
Universitätsklinikum
Hamburg-Eppendorf

# Allogeneic Transplantation in AML and MDS

***Unmet Challenges in High Risk Haematological Malignancies:***
***From Benchside to Clinical Practice***
***Turin, September 13-14,2021***

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**Dept of Stem Cell Transplantation**
**University Hospital Hamburg/Germany**

# Disclosures

Novartis: Research grant, Honoraria

Sanofi: Honoraria

Jazz: Honoraria

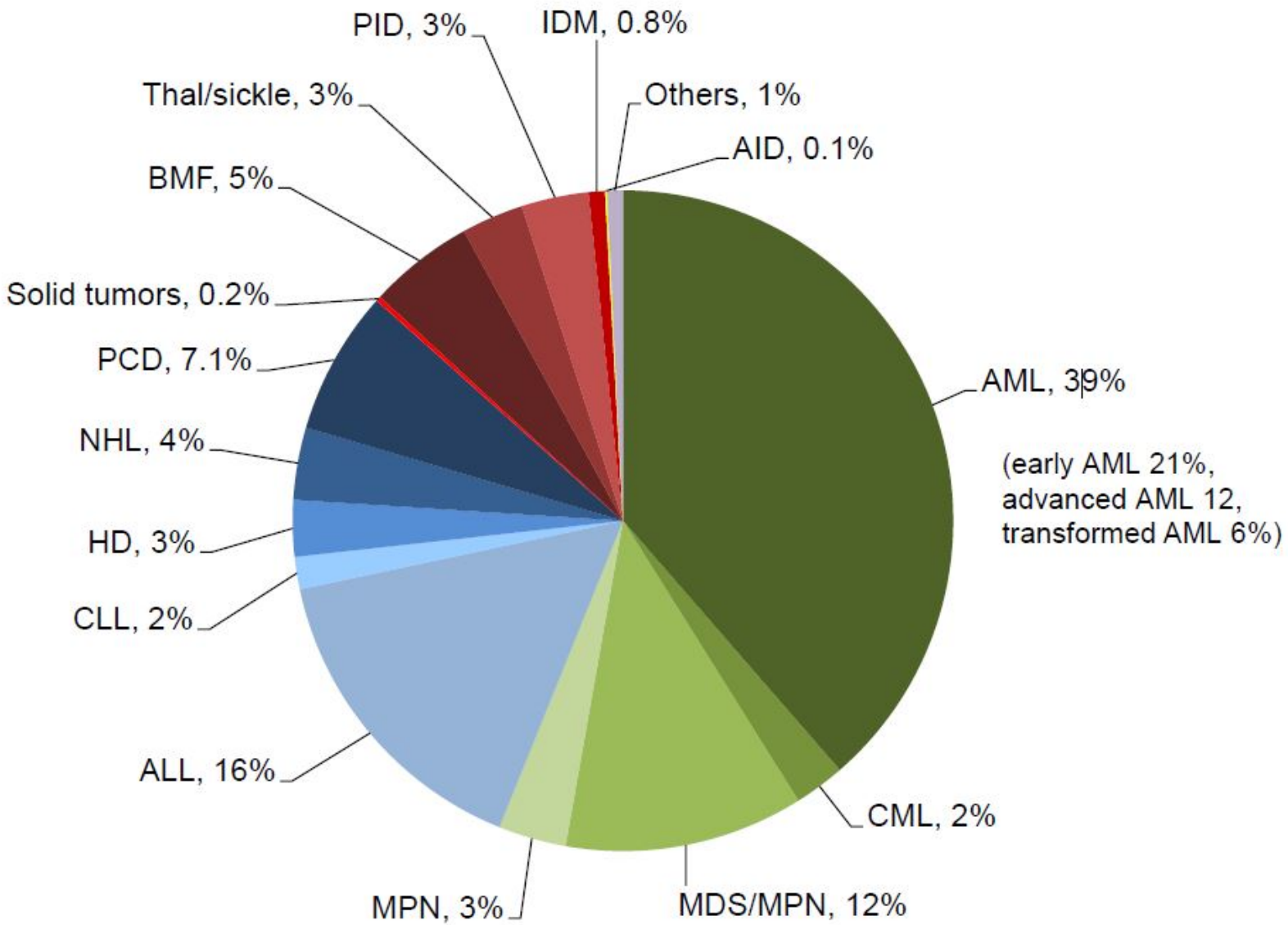
Riemser: Research grant, Honoraria

Neovii: Research grant, Honoraria

Celgene/BMS: Research grant, Honoraria

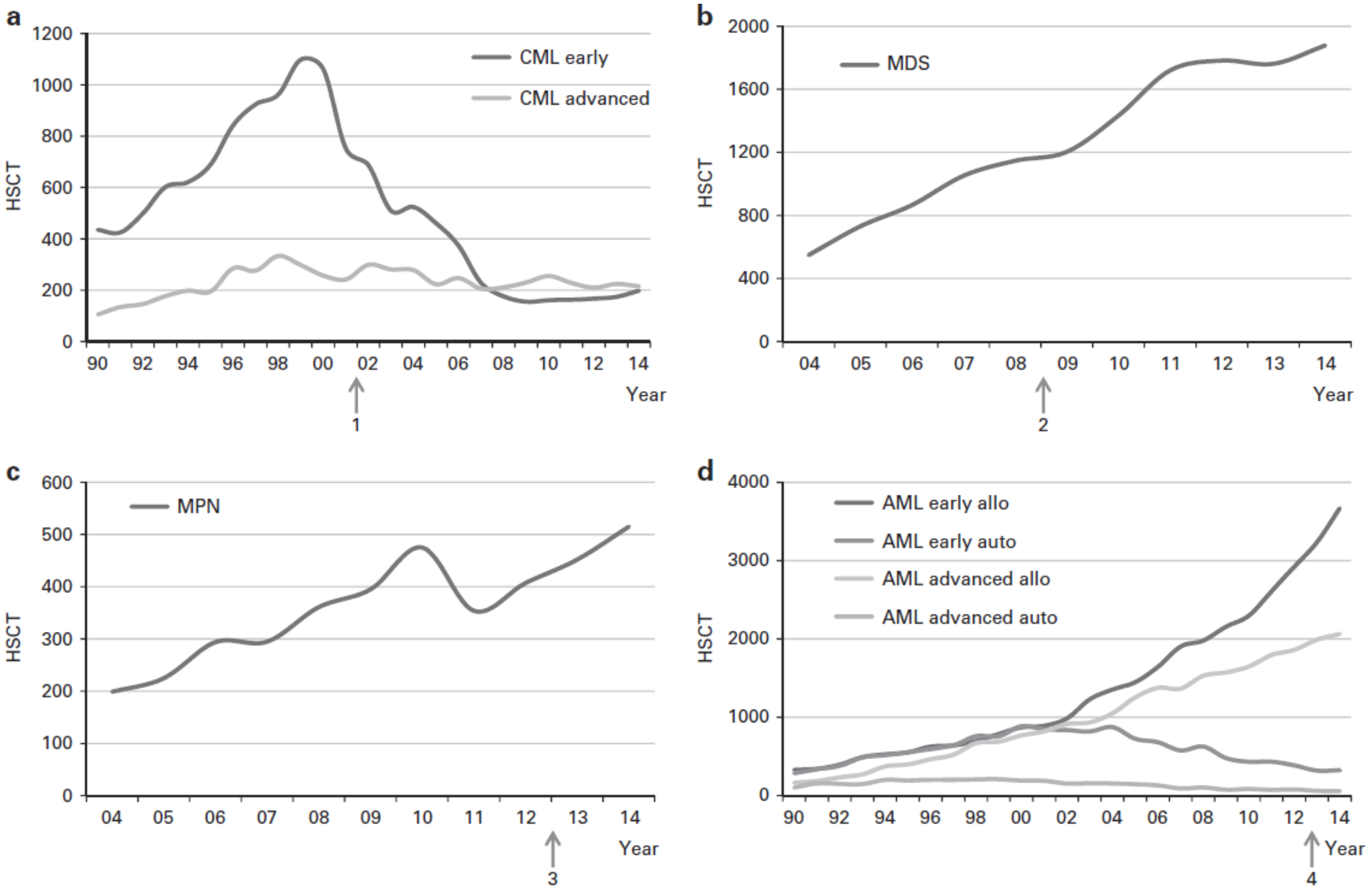
Kite-Gilead: Honoraria

# Allogeneic HSCT in Europe 2019




*Passweg et al., BMT 2021*

# Allogeneic SCT: Myeloid Malignancies



# ELN Risk Classification according genetics

| Risk category* | Genetic abnormality |
|---|---|
| Favorable | t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* |
| | inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* |
| | Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low}$† |
| | Biallelic mutated *CEBPA* |
| Intermediate | Mutated *NPM1* and *FLT3*-ITD$^{high}$† |
| | Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD$^{low}$† (without adverse-risk genetic lesions) |
| | t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ |
| | Cytogenetic abnormalities not classified as favorable or adverse |
| Adverse | t(6;9)(p23;q34.1); *DEK-NUP214* |
| | t(v;11q23.3); *KMT2A* rearranged |
| | t(9;22)(q34.1;q11.2); *BCR-ABL1* |
| | inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* |
| | −5 or del(5q); −7; −17/abn(17p) |
| | Complex karyotype,§ monosomal karyotype‖ |
| | Wild-type *NPM1* and *FLT3*-ITD$^{high}$† |
| | Mutated *RUNX1*¶ |
| | Mutated *ASXL1*¶ |
| | Mutated *TP53*# |

*Döhner et al. Blood 2017; 129:424-447*

# ELN recommendation 2017

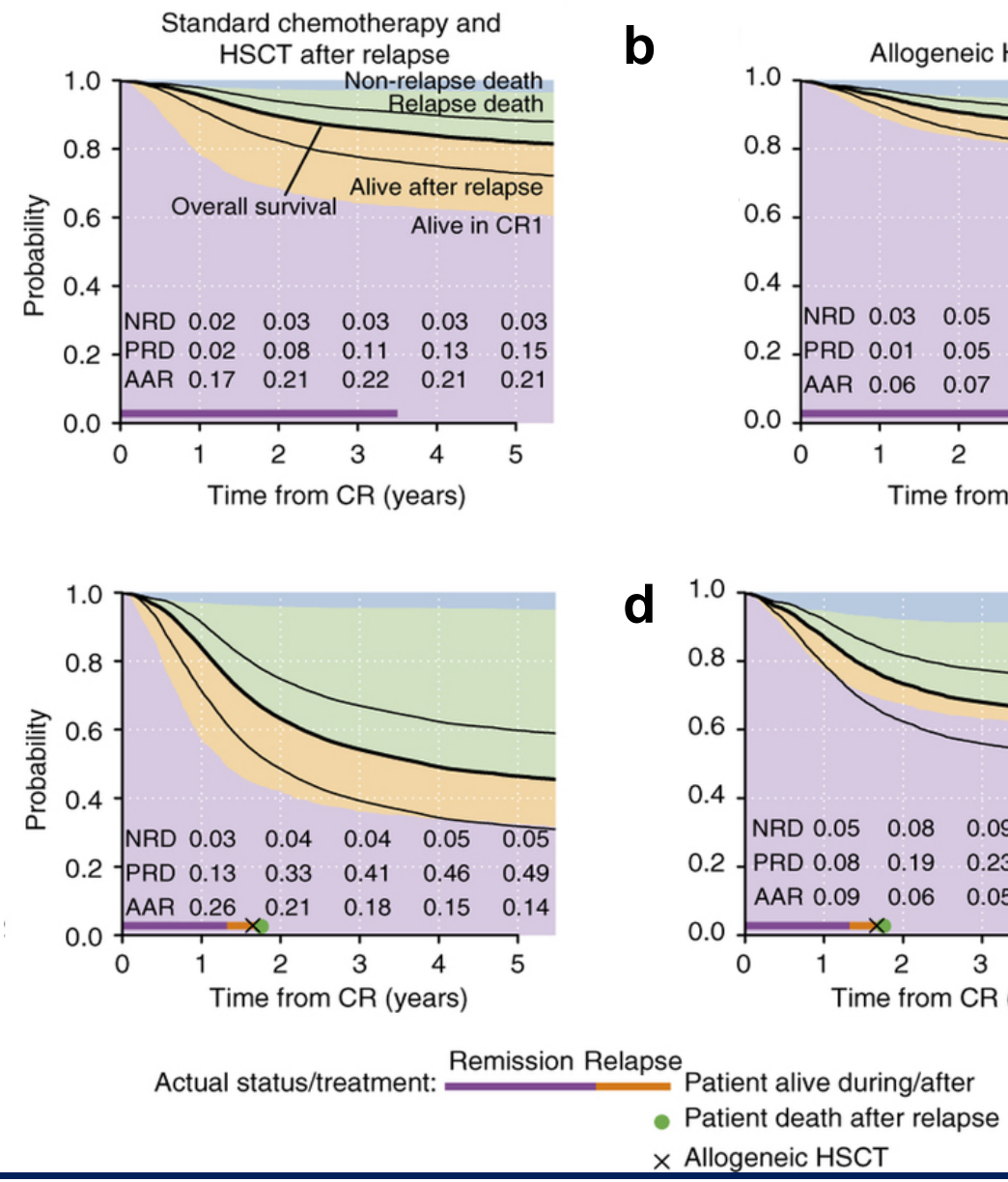
| | |
|---|---|
| **Patients eligible for intensive chemotherapy** | |
| Induction therapy (all ages) ("7+3")*,†,‡ | • 3 d of an IV anthracycline: daunorubicin at least 60 mg/m$^2$; idarubicin 12 mg/m$^2$; or mitoxantrone 12 mg/m$^2$, and 7 d of continuous infusion cytarabine (100-200 mg/m$^2$) |
| Consolidation therapy‡,§ | |
| Younger patients (18-60/65 y) | |
| • Favorable-risk genetics | • 2-4 cycles of IDAC (1000-1500 mg/m$^2$ IV over 3 h q12h, d1-3; or 1000-1500 mg/m$^2$ IV over 3 h d1-5 or 6) |
| • Intermediate-risk genetics | • Allogeneic HCT from matched-related or unrelated donor |
| | • 2-4 cycles of IDAC (1000-1500 mg/m$^2$ IV over 3 h q12h, d1-3; or 1000-1500 mg/m$^2$ IV over 3 h d1-5 or 6), or |
| | • High-dose therapy and autologous HCT |
| • Adverse-risk genetics | • Allogeneic HCT from matched-related or unrelated donor |
| Older patients (>60/65 y) | |
| • Favorable-risk genetics | • 2-3 cycles of IDAC (500-1000 mg/m$^2$ IV over 3 h q12h, d1-3; or 500-1000 mg/m$^2$ IV over 3 h d1-5 or 6) |
| • Intermediate/adverse-risk genetics | • No established value of intensive consolidation therapy; consider allogeneic HCT in patients with low HCT-Comorbidity Index, or investigational therapy |

*Döhner et al., Blood 2017*

# Indication for allogeneic SCT in AML refining by molecular genetics n= 1540

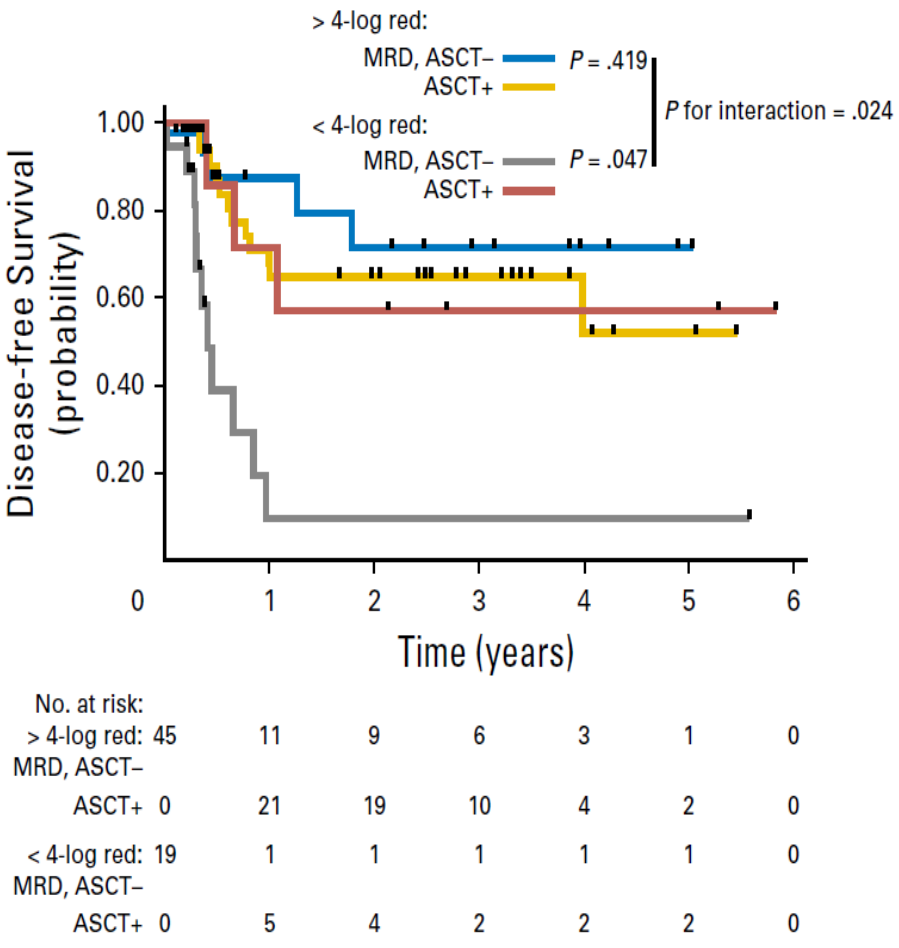
**29y female**
**AML (8;21)**
**ELN: favorable**

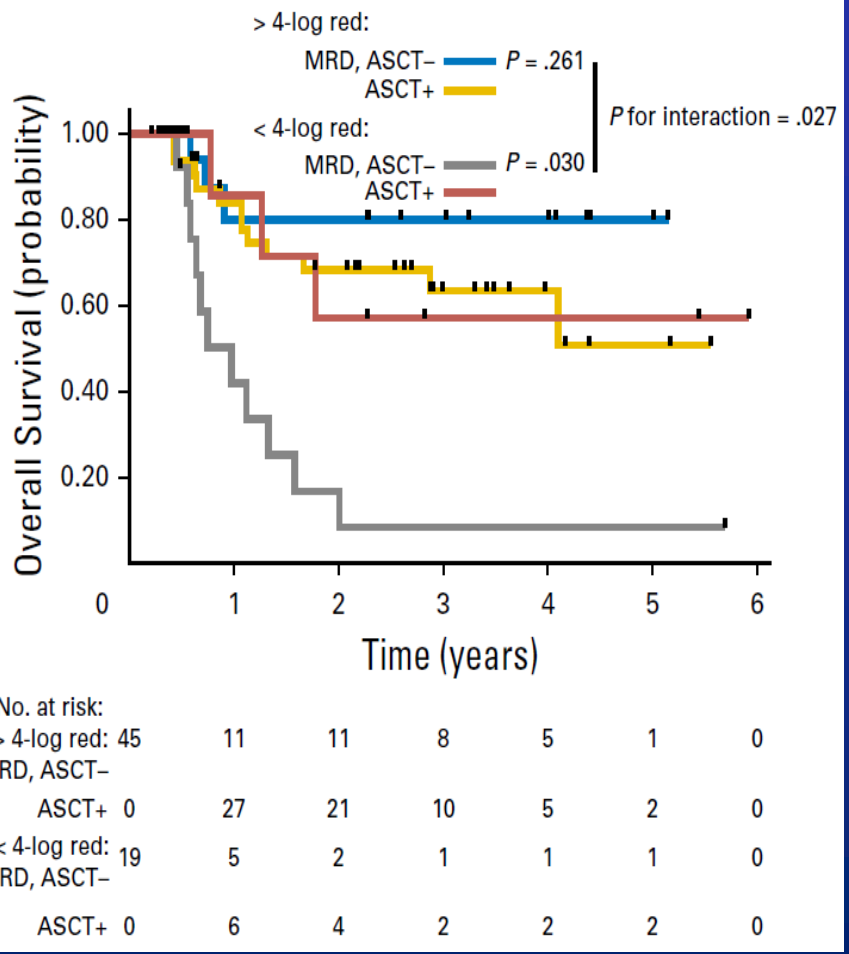
**49y male**
**AML: NPM1+**
**DNMT3A+**
**IDH1+**
**ELN: favorable**




*Gerstung et al., Nature Genetics 2017*

# NPM1 MRD in peripheral blood after induction:



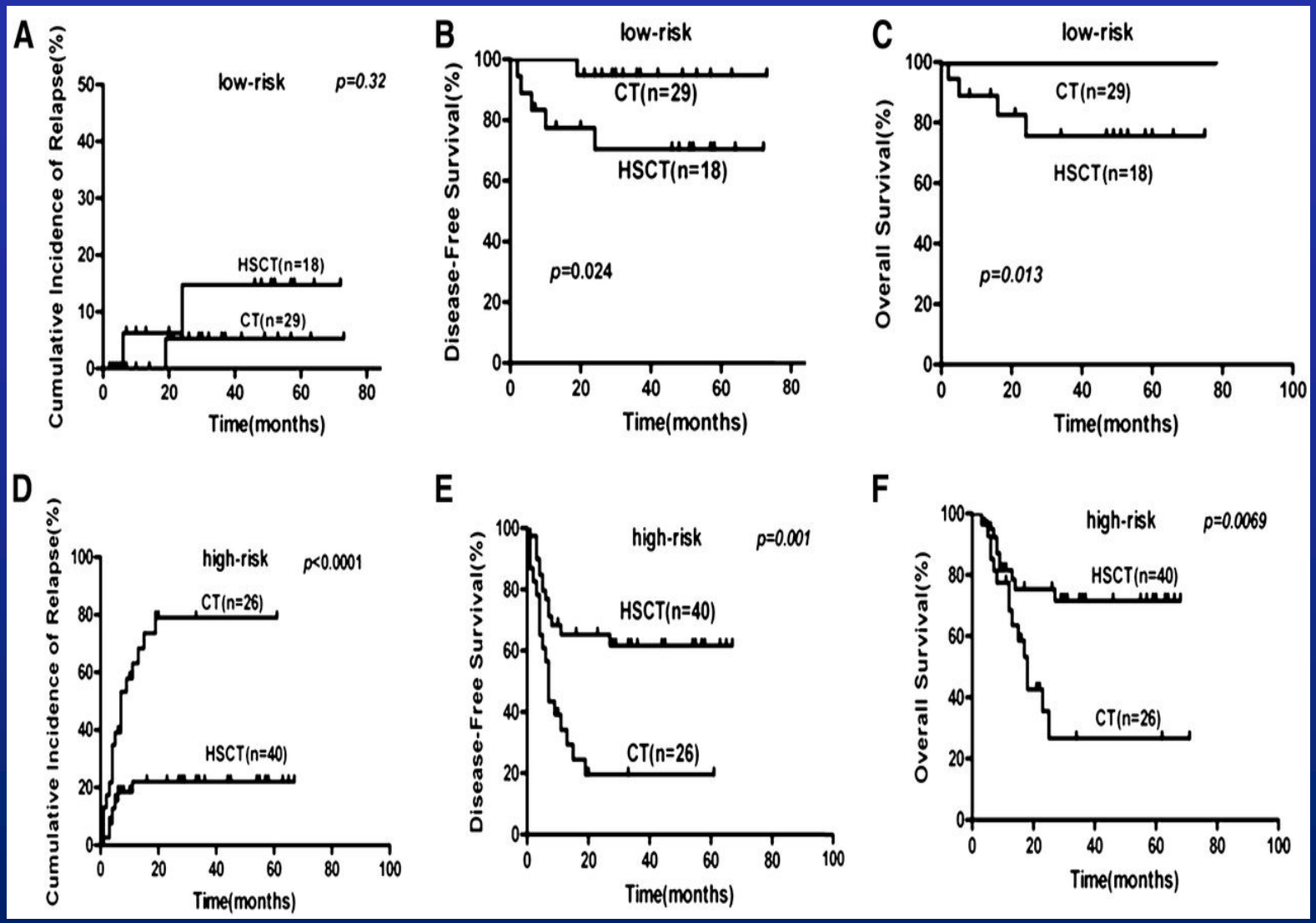




- Balsat et al. J Clin Oncol 2017; 35: 185-193

# MRD positive CBF patients benefit from allogeneic hematopoietic cell transplantation

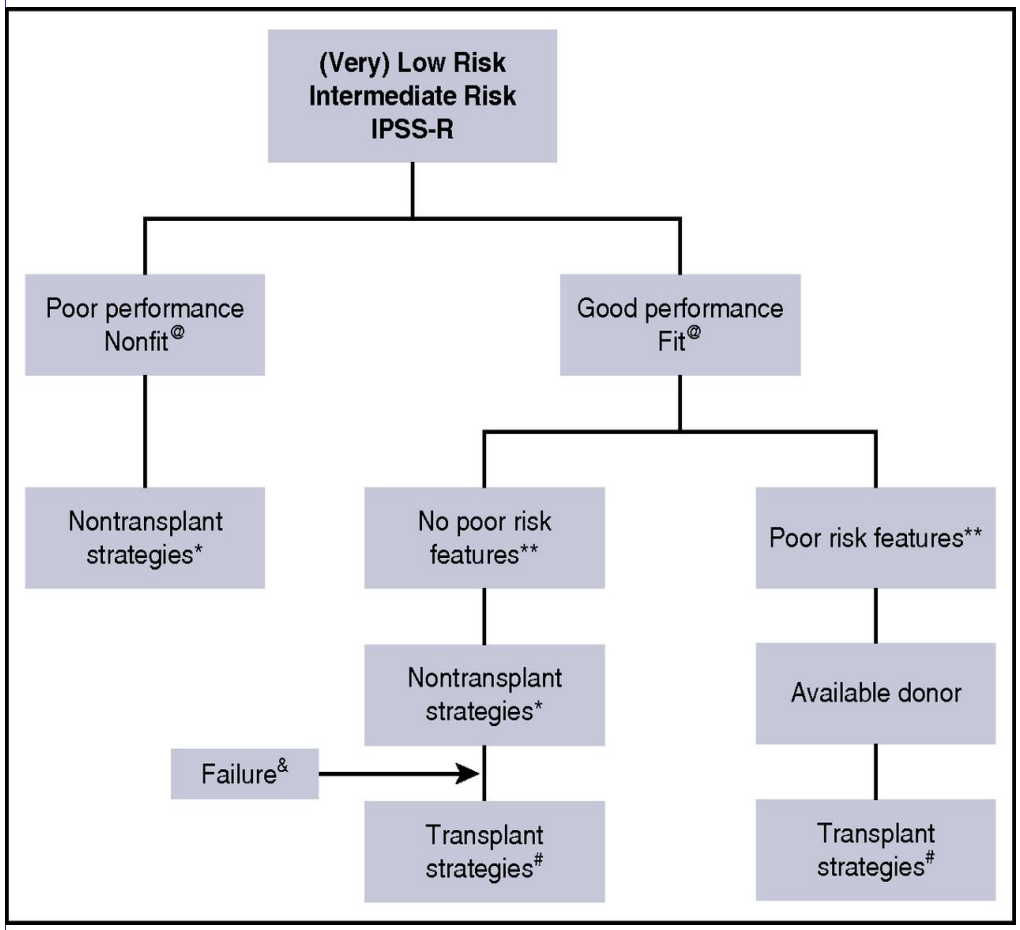
**MRD negative CBF AML**

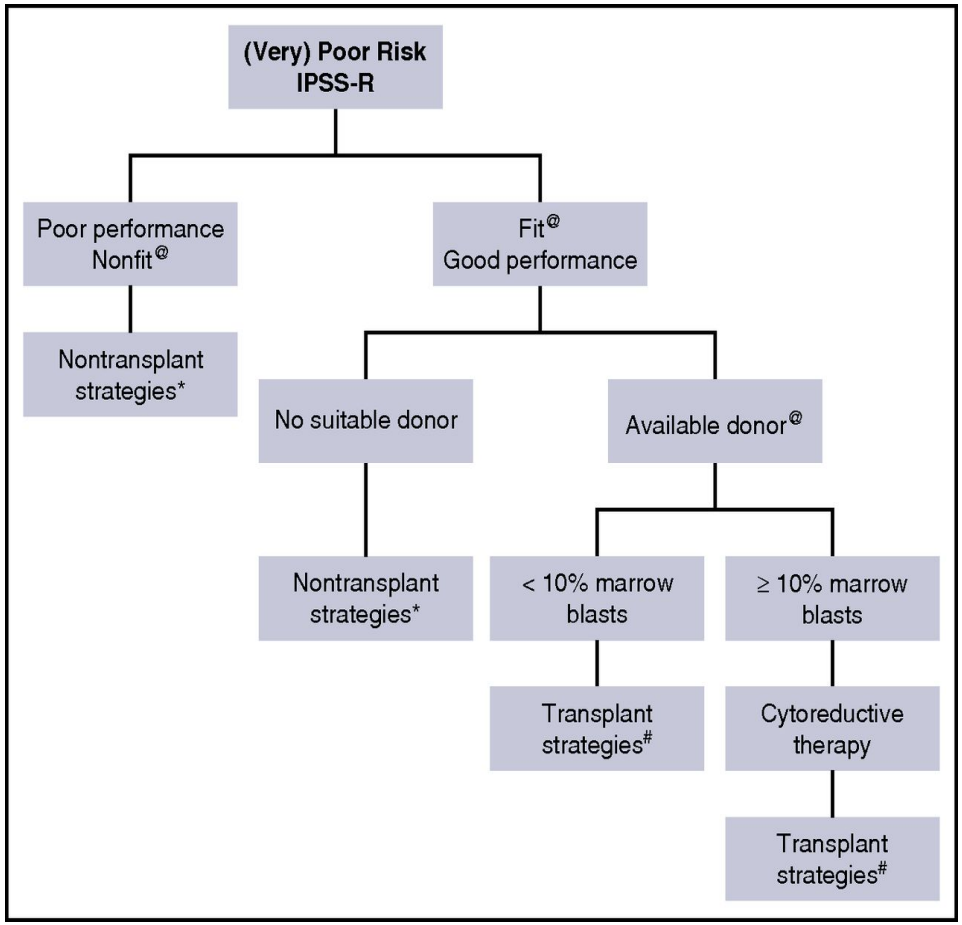
**MRD positive CBF AML**




- Zhu et al. Blood 2013; 121: 4056-4062

# Allogeneic SCT for MDS (EBMT/ELN)




Theo de Witte et al. Blood 2017;129:1753-1762

# Prospective Vidaza-allo study in elderly MDS

MDS (age 55-70 years) IPSS: intermediate II or high risk
(and intermediate I with high risk cytogenetic)

Registration

↓

*5-Azacytidine (Vidaza®) 7x75 mg/m² s.c. (q28d)*
*4 cycles plus donor search (HLA-identical sibling or matched unrelated donor (10/10)*

↓

After 4 (max 6) cycles of Vidaza®

↙ ↘

**No donor available:**
Continue with Vidaza® treatment until progress or unacceptable toxcities

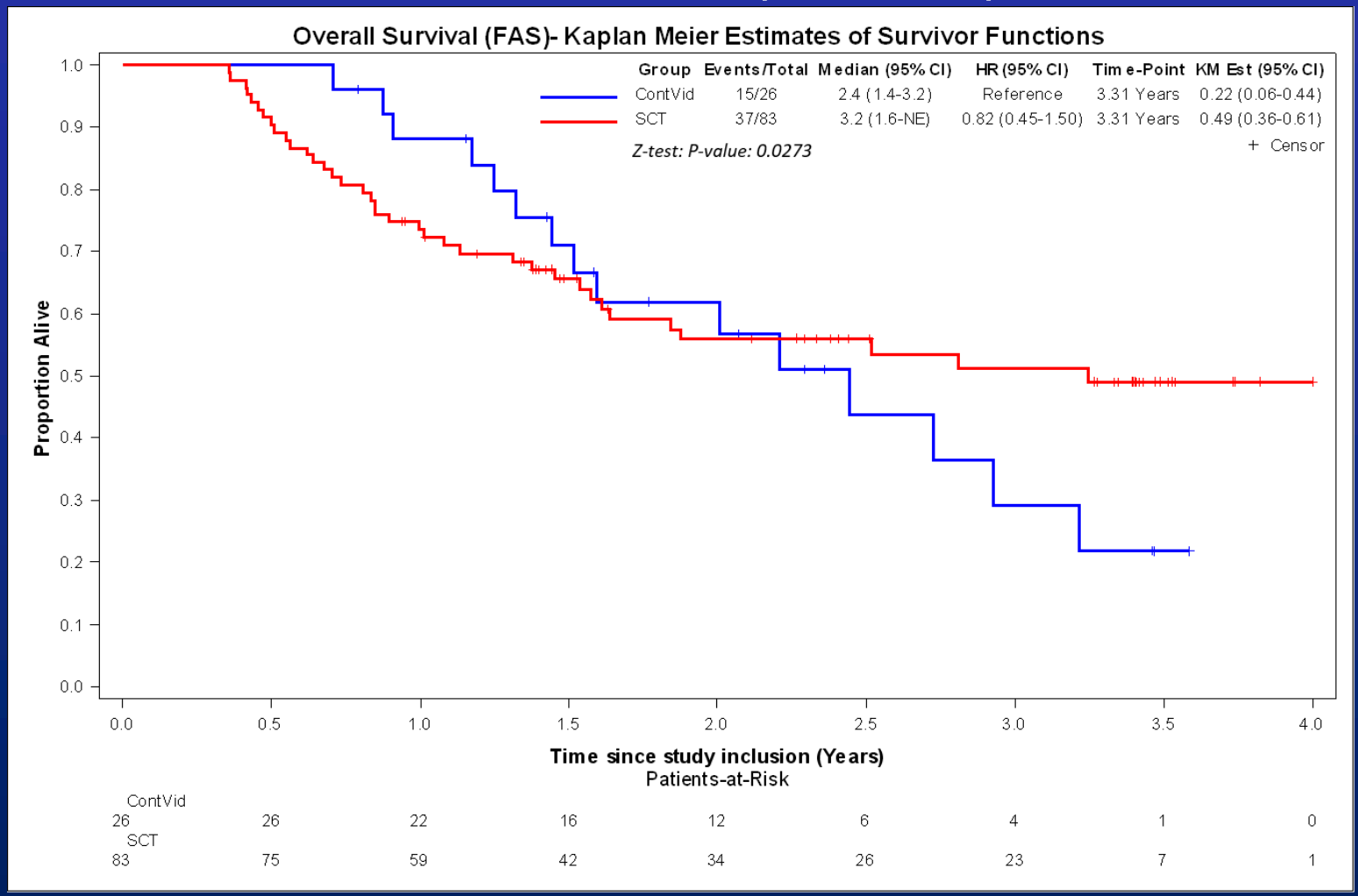
**Donor available:**
Allogeneic stem cell transplantation after reduced intensity conditioning*

possible RIC regimen:

- Busulfan 8 mg/kg (or Busilvex 6,4 mg/kg) plus Fludarabine (150 mg/m²)
- FLAMSA plus Busulfan 8 mg/kg (or Busilvex 6,4 mg/kg) plus Fludarabine (60 mg/m²)

# Prospective Vidaza-allo study

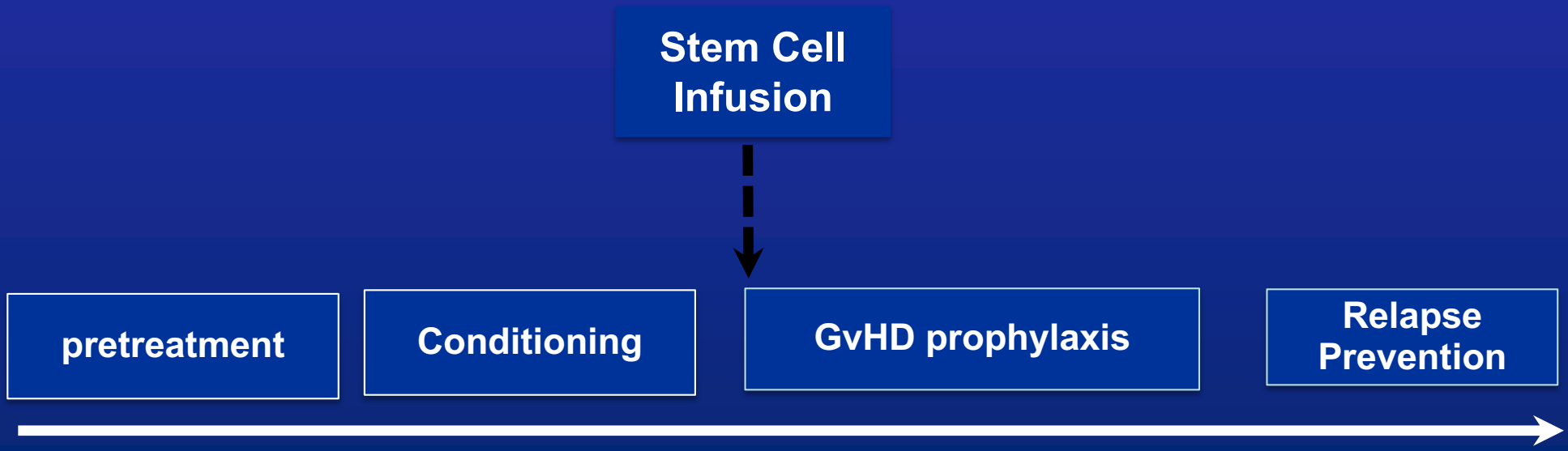
**Between June 2011 and November 2016 190 patients with a median age of 63 years (range, 55 to 72y) from 14 German centers were included**
**43% (n= 81) could not be selected after 5 Aza induction for one of the treatment arm because of progressive disease (n=25; 31%), mortality (n=14; 17%), inclusion or exclusion criteria not fulfilled (n=18, 22%),**



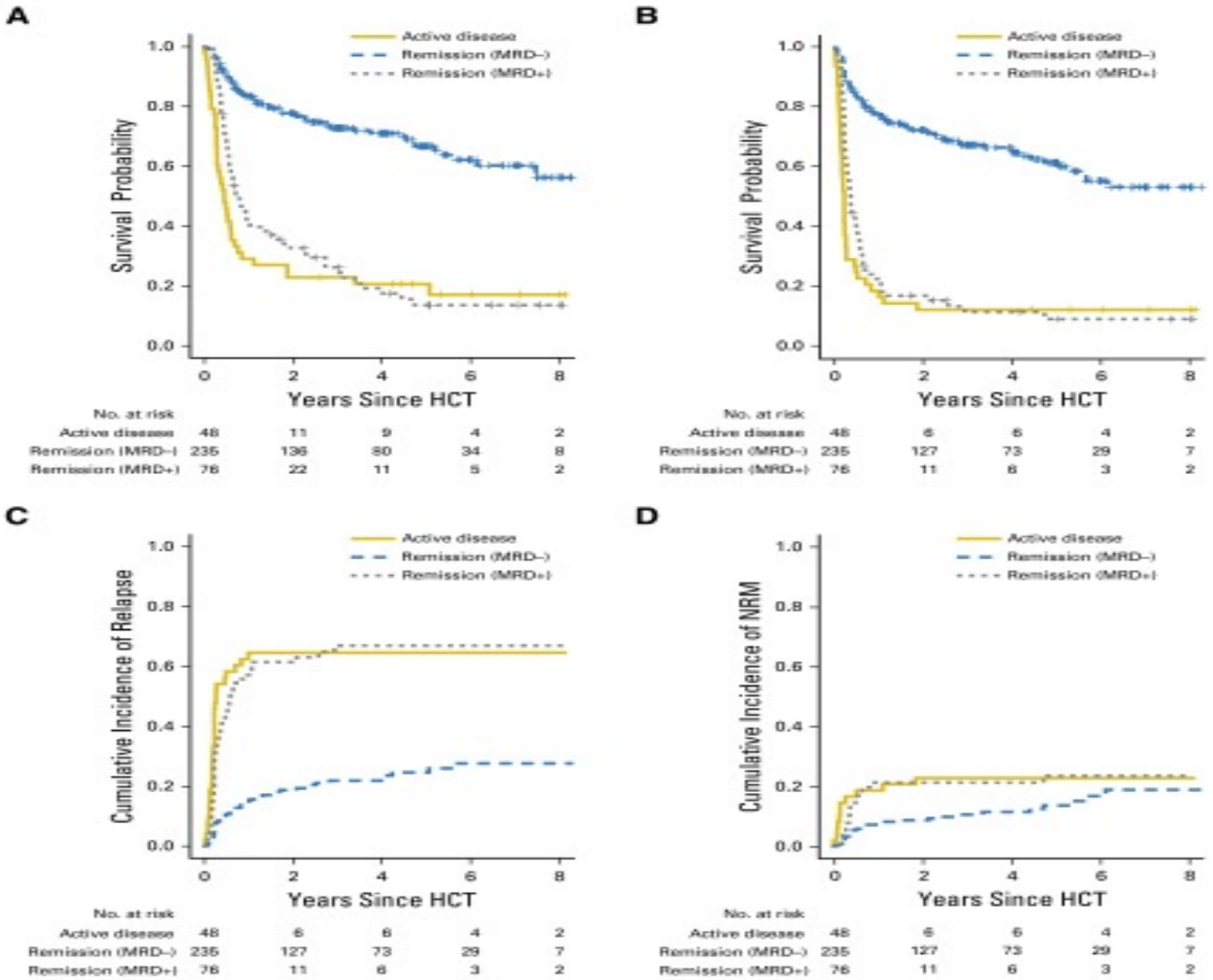

Kröger et al JCO 2021

# Optimizing allogeneic stem cell transplantation

1. Cure
2. Relapse
3. Non-relapse mortality



# Impact of MRD prior to allogeneic SCT in AML




*Walter RB et al., JCO 2016*

# GIMEMA AML1310 trial

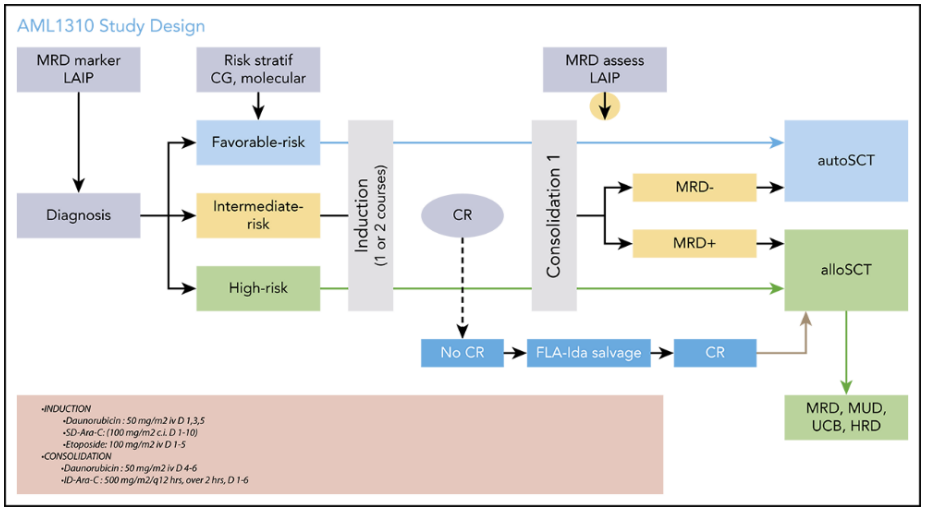
blood Regular Article

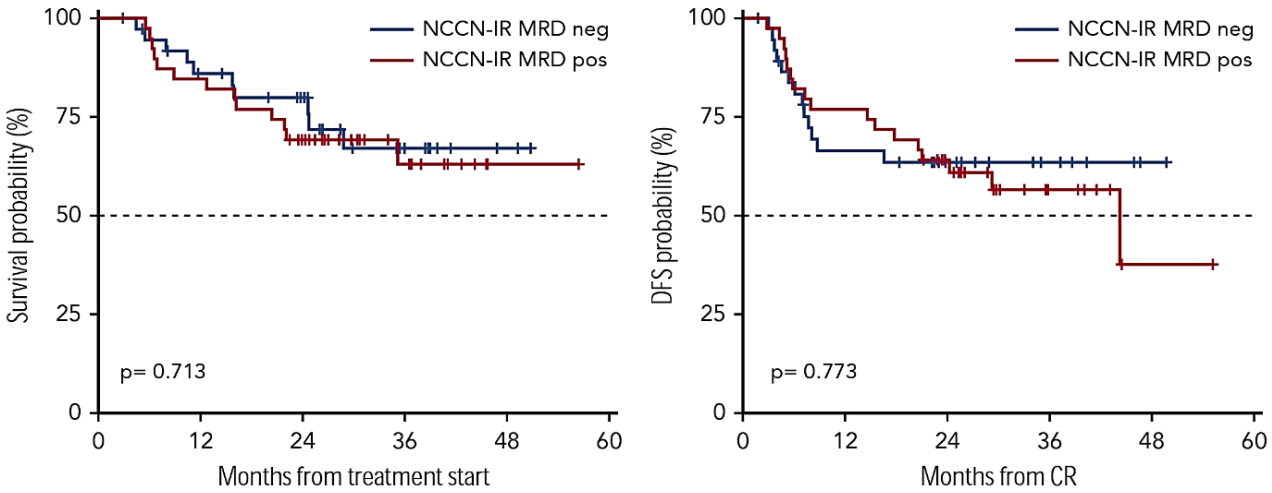
CLINICAL TRIALS AND OBSERVATIONS

## GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia

Adriano Venditti,[1,2] Alfonso Piciocchi,[3] Anna Candoni,[4] Lorella Melillo,[5] Valeria Calafiore,[6] Roberto Cairoli,[7] Paolo de Fabritiis,[8] Gabriella Storti,[9] Prassede Salutari,[10] Francesco Lanza,[11] Giovanni Martinelli,[12,13] Mario Luppi,[14] Patrizio Mazza,[15] Maria Paola Martelli,[16] Antonio Cuneo,[17] Francesco Albano,[18] Francesco Fabbiano,[19] Agostino Tafuri,[20] Anna Chierichini,[21] Alessia Tieghi,[22] Nicola Stefano Fracchiolla,[23] Debora Capelli,[24] Robin Foà,[25] Caterina Alati,[26] Edoardo La Sala,[3] Paola Fazi,[3] Marco Vignetti,[3] Luca Maurillo,[2] Francesco Buccisano,[1,2] Maria Ilaria Del Principe,[1,2] Maria Irno-Consalvo,[1] Tiziana Ottone,[1] Serena Lavorgna,[1] Maria Teresa Voso,[1,2] Francesco Lo-Coco,[1,2] William Arcese,[1,2] and Sergio Amadori[3]

*Blood.* 2019;134(12):935-945

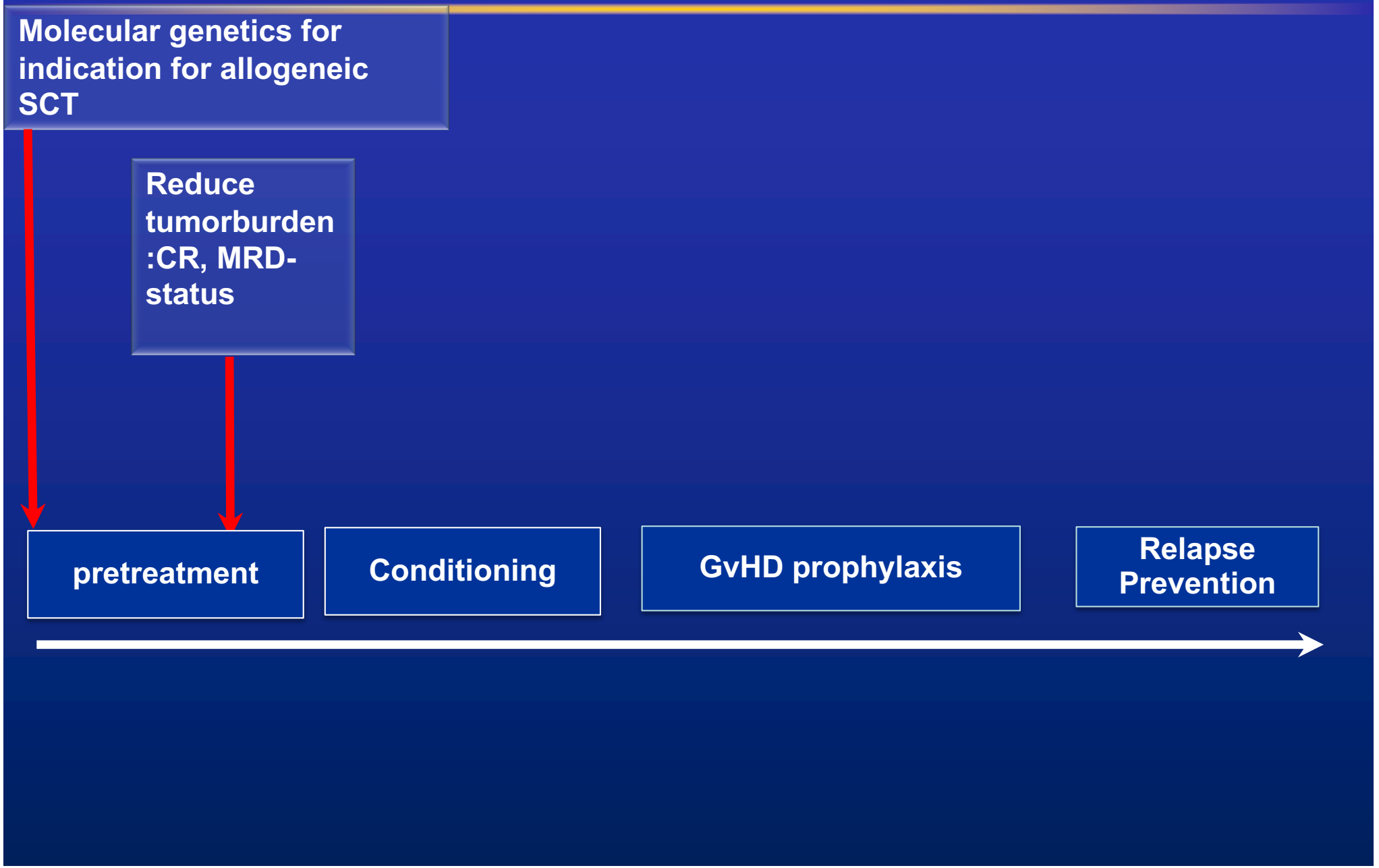


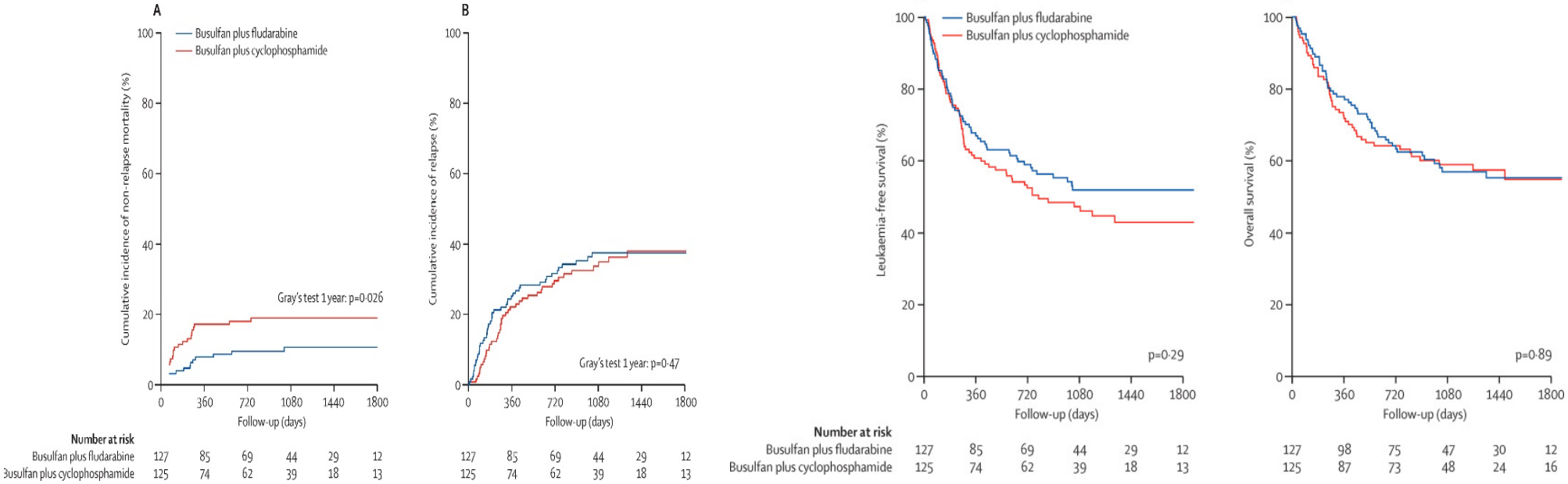

110/177 (62%) and 130/188 (71%) AuSCT or AlloSCT candidates received it

Vendetti et al. Blood 2019;134:935–945.

# Optimizing allogeneic stem cell transplantation

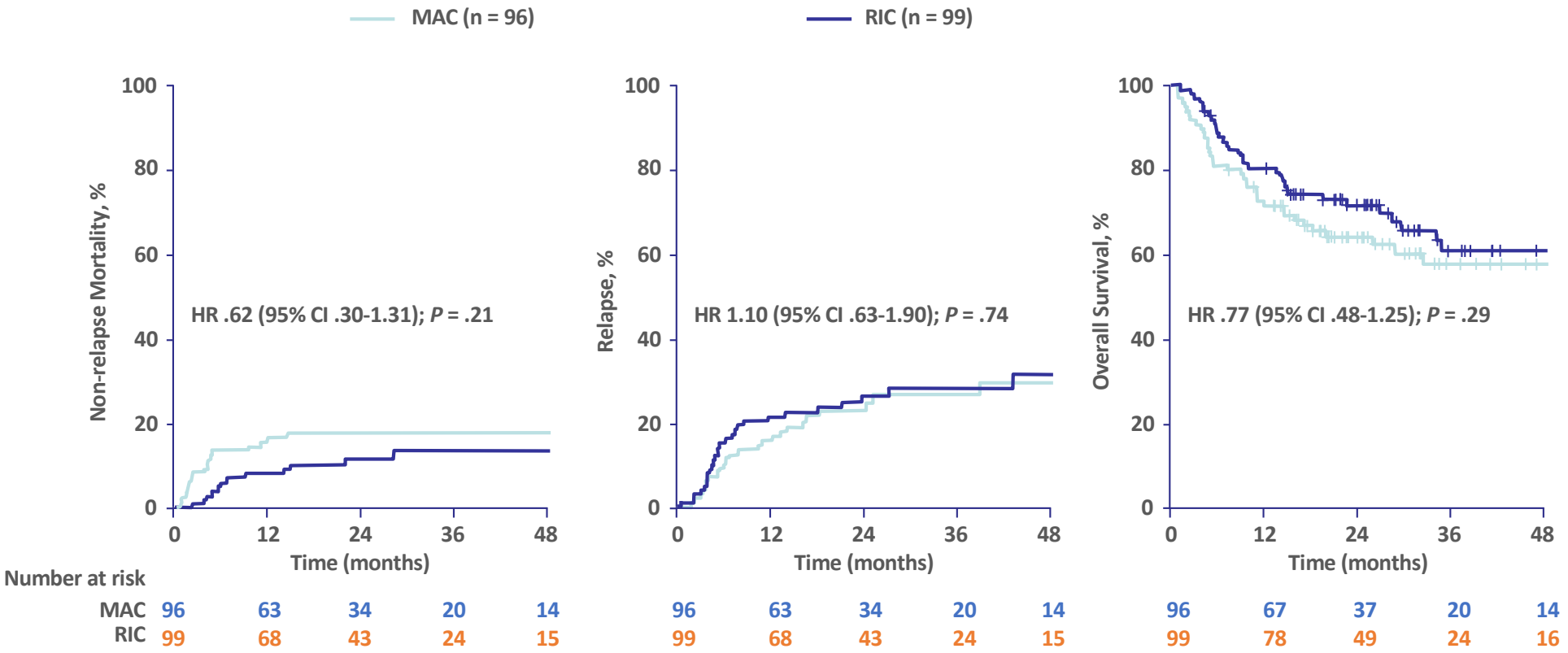


# Busulfan/Cyclophosphamide vs Busulfan/Fludarabine in AML a randomized study



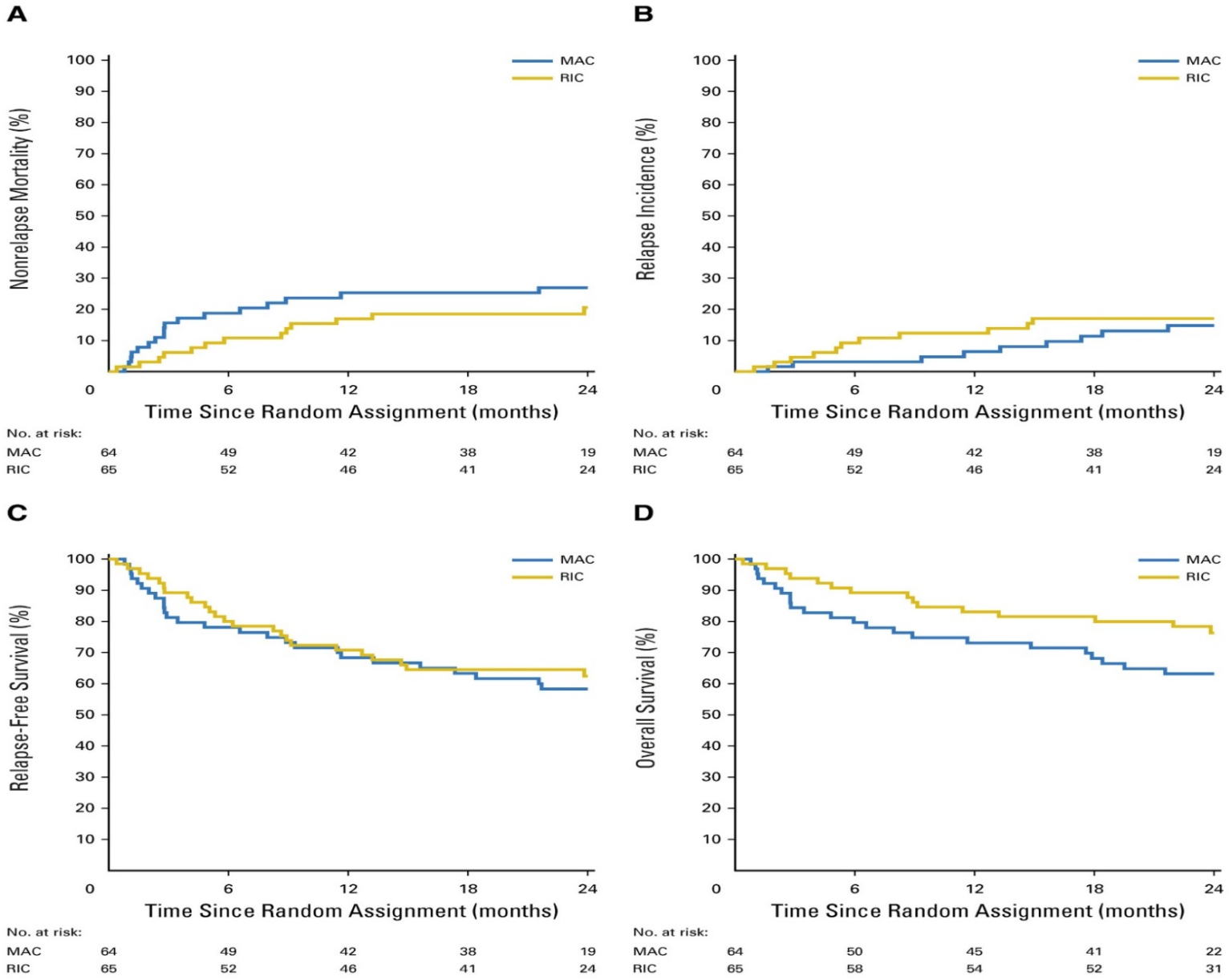

*Rambaldi et al Lancet Oncol 2015*

# RIC vs. MAC AML CR1: German Randomized Study TBI12/Cy vs TBI8/Flu



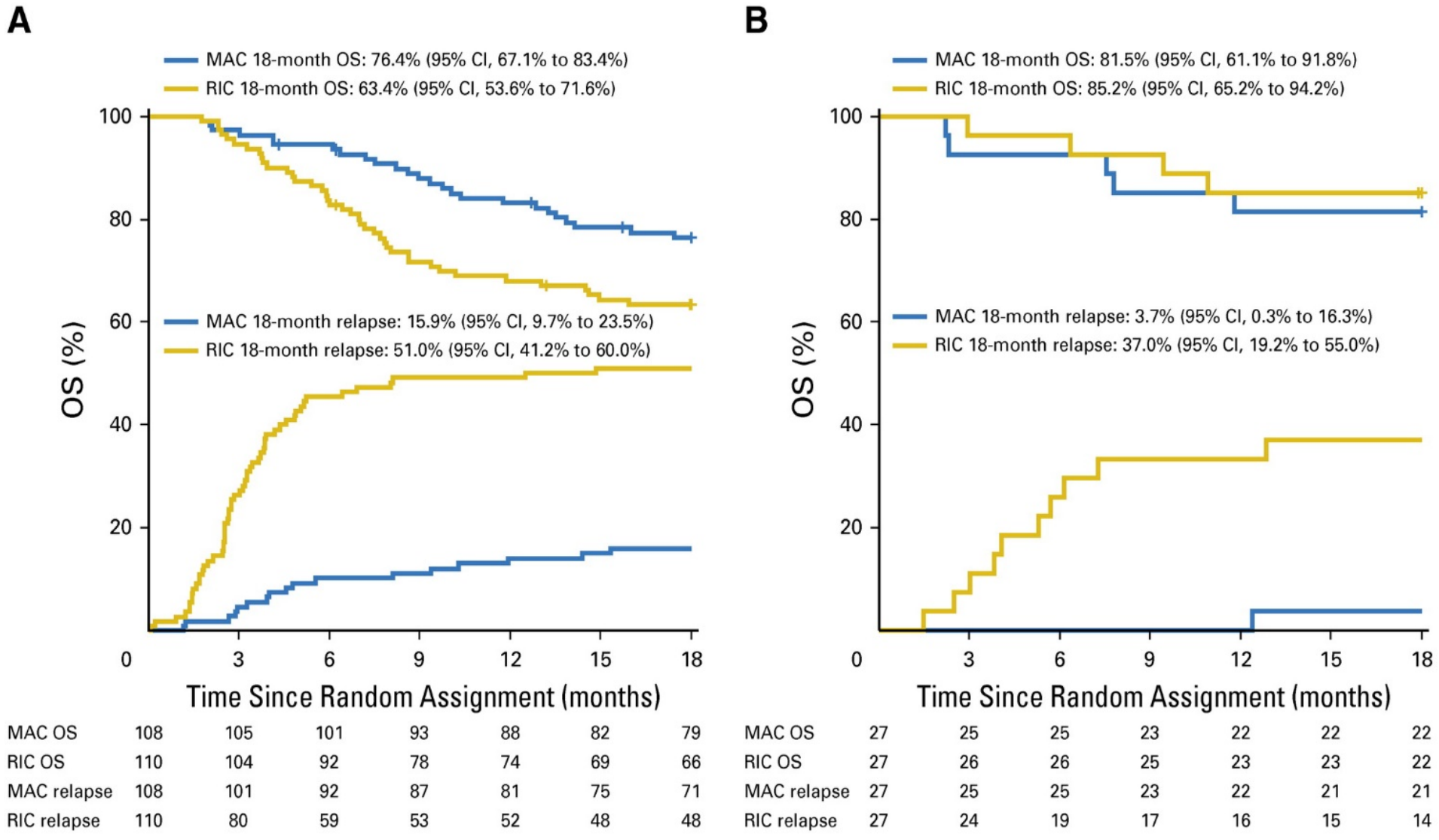

Bornhäuser M, et al. *Lancet Oncology.* 2012;13:1035-1044.

# RIC vs MAC in MDS/sAML ( EBMT prospective RICMAC Study)



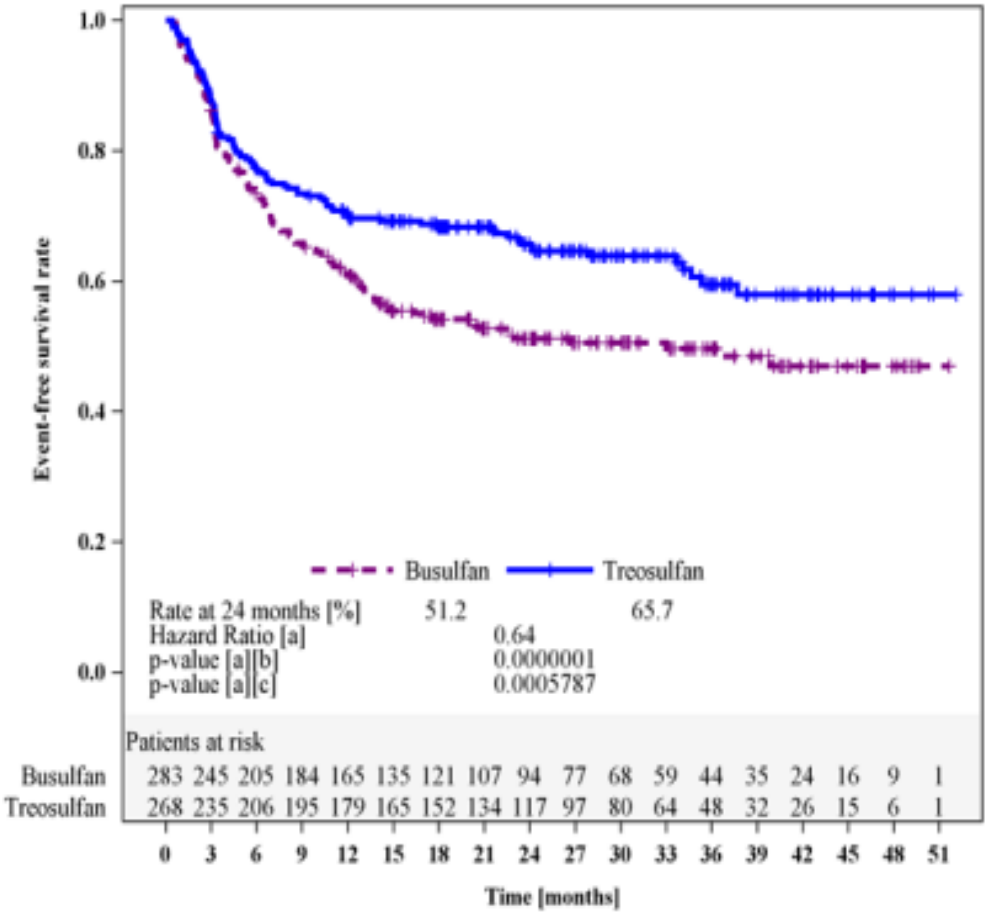

*Kröger et al., JCO 2017*

# Role of Conditioning Regimen: MAC vs RIC: BMT CTN prospective Study

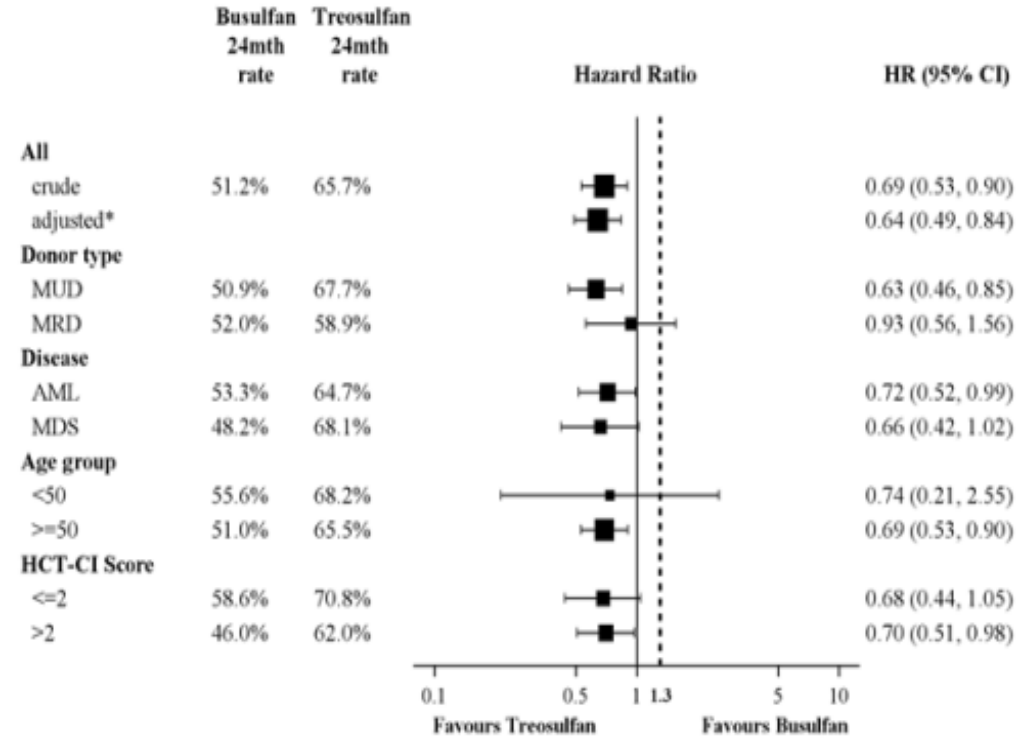



*Scott et al., JCO 2017*

# Treosulfan or busulfan plus fludarabine for older patients with AML or MDS: a randomised, non-inferiority, phase 3 trial




[a] adjusted for donor type as factor, and risk group and centre as strata using Cox regression model
[b] for testing non-inferiority of Treosulfan compared to Busulfan
[c] for testing superiority of Treosulfan compared to Busulfan




* adjusted for donor type as factor, and risk group and centre as strata using Cox model.

*Beelen et al Lancet Haemat 2020*

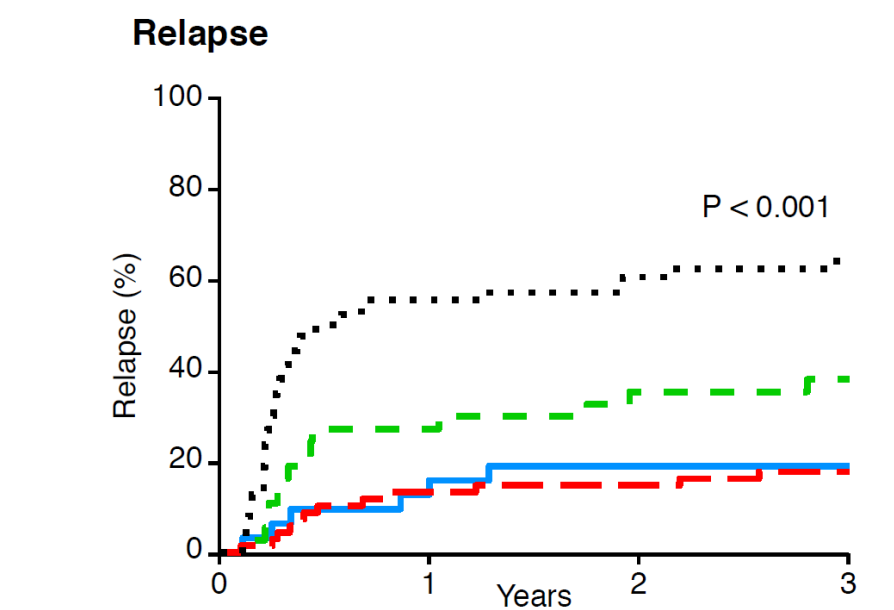
# Prospective Studies comparing different intensity of conditioning regimen in AML and MDS

| Trial | Population | Regimen | | RFS % (*P*) | Relapse % (*P*) | NRM % (*P*) | OS % (*P*) |
|---|---|---|---|---|---|---|---|
| Toxicity reduced MAC *vs.* MAC or RIC | | | | | | | |
| Rambaldi *et al.*[20] | AML<br>Age >40 y | BuFlu (MAC) | BuCy (MAC) | 40 *vs.* 47<br>(ns) | 24 *vs.* 21<br>(ns) | 8 *vs.* 18<br>(0.03) | 27 *vs.* 35<br>(ns) |
| Bornhäuser *et al.*[16] | AML CR1<br>Age 18-60 y<br>IR/HR cytogenetics | 8 GyTBIFlu (MAC) | 12 GyTBI/Cy (MAC) | 58 *vs.* 56<br>(ns) | 28 *vs.* 26<br>(ns) | 13 *vs.* 18<br>(ns) | 61 *vs.* 58<br>(ns) |
| Beelen *et al.*[24] | AML/MDS<br>Age ≥50 y and/or<br>CI >2/KPS >60% | TreoFlu (MAC) | BuFlu (RIC) | 64 *vs.* 50<br>(0.001) | 25 *vs.* 23<br>(ns) | 11 *vs.* 23<br>(0.05) | 71 *vs.* 56<br>(0.01) |
| RIC *vs.* NMA | | | | | | | |
| Blaise *et al.*[2] | Hematologic malignancies | BuFlu (RIC) | FluTBI (NMA) | 35 *vs.* 23<br>(ns) | 27 *vs.* 54<br>(<0.01) | 38 *vs.* 22<br>(0.03) | 41 *vs.* 41<br>(ns) |
| RIC *vs.* MAC | | | | | | | |
| Ringdén *et al.*[90] | AML/CML<br>Age ≤60 y | BuFlu (RIC)<br>incl n=4 CML (NMA) | BuCy(MAC) | NR | 12 *vs.* 35<br>(ns) | 11 *vs.* 11<br>(ns) | 76 *vs.* 62<br>(ns) |
| Scott *et al.*[26] | AML/MDS in CR<br>Age 18-65 y | BuFlu; FluMel (RIC) | BuFlu; BuCy; TBICy (MAC) | 47 *vs.* 68<br>(<0.01) | 48 *vs.* 14<br>(<0.001) | 4 *vs.* 16<br>(<0.01) | 78 *vs.* 68<br>(0.07) |
| Kröger *et al.*[25] | MDS/sAML<br>Age 18-60 y UD<br>Age 18-65 RD | BuFlu (RIC) | BuCy (MAC) | 62 *vs.* 58<br>(ns) | 17 *vs.* 15<br>(ns) | 17 *vs.* 25<br>(ns) | 76 *vs.* 63<br>(0.08) |
| RIC *vs.* sequential RIC | | | | | | | |
| Craddock *et al.*[14] | AML /MDS<br>Age 18-75 y | FLAMSA-Bu (seq RIC) | Bu/Flu or Mel/Flu (RIC) | 54 *vs.* 49<br>(ns) | 27 *vs.* 30<br>(ns) | 21 *vs.* 17<br>(ns) | 61 *vs.* 59<br>(ns) |

RIC: reduced intensity conditioning; MAC: myeloablative conditioning; NMA: nonmyeloablative; RFS: relapse-free survival; NRM: non-relapse mortality; OS: overall survival; (s)AML: (secondary) acute myeloid leukemia; CML: chronic myeloid leukemia; CR: complete remission; Cy: cyclophosphamide; Treo: treosulfan; Flu: fludarabine; TBI: total body irradiation; Bu: busulfan; IR: intermediate-risk; HR: high-risk; Mel: melphalan; MDS: myelodysplastic syndrome; UD: unrelated donor; RD: related donor; ns: not significant; y: years; CI: comorbidity index; KPS: Karnofsky performance status; NR: not reported; seq: sequential.

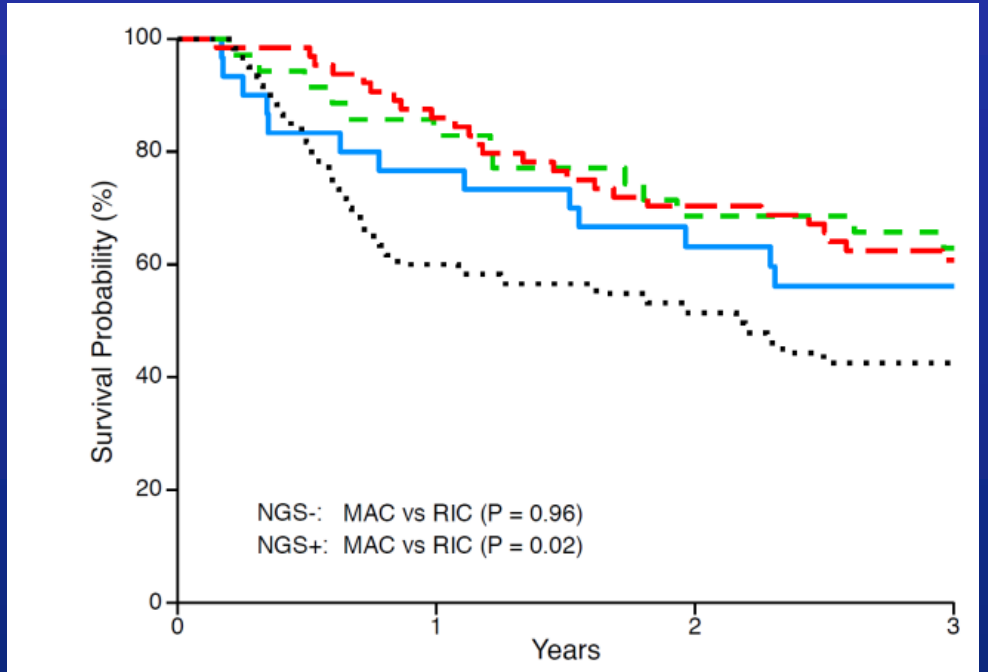
*Gagelmann, Kröger Haematologica 2021*

# MRD by NGS and outcome after RIC vs MAC


**No. at Risk**

| | | | | |
|---|---|---|---|---|
| NGS- | | | | |
| MAC | 30 | 21 | 16 | 15 |
| RIC | 35 | 24 | 20 | 18 |
| NGS+ | | | | |
| MAC | 65 | 50 | 43 | 32 |
| RIC | 60 | 23 | 17 | 13 |

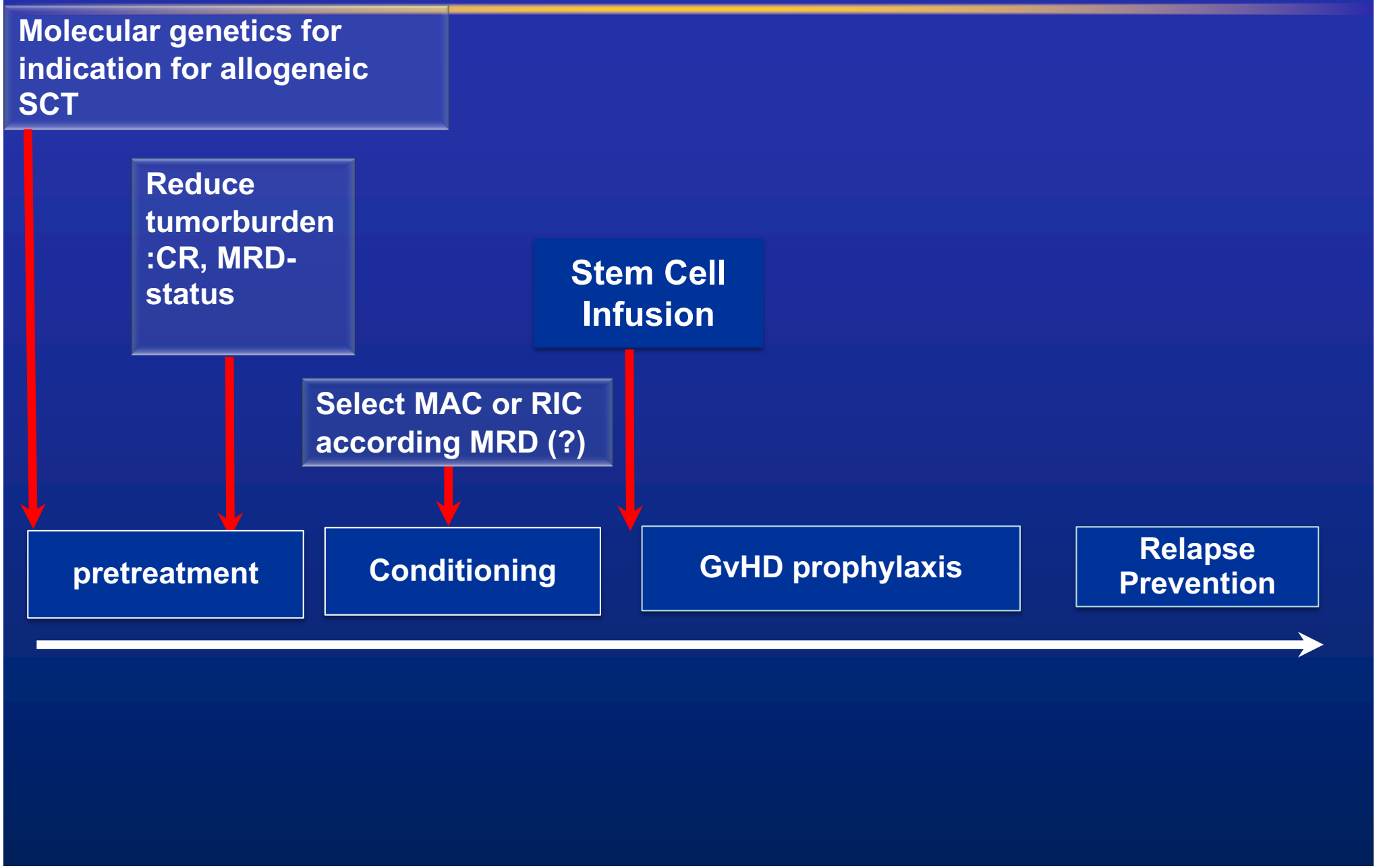



**No. at Risk**

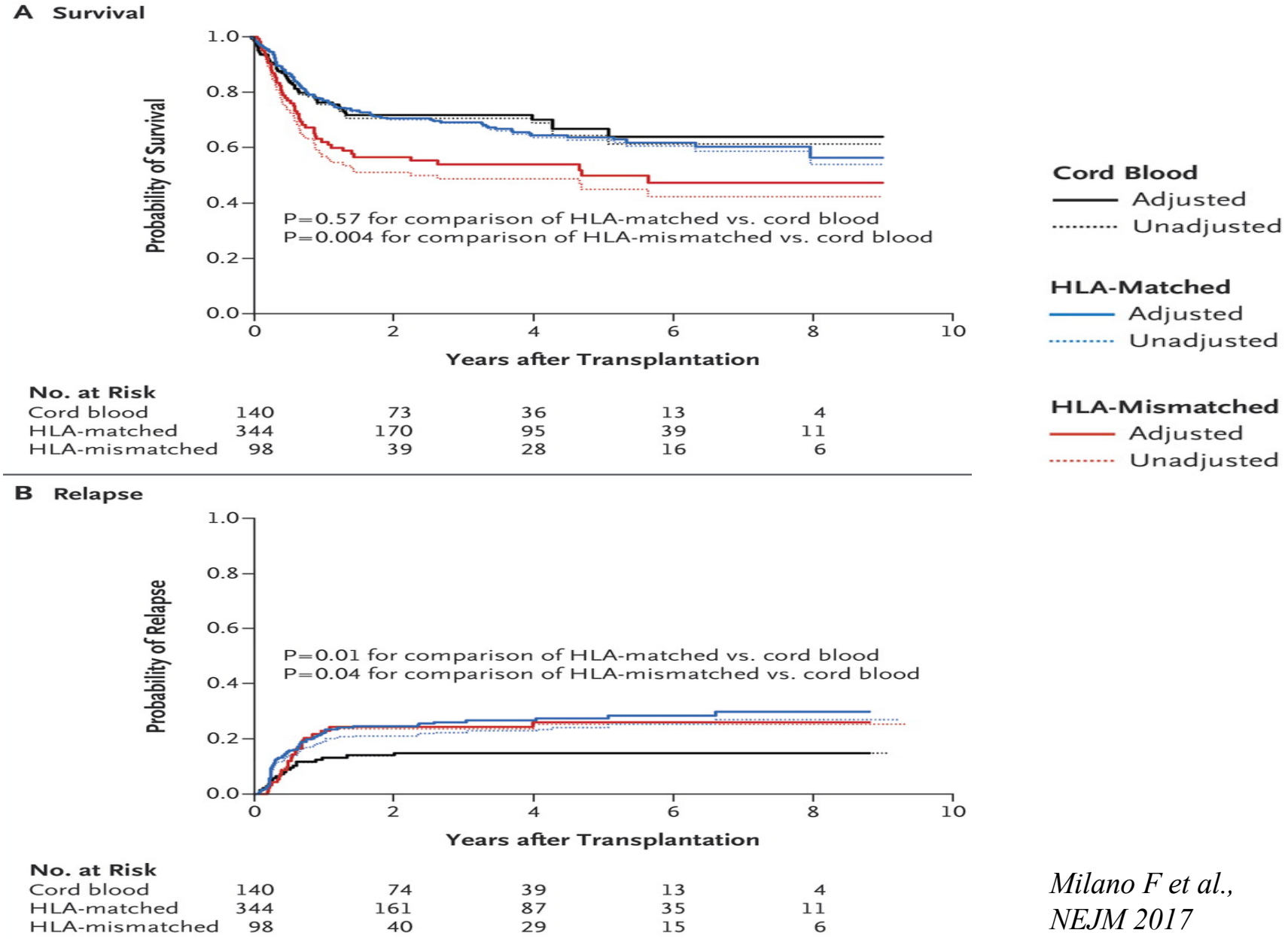
| | | | | |
|---|---|---|---|---|
| NGS- | | | | |
| MAC | 30 | 23 | 18 | 16 |
| RIC | 35 | 29 | 24 | 22 |
| NGS+ | | | | |
| MAC | 65 | 55 | 45 | 35 |
| RIC | 60 | 36 | 29 | 24 |

Hourigan et al. JCO 2020

# Optimizing allogeneic stem cell transplantation

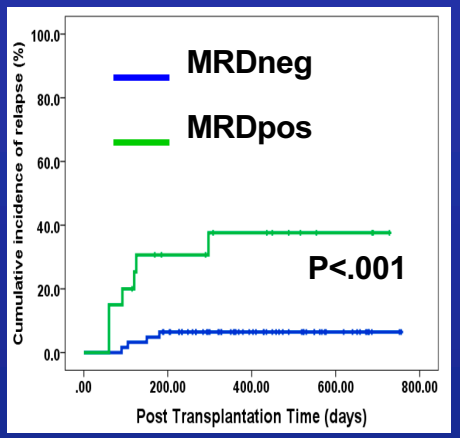
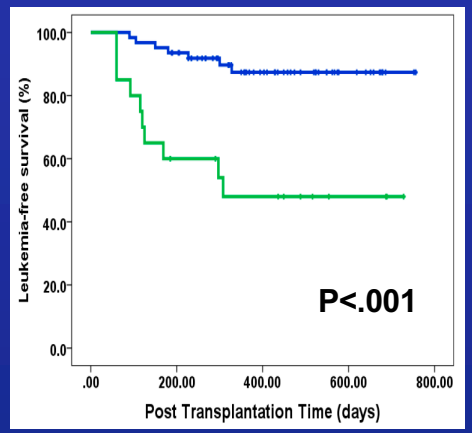
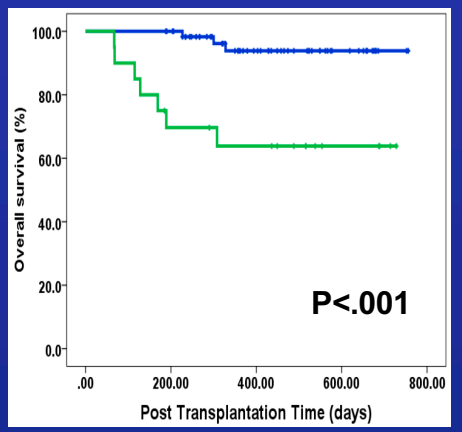
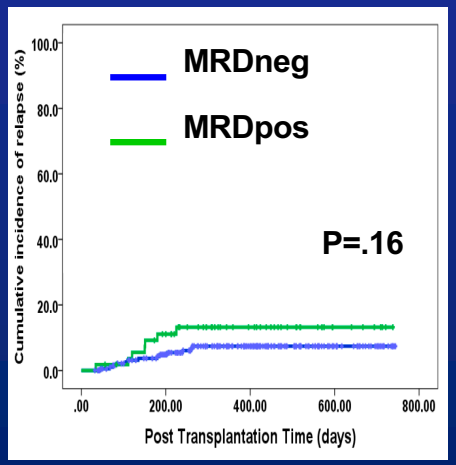
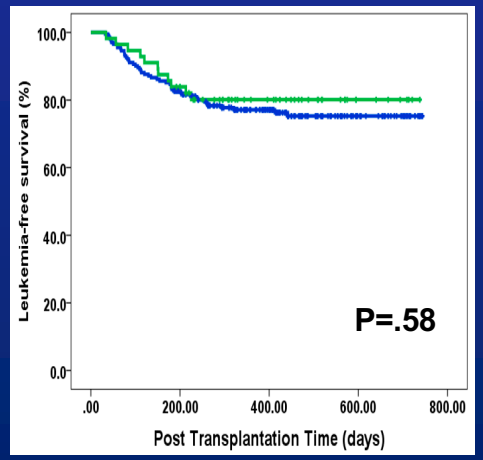
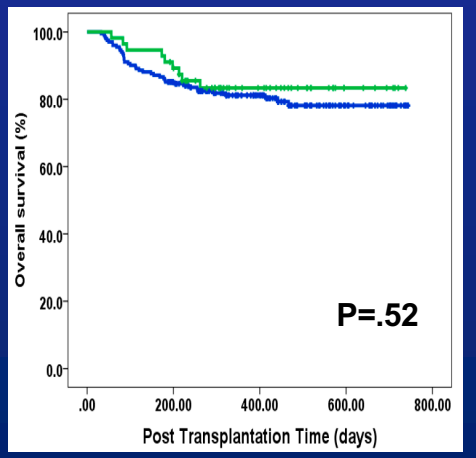


# Cordblood for MRD positive leukemia




*Milano F et al., NEJM 2017*

# Haplo-identical vs HLA-identical SCT for MRD positive (Flow) patients

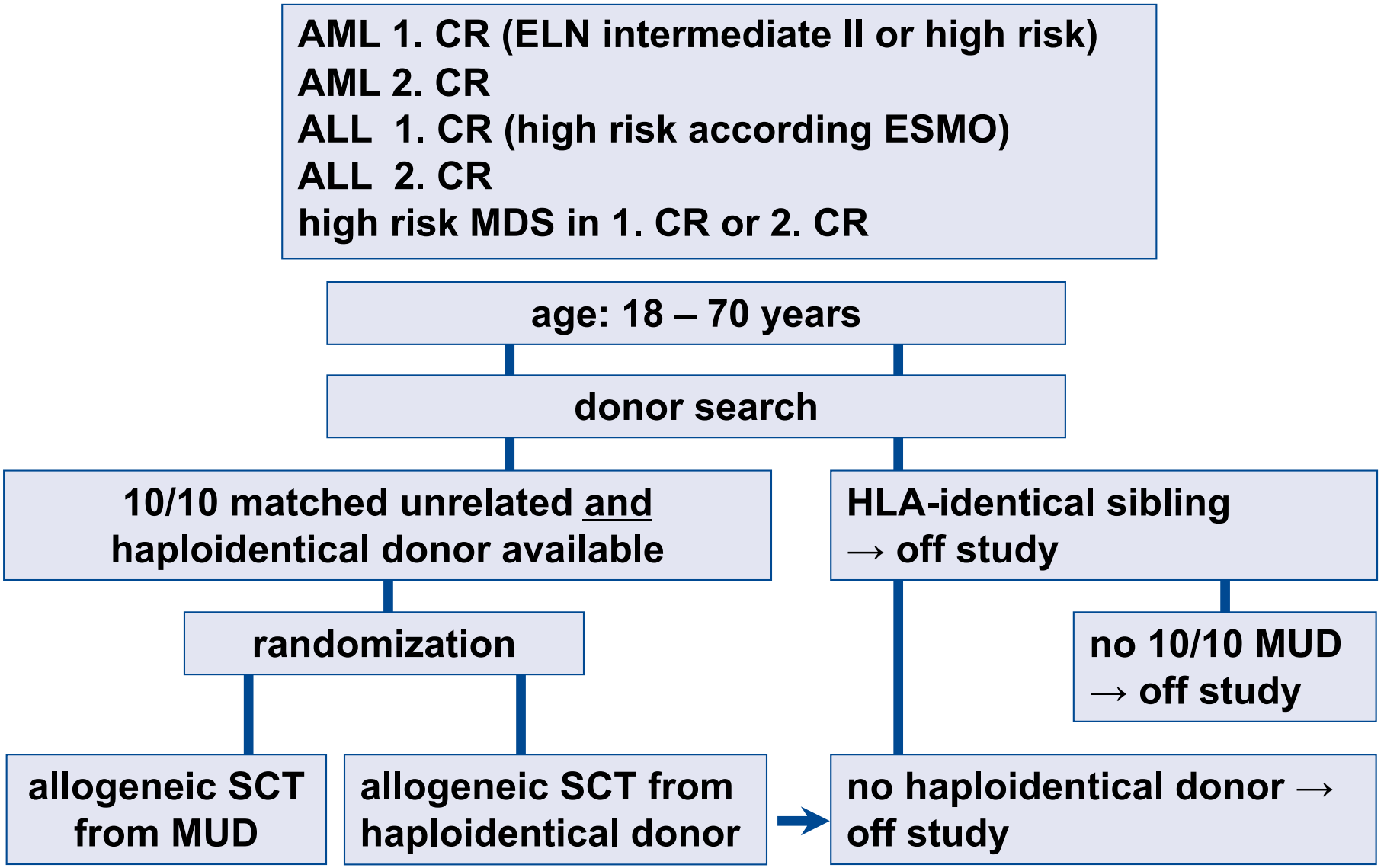
| | Relapse incidence | Leukemia-free survival | Overall survival |
|---|---|---|---|
| MSD (n=82) |  |  |  |
| Haplo (n=258) |  |  |  |



Chang et al. J Hematol Oncol 2017; 10: 134

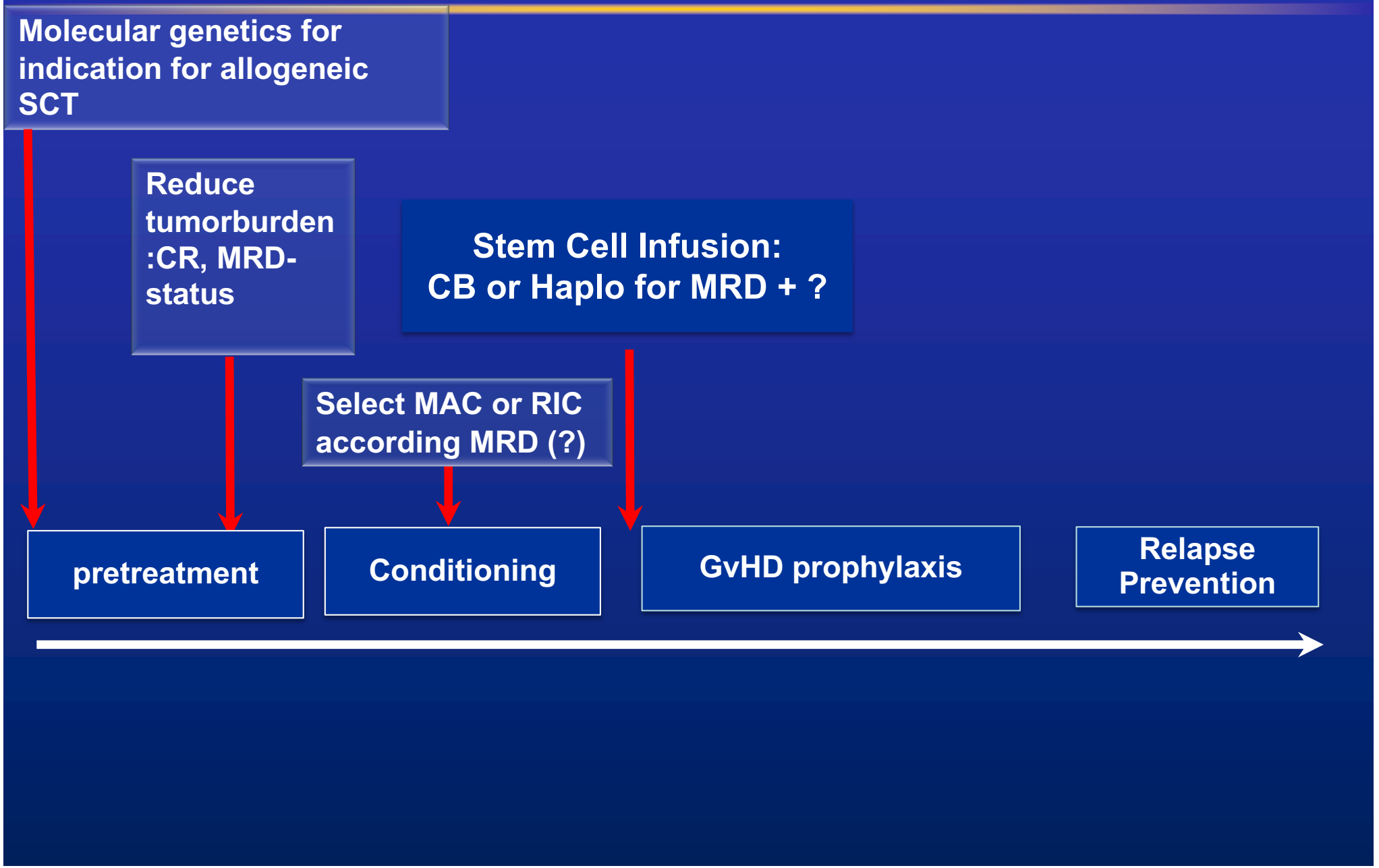
# European HaploMUD Study

## European Multicenter Study (9 countries)

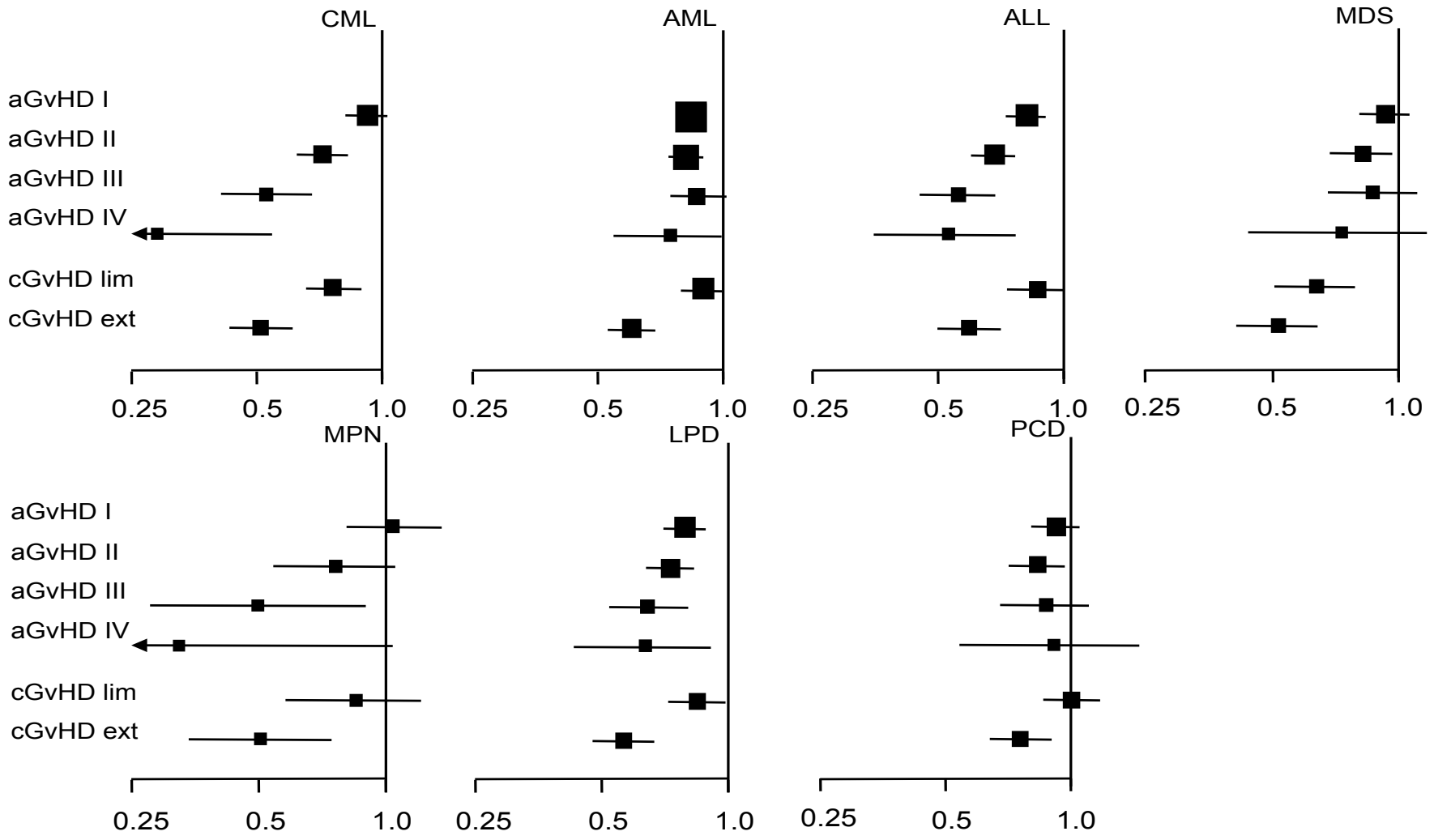



*DKMS funded study*

# Optimizing allogeneic stem cell transplantation



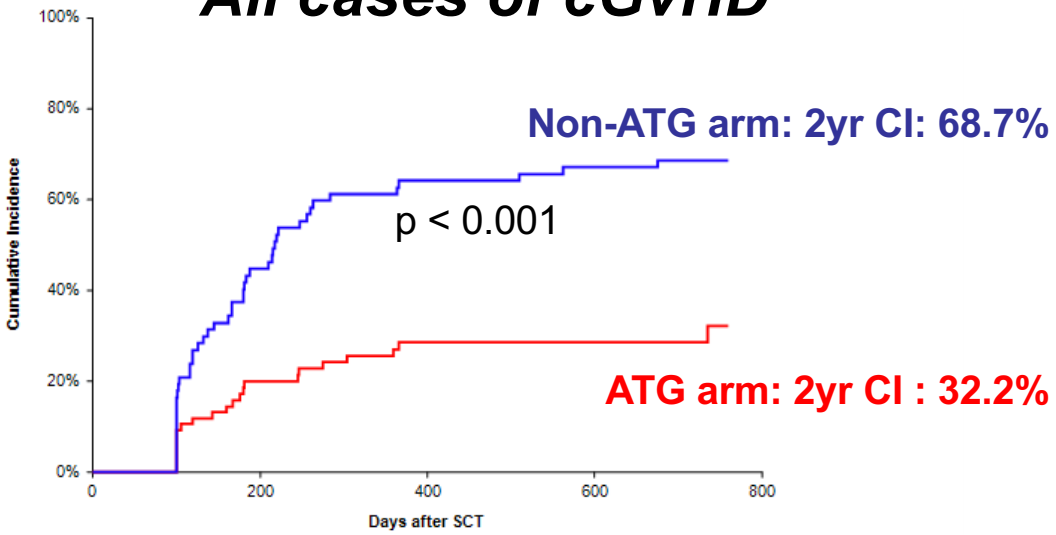
# Impact of GvHD on relapse in different diseases: EBMT Megafile (> 60.000 pts)



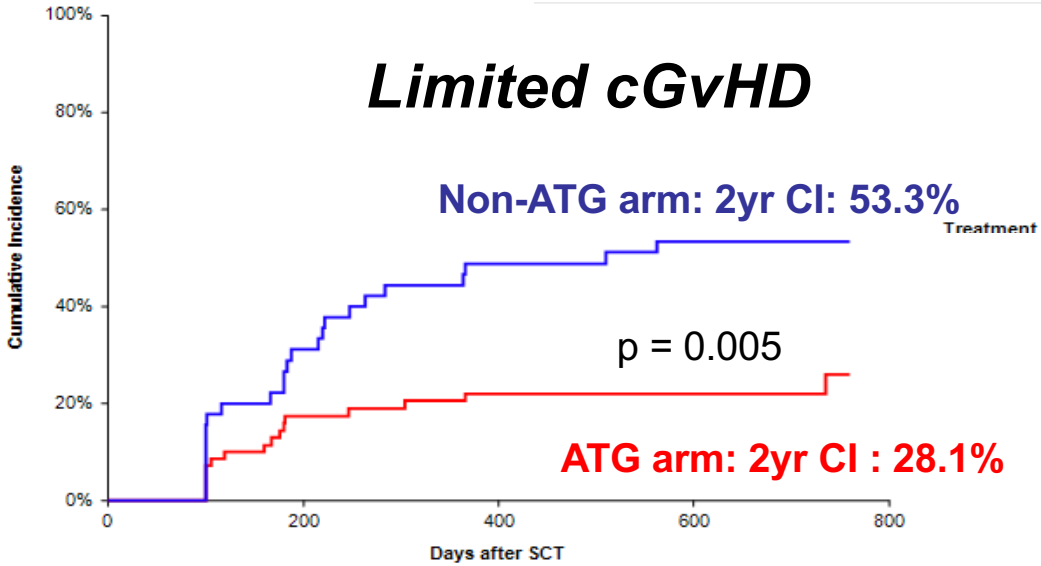

*M Stern et al., Leukemia 2014*

# Effect of ATLG on cGvHD after HLA-identical allogeneic SCT for acute leukemia

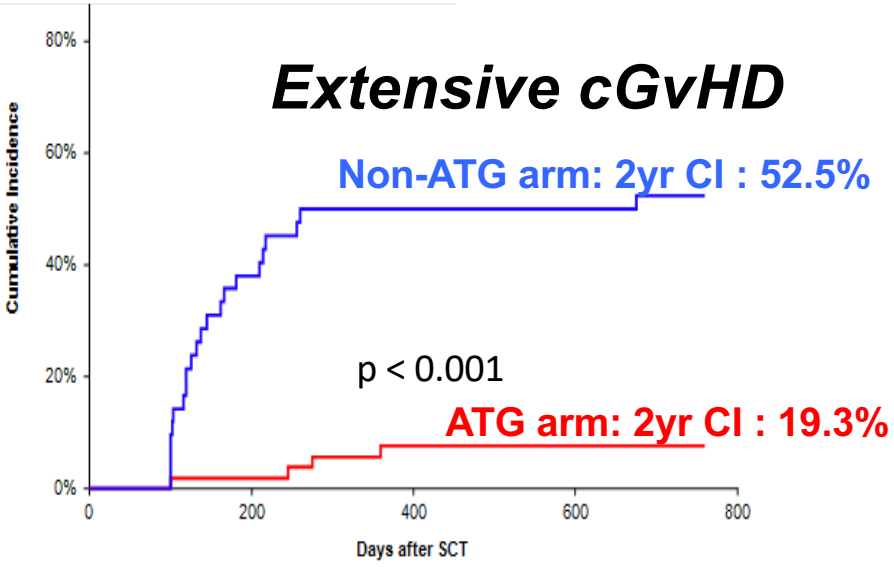
## *All cases of cGvHD*




## *Limited cGvHD*



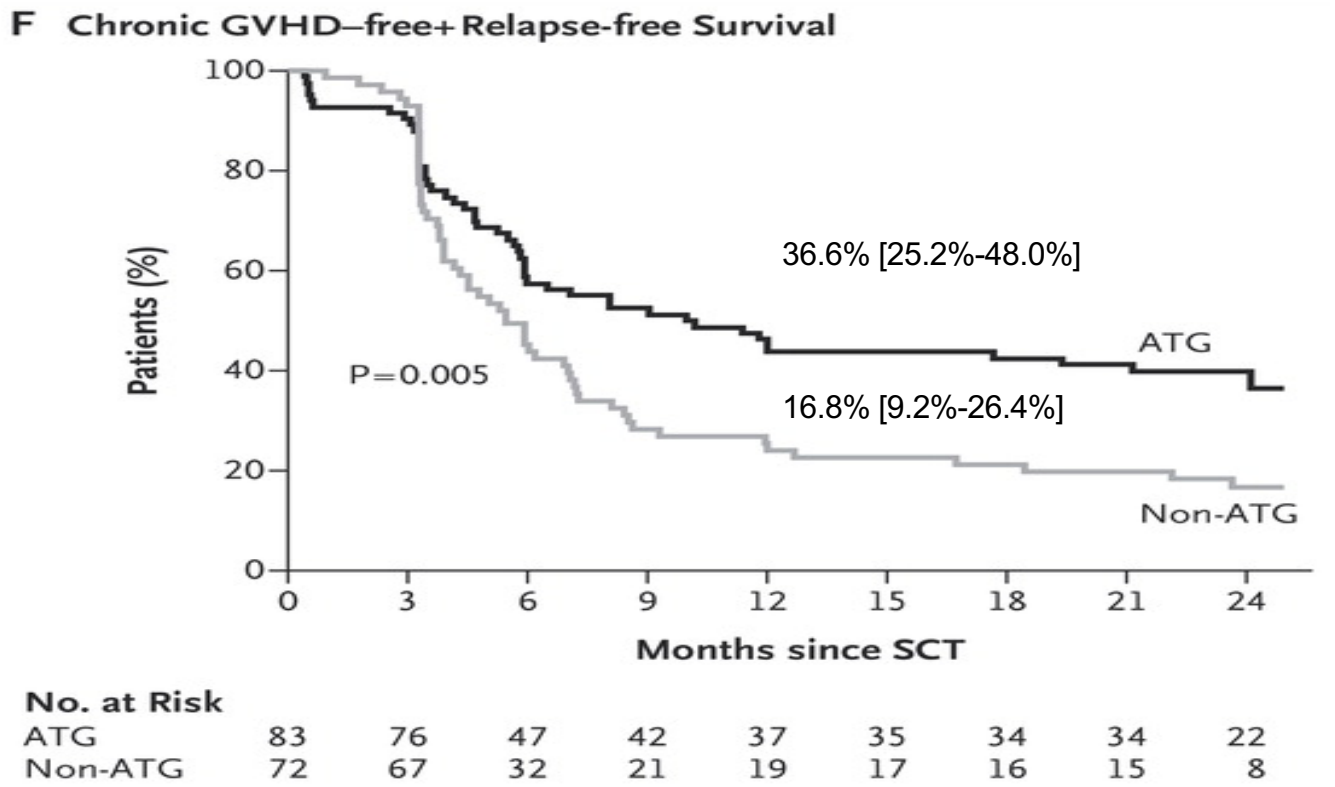

## *Extensive cGvHD*




Kröger, Solano… Bonifazi NEJM 2016

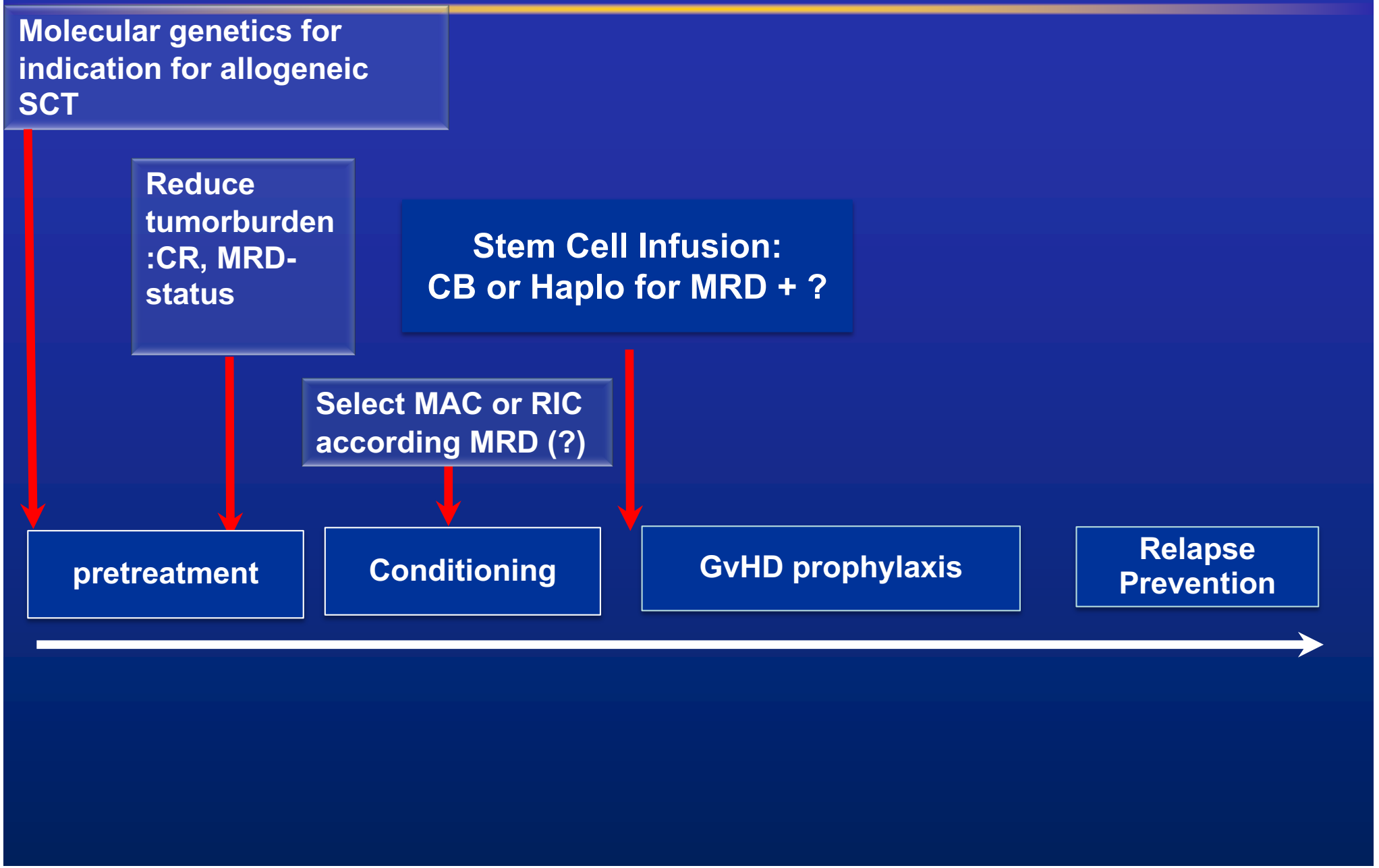
# ATLG in sibling transplants: Results from a randomized study

**cGRFS**

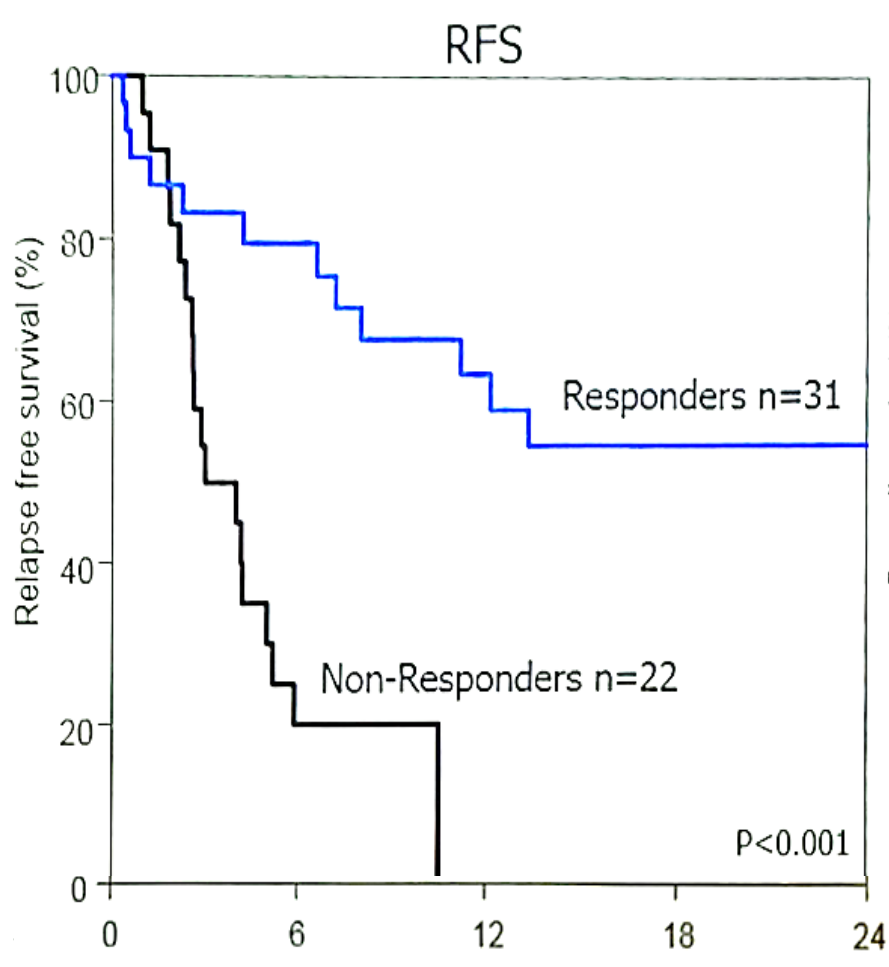


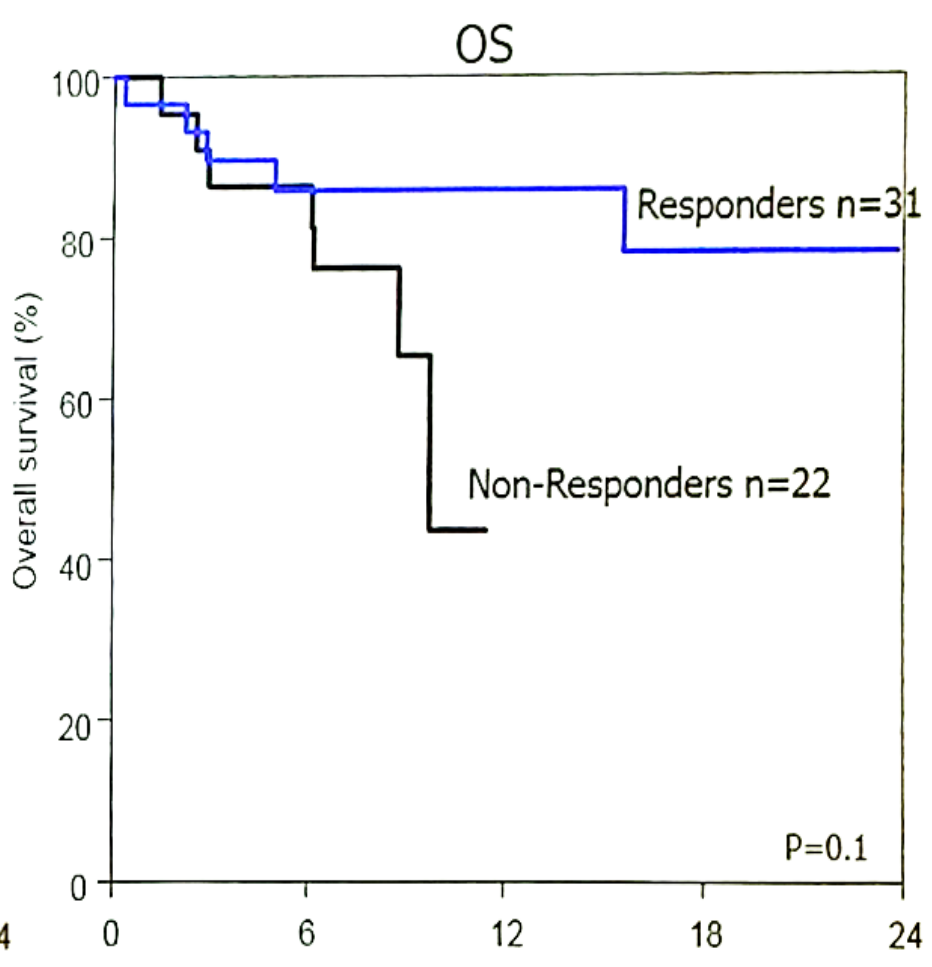

*Kröger N et al. NEJM 2016; Bonifazi F et al Lancet Haemtologica 2019*

# Optimizing allogeneic stem cell transplantation



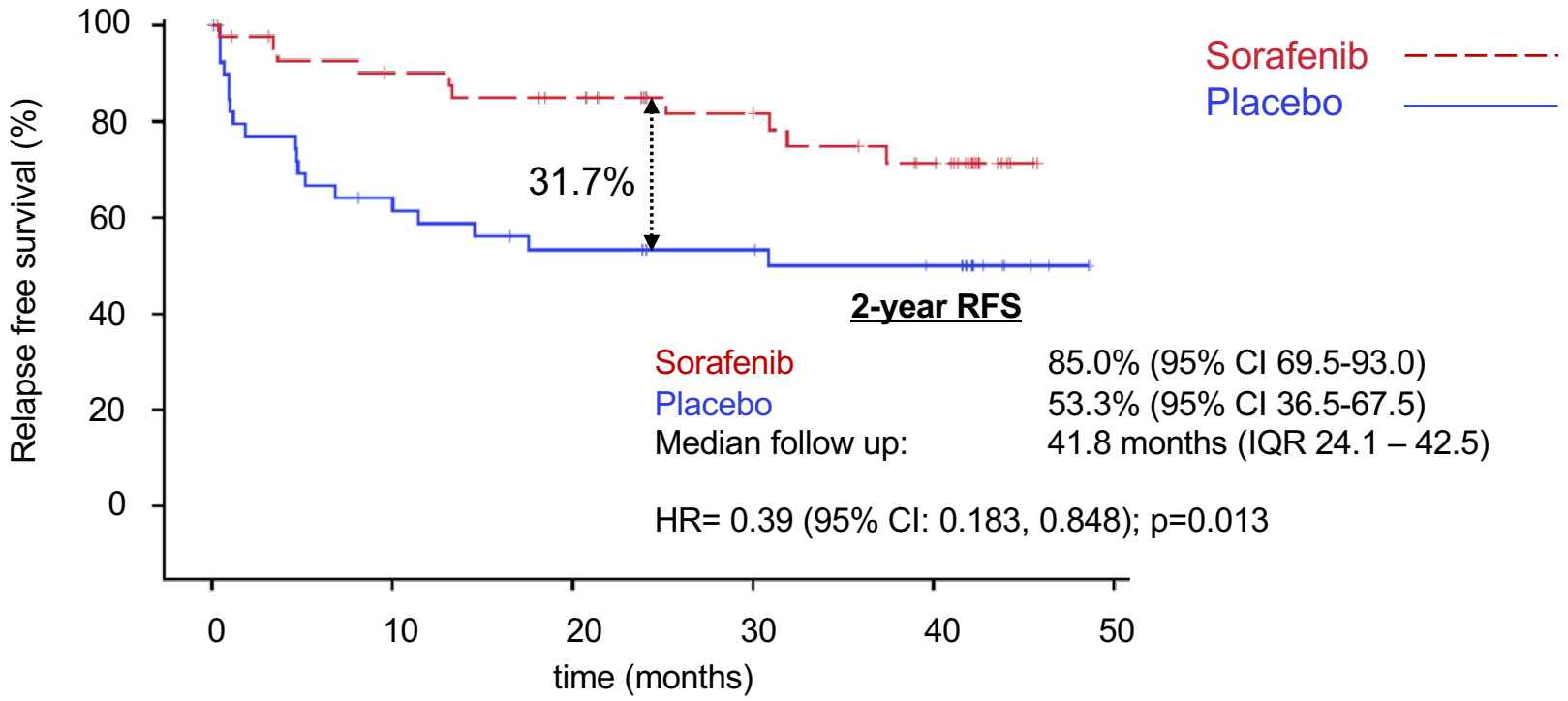
# Azacitidine for MRD positive AML/MDS




Platzbecker et al. Lancet Oncol 2018

# Sorafenib maintenance for pts with FLT3-ITD acute myeloid leukaemia in 1st complete remission (SORMAIN study) Relapse free survival




*Burchert et al., JCO 2020*

# Selected Ongoing Phase 2/3 AML Maintenance Trials post allograft in AML or MDS

| Trial[1-9] | Phase | Description |
|---|---|---|
| **Maintenance post-transplant** | | |
| AMADEUS*<br>NCT04173533 | III | Oral-AZA versus placebo upon engraftment for up to 12 months maintenance (MDS and AML patients) |
| VIALE-T*<br>NCT04161885 | III | Maintenance therapy with VEN + inj. AZA + BSC post-allo-HSCT in patients with AML<br>• VEN + inj. AZA + BSC during part 1 (dose confirmation)<br>• VEN + inj. AZA + BSC versus BSC during part 2 (randomization) |
| MORPHO†<br>NCT02997202 | III | Gilteritinib maintenance post-allo-HSCT in patients in CR1 with *FLT3*-ITD AML |
| NCT02400255† | II | Crenolanib maintenance in *FLT3*-ITD AML patients (i) in CR and (ii) not in CR at the time of allo-HSCT |

# Optimizing allogeneic stem cell transplantation