Dose-Reduced Versus Standard Conditioning Followed by Allogeneic Stem Cell Transplantation in Patients With MDS or Secondary AML:

A Randomized Phase III Study of the Chronic Malignancies Working Party (EBMT)

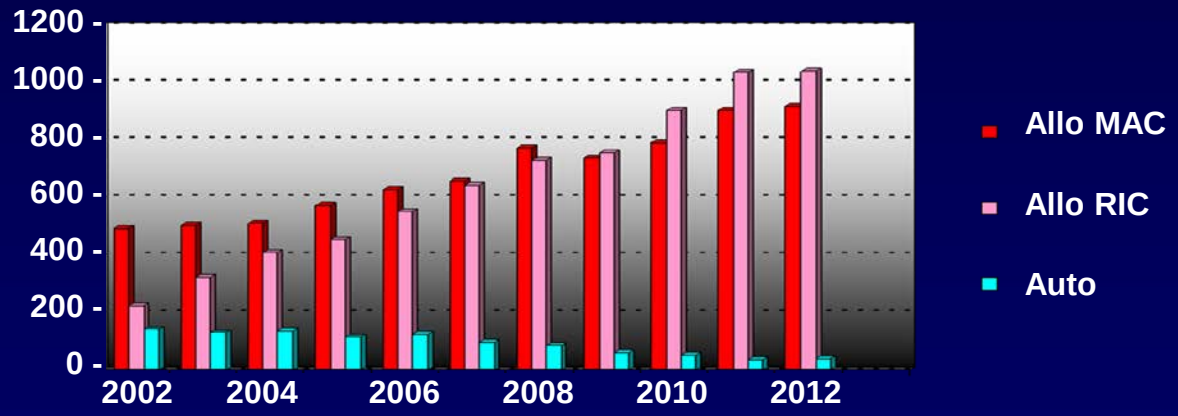
Abstract 320

Kröger N, Brand R, Iacobelli S, Uddin R, Niederwieser D, Platzbecker U, Hübel K, Afanasyev B, Robin M, Stelljes M, Weber T, Heim D, Onida F, Dreger P, Bethge W, Gramatzki M, Guidi S, Pini M, Volin L, Kobbe G, Poire X, de Witte T

Background

While advances are being made in the biology of MDS leading to more effective therapies, such as hypomethylating agents, allogeneic transplantation is currently shown to be the most effective and curative treatment.

Dose-reduced conditioning is now more frequently used in patients with MDS because of lower conditioning-related toxicity; however, there are some concerns regarding a higher risk of relapse as shown in retrospective studies



The Chronic Malignancies Working Party (CMWP) of EBMT performed a multicenter, prospective phase III-study comparing dose-reduced versus standard conditioning followed by allogeneic stem cell transplantation from related or unrelated donors in patients with MDS or secondary AML.

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

EBMT-Study: MDS/sAML

Randomization

ARM A

Standard Myeloablative Conditioning (MAC)

Busulfan 12.8 mg/kg IBW iv
(or Busulfan 16 mg/kg BW po)
Cyclophosphamide
120 mg/kg BW iv

ARM B

Reduced Intensity Conitioning (RIC)

Bulsulfan 6.4 mg/kg IBW iv
(or Busulfan 8 mg/kg BW po)
Fludarabine 5 x 30 mg/m² iv

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Aims of the Study

Primary endpoint

The hypothesis is that a dose-reduced conditioning will reduce the nonrelapse mortality from 40% to 20% at one year after allogeneic stem cell transplantation.

Secondary endpoints were:

- **Incidence of acute graft-versus-host disease**
- **Incidence of chronic graft-versus-host disease ("limited" or "extensive")**
- **Comparison of overall survival post-transplant at two years**
- **Comparison of event-free survival post-transplant at two years**
- **Cumulative incidence of relapse post-transplant at two years between both groups**

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Inclusion Criteria

- **Disease: Cytologically proven myelodysplastic syndrome (MDS), either as:**
  - **Refractory anemia (RA)**
  - **Refractory anemia with ring sideroblasts (RARS)**
  - **Refractory anemia with excess of blasts (RAEB)**
  - **Refractory anemia with excess of blast in transformation (RAEB-T)**
- **Chronic myelomoncytic leukemia (CMML dysplastic type)**
  - **Or secondary acute myeloid leukemia (sAML)**
- **Blast count <20% with or without chemotherapy at time of transplantation.**

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Inclusion Criteria

- Patient eligible for standard and dose-reduced conditioning
- HLA-matched unrelated (HLA-A, HLA-B, HLA-DBR1) (one mismatch allowed): Age 18 - 60 years
- HLA-matched related donor (HLA-A, HLA-B, HLA-DBR1) (one antigen-mismatch allowed): Age 18 - 65 years
- No major organ dysfunction
- Written informed consent of the patient

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Exclusion Criteria

- Blasts >20% at time of transplantation
- No written informed consent
- Central nervous system involvement
- Severe irreversible renal, hepatic, pulmonary, or cardiac disease, such as
  - Total bilirubin >2 times upper the normal level
  - Left ventricular ejection fraction <30%
  - Creatinine clearance <30 ml/min
  - DLCO <35% and/or receiving supplementary continuous oxygen
- Positive serology for HIV
- Pregnant or lactating women
- Patients with a life expectancy of less than six months because of another debilitating disease
- Serious psychiatric or psychological disorders

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Study

Study design

- Prospective randomized phase III multicenter study
- Start of the study: 5/2006
- Accrual: 6 years
- 18 centers from 7 nations participated

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Statistical Consideration

Stratification factor	*Applied….*
Related versus unrelated	Always
Blast count <5% versus ≥5% prior to transplant	Only if in BOTH the “related” and “unrelated” strata, 4 or more patients are expected to participate
Age <45 versus ≥45 years	Only if in all 4 strata resulting from the 2 factors above, we expect at least 4 patients

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

RICMAC Study

Study was prematurely stopped in 12/2012 due to slow recruitment. Analysis is based on 129 pts (2 pts did not receive SCT and were excluded)

	Arm A (MAC) n = 62	Arm B (RIC) n = 65
Median age	50 yrs	51 yrs
<45 yrs	15 (24%)	16 (25%)
>45 yrs	47 (76%)	49 (75%)
Blasts at SCT	med. 4%	med. 5%
<5%	45 (73%)	35 (54%)
>5%	17 (27%)	28 (46%)
Diagnosis		
MDS/CMML	53 (87%)	61 (94%)
sAML	9 (13%)	4 (6%)
Donor		
HLA ident sibling or relatives	17 (27%)	16 (25%)
Unrelated	36 (58%)	38 (58%)
Mismatch related/unrelated	9 (15%)	11 (17%)

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

RICMAC Study

	Arm A (MAC) n = 62	Arm B (RIC) n = 65
GvHD prophylaxis for unrelated		
ATG	31 (64%)	30 (64%)
Alemtuzumab	--	--
No antibody (CSA + MTX only)	15 (33%)	17 (36%)
IPSS at diagnosis (only MDS)	(n = 50)	(n = 52)
low	2 (4%)	2 (4%)
intermediate I	28 (56%)	23 (42%)
intermediate II	16 (32%)	24 (43%)
high	4 (8%)	6 (11%)
Chemotherapy before SCT		
No	39 (63%)	44 (68%)
Yes	23 (37%)	21 (32%)

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Results

	Arm A (MAC) n = 62	Arm B (RIC) n = 65
Primary graft failure	1	2
Leucocyte engraftment		
>1.0 x 10^9/L	14 d (10-26)	15 d (0-25)
Platelet engraftment		
>20 x 10^9/L	14 d (9-25)	15 d (0-25)
Acute GvHD		
I - IV	31 (51%)	32 (50%)
II - IV	23 (38%)	20 (33%)
III - IV	8 (13%)	8 (13%)
Chronic GvHD (total 106)		
no	18 (37%)	20 (35%)
limited	11(22%)	15 (26%)
extensive	20 (41%)	22 (38%)

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

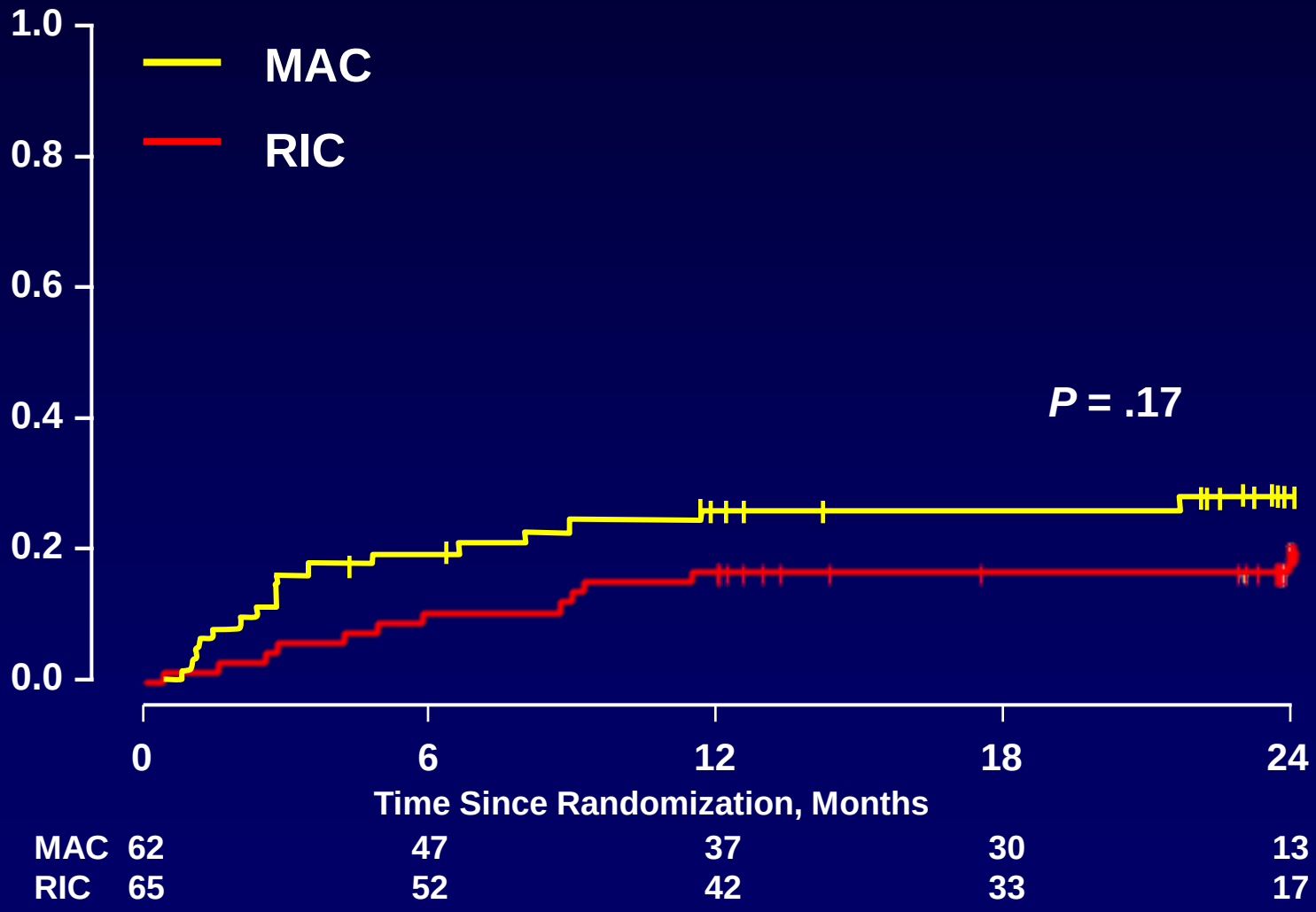
RICMAC Study

	Arm A (MAC)	Arm B (RIC)	*P* value
NRM at 1yr at 2 yrs	 26 %(15%-37%) 28% (17%-40%)	 17% (8%-26%) 20% (9%-30%)	.17 (Gray-test)
Relapse incidence at 2 yrs	15% (5%-25%)	18% (8%-27%)	.51 (Gray-test)
Relapse-free survival at 2 yrs	57% (44%-70%)	62% (50%-75%)	.49 (log-rank)
Overall survival at 2 yrs	62% (49%-75%)	76% (65%-87%)	.06 (log-rank)

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Results

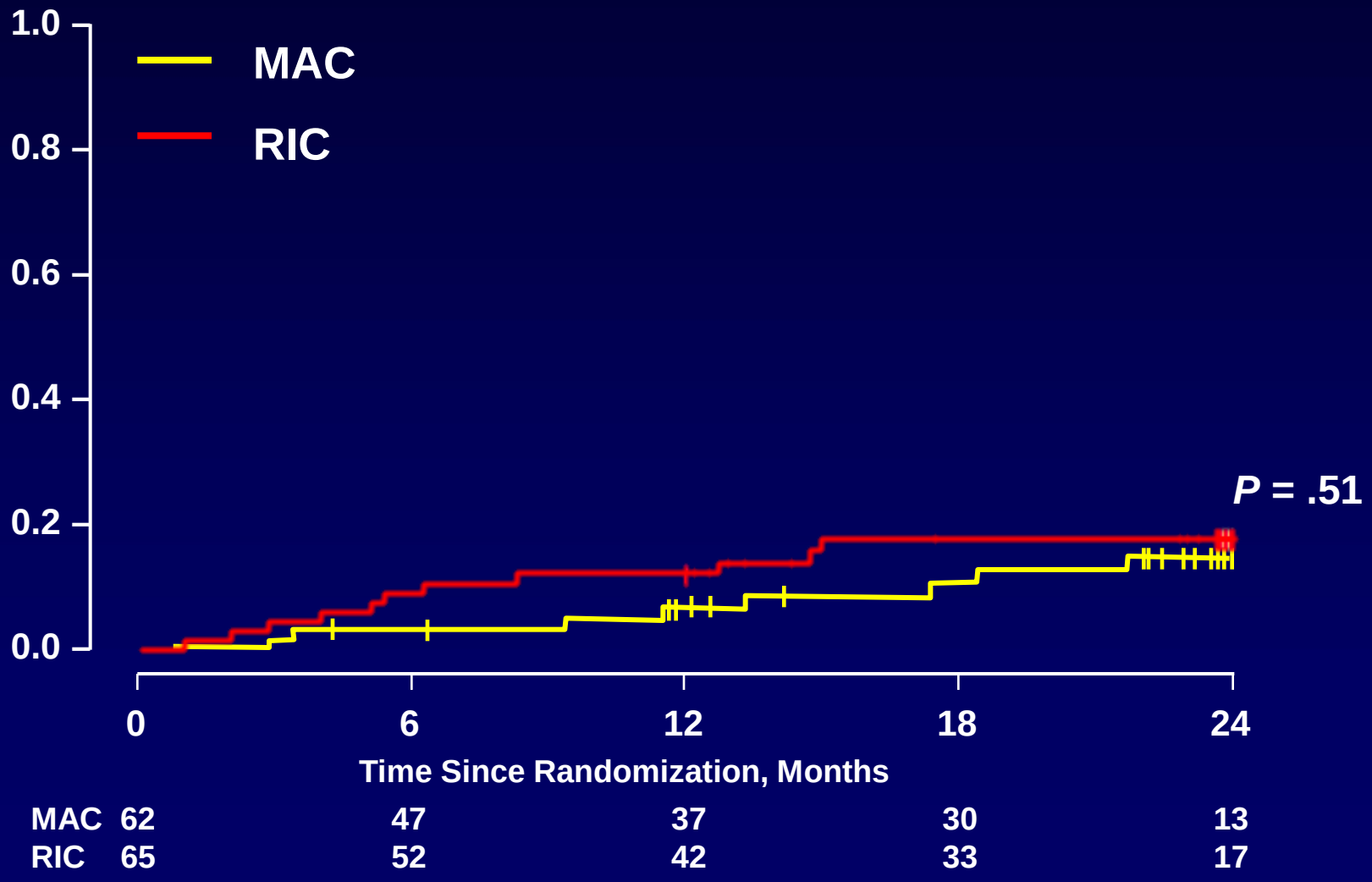
Non-Relapse Mortality



Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Results

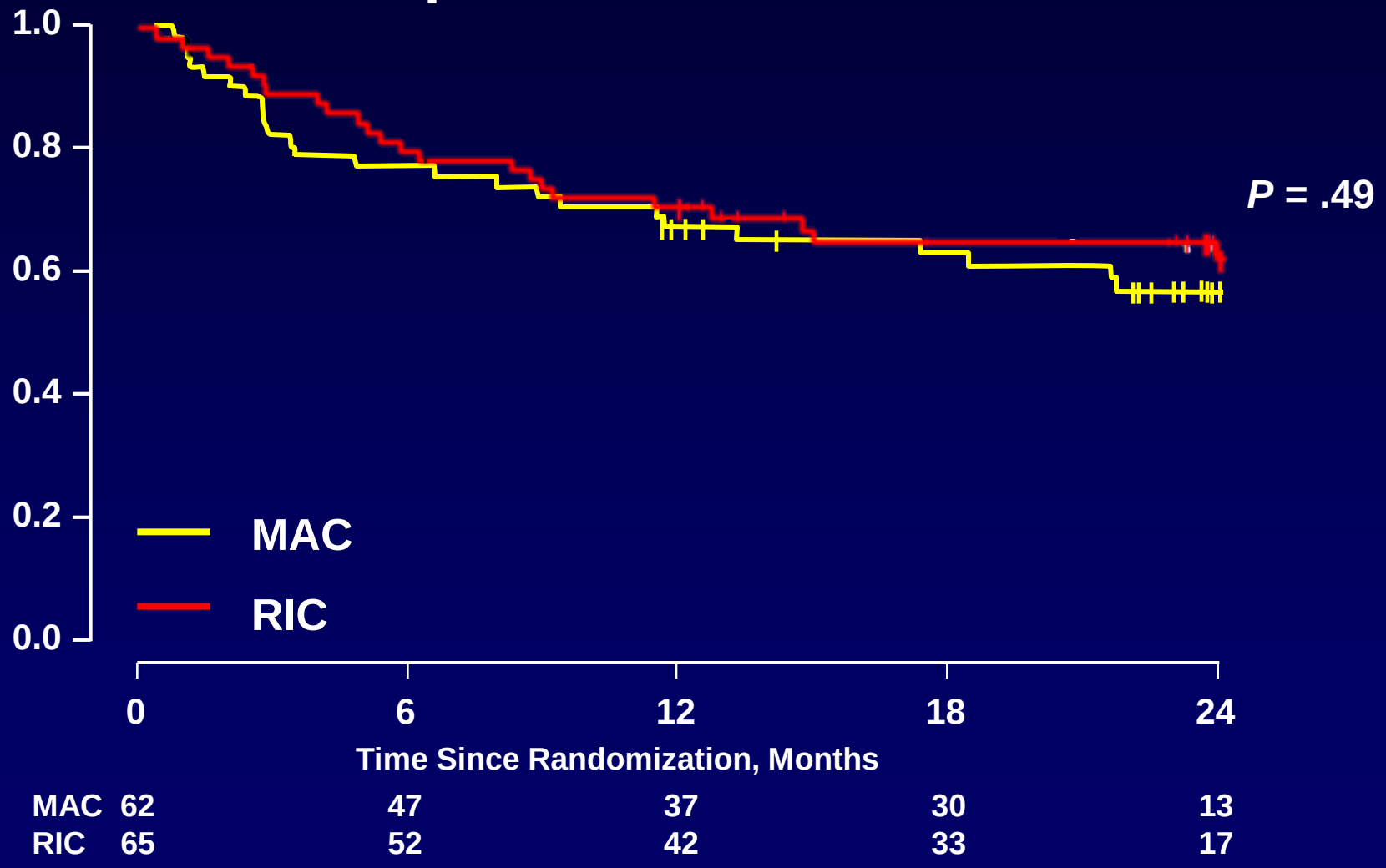
Relapse Incidence



Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Results

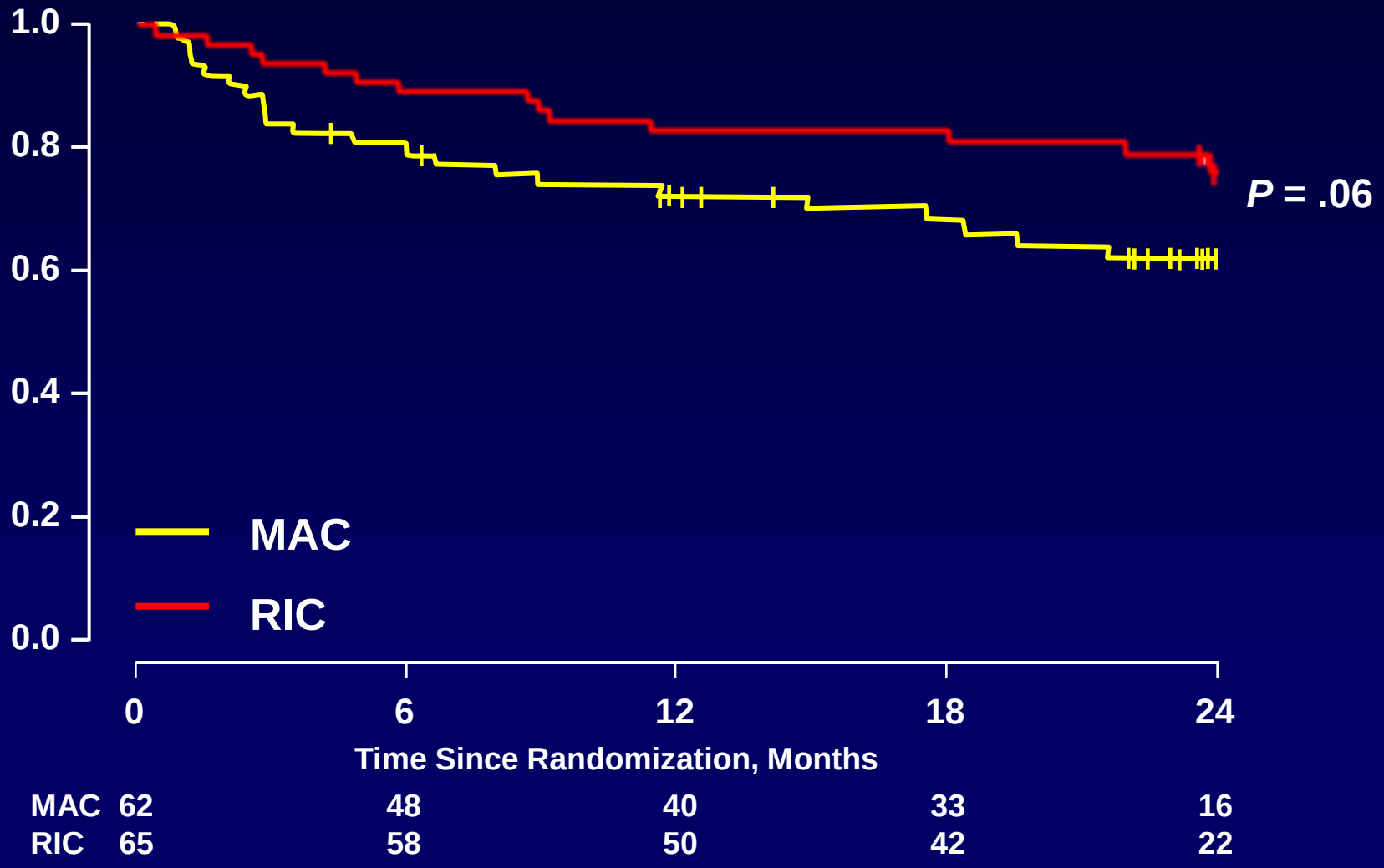
Relapse-Free Survival



Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Results

Overall Survival



Kröger N, et al. *Blood.* 2014;124: Abstract 320.

RICMAC Study: Cox Model

	OS (HR)	RFS (HR)	Relapse (HR)	NRM (HR)
RIC vs MAC	**0.42** ***P* = .03**	**0.82** ***P* = .48**	**1.51** ***P* = .38**	**0.57** ***P* = .18**
Performance status 1-3 vs 0	**2.58** ***P* = .04**	-	-	**4.92** ***P* = .01**
Prior Chemo	-	-	**3.36** ***P* = .01**	
Age >51y	-	**1.93** ***P* = .03**	-	-

Subanalysis among cytogenetic risk on OS:

RIC vs MAC:	low risk:	HR: 0.14, *P* = .002
	interm risk:	HR: 0.86, *P* = .9
	high risk:	HR: 1.70, *P* = .39

Kröger N, et al. *Blood.* 2014;124: Abstract 320.

Conclusions

1. These data from the prospective, randomized EBMT study comparing RIC vs MAC in MDS patients suggest that RIC (Bu/Flu) results in at least aquivalent results in comparison to MAC (Bu/Cy)
2. The borderline significant improved survival of RIC *(P* = .06) is mainly due to an improved survival in the cytogenetic low-risk group
3. Longer follow-up is necessary to confirm these data

Kröger N, et al. *Blood.* 2014;124: Abstract 320.