# Treatment of t-MDS/AML: the role of allogeneic transplantation

FIFTH
INTERNATIONAL SYMPOSIUM ON
SECONDARY LEUKEMIA
AND LEUKEMOGENESIS

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**Alessandro Rambaldi**

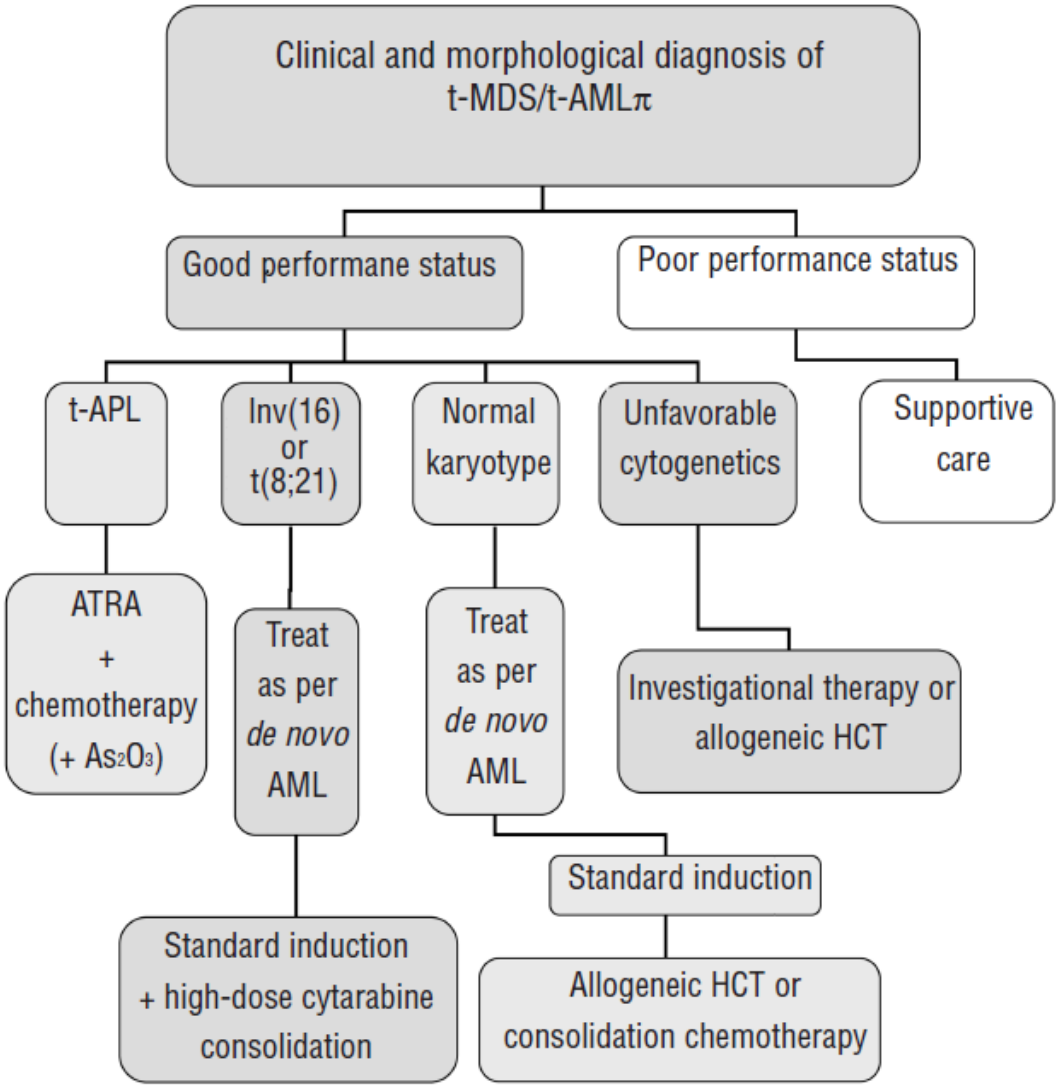
UNIVERSITÀ DEGLI STUDI DI MILANO

Azienda Ospedaliera
Papa Giovanni XXIII
Bergamo

# Program overview

1. Prognostic factors for t-MN undergoing AlloHSCT
   a. Previous diseases/treatments
   b. Cytogenetics
2. How to perform an AlloHSCT for t-MN
   a. Should we give induction chemotherapy before transplant?
   b. Is there a best conditioning regimen?
   c. Do we have new hopes from alternative donors and cellular therapy?

# Decision tree for the management of therapy-related myeloid neoplasms

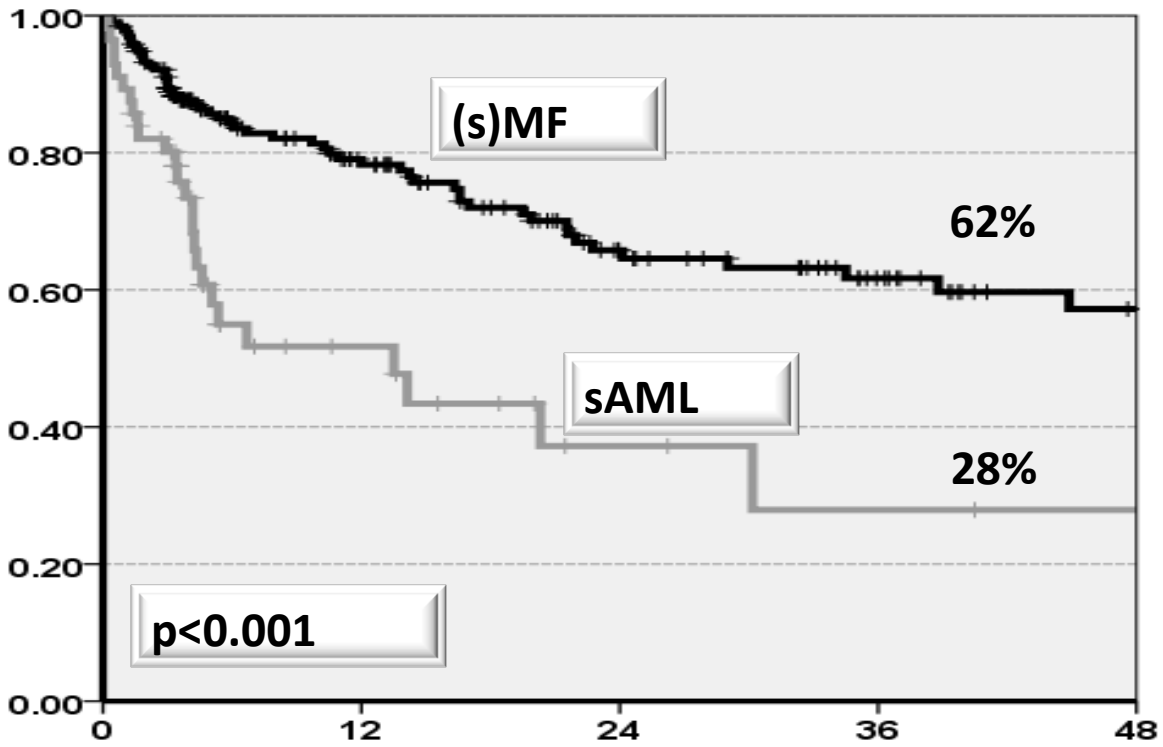



*Larson, RA Haematologica. 2009;94(4):454-459*

# Prognostic factors

- Previous disease/treatments
- Cytogenetics
- CR at transplant

# Overall Survival of (s)MF and s(AML) after AlloHSCT: EBMT data

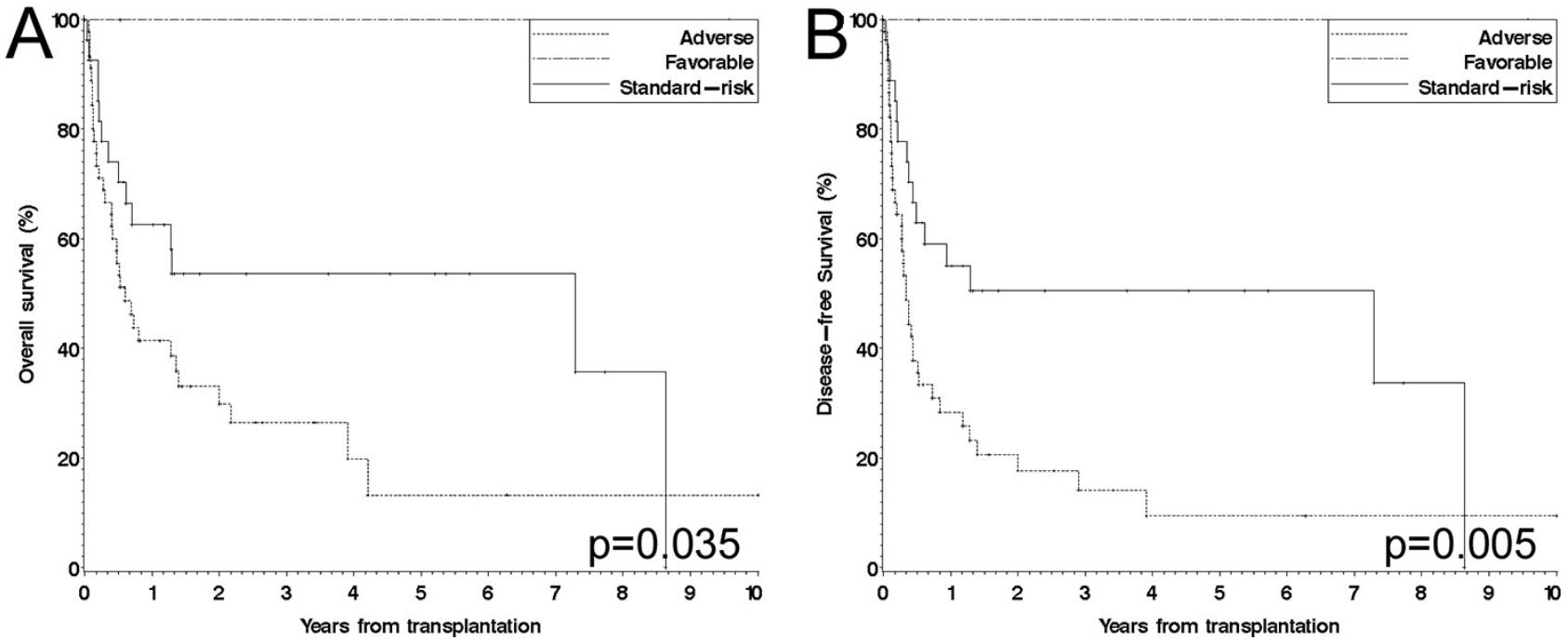



Federico Lussana et al. Haematologica 2014; 99:916-921



haematologica
Journal of the European Hematology Association
Published by the Ferrata Storti Foundation

# *Overall Survival and Disease Free Survival according to Cytogenetics*




*Armand P et al.: Biology of Blood and Marrow Transplantation* 2007 13, 655-664DOI: (10.1016/j.bbmt.2007.01.079)

# Characteristics of patients who underwent allogeneic HCT for a therapy-related MDS and AML reported to the CIBMTR between 1990 and 2004

| | | |
|---|---|---|
| **Disease†** | 868 | |
| t-AML | | 545 (63) |
| t-MDS | | 323 (37) |
| **Prior disease†** | 868 | |
| Hodgkin lymphoma | | 199 (23) |
| Non-Hodgkin lymphoma | | 183 (21) |
| Breast cancer | | 139 (16) |
| Acute lymphoblastic leukemia | | 101 (12) |
| Chronic lymphocytic leukemia | | 9 (1) |
| Plasma cell disorder | | 12 (1) |
| Sarcoma/Ewing | | 72 (8) |
| Wilms tumor/neuroblastoma | | 10 (1) |
| Testis/ovarian/germ cell | | 50 (6) |
| CNS | | 15 (2) |
| Autoimmune‡ | | 38 (4) |
| Other solid tumors§ | | 33 (4) |
| Rheumatoid arthritis | | 4 (1) |
| Others‖ | | 3 (<1) |

*Litzow, MR Blood. 2010;115:1850-1857)*

# Allogeneic HCT for therapy-related MDS and AML reported to the CIBMTR between 1990 and 2004

| Prognostic factors | Overall survival | Non Relapse Mortality | Relapse |
|---|---|---|---|
| **Age at HSCT older than 35** | .001 | .003 | .003 |
| **Poor/unfavourable Cytogenetics** | < .001 | NS | <.001 |
| **Disease status prior to HSCT** | | | |
| AML not in CR | <.001 | .09 | <.001 |
| t-MDS early | .035 | .001 | NS |
| T-MDS advanced | .001 | .005 | .002 |
| **Type of donor** | | | |
| URD mismatched | .001 | .001 | NS |
| Other relative | <.001 | <.001 | NS |

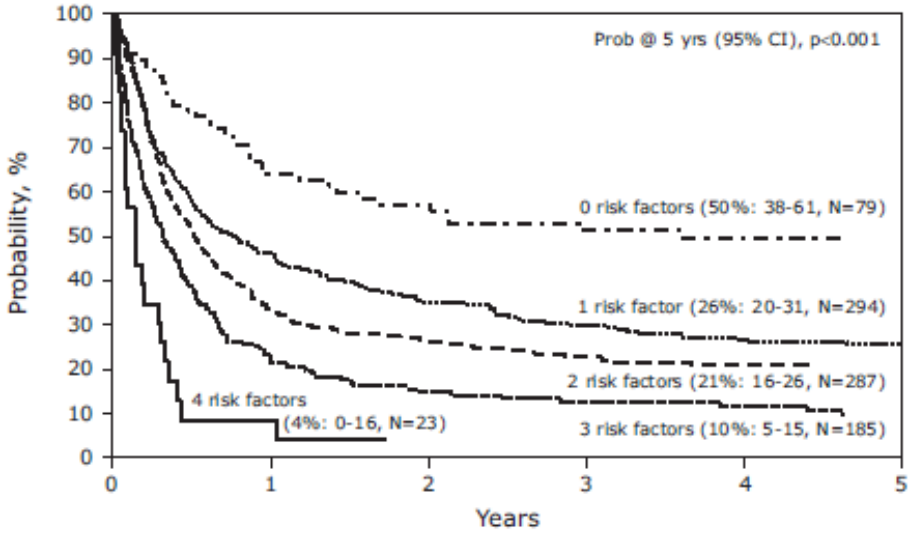
***Adapted from Litzow, MR Blood. 2010;115:1850-1857)***

# Characteristics of patients who underwent allogeneic HCT for a therapy-related MDS and AML reported to the CIBMTR between 1990 and 2004

## Risk Factors

- Age older than 35
- Poor risk cytogenetics
- Non sibling donor
- No CR at conditioning

## Overall Survival




*Litzow, MR Blood. 2010;115:1850-1857)*

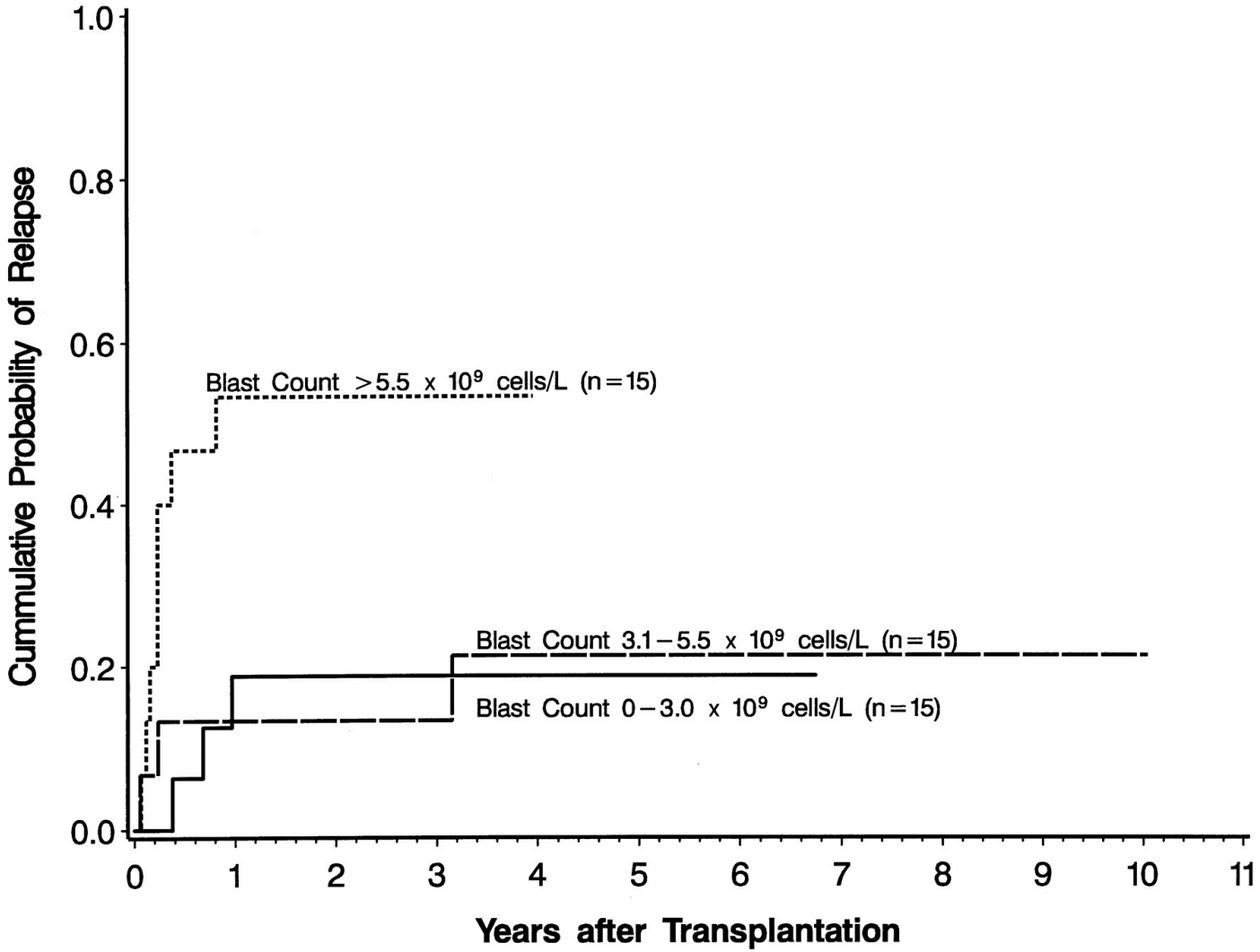
# How to perform an AlloHSCT for t-MN

a. Should we give induction chemotherapy before transplant?

b. Is there a best conditioning regimen?

c. Do we have new hopes from alternative donors and cellular therapy?

# Relapse according to PB blast count before the start of the transplant preparative regimen

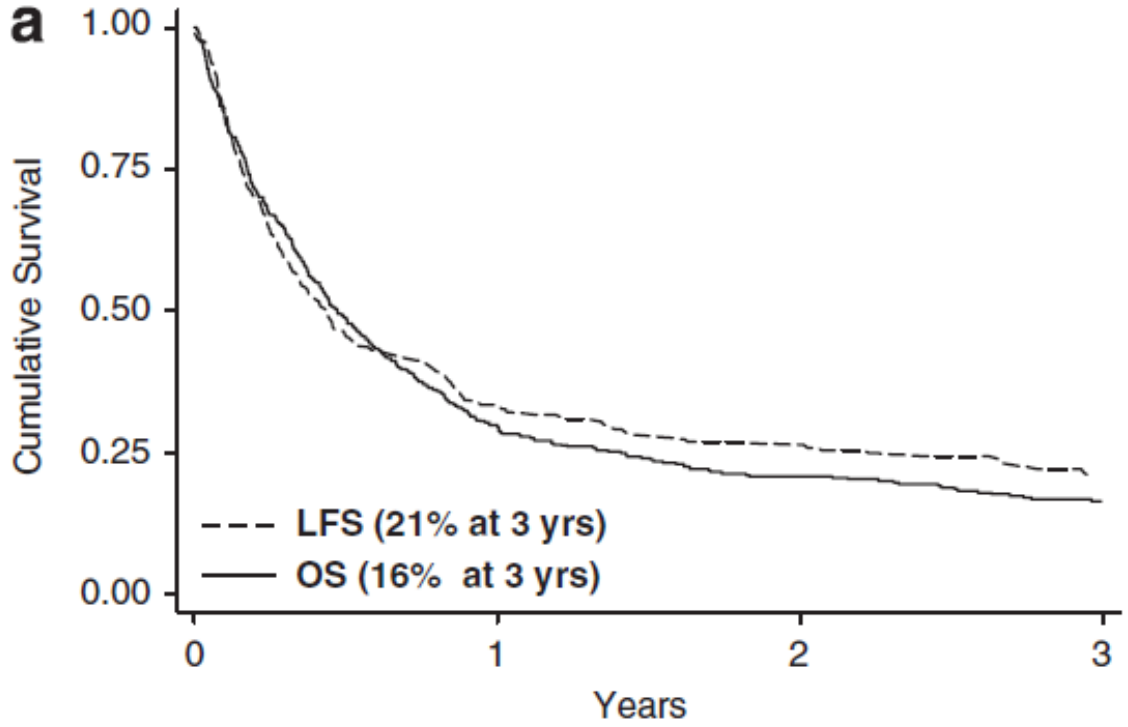



Jeanne E. Anderson et al. Blood 1997;89:2578-2585



blood

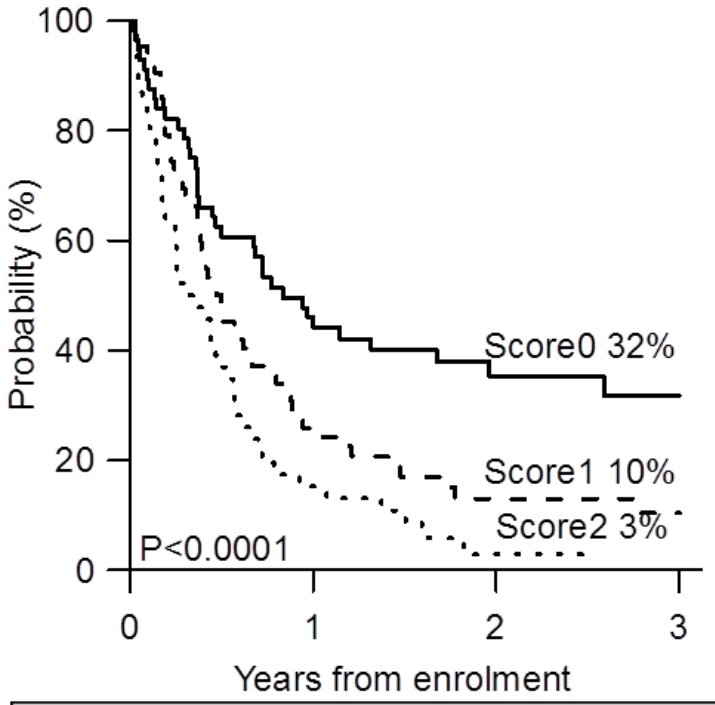
# The CIBMTR score predicts survival of AML patients undergoing allogeneic transplantation with active disease after a myeloablative or reduced intensity conditioning: a retrospective analysis of the Gruppo Italiano Trapianto Di Midollo Osseo




*Todisco E et al, Leukemia (2013) 27, 2086–2091*

# AlloHSCT in Refractory AML: a GITMO score

| Score Variables | Score | Data Available | N (%) |
|---|---|---|---|
| ***Chemotherapy cycles*** | | 220 | |
| ≤2 | 0 | | 122 (55) |
| >2 | 1 | | 98 (45) |
| ***Blast infiltration*** | | 197 | |
| BM<25% or no PB | 0 | | 78 (40) |
| BM≥25% or any PB | 1 | | 119 (60) |
| ***Age*** | | 227 | |
| ≤60 | 0 | | 187 (82) |
| >60 | 1 | | 40 (18) |
| ***Cytogenetics/ molecular biology*** | | 191 | |
| Favorable/Intermediate I | 0 | | 81 (42) |
| Intermediate II /Adverse | 1 | | 110 (58) |




| Score | Risk Factor | N=165 | HR (95% CI) | P | OS at 3 years |
|---|---|---|---|---|---|
| 0 | 0-1 | 56 (34) | | | 32% |
| 1 | 2 | 63 (38) | 1.73 (1.13-2.63) | 0.0112 | 10% |
| 2 | 3-4 | 46 (28) | 2.62 (1.68-4.10) | <0.0001 | 3% 2 yrs |

***Todisco, E et al.: under minor revision***

# How to perform an AlloHSCT for t-MN

a. Should we give induction chemotherapy before transplant?

**b. Is there a best conditioning regimen?**

c. Do we have new hopes from alternative donors and cellular therapy?

# Study treatments

***BuCy2***

| Day | -9 | -8 | -7 | -6 | -5 | -4 | -3 | -2 | -1 | 0 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Busulfan (0.8 mg/kg x 4/day)** | X | X | X | X | | | | | | |
| **Cyclophosphamide (60 mg/Kg/day)** | | | | | | X | X | | | |
| **If URD: ATG (anti-thymocyte globulin) (0.5-2-2.5 mg/kg/day)** | | | | | | | X | X | X | |
| **Allogeneic stem-cell transplantation** | | | | | | | | | | X |

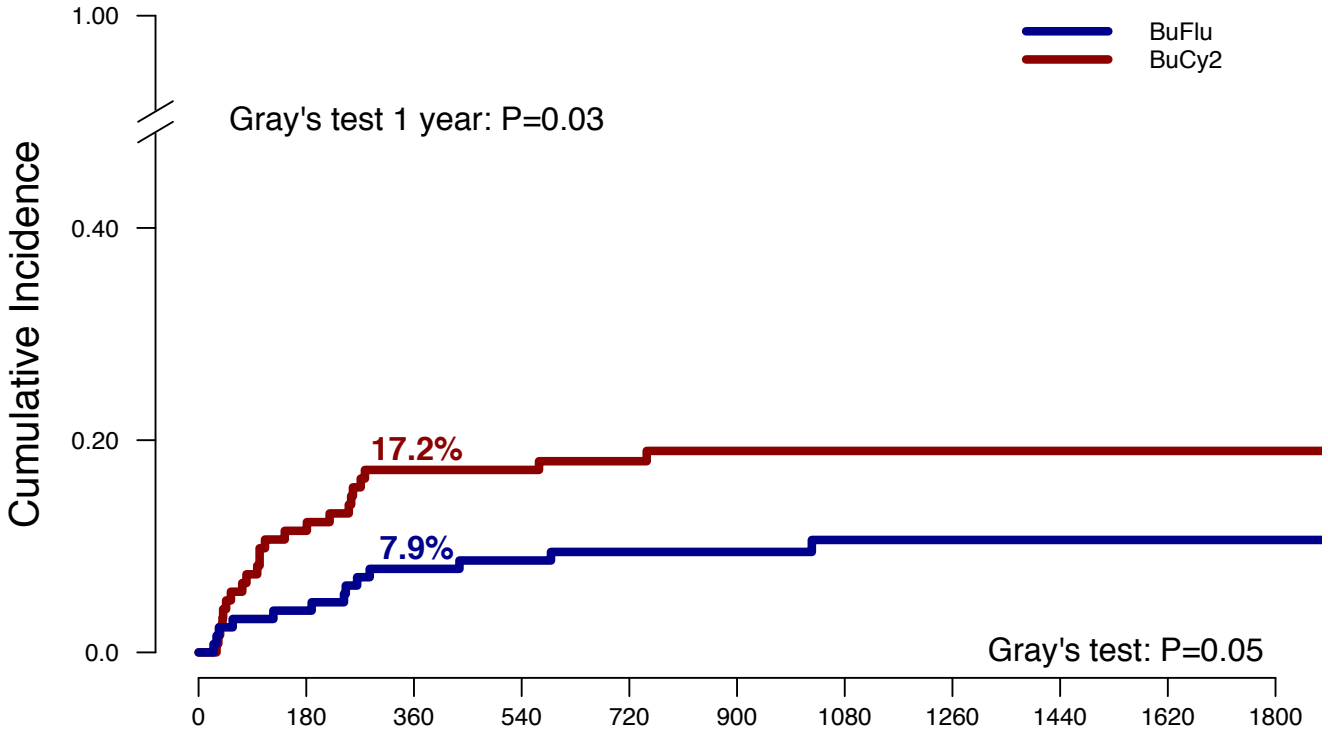
***BuFlu***

| Day | -9 | -8 | -7 | -6 | -5 | -4 | -3 | -2 | -1 | 0 |
|---|---|---|---|---|---|---|---|---|---|---|
| **Busulfan (0.8 mg/kg x 4/day)** | | | | X | X | X | X | | | |
| **Fludarabine i.v. (40 mg/m²/day)** | | | | X | X | X | X | | | |
| **If URD: ATG (anti-thymocyte globulin) (0.5-2-2.5 mg/kg/day)** | | | | | | | X | X | X | |
| **Allogeneic stem-cell transplantation** | | | | | | | | | | X |

*A. Rambaldi et al.: The Lancet Oncology, 2015*

# Non Relapse Mortality

(intent to treat population)

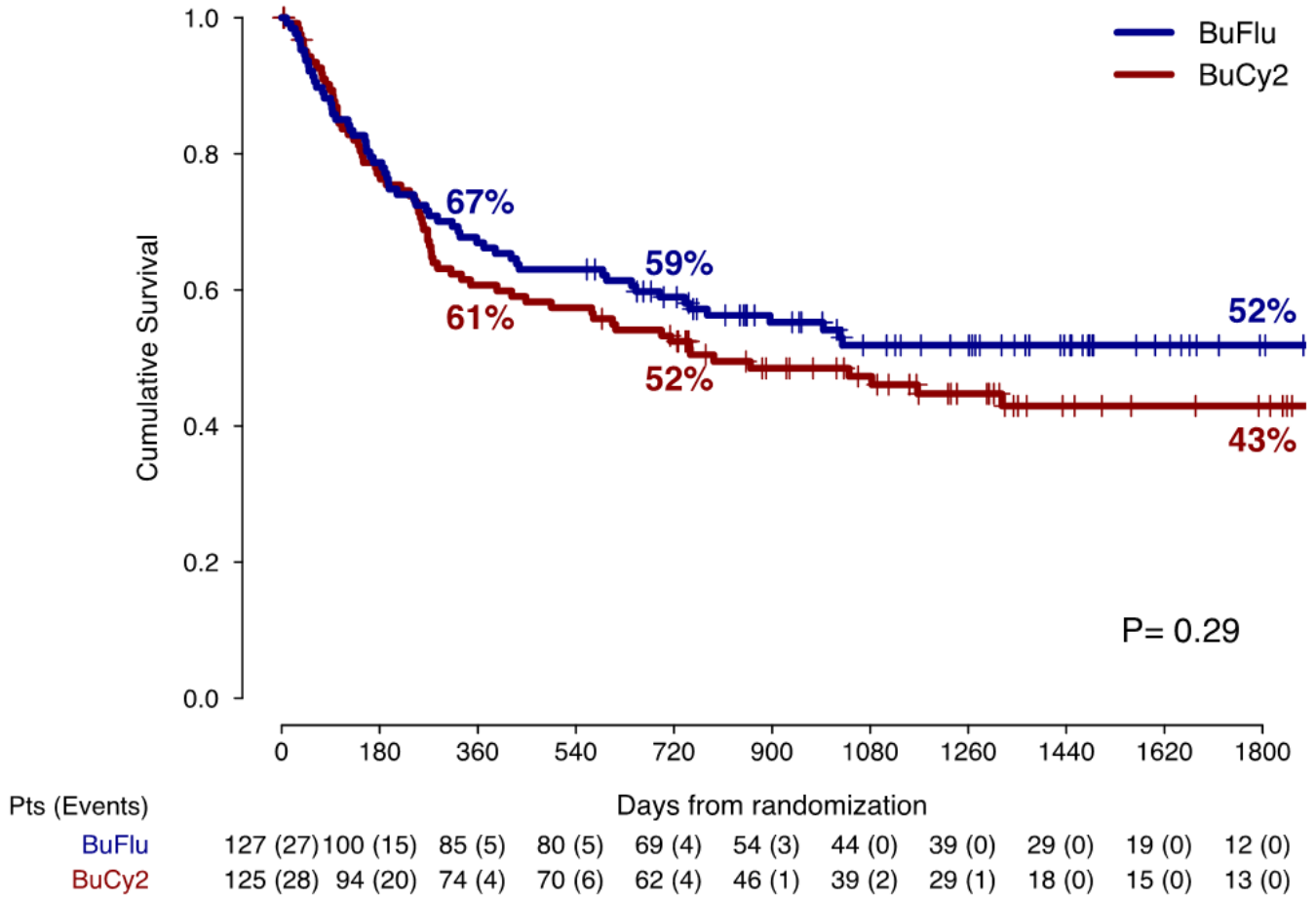



| Pts (Events) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| BuFlu | 127 (0) | 100 (5) | 85 (5) | 80 (1) | 69 (1) | 54 (0) | 44 (1) | 39 (0) | 29 (0) | 19 (0) | 12 (0) |
| BuCy2 | 125 (0) | 94 (14) | 74 (7) | 70 (0) | 62 (1) | 46 (1) | 39 (0) | 29 (0) | 18 (0) | 15 (0) | 13 (0) |

*A. Rambaldi et al.: The Lancet Oncology, 2015*

# Leukemia Free Survival

(intent to treat population)




*A. Rambaldi et al.: The Lancet Oncology, 2015*

# How to perform an AlloHSCT for t-MN

a. Should we give induction chemotherapy before transplant?

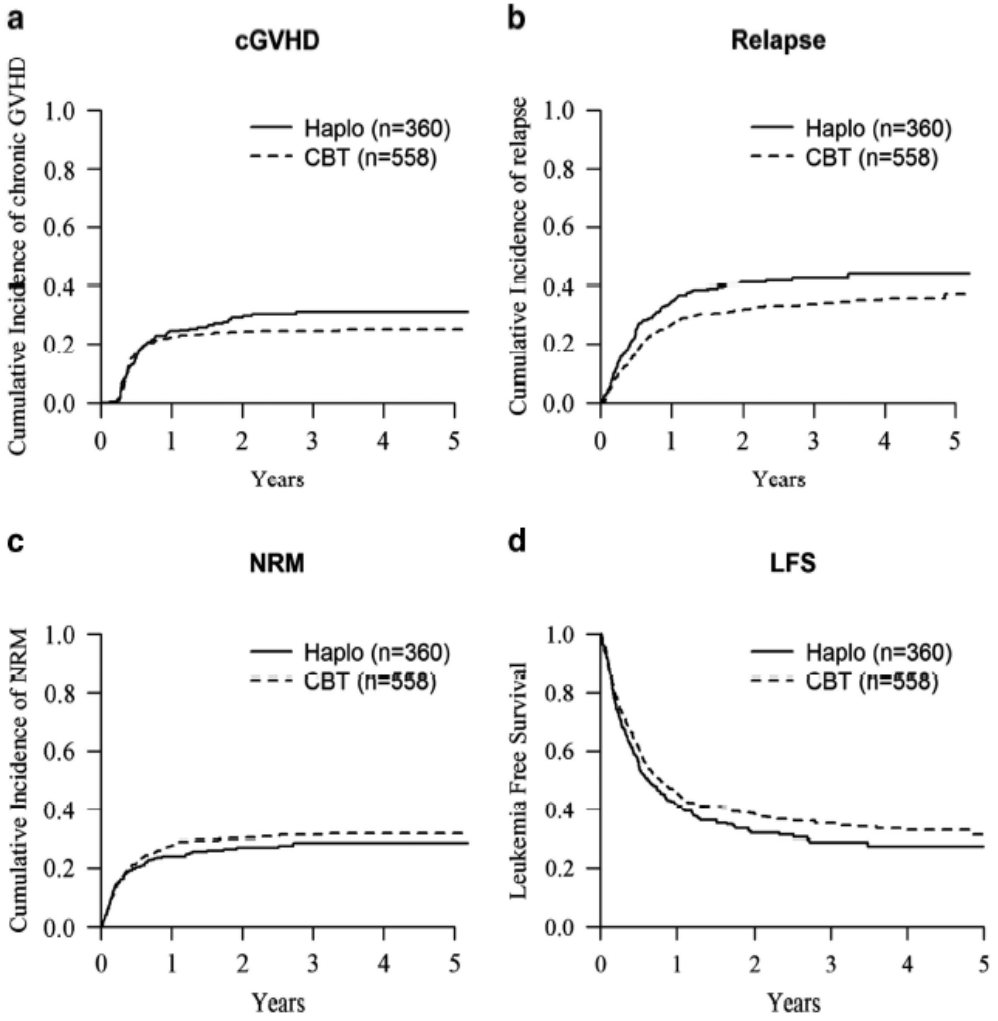
b. Is there a best conditioning regimen?

c. **Do we have new hopes from alternative donors and cellular therapy?**

Leukemia

ORIGINAL ARTICLE

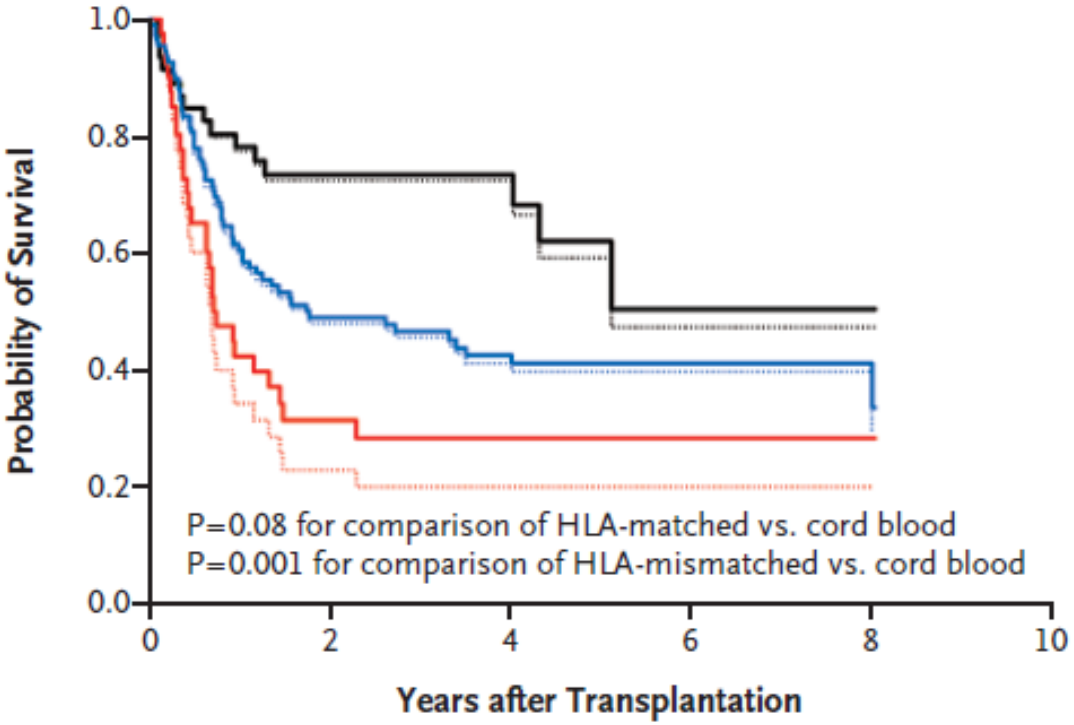
# Comparison of outcomes after unrelated cord blood and unmanipulated haploidentical stem cell transplantation in adults with acute leukemia




*Ruggeri A et al.: Leukemia (2015) 29, 1891–1900*

The NEW ENGLAND JOURNAL of MEDICINE

**A Survival among Patients with Minimal Residual Disease**



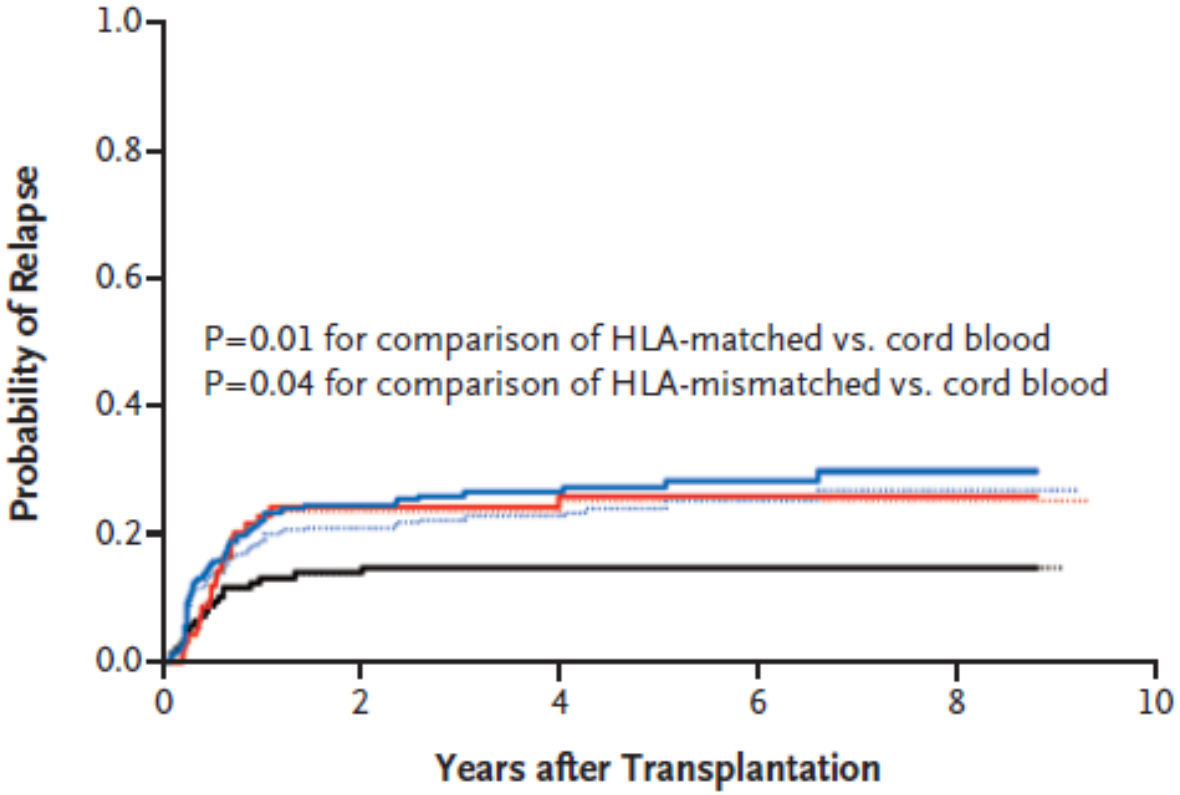

**No. at Risk**

| | | | | | |
|---|---|---|---|---|---|
| Cord blood | 45 | 22 | 9 | 2 | 1 |
| HLA-matched | 104 | 35 | 25 | 12 | 3 |
| HLA-mismatched | 35 | 7 | 6 | 3 | 1 |

*F. Milano et al. NEJM, 2016; 375: 944-953*

The NEW ENGLAND JOURNAL of MEDICINE

**B** Relapse




**No. at Risk**

| | | | | | |
|---|---|---|---|---|---|
| Cord blood | 140 | 74 | 39 | 13 | 4 |
| HLA-matched | 344 | 161 | 87 | 35 | 11 |
| HLA-mismatched | 98 | 40 | 29 | 15 | 6 |

*F. Milano et al. NEJM, 2016; 375: 944-953*

# Cellular therapy for untreatable AML

# Immunotherapy of older AML with NK Cells

- AML patients, in first CR (median age 64)
- Flu/Cy immunosuppressive chemotherapy
- CD56+CD3- NK cells from haplo KIR-mismatched donors and IL-2
- feasible in elderly patients with AML as post-CR consolidation
- donor NK alloreactivity has a predictive role on outcome

Antonio Curti et al. Blood 2014;124:624

Curti, A et al Clin Cancer 22 Issue 8, pp. 1914-1921

blood

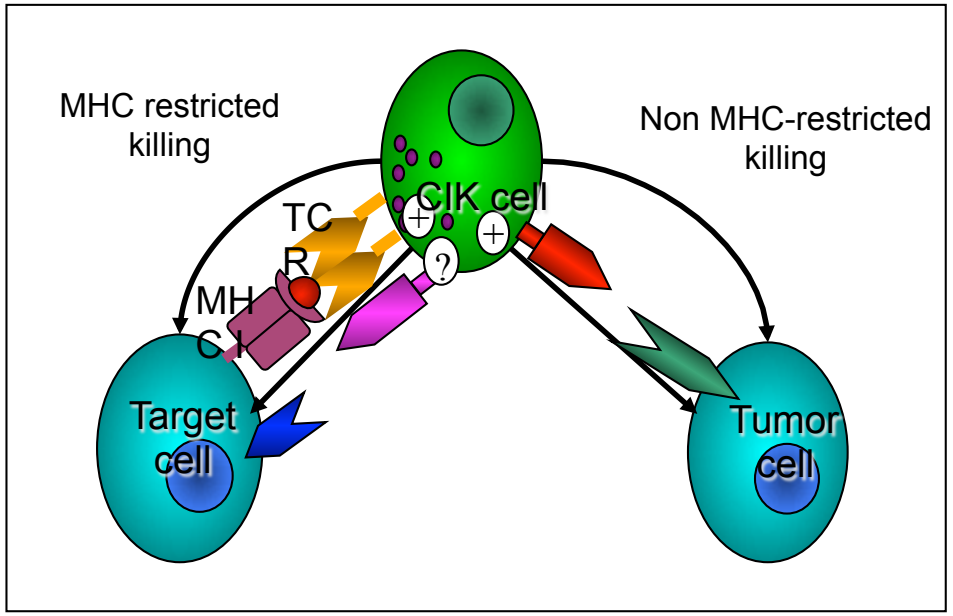
AACR
American Association for Cancer Research

# Cellular therapy with Cytokine Induced Killer (CIK) cells

- *CIK cells are NK-T cells (CD56+CD3+) expanded from peripheral blood mononuclear cells (first described in NK cell clones by T. Hercend)*

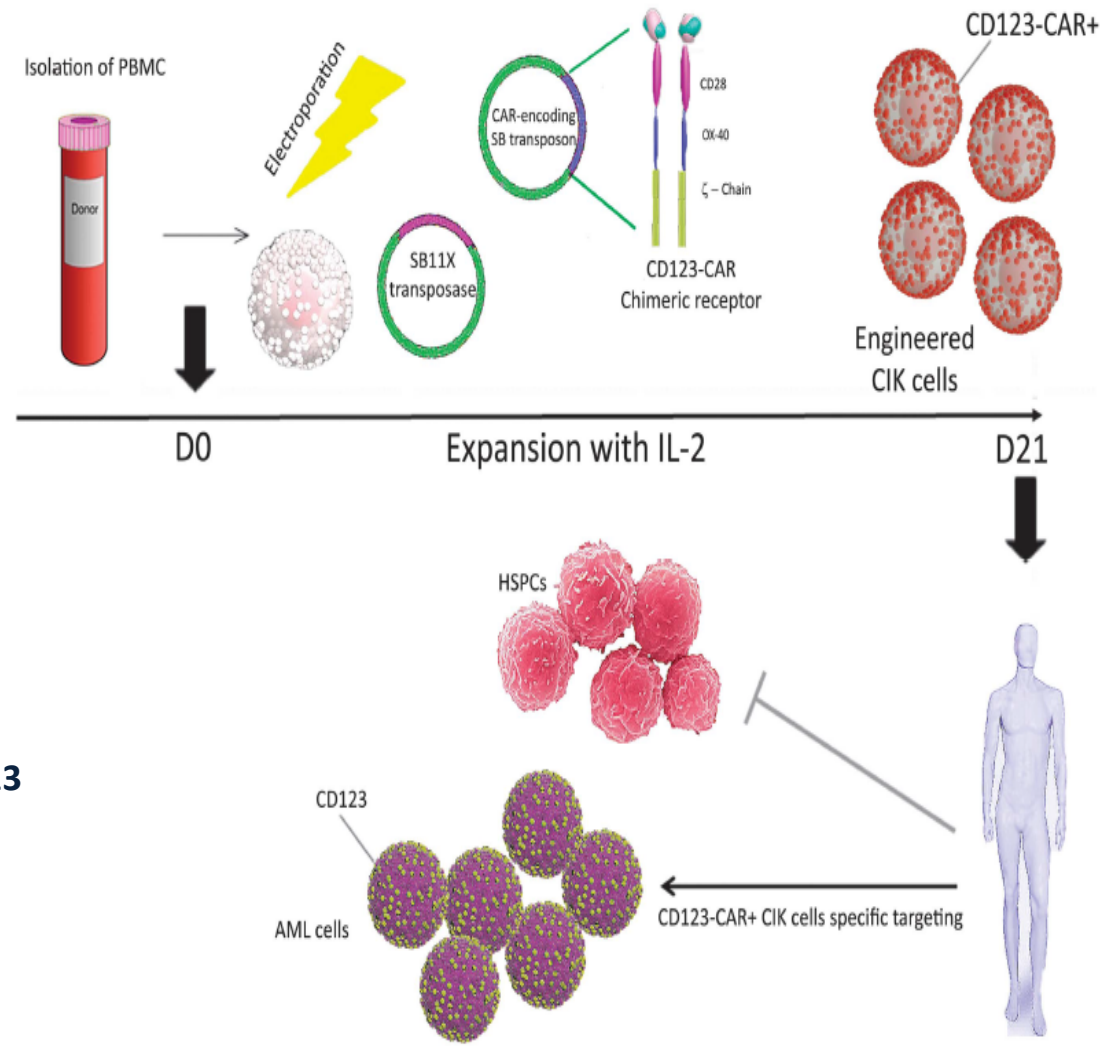
- *CIK cells show non-specific anti-tumor activity and home to tumors without significant GVHD in several animal models*

- *CIK cells can be reproducibly expanded in vitro under strict GMP conditions*




*Introna et al, BMT, 2006*
*Marin et al, Exp. Hematol,2006*
*Franceschetti et al, Exp Hematol, 2009*
*Introna et al, BBMT, 2010*
*Pievani et al, Blood, 2011*
*Pievani et al, Blood, 2011*

# Human CIK cells transduced with CD123 CAR and CD33 CARs have shown activity in vitro and in vivo against AML




- Marin et al., Haematologica 2010
- Tettamanti et al., Br. J. Hemat. 2013
- Pizzitola et al., Leukemia 2014
- Rambaldi A. et al., Leukemia 2015

# CONCLUSIONS

- T-MN are an heterogeneous group of malignancies with different outcome depending on patient and disease characteristics but also on treatment intensity and quality

- AlloHSCT may represent a therapeutic option for some patients and alternative donors (CB and Haplo) should be always considered

- Post-transplant approaches with cells or drugs should be considered for patients at very high risk of disease recurrence