GITMO

GRUPPO ITALIANO PER IL TRAPIANTO DI MIDOLLO OSSEO, CELLULE STAMINALI EMOPOIETICHE E TERAPIA CELLULARE

Timing del Trapianto nella Mielofibrosi

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Haematopoietic Stem Cell Transplantation in Myelofibrosis

- ✓ Hematopoietic stem cell transplantation is the only curative therapy for primary (PMF) and secondary (post-TE or post-PV) myelofibrosis;
- ✓ It's associated with significant risk of treatment-related morbidity and mortality ;
- ✓ The optimal timing of HSCT for MF has been a matter of debate;
- ✓ The complexity of decision-making for transplantation has increased further following the wider availability of JAK1/2 inhibitor therapy.

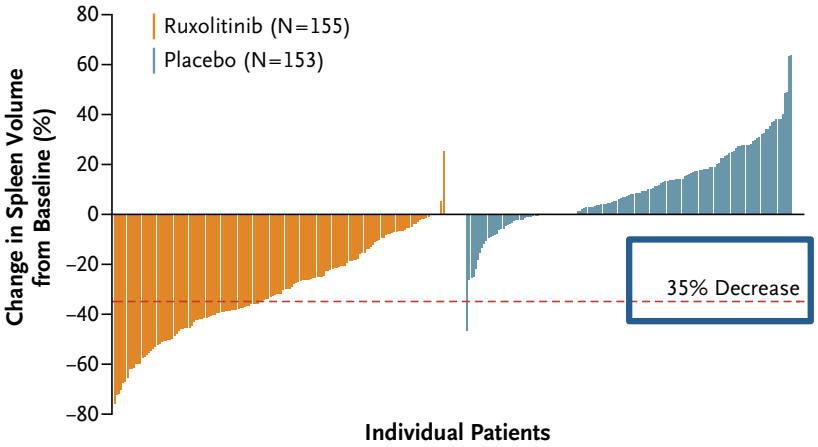
Allogeneic Stem Cell Transplant: NRM

Reference	Timeline of HCT	N	Median age, y (range)	Conditioning regimen	% of patients with RIC	% with MRD	NRM	PFS	OS
Guardiola[11]	1979-1997	55	42 (4-53)	TBI based (63%)	0	90	27% at 1 y	39% at 5 y	47% at 5 y
Deeg[10]	1980-2002	56	43 (10-66)	Bu/Cy in 78%	0	64	14% at 3 mo	NR	58 at 3 y
Daly[9]	1990-2002	25	48 (45-50)	TBI based (92%)	0	52	48% at 1 y	NR	41 at 2 y
Rondelli[66]	NR	21	54 (27-68)	Multiple	100	85	10% at 1 y	81% at 2.7 y	85% at 2.7 y
Kerbauy[58]	NR	104	49 (18-70)	Multiple, Bu/Cy (62%)	9	50	35% at 5 y	NR	61% at 5 y
Patriarca[65]	1986-2006	100	49 (21-68)	Multiple, Bu/Cy 50% of full intensity; Thiotepa + Cy in 46% of RIC	52	78	43% at 3 y	35% at 3 y	42% at 3 y
Kroger[54]	2002-2007	103	55 (32-68)	Flu-Bu (100%)	100	32	16% at 1 y	51% at 5 y	67% at 5 y
Gupta[64]	1998-2005	46	47 y MAC; 54 y RIC	Multiple, Cy TBI (96%) for MAC; Flu Bu (70%) for RIC	50	54	48% for MAC and 27% for RIC at 3 y	43% for MAC and 58% for RIC at 3 y	48% for MAC and 68% for RIC at 3 y
Ballen[56]	1989-2002	289	47 (18-73)	Multiple, Bu/Cy (43%)	21	56	35% siblings 50% for URD at 5 y	33% siblings 27% for URD at 5 y	37% siblings 30% for URD at 5 y
Alchalby[71]	1999-2009	162	56 (32-73)	Flu-Bu in 96%	100	27	22% at 1 y	46% at 5 y	62% at 5 y
Bacigalupo[63]	1994-2007	46	51 (24-67)	Thiotepa-Cy + melphalan	100	65	24% at 5 y	NR	45% at 5 y
Stewart[76]	1989-2005	51	49 (19-64)	Multiple, RIC in 47%	47	65	41% at 2 y	44% and 24% at 3 y for MAC and RIC	44% and 31% at 3 y for MAC and RIC
Robin[92]	1997-2008	147	53 (20-68)	Multiple	69	61	39% at 4 y	32% at 4 y	39% at 4 y
Samuelson[13]	1999-2007	30	65 (60-78)	Multiple	63	50	13% at day 100	40% at 3 y	45% at 3 y
Abelsson[67]	1982-2009	92	46 for MAC, 55 for RIC	Multiple	56	40	32% for MAC and 24% for RIC at 2 y	NR	49% for MAC and 59% for RIC at 5 y
Nivison-Smith[69]	1993-2005	57	47 (16-71)	Multiple	26	68	25% at 1 y		58% at 5 y
Ditschkowski[70]	1994-2010	76	50.5 (22-67)	Multiple	NR	35	36% at 5 y	50% at 5 y	53% at 5 y
Scott[57]	1990-2009	170	51.5 (12-78)	Multiple	NR	50	34% at 5 y	57% at 5 y	57% at 5 y

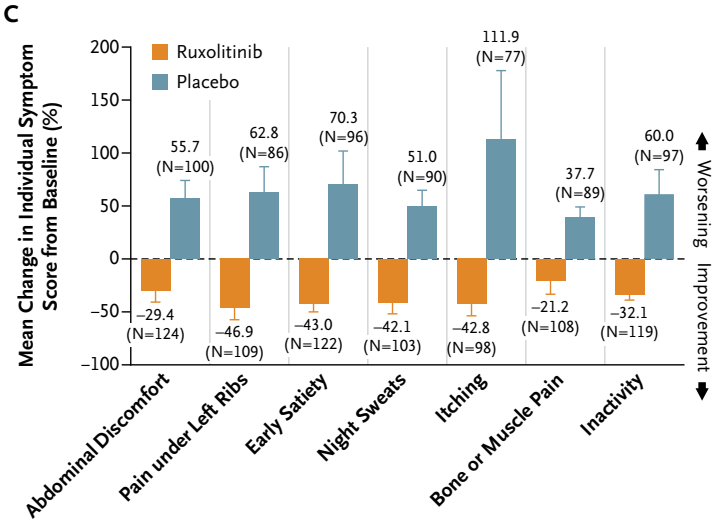
Gupta V et Al. Blood 2012

Efficacy of Ruxolitinib in MF

Spleen Volume

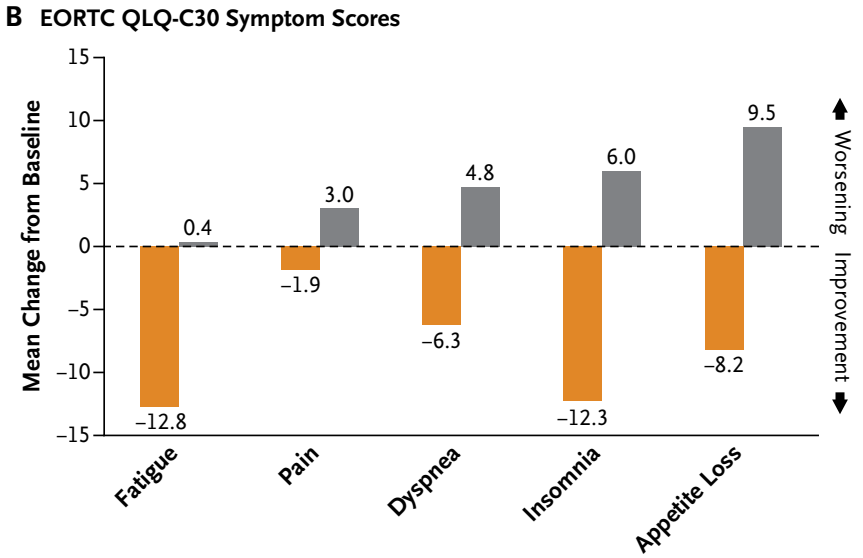


Constitutional symptoms



Verstovsek S et Al New Engl J Med 2012

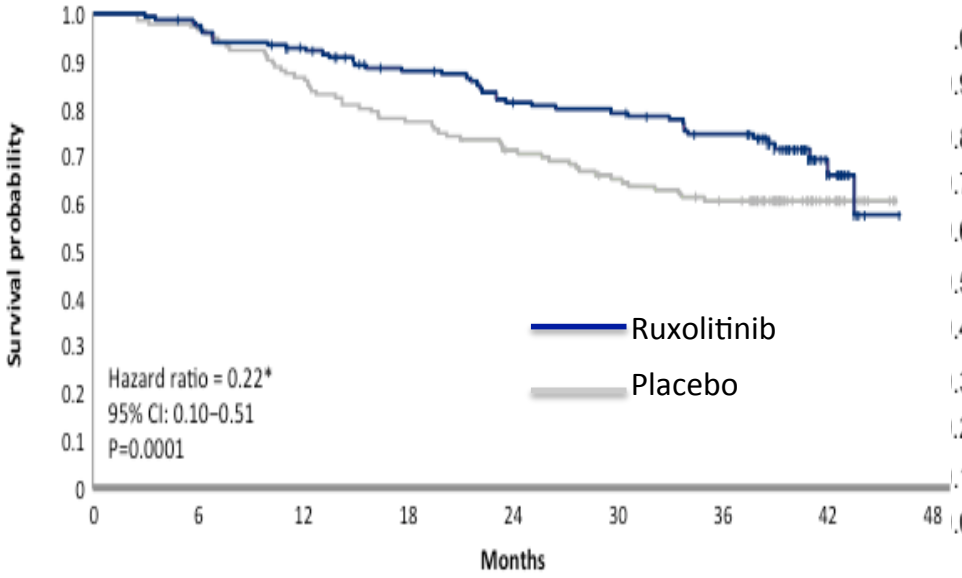
QoL



Harrison C et Al New Engl J Med 2012

Efficacy of Ruxolitinib in MF
OS

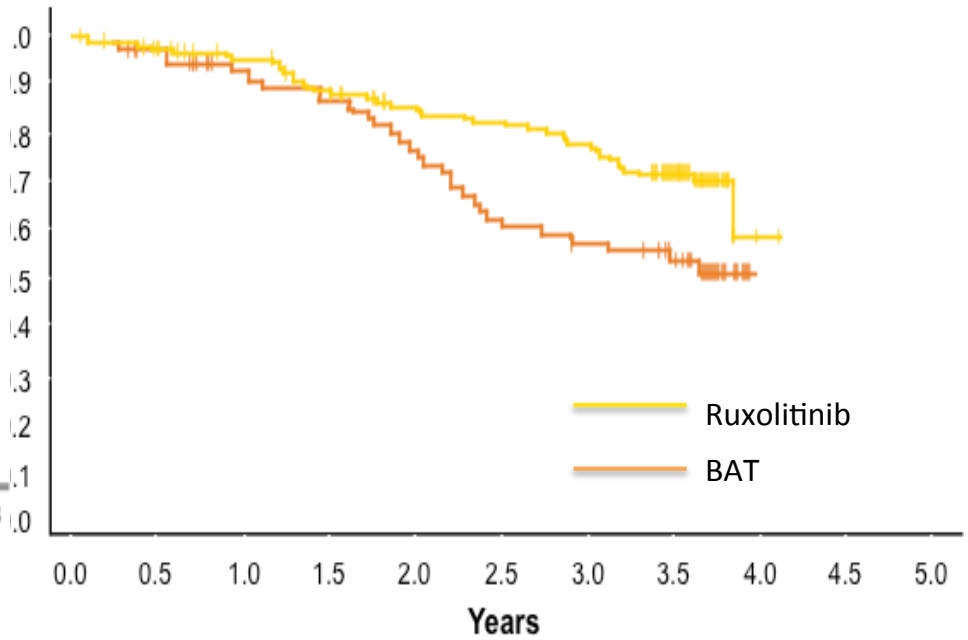
COMFORT-I
(3 year-follow-up)



Overall survival favored patients originally randomized to ruxolitinib compared with patients originally randomized to placebo

Verstovsek S 2013

COMFORT-II
(3.5 year-follow-up)

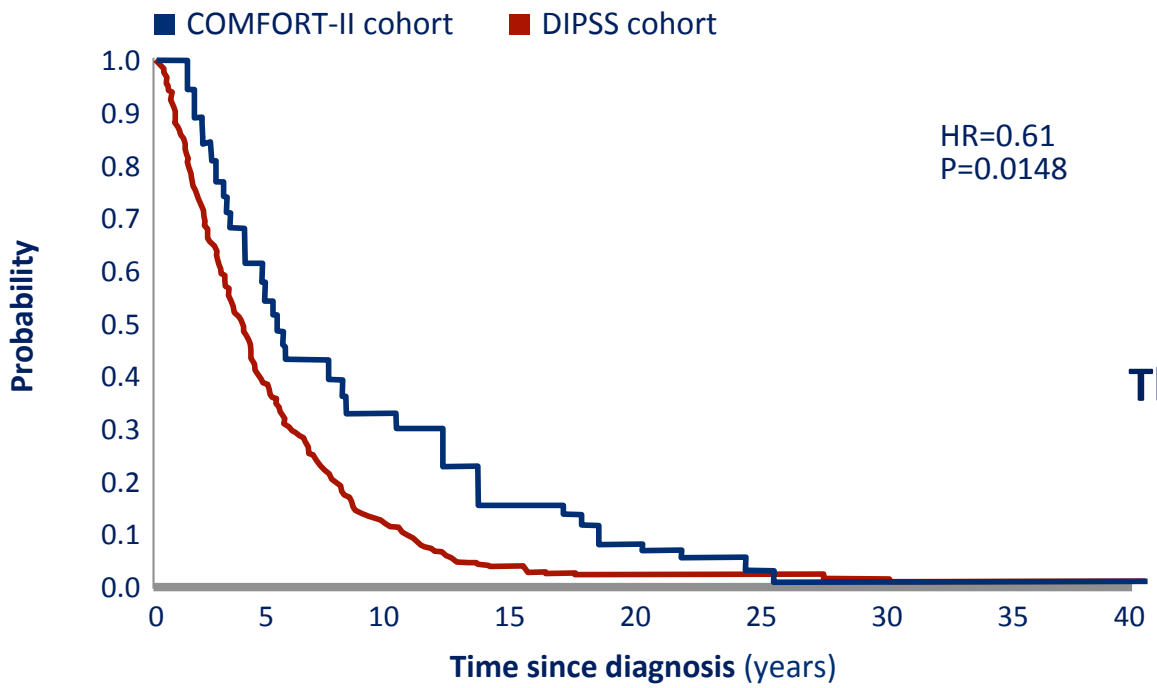


- The estimated survival probability at 3.5 years was 0.71(95% CI, 0.63-0.78) in the ruxolitinib arm and 0.54 (95% CI, 0.41-0.65) in the BAT arm, with a 42% reduction in the risk of death.

Harrison C 2014

Impact Of Ruxolitinib On The Natural History Of Patients With Primary Myelofibrosis

Survival estimate from diagnosis of PMF patients treated with ruxolitinib or BAT



The risk of death might be reduced by ~40% by introducing ruxolitinib in the treatment of PMF patients

The 8-year survival probability from initial diagnosis was 32.2% for COMFORT-II and 15.9% for DIPSS

Passamonti F, et Al Blood 2014

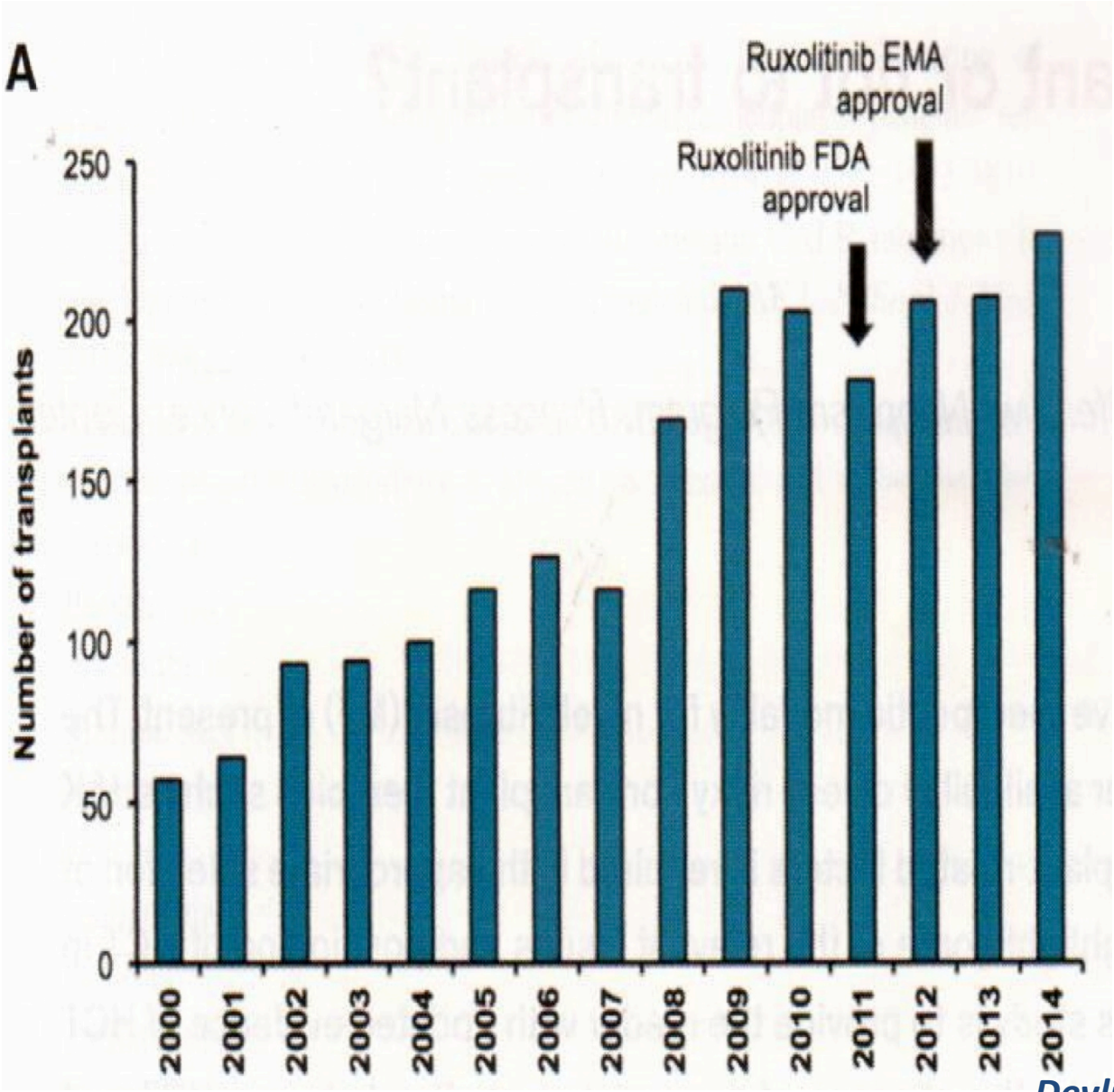
Three-year efficacy, safety, and survival findings from COMFORT-II, a phase 3 study comparing ruxolitinib with best available therapy for myelofibrosis

n (%)	Ruxolitinib (n = 146)	BAT (n = 73)	Ruxolitinib after BAT (n = 45)
Still on treatment	66 (45.2)	0	—
Discontinued	80 (54.8)	28 (38.4)	—
Crossed over*	—	45 (61.6)	—
After qualifying progression event	—	26 (35.6)	—
After protocol amendment 5	—	13 (17.8)	—
Other†	—	6 (8.2)	—
Still on treatment after crossover	—	—	22 (48.9)
Discontinued after crossover	—	—	23 (51.1)
Primary reasons for discontinuation			
AE	24 (16.4)	5 (6.8)	6 (13.3)
Consent withdrawn	9 (6.2)	9 (12.3)	0
Protocol deviation	2 (1.4)	0	5 (11.1)
Disease progression	22 (15.1)	4 (5.5)	6 (13.3)
Noncompliance with study medication	3 (2.1)	0	1 (2.2)
Noncompliance with study procedures	0	1 (1.4)	0
Unsatisfactory therapeutic effect	5 (3.4)	0	1 (2.2)
Other‡	15 (10.3)	9 (12.3)	4 (8.9)

About 50% of patients will discontinue ruxolitinib by 3 years due either to side effects or loss of response

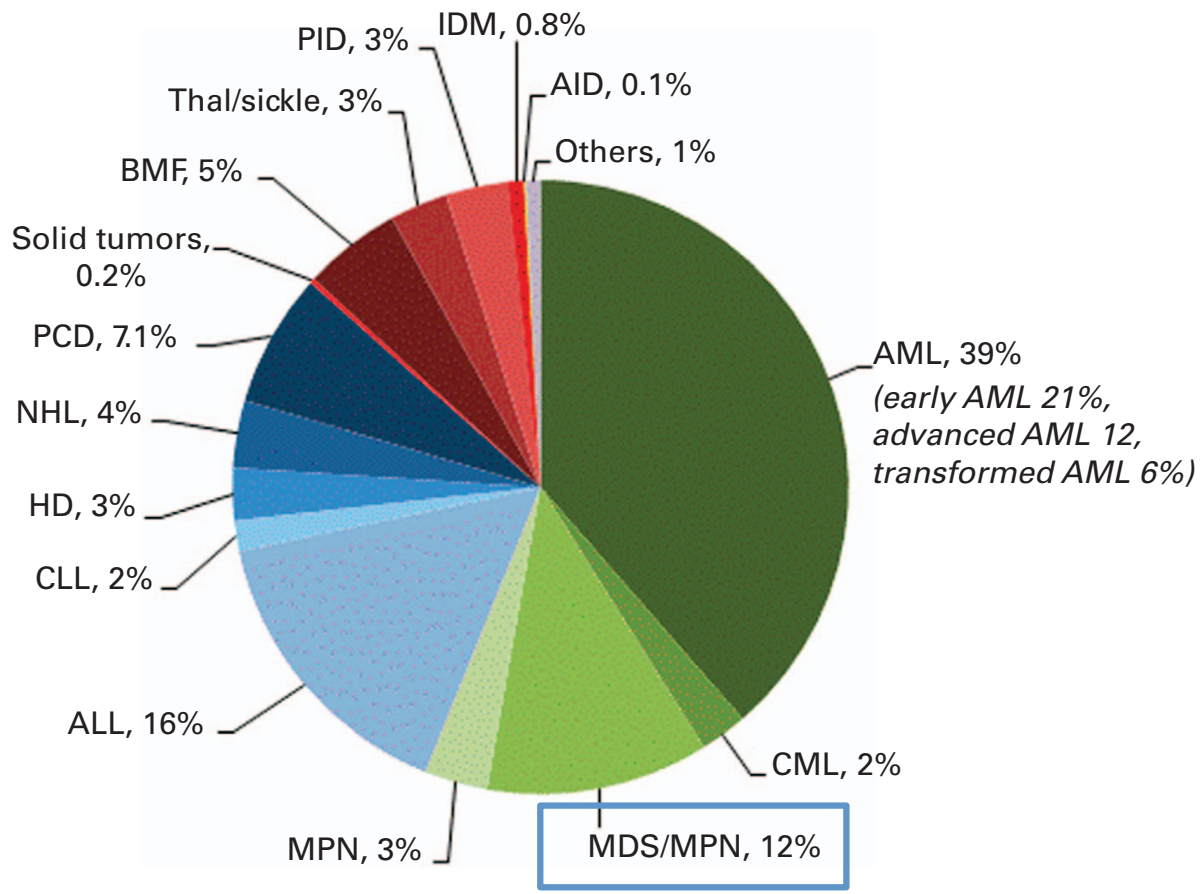
Cervantes F et Al. Blood 2013

CIBMTR: trends in HCT for primary MF between 2000 and 2014



Devlin R et Al. ASH 2016

EBMT: the 2015 Transplant activity survey

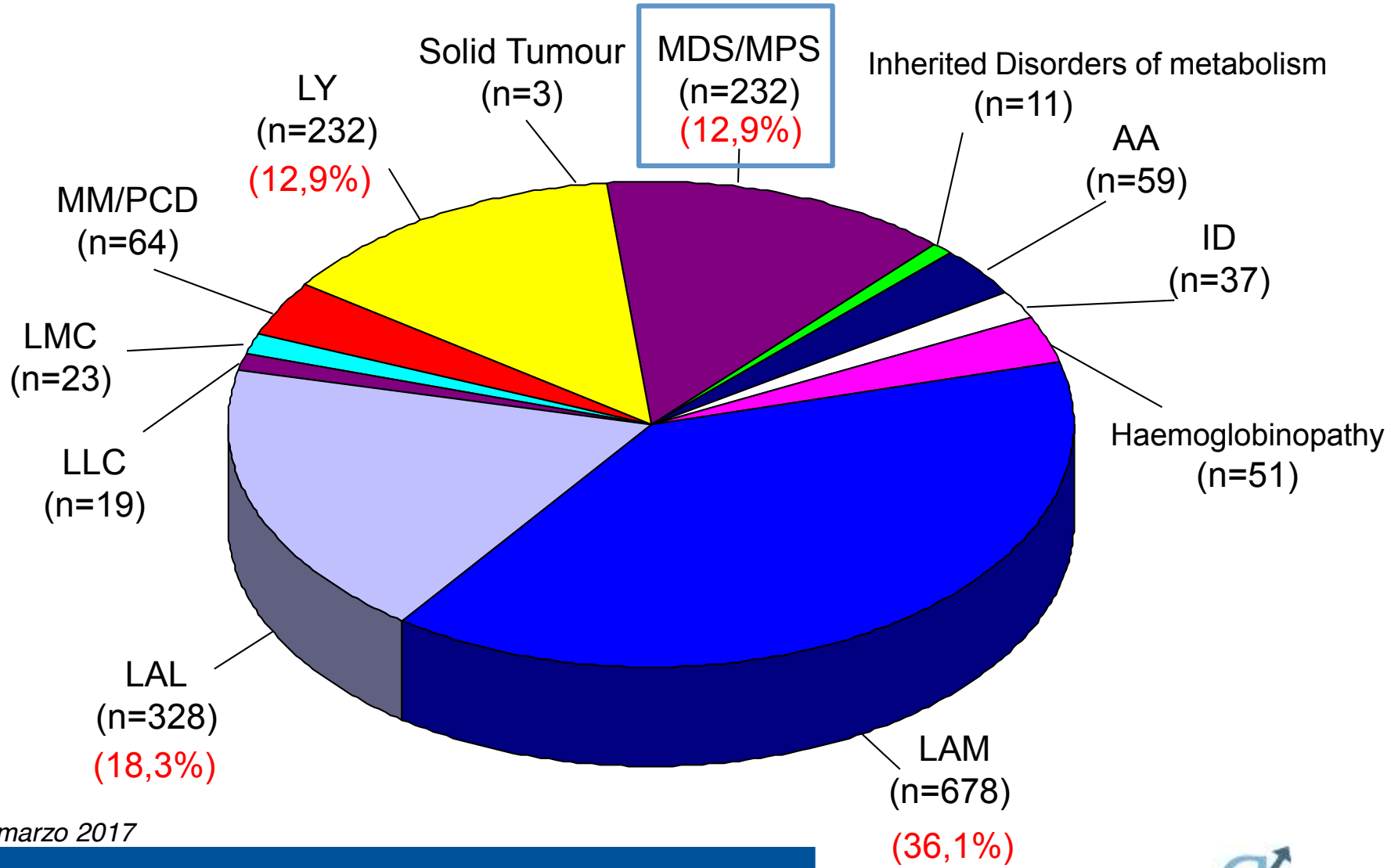


Passweg JR et Al. Bone Marrow Transplant 2017

GITMO Trapianto Allogenico

Numero Trapianti per principali Patologie

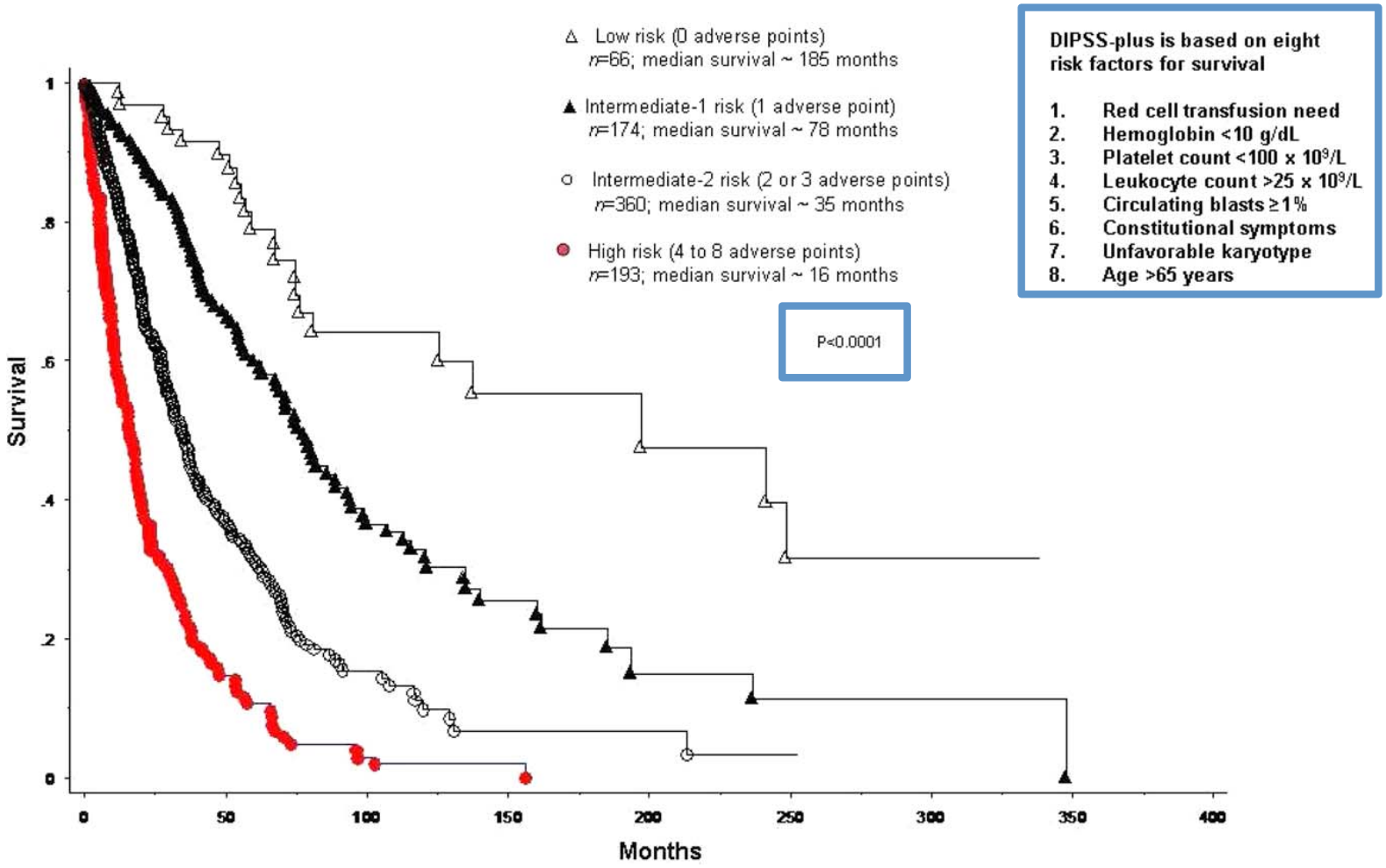
Attività 2016



al 22 marzo 2017

GITMO

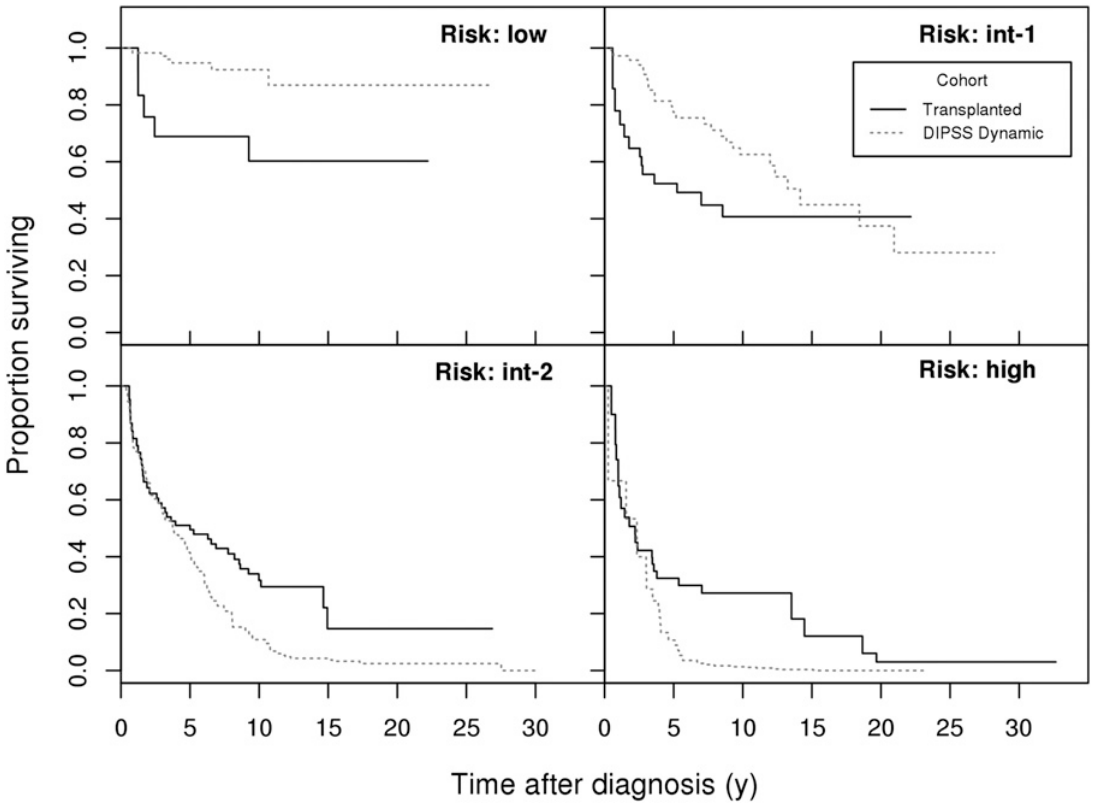
Current guidelines recommend that HCT be offered to patients predicted to have a poor survival based on prognostic risk score



Tefferi A et Al. Am J Haematol 2014

Impact of allogeneic stem cell transplantation on survival of patients less than 65 years of age with primary myelofibrosis

Survival probalities of 4 DIPSS subgroups at stem cell transplant



- ***Long-term outcome of int-2 and high risk pts better with HCT than non-transplant therapies***,
- equivalent outcome for Int-1 pts;
- ***in low-risk pts better outcome for non-transplant therapies***

Shortcomings: retrospective study, age restriction (65y), non-transplant therapies antedated to JAK inhibitors

Kroger Net Al. Blood 2015

Current issues

- Should there be an upper age limit for transplantation?
- Is there a role for transplantation in intermediate-1 risk disease?
- What is the optimal timing of HCT in patients with MF in the era of JAK inhibitors?

Current issues

- **Should there be an upper age limit for transplantation?**
- *Is there a role for transplantation in intermediate-1 risk disease?*
- *What is the optimal timing of HCT in patients with MF in the era of JAK inhibitors*?

Hematopoietic cell transplantation as curative therapy for patients with myelofibrosis: Long-term success in all age groups

Reference	Timeline of HCT	N	Median age (range), years	Conditioning regimen	% of patients with RIC	NRM	PFS	OS
Rondelli [34]	NR	21	54 (27–68)	Multiple	100	10% at 1 y	81% at 2.7 y	85% at 2.7 y
Kerbauy [35]	NR	104	49 (18–70)	Multiple, Bu/Cy (62%)	9	35% at 5 y	NR	61% at 5 y
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Ballen [10]	1989–2002	289	47 (18–73)	Multiple, Bu/Cy (43%)	21	35% siblings 50% for URD at 5 y	33% siblings 27% for URD at 5 y	37% siblings 30% for URD at 5 y
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Robin [38]	1997–2008	147	53 (20–68)	Multiple	69	39% at 4 y	32% at 4 y	39% at 4 y
Samuelson [20]	1999–2007	30	65 (60–78)	Multiple	63	13% at day 100	40% at 3 y	45% at 3 y
Ditschkowski [13]	1994–2010	76	50.5 (22–67)	Multiple	NR	36% at 5 y	50% at 5 y	53% at 5 y

REDUCED INTENSITY HEMATOPOIETIC CELL TRANSPLANTATION FOR PATIENTS WITH PRIMARY MYELOFIBROSIS: A COHORT ANALYSIS FROM THE CENTER FOR INTERNATIONAL BLOOD AND MARROW TRANSPLANT RESEARCH

Studies using cohorts transplanted more recently and/ or undergoing RIC show no association between age and poor HCT outcomes after controlling for other factors

Grade 2–4 acute GVHD					
Donor type					0.02
HLA-identical sibling	79	1			
Well-matched URD	104	1.98	0.006	1.22–3.22	
Partially matched/mismatched URD	50	1.52	0.18	0.83–2.80	
Contrast					
Well-matched URD vs. Partially matched/mismatched URD		1.30	0.33	0.76–2.23	
Relapse/Progression					
DIPSS					
Low/Intermediate-1	141	1			0.04
Intermediate-2/high	89	0.65	0.04	0.42–0.99	
NRM					
DIPSS					
Low/Intermediate-1	141	1			0.07
Intermediate-2/high	89	1.70	0.07	0.96–3.01	
Donor type					
HLA-identical sibling	79	1			< 0.001
Well-matched URD	104	3.92	0.006	1.50–10.33	
Partially matched/mismatched URD	50	9.37	< 0.001	3.49–25.17	
Contrast					
Well-matched URD vs. Partially matched/mismatched URD		0.42	0.005	0.23–0.77	
PFS					
Donor type					0.03
HLA-identical sibling	79	1			
Well-matched URD	104	1.17	0.42	0.80–1.69	
Partially matched/mismatched URD	50	1.75	0.01	1.14–2.68	
Overall Survival					
Donor type					
HLA-identical sibling	79	1			0.002
Well-matched URD	104	1.57	0.05	1.01–2.46	
Partially matched/mismatched URD	50	2.48	0.0003	1.51–4.04	

Gupta V et Al Biol Blood Marrow Transplant 2014

Allogeneic hematopoietic stem cell transplantation in patients with polycythemia vera or essential thrombocythemia transformed to myelofibrosis or acute myeloid leukemia: a report from the MPN Subcommittee of the Chronic Malignancies Working Party of the European Group for Blood and Marrow Transplantation

registry between 1994 and 2010. Their median age was 56 years (range, 22-75) and in 52% of cases the interval between diagnosis and transplantation was 10 years or more. With a median follow-up from transplantation of 13 months, the 3-year overall survival rate and relapse incidence were 55% and 32%, respectively. In univariate analysis, the main parameters that negatively affected post-transplantation outcomes were older age (>55 years), a diagnosis at transplant of acute myeloid leukemia and the use of an unrelated donor. The overall 3-year cumulative incidence of non-relapse mortality was 28%, but was significantly higher in older patients than in younger ones (>55 years, 35% *versus* 20%, *P*=0.032), in those transplanted from an unrelated donor rather than a related donor (34% *versus* 18%, *P*=0.034) and in patients with a diagnosis of acute myeloid leukemia compared to myelofibrosis (29% *versus* 27%, *P*=0.045). This large retrospective study confirms that transplantation is potentially curative for patients

Univariate analysis for outcomes at 36 months

Risk factor	N.	OS (%) at 3-year	*P*	RI (%) at 3-year	*P*	NRM (%) at 3-year	*P*
Overall	250	55		32		28	
Age, years							
<55	114	65	-	27	-	20	-
≥55	136	47	0.015	39	0.047	35	0.032
Diagnosis at TRX							
AML	57	28	-	53	-	29	-
MF	193	62	<0.001	28	0.001	27	0.045
Donor type							
Related	115	65	-	35	-	18	-
Unrelated	124	50	0.085	30	0.562	34	0.034
Mismatched	11	30	0.390	35	0.775	49	0.342

Causes of death	N.	(%)
Relapse/progression	29	35
Infection	24	29
GVHD	20	25
Organ damage/failure	1	<1
Cerebral hemorrhage	1	<1
Other causes	10	4

Lussana F et Al. Haematologica 2014

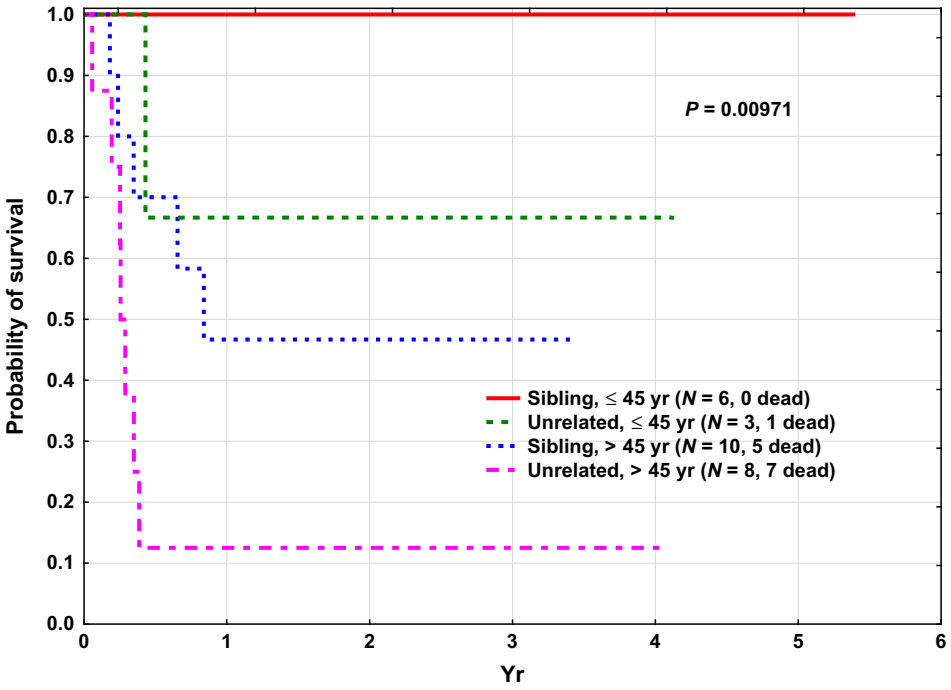
Safety and outcome of allogeneic stem cell transplantation in myelofibrosis

Multivariate analysis for OS

Factor	Hazard ratio	95% CI	*P*
Age			
≤45	1.00		
>45	10.55	1.35–82.55	0.025
Donor type			
MRD	1.00		
MUD	3.73	1.18–11.84	0.026

- 3-y OS for patients < 45y with MUD donor and > 45y with MRD donor 66% and 47% , respectively;
- Allo-HCT in patients > 45 y with MUD is associated with high rate NRM

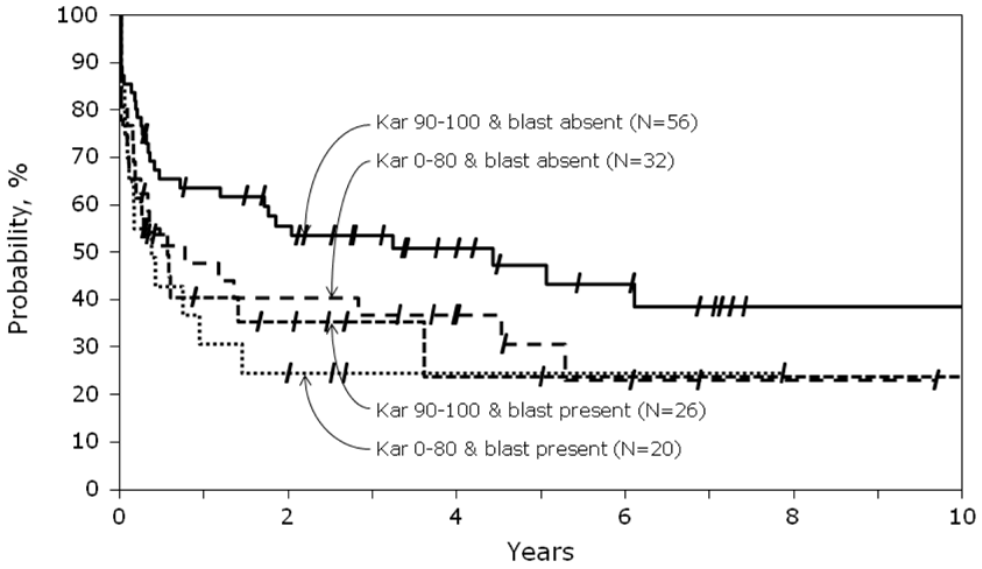
OS post-HCT by donor and age



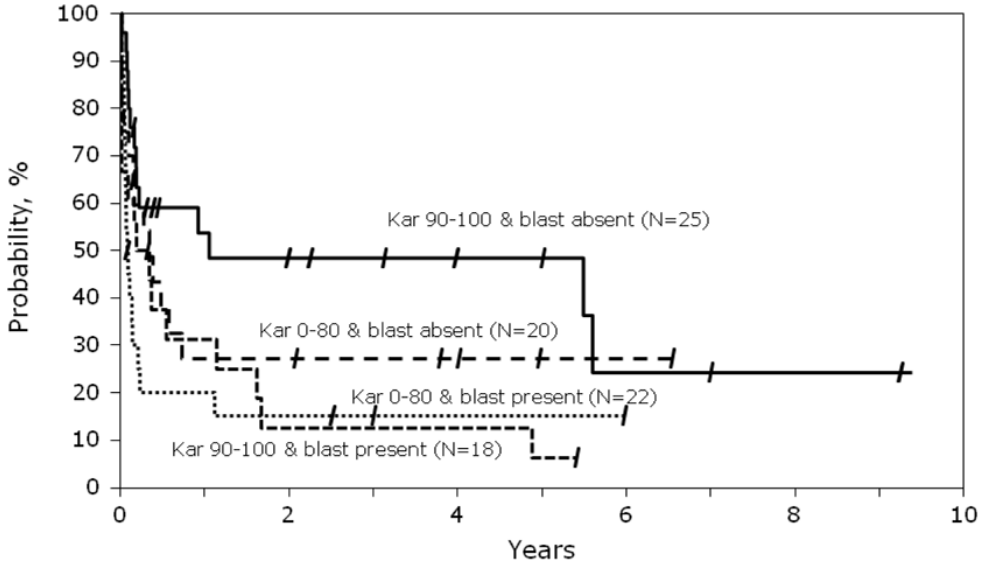
Markiewicz M et Al. Eur J Haematol 2015

Performance status and comorbidities /NRM and OS

HLA-identical sibling HCT

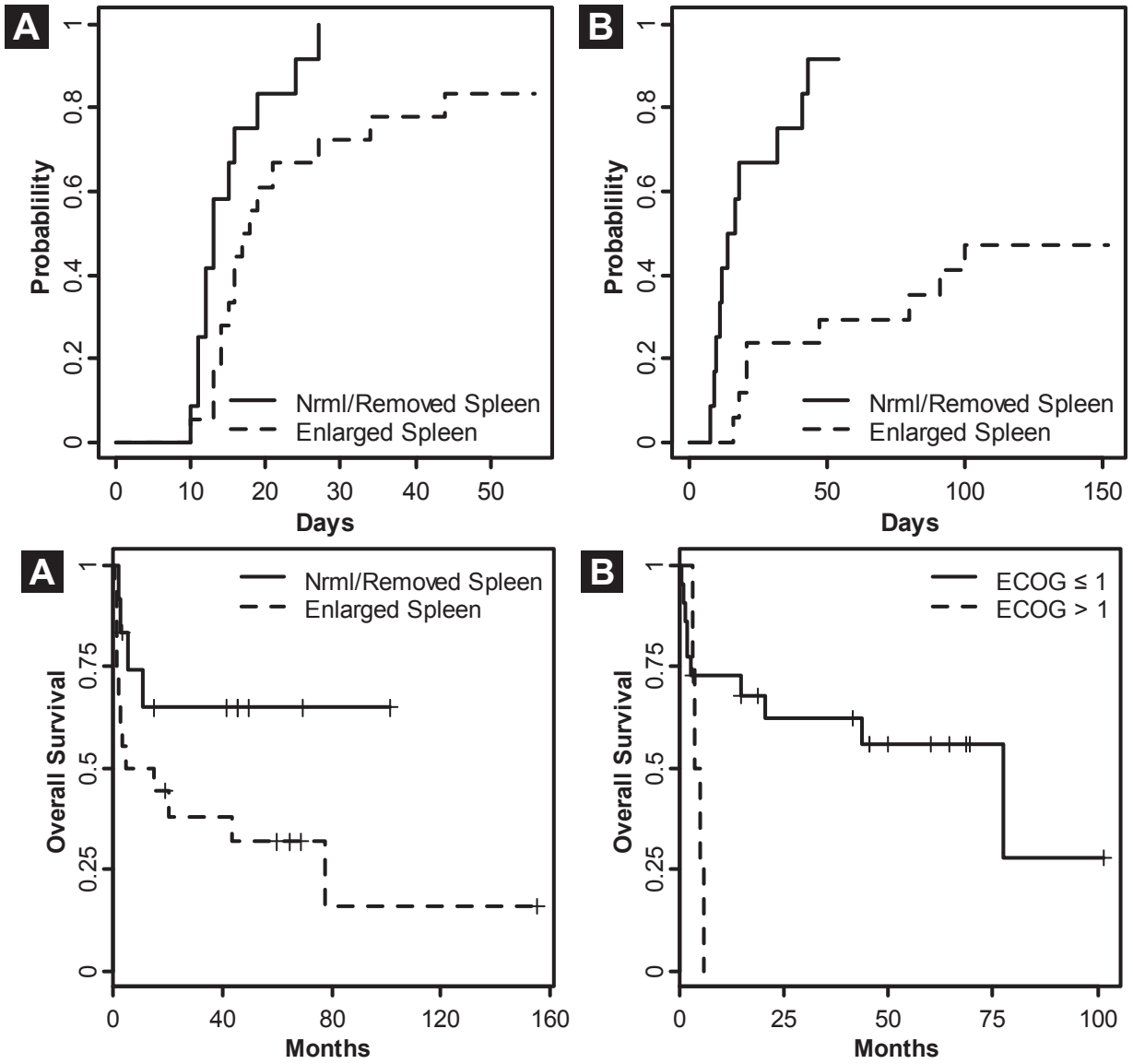


Unrelated donor allogeneic HCT



Ballen kk et Al Biol Blood Marrow Transplant 2010

Effects of spenomegaly and high serum LDH on engraftment and outcome



Gergis U et Al. Clin Lymph., Myeloma & Leukemia 2016

Allogeneic hematopoietic cell transplantation for myelofibrosis in patients pretreated with the JAK1 and JAK2 inhibitor ruxolitinib

Patient no.	*Reason for commencing ruxolitinib*		*Best response to ruxolitinib*		*Durability of response until allogeneic HCT*	*Outcome after allogeneic HCT*
	Splenomegaly[a] *(cm)*	*MF-related symptoms*	*Reduction in spleen size*[a] *(cm)*	*Decrease in MF-related symptoms from baseline (%)*		
1	Yes (24)	Yes	Yes (19)	50	Yes	Died 10 months after HCT (sepsis)
2	Yes (12)	Yes	No	34	No[b]	Died 2 months after HCT (relapse of AML)
3	Yes (11)	Yes	Yes (7)	50	Yes	Remission
4	—	Yes	—	66	Yes	Remission +
5	Yes (8)	—	Yes (0)	—	No[c]	Remission
6	—	Yes	—	100	Yes	Remission
7	—	Yes	—	50	Yes	Remission
8	Yes (7)	Yes	Yes (3)	66	Yes	Remission +
9	Yes (10)	Yes	Yes (5)	50	Yes	Remission
10	Yes (16)	Yes	Yes (6)	55	Yes	No engraftment. Restarted on ruxolitinib with a very good response
11	Yes (25)	Yes	No	33	Yes	Progression of MF. Died 9.5 months after HCT
12	Yes (10)	Yes	Yes (8)	80	No[d]	Second CR + after relapse with AML 4 months after allogeneic HCT treated with chemotherapy and withdrawal of immunosuppression
13	Yes (10)	Yes	Yes (6)	100	Yes	Remission
14[e]	Yes (17)	Yes	Yes (10)	60	Yes	Remission

Treatment with JAK inhibitor therapy may improve the performance status in some patients, and may take some patients eligible for transplant who were initially considered ineligible

Jaekel N et Al. Bone Marrow Transplant 2014

- …… decisions regarding HCT not be made on the basis of age alone but in the context of patient disease, fitness, and other characteristics that affect translant outcomes , and if a transplant is otherwise indicated, should not be deemed due solely to age

- ….. careful attention to performance status and comorbidities in potential HCT candidates. Patients with poor performance status mey benefit form a trial of jAK inhibitor therapy, and re-assessment for HCT candidacy after 3 or 6 months oh therapy

Devlin R and Gupta V ASH 2016

Current issues

- *Should there be an upper age limit for transplantation?*
- **Is there a role for transplantation in intermediate-1 risk disease?**
- *What is the optimal timing of HCT in patients with MF in the era of JAK inhibitors?*

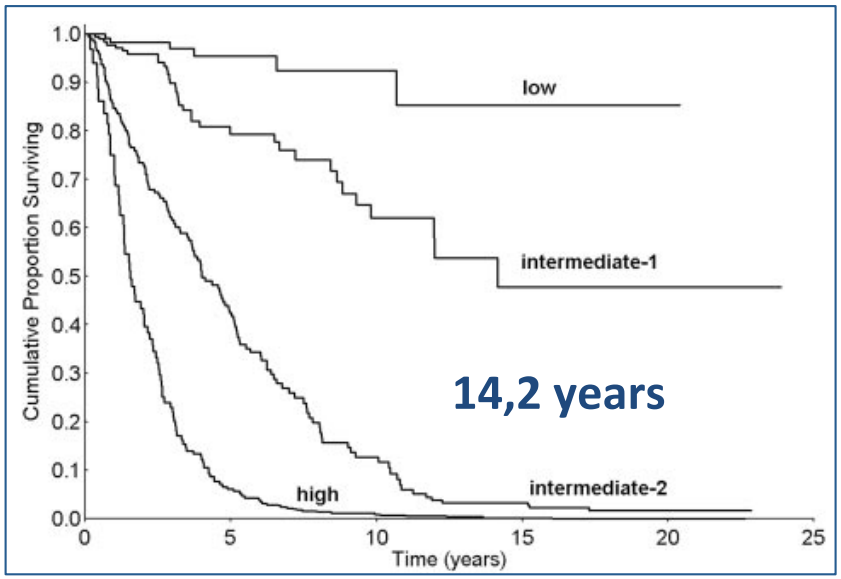
Intermediate-1 risk MF: OS according to DIPSS and aaDIPSS (pre-JAK inhibitors era)

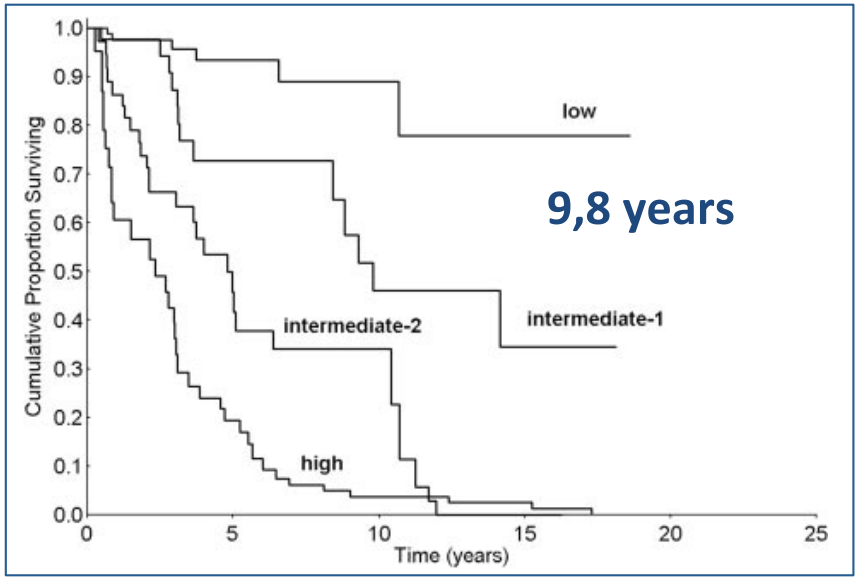
Table 3. DIPSS for survival in primary myelofibrosis

	Value		
Prognostic variable	**0**	**1**	**2**
Age, y	≤ 65	> 65	
White blood cell count, $\times 10^9$/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1	≥ 1	
Constitutional symptoms, Y/N	N	Y	

Table 4. Age-adjusted DIPSS for survival in primary myelofibrosis

	Value		
Prognostic variable	**0**	**1**	**2**
White blood cell count, $\times 10^9$/L	≤ 25	> 25	
Hemoglobin, g/dL	≥ 10		< 10
Peripheral blood blast, %	< 1		≥ 1
Constitutional symptoms, Y/N	N		Y

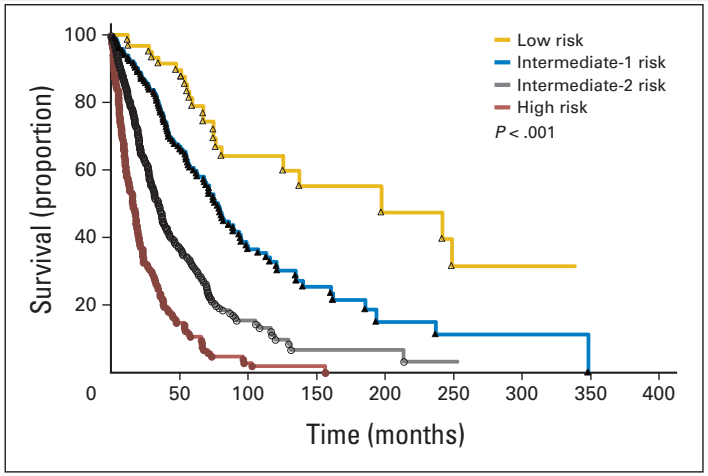


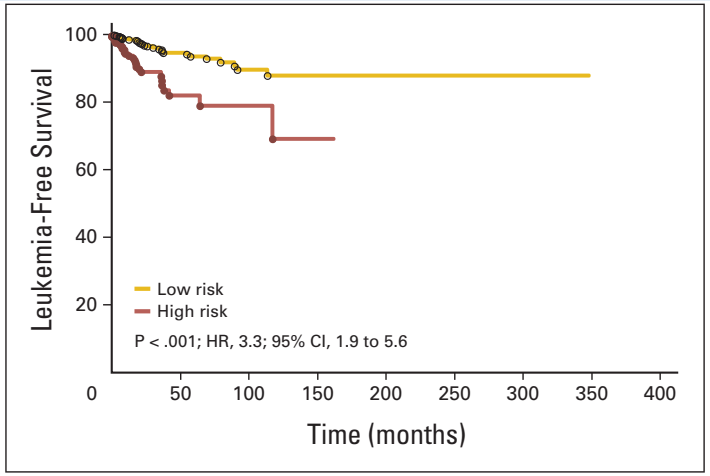


Passamonti F et Al. Blood 2010

Decision-making process in intermediate-1 risk patients
Risk Factors: Cytogenetics and Transfusion-requiring anemia (DIPSS plus)

Survival	Patients Referred Within 1 Year of Diagnosis (n = 428) 95% CI	Hazard Ratio	*P*	Patients Referred After 1 Year From Diagnosis (n = 365) 95% CI	Hazard Ratio	*P*
Overall survival						
DIPSS risk						
High	4.0 to 13.3	7.3	< **.001**	2.9 to 15.9	6.8	< **.001**
Intermediate-2	2.1 to 6.0	3.6	< **.001**	2.1 to 10.3	4.6	**.0002**
Intermediate-1	1.2 to 3.1	1.9	**.01**	1.4 to 7.0	3.2	**.005**
Unfavorable karyotype*	1.7 to 3.4	2.4	< **.001**	1.2 to 2.3	1.7	**.001**
Platelets < 100 × 10^9/L	1.2 to 2.2	1.6	**.0009**	1.1 to 1.9	1.4	**.02**
Red cell transfusion dependent	1.1 to 2.0	1.4	**.01**	0.9 to 1.6	1.2	.16
Leukemia-free survival, N = 793						
DIPSS risk						
High	0.9 to 26	5.0	.06			
Intermediate-2	0.7 to 15	3.3	.12			
Intermediate-1	0.9 to 16	3.7	.08			
Unfavorable karyotype*	1.1 to 4.3	2.2	**.02**			
Platelets < 100 × 10^9/L	1.4 to 4.6	2.5	**.003**			
Red cell transfusion dependent	0.6 to 2.3	1.2	.65			

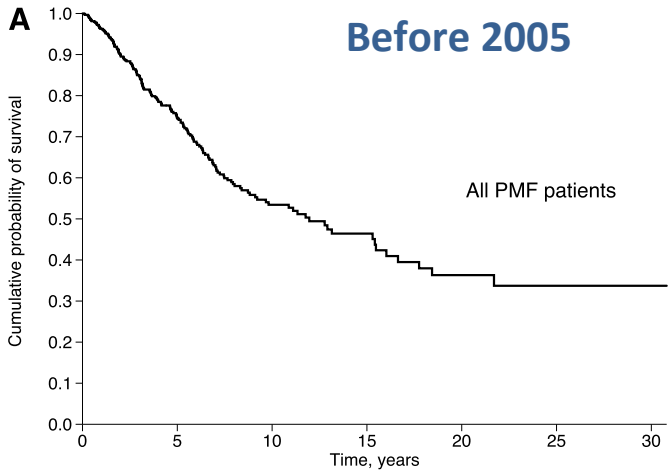


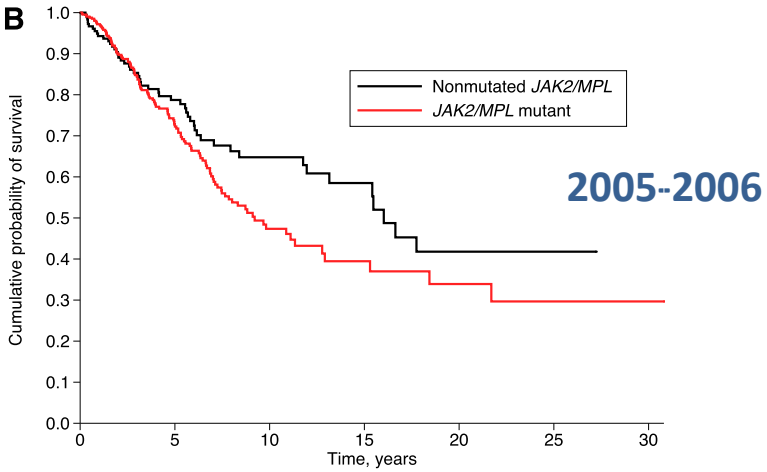


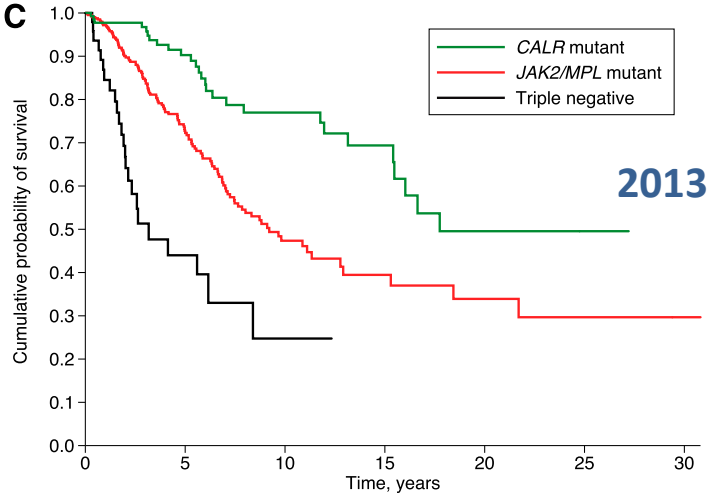
Gangat N et Al JCO 2011

Decision-making process in intermediate-1 risk patients
Risk Factors: MPN driver mutations

Kaplan-Meier analysis of OS of PMF patients according to the genotype/ different times of diagnosis



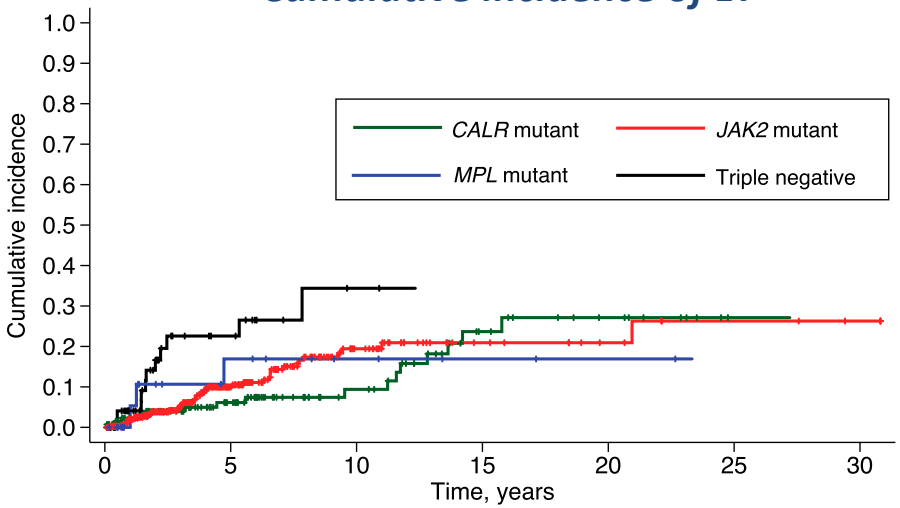




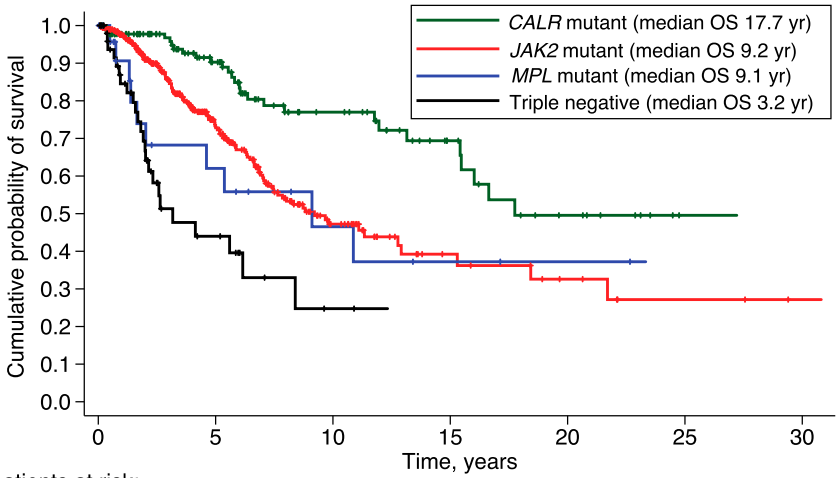
Rumi E et Al. Blood 2014

Clinical effect of driver mutations of *JAK2*, *CALR*, or *MPL* in primary myelofibrosis

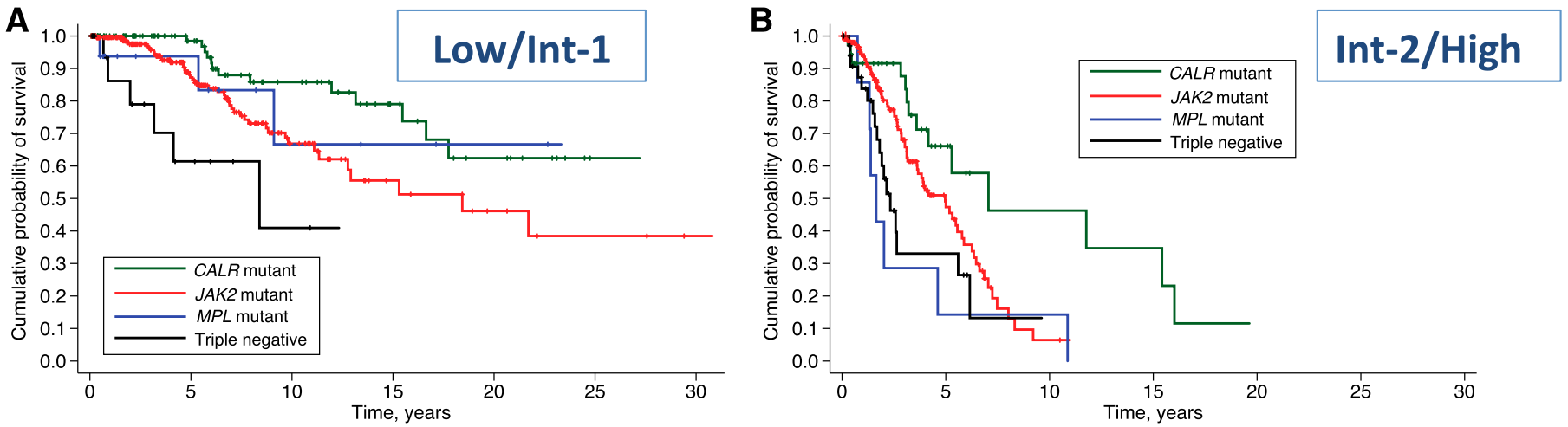
Cumulative incidence of LT



Analysis of OS according to driver mutation



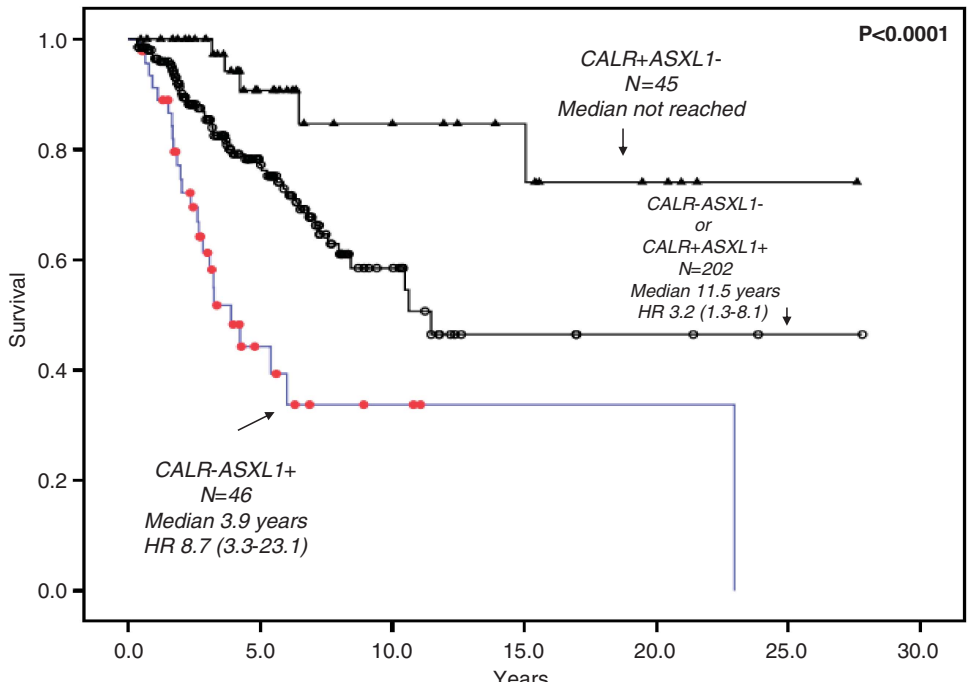
Analysis of OS according to driver mutation and IPSS stratification



Rumi E et Al. Blood 2014

CALR and *ASXL1* mutations-based molecular prognostication in primary myelofibrosis: an international study of 570 patients

Kaplan Meier estimates of OS in Italian series (pt 293)/ mutational status CALR/ASXL1



The presence of ASXL1 mutation in CALR-mutated cases is associated with higher rate of marked leukocytosis, circulating peripheral blasts and thrombocytopenia

Mayo Clinic CALR/ASXL1 mutation-based prognostic model/OS:

- Low risk pts (CALR+/ASXL1 -) not reached;
- Intermediate risk (CALR+/ASXL1+ or (CALR+/ASXL1) 11,5 years;
- High risk (CALR-/ASXL1 +) 3,2 years

Tefferi A et Al. Leukemia 2014

MIPSS: Molecular International Prognostic Score System

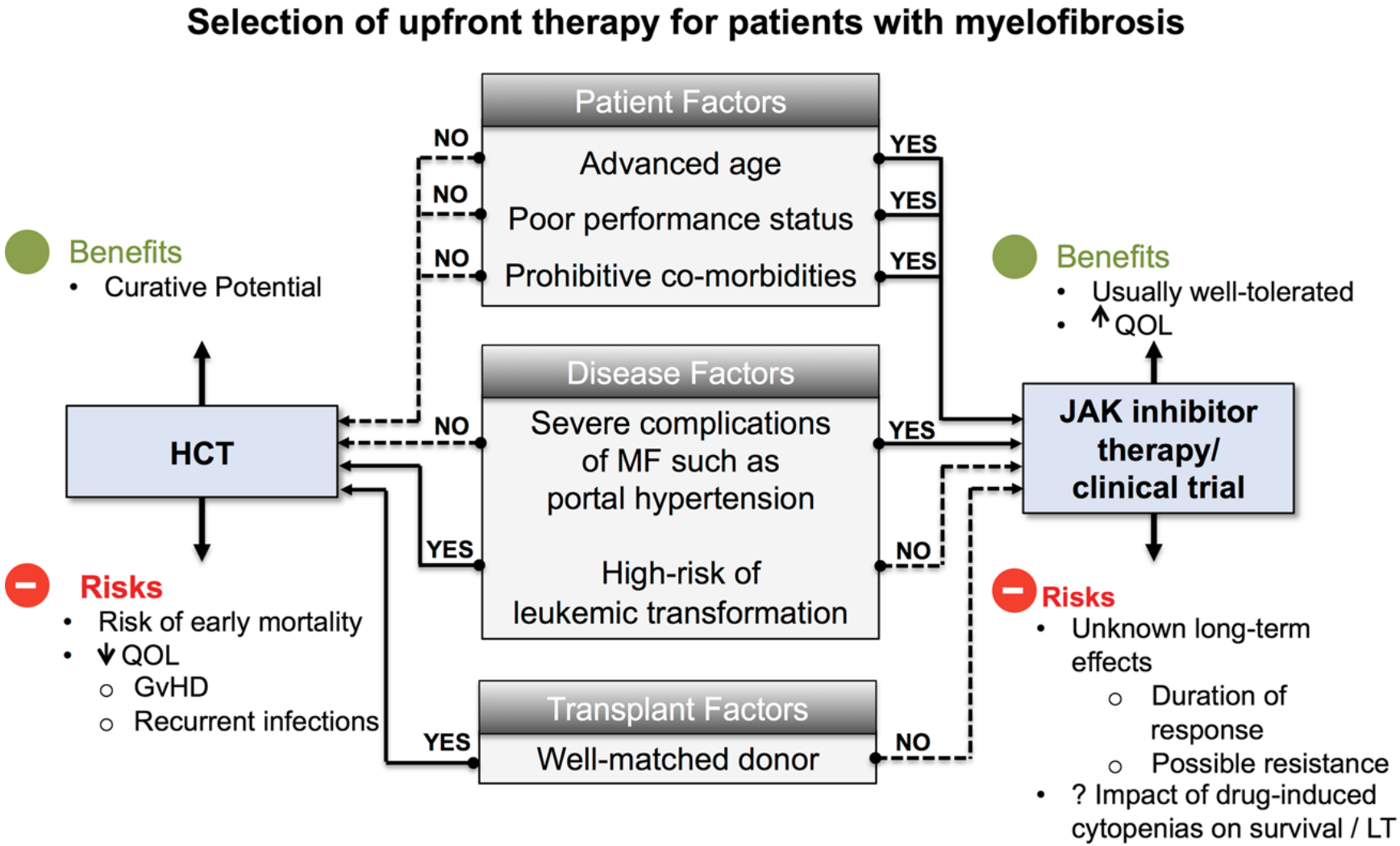
MULTIVARIATE ANALYSIS			Weighted value
Variables	***HR(95% CI)***	***P***	
Age >60 yrs	3.8 (2.60-5.51)	< 0.0001	1.5
Hb <100 g/L	1.4 (1.01-1.99)	0.04	0.5
Constitutional Symptoms	1.5 (1.13-2.16)	0.007	0.5
PLT < $200x10^9$/L	2.5 ((1.77-3.42)	< 0.0001	1.0
Triple negativity	3.9 (2.20-6.80)	< 0.0001	1.5
JAK2/MPL mutation	1.8 (1.11-2.90)	0.016	0.5
ASXL1 mutation	1.4 (1.06-1.99)	0.02	0.5
SRSF2 mutation	1.7 (1.08-2.58)	0.02	0.5

Vannucchi A et Al Leukemia 2013

Factors influencing the choice between HCT vs non transplant therapies

Characteristics	Reason for poorer outcomes with nontransplant therapy
Severe thrombocytopenia ($<50x10^{9/L}$)	No data on the use of ruxolitinib in this subgroup Challenging to safely deliver adequate doses of ruxolitinib in severely thrombocytopenic patients
Heavily transfusion-dependent anemia	Anemia is a major toxicity of JAK inhibitor therapy, and may worsen with treatment
≥ 3 mutations	Shorter time to treatment failure with ruxolitinib Increased risk of LT
High-risk cytogenetics	Increased risk of LT Impact of high-risk cytogenetics on ruxolitinib-treated patients not well studied
Increasing blasts in peripheral blood	Increasing blasts is a risk factor for LT
Characteristics	**Reason for poorer outcomes with HCT**
Poor performance status	Increased NRM and decreased survival
Comorbidities	Severe comorbidities result in higher NRM
Advanced age	Very advanced age adversely impacts HCT outcomes Response to JAK inhibitor therapy is not impacted by advanced age
Mismatched donor	Mortality almost double compared with MSD/well-matched URD
Severe portal hypertension	Possible increase in regimen-related hepatotoxicity

Aids to decision making in selection of initial therapy (drug therapy vs HCT) in patients with MF



Gupta V et Al Blood 2012

At present, the decision regarding HCT in Intermediate-1 risk patients is **individualized** after carefully consideration of

Severe thrombocytopenia

- High PB blasts %
- High-risk cytogenetics
- Refractory transfusion-requiring anemia
- Triple negative mutation status or presence of HMR mutations

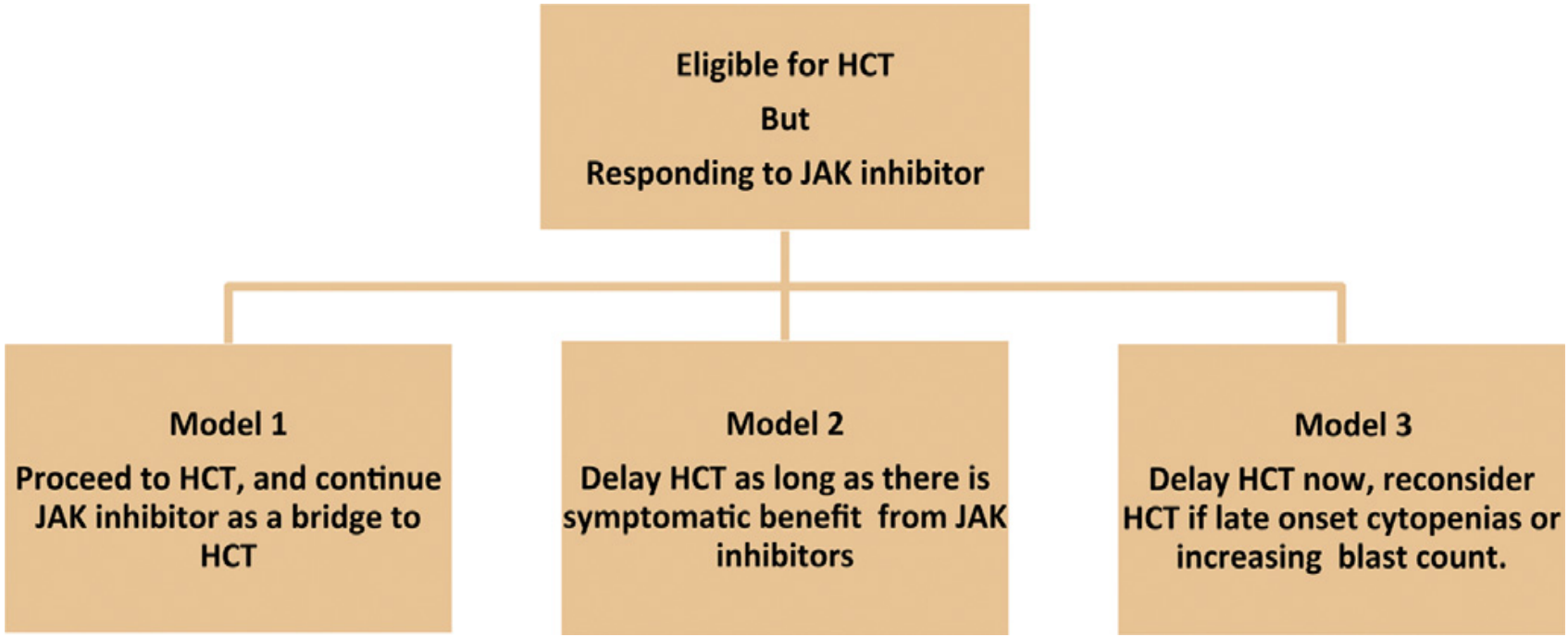
Current issues

- *Should there be an upper age limit for transplantation?*
- *Is there a role for transplantation in intermediate-1 risk disease?*
- **What is the optimal timing of HCT in patients with MF in the era of JAK inhibitors?**

What is the optimal timing of HCT in patients with MF in the era of JAK inhibitors?

- **Early vs delayed HCT in patients responding to JAK inhibitor therapy?**
- Does donor type play a part in decision about the timing of HCT ?
- Are there any factors predicting poor response to JAK inhibitor therapy ?
- Do JAK inhibitors have a role as part of HCT procedure?

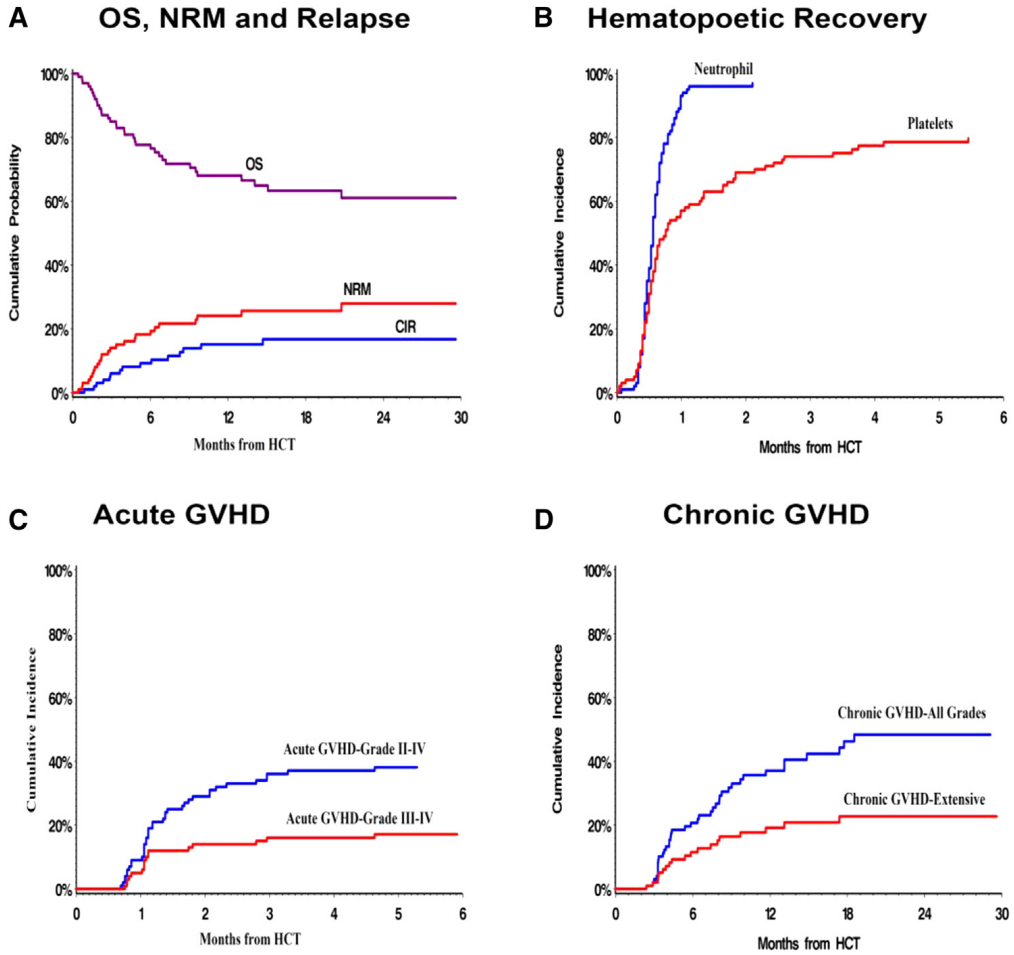
Timing of HCT in patients responding to JAK inhibitors



Shavanas M et Al. Best Prac Res Clin Haematol 2014

Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis with Prior Exposure to Janus Kinase 1/2 Inhibitors

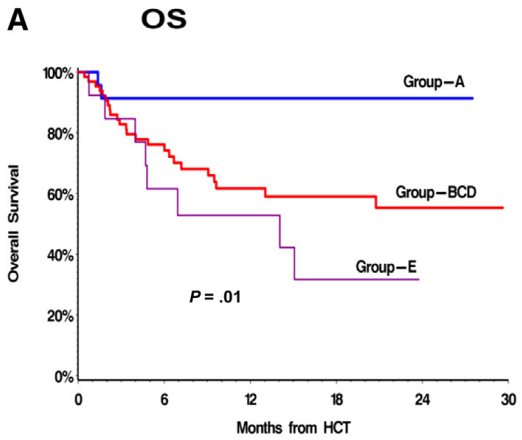
Retrospective multucenter study on 100 pts undervent HCT after JAK1/2 inhibitor exposure between 2009 and 2014 ; median duration of JAK1/2 inhibitor therapy 5 months (1-56)



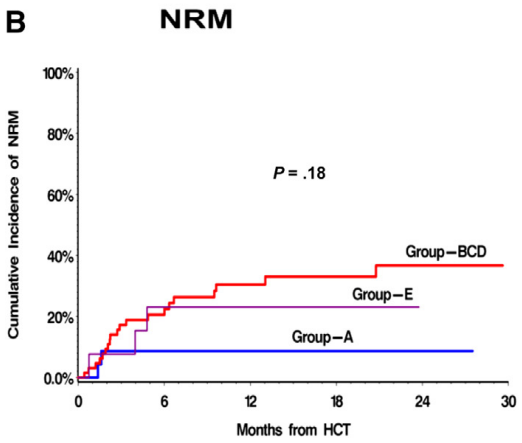
- aGVHD II-IV and III-IV by 100 days 37% and 16% respectively;
- cGVHD by 2 years 48%, 23% extensive;
- CIR by 2 years 17%
- NRM by 2 years 28%
- Probability of OS at 2 years 61%

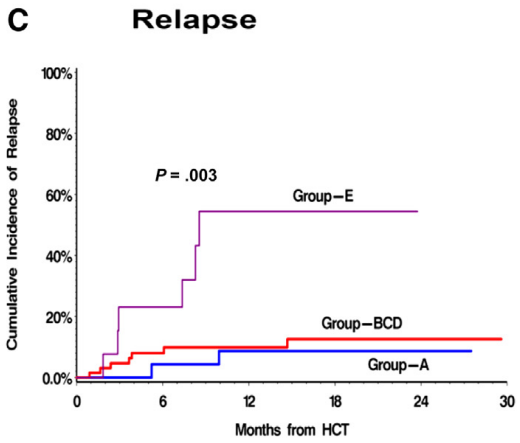
Shavanas M et al Biol Blood Marrow Transplant 2016

Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis with Prior Exposure to Janus Kinase 1/2 Inhibitors



Comparison of groups based on response to JAK1/2 inibitors





- 2y-OS group A 91% vs 55% group BCD vs 32% group E (group A vs E p .01)
- 2y-NRM group A 9% vs 37% group BCD (p . 07)

No differences in baseline charcateristics of disease between patients responders or not to JAK1/2 inhibitors

Multivariable Analysis of OS

Variable	Death	
	HR (95%CI)	*P*
Response: 3 groups		.03
Group A (n = 23)	1	
Group BCD (n = 64)	5.4 (1.5-20.0)	
Group E (n = 13)	8.0 (1.6-39.6)	
DIPSS score before JAK1/2 inhibitor		.003
Intermediate-1 (n = 40)	1	
Intermediate-2 (n = 48)	1.1 (.5-2.6)	
High risk (n = 6)	8.7 (2.4-31.8)	
Donor		.006
Matched sibling (n = 36)	1	
Matched unrelated (n = 50)	1.03 (.4-2.6)	
Other (n = 14)	4.3 (1.5-12.4)	
Intensity of conditioning		.10
Full intensity (n = 44)	1	
Reduced intensity (n = 56)	2.0 (.9-4.4)	

Shavanas M et al Biol Blood Marrow Transplant 2016

What is the optimal timing of HCT in patients with MF in the era of JAK inhibitors?

- Early vs delayed HCT in patients responding to JAK inhibitor therapy?
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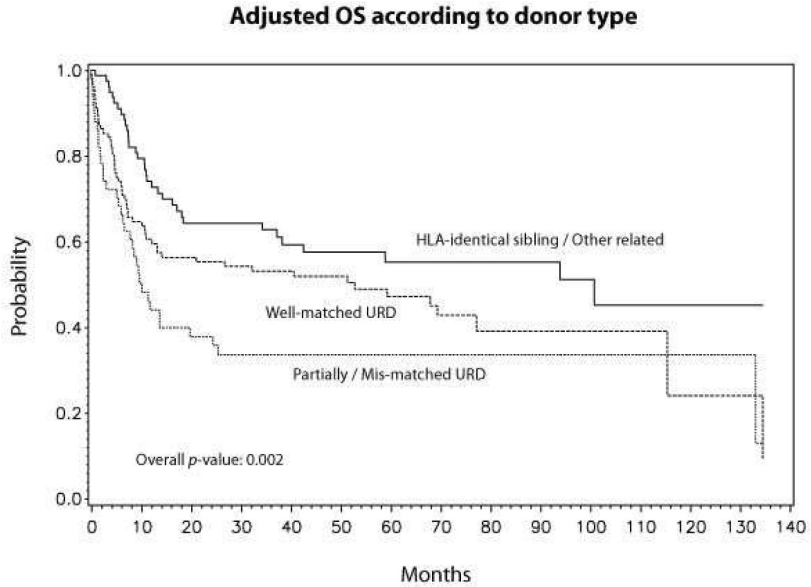
Table 1 Prospective studies of reduced-intensity transplantation in myelofibrosis

	European Group for Blood and Marrow Transplantation (EBMT) study [13] (*N*=103)	Myeloproliferative diseases research consortium (MPD_RC) study [14•] (*N*=66)
Conditioning	Flu-bu+ATG	Flu-Mel±ATG
Low-risk patients, %	17	4.5
URD, %	68	52
Survival, %	68 % at 5 years	75 % at 25 months (RD); 32 % at 25 months (URD)
NRM vs. relapse death, %	21 vs. 22 % at 3 years	22 vs. 4 % at 25 months (RD); 59 vs. 3 % at 25 months (URD)
Leukemia-free survival, %	40 % at 5 years	NR
Overall graft failure, %	2 %; 11 % needed stem cell boost	6 % (RD); 36 % (URD)

Viswabandya A et Al Curr Hematol Malig Rep 2016



Gupta V et AL Biol Blood Marrow Transplant 2014

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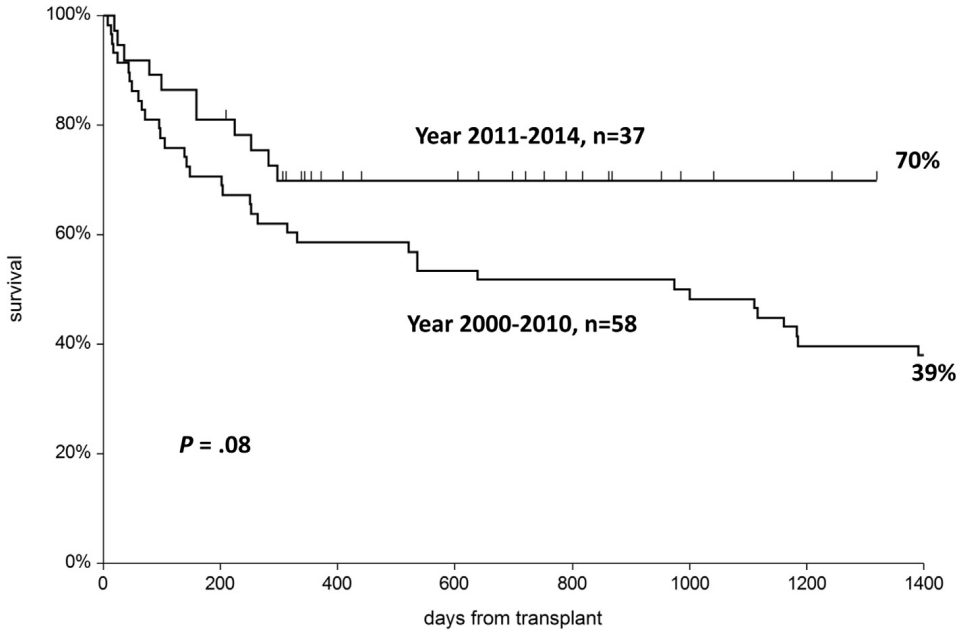
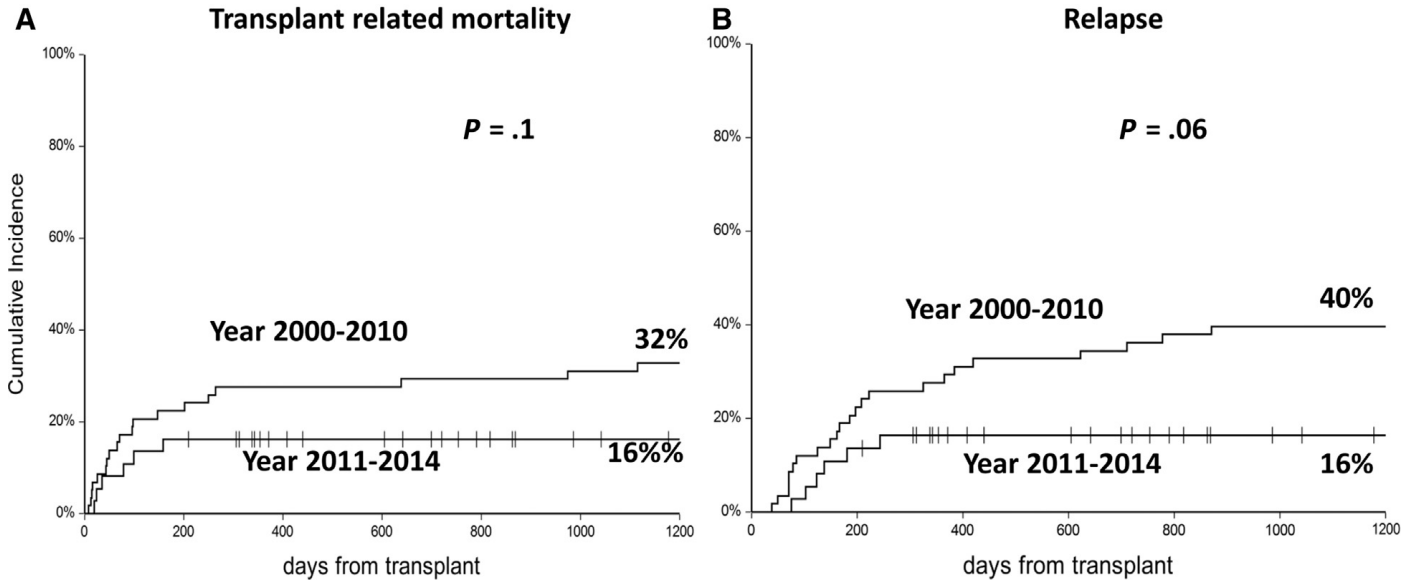
Shavanas M et al Biol Blood Marrow Transplant 2016

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

Clinical Data of Patients with Myelofibrosis

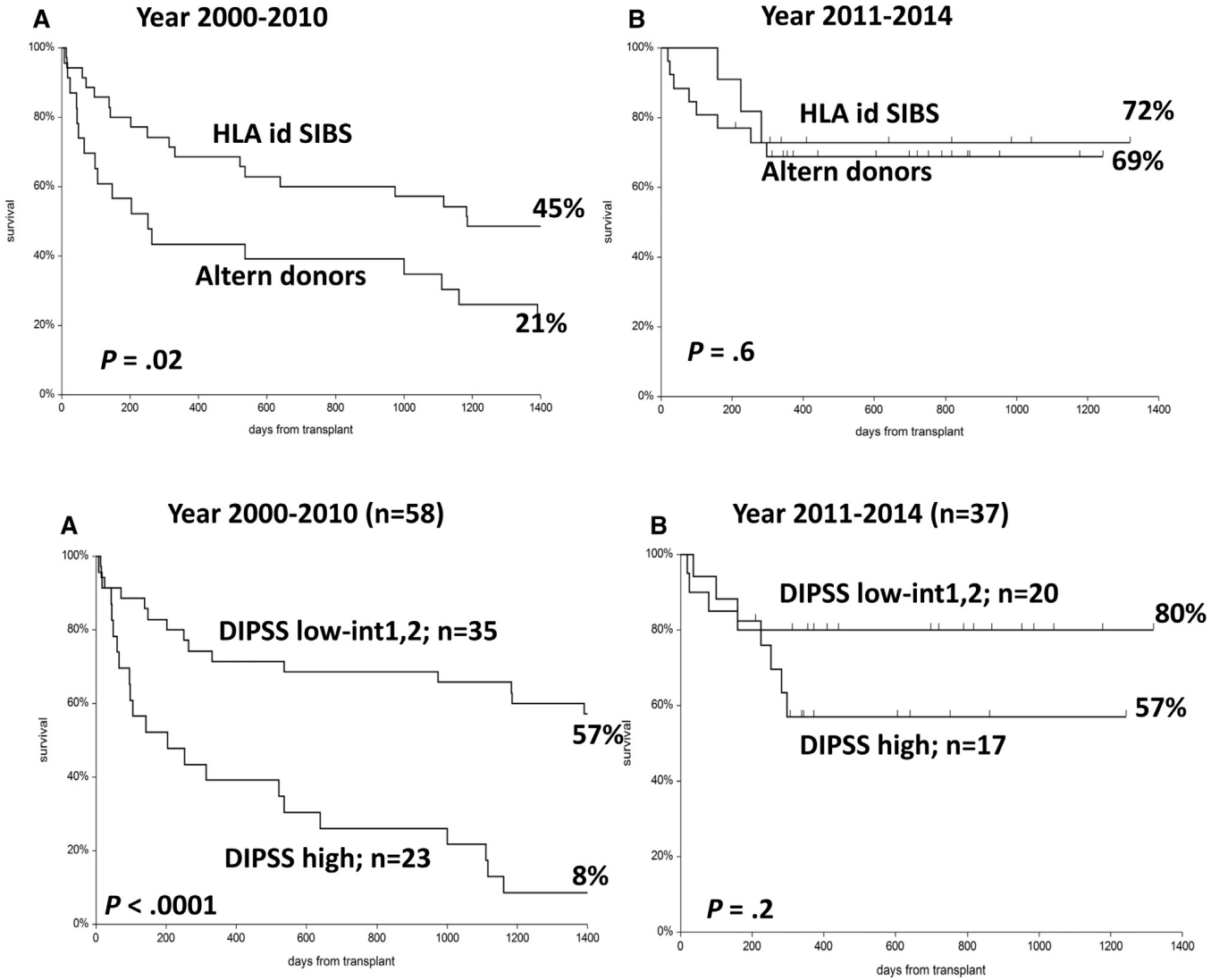
	Year of Transplantation	2000 to 2010	2011 to 2014	*P* Value
	No. of patients	58	37	
*	Age, median (range), yr	53 (24-67)	58 (37-69)	.004
	DIPSS low-int 1/int 2/high	11/24/23	8/12/17	.60
	Spleen size, median (range), cm	23 (12-40)	20 (14-30)	.04
	JAK2 mutated	20 (44%)	18 (51%)	.50
	CD34 cells in PB/μL	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





Bregante S et Al biol Blood Marrow Transplant 2016

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



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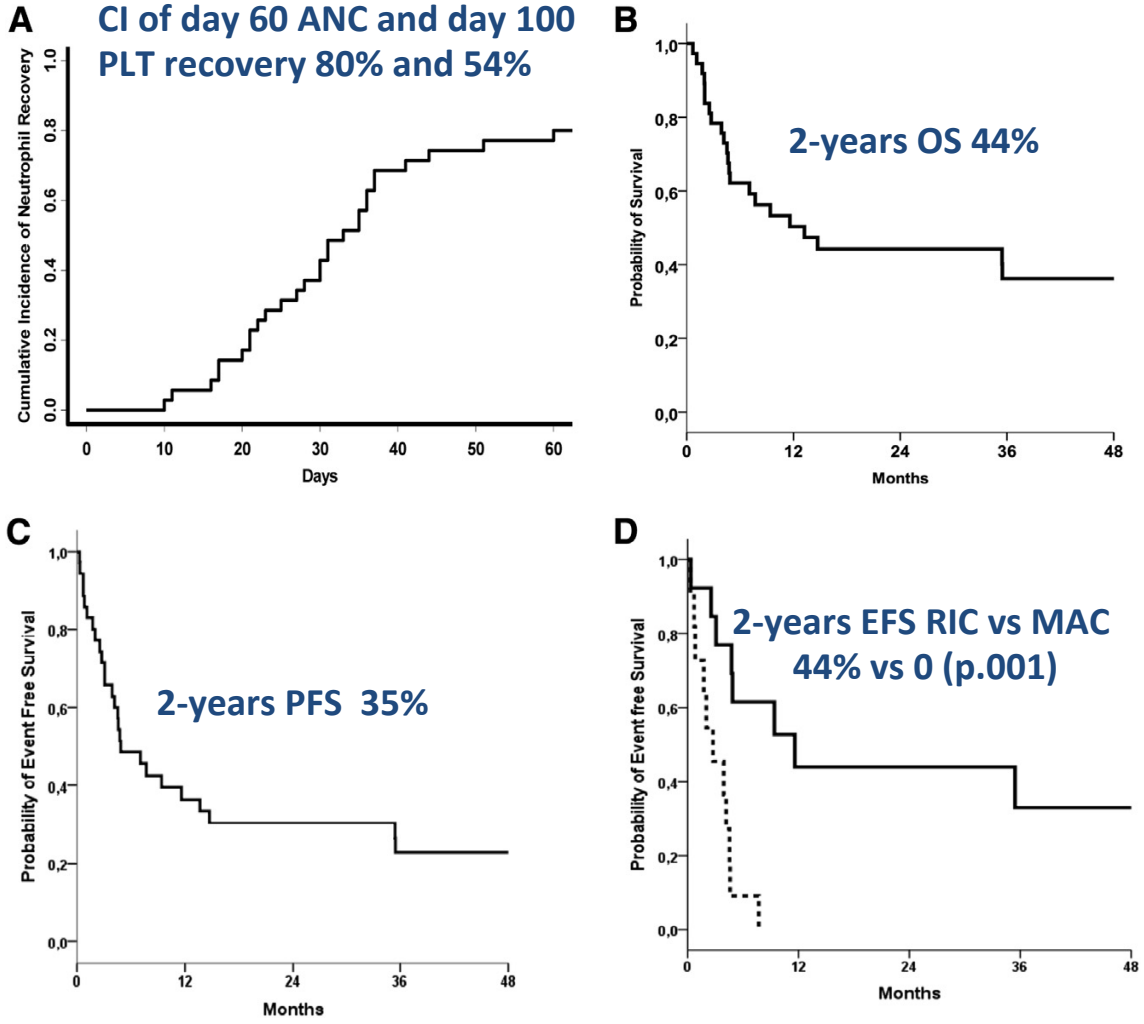
Unrelated Cord Blood Transplantation for Patients with Primary or Secondary Myelofibrosis



- Thirty five pts with PMF/ SMF underwent a single or double UCB transplant after RIC (69%) or MAC (31%) conditioning
- ***Median age 54 (28-53)***
- Seven pts in LT at Tx
- ***CB units 5/6 and 4/6 HLA matched in 23% and 77% respectively***
- ***Graft Failure 40% (14/35 pts)***
- CI of 2-years TRM 35%

Robin M et Al Biol Blood Marrow Transplant 2014

- In patients who are responding to JAK 1/2 inhibitor therapy, HCT can be considered early if a suitable matched sibling donor or well-matched donor is available

- Conversley, HCT with alternative donors can be considered in delayd in those patients who are at very high risk of leukemic transformation, or those who loss response to, or became intolerant to JAK inhibitors

What is the optimal timing of HCT in patients with MF in the era of JAK inhibitors?

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- Does donor type play a part in decision about the timing of HCT ?
- **Are there any factors predicting poor response to JAK inhibitor therapy ?**
- Do JAK inhibitors have a role as part of HCT procedure?

Correlation of mutation profile and response in patients with myelofibrosis treated with ruxolitinib

Time to treatment failure stratified by (A) molecular risk group and (B) number of mutations

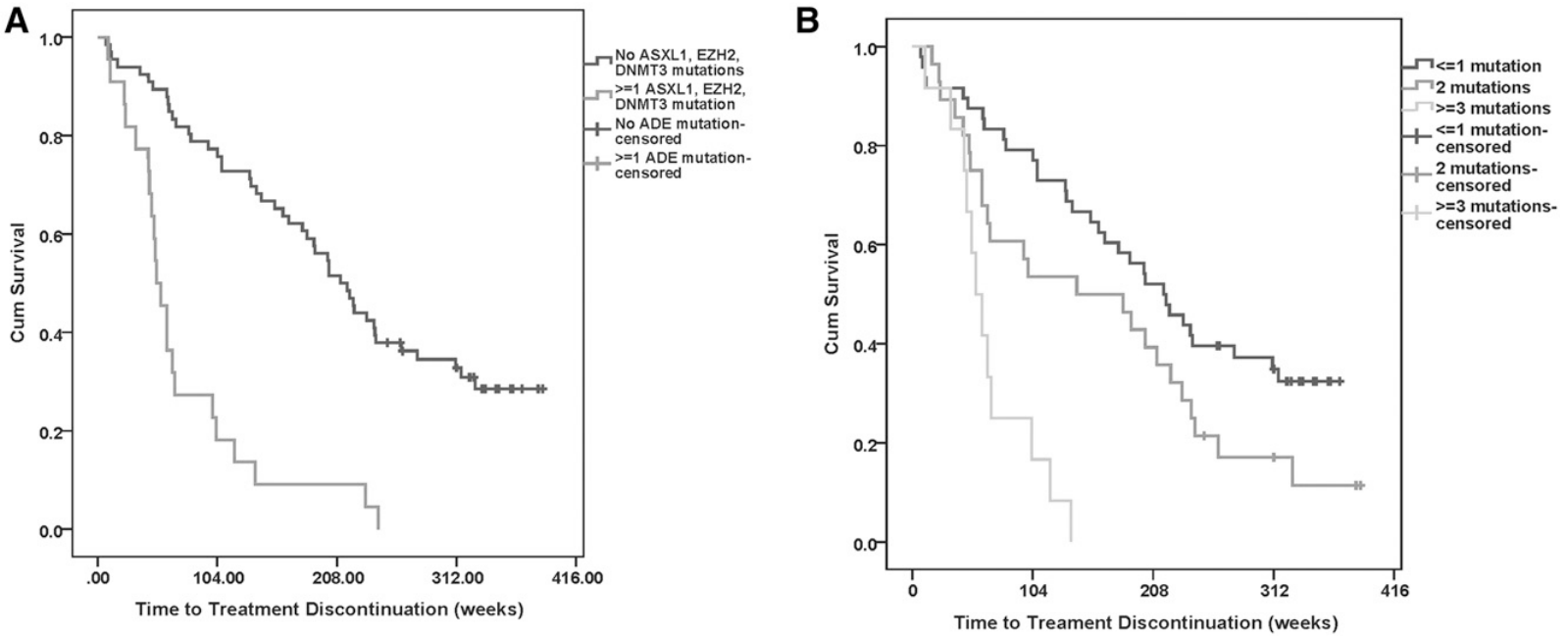

Table 4. Multivariable Cox regression analysis of TTD

Variable	HR	95% CI	*P* value
Number of mutations			
≤1	Reference		
2	2.56	1.35-4.86	**.004**
≥3	3.74	1.53-9.10	**.004**
Transfusion dependence	1.65	0.823-3.31	.158
Diagnosis			
PPV-MF	Reference		
PMF	1.85	0.959-3.57	.066
IWG-defined spleen response	0.372	0.179-0.776	**.008**

- **Spleen response** (≥ 50%reduction in palpable spleen size) is inversely correlated with number of mutations;
- Patients with **≥ 3 mutations** also have a shorter time to treatment discontinuation and OS than those with fewer mutations

Patel KP et al. Blood 2015

What is the optimal timing of HCT in patients with MF in the era of JAK inhibitors?

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- Does donor type play a part in decision about the timing of HCT ?
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- **Do JAK inhibitors have a role as part of HCT procedure?**

Study	No. of patients	Study design	Results	Conclusions
Jackel et al. 2014 [24]	14	Retrospective	Engraftment in 13 patients (93 %); graft fibrosis (n=1) and treatment-related sepsis (n=1)	Tapering ruxolitinib until conditioning did not result in unexpected SAEs
Shanavas et al. 2014 [25]	6	Retrospective	No adverse impact on early post-HCT outcomes	Tapering ruxolitinib until conditioning did not result in unexpected SAEs
Stübig et al. 2014 [26]	22	Retrospective	1-year OS of 100 % in patients with a good response to ruxolitinib vs. 60 % in others	Continuing ruxolitinib until conditioning without taper resulted in no unexpected SAEs
Lebon et al. 2013 [27]	11	Retrospective	Good engraftment rates	Differing schedules of ruxolitinib tapering associated with high engraftment rates
Shanavas et al. 2015 [11]	100	Retrospective	No adverse impact on early outcomes of HCT	Continuing JAK inhibitor therapy near to start of conditioning therapy is associated with very low risk of withdrawal symptoms

Pros

- Improvment of constitutional symptoms and splenomegaly;
- Potential benefit of reduced incidence of acute GVHD (cytokines downregulation)

Cons

- “Withdrawal symptoms”;
- Immunosuppression;
- Increased risk of infections
- Tumor lysis syndrome

Viswbandya A et Al. Curr Hematol Malig Rep 2016

JAK 1/2 inhibition in transplant eligible patients

At present, there are no convincing data to demonstrate the beneficial impact of JAK inhibitor therapy in the transplant procedure. We recommend that the combination of JAK inhibitors in transplant protocols should be used with caution either as part of clinical trials or at experienced centers. For patients who are on JAK inhibitors prior to HCT, we recommend that JAK inhibitors should be continued near to the transplant, and a gradual taper over 4 to 5 days prior to the start of conditioning therapy is recommended.

Viswabandya A et Al. Curr Hematol Malig Rep 2016

Recommendations on allo-HCT in MPN-MF

	British Committee for Standards in Hematology (2012)[67]	*ELN/EBMT (2015)*
Patient selection and conditioning regimen	Transplant eligible patients <45 years of age, with an IPSS risk of intermediate-2 or high, especially with transfusion dependence and/or adverse cytogenetic abnormalities, should be considered for myeloablative allo-SCT Transplant eligible patients with an IPSS risk of intermediate-2 or high, especially with transfusion dependence and/or adverse cytogenetic abnormalities, together with an HSCT comorbidity index $\geqslant 3$, or who are aged over 45 years, should be considered for RIC allo-HSCT. Patients should be transplanted before they have received more than 20 units of red cells. Use of oral busulfan should be recommended by targeted dosing according to plasma levels. Alternatively, intravenous busulfan can be used, guided by plasma levels where possible.There is no conclusive evidence to support use of a specific MA or RIC conditioning regimen, although favorable results have been achieved following BUCY and FLUBU and anti-lymphocyte globulin. Every effort should be made to enroll patients in prospective clinical studies and data should be reported to National and International Registries	All patients with intermediate-2 or high-risk disease according to IPSS, DIPSS or DIPSS+, and age <70 years, should be considered candidates for allo-SCT. Patients with intermediate-1-risk disease and age <65 years should be considered candidates for allo-SCT if they present with either refractory, transfusion-dependent anemia, or a percentage of blasts in peripheral blood greater than 2%, or adverse cytogenetic. Patients with low-risk disease should not be considered candidates for allo-SCT. The optimal intensity of the conditioning regimen still needs to be defined. For patients with higher age and/or comorbidities, a lower Intensity regimen is more appropriate, while for patients with advanced disease and good performance status a more intensified regimen should be selected. A spectrum of reduced intensity conditioning regimens and protocols has shown acceptable transplant-related mortality and overall survival There is no direct evidence to recommend which of these regimens should be preferentially adopted. The Panel identified this as an area of a major unmet clinical need.

Kroger NM et Al. Leukemia 2015

Conclusions

- Hematopoietic stem cell transplantation is the only curative therapy for primary (PMF) and secondary (post-TE or post-PV) myelofibrosis;
- The optimal timing of HSCT for MF has been a matter of debate; the decision of transplantation should be individualized in each patient considering also factors such as young age, good performance status that may tilt the balance towards transplantation;the early HTC might be a valid option for JAK inhibitor rersponsive patients with MRD or well Machetd UD
- The complexity of decision-making for transplantation has increased further following the wider availability of JAK1/2 inhibitors , taking into account there role on the outcome of the transplant.