Universitätsklinikum Hamburg-Eppendorf

Allogeneic Stem Cell Transplant for Myelofibrosis

When and How?

New Drugs in Hematology

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Disclosures: Nicolaus Kröger

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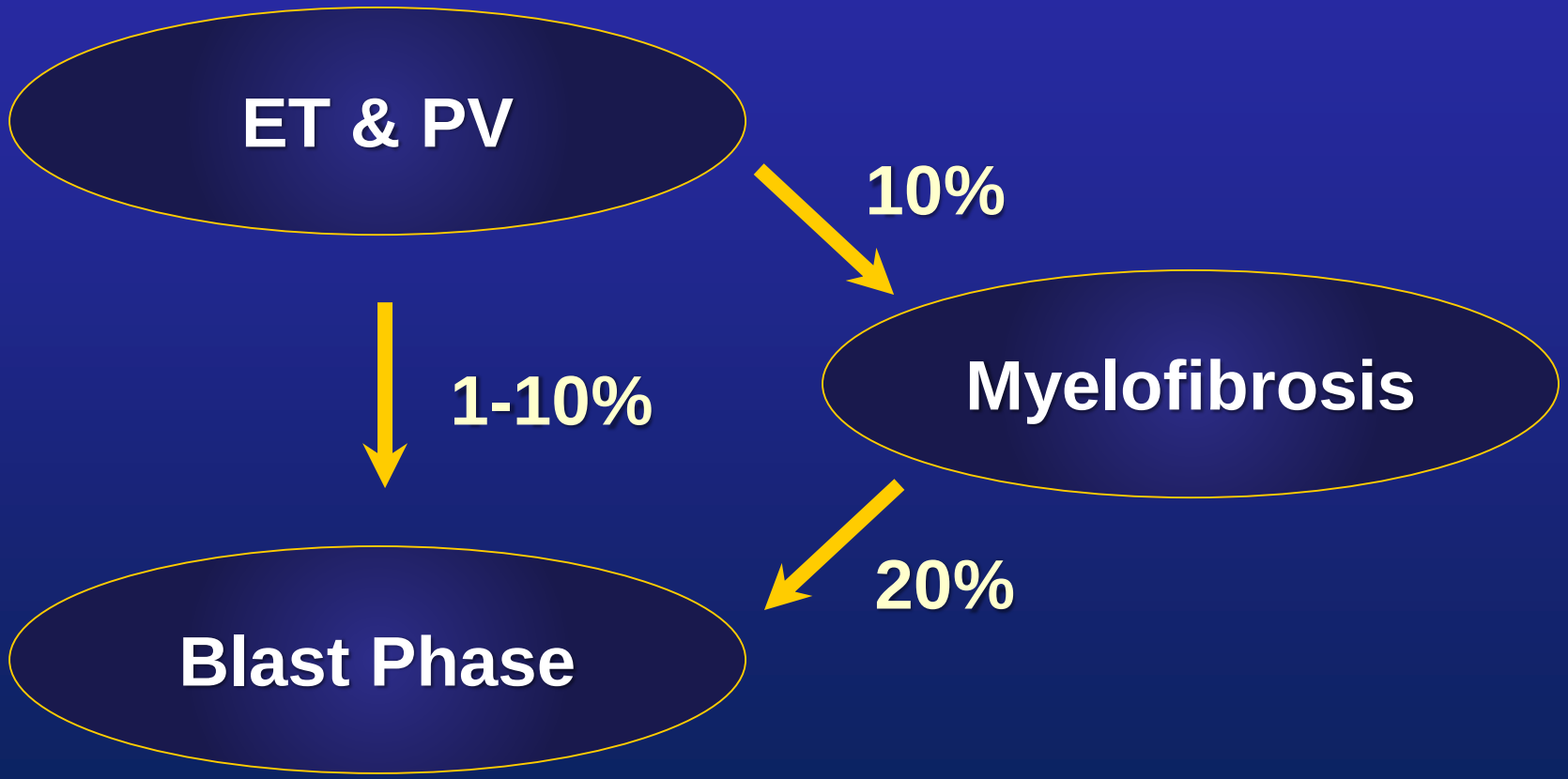
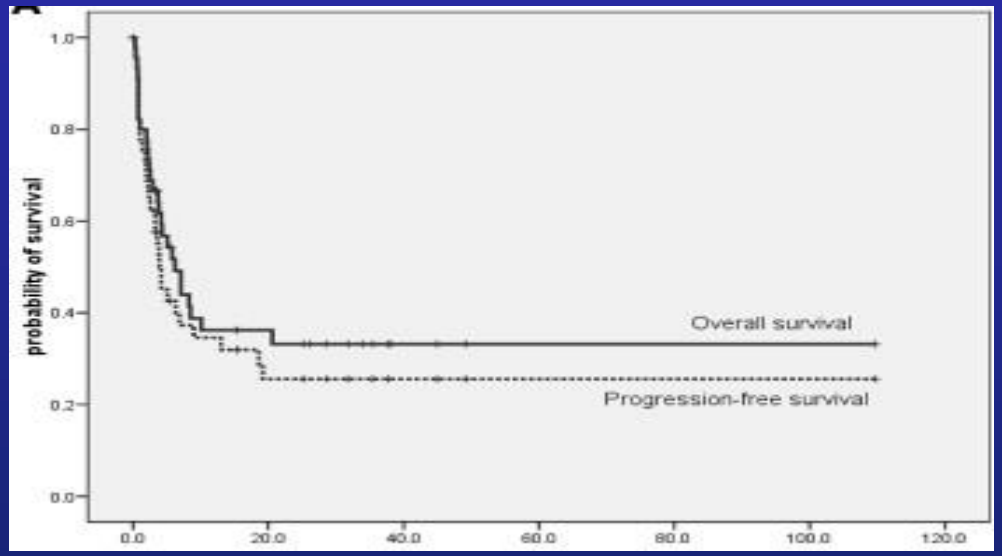
- AOP Orphan Pharmaceutical: honorarium
- Riemser: Research Grant
- Neovii: Research Grant

Progression in the MPNs



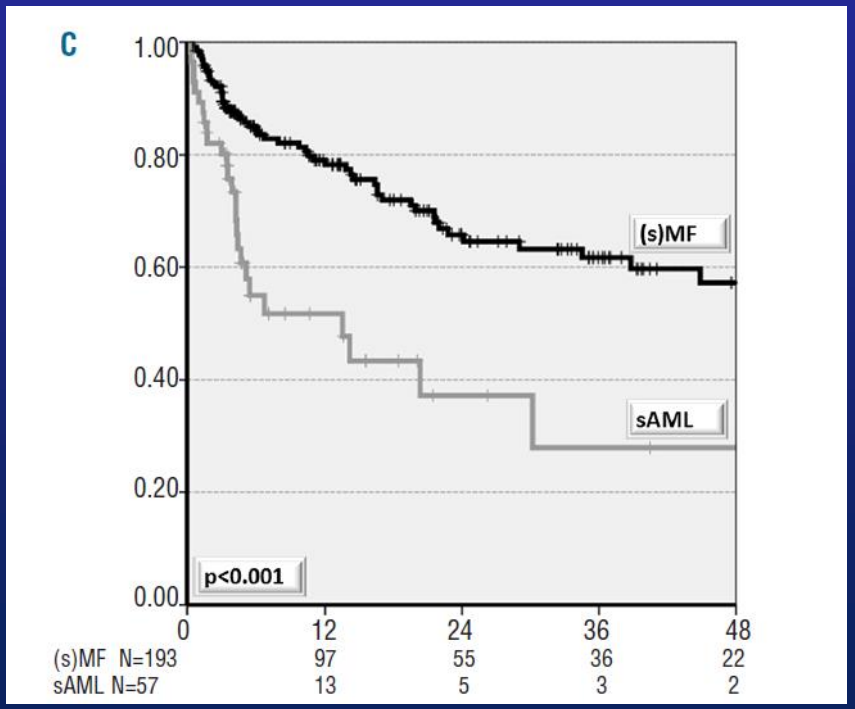
Allogeneic stem cell transplantation for blast phase of PV or myelofibrosis (EBMT data)

Transformed Leukemia after myelofibrosis



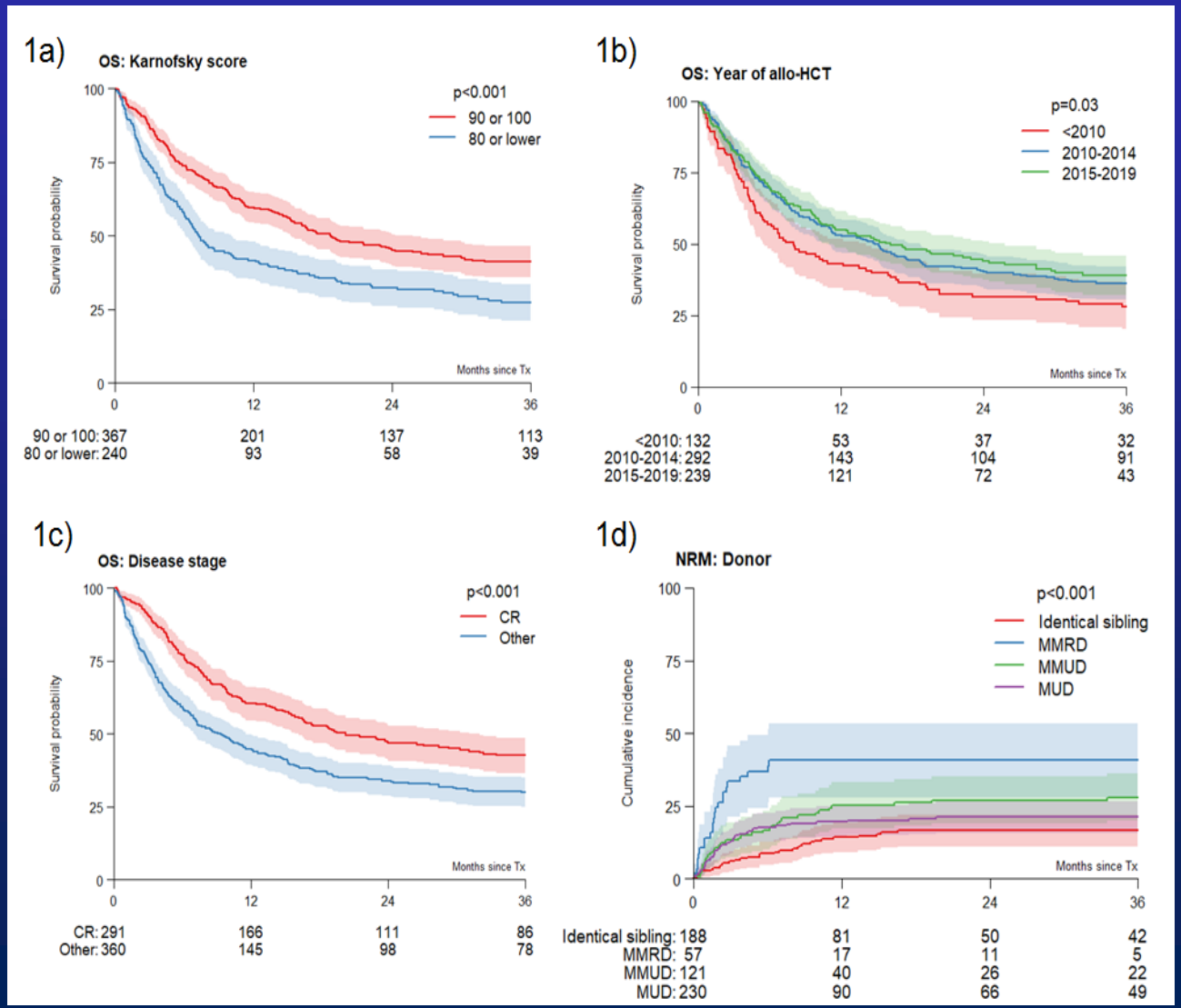
Alchalby et al BBMT 2014

PV transformed to sMF or sAML



Lussana et al Haematologica 2014

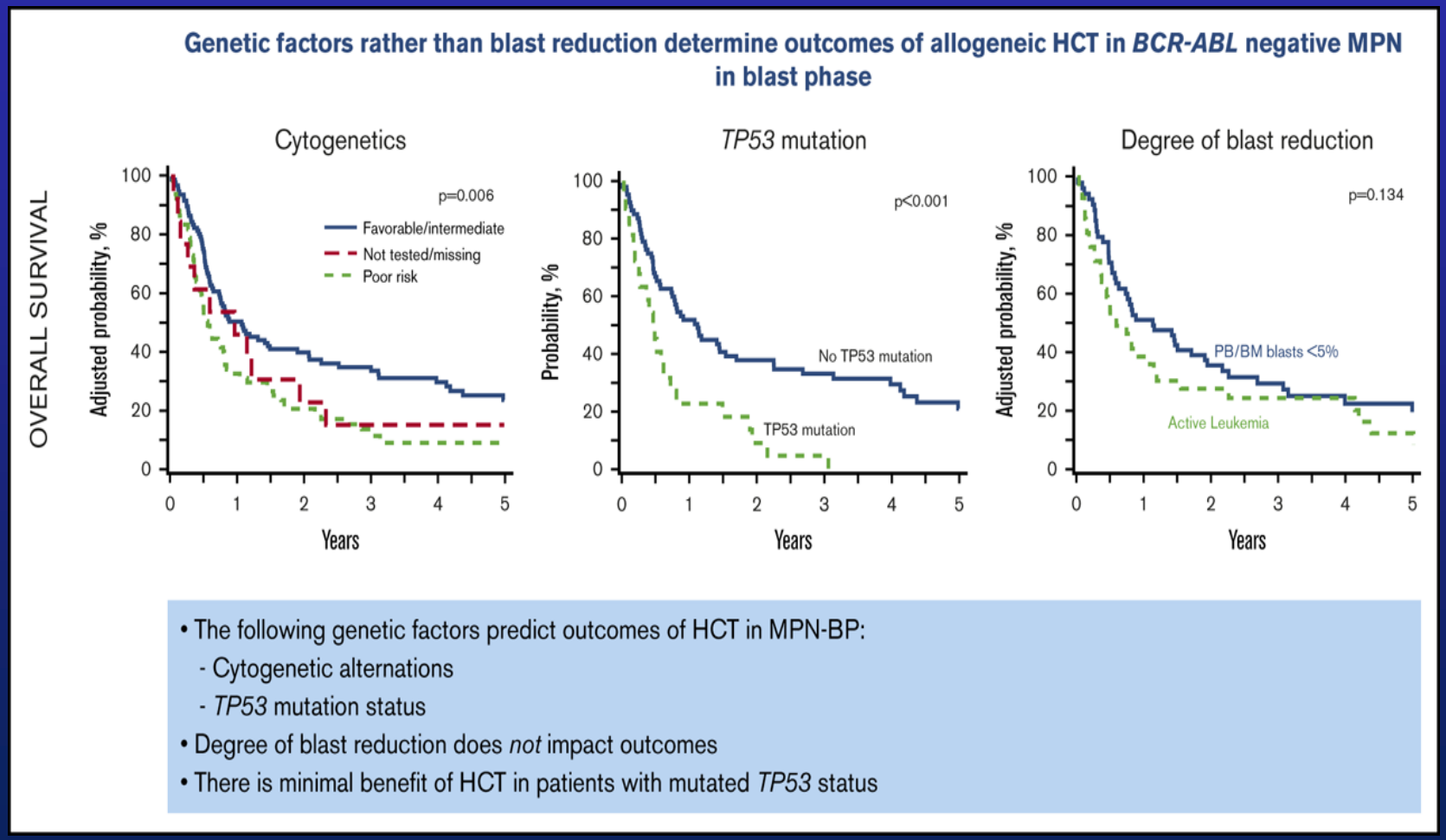
Allogeneic Stem Cell Transplantation for blastic phase MPN: EBMT /CMWP data



EBMT study:
N=662
TRM at 1 y: 24%
Relapse at 3 y: 48%
PFS at 3 y: 28%
OS at 3 y: 36%

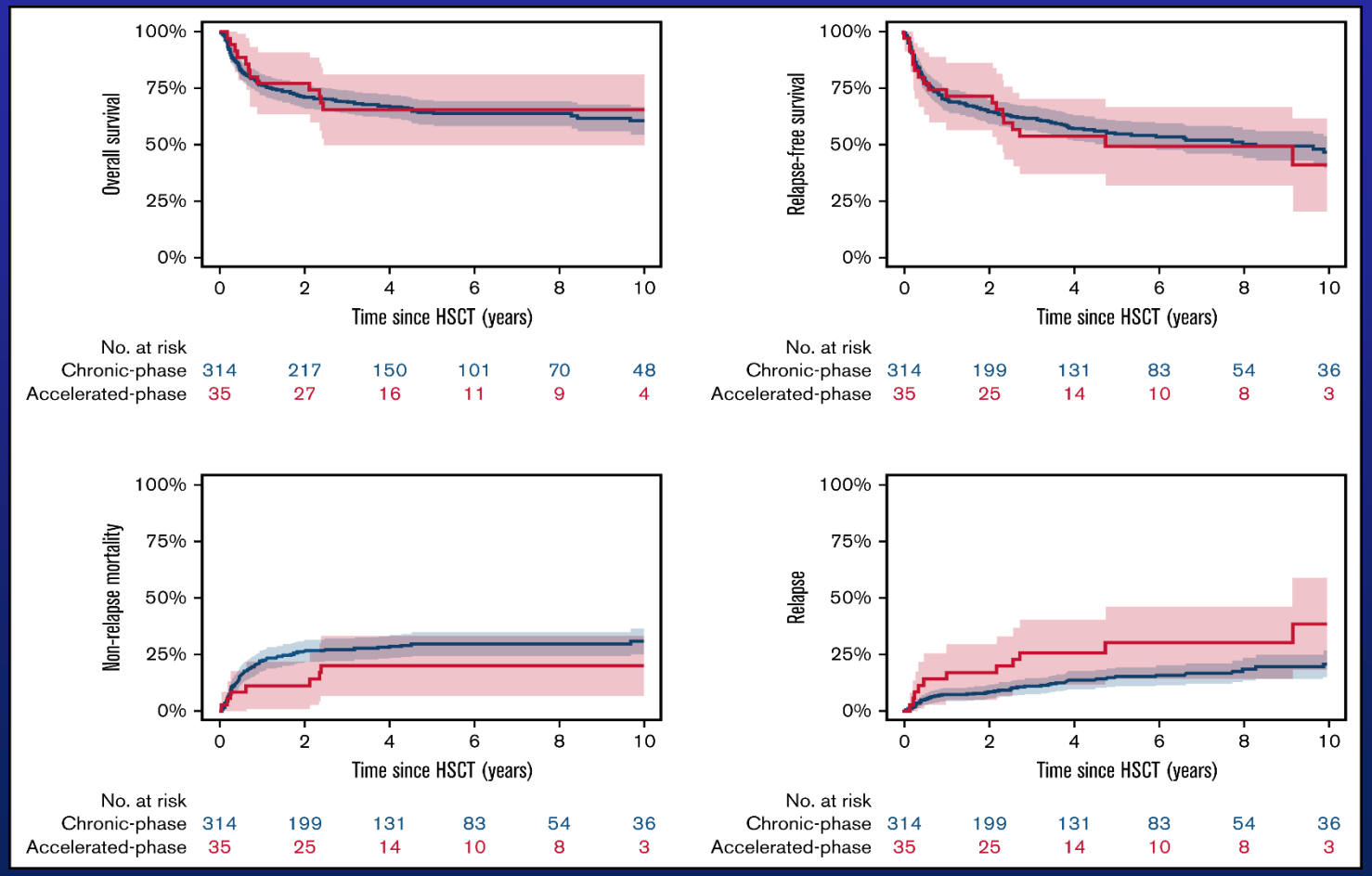
Orti et al EBMT congress 2022

Genetic factors rather than blast reduction determine outcomes of allogeneic HCT in BCR-ABL–negative MPN in blast phase (CIBMTR data)



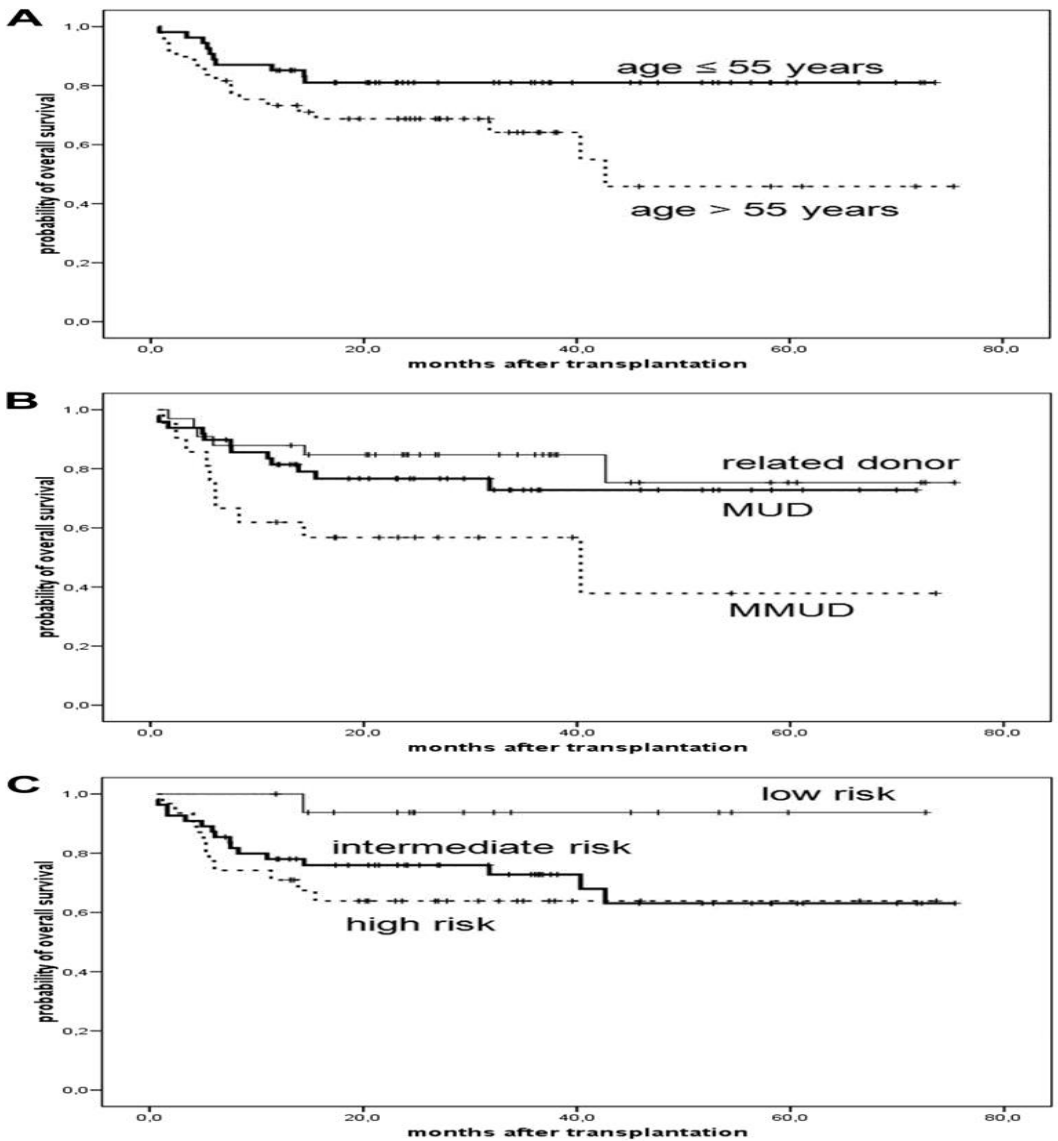
Gupta et al, Blood Adv 2020

Reduced intensity hematopoietic SCT for accelerated-phase myelofibrosis (n=35) in comparison to chronic phase (n=314)



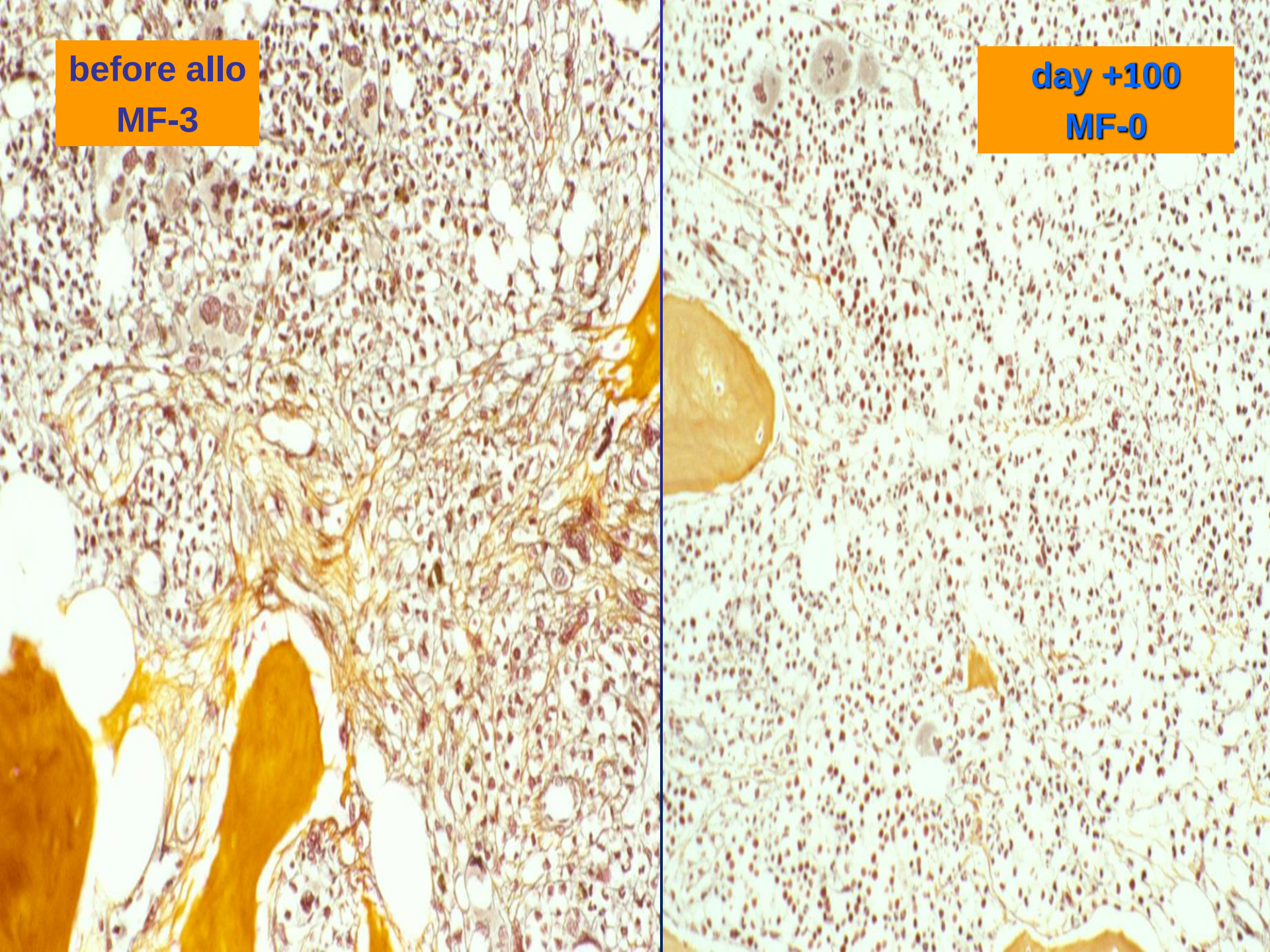
Gagelmann N et al Blood Adv 2022

Survival of pts with myelofibrosis after busulfan/fludatabine based reduced-intensity allogeneic stem cell transplantation. Prospective EBMT study (n=103; med age 55y)

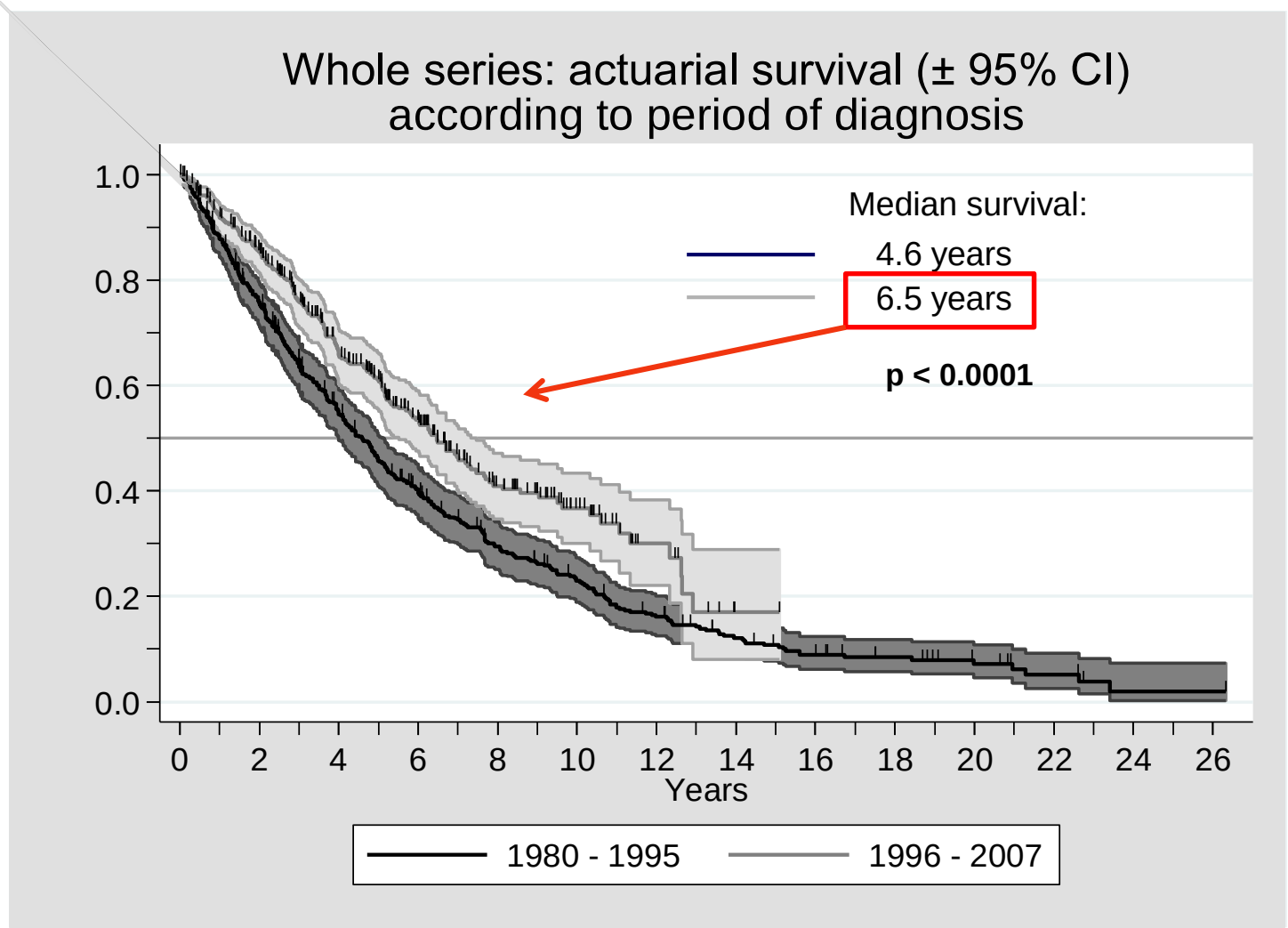


EBMT

Kröger et al. Blood 2009;114:5264-5270


before allo
MF-3
day +100
MF-0

Primary Myelofibrosis: Survival between 1980 and 1995 and between 1996 and 2007



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

Evolving Prognostic Scores in Myelofibrosis

	Lille	*IPSS*	*DIPSS*	*DIPSS -Plus*
Anemia	X	X	X	X
Leukocytes	X	X	X	X
Blasts		X	X	X
Constitutional Symptoms		X	X	X
Age >65		X	X	X
Karyotype (-8,-7,-5, i17q,12p-,inv3, 11q23 or Complex)				X
PLT <100				X
RBC Transfusion Dep				X

Dupriez B, et al. Blood. 1996;88:1013-1018.
Cervantes F, et al. Blood. 2009;113:2895-2901.
Gangat N, et al. J Clin Oncol. 2011;29:392-397.
Passamonti F, et al. Blood. 2010;115:1703-1708.

Dupriez 1996	*Cervantes 2009*	*Passamonti 2010*	*Gangat 2011*

Risk scoring system

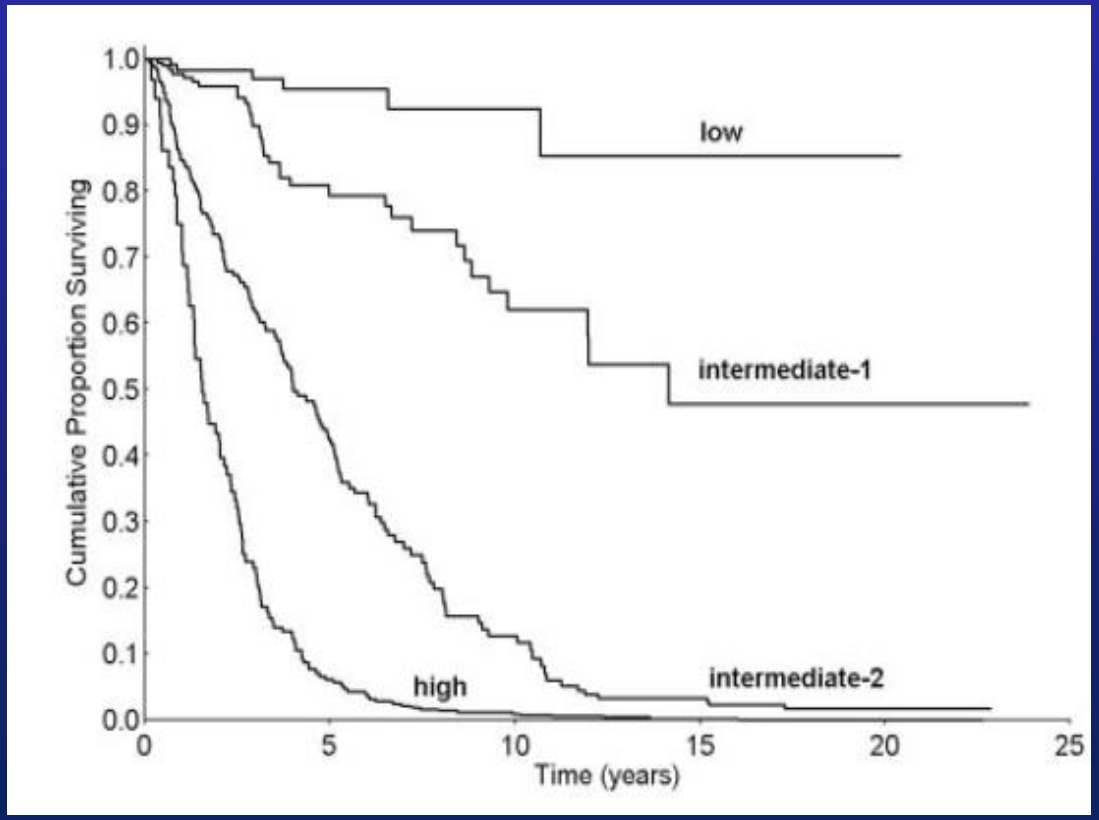
Factors

• Age > 65 years	1
• Constitutional symptoms	1
• Hb < 10 g/dL	2
• Leukocytes > 25 x 10^9/L	1
• Blood blasts ≥ 1%	1

Risk groups

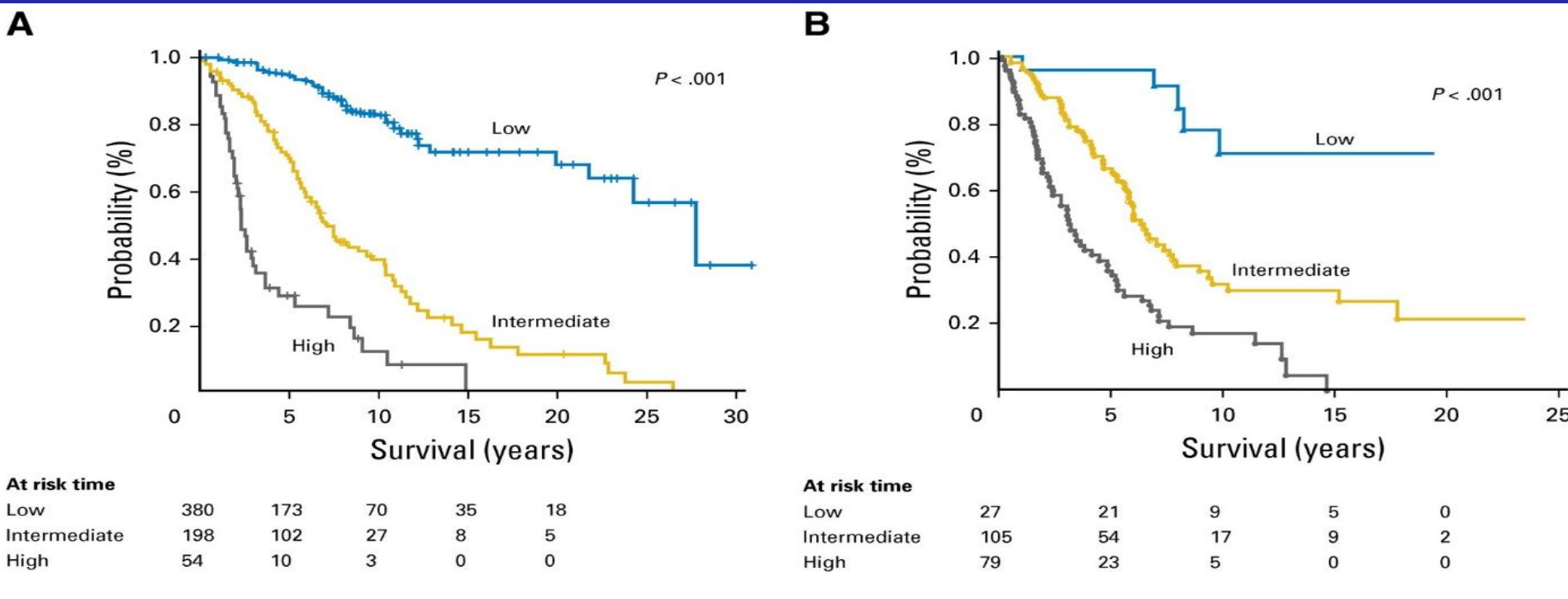
• Low	0
• Intermediate-1	1-2
• Intermediate-2	3-4
• High	≥ 5

DIPSS: Dynamic International Prognostic Scoring System for PMF



Passamonti F et al., Blood 2010, 115:1703-8

Overall survival (OS) in (A) training and (B) validation cohorts by the MIPSS70 prognostic scoring system risk classification



median OS
Low 27.7 y
Interm. 7.1 y
High 2.3 y

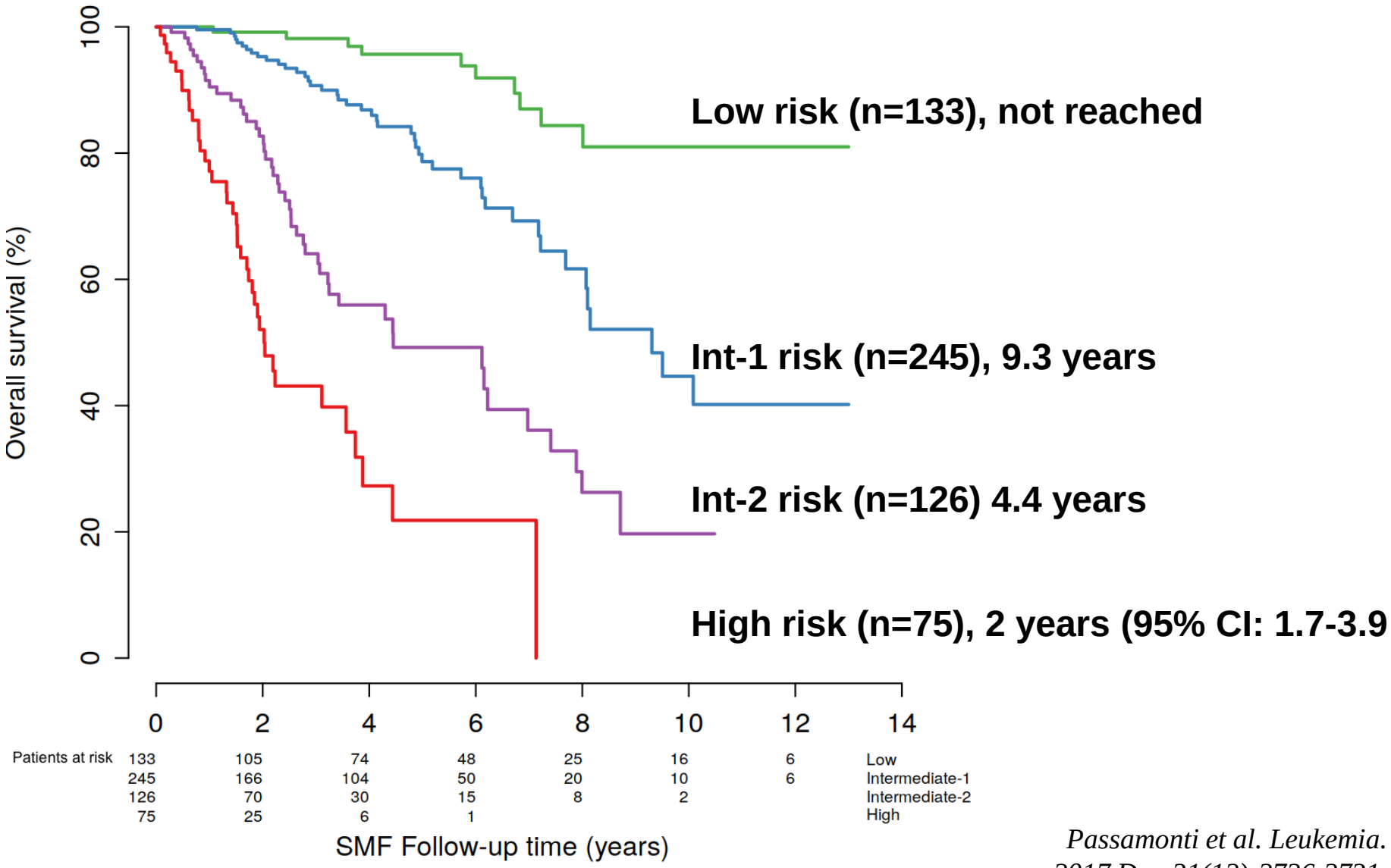
Guglielmelli et al., JCO 2018

The MYSEC-PM score for Post ET/PV myelofibrosis

Factor	Score values			
Age, years	*0.15			
	0	1	2	
Constitutional symptoms	No	Yes		
Blood blasts, %	<3		≥3	
Platelets, x 10^9/l	≥150	<150		
CALR-unmutated genotype	No		Yes	
Hemoglobin, x10^9/l	≥11		<11	
Overall	**<11**	**11 to <14**	**14 to <16**	**≥16**
Risk groups	**Low**	**Intermediate-1**	**Intermediate-2**	**High**

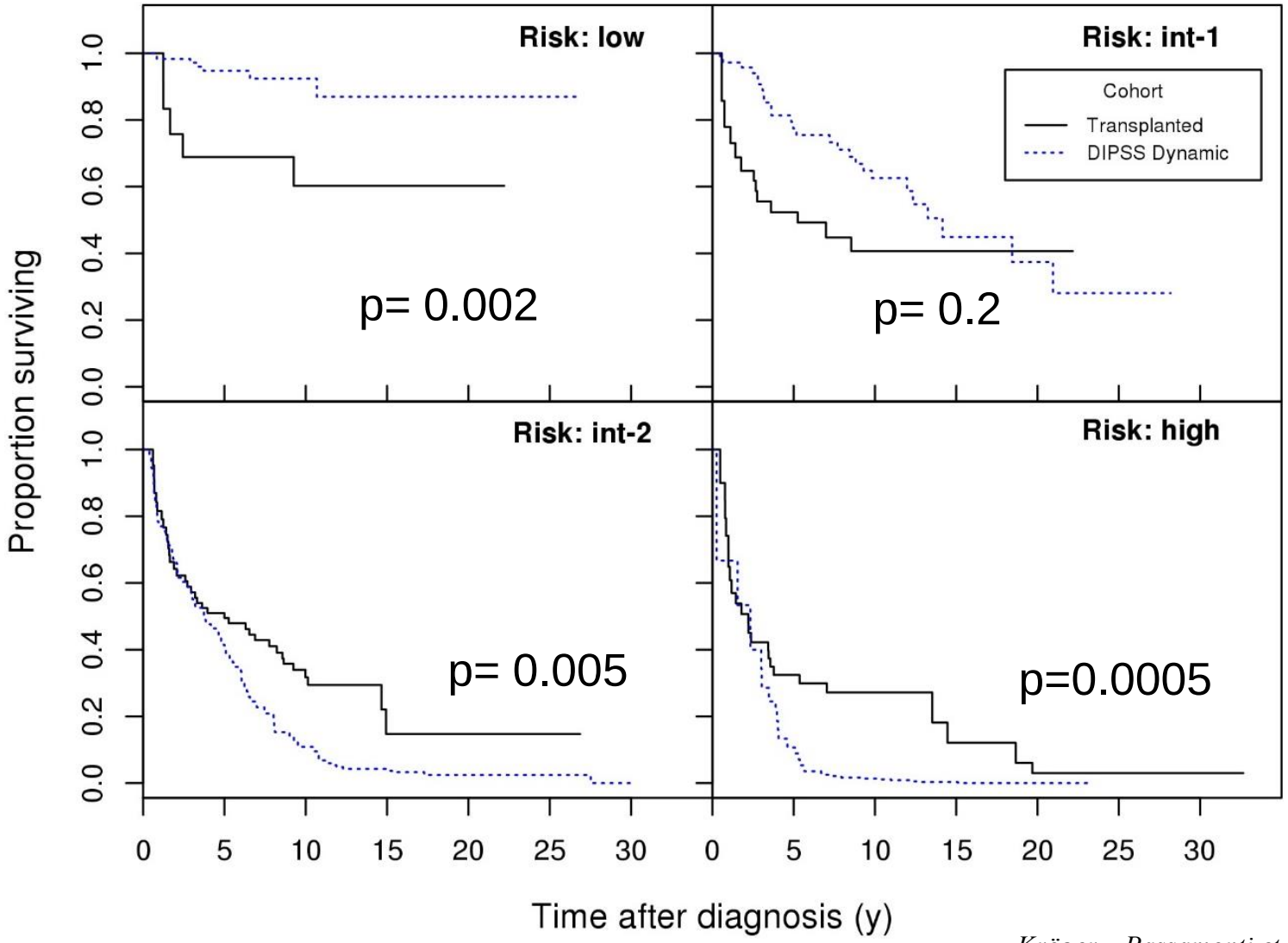
Passamonti et al. Leukemia. 2017 Dec;31(12):2726-2731

The MYSEC-PM estimate of survival in SMF



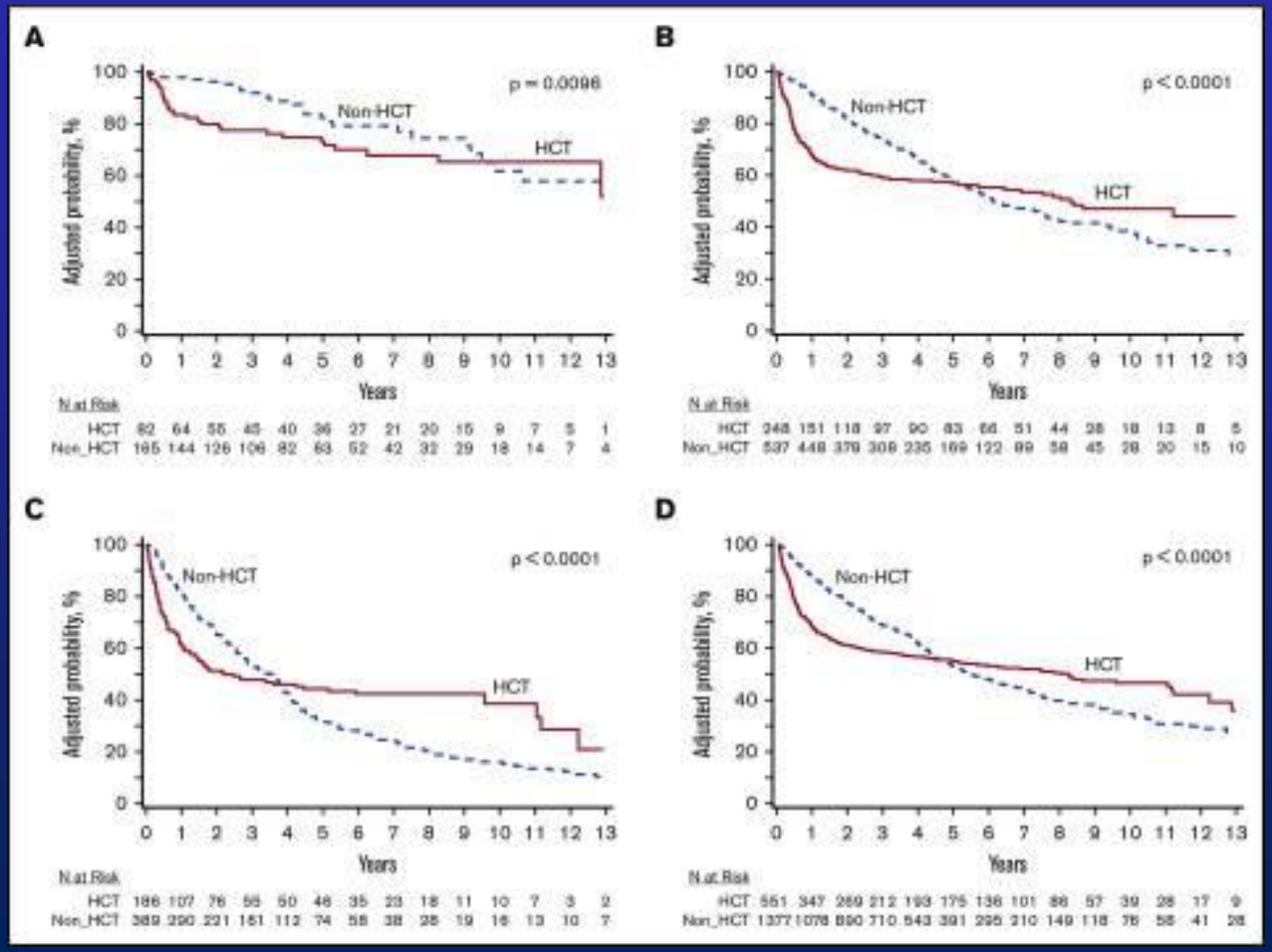
Passamonti et al. Leukemia. 2017 Dec;31(12):2726-2731.

Results of transplant vs non-transplant according DIPSS after left truncation



Kröger .. Passamonti et al., Blood 2015

Survival probabilities for the DIPSS risk groups in MF receiving HCT vs non-HCT therapy. (A) DIPSS low risk. (B) DIPSS Int-1. (C) DIPSS Int-2 or higher. (D) Overall (all DIPSS groups). CIBMTR data



Gowin et al Blood Advances 2020

Recommendation from EBMT/ELN regarding patient selection

1. All patients with intermediate-2– or high-risk disease according IPSS, DIPSS, or DIPSS-Plus, and age <70 y should be considered candidates for alloHSCT
2. Patients with intermediate-1–risk disease and age <65 y should be considered candidates for alloHSCT if they present either with refractory transfusion-dependent anemia, a percentage of blasts in peripheral blood >2%, or adverse cytogenetics
3. Patients with low-risk disease should not be considered candidates for alloHSCT; they should be monitored and evaluated for transplant when disease progression occurs

Leukemia. 2015;29:2126-2133.

Recommendation for Transplantation

Are available prognostic risk scores for Myelofibrosis also predictive for outcome after stem cell transplantation?

How important are „transplant-specific“ and „patient-specific“ risk factors to predict outcome after stem cell transplantation?

Transplant Risk score for myelofibrosis (n=361)

Variable	Hazard ratio	95% CI	P	Scoring
Leukocyte count, x 10^9/l			0.007	
≤ 25	reference			**1**
> 25	1.70	1.16 to 2.61		
Karnofsky performance score			0.021	
90 to 100	reference			**1**
< 90	1.50	1.06 to 2.13		
CALR-/MPL-unmutated genotype	2.20	1.10 to 4.51	0.032	**2**
Platelet count, x 10^9/l			0.006	
≥ 150	reference			**1**
< 150	1.67	1.16 to 2.40		
Age, years			0.006	
≥ 57	reference			**1**
< 57	1.65	1.15 to 2.36		
HLA-mismatch unrelated donor	2.08	1.45 to 2.97	< 0.001	**2**
ASXL1	1.42	1.01 to 2.01	0.041	**1**

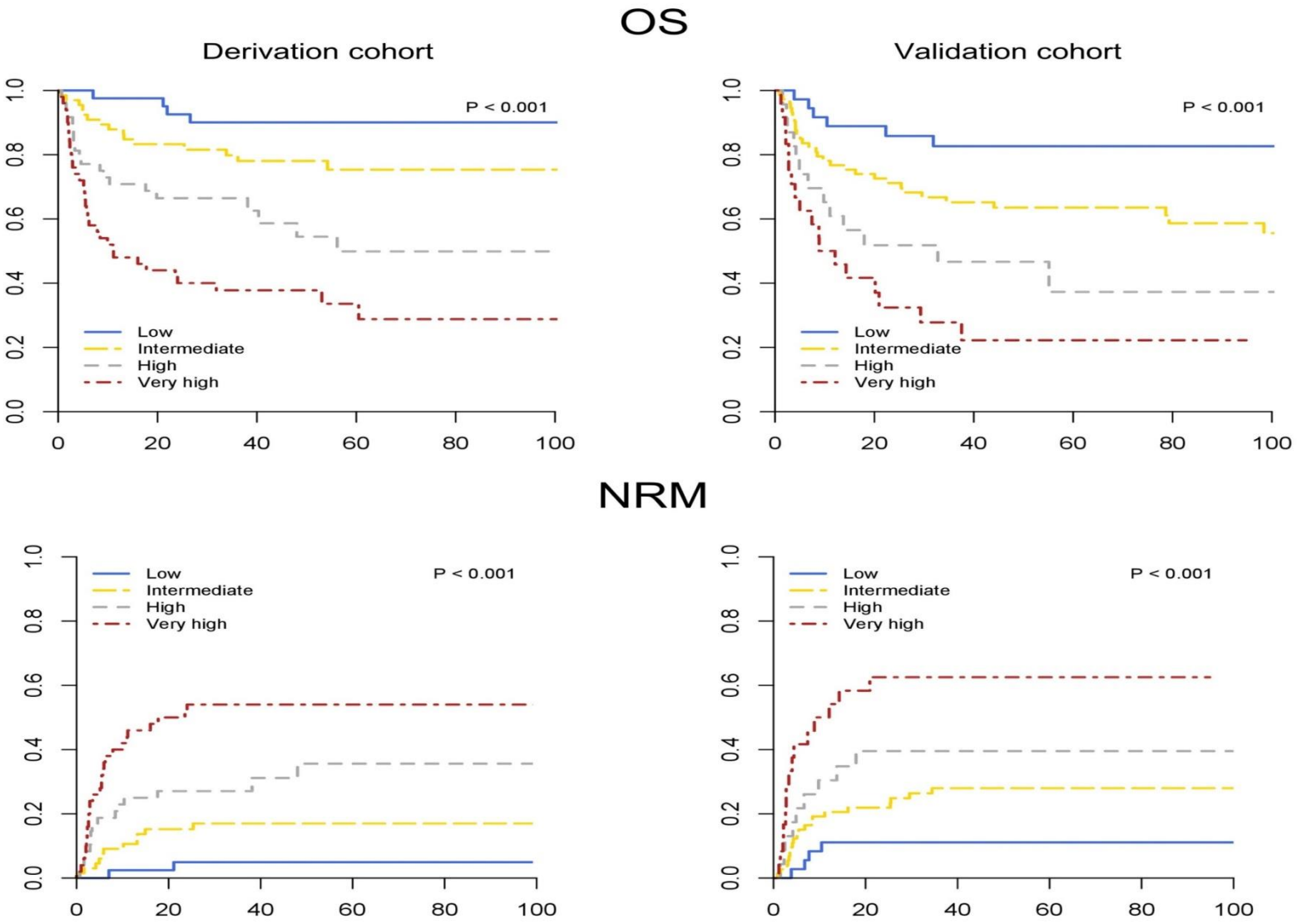
Gagelmann et al Blood 2019

Transplant-risk score for PMF and post ET / PV PMF

Leucocytes > 25 x 10^9/L	1
Karnofsky ≤ 90	1
CALR + MPL unmutated	2
Platelets ≤ 150 x 10^9/L	1
Age > 57 yrs	1
Mismatch unrelated donor	2
ASXL-1	1

		5 y OS	NRM
0-2	low	90%	10%
3-4	intermediate	77%	22%
5	high	50%	36%
≥ 6	very high	34%	57%

Transplant Risk score for myelofibrosis

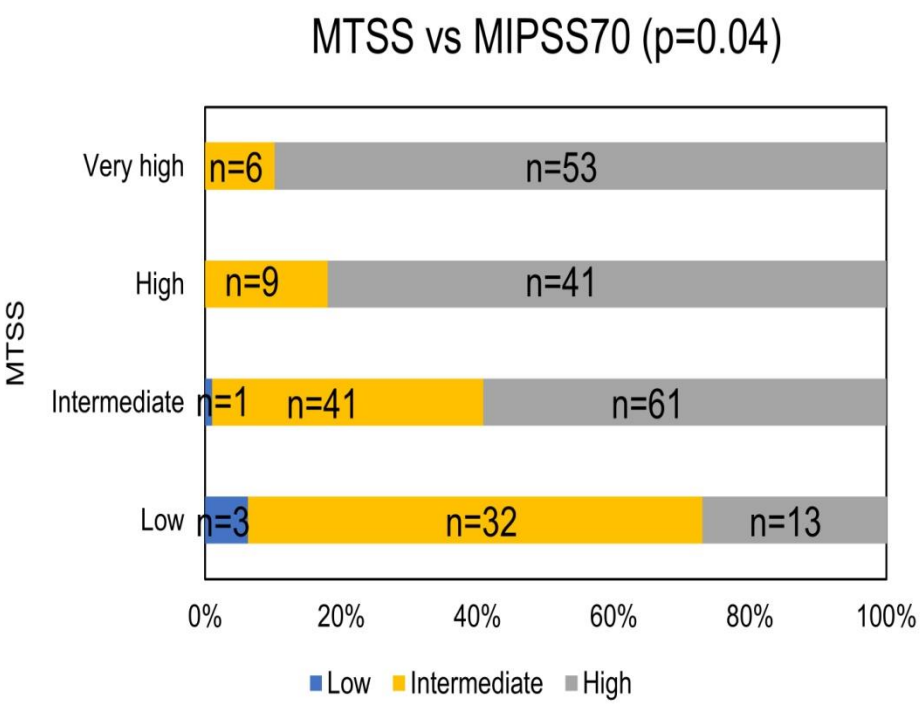


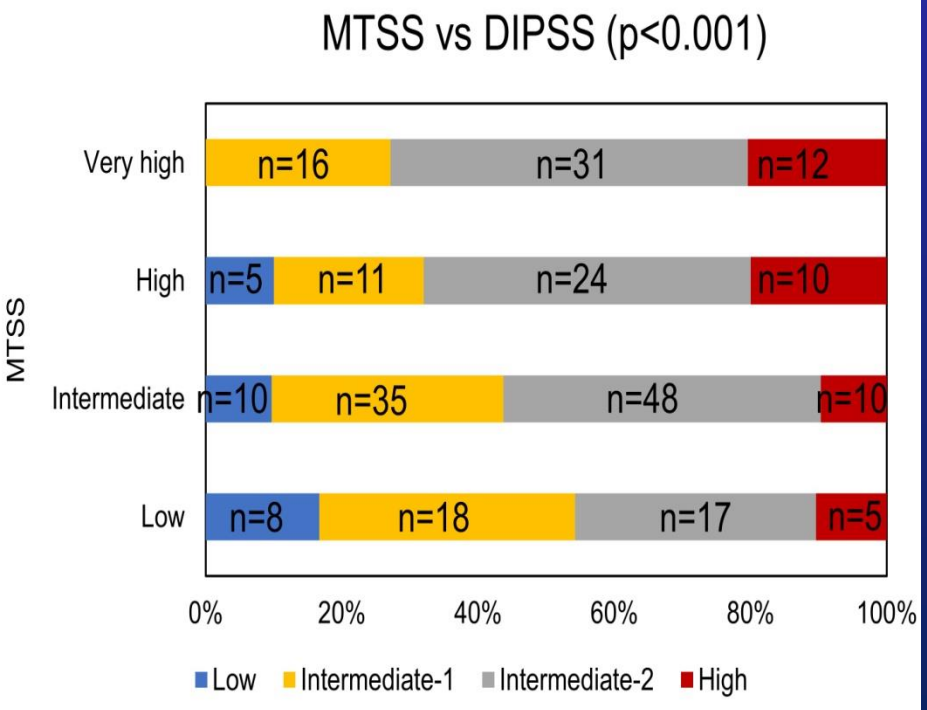
Gagelmann et al., Blood 2019

Comparison of the existing prognostic systems for 5-year survival after allogeneic SCT

System	Components	No.	C-index (95% CI)	Bootstrap C-index (95% CI)
DIPSS	hemoglobin < 10 g/dL, age > 65 years, constitutional symptoms, leukocytes > 25 x 10^9/L, circulating blasts ≥ 1%	260	0.573 (0.664 to 0.582)	0.566 (0.557 to 0.575)
DIPSS-plus	DIPSS, transfusion-dependence, unfavorable karyotype, platelets < 100 x 10^9/L	149	0.557 (0.546 to 0.568)	0.442 (0.531 to 0.553)
MIPSS70	hemoglobin < 10 g/dL, leukocytes > 25 x 10^9/L, platelets < 100 x 10^9/L, circulating blasts ≥ 2%, fibrosis grade ≥ 2, constitutional symptoms, absence of CALR type 1–like mutation, HMR category, ≥ 2 HMR mutations.	260	0.587 (0.578 to 0.596)	0.581 (0.572 to 0.590)
MIPSS70-plus	hemoglobin < 10 g/dL, circulating blasts ≥ 2%, constitutional symptoms, absence of CALR type 1–like mutation, HMR category,[7] ≥ 2 HMR mutations, unfavorable karyotype	149	0.547 (0.536 to 0.558)	0.540 (0.530 to 0.550)
MYSEC-PM	CALR-unmutated genotype, hemoglobin < 11 g/dL, platelets < 150 x 10^9/L, circulating blasts ≥ 3%, age, constitutional symptoms	101	0.605 (0.593 to 0.617)	0.594 (0.582 to 0.606)
MTSS	platelets < 150 x 10^9/L, leukocytes > 25 x 10^9/L, KPS < 90%, HLA-mismatched unrelated donor, ASXL1 mutation, CALR-/MPL-unmutated genotype, age < 57 years	260	0.718 (0.710 to 0.726)	0.710 (0.701 to 0.719)
		101	0.701 (0.690 to 0.711)	0.690 (0.679 to 0.701)

Transplant Riskscore (MTSS vs MIPSS 70 and DIPSS) after allogeneic stem cell transplantation





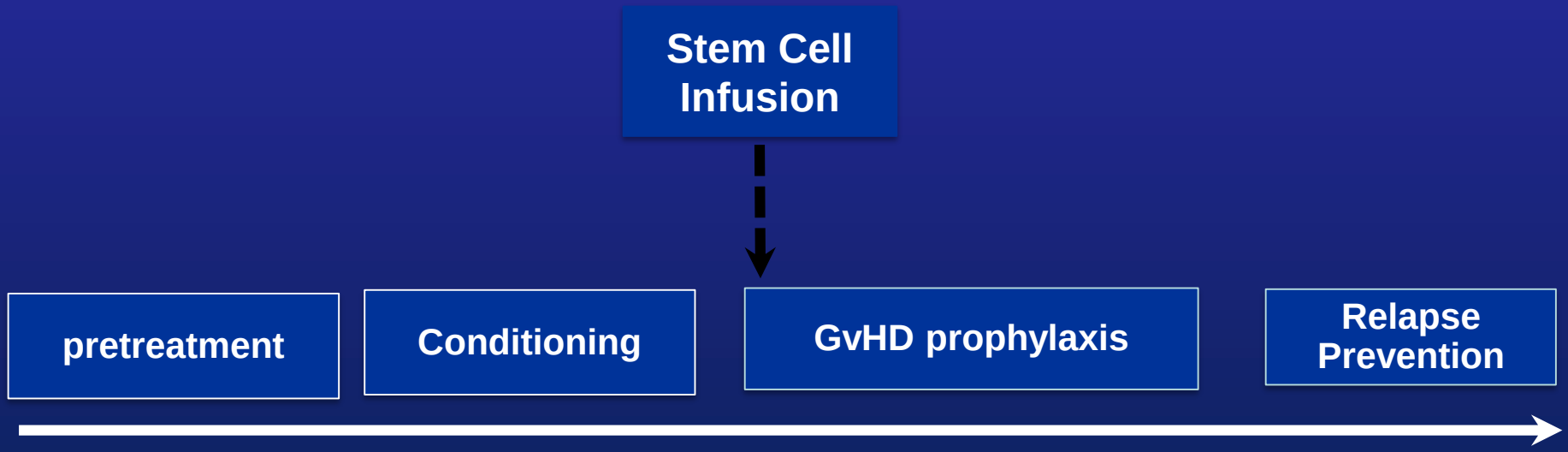
Summary (1)

1. **Allogeneic stem cell transplantation is currently the only curative treatment approach for PMF or post ET/PV MF**
2. **Pts with transformed PV/ET or MF are candidates for allogeneic SCT**
3. **According guidelines pts with PMF and DIPSS intermediate II and high risk are candidates for allogeneic SCT**
4. **To balance the risk of therapy-related complication and potential cure a careful selection of patients with Disease specific and Transplant specific risk scores is needed**

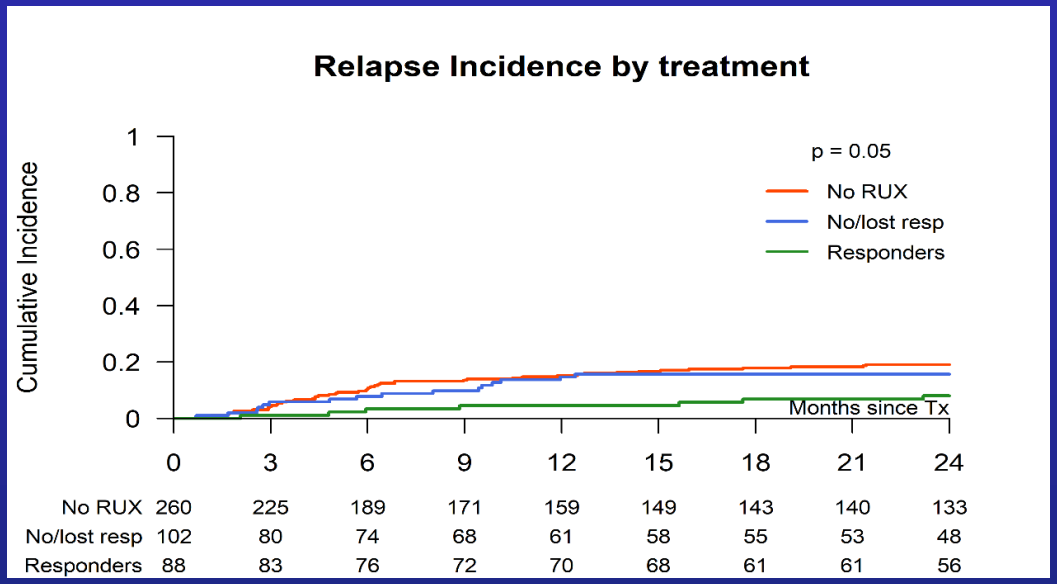
Allogeneic stem cell transplantation for Myelofibrosis

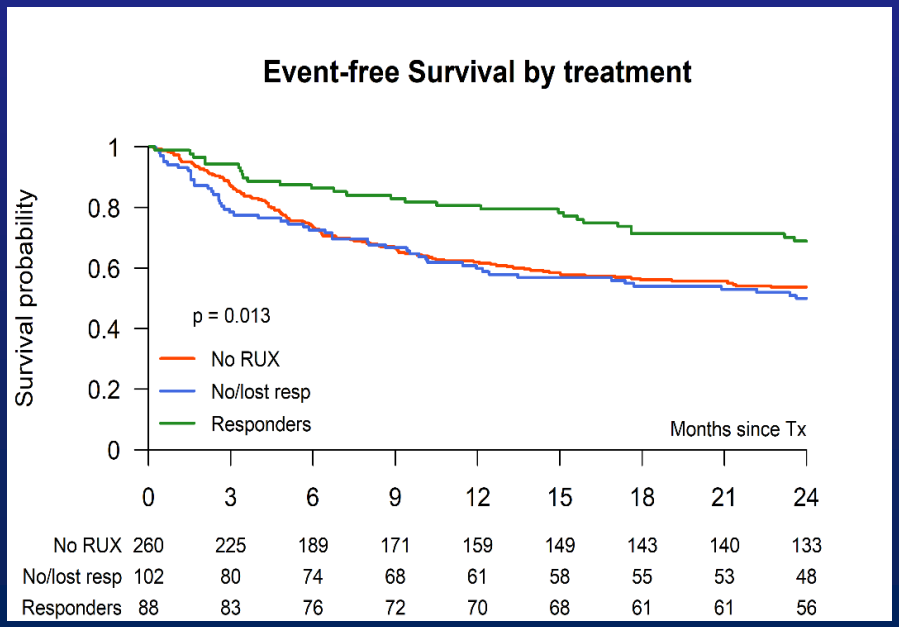
How?

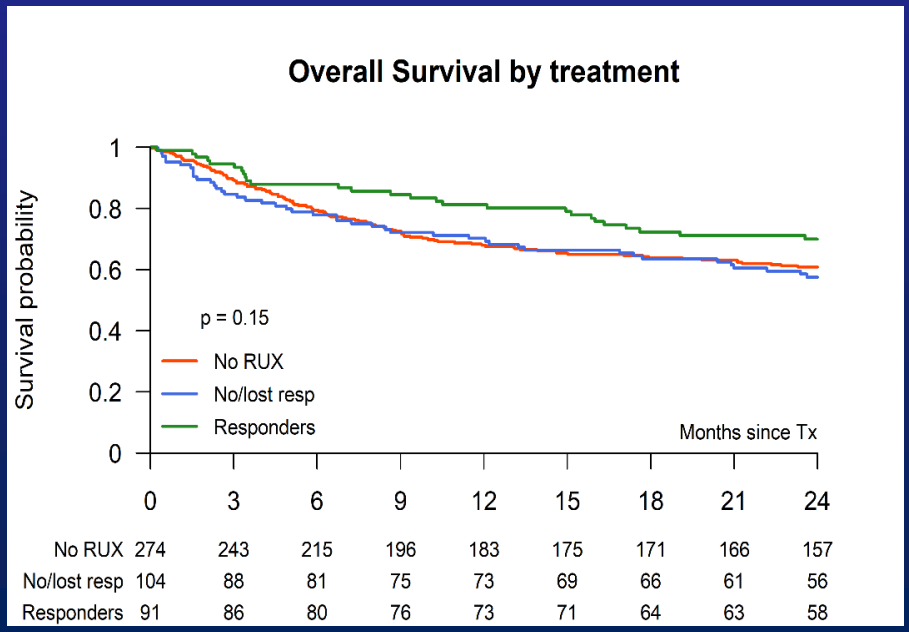
Optimizing stem cell transplantation in myelofibrosis



Ruxolitinib (n=277) vs no Ruxo (n=274)prior to allogeneic SCT (EBMT study)







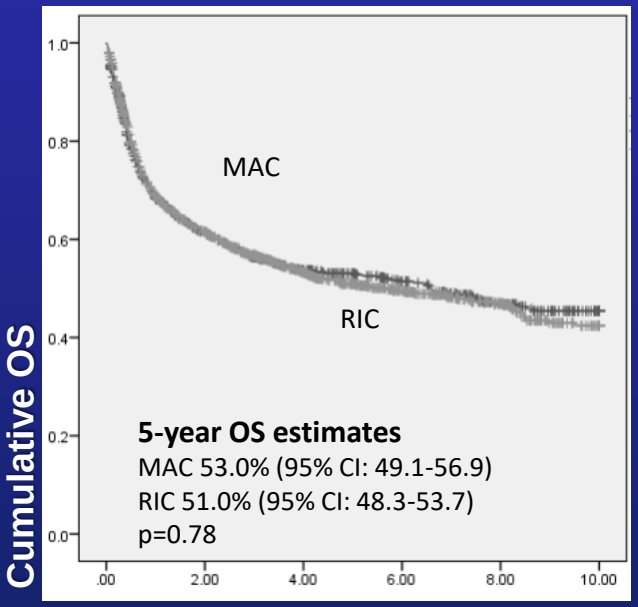
Leukemia 2020

Optimizing stem cell transplantation in myelofibrosis

1. Pretreatment
2. Conditioning regimen

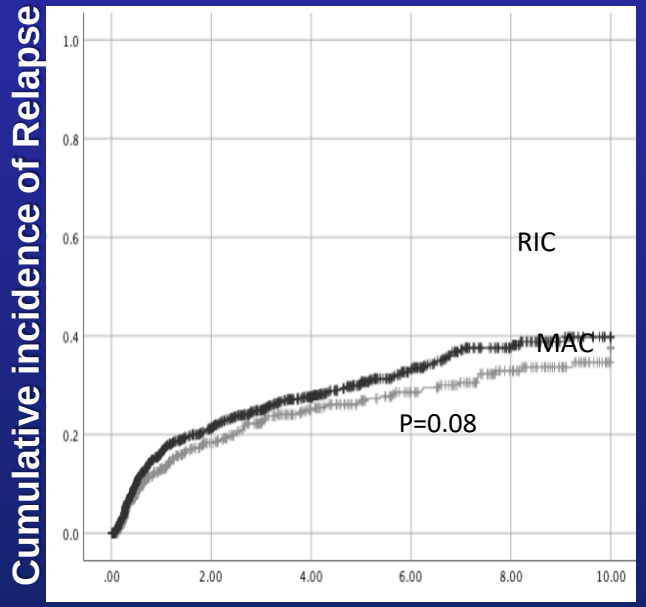
Reduced Intensity vs Myeloablative Conditionig in Myelofibrosis: EBMT data

(a)



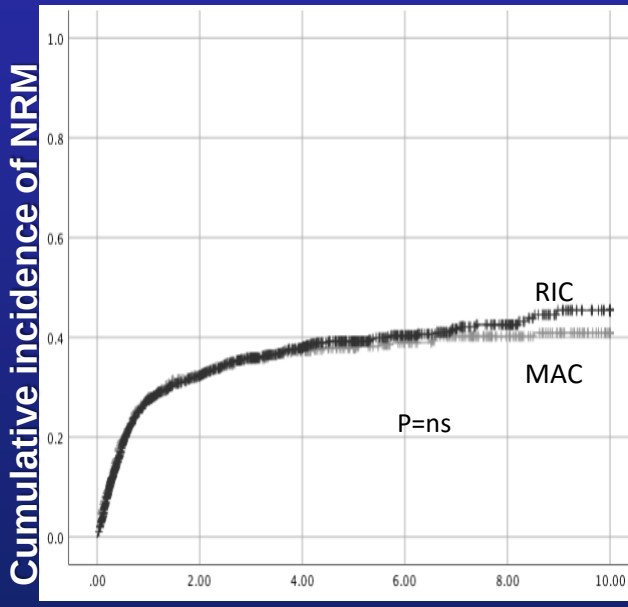
Years post allo-SCT

(b)



Years post allo-SCT

(c)



Years post allo-SCT

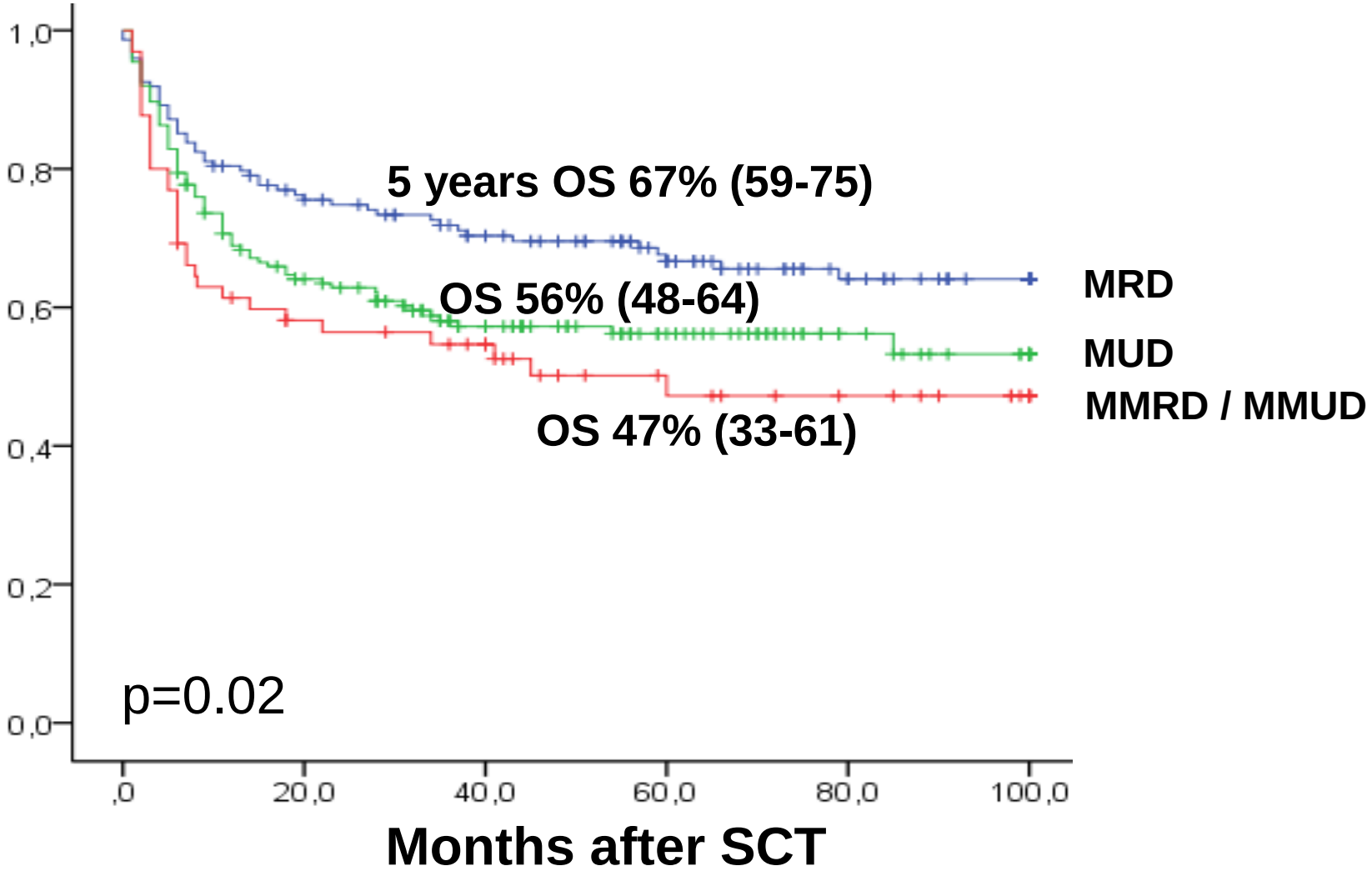
McLonal et al., BBMT 2019

Optimizing stem cell transplantation in myelofibrosis

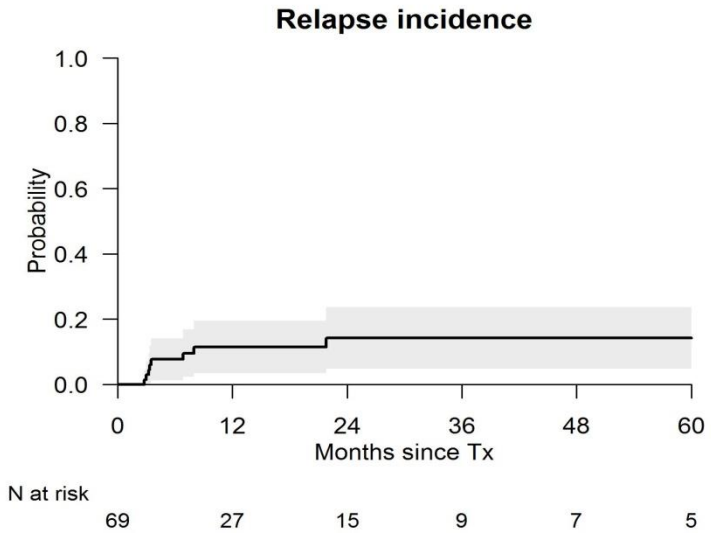
1. Pretreatment
2. Conditioning regimen
3. Donor source

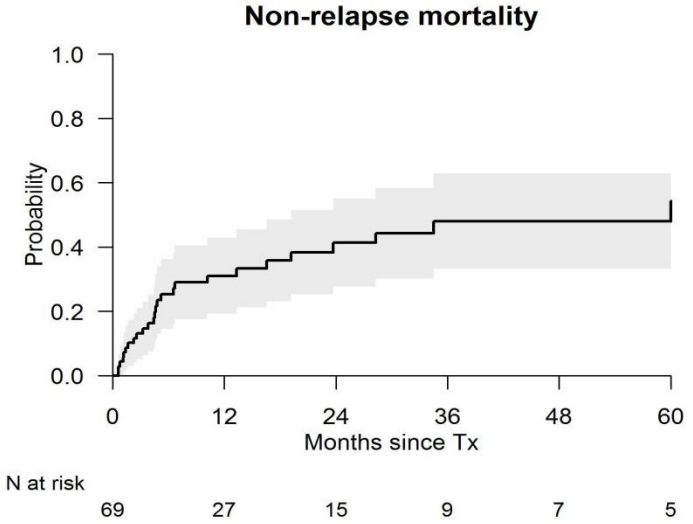
MRD vs MUD vs MMUD/MRD (n=388)

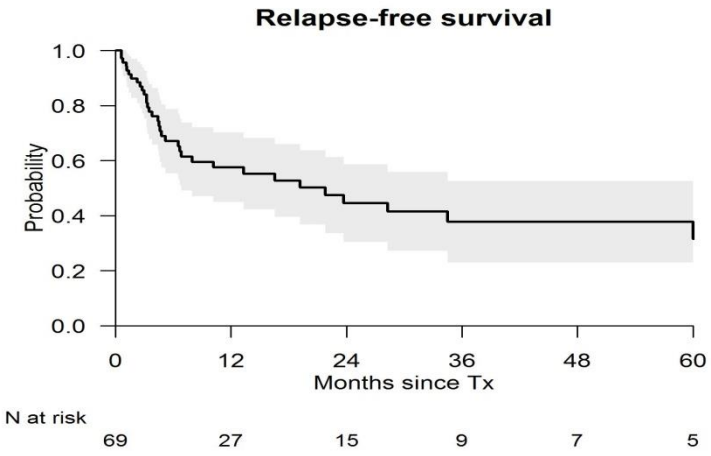
Probability of overall survival

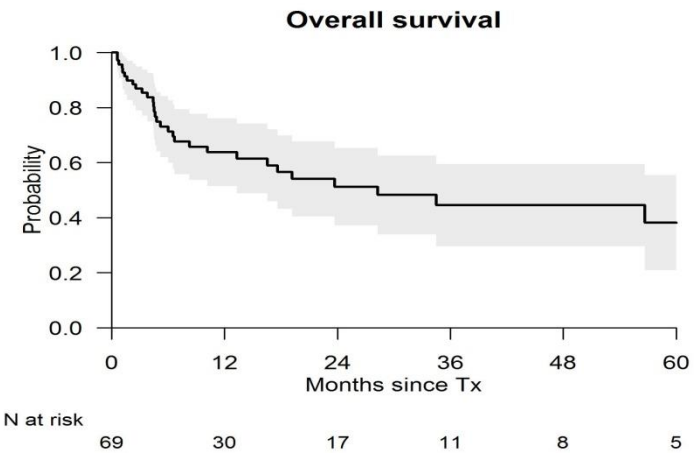


Outcome of haploidentical SCT for Myelofibrosis within EBMT (n=69)







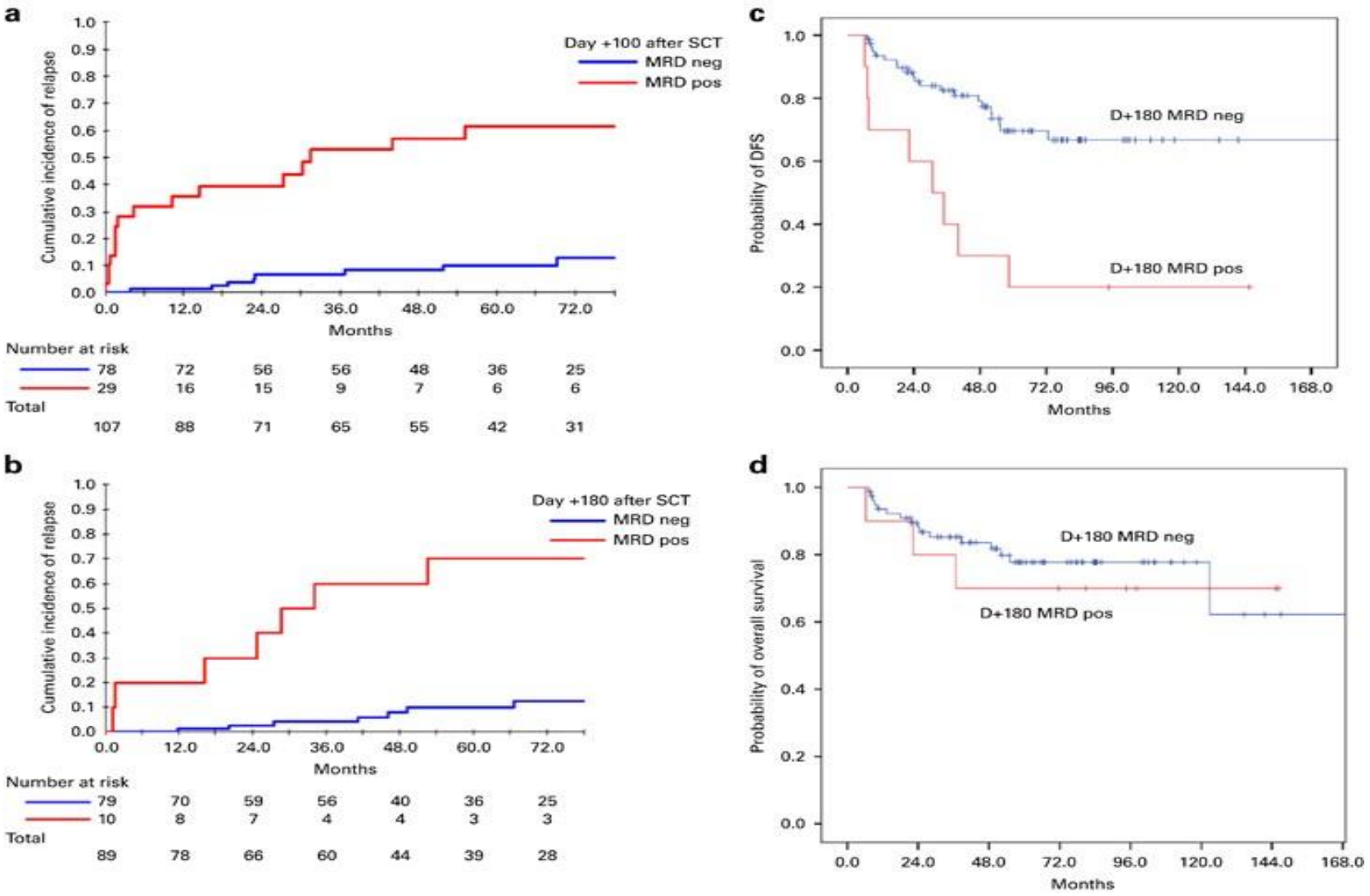


Raj et al BMT 2019

Optimizing stem cell transplantation in myelofibrosis

1. Pretreatment
2. Conditioning regimen
3. Donor source
4. Relapse prevention

Detection of JAK2/CALR or MPL post transplant (day 180)



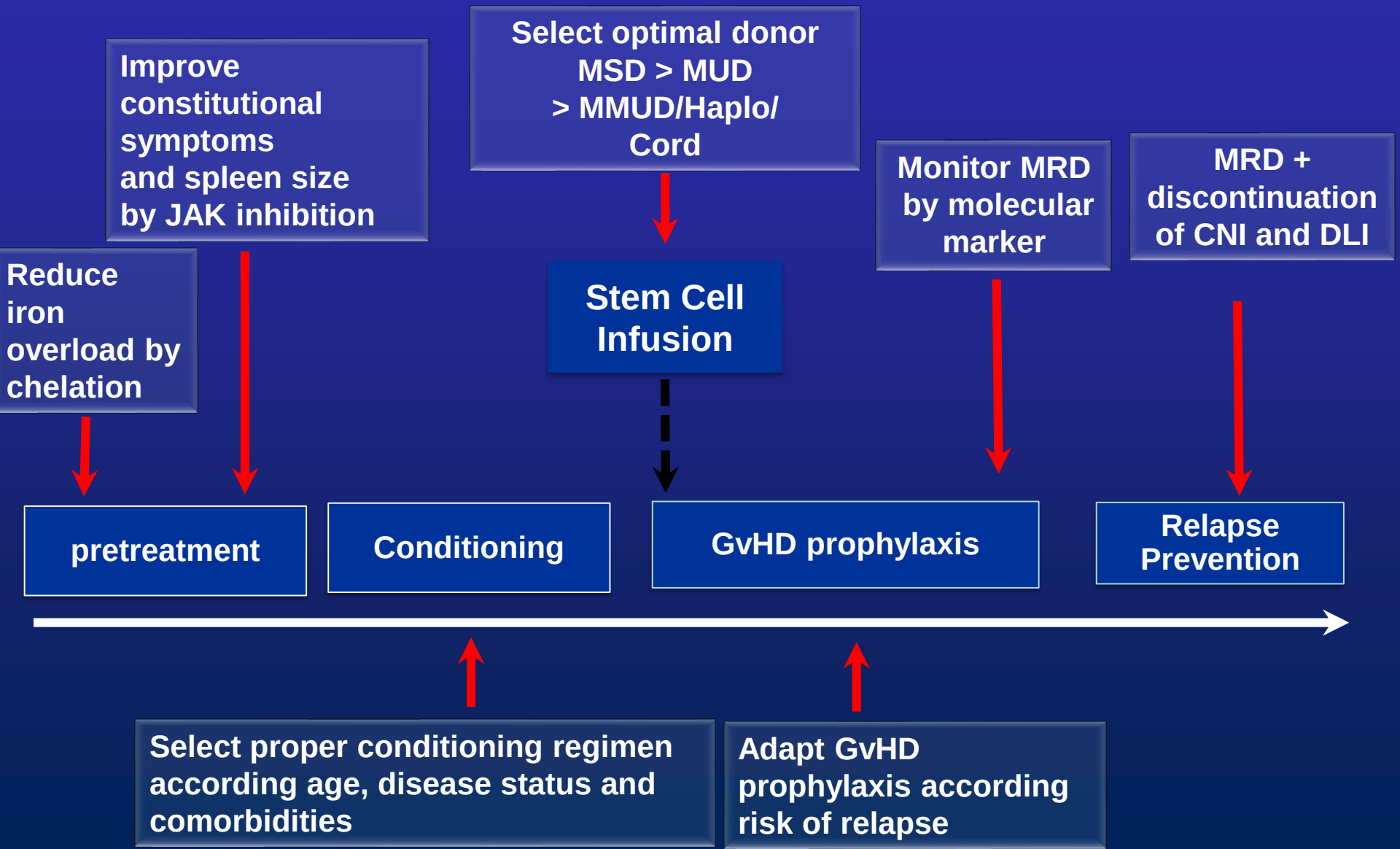
Wolschke et al BMT 2017

JAK2 monitoring after DLI for MRD or relapse after allo SCT for Myelofibrosis

	Molecular response	*Acute GvHD II/IV*	*Median number of DLIs to achieve CR*
Salvage DLI (n = 9)	**44 % CR**	**22 %**	**2**
Pre-emptive DLI (n = 7)	**100 % CR**	**0 %**	**1**

Kröger et al., Blood. 2009 Feb 19;113(8):1866-8

Summary :Optimizing stem cell transplantation in myelofibrosis



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