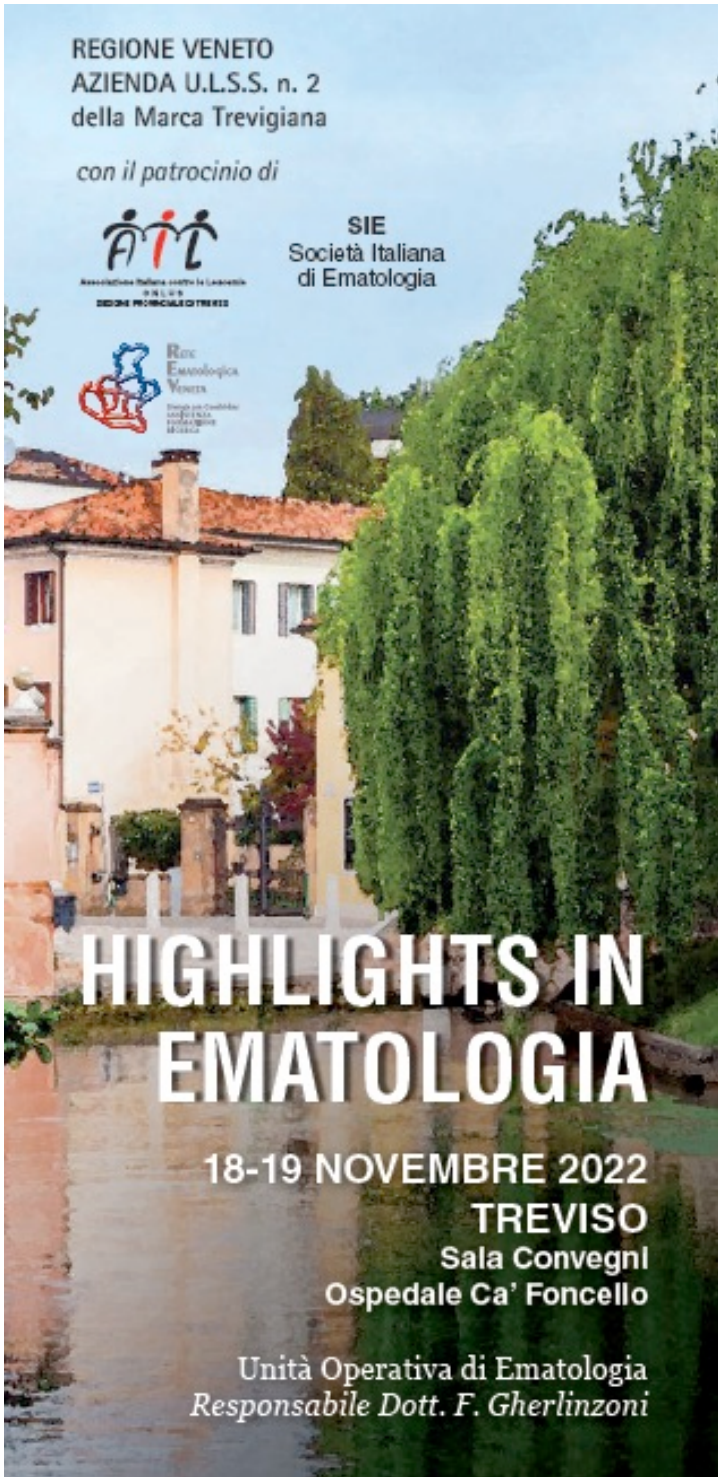


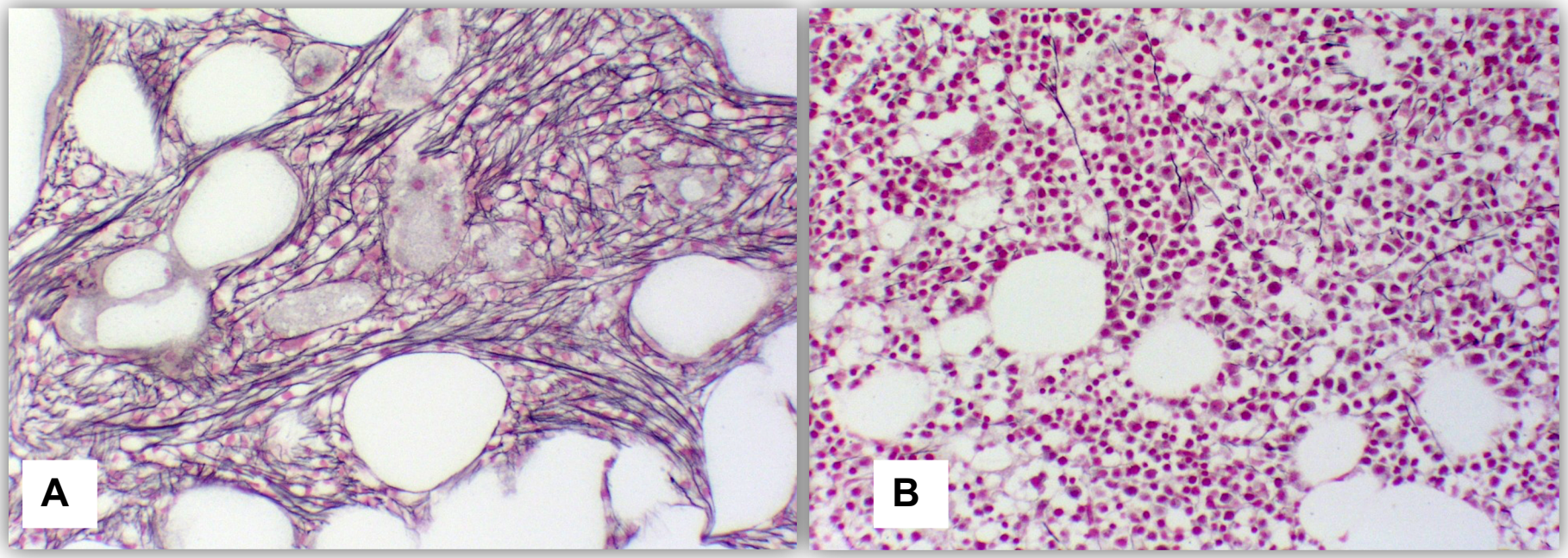
La mielofibrosi vista dal trapiantologo

Damiano Rondelli, MD
Michael Reese Professor of Hematology
Chief, Division of Hematology/Oncology
Director, BMT&CT Program
UI Health / University of Illinois at Chicago
Chicago, IL
USA

THE UNIVERSITY OF ILLINOIS AT CHICAGO
UIC

no conflict of interest to disclose

At present, allogeneic **hematopoietic stem cell transplantation (HSCT)** is the only treatment modality that has the potential to cure myelofibrosis



Reticulin fibrosis in an IM patient before and after allogeneic stem cell transplant. (A) represents bone marrow before transplant; (B) represents bone marrow 12 months post transplant.

Volume Density of Reticulin Fibers (%)

	Pre-transplant	***Post-transplant***			
		1 mo.	*3 mo.*	*6 mo.*	*12 mo.*
N=4	51.3 ± 19.8	31.2 ± 26	11.5 ± 6	8 ± 5.4	6 ± 1.4

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Hongyu Ni, Barosi G, Rondelli D, Hoffman R. Am J Clin Pathol 2005

Questions on HSCT in MF

1. What risk factors identify a **candidate for HSCT**?
2. Is an unrelated or haploidentical **donor** a valid option?
3. RIC or MAC **regimen**?
4. Splenomegaly vs **splenectomy**?
5. Role of **Jak-inhibitors** prior to tx?
6. What are the **prognostic factors** for BMT in MF?

International Prognostic Score System (IPSS) in MF

Cervantes, F. et al. Blood 2009;113:2895-2901

Table 2. Risk factors at presentation of primary myelofibrosis selected at the stepwise Cox regression model for significant association with shorter survival*

Risk factor	Frequency in the series, %	Hazard ratio (95% CI)	z test	*P*
Age > 65 y	44.6	1.95 (1.61-2.36)	6.84	< .001
Constitutional symptoms	26.4	1.97 (1.62-2.40)	6.77	< .001
Hb < 10 g/dL	35.2	2.89 (2.46-3.61)	11.24	< .001
WBC count > 25 x 10^9/L	9.6	2.40 (1.83-3.14)	6.37	< .001
Blood blasts > 1%	36.2	1.80 (1.50-2.17)	6.29	< .001

* In 1001 patients with the 5 variables available.

Dynamic IPSS/Plus

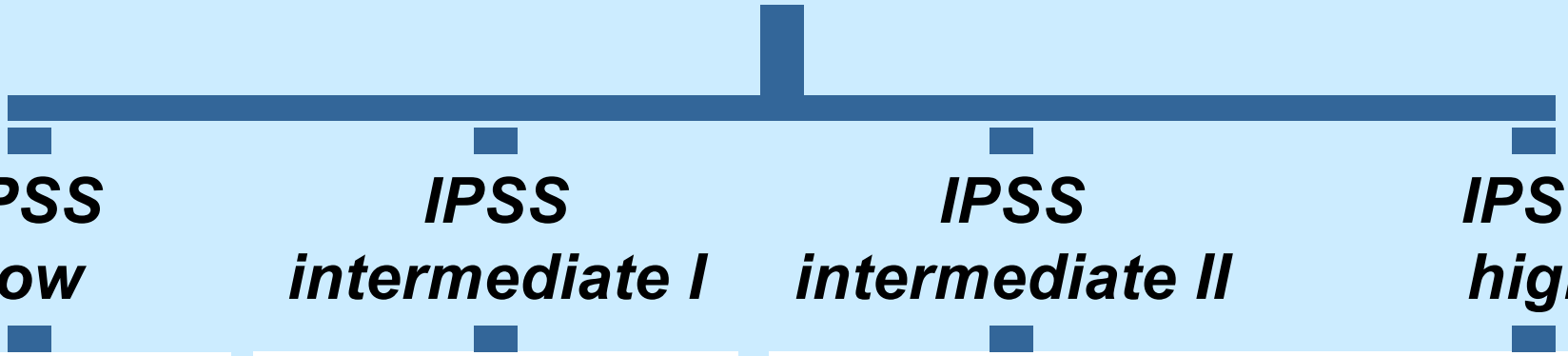
Risk Model	Risk Factors	Risk Stratisfaction		Median Survival (months)
Dynamic IPSS[1]	•Age > 65 years •Hgb < 10g/dL (2 pts) •WBC > $25x10^9$/L •Circulating blasts ≥1% •Constitutional symptoms	•Low: •Intermed-1: **•Intermed-2:** **•High:**	0 1-2 **3-4** **5-6**	•Not Reached •118 **•58** **•27**
DIPSS-Plus[2]	DIPSS Risk + •Platelet < $100x10^9$/L •Unfavorable cytogenetics* •Transfusion requirement	•Low: •Intermed-1: **•Intermed-2:** **•High:**	0 1 **2-3** **4-6**	•180 •80 **•35** **•16**

*Unfavorable cytogenetics included complex karyotype, +8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), 11q23 rearrangement

1. Passamonti et al. Blood 2010
2. Gangat et al. JCO 2011

Indications to allogeneic BMT in MF

Consensus EBMT/ELN WG (Kröger N et al Leukemia 2015)

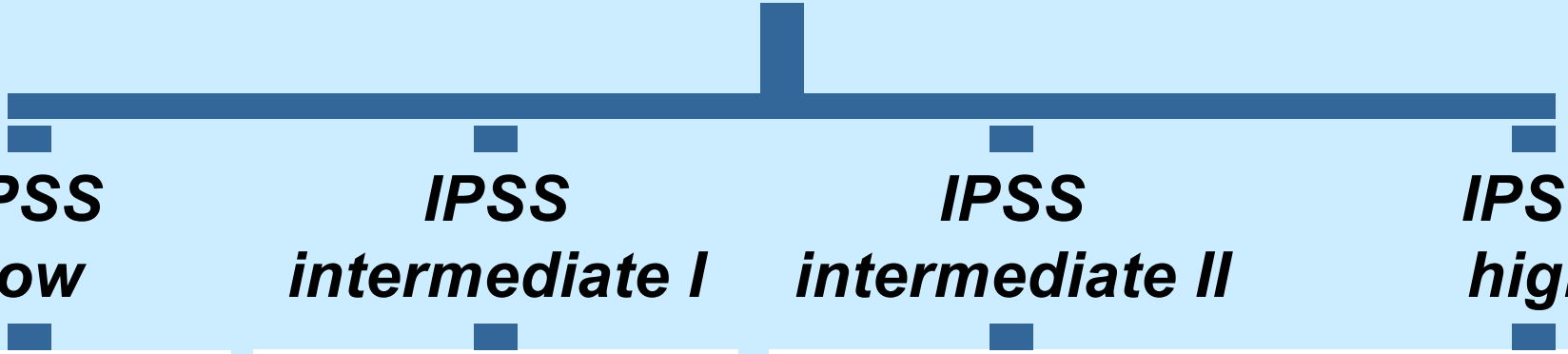


no transplant
no JAK inhibitors

Consider BMT if signs of progression

Indications to allogeneic BMT in MF

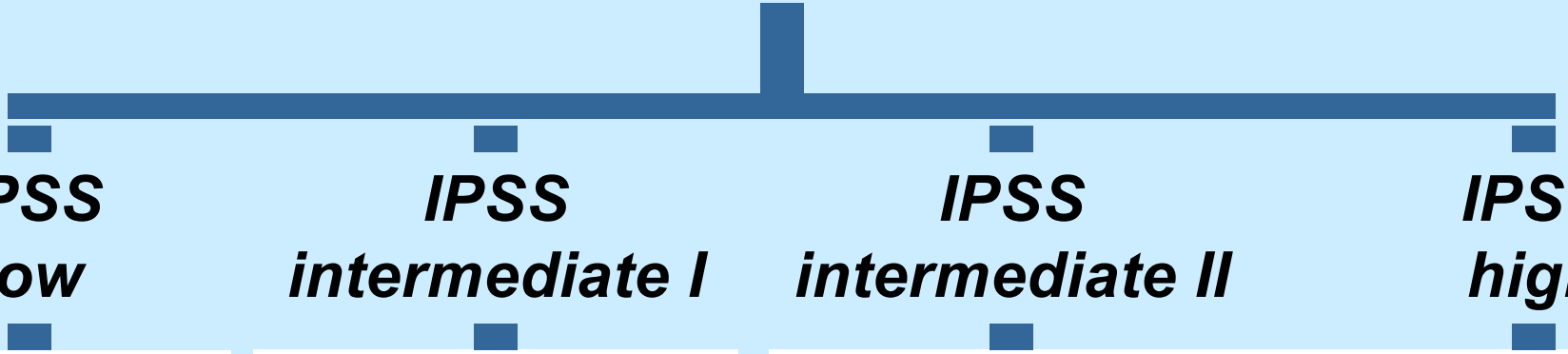
Consensus EBMT/ELN WG (Kröger et al Leukemia 2015)



IPSS low	***IPSS intermediate I***	***IPSS intermediate II***	***IPSS high***
no transplant **no JAK inhibitors** **Consider BMT if signs of progression**	**general: no transplant unless <65yo with:** **refractory transf-dep. anemia** **or** **->2% PB blasts** **or** **- Adv. cytogenetics** **no JAK inhibitors (except: constitutional symptoms or/and splenomegaly)**		

Indications to allogeneic BMT in MF

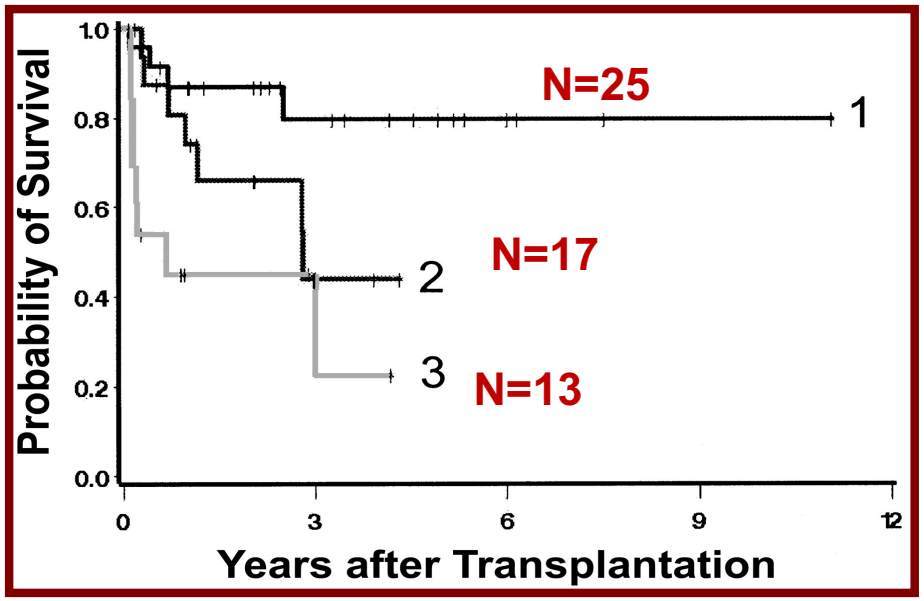
Consensus EBMT/ELN WG (Kröger et al Leukemia 2015)



IPSS low	*IPSS intermediate I*	*IPSS intermediate II*	*IPSS high*
no transplant **no JAK inhibitors** **Consider BMT if signs of progression**	**general: no transplant unless <65yo with:** **refractory transf. dep anemia** **or** **->2% PB blasts** **or** **- Adv. cytogenetics** **no JAK inhibitors (except: constitutional symptoms or/and splenomegaly)**	**consider transplant (≤ 70 yrs)** **if splenomegaly or/and constitutional sympt: JAK2 inhibitor prior transplant** **If no transplant eligible:** **- JAK inhibitors (only if splenomegaly or/and constitutional sympt.)** **- Clinical trials**	

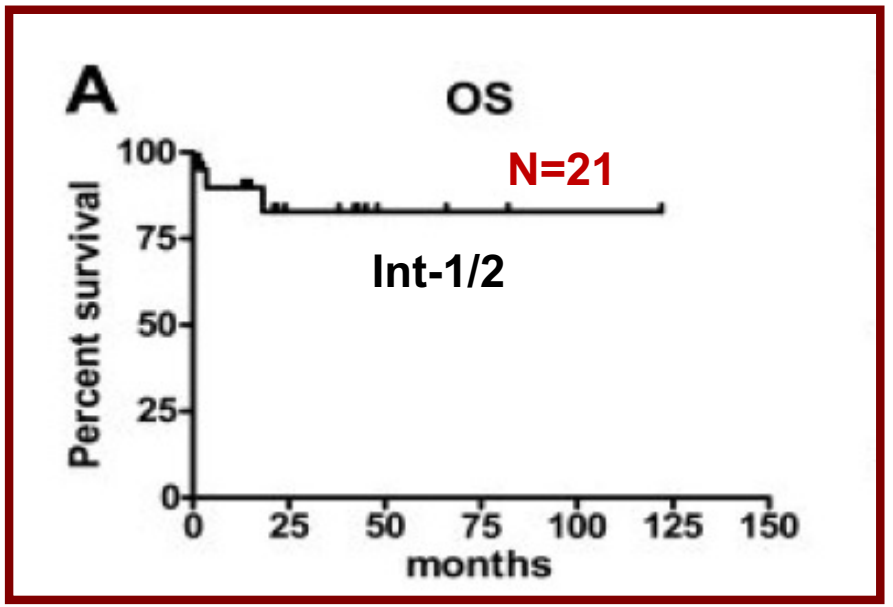
Conditioning regimens in myelofibrosis

Myeloablative (median age:43)



Deeg JH et al. Blood 2003; 12:3912

Reduced Intensity (median age:54)



Rondelli D et al. Blood 2005; 105:4115

First prospective study of allo-SCT (RIC) in MF

(n=105 pts)

blood

JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

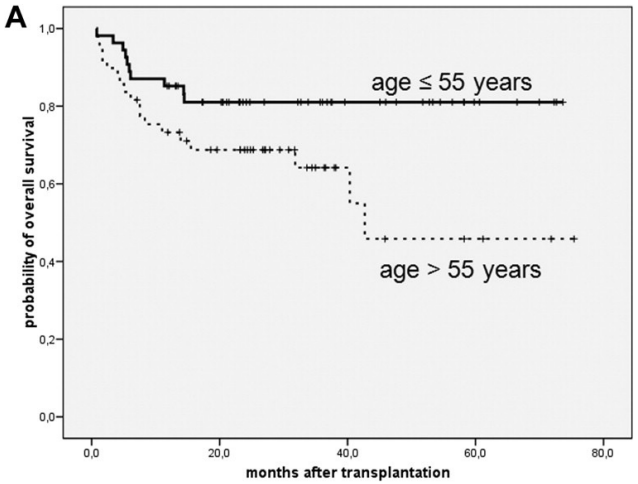
Low dose busulfan

10 mg/kg orally or 8mg/kg i.v),

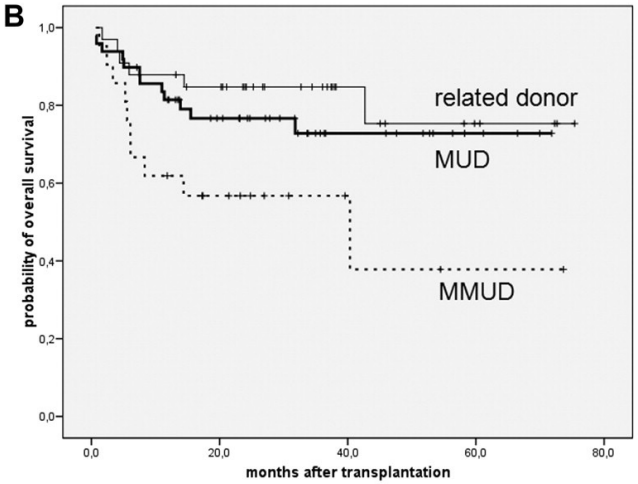
fludarabine

(180 mg/m2)

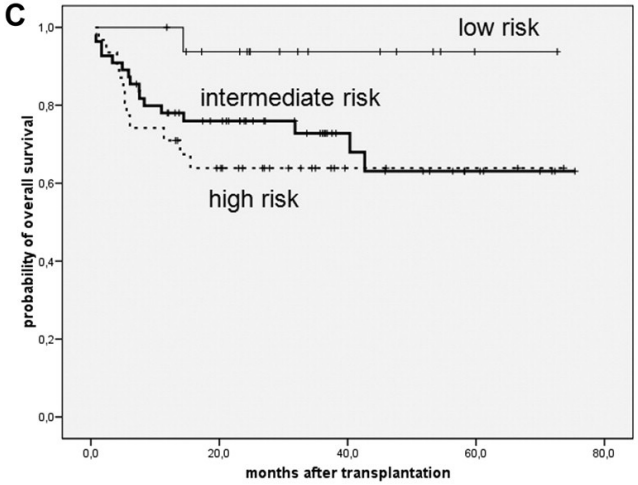
anti-thymocyte globulin



Age



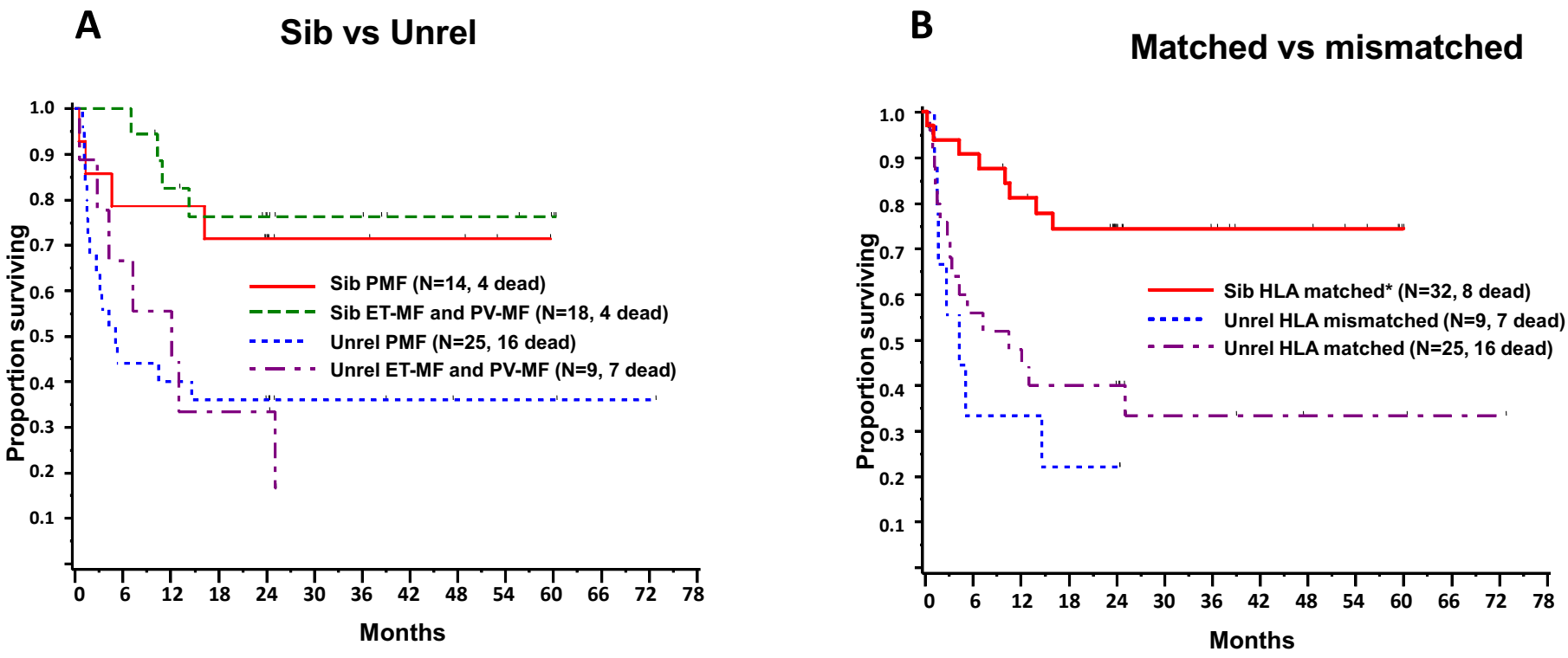
HLA



Lille score

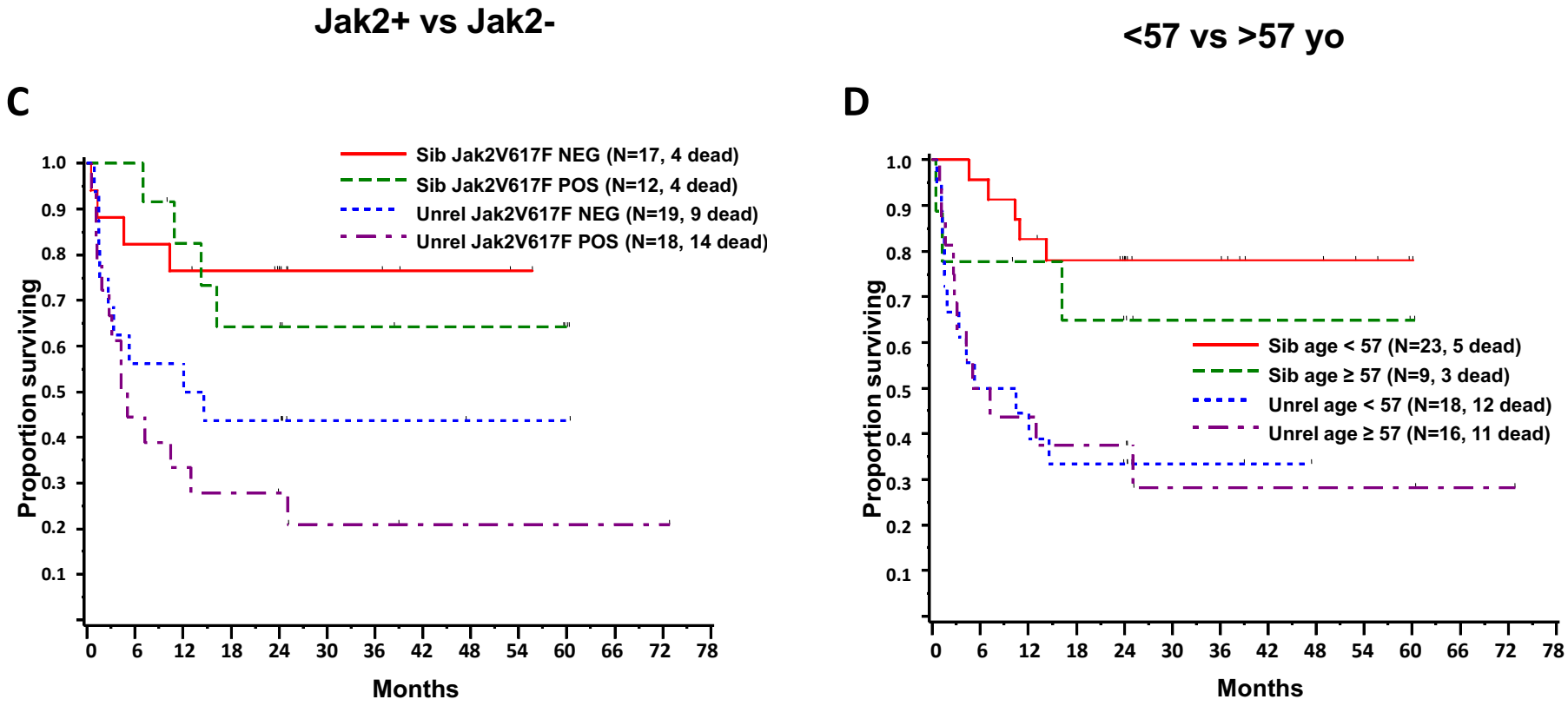
Kroger, N. et al. Blood 2009;114:5264

MPD-RC 101:Prospective study of RIC BMT in myelofibrosis FLU/MEL ± ATG



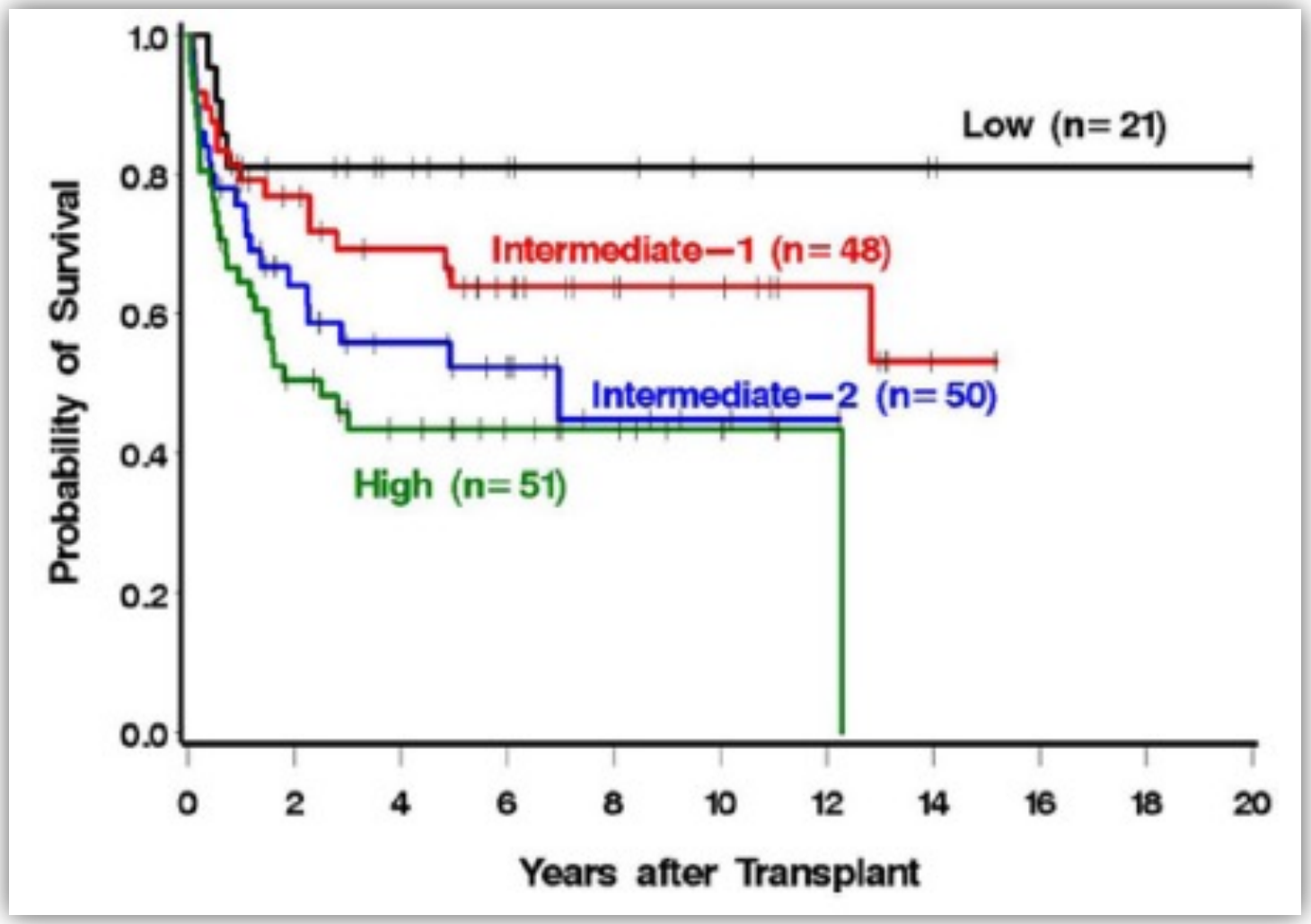
Rondelli D et al. Blood. 2014;124:1183-91

no prognostic effect of Jak2 status



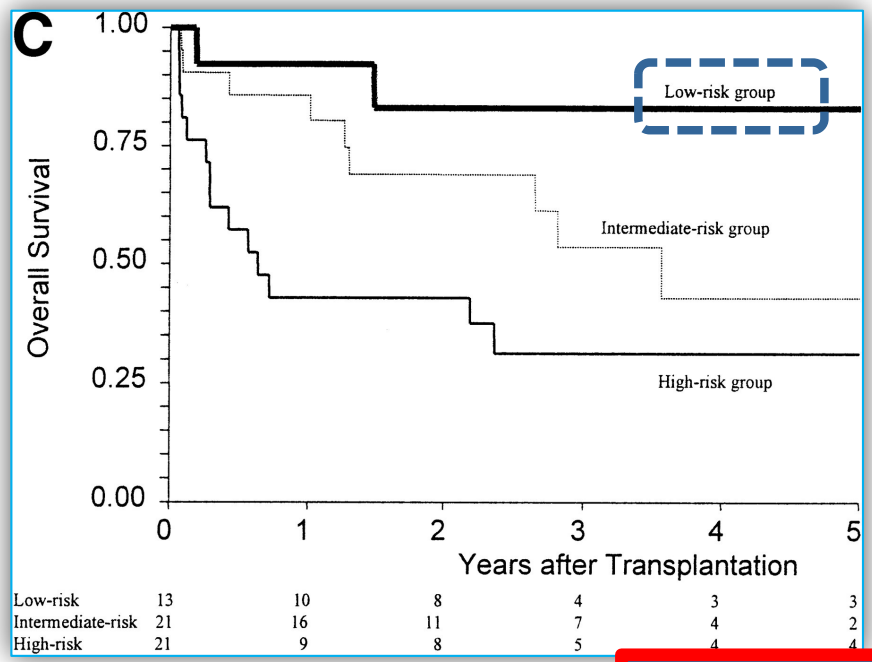
Rondelli D et al. Blood. 2014;124:1183-91

First results by IPSS score analysis

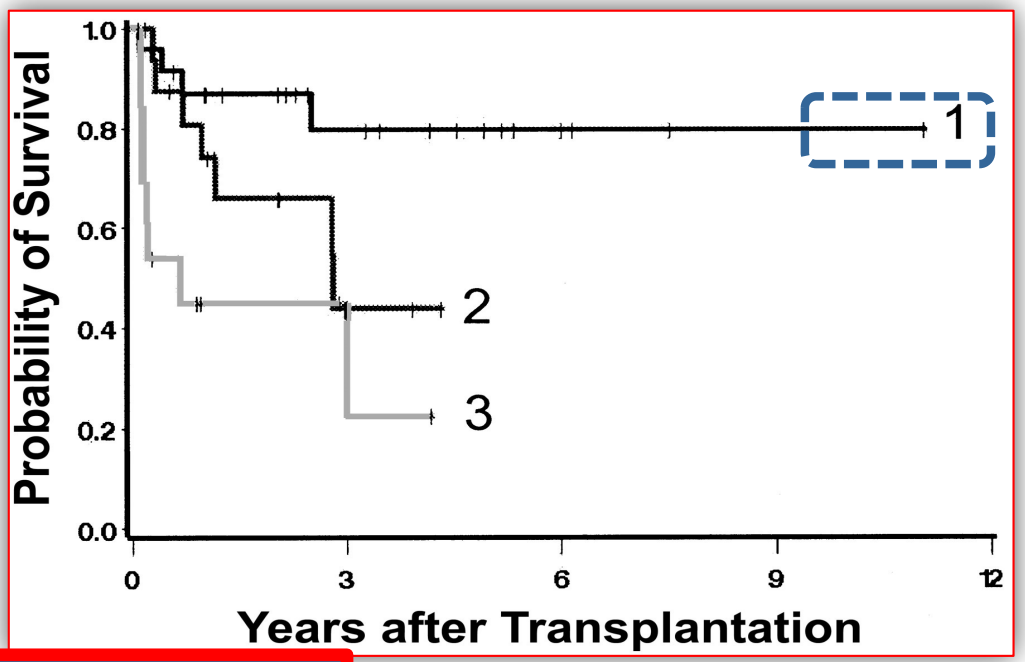


Scott B et al. Blood 2012; 119:2657-2664

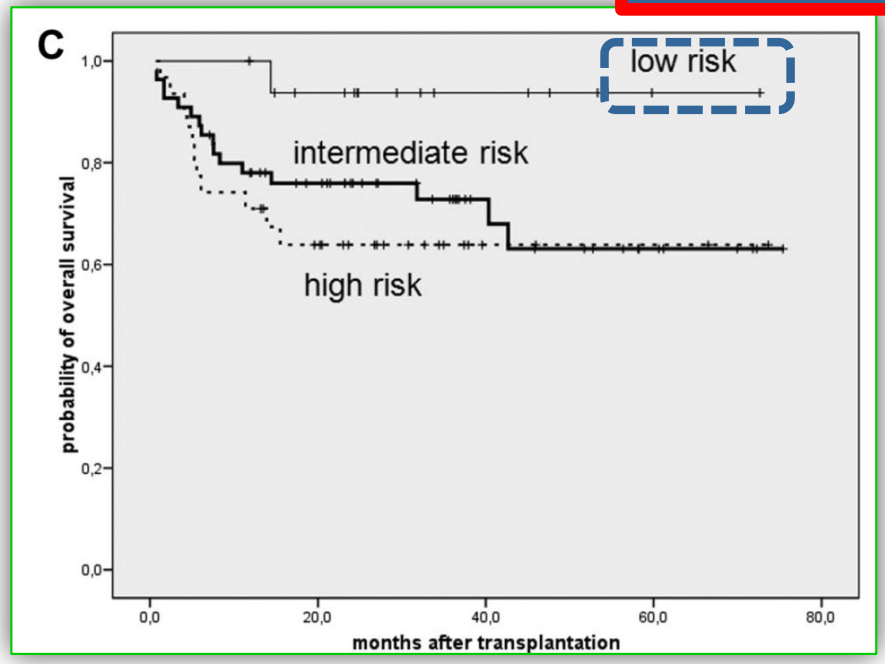
BMT in low/Int-1 risk



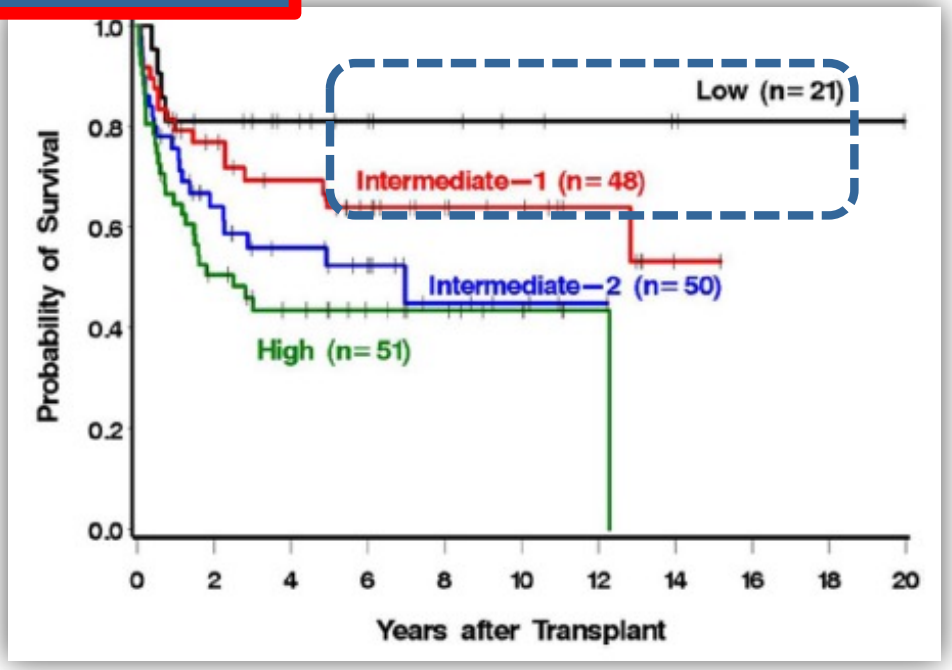
Guardiola P et al. Blood, 1999; 93:2831



Deeg JH et al. Blood 2003;12:3912



Kröger, N. et al. Blood 2009;114:5264



Scott B et al. Blood 2012; 119:2657-2664

HSCT in myelofibrosis: retrospective studies

Table 2 Allogeneic transplantation in myelofibrosis: main results after myeloablative conditioning regimens

Reference	No. of pts	Median age (years)	Intermediate/high risk (%)	TRM at 1 year (%)	Overall survival at 1 year (%)
Guardiola [10]	55	42	76	27	14 (>45 years) 62 (<45 years)
Przepiorka [56]	5	43		20	60
Daly [57]	25	48	84	48	41
Deeg [58]	56	43	54	32	58
Mittal [59]	5	54		40	60
Ditschkowski [60]	20	37	65	20	38
Kerbauy [11]	95	51	54	32	61

Table 3 Allogeneic transplantation in myelofibrosis: main results after reduced intensity conditioning regimens

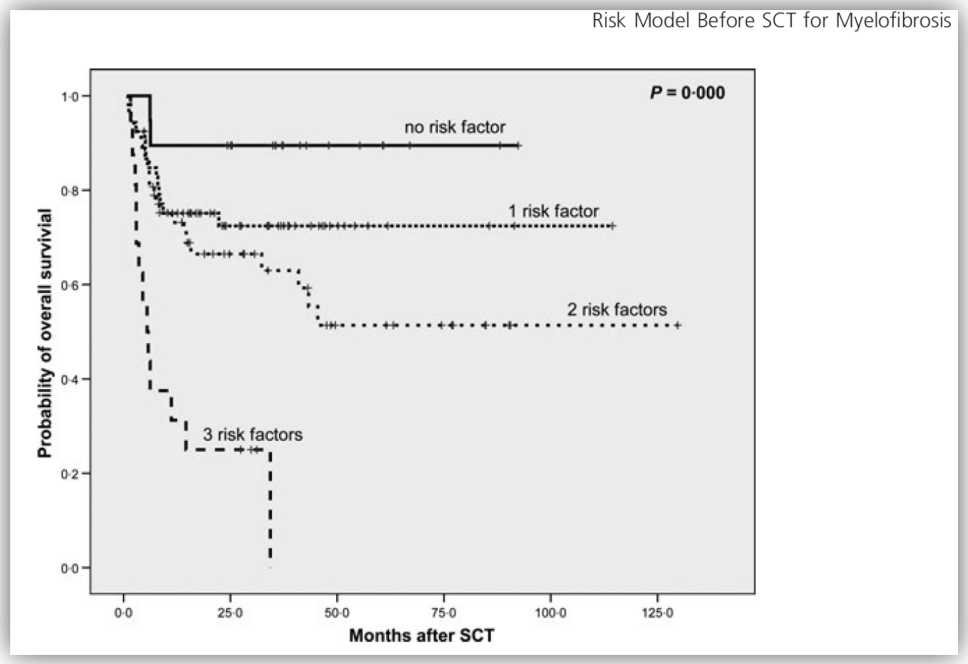
Reference	No. of pts	Median age (years)	Intermediate/high risk (%)	TRM (%)	OS (%)
Devine [13]	4	56	100%	0	100
Rondelli [14]	21	54	100	10	85
Merup [61]	10	58	70	10	90
Snyder [62]	9	54	89	44	55
Patriarca [15]	52	53	89	35	54
Bacigalupo [17]	46	51	91	24	45

Rambaldi A, Int J Hematol 2010; 91:180

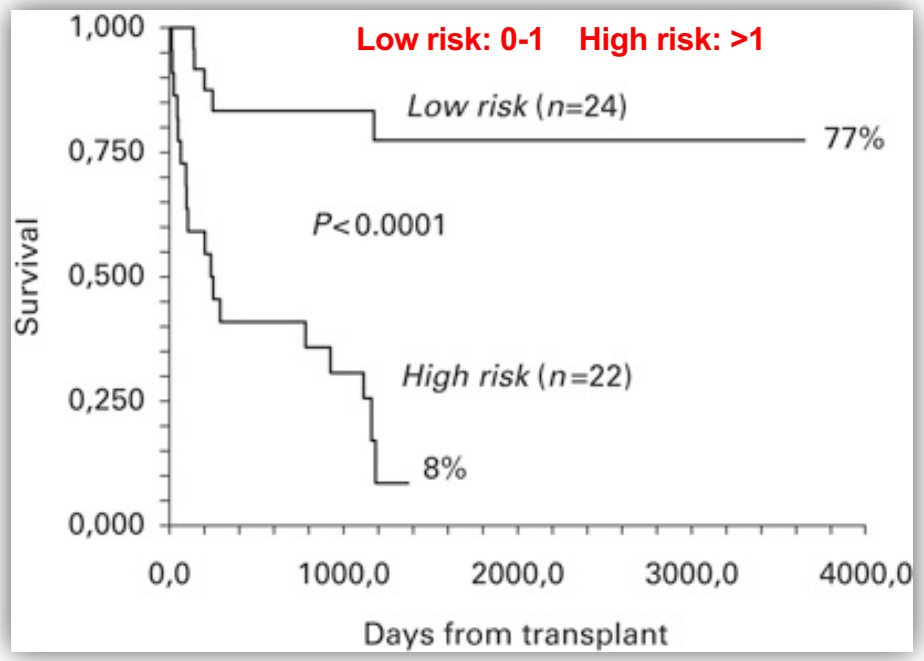
PROGNOSTIC FACTORS IN SCT FOR MYELOFIBROSIS

Prognostic factors in Tx for MF
Jak2 V617F wild type
Age >57
Constitutional symptoms

Prognostic factors in Tx for MF
Spleen >22 cm
RBC transfusions >20
Donor other than matched sibling



Alchalby H et al. Br J Haematol 2012, 157:75-85.



Bacigalupo A et al, BMT 2010;45:458-63

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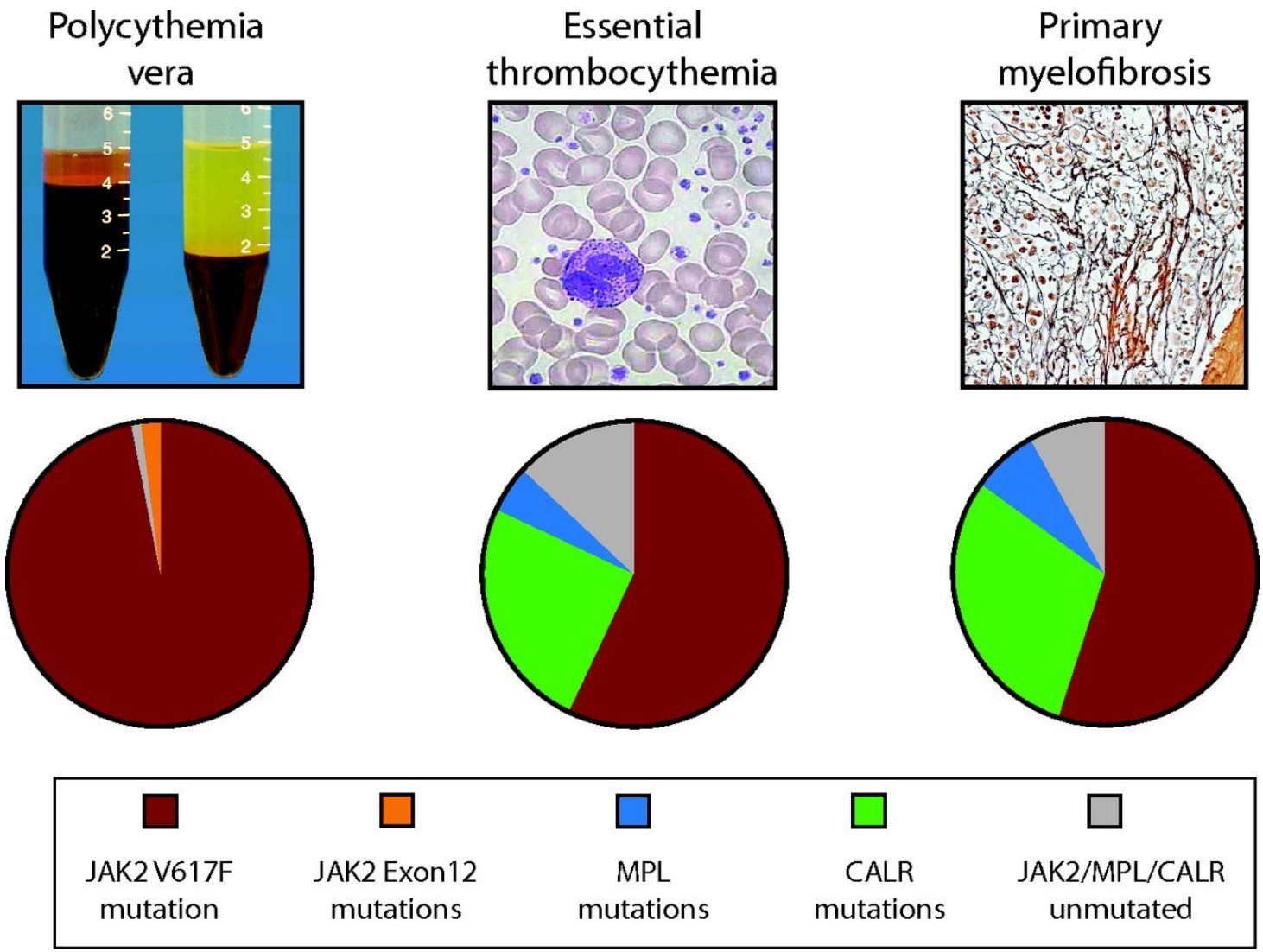
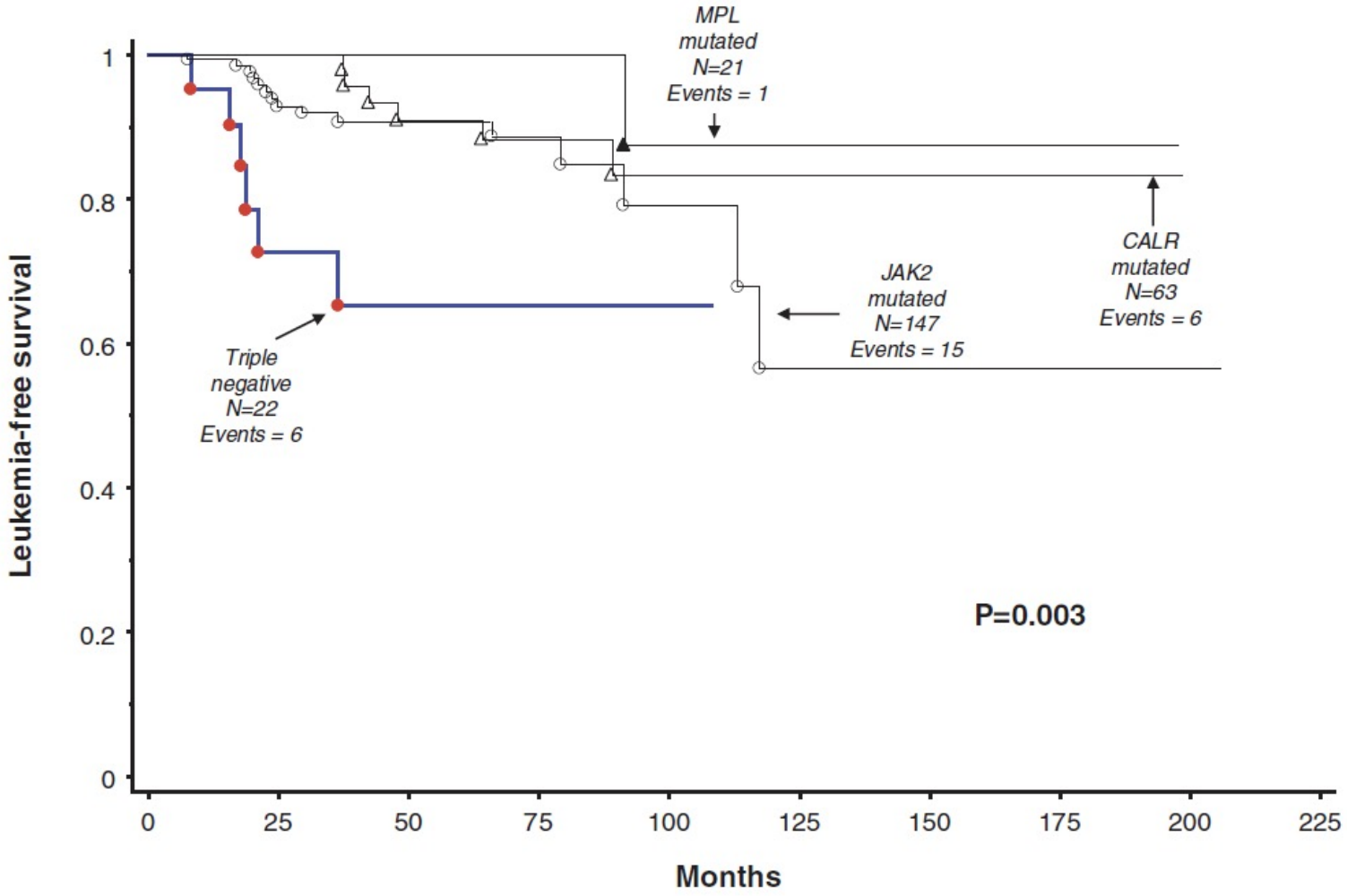
Genomic landscape of MPNs



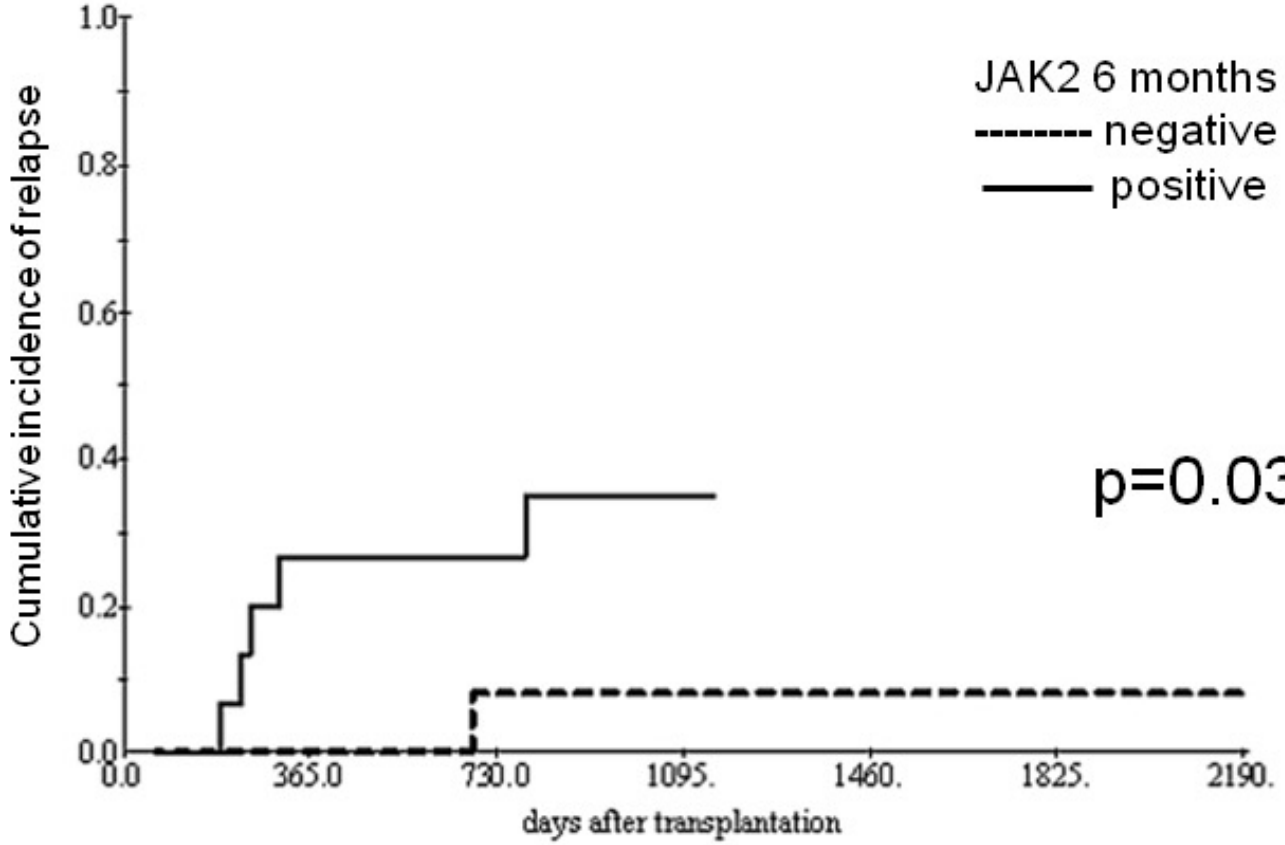
Jyoti Nangalia, and Tony R. Green Hematology 2014;2014:287-296

Poor outcome in Triple negative MF



Tefferi et al. Leukemia 2014; 28:1472-1477

Persistence of JAK2 mutation post- RIC SCT correlates with relapse



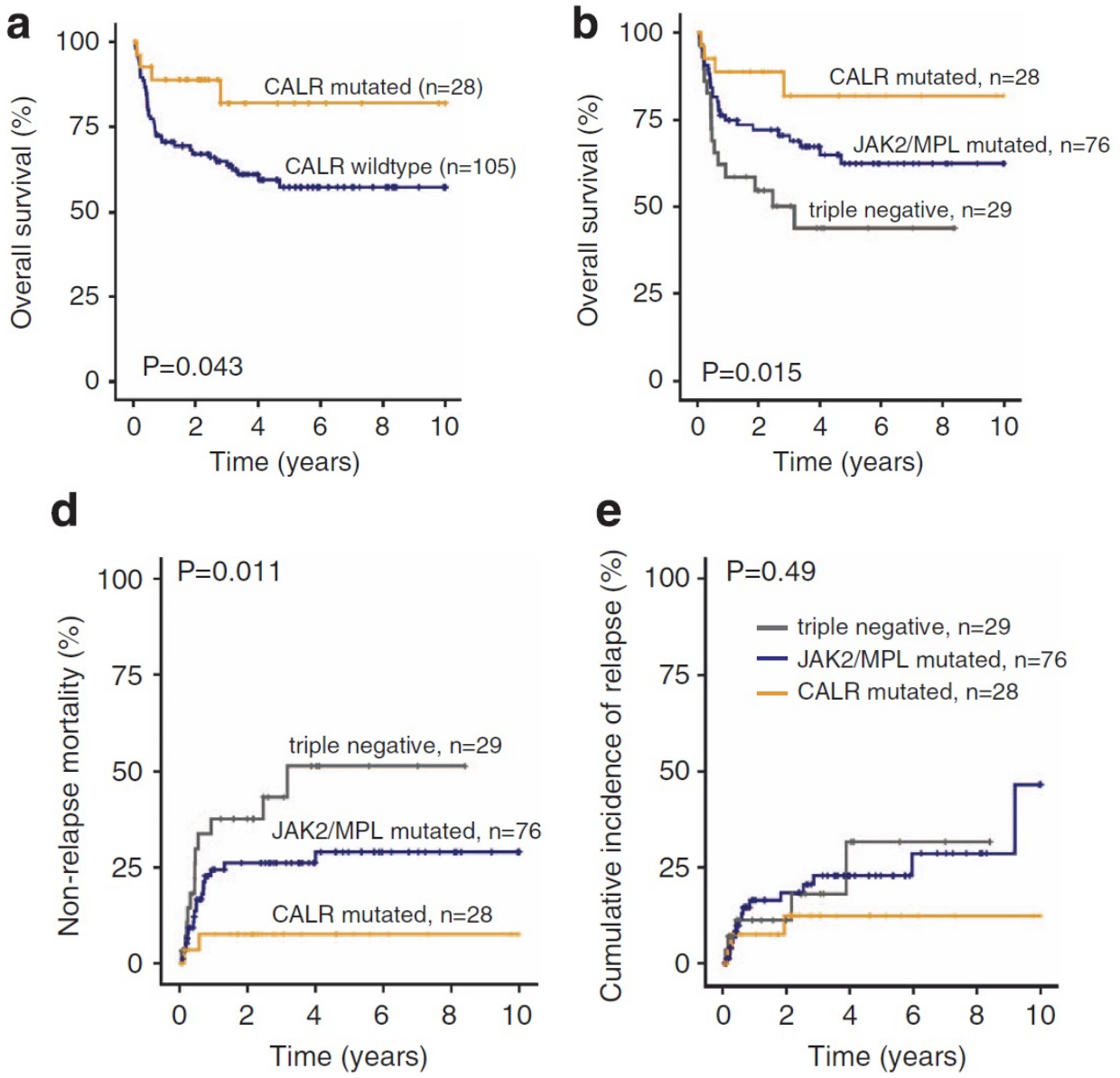
Number at Risk							
negative	23	23	11	11	11	11	11
positive	15	11	11	7	2	2	2
Total	38	34	22	18	13	13	13

Alchalby et al., Blood. 2010 Nov 4;116(18):3572-81

LETTER TO THE EDITOR

Prognostic effect of calreticulin mutations in patients with myelofibrosis after allogeneic hematopoietic stem cell transplantation

Panagiota V et al, Leukemia 2014



Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Comparison of Dynamic International Prognostic Scoring System and MYelofibrosis SECondary to PV and ET Prognostic Model for Prediction of Outcome in Polycythemia Vera and Essential Thrombocythemia Myelofibrosis after Allogeneic Stem Cell Transplantation

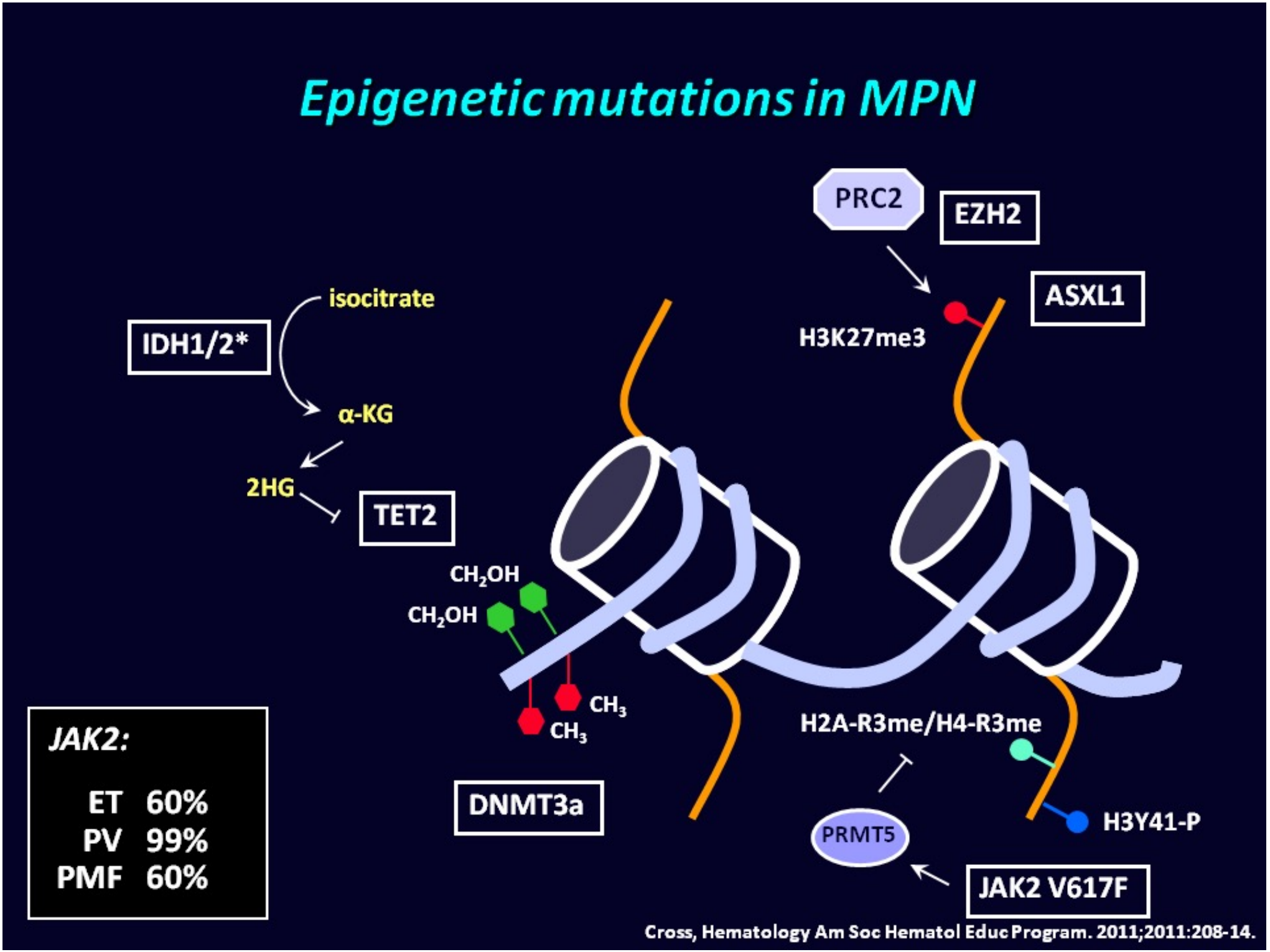
Nico Gagelmann[1], Diderik-Jan Eikema[2], Liesbeth C d

Table 2

Multivariate Analysis Predictive Factors According to DIPSS and MYSEC-PM for the Outcome of Allogeneic Transplant in Post-PV and Post-ET MF

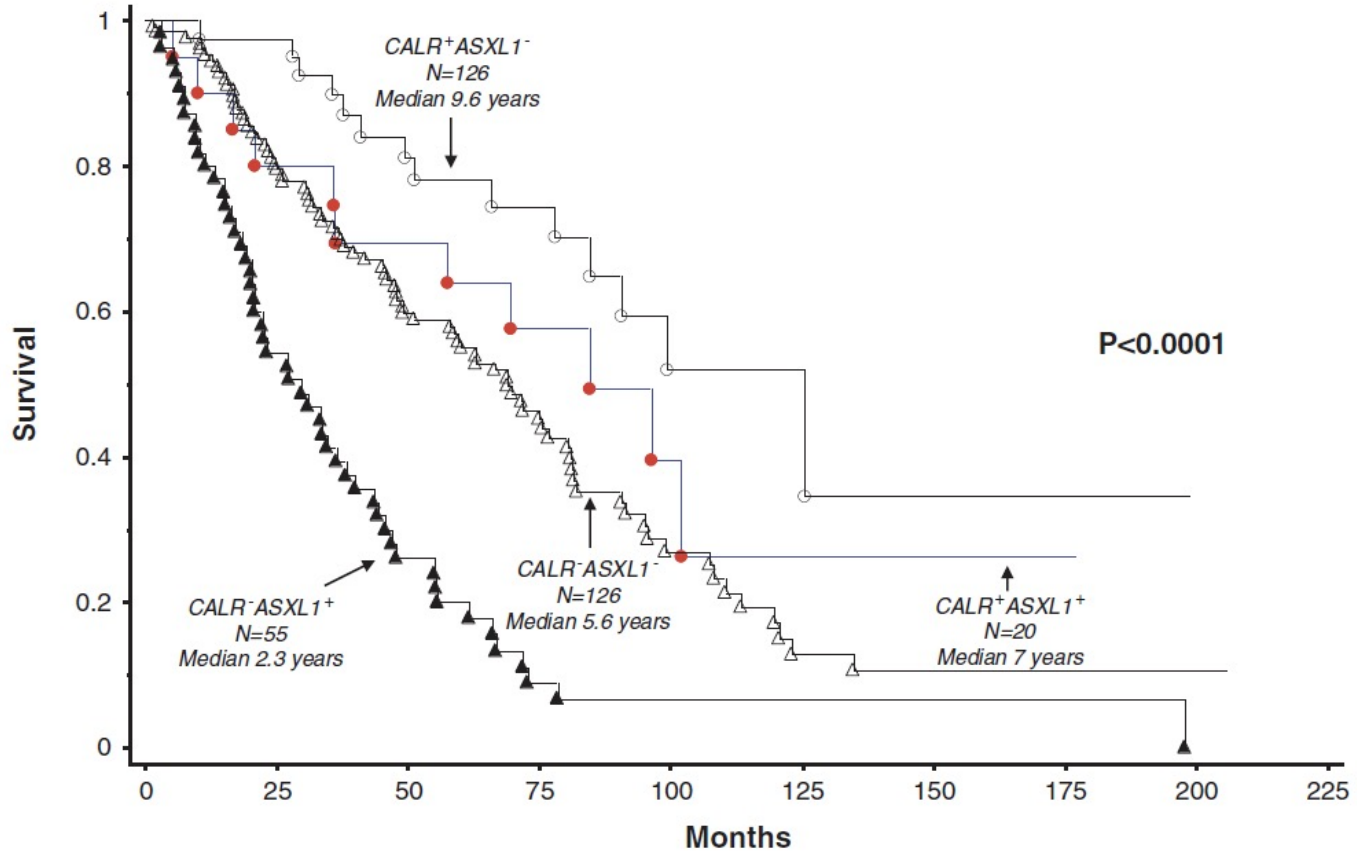
Clinical Variables	HR	95% CI	*P*
DIPSS			
Hemoglobin < 10 g/dL	1.05	.65-1.72	.84
WBC count > 25 × 109/L	1.58	.87-2.87	.14
Blood blasts > 0%	.83	.49-1.41	.50
Age > 65 yr	1.34	.70-2.54	.37
Constitutional symptoms	1.41	.84-2.39	.20
MYSEC-PM			
CALR-unmutated	3.02	1.19-7.63	.02
Blood blasts > 2%	1.34	.79-2.30	.28
Hemoglobin < 11 g/dL	.97	.54-1.76	.44
Platelets < 150 × 109/L	1.29	.76-2.18	.35
Constitutional symptoms	1.22	.73-2.02	.45
Age, yr	1.24	1.01-1.52	.04

Epigenetic mutations in MPN



Cross, Hematology Am Soc Hematol Educ Program. 2011;2011:208-14.

ASXL1 mutation is an adverse prognostic factor in MF



Tefferi et al. Leukemia 2014; 28:1472-1477

“triple negative” or **CALR- ASXL1+** patients have a worse prognosis independently of DIPSS.

Biol Blood Marrow Transplant 25 (2019) 1142–1151

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

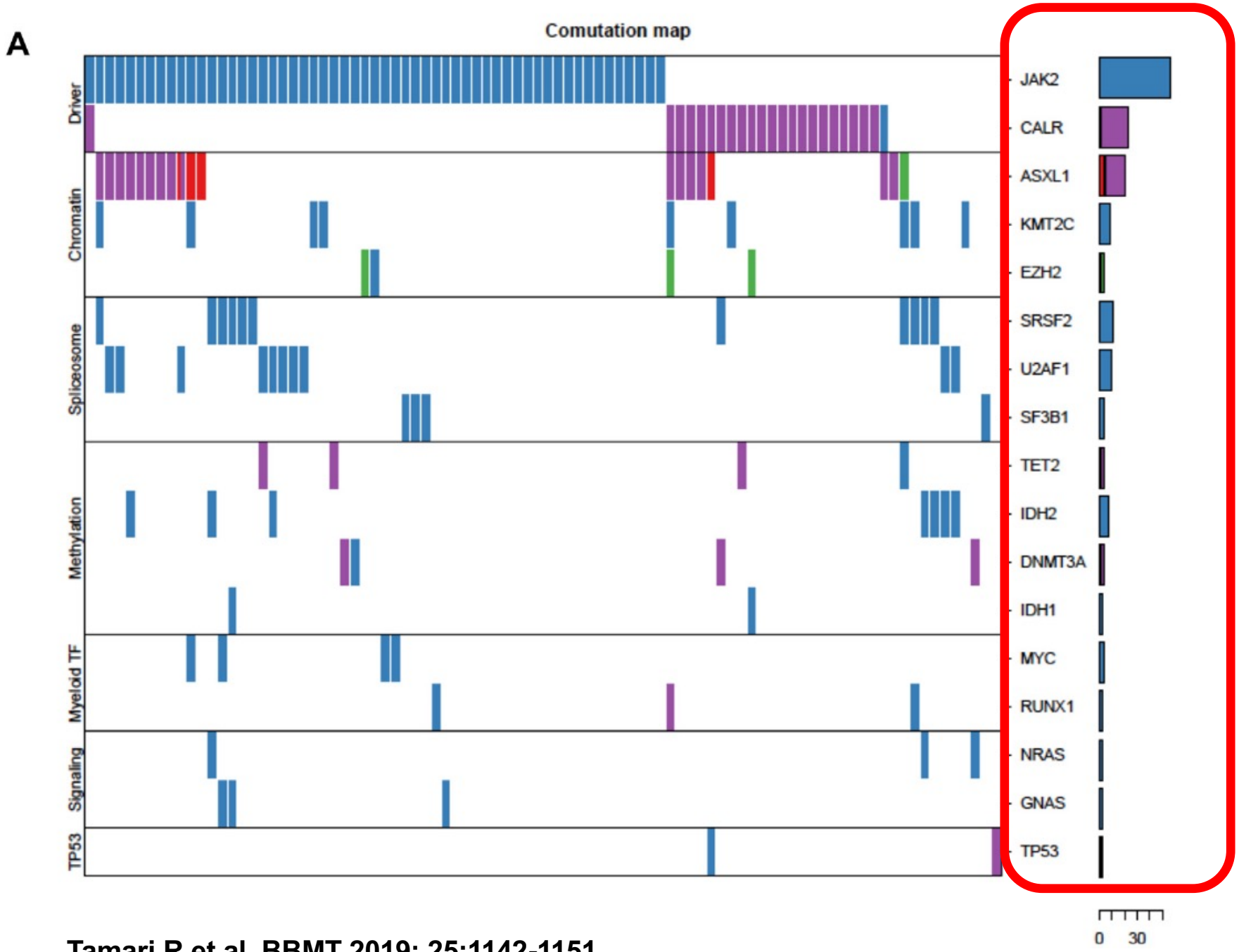
Impact of High-Molecular-Risk Mutations on Transplantation Outcomes in Patients with Myelofibrosis

Roni Tamari[1], Franck Rapaport[2], Nan Zhang[3], Caroline McNamara[4], Andrew Kuykendall[5], David A. Sallman[5], Rami Komrokji[5], Andrea Arruda[4], Vesna Najfeld[6], Lonette Sandy[6], Juan Medina[1], Rivka Litvin[1], Christopher A. Famulare[1], Minal A. Patel[1], Molly Maloy[1], Hugo Castro-Malaspina[1], Sergio A. Giralt[1], Rona S. Weinberg[6], John O. Mascarenhas[6], Ruben Mesa[3], Damiano Rondelli[7], Amylou C. Dueck[3], Ross L. Levine[1], Vikas Gupta[4], Ronald Hoffman[6], Raajit K. Rampal[1,*]

N=101 allotransplants in MF

18% MAC HSCT

82% RIC HSCT

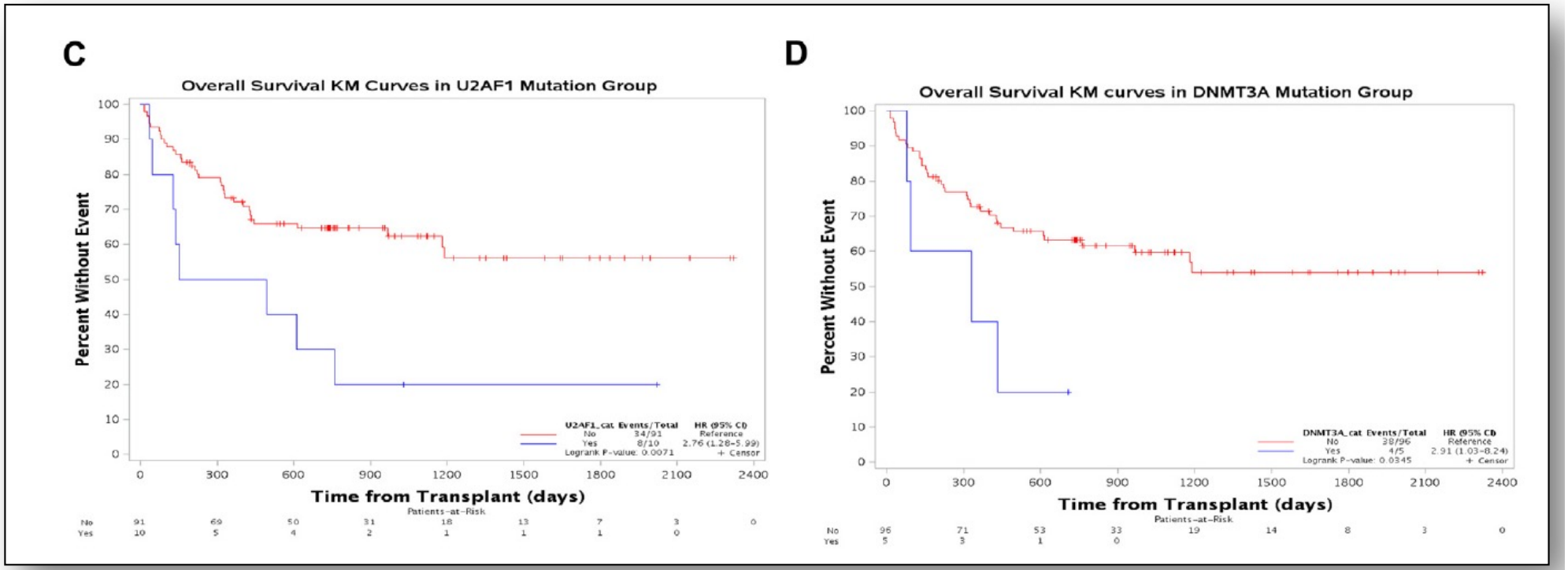


Tamari R et al. BBMT 2019; 25:1142-1151

Table 2
Univariate Analysis of Clinical Characteristics and Mutation Analysis for OS

Effect	Level	HR (95% CI)	P value	
Age at transplant	50 - 65 vs. < 50	1.10 (0.43,2.84)	0.9635	
	> 65 vs. < 50	1.01 (0.31,3.31)		
Gender	F vs. M	0.95 (0.51,1.76)	0.8613	
Cytogenetic risk	unfavorable vs. favorable	2.01 (1.01,4.00)	0.0547	*
	NA vs. favorable	2.19 (0.96,4.98)		
DIPSS	High Risk vs. Low Risk	1.33 (0.40,4.42)	0.4426	
	Int-1 vs. Low Risk	1.24 (0.42,3.68)		
	Int-2 vs. Low Risk	0.73 (0.24,2.24)		
Spleen status	Splenectomy vs. No splenomegaly	1.95 (0.67,5.63)	0.4527	
	Splenomegaly vs. No splenomegaly	1.43 (0.65,3.14)		
Conditioning intensity	RIC vs. MAC	5.94 (1.43,24.62)	0.0052	*
Time from diagnosis to transplant	>2 years vs. <= 2 years	1.07 (0.58,1.95)	0.8363	
Primary vs seconday MF	Other dx vs. PMF	0.75 (0.40,1.43)	0.3816	
Donor	Unrelated vs. Related	1.59 (0.85,2.96)	0.1436	
Donor age	>=50 vs. <50	0.91 (0.46,1.80)	0.2808	
	NA vs. <50	0.46 (0.18,1.22)		
Mutations	At least one positive vs. triple negative	1.22 (0.56,2.64)	0.6145	
HMR presence	Yes vs. No	1.36 (0.73,2.56)	0.3334	
3 or more somatic mutations	Yes vs. No	1.22 (0.64,2.31)	0.5467	
JAK2	Yes vs. No	1.34 (0.71,2.53)	0.3572	
CALR	Yes vs. No	0.72 (0.32,1.63)	0.4328	
ASXL1	Yes vs. No	1.39 (0.67,2.92)	0.3755	
SRSF2	Yes vs. No	0.95 (0.37,2.42)	0.9174	
KMT2C	Yes vs. No	0.78 (0.28,2.19)	0.6342	
U2AF1	Yes vs. No	2.76 (1.28,5.99)	0.0071	*
TET2	Yes vs. No	1.60 (0.63,4.08)	0.317	
IDH2	Yes vs. No	2.23 (0.94,5.29)	0.0626	
DNMT3A_cat	Yes vs. No	2.91 (1.03,8.24)	0.0345	*
MIPSS-70	High Risk vs. Intermediate/low risk	1.25 (0.62,2.52)	0.5372	

U2AF1
DNMT3A



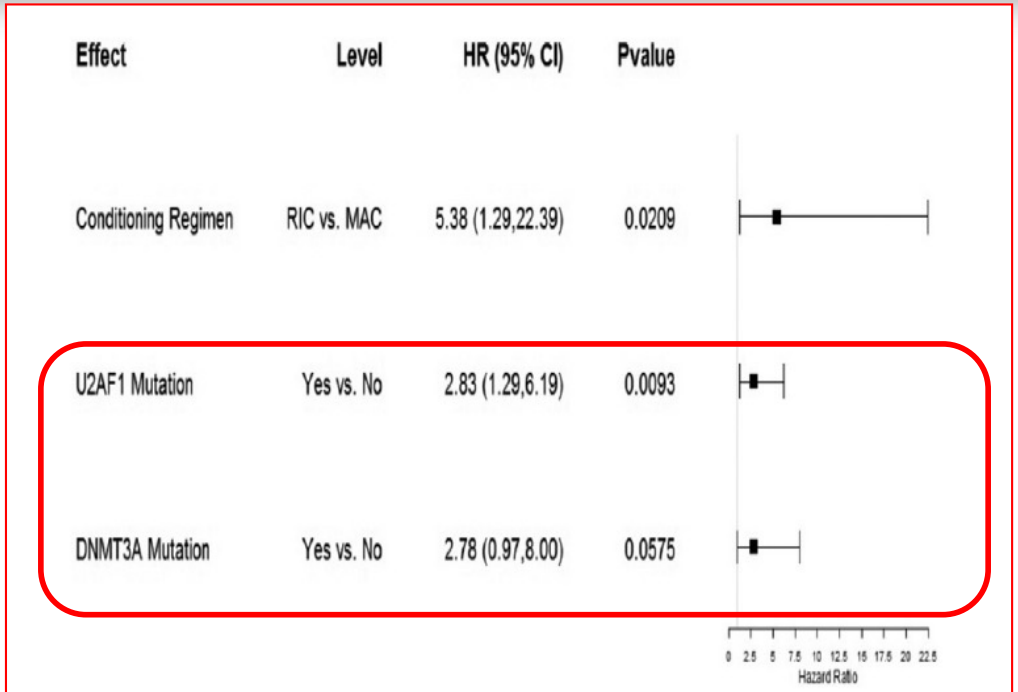


Figure 4. Multivariate analysis for OS as a forest plot.

Tamari R et al. BBMT 2019; 25:1142-1151

Do High Risk patients benefit from a myeloablative conditioning (MAC)?

HemaSphere

EHA

Article
Open Access

High Molecular and Cytogenetic Risk in Myelofibrosis Does Not Benefit From Higher Intensity Conditioning Before Hematopoietic Cell Transplantation: An International Collaborative Analysis

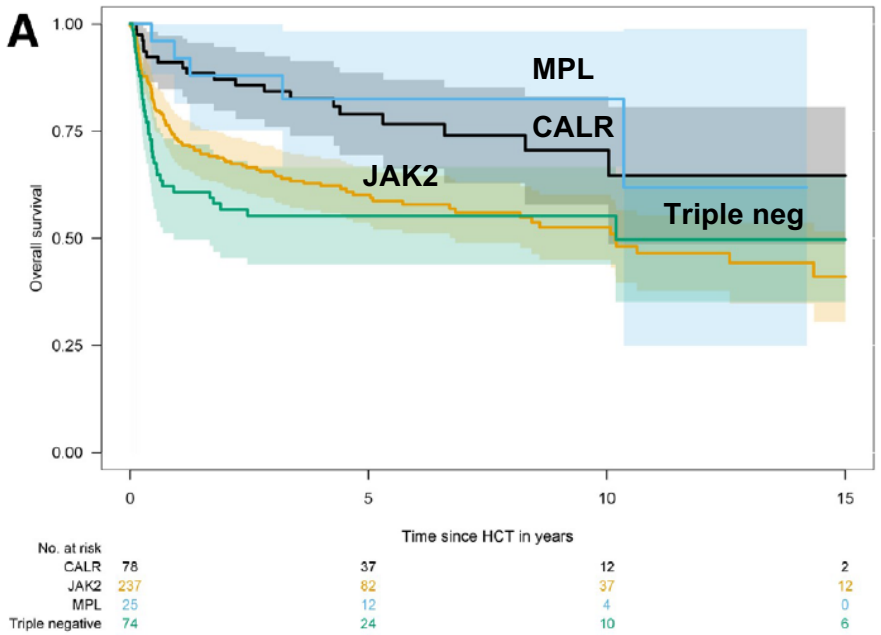
Patients and Transplant Characteristics

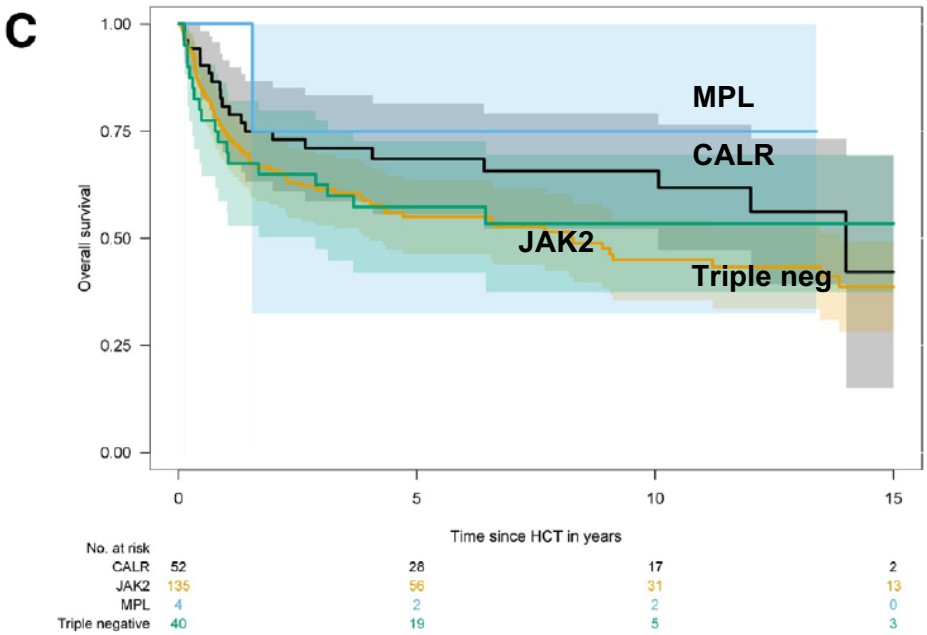
Characteristic	RIC (n = 414)	MAC (n = 231)	*P*
Age at HCT in years, median (range)	58 (18–78)	54 (21–71)	<0.001
Female sex, n (%)	165 (40)	106 (46)	0.15
Diagnosis, n (%)			0.001
PMF	290 (70)	133 (58)	
SMF	124 (30)	98 (42)	
Transfusion dependence	202 (49)	127 (55)	0.16
Blood levels, median (range)			
Hemoglobin, g/dL	9.5 (5.6–17.6)	9.9 (5.6–16.0)	0.12
Circulating blasts, %	1 (0–19)	1 (0–19)	0.51
Platetels, $\times 10^6$/L	144 (5–2437)	165 (4–3506)	0.18
Leukocytes, $\times 10^6$/L	8.1 (0.6–168.8)	8.6 (0.4–93.7)	0.70
Karnofsky performance status, n (%)			0.03
90%–100%	244 (59)	159 (69)	
<90%	170 (41)	72 (31)	
Driver mutation genotype, n (%)			0.07
CALR	78 (19)	52 (23)	
MPL	25 (6)	4 (2)	
JAK2	237 (57)	135 (58)	
Triple negative	74 (18)	40 (18)	
ASXL1 mutation present[a]	119 (29)	50 (29)	0.97
HMR present[b]	148 (41)	59 (38)	0.55

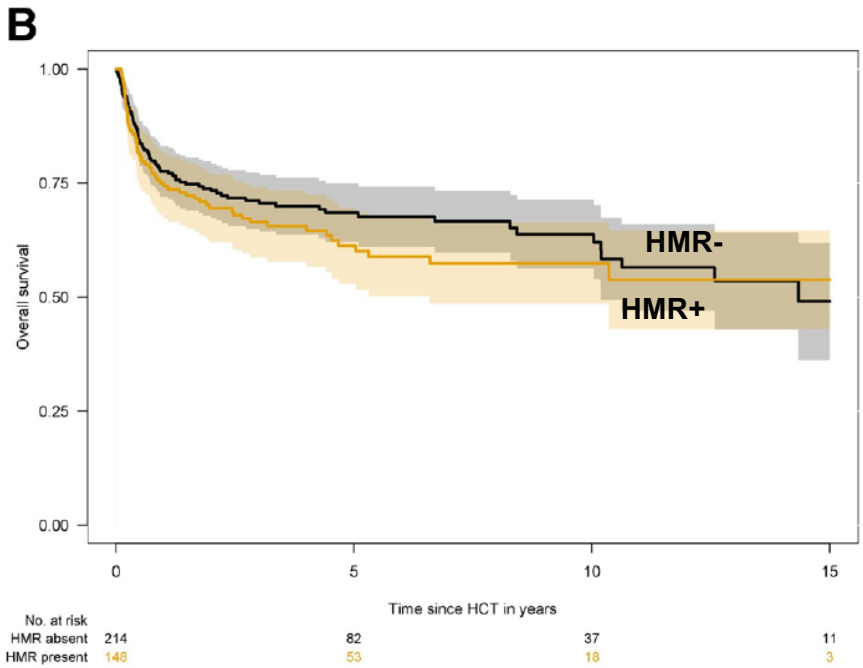
Gagelmann N…Kroeger N, HemaSphere 2022; 6:10(e784)

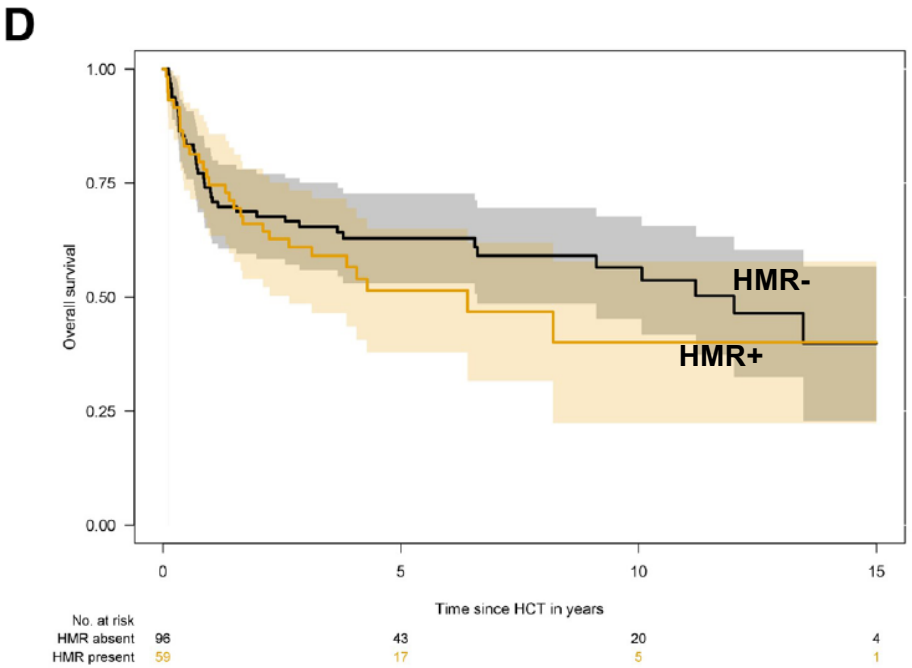
RIC

MAC


A
1.00
0.75
0.50
0.25
0.00
Overall survival
MPL
CALR
JAK2
Triple neg
0
5
10
15
Time since HCT in years
No. at risk
CALR 78 37 12 2
JAK2 237 82 37 12
MPL 25 12 4 0
Triple negative 74 24 10 6


C
1.00
0.75
0.50
0.25
0.00
Overall survival
MPL
CALR
JAK2
Triple neg
0
5
10
15
Time since HCT in years
No. at risk
CALR 52 28 17 2
JAK2 135 56 31 13
MPL 4 2 2 0
Triple negative 40 19 5 3


B
1.00
0.75
0.50
0.25
0.00
Overall survival
HMR-
HMR+
0
5
10
15
Time since HCT in years
No. at risk
HMR absent 214 82 37 11
HMR present 148 53 18 3


D
1.00
0.75
0.50
0.25
0.00
Overall survival
HMR-
HMR+
0
5
10
15
Time since HCT in years
No. at risk
HMR absent 96 43 20 4
HMR present 59 17 5 1

Do patients in accelerated-phase (blasts: 10-19%) benefit from a reduced intensity conditioning (RIC) vs patients in chronic-phase?

REGULAR ARTICLE

blood advances

Check for updates

Reduced intensity hematopoietic stem cell transplantation for accelerated-phase myelofibrosis

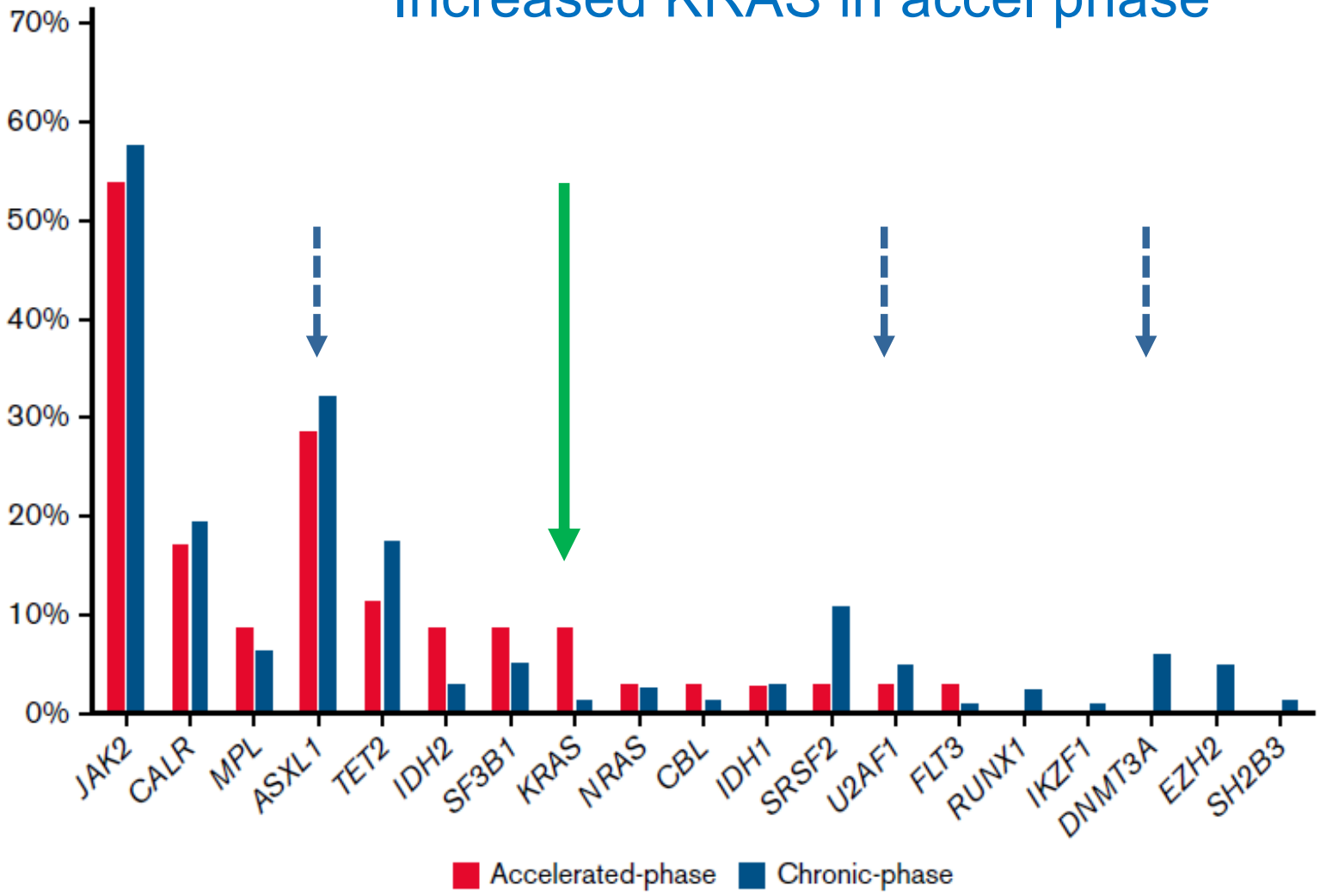
Nico Gagelmann,[1] Christine Wolschke,[1] Rachel B. Salit,[2] Thomas Schroeder,[3] Markus Ditschkowski,[3] Victoria Panagiota,[4]

chronic phase: N. 314
accel phase: N. 35
Median age: 58 yrs in both groups

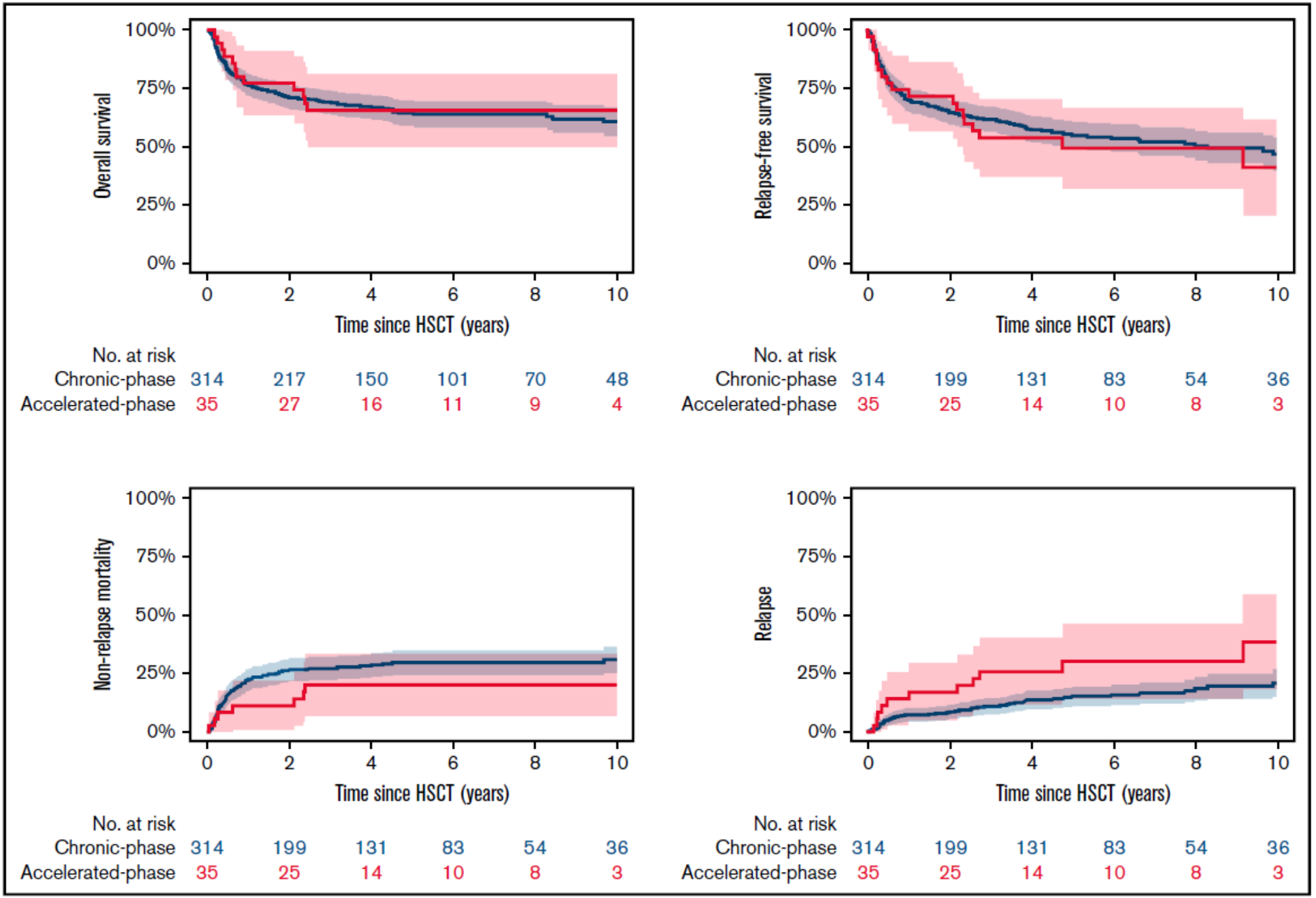
Characteristic	Entire cohort	Chronic-phase	Accelerated-phase	*P*
DIPSS, no. (%)				.05
Low	15	15 (6)	0	
Intermediate-1	75	72 (31)	3 (14)	
Intermediate-2	123	112 (49)	11 (52)	
High	39	32 (14)	7 (34)	
Triple negative	59	52 (17)	7 (20)	
HMR, no. (%)				.86
Present	140	126 (40)	14 (40)	
Donor relation, no. (%)				.36
Matched related	89	81 (26)	8 (23)	
Matched unrelated	174	152 (48)	22 (63)	
Mismatched related	2	2 (1)	0	
Mismatched unrelated	84	79 (25)	5 (14)	
Regimen				.92
Busulfan-fludarabine	293	264 (74)	29 (83)	
Fludarabine-melphalan	55	49 (15)	6 (17)	
TBI-fludarabine	1	1 (1)	0	
Time to transplant, y				.36
Median (range)	2.2 (0.1-47.3)	2.1 (0.1-47.3)	3.2 (0.2-47.2)	
Ruxolitinib pretransplant, no. (%)	117	102 (33)	15 (43)	.26
Follow-up, y				.62
Median (range)	6.0 (5.2-6.7)	6.0 (5.2-6.7)	5.9 (2.8-9.0)	

Gagelmann N, et al, Blood Adv 2022; 6(4); 1222-1231

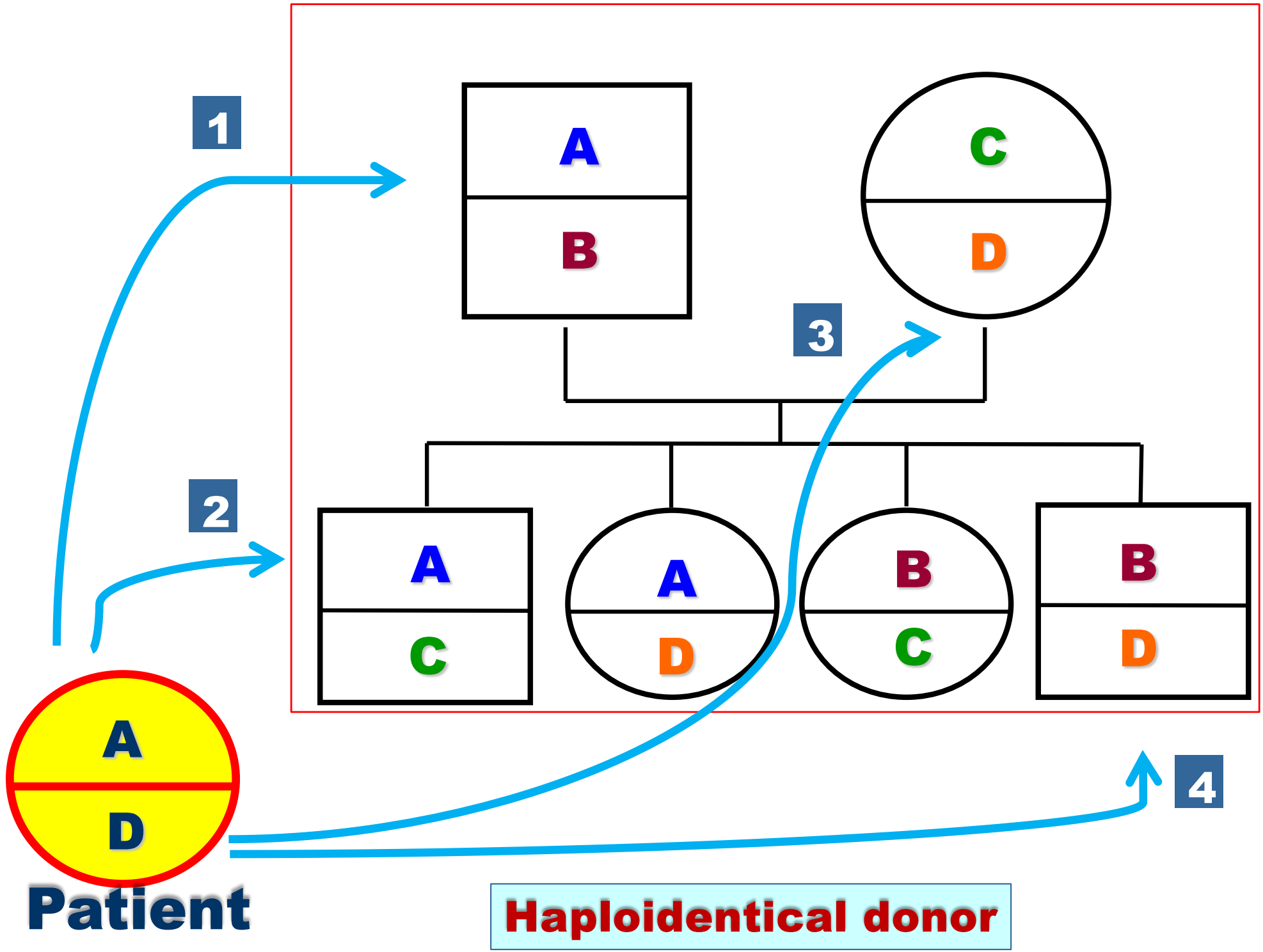
Increased KRAS in accel phase



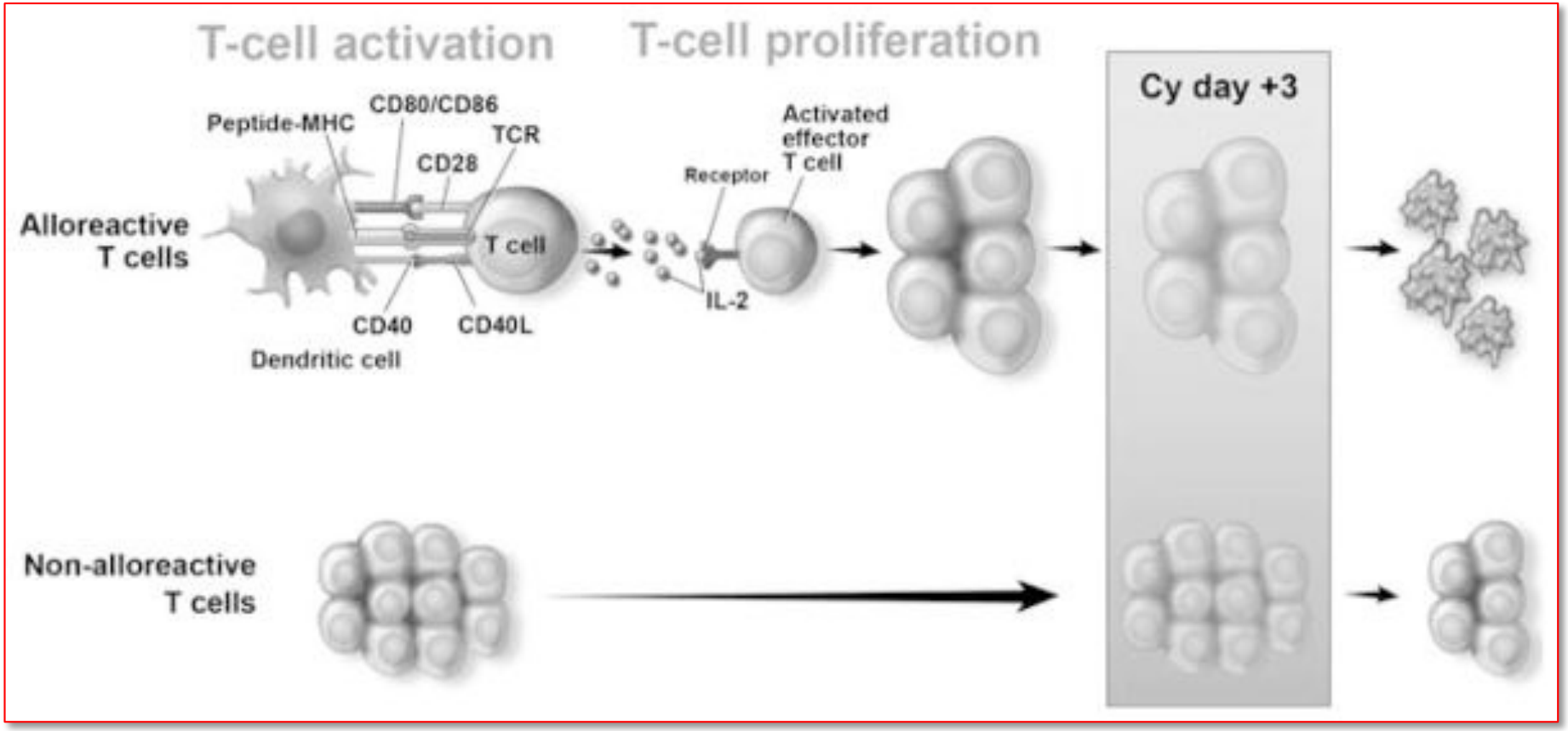
Gagelmann N, et al, Blood Adv 2022; 6(4); 1222-1231



Gagelmann N, et al, Blood Adv 2022; 6(4); 1222-1231


1
A
B
C
D
3
2
A
C
A
D
B
C
B
D
A
D
4
Patient
Haploidentical donor

The PTCy Strategy

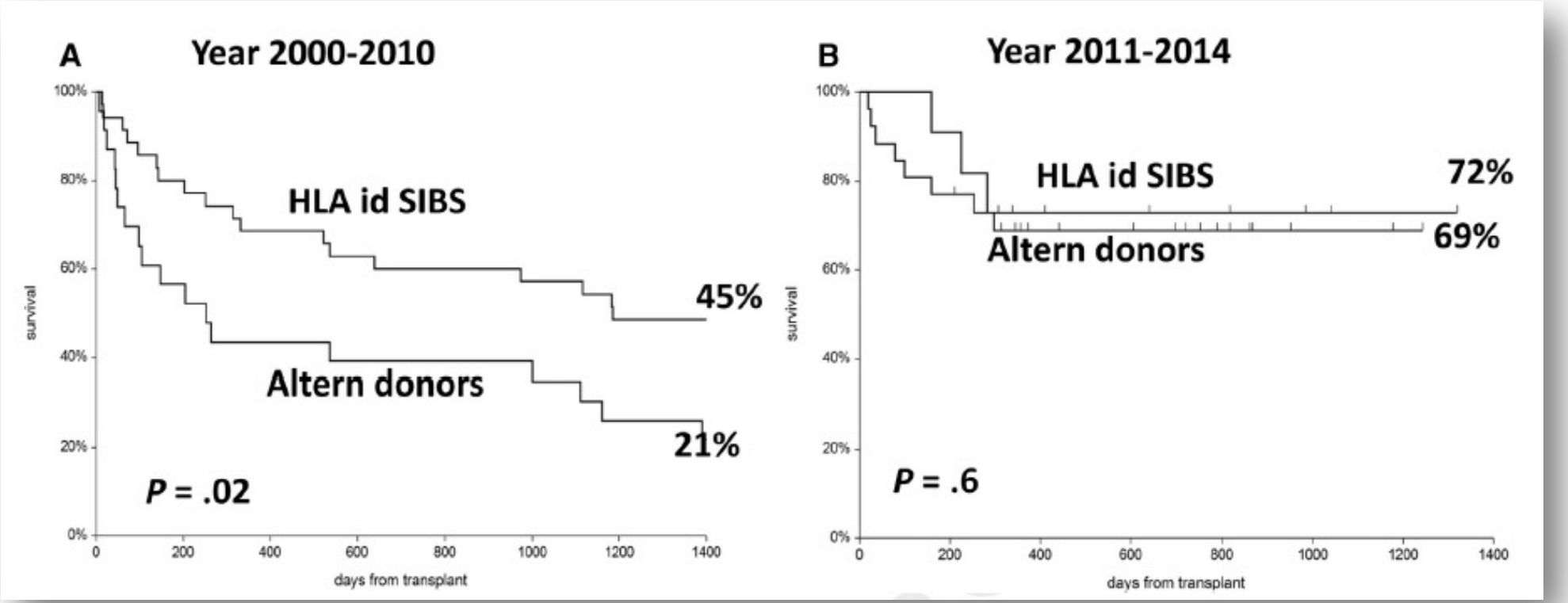


1) Depletion of alloreactive T cells
2) Preservation of stem cells due to chemo-resistance
3) Expansion of Tregs

THE UNIVERSITY OF ILLINOIS AT CHICAGO

Improved Outcome of Alternative Donor Transplantations in Patients with Myelofibrosis: From Unrelated to Haploidentical Family Donors

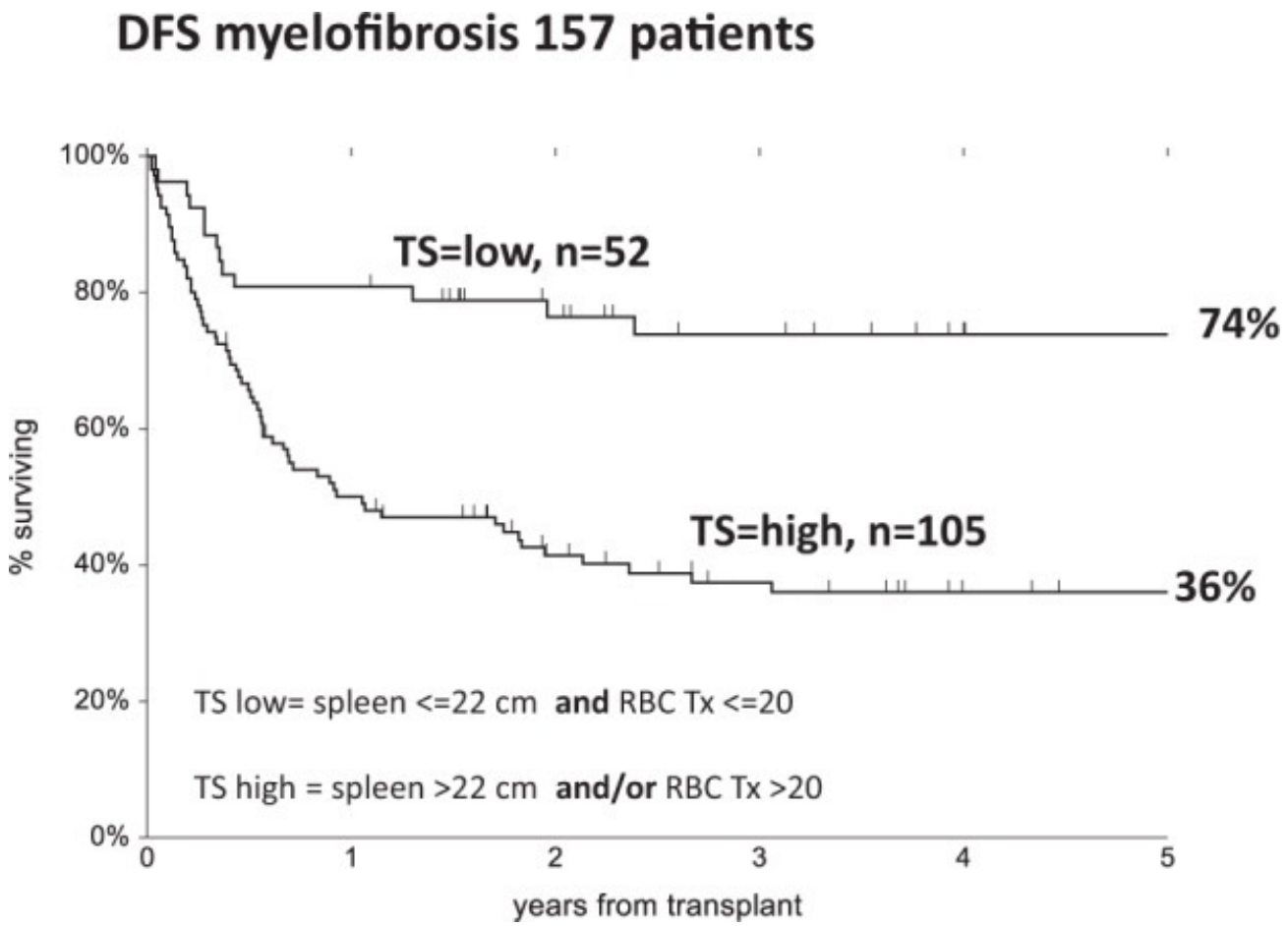
Bregante S,.. Bacigalupo A. BBMT 2015



2000-2010
Cytoxan
Thiotepa

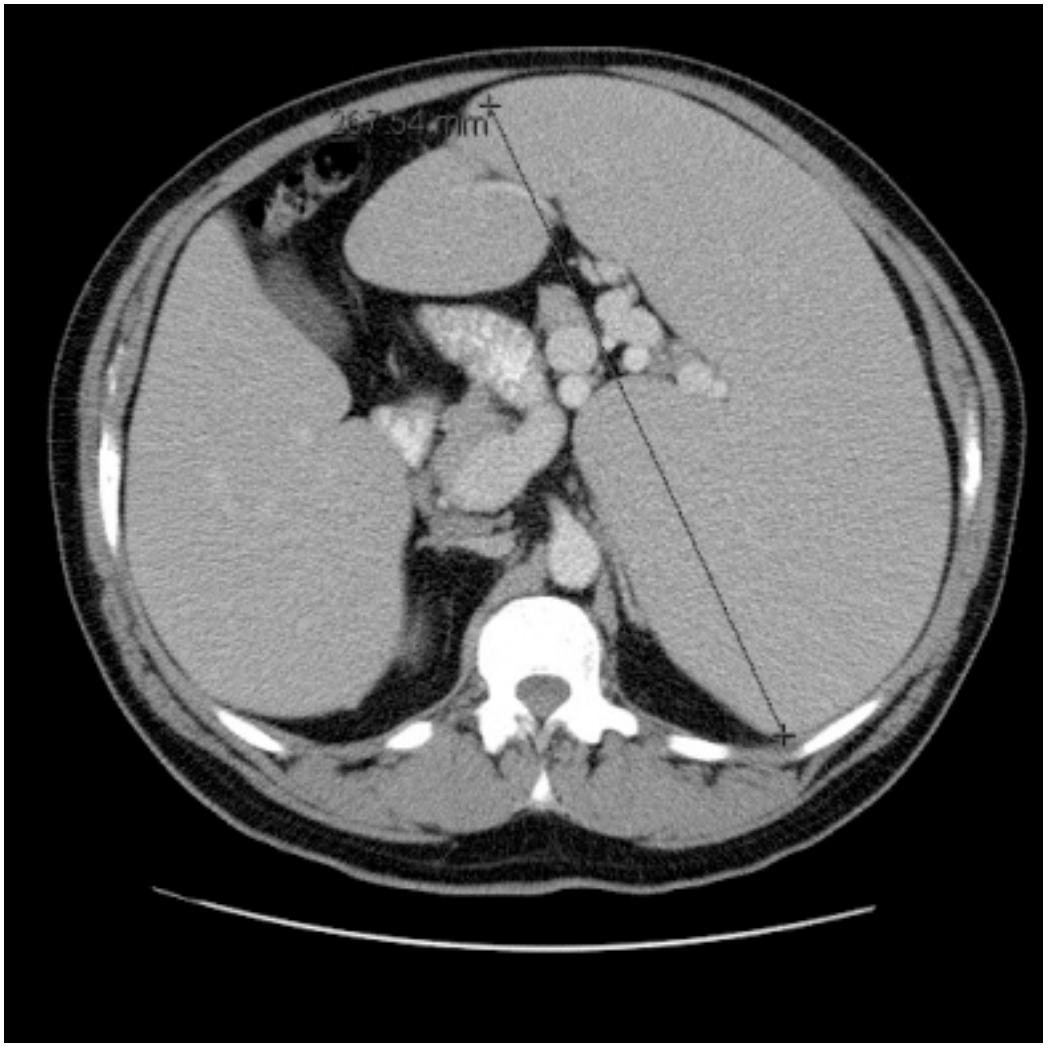
2011-2014
Fluda
Thiotepa
Bus

Sora F et al., Blood Cancer J. 2022 Jul; 12(7): 111.



A low transplant score (TS) is identified as red blood cell transfusions (RBC Tx) <20 units and spleen size less than 22 cm. A high TS is identified as red blood cell transfusions (RBC Tx) >20 units and/or spleen size than >22 cm.

EXTENSIVE SPLENOMEGALY PRIOR TO ALLOGENEIC STEM CELL TRANSPLANTATION

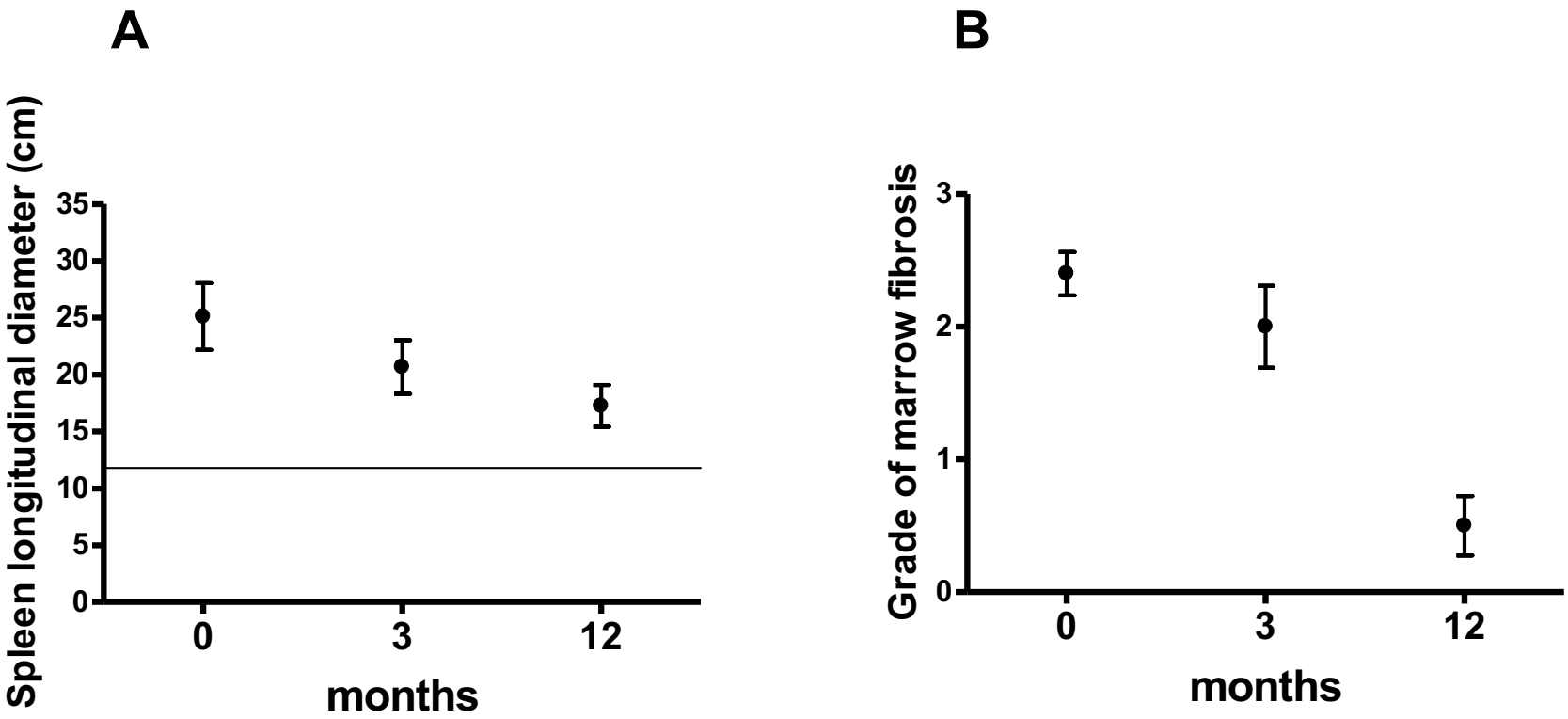


EXTENSIVE SPLENOMEGALY PRIOR TO ALLOGENEIC STEM CELL TRANSPLANTATION: engraftment

Pt. No	Spleen long. diameter at DX (cm)	BM fibrosis at DX (grade)	Dx to Tx (mo)	ANC >500 (days)	PLT >20K (days)	Follow-up (mo)	Spleen long. diameter at last follow-up (cm)	Clinical response§
1	34	3	6	18	77	81+	21	CRp
2	12.5	2	12	16	N/A*	2	10.5	N/A
3	32	2	7	15	15	54+	15	CR
4	21	3	6	12	15	55+	14	CR
5	30.5	3	24	28	256	14+	24.5	CI
6	12	3	6	12	12	57+	9.5	CR
7	20.5	2	12	15	8	79+	13.5	CR
8	30	2	2	12	12	48+	25	CR
9	33.5	3	264	19	14	6+	23	CI
10	34	2	22	15	15	5+	23	CRp

Ciurea et al, Brit J Haematol, 2008

Decreased fibrosis after allo SCT in pts with extensive splenomegaly



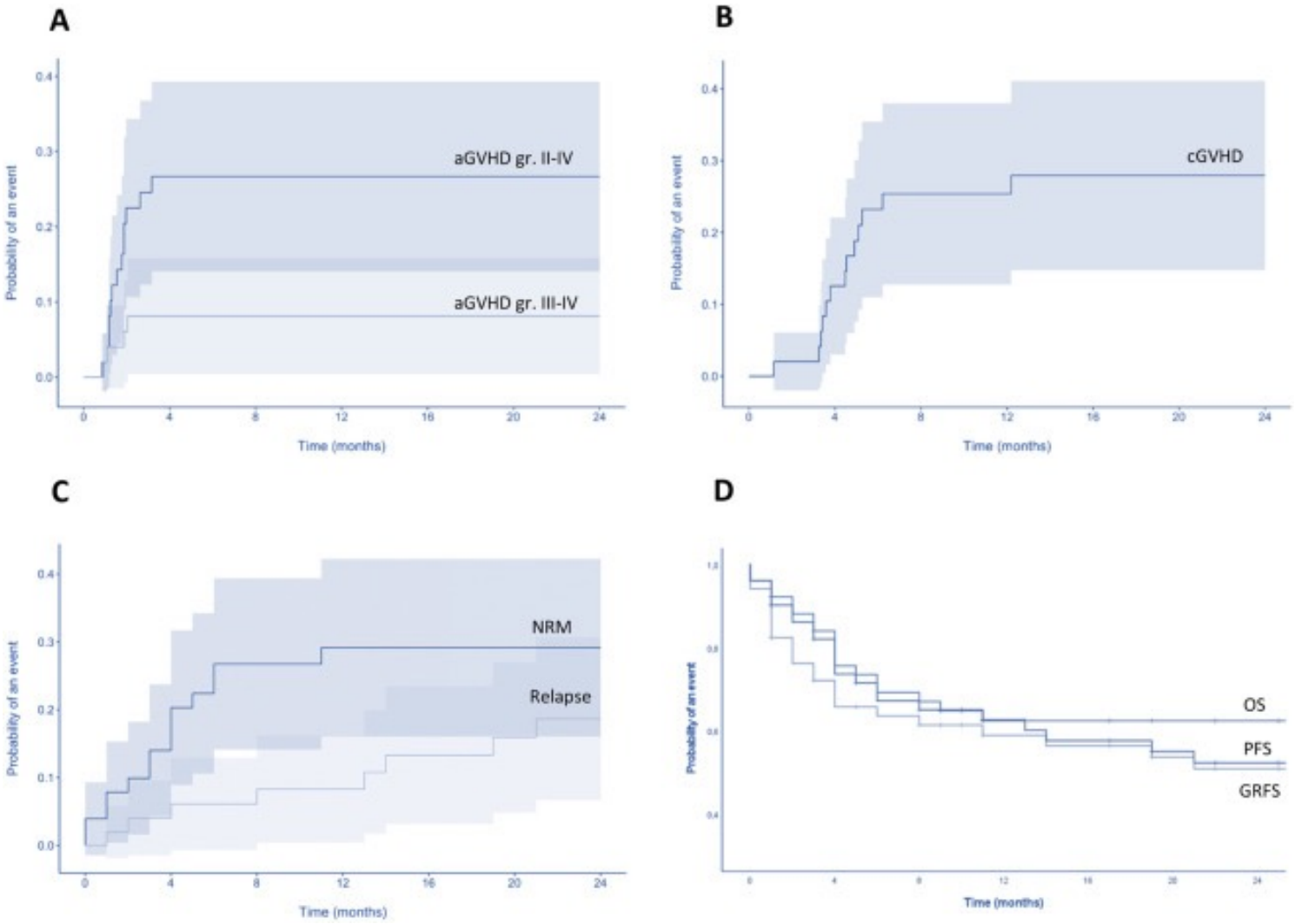
Ciurea et al, Brit J Haematol 2008;141:80-83

Haploidentical hemopoietic cell transplantation for myelofibrosis, in ruxolitinib era

2012-2020
N.51 pts
Age: 58 (42-72)
Splenectomy: 14

Cond Regim
TBF2: 32
TBF3: 19

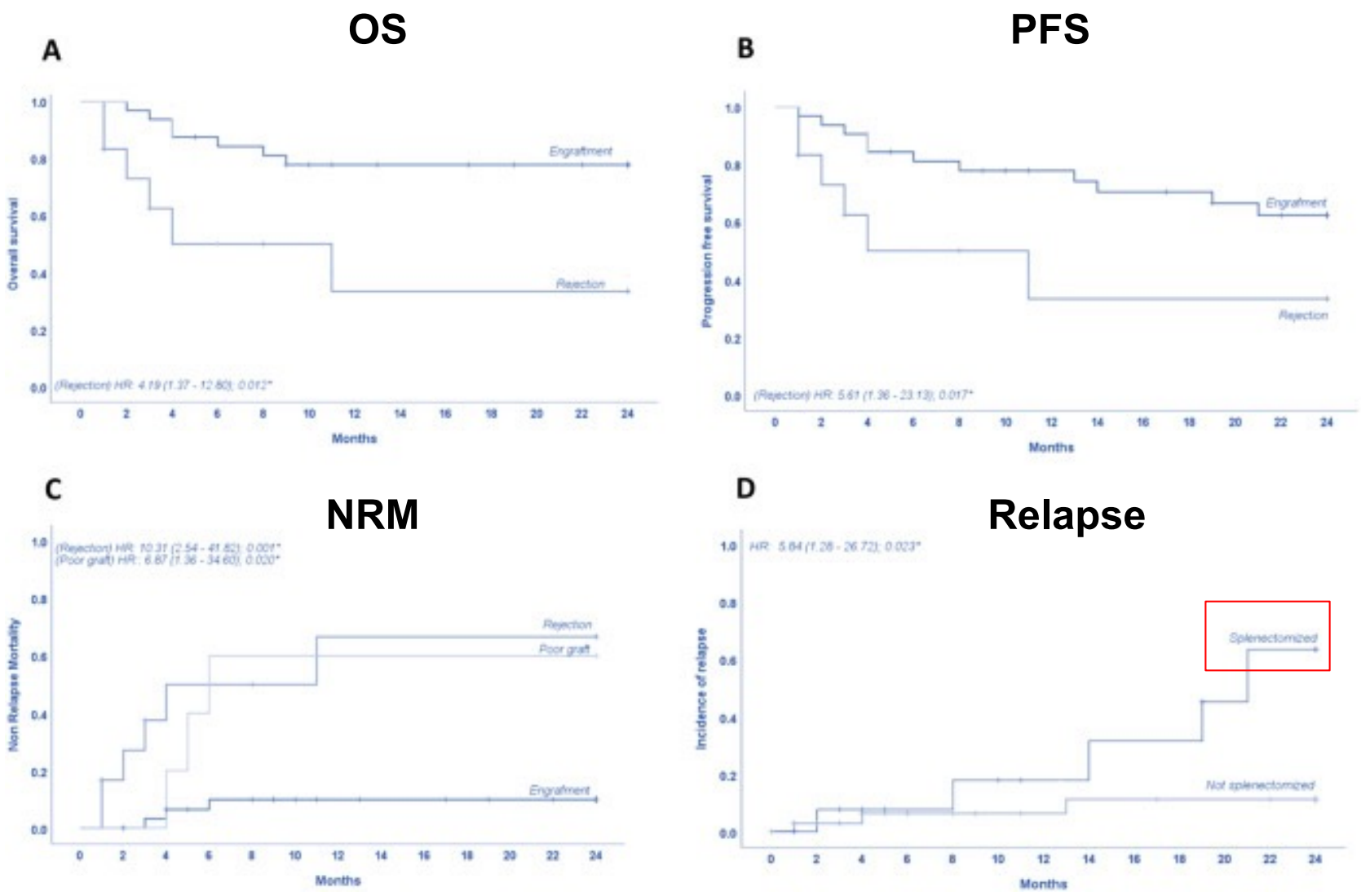
GVHD prophyl
PTCy
CsA x 180 dd
MMF x 28 d



Gambella M, et al. Transplantation and Cellular Therapy (2022)

Splenectomy pre-HSCT: good for engraftment and bad for relapse?

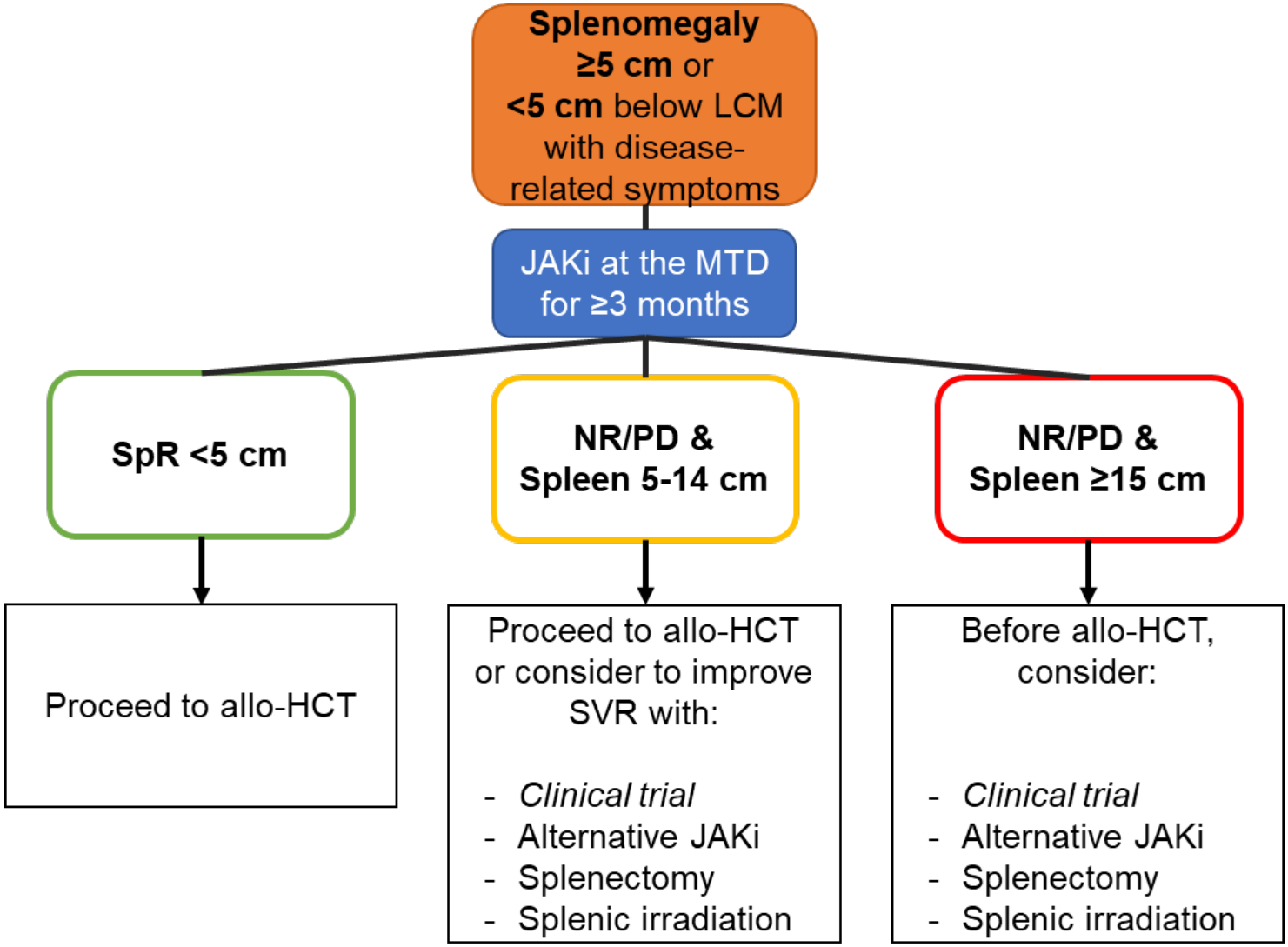
Gambella M, et al. Transplantation and Cellular Therapy (2022)



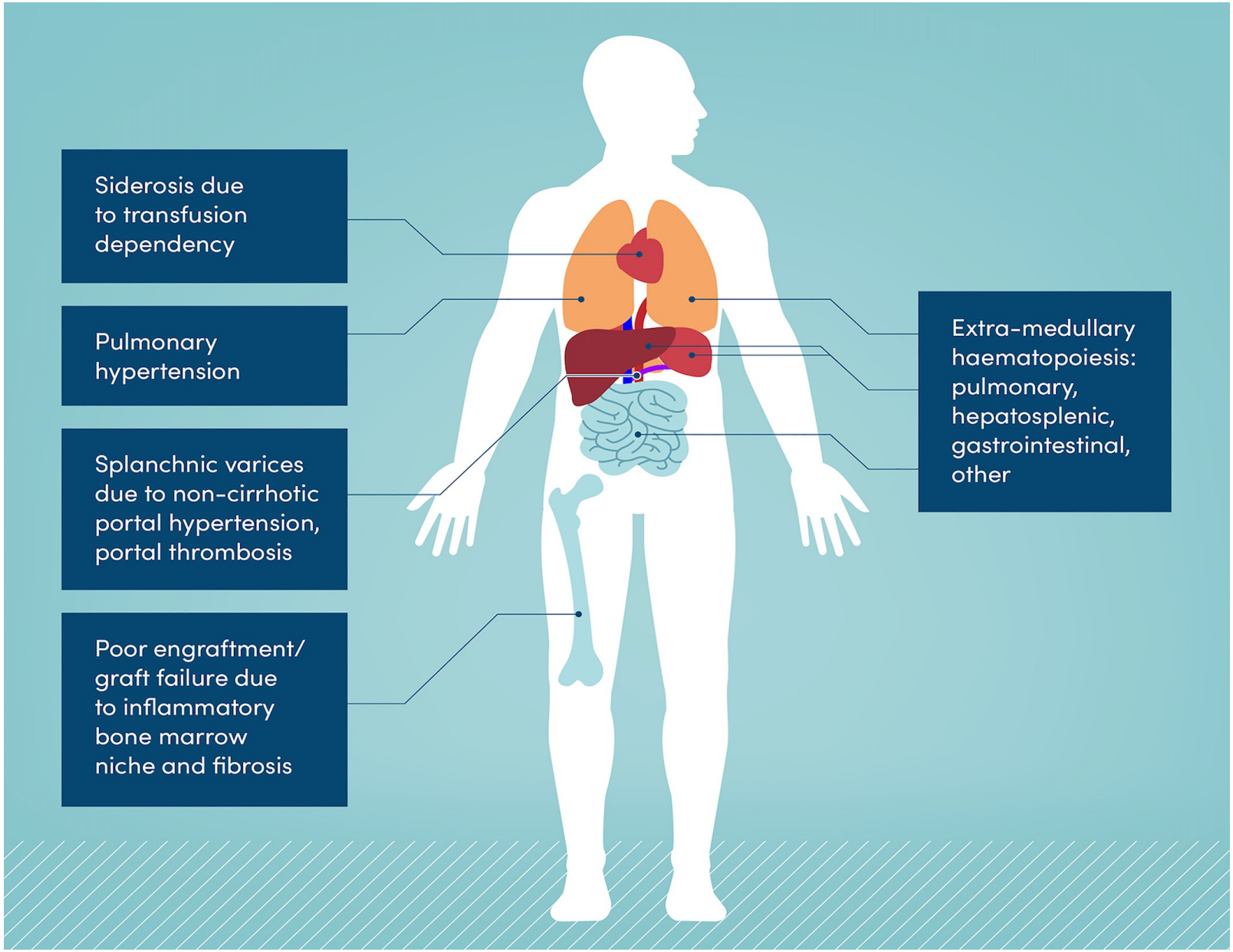
In multivariate analysis: splenectomy correlated with PFS (0.026) and with relapse (0.023), graft failure correlated with OS (0.012)

MANAGEMENT OF SPLENOMEGALY IN PATIENTS WITH PRIMARY OR SECONDARY MYELOFIBROSIS WHO ARE CANDIDATES FOR ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: A POSITION PAPER ON BEHALF OF THE CHRONIC MALIGNANCIES WORKING PARTY OF EBMT

Polverelli N, et al Lancet Haematol 2022



Factors potentially contributing to poor transplant outcomes



Perram J, et. American J Hematol, Volume: 97, Issue: 11, Pages: 1464-1477, First published: 08 July 2022, DOI: (10.1002/ajh.26654)

A few answers on HSCT in MF

1. **DIPPS score, cytogen and molec studies needed**
2. **Consider HSCT if transfusion dependent or increasing spleen size**
3. **Jak inhib (≥ 3 months) useful to reduce spleen pre-HSCT**
4. **HSCT is successful with MRD, MUD or haplo- donors**
5. **MAC not superior to RIC. RIC can be used also in HR or accel phase patients**
6. **Very large spleen can affect engraftment (and survival), but splenectomy can increase the risk of relapse. Yes, splenectomy in symptomatic patients**

thank you!

UNIVERSITY OF ILLINOIS
Hospital & Health Sciences System
Hematology/Oncology