Il trapianto allogenico integrato nella strategia terapeutica delle malattie ematologiche

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Sistema Socio Sanitario
Regione Lombardia
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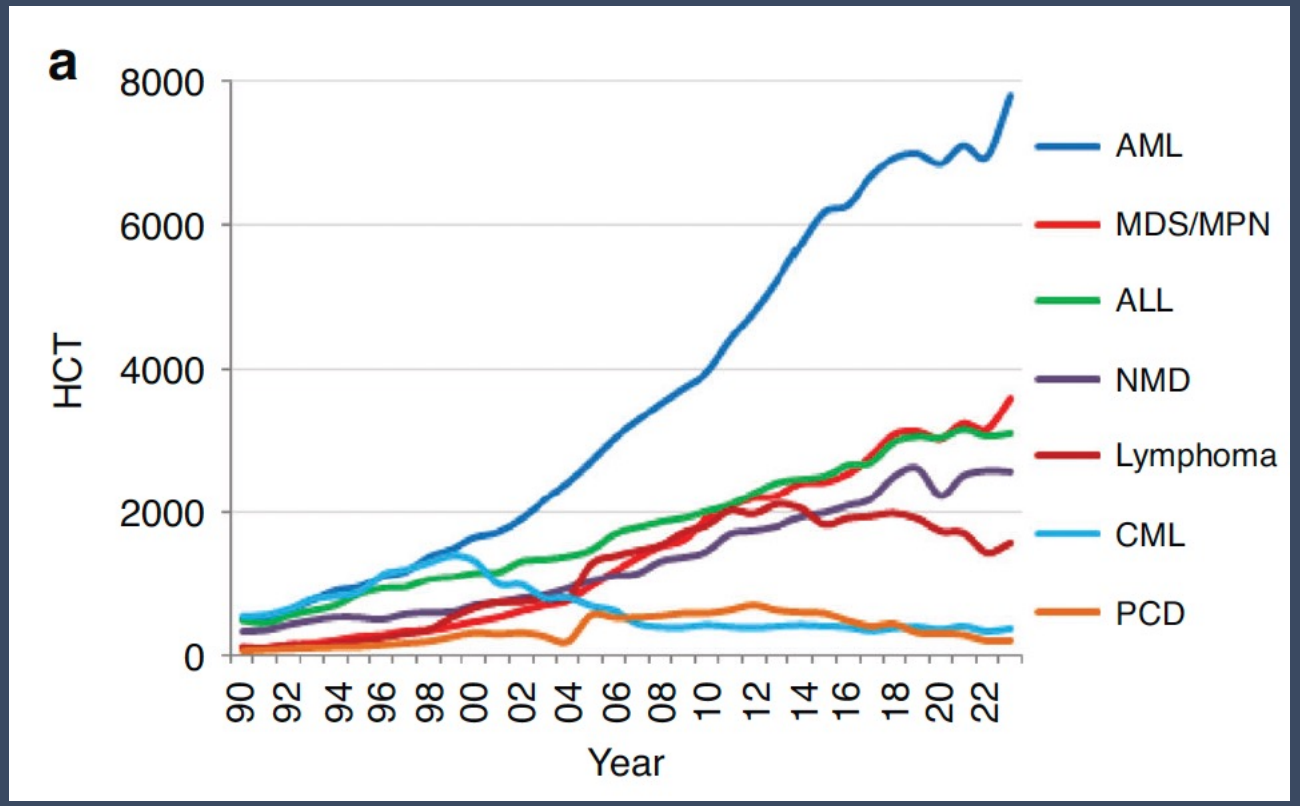
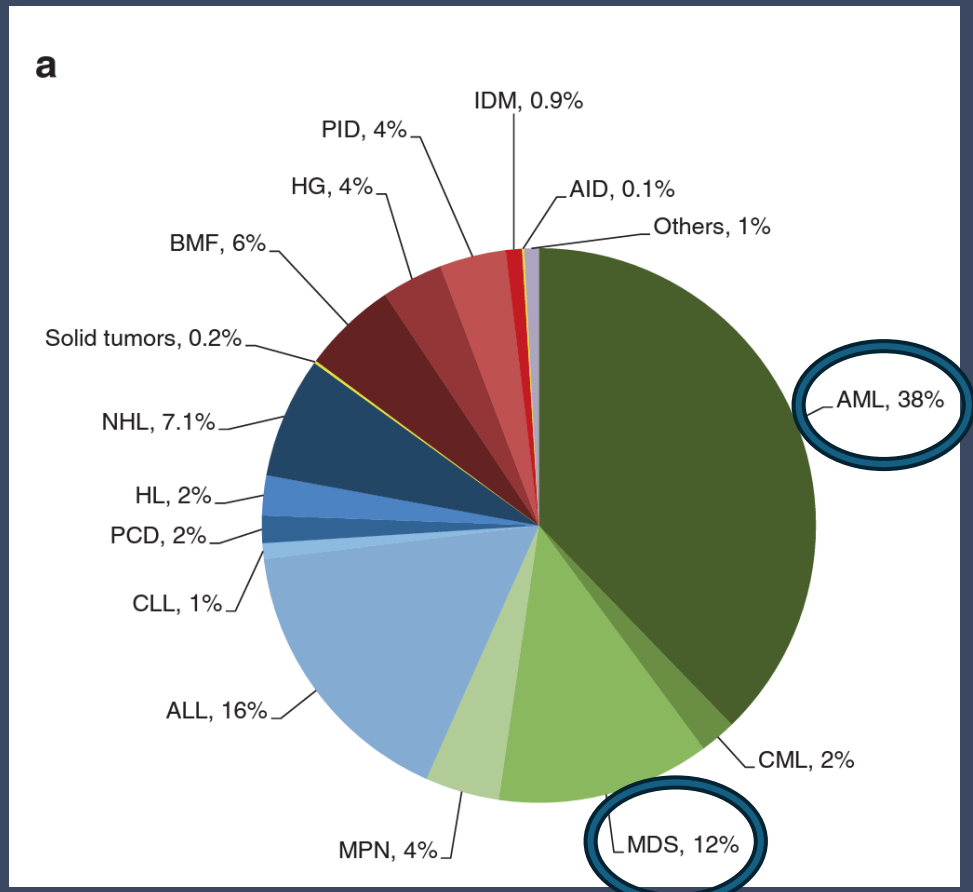
Unità di Malattie del Sangue e Trapianto Midollo Osseo - Programma Terapie Cellulari e Ricerca in Ematologia
Unit of Blood Diseases and Bone Marrow Transplantation - Cell Therapies and Hematology Research Program

Disclosures

	Jazz Pharmaceuticals	Pfizer	Mallinckrodt/ Therakos	Sanofi	Alexion	Novartis	Medac Pharma
Speaking	X	X	X	X	X		X
Research grant			X	X			
Advisory board		X		X	X	X	
Travel Grant	X			X			X

TRENDS IN TRANSPLANT PRACTICE IN EUROPE





Passweg JR et al Hematopoietic cell transplantation and cellular therapy survey of the EBMT: monitoring of activities and trends over 30 years. Bone Marrow Transplant. 2021 Jul;56(7):1651-1664.

Passweg JR et al The 2023 EBMT report on hematopoietic cell transplantation and cellular therapies. Increased use of allogeneic HCT for myeloid malignancies and of CAR-T at the expense of autologous HCT. Bone Marrow Transplant. 2025 Apr;60(4):519-528.

ALLOHSCT IN ELDERLY PATIENTS – CIBMTR

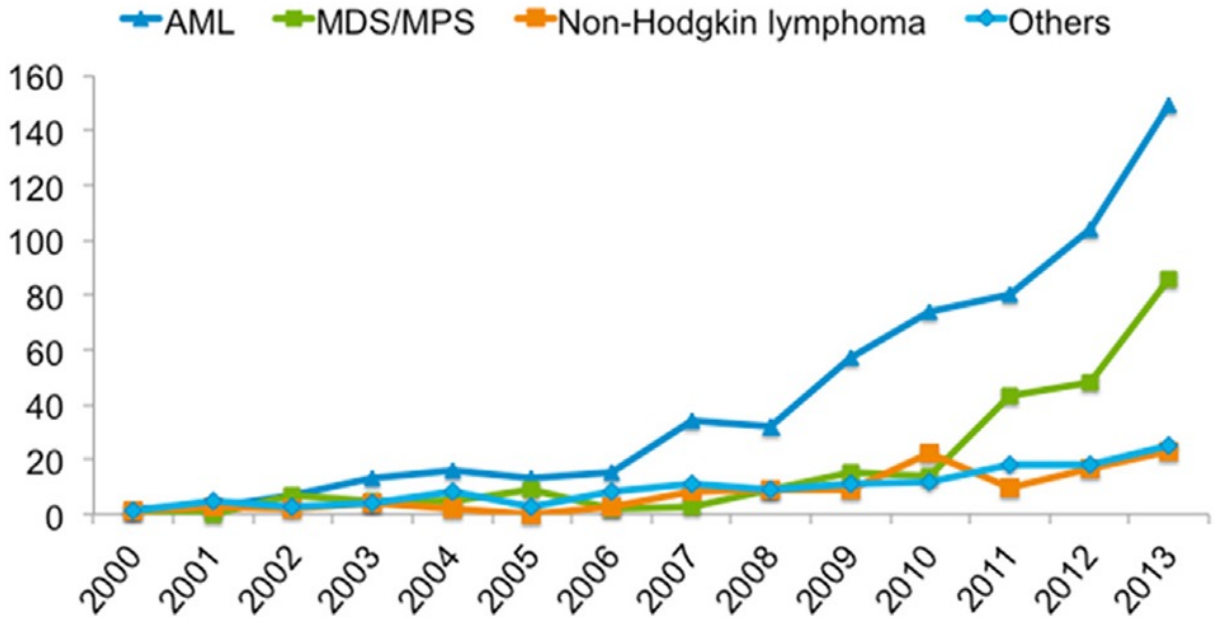


Figure 1. Absolute number of allogeneic transplants in recipients 70 years and older from 2000 to 2013 reported to the CIBMTR by disease category.

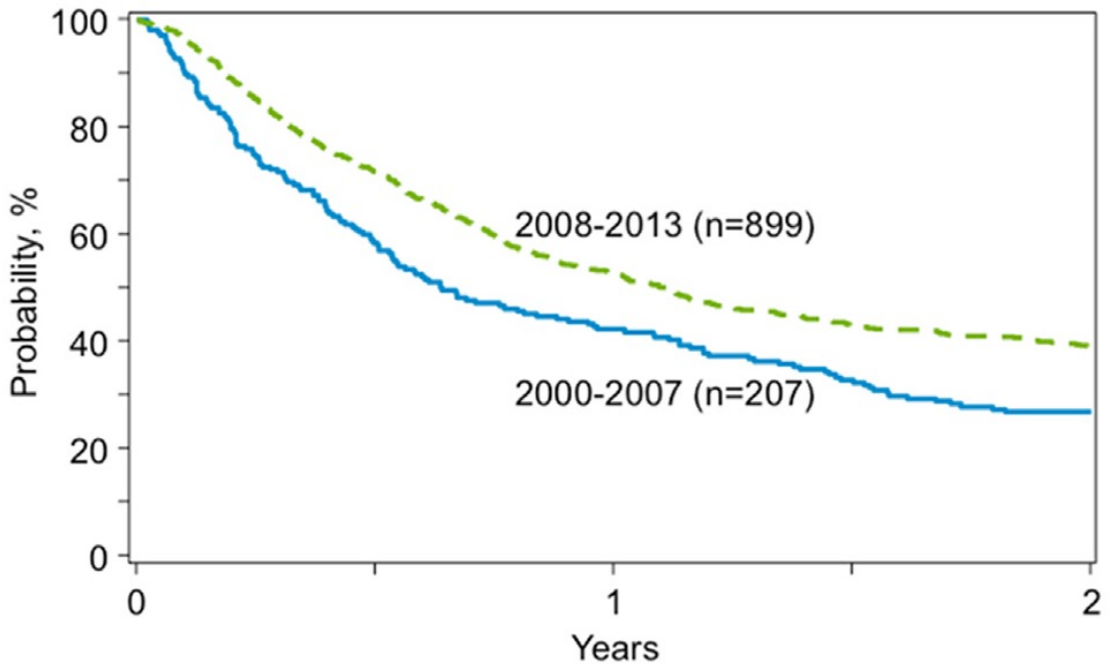
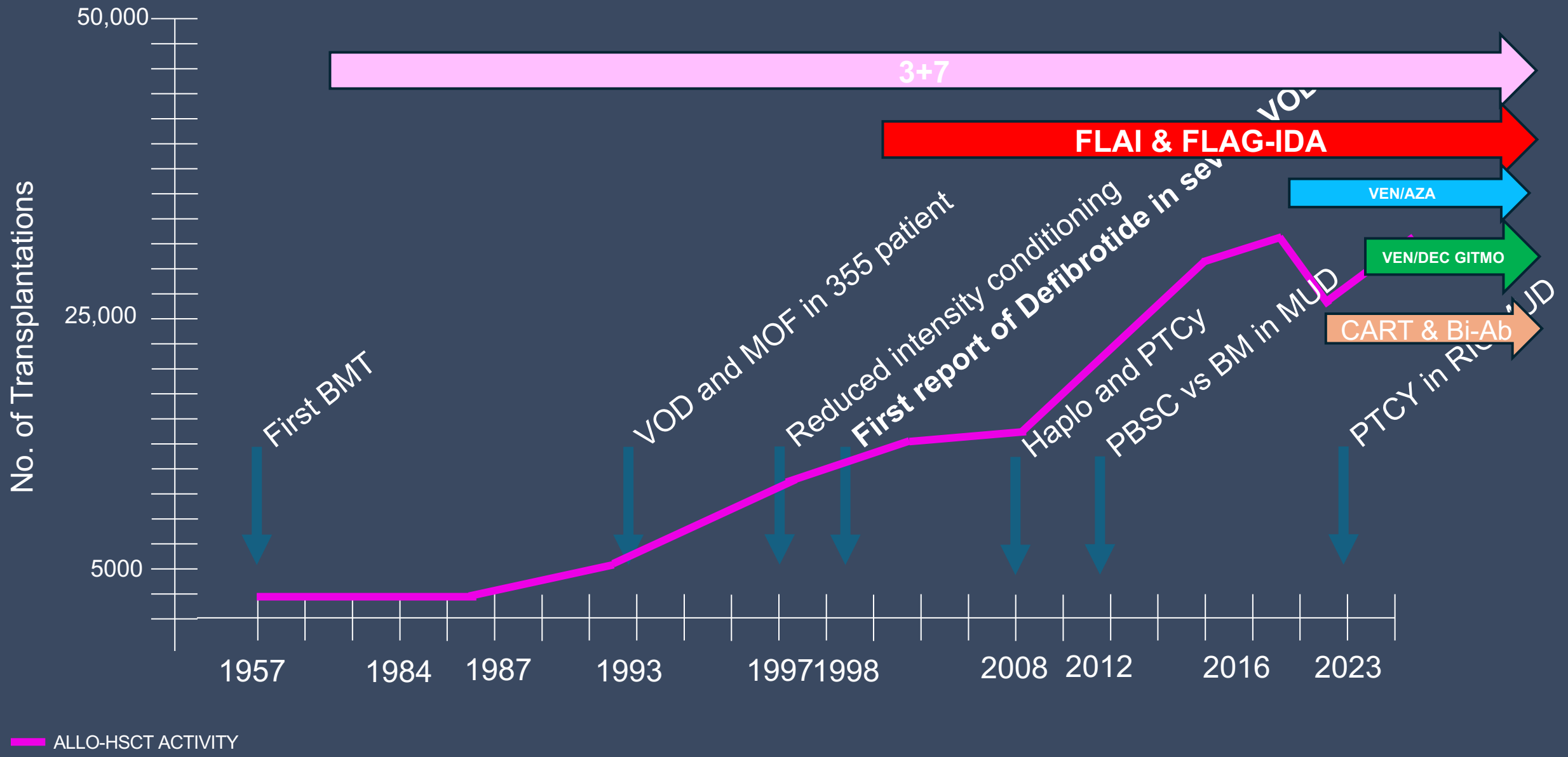


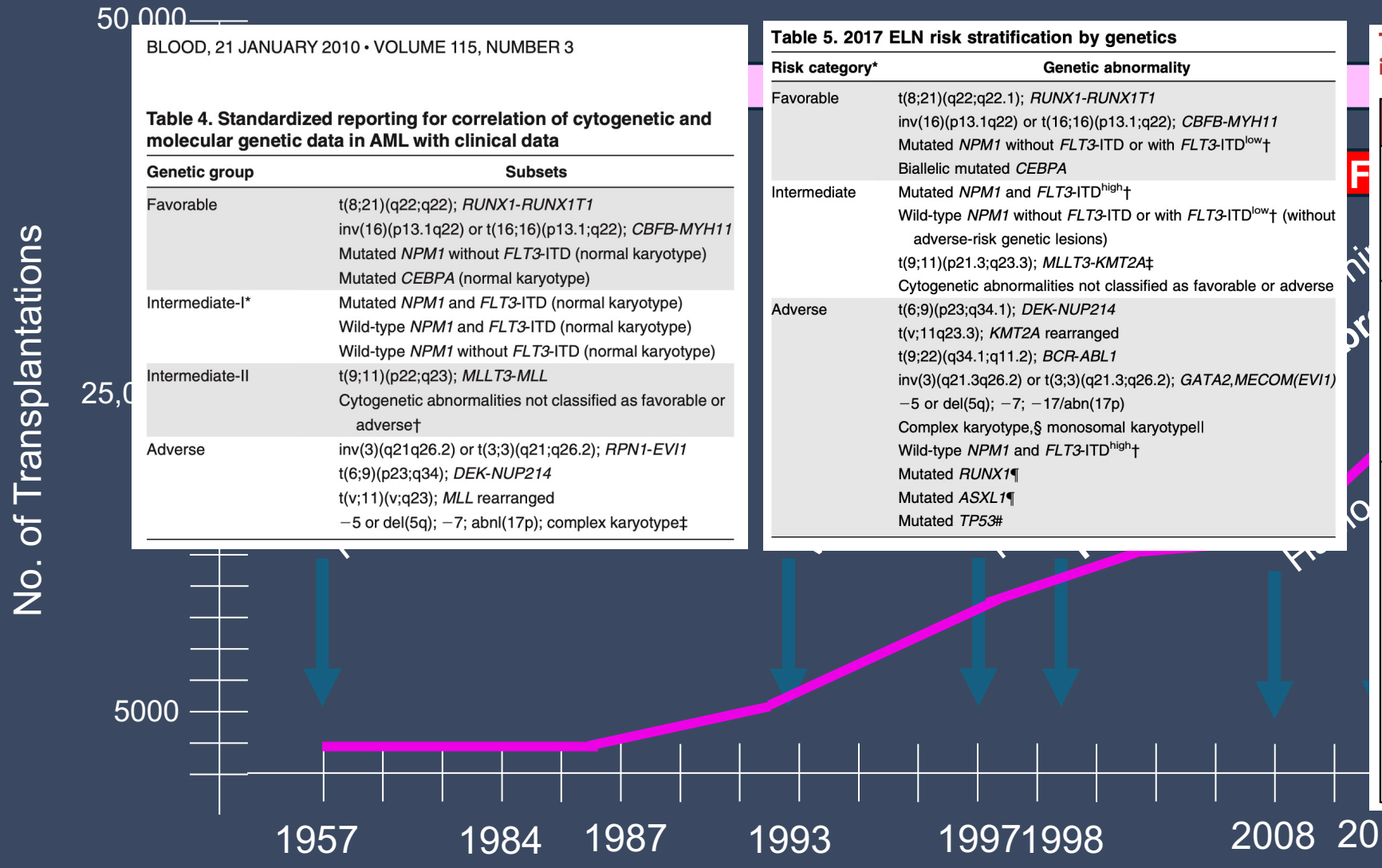
Figure 2. OS for allogeneic HCT recipients 70 years and older transplanted between 2000-2007 and 2008-2013.

Increasing Use of Allogeneic Hematopoietic Cell Transplantation (HCT) in Patients Age 70 Years and Older: A CIBMTR Study of Trends and Outcomes
1.Muffly, Lori et al. Biology of Blood and Marrow Transplantation, Volume 22, Issue 3, S68 - S69

ALLO-HSCT activity across two centuries



ALLO-HSCT activity across two centuries



BLOOD, 21 JANUARY 2010 • VOLUME 115, NUMBER 3

Table 4. Standardized reporting for correlation of cytogenetic and molecular genetic data in AML with clinical data

Genetic group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD (normal karyotype) Mutated *CEBPA* (normal karyotype)
Intermediate-I*	Mutated *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* and *FLT3*-ITD (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD (normal karyotype)
Intermediate-II	t(9;11)(p22;q23); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse†
Adverse	inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1* t(6;9)(p23;q34); *DEK-NUP214* t(v;11)(v;q23); *MLL* rearranged −5 or del(5q); −7; abnl(17p); complex karyotype‡

Table 5. 2017 ELN risk stratification by 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*#

Table 6. 2022 ELN risk classification by genetics at initial diagnosis*

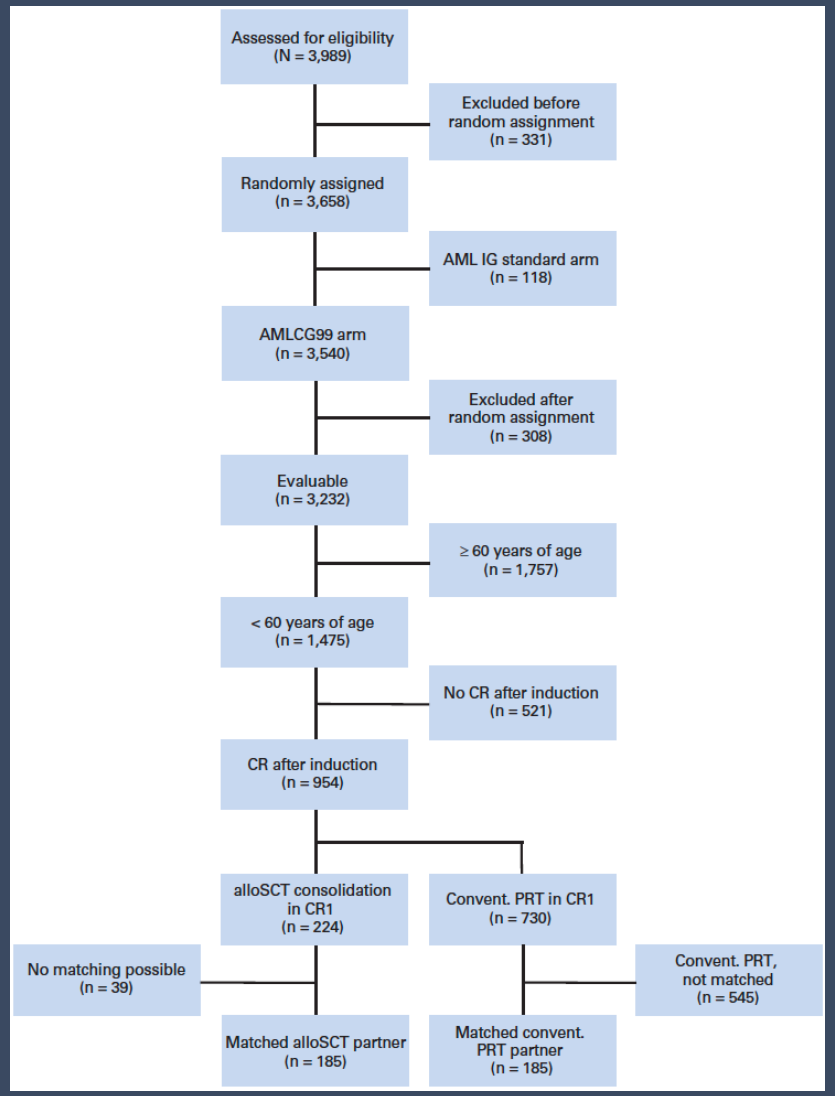
Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (without adverse-risk genetic lesions) • t(9;11)(p21.3;q23.3)/*MLLT3*::*KMT2A*†,¶ • Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	• t(6;9)(p23.3;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged# • 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)*-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,** monosomal karyotype†† • Mutated *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and/or *ZRSR2*‡‡ • Mutated *TP53*[a]

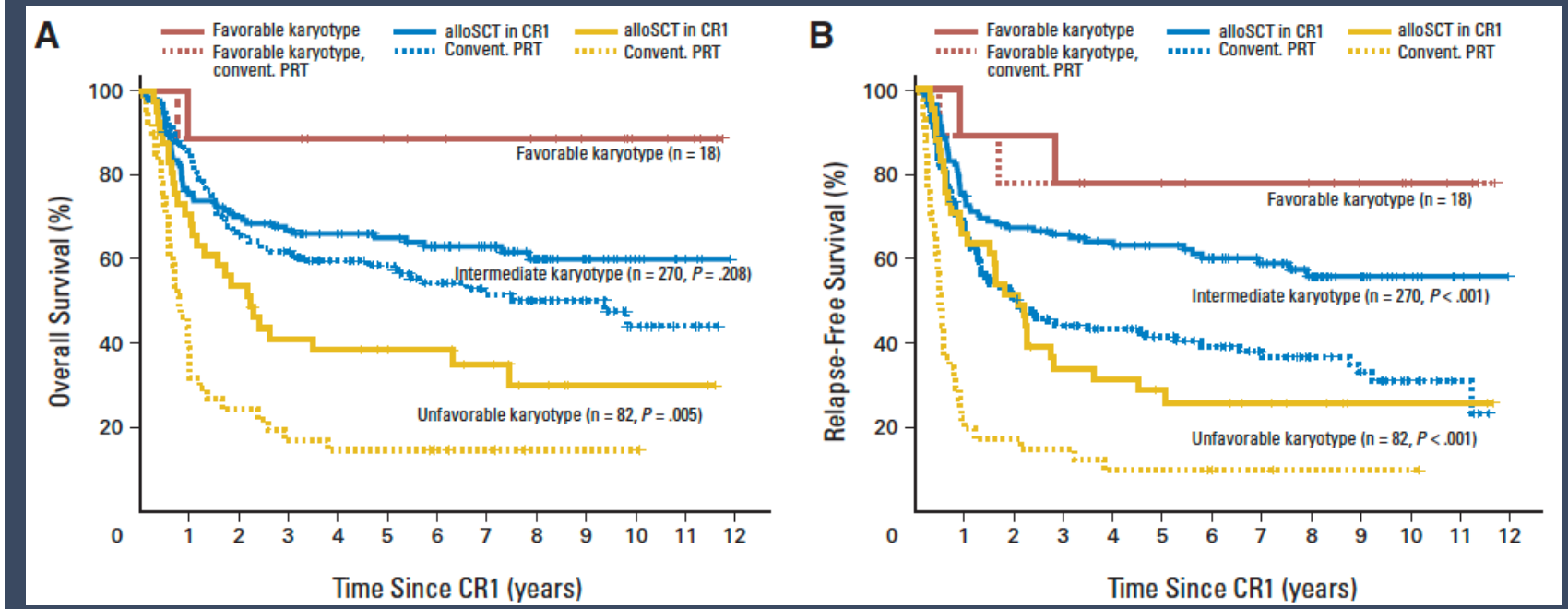
Allogeneic Transplantation Versus Chemotherapy as Postremission Therapy for Acute Myeloid Leukemia: A Prospective Matched Pairs Analysis

Matthias Stelljes, Utz Krug, Dietrich W. Beelen, Jan Braess, Maria C. Sauerland, Achim Heinecke, Sandra Ligges, Tim Sauer, Petra Tschanter, Gabriela B. Theuvissen, Björna Berning, Hans J. Kolb

VOLUME 32 · NUMBER 4 · FEBRUARY 1 2014

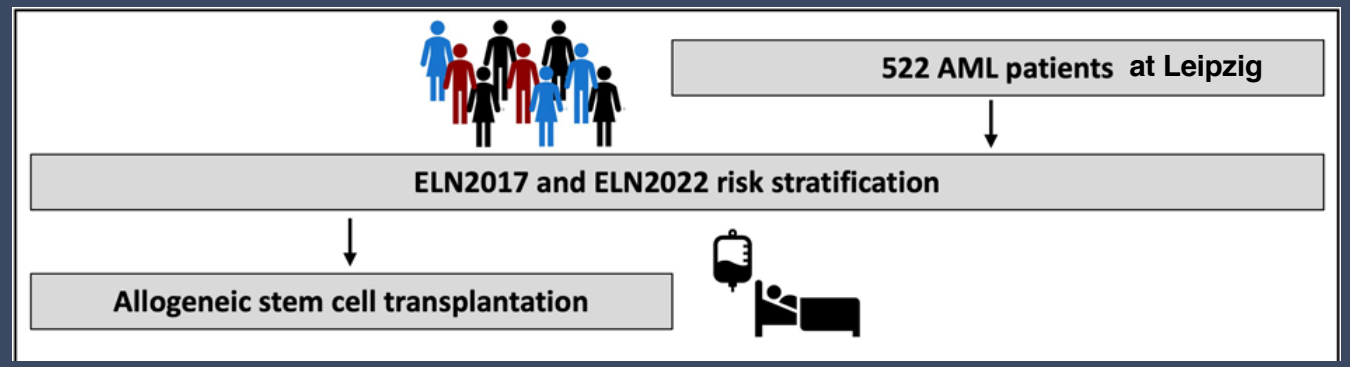
JOURNAL OF CLINICAL ONCOLOGY

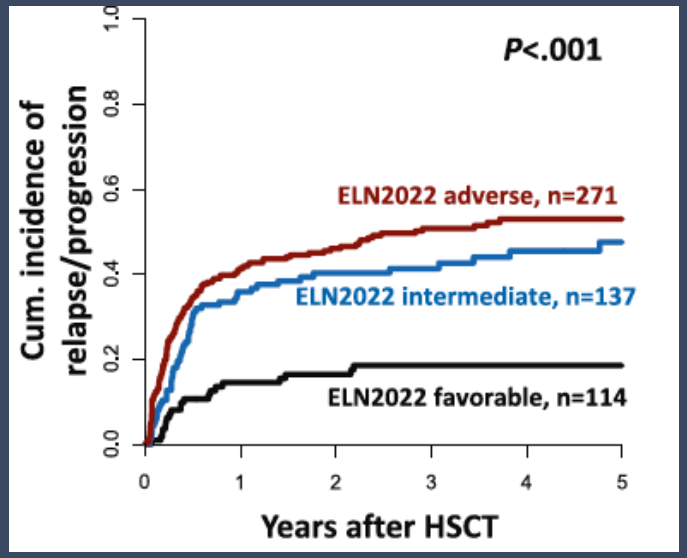


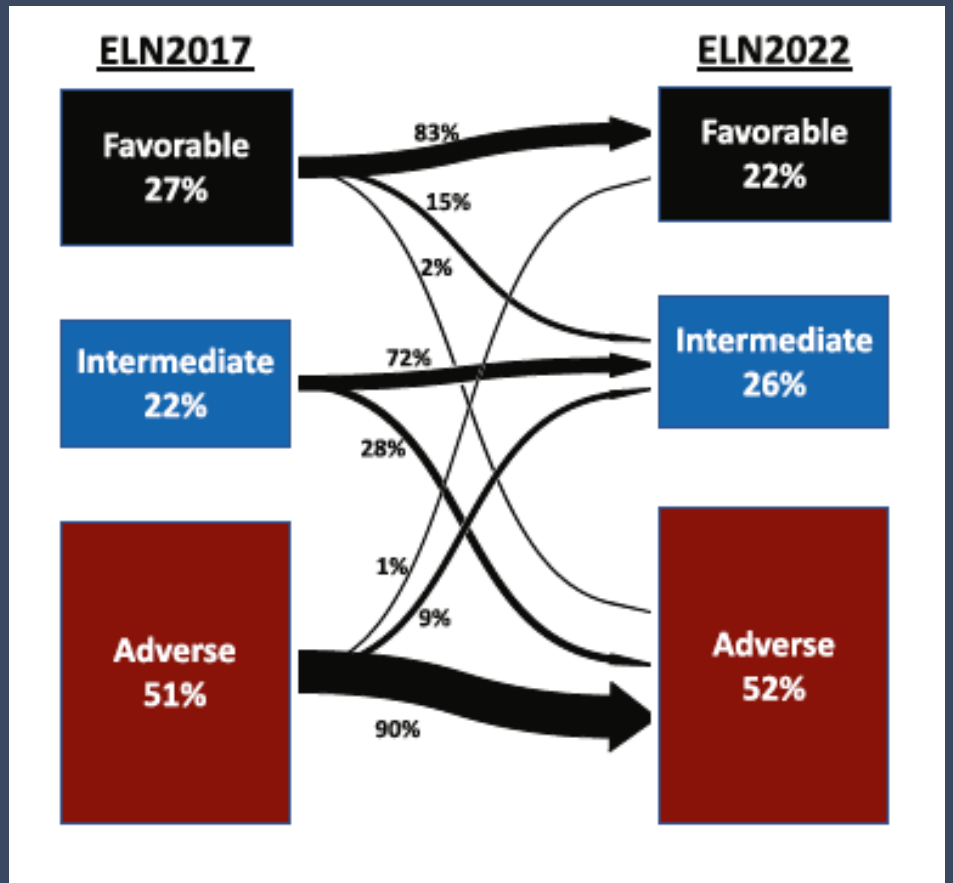


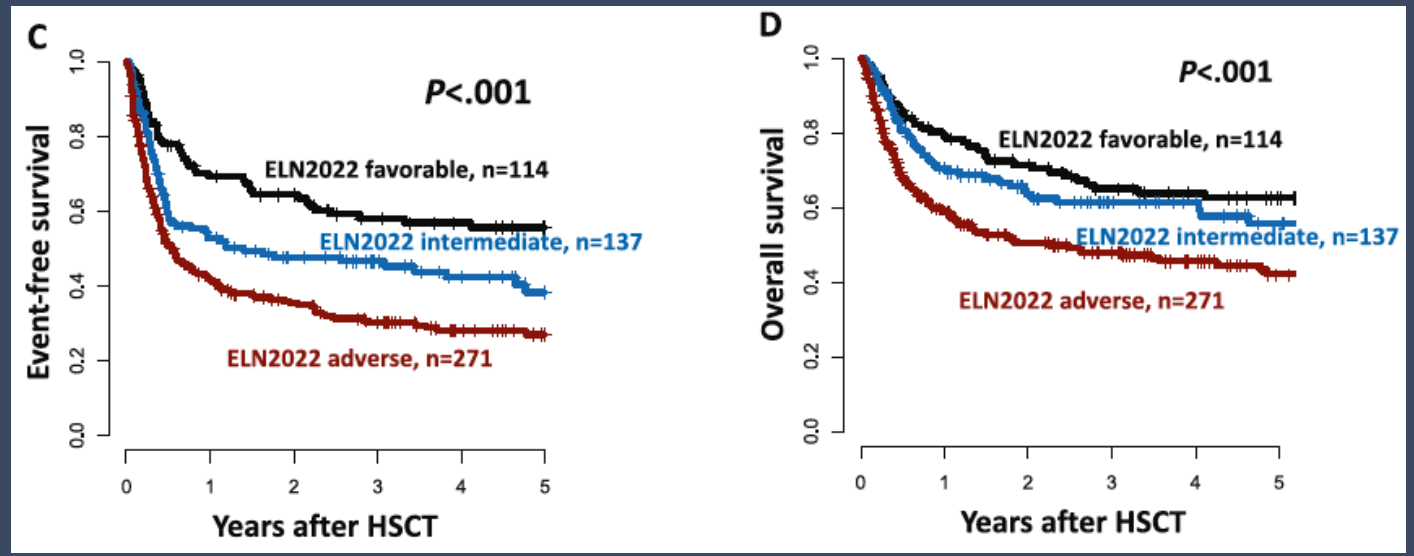
AlloSCT in CR1 (linea cont.) Vs. Chemiotherapy (dotted line)

AML_ELN22 new classification_validation





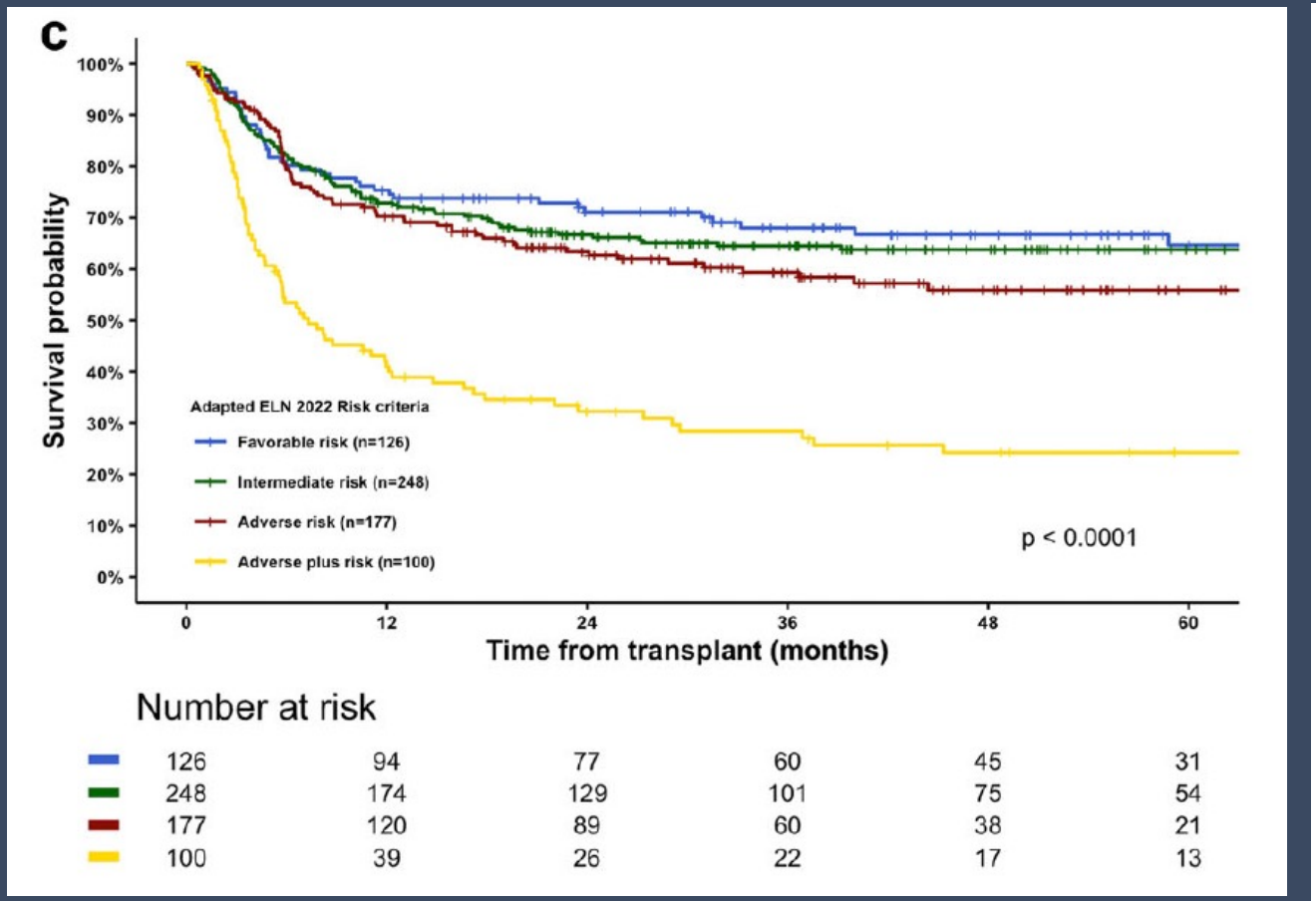


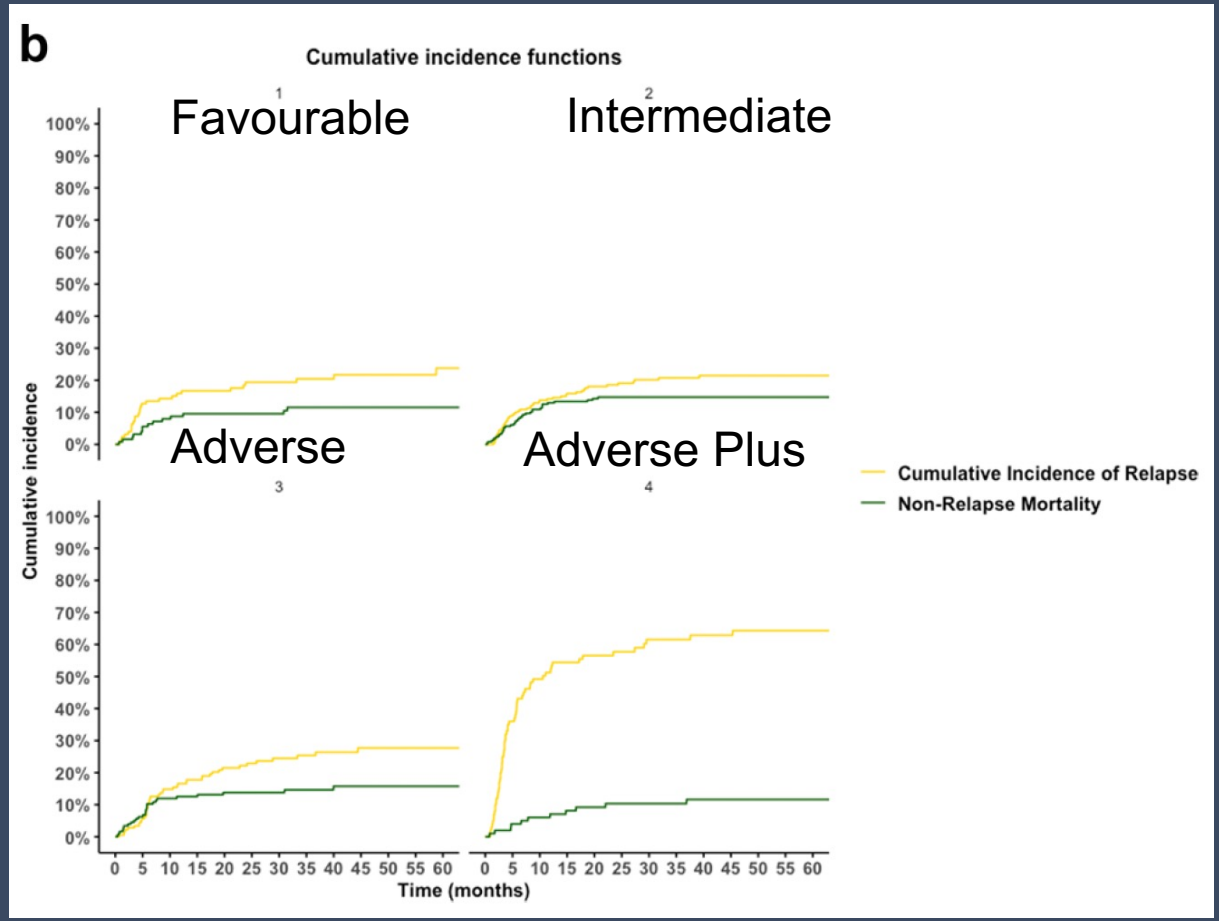


Jentzsch et al., Blood Cancer Journal, 2022

Allo-HCT refined ELN 2022 risk classification: validation of the Adverse-Plus risk group in AML patients undergoing allogeneic hematopoietic cell transplantation within the Spanish Group for Hematopoietic Cell Transplantation (GETH-TC)

Carlos Jiménez-Vicente[1], Jordi Esteve[1], Mónica Baile-González[2], Estefanía Pérez-López[2], Carmen Martin Calvo[3], Clara Aparicio[3], Itziar Oiartzabal Ormategi[4], Albert Esquirol[5], Felipe Peña-Muñoz[6], Sara Fernández-Luis[7], Inmaculada Heras Fernando[8], Ana Pilar González-Rodríguez[9], Alberto López-García[10], Jose Luis López-Lorenzo[10], Tamara Torrado[11], Adolfo Jesús Sáez Marín[12], Cynthia Acosta Fleytas[13], Lucía García[14], Sara Villar[15], Silvia Filaferro[16], Pascual Balsalobre[16], María Jesús Pascual Cascón[16,17] and María Queralt Salas[1]✉





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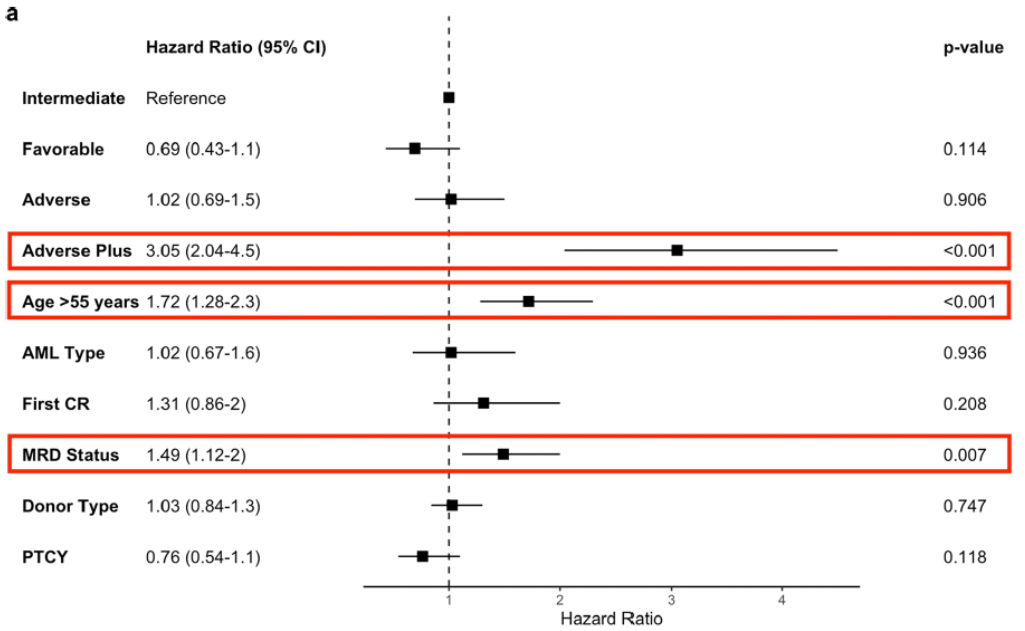
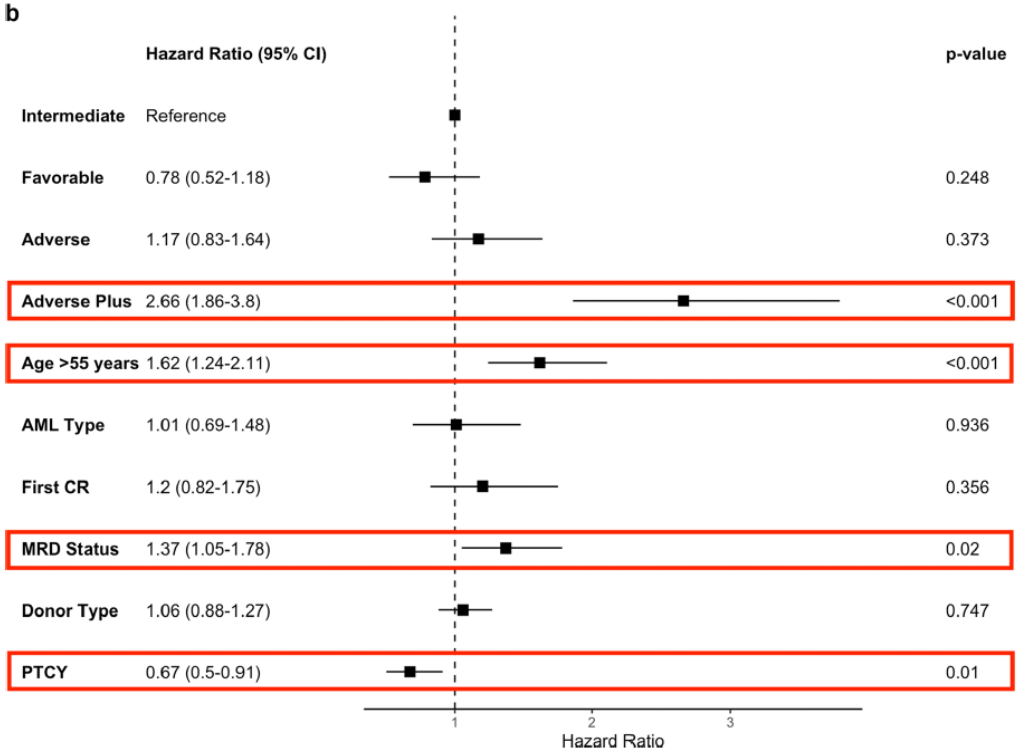
- The Allo-HCT–Refined ELN 2022 classification further stratifies adverse-risk AML into Adverse* and Adverse-Plus (AdvP), identifying a subgroup with significantly inferior outcomes after allo-HCT.
- Patients classified as AdvP (complex karyotype, MECOM(EVI1) rearrangement, and/or TP53 mutation/deletion) showed markedly reduced 5-year OS (≈28–32%) and LFS (≈24%) with a very high cumulative incidence of relapse (≈64%).
- In multivariable analysis, AdvP status, age >55 years, and pre-transplant MRD positivity were independently associated with worse OS and LFS, while PTCY-based GVHD prophylaxis was associated with improved LFS.

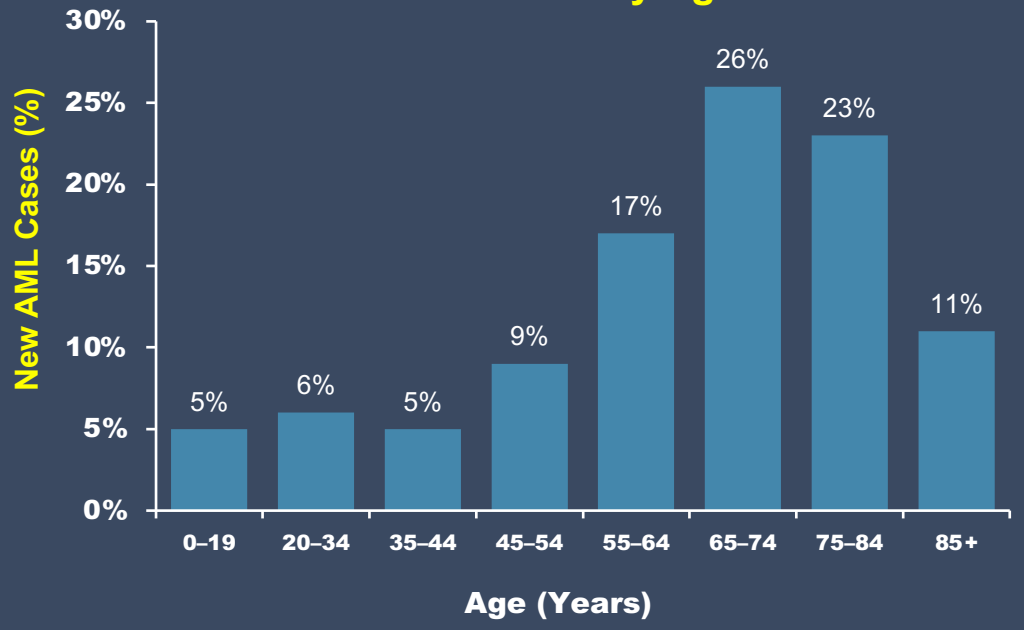




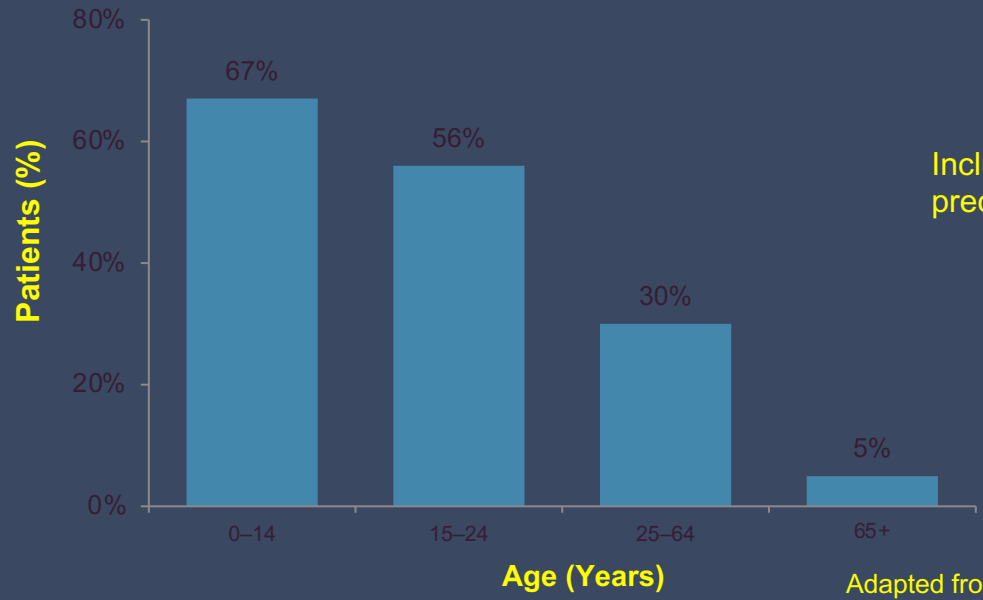
AML IS MOST FREQUENTLY DIAGNOSED IN OLDER ADULTS[1]

- Prognosis worsens with increasing age[2]

New AML Cases by Age[1]



5-Year Relative Survival in AML by Age[2]



Includes related precursor neoplasms

Adapted from Visser *et al*. 2012

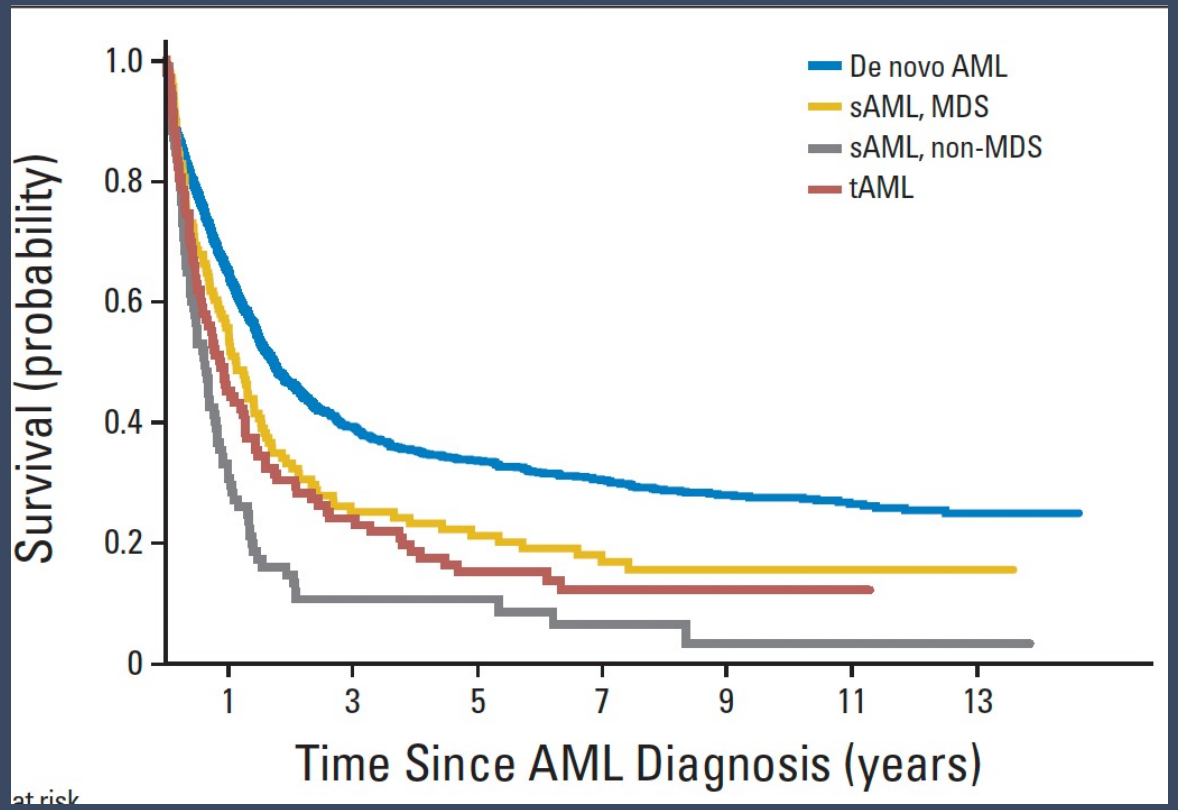
Older patients can be challenging to treat[3]

- Significant comorbidities
- Increased likelihood of prior treatment for malignancies or haematological disorders
- Complex genetic and molecular leukaemia biology

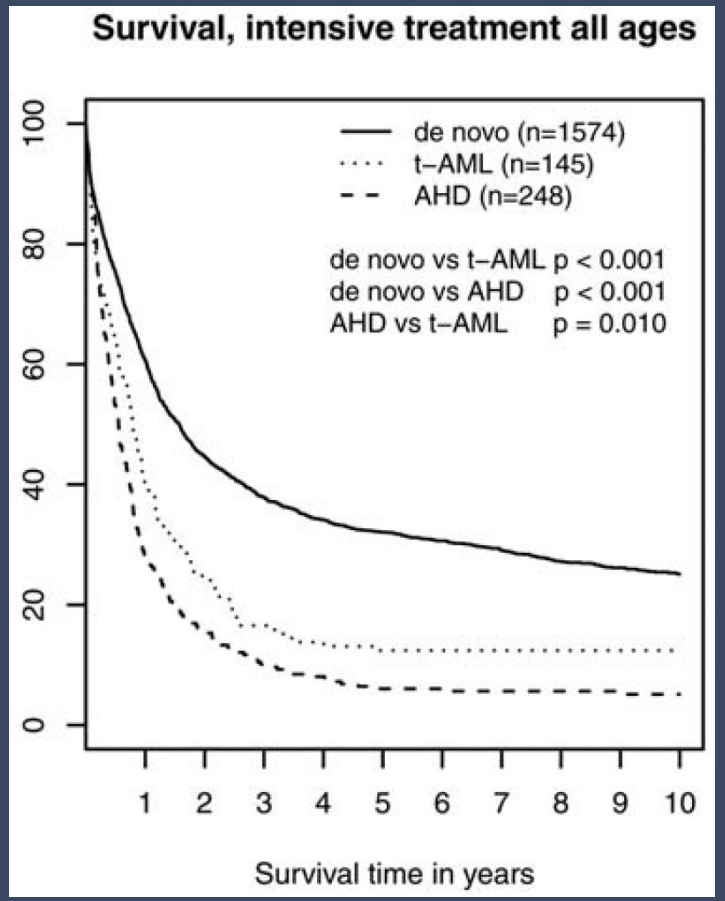
References: 1. National Cancer Institute. SEER. https://seer.cancer.gov/statfacts/html/amyl.html Last accessed, Nov 2021, 2. Visser O, et al. Eur J Cancer 2012;48(17):3257–3266, 3. Bhatt VR, et al. Leuk Lymphoma 2018;59(1):29–41, 3. Kaiser S et al – Blood 2011 Feb 17;117(7):2137-45
Acronyms: AML, acute myeloid leukaemia

NOT ALL THE AML ARE THE SAME

Granfeldt Østgård et al – Sweden group



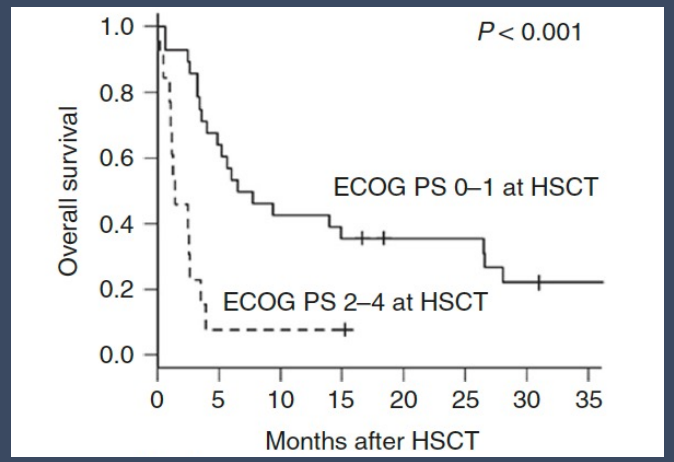
Erik Hulegårdh et al - Danish group



Erik Hulegårdh et al Am. J. Hematol. 90:208–214
Granfeldt Østgård et al. J Clin Oncol 33:3641-3649

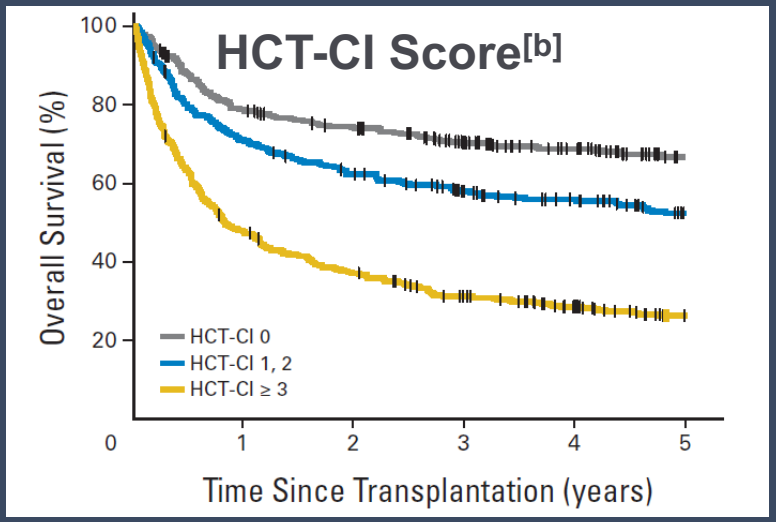
Eligibility for Allo-SCT in Older Adult Patients Is Challenging

Performance Status[a]



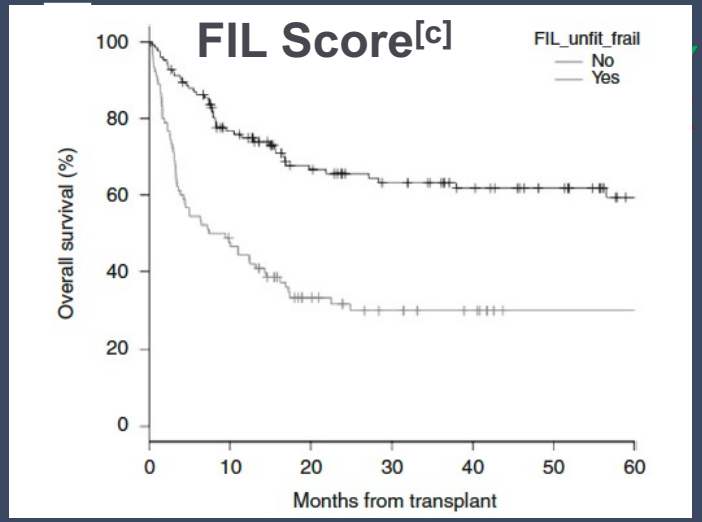
✓ Simple
X Too limited
X Functional status

HCT-CI Score[b]



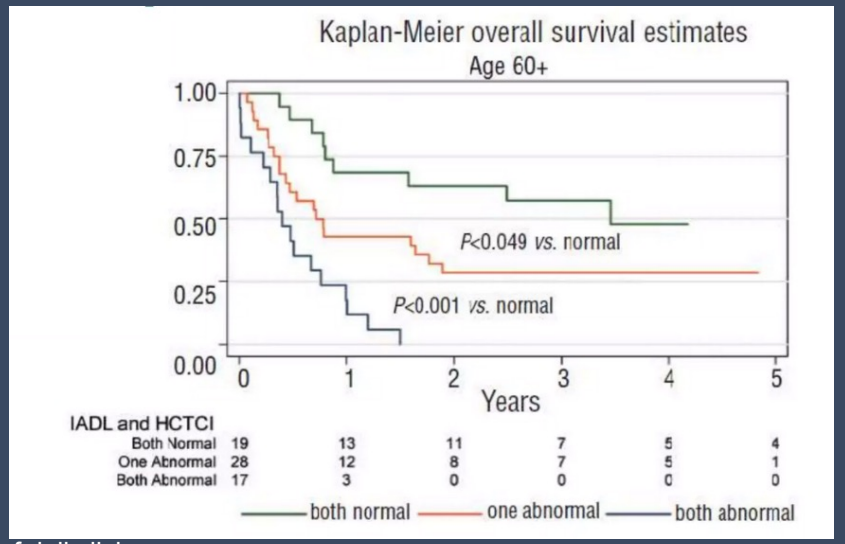
✓ Comorbidity
✓ Choice conditioning regimen
X Frailty

FIL Score[c]



✓ Frailty
X Comorbidity

Geriatric Assessment[d]



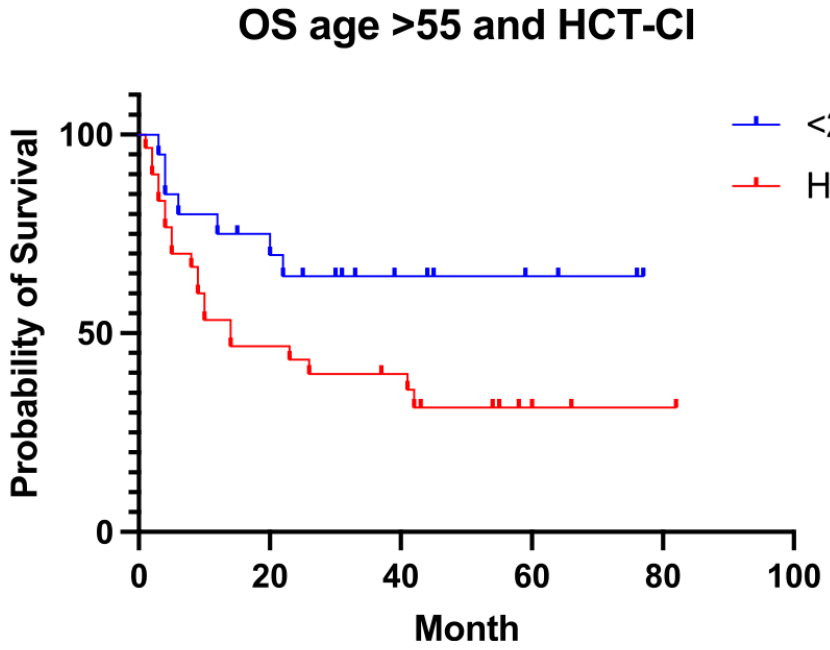
✓ Simple
✓ Frailty
X Comorbidity

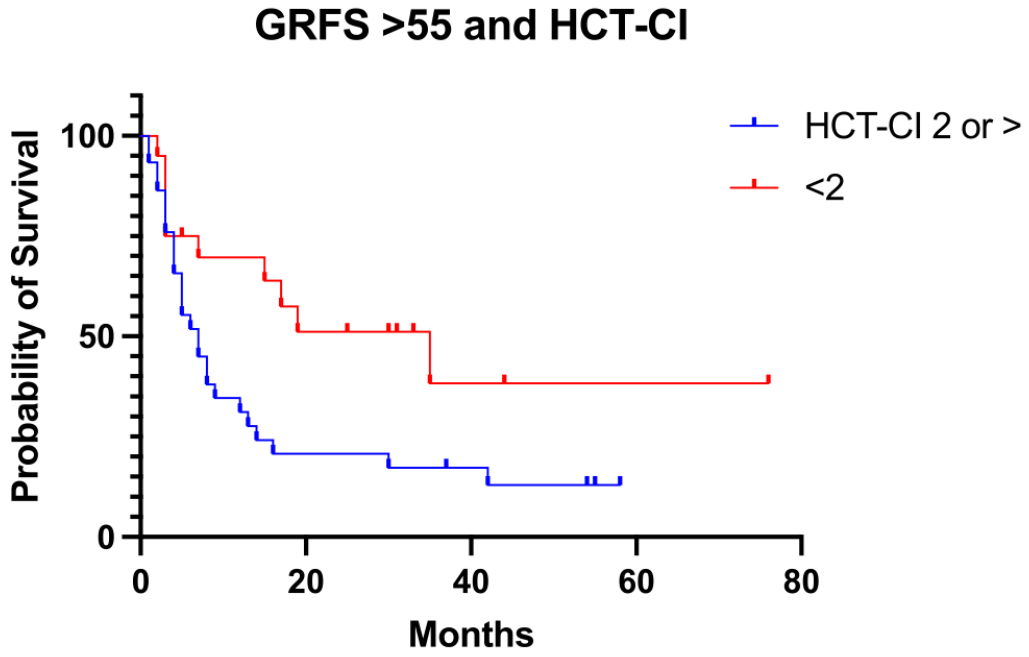
FIL, Fondazione Italiana Linfomi; HSCT, hematopoietic stem cell transplant; IADL, instrumental activities of daily living.

a. Muffly LS, et al. Haematologica. 2014;99:1373-1379; b. Sorror ML, et al. J Clin Oncol. 2014;32:3249-3256; c. Polverelli N, et al. Bone Marrow Transplant. 2020;55:2224-2233; d. Tomori S, et al. Bone Marrow Transplant. 2020;55:233-241.

A deeper T-Cell depletion is the right answer?

103 AML and MDS-EB after FB4-CAMPATH



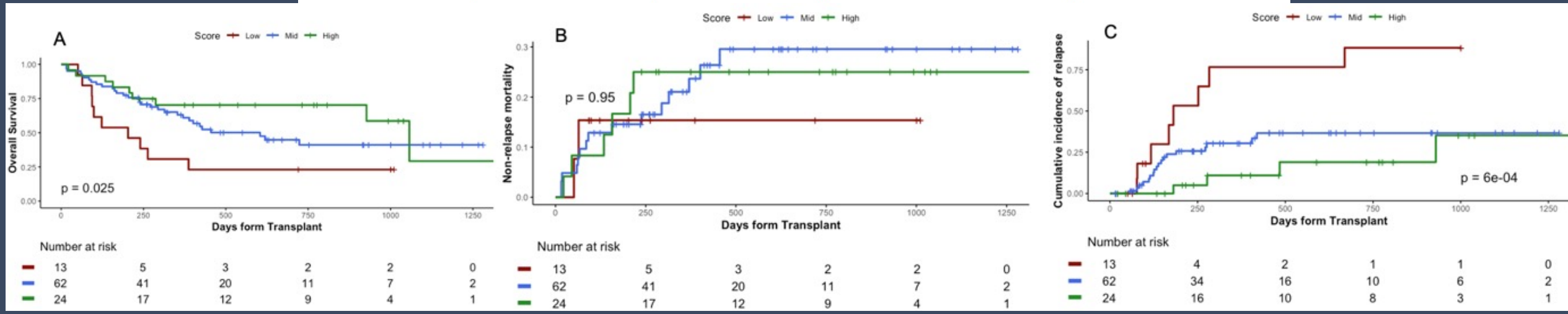


Moderate and severe chronic GVHD are only 16% and 4%, respectively.
Relapse and TRM 30% and 26%
Causes of TRM: Infections (65% of total TRM), GVHD (5%), CNS bleeding (5%), and stroke (5%).

Avenoso D, et al. Transplant Cell Ther. 2023 Nov;29(11):698.e1-698.e6. doi: 10.1016/j.jtct.2023.08.012. PMID: 37579918.

Development of a Simplified Geriatric Score-4 (SGS-4) to Predict Outcomes After Allogeneic Hematopoietic Stem Cell Transplantation in Patients Aged over 50

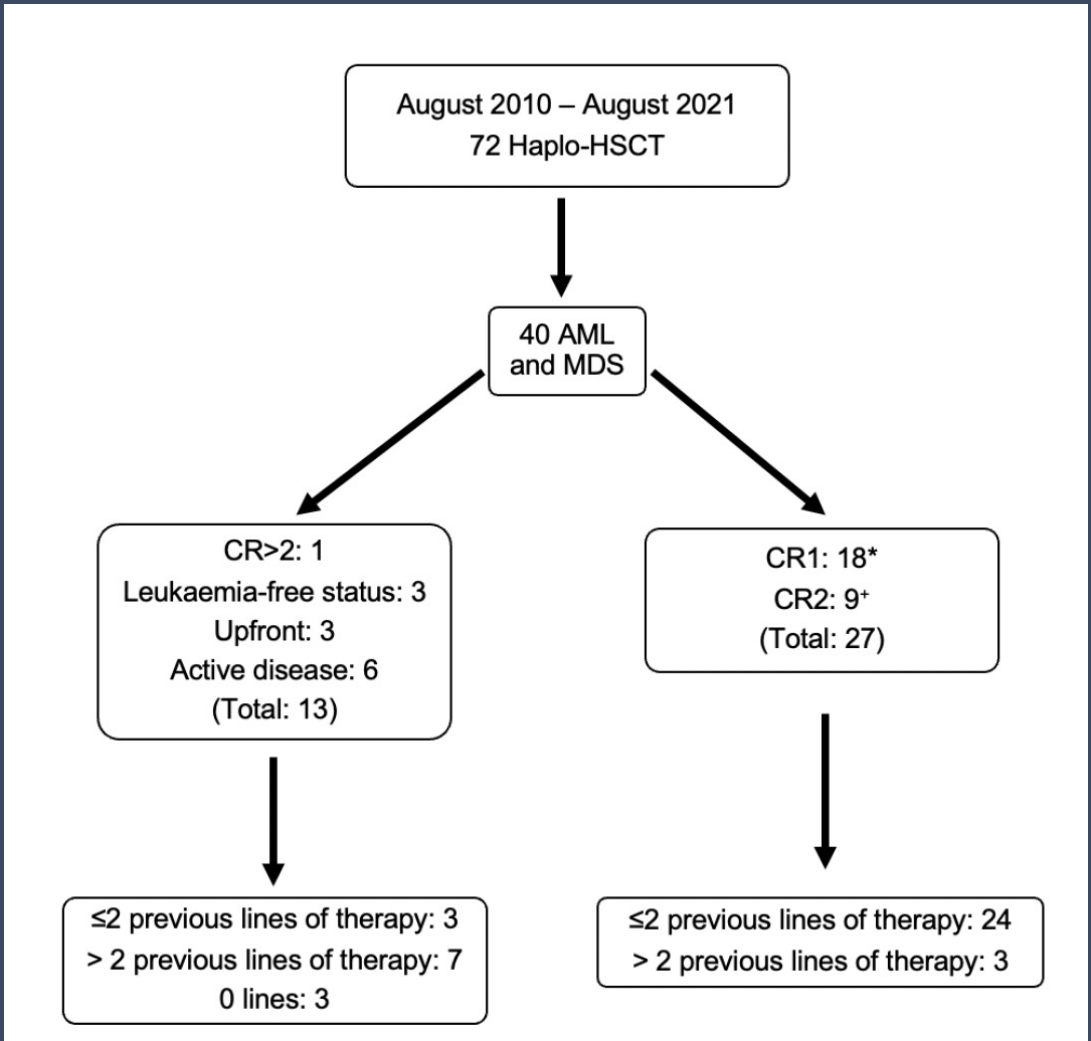
Eugenia Accorsi Buttini [1,2,*], Alberto Zucchelli [1,3], Paolo Tura [1], Gianluca Bianco [1], Daniele Avenoso [1,4], Giovanni Campisi [5], Mirko Farina [1,4], Gabriele Magliano [4], Enrico Morello [4], Vera Radici [1,4], Nicola Polverelli [6], Domenico Russo [1,4], Alessandra Marengoni [1,3,†] and Michele Malagola [1,4,†]

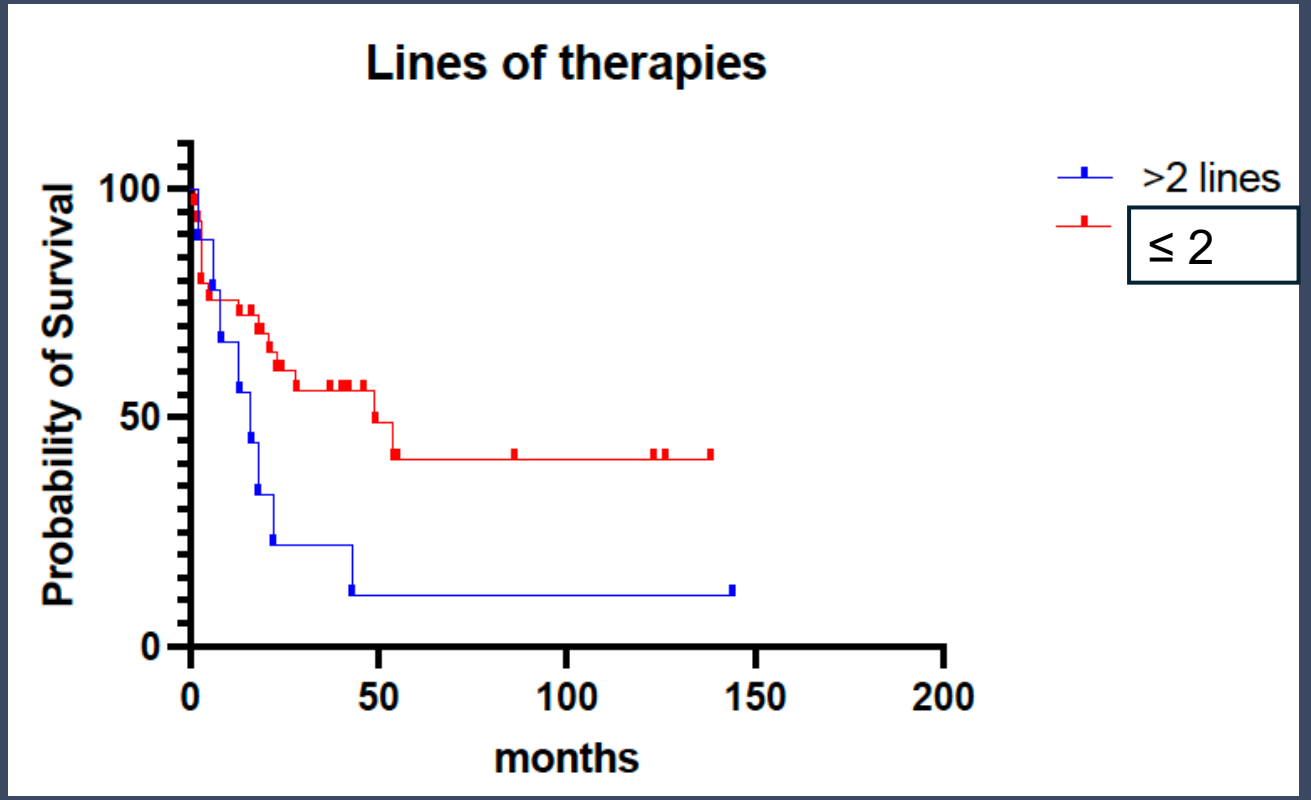


Outcome	Low (%)	Intermediate (%)	High (%)	p-value
OS @ 1 yr	32.7	62.7	70.3	0.025
NRM @ 1 yr	16.1	20.6	25.0	0.95
CIR @ 1 yr	69.2	30.4	10.9	<0.01

- **Score Components**
- Developed via Factor Analysis: **Gait speed**, **Hand grip**, **G8**, **Sex**
- Score ranges stratified patients into:
  - **Low fitness (≤13)**: n=13
  - **Intermediate fitness (>13–22.5)**: n=62
  - **High fitness (>22.5)**: n=24

If no HLA-identical donor available, go for HAPLO. The sooner, the better.





OS / PFS: 1- and 3-year OS were 62% and 43% (median OS 22 months). Patients with ≤2 prior therapy lines had superior OS (3-year: 55% vs 22%, p=0.04). One- and 3-year PFS were 57% and 46%.

CIR: Overall relapse incidence was 25% (median time to relapse 5 months). Patients with >2 prior therapy lines had higher 3-year CIR than those with ≤2 (49% vs 17%, p=0.05).

Avenoso D *et. al* Mediterr J Hematol Infect Dis. 2024 Jan 1;16(1):e2024002. doi: 10.4084/MJHID.2024.002. PMID: 38223487.

Haploidentical bone marrow transplantation for AML in remission after TBF conditioning: a long-term follow-up

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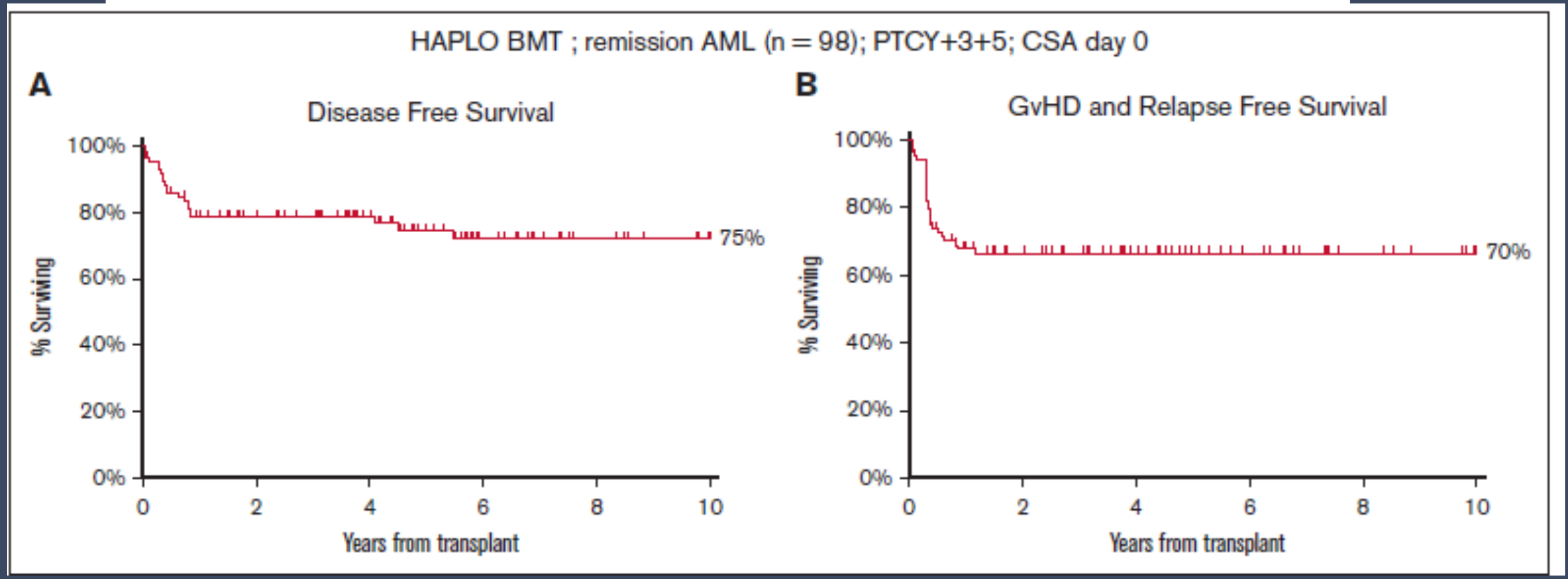
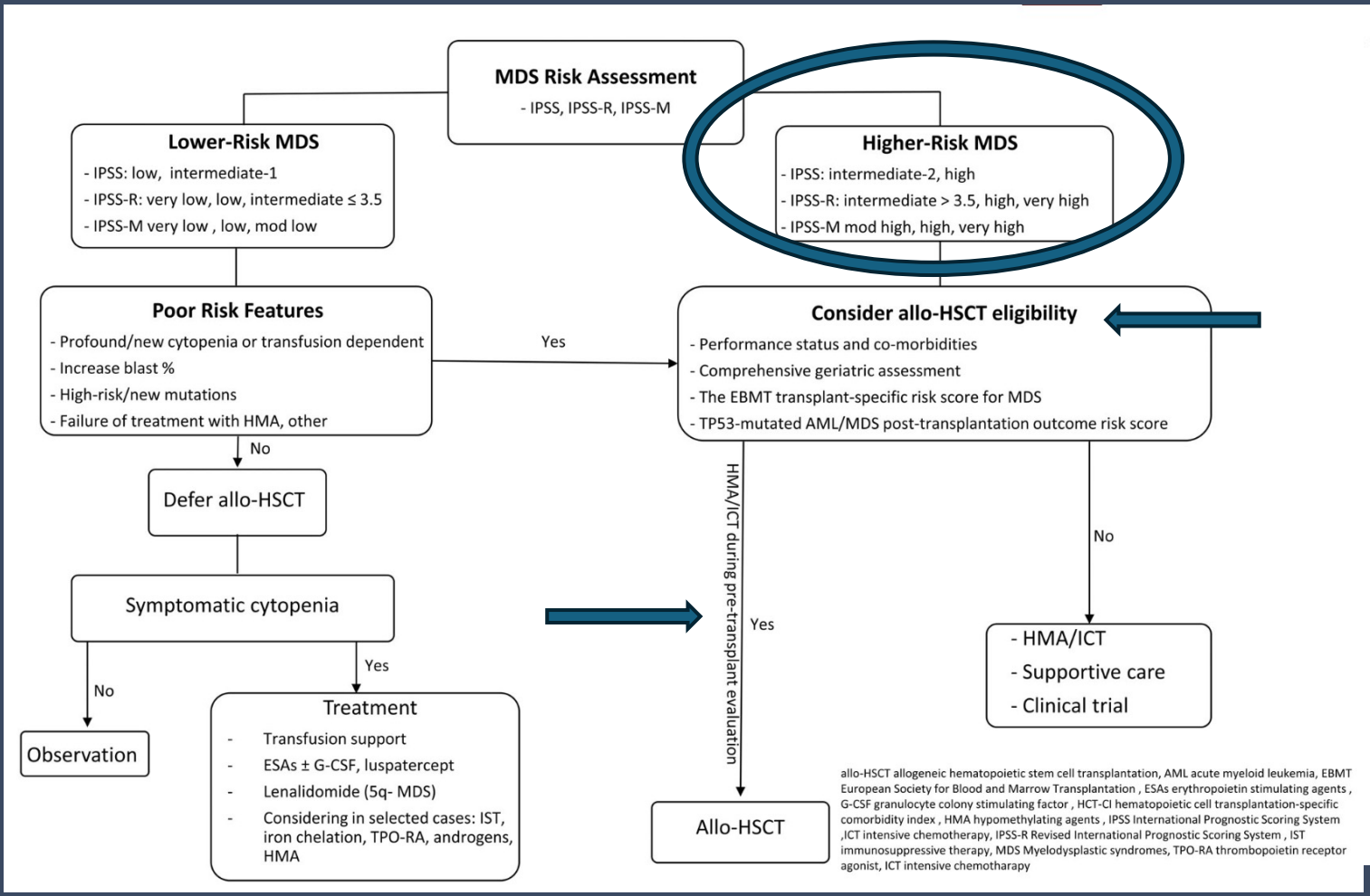
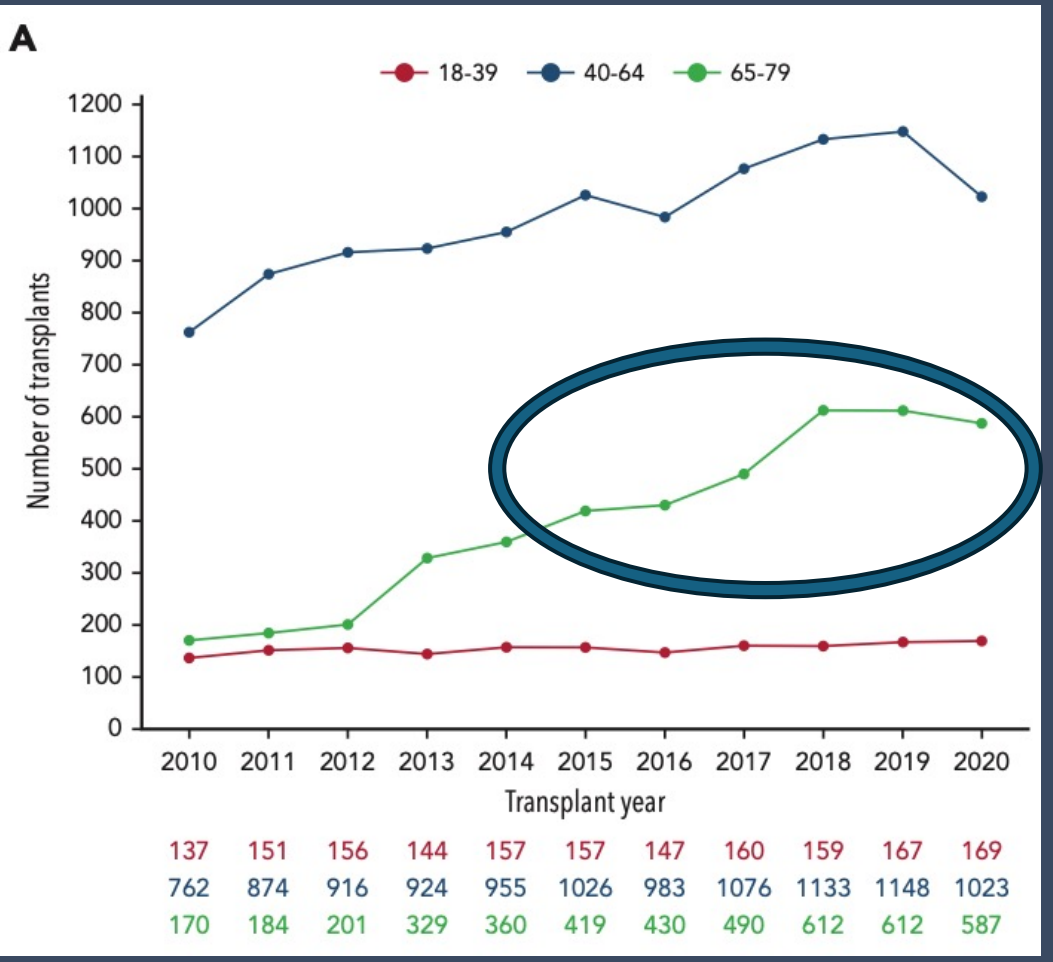


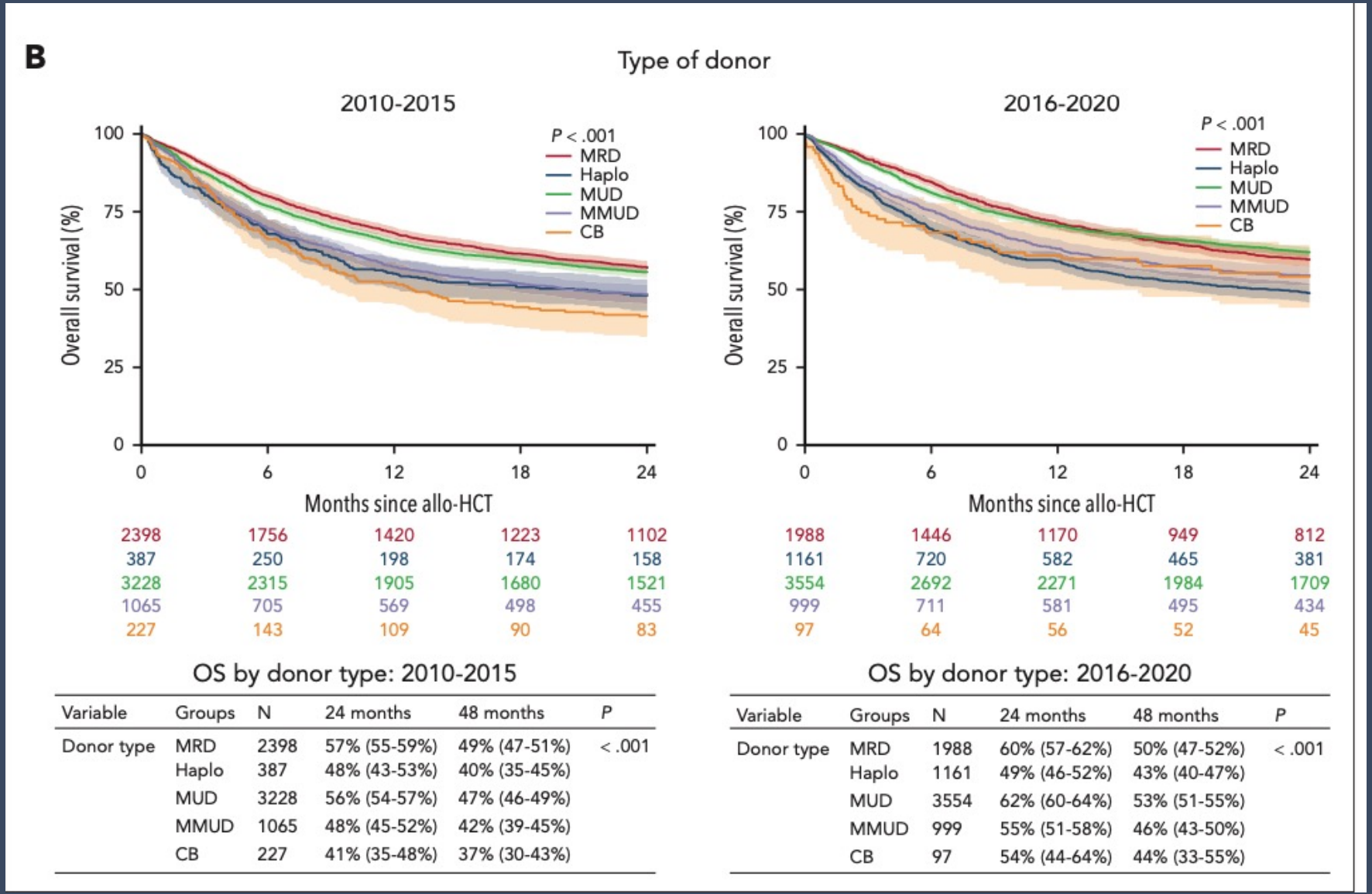
MDS state of art





Vittayawacharin P. et al Am J Hematol. 2023;98:322–337
Gurnari C. et al, Blood. 2025 May 1;145(18):1987-2001

Allo-HSCT as a curative strategy



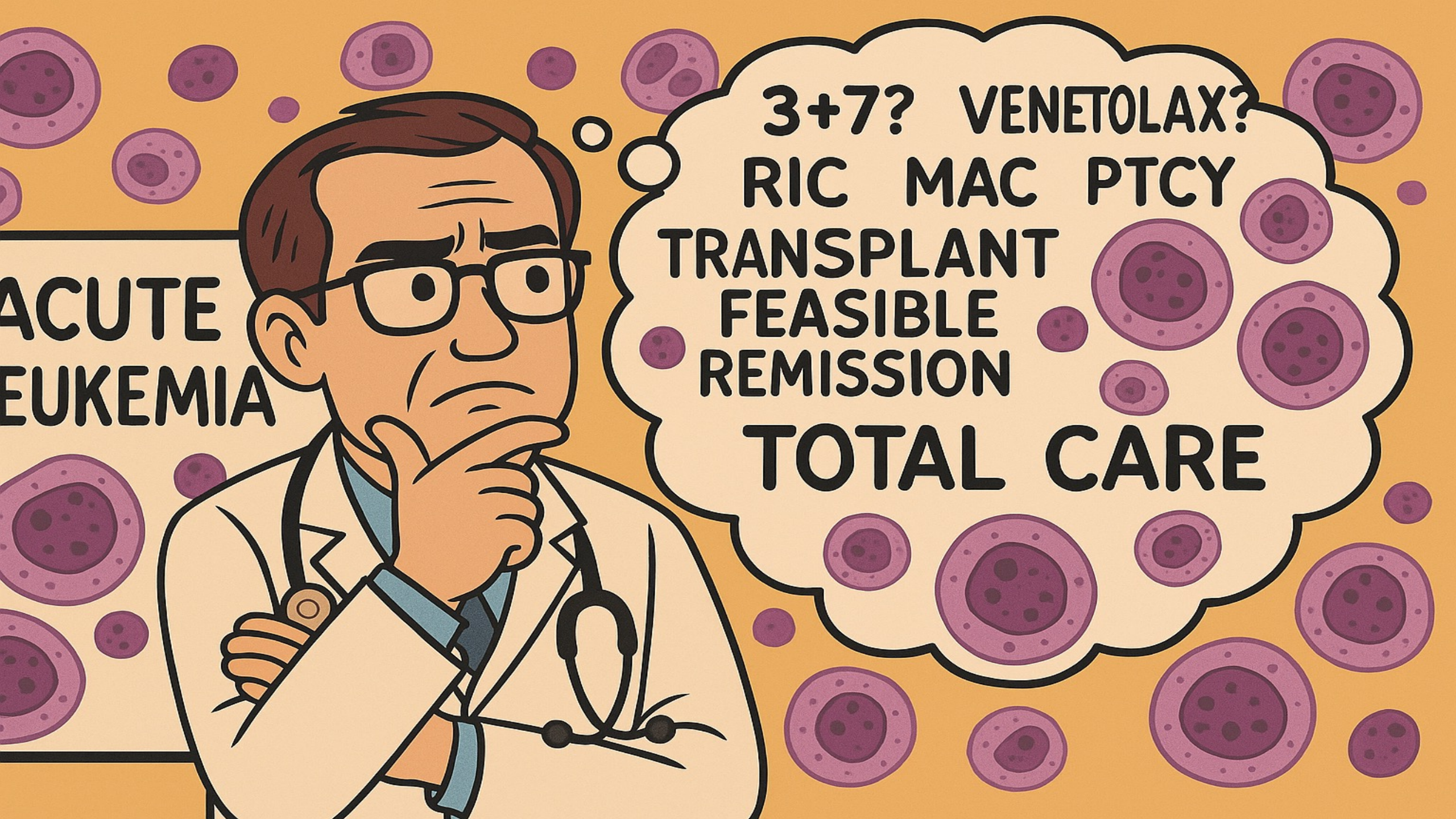
OS by donor type: 2010-2015

Variable	Groups	N	24 months	48 months	P
Donor type	MRD	2398	57% (55-59%)	49% (47-51%)	< .001
	Haplo	387	48% (43-53%)	40% (35-45%)	
	MUD	3228	56% (54-57%)	47% (46-49%)	
	MMUD	1065	48% (45-52%)	42% (39-45%)	
	CB	227	41% (35-48%)	37% (30-43%)	

OS by donor type: 2016-2020

Variable	Groups	N	24 months	48 months	P
Donor type	MRD	1988	60% (57-62%)	50% (47-52%)	< .001
	Haplo	1161	49% (46-52%)	43% (40-47%)	
	MUD	3554	62% (60-64%)	53% (51-55%)	
	MMUD	999	55% (51-58%)	46% (43-50%)	
	CB	97	54% (44-64%)	44% (33-55%)	

Gurnari C. et al, Blood. 2025 May 1;145(18):1987-2001


ACUTE
EUKEMIA
3+7? VENETOLAX?
RIC MAC PTCY
TRANSPLANT
FEASIBLE
REMISSION
TOTAL CARE

The optimal AML/MDS patient journey:
Highly effective and Less Toxic and Tailored.

Diseases (High/Int)	**AML > MDS > MPN > ALL > NHL**
Age	**> 50yy – 75yy**
MRD	**CR1 mrd-/mrd+ > CR2**
Fitness	**FIT > Frail**
Pre-Transplant Treat-Prog *With CHT (3+7 or similar)*	Highly effective and Less Toxic *no more than 15% of PTS get a Transplant*

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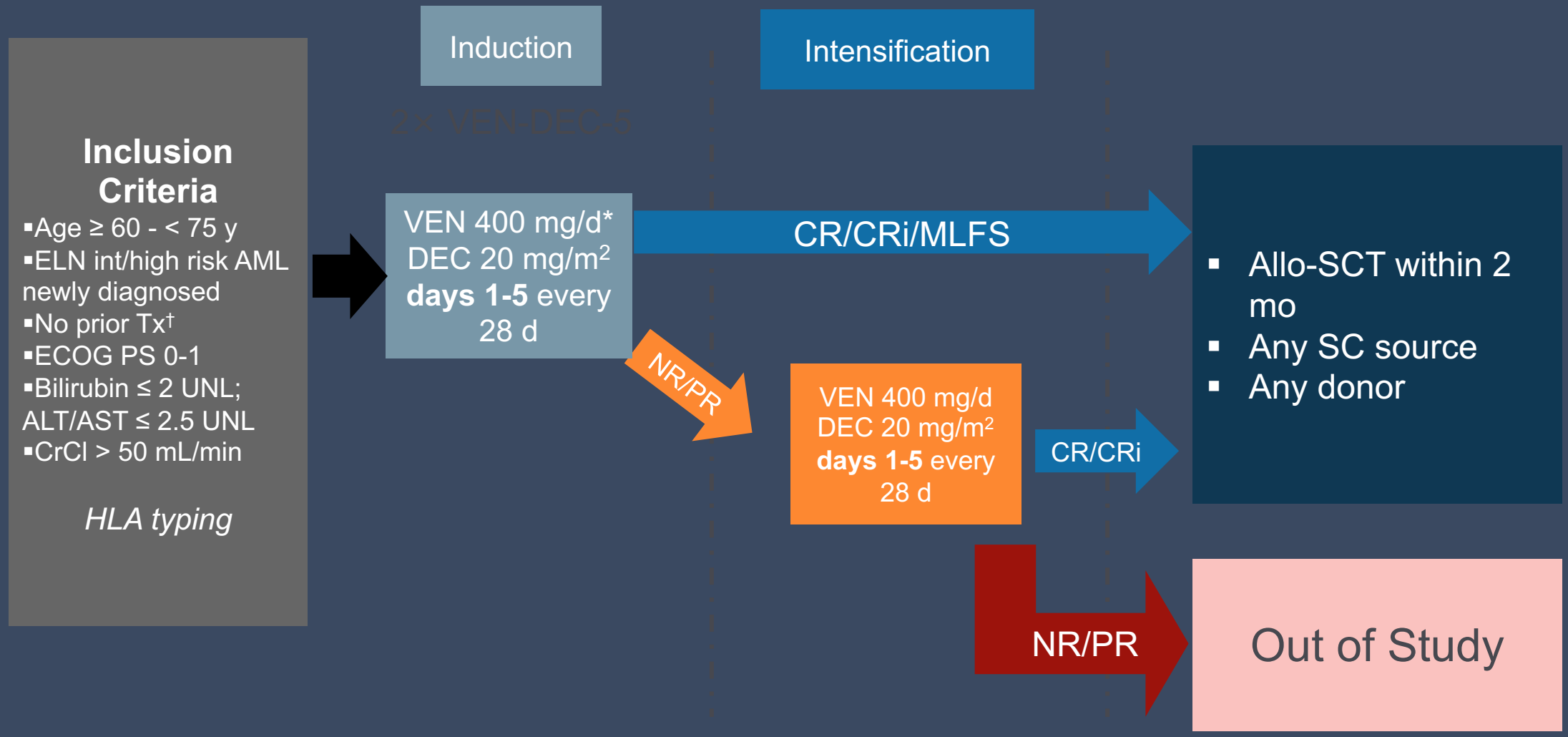
Phase 2 VEN-DEC GITMO Trial as "Bridge" to Allo-SCT
Study Design



*VEN ramp up: 100 mg on day 1, 200 mg on day 2, and 400 mg from day 3 (only for first cycle). †HU is allowed in case of WBC count > 25 000

ClinicalTrials.gov. Accessed March 28, 2023. https://clinicaltrials.gov/ct2/show/NCT04478199.

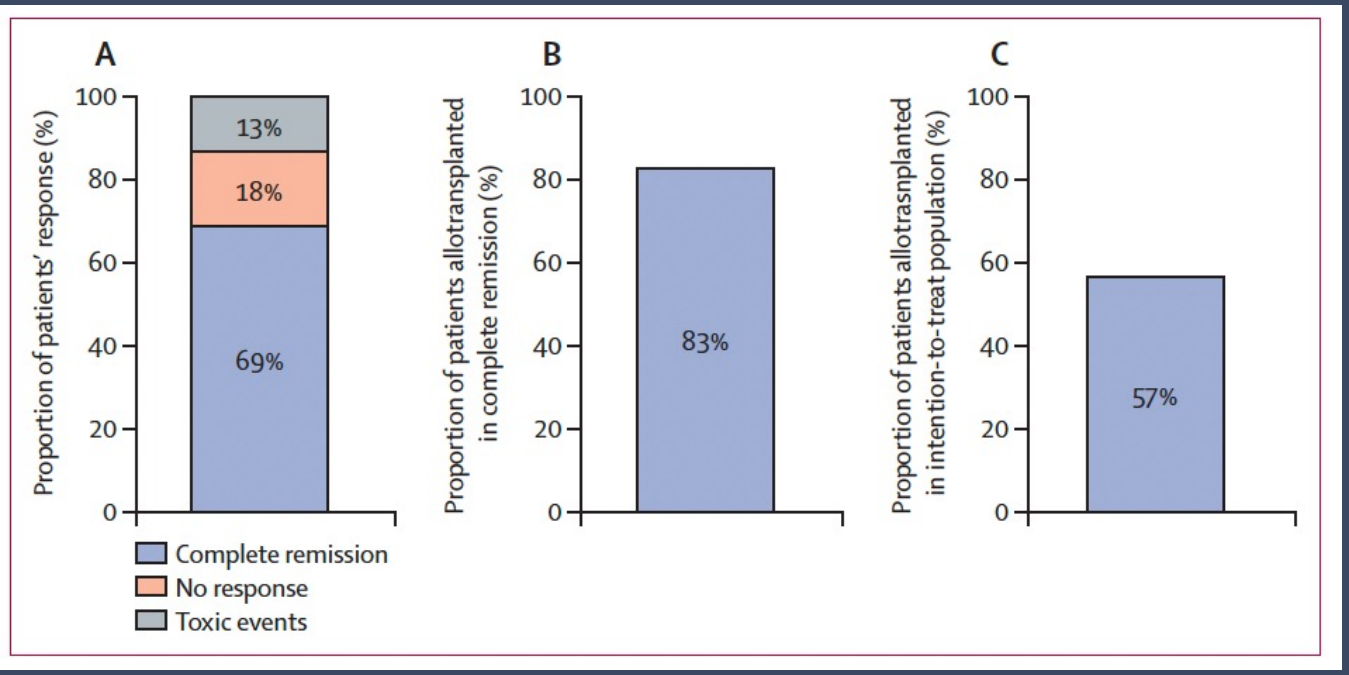
Russo et al., Lancet Haematology Sept. 2024

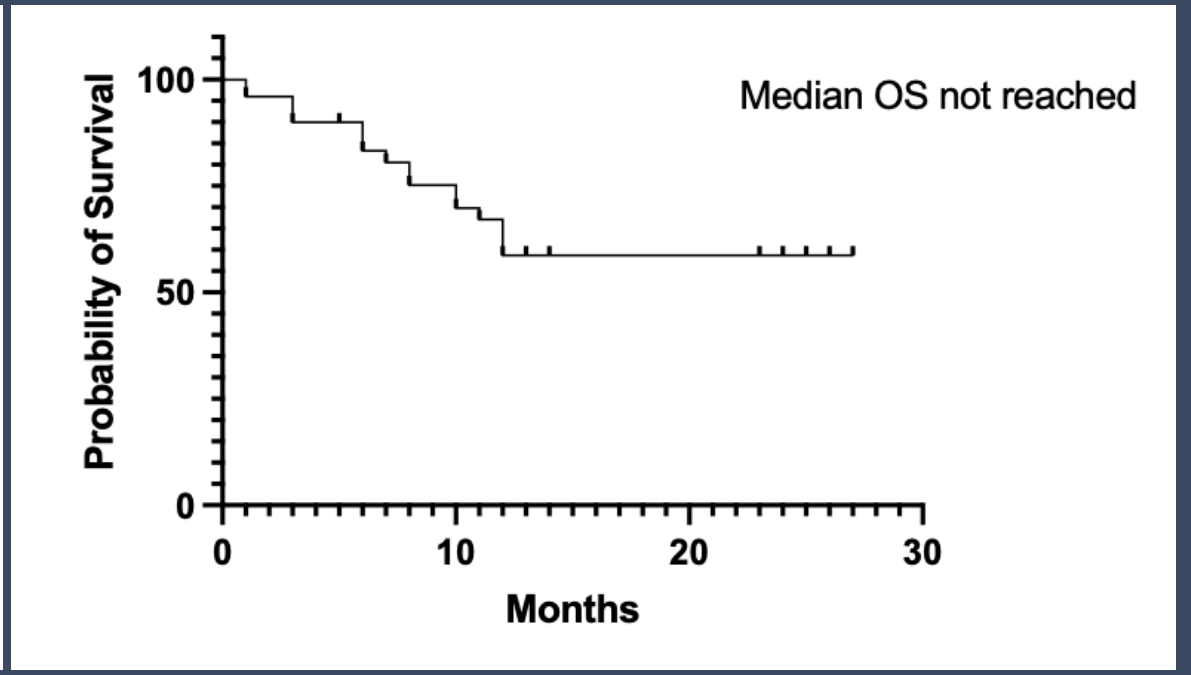
Transplant Feasible Remission (TFR) in AML

65/93 (=69%) achieved CR

53/65 CR patients (=83%) underwent allo-SCT

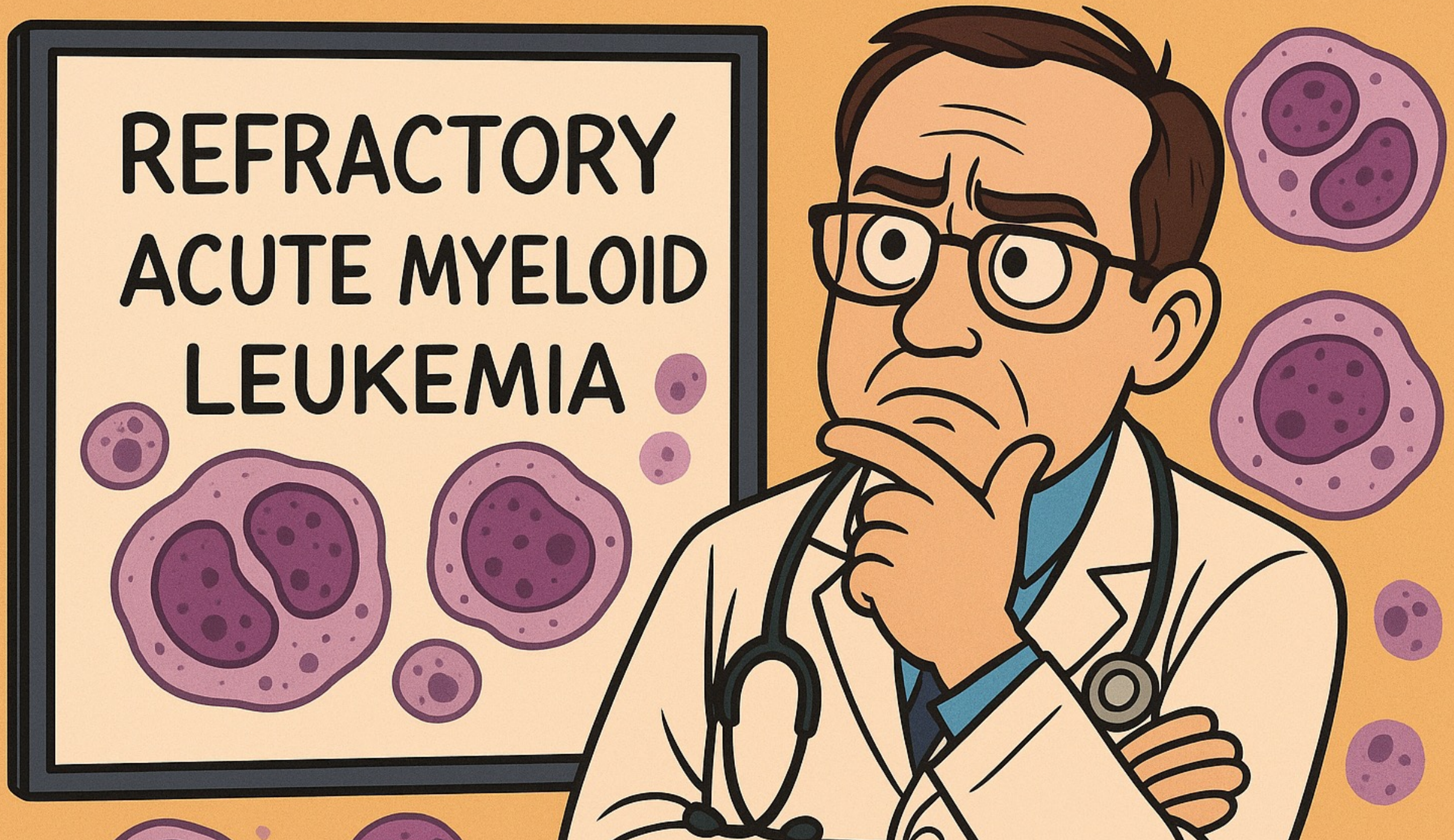
53/93 treated patients (=57%) underwent allo-SCT





Russo D. Et Al . Venetoclax Plus Decitabine As A Bridge To Allogeneic Haematopoietic Stem-cell Transplantation In Older Patients With Acute Myeloid Leukaemia (VEN-DEC GITMO): Final Report Of A Multicentre, Single-arm, Phase 2 Trial. Lancet Haematol. 2024

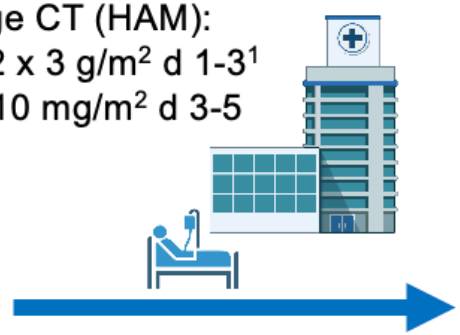
Avenoso D.*, Farina M.* Et Al. Venetoclax-decitabine Followed By Allogeneic Stem Cell Transplant Improves The Outcome Of Elderly High-risk Acute Myeloid Leukaemia: Ven-dec-gitmo Study Mid-term Update Of Allo-transplanted Patients – Bone Marrow Transplantation (2025) 60:183 – 887 - *Joint first authorship.


REFRACTORY
ACUTE MYELOID
LEUKEMIA

Hypothesis: salvage chemotherapy prior to alloHCT would not provide a net benefit.

RIST

Salvage CT (HAM):
AraC 2 x 3 g/m^2 d 1-3[1]
Mitox 10 mg/m^2 d 3-5



Conditioning Intensity tailored to amount of residual AML

R

281 patients, rando 1:1

Primary Endpoint:

Treatment success

OS from Rando

DisC

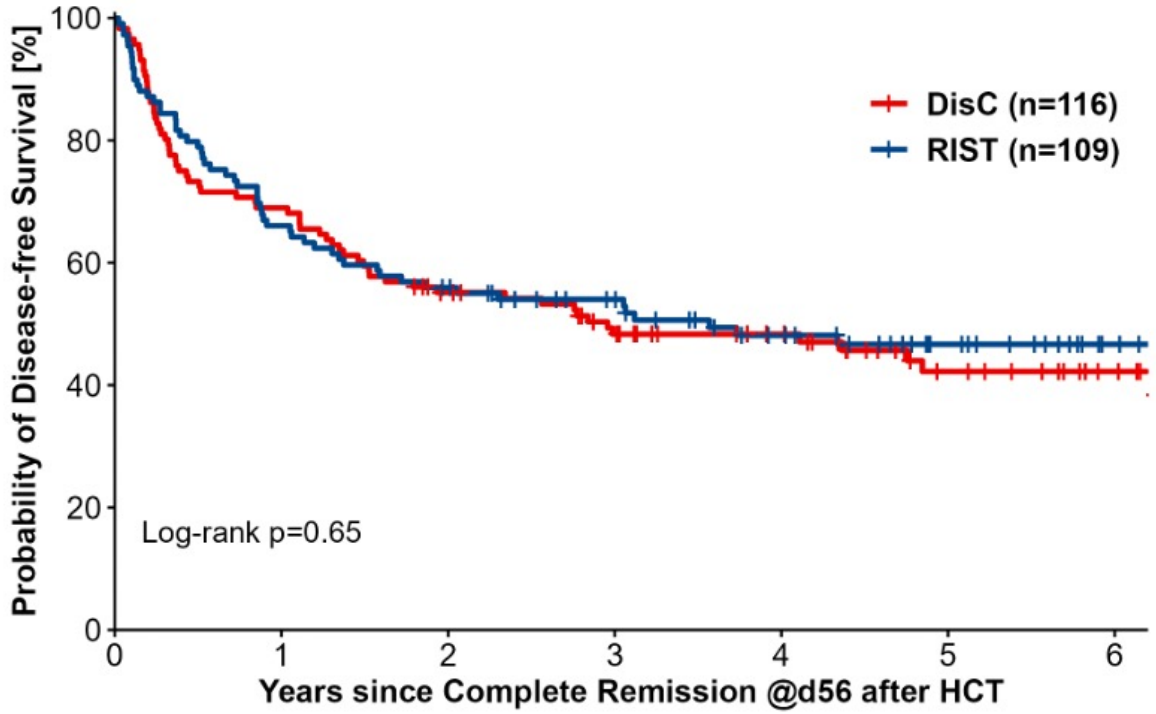
watchful waiting
or
low-dose AraC
or
Mitoxantron 10 mg/m^2

Sequential conditioning
FLAMSA-RIC or
Mel/Flu/TBI

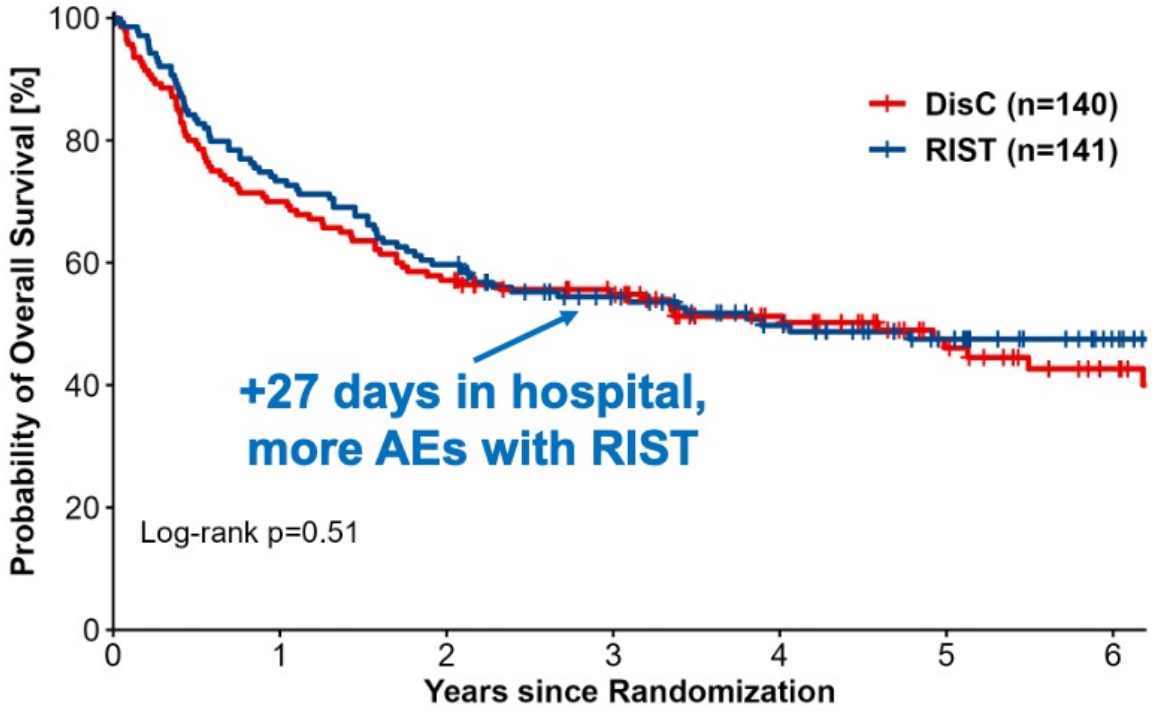
Stelljes, Lancet Hematology 2024

No difference in DFS! No difference in OS from randomization!

Disease-free Survival from d56

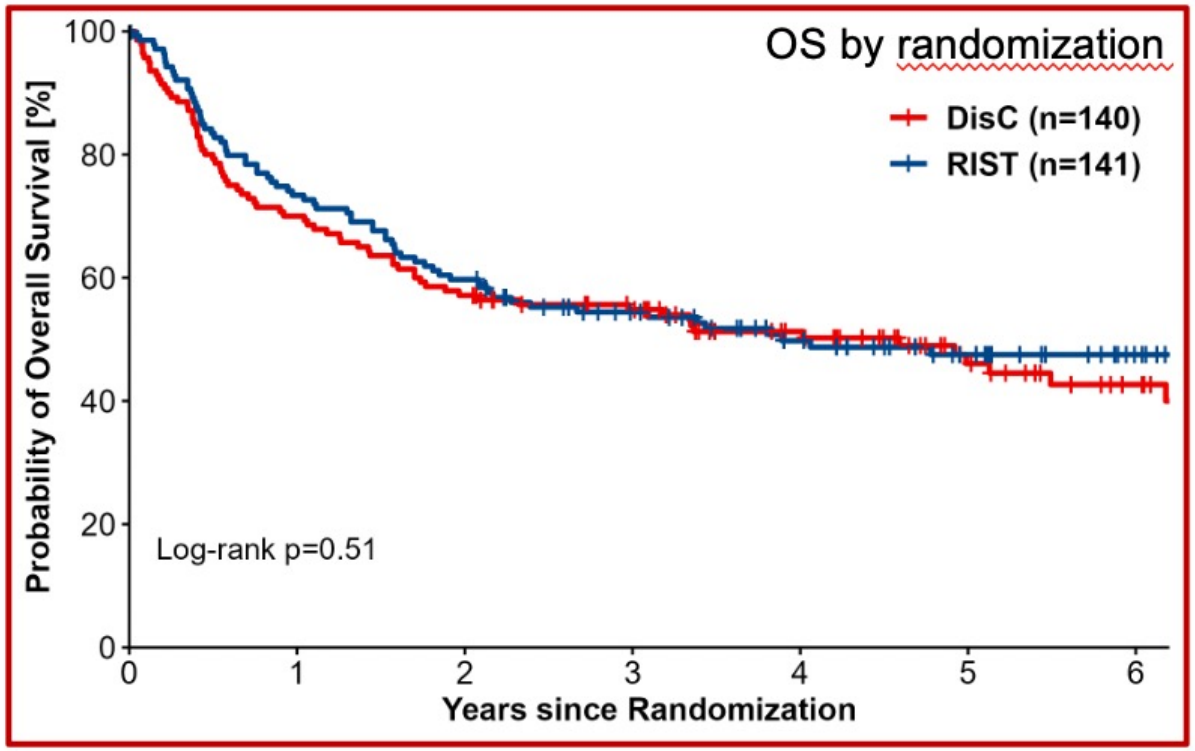


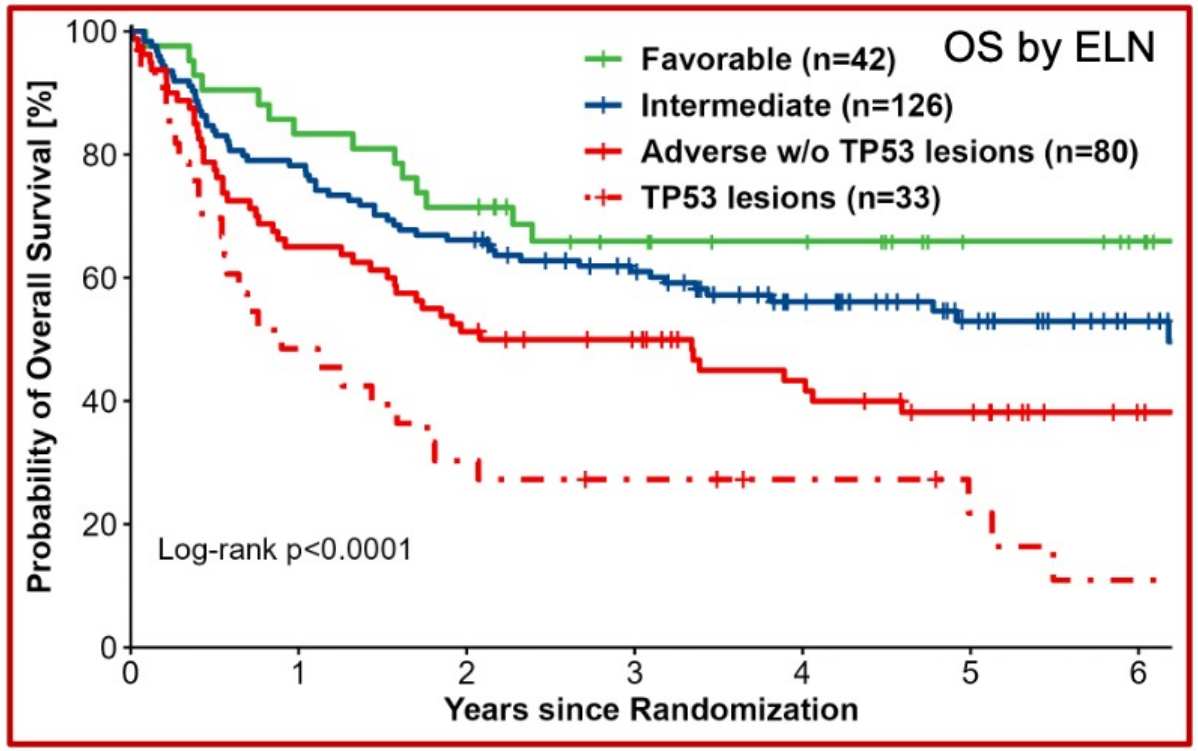
Overall Survival from randomization



Median follow-up from randomization: 60 months

Summary: AML biology matters, but not: depth of remission

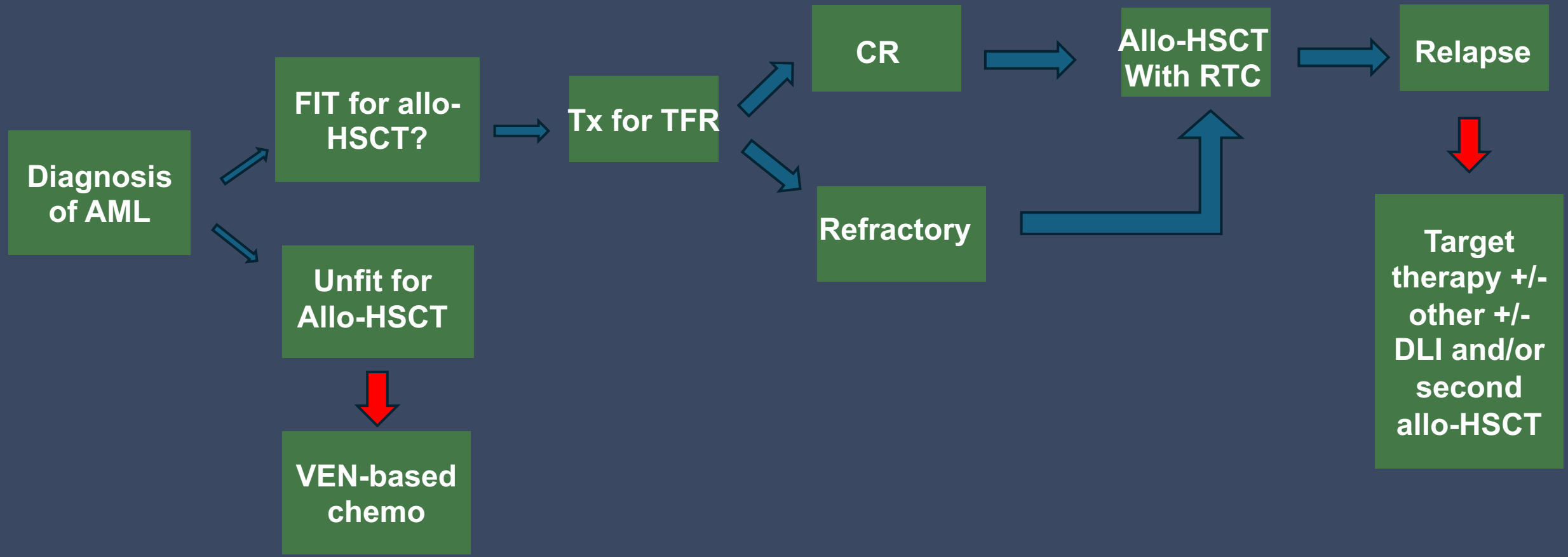




- Long-term follow-up of ASAP trial shows no advantage of remission induction prior to alloHCT
- Sequential conditioning for patients with AML not in remission needs to be improved in frame-work of RCT
- Especially for adverse risk AML bridging, conditioning, and maintenance after HCT need to be improved.

Stelljes et al., ASH 2024

The AML pathway in 2030?



Speaker personal's opinion (& dream).

Conclusions and open questions

- Allo-HSCT remains a central curative strategy in AML, with growing use in older patients and in high-risk disease, supported by refined risk stratification (ELN 2022 AdvP) and by the emerging concept of Transplant Feasible Remission within a comprehensive treatment journey.

- In older and high-risk AML, venetoclax-based therapies (e.g. VEN-DEC GITMO) enable a higher proportion of patients to reach transplant and may redefine the concept of remission as “transplant-oriented” rather than purely morphological.

- PTCY platforms, haploidentical donors, and reduced-intensity conditioning have expanded transplant eligibility, but relapse and non-relapse mortality remain major limitations, especially in AdvP and heavily pretreated patients.

Open questions: Can TFR become a standardized endpoint in AML? How should we integrate MRD, fitness scores and biological risk to personalize conditioning, donor choice and post-transplant strategies (maintenance, DLI, second allo-HSCT) in the 2030 AML pathway?