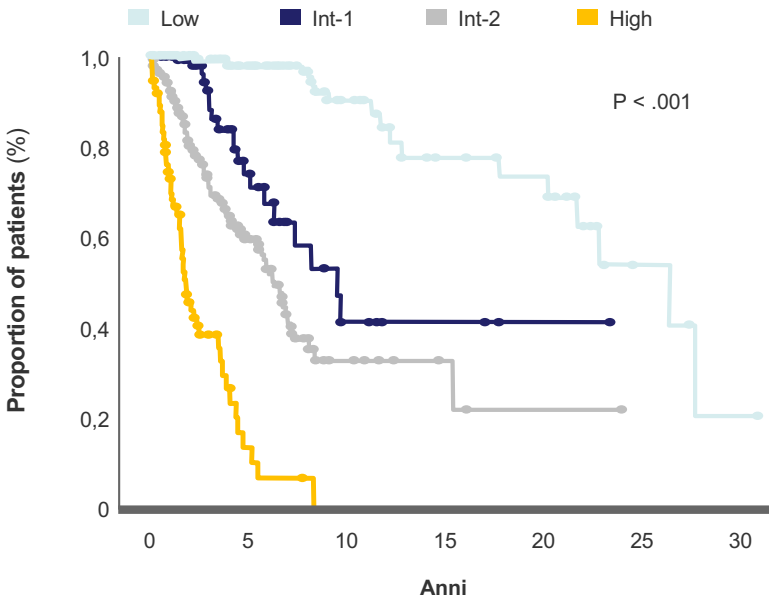
	IPSS		DIPSS		DIPSS-plus	
Risk category	Score	Median OS (years)	Score	Median OS (years)	Score	Median OS (years)
Low	0	11.2	0	NR	0	15.0
Int-1	1	7.9	1–2	14.2	1–2	6.6
Int-2	2	4.0	3–4	4.0	3–4	2.1
High	≥ 3	2.2	≥ 5	1.5	5–6	1.3

Cervantes F, et al. Blood. 2009;113:2895-901.
Gangat N, et al. J Clin Oncol. 2011;29:392-7.
Passamonti F, et al. Blood. 2010;115:1703-8.

High Molecular Risk (HMR) : How Many Patients Would be Reclassified?

IPSS Risk Categories	*ASXL1* N. (%)	*EZH2* N. (%)	*SRSF2* N.(%)	*IDHs* N. (%)	N (%) Of HMR patients
LOW	24/162 (14.8%)	6/165 (3.6%)	7/151 (4.6%)	2/157 (1.3%)	**35/166 (21.1%)**
INT- 1	28/142 (19.7%)	6/143 (4.2%)	6/136 (4.4%)	6/142 (4.2%)	**34 /146 (23.4%)**
INT- 2	23/100 (23.0%)	4/99 (4.0%)	9/97 (9.3%)	2/96 (2.1%)	**31 /104 (29.8%)**
HIGH	27/65 (41.5%)	8/66 (12.1%)	16/63 (25.4%)	1/60 (1.7%)	**39/68 (57.3%)**

Towards refined prognostic scores: MIPSS



Variables

- age
- Hb
- PLTs
- Symptoms
- Triple negative *JAK2/MPL , ASXL1, SRSF2*

Risk category	Points	% of patients	OS yrs)	HR
low	0-0,5	27	26,4	1
Int-1	1-1,5	14	9,7	4,7
Int-2	2-3,5	46	6,4	9,9
high	≥4	13	1,9	36,5

MIPSS is better performing in predicting overall survival compared with IPSS

Vannucchi AM et al, ASH 2014

Mutation enhanced international prognostic scoring system for patients <70 yrs

MIPSS70 Risk Score: Variables Associated With Reduced OS

Variables	Weighted value
Hb < 100g/L	1
WBC > $25x10^9$/L	2
PLT < $100x10^9$/L	2
PB blasts ≥ 2%	1
Constitutional symptoms	1
Grade ≥ 2 BM fibrosis	1
Absence of *CALR* Type 1	1
HMR category*	1
≥ 2 HMR mutations	2

*Any mutation in: ASXL1, EZH2, SRSF2, IDH1/2
Guglielmelli P, et al. *J Clin Oncol.* 2018;36:310-318.

Guglielmelli P et al. JCO 2018

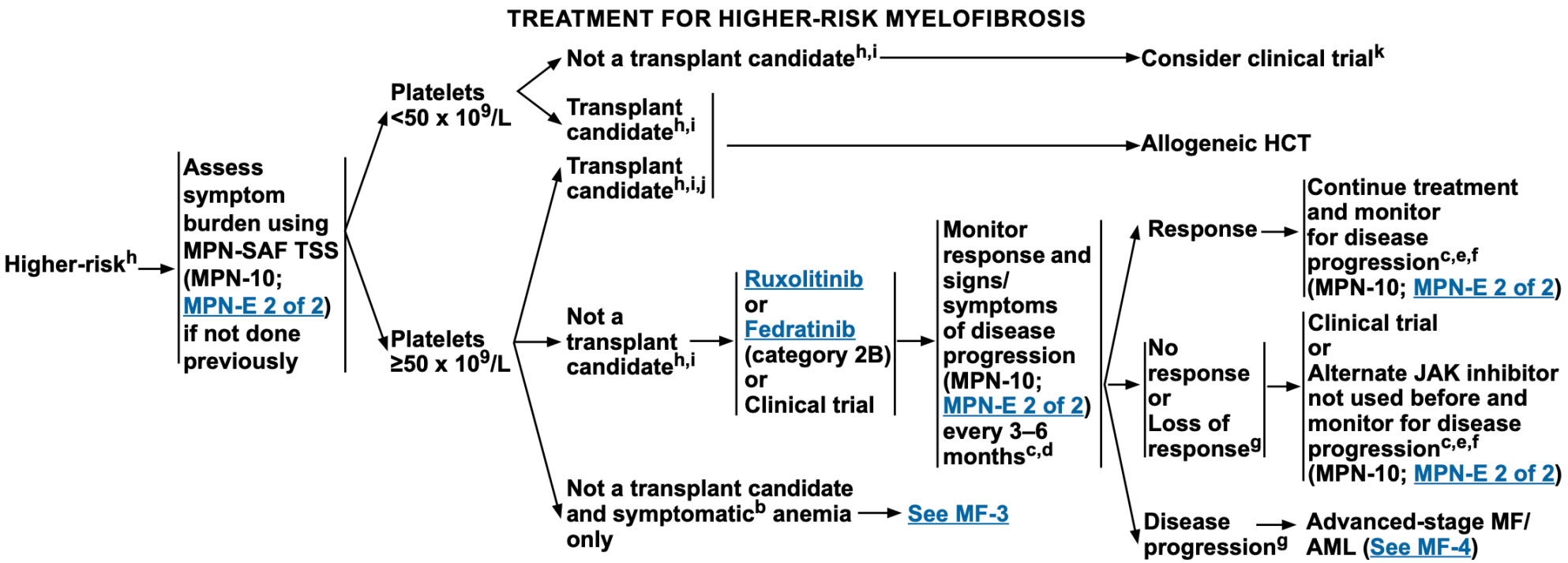
MIPSS70+ version 2.0

Hb
Circulating blasts
Symptoms

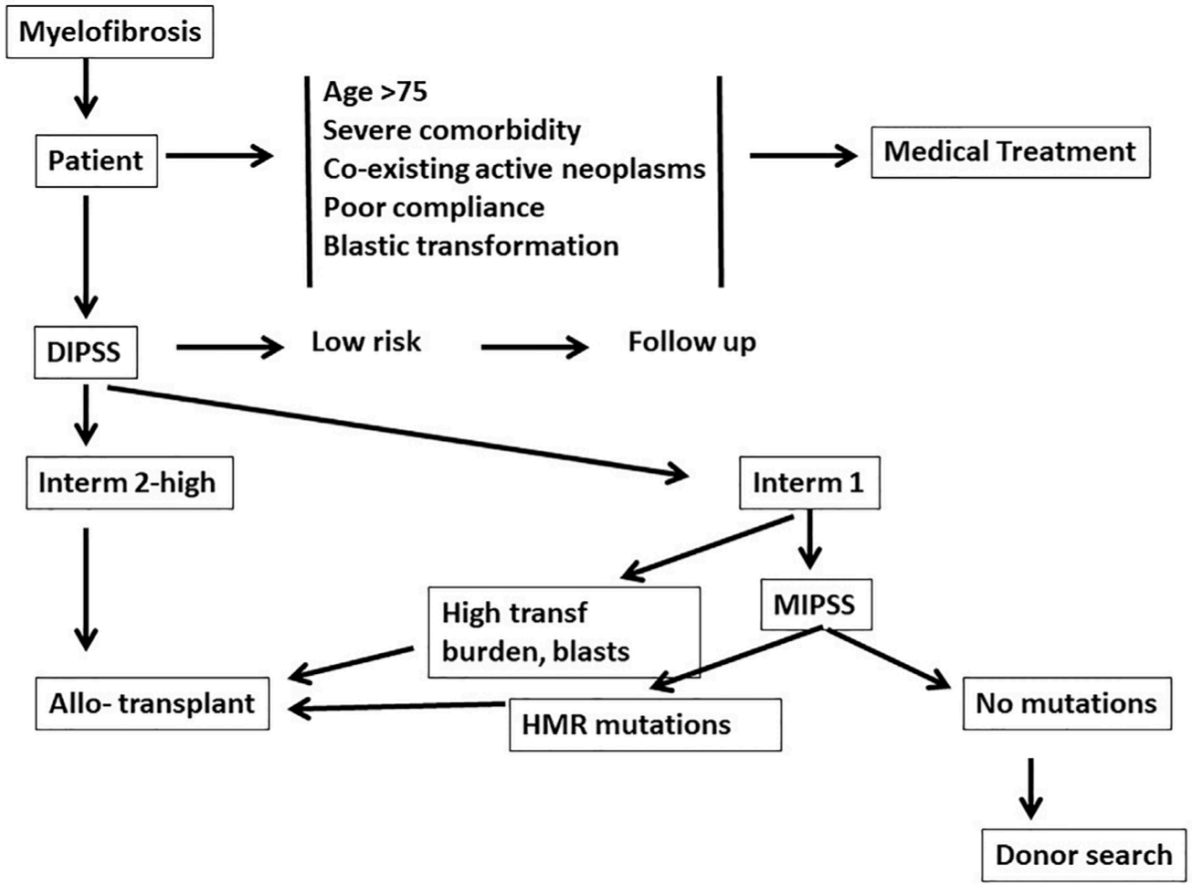
Molecular abnormalities
Cytogenetic

Tefferi JCO 2018

NCCN guidelines for the treatment of high risk myelofibrosis



Allogeneic Hemopoietic Stem Cell Transplantation for Myelofibrosis: 2021

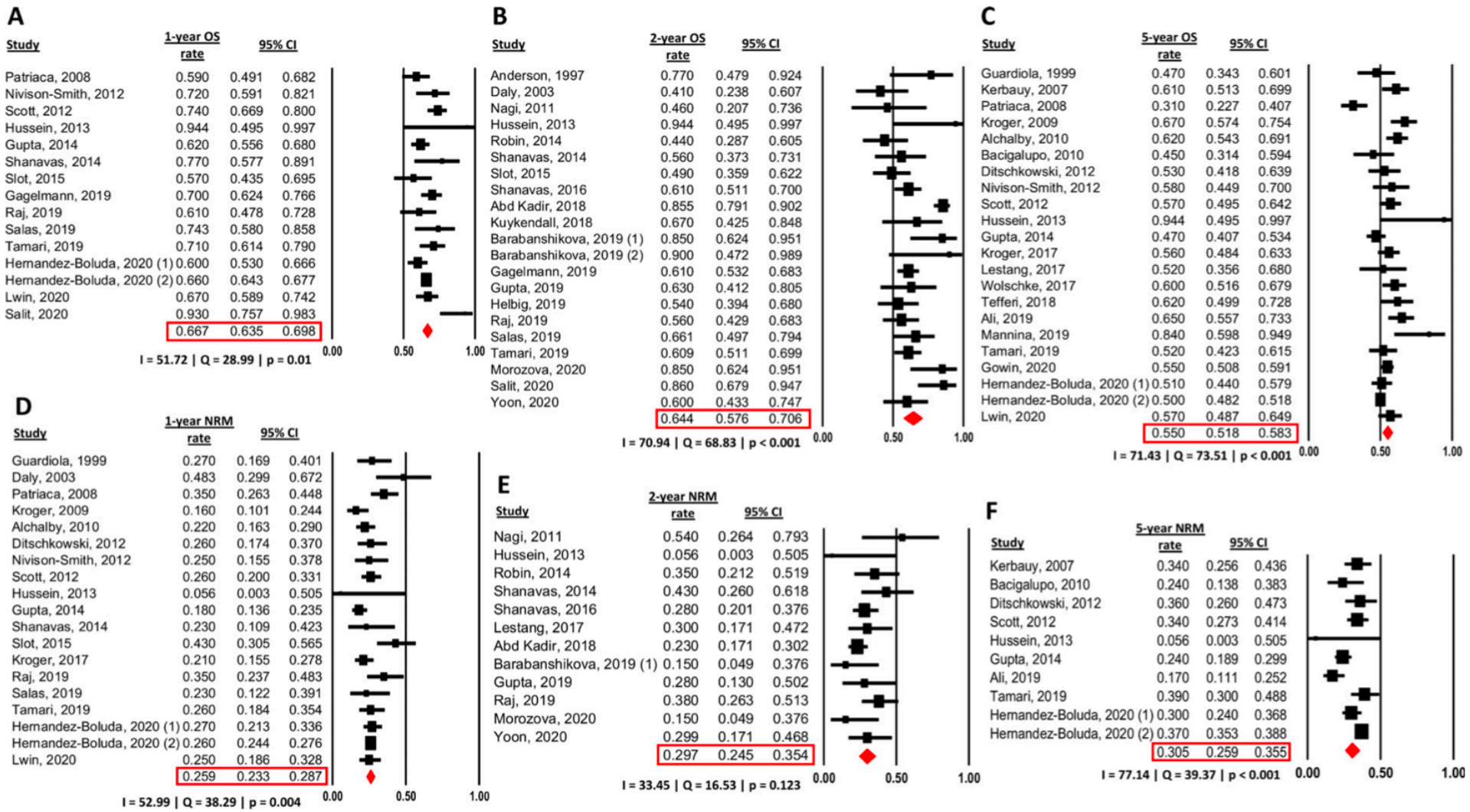


Bacigalupo et al. Frontiers in Immunology 2021

Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients With Myelofibrosis—A Systematic Review and Meta-Analysis

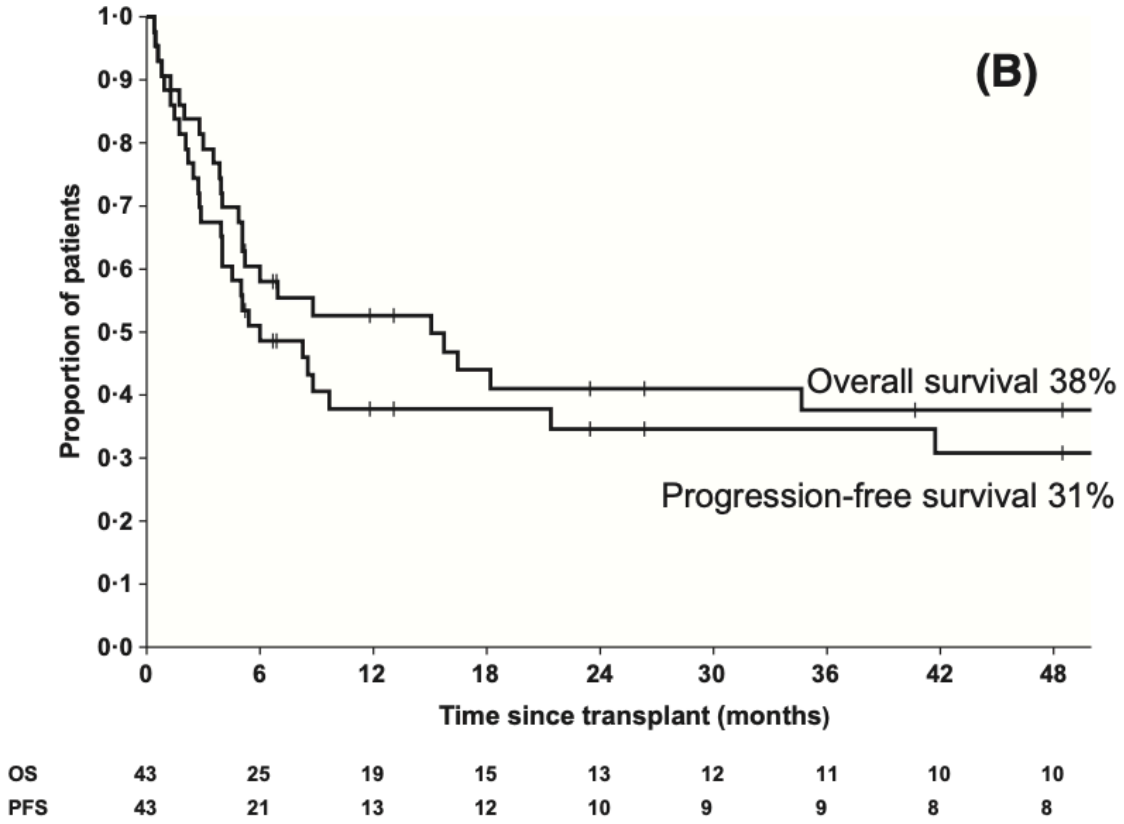
43 studies with 8739 pts

Jan Philipp Bewersdorf[1], Amar H. Sheth[2], Shaurey Vetsa[3], Alyssa Grimshaw[4], Smith Giri[5], Nikolai A. Podoltsev[1,6], Lohith Gowda[1], Roni Tamari[7], Martin S. Tallman[8], Raajit K. Rampal[8], Amer M. Zeidan[1,6,†], Maximilian Stahl[9,*,†]



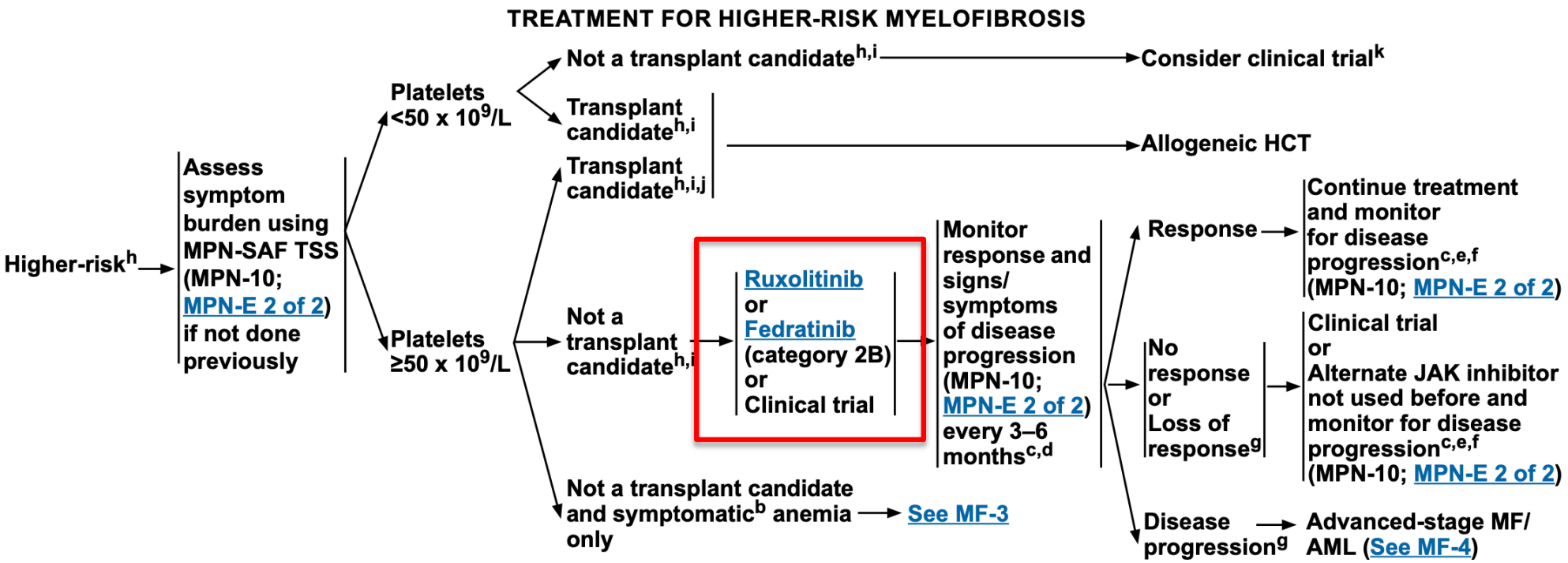
Transplantation and Cellular Therapy, 2021

Allogeneic stem cell transplant for patients with myeloproliferative neoplasms in blast phase: improving outcomes in the recent era



Shah et al. BJH 2021

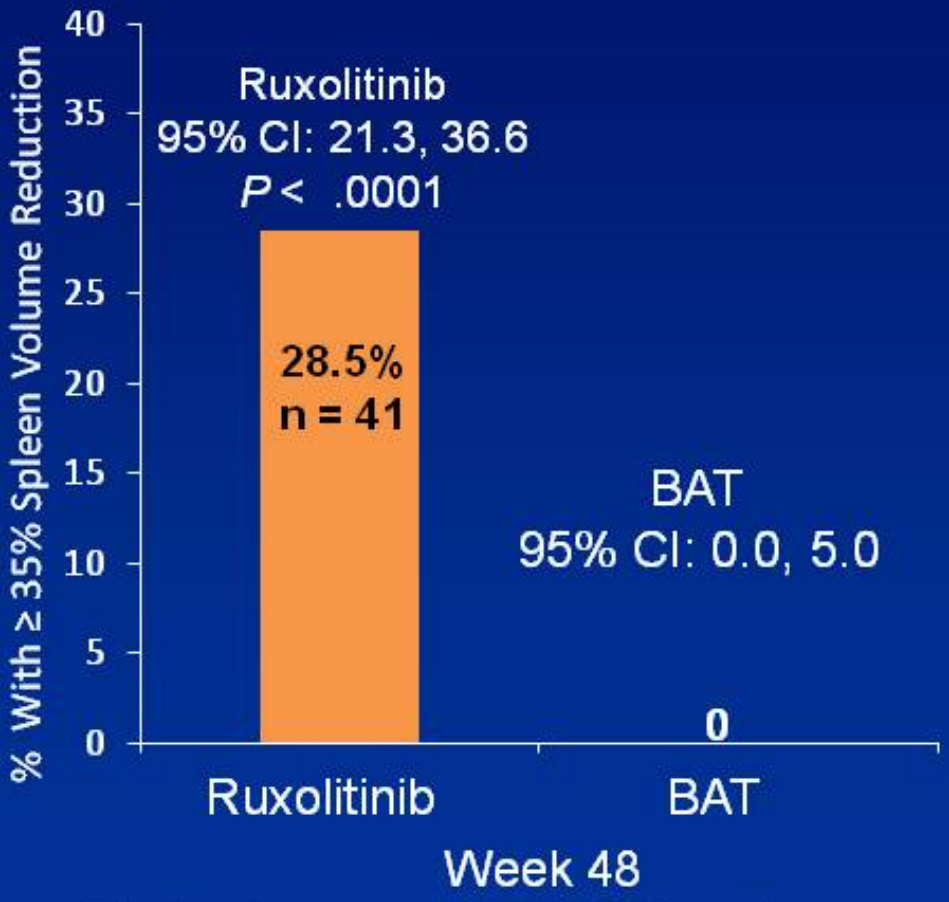
NCCN guidelines for the treatment of high risk myelofibrosis



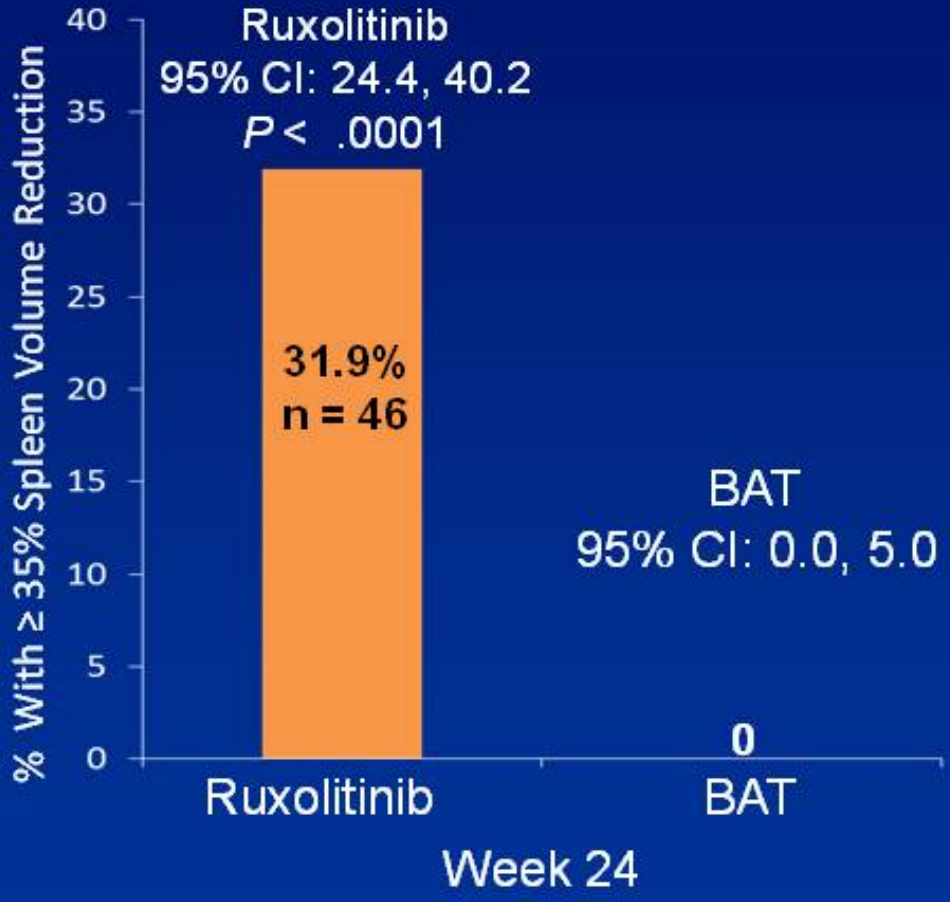
COMFORT-II

Efficacy Results (ITT)

Primary Endpoint



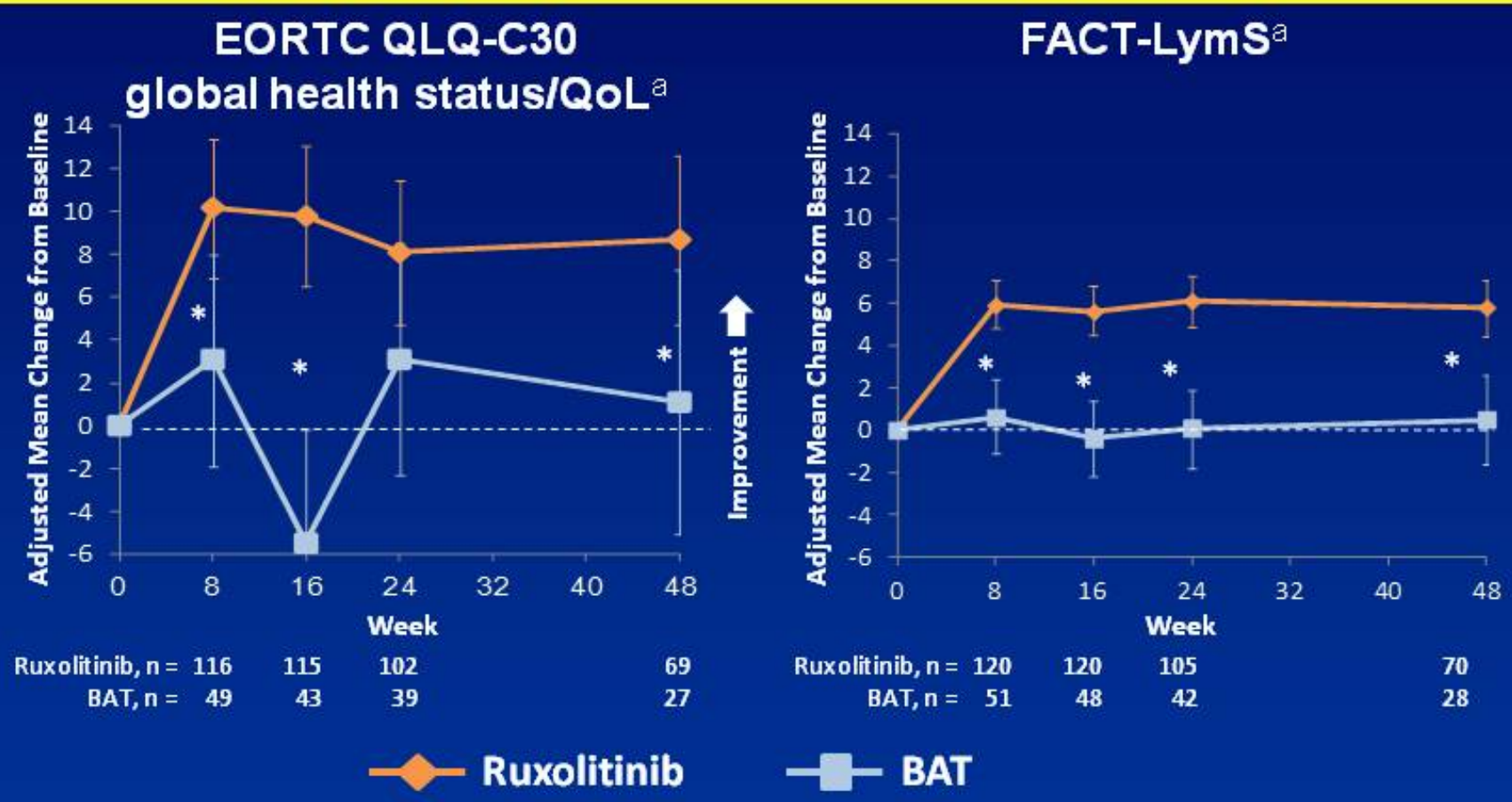
Key Secondary Endpoint



- Median time to response, 12.29 weeks
- Median duration has not been reached

Harrison C. et al. N Engl J Med. 2012 Mar 1;366(9):787-98.

Change from Baseline in EORTC QLQ-C30 Global Health Status/QoL and FACT-LymS



Compared with the BAT arm, Global Health Status/QoL and the FACT-LymS were significantly improved in the ruxolitinib arm at weeks 8, 16, and 48

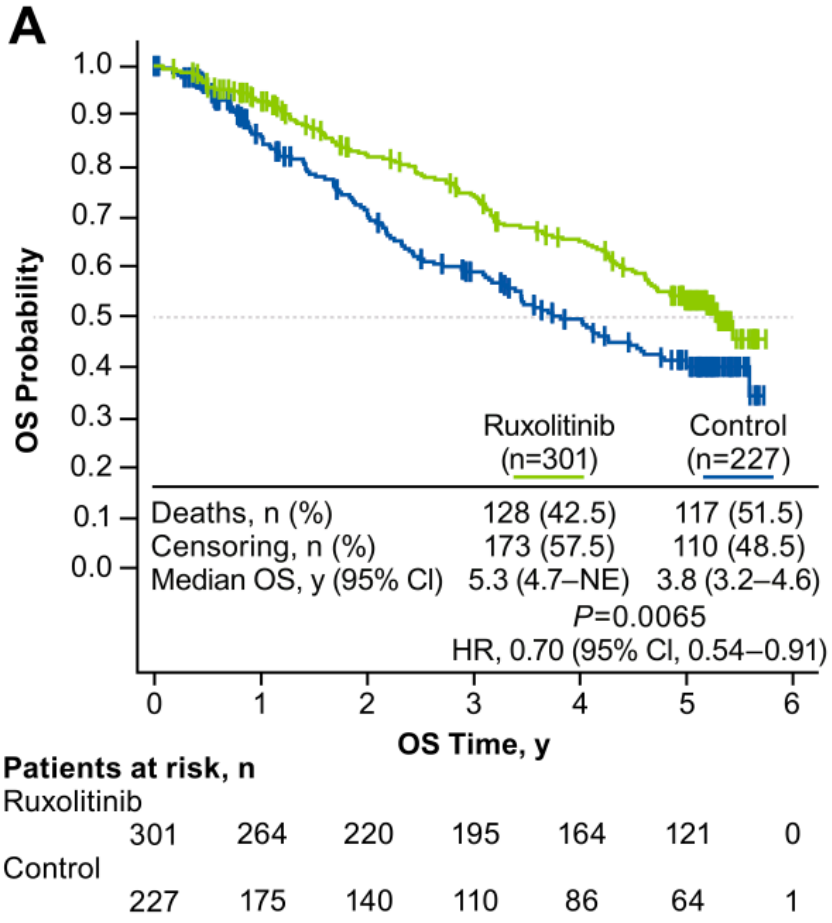
[a] Adjusted for age, sex, baseline score, and prognostic risk category.

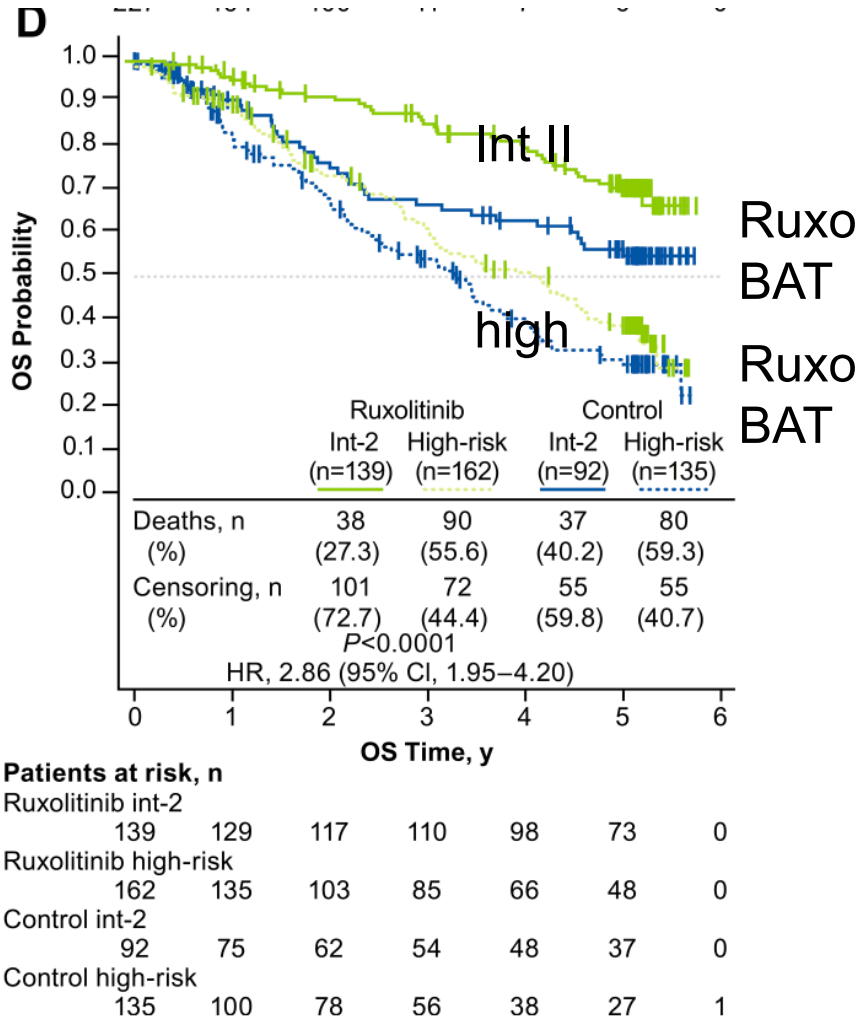
* $P < .05$ for treatment difference (from the mixed model).

Harrison C, et al. Oral presentation at ASH Annual Meeting; Dec 10-13, 2011. Abstract 795.

Long-term survival in patients treated with ruxolitinib for myelofibrosis: COMFORT-I and -II pooled analyses

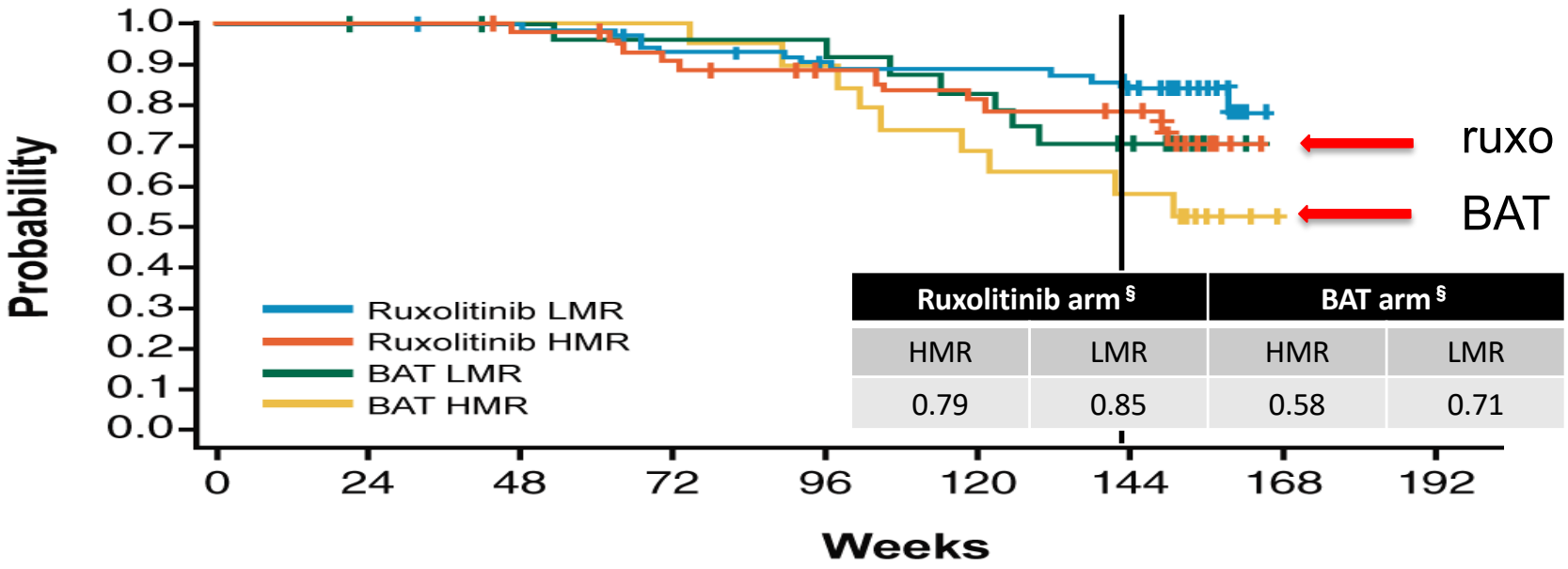
30% reduction of the risk of death compared to BAT after 5 yrs





Verstovsek S.et al. J Hematol Oncol 2017

Survival Estimates in Patients in COMFORT-II Stratified by Treatment and Molecular Score



Ruxolitinib arm §		BAT arm §	
HMR	LMR	HMR	LMR
0.79	0.85	0.58	0.71

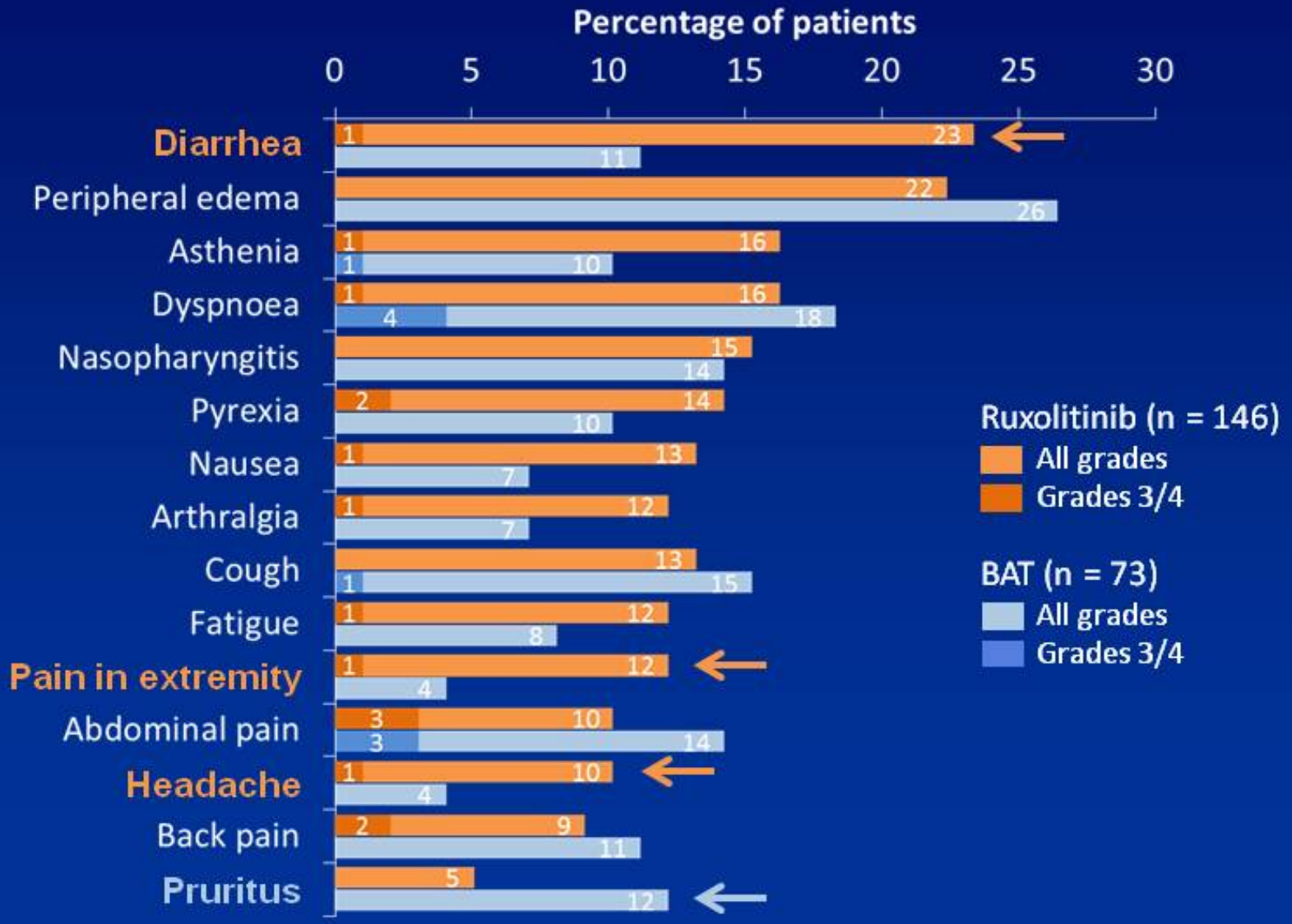
- In multivariate analysis of overall survival by treatment and molecular risk, the HR for treatment (ruxolitinib vs BAT) was 0.57 (95%CI= 0.30-1.08) and for LMR vs HMR the HR was 0.62 (95%CI=0.33-1.16)

§ Median follow up= 151 weeks; Kaplan Meier estimates at 144 weeks

Guglielmelli P, et al. *Blood.* 2014; 123:2157-60

COMFORT-II

Nonhematologic Adverse Events Regardless of Study Drug Relationship (≥ 10% in Any Group)



Harrison C, et al. Oral presentation at 16th Congress of EHA; June 9-12, 2011. Abstract 1020.

JAK2 inhibitors

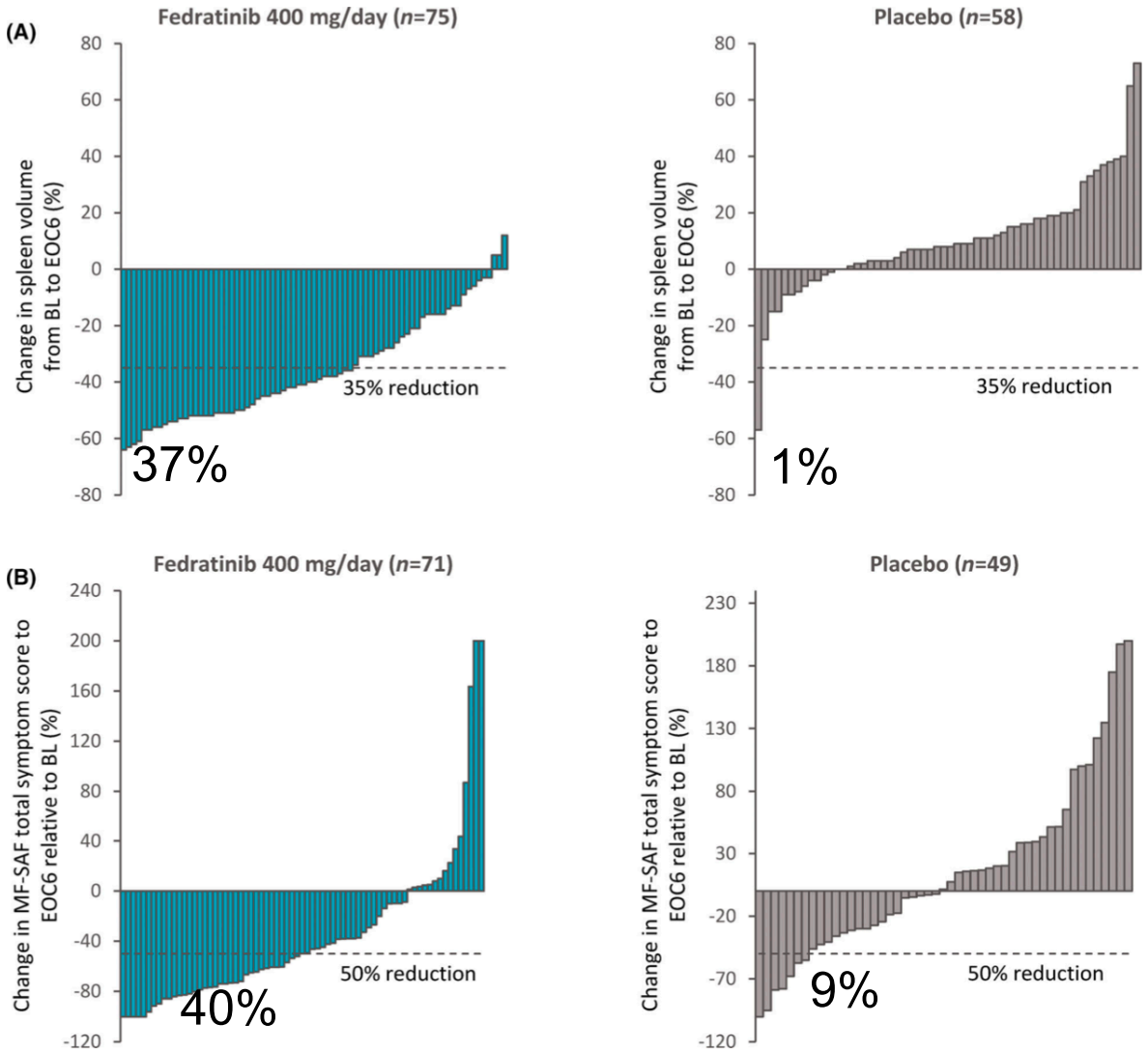
Table 1. Kinase profiles of current JAK2 inhibitors

	Enzyme IC_{50}, nM			
Kinase	**Fedratinib**	**Ruxolitinib**	**Pacritinib**	**Momelotinib**
JAK1	105	3.3	1280	11
JAK2	3	2.8	23	18
JAK3	1002	428	520	155
TYK2	405	19	50	17

Fedratinib (JAK2 and FLT3 inhibitor)

- 2011 Jakarta studies:
  - Jakarta I: Fedratinib vs placebo in first line MF
  - Jakarta II in Jakavi refractory or intolerant MF
- 2013: FDA put on hold the trials
- 2017 hold was lifted
  - FREEDOM I and FREEDOM II (Refractory/Intolerant)
- 2019 FDA approval for patients with int II or high risk MF in first line or R/I

Updated results of the placebo-controlled, phase III JAKARTA trial of fedratinib in patients with intermediate-2 or high-risk myelofibrosis

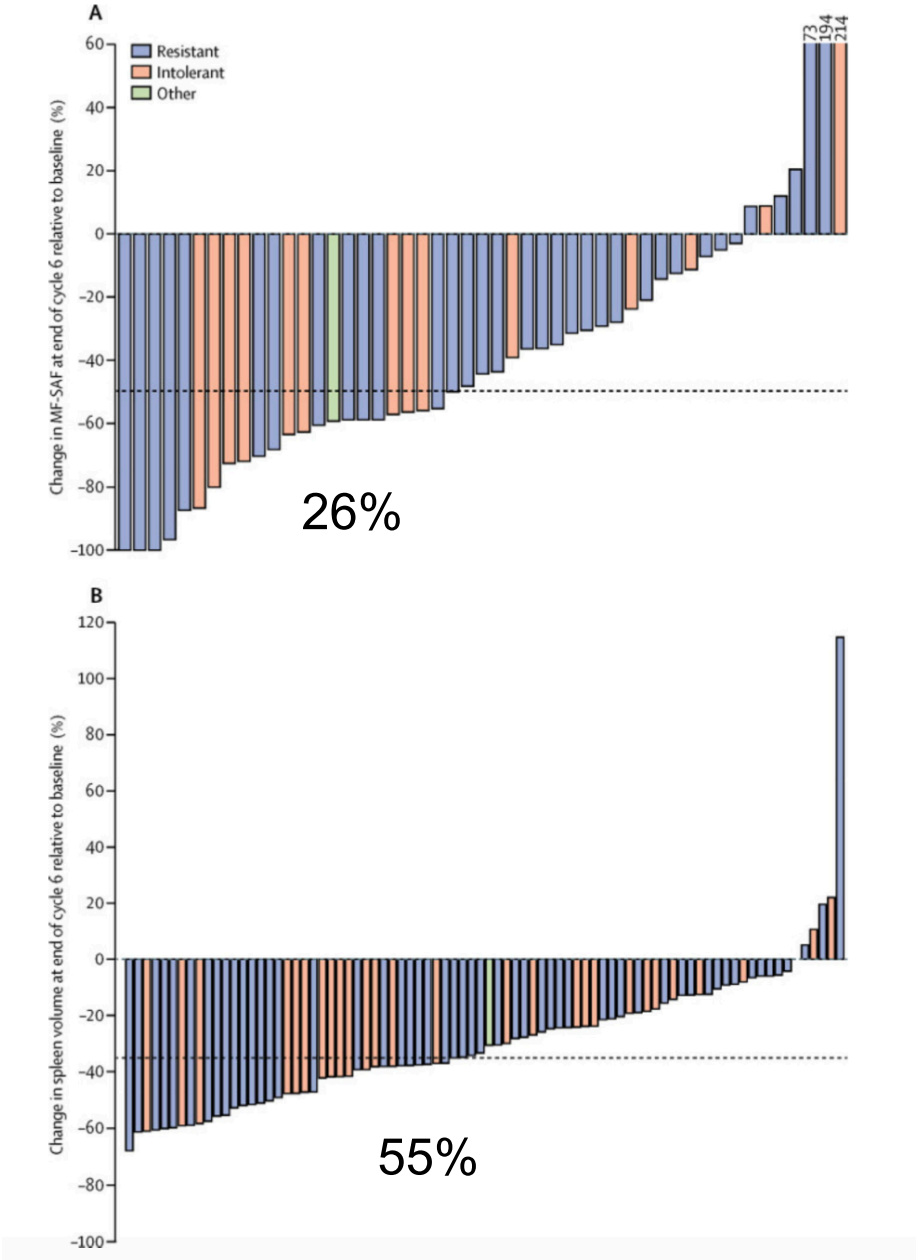


Pardanani et al. BJH 2021

	Fedratinib 400 mg (n = 96)		Placebo (n = 95*)	
	All grades %	Grade ≥3†	All grades	Grade ≥3
Adverse events‡				
Diarrhoea	66	5	16	0
Nausea	62	0	15	0
Anaemia	40	30	14	7
Vomiting	39	3·1	5	0
Fatigue or asthenia	19	5	16	1·1
Muscle spasms	12	0	1·1	0
Blood creatinine increased	10	1	1·1	0
Pain in extremity	10	0	4·2	0
ALT increased	9	0	1·1	0
Headache	9	0	1·1	0
Weight increased	9	0	4·2	0
Dizziness	8	0	3·2	0
Bone pain	8	0	2·1	0
Urinary tract infection§	6	0	1·1	0
Dysuria	6	0	0	0
AST increased	5	0	1·1	0
Laboratory parameters				
Haematology				
Anaemia	74	34	32	10
Thrombocytopenia	47	12	26	10
Neutropenia	23	5	13	3·3
Biochemistry				
Creatinine increased	59	3·1	19	1·1
ALT increased	43	1	14	0
AST increased	40	0	16	1·1
Lipase increased	35	10	7	2·2
Hyponatremia	26	5	11	4·3
Amylase increased‖	24	2·1	5	0

Pardanani et al. BJH 2021

Janus kinase-2 inhibitor fedratinib in patients with myelofibrosis previously treated with ruxolitinib (JAKARTA-2): a single-arm, open-label, non-randomised, phase 2, multicentre study



Efficacy on symptoms

Efficacy on spleen volume

Harrison et al. Lancet Haematol. 2017

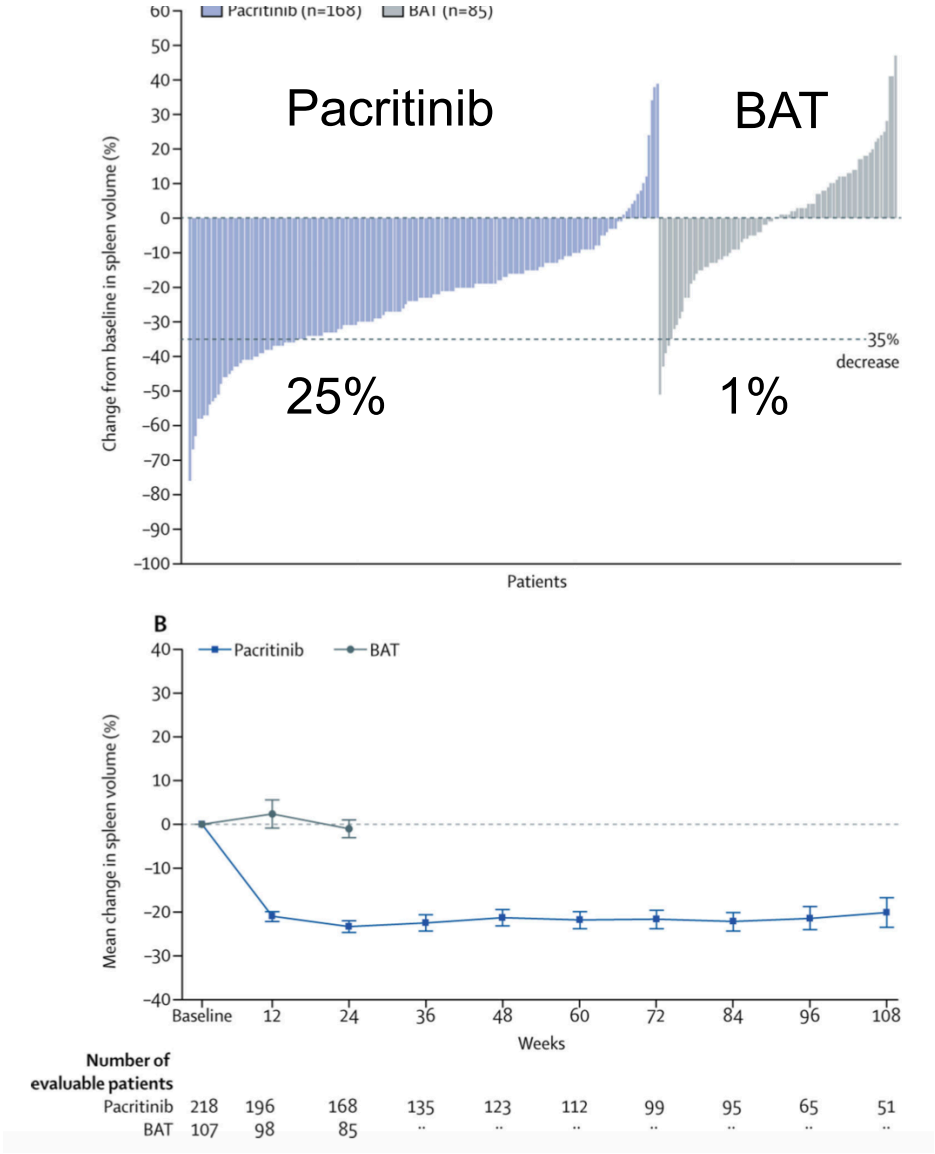
What's next?

Table 1. Kinase profiles of current JAK2 inhibitors

	Enzyme IC_{50}, nM			
Kinase	**Fedratinib**	**Ruxolitinib**	**Pacritinib**	**Momelotinib**
JAK1	105	3.3	1280	11
JAK2	3	2.8	23	18
JAK3	1002	428	520	155
TYK2	405	19	50	17

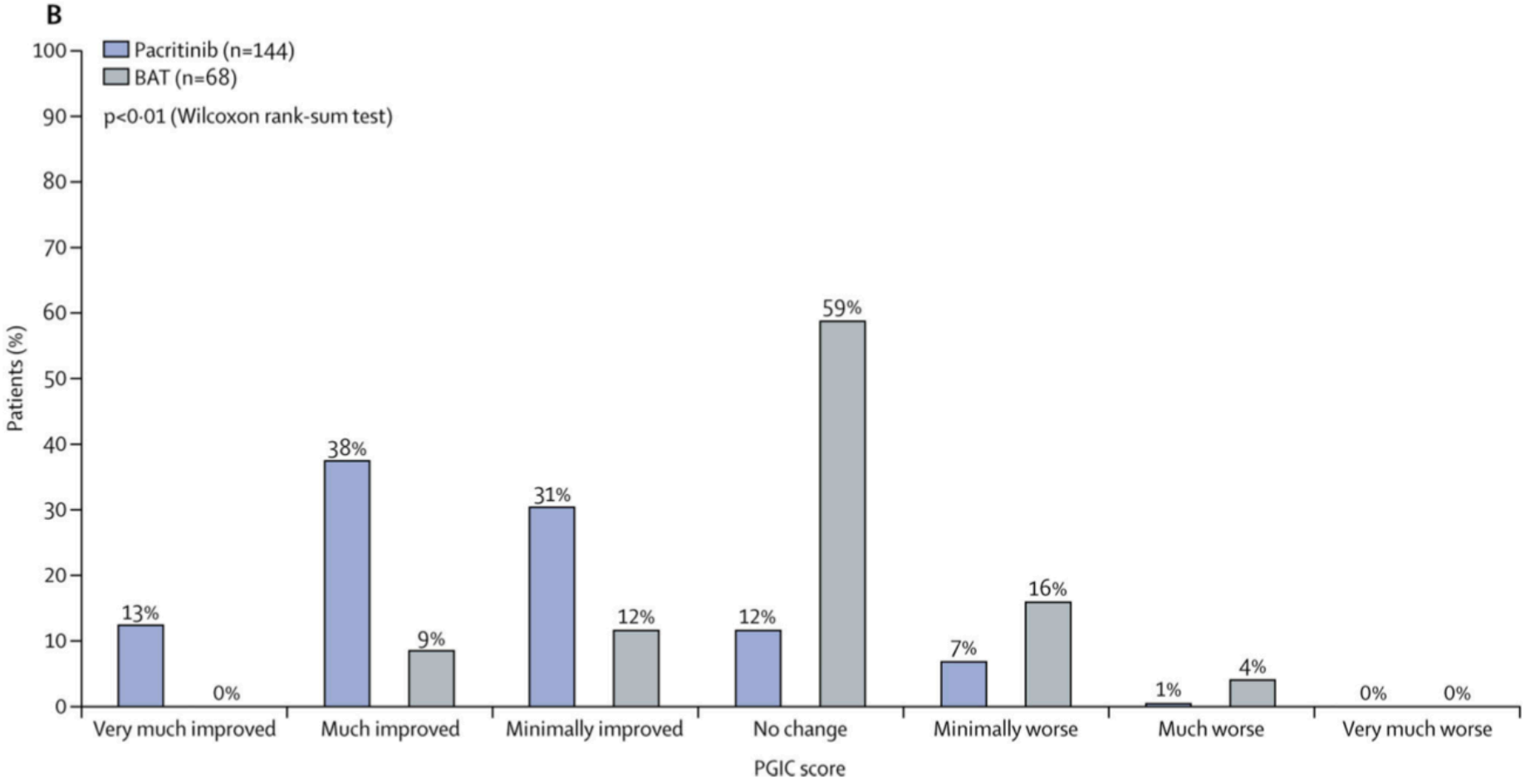
Anemia
Thrombocytopenia

Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial



Mesa et al. Lancet Hematol 2017

Pacritinib versus best available therapy for the treatment of myelofibrosis irrespective of baseline cytopenias (PERSIST-1): an international, randomised, phase 3 trial

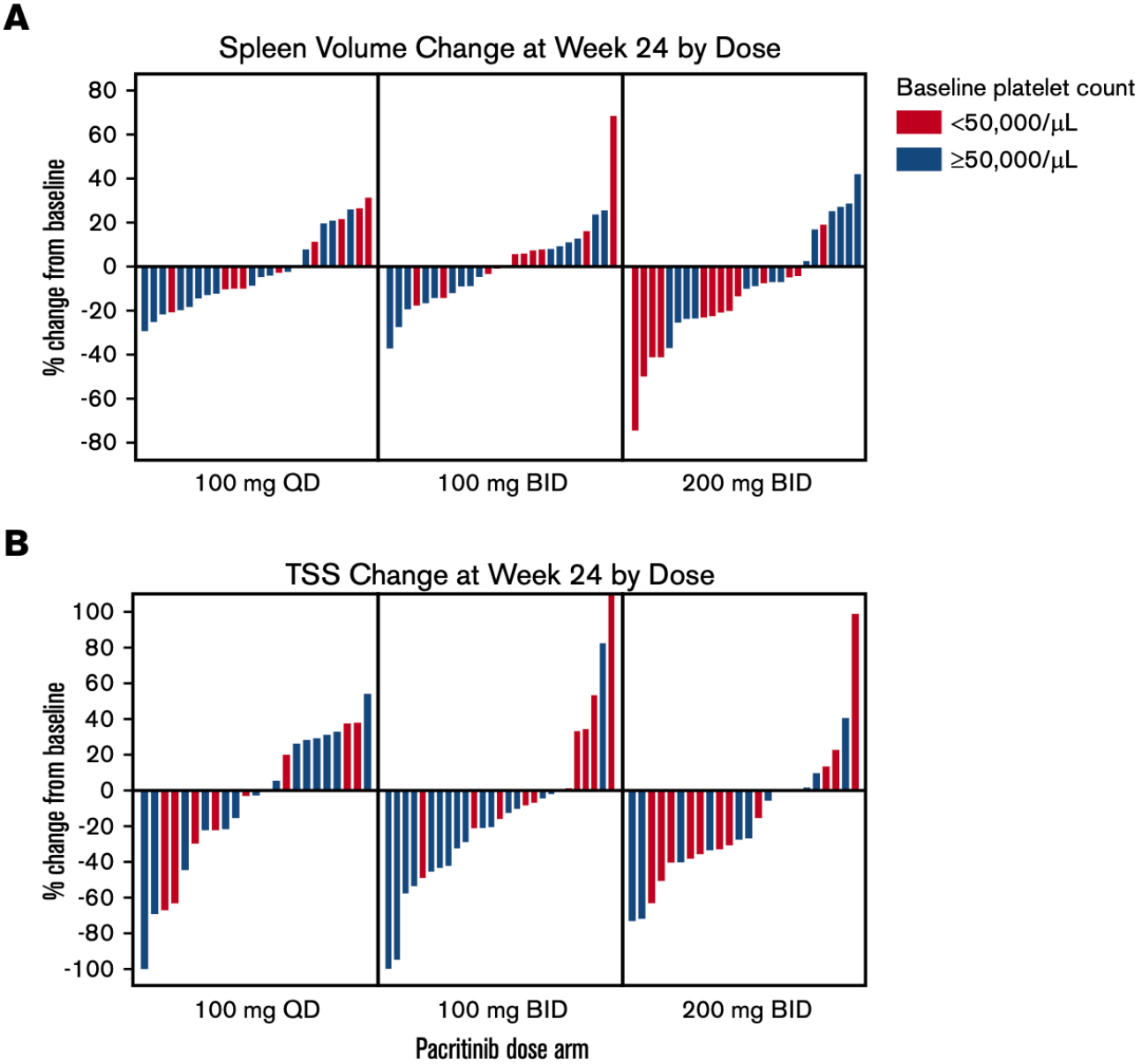


Mesa et al. Lancet Hematol 2017

Pacritinib vs best available therapy in patients with myelofibrosis and thrombocytopenia

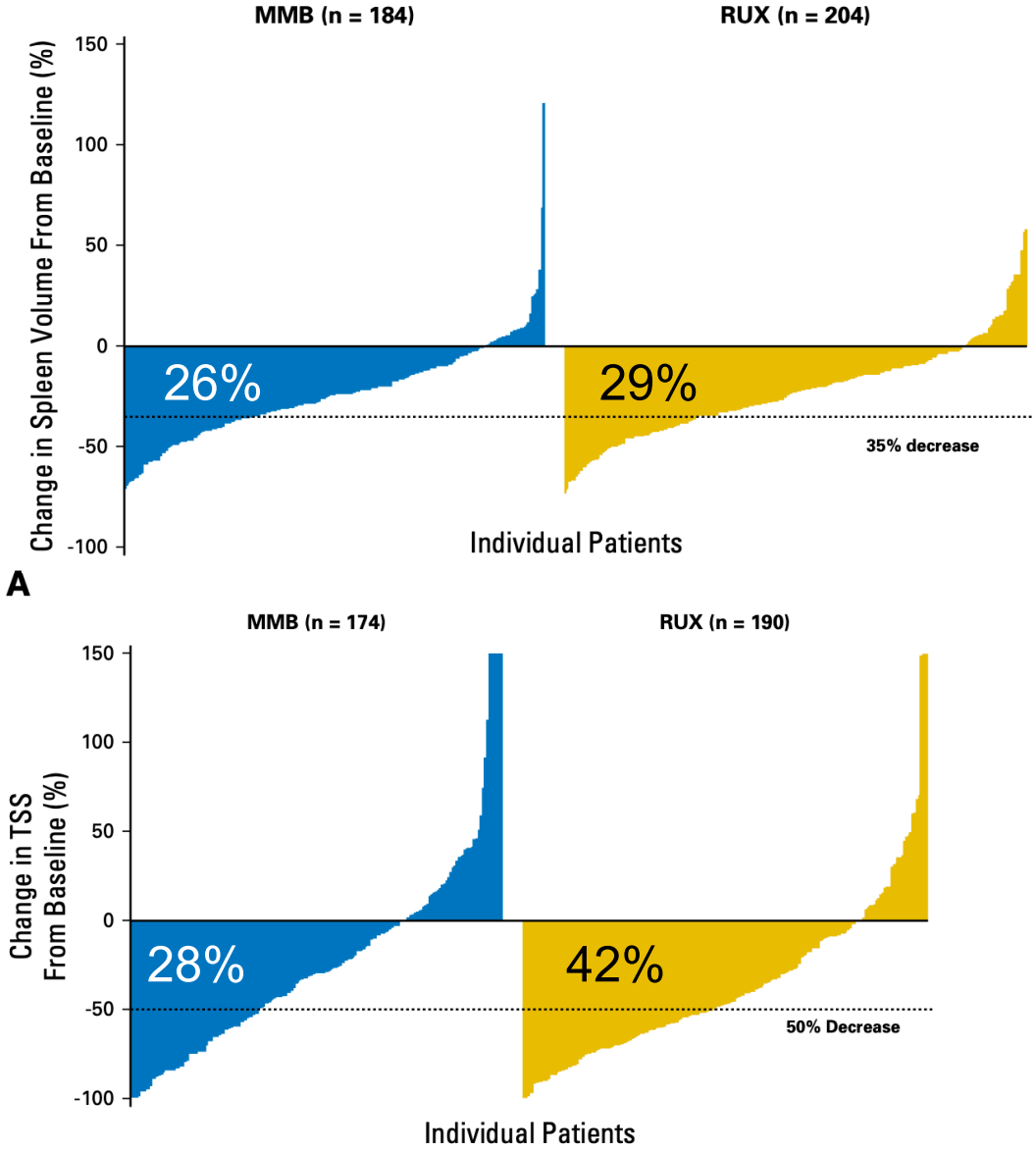
Mascarenhas et al. Jama Oncol 2018

Pacritinib can be used in patients with thrombocytopenia



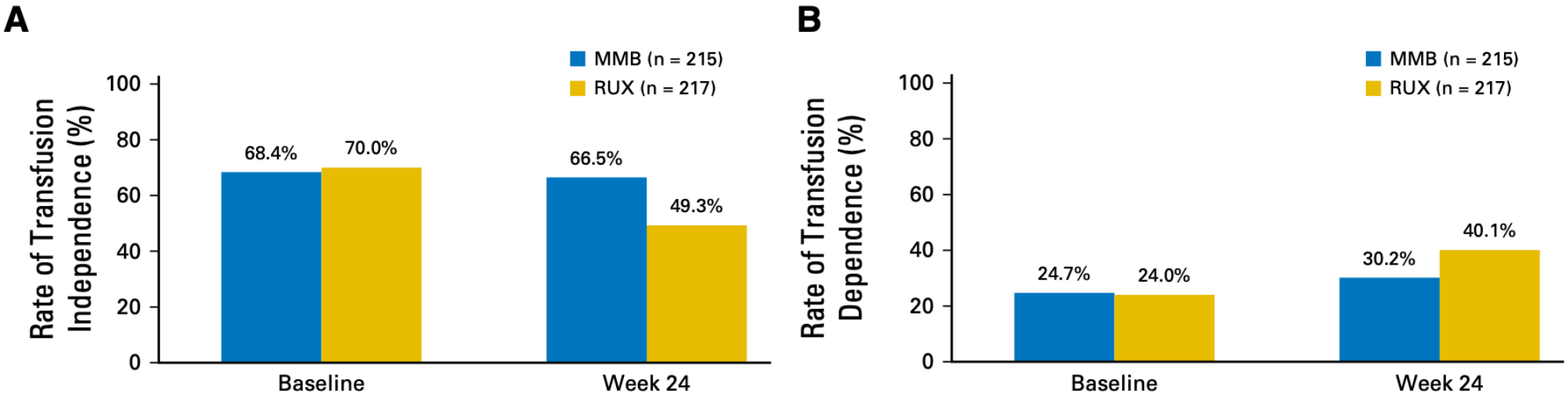
Gerds et al. Blood adv 2020

SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor–Naïve Patients With Myelofibrosis



Mesa R. et al. JCO 2017

SIMPLIFY-1: A Phase III Randomized Trial of Momelotinib Versus Ruxolitinib in Janus Kinase Inhibitor–Naïve Patients With Myelofibrosis



Memelotinib may offer:

- Less symptoms control
- Comparable spleen response
- Benefit in terms of transfusion independence

Mesa R. et al. JCO 2017

New molecules in clinical trials

BET inhibitors prevent protein-protein interaction between BET proteins and acetylated histones and transcription factors

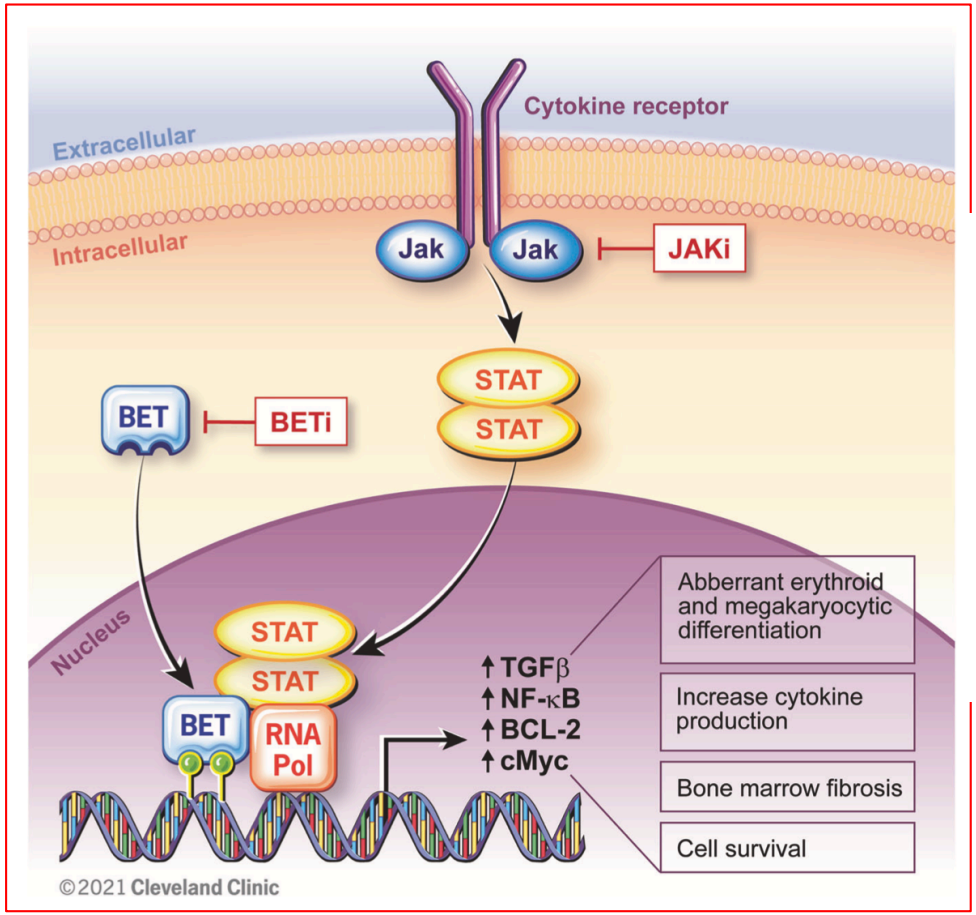
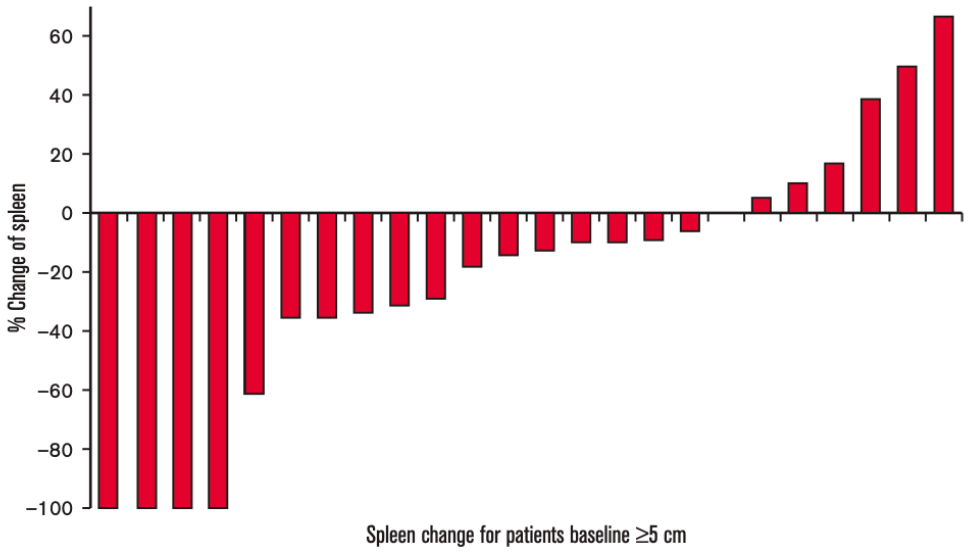


Table 1. BET inhibitors in clinical development for myelofibrosis.

Agent	BET selectivity	Phase trial	NCT identifier
Pelabresib (CPI-0610)	Pan BET inhibitor	2	NCT02158858
Pelabresib (CPI-0610)	Pan BET inhibitor	3	NCT04603495
INCB057643	Pan BET inhibitor	1/2	NCT04279847
ABBV-744	BD2 selective inhibitor	1	NCT04454658
Mivesbresib	Pan BET inhibitor	1	NCT04480086

Final results of a phase 2 clinical trial of LCL161, an oral SMAC mimetic for patients with myelofibrosis

C



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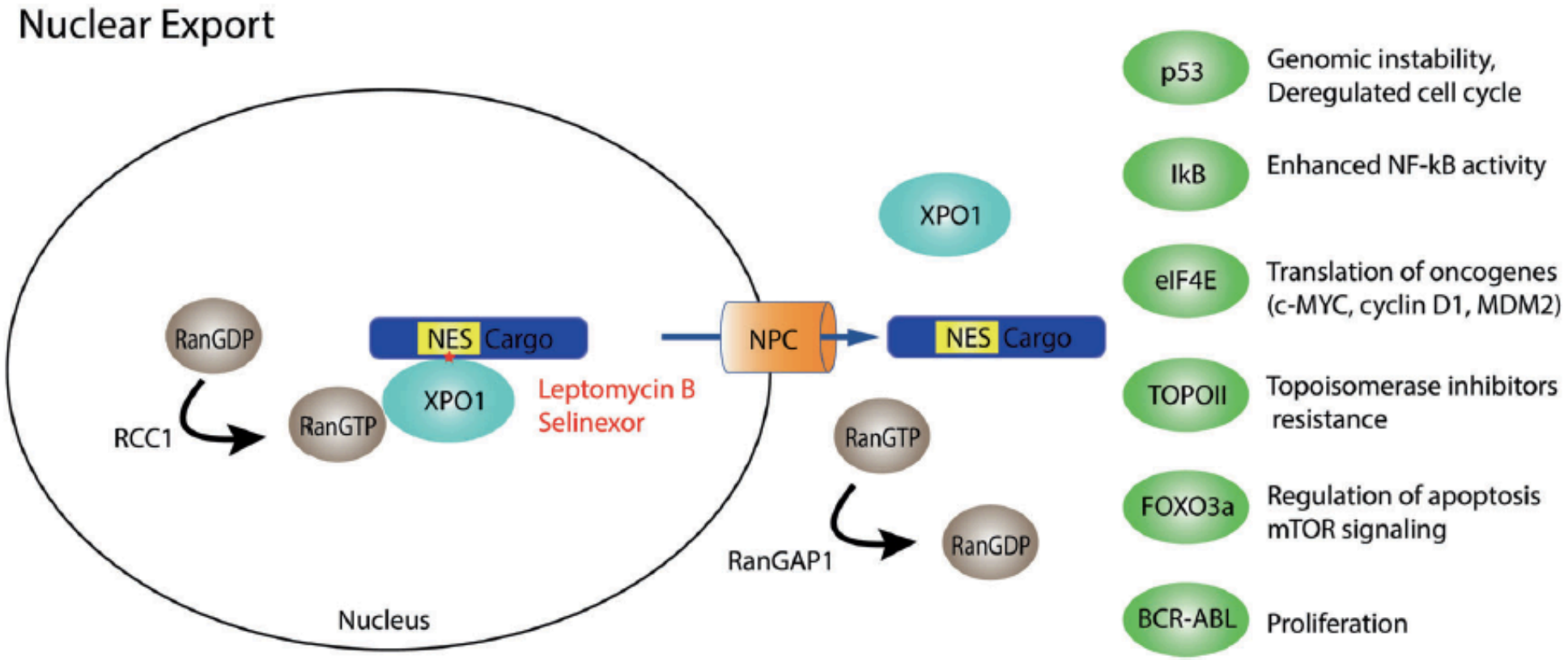
Patient	Hemoglobin Baseline (g/dL)	Peak Hemoglobin (g/dL)	Response duration (months)	Treatment Duration (months)
1	4.4	10.7	5.8	16.3
11	9	15.6	25.6	32.5
18	7	10.4	8.4	21.0
25	6.6	12.7	35.0	39.8
30	8.9	12.4	5.5	9.0
40	8.2	12.5	17.5	26.6

Blood Advances 24 August 2021

Selinexor targets nuclear export (Exportin 1) enhances p53 activity



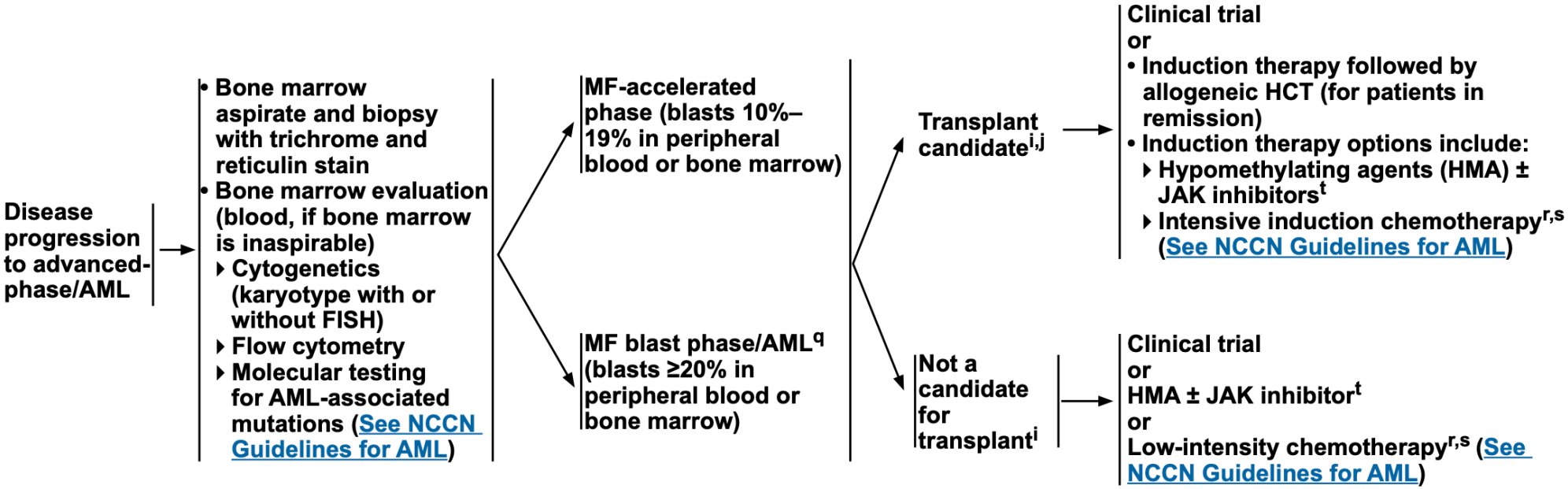
Nachmias B. et al. Leukemia 2020

MYLOX-1 study: An open-label, phase IIa study of the safety, tolerability, pharmacokinetics and pharmacodynamics of oral GB2064 ***(a LOXL2 inhibitor****) in participants with myelofibrosis*

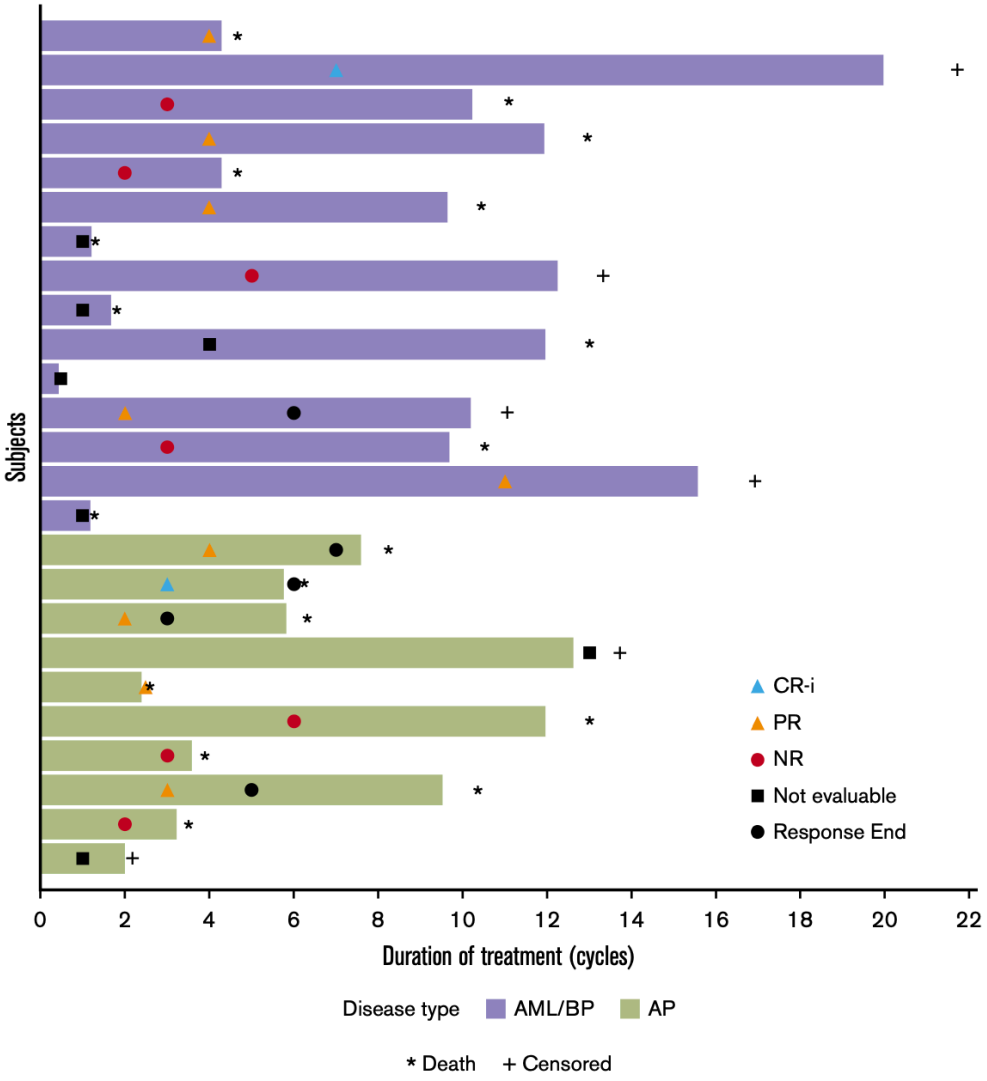
Patients refractory or intolerant to ruxolitinib

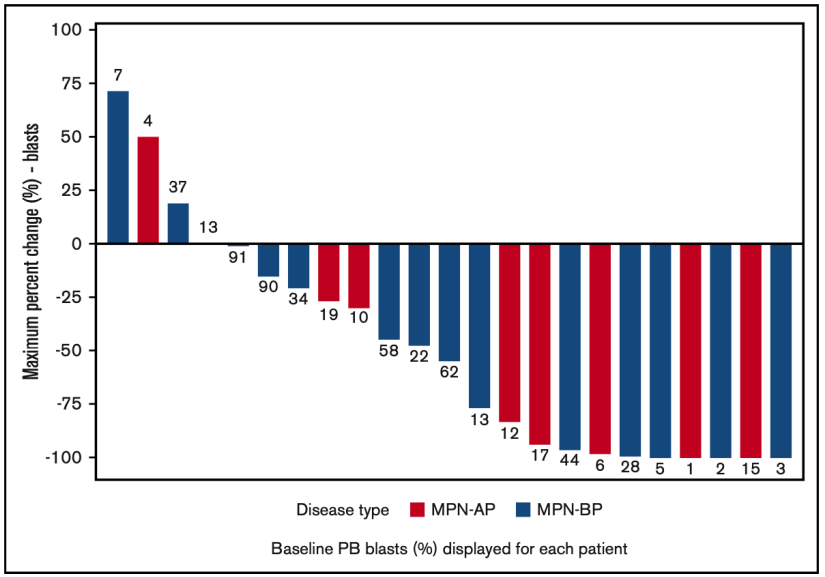
Ruxolitinib Combinations				
Ruxolitinib + thalidomide	NCT03069326	JAK1-/JAK2-inhibitor + immunomodulator	II	Primary or secondary myelofibrosis
Ruxolitinib + pomalidomide	NCT01644110	JAK1-/JAK2-inhibitor + immunomodulator	I/II	Primary or secondary myelofibrosis
PIM447 (pan-pim inhibitor) + ruxolitinib (doublet), LEE011 (CDK4/6 inhibitor) + ruxolitinib (doublet), PIM447 + ruxolitinib + LEE 011 (triple combination)	NCT02370706	JAK1-/JAK2-inhibitor + pan-pim inhibitor or CDK4/6 inhibitor	Ib	JAK2V617F-positive primary or secondary MF
Open-Label of Navitoclax (ABT-263) Alone or in Combination With Ruxolitinib	NCT03222609	Bcl-2 inhibitor ± JAK1-/JAK2-inhibitor	II	Intermediate or high-risk primary Myelofibrosis, post polycythemia Vera Myelofibrosis or post-essential thrombocythemia myelofibrosis
Pevonedistat (MLN4924) + ruxolitinib	NCT03386214	NEDD8 inhibitor ± JAK1-/JAK2-inhibitor	I	Primary or secondary myelofibrosis classified as high risk, intermediate-2 risk, or intermediate 1 risk by IPSS; tolerating 3 months of ruxolitinib before enrolment
Itacitinib (INCB039110) in Combination With Low-Dose Ruxolitinib or Itacitinib Alone	NCT03144687	JAK1 inhibitor ± JAK1-/JAK2-inhibitor	II	Primary or secondary myelofibrosis, tolerating 2 months of and response to ruxolitinib before enrolment
Ruxolitinib + azacytidine SC or IV for 5 days for up to 15 28-day cycles	NCT01787487	JAK1-/JAK2-inhibitor + hypomethylating agent	II	Patients with myelofibrosis, myelodysplastic syndromes/ myeloproliferative neoplasms (MDS/ MPN), chronic myelomonocytic leukemia (CMML), atypical chronic myeloid leukemia, myelodysplastic syndromes/myeloproliferative neoplasms, unclassifiable (MDS/MPN-U)

Disease progression to advanced phase/AML



Phase 2 study of ruxolitinib and decitabine in patients with myeloproliferative neoplasm in accelerated and blast phase





Mascarenhas J.O. et al Blood Advances 2020

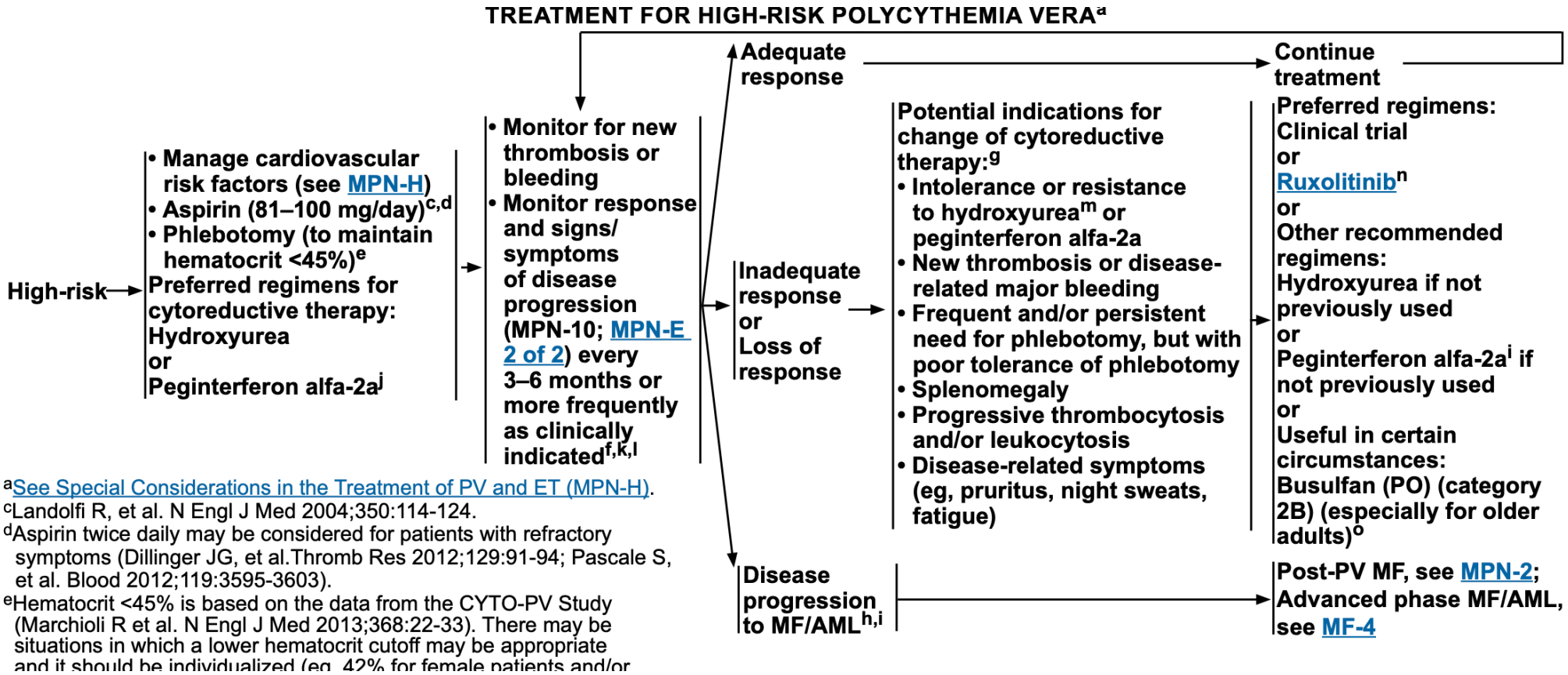
Summary for high risk myelofibrosis

First line therapy :
Allo HSCT
Ruxolitinib – Fedratinib

Second line
Fedratinib
Momelotinib (pts with anemia)
Pacritinib (pts with thrombocytopenia)
Clinical trials with new agents

Accelerated or blastic phase
Chemotherapy+ HSCT
Low dose chemotherapy
HMA + ruxolitinib
Clinical trials

High risk PV



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

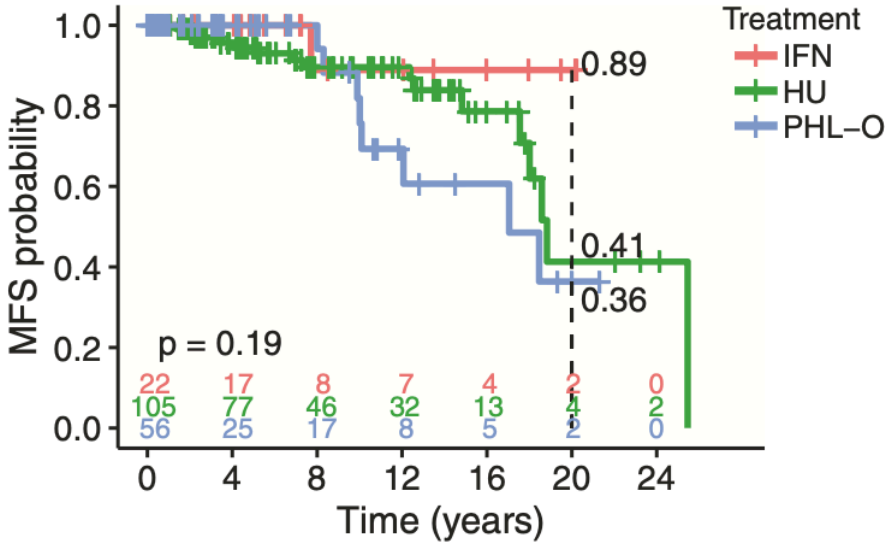
[c] Landolfi R, et al. N Engl J Med 2004;350:114-124.

[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).

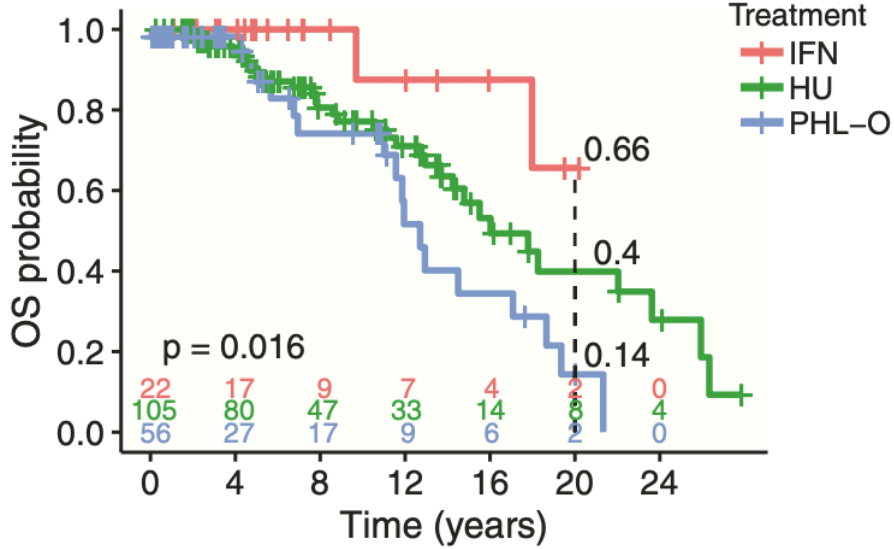
[e] Hematocrit <45% is based on the data from the CYTO-PV Study (Marchioli R et al. N Engl J Med 2013;368:22-33). There may be situations in which a lower hematocrit cutoff may be appropriate and it should be individualized (eg, 42% for female patients and/or

Interferon-alpha for treating polycythemia vera yields improved myelofibrosis-free and overall survival

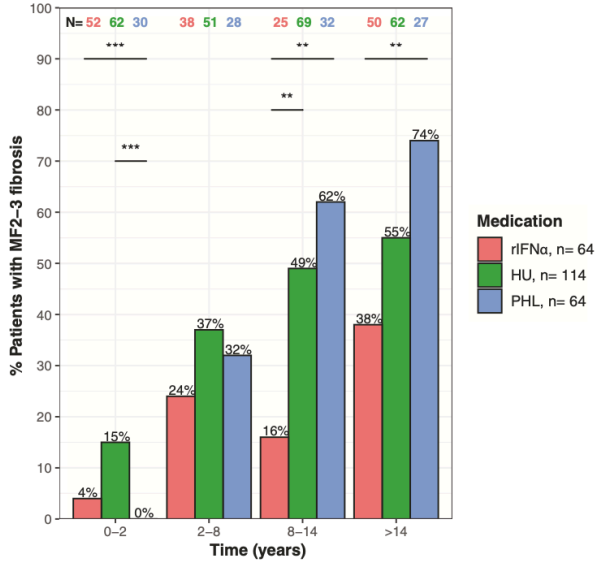
G. MFS: high-risk patients by treatment group



H. OS: high-risk patients by treatment group



IFN= Interferon
HU= Hydroxyurea
PHL-O Phlebotomy only



Grade II/III fibrosis over time

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