Trasplante alogénico en la mielofibrosis

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Inmunoterapia & Hemopatías
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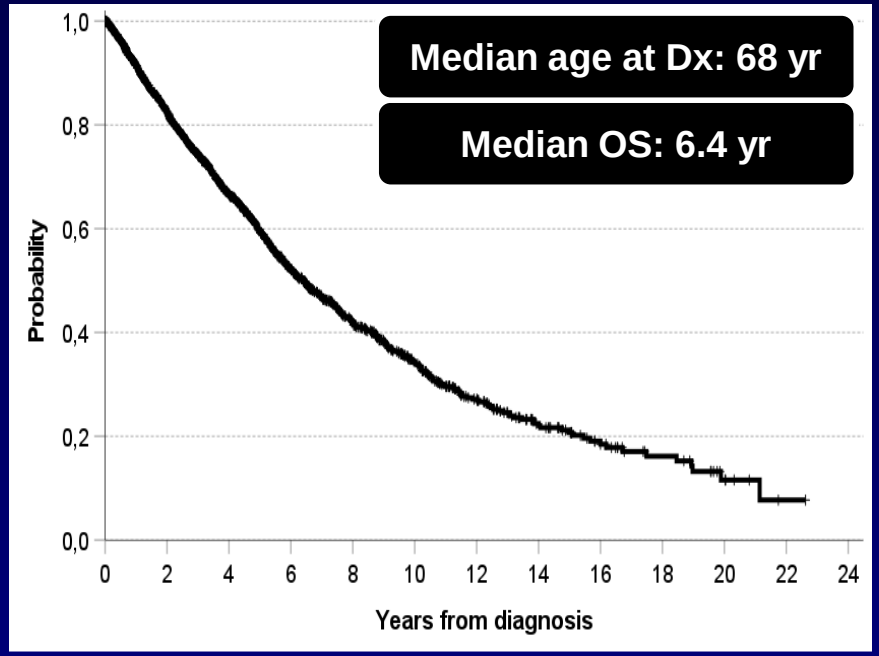
Conflicts of interest

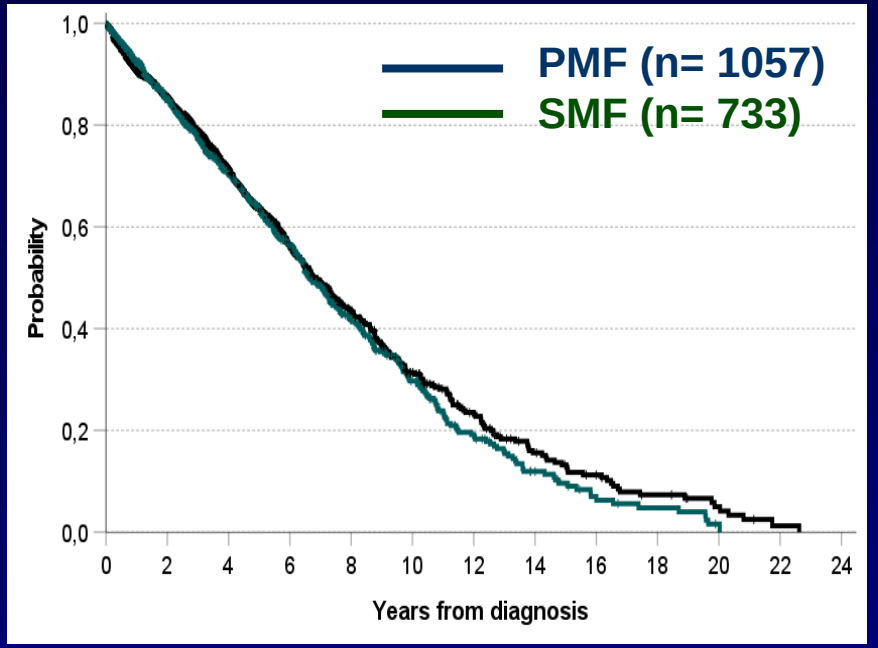
- Advisory honoraria from BMS and AOP Orphan
- Travel support from Incyte and Pfizer
- Speaker fees from Pfizer, Novartis, BMS, and Incyte

Outline

- General considerations
- Disease risk stratification in myelofibrosis
- Transplant risk stratification in myelofibrosis
- Patient / clinician perceptions on the risk-benefit balance of transplant
- Optimal timing of transplant in myelofibrosis
- Take-home messages

Survival of myelofibrosis patients (Dx 2000-2023; n=1790)



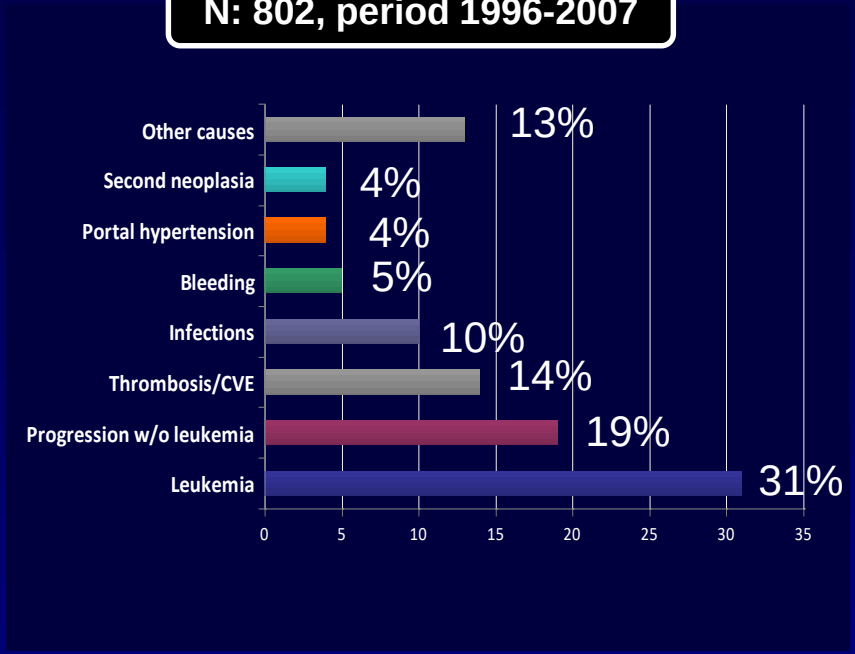


Median follow-up: 6.7 años

Spanish Myelofibrosis Registry, unpublished data

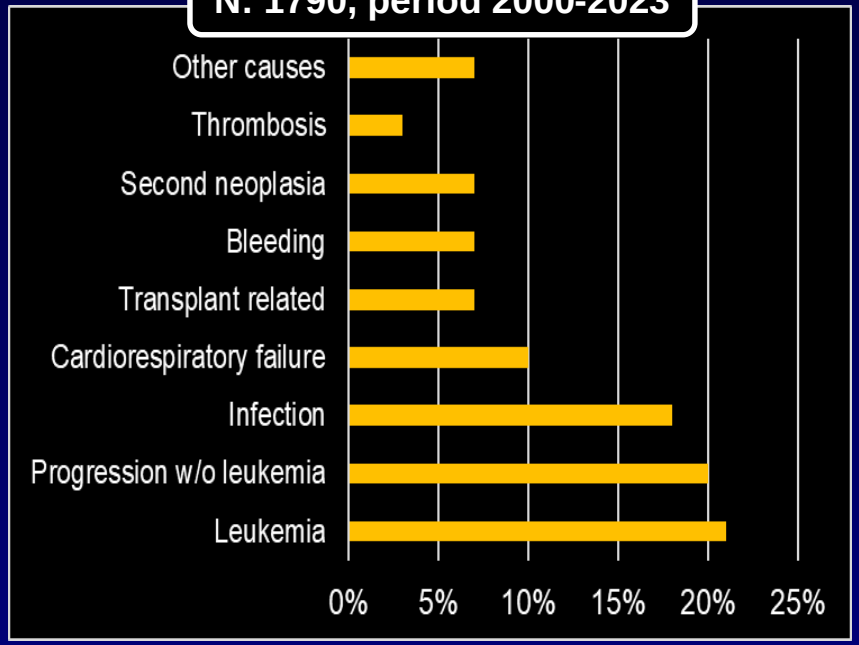
Causes of mortality in myelofibrosis

N: 802, period 1996-2007



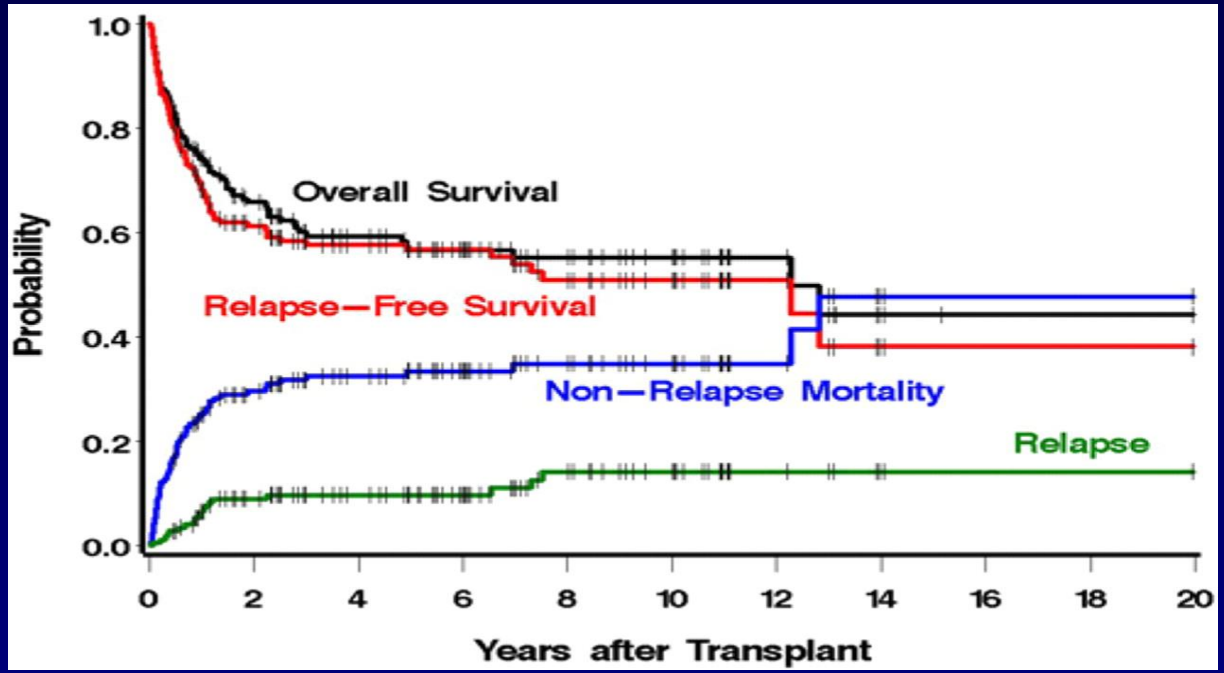
Cervantes F et al, JCO 2012;30:2981-7

N: 1790, period 2000-2023



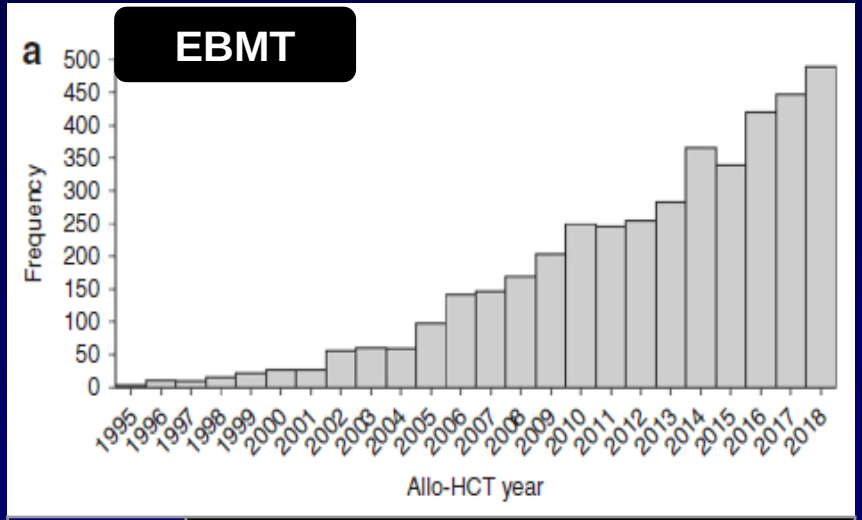
GEMFIN Registry, unpublished data

Allo-HCT is curative for myelofibrosis



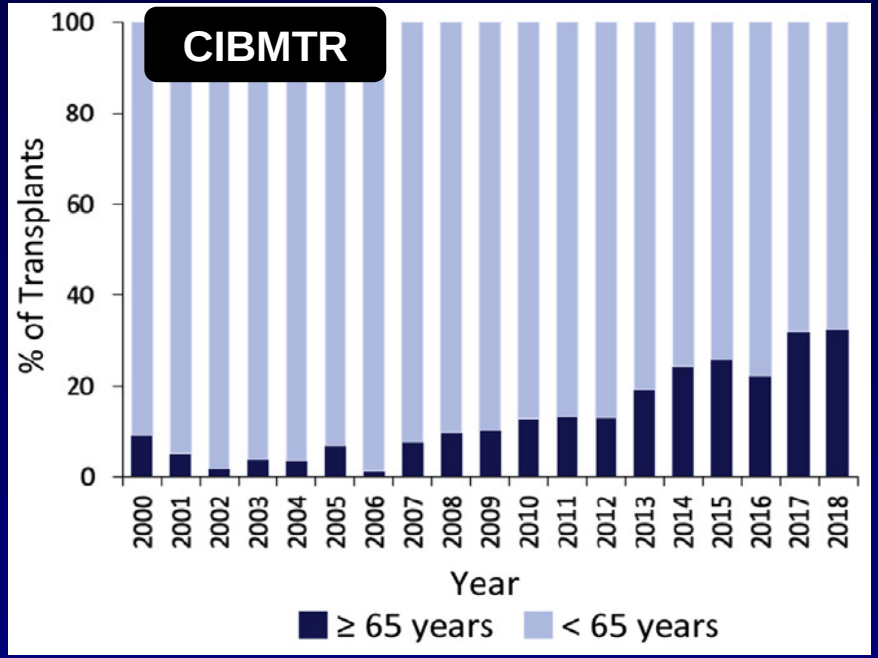
Scott BL et al. Blood 2012;119:2657-64

Trends in allo-HCT for myelofibrosis



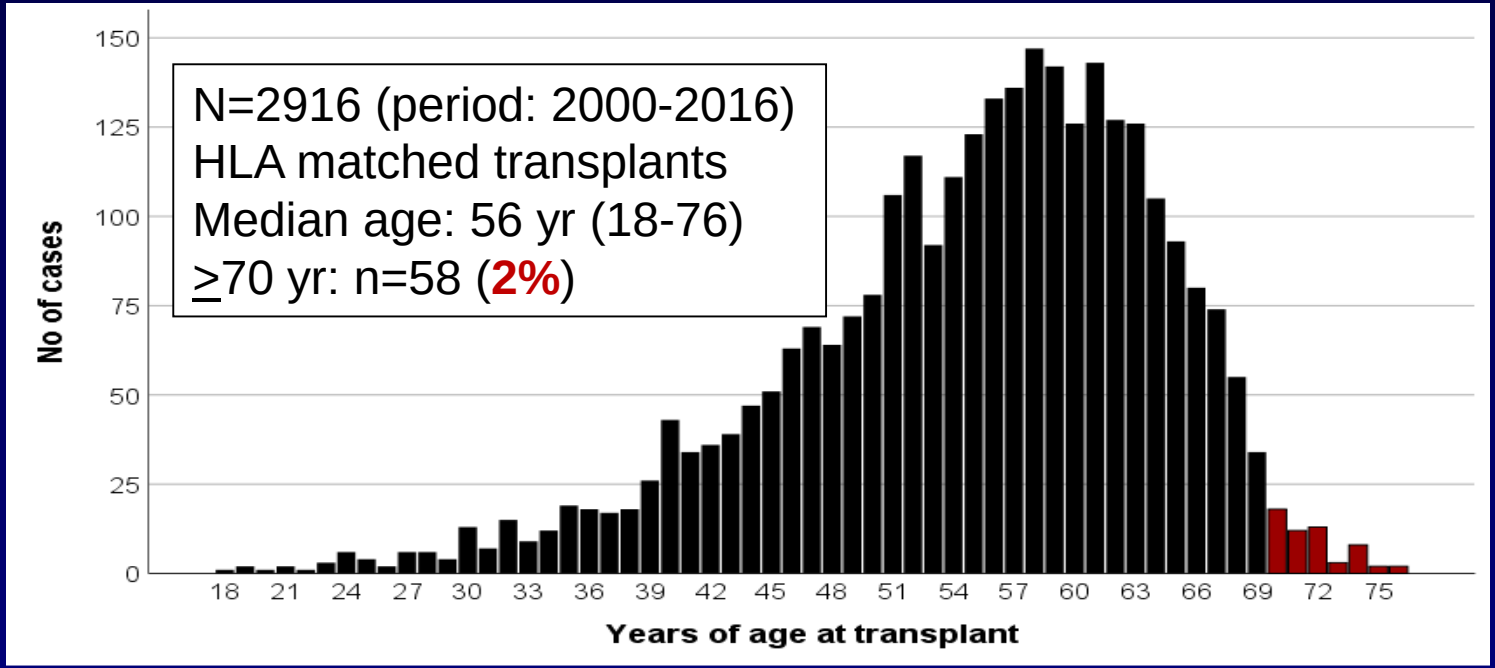
	Period			
Age	**<2006**	**2006-10**	**2011-14**	**2015-18**
Median, yr	49.4	55.6	57.8	59.3

McLornan DP et al. BMT 2021;56(9):2160-72



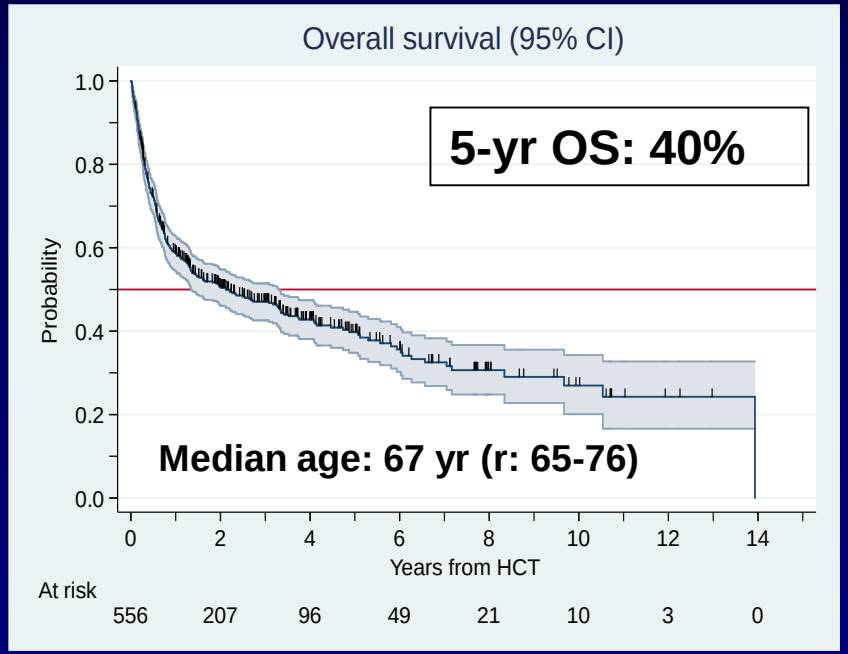
Davidson MB & Gupta V.
Hematol Oncol Clin N Am 2021;35:391-407

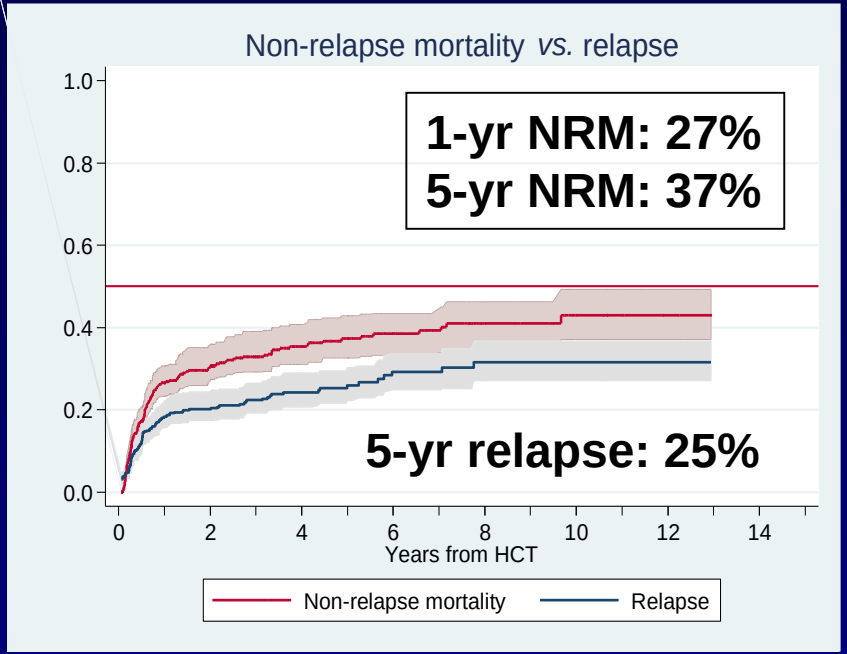
Age distribution at transplant in MF EBMT data



Hernandez-Boluda JC et al. Leukemia 2021:35(1):215-24

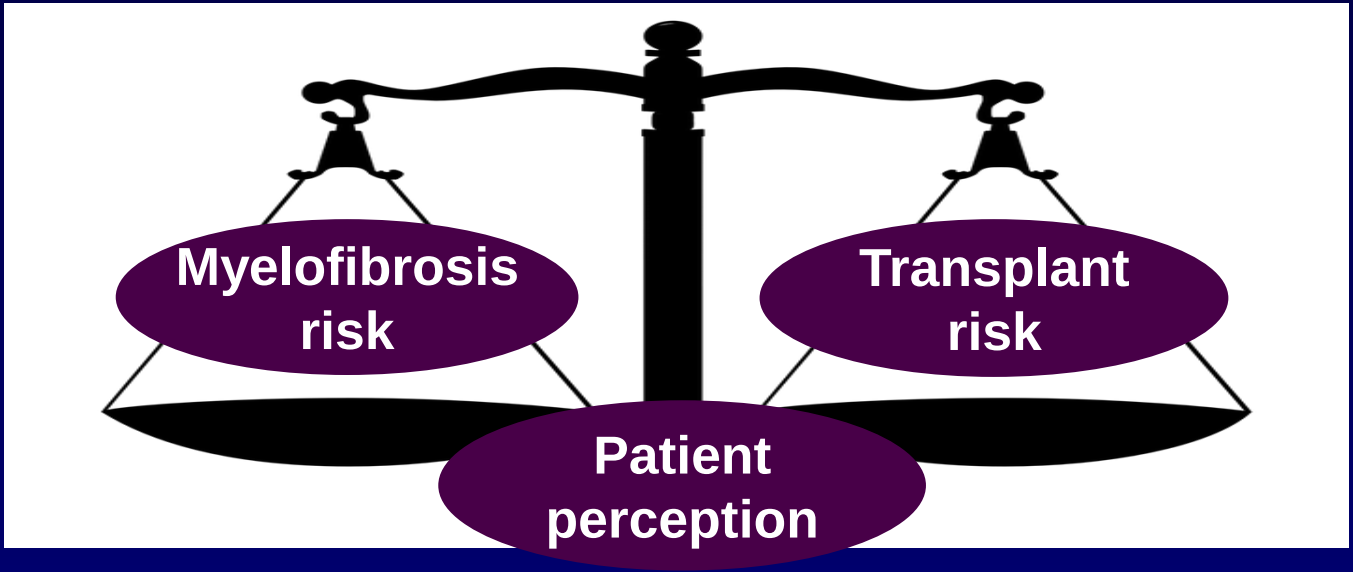
Allo-HCT in MF patients ≥ 65 yr
EBMT data (2000-2017)





Hernandez-Boluda JC et al, AJH 2021;96(10):1186-94

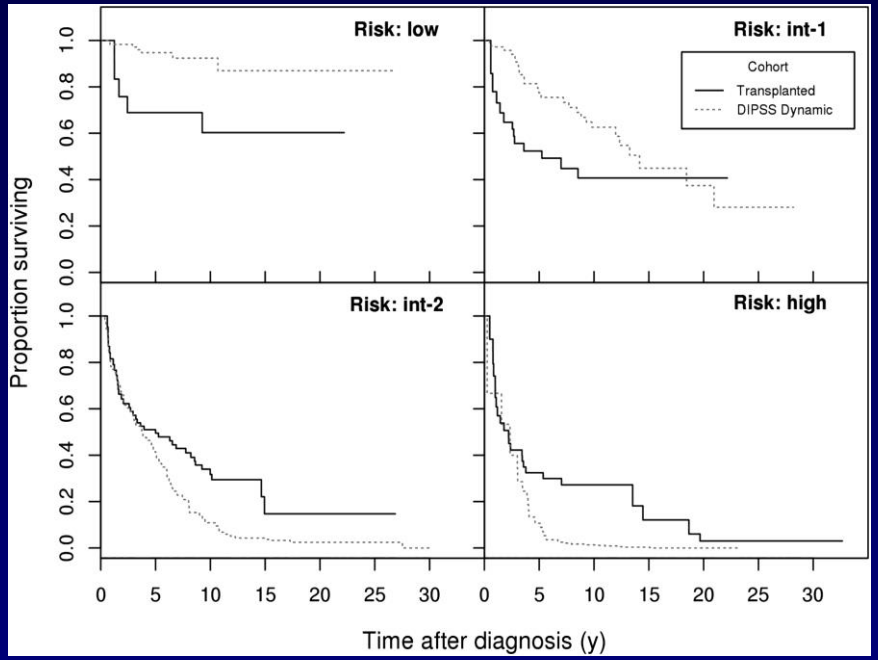
Transplant decision in myelofibrosis



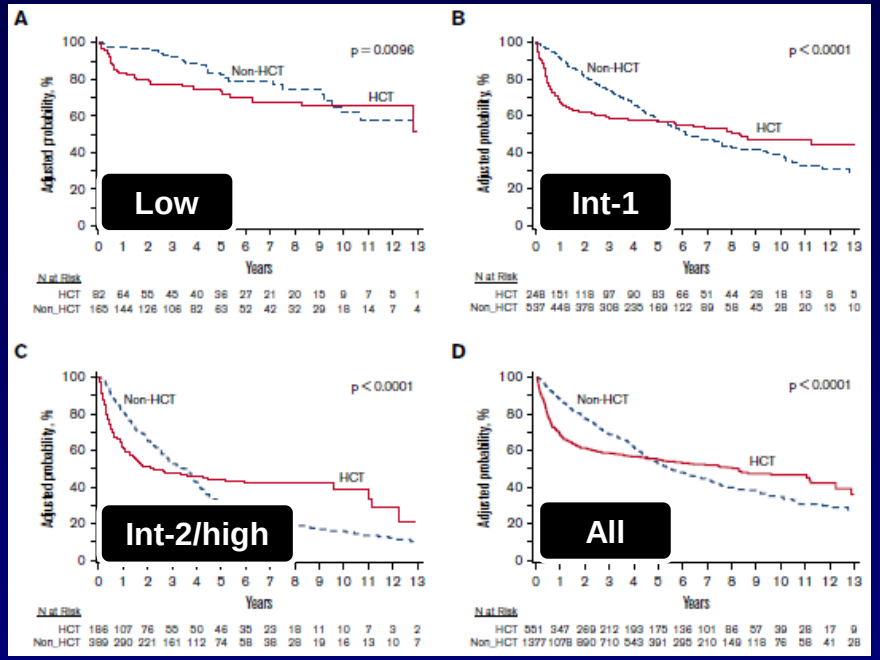
Patients with an expected survival of **less than 5 years** with conventional treatment should be considered as candidates for transplantation.

Kröger NM et al, Leukemia 2015;29(11):2126-33

Allo-HCT *vs*. No HCT
OS by DIPSS (< 65-70 yr)



Kröger N et al. Blood 2015;125:3347-50



Gowin K et al. Blood Adv 2020;4(9):1965-73

1) Disease risk stratification in myelofibrosis

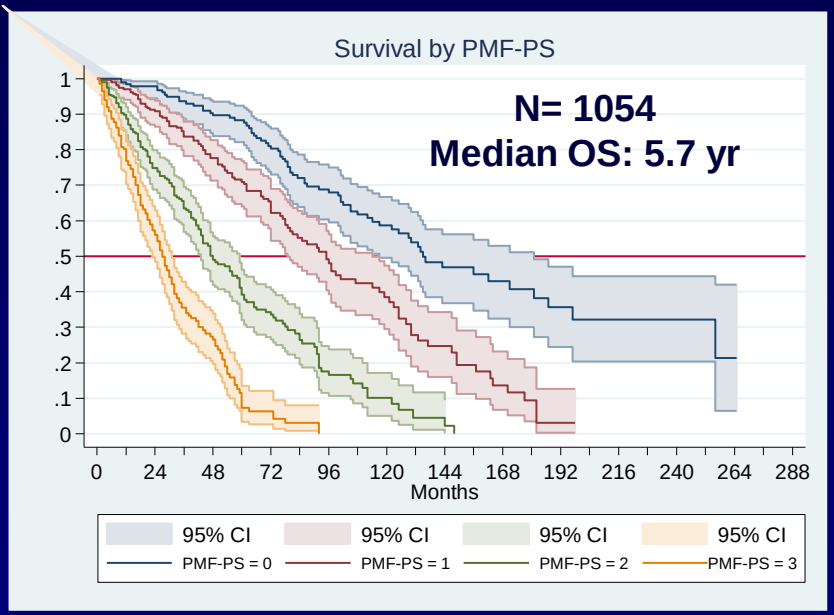
Identification of patients with an expected survival of less than 5 years

Prognostic models for OS in MF

	IPSS	DIPSS	DIPSS+	AIPSS-MF	MIPSS70	MIPSS70+ v2.0	MYSEC-PM	MPN risk calculator
MF type	PMF	PMF	PMF	All	PMF	PMF	SMF	All
Time-point	Dx	Follow-up	Any time	Dx	Any time	Any time	Dx	Dx
Prognostic factors	Clinical	Clinical	Clinical Cytog	Clinical	Clinical Histology Driver mut HRM*	Clinical Driver mut HRM* Cytog	Clinical Driver mut	Clinical Driver mut BMP** Cytog
Reference	Cervantes 2009	Passamonti 2010	Gangat 2011	Mosquera 2022	Guglielmelli 2017	Tefferi 2018	Passamonti 2017	Grinfeld 2018

*High risk mutations; **Broad mutational profile.

International Prognostic Scoring System (IPSS) for PMF

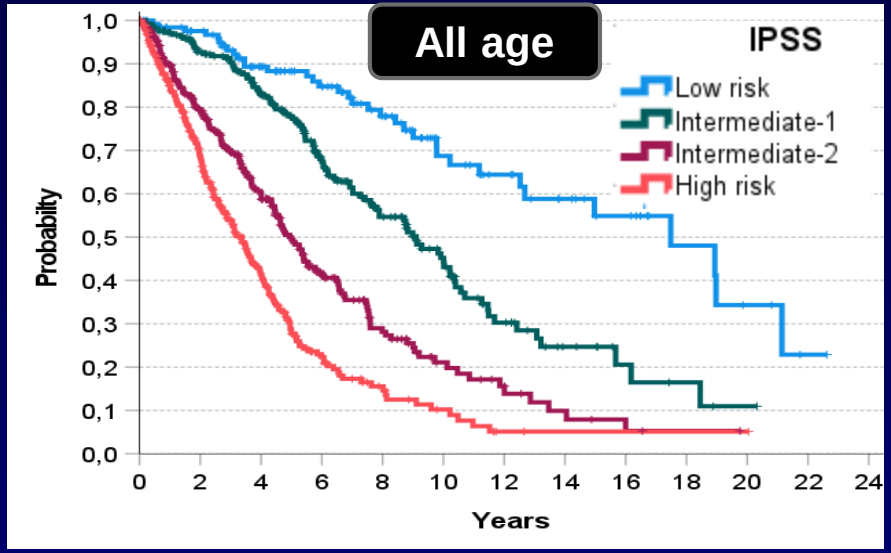


Prognostic variable	Hazard ratio	p
Age > 65 yr	1.950	< 0.0001
Constitutional symptoms	1.973	< 0.0001
Hb < 10 g/dL	2.989	< 0.0001
WBC > 25 x 10^9/L	2.400	< 0.0001
Blood blasts ≥ 1%	1.809	< 0.0001

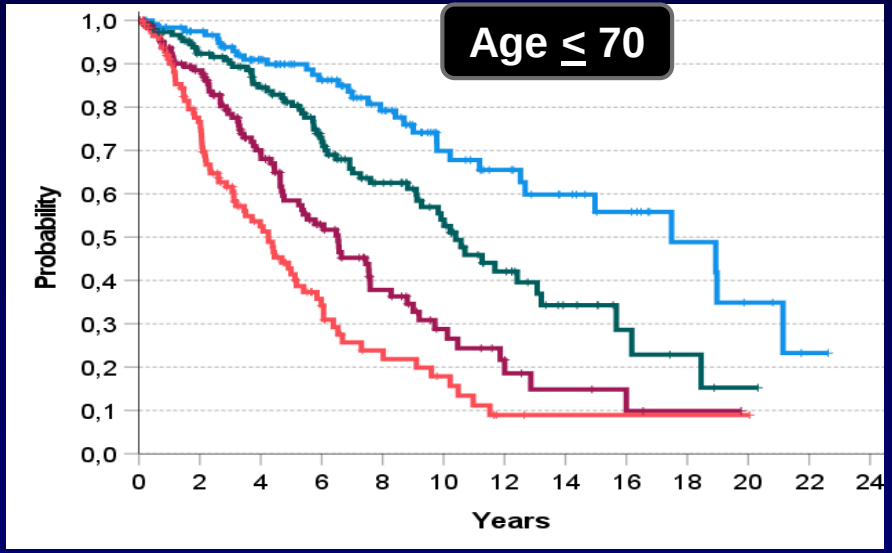
Risk Group	No. factors	No. cases (%)	Median OS (months)
Low	0	224 (22%)	135
Int-1	1	292 (29%)	95
Int-2	2	283 (28%)	**48**
High	≥ 3	202 (21%)	**27**

Cervantes F et al, Blood 2009;113(13):2895-901

IPSS for PMF (GEMFIN registry)

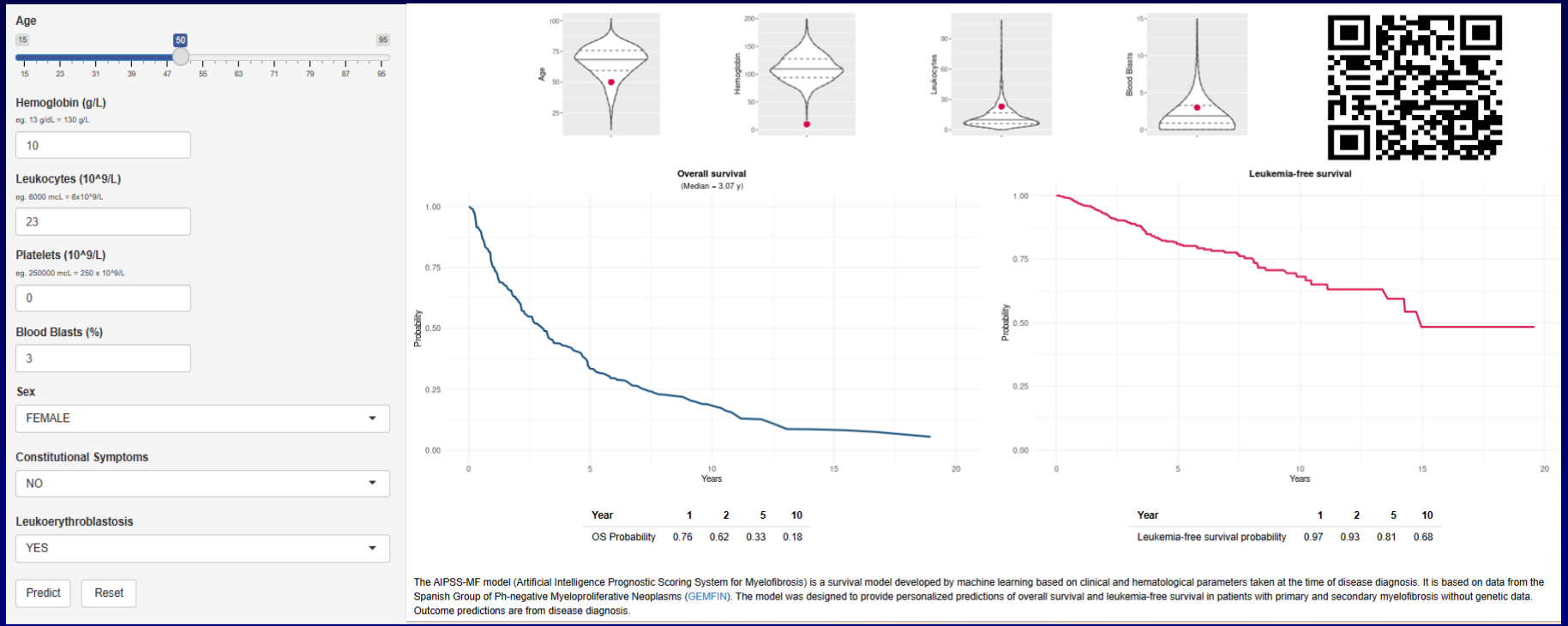


Risk	N	Median OS (yr)
Low	129 (13%)	17.5
Int-1	253 (26%)	9.1
Int-2	306 (31%)	4.9
High	288 (30%)	3.4



Risk	N	Median OS (yr)
Low	126 (23%)	17.5
Int-1	158 (29%)	10.4
Int-2	150 (27%)	6.5
High	118 (21%)	4.3

Artificial Intelligence Prognostic Scoring System for MF (AIPSS-MF)



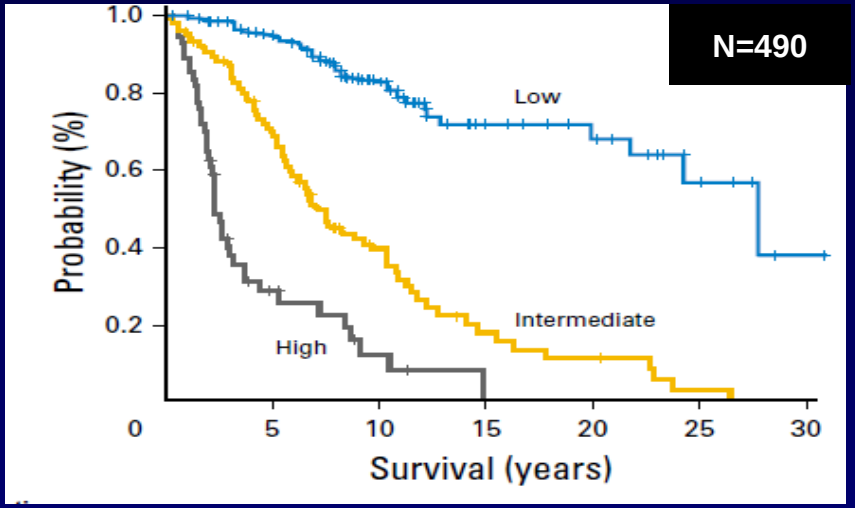
https://geneticsoncohematology.com/MF/

Mosquera-Orgueira A et al, Hemasphere 2022;20;7(1):e818

MIPSS70: Mutation-enhanced International Prognosis Score System for PMF ≤ 70 yr

Risk factor	Points
Constitutional symptoms	1
Hb < 10 g/dL	1
Blood blasts ≥ 2%	1
Marrow fibrosis ≥ 2	1
No *CALR* type 1	1
High risk mutation*	1
WBC > 25 x 10^9/L	2
Platelets < 100 x 10^9/L	2
High risk mutations* ≥ 2	2

*ASXL1, EZH2, SRSF2, IDH1, IDH2



Risk	Score	No. cases (%)	Median OS (yr)
Low	0-1	238 (49%)	27.7
Int	2-4	198 (40%)	7.1
High	≥ 5	54 (11%)	**2.3**

http://www.mipss70score.it/

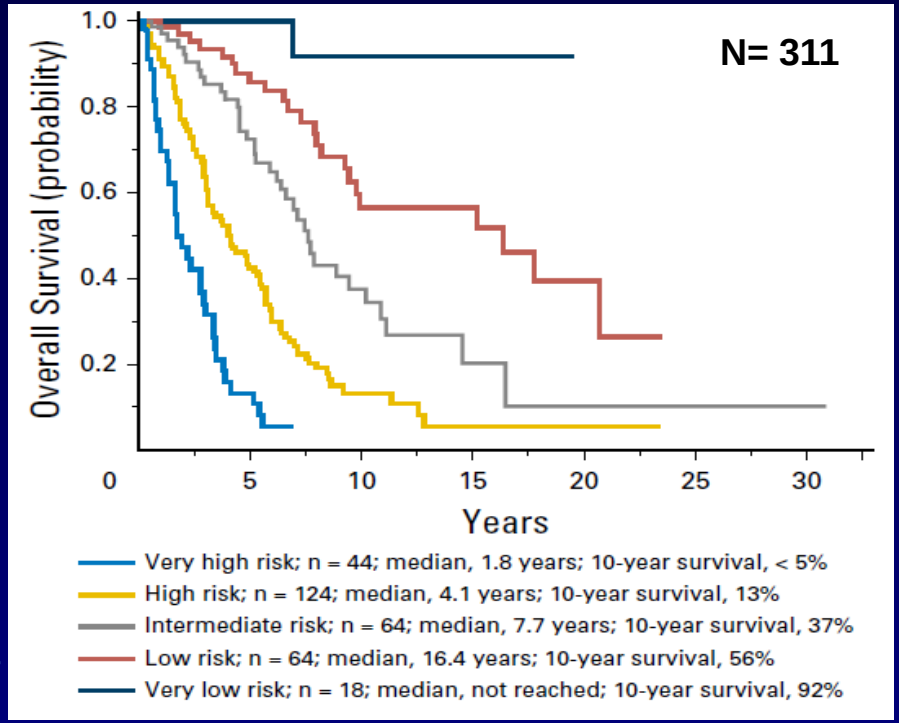
Guglielmelli P et al, JCO 2018;36(4):310-8

MIPSS70-plus version 2.0

Risk factor	Points
Moderate anemia*	1
Blood blasts ≥ 2%	1
Constitutional symptoms	2
Severe anemia**	2
No *CALR* type 1	2
High risk mutation***	2
High risk mutations*** ≥ 2	3
Unfavorable karyotype	3
Very high risk karyotype	4

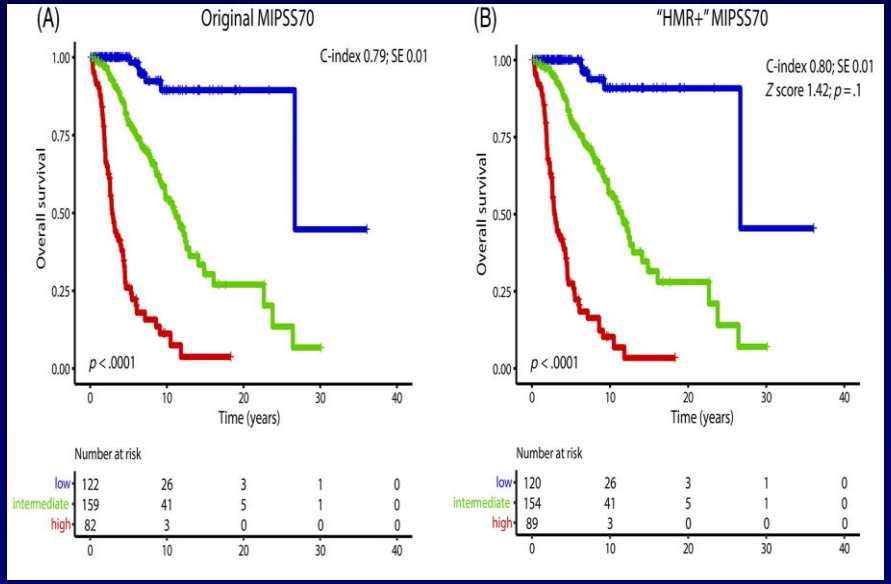
*Hb 8-9.9 g/dL (♀) or < 9-10.9 g/dL (♂)
**Hb < 8 g/dL (♀) or < 9 g/dL (♂)
***ASXL1, EZH2, SRSF2, IDH1/2, U2AF1Q157

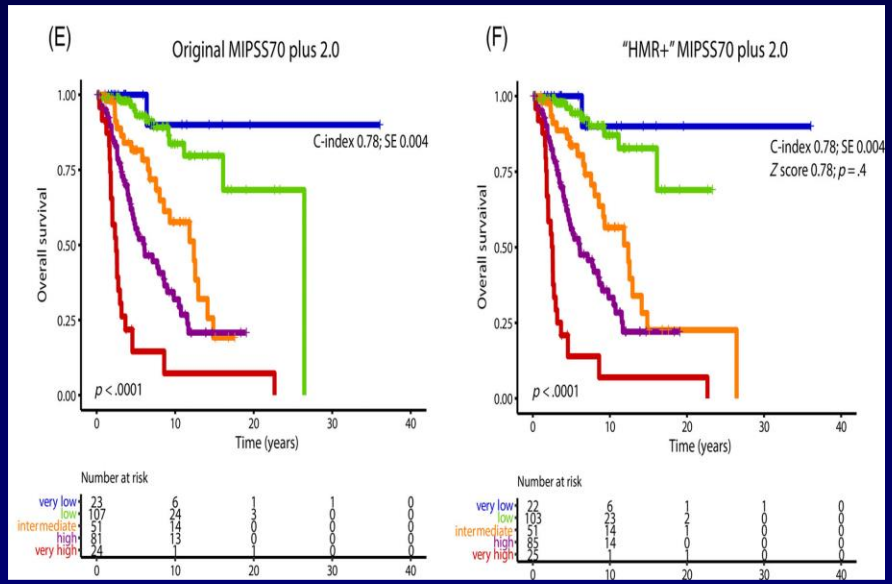
http://www.mipss70score.it/



Tefferi A et al, JCO 2018;36(17):1769-70

Prognostic contribution of *CBL*, *KRAS*, *NRAS*, *RUNX1* and *TP53* mutations on the MIPSS70 scores in PMF



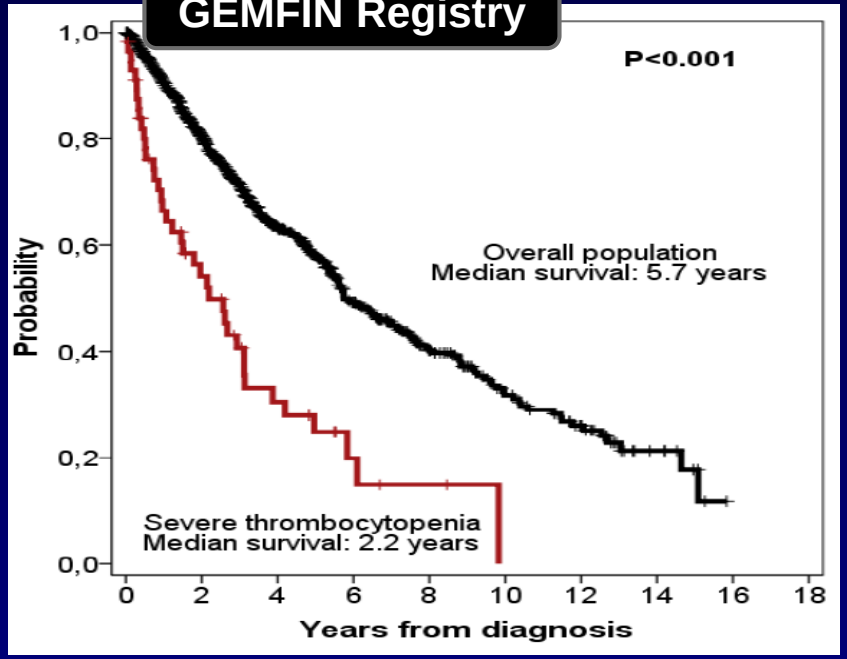


Overall, no significant improvement of score performances. However, ***TP53* mutations should be included** due to their independent role in predicting a dismal outcome.

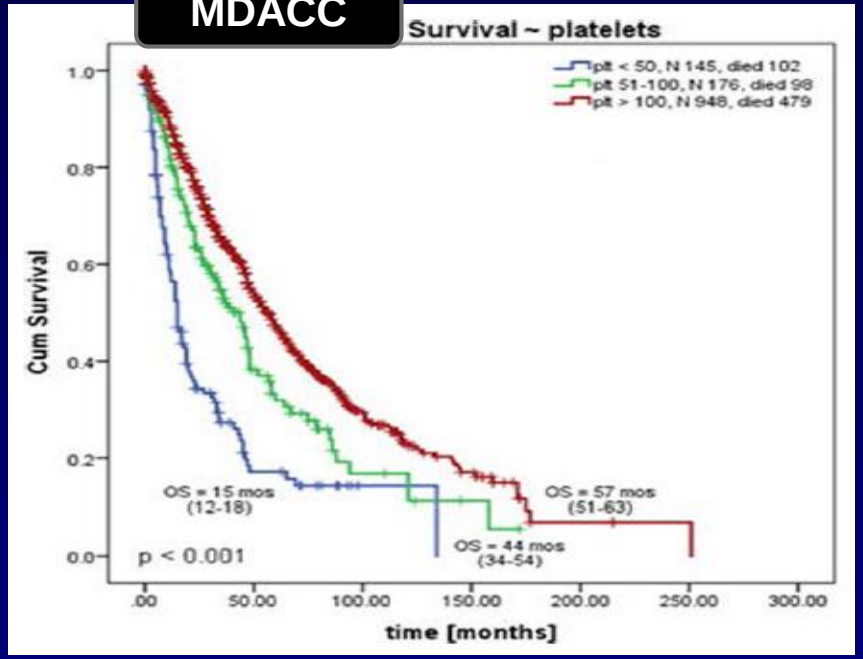
Loscocco GG et al, AJH 2023; prepublished

MF with severe thrombocytopenia

GEMFIN Registry



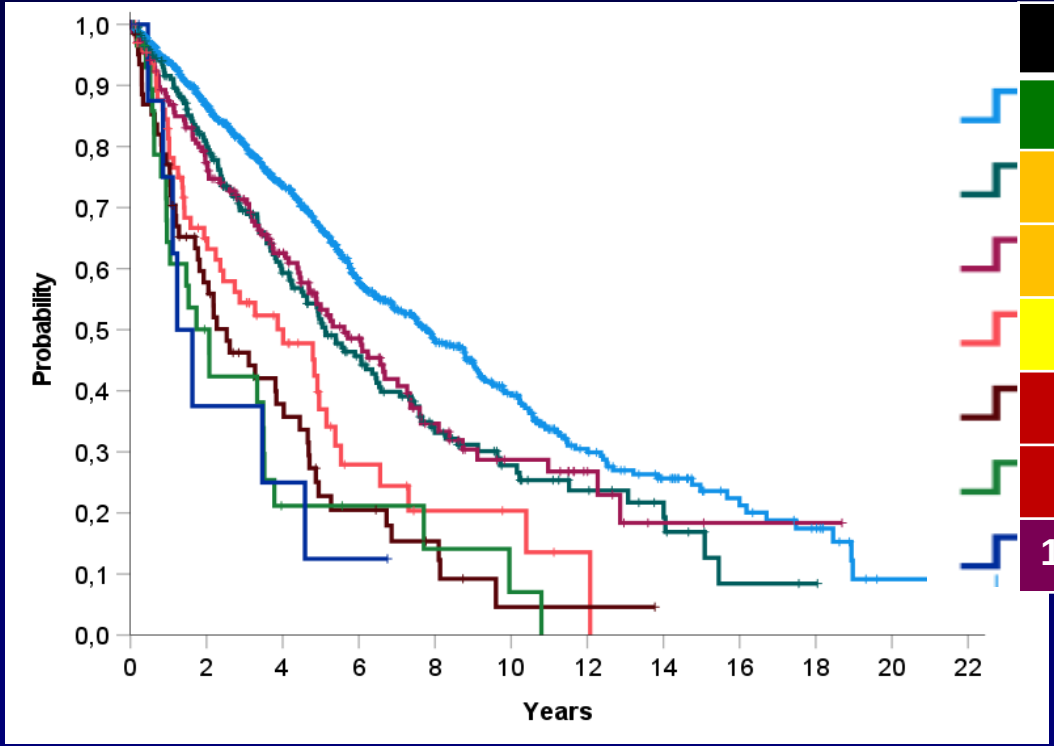
MDACC



Hernandez-Boluda JC et al. BJH 2018;181(3):397-400

Masarova L et al. Leuk Res 2020 (91):106338

Blood blasts at diagnosis and OS in MF

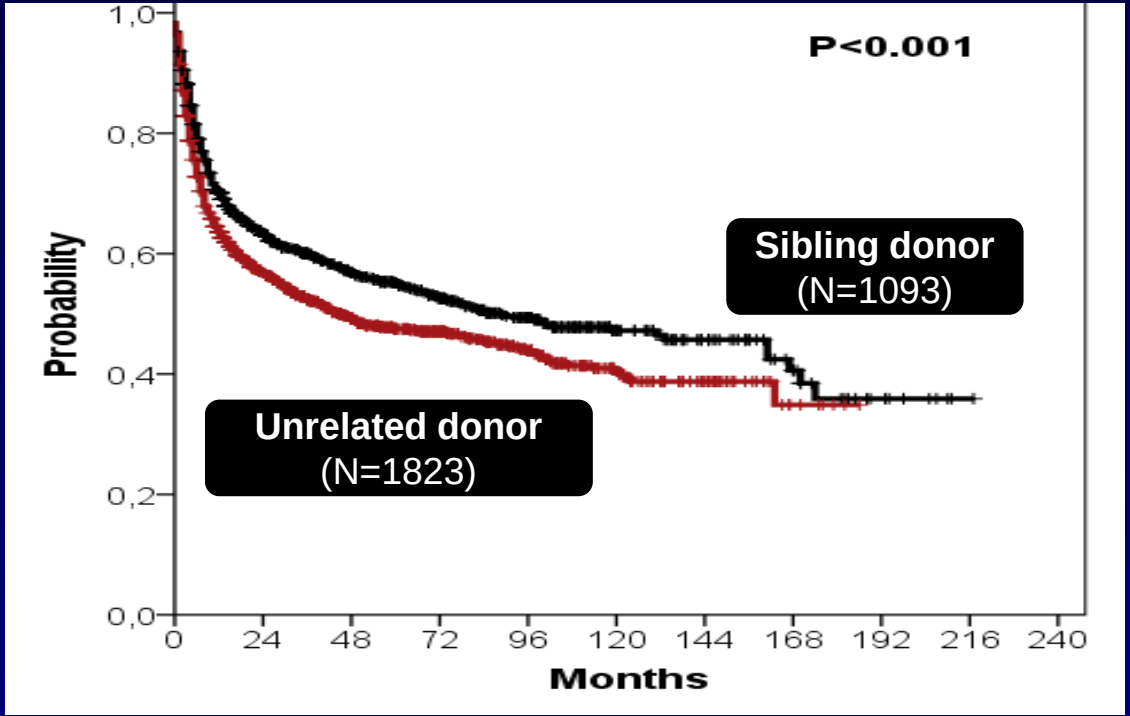


%	N	Median OS
0	862 (60%)	7.8 yr
1	227 (16%)	5.1 yr
2	173 (12%)	5.6 yr
3	68 (5%)	4.0 yr
4-5	62 (4%)	2.5 yr
6-9	29 (2%)	2.1 yr
10-19	10 (<1%)	1.2 yr

Spanish Registry of Myelofibrosis (n=1431), unpublished data

2) Transplant risk stratification in myelofibrosis

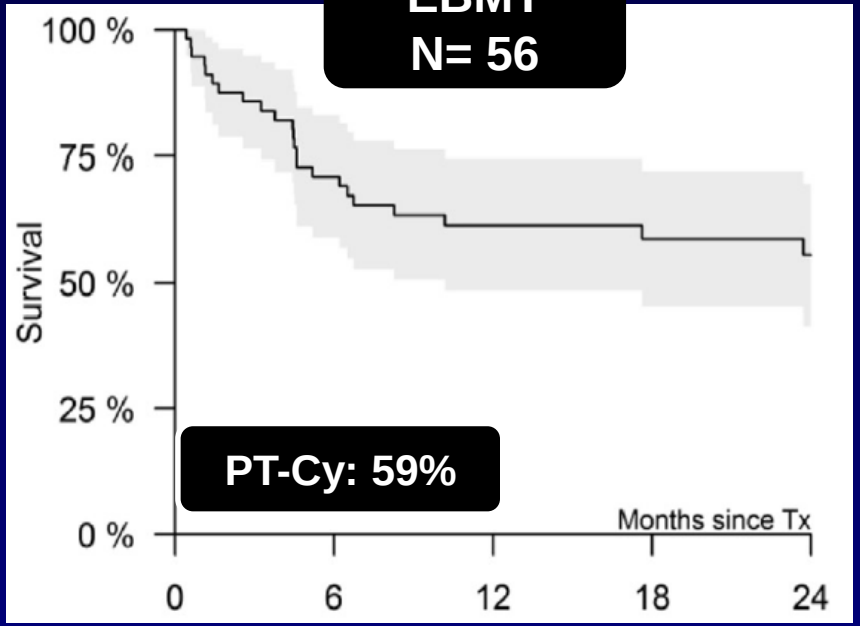
OS after HLA-matched transplant in MF EBMT data



Hernandez-Boluda JC et al. Leukemia 2021:35(1):215-24

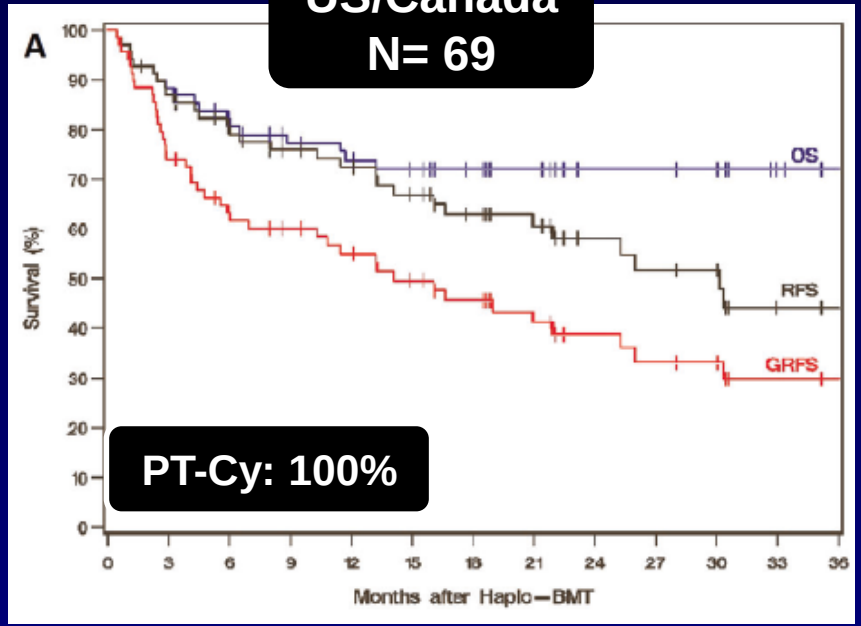
Allo-HCT in MF: haploidentical donor

EBMT
N= 56



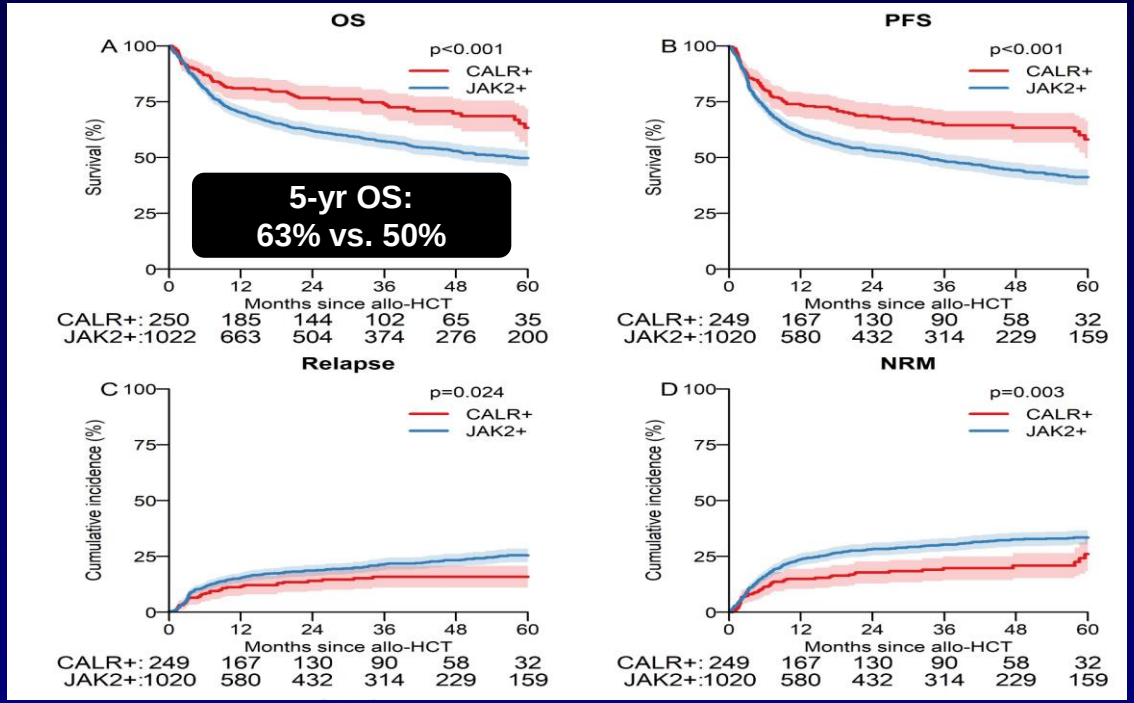
Raj K et al. BBMT 2019;25(3):522-8

US/Canada
N= 69



Kunte S et al. Leukemia 2022;36:856-64

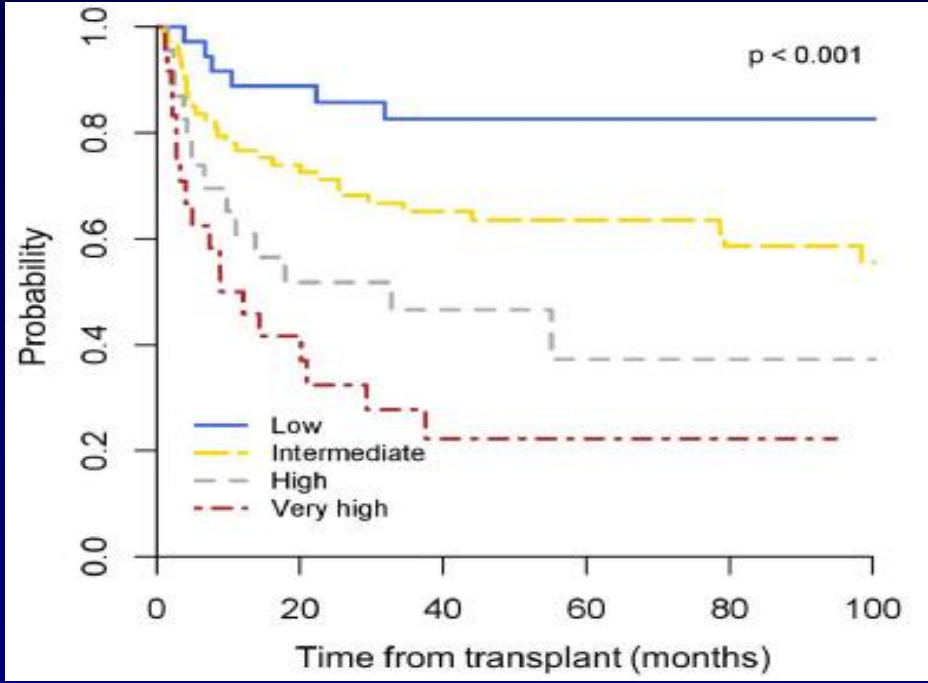
Impact of driver mutations on OS after allo-HCT in MF



PMF and post-ET MF only

Hernandez-Boluda JC et al. BMT 2023: prepublished

Myelofibrosis Transplant Scoring System (MTSS)

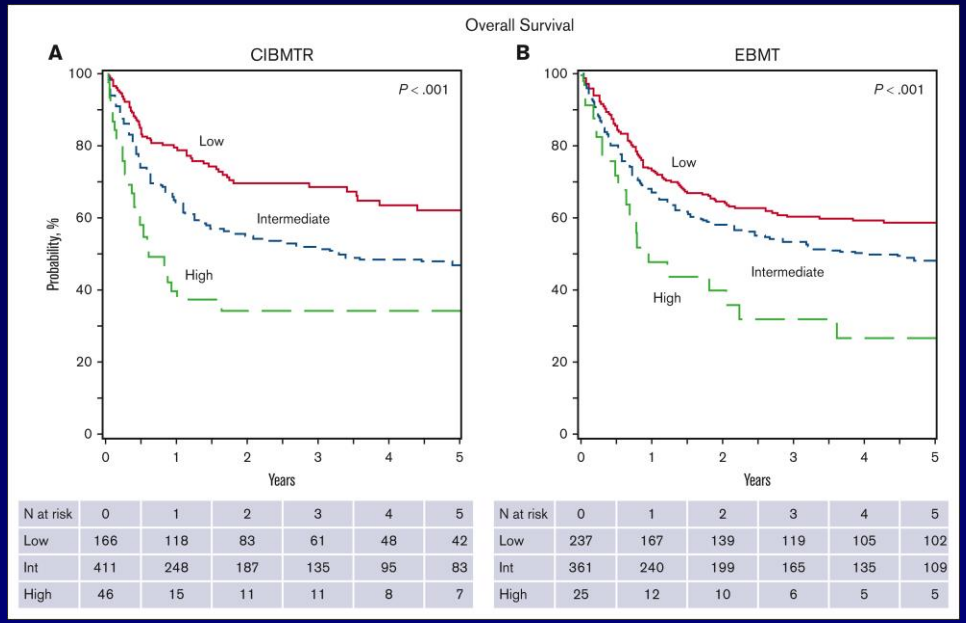


Gagelmann N et al. Blood 2019;133(20):2233-42

Risk factor	Points
Age ≥ 57 yr	1
KPS < 90%	1
WBC > 25 x 10^9/L	1
Platelets < 150 x 10^9/L	1
ASXL1 mutation	1
JAK2+/triple negative genotype	2
Mismatched unrelated donor	2

Risk	Score	% pts	5-yr OS
Low	0-2	23	83%
Int	3-4	47	64%
High	5	15	**37%**
Very high	≥ 6	15	**22%**

A simple Prognostic Scoring System for Allo-HCT in MF (CIBMTR/EBMT)



N at risk	0	1	2	3	4	5
Low	166	118	83	61	48	42
Int	411	248	187	135	95	83
High	46	15	11	11	8	7

N at risk	0	1	2	3	4	5
Low	237	167	139	119	105	102
Int	361	240	199	165	135	109
High	25	12	10	6	5	5

Risk factor	Points
Age > 50 yr	1
Unrelated donor	1
Hb < 100 g/L at transplant	2
Mismatched unrelated donor	2

Risk group	Score	CIBMTR 3-yr OS
Low	0-2	69%
Intermediate	3-4	51%
High	5	**34%**

High risk category comprises 4-7% of patients only

Tamari R et al. Blood Adv 2023;7(15):3993-4002

Treatment decision

- Patients with DIPSS int-2/high-risk or MIPSS70/MIPSS70+ high-risk or MYSEC-PM int-2/high-risk (for secondary MF) and MTSS low/intermediate-risk **should be considered candidates** for allo-HCT.

- Patients with DIPSS int-1 risk or MIPSS70/MIPSS70+ intermediate-risk and MTSS low-risk **should be offered allo-HCT**, balancing patient preferences, actual treatment options including clinical trials and other risk features (including presence of *TP53* mutations).

- In patients aged more than 70 years, allo-HCT **may be offered** on an individual basis, balancing patient preferences and disease- and patient-associated features.

Indication and management of allo-HSCT in MF: Updated recommendations by the EBMT/ELN
Kröger NM et al, Lancet Haematol 2023; prepublished

Treatment decision

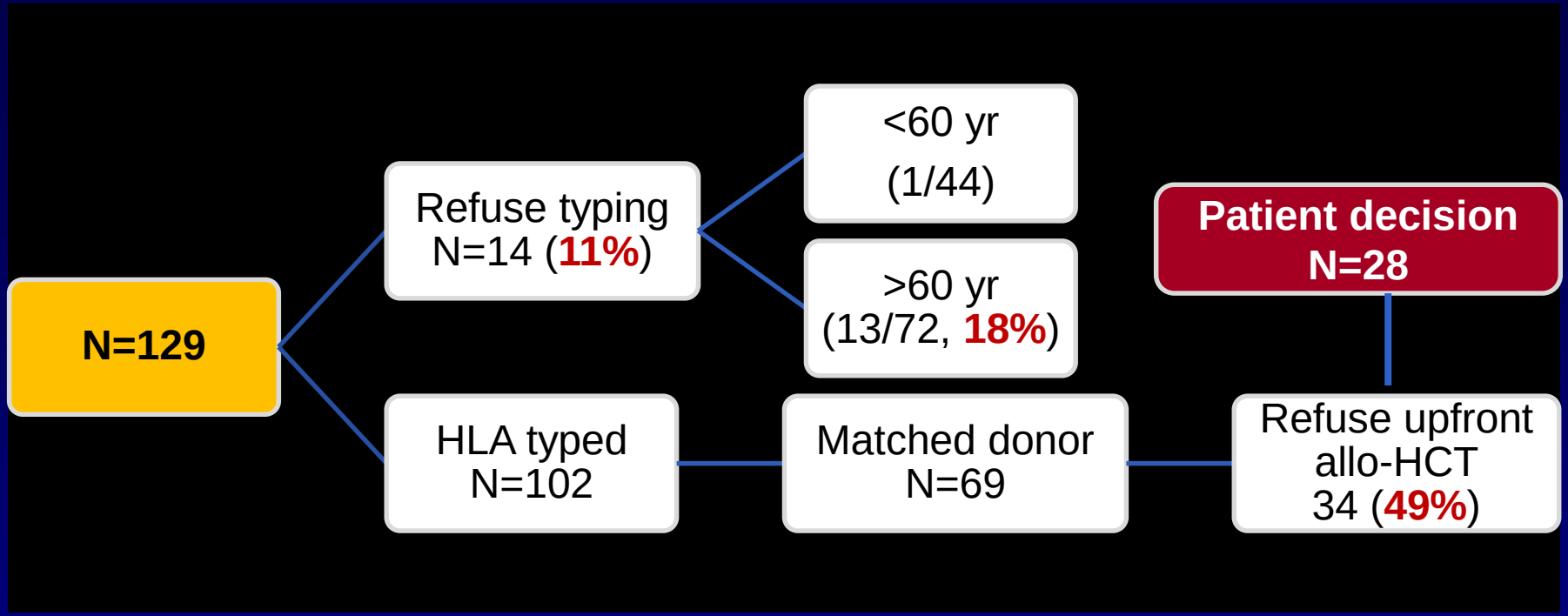
	MIPSS70	MIPSS70+ v2.0
Disease risk group	High	High
Predicted Median OS	2.3 yr	4.1 yr

	MTSS
Transplant risk group	Low
Predicted 5-yr OS	83%

Discuss with the patient the risk-benefit balance including its optimal timing

3) Patient / clinician perceptions on the risk-benefit balance of transplant in myelofibrosis

Patient perceptions regarding allo-HCT in MF
Princess Margaret



Smith E et al, Transplant Cell Ther 2021;27(7):600.e1-e8

How many MF patients undergo transplant ?

Spanish Myelofibrosis Registry
Calendar year: 2000-2023
N=1790, 60 centers

Median follow-up: 6.7 yr

Allo-HCT: 168 (9.4%)

Time from Dx	N*
Year 1	51 (32%)
Year 2	39 (24%)
Year 3	10 (6%)
Later on	61 (38%)

*Available in 161 cases

Median time from MF Dx to HCT:

645 days (range: 51-7099)

Unpublished data

How many MF patients diagnosed at age 70 or younger undergo transplant ?

IPSS	Age ≤ 70 yr (N= 961)
Low	202 (21%)
Int-1	291 (30%)
Int-2	272 (28%)
High	196 (21%)

Allo-HCT: 167 / 1,033 (16%)

Time Dx- HCT

1461 days (201-7099)

Allo-HCT

69 (14%)

Time Dx- HCT

371 days (51-5343)

Allo-HCT

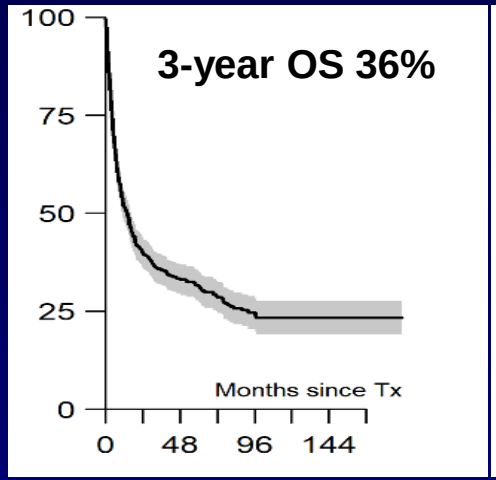
91 (19%)

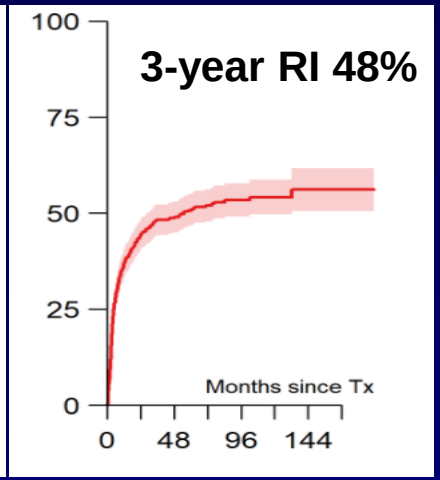
GEMFIN Registry, unpublished data

4) Optimal timing of transplant in myelofibrosis

Allo-HCT in blast phase MPNs (EBMT)

N=663
RIC: 65%



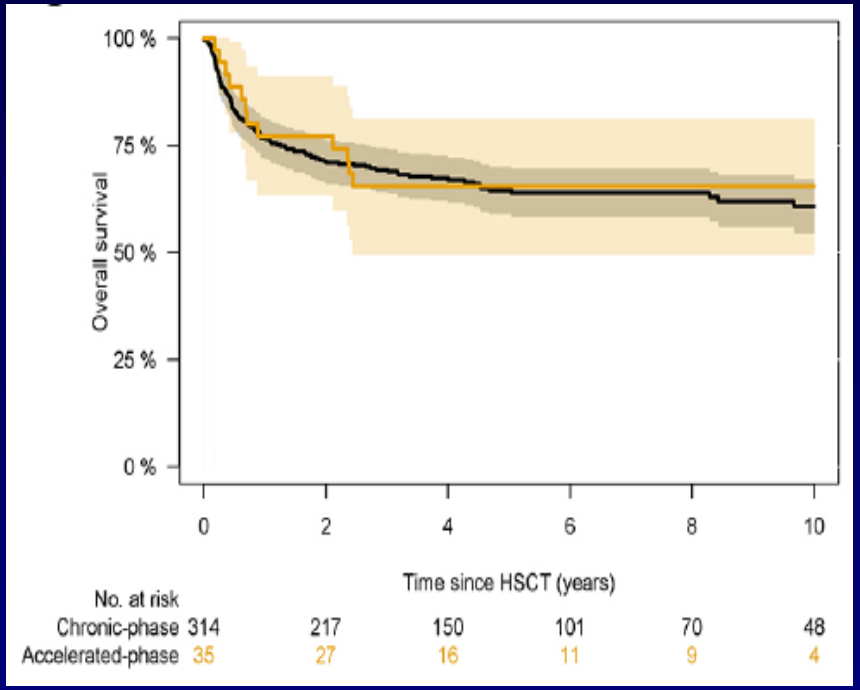


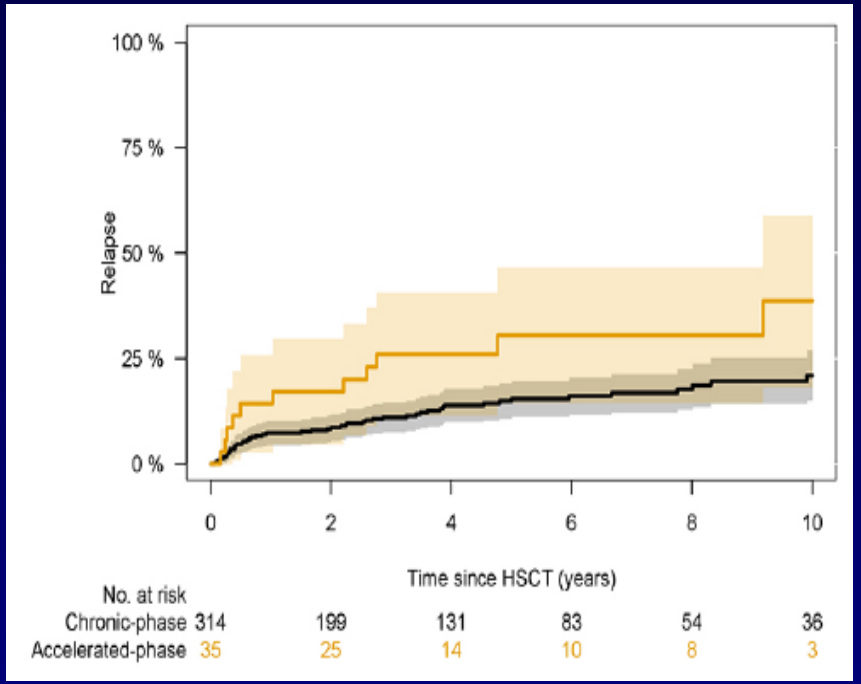
Conditioning intensity was not asociated with relapse risk

	Relapse	
	HR (95% CI)	(Overall) p
Age at allo-HCT (per 10 year increase)	1.02 (0.89–1.18)	0.76
Sex		
Male	1.00	
Female	0.98 (0.77–1.26)	0.89
Karnofsky prognostic score		
≥90	1.00	
<90	1.11 (0.86–1.43)	0.42
Year of allo-HCT (per year later)	0.95 (0.92–0.99)	0.008
Donor type		(0.92)
MSD	1.00	
MMRD	0.97 (0.56–1.67)	0.9
MMUD	1.06 (0.75–1.49)	0.73
MUD	0.93 (0.69–1.25)	0.62
Interval diagnosis—AML (per year later)	1.00 (0.99–1.02)	0.62
Disease stage at allo-HCT		
CR	1.00	
Active disease	1.32 (1.04–1.68)	0.02

Orti G et al, AJH 2023;98(4):628-38

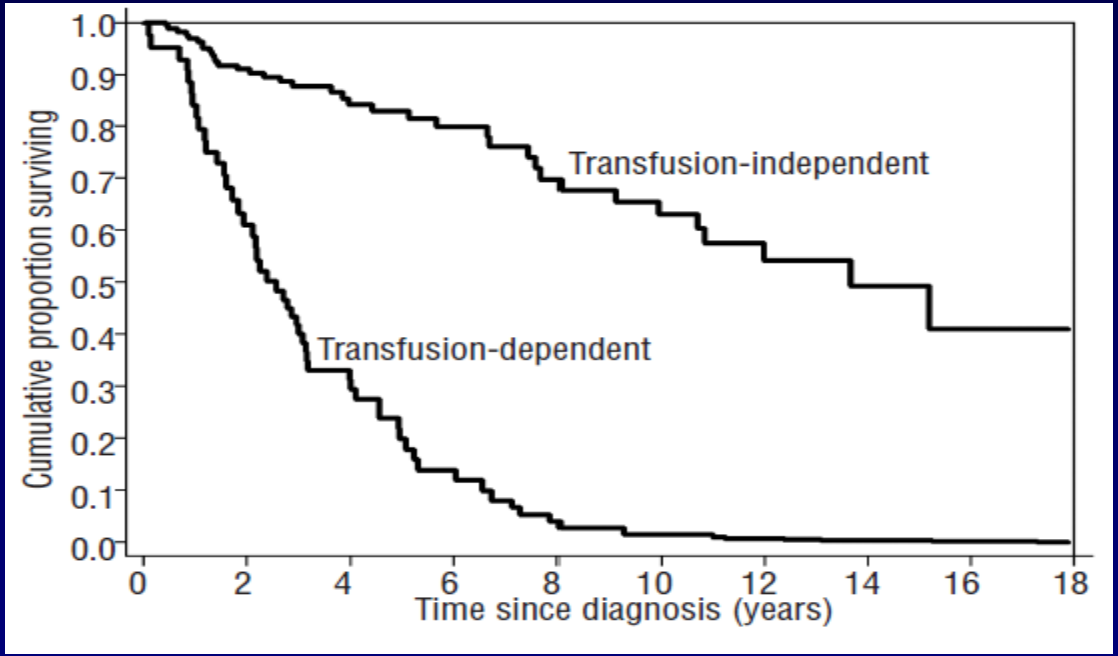
Allo-HCT for accelerated phase MF





Gagelmann N et al, Blood Adv 2022:6(4):1222-31

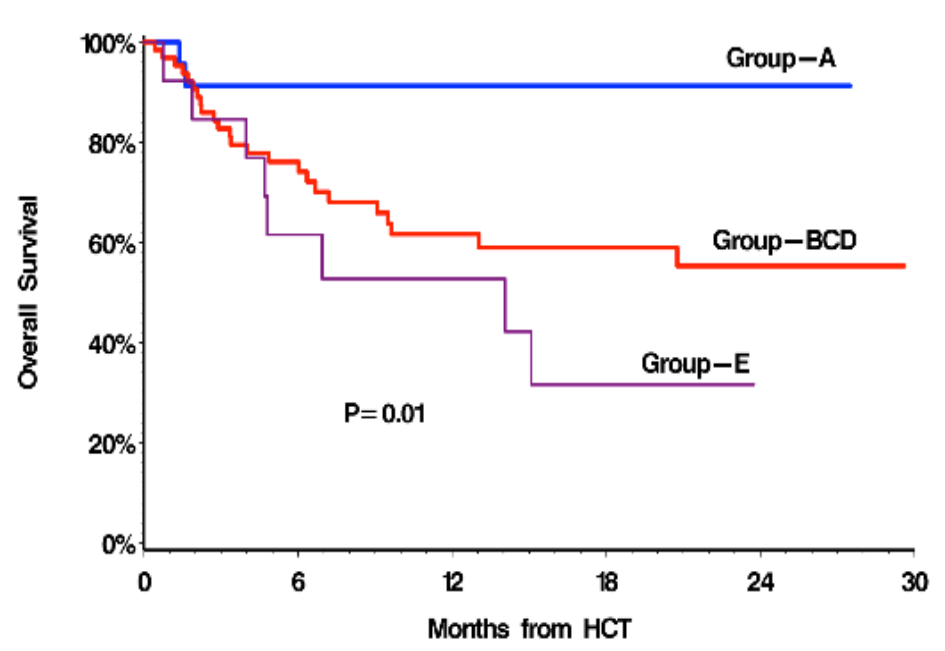
Red blood cell transfusion-dependency implies poor OS irrespective of IPSS/DIPSS



RBC-dependency as time-dependent variable

Chiara E et al. Haematologica 2011;96(1):167-70

Survival after allo-HCT depending on response to ruxolitinib at transplant

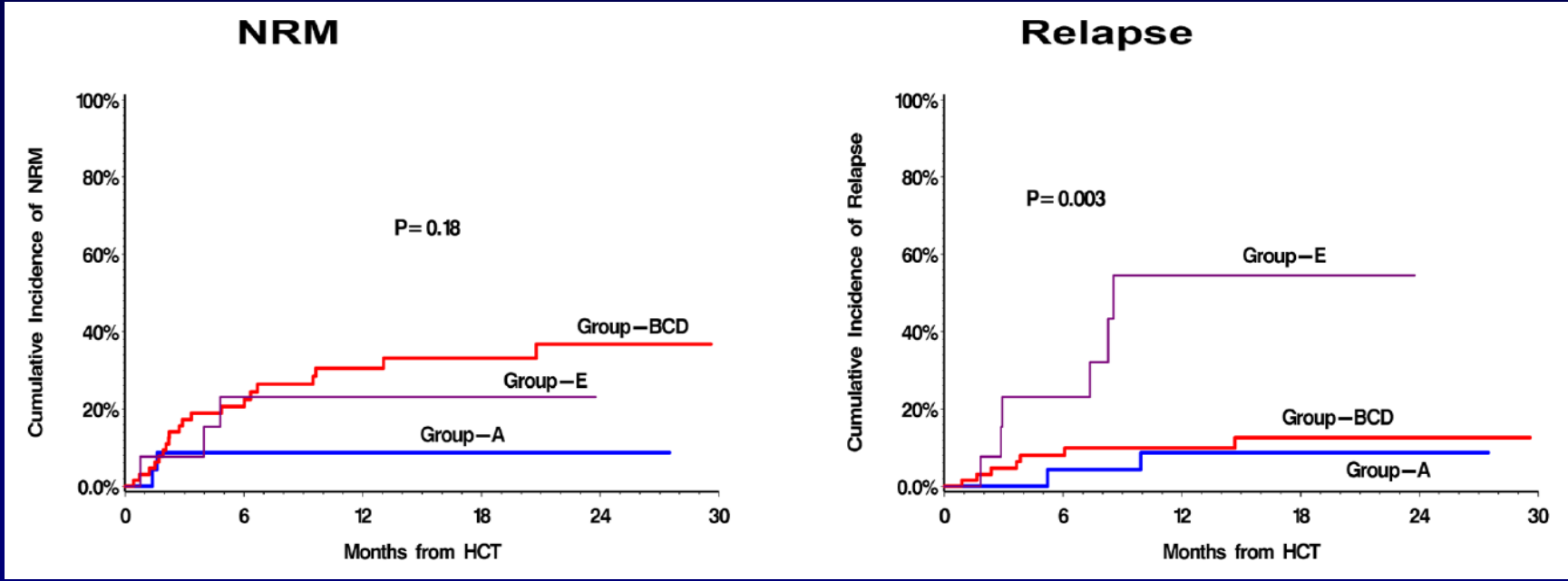


Response to JAK#, n	
Group A: Clinical Improvement	23
Group B: Stable disease	31
Group C: New onset cytopenia or increasing blasts	15
Group D: Progressive disease: Splenomegaly	18
Group E: Progressive disease: Leukemic Transformation	13

Clinical improvement:
≥ 50% spleen size reduction

Shanavas M et al. BBMT 2016;22(2):432-40

Survival after allo-HCT depending on response to ruxolitinib at transplant



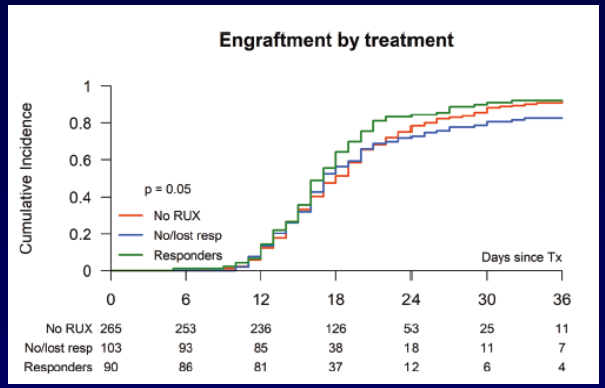
Shanavas M et al. BBMT 2016;22(2):432-40

Pretransplant use of JAKi: EBMT series

Transplant period
2012-2016

Spleen response to RUX:
≥ 25% spleen size reduction

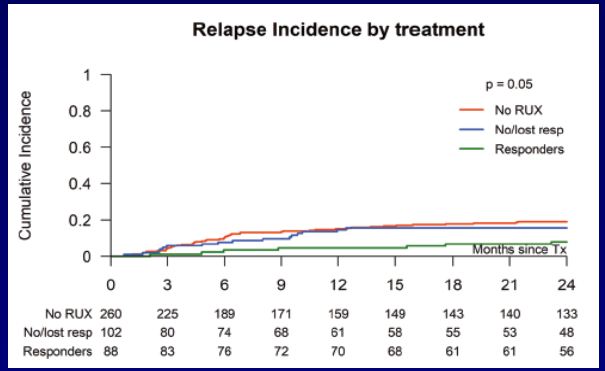
A) RUX responders (n=91)
B) RUX no/lost response (n=104)



Graft failure

6% RUX resp

15% No or lost response



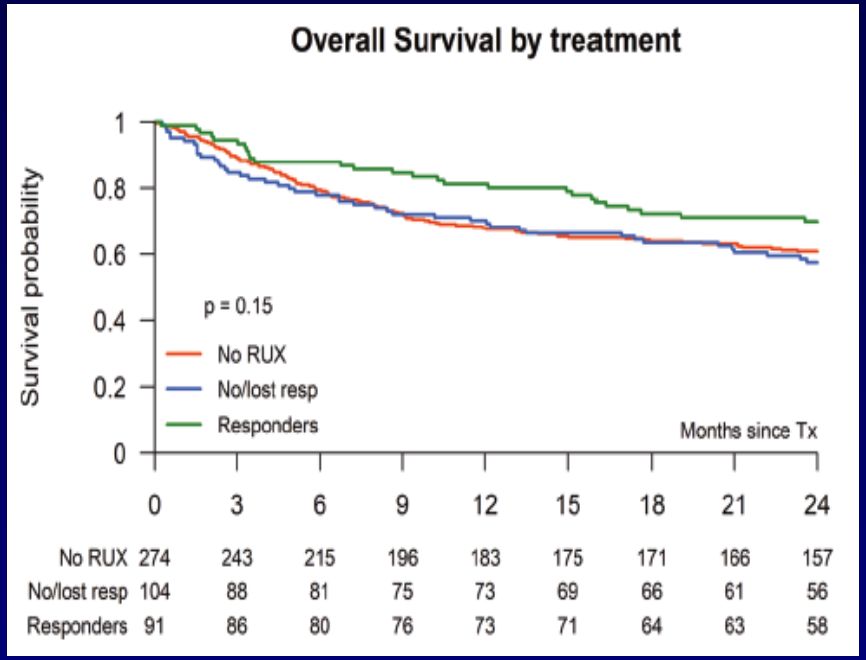
2-yr relapse incidence

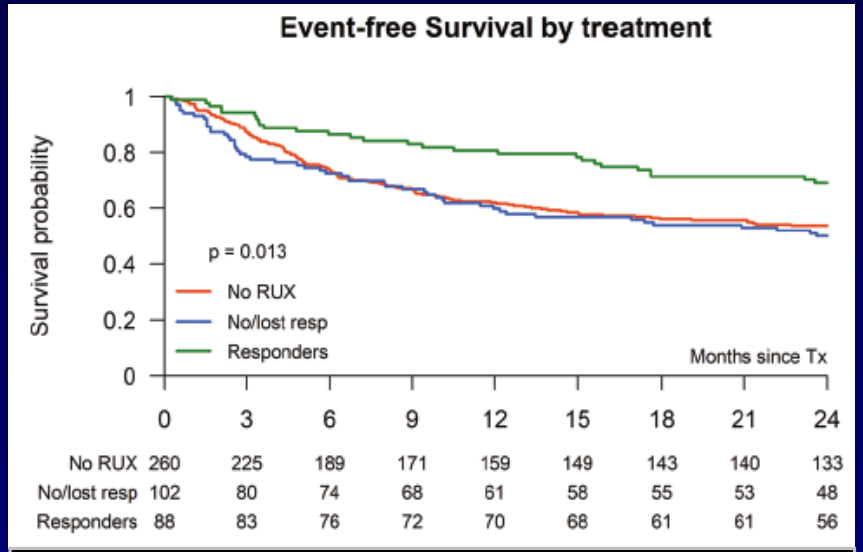
8% RUX resp

16% No or lost response

Kröger NM et al, Leukemia 2021;35(12):3551-60

Pretransplant use of JAKi: EBMT series





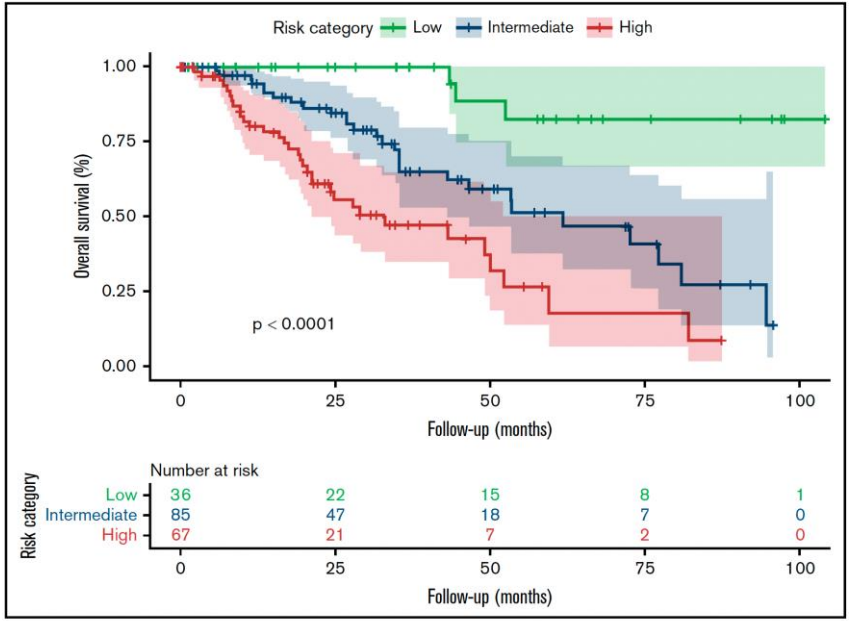
2-yr EFS:
69% RUX resp vs 50% No/lost response

Kröger NM et al, Leukemia 2021;35(12):3551-60

RR6, a Model to Predict Survival After 6 Months of Ruxolitinib in MF

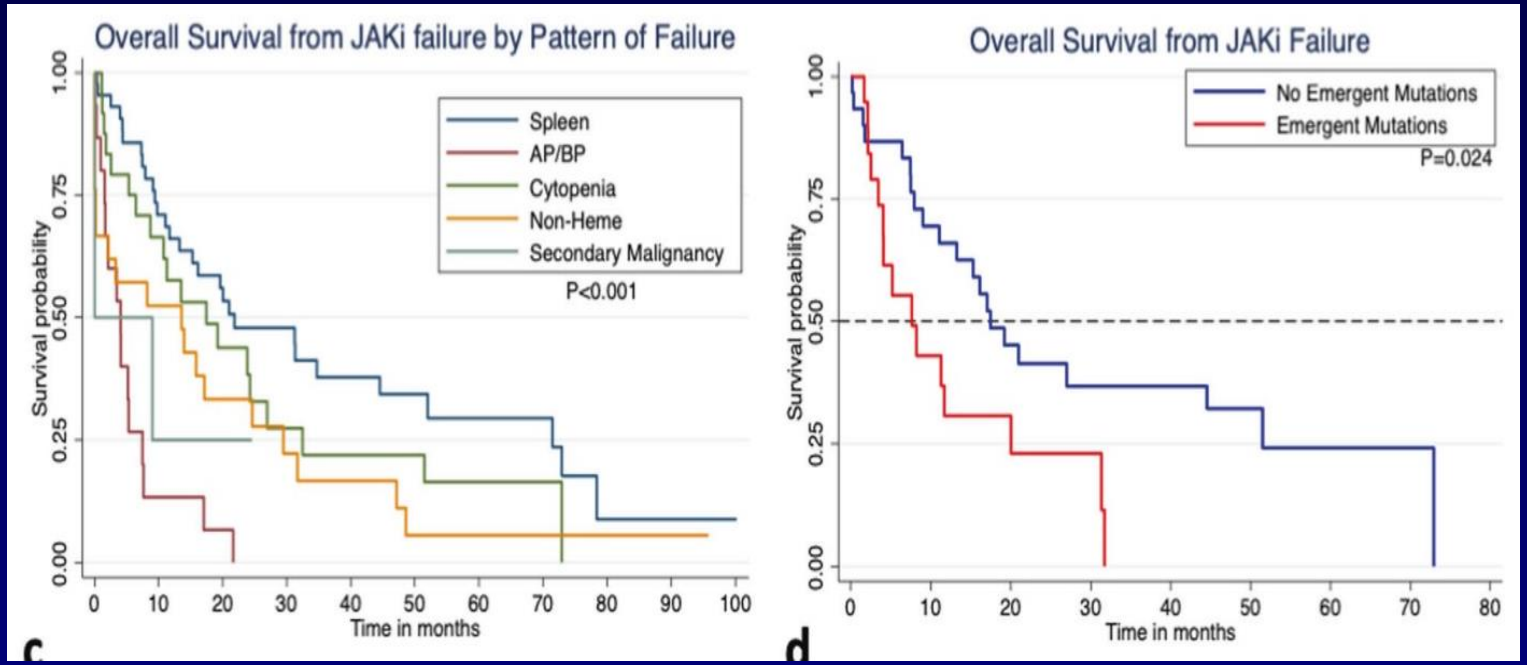
Parameters	Points
RUX dose <20 mg BID at BL, M3, M6	1
≤30% spleen length reduction at M3 & M6	1.5
RBC transfusions at M3 and/or M6	1
RBC transfusions at BL, M3, and M6	1.5

Risk category	%. of pts	OS (months)	Score
Low	19	NR	0
Intermediate	45	61	1-2
High	36	**33**	≥2.5



Maffioli M et al, Blood Adv 2022;6:1855-64

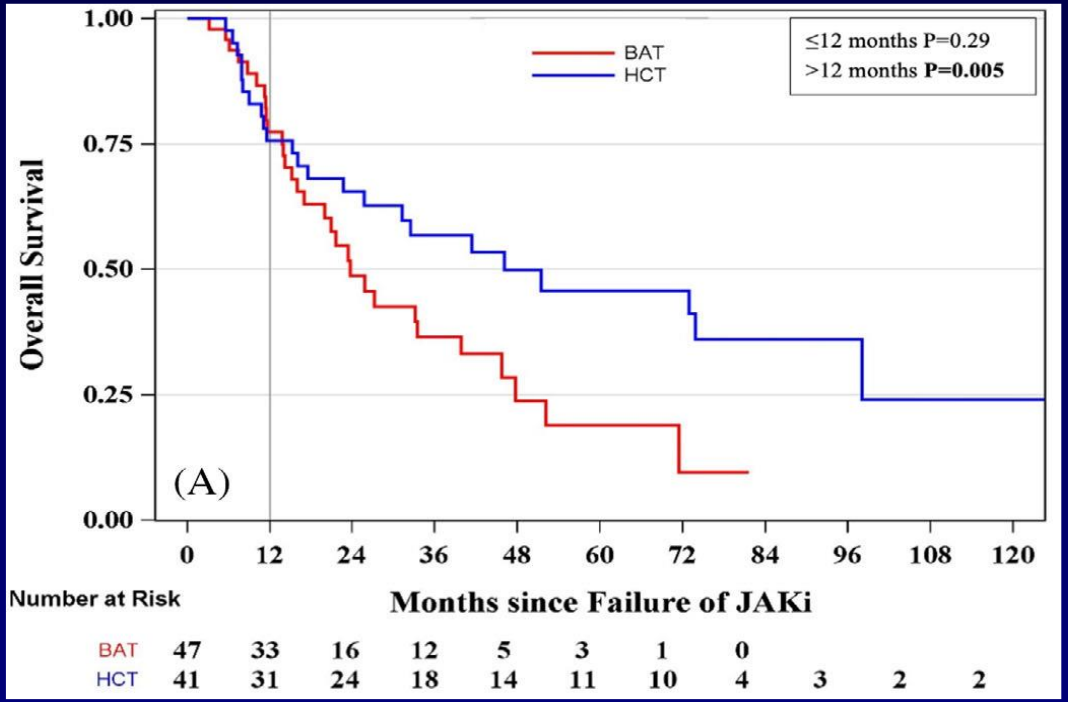
Overall survival from JAKi failure



Median OS: 14 months

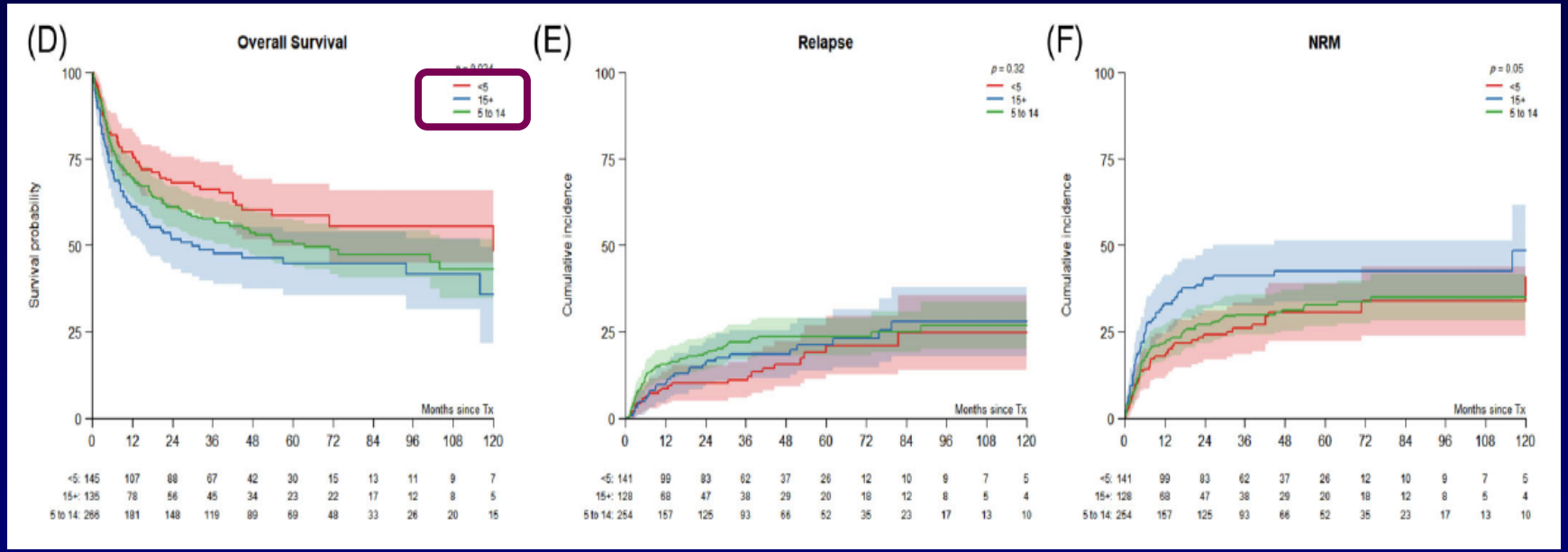
England JT et al. Leukemia 2022;36(6):1689-92

Overall survival from JAKi failure
Allo-HCT vs BAT



England JT et al. AJH 2023;98:E127-9

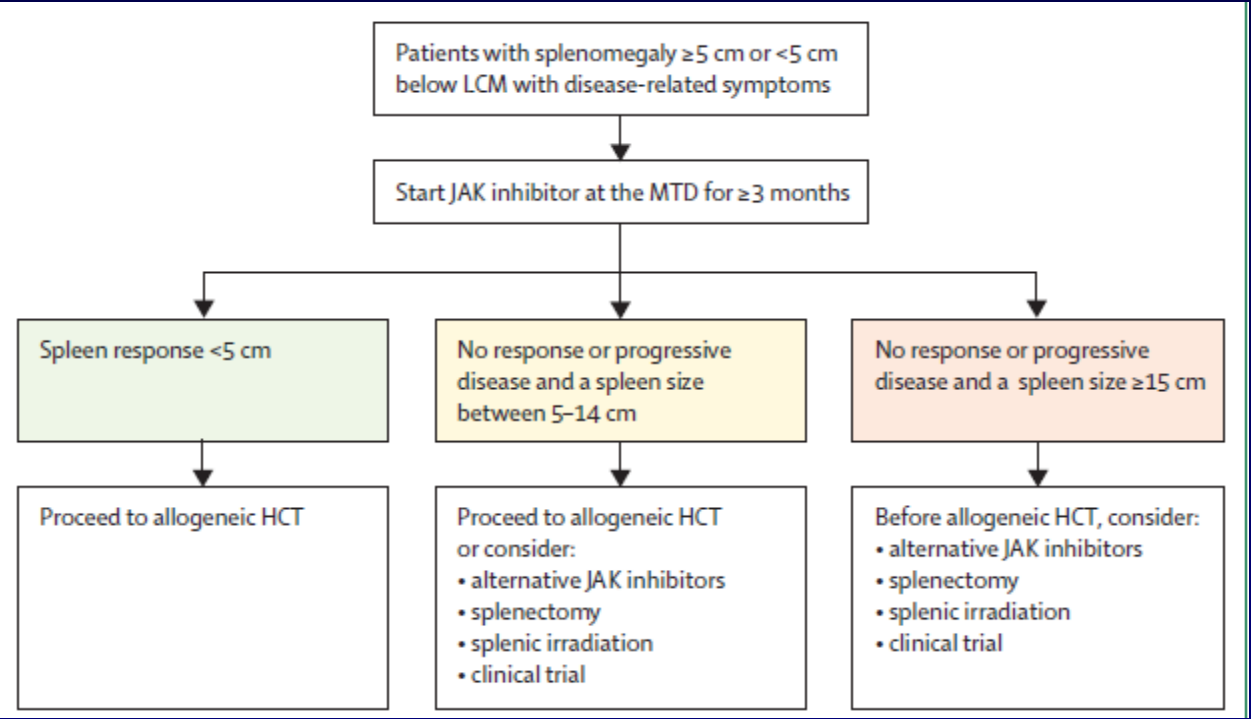
Impact of spleen size on allo-HCT outcomes



The effect of spleen size on OS was not significant in MAC transplants

Polverelli N et al. AJH 2021;96(1):69-79

Management of splenomegaly in transplant candidates



Polverelli N et al. Lancet Haematol 2023;10(1):e59-e70

Take-home messages

- The activity of allo-HCT in myelofibrosis is increasing over time, with a more frequent use in older patients. Despite this trend, a significant proportion of patients decide not to receive this potential life-saving therapy.

- The decision to undergo transplant and its timing should be based on the myelofibrosis-risk, the transplant-risk and the patient perceptions on the risk-benefit ratio of the procedure.

- Proper timing of transplant is crucial to optimize the results (i.e., before clinical deterioration, ruxolitinib failure and leukemic transformation).