
Optimal Timing and Patient Selection for Allogeneic Transplantation in Myelofibrosis

New Drugs in Hematology

Bologna , Royal Hotel Charlton,

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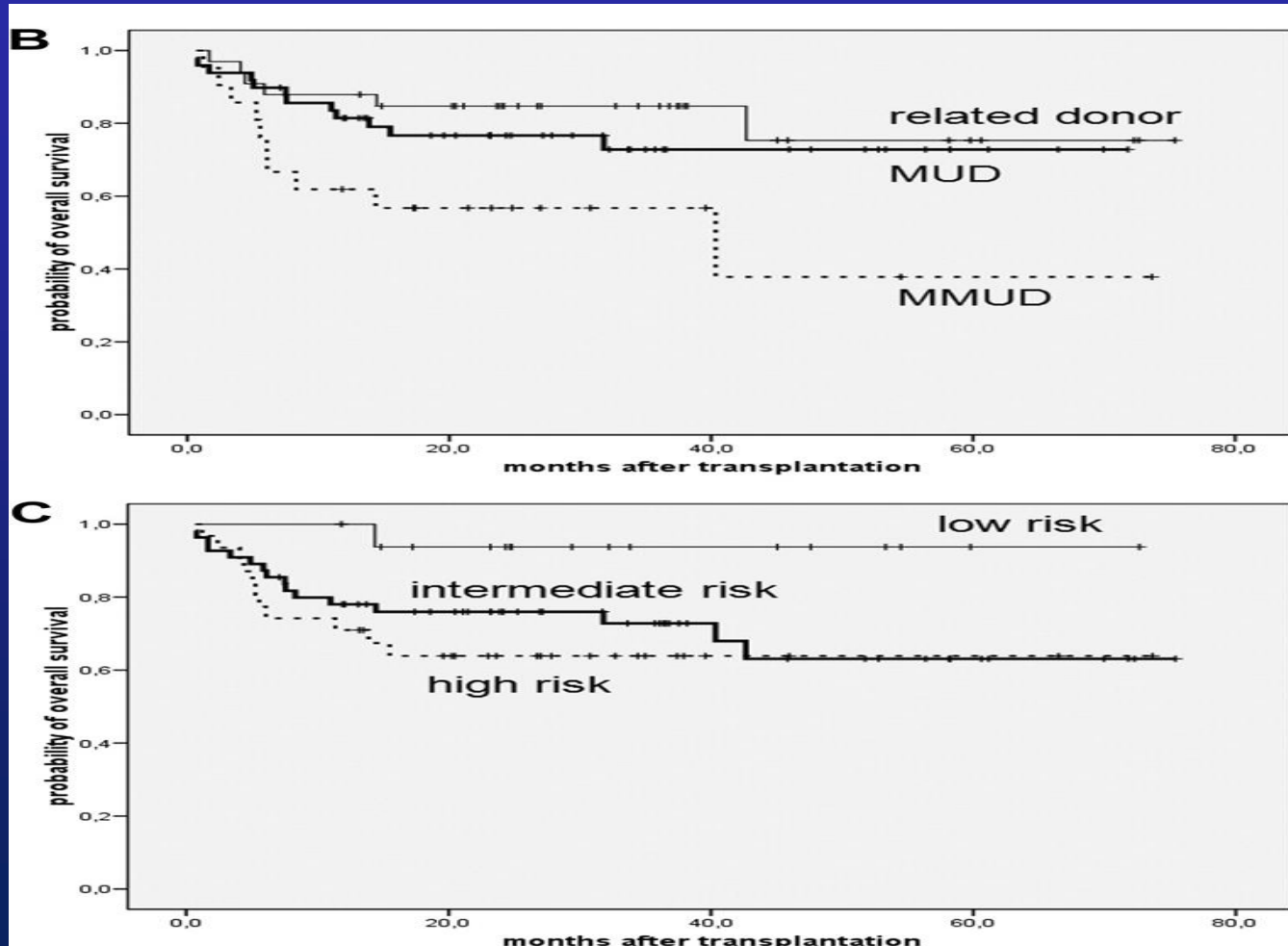
University Medical Center Essen/Germany

Conflict of Interest

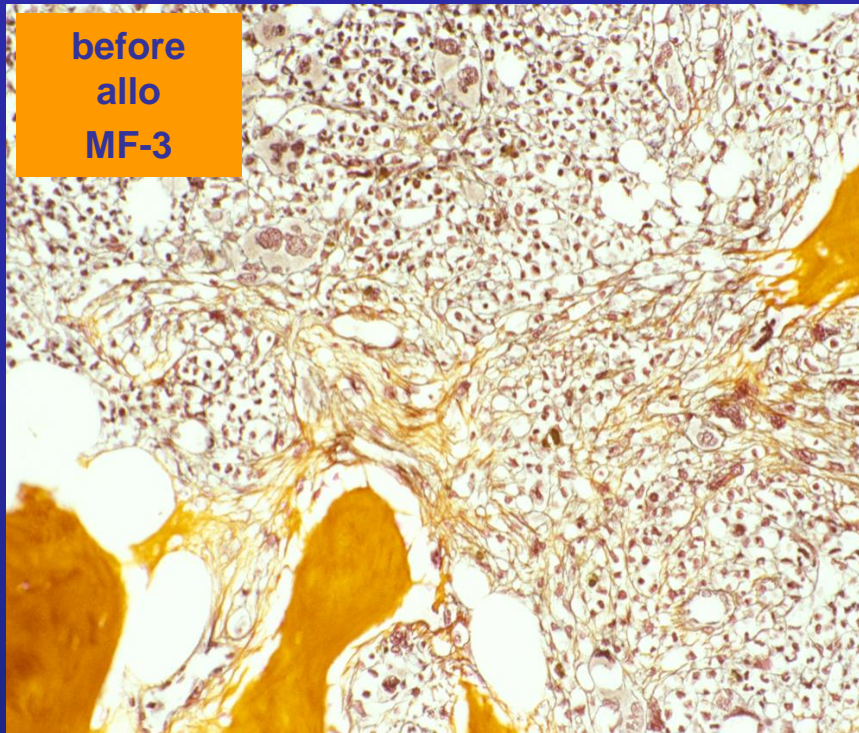
Name of Company	Research support	Employee	Consultant	Major Stockholder	Speaker's Bureau	Advisory Board	Honarium for lectures
Neovii	x		x			x	x
Novartis	x					x	x
BMS	x					x	x
Janssen						x	x
Jazz						x	x
Riemser	x						
GSK							x

Survival of pts with myelofibrosis after busulfan/fludaabine based reduced-intensity allogeneic stem cell transplantation.

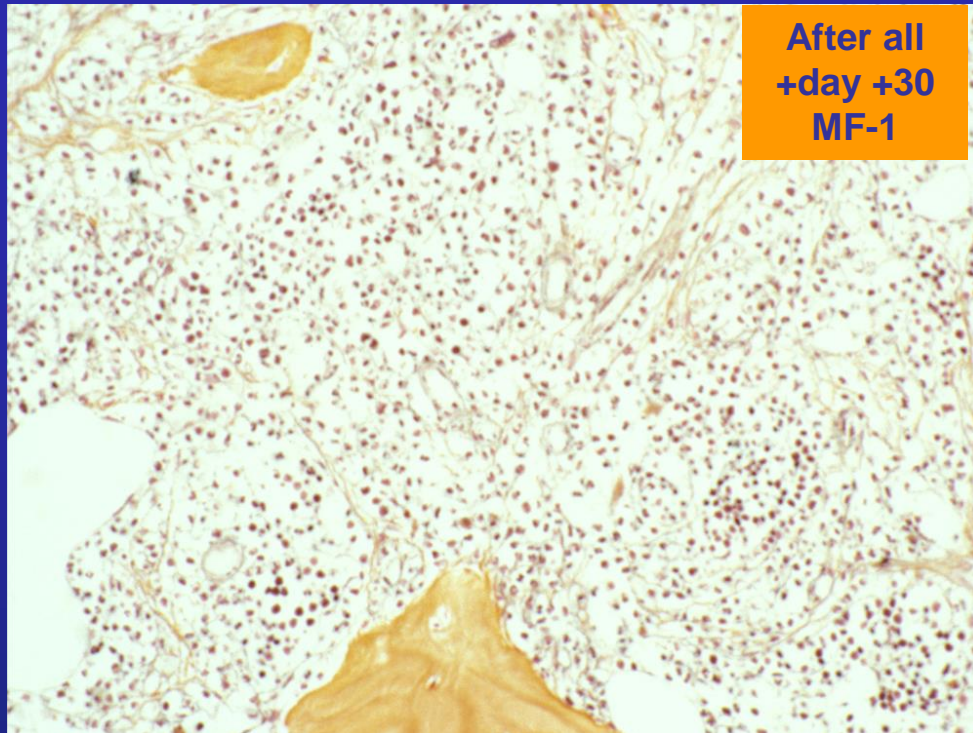
Prospective EBMT study (n=103; med age 55y)



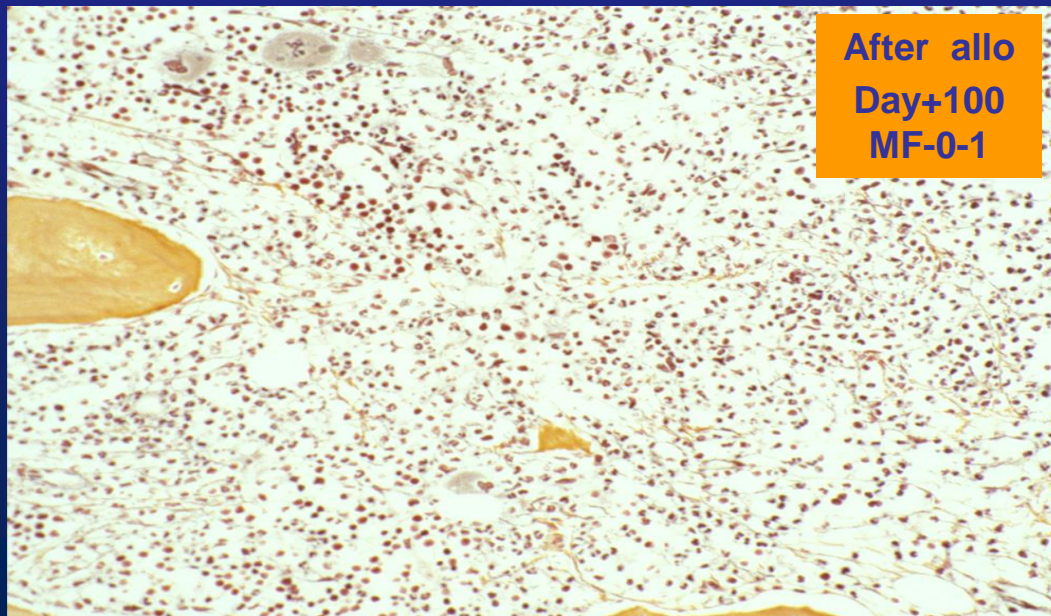
before
allo
MF-3



After all
+day +30
MF-1



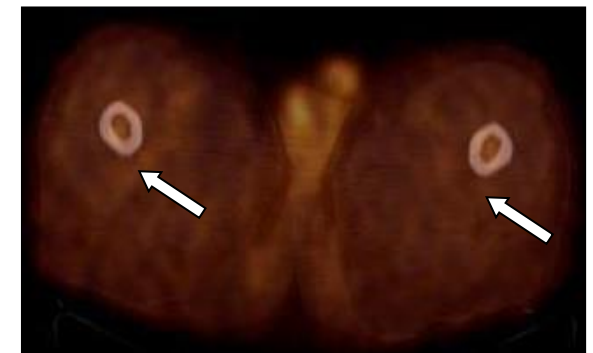
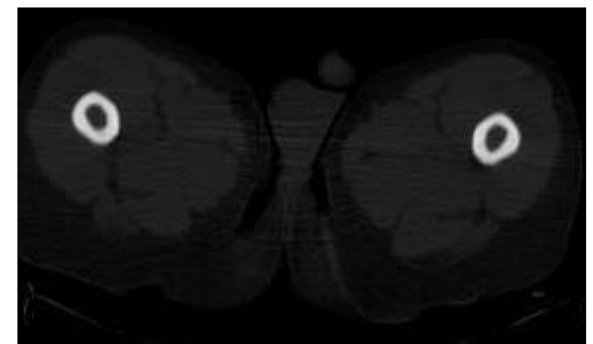
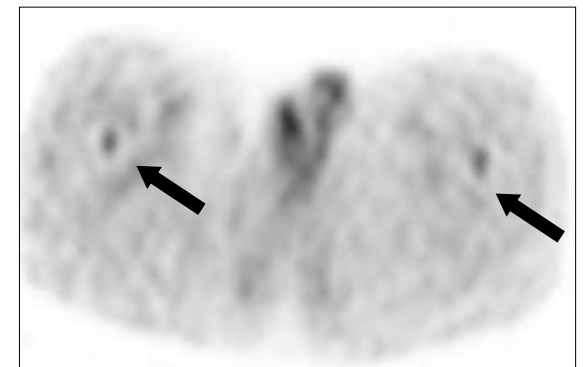
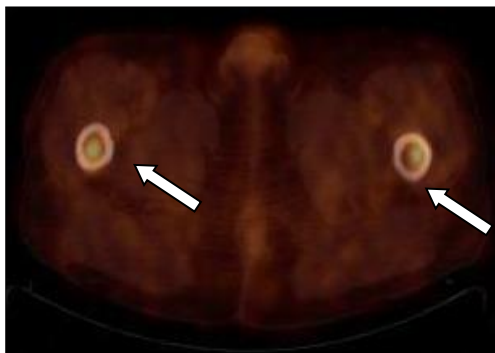
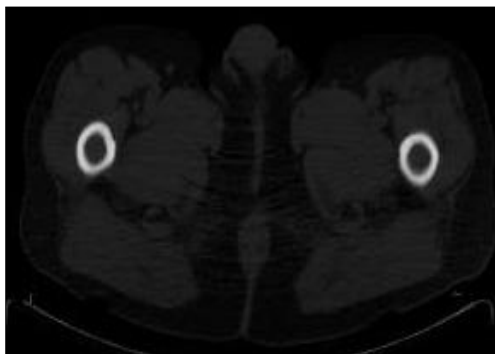
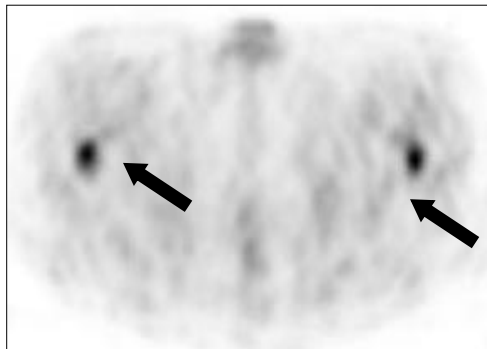
After allo
Day+100
MF-0-1



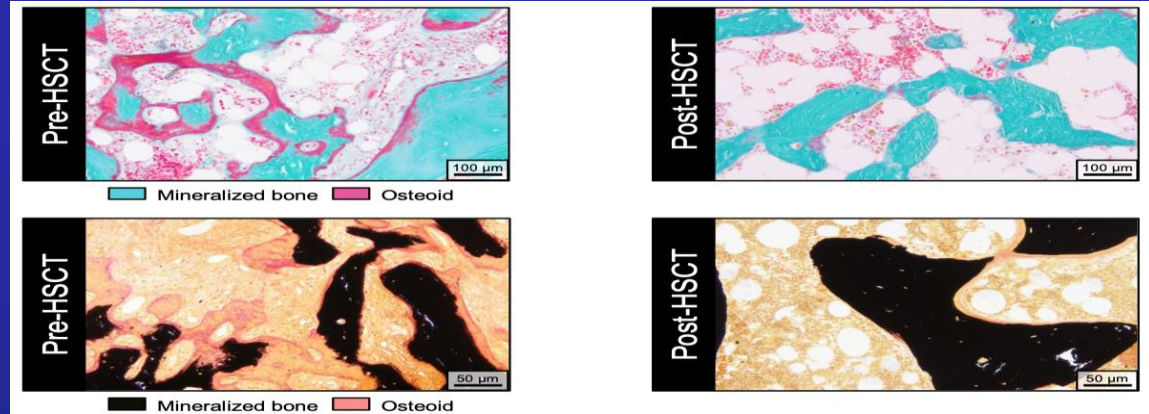
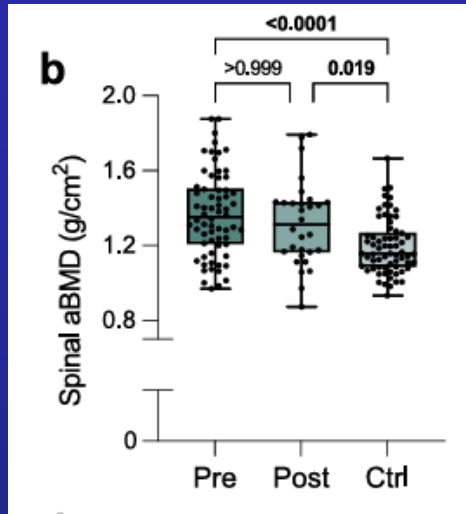
Molecular remission of driver mutation after allo in MF (n=324)

	JAK2	CALR	MPL	P
Day 100	63%	82%	100%	<0.001

PET CT in Myelofibrosis pre and post allogeneic SCT (+100d)

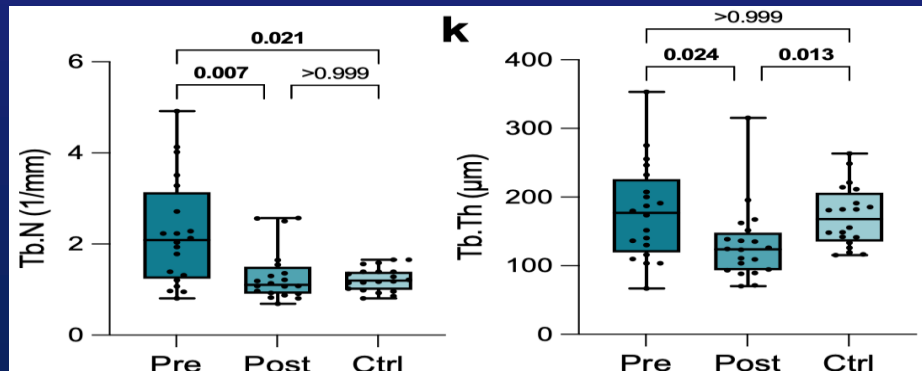


Reconstruction of skeletal homeostasis and resolution of osteosclerosis

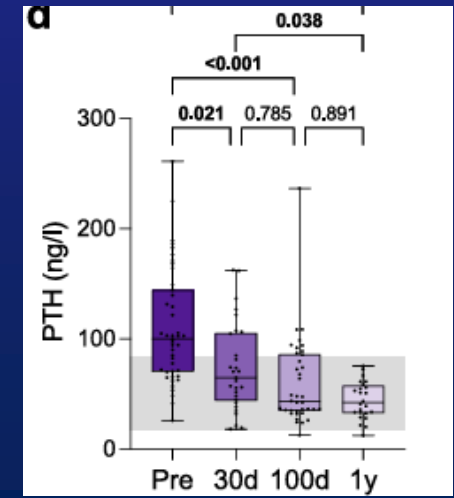
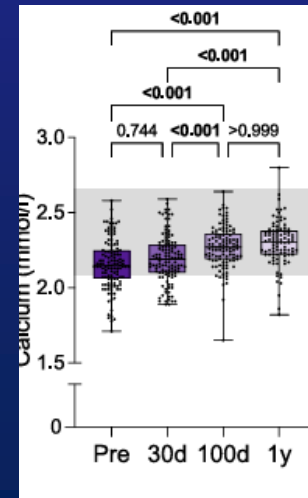


Histological images of trichrome Masson-Goldner-stained sections (top) and of von Kossa-stained sections (bottom) before and after transplantation.

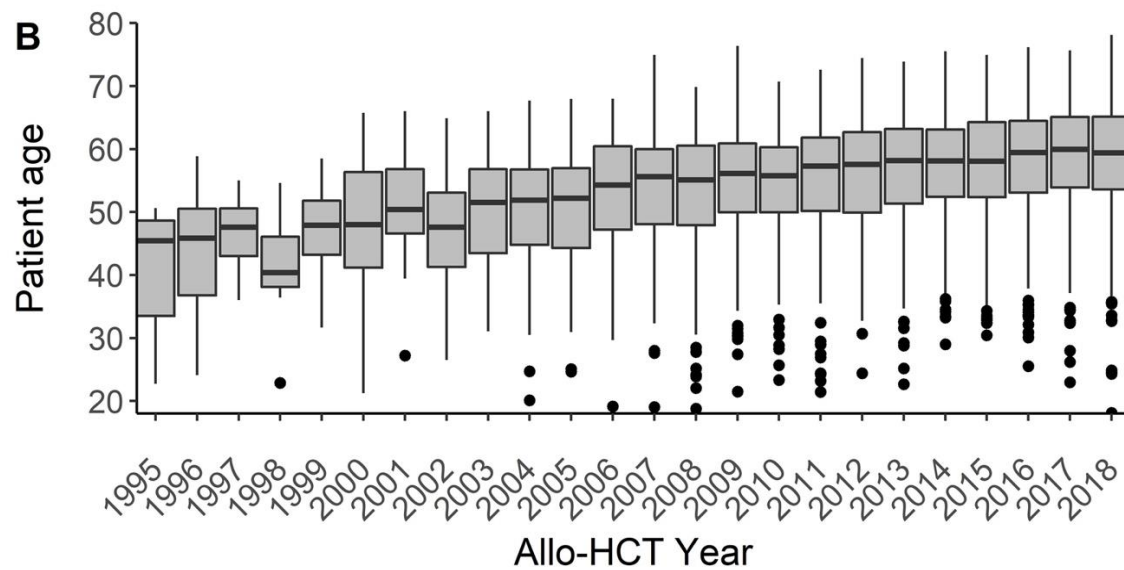
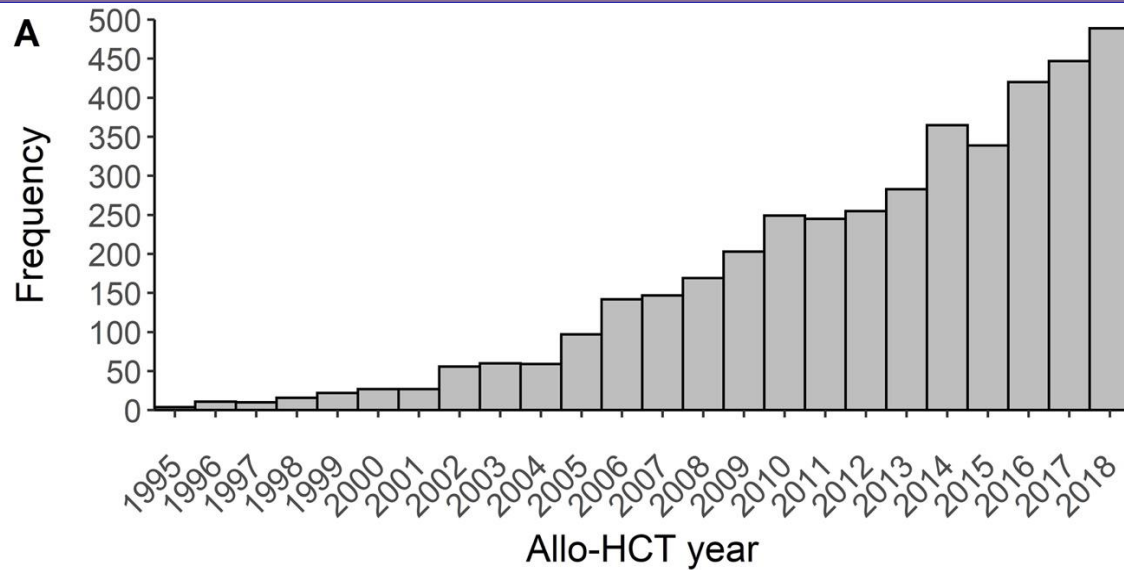
Normalization of increased areal bone mineral density (aBMD).



Trabecular number (Tb.N) and Trabecular thickness (Tb.Th)



Allogeneic SCT in Myelofibrosis over time (EBMT data base)



Optimizing outcome after allogeneic stem cell transplantation for myelofibrosis

1. Cure: ca. 60%
2. Relapse: ca 20-25%
3. TRM: ca 15-20%

Stem Cell
Infusion



Patient
Selection

Pre-
treatment

Conditioning

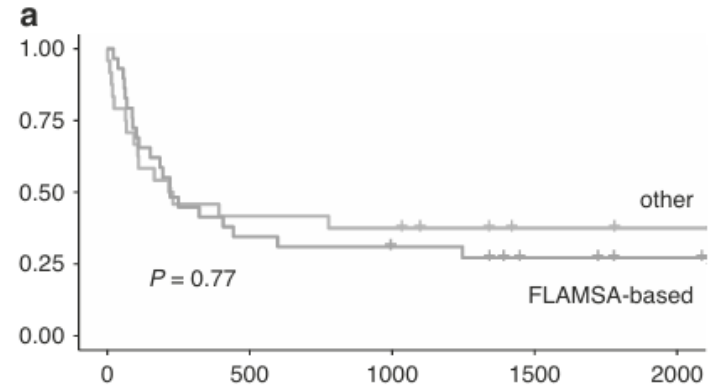
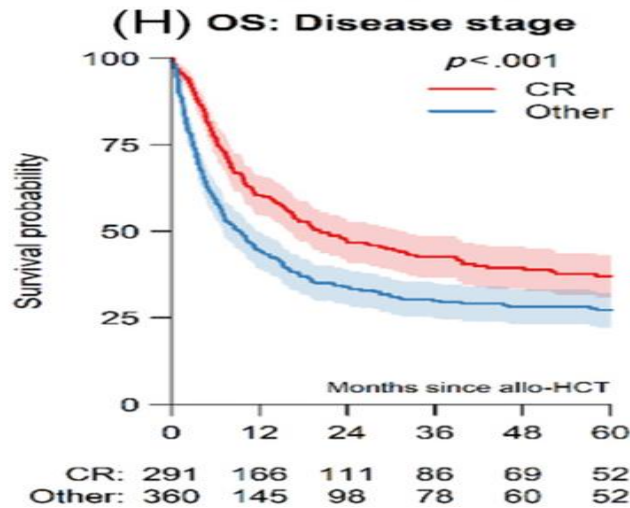
GvHD prophylaxis

Relapse
Prevention



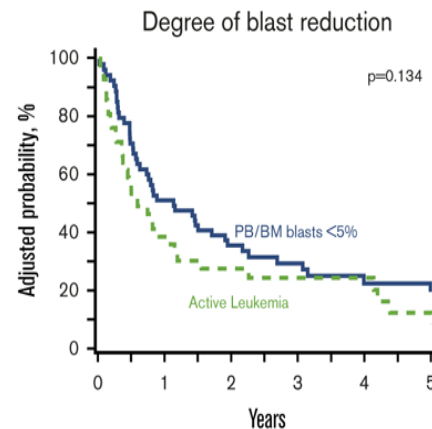
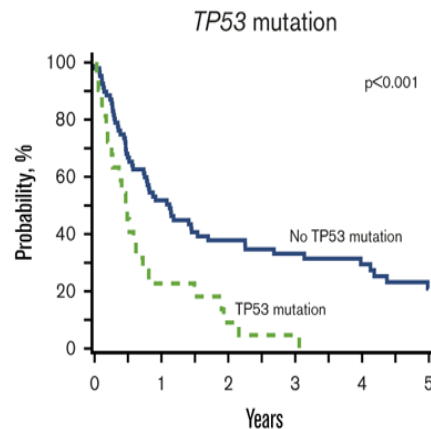
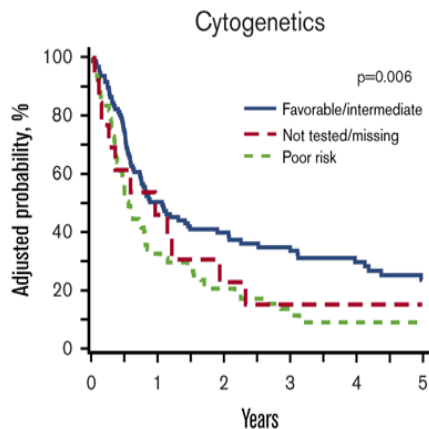
Allogeneic SCT for blast phase of myelofibrosis

Transformed Leukemia after myelofibrosis



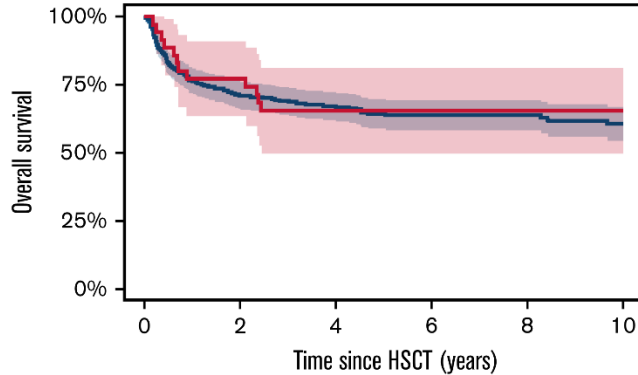
Genetic factors rather than blast reduction determine outcomes of allogeneic HCT in *BCR-ABL* negative MPN in blast phase

OVERALL SURVIVAL

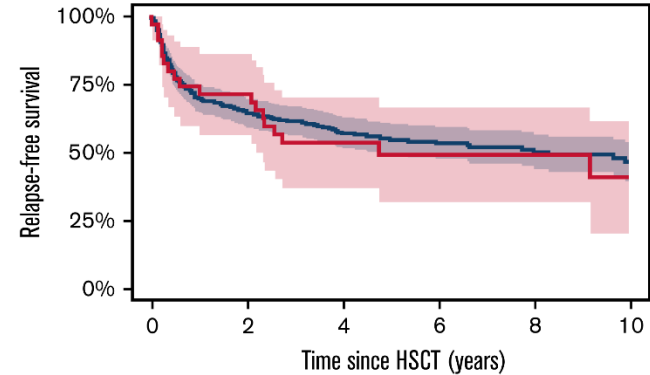


Alchalby et al BBMT 2014
Gupta et al, Blood Adv 2020
Orti et al AJH 2023
Barbulushi et al BMT 2026

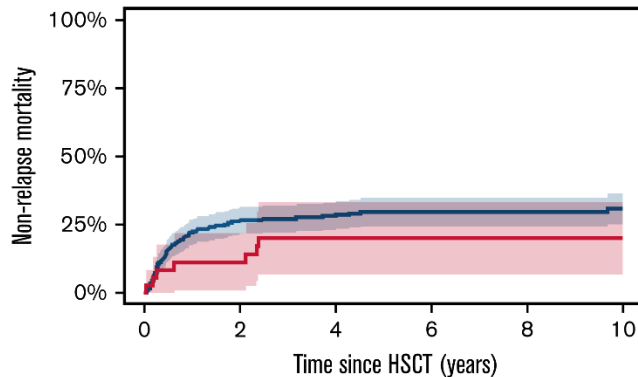
Allogeneic HSCT for Accelerated phase in MF (10-19% Blasts)



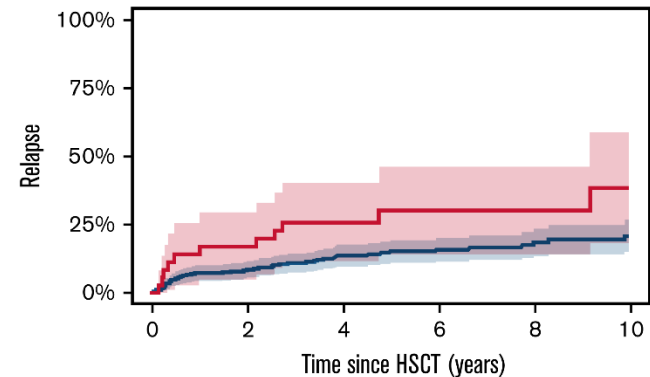
No. at risk		0	2	4	6	8	10
Chronic-phase	314	217	150	101	70	48	
Accelerated-phase	35	27	16	11	9	4	



No. at risk		0	2	4	6	8	10
Chronic-phase	314	199	131	83	54	36	
Accelerated-phase	35	25	14	10	8	3	

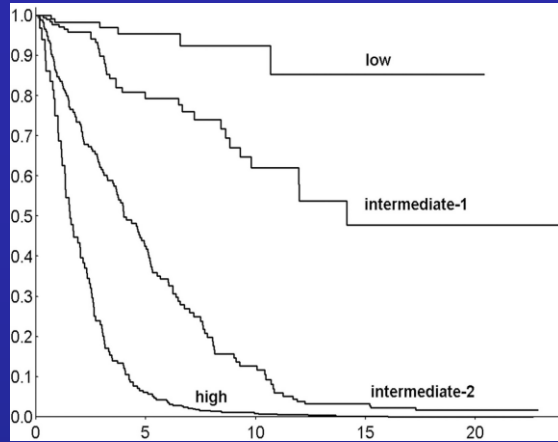


No. at risk		0	2	4	6	8	10
Chronic-phase	314	199	131	83	54	36	
Accelerated-phase	35	25	14	10	8	3	

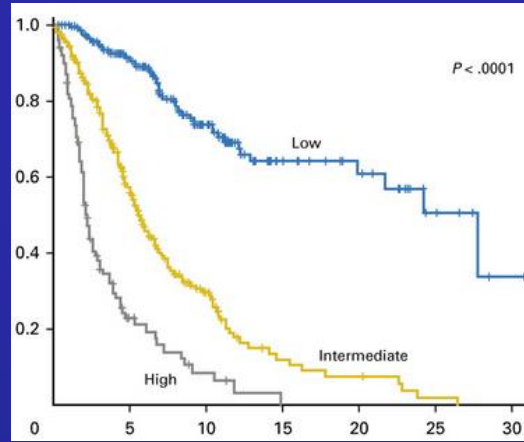


No. at risk		0	2	4	6	8	10
Chronic-phase	314	199	131	83	54	36	
Accelerated-phase	35	25	14	10	8	3	

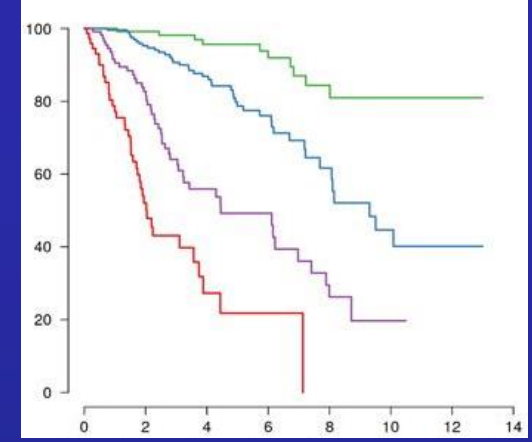
Disease specific scoring systems for myelofibrosis



DIPSS



MIPSS70

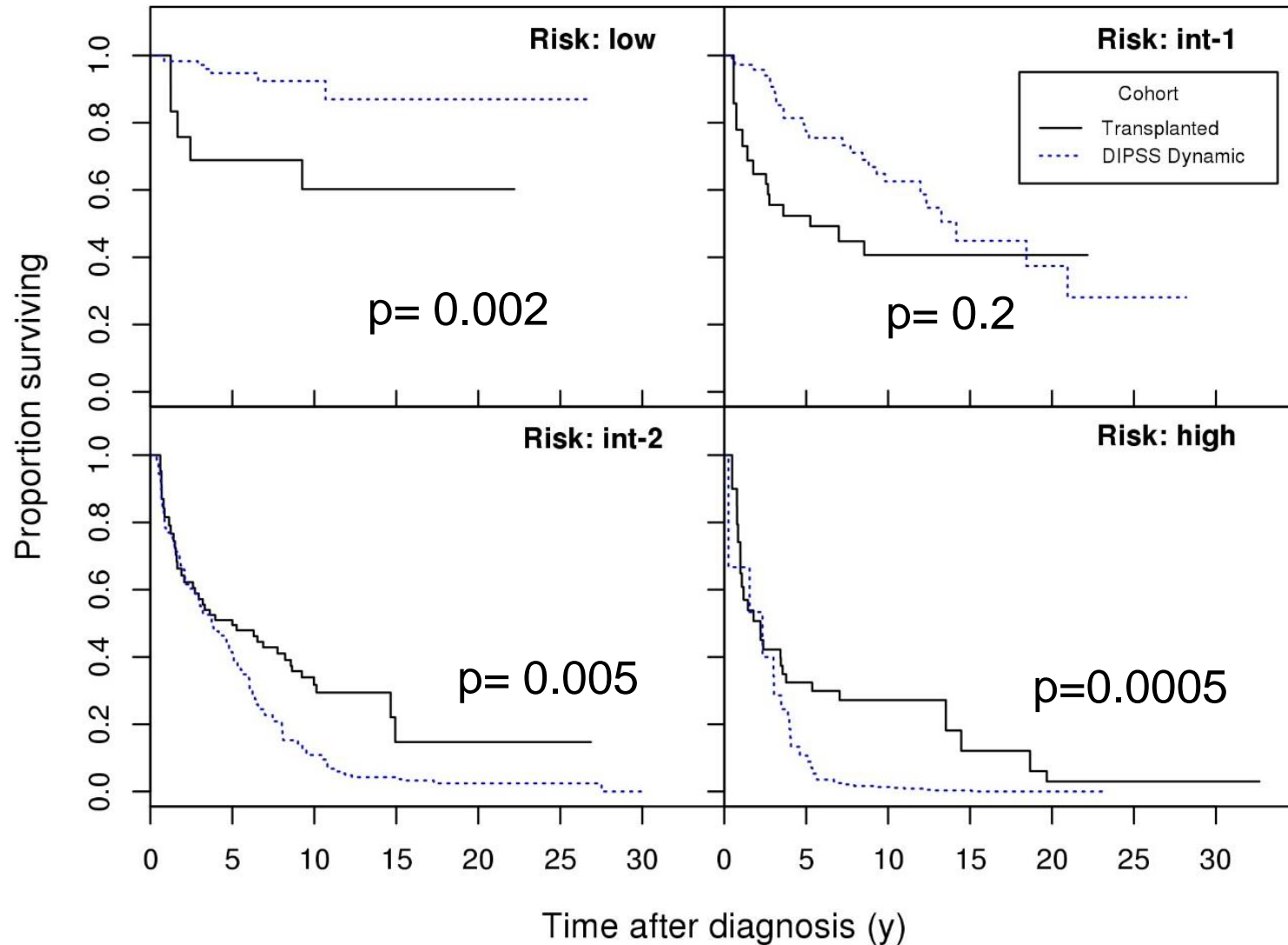


MYSEC

Risk factors

DIPSS	Leukocytes >25 x 10⁹/l	Hb <10 g/dl	Constitutional symptoms	Age >65	Blasts ≥1%				
Score	1	2	1	1	1				
MIPSS70	Leukocytes >25 x 10⁹/l	Hb <10 g/dl	Constitutional symptoms	Fibrosis ≥2	Blasts ≥2%	Non- CALR type 1	Platelets <100 x 10⁹/l	HMR *	HMR* ≥2
Score	2	1	1	1	1	1	2	1	2
MYSEC (post ET/PV)	Platelets <150 x 10⁹/l	Hb <11 g/dl	Constitutional symptoms	Age, years	Blasts ≥3%	Non- CALR			
Score	1	2	1	x 0.15	2	2			

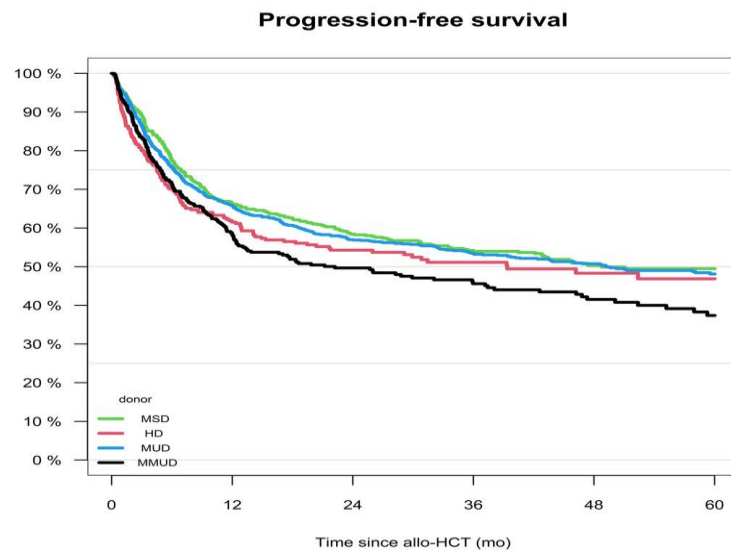
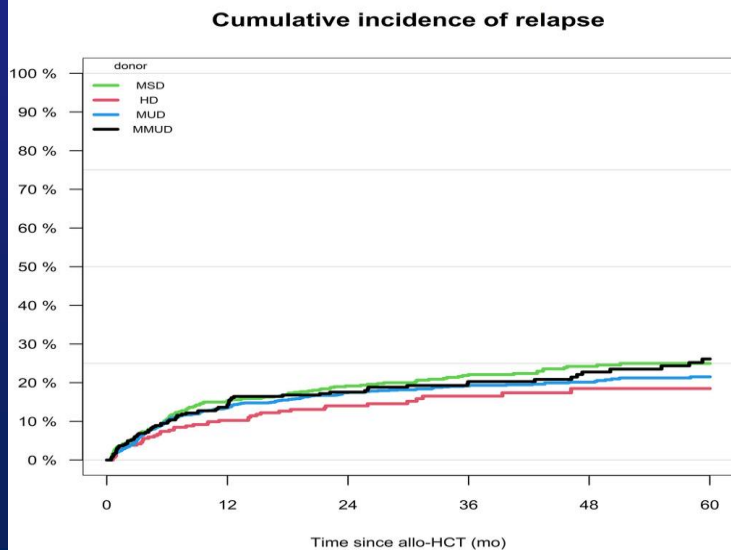
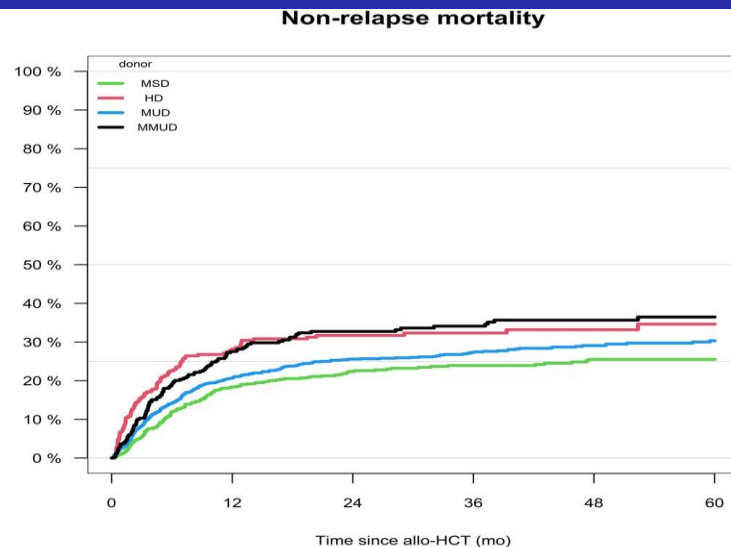
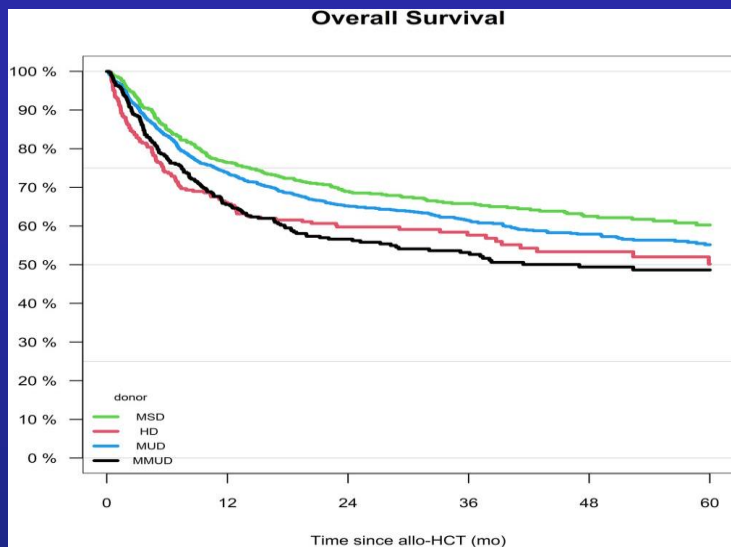
Results of transplant vs non-transplant according DIPSS after left truncation



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

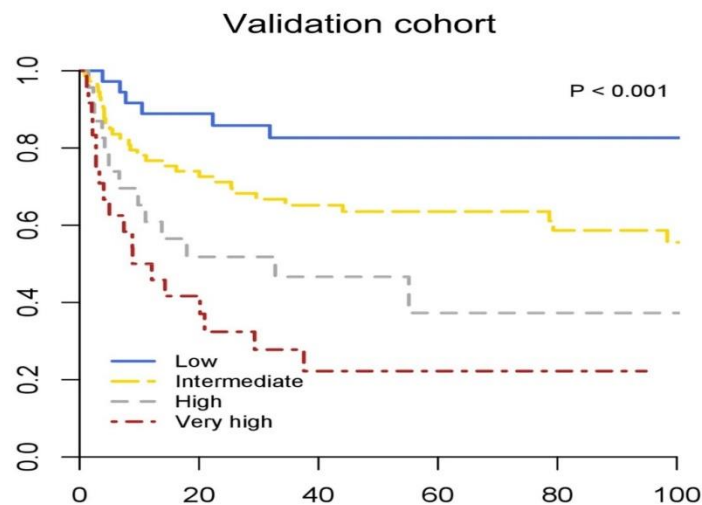
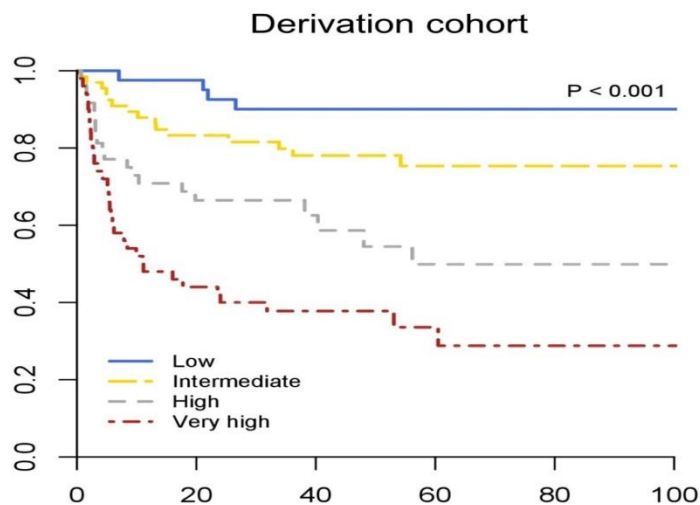
				5 y OS	NRM
Leucocytes > 25 x 10 ⁹ /L	1	0-2	low	90%	10%
Karnofsky ≤ 90	1				
CALR + MPL unmutated	2	3-4	intermediate	77%	22%
Platelets ≤ 150 x 10 ⁹ /L	1	5	high	50%	36%
Age > 57 yrs	1				
Mismatch unrelated donor	2	≥ 6	very high	34%	57%
ASXL-1	1				

Impact of Donor Type on Outcomes After Allogeneic Hematopoietic Cell Transplantation in Myelofibrosis: A Study of EBMT (n=2809)

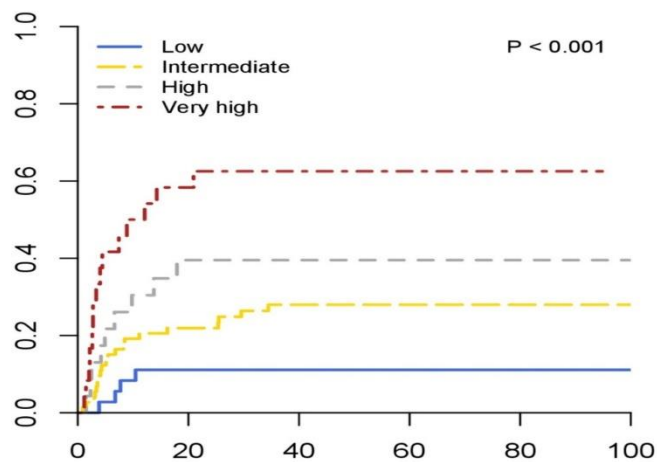
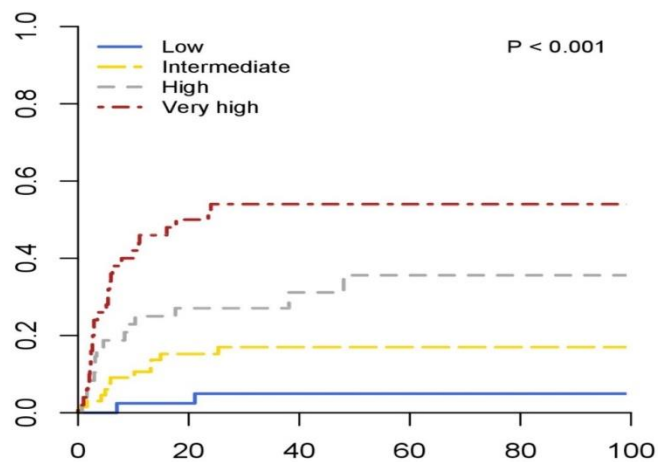


Transplant Risk score for myelofibrosis

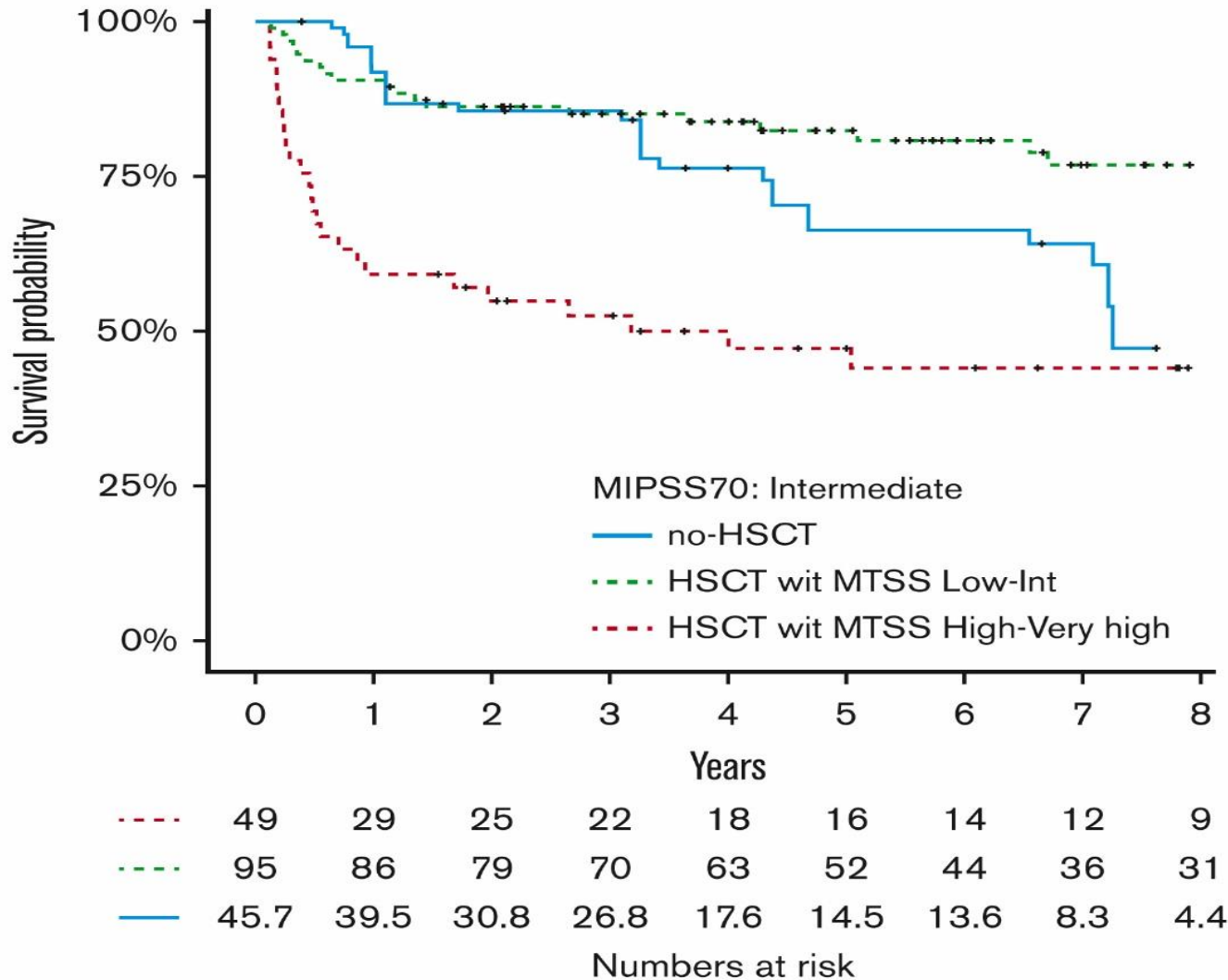
OS



NRM

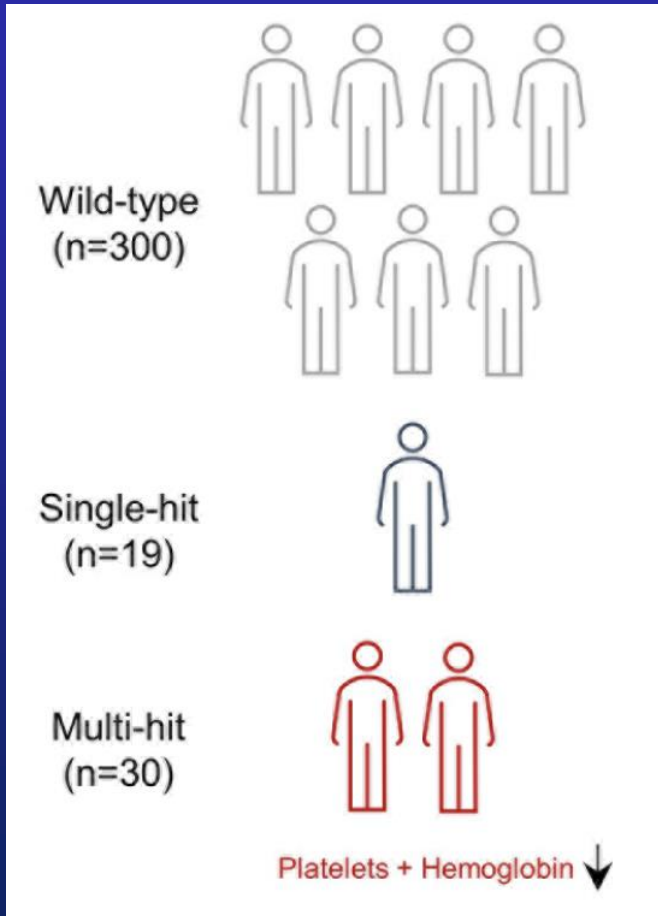


Role of MTSS in transplantation decisions for patients with intermediate MIPSS in primary myelofibrosis (SCT n=241, no SCT n=105)

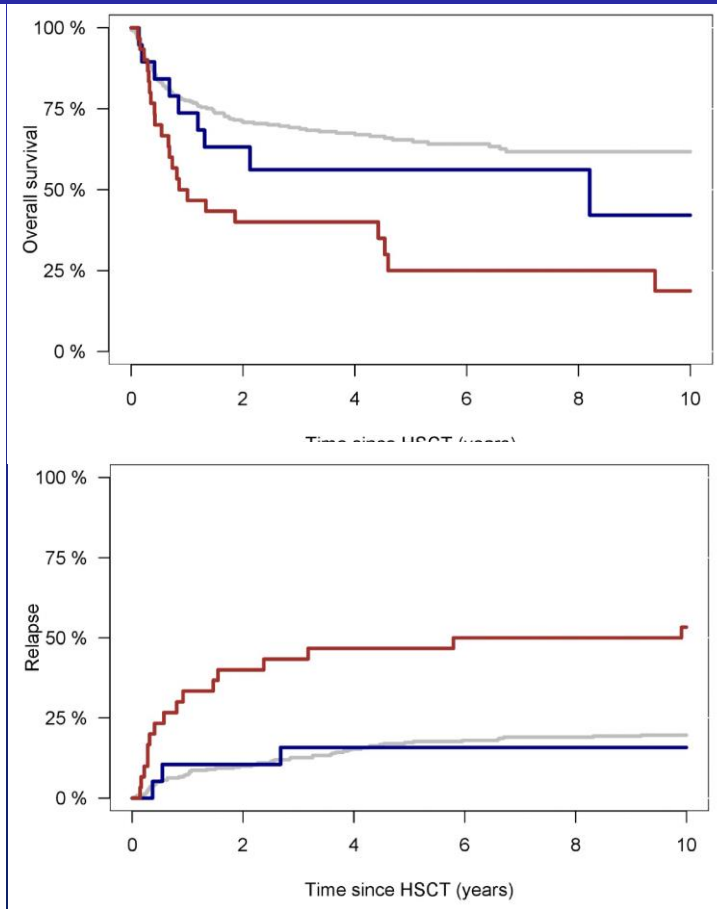


TP53 allelic state and clinical outcomes in patients with myelofibrosis undergoing allogeneic SCT

TP53 allelic state



Clinical outcomes



TP53 multi-hit state defines a high-risk subgroup of patients with myelofibrosis undergoing allogeneic stem cell transplantation.

New updated MTSS2.0

Patient

Older age (>60 years)
Performance status

Disease

Anemia,
thrombocytopenia,
severe leukocytosis and
leukopenia

Shorter time to SMF
Portal vein thrombosis

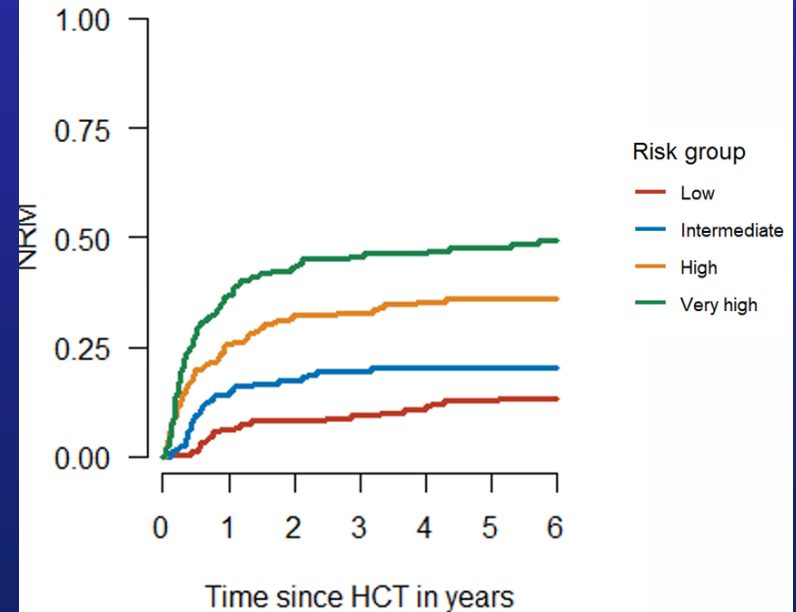
Molecular

Complex karyotype
Non-CALR/MPL
ASXL1, TP53, U2AF1, and
RAS pathway mutations

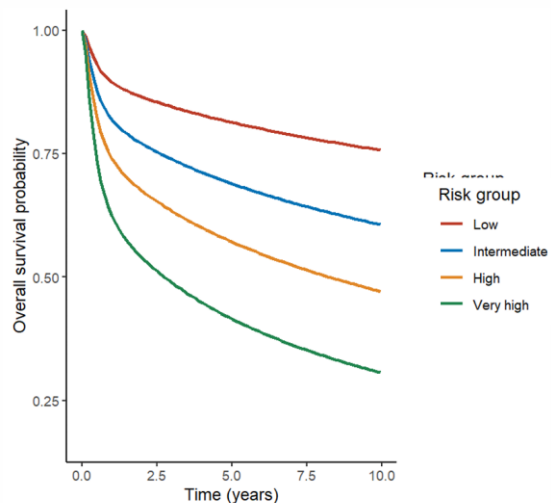
Transplant

Haploidentical and
mismatched unrelated
donors

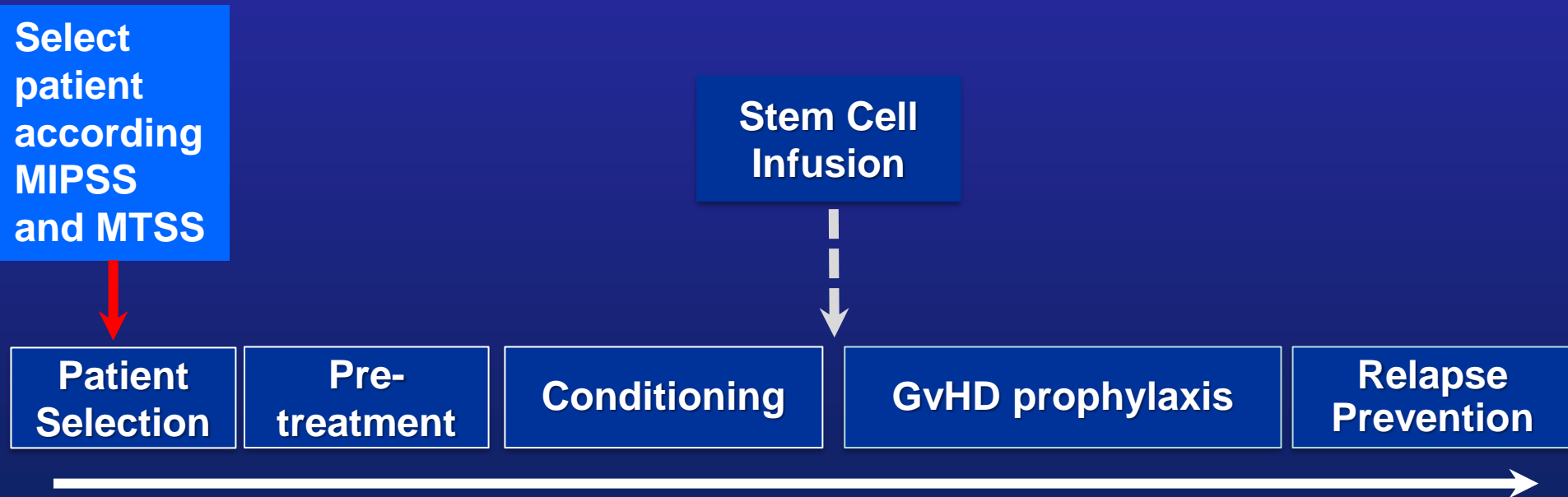
Non-relapse mortality



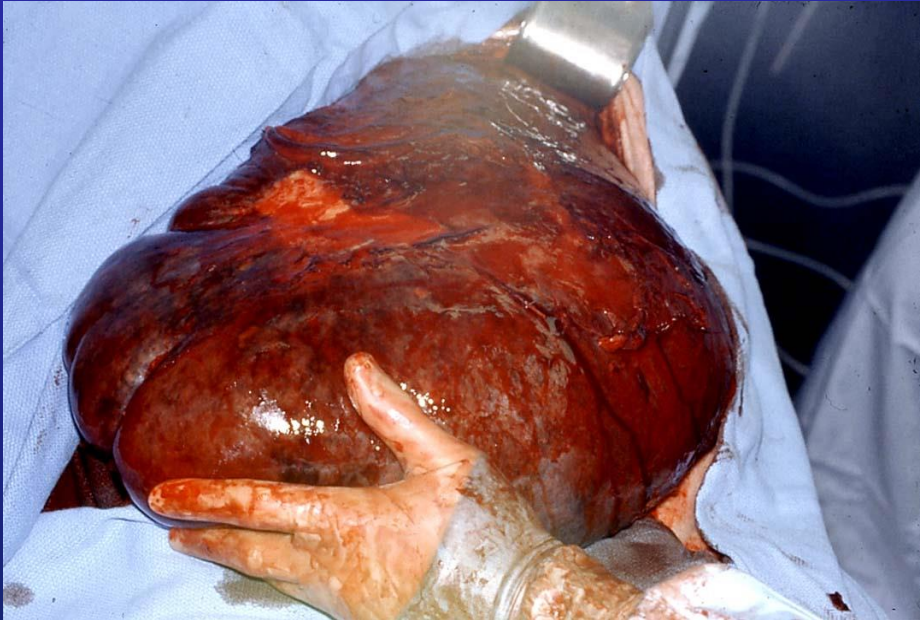
Overall survival



Approaches to improve outcome after allogeneic stem cell transplantation



Splenomegalie bei MPN

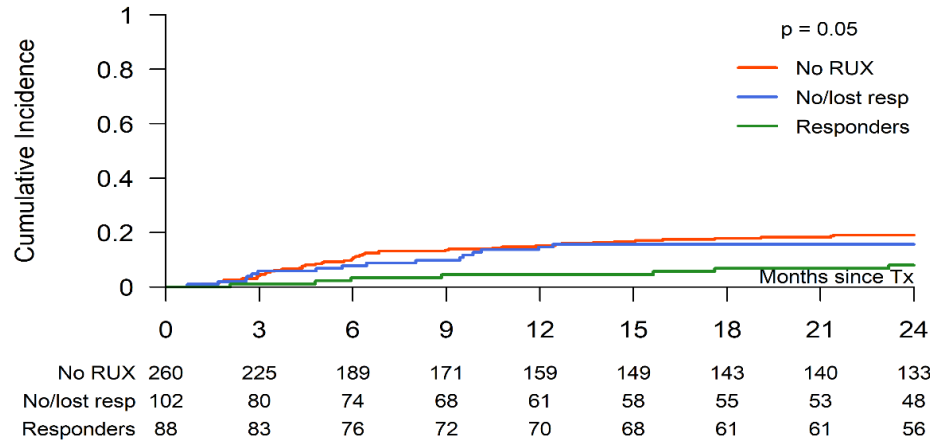


Reducing the spleen size by:

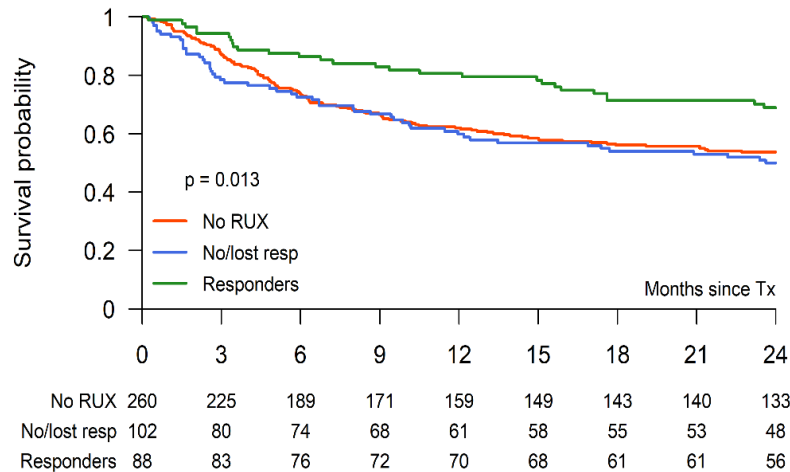
1. JAK inhibitor
2. Splenectomy
3. Splenic irradiation

JAK inhibitor prior alloSCT

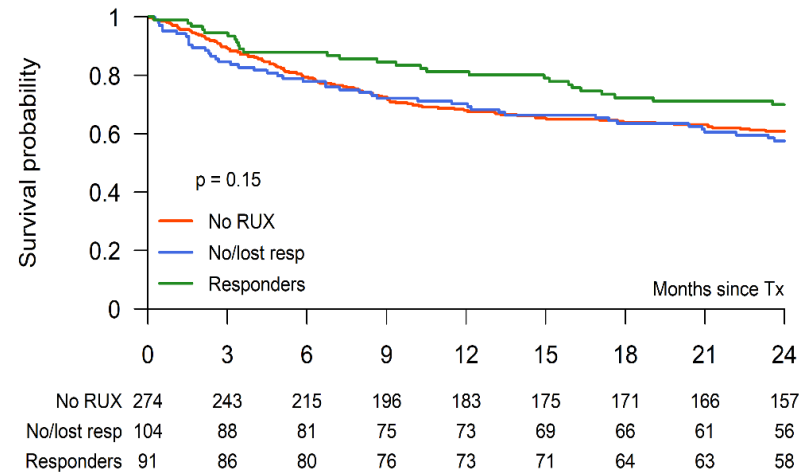
Relapse Incidence by treatment



Event-free Survival by treatment



Overall Survival by treatment



JAK inhibitor as GvHD prophylaxis (peri-transplant)

PERI-group

n = 33

30
3

OR

Time in days: -9, -8, -7, Bu/Flu conditioning (RIC), -1, 0, +1, +2, +3, +4, +5, +6, +21, +22, +27, +28, +29

Ruxolitinib: 2 x 5 mg daily (days -1 to +6), 1 x 5 mg daily (days +21 to +29)
 Fedratinib: 1 x 200 mg daily (days -1 to +6), 1 x 100 mg daily (days +21 to +29)

Stem cell infusion

PRE-group

n = 38

33
5

OR

Time in days: -9, -8, -7, Bu/Flu conditioning (RIC), -1, 0, +1, +2, +3, +4, +5, +6, +21, +22, +27, +28, +29

Ruxolitinib: tapering (days +1 to +6)
 Fedratinib: tapering (days +1 to +6)

Stem cell infusion

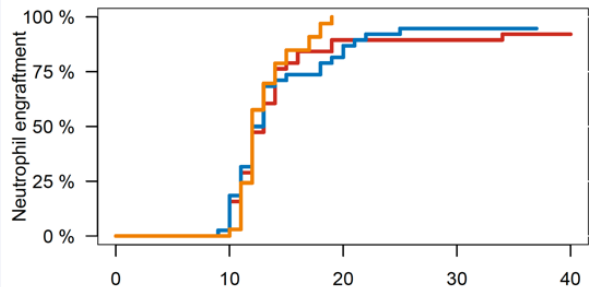
NON-group

n = 38

OR

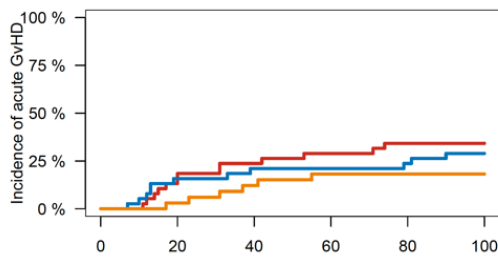
Time in days: -9, -8, -7, Bu/Flu conditioning (RIC), -1, 0, +1, +2, +3, +4, +5, +6, +21, +22, +27, +28, +29

Ruxolitinib: X
 Fedratinib: X



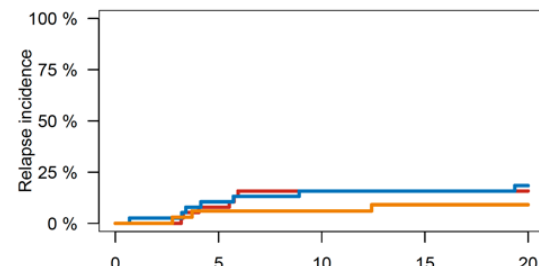
No. at risk	Time since transplant (days)			
	0	10	20	30
NON 38	37	4	4	3
PRE 38	37	6	1	0
PERI 33	33	0	0	0

Acute GvHD grade II-IV



JAKinhibition	Time since transplant (days)				
	0	20	40	60	80
NON 38	33	29	27	24	23
PRE 38	31	28	28	27	23
PERI 33	32	29	27	27	26

Relapse



JAKinhibition	Time since transplant (months)			
	0	5	10	20
NON 38	33	29	26	26
PRE 38	30	21	20	14
PERI 33	28	20	10	9

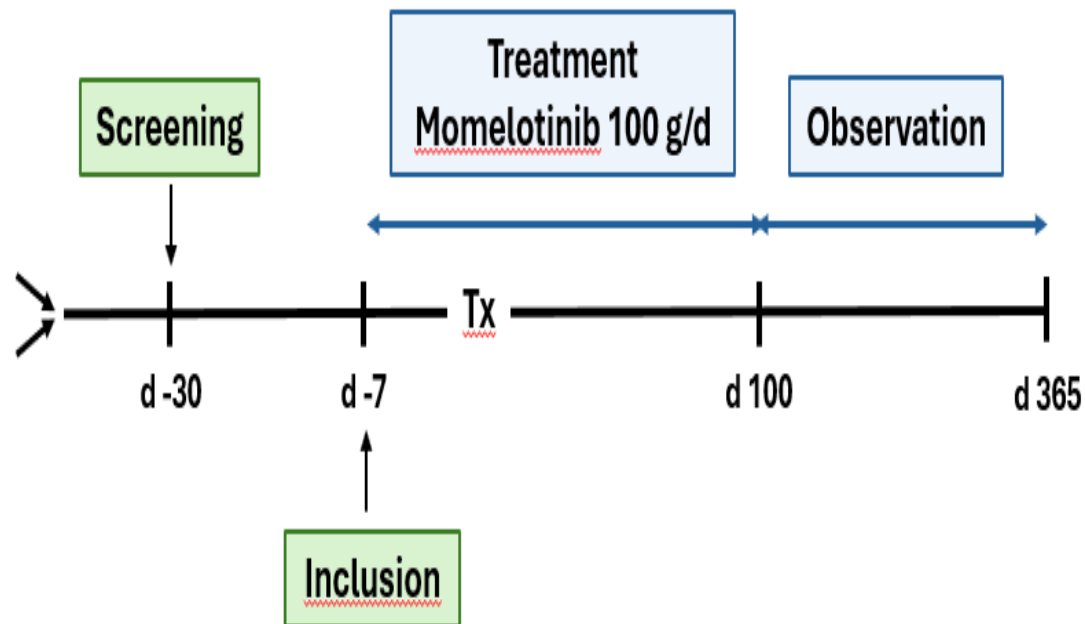
MoST-MF: A Phase 1/2 Study of Peri- and Post-Transplant Mometotinib in Allogeneic Hematopoietic Cell Transplantation for Myelofibrosis

Patients, n = 50:

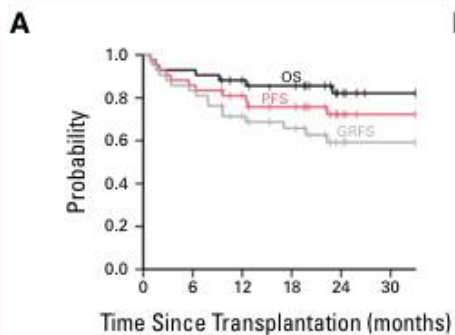
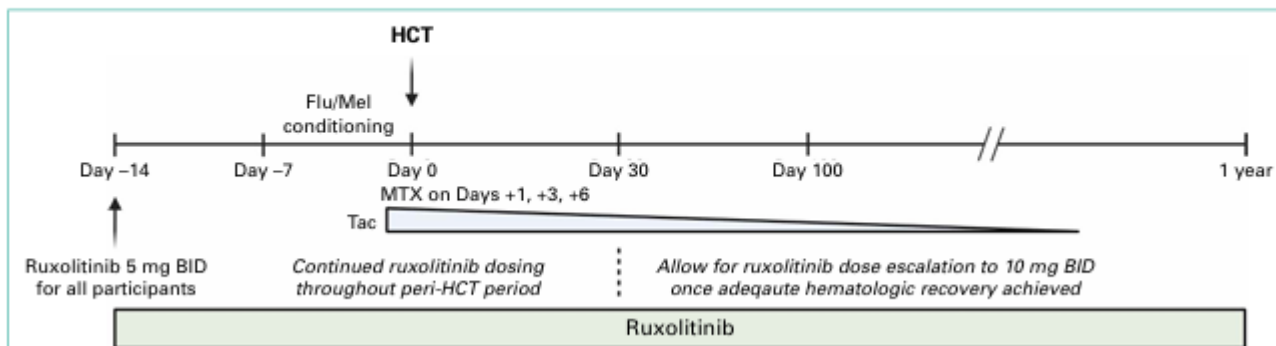
- ≥ 18 years
- First allo HCT
- Diagnosis WHO:
PMF, post-PV, post-ET
- Chronic-phase
- DIPSS ≥ intermediate
- MIPSS70+v2.0 ≥ intermediate



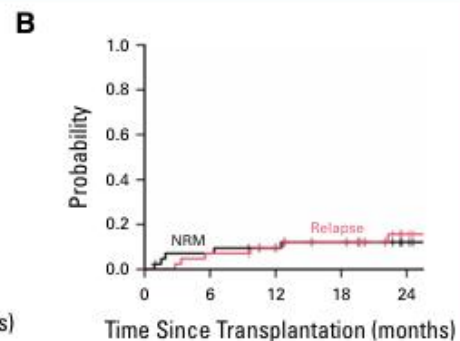
Mometotinib
or
other JAK inhibitor



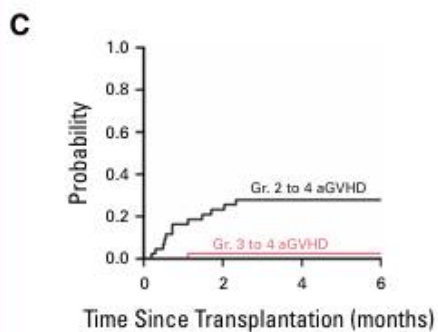
Ruxolitinib During and After HCT for Myelofibrosis



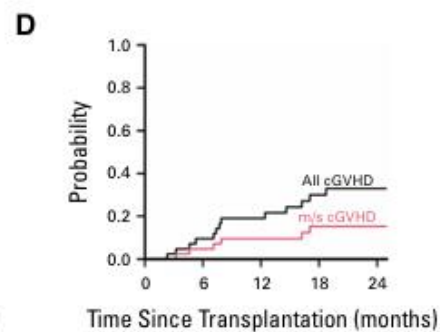
No. at risk	0	6	12	18	24	30
OS	43	39	34	31	22	18
PFS	43	36	31	27	18	15
GRFS	43	35	27	23	15	13



No. at risk	0	6	12	18	24
NRM	43	36	31	27	18
Relapse	43	36	31	27	18

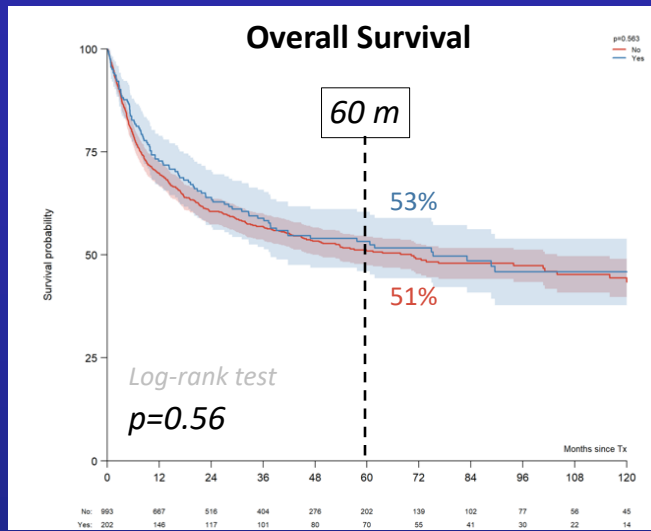


No. at risk	0	2	4	6
Gr 2 to 4 aGVHD	43	32	29	28
Gr 3 to 4 aGVHD	43	39	37	36

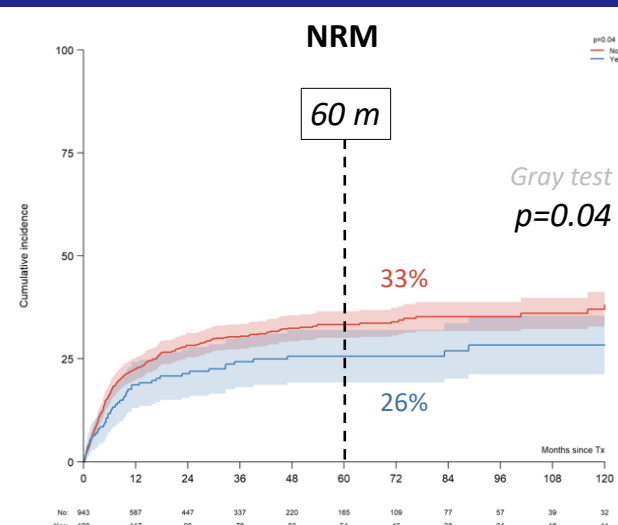
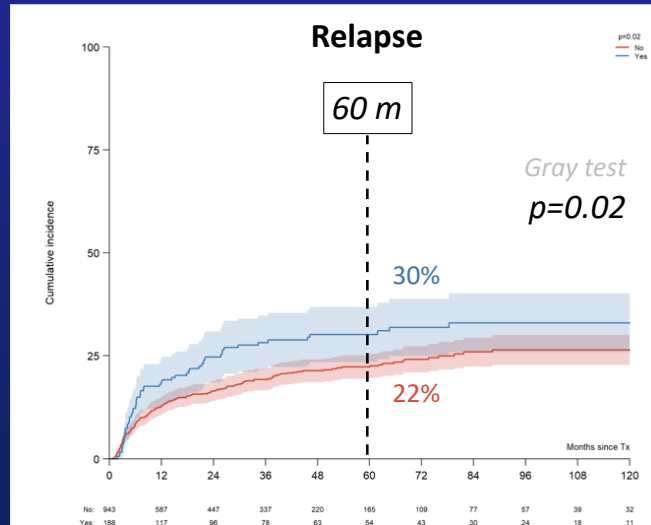


No. at risk	0	6	12	18	24
All cGVHD	43	32	25	18	11
m/s cGVHD	43	34	27	21	14

Splenectomy and impact on allo-HCT (EBMT data)

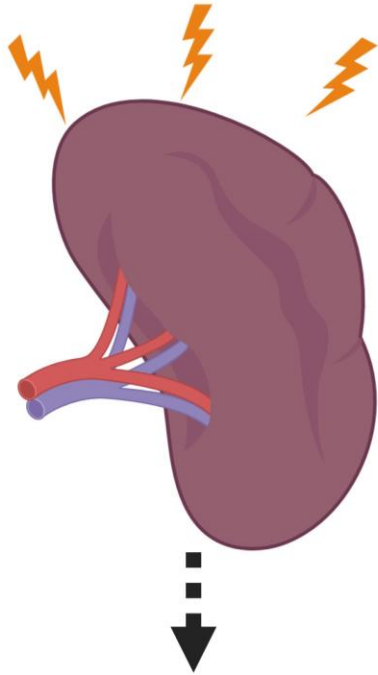


- Total of 1195 patients
- Median age=57.9
- PMF=70%
- Splenectomy; n=202 (16.9%)
- Flu Mel 77.9%; Flu Bu 22.1%



MVA: Splenectomy associates with improved engraftment and lower NRM counterbalanced by higher RI, with no resultant OS advantage.

Splenic irradiation – global collaborative analysis



as part of transplant platform within 2 weeks before transplant

Significantly reduces

- spleen size
- relapse incidence

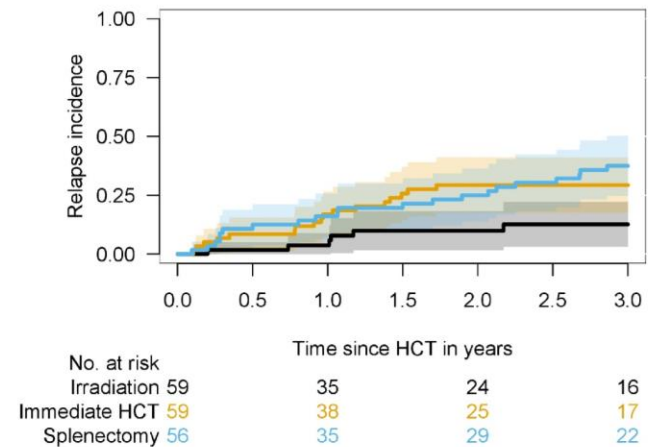
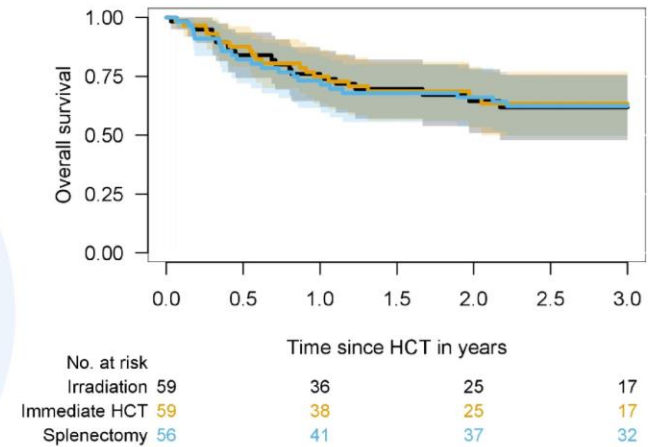
and shows similar

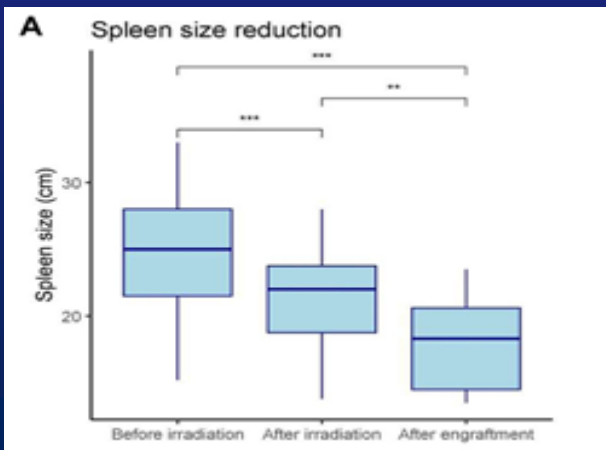
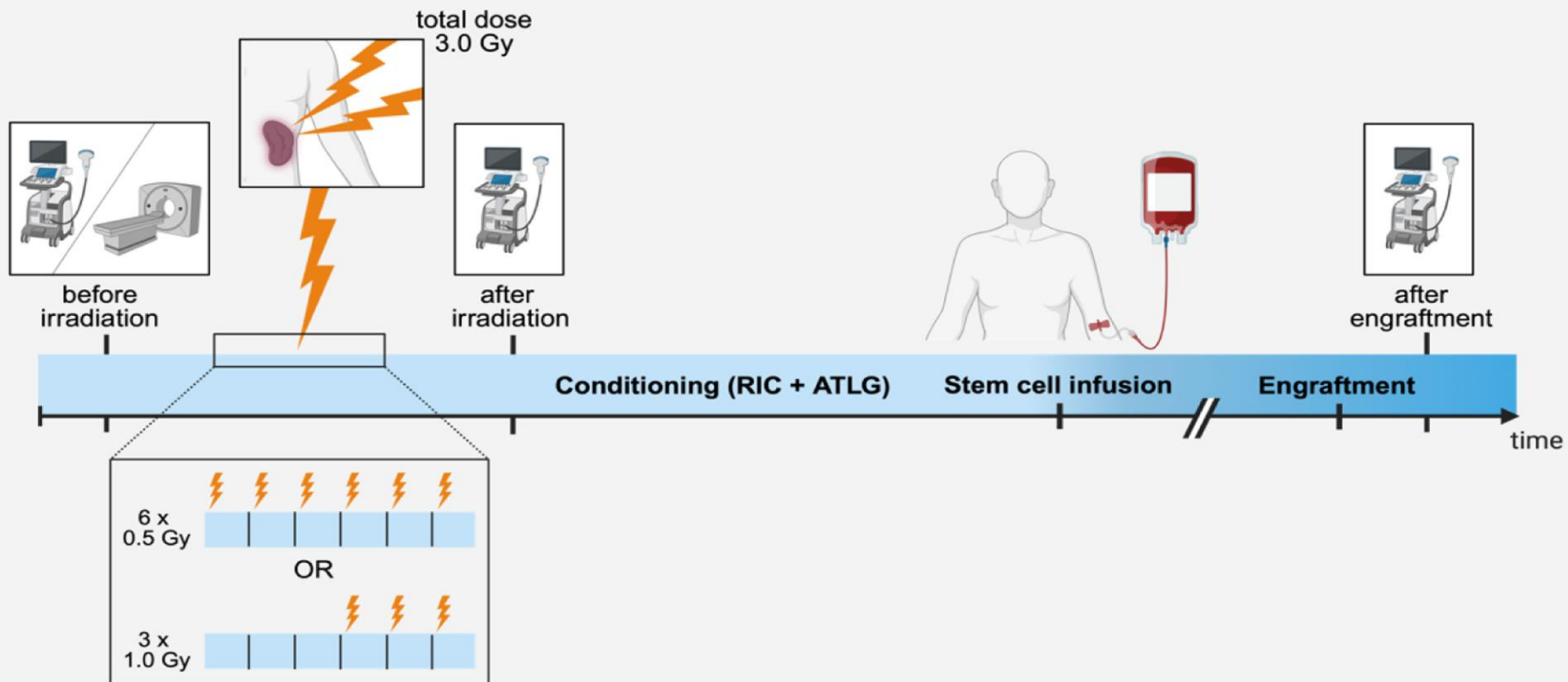
- overall survival
- non-relapse mortality

versus

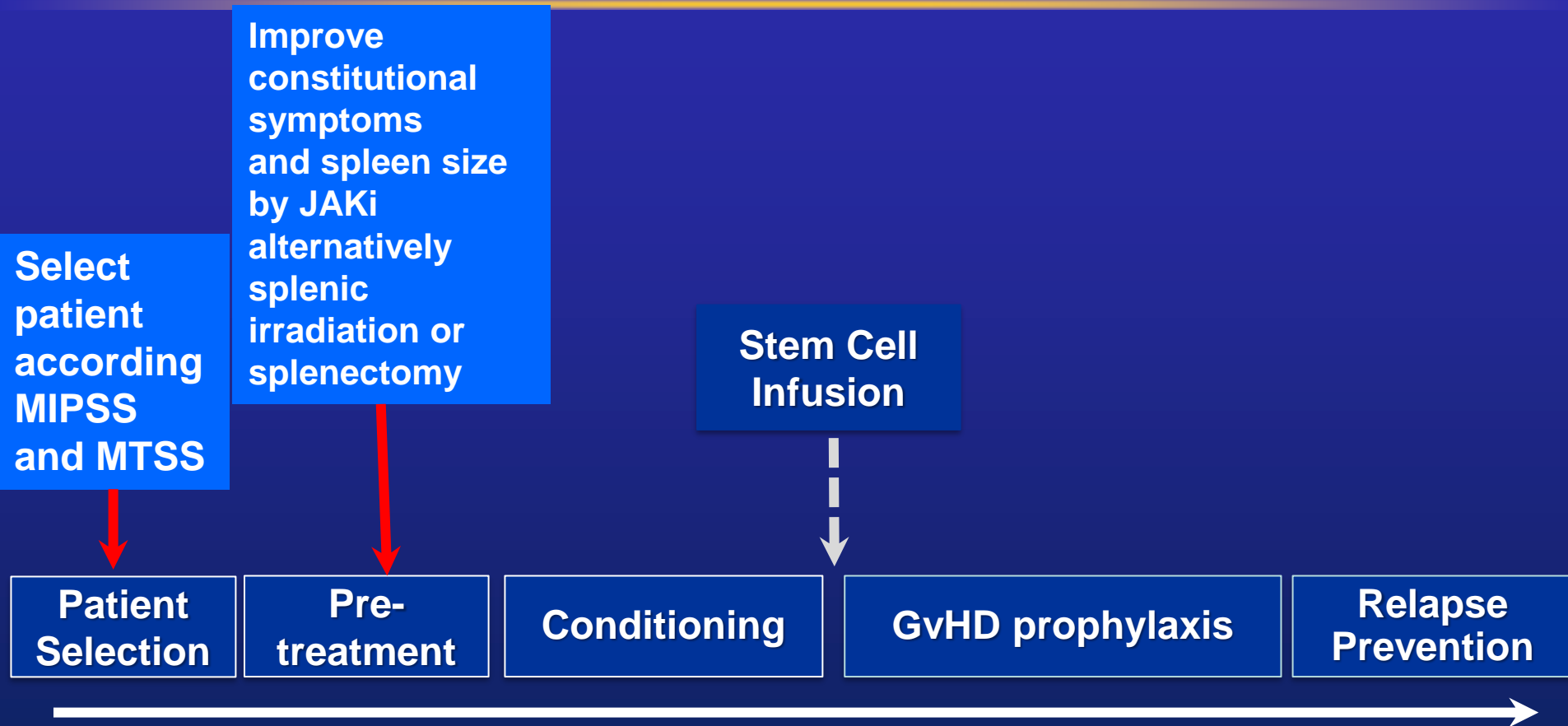
- splenectomy
- immediate transplant

	Pre-irradiation	Post-irradiation/ pretransplant	P
Spleen size, cm	23 (14-35)	18 (10-29)	0.04
Hemoglobin, g/dl	8.9 (6.2-13.7)	8.5 (9.0-13.0)	0.43
Platelets	92 (8-722)	39 (2-400)	0.03
Leukocytes	9.5 (0.1-163)	2.2 (0.1-55)	0.03





Approaches to improve outcome after allogeneic stem cell transplantation

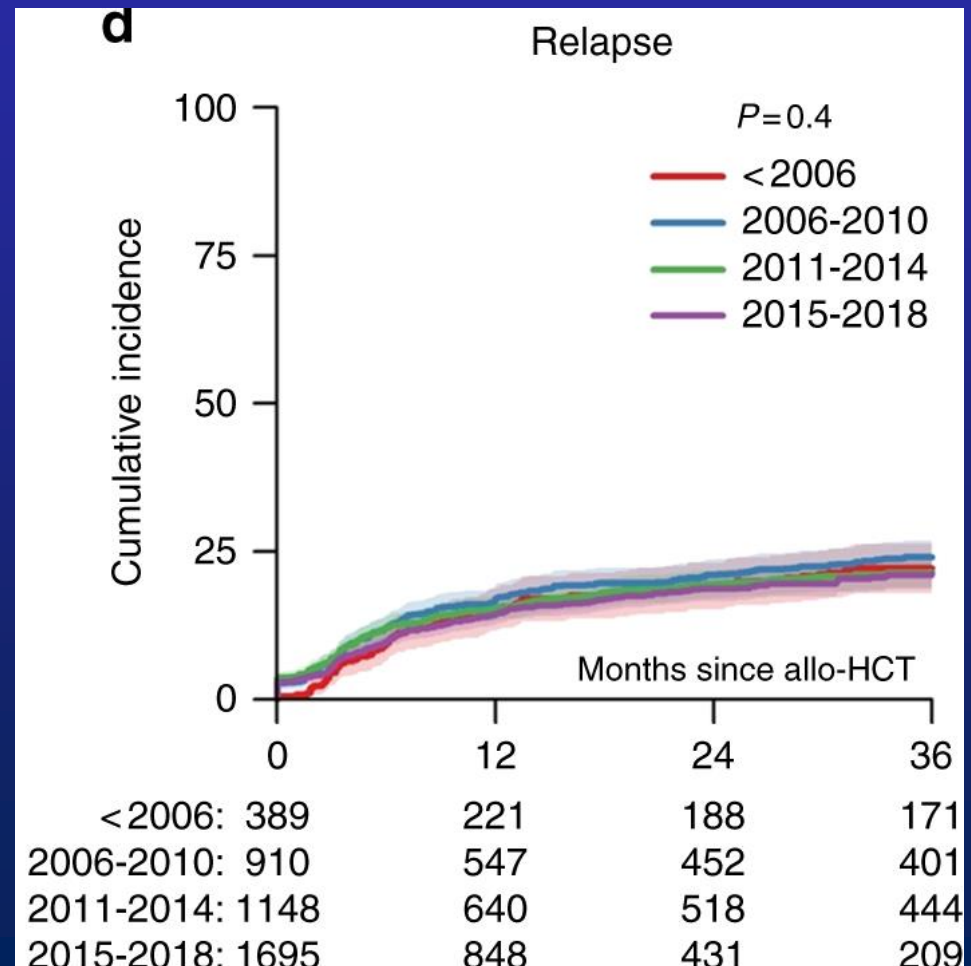


Outcome of patients with Myelofibrosis relapsing after allogeneic stem cell transplant: a retrospective study by the Chronic Malignancies Working Party of EBMT (n=1371)

Relapse : n= 251: cumulative incidence of 18%

The median time to relapse:
7,1 months (range 1.4–111 months)

Median survival early relapsing
<7.1 months vs late > 7.1 months :
12.9 vs 36.9 months : $P < 0.002$



ORIGINAL ARTICLE

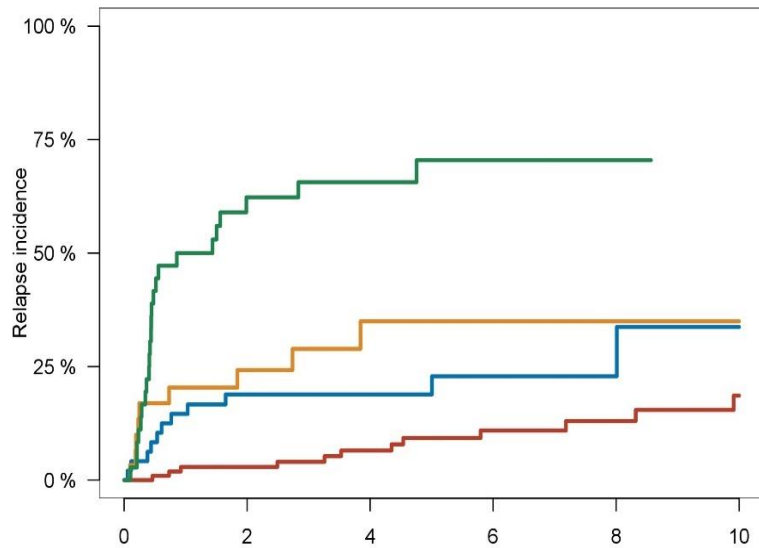
Clearance of Driver Mutations after Transplantation for Myelofibrosis

Nico Gagelmann, M.D., Marie Quarder, M.D., Anita Badbaran, M.Sc.,
Kristin Rathje, M.D., Dietlinde Janson, M.D., Catherina Lück, M.D.,
Johanna Richter, M.D., Franziska Marquard, M.D., Sofia Oechsler, M.D.,
Radwan Massoud, M.D., Evgeny Klyuchnikov, M.D., Ina Rudolph, M.D.,
Mathias Schäfersküpper, M.D., Christian Niederwieser, M.D.,
Silke Heidenreich, M.D., Carolina Berger, M.D., Ph.D., Boris Fehse, M.D., Ph.D.,
Christine Wolschke, M.D., Francis Ayuk, M.D., and Nicolaus Kröger, M.D.

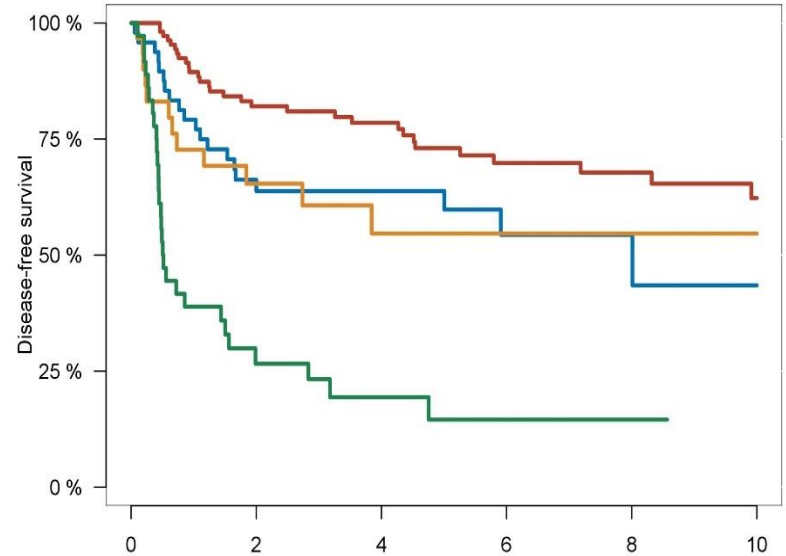
- **JAK V617F** **n = 238**
- **MPL** **n = 13**
- **CALR** **n = 73**
- **Sensitive qPCR or digital PCR for JAK V617F, MPL, CALR**
- **Screened on day +30,+100 and + 180 post allograft**

Impact on Drivermutation Clearance at day 30 , 100 and 180 (n= 324)

	JAK2	CALR	MPL	P
Day 30	42%	73%	46%	<0.001
Day 100	63%	82%	100%	<0.001
Day 180	77%	90%	100%	0.05

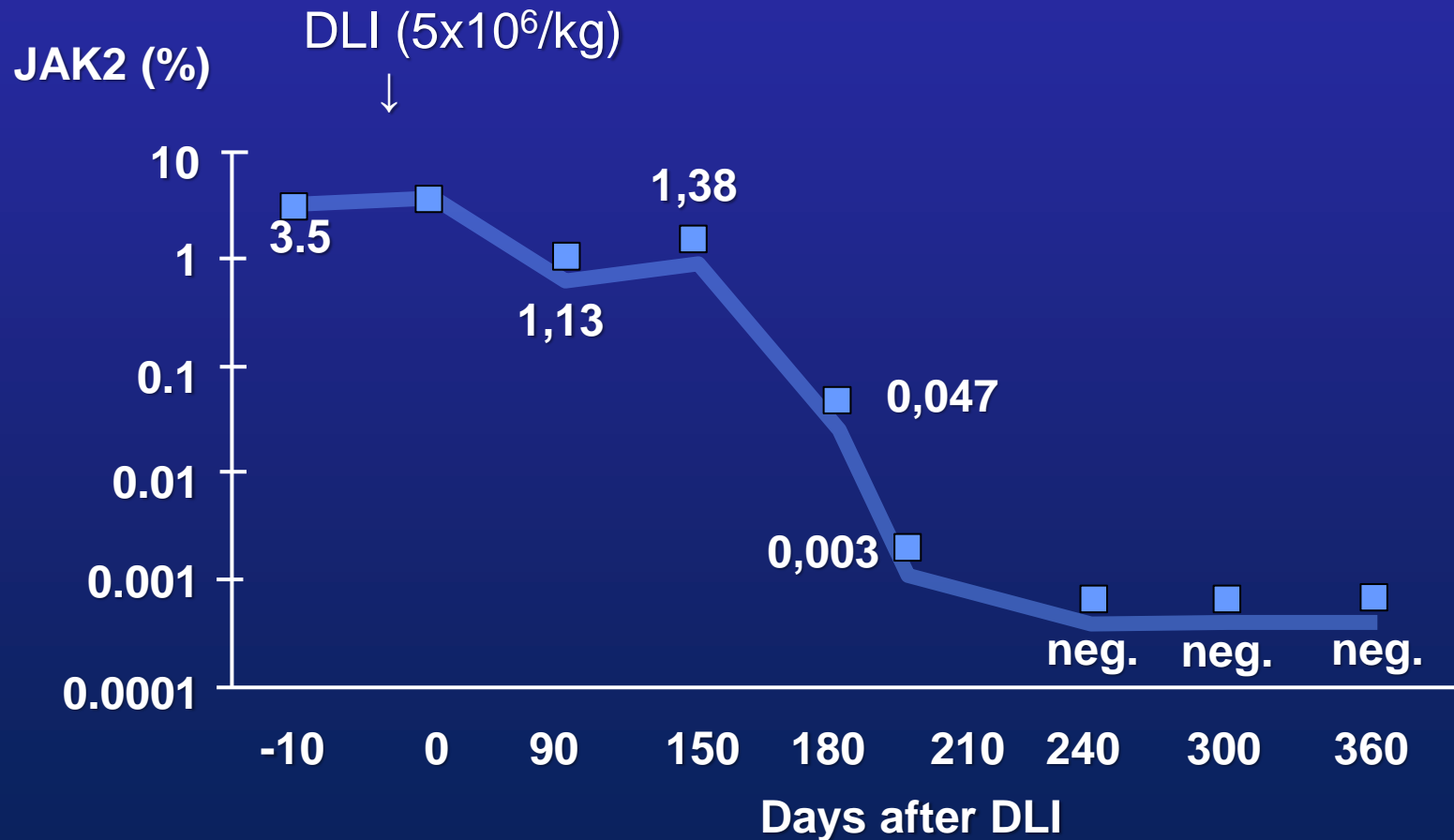


No. at risk	0	2	4	6	8	10
Always negative	111	75	60	40	31	20
Day 100 negative	48	27	22	9	5	2
Day 180 negative	30	15	9	5	4	1
Never negative	36	8	4	1	1	0

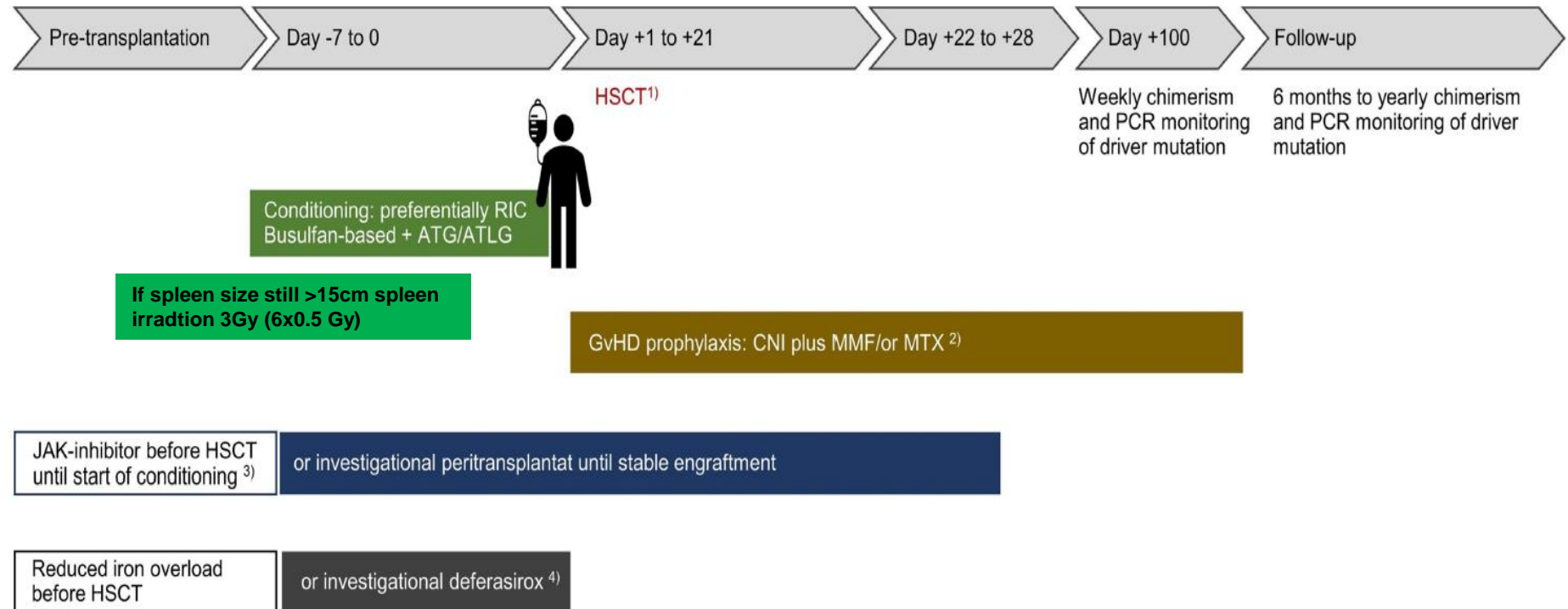


No. at risk	0	2	4	6	8	10
Always negative	111	75	60	40	31	20
Day 100 negative	48	27	22	9	5	2
Day 180 negative	30	15	9	5	4	1
Never negative	36	8	4	1	1	0

JAK2 Monitoring after DLI in MF Patient with residual disease after allografting for myelofibrosis



Transplant platform



¹⁾ Donor choice: matched sibling > matched unrelated > mismatched unrelated or haploidentical

²⁾ If no pretransplant ATG/ATLG, consider post-transplant cyclophosphamide

³⁾ Alternative: If JAK-inhibitor failed and persistent excessive spleen size: consider spleen irradiation before conditioning or splenectomy

⁴⁾ Investigational if ferritin is high during conditioning to reduce labile plasma iron (LPI), with busulfan pharmacokinetic