46th Annual Meeting of the EBMT
14th March 2021

The impact of HSCT at the ruxolitinib era

Marie Robin, MD, PhD
Hôpital Saint-Louis, AP-HP
INSERM1131, Université Paris, France

Timeline

- Expectations with ruxolitinib
- Expectations with transplantation
- The effect of transplantation in MF patients
- The use of ruxolinitib before HSCT
- The use of ruxolitinib after HSCT

DISCLOSURES OF COMMERCIAL SUPPORT

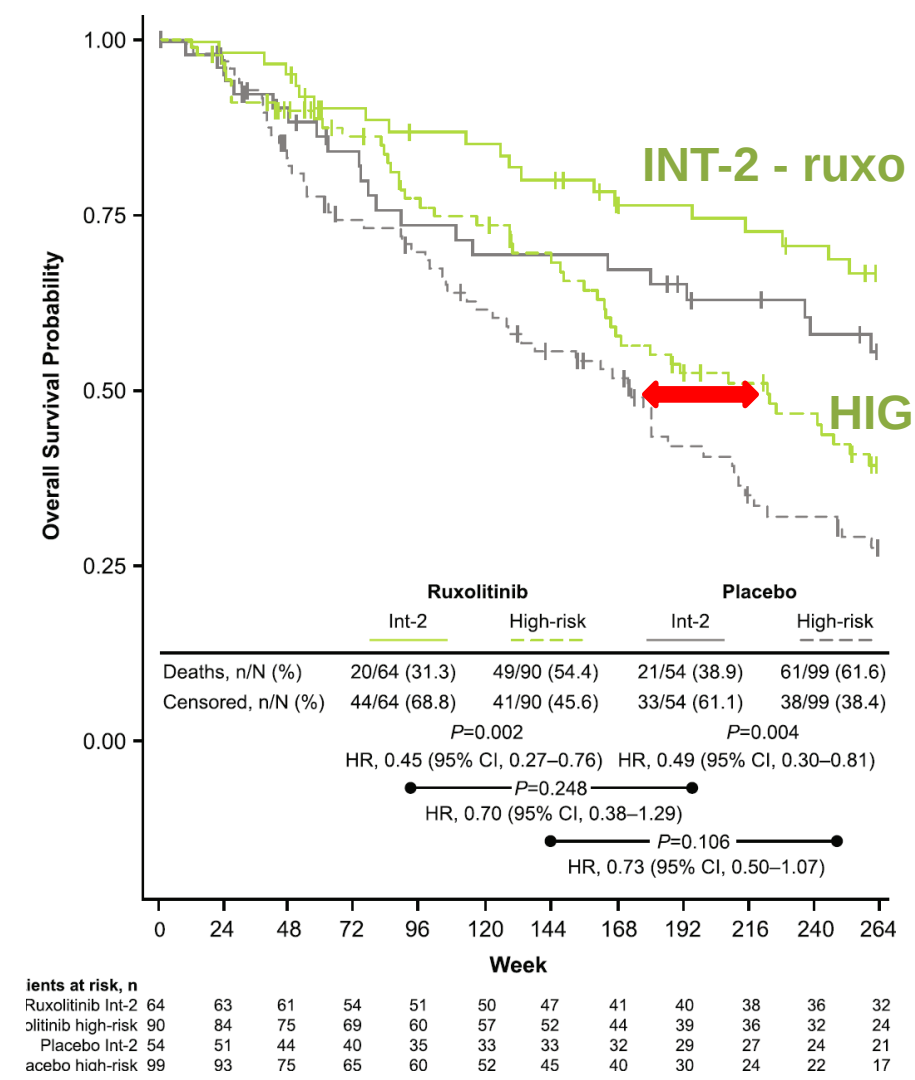
Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Novartis	**X**						
Neovii	**X**						
Medac	**X**						

Expectations with ruxolitinib

PRO	CON
• approved drug in MF	• no CR
• pills	• small proportion of PR
• good tolerance	• limited duration of remission
• quickly efficient	• cytopenia
• symptoms relief	• immune defect
• survival advantage	• effect on survival?
	• effect on AML transformation?

Long-term COMFORT I

at 5 years

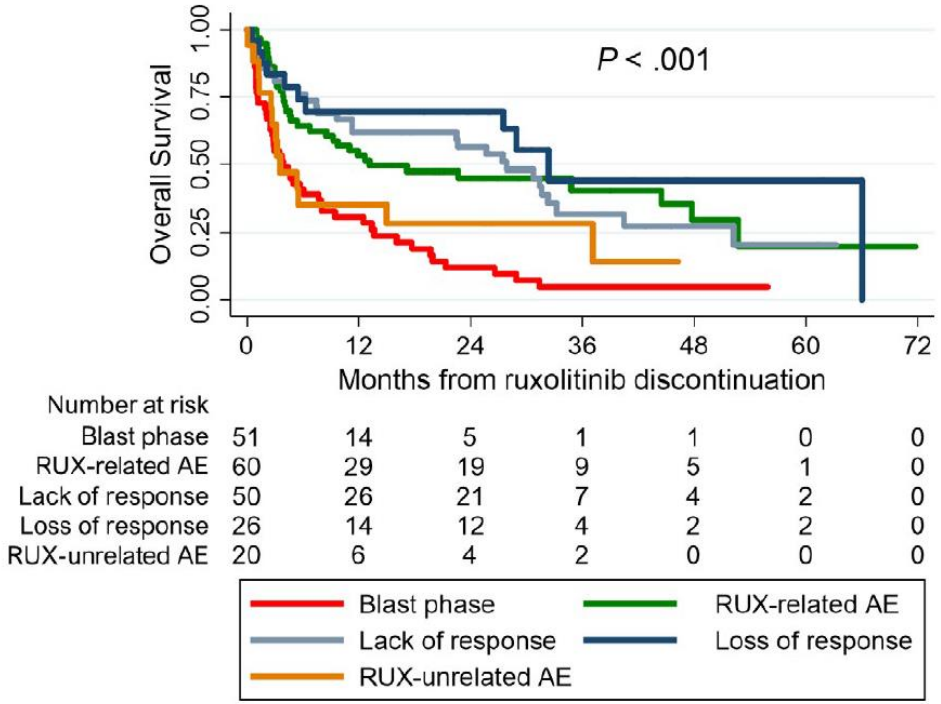


- Advantage in survival
- Constant risk of death

Verstovsek *et al. Journal of Hematology & Oncology* (2017) 10:55

Poor life expectancy after rux discontinuation

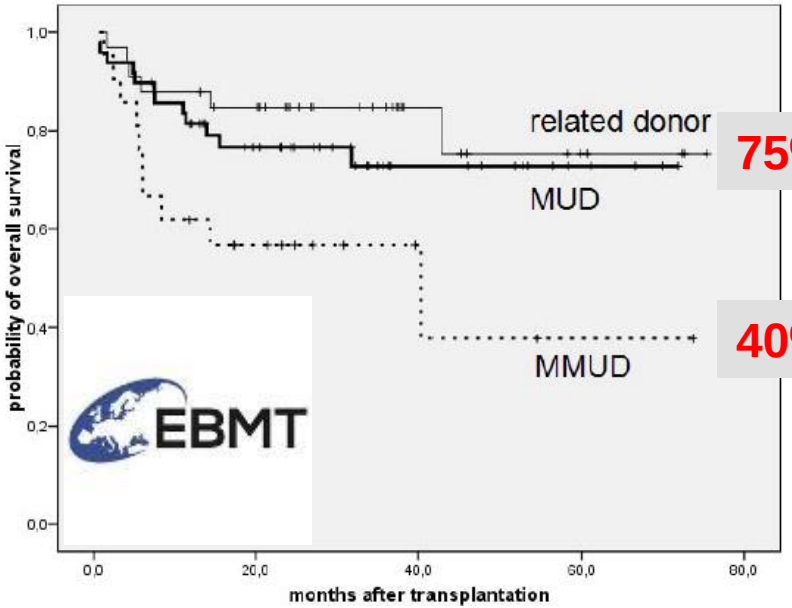
- ✓ A centralized European data base 524 patients received ruxolitinib
- ✓ At 3 years, 40.8% had stopped



Cancer 2020. Palandri

Expectations with transplantation

PRO	CON
• curative • long-term survivors • long-term data • decreases the risk of transformation and progression	• not possible for all • invasive: hospitalization... • immune failure • GVHD • rejection



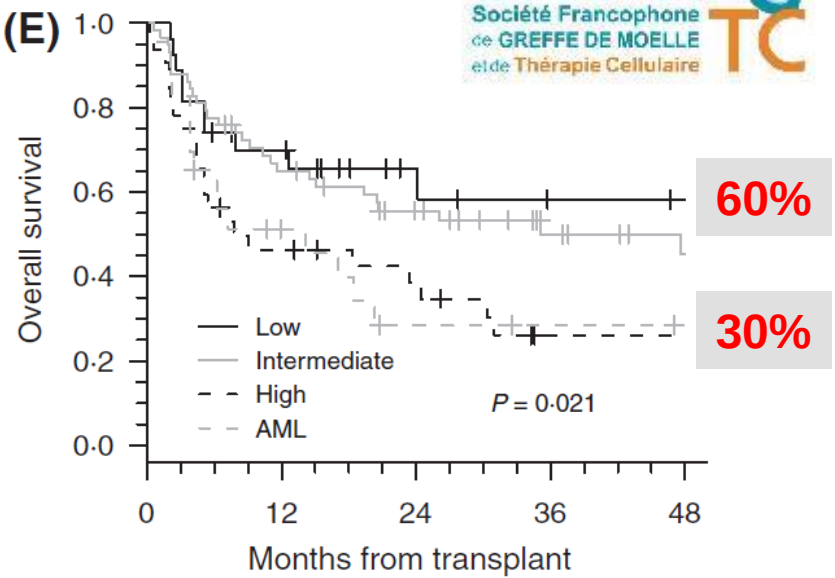
75%

40%

Blood 2009. N Kroger

- Risk factors related to disease risk, donor and patient (age)

- The majority of events (GVHD, death, relapse, rejection) occurs within 24 months

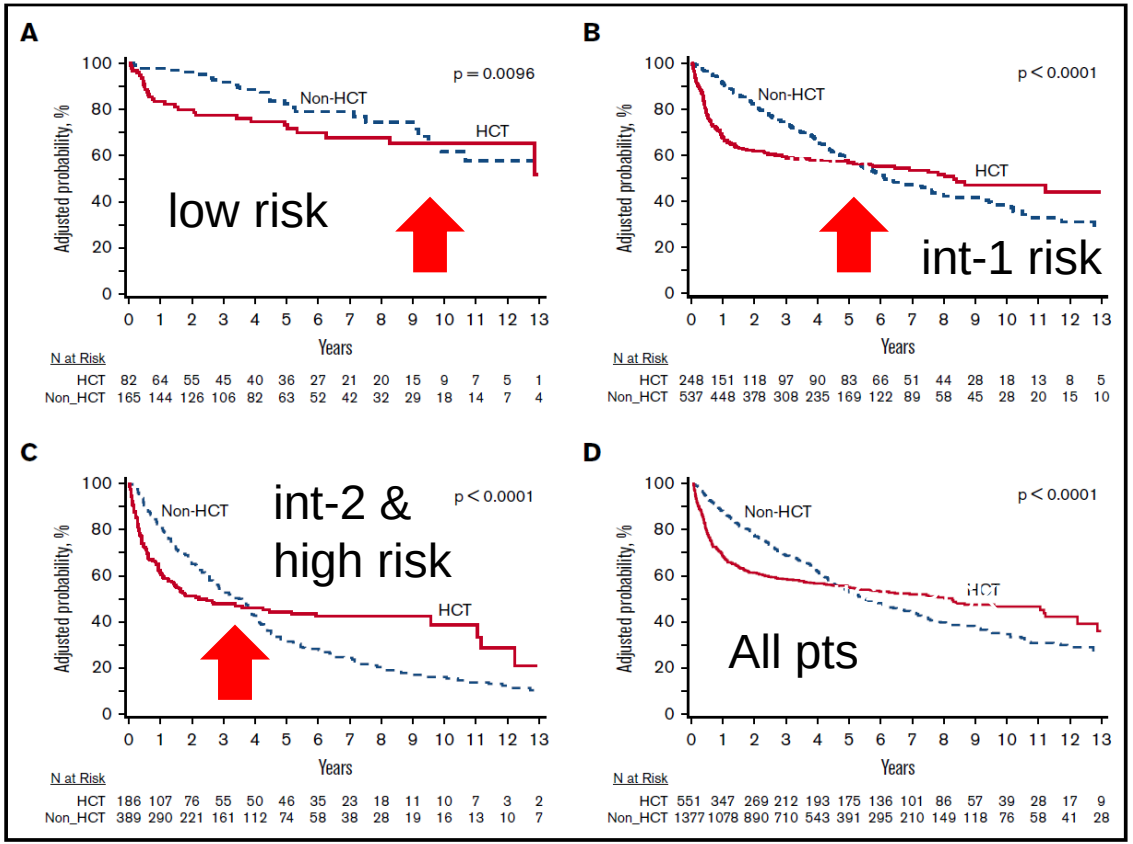


60%

30%

BJH 2011. M Robin

Early mortality vs long-term survivors

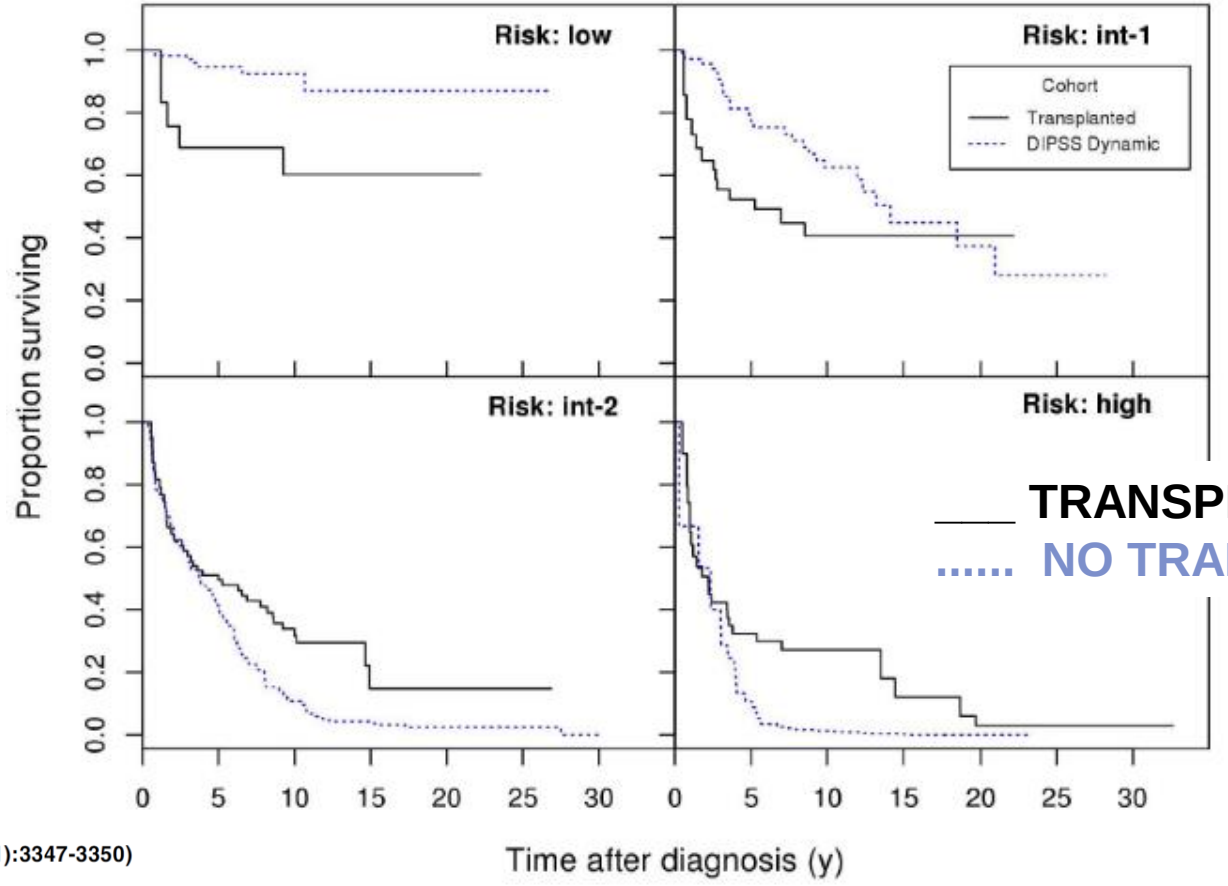


- ✓ 2000-2014
- ✓ CIBMTR & MNRC
- ✓ Excess of mortality the first year for all groups
- ✓ No difference in survival in allo but low risk after one year
- ✓ advantage of long-term survival
- ✓ multivariable model confirmed the advantage of OS

Goldwin et al

12 MAY 2020 • VOLUME 4, NUMBER 9 blood advances

Early mortality vs long-term survivors



___ TRANSPLANT, N=190

..... NO TRANSPLANT, N=248

blood

(*Blood*. 2015;125(21):3347-3350)

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

Nicolaus Kröger,[1] Toni Giorgino,[2] Bart L. Scott,[3] Markus Ditschkowski,[4] Haefaa Alchalby,[1] Francisco Cervantes,[5] Alessandro Vannucchi,[6] Mario Cazzola,[7] Enrica Morra,[8] Tatjana Zabelina,[1] Margherita Maffioli,[9] Arturo Pereira,[5] Dietrich Beelen,[4] H. Joachim Deeg,[3] and Francesco Passamonti[9]

(*Blood*. 2015;125(21):3347-3350)

Survival proportion†	Transplant-cohort Year			Non-transplant-cohort Year		
	1	5	10	1	5	10
Low risk	100	69 (48-99)	60 (38-95)	(96-100)	(90-99)	92 (86-99)
Int-1	78 (55-100)	52 (33-83)	41 (24-70)	(93-100)	(67-89)	63 (51-77)
Int-2	82 (68-98)	50 (37-67)	32 (21-48)	(67-88)	(32-54)	11 (5-22)
High risk	65 (46-92)	32 (19-56)	27 (15-49)	(30-100)	(3-44)	1 (0-10)

- HSCT improves OS in int-2 and high MF patients
- no patient were treated by ruxolitinib

“

But patients arrived now at HSCT on ruxolitinib so what is the impact on post-transplant outcome?

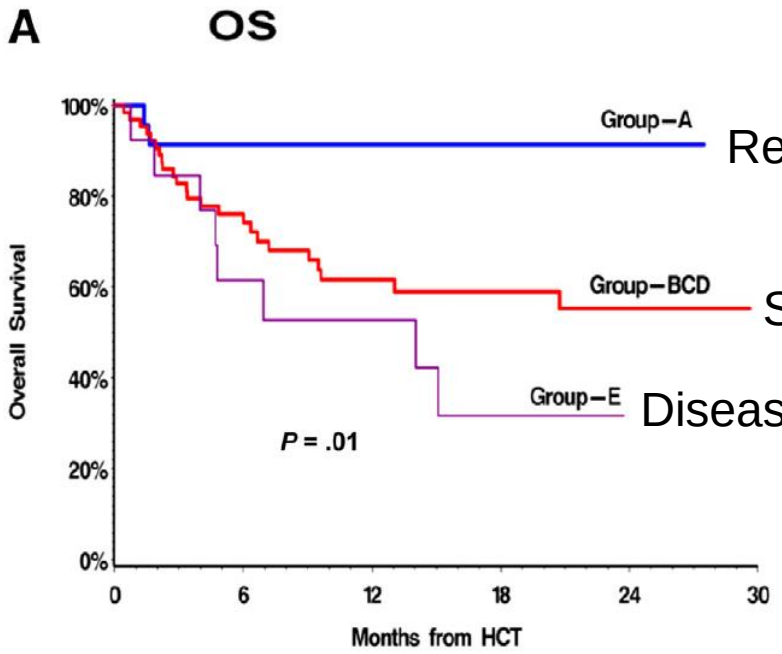
”

Rux before HSCT

Ruxolitinib could improve post-HSCT outcome of patients by:

- decreasing general symptoms and improving performance status
- reducing spleen size
- decreasing inflammatory cytokines

Ruxolitinib before HSCT



Responders, N=23

Stable or ⇑ blast only, N=64

Disease progression, N=13

A multicenter collaborative retrospective including centres from CA, US, UK

Biol Blood Marrow Transplant 22 (2016) 432–440

In patients who are progressive under ruxolitinib, outcome after HSCT is worse

Ruxolitinib & / or HSCT

Multiple variables model; transplant no transplant, CIBMTR study

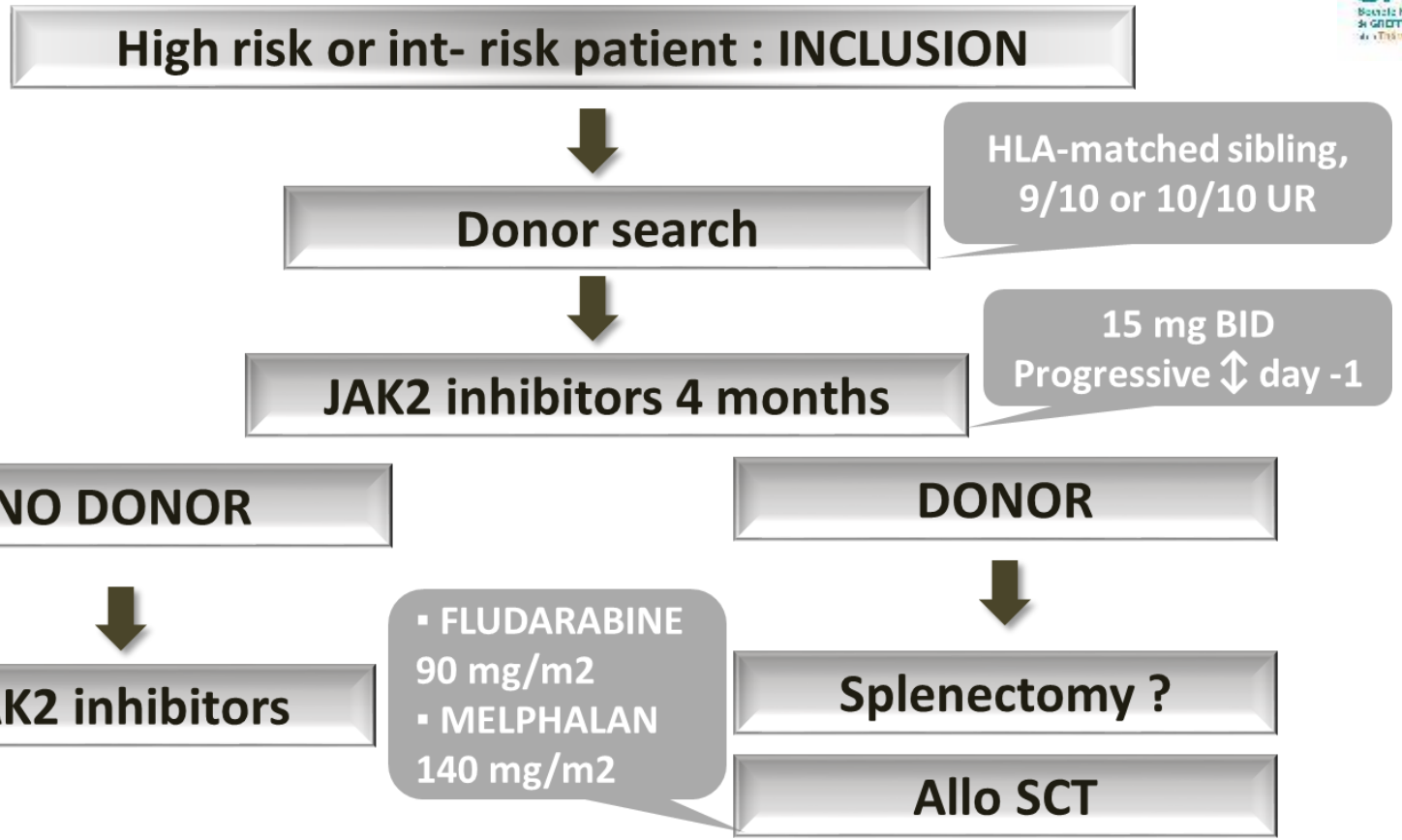
	HR	95% CI	Overall *P*
OS (≤12 mo)			<.0001
HCT	1		
Non-HCT	0.325	0.260, 0.406	
OS (>12 mo)			<.0001
HCT	1		
Non-HCT	2.109	1.656, 2.685	
Ruxolitinib			<.0001
No	1		
Yes	0.530	0.444, 0.633	

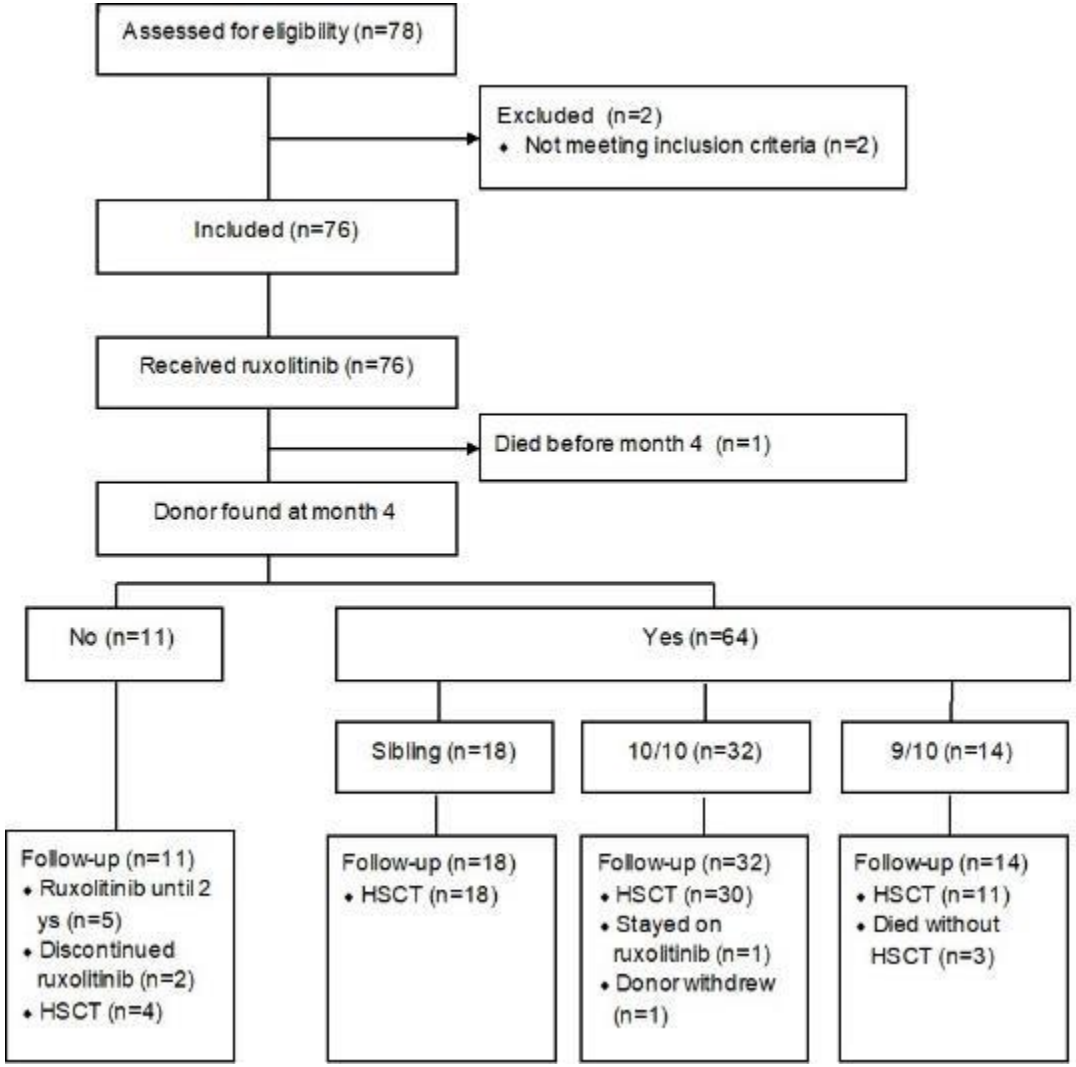
- **DIPSS, Cytogenetics, KPS are also prognostic**

Goldwin et al

12 MAY 2020 · VOLUME 4, NUMBER 9 blood advances

JAK ALLO

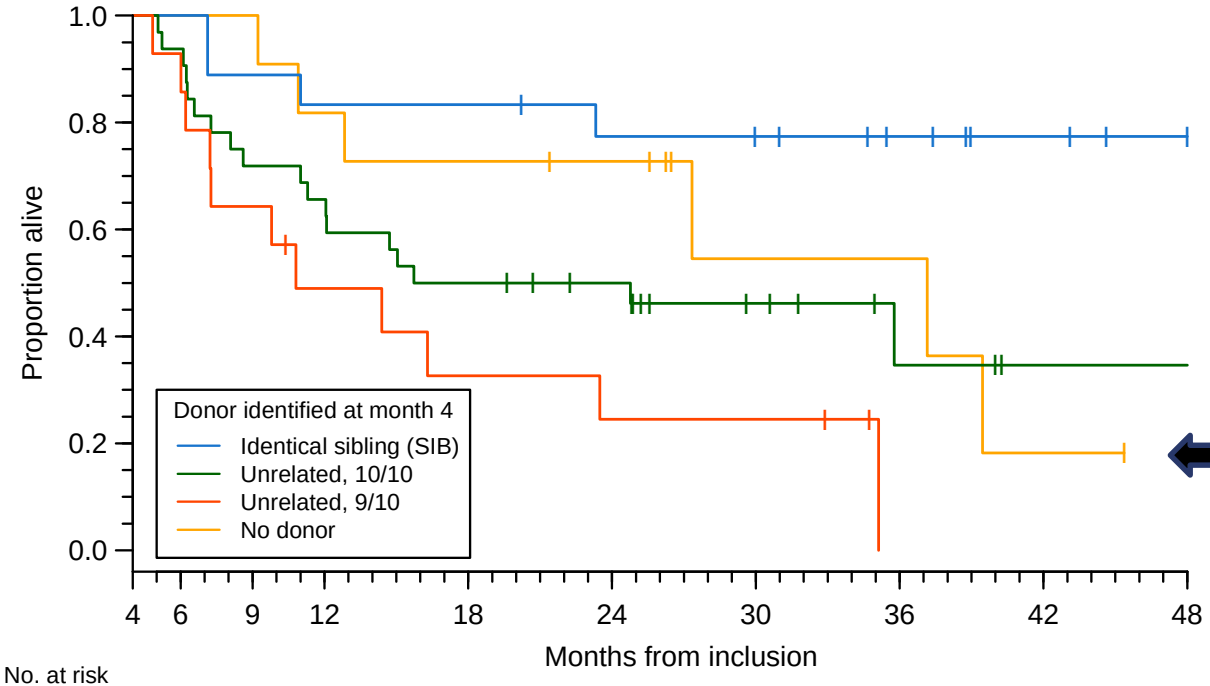

High risk or int- risk patient : INCLUSION
Donor search
HLA-matched sibling, 9/10 or 10/10 UR
JAK2 inhibitors 4 months
15 mg BID
Progressive ↕ day -1
NO DONOR
DONOR
JAK2 inhibitors
▪ FLUDARABINE 90 mg/m2
▪ MELPHALAN 140 mg/m2
Splenectomy ?
Allo SCT



31% of PR after 4 months rux

92% of rux treated patients received HSCT

Ruxolitinib vs HSCT



HLA matched sibling donor

No donor / No CR

Overall P = 0.002

No. at risk

SIB	18	18	16	15	15	13	12	9	6	4
10/10	32	30	23	21	16	13	7	3	1	1
9/10	14	13	9	6	4	3	3	0	0	0
No	11	11	11	9	8	7	3	3	1	0

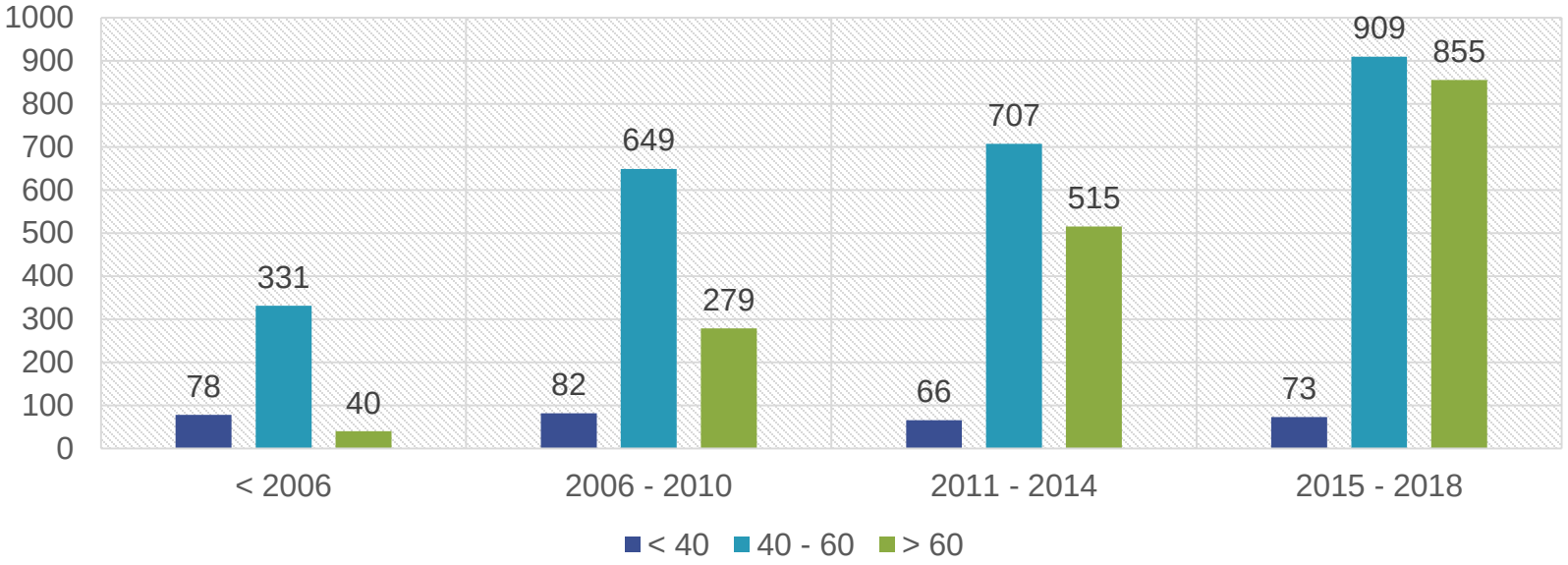
“

- ✓ *Long-term survivors are observed after HSCT, the benefit of HSCT is late as compared to ruxo therapy.*
- ✓ *HSCT remains the only curative therapy*
- ✓ *HSCT is increasingly used in MF patients*

”

EBMT European Society for Blood and Marrow Transplantation

Development of allogeneic HSCT of myelofibrosis in Europe (EBMT)



Phase 2 studies

testing pre-transplantation ruxolitinib

- MDRC114: graft failure and NRM / previous MRC110 trial (BBMT 2019. Gupta)
- FHRC: 2-year OS / historical (BBMT 2020 Salit)
- JAK-ALLO: 1-year DFS / historical (BMT 2020 Robin)

Procedure	Pre-graft response	Graft failure/ NRM	OS	AGVHD/ CGVHD
Pts < 6m Ruxo Tapering → D-5* FB4+/-ATG N=21				
Pts on ruxo Flu mel / Bu Cy Tapering → D-4* N=28				
Ruxo at inclusion Flu mel+/-ATG Tapering / abrupt stop N=58 (transplanted)				

*overlap conditioning regimen

Procedure	Pre-graft response	Graft failure/ NRM	OS	AGVHD/ CGVHD
Pts < 6m Ruxo Tapering → D-5* FB4+/-ATG N=21	47%			
Pts on ruxo Flu mel / Bu Cy Tapering → D-4* N=28	NA			
Ruxo at inclusion Flu mel+/-ATG Tapering / abrupt stop N=58 (transplanted)	31% PR			

*overlap conditioning regimen

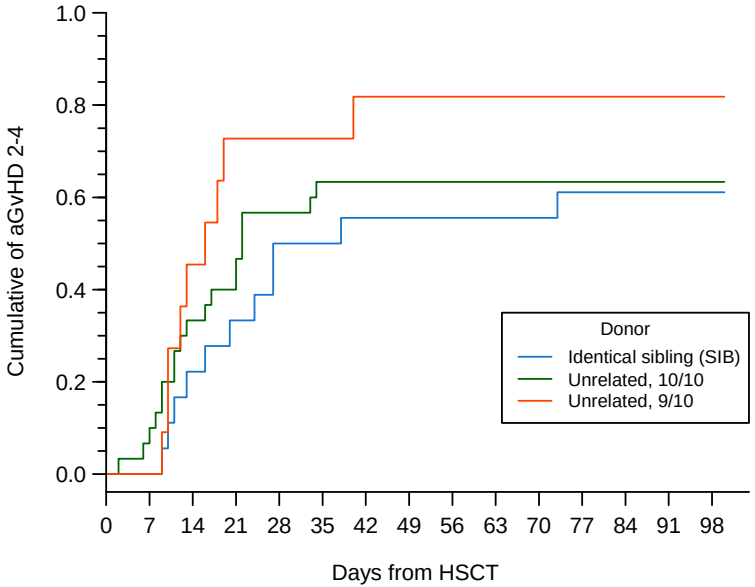
Procedure	Pre-graft response	Graft failure/ NRM	OS	AGVHD/ CGVHD
Pts < 6m Ruxo Tapering → D-5* FB4+/-ATG **N=21**	47%	3 GF 28% at 2-y	61% at 2-y	
Pts on ruxo Flu mel / Bu Cy Tapering → D-4* **N=28**	NA	No GF 2 pts	86% at 2-y	
Ruxo at inclusion Flu mel+/-ATG Tapering / abrupt stop **N=58** (transplanted)	25% PR	1 GF	55% at 2-y	

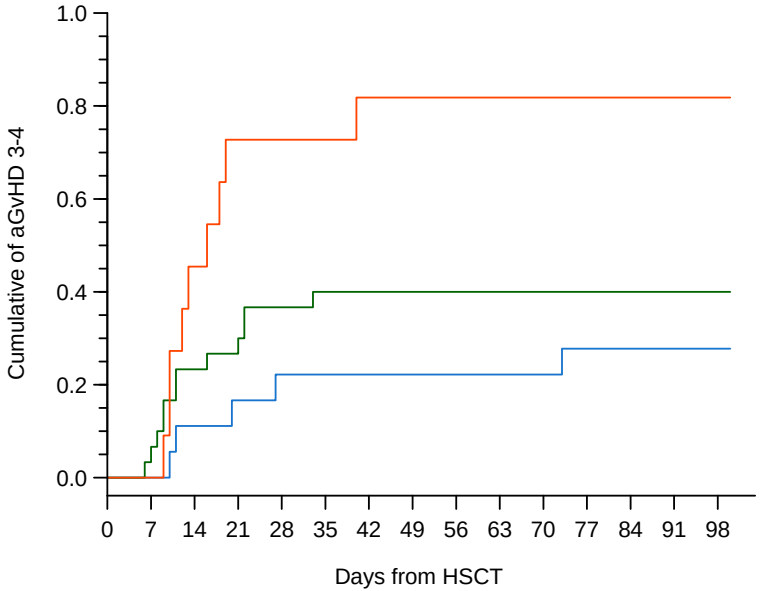
*overlap conditioning regimen

Procedure	Pre-graft response	Graft failure/ NRM	OS	AGVHD/ CGVHD
Pts < 6m Ruxo Tapering → D-5* FB4+/-ATG N=21	47%	3 GF 28% at 2-y	61% at 2-y	64%/76%
Pts on ruxo Flu mel / Bu Cy Tapering → D-4* N=28	NA	No GF 2 pts	86% at 2-y	78%/41%
Ruxo at inclusion Flu mel+/-ATG Tapering / abrupt stop N=58 (transplanted)	25% PR	1 GF	55% at 2-y	66%/ND

*overlap conditioning regimen

Hyper acute and severe GVHD





JAK ALLO trial

in press BMT. Robin et al

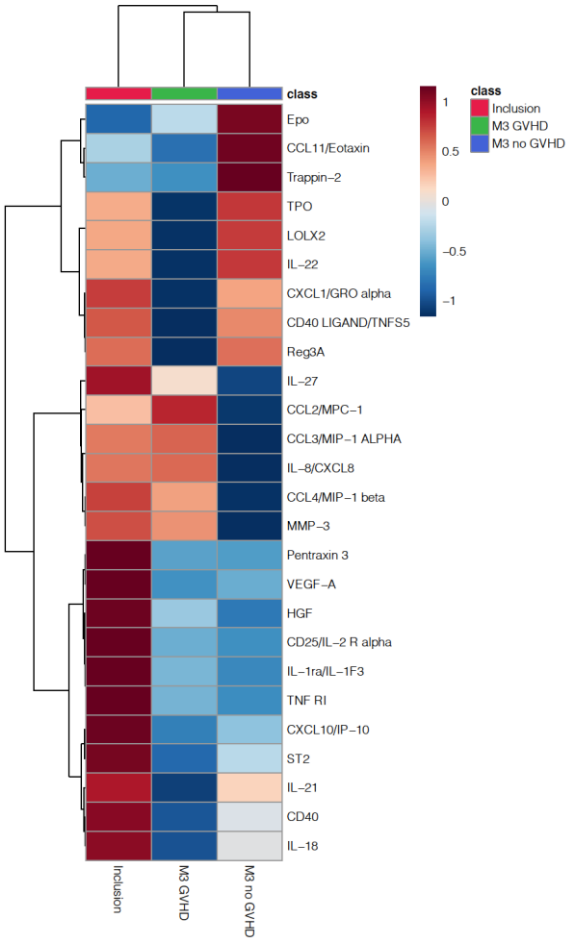
Is incidence of GVHD higher after ruxolitinib?

What were incidences of acute GVHD before ruxolitinib era in MF?

Studies	N=	TRM	Survival
Blood 1999	55	27% (1 y)	47% (5 y)
Blood 2003	56	32% (3 y)	58% (3 y)
BBMT 2007	104	ND	61% (5 y)
Haem 2008	100	43% (3 y)	42% (3 y)
Blood 2009	**103**	**16% (1y)**	**67% (5 y)**
BBMT 2009	289	35-50%(5 y)	37% (5 y)
BJH 2011	147	29% (4 y)	39% (4 y)
Haem 2012	76	28% (1y)	53% (5y)
BBMT 2014	233	24% (5 y)	47% (5y)
Blood 2014	**66**	**22 (S) vs 59 (UR)**	**72 vs 32%**
BBMT 2017	223	20% - 40 (HR)%	75%- 35% (5y)

Studies	N=	AGVHD	TRM	Survival
Blood 1999	55	60%/33%	27% (1 y)	47% (5 y)
Blood 2003	56	68%	32% (3 y)	58% (3 y)
BBMT 2007	104	64%	ND	61% (5 y)
Haem 2008	100	41%	43% (3 y)	42% (3 y)
Blood 2009	**103**	**27%**	**16% (1y)**	**67% (5 y)**
BBMT 2009	289	43%	35-50%(5 y)	37% (5 y)
BJH 2011	147	43%	29% (4 y)	39% (4 y)
Haem 2012	76	32%	28% (1y)	53% (5y)
BBMT 2014	233	37%	24% (5 y)	47% (5y)
Blood 2014	**66**	**39%**	**22 (S) vs 59 (UR)**	**72 vs 32%**
BBMT 2017	223	66%	20% - 40 (HR)%	75%- 35% (5y)

Pro-inflammatory cytokines



A specific profile is associated with patients with GVHD

JAK ALLO trial

in press BMT. Robin et al

Can we use ruxolitinib to prevent GVHD?

Ruxolitinib has been approved by FDA for steroid resistant GVHD

Peri-transplant ruxolitinib

- A pilot study of 12 patients
- 5mg BID from conditioning to engraftment stopped on day +28
- 2/10 had to stop before D+28 because of cytopenia
- 3 patients developed late acute GVHD
- No death (FU 17 months)
- Decrease in some pro-inflammatory cytokines at time of HSCT

Biol Blood Marrow Transplant 24 (2018) 2152–2156 Kroger et al

Conclusion

- Ruxolitinib may be useful to improve general performance status and reduce spleen size before HSCT
- Ruxolitinib does not replace HSCT
- Candidates to transplant should not be treated by ruxolitinib until progression
- The timing for ruxolitinib peri-transplantation remains to determine
- Small doses after HSCT may prevent GVHD efficiency

EBMT European Society for Blood and Marrow Transplantation

SFGM TC Société Francophone de GREFFE DE MOELLE et de Thérapie Cellulaire

CMWP

I Yakoub Agha
N Kröger
D Mc Lornan
T Czerw
JC Hernandez-Boluda
P Hayden
C Scheid
F Onida
S Schoenland
O Tournilhac
L Garderet
M van Gelder

ASSISTANCE PUBLIQUE HÔPITAUX DE PARIS

Hôpitaux Universitaires SAINT-LOUIS LARIBOISIERE FERNAND-WIDAL

G Socié
R Peffault
F Sicre
D Michonneau
A Xhhard
JJ Kiladjian
S Giraudier
B Cassinat
MH Schlageter

A Huynh
Y Beguin
JH Dalle
S N Guyen
R Devillier
E Daguindaux
Y Chalandon
JO Bay
E Baudoux
H Labussiere

F Colledani
E Forcade
P Turlure
T Guillaume
C Pochon
AP Pickaert
A Wallart
N Raus
M Pereira
MT Rubio