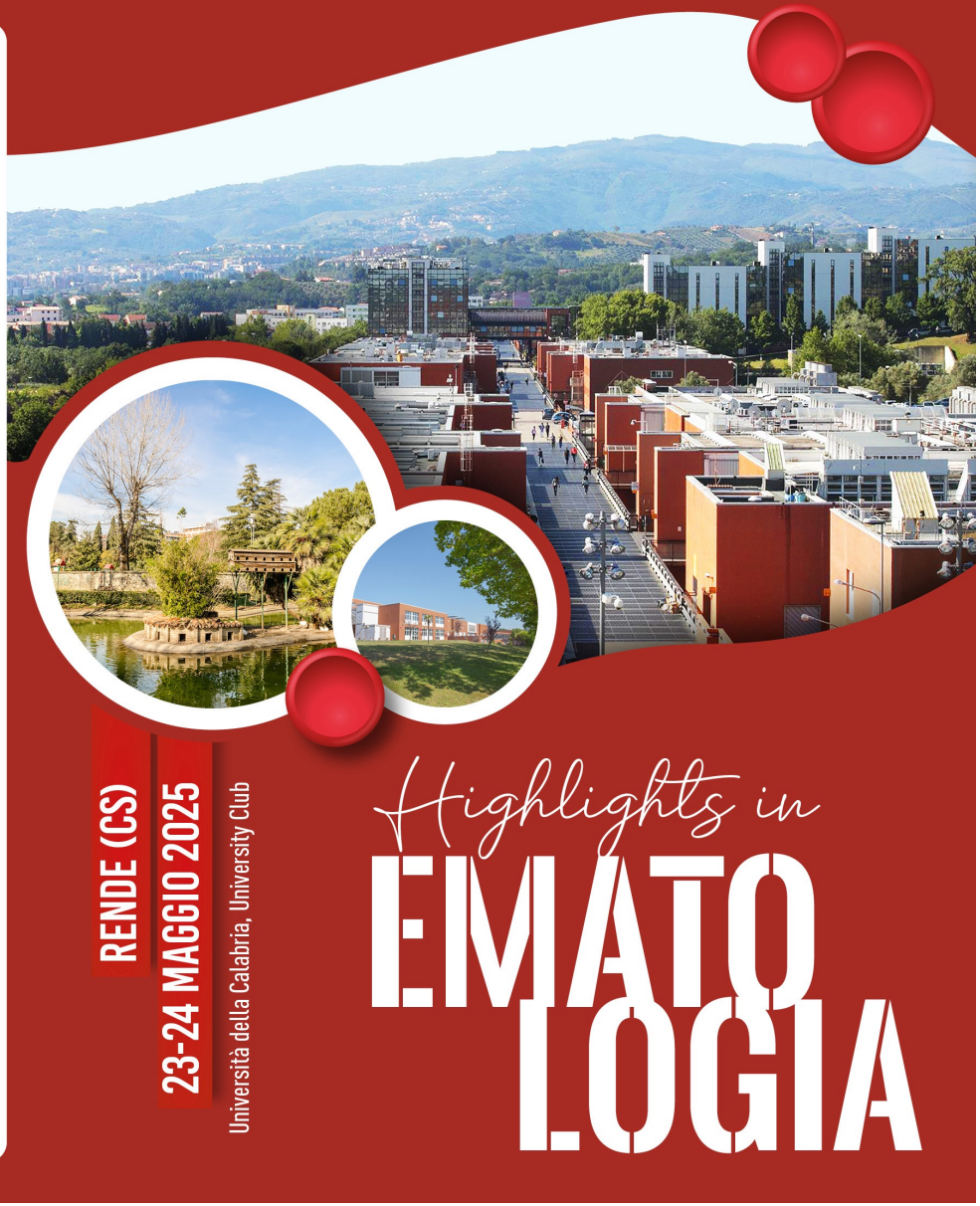
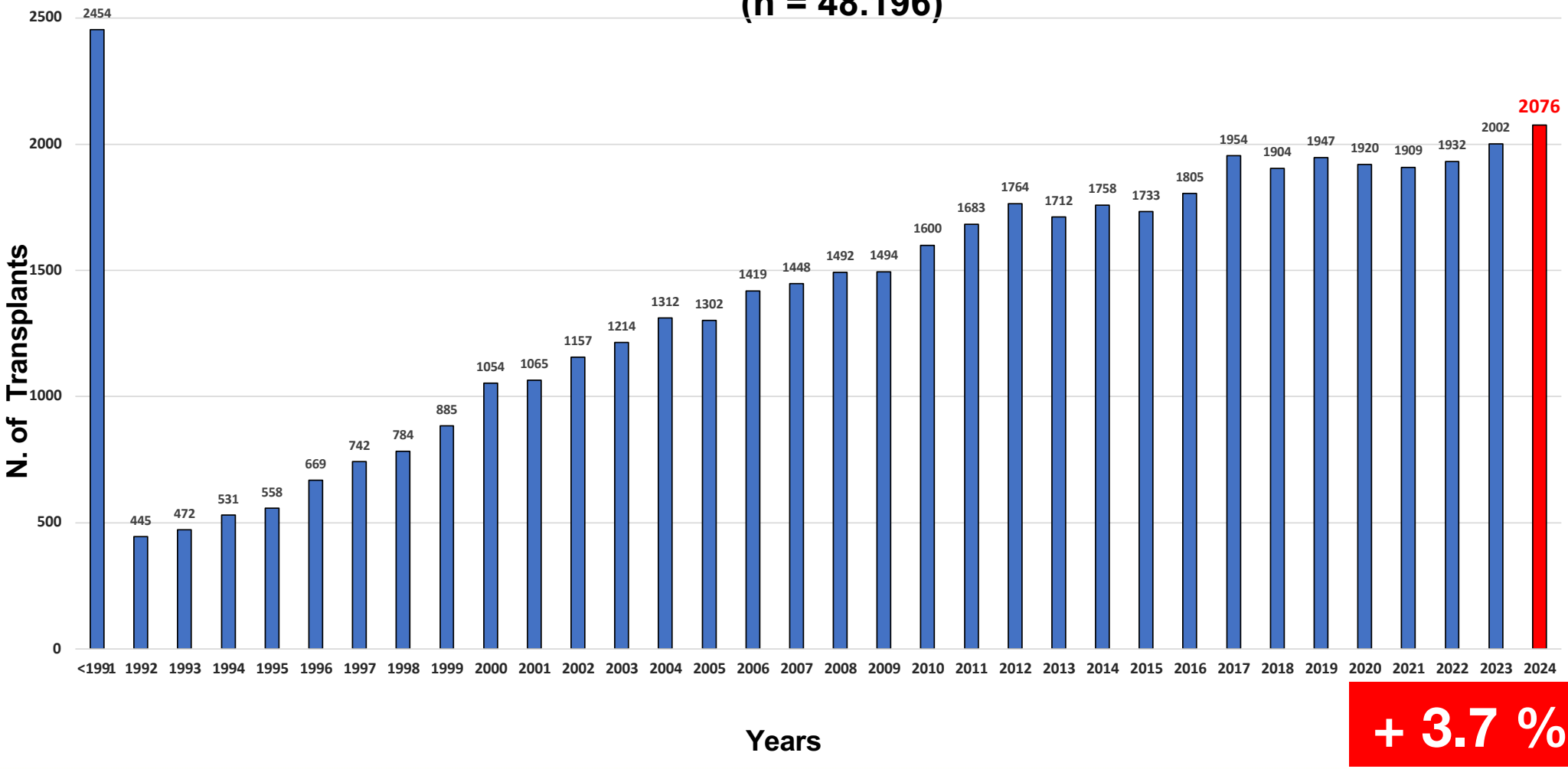
Ruolo del trapianto allogenico nella leucemia acuta

Massimo Martino - Reggio Calabria



Allogeneic Transplants

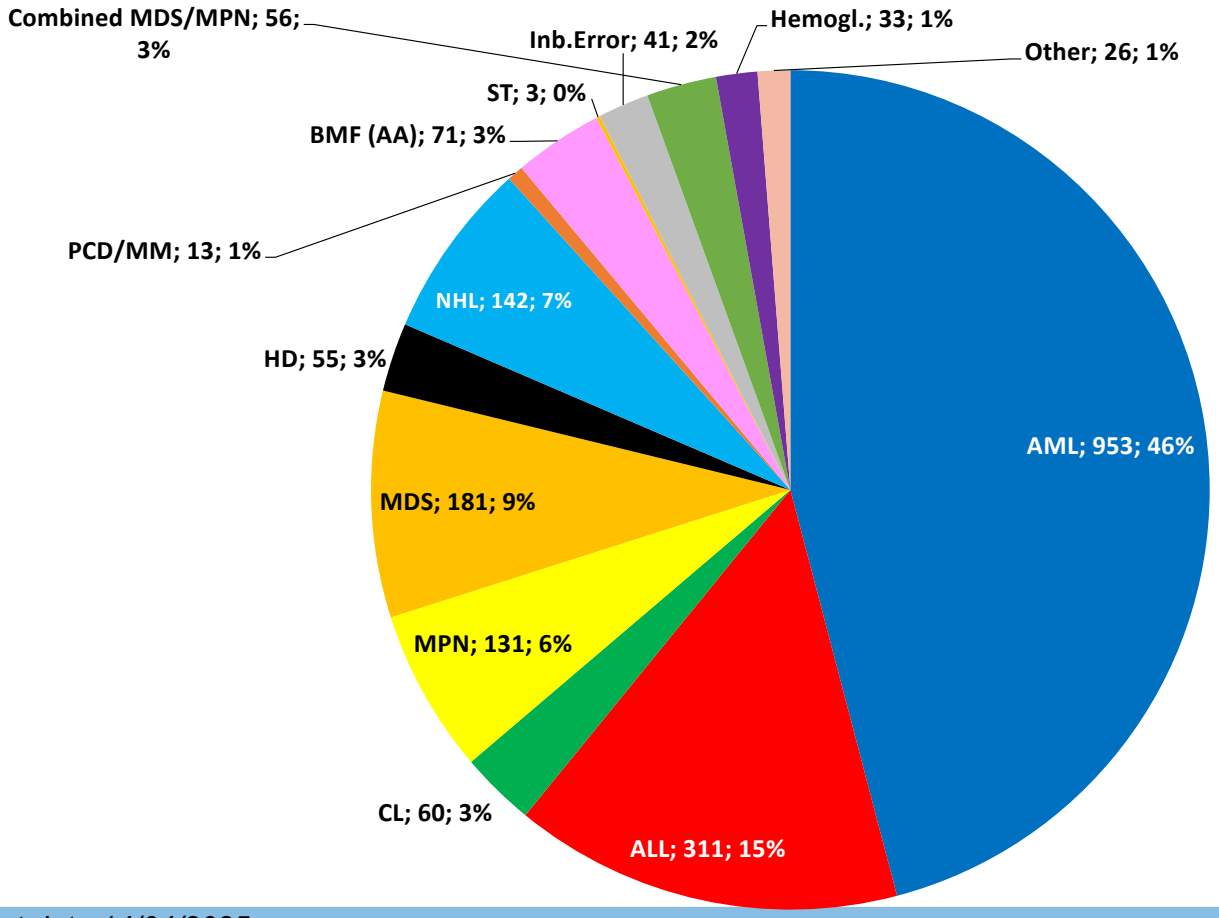
(n = 48.196)



+ 3.7 %

Export date 14/04/2025

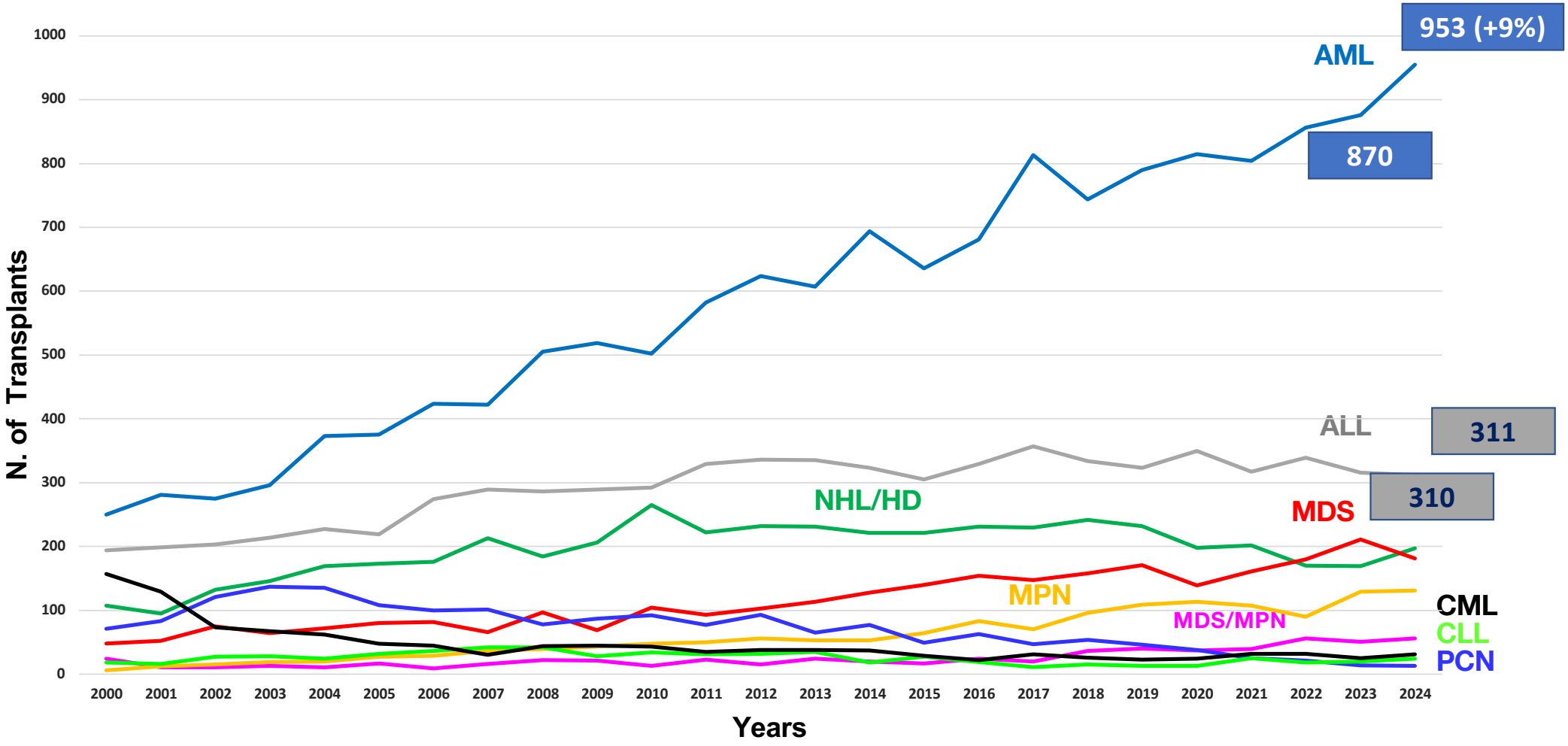
Allogeneic Transplants (n. 2076) - Indications 2024



Disease	%
AML	46
ALL	15
MDS	9
NHL	7
MPN	6
HD	3

Export date 14/04/2025

Number of Allogeneic HCTs in Italy by Selected Disease



Export date 14/04/2025

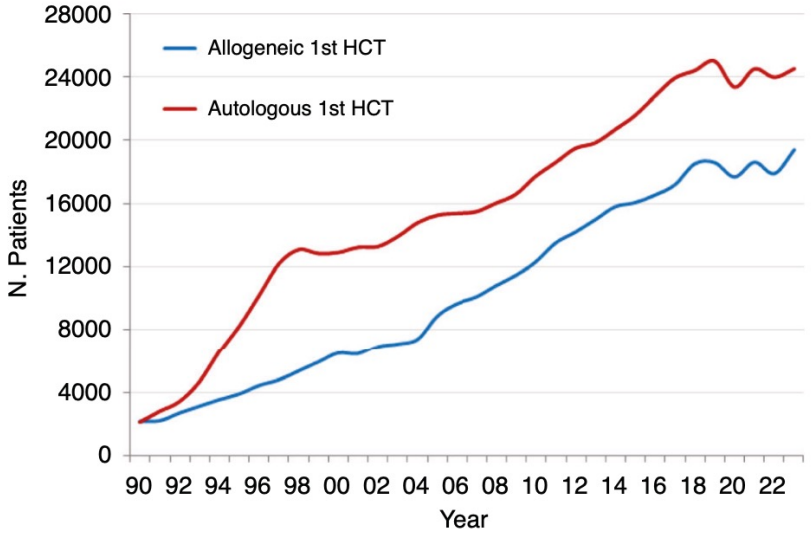
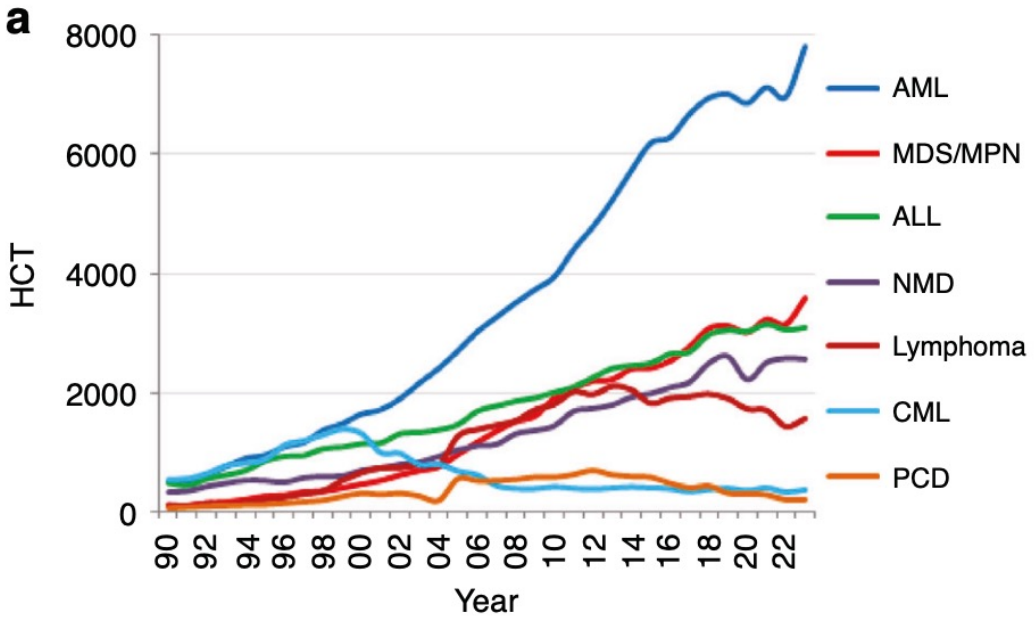
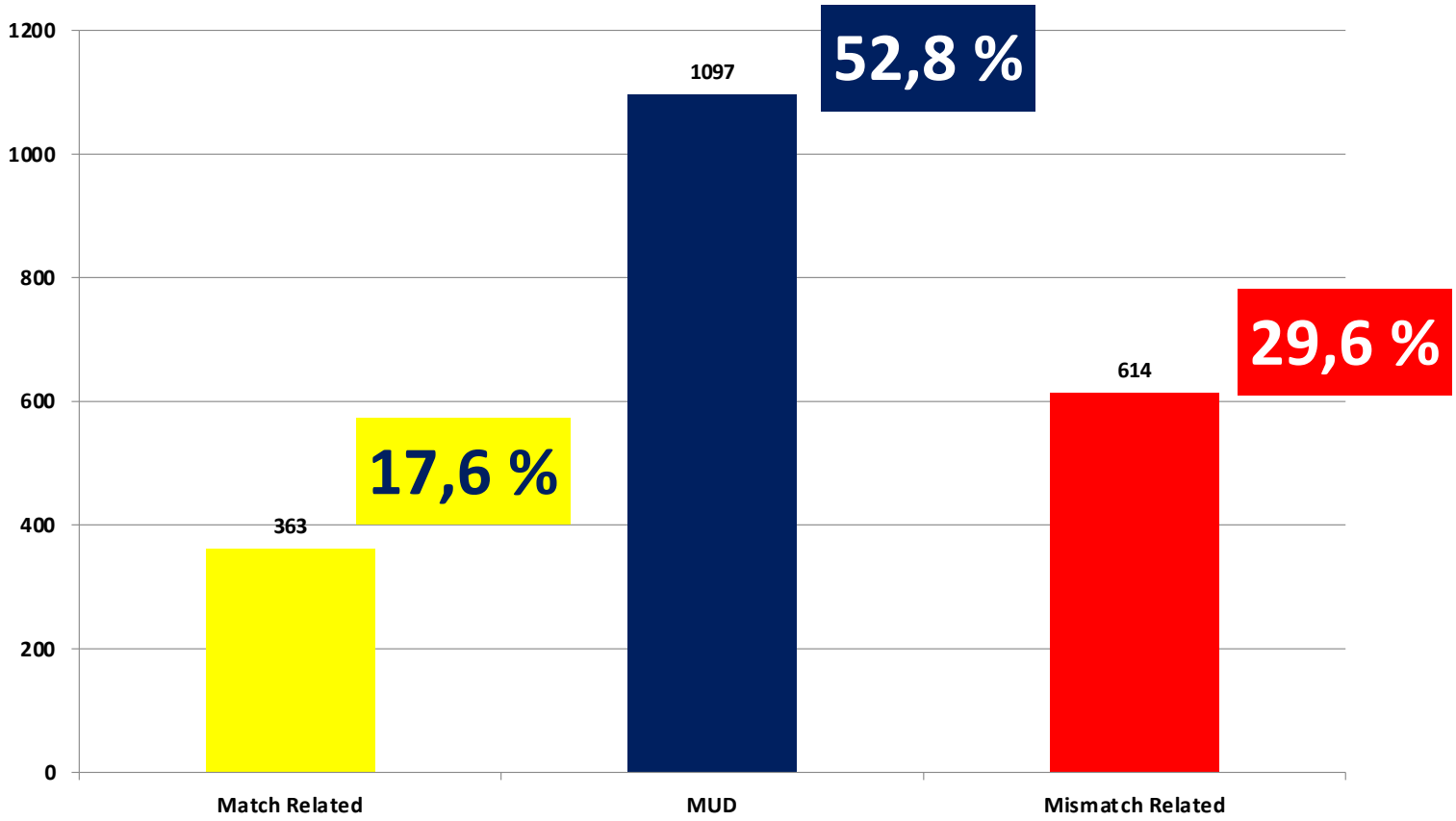


Fig. 1 Number of patients receiving the first allogeneic or autologous HCT from 1990 to 2023.



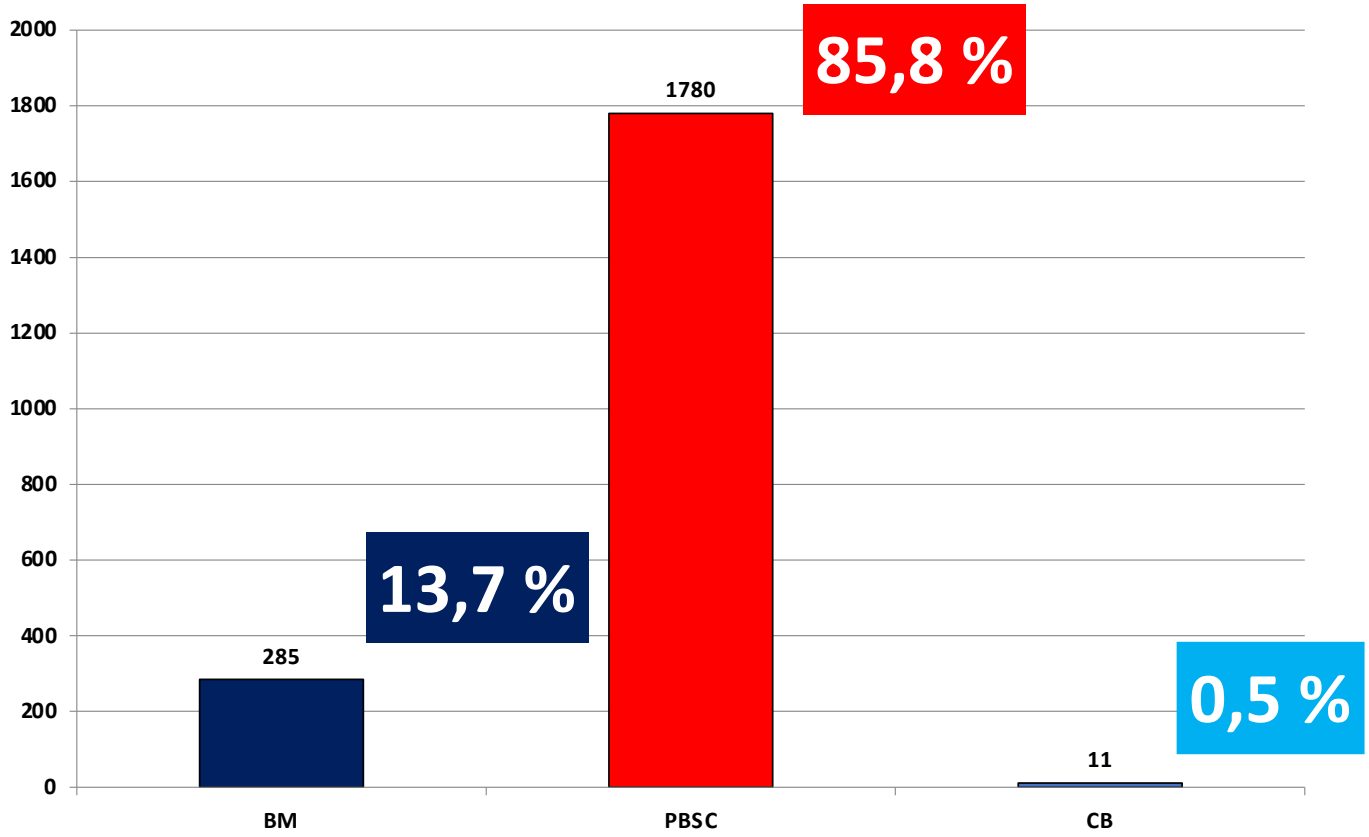
Passweg JR, et al. Bone Marrow Transplant. 2025 Feb 12. doi: 10.1038/s41409-025-02524-2.

2024: Allogeneic Transplants (n. 2076) – Donor type



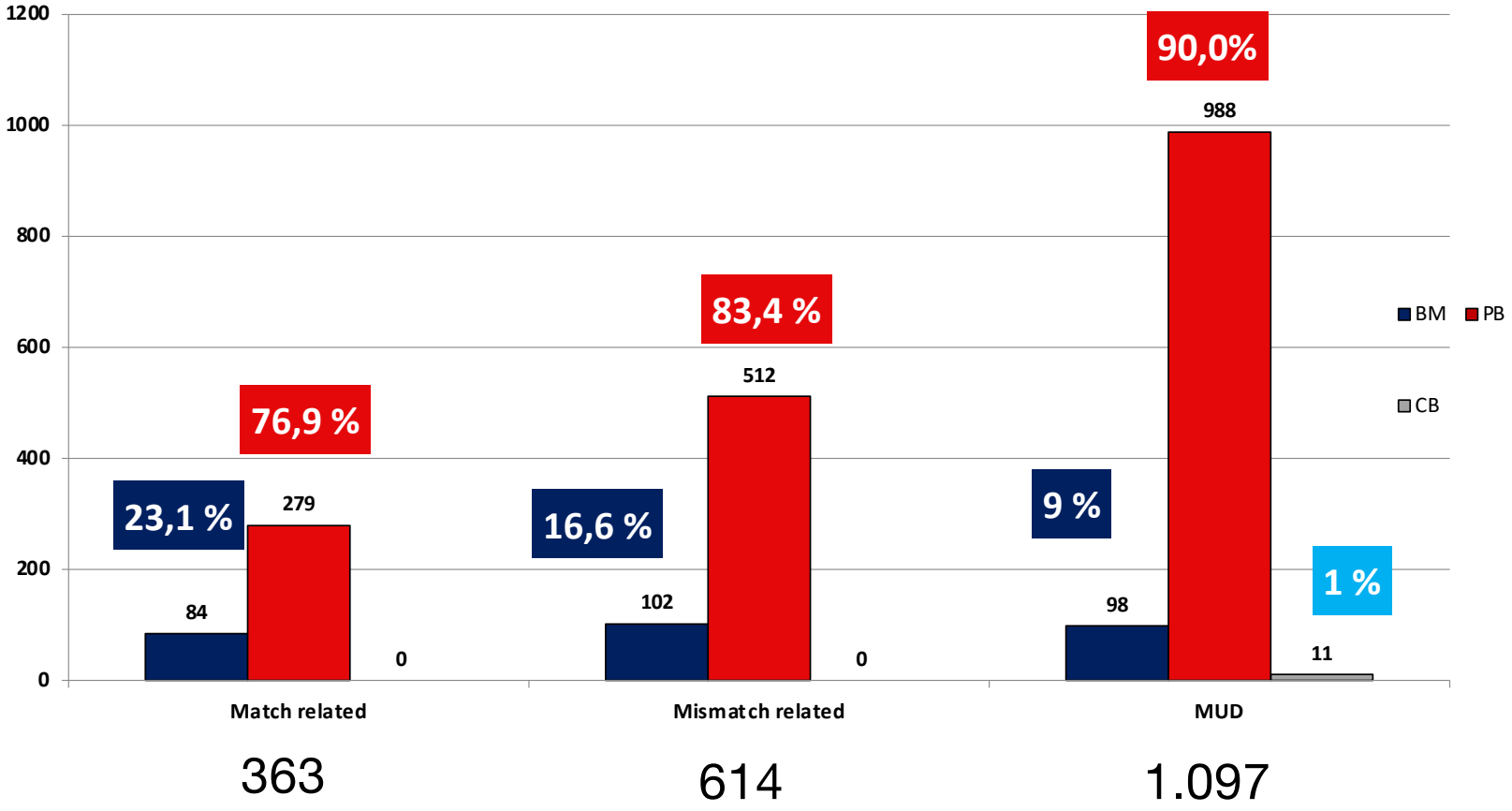
Export date 14/04/2025

2024: Allogeneic Transplants (n. 2076) – Source of HSC



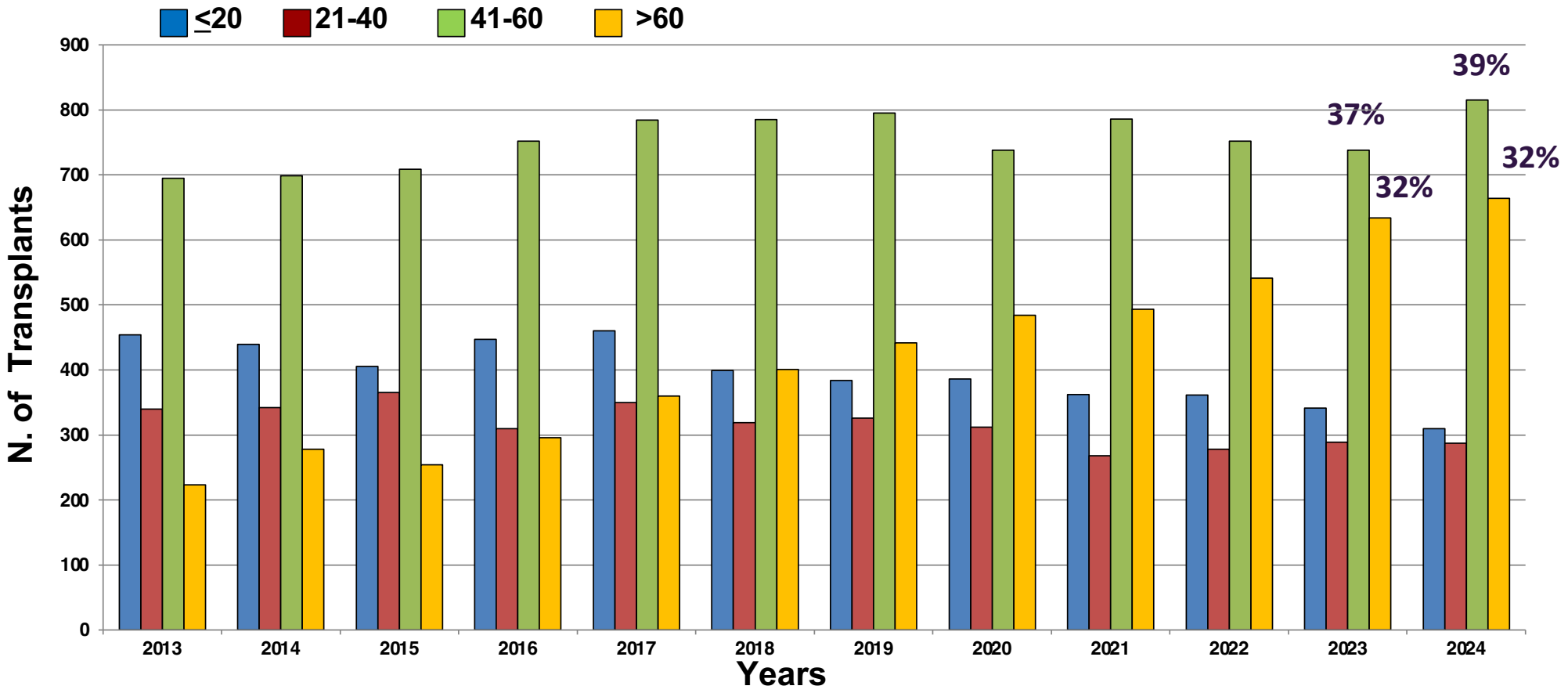
Export date 14/04/2025

2024: Allogeneic Transplants (n. 2076) – Donor and Source of HSC



Export date 14/04/2025

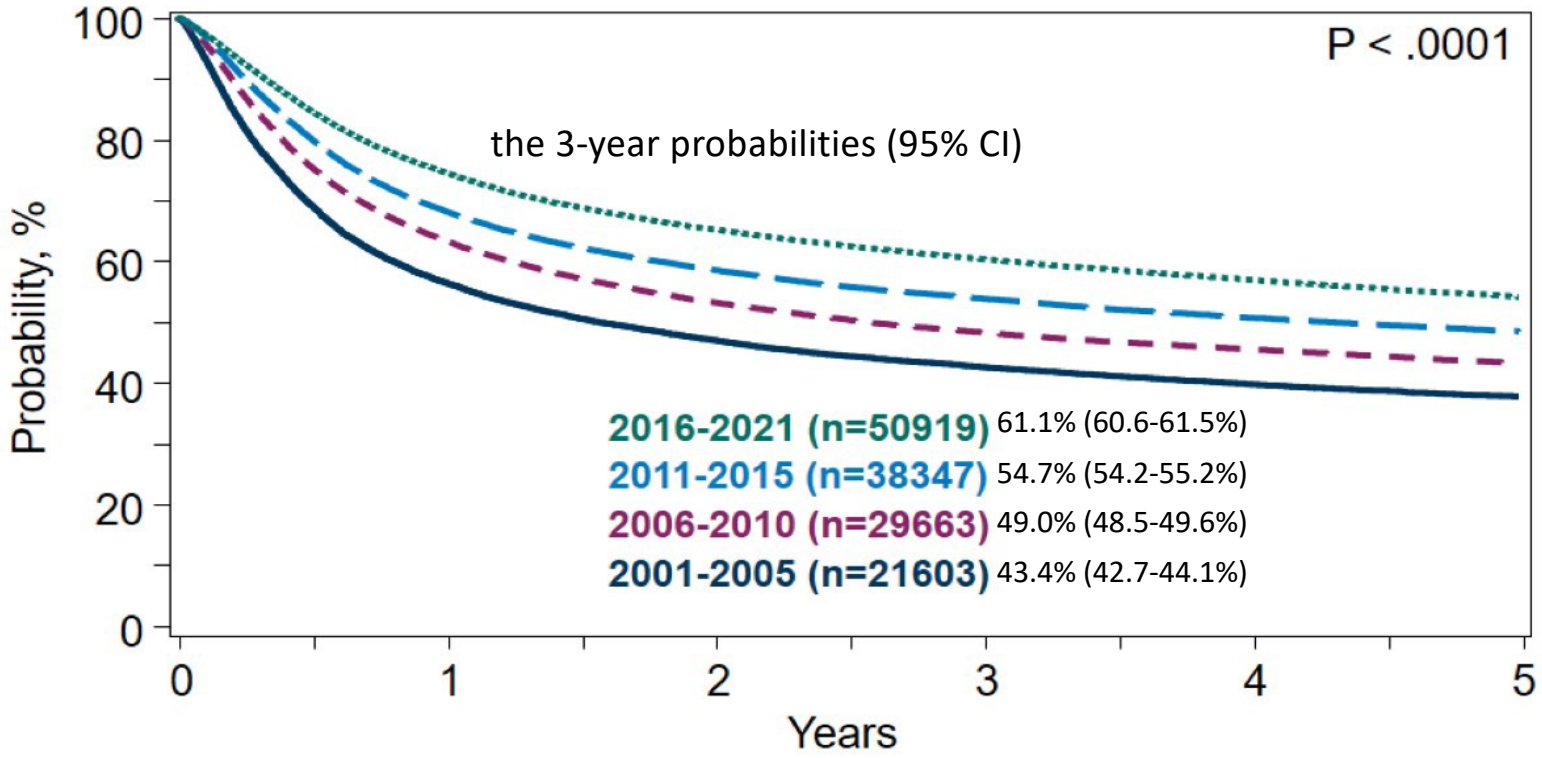
2024 - Allogeneic Transplants: Patient age at transplantation



Export date 14/04/2025

Trends in Survival after Allogeneic HCTs, in the US, 2001-2021

140,532 patients receiving **allogeneic** HCT



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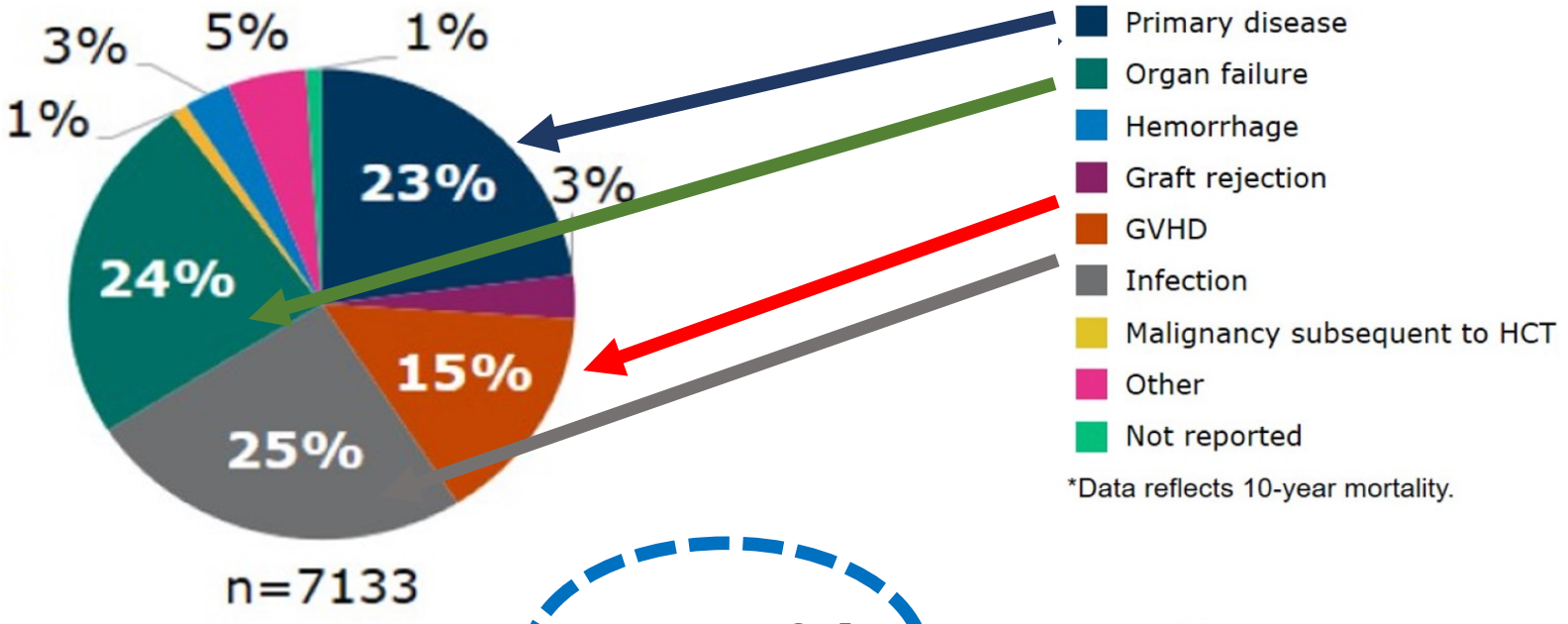
Spellman S, et al. **Current Uses and Outcomes of Cellular Therapies in the US: CIBMTR Summary Slides, 2024.**

Causes of Death after Allogeneic HCTs in the US, 2012-2022

Age ≥18 years
Total transplants = 75507

Data reflects 100-days mortality



*Data reflects 10-year mortality.

9.6 %

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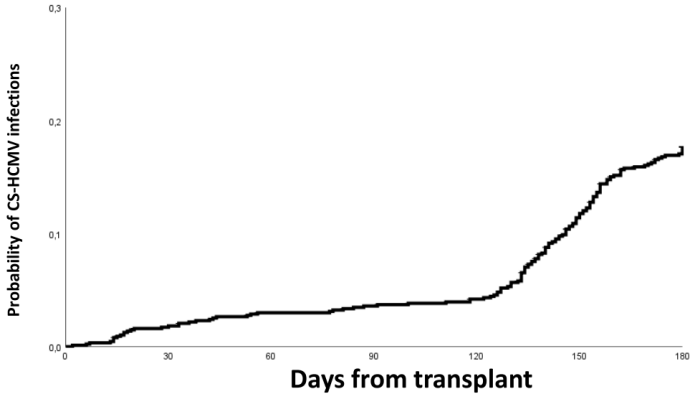
The GITMO CYTO-ALLO STUDY

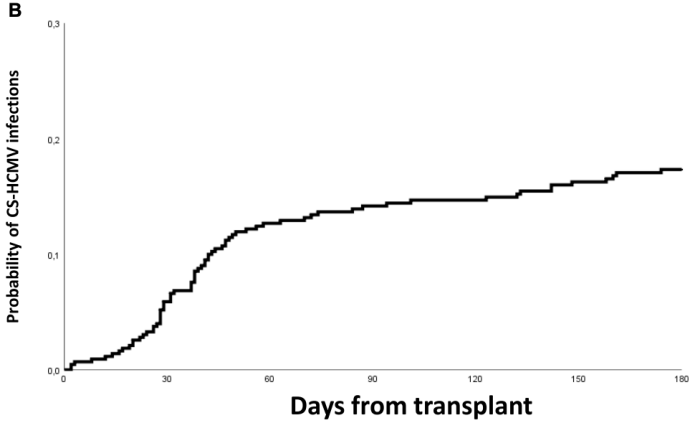
A



100 days Cum Inc. 3.8% (95% CI 2.6%-5.2%)
180 days Cum Inc. 16% (95% CI 14%-19%)

cumulative incidence of clinically significant HCMV infections (CS-HCMV-i) at 100 days and 180 days from allo-HSCT in patients who received letermovir primary prophylaxis (LET-PP). The low rate of infections during the prophylaxis period was balanced by a rebound of infections in the late post-transplant phase, when prophylaxis was discontinued

B



100 days Cum Inc. 14% (95% CI 11%-17%)
180 days Cum Inc. 17% (95% CI 13%-20%)

The cumulative incidence of CS-HCMV-i at 100 days and 180 days from allo-HSCT in patients who did not receive LET-PP

Girmenia et al. Open Forum Infectious Diseases 2025

GVHD: consensus recommendations of the European Society for Blood and Marrow Transplantation

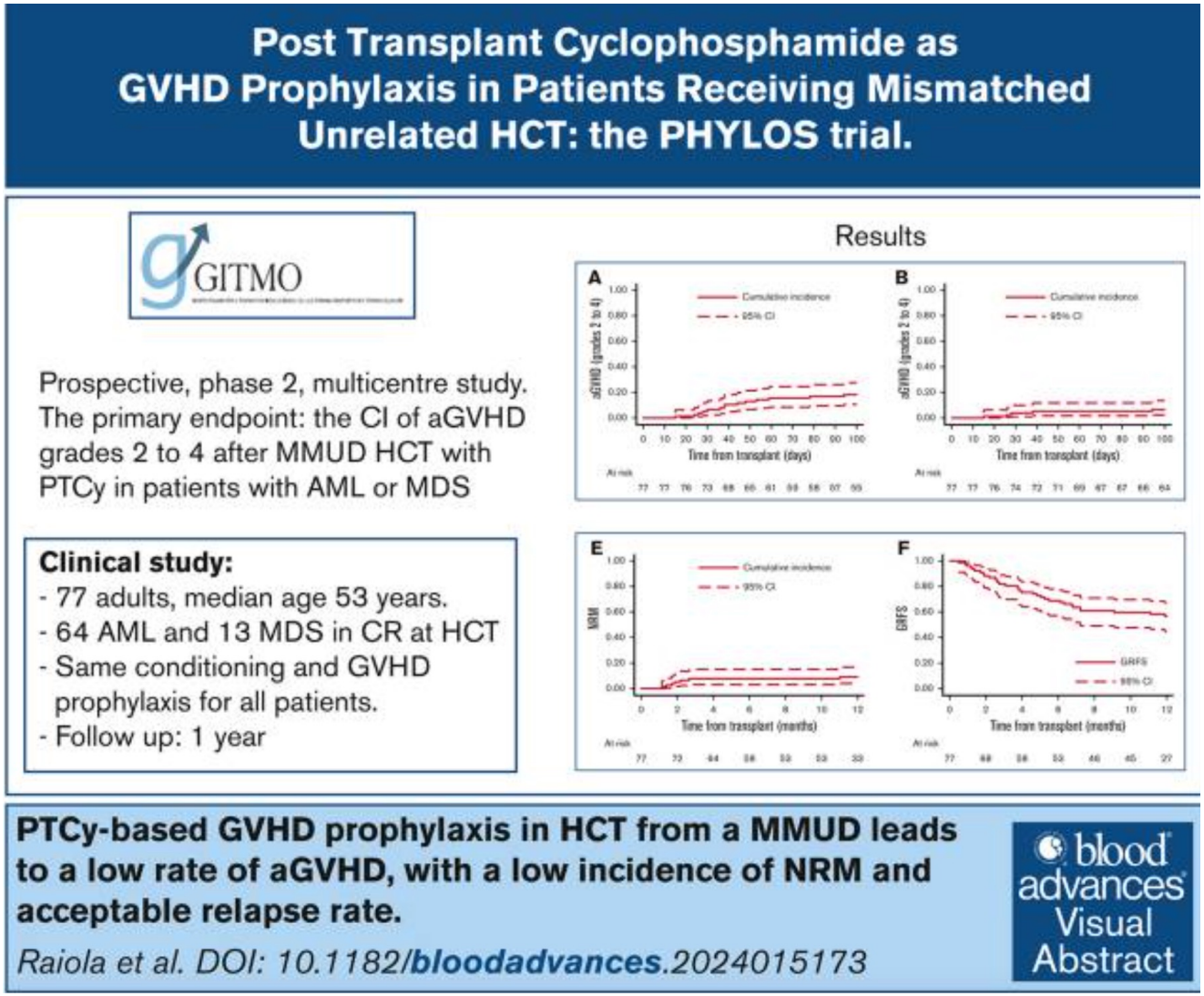
Key updates to the recommendations include:

(1) primary use of ruxolitinib in steroid-refractory acute GVHD and steroid-refractory chronic GVHD as the new standard of care,

(1) use of rabbit anti-T-cell (thymocyte) globulin or post-transplantation cyclophosphamide as standard GVHD prophylaxis in peripheral blood stem-cell transplantations from unrelated donors, and

(2) the addition of belumosudil to the available treatment options for steroid-refractory chronic GVHD

Penack O, et al.. Lancet Haematol. 2024

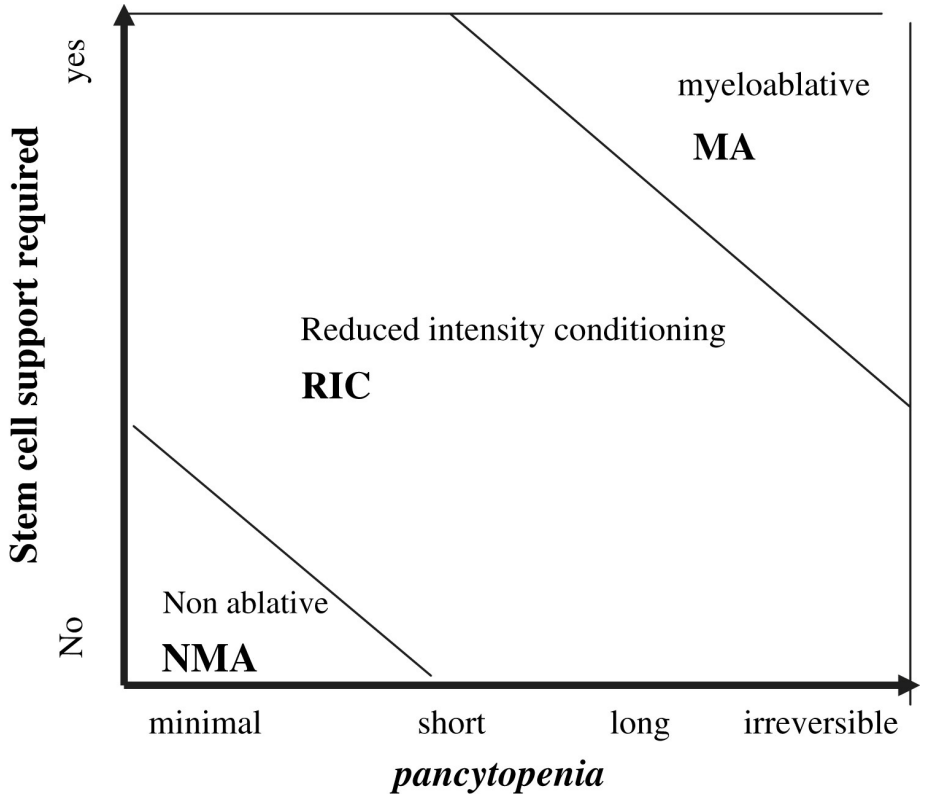


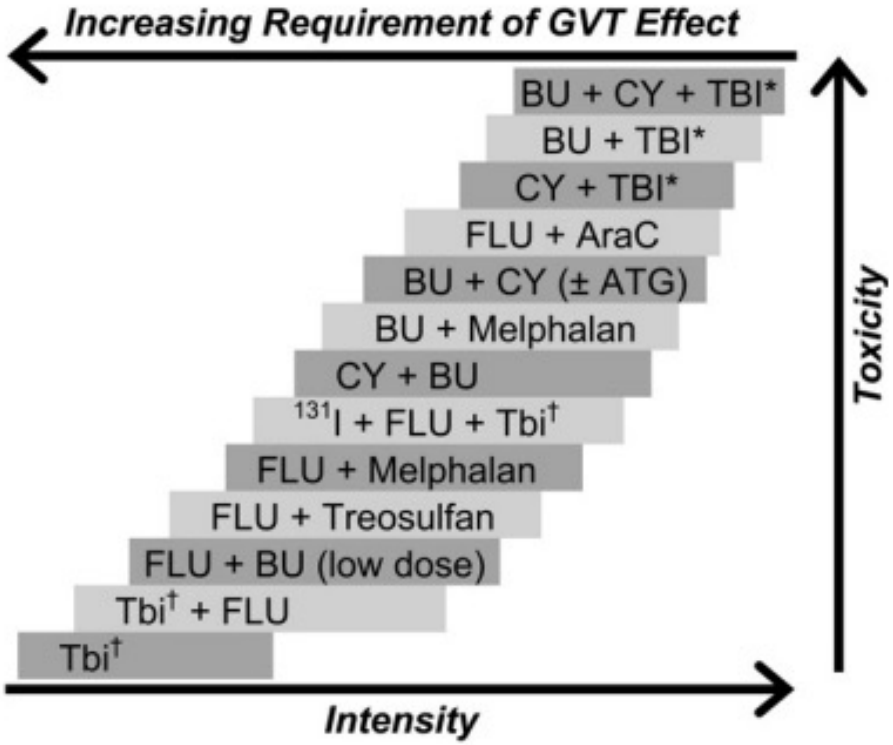
The 100-day cumulative incidence of grades 2 to 4 aGVHD was 18.2% (95% CI, 10.6-27.6) and of grades 3 to 4 was 6.5% (95% CI, 3.1-15.1)

One-year cumulative incidence of chronic GVHD was 13.4% (95% CI, 6.9-22.1). One-year cumulative incidence of nonrelapse mortality was 9.1% (95% CI, 4.0-16.9), and the relapse rate was 23.8% (95% CI, 14.9-33.9). One-year overall survival and graft relapse-free survival were 78.6% (95% CI, 67.4-86.3) and 55.3% (95% CI, 43.4-65.7),

Raiola AM, et al. Blood Adv. 2025

Classification of Conditioning Regimens



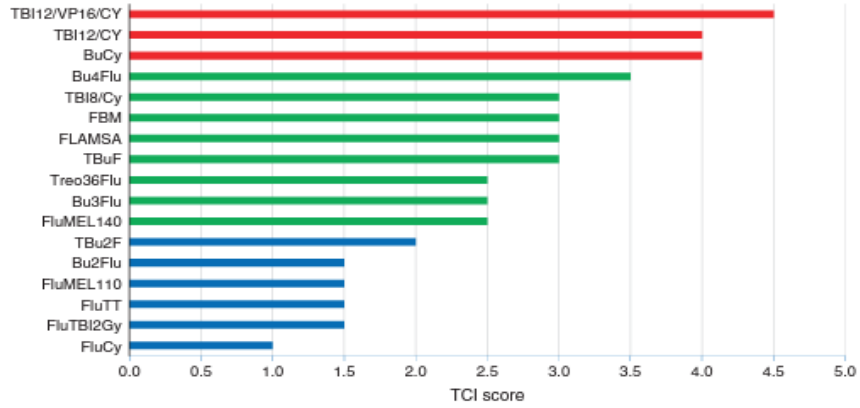


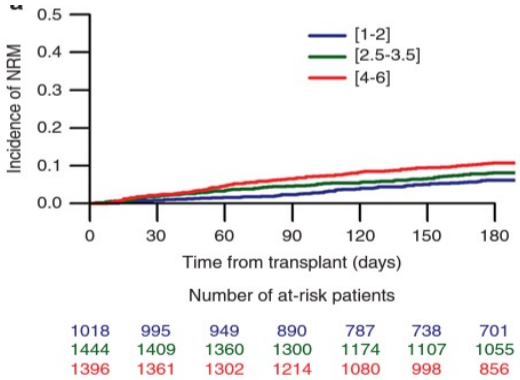
- AraC, cytarabine; ATG, anti-T-lymphocyte immunoglobulin; CY, cyclophosphamide; GVT, graft vs tumor; Tbi/TBI, total body irradiation.
- Bacigalupo A, et al. Biol Blood Marrow Transplant. 2009;15:1628-1633; Gyurkocza B, et al. Blood. 2014;124:344-353.

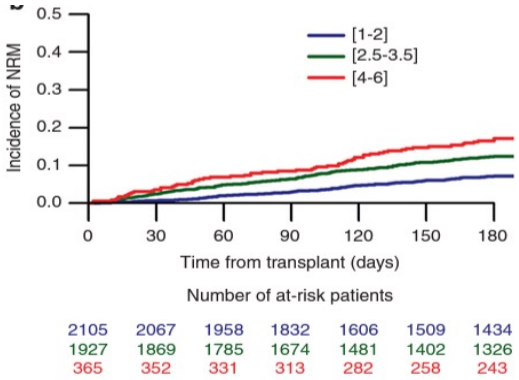
Transplant Conditioning Intensity Score
EBMT

The concept of MAC vs RIC has been expanded by recently developed Reduced Toxicity Conditioning (RTC) regimens including well-established agents

Component	Dose level			Added points for each dose level
	Low	Intermediate	High	
TBI fractionated (Gray)	≤5	6–8	≥9	1
Busulphan (mg/kg)	≤6.4 iv & ≤8 po	9.6 iv & 12 po	12.8 iv & 16 po	1
Treosulfan (g/m2)	30	36	42	1
Melphalan (mg/m2)	<140	≥140	≥200	1
Thiotepa (mg/kg)	<10	≥10	≥20	0.5
Fludarabine (mg/m2)	≤160	>160		0.5
Clofarabine (mg/m2)	≤150	>150		0.5
Cyclophosphamide (mg/kg)	<90	≥90		0.5
Carmustine (mg/m2)	≤250	280–310	≥350	0.5
Cytarabine (g/m2)	<6	≥6		0.5
Etoposide (mg/kg)	<50	≥50		0.5





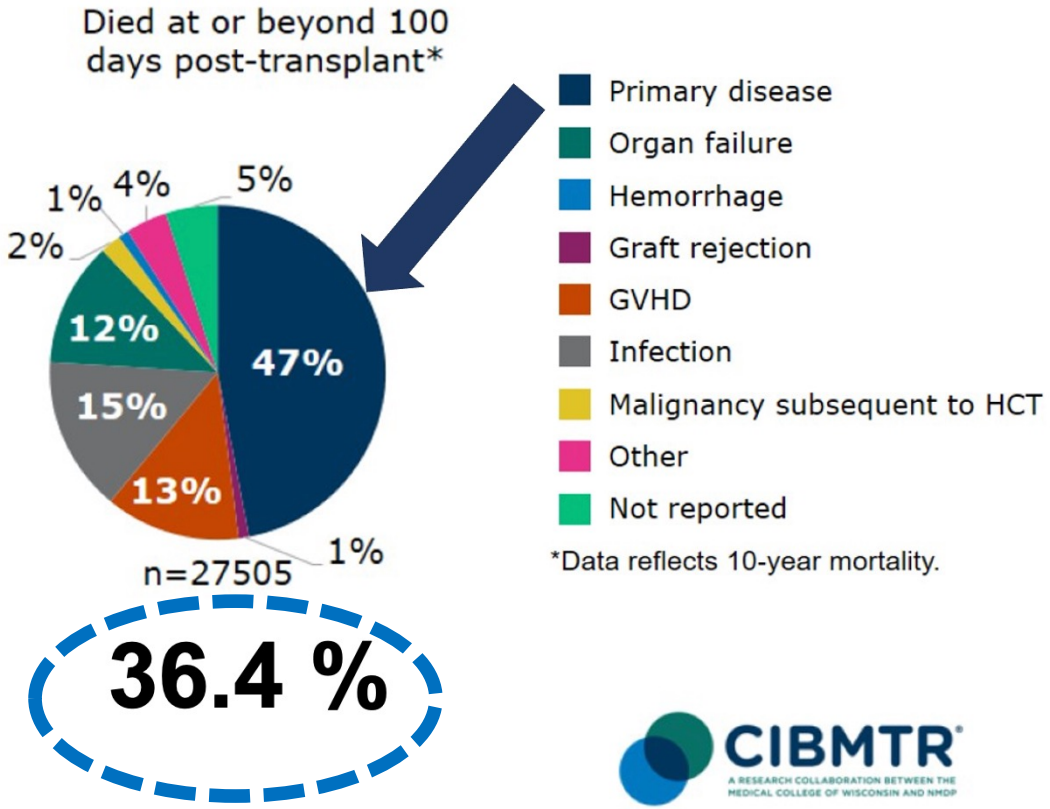


- TCI, transplant conditioning intensity.
- Spyridonidis A, et al. Bone Marrow Transplant. 2020;55:1114-1125.

Causes of Death after Allogeneic HCTs in the US, 2012-2022

Age ≥18 years
Total transplants = 75507

Data reflects 10-year mortality



36.4 %

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In 1977 Thomas and colleagues published their landmark article in *Blood* describing outcomes of 100 consecutive subjects with advanced acute lymphoid or myeloid leukemia receiving transplants from HLA-identical siblings

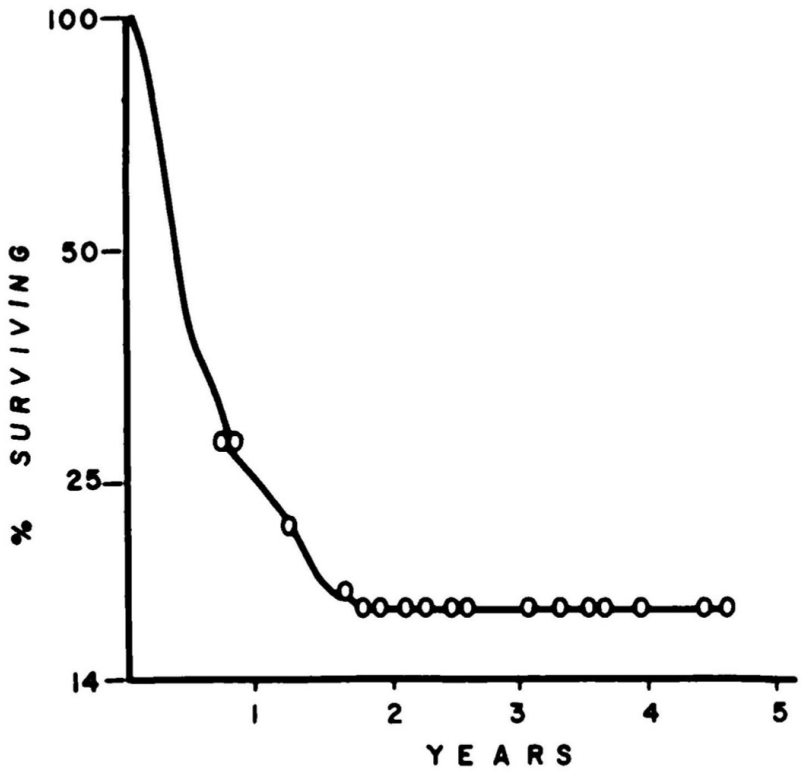


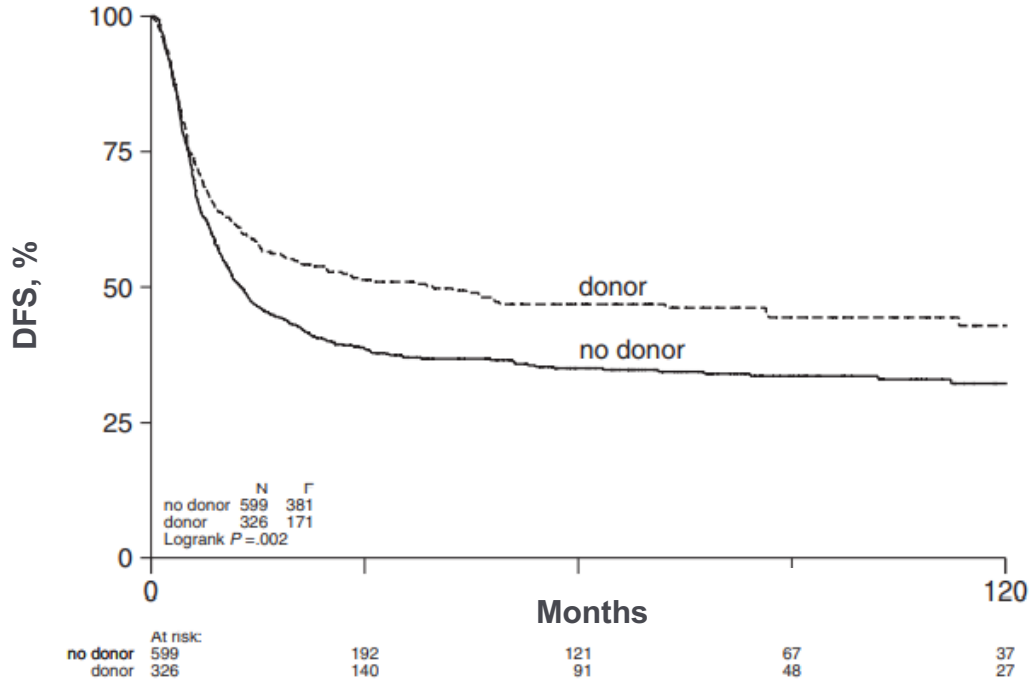
Figure 1. Kaplan-Meier plot of survival of the 100 patients with acute leukemia transplanted in the study by Thomas *et al*. Open circles represent surviving patients. Figure reproduced, with permission, from *Blood*.[1]

They reported median survival of about 4 months with 13 alive in remission 1-4½ years after transplantation (Figure 1). The authors noted subjects in a "*fair clinical condition*" did the best, concluding: "*[M]arrow transplantation should now be undertaken earlier in the management of people with acute leukemia who have an HLA-matched sibling marrow donor.*"

. Thomas ED, Buckner CD, Banaji M, et al. One hundred patients with acute leukemia treated by chemotherapy, total body irradiation, and allogeneic marrow transplantation. Blood. 1977;49(4):511-533.

Where Are We in Allogeneic HCT for Patients With AML?

- **DFS of patients with AML in first CR <u>according to donor</u>**

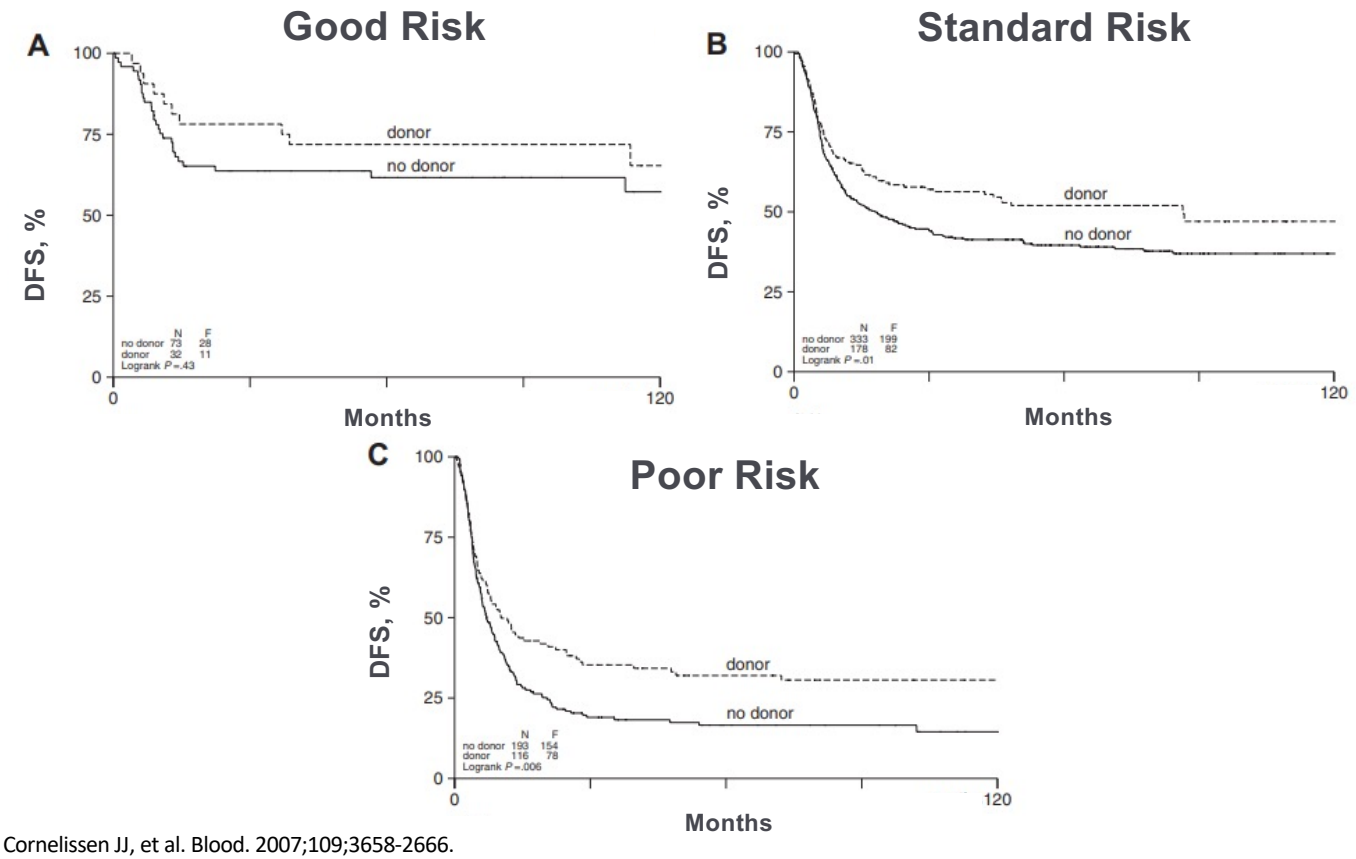


- Lower relapse rate and an increased TRM in the donor group resulted in a significantly better DFS in the donor group than in the no-donor group
- (48% vs 27%; *P* < .001)

- DFS, disease-free survival.
- Cornelissen JJ, et al. Blood. 2007;109;3658-2666.

Where Are We in Allogeneic HCT for Patients With AML?

- **DFS of patients with AML in first CR according to risk category and donor availability**

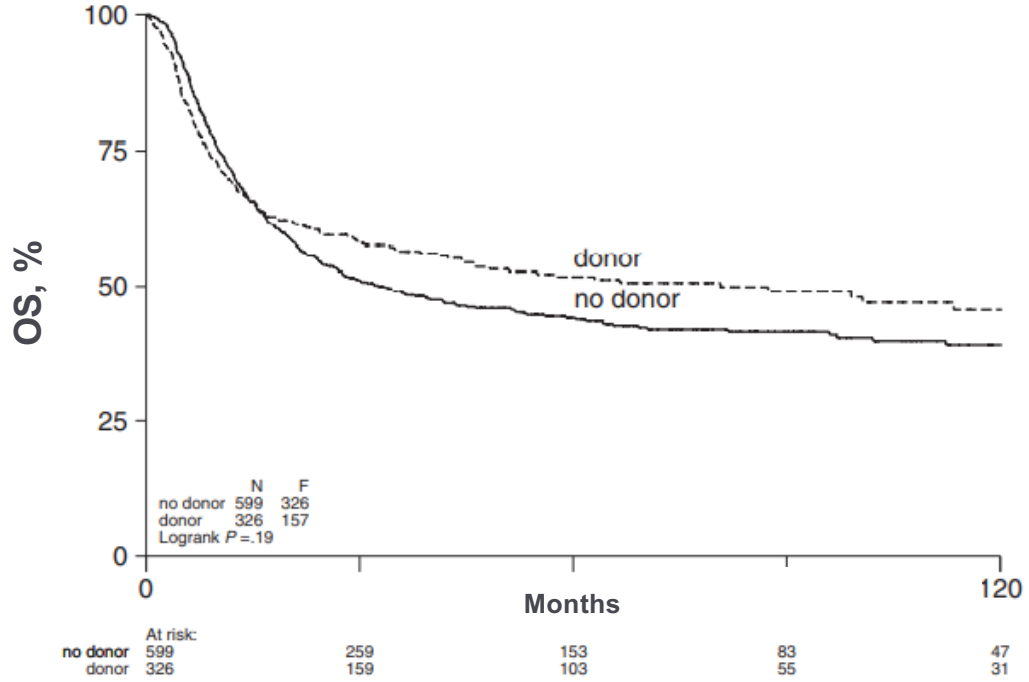


- A DFS improvement was observed in all AML prognostic risk categories but was significant only in intermediate- and poor-risk patients
- (estimated HRs 0.74-0.67)

- Cornelissen JJ, et al. Blood. 2007;109;3658-2666.

Where Are We in Allogeneic HCT for Patients With AML?

- **OS of patients with AML in first CR according to donor availability**



- The improved DFS translated into a better OS
- (54% vs 46%; *P* = .07)

- OS, overall survival.
- Cornelissen JJ, et al. Blood. 2007;109;3658-2666.

ELN Risk Stratification

Risk Group	Genetic Abnormality
Favorable	▪ t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* ▪ inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* ▪ *NPM1*^{mut} without *FLT3*-ITD ~~or *FLT3*-ITD^{low}*~~ ▪ Biallelic mutated *CEBPA*
Intermediate	▪ *NPM1*^{mut} and *FLT3*-ITD^{high} ▪ Wild-type *NPM1* without *FLT3*-ITD or *FLT3*-ITD^{low}* (without adverse-risk genetic lesions) ▪ t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* ▪ Cytogenetic abnormalities not classified as favorable/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)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM(EVI1)* ▪ –5 or del(5q); –7; –17/abn(17p) ▪ Complex karyotype (≥ 3 unrelated chromosomal abnormalities) ▪ Monosomal karyotype ▪ ~~Wild-type *NPM1* and *FLT3*-ITD^{high}*~~ ▪ *RUNX1*^{mut}, *ASXL1*^{mut}, or *TP53*^{mut}

Risk Group	Genetic Abnormality
Favorable	▪ t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* ▪ inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* ▪ *NPM1*^{mut} without *FLT3*-ITD ▪ **bZIP in-frame mutated *CEBPA***
Intermediate	▪ **Mutated *NPM1* and *FLT3*-ITD** ▪ **Wild-type *NPM1* with *FLT3*-ITD** ▪ t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* ▪ Cytogenetic abnormalities not classified as favorable/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* ▪ ***t(8;16)(p11;p13)/KAT6A::CREBBP*** ▪ inv(3)(q21.3;q26.2) or t(3;3)(q21.3;q26.2); *GATA2*, *MECOM(EVI1)* ▪ ***t(3q26.2;v)/MECOM(EVI1)-rearranged*** ▪ –5 or del(5q); –7; –17/abn(17p) ▪ Complex karyotype (≥ 3 unrelated chromosomal abnormalities), monosomal karyotype ▪ *Mutated ASXL1*, ***BCOR, EZH2,*** *RUNX1*, ***SF3B1, SRSF2, STAG2, U2AF1,*** **or *ZRSR2*** ▪ Mutated *TP53*

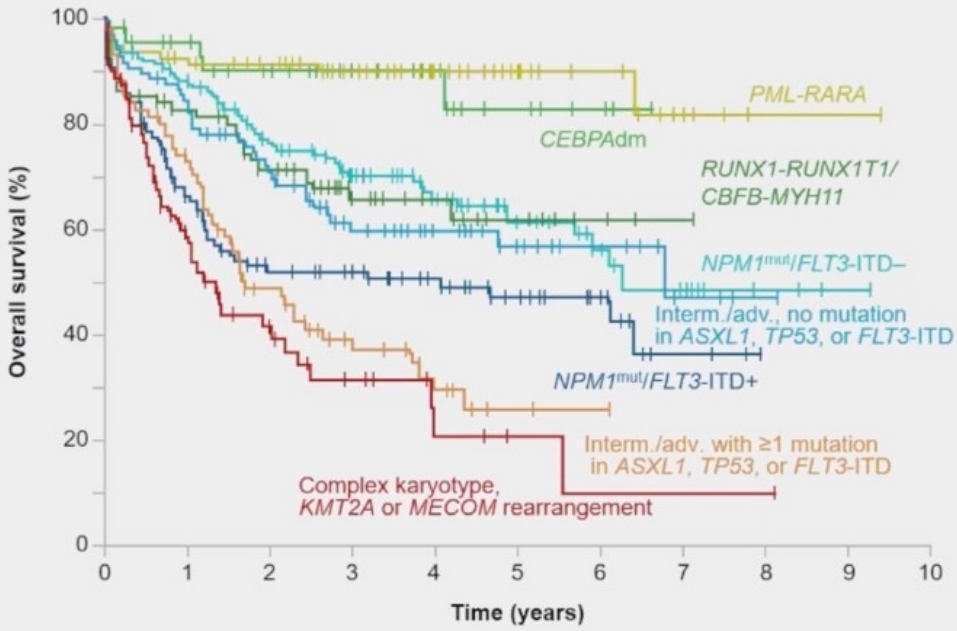
Döhner H, et al. Blood. 2017;129:424-447; Döhner H, et al. Blood. 2022;140:1345-1377.

AML classification highlights the differential outcomes with standard intensive chemotherapy : AML is not one disease!

ELN 2022[1]

Favorable	• t(8;21)(q22;q22.1)/*RUNX1::RUNX1T1* • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB::MYH11* • Mut *NPM1* w/o *FLT3*-ITD • bZIP in-frame mut *CEBPA*
Intermediate	• Mut *NPM1* with ***FLT3*-ITD** • Wt *NPM1* with ***FLT3*-ITD** • t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A* • Cytogenetic and/or molecular
Adverse	• t(6;9)(p23.3;q34.1)/*DEK::NUP214* • t(v;11q23.3)/*KMT2A*-rearr • t(9;22)(q34.1;q11.2)/*BCR::ABL1* • t(8;16)(p11.2;p13.3)/*KAT6A::CREBBP* • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/*GATA2,MECOM(EVI1)* • t(3q26.2;v)/*MECOM(EVI1)*-rearr • −5 or del(5q); −7; −17/abn(17p) • Complex/monosomal karyotype • Mut *ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1,* or *ZRSR2* • Mut *TP53*

OS in patients aged <60 years with *de novo* AML (N=867)[2]

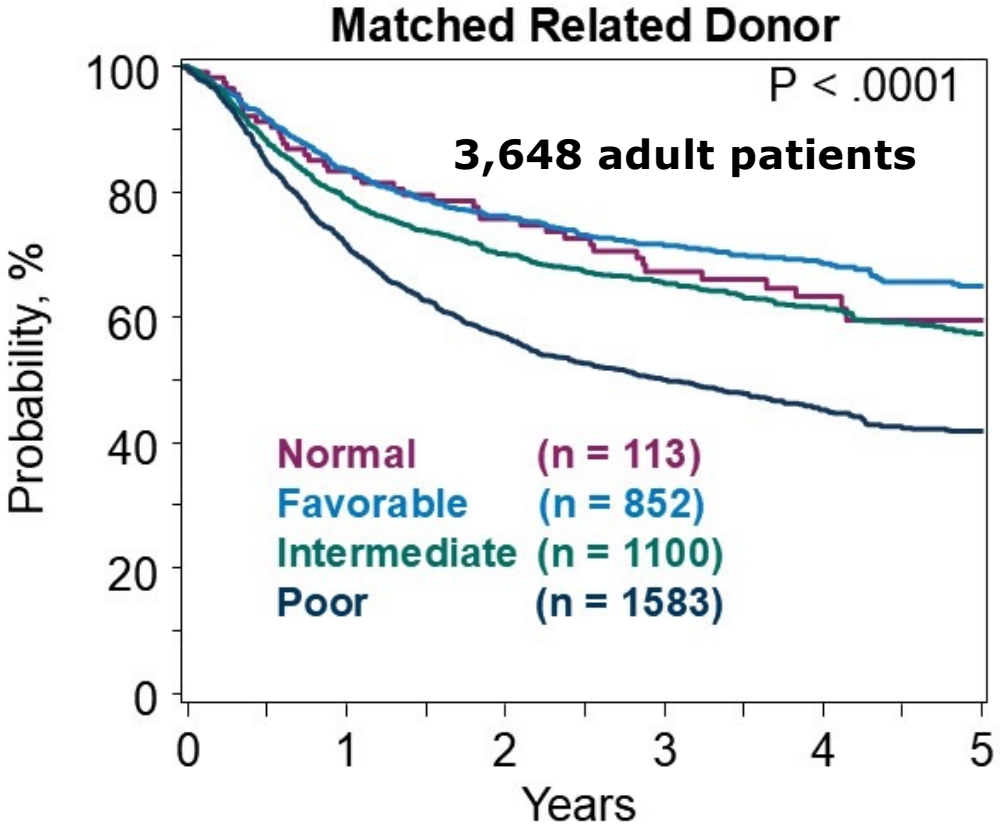


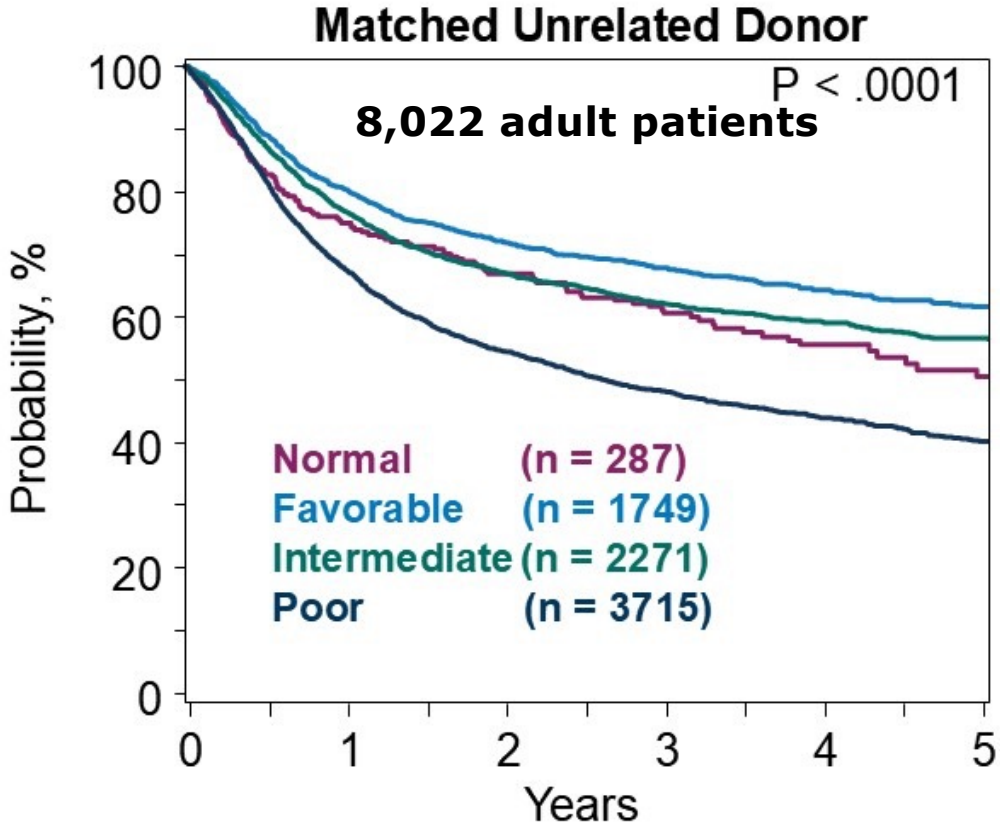
*** This population of patients had been treated with standard intensive chemotherapy.**

ELN, European LeukemiaNet

1. Döhner H, *et al. Blood* 2022; **144:**1345–1377; 2. Adapted from Haferlach C, *et al. Blood* 2016; **128:**286.

Survival after Allogeneic HCTs for Acute Myeloid Leukemia, Using Matched Donors in the US, 2017-2022, Adults, by ELN Cytogenetic Risk Score





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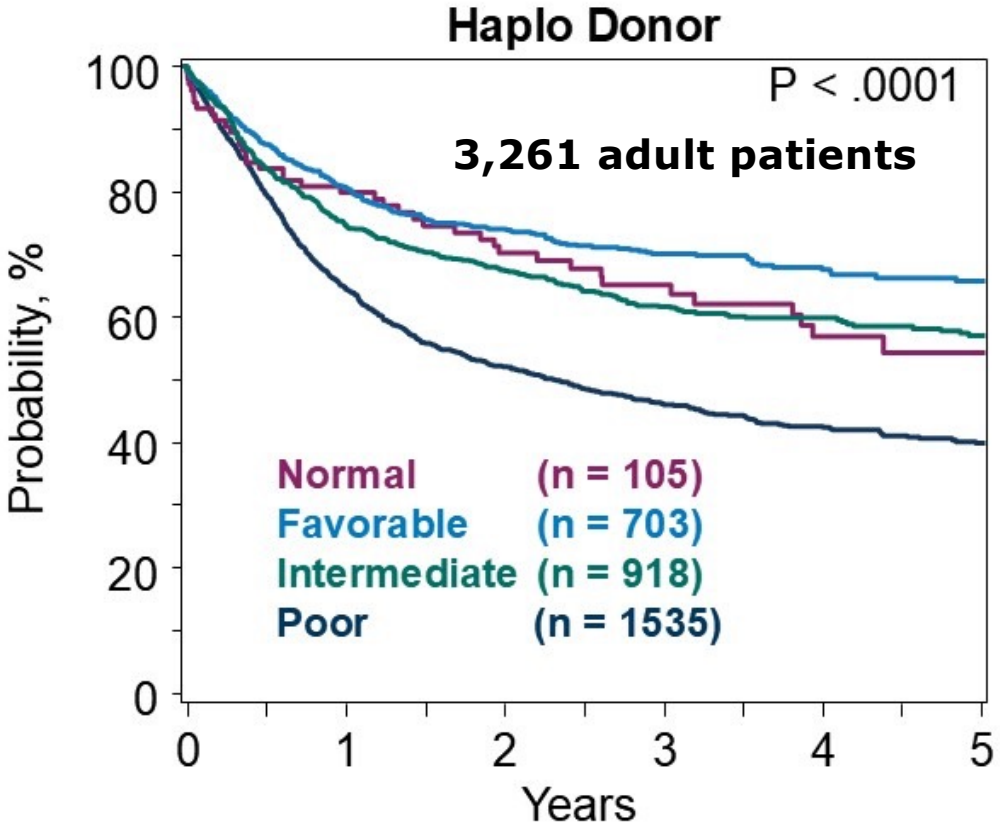
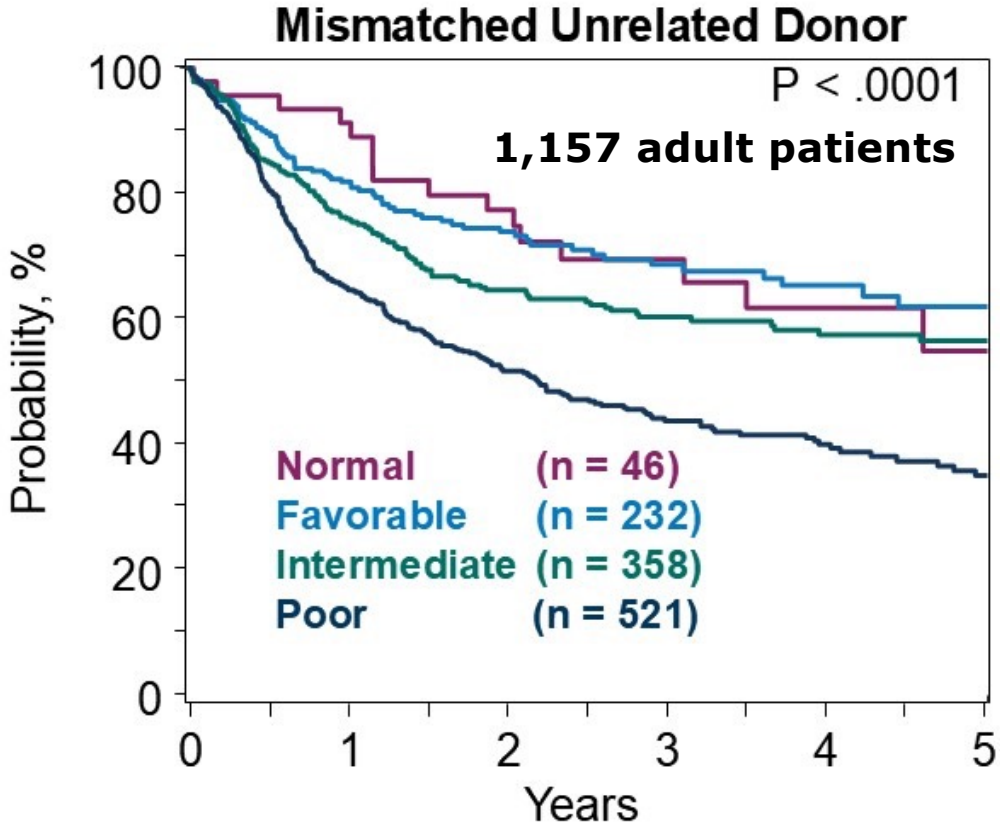
Abbreviations: ELN, European LeukemiaNet; HCT, hematopoietic cell transplantation.

Survival after Allogeneic HCTs for Acute Myeloid Leukemia, Using Mismatched Donors in the US, 2017-2022, Adults, by ELN Cytogenetic Risk Score





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Abbreviations: ELN, European LeukemiaNet; haplo, haploidentical; HCT, hematopoietic cell transplantation.

PERSPECTIVE OPEN

ACUTE MYELOID LEUKEMIA

A *modest proposal* to the transplant publik to prevent harm to people with acute myeloid leukaemia in 1st complete remission cured by chemotherapy

R. P. Gale[1]✉, G. L. Phillips[2] and H. M. Lazarus[3]

Leukemia (2024) 38:1663–1666; https://doi.org/10.1038/s41375-024-02214-w

Transplants cure some people with acute myeloid leukaemia in 1st complete remission. However, some of these people were already cured by chemotherapy. In these persons a transplant cannot be of benefit but has the potential to be harmful.

who were not. The usual approach is to consider co-variates *at diagnosis* correlated with failing chemotherapy. There are many risk classification models used for this such as the European LeukaemiaNet (ELN), National Comprehensive Cancer Network (NCCN) and Medical Research Council (MRC) risk classifications [2–4]. However, these models are only modestly accurate with

But there are other important limitations. 1st, these models are neither dynamic nor representative. They are based predominately on data from persons < 60 years receiving cytarabine and daunorubicin induction therapy followed by high-dose cytarabine consolidation. Several fail to account for recent developments such as *FLT3*-inhibitors or venetoclax/azacitidine regimens. But more importantly, they lose accuracy when applied to someone in 1st complete remission for a few months when a transplant is being considered. Much of the prediction accuracy of these

Our *modest proposal* differs from recommendations from many clinical practice guidelines and expert consensus panels. For example, Summing up, the 2022 ELN AML recommendations state: *Allogeneic HCT should be considered when the relapse probability without the procedure is predicted to be 35 to 40%*. To support this recommendation the ELN authours cite a 2016 article in *BLOOD* [24] However, the article contains no conceptual-, scientific-, statistical or evidence-based data supporting this recommendation. There are other relevant publications [25].

Hematopoietic stem cell transplantation for patients with AML in first complete remission

Jan J. Cornelissen[1] and Didier Blaise[2]

BLOOD, 7 JANUARY 2016 • VOLUME 127, NUMBER

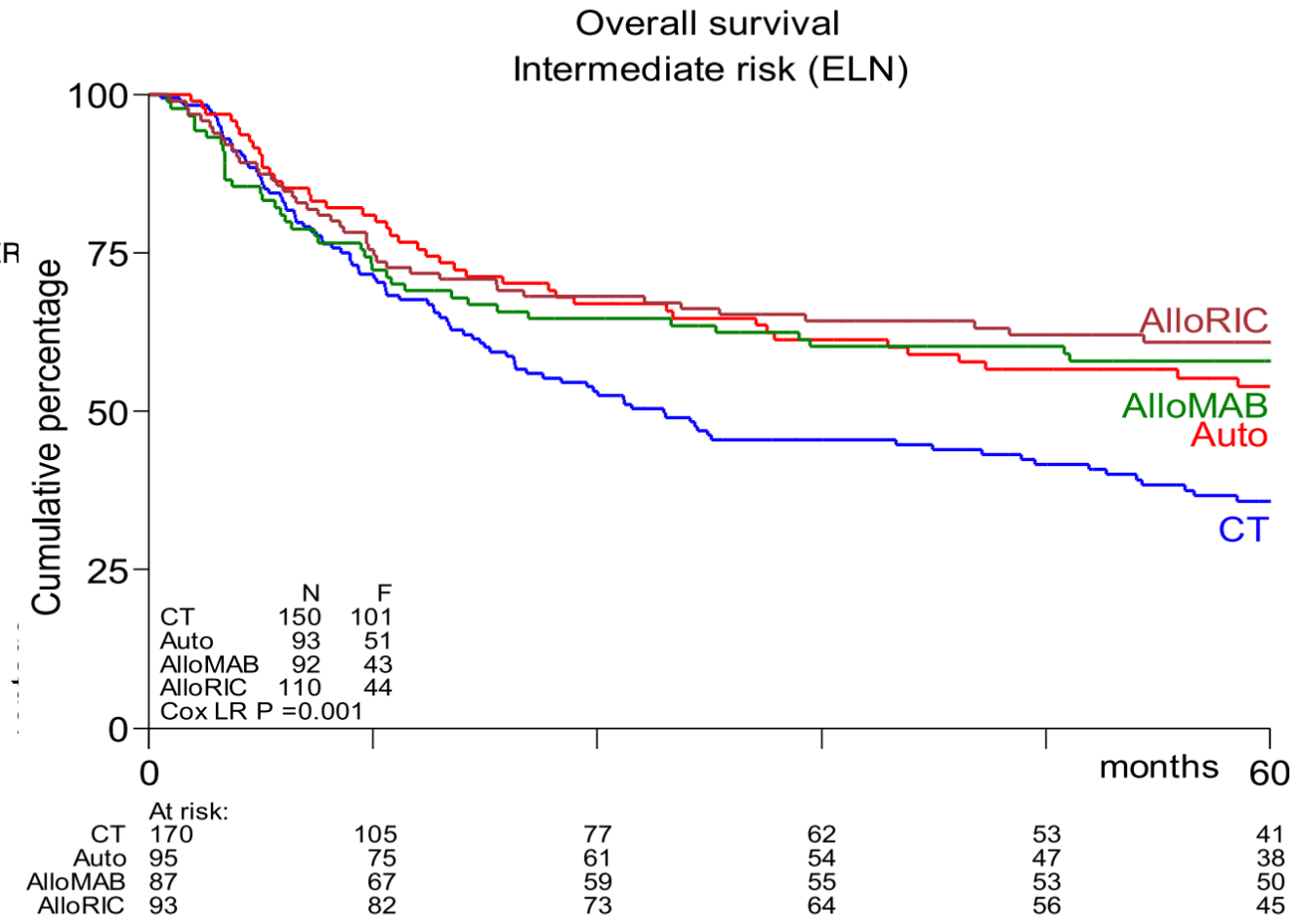
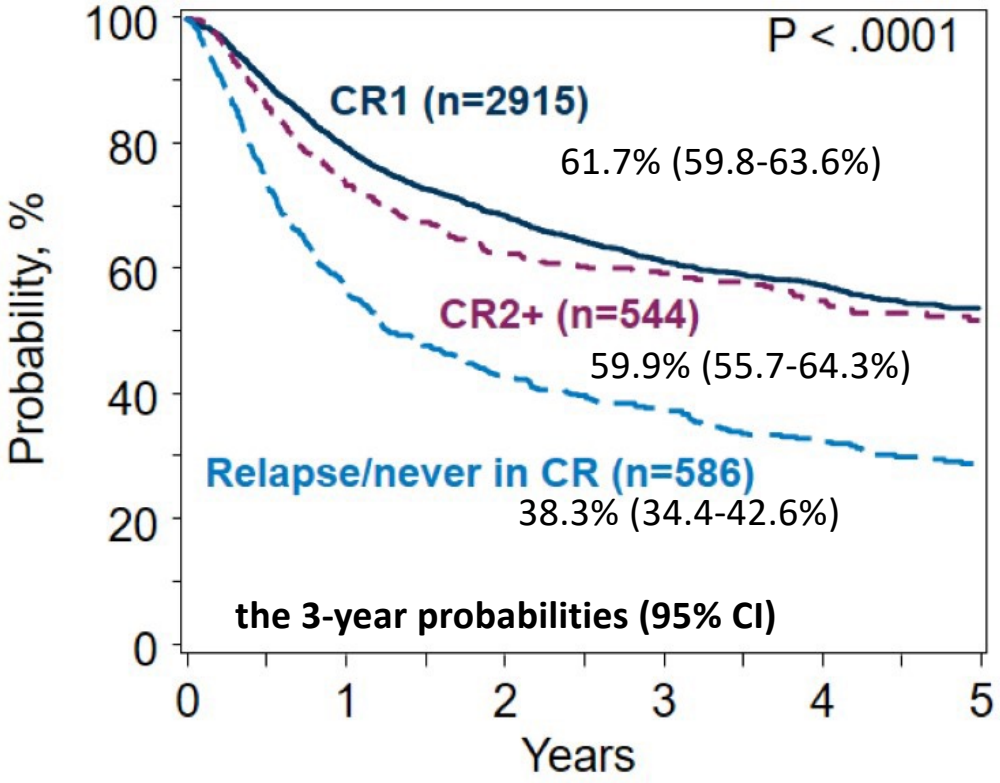


Figure 1. Kaplan-Meier estimates of overall survival of AML intermediate-risk patients in CR1, age 40 to 60 years, by type of postremission therapy (updated results from Cornelissen et al[53]). HSCT recipients showed significantly better OS than patients receiving chemotherapeutic postremission therapy (P = .001). AlloMAB, myeloablative alloHSCT; AlloRIC, reduced intensity conditioning alloHSCT; Auto, autologous HSCT; CT, chemotherapy; ELN, European Leukemia Net. F, female; LR, logistic regression.

Survival after Allogeneic HCTs for Acute Myeloid Leukemia, Using Matched Donors in the US, 2016-2021, Adults

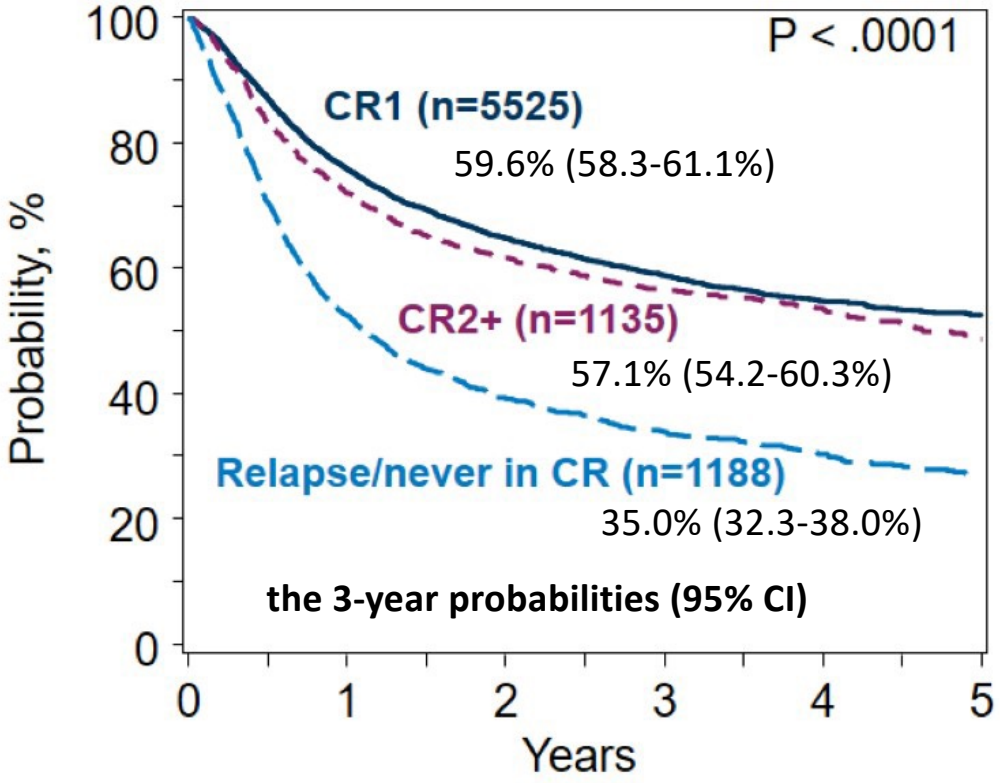
4,045 adult patients

Matched Related Donor



7,848 adult patients

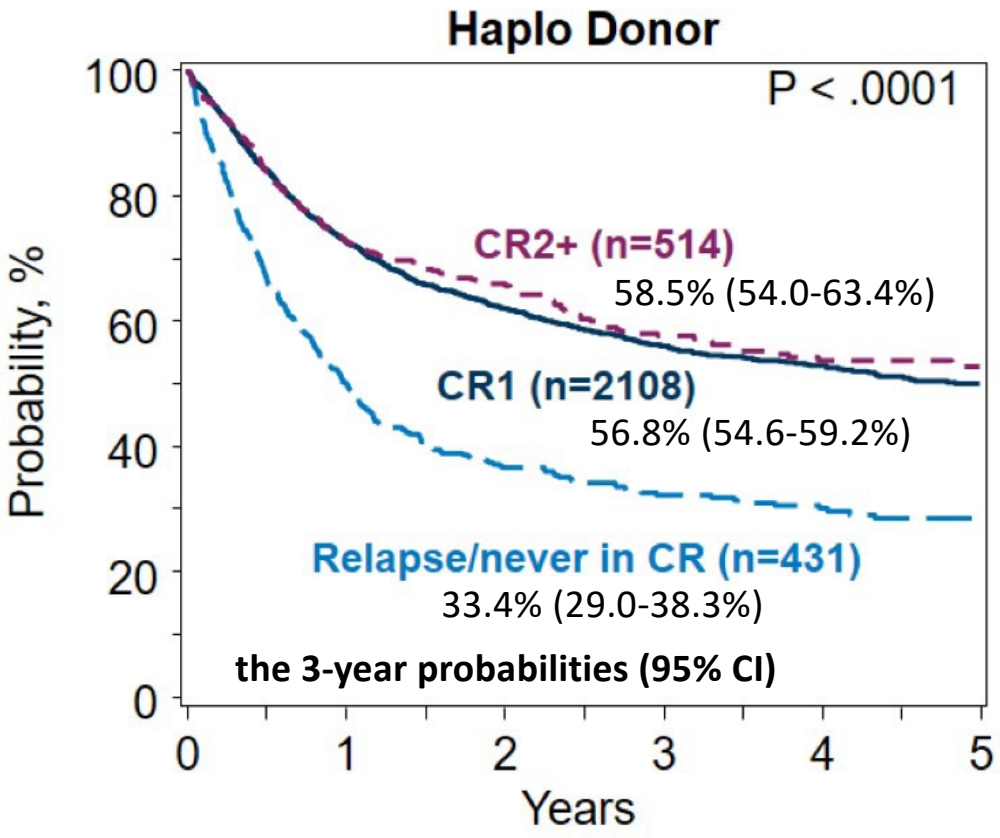
Matched Unrelated Donor

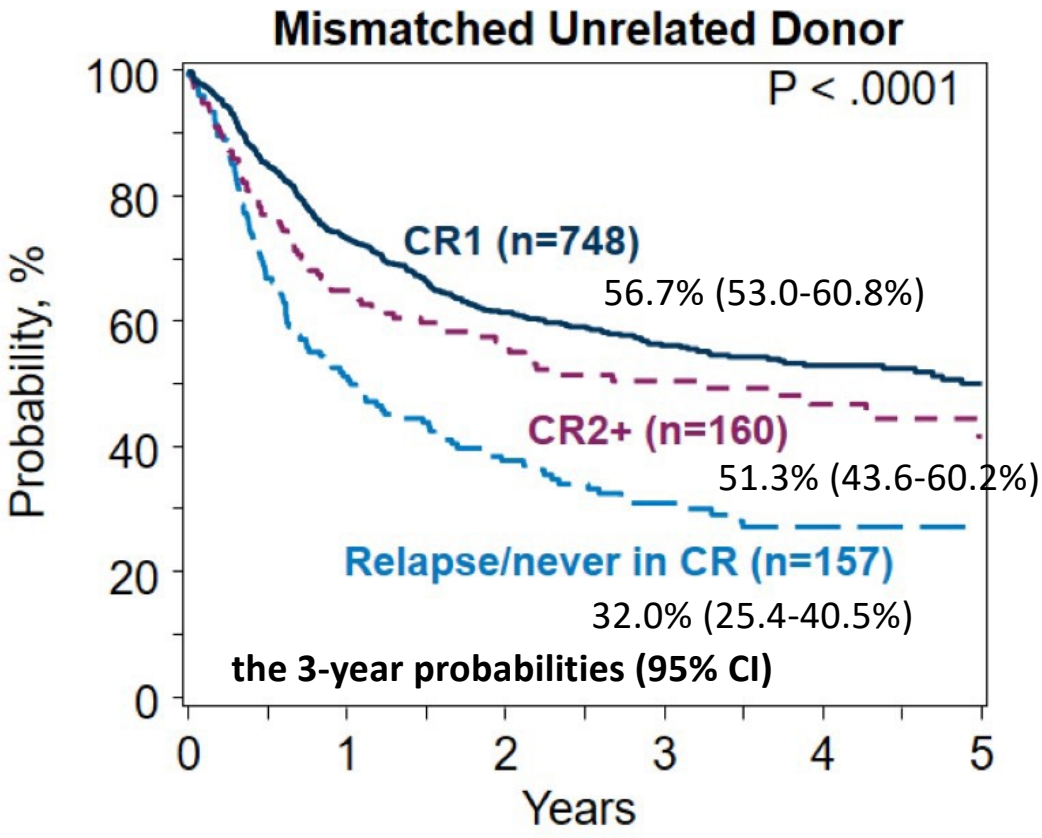


CIBMTR
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Abbreviations: CR, complete remission; CR1, first complete remission; CR2+, second or greater complete remission.

Survival after Allogeneic HCTs for Acute Myeloid Leukemia, Using Mismatched Donors in the US, 2016-2021, Adults



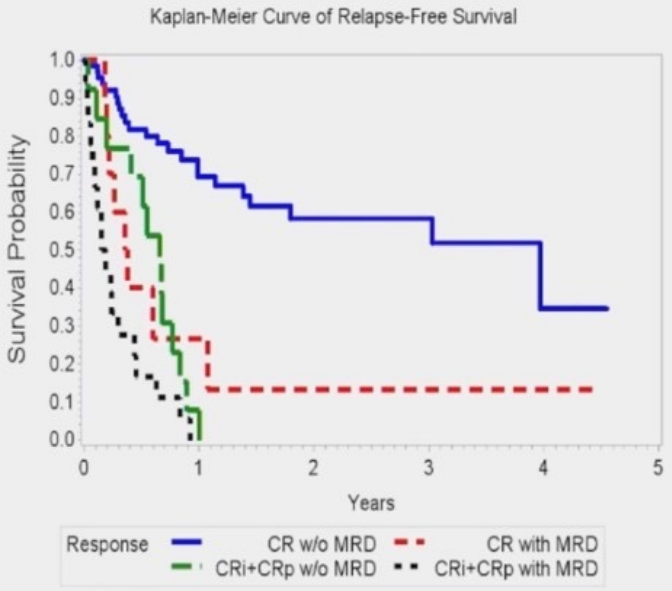


CIBMTR
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

Abbreviations: CR, complete remission; CR1, first complete remission; CR2+, second or greater complete remission; haplo, ≥ 2 HLA antigen mismatch; mismatched unrelated donor, ≤7/8 HLA allele match, excluding umbilical cord blood.

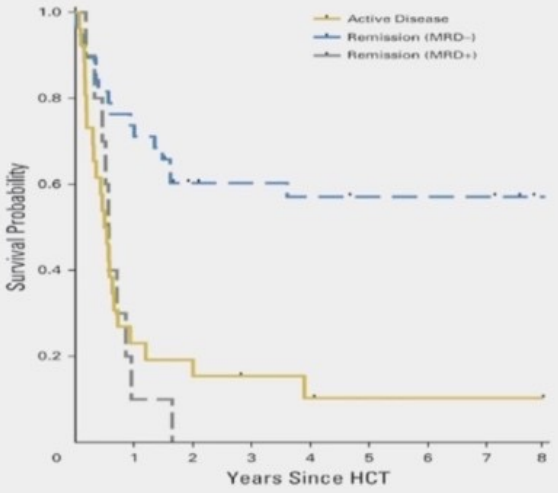
MRD associated with poor outcome after chemo or BMT

Chemotherapy



[1]*Chen et al. JCO 33:1258, 2015*

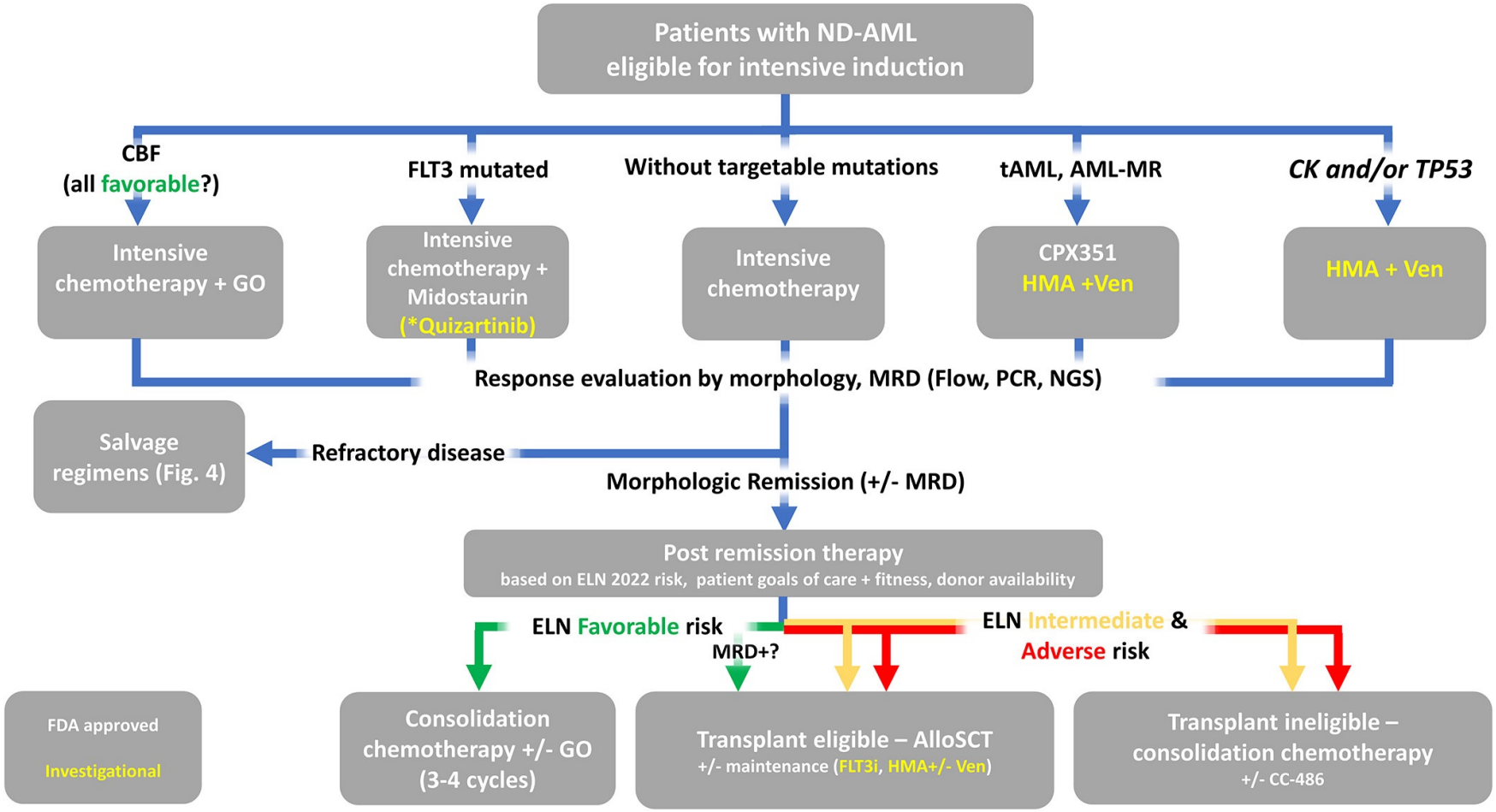
Transplant



Hourigan *et al.*, JCO 2016

Radich J, ASH 2024 Educational program

Acute myeloid leukemia: update on diagnosis, risk-stratification, and management



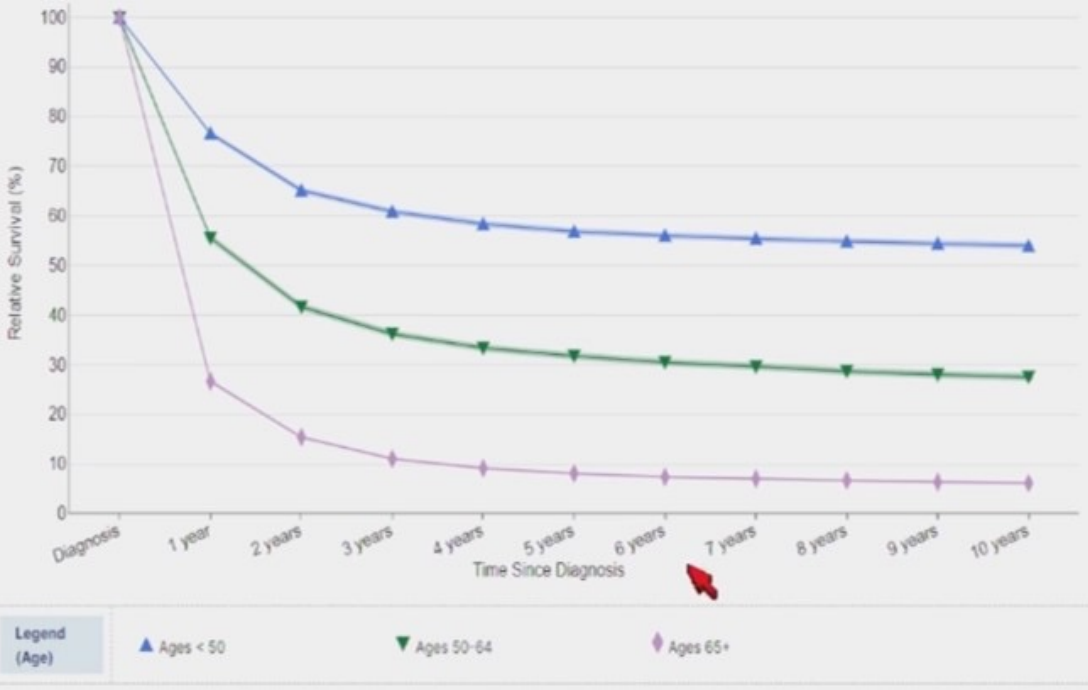
American J Hematol, Volume: 98, Issue: 3, Pages: 502-526, First published: 02 January 2023, DOI: (10.1002/ajh.26822)

AML Epidemiology

Median age at diagnosis:
69 years

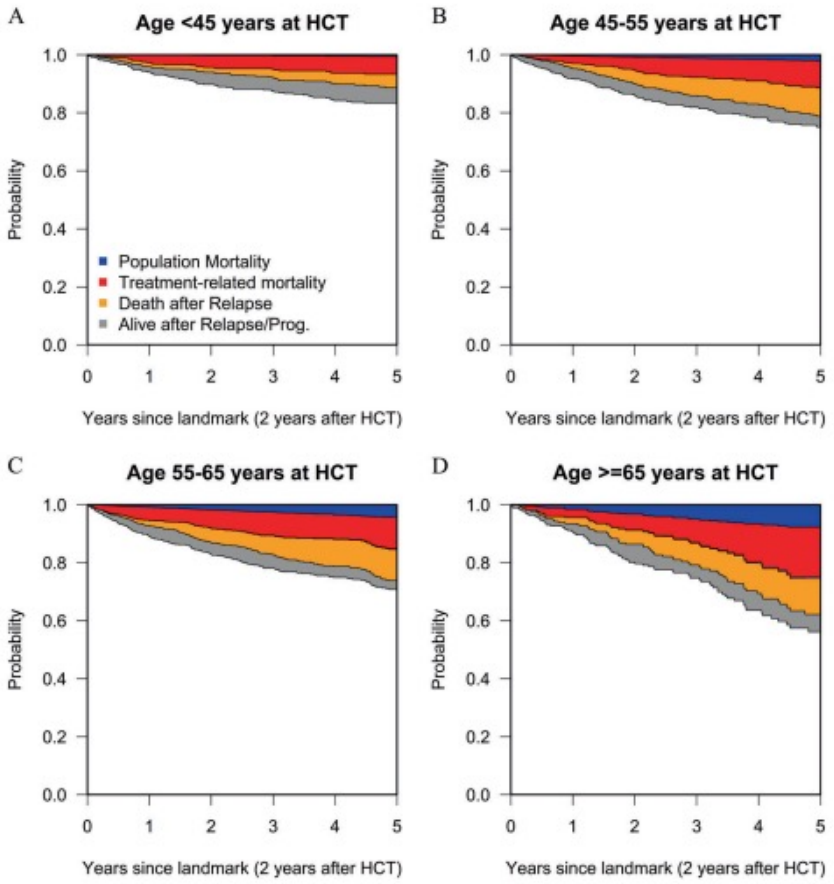
Incidence by Age Group

Survival by Age Group



SEER 2024 data
https://seer.cancer.gov/statfacts/html

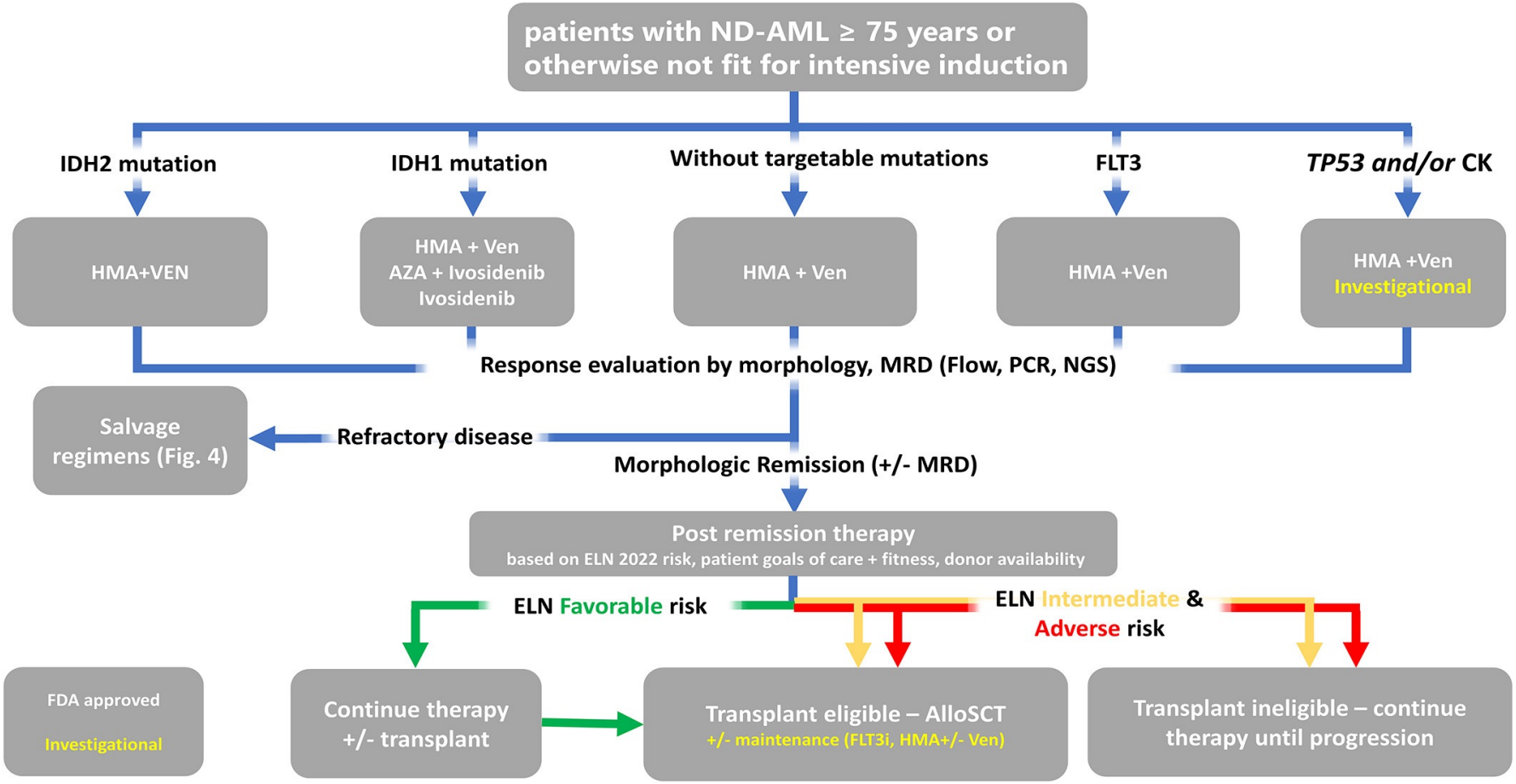
Mortality by Age for MDS and sAML



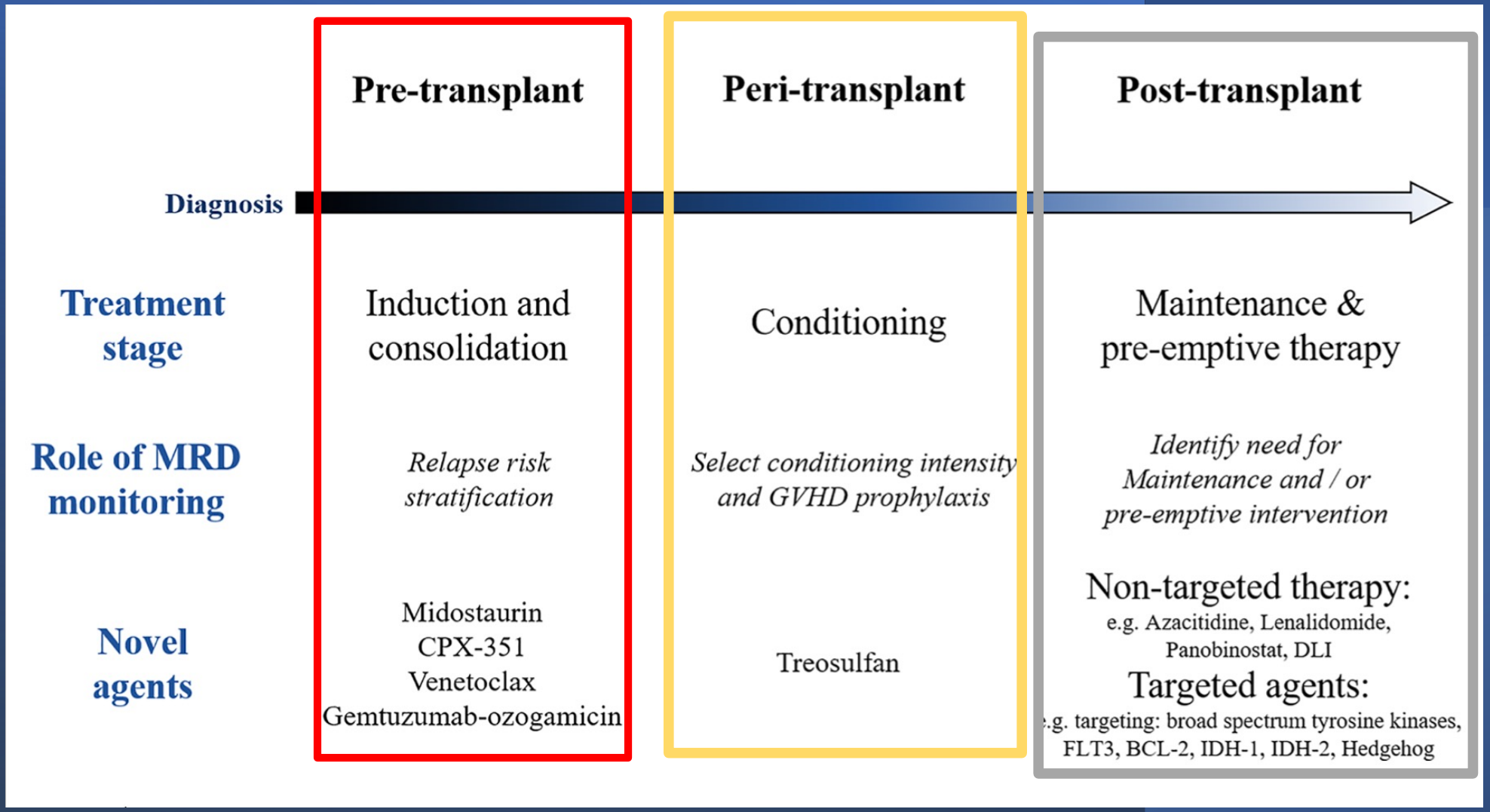
- N = 6434 who received a first allogeneic HCT
- For patients **< 45 y** at allogeneic HCT, the estimated 5-y population mortality was **0.5%**, compared with **8%** for patients who were **≥ 65 y** at transplantation
- Estimated 5-y TRM rates of these populations were 6% and 17% for these age groups, respectively

Schetelig J, et al. Leukemia. 2019;33:686-695.

Acute myeloid leukemia: update on diagnosis, risk-stratification, and management



American J Hematol, Volume: 98, Issue: 3, Pages: 502-526, First published: 02 January 2023, DOI: (10.1002/ajh.26822)



Loke J, Buka R and Craddock C (2021) Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia: Who, When, and How? Front. Immunol.

What defines an UNFIT "Transplant Ineligible" patient?

- Age ≥ 75*ish*
- ECOG PS ≥2
- Underlying organ dysfunction
  - Renal failure, liver disease, cardiomyopathy
- *Prior (especially treated) antecedent hematologic disorders?*
- *Unfavorable / high risk genetics?*
  - *Especially pts with TP53 mutations*
- *MRD positivity?*

Di Nardo C, Ash educational program, 2024

Transplant in ALL: who, when, and how?

Table 3. **Summary of recommendations for transplant consolidation in adult ALL**

Indication for transplant*	
**Early referral of high-risk patients for prompt donor search and personalized/collaborative decision-making is critical*	
Immunophenotype	Early T-cell precursor
Karyotype	Complex karyotype; low hypodiploid (32–39 chromosomes); near haploid (24–31 chromosomes)
Unfavorable molecular genetic profile	*IKZF1; BCR::ABL1-like* (Ph-like); *KMT2A* rearranged; *MEF2D* rearranged; *MYC* rearranged; *TP53*; *iAMP21*
Slow response to therapy	Time to morphologic CR >4 weeks
	Persistent MRD post-induction using flow or NGS
No added benefit to transplant consolidation	
BCR::ABL1 rearranged (Ph+) • With incorporation of TKI therapy, studies suggest no benefit to HCT in patients who develop prompt, deep response AND have no evidence for unfavorable molecular features.	
Absence of high-risk molecular genetic features AND prompt, deep response to induction therapy.	
Role of transplant consolidation not clear	
Consolidation post-CAR-T therapy • Patients with very high risk features and patients with evidence for MRD following CAR-T likely benefit from HCT consolidation; toxicity from extensive prior therapy may result in adverse survival in other patients.	

How I treat newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia

Diagnostics/evaluation	**Patient:** Age, fitness/frailty, cardiovascular risk factors, support **Disease:** *Genetic risk:* cytogenetic, molecular (*IKZF1*; *IKZF1* plus) *MRD monitoring:* RT-PCR p190 vs p210; NGS or PCR for clonal tracking
AlloHCT, in CR1	**Favoring yes** 1. High-risk genetic features (chromosomes: complex, "double" Ph; *IKZF1* plus) 2. No achievement of CMR by 3 months (with TKI+/− chemotherapy) 3. Fit, appropriate donor 4. No blinatumomab available or not tolerated **Favoring no** 1. No high-risk genetic features 2. Achievement of CMR by 3 months (with TKI+/− chemotherapy) 3. Blinatumomab **Unknown** 1. Poor response to TKI+/− chemo but CMR with blinatumomab 2. High-risk genetics but optimal MRD response

Marlise R. Luskin - Hematology 2024 | ASH Education Program

Impact of pre-transplantation minimal residual disease on the outcomeof Allogeneic hematopoietic stem cell transplantation for ALL

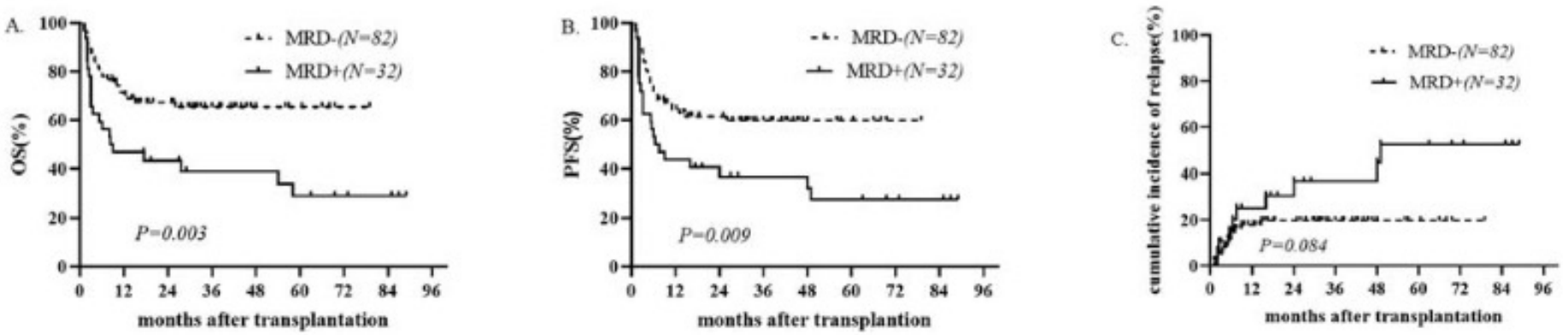
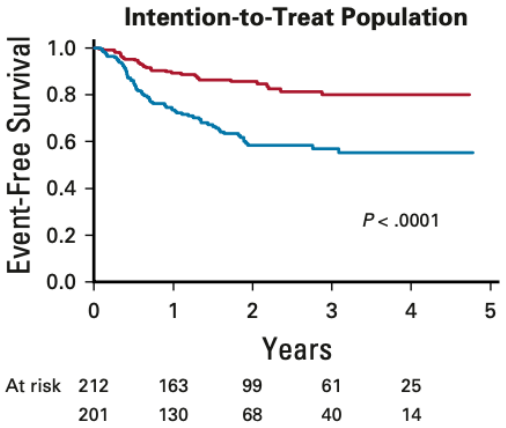


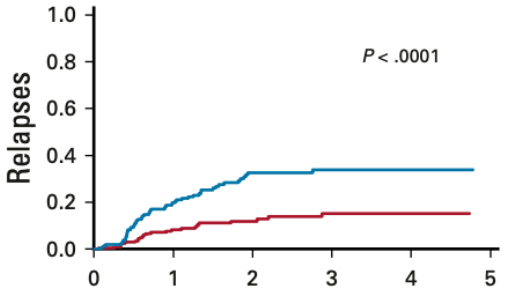
Figure 1. Kaplan–Meier curves of (A) overall survival (OS), (B) progression-free survival (PFS), (C) cumulative incidence of relapse between the MRD+ group and MRD– group.

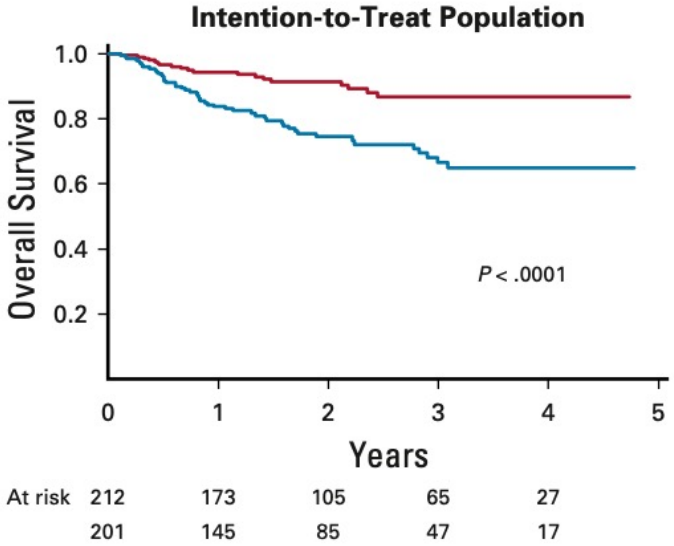
HEMATOLOGY 2021

ALL: TBI- vs non-TBI-based conditioning



	Patients	Eval.	Events	2-year EFS
TBI	212	209	31	0.86 (0.79-0.90)
CHC	201	200	72	0.58 (0.50-0.66)





	Patients	Eval.	Deaths	2-year OS
TBI	212	209	19	0.91 (0.86-0.95)
CHC	201	200	49	0.75 (0.67-0.81)

Peters C, Dalle JH, LocatelliF, et al. *J Clin Oncol*. 2021;39(4):295-307.

Summary:

•Allo-SCT offers a potentially curative option for patients with AML, especially for those with high-risk or relapsed disease.

•In ALL, MRD has emerged as a powerful predictor of relapse irrespective of treatment strategy, challenging the necessity of transplant in MRD-negative patients. Immunotherapies and targeted treatments are increasingly integrated into both initial and relapsed treatment protocols yielding deep remis- sion and allowing for successful transplant in patients with a history of advanced disease.

•While it can be highly effective due to the GVL effect, it comes with significant risks, including GVHD and infection.

•Advances in GVHD prevention, conditioning regimens, and post-transplant therapies are improving outcomes, but the decision to proceed with allogeneic HSCT must be carefully individualized based on the patient's overall health, disease risk, and available donor options.

•.Expanded donor options, particularly haploidentical transplantation coupled with reduced intensity conditioning, have extended the applicability of allo-HCT to a broader range of patients.