III SESSIONE:
MIELOFIBROSI E COMPLICANZE:

Inibitori di JAK2 e trapianto nella mielofibrosi

Francesca Patriarca
Università di Udine

RECOMMENDATIONS
FOR ALLO-TRANSPLANT IN MYELOFIBROSIS

prognosis of the disease

non-transplant-treatments

risk of non-relapse-mortality

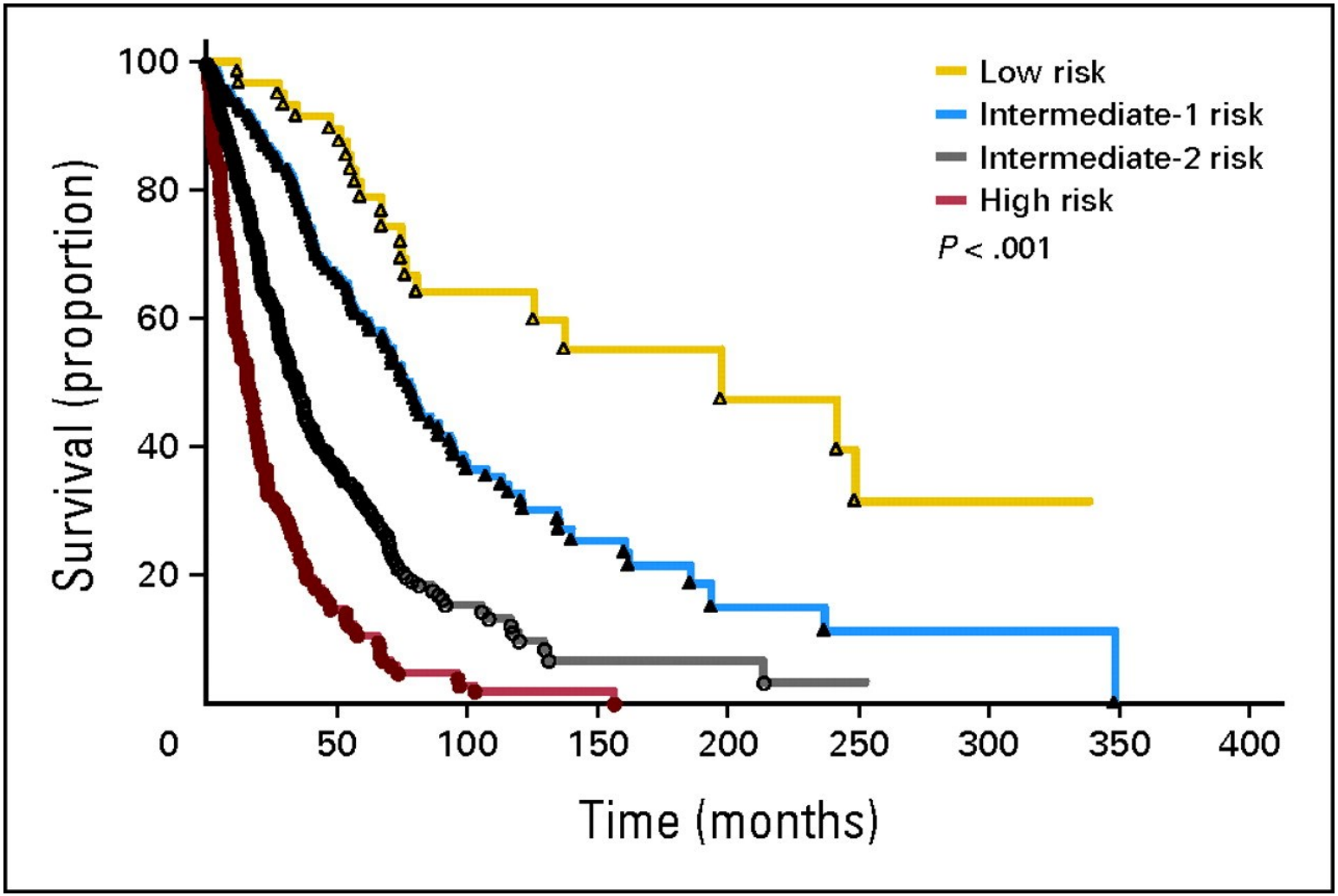
risk of morbility due to chronic GVHD

relapse after transplant

PROGNOSTIC SCORES IN MYELOFIBROSIS

score	Lille score Dupriez et al, 1996	IPSS Cervantes et al, 2008	DIPSS Passamonti 2010	DIPSS-plus Gangat 2011
Adverse factors	• Hb<10g/dL • WCc<4 or >30x10^6/L	•Age >65y •Hb<10g/dL •Blasts >1% •Constitutional symptoms •WCc >25x10^6/L	•Age >65y •Hb<10g/dL •Blasts >1% •Constitutional symptoms •WCc >25x10^6/L	•Age >65y •Hb<10g/dL •Blasts >1% •Constitutional symptoms •WCc >25x10^6/L • platelets <100x109/L •RBC need •Unfavourable karyotype:+8,-7,-5,17p,11q23,12p-
score	1 point each	1 point each	1 point each Hb: 2 points	The sum of the DIPSS score (int-1: 1 point, int-2: 2 points; high 3 points) plus 1 additional to platelets, karyo, RBC needs
risk	LOW 0 INT 1 HIGH 2	LOW 0 NT-1 1 NT-2 2 HIGH 3	LOW 0 INT-1 1-2 INT-2 3-4 HIGH 5-6	LOW 0 INT-1 1 INT-2 2-3 HIGH 4-6

Dinamic International Scoring system–plus



Survival data of 793 patients with primary myelofibrosis evaluated at time of their first Mayo Clinic referral and stratified by their Dynamic International Prognostic Scoring System (DIPSS) + karyotype + platelet count + transfusion status prognostic scores.

Naseema Gangat et al. JCO 2011;29:392-397

RECOMMENDATIONS FOR ALLO-TRANSPLANT IN MYELOFIBROSIS

prognosis of the disease: median OS <3 years in int-2 and high-risk pts

non-transplant-treatments:

conventional chemotherapy

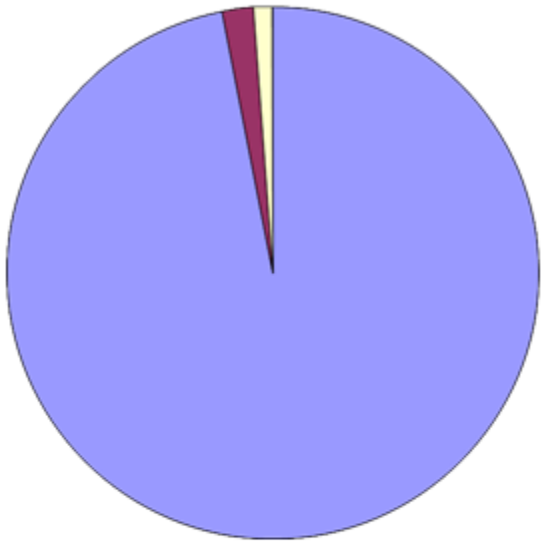
JAK2 inhibitors

risk of non-relapse-mortality

risk of morbility due to chronic GVHD

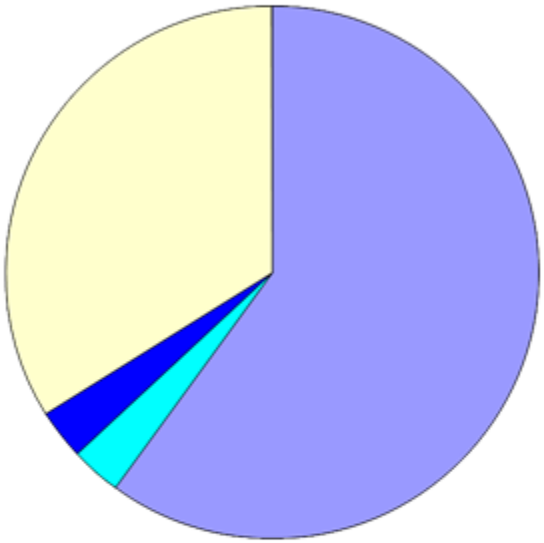
relapse after transplant

JAK2 activation and signalling defects



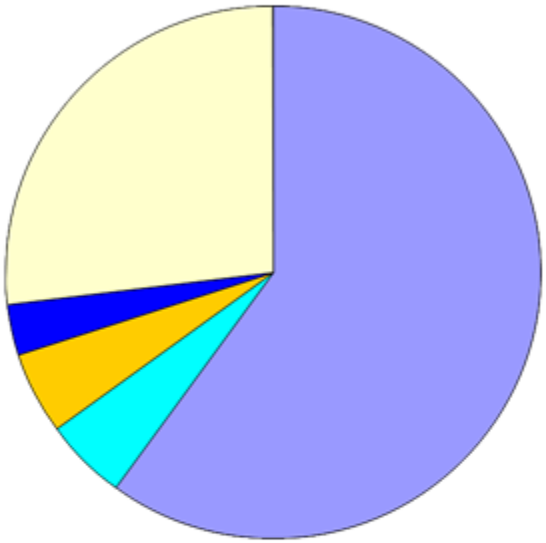
PV

- 97% *JAK2* V617F
- 2% *JAK2* ex 12
- 1% ?



ET

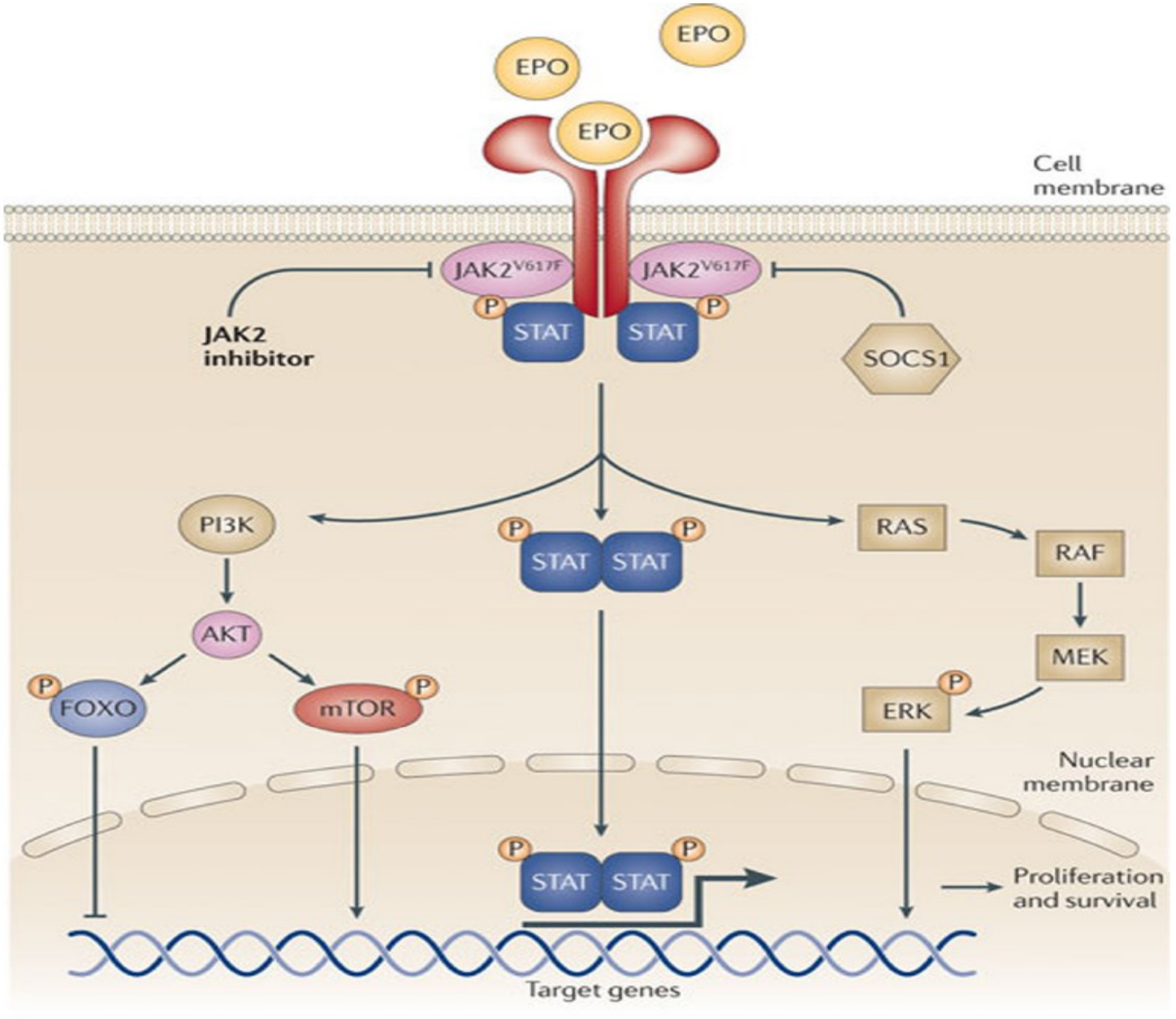
- 60% *JAK2* V617F
- 3% *MPL* ex 10
- 3% *SH2B3 (LNK)*
- 34% ?



PMF

- 60% *JAK2* V617F
- 5% *MPL* ex 10
- 5% *CBL*
- 3% *SH2B3 (LNK)*
- 27% ?

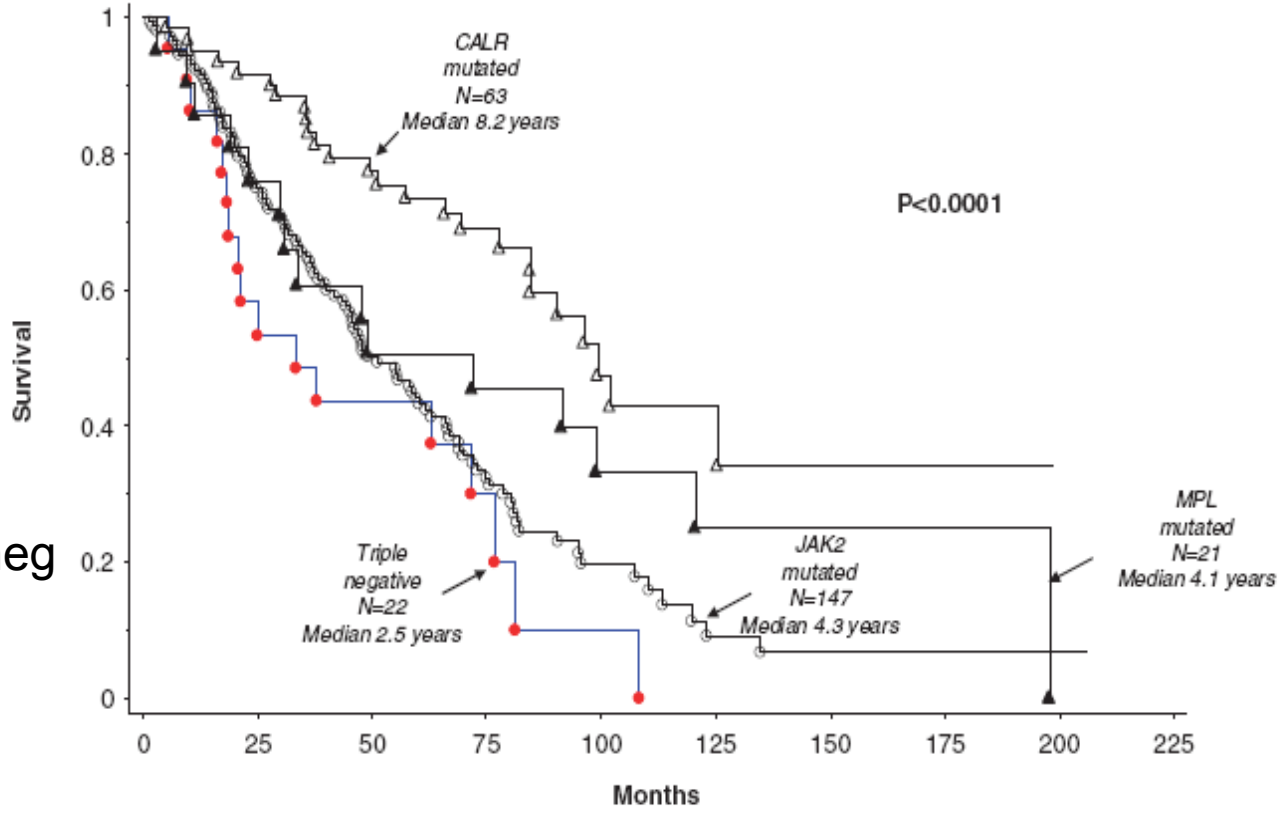
From Cross, Hematology Am Soc Hematol Educ Program.2011;2011: 208-14.


EPO
EPO
EPO
Cell membrane
JAK2V617F
JAK2V617F
P
P
STAT
STAT
JAK2 inhibitor
SOCS1
PI3K
P
STAT
STAT
P
RAS
RAF
AKT
MEK
P
FOXO
mTOR
P
ERK
P
Nuclear membrane
P
STAT
STAT
P
Proliferation and survival
Target genes

PROGNOSTIC SIGNIFICANCE OF MUTATIONAL STATUS

254 pts

147 (52%) JAK2
63 (25%) CALR
21 (8%) MPL
22 (9%) triple neg



Tefferi A et al, Leukemia 2014

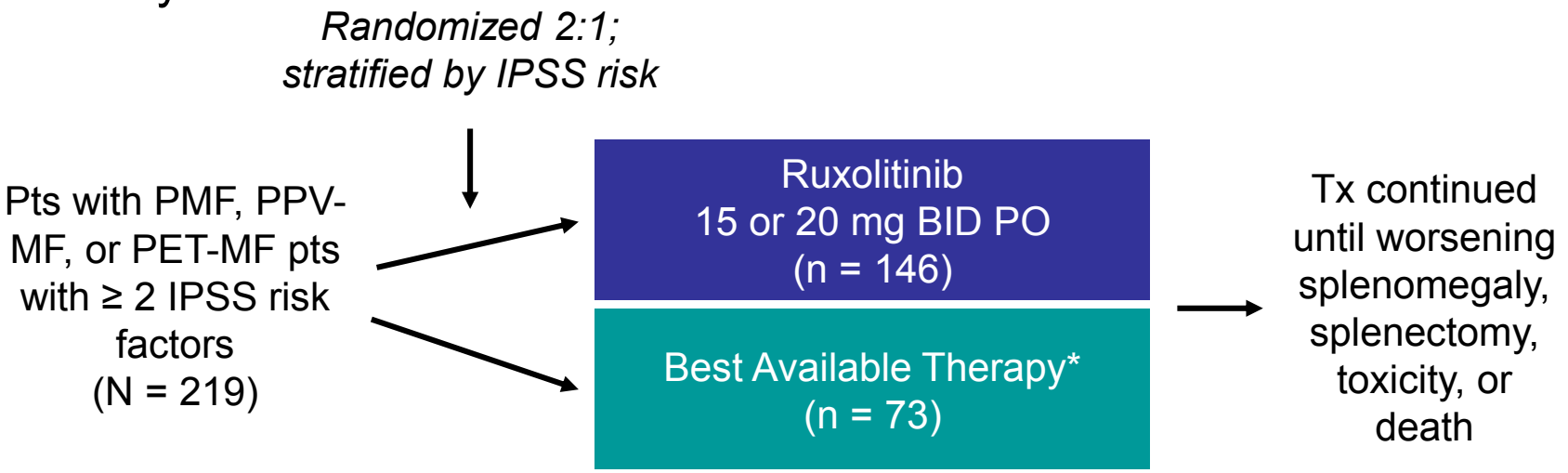
JAK1/2 INHIBITORS

JAK2 inhibitors	Study phase
ruxolitinib	approved FDA in 2011 and EMA 2012
TG101348 (SAR302503)	2
SB1518	2
CEP701 (lestauritinib)	2
CYT3871	1
LY2784J44	1

Adapted from Mesa et al, Hematology 2010

COMFORT-II: Study Design

- 5-year follow-up of multicenter, open-label, randomized phase III study[1-3]



*Crossover from BAT to ruxolitinib permitted.

- Ruxolitinib tx maintained until splenic volume increased ≥ 25% above on-study low/baseline

1. Harrison C, et al. N Engl J Med. 2012;366:787-798.
2. Cervantes F, et al. Blood. 2013;122:4047-4053.
3. Harrison C, et al. ASH 2015. Abstract 59.

COMFORT-II: 5-Yr Efficacy

- **Achieved ≥ 35% spleen volume reduction** in:
  - 53% (78/146) ruxolitinib-randomized pts
  - 42% (19/45) ruxolitinib crossover pts
  - 67% (34/51) of all pts remaining on tx at 5 yrs
- **Median duration of spleen volume reduction** with ruxolitinib was 3.2 yrs with 0.48 (95% CI: 0.35-0.60) probability of maintenance at 5 yrs
- **JAK2 V617F allele burden reduced** from baseline in 74% (35/47) ruxolitinib-randomized pts at Wk 168, 83% (35/42) at Wk 192
- **Bone marrow fibrosis improved or stabilized in** 48% (70/146) ruxolitinib-randomized pts, worsened in 19% (27/146)
- **Median OS improved** vs BAT (NR vs 4.1 yrs; HR: 0.67; 95% CI: 0.44-1.02; *P* = .06)
  - Adjusting for crossover to ruxolitinib arm with Rank-Preserving Structural Failure Time analysis, OS for pts on BAT arm was 2.7 yrs (HR 0.44; 95% CI: 0.18-1.04) in favor of ruxolitinib
- **Risk of death reduced 33% with ruxolitinib tx**

Harrison C, et al. ASH 2015. Abstract 59.

COMFORT-II: 5-Yr Safety

- Safety/tolerability profile comparable to 3-yr analysis with no new or unexpected AEs

Most Commonly Reported AEs, %	Any Ruxolitinib
AE	
▪ Thrombocytopenia	52
▪ Anemia	49
▪ Diarrhea	36
▪ Peripheral edema	33
Grade 3/4 AE	
▪ Anemia	23
▪ Thrombocytopenia	19
▪ Pneumonia	6
▪ Health deterioration	4
▪ Dyspnea	4

Harrison C, et al. ASH 2015. Abstract 59.

COMFORT-II: Discontinuations

- 50 pts (22.8%) completed 5 yrs of ruxolitinib treatment/ follow-up
  - Ruxolitinib randomized (n = 39)
  - BAT with crossover to ruxolitinib (n = 11)
- AEs accounted for 22% to 25% of ruxolitinib treatment discontinuations

Reason for Discontinuation, n (%)	Ruxolitinib (n = 146)	BAT (n = 73)	Ruxolitinib After Crossover (n = 45)
All combined	107 (73)	28 (38)	34 (76)
▪AE	35 (24)	5 (7)	10 (22)
▪Disease progression	32 (22)	4 (6)	7 (16)
▪Consent withdrawn	10 (7)	9 (12)	0
▪Other (including stem cell transplant)	16 (11)	9 (12)	6 (13)

Harrison C, et al. ASH 2015. Abstract 59.

RECOMMENDATIONS
FOR ALLO-TRANSPLANT IN MYELOFIBROSIS

prognosis of the disease:
median OS <3 years
In int-2 and high-risk pts

risk of non-relapse-mortality

Ruxolitinib treatment:

- **spleen reduction in 50% of pts**
- **≥ 5 y-clinical benefit in 20% of pts**
- **severe hematological AE in 20% of pts**

risk of morbility due to chronic GVHD

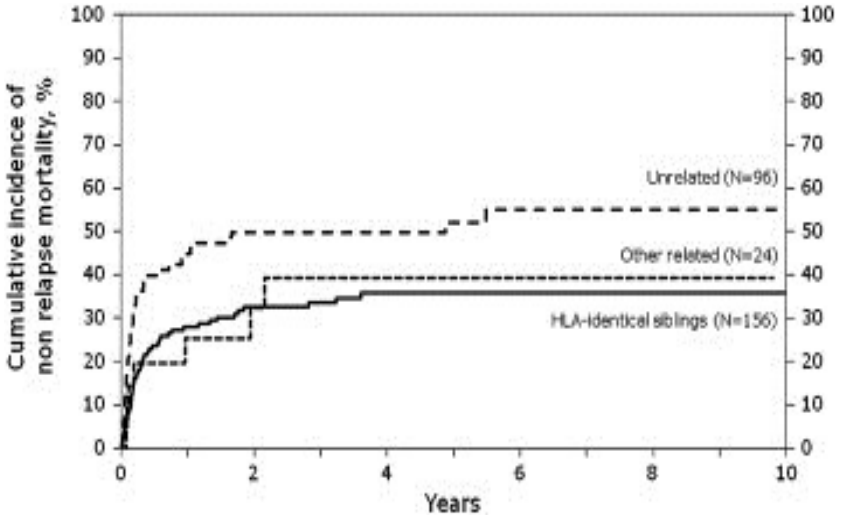
relapse after transplant

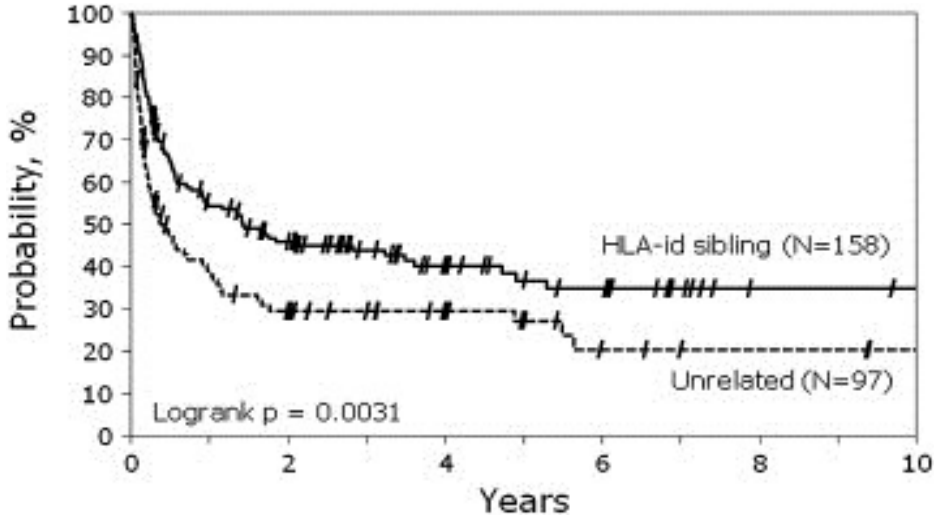
ALLOGENEIC SCT AFTER STANDARD MYELOABLATIVE CONDITIONING

	Guardiola Blood '99	Daly 2004	Ditshkowski '04	Kerbauy BBMT 2007	GITMO Haemat 2008	Stewart 2010	Ballen CIBMTR BBMT2010
N° pts	55	25	20	104	100	51	289
Median age	42 (4-53)	48 (46-50)	45 (22-57)	49 (18-70)	49 (21-68)	49 (19-64)	47 (18-73)
Conditioning	myelo	myelo	myelo	91% Myelo	49% myelo	52% Myelo	86% myelo 57% Bu-Cy
Donor Rel/unrel	49/6	15/10	13/2	59/45	82/18	33/18	162/127
Graft failure	9%	9%	n.v	10%	12%	8% all RIC	18%
NRM	27% (1y)	48% (1y)	40% (3y)	34% (5y)	43% (5y)	41% myelo 32% RIC (3y)	36% (5y)
relapse	23% (5y)	/	15% (2y)	10% (3y)	41% (2y)	15% (myelo) 46% (RIC)	32% (sibling) 23% (MUD) 40% (alternative)
OS	47% (5y)	41% (2y)	38% (3y)	51% (5y)	42% (5y)	44% myelo 31% RIC (3y)	36% (5y)

OUTCOME OF TRANSPLANT FOR MYELOFIBROSYS: THE CIMTR registry (between 1989-2002)

289 pts, 56% sibling, 86% myeloablative conditioning





Ideal candidate for myeloablative transplant:

- Age younger than 40 years
- Anemia or leukocytosis
- No comorbidity
- HLA- identical sibling

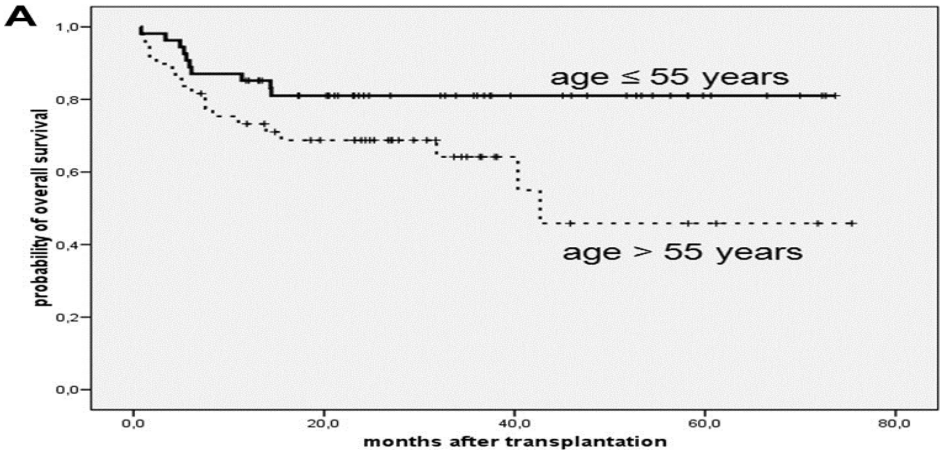
Ballen et al, BBMT 2010

ALLO-SCT AFTER REDUCED-INTENSITY CONDITIONING: retrospective analyses

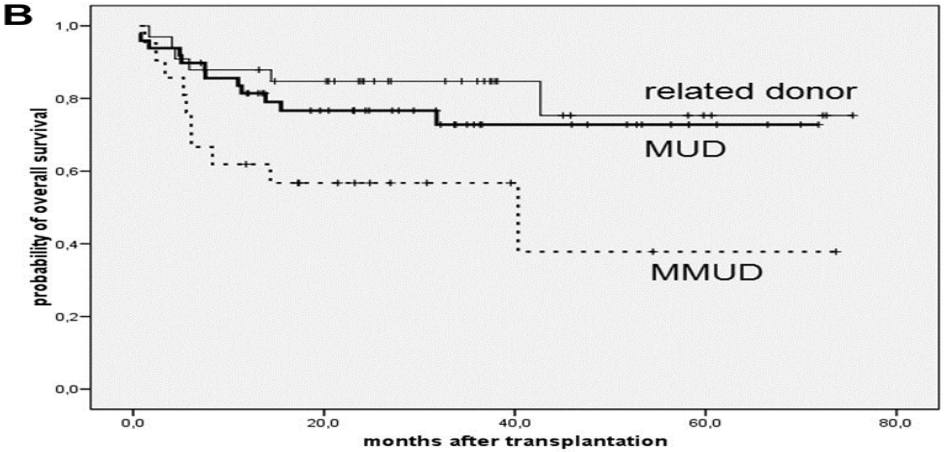
	Rondelli 2005	Merup 2006	Synder 2006	Bacigalupo 2009	Nagi 2011	Samuelson 2011	Gupta 2013 CIBMTR
N° pts	21	10	9	46	11	30	233
Median age	54 (27-68)	40 (5-63)	54 (46-68)	55 (32-68)	51 (46-62)	65 (60-78)	55 (19-79)
Conditioning	Flu-bu Thiotepa-cy Flu-melph Flu-TBI	Flu-bu Flu-cy-mel	Flu-mel Flu-TBI	Thiotepa-cy± mel	Flu-bu-aletuzumab	Flu-TBI Flu-BU Flu Mel BU-Cy	Flu-TBI Flu-Bu Flu-Mel ± ATG
Donor Rel/unrel	19/2	20/7	2/7	32/14	11	15/15	79/154
NRM	9% (1y)	29% (4y)	44% (3y)	24% (1y)	54% (2y)	30% (1y)	24% (5y)
3y-relapse	9% (3y)	NE	0% (3y)	19% (3y)	0	30% (3y)	48% (5y)
OS	78% (2y)	70% (4y)	56% (3y)	45% (5y)	46% (2y)	45% (3y)	56%/48%/34% (5y)

ALLO-SCT AFTER REDUCED-INTENSITY CONDITIONING: prospective studies

	EBMT (Kroger) 2009	Rondelli 2014
N° pts	104	66
Median age	55 (32-68)	54,5
Conditioning	Fluda-Bu ATG	Flu-Mel ±ATG
Donor: Rel/unrel	34/70	32/34
NRM	16% (1y)	22% sibling 59% unrelated (2y)
Graft failure	3% Poor graft function 11%	36%(unrelated pts)
OS	67% (5y)	75% sibling 32% unrelated (2y)

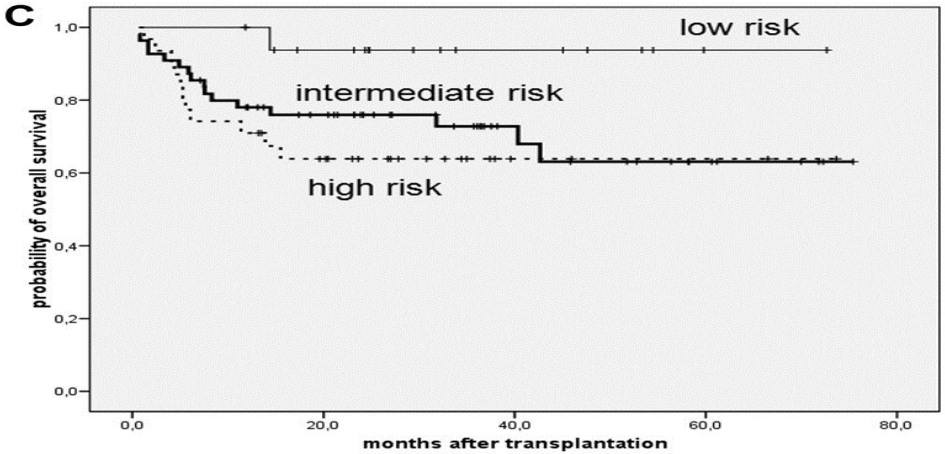


5-y OS=67%



Age > 55 years
Mismatched MUD donors
absence of JAK mutation

are negative predictors of OS

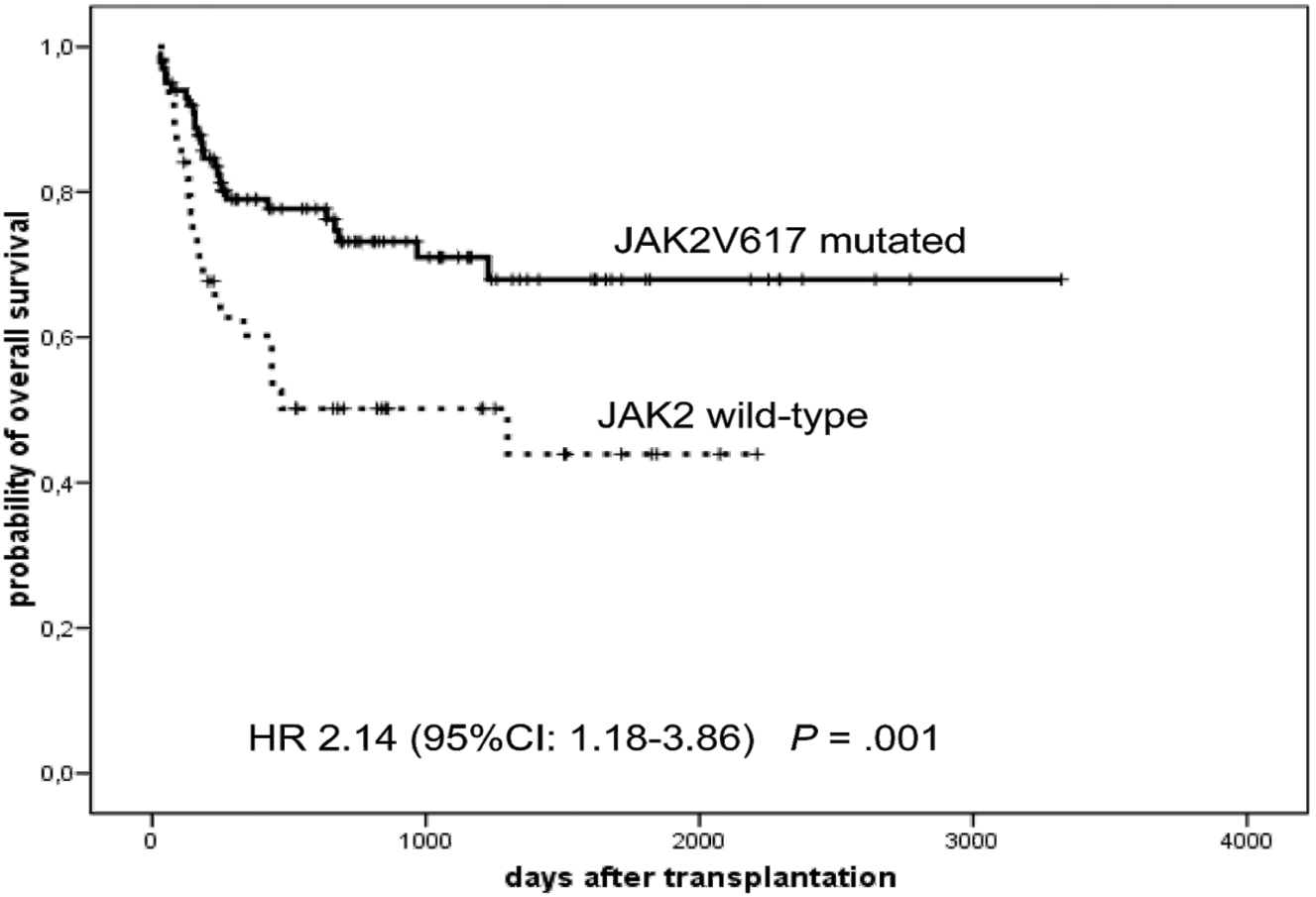


Lille high-risk score

is significative factor for increase risk of relapse

Kroeger, Blood 2009

IMPACT OF JAK2 V617F MUTATION

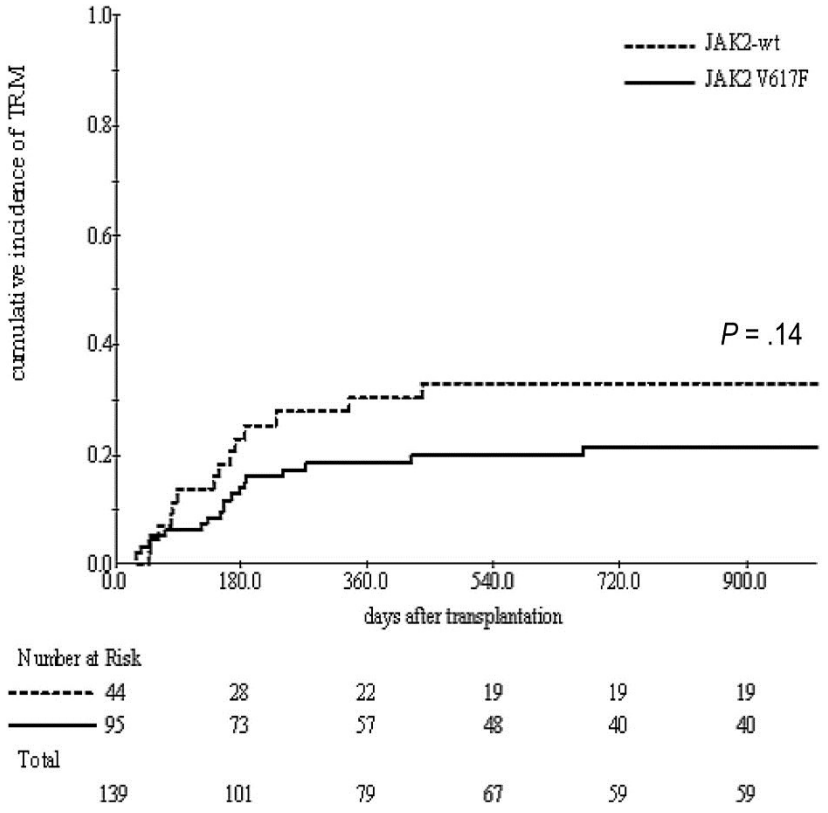


139 pts
95 pts (68%) JAK2 mut
44 pts JAK-wt

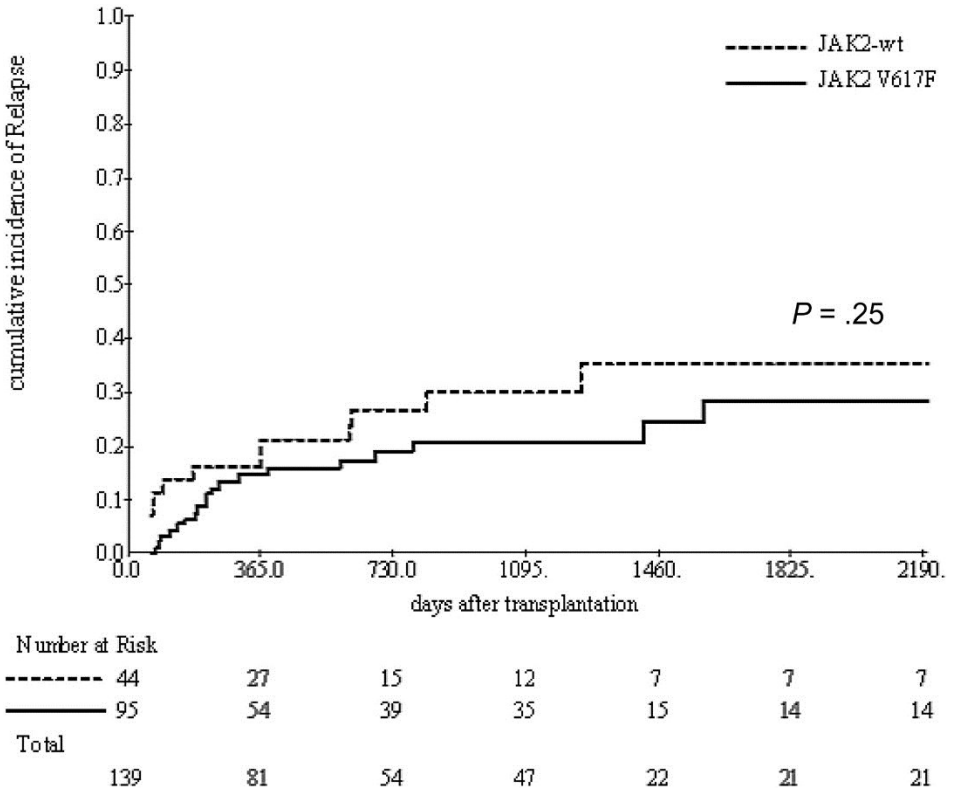
Probability of OS according to JAK2 status.

Alchalby H et al. Blood 2010;116:3572-3581

IMPACT OF JAK2 V617F MUTATION



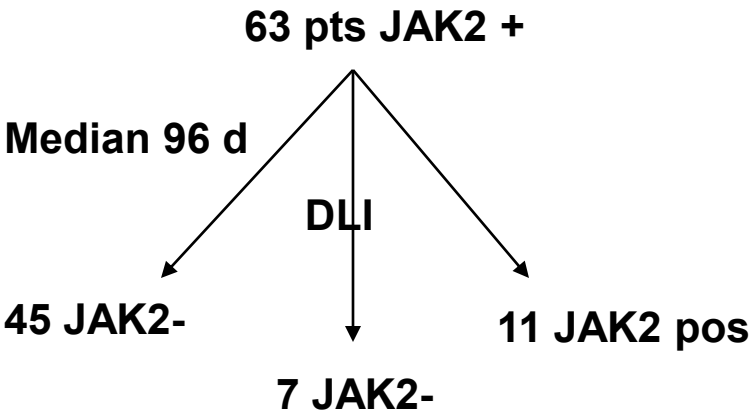
Cumulative incidence of TRM according to JAK2 status.

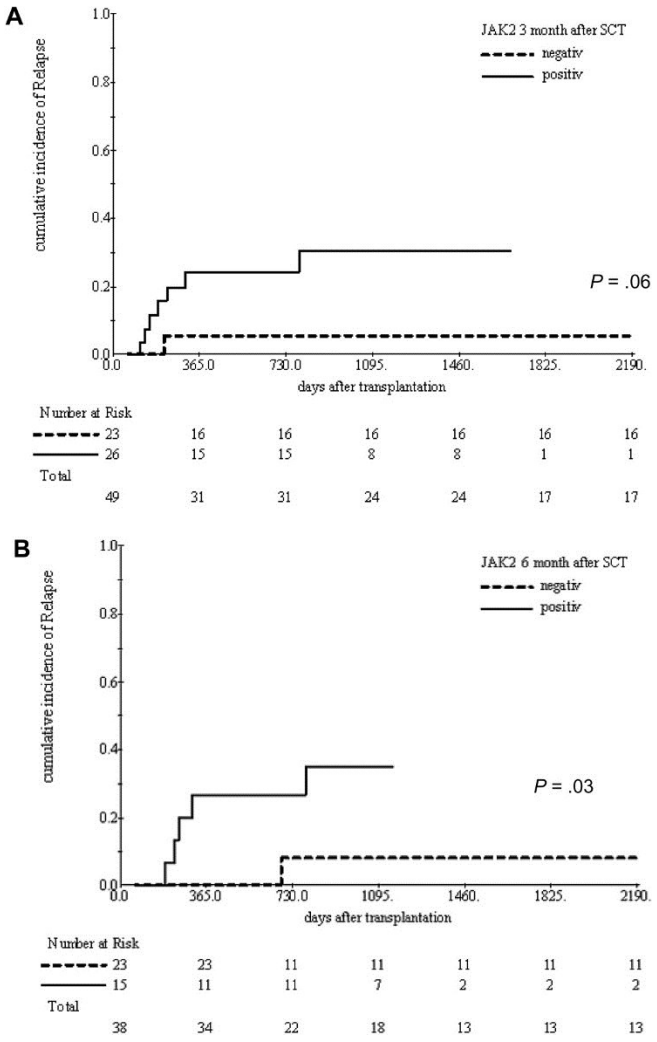


Cumulative incidence of relapse according to JAK2 status.

Alchalby H et al. Blood 2010;116:3572-3581

CLINICAL IMPACT OF JAK2 V 617F CLEARANCE AFTER allo-SCT





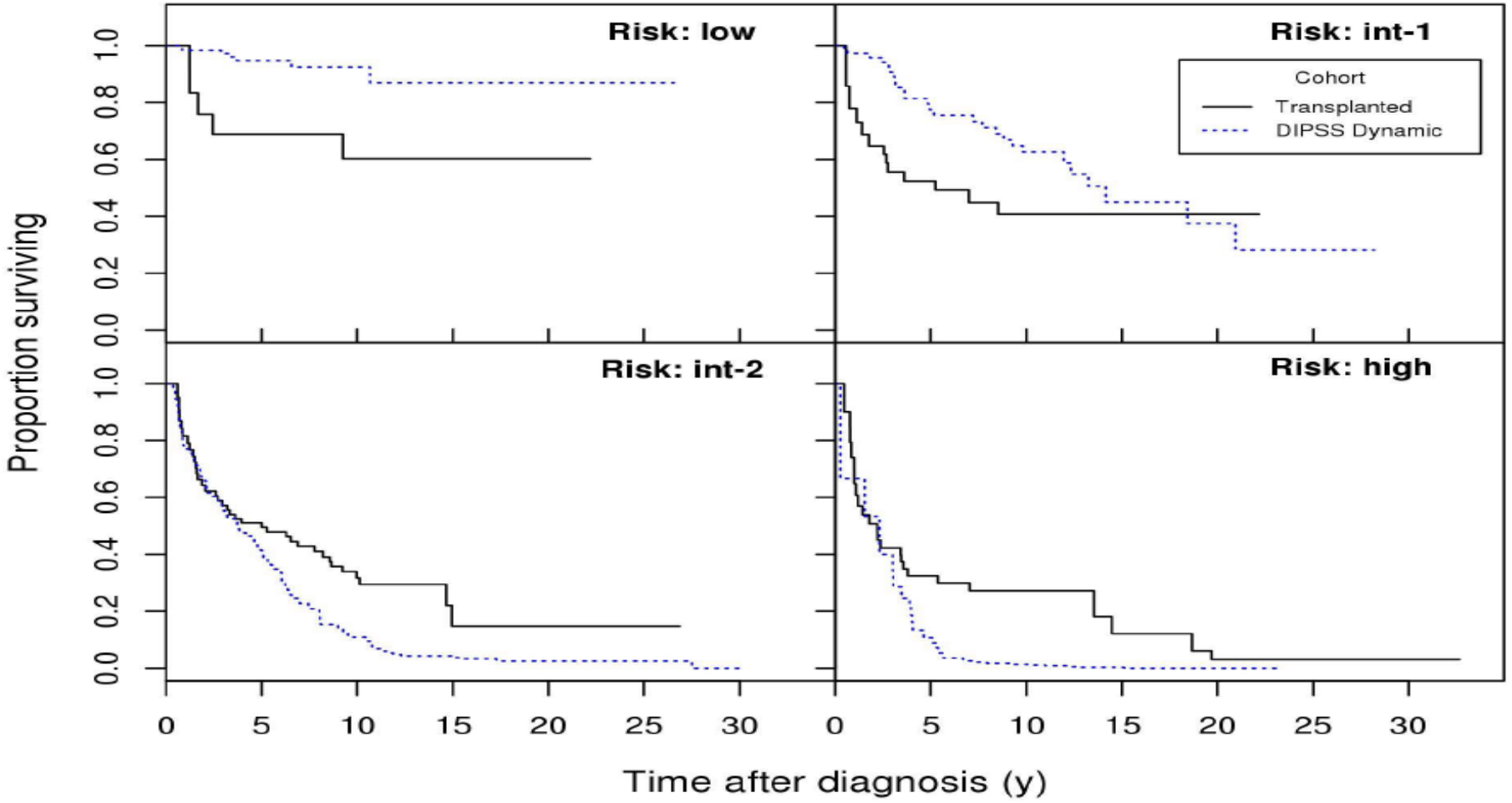
Cumulative incidence of relapse at 3 and 6 months after ASCT according to JAK2V617F clearance status.

Alchalby H et al. Blood 2010;116:3572-3581

blood
Prepublished online March 17, 2015;
doi:10.1182/blood-2014-10-608315

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

Nicolaus Kröger, Toni Giorgino, Bart L. Scott, Markus Ditschkowski, Haefaa Alchalby, Francisco Cervantes, Alessandro Vannucchi, Mario Cazzola, Enrica Morra, Tatjana Zabelina, Margherita Maffioli, Arturo Pereira, Dietrich Beelen, H. Joachim Deeg and Francesco Passamonti



CONSENSUS by EBMT/ELN International Working Group

ELEGIBILITY:

• 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.

•Pts with intermediate-1-risk disease and age <65 years should be considered candidates for allo-SCT if they present with transfusion-dependent anemia, or blasts in PB > 2%, or adverse cytogenetic.

Patients with low-risk disease should not be considered candidates for allo-SCT.

PROCEDURE:

•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 TRM and OS.

The Panel identified this as an area of a major unmet clinical need

Kroger et al, LEUKEMIA 2015

RECOMMENDATIONS
FOR ALLO-TRANSPLANT IN MYELOFIBROSIS

prognosis of the disease:
median OS <3 years
In int-2 and high-risk pts

Ruxolitinib treatment:

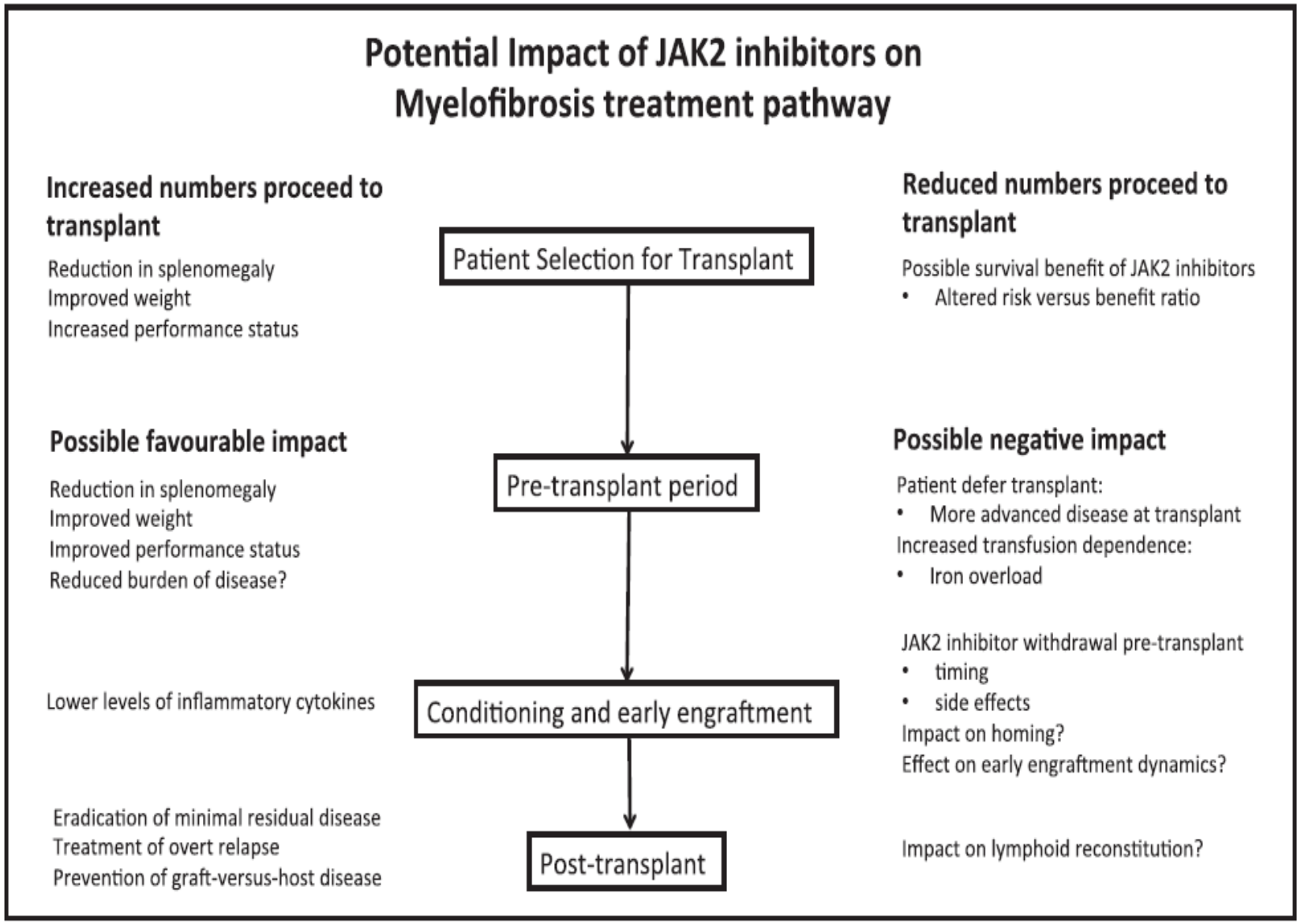
- **spleen reduction in 50% of pts**
- **≥ 5 y-clinical benefit in 20% of pts**
- **severe hematological AE in 20% of pts**

20-30% risk of non-relapse-mortality:

10%risk of graft failure

10-20% risk of relapse after transplant

COMBINATION OF ALLO-SCT AND RUXOLITINIB



McLornan BP British J Hematol 2012

PROSPECTIVE PHASE II TRIAL ClinicalTrial.gov:NCT01795677

Sponsored by Goleam-FIM in collaboration with SFGMTC

- Primary endpoint: achievement of DFS at 1 year > 50%
- Inclusion criteria: Lille or IPSS intermediate or high risk score
- Sample size : 53 pts
- Ruxolinib treatment: daily dose of 20 mg (if PLT< 100) or 30 mg (if PLT>100) and allo-SCT within 120 days
- Conditioning regimen : fludarabine-melphalan started after RUXO tapering and discontinuation.

- **First results (Robin M et al, ASH 2013 6a):**

  3 SAE during ruxolinib treatment (pancytopenia 2, cranial nerve palsy 1)

  10 SAE reported within 21 days after RUXO discontinuation (febrile cardiogenic shocks in 2 pts, tumour lysis syndrome in 3 pts, 2 fatal grade III-IV acute GVHD)

- Protocol amendement: shorter duration (10 days) of RUXO tapering associated with 0.5 mg/Kg steroids and conditioning starting with melphalan

VOLUME 31 · NUMBER 29 · OCTOBER 10 2013

JOURNAL OF CLINICAL ONCOLOGY DIAGNOSIS IN ONCOLOGY

Ruxolitinib Withdrawal Syndrome Leading to Tumor Lysis

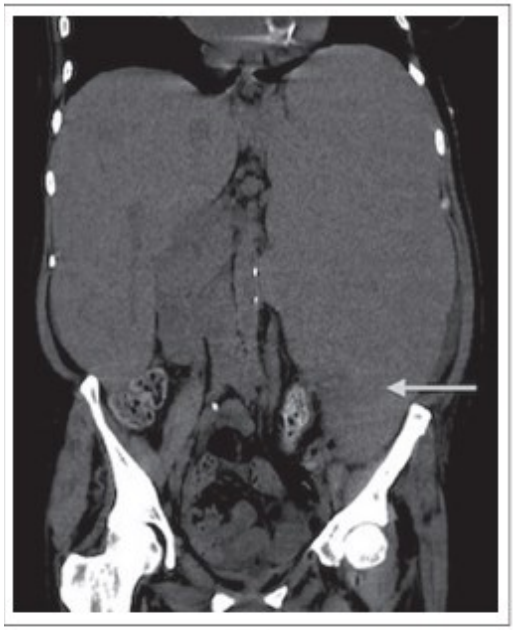


Fig 1.

70 y-old woman with history of JAK2 + secondary MF, treated with pegylated IFN, hydrossiurea and the 10 mg/day ruxolitinib due to B- symptoms and splenomegaly.

Ruxolinib was reduced to 5 mg and then stopped due to grade IV anemia and thrombocytopenia .

The pt was admitted to the emergency room 4 weeks after discontinuing ruxolitinib with abdominal pain and massive splenomegaly,acute renal failure, hyperkalemia, hyperuricemia, hypocalcemia,and hyperphosphatemia.

She was treated for a presumptive diagnosis of tumor lysis syndrome with aggressive hydration and rasburicase , and insulin glucose infusion were administered. She was discarged after 5 days .

Long-term follow-up of the initial phase I/II study reported that after discontinuation of the drug due to treatment toxicity, loss or lack of response,most patients experienced acute relapse of their symptoms and worsening Splenomegaly. Additionally,11%(five out of 47) of the patients who discontinued ruxolitinib exhibited a wide range of serious adverse events resulting in hospitalization (3 respiratory distress requiring intubation, 1 splenic infarction, 1 septic shock)

These severe adverse effects are attributed to a rapid rebound of inflammatory cytokines and can be prevented by slowly tapering rather than abruptly discontinuing ruxolitinuib .

Tefferi A, Mayo Clin Proc. 2011

CLINICAL DATA ON RUXO TREATMENT BEFORE ALLO-SCT

study	Retrospective SFGM-TC	retrospective	retrospective
author	Lebon et al, ASH 2013, 2111a	Kroger et al, Leukemia 2014	Jaekel et al, BMT 2014
N° pts	11	22	14
Median age	54 (44-66)	59 (42-74)	58
Ruxolinib indication	Splenomegaly (11) Symptoms (8)	Splenomegaly (22) Symptoms (21)	Splenomegaly (14) Symptoms (14)
Median time Start ruxolitinib-SCT	80 days	133 days (27-324)	175
Median time End ruxolitinib-allo-SCT	10 days	0 in 82% pts	0
Daily dose ruxolitinib	/	10 mg (5) 30 mg (5) 40 mg(12)	15 mg (1) 30 mg (7) 40 mg (6)
Response to ruxolinib	↓ spleen (8) Splenectomy (2)	↓ spleen (16) ↓ symptoms (19)	↓ spleen (7) ↓ symptoms (10)
Grade 3-4 toxicity	hematologic t. (1)	Hematologic t (1)	Hematologic t (2)

CLINICAL DATA ON RUXO TREATMENT BEFORE ALLO-SCT

study	Retrospective SFGM-TC	retrospective	retrospective
author	Lebon et al, ASH 2013, 2111a	Kroger et al, ASH 2013, 392 a	Jaekel et al, BMT 2014
N° pts	11	22	14
Conditioning regimen	RIC (11)	Busulfan 16/22 Treosulfan 3/22 Melphalan 3/22	RIC 11 Myelo 3
PB source	10/11	21/22	14
HLA-id sibling donor Matched unrelated Mismatched unrelated	4/11 3/11 4/11	2/22 14/22 6/22	3/14 11/14
engrafment	Full chimerism 8/11	22/22	13
all grade acute GVHD grade III-IV acute GVHD	5/11 2/11	11/22 4/22	2/14
NRM	1/11	1-y CI 14%	1y-CI 7%
OS	9/11	1 y-OS 81% 1y-DFS 76%	1 y-OS 78% 1y-DFS 76%

CLINICAL DATA ON RUXO TREATMENT BEFORE ALLO-SCT

Retrospective studies on 100 pts treated with ruxo before allo-SCT among different Canadian and American Centers

Outcome of ruxo treatment before allo-SCT

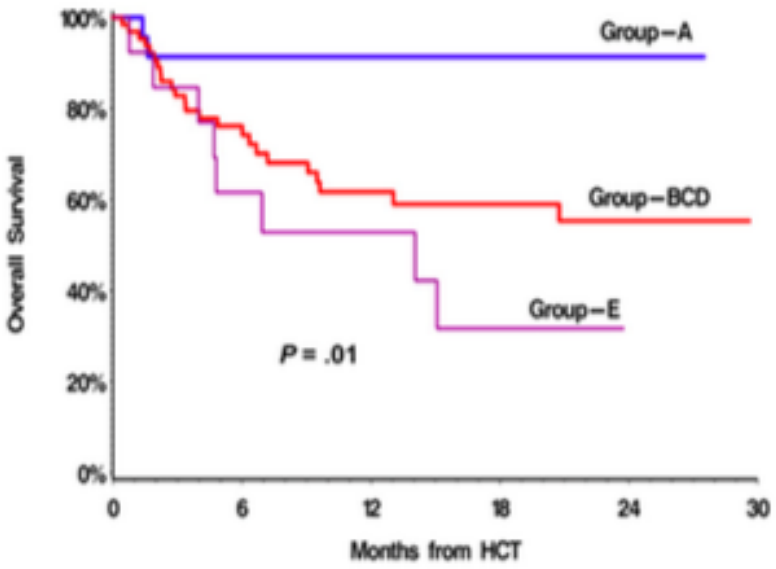
A. Clinical improvement (23 pts)
B. Stable disease (31 pts)
C. New cytopenia/intolerance/increasing blasts (18 pts)
D. Progressive disease:splenomegaly (18 pts)
E. Progressive disaese: leukemic transformation: (13 pts)

Response to JAK2 inhibitors, DIPSS and donor type were independent predictor for OS

10 AE (2 SAE) among the 66 pts who continued ruxo until transplant, significantly more common in pts who started tapering or stopped $\geq$ 6 days before SCT

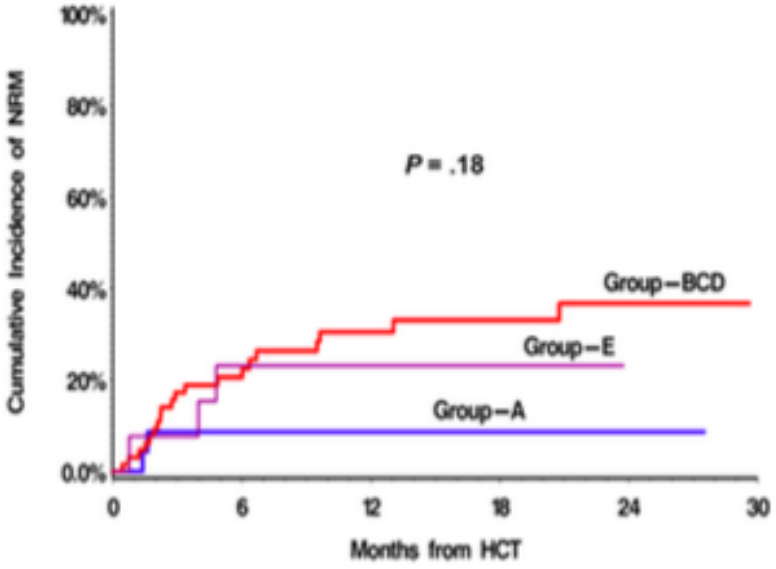
Shanavas et al, BBMT 2015

A

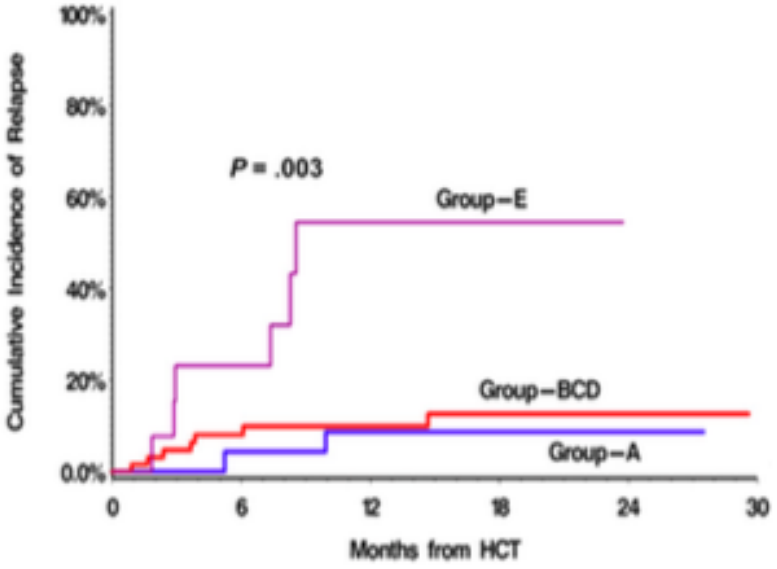


Comparison of groups based on response to JAK1/2 inibitors

B



C



CONSENSUS by EBMT/ELN International Working Group

- **Pre-transplant JAK inhibitor therapy with ruxolitinib is indicated in patients with a symptomatic spleen and/or constitutional symptoms.**

- **The drug should be initiated at least 2 months before transplant and should be titrated to the maximum tolerated dose. Weaning starting 5–7 days prior to conditioning should be implemented in the attempt to avoid a rebound phenomenon, with the drug stopping the day before conditioning.**

- **JAK2 inhibitors alone may reduce the spleen size and persistent constitutional symptoms, but there is no evidence that suggests modulation of donor cell chimerism or clearance of minimal residual disease.**

Kroger et al, Leukemia 2015

BIOLOGICAL IMPLICATIONS OF RUXOLITINIB TREATMENT

- Oral administration of the JAK1/ 2 inhibitor tofacitinib prevented GVHD-like disease manifested by weight loss and mucocutaneous lesions in a murine model of GVHD.
- Tofacitinib was also effective in reversing established disease.
- Tofacitinib diminished the expansion and activation of murine CD8 T cells and also inhibited the expression of interferon-γ-inducible cell death of keratinocytes

Okiyama et al, J Investigative Dermatology 2013

RUXOLITINIB IN GVHD

Retrospective studies on 95 pts with steroid refractory GVHD treated with a median of 3 lines of immunosuppressants from 19 European and American Centers

	grade 3-4 acute GVHD	moderate&severe chronic GVHD
overall response	44/51 (81%)	35/41 (85%)
complete response	25/54 (46%)	3/41 (7%)
6 month- OS	79%	97%
GVHD-relapse	3/44 (7%)	2/35 (6%)
cytopenias	30/54 (55%)	7/41 (17%)
CMV reactivation	18/54 (33%)	6/41 (15%)
disease relapse	5/54 (9%)	1/41 (2%)

Zeiser R et al, ASH 2015

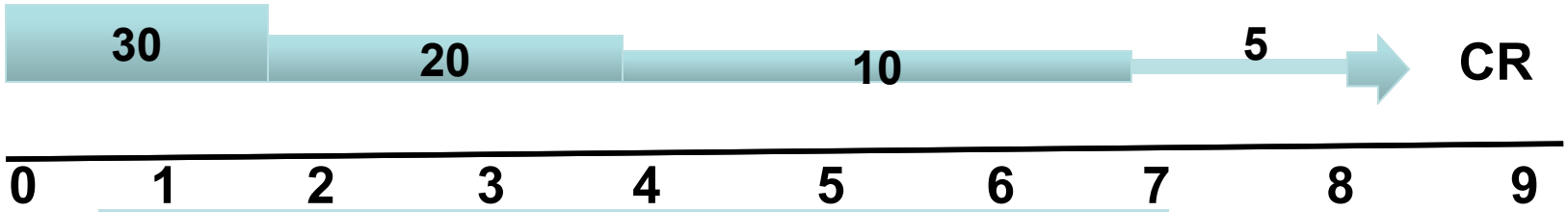
UDINE EXPERIENCE IN STEROID-REFRACTORY GVHD

1. Day + 52 secondary treat: pentostatin
   grade IV a GVHD
   skin1,liver 4,gut 1

30 † Exitus due to GVHD progression

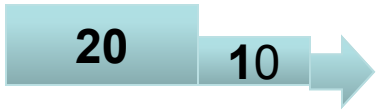
2. Day + 36 secondary treat: etanercept, photophoresis
   grade IV a GVHD
   skin 4,liver 4,gut 4

3. Day + 54 secondary treat: etanercept, photophoresis, pentostatin
   grade IV a GVHD
   skin 3,liver 4,gut 4



UDINE EXPERIENCE IN STEROID-REFRACTORY GVHD

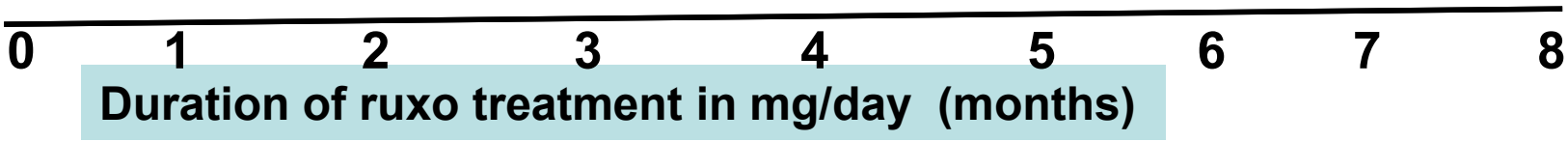
1. Day + 29 secondary treatments: photophpresis
   grade II a GVHD
   skin 3



CR

2. Day + 970 secondary treatments: photophoresis, imatinib
   severe chronic GVHD
   skin, mouth,liver,lung

stable



CONCLUSIONS

- **In the era of JAK2 inhibitors, allogeneic transplant is still the only curative approach for patients with myelofibrosis.**
- **Patients with DIPSS intermediate-2 and high-risk myelofibrosis or RBC transfusion dependent or with unfavourable karyotype should be candidated to allogeneic transplant due to median OS < 3 years .**
- **The choice of the appropriate conditioning regimen is an unmet clinical need.**
- **Ruxolitinib could be effective to reduce spleen and control symptoms before allo-SCT in about 50% of patients.Ruxolitinib could be stopped the day before conditioning to avoid rebound phenomenon.**
- **Ruxolitinib is a promising treatment of steroid refractory GVHD.**

ACKNOWLEDGMENTS

Hematology Division and Transplant Unit
Udine University Hospital

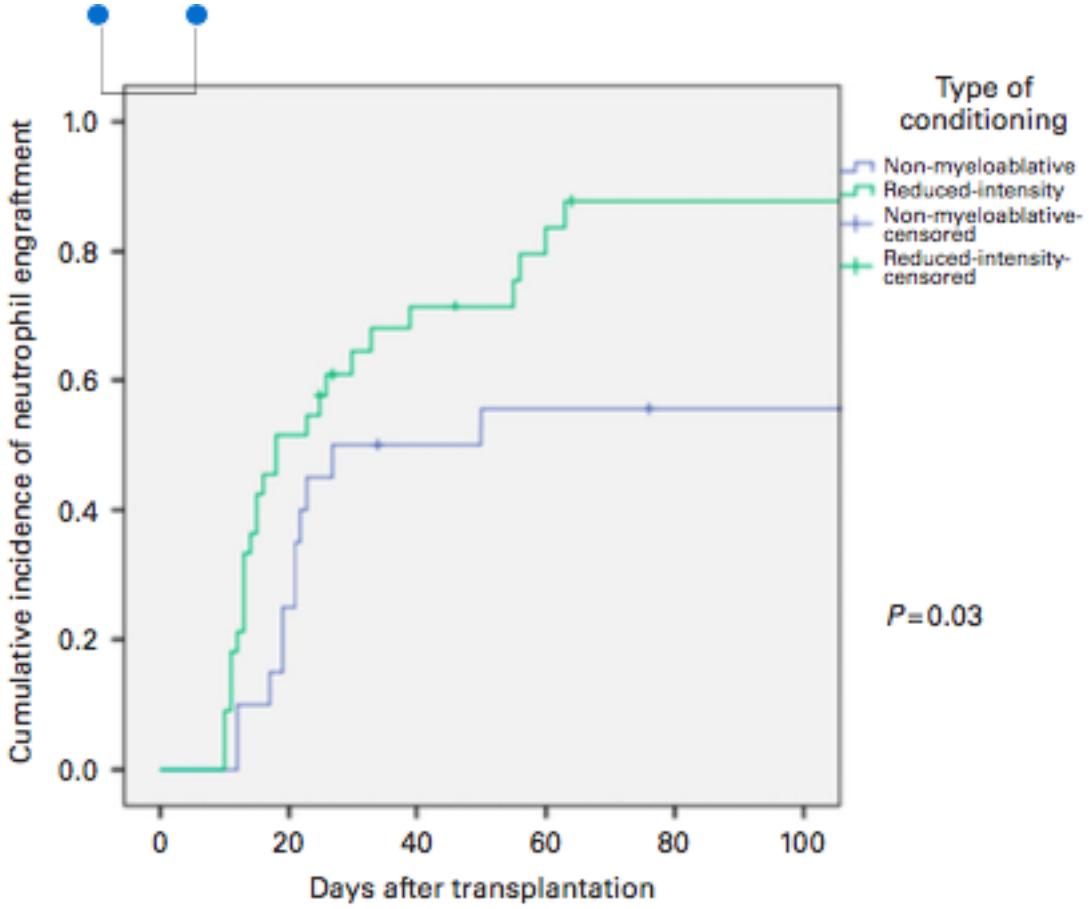
Renato Fanin Director
Marta Battista
Antonella Geromin
Michela Cerno
Alessandra Sperotto
Chiara Cigana
Davide Lazzarotto
Giovanna Ventura
Marta Medeot
Francesca Patriarca
Francesco Zaja
Anna Candoni
Mario Tiribelli
Erica Simeone
Silvia Buttignol
Raffaella Stocchi
Daniela Damiani
Stefano Volpetti
Fabrizia Colasante

Data manager, nurses, the patients and their family

ROLE OF CONDITIONING REGIMEN

20 pts NMA regimens mainly Flu-TBI 2Gy

33 pts RIC regimens Flu-Mel or Flu-CTX-TBI 4Gy



Slot S et al, BMT 2015