# The conundrum of TP53 mutations in HSCT

Alessandro Rambaldi

Fondazione per la Ricerca Clinica Ospedale Papa Giovanni XXIII Bergamo

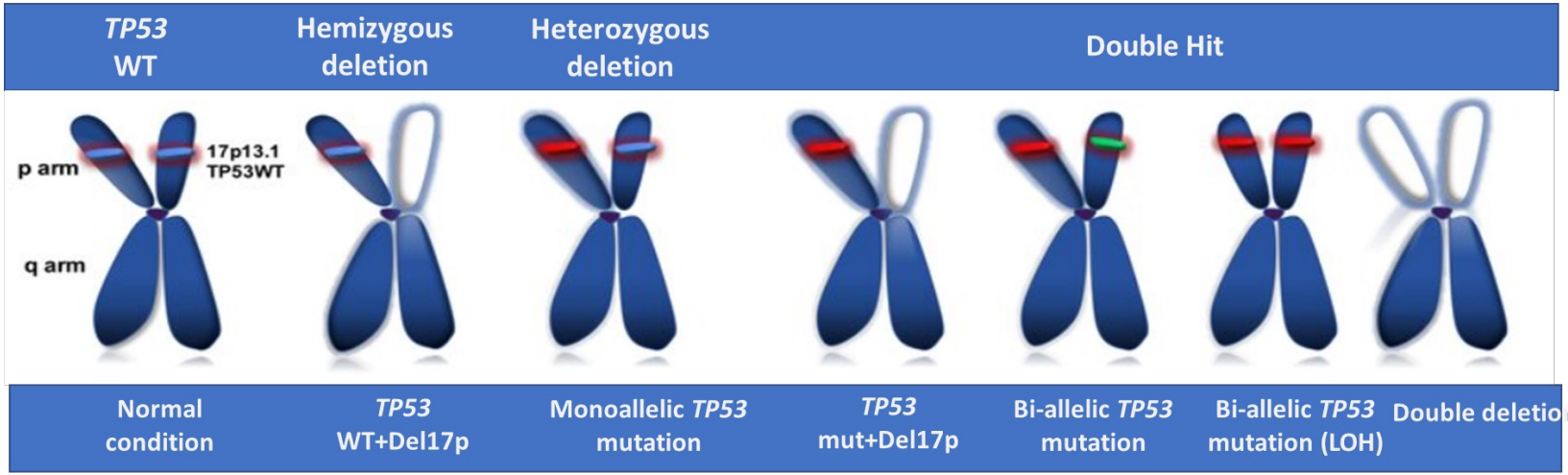
# Disclosure statement

| Company name | Research support | Employee | Consultant | Stockholder | Speakers bureau | Advisory board | Other |
|---|---|---|---|---|---|---|---|
| Amgen | | | ✓ | | | ✓ | ✓ |
| Pfizer | | | ✓ | | | | |
| Novartis | | | ✓ | | | ✓ | |
| Kite Gilead | | | ✓ | | | ✓ | ✓ |
| Jazz | | | ✓ | | | ✓ | ✓ |
| Omeros | | | ✓ | | | ✓ | ✓ |
| Incyte | | | ✓ | | | | |
| Sanofi | | | ✓ | | | | |
| Pierre Fabre | | | ✓ | | | ✓ | |
| Italfarmaco | | | ✓ | | | ✓ | ✓ |

# TP53 mutations in myeloid malignancies

Not all mutations are equal…at least when planning a transplant

# TP53 deletions/mutations: definition matters



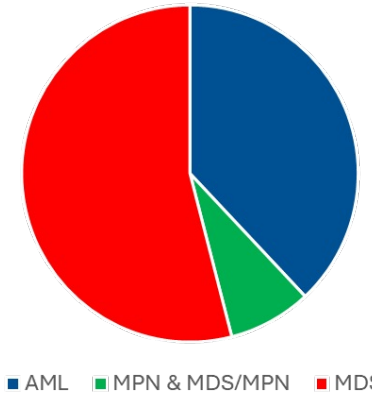

Definition of *TP53* double-hit (or biallelic inactivation) refers to the loss of both functional copies of the *TP53* tumor suppressor gene. It is defined by two hits to the gene, such as a deletion (del(17p)) combined with a mutation, two separate mutations, or a mutation with high variant allele frequency (VAF) that resulted from LOH.

# Survival after allo-HCT in patients with MDS/AML with TP53 loss of function and concurrent high-risk cytogenetics

| Author | Study type | Disease | Pts with *TP53* LOF receiving allo-HCT | Subset with high-risk cytogenetics | DFS from time of HCT | OS from time of HCT |
|---|---|---|---|---|---|---|
| **MDS*** | | | | | | |
| Lindsley et al[25] | Registry | MDS | *TP53* mut: 289 pts | Not listed | Not listed | 3-y OS: ~15% (complex) |
| Yoshizato et al[26] | Registry | MDS including subset with sAML | *TP53* mut: 98 pts | Complex: 86 pts | Not listed | Median OS: 4.3 mo<br>3-y OS: ~10% (complex) |
| **AML** | | | | | | |
| Middeke et al[23] | Registry | AML | 17p abnl: 201 pts | Monosomal: 77 pts<br>Complex: 180 pts | 3-y EFS: 9% (monosomal)<br>3-y EFS: 9% (complex) | 3-y OS: 11% (monosomal)<br>3-y OS: 11% (complex) |
| Middeke et al[22] | 3 multicenter clinical trials | AML | *TP53* mut: 40 pts | Adverse†: 40 pts | 3-y PFS: 7.5% (adverse) | 3-y OS: 10% (adverse) |
| Luskin et al[27] | Single center | AML | *TP53* mut: 9 pts | Adverse‡: 6 pts | All relapsed (adverse; range, 1.6-18.6 mo after HCT) | Not listed |
| Poire et al[24] | Registry | AML | 17p abnl: 125 pts | Monosomal: 86 pts<br>–5/5q-: 58 pts | 2-y: 17% (monosomal)<br>2-y: 11% (–5/5q-) | 2-y OS: 19% (monosomal)<br>2-y OS: 16% (–5/5q-) |
| Najima et al[28] | Single center | AML (nonremission) | *TP53* mut: 23 pts | Monosomal: 11 pts | Not listed | All died within 12 mo post allo-HCT (monosomal) |
| Grob et al[18] | 4 multicenter clinical trials | MDS-EB<br>AML | *TP53* mut: 59 pts | Complex: 48 pts | Not listed | 3-y OS: ~10% (complex) |
| Loke et al[21] | Registry | AML | *TP53* mut: 179 pts | 17p loss and/or complex: 126 pts | 2-y PFS: 15.2% (17p loss and/or complex) | 2-y OS: 24.6% (17p loss and/or complex) |

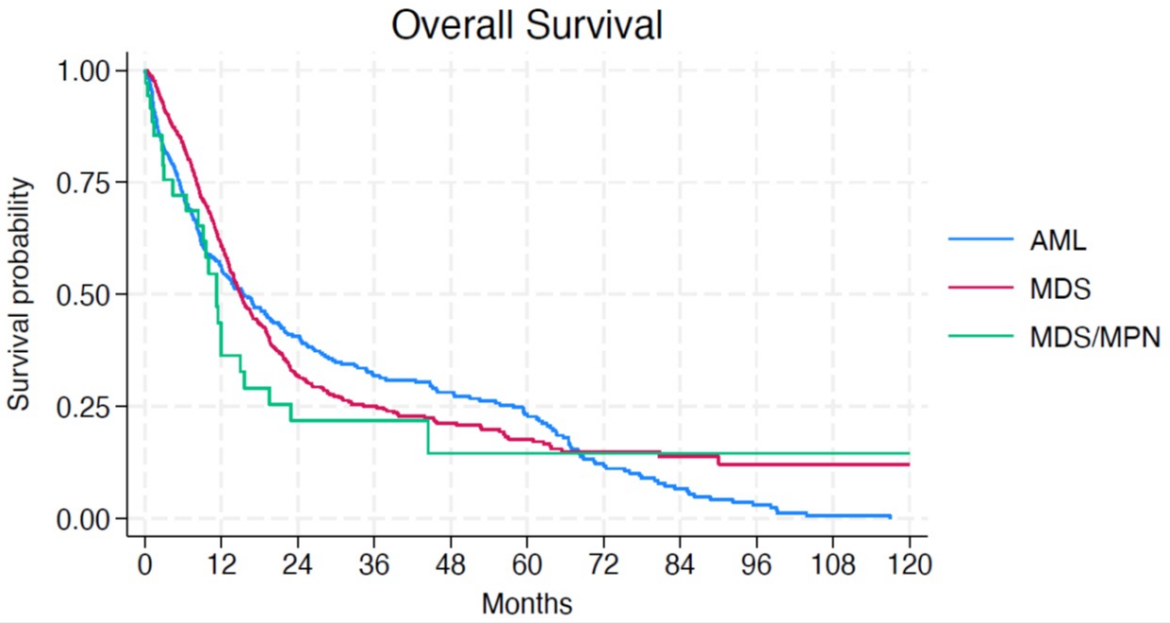
*Nawas MT and Kosuri S Blood Advances 2024*

# MN with biallaleic TP53 is a unique clinical entity




MN with TP53 mutations (bi-allelic inactivation)

N= 2352




*Lanino L et al, JCO in press and by courtesy of Prof Della Porta MG.*

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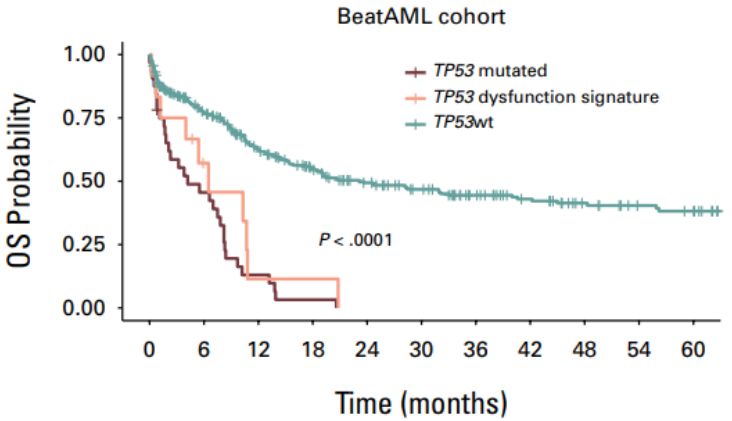
# TP53: not only deletions and mutations

- A subset of MDS (5%) characterized by TP53 wild-type and hyperexpression of abnormal p53 protein in bone marrow progenitors that exhibit dismal outcome.
- These patients presented upstream p53 signaling aberrations in Pi3K cascade; RAS, WNT, and NF-KB pathways; and MDM2 gene amplification, together with a downstream dysregulation of p53 targets




No. at risk:

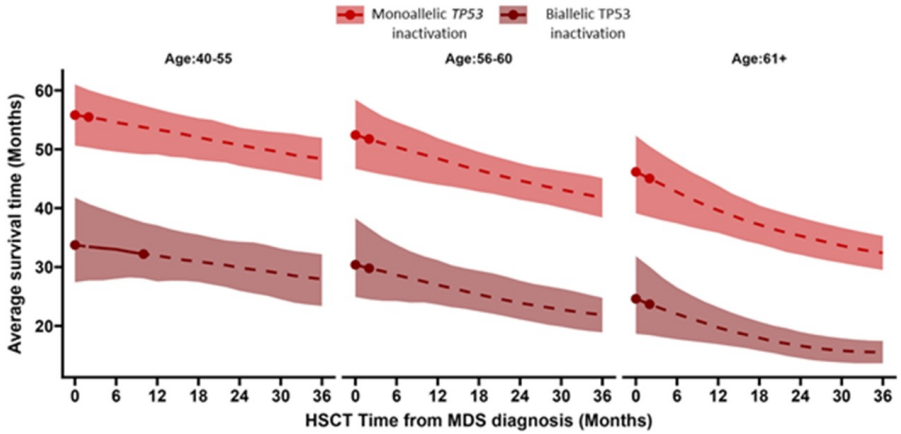
| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| *TP53* mutated | 32 | 14 | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *TP53* dysf signature | 12 | 5 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| *TP53wt* | 318 | 212 | 155 | 122 | 99 | 85 | 67 | 55 | 44 | 36 | 33 |

*Zampini et al. JCO 2025; Lanino L et al, JCO in press and by courtesy of Prof Della Porta MG.*

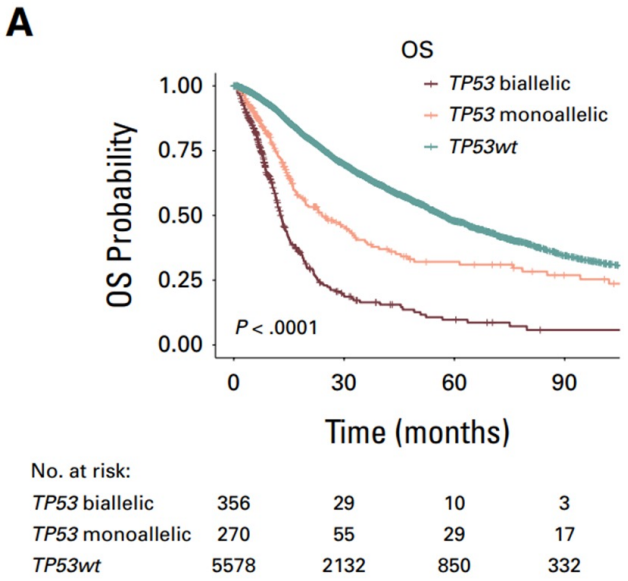
# AlloHSCT for TP53-mutated MDS/AML: utility or futility?

# Should we transplant a patient with a MN and TP53 deletions, mutations or inactivation?

## Optimal Transplantation policies in patients with MDS carrying TP53 mutations



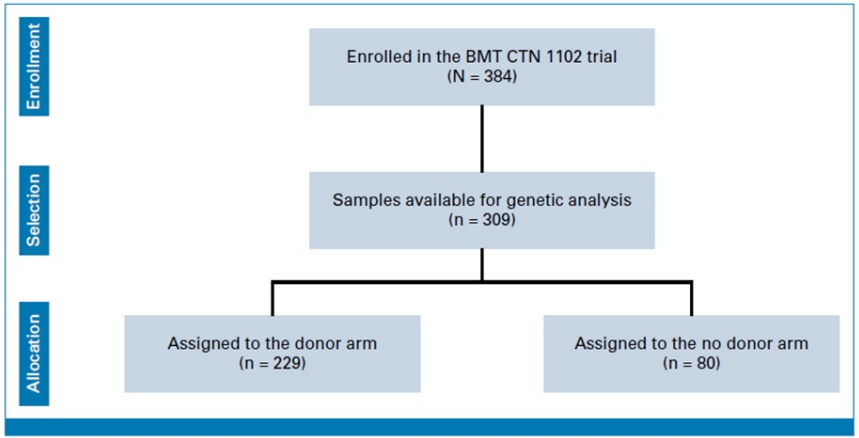

## Overall Survival



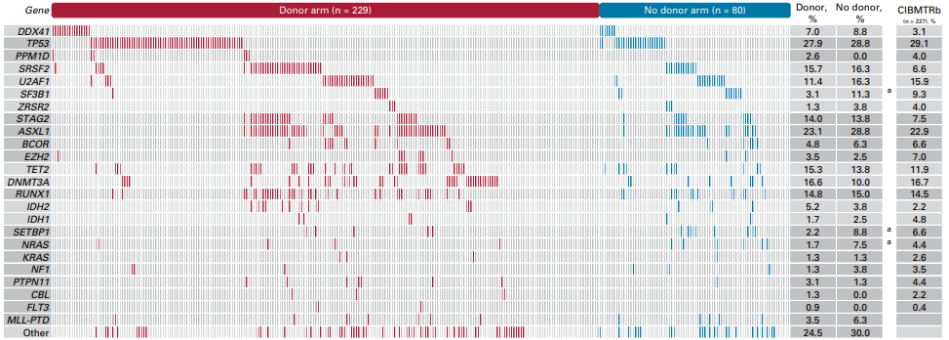

*Tentori et al.: JCO 2024; Zampini et al. J Clin Oncol 2025; Lanino et al. J Clin Oncol 2026 in press*

# AlloHSCT in MDS Across High-Risk Genetic Subgroups: Genetic Analysis of the BMT CTN 1102 Study

Patients included in the BMT CTN 1102 study

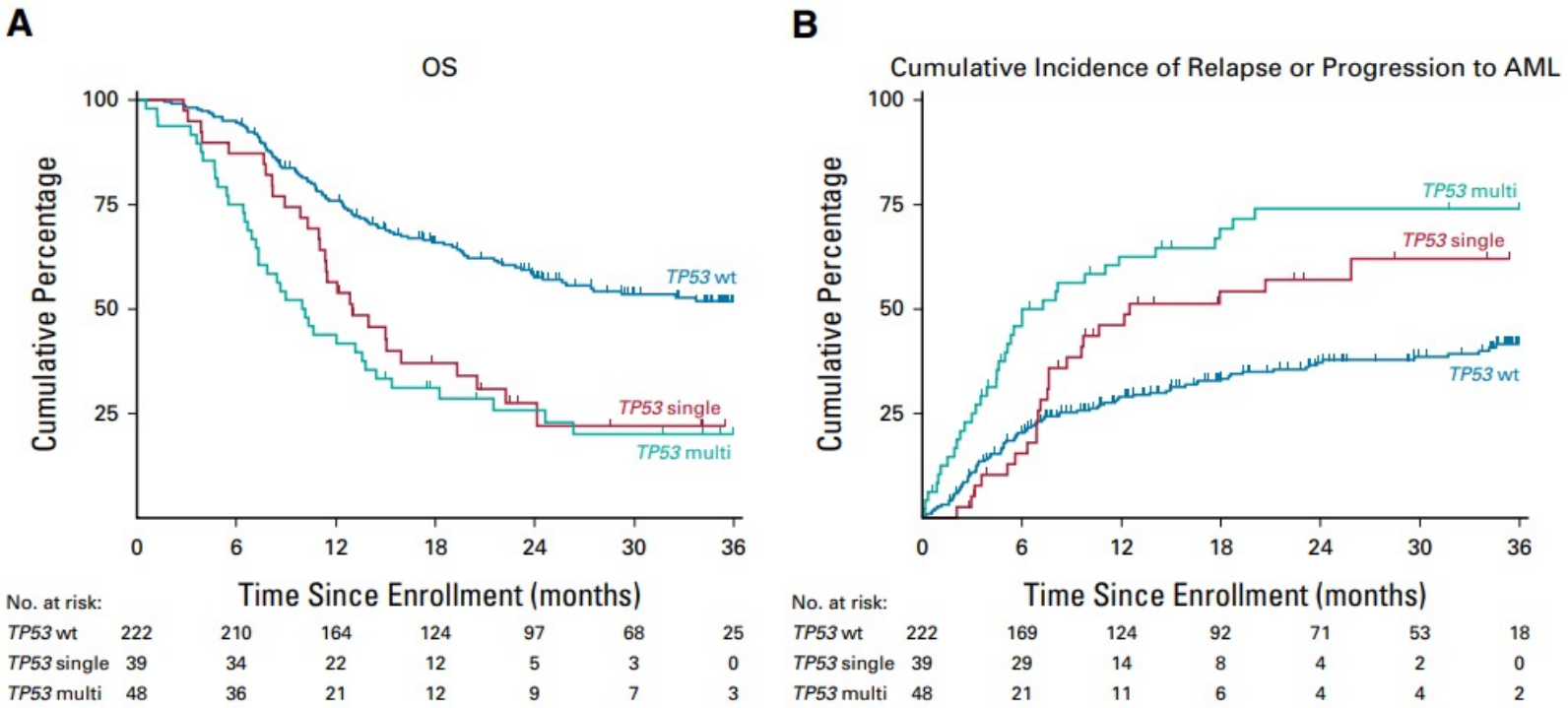



Spectrum of myeloid driver mutations in the BMT CTN 1102 study




*Versluis J. et al.: J Clin Oncol 41:4497-4510, 2023 DOI https://doi.org/10.1200/JCO.23.00866*

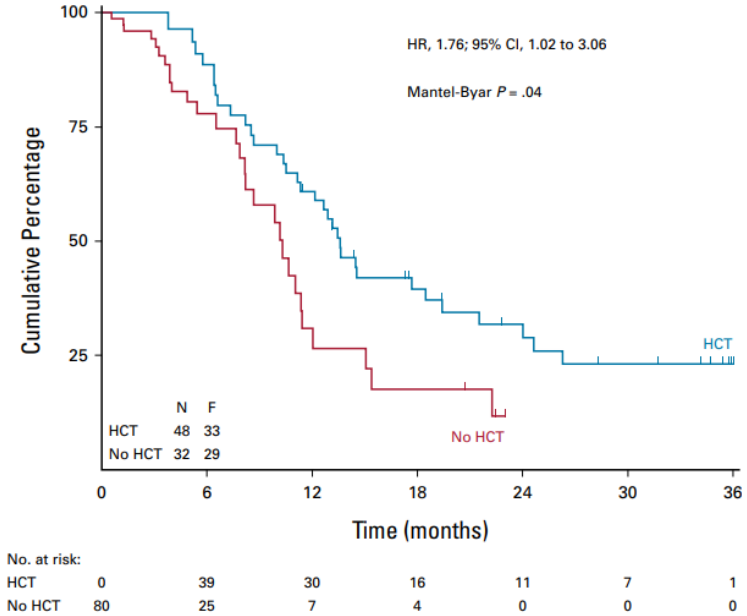
# Clinical outcomes by TP53 allelic state in the BMT CTN 1102 Study



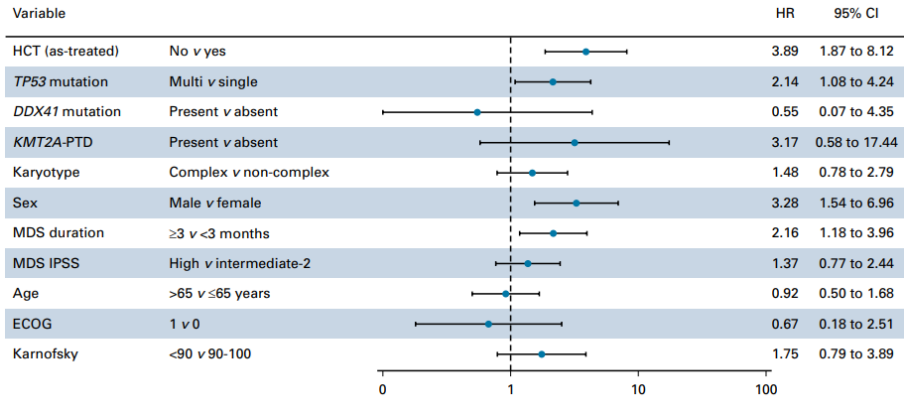

*Versluis J. et al.: J Clin Oncol 41:4497-4510, 2023 DOI https://doi.org/10.1200/JCO.23.00866*

# AlloHSCT improves Overall Survival of patients with mutated TP53

OS in Patients WithTP53 mutations With HCT as Time-Dependent Covariate




Forest plot of subgroup analyses in patients with mutated TP53



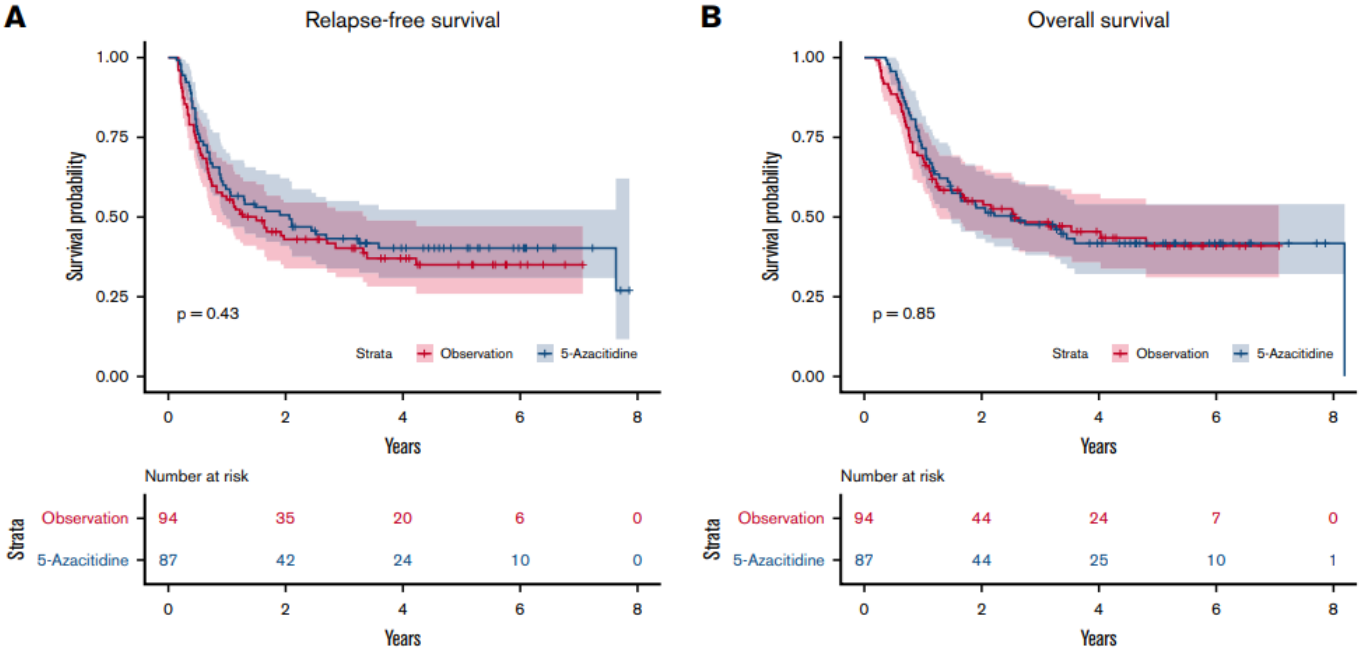
| Variable | | HR | 95% CI |
|---|---|---|---|
| HCT (as-treated) | No *v* yes | 3.89 | 1.87 to 8.12 |
| *TP53* mutation | Multi *v* single | 2.14 | 1.08 to 4.24 |
| *DDX41* mutation | Present *v* absent | 0.55 | 0.07 to 4.35 |
| *KMT2A*-PTD | Present *v* absent | 3.17 | 0.58 to 17.44 |
| Karyotype | Complex *v* non-complex | 1.48 | 0.78 to 2.79 |
| Sex | Male *v* female | 3.28 | 1.54 to 6.96 |
| MDS duration | ≥3 *v* <3 months | 2.16 | 1.18 to 3.96 |
| MDS IPSS | High *v* intermediate-2 | 1.37 | 0.77 to 2.44 |
| Age | >65 *v* ≤65 years | 0.92 | 0.50 to 1.68 |
| ECOG | 1 *v* 0 | 0.67 | 0.18 to 2.51 |
| Karnofsky | <90 *v* 90-100 | 1.75 | 0.79 to 3.89 |



*Versluis J. et al.: J Clin Oncol 41:4497-4510, 2023 DOI https://doi.org/10.1200/JCO.23.00866*

# How to improve these results?
## Posttransplant maintenance strategies

# A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS




*Oran B et al.: Blood advances 2020 DOI 10.1182/bloodadvances.2020002544.*

# Maintenance therapy with oral decitabine plus cedazuridine after alloHSCT for MDS

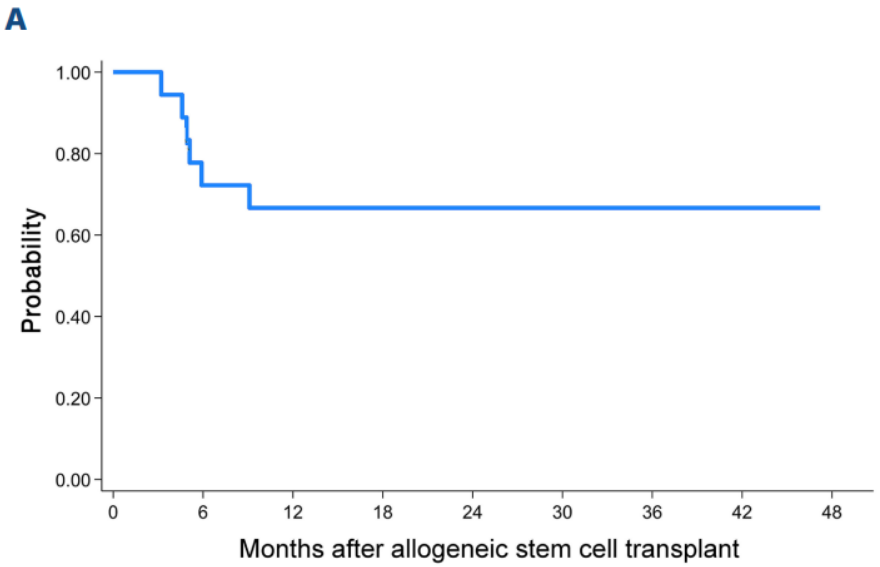
| Baseline characteristics | Values |
|---|---|
| Age in years, median (range) | 62.5 (28-76) |
| Sex, N (%)<br>Male<br>Female | <br>12 (66.6)<br>6 (33.3) |
| *TP53* mutated, N (%) | 8 (44) |
| BM blast count % at diagnosis, median (range) | 5 (2-15) |
| IPPS-R, high and very high risk, N (%) | 9 (50) |
| Pre-HSCT BM blast count %, median (range) | 2 (1-4) |
| Stem cell source, N (%)<br>Bone marrow<br>Peripheral blood stem cells | <br>1 (5)<br>17 (95) |
| Conditioning regime, N (%)<br>Fludarabine/melphalan-based<br>Busulfan-based<br>Fludarabine-TBI | <br>3 (17)<br>14 (78)<br>1 (5) |
| Donor type, N (%)<br>Matched unrelated donor<br>Matched sibling<br>Haploidentical | <br>10 (56)<br>7 (39)<br>1 (5) |

- Oral decitabine 35 mg - cedazudirine 100 mg
- maintenance start within 180 days post-HSCT
- Patients included were in CR, defined as <5% BM blasts and MRD- by Flow Cytometry
- No active GVHD and active infection at time of maintenance initiation

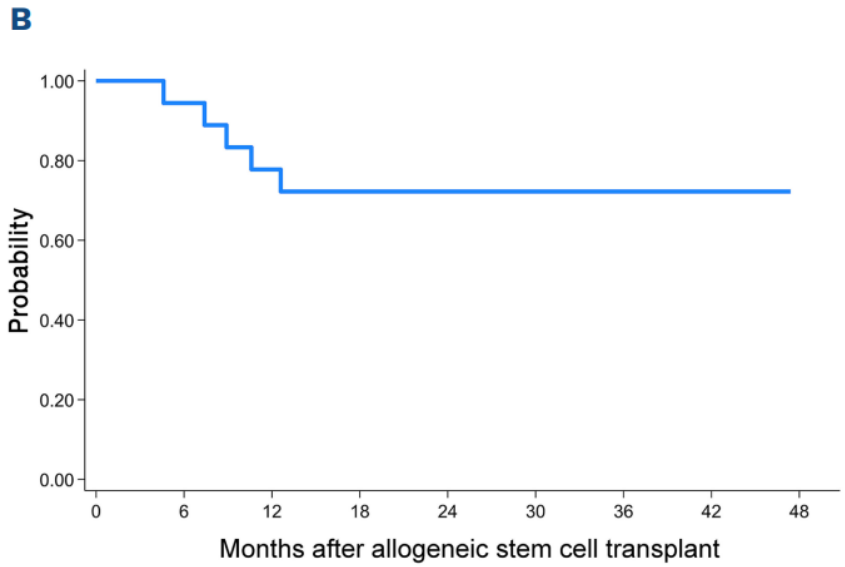
*Smallbone P et al.: Haematologica Vol. 110 No. 8 (2025): August, 2025 https://doi.org/10.3324/haematol.2024.287177*

# Maintenance therapy with oral decitabine plus cedazuridine after alloHSCT for MDS

Progression-free survival




Overall survival



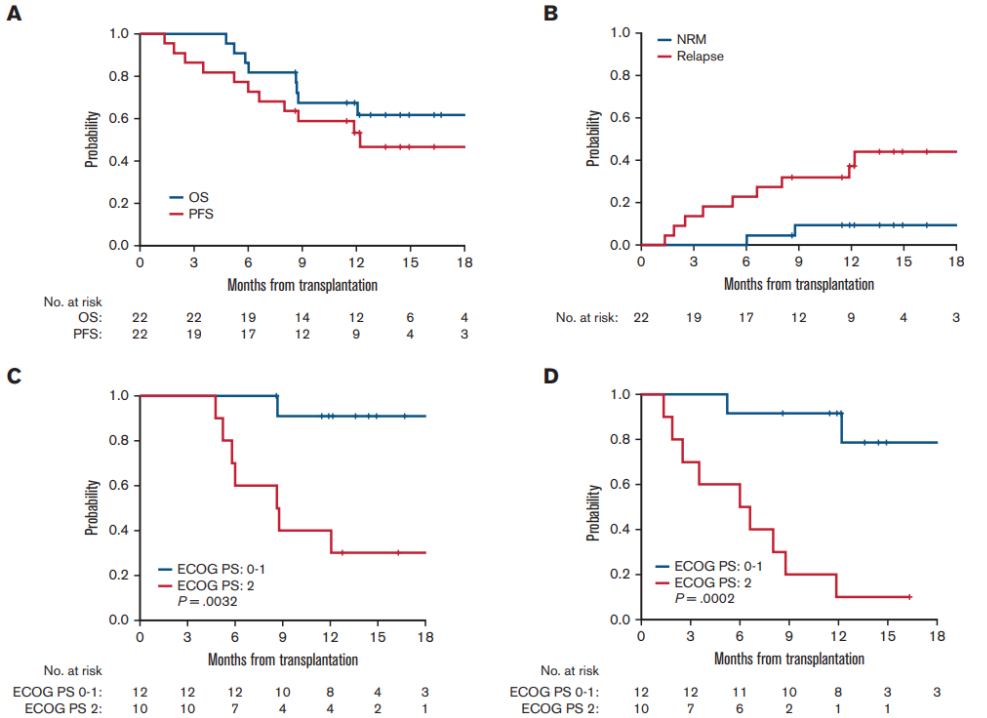

*Smallbone P et al.: Haematologica Vol. 110 No. 8 (2025): August, 2025 https://doi.org/10.3324/haematol.2024.287177*

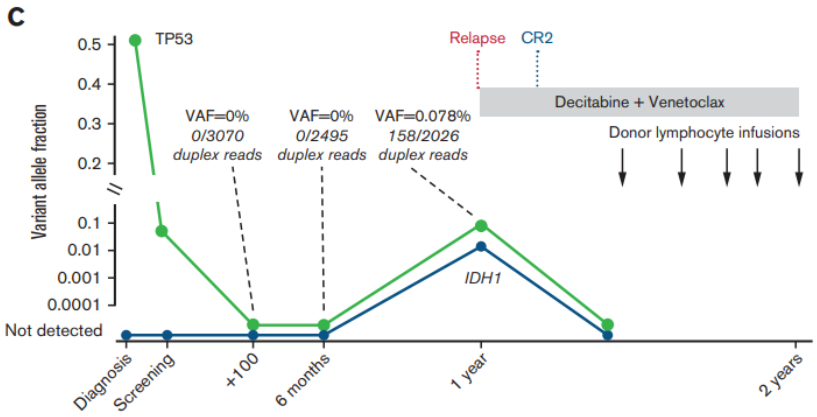
# Ongoing Randomized clinical trials

- **Safety and Efficacy of Venetoclax in Combination With Azacitidine Versus Standard of Care After AlloHSCT in AML (VIALE-T, NCT04161885)**
  - Randomized, Open Label Phase 3 Study in **AML** who received alloHCT within the past 60 days

- **Randomised Study of Oral Azacitidine vs Placebo Maintenance in AML or MDS After Allo-HSCT (AMADEUS, NCT04173533)**
  - A Double-Blind, Phase III, Randomised Study to Compare the Efficacy and Safety of Oral Azacitidine (CC-486) Versus Placebo in Subjects With **AML or MDS** as Maintenance After Allogeneic Haematopoietic Stem Cell Transplantation

# Adding venetoclax to fludarabine/busulfan RIC transplant for high-risk MDS and AML is feasible, safe, and active

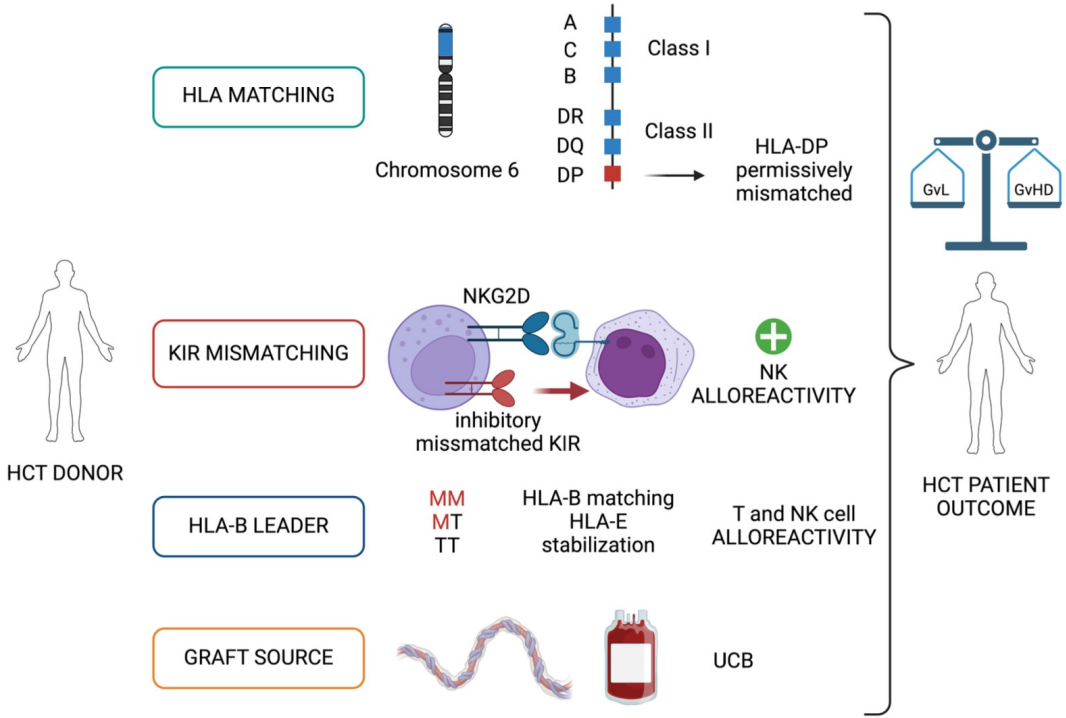



MRD monitoring before and after transplant

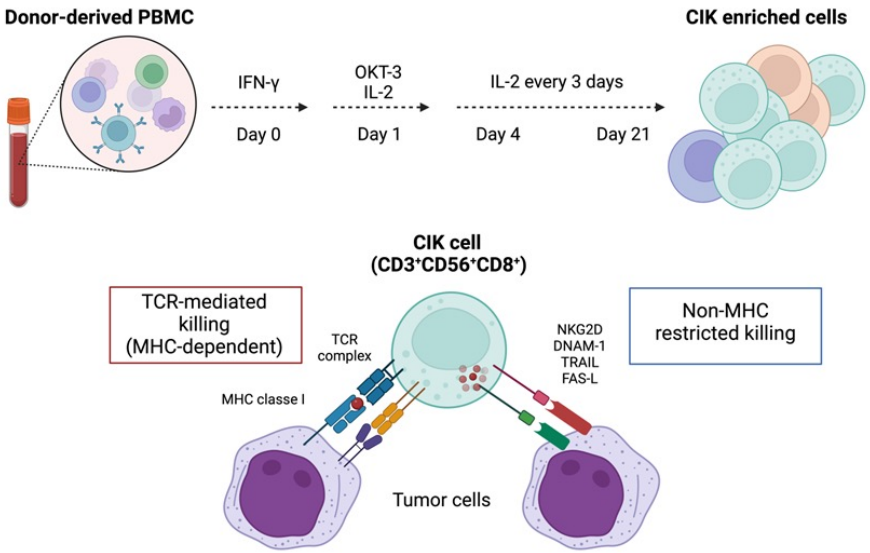
*Garcia JS et al.: Blood Advances 2021 DOI 10.1182/bloodadvances.2021005566*

# Graft versus Leukemia (GvL) immunological basis: donor selection through HLA, KIR matching and graft source




Rambaldi B et al., *Front Immunol* 2024

# Allogeneic CIK cells to enhance GvL hampering GvHD effect: background and patients characteristics

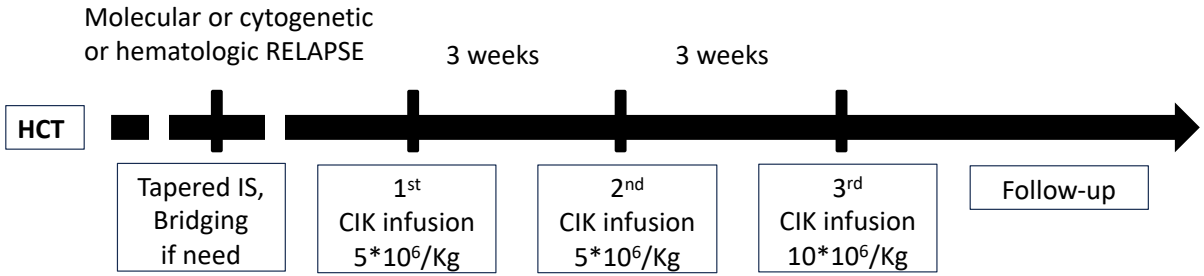



| | N (%) |
|---|---|
| Age | 61.9 (54.1-65.3) |
| Sex (M) | 16 (57.1) |
| Disease<br>AML<br>MF<br>ALL<br>MDS | <br>21 (75)<br>5 (17.9)<br>1 (3.6)<br>1 (3.6) |
| Donor type (haploidentical) | 19 (67.9) |
| Time from HCT to relapse (months) | 5.3 (2.8-19.4) |
| Bridging therapy | 9 (32.1) |
| Status of disease at CIK infusion<br>Active disease<br>RC MRD+ / MC<br>FC / RC MRD - | <br>5 (17.9)<br>17 (60.7)<br>6 (21.4) |
| DLI pre-CIK | 6 (21.4) |
| Concomitant therapy with CIK | 7 (25) |

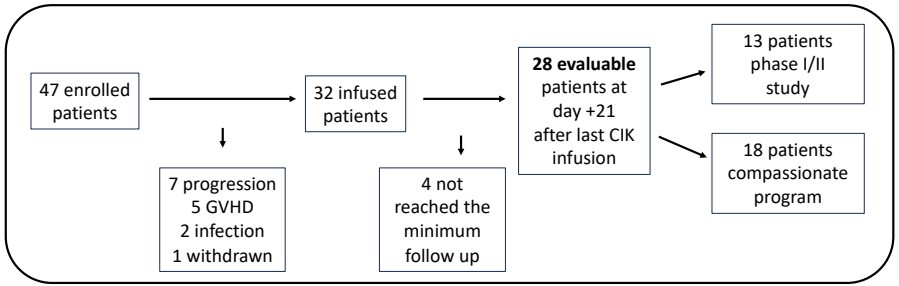
1 Introna M, et al. Bone Marrow Transplant. 2006; 2 Pievani et al, Blood, 2011; 3 Linn et al. Journal of Biomed and Biotech 2010; 4 Sangiolo et al. Journal of Cancer 2011; 5 Introna et al, Haematologica 2007; 6 Rambaldi A (2015) Leukemia 29(1):1-10; 7 Introna M (2017) Biol Blood Marrow Transplant. 23(12):2070-8; 8 Golay J etal.: Cytotherapy. 2018 Aug;20(8):1077-1088 ; 9 Magnani C et al.: Journal of Clinical Investigation 2020

# Allogeneic CIK cells to enhance GvL hampering GvHD effect: background and patients characteristics

- Phase I/II trial using haplo or HLA-mismatched donor-derived CIK cells for post-HCT relapse (NCT03821519)



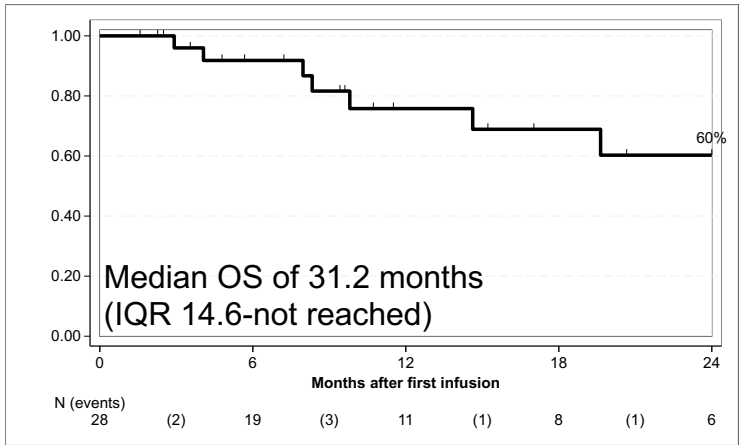

- The primary endpoint was the incidence of acute grade II-IV GvHD at day +100 after the last infusion of CIK cells



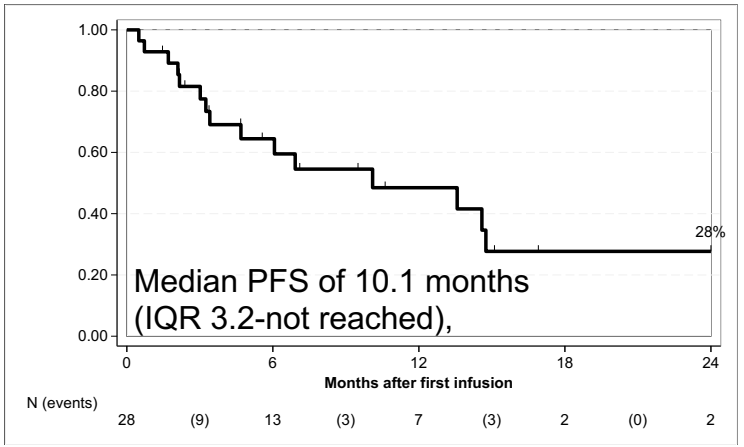

*Rambaldi B et al. ASH 2025*

# Outcomes

**OS**




**PFS**




- No acute GvHD was reported
- One patient developed mild chronic GvHD

*Rambaldi B et al. ASH 2025*

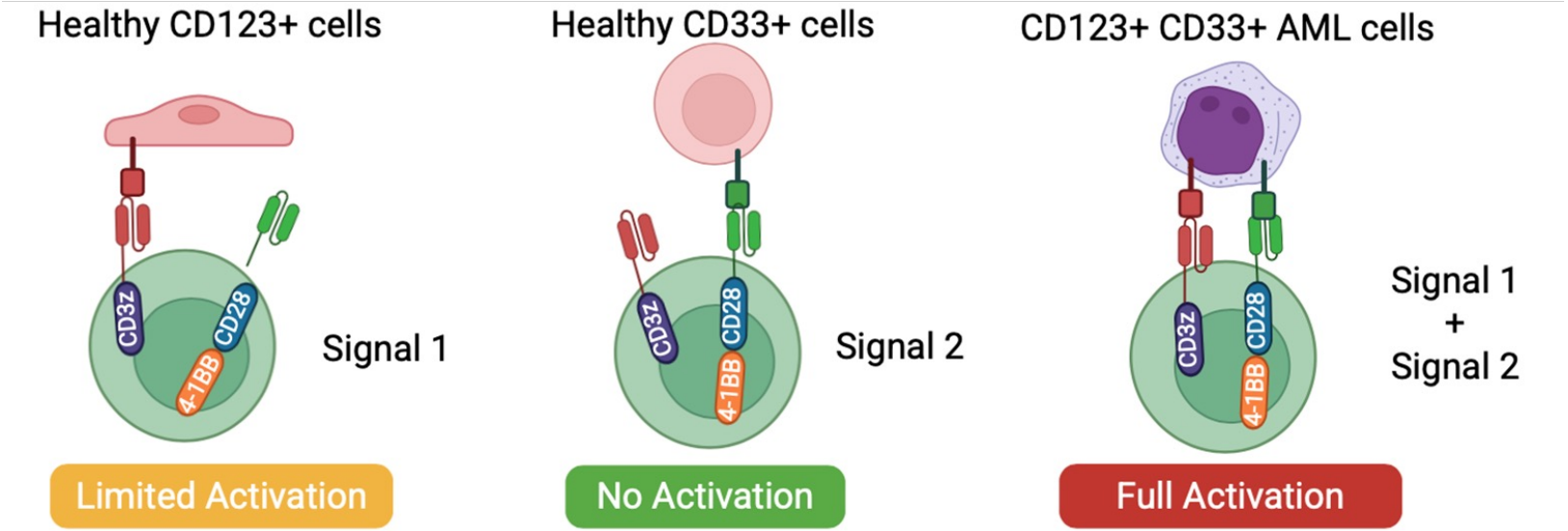
# A new trial with CIK cells: study design

- Prophylactic donor derived CIK cells will be infused in high-risk AML patients
- CIK cells will be manufactured from donor peripheral blood mononuclear cells (PBMCs) in case of BM donation or directly from the left over of the leukapheresis in the case of PBSC source.
- Infusions of donor CIK cells will be administered by 4 weeks intervals at increasing dose levels ($1x10^6$, $5x10^6$ and $10x10^6$ CD3+CD56+ cells/Kg) at 30, 60 and 90 days after transplant, according to the dose escalating program already adopted

*Rambaldi B et al. In preparatiuon*

# First-in-Human Anti-CD123/CD33 Chimeric Antigen Receptor Cytokine-Induced Killer (DualCARCIK-CD123/33) Cells for AML

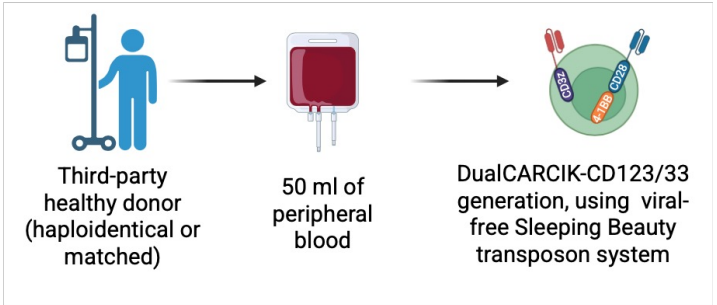
## Targeting Strategy




*Tettamanti S. et al*

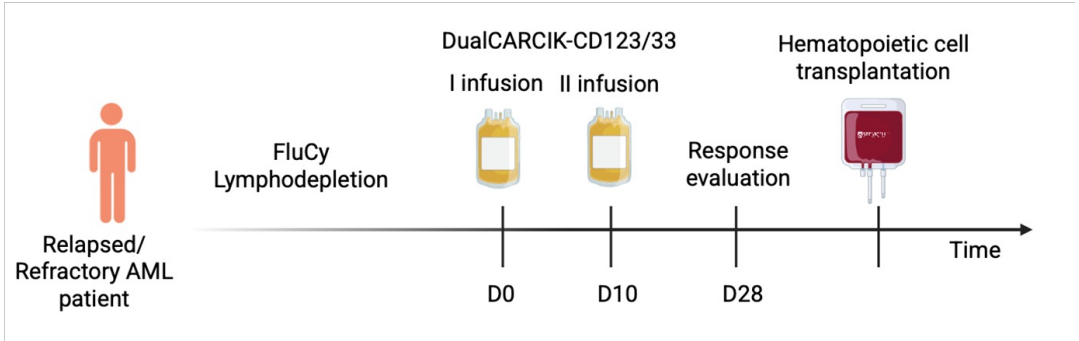
# First-in-Human Anti-CD123/CD33 Chimeric Antigen Receptor Cytokine-Induced Killer (DualCARCIK-CD123/33) Cells for AML

## Manufactory




## Clinical Trial

**A phase I/II single-arm, clinical trial to evaluate the safety, efficacy and feasibility of DualCARCIK-CD123/33 cells for R/R AML**

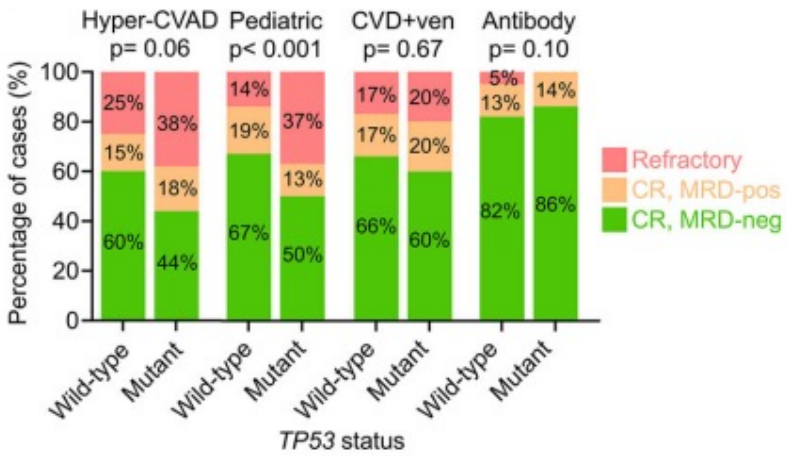



*Rambaldi B, Ottaviano G and Tettamanti S*

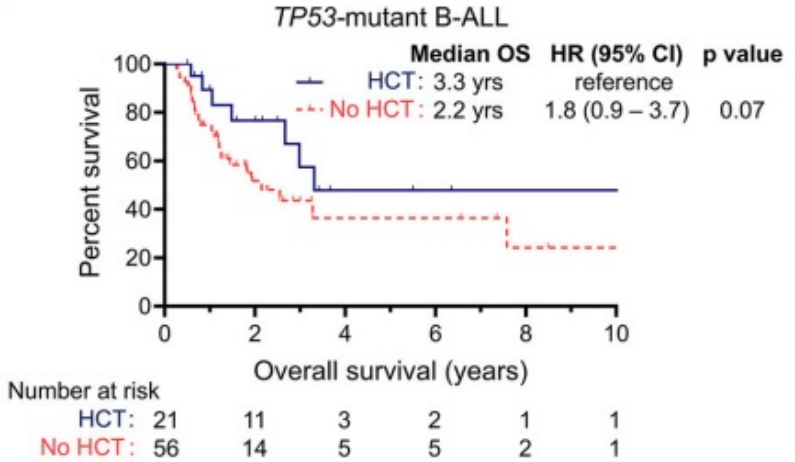
# TP53 mutations in B cell precursor ALL

# Clinical outcomes in TP53-mutant B-ALL

CR with flow MRD negativity rates by different first-line approaches



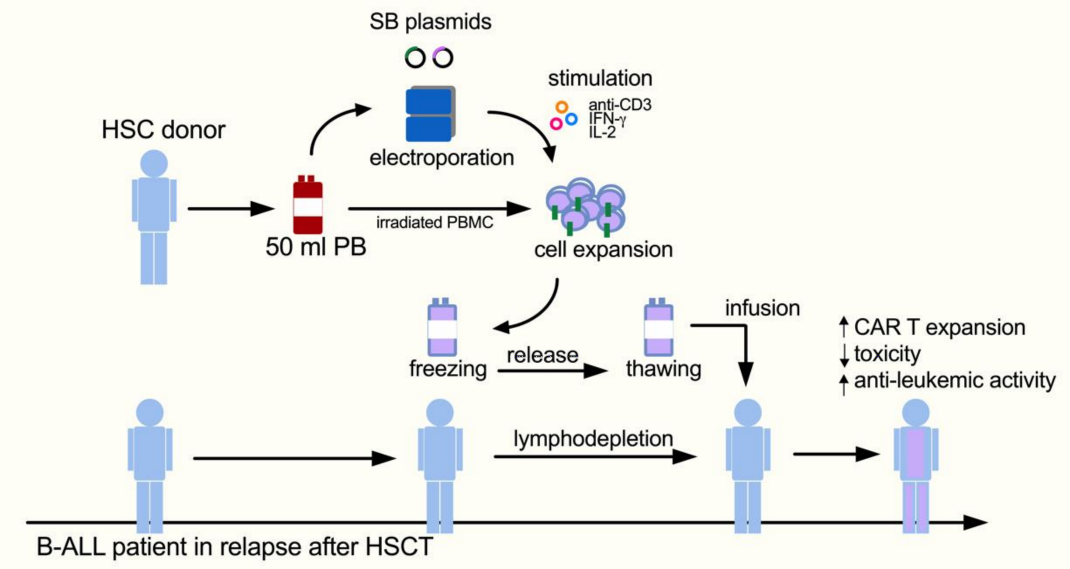

Overall survival by performance of AlloHSCT




*Harris EJ et al.: Blood Cancer Journal (2025) 15:138 ; https://doi.org/10.1038/s41408-025-01350-5*

# DONOR-DERIVED CARCIK-CD19 CELLS ENGINEERED WITH SB TRANSPOSON IN B-ALL RELAPSED AFTER ALLO-SCT

**36 adult and pediatric patients enrolled at 2 sites**




## Safety

- **CRS:** Grade 1-2 = 41%, Grade 3+ = 0%
- **ICANS:** Grade 1-2 = 3%; Grade 3+ = 0%
- **GVHD:** 0%

*Magnani CF et al., J Clin Invest. 2020;130(11):6021-6033*
*Lussana F et al., Blood Cancer J. 2025;15(1):54.*

# Conclusions

- The clinical outcome of TP53 mutated AML, MDS and MPN is largely suboptimal but alloHSCT is the only potentially curative treatment option for these patients
- Each patient with these molecular characteristics should be promptly referred to transplant
- Post-Transplant treatment with well tolerated drugs would be paramount if supported by ongoing clinical trials
- Post transplant treatment with donor derived lymphocytes or CAR-T cells would be equally welcome but feasibility, safety and efficacy of this approach remains to be demonstrated

# ACKNOWLEDGMENTS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**The Molecular Lab Paolo Belli, Bergamo**
Silvia Salmoiraghi
Emanuela Carlotti
Cristian Meli
Anna Salvi
Manuela Tosi
Roberta Cavagna
Clara Belotti
Orietta Spinelli

**Cell Therapy Lab Gilberto Lanzani, Bergamo**
Chiara Capelli
Josee Golay
Elisa Gotti
Silvia Panna
Irene Cattaneo
Olga Pedrini
Martino Introna

**Cell Therapy Lab Stefano Verri, IRCCS San Gerardo Monza**
**Giuseppe Gaipa**
Chiara Magnani
Daniela Belotti
Giada Matera
Stefania Cesana
Valentina Colombo
Michele Quaroni

**Fondazioni Tettamanti, Monza and Clinica Pediatrica Università di Milano Bicocca**
**Andrea Biondi**
Sarah Tettamanti
Marta Serafini


Ospedale di Bergamo
Regione Lombardia
ASST Papa Giovanni XXIII

Fondazione IRCCS San Gerardo dei Tintori