Transplantation with an Alternative Donor: Results and Perspective

"Dilemma in allogeneic hematopoietic transplantation for myelofibrosis"

-SFGM-TC non profit symposium-

14.3.2021 EBMT virtual Annual Meeting 2021

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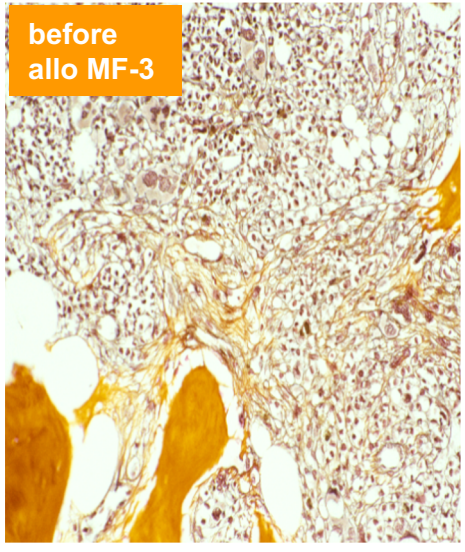
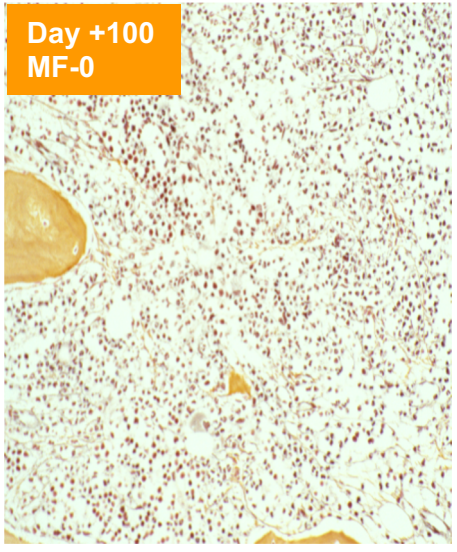
Background

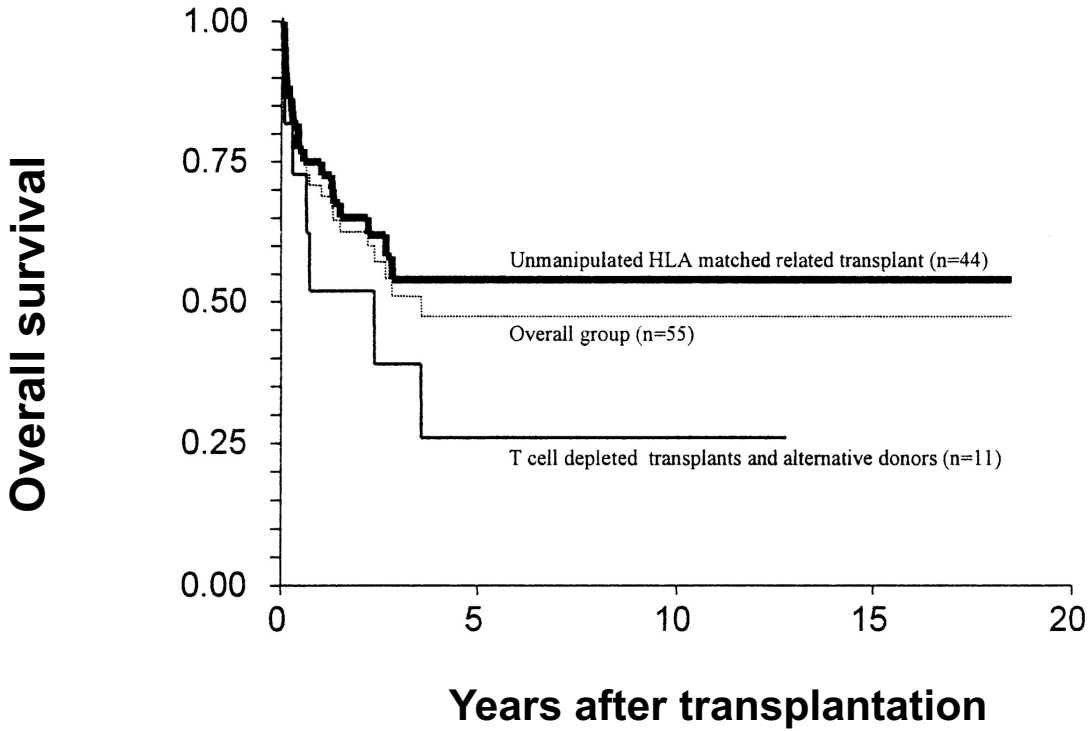
Allogeneic hematopoietic stem cell transplantation is a curative treatment for patients With primary or post ET/PV Myelofibrosis and induces:

- Molecular remission
- Complete resolution of bone marrow fibrosis





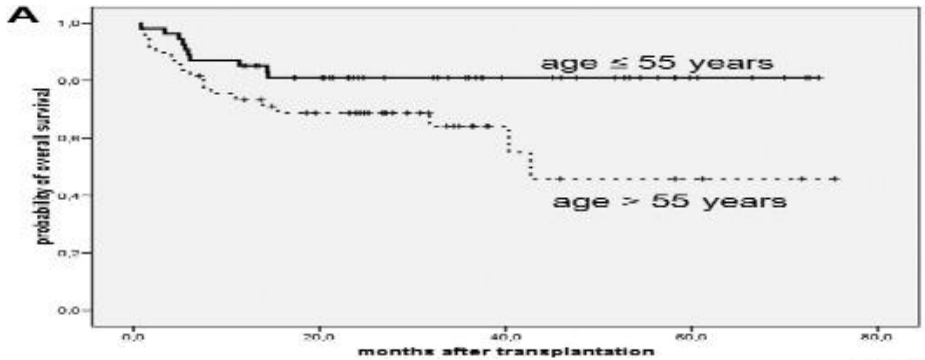
Allogeneic stem cell transplantation for agnogenic myeloid metaplasia: A EBMT, SFGM, GITMO, FHCRC Collaborative Study (n=55; med age 42 y)

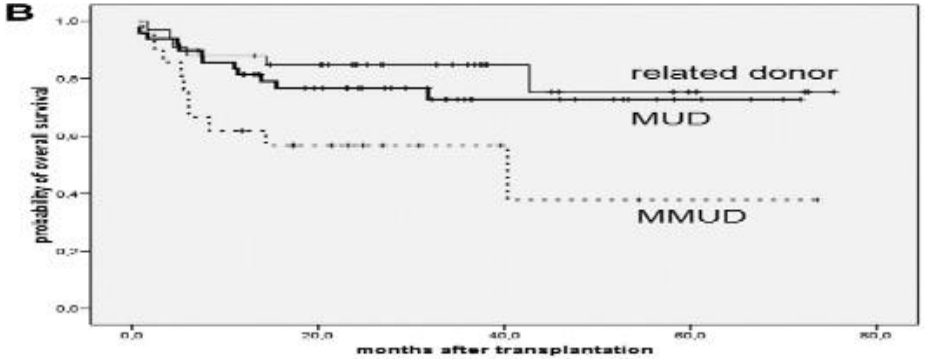


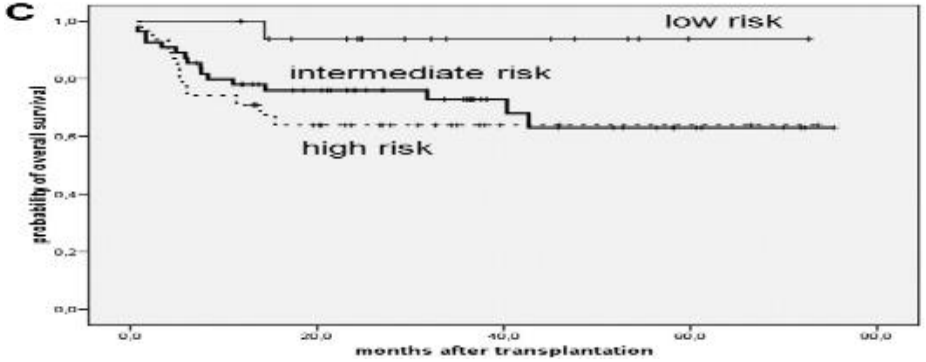
Guardiola et al. Blood 1999;93:2831-2838 [3]

Survival of pts with myelofibrosis after busulfan/ fludarabine (+ATG) based reduced-intensity allogeneic SCT

Prospective EBMT study (n=103; med age 55y)

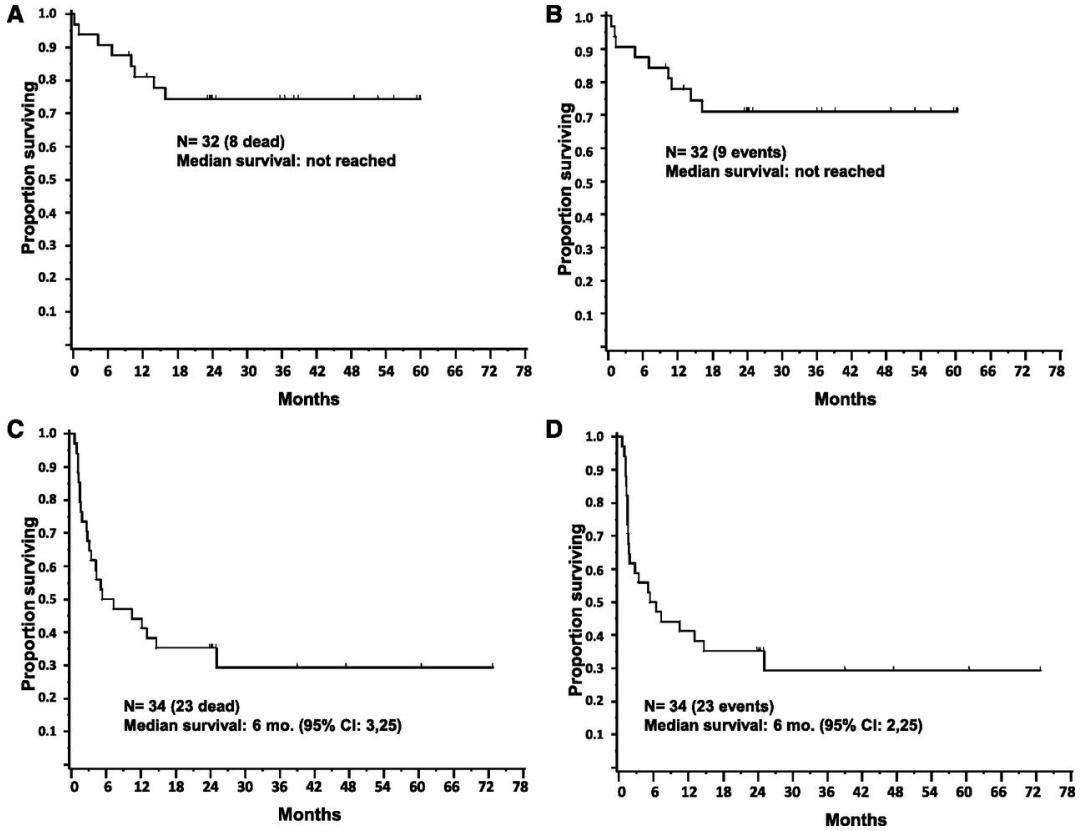






Kröger et al. Blood 2009;114:5264-5270

MPD-RC 101 prospective study of reduced-intensity allogeneic stem cell transplantation in patients with myelofibrosis (Mel/Flu +/-ATG)



HLA ident sibling

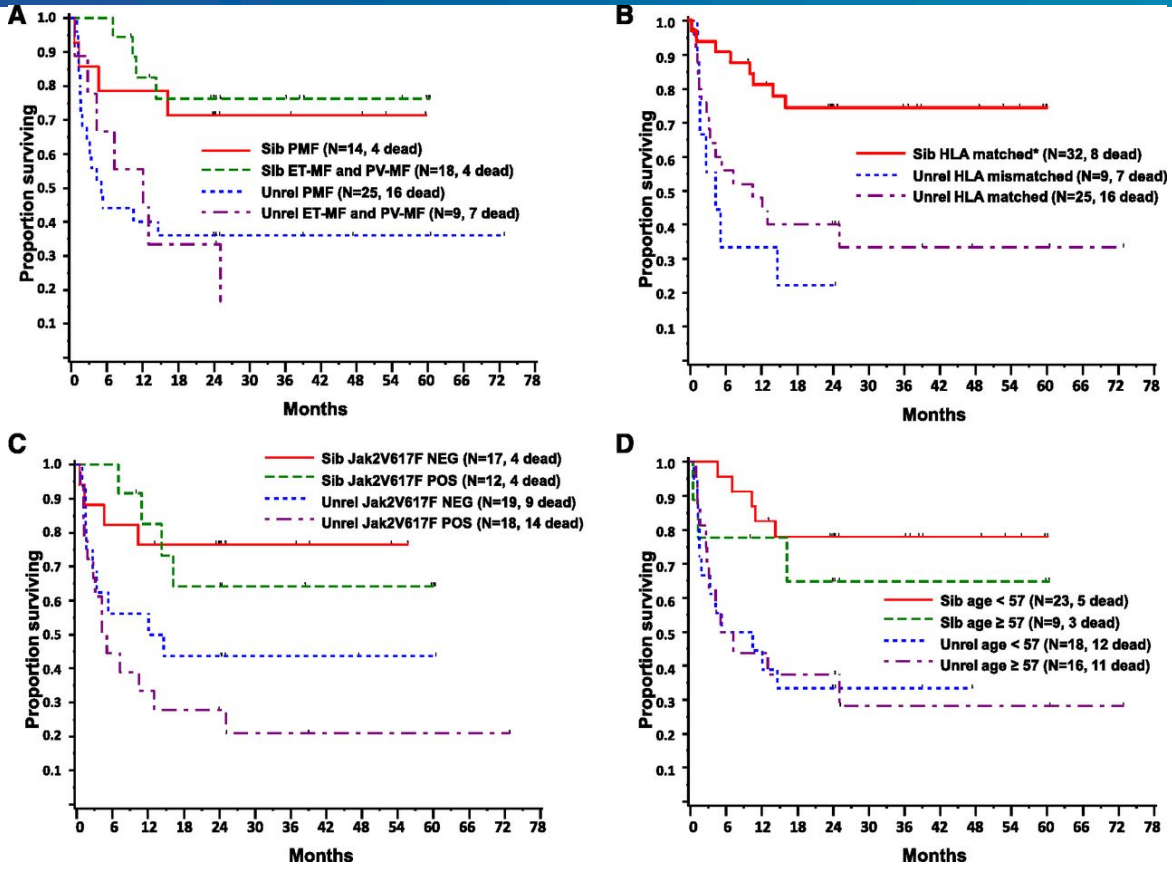
Matched unrelated

24% primary graft failure

12% secondary graft failure

Rondelli et al Blood 2014

MPD-RC 101 prospective study of reduced-intensity allogeneic stem cell transplantation in patients with myelofibrosis



Rondelli et al Blood 2014

Allogeneic haematopoietic stem cell transplantation for myelofibrosis: a report of the SFGM-TC

Multiple model analysis for overall survival.

	Selected model		Adjusted on Lille score	
	Adjusted HR (95%CI)	***P***	**Adjusted HR (95%CI)**	***P***
Male without splenectomy	3·45 (2·07–5·77)	<0·0001	3·10 (1·81–5·3)	<0·0001
Non HLA-identical sibling	1·86 (1·12–3·07)	0·016	1·79 (1·07–2·99)	0·027
Non chronic phase disease	1·81 (1·02–3·21)	0·043	1·69 (0·94–3·04)	0·078
Modified Lille score				
Low			1	
Intermediate			1·24 (0·63–2·43)	0·53
High			1·69 (0·85–3·38)	0·14

Robin et al. BJH 2010

Allogeneic haematopoietic stem cell transplantation for myelofibrosis: a report of the GITMO

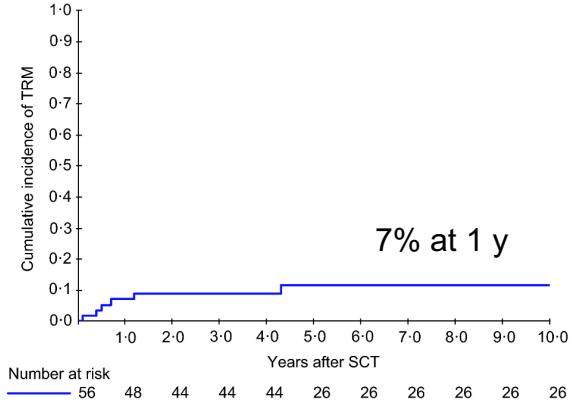
Multiple model analysis for TRM.

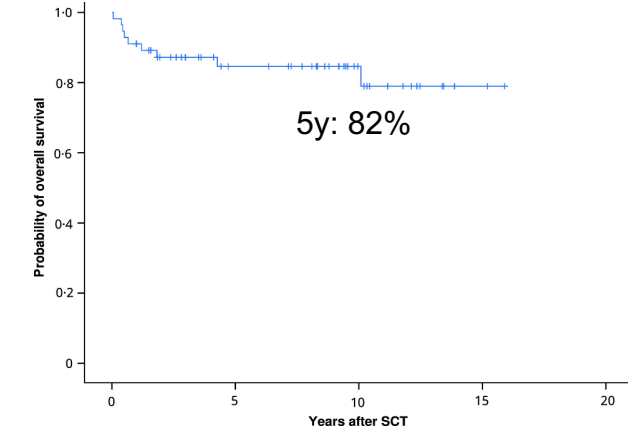
Factor	*TRM*		
Transplant time	HR	95%CI	p
<1995	1		
1996-2000	0.37	0.14-0.96	0.041
>2001	0.24	0.10-0.58	0.001
Time from diagnosis to SCT modeled as a continuous variable	1.01	1.001-1.011	0.007
Donor			
Matched sibling	1		
Unrelated or mismatched	2.49	1.19-5.23	0.016

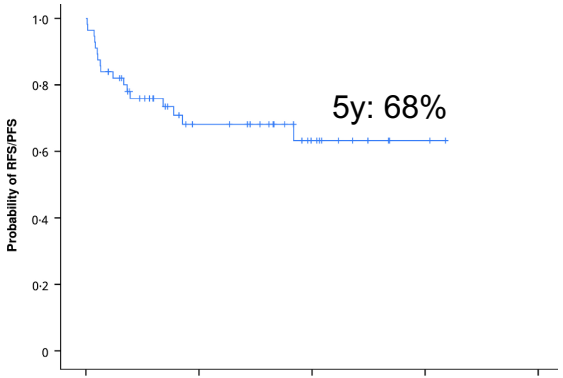
SCT: stem cell transplantation.

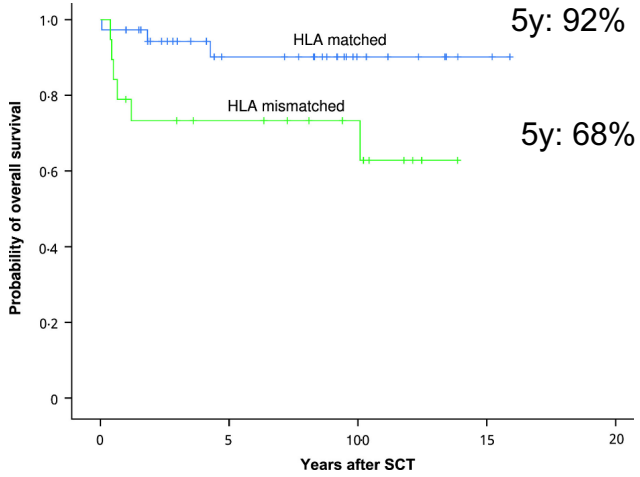
Patriarca et al. Haematologica 2008

Reduced intensity allogeneic SCT for younger patients (< 55y) with myelofibrosis (n=58) Bu/Flu plus ATG









Mannina et al. BJH 2010

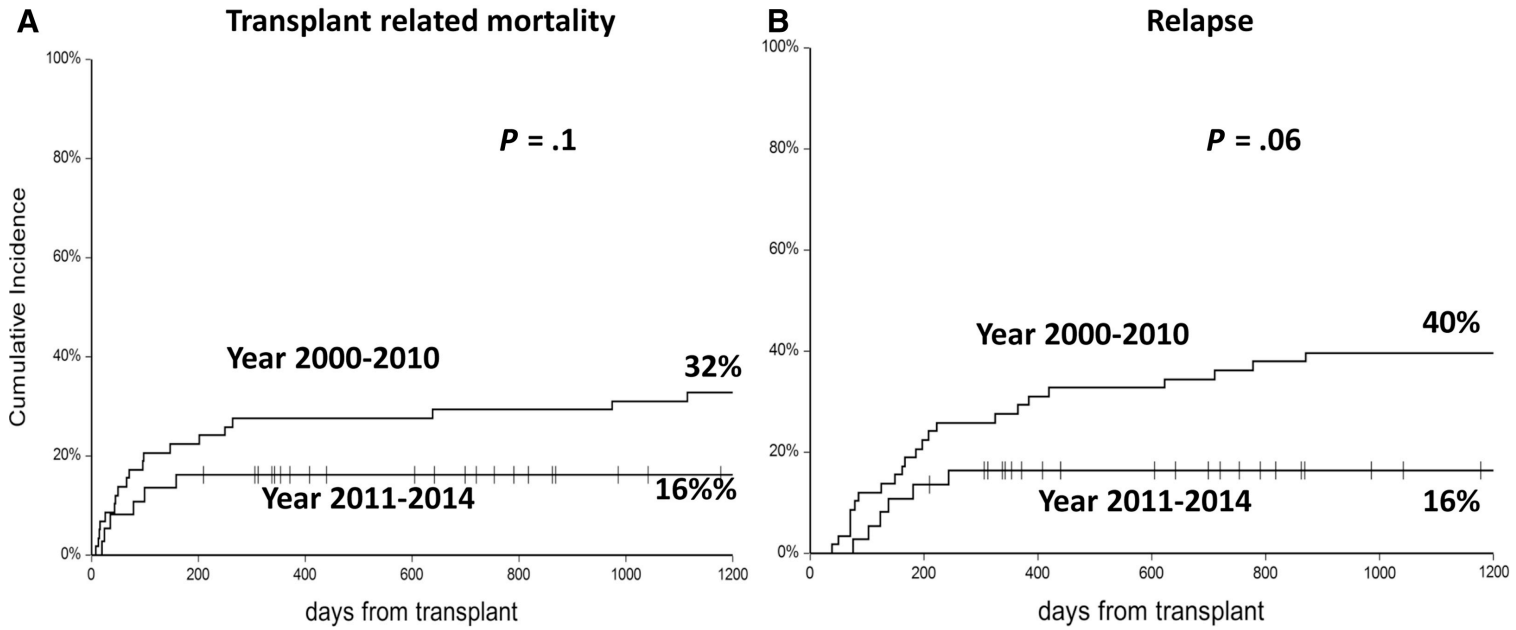
Improvement in outcome after allogeneic stem cell transplantation with alternative donors for Myelofibrosis

Year of Transplantation	2000 to 2010	2011 to 2014	*P* Value
No. of patients	58	37	
Age, median (range), yr	53 (24-67)	58 (37-69)	.004
DIPSS low-int 1/int 2/high	11/24/23	8/12/17	.60
Spleen size, median (range), cm	23 (12-40)	20 (14-30)	.04
JAK2 mutated	20 (44%)	18 (51%)	.50
CD34 cells in PB/µL	104 (0-5280)	120 (2-354)	.90
Splenectomy	46 (79%)	9 (24%)	<.0001
Transfusions >20 units	33 (57%)	13 (35%)	.03
MTS: low, int, high	11/27/20	19/13/6	.006
Interval Dx-Tx, median, d	889	745	.40
Ruxolitinib	0 (0%)	6 (16%)	.001
Donors: SIBS/UD/Haplo	35/20/3	11/6/20	<.0001
Stem cell source BM/PB	50/8	32/5	.90
Myeloablative regimens	9 (15%)	26 (70%)	<.0001
TBF regimen, n (%)	1 (2%)	26 (70%)	<.0001

Int indicates intermediate; PB, peripheral blood; BM, bone marrow; Dx, diagnosis; Tx, treatment; SIBS, HLA-identical siblings.

Bregante et al BBMT 2016

Improvement in outcome after allogeneic stem cell transplantation with alternative donors for Myelofibrosis



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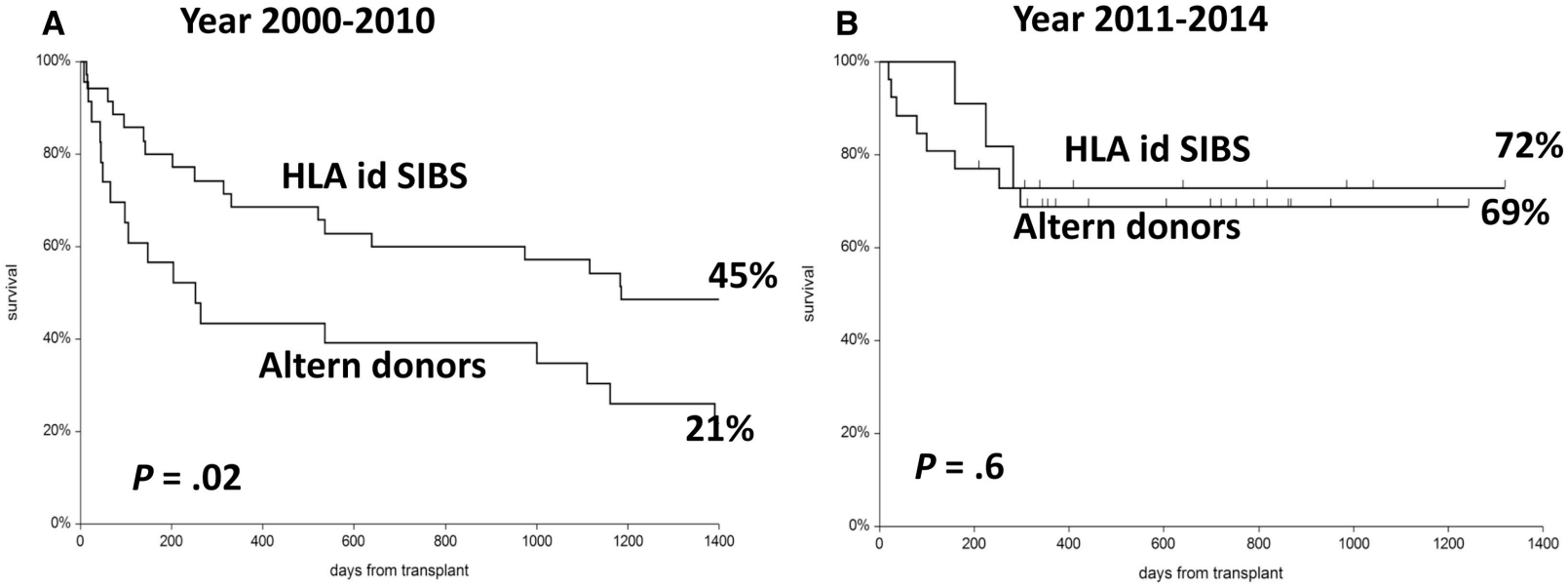
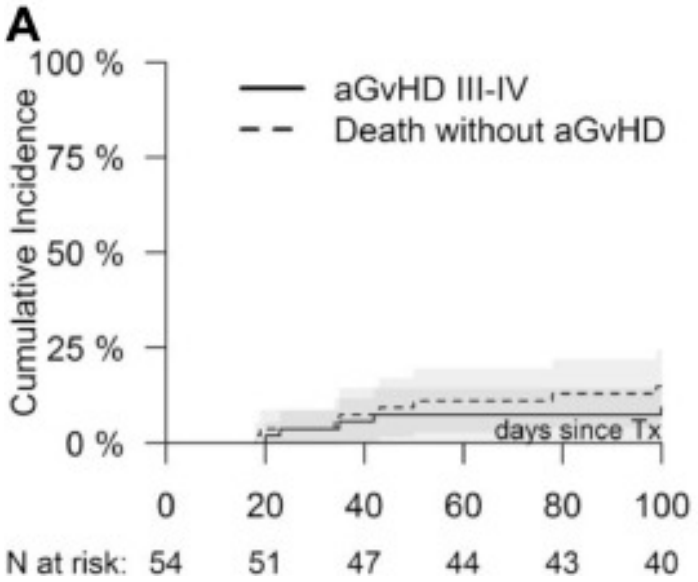
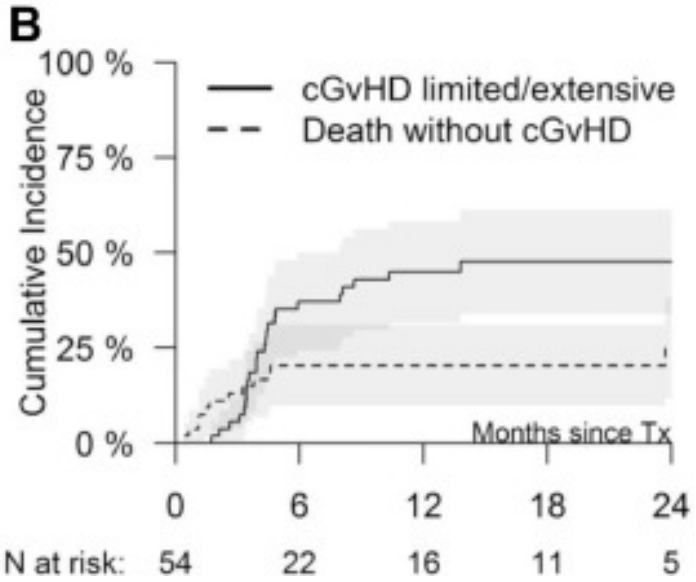


Death within 1 yr	2000-2010	2011-2014
Matched siblings	11 (31%)	3 (27%)
Alternative donors	13 (56%)	8 (31%)

Bregante et al BBMT 2016

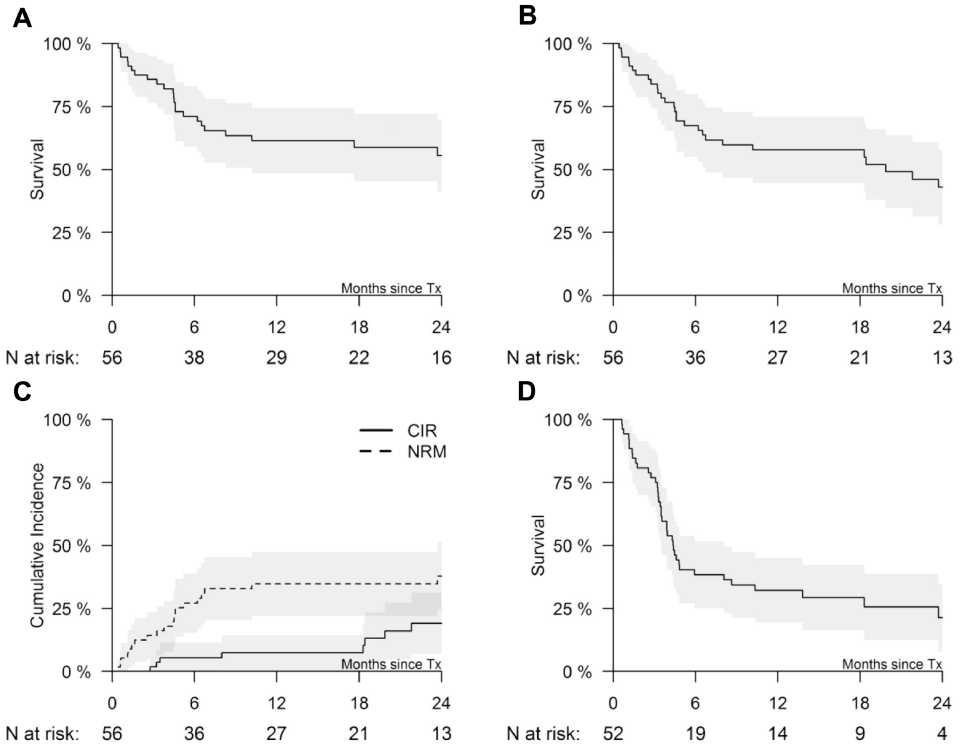
Outcome of mismatched Family (Haplo) Donor transplantation in PMF pts (n= 57 EBMT data) (80% PtCy)





Raj et al, BBMT 2019

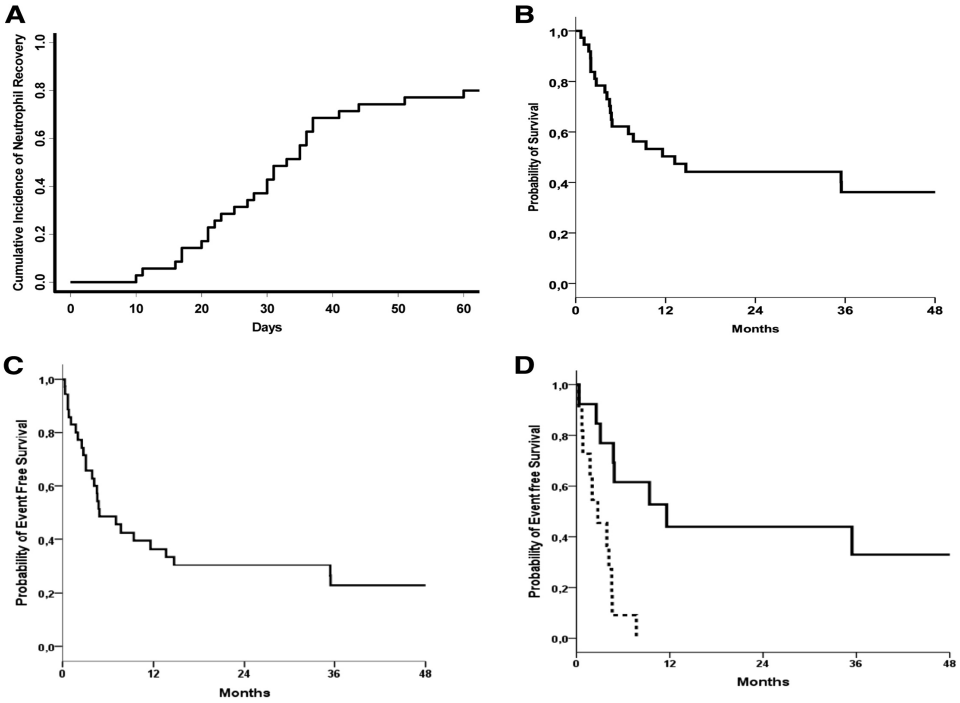
Outcome of mismatched Family (Haplo) Donor transplantation in PMF pts (n= 57 EBMT data) (80% PtCy)



Primary GF: 9%
Secondary GF: 16%

Raj et al, BBMT 2019

Outcome of Cord blood transplantation in PMF pts (n= 35 EBMT data)



A) Neutrophil engraftment: 80%
B) OS: 2-year: 44%
C) EFS:2-year: 30%,
D) EFS in RIC population TCF:44%

NRM at 2 y: 35%

Robin et al, BBMT 2019

Transplant Risk score for myelofibrosis (n=361)

Variable	*Hazard ratio*	*95% CI*	*P*	Scoring
Leukocyte count, x 10^9/l			0.007	1
≤ 25	reference			
> 25	1.70	1.16 to 2.61		
Karnofsky performance score			0.021	1
90 to 100	reference			
< 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	1
≥ 150	reference			
< 150	1.67	1.16 to 2.40		
Age, years			0.006	1
≥ 57	reference			
< 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

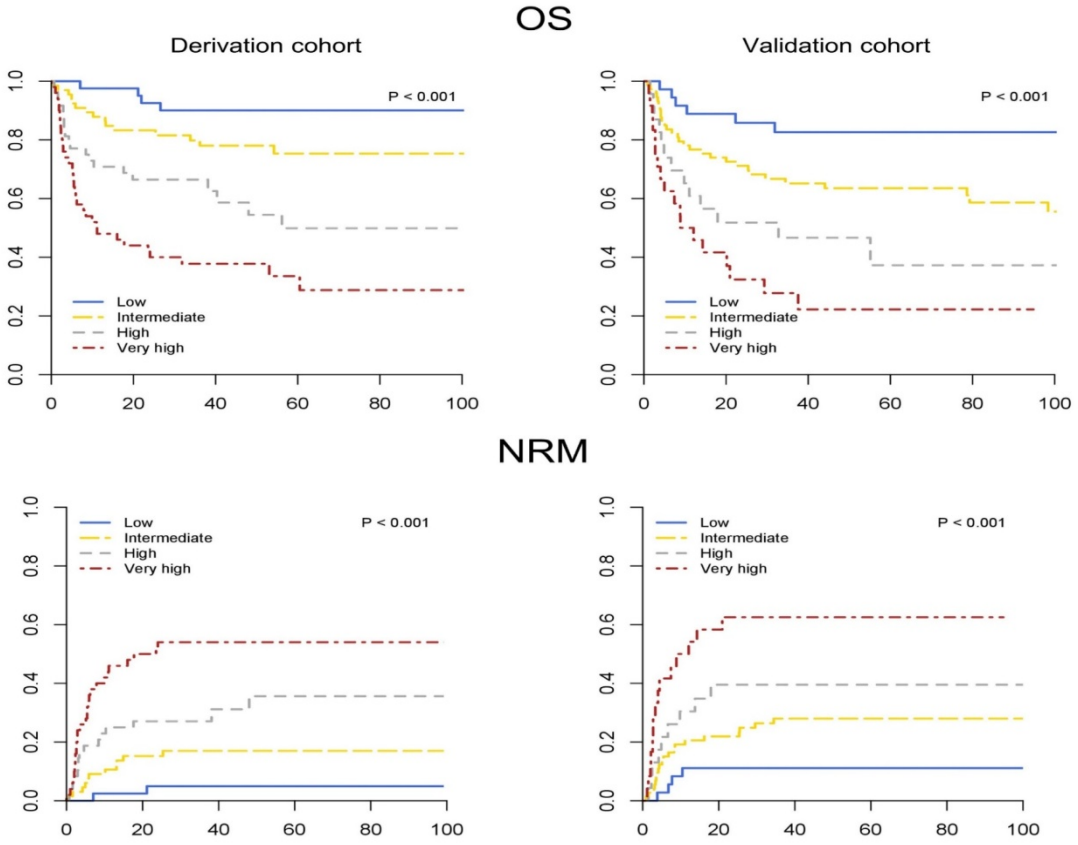
Gagelmann et al., Blood 2019

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

Allogeneic stem cell transplantation from alternative donors in Myelofibrosis: Summary

- Significant worse outcome of alternative donor for myelofibrosis is reported in most of the studies
- Main reason for worse outcome is a higher NRM caused mainly be graft failure but also of GvHD
- Mismatched unrelated donor seems to be worse than matched unrelated donors
- In contrast to other haematological malignancies outcome after Haplo-identical SCT with post Cyclophosphamide is less favourable
- Donor selection remains crucial for myelofibrosis and influences treatment outcome substantially
- Better strategies to prevent graft failure after alternative donor transplantation are needed: e.g Spleensize reduction , DSA?,

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Thanks!

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