Should intermediate risk fit patients undergo alloHSCT in CR1?
YES

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

No disclosures

INDICAZIONE AD ALLOTRAPIANTO

Cosa intendiamo per LMA a rischio intermedio?

Recommendations from an international expert panel on behalf of the ELN

2010 ELN risk stratification by genetics

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‡

Blood. 2010 Jan 21; 115

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}† (with adverse-risk genetic lesions) t(9;11)(p21.3;q23.3); *MLLT3-KMT2A*‡ Cytogenetic abnormalities not classified as favorable or adver
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(EV* −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*#

Blood. 2017 Jan 26; 129

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

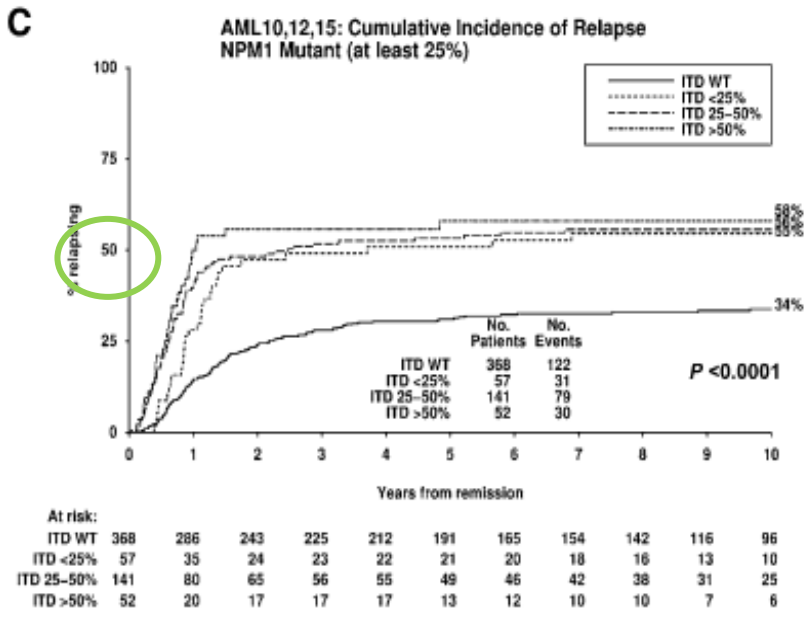
Risk category†	Genetic abnormality
Favorable	• t(8;21)(q22;q22.1)/*RUNX1*::*RUNX1T1*†,‡ • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/*CBFB*::*MYH11*†,‡ • Mutated *NPM1*†,§ without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*‖
Intermediate	• Mutated *NPM1*†,§ with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD (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]

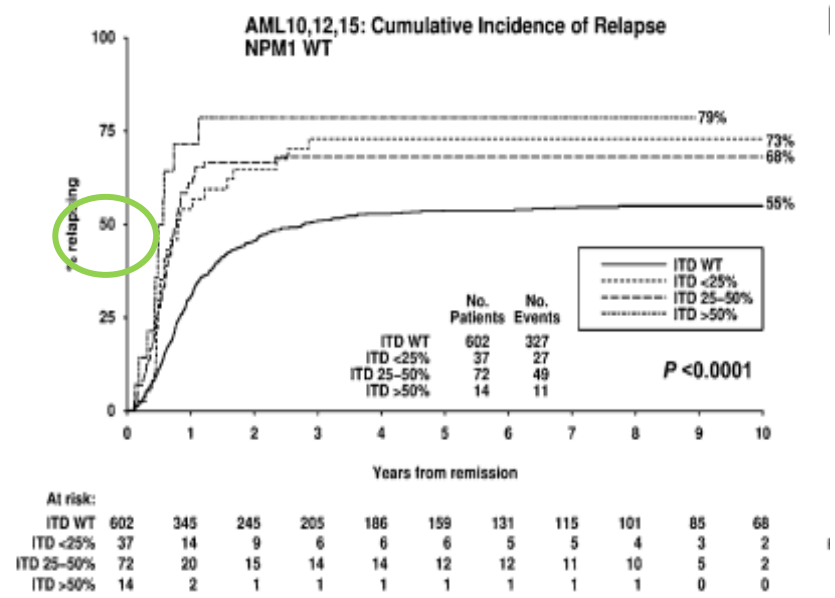
Blood, 2022 Sep 22; 140

Cosa intendiamo per LMA a rischio intermedio?

- Diagnosi spesso di esclusione

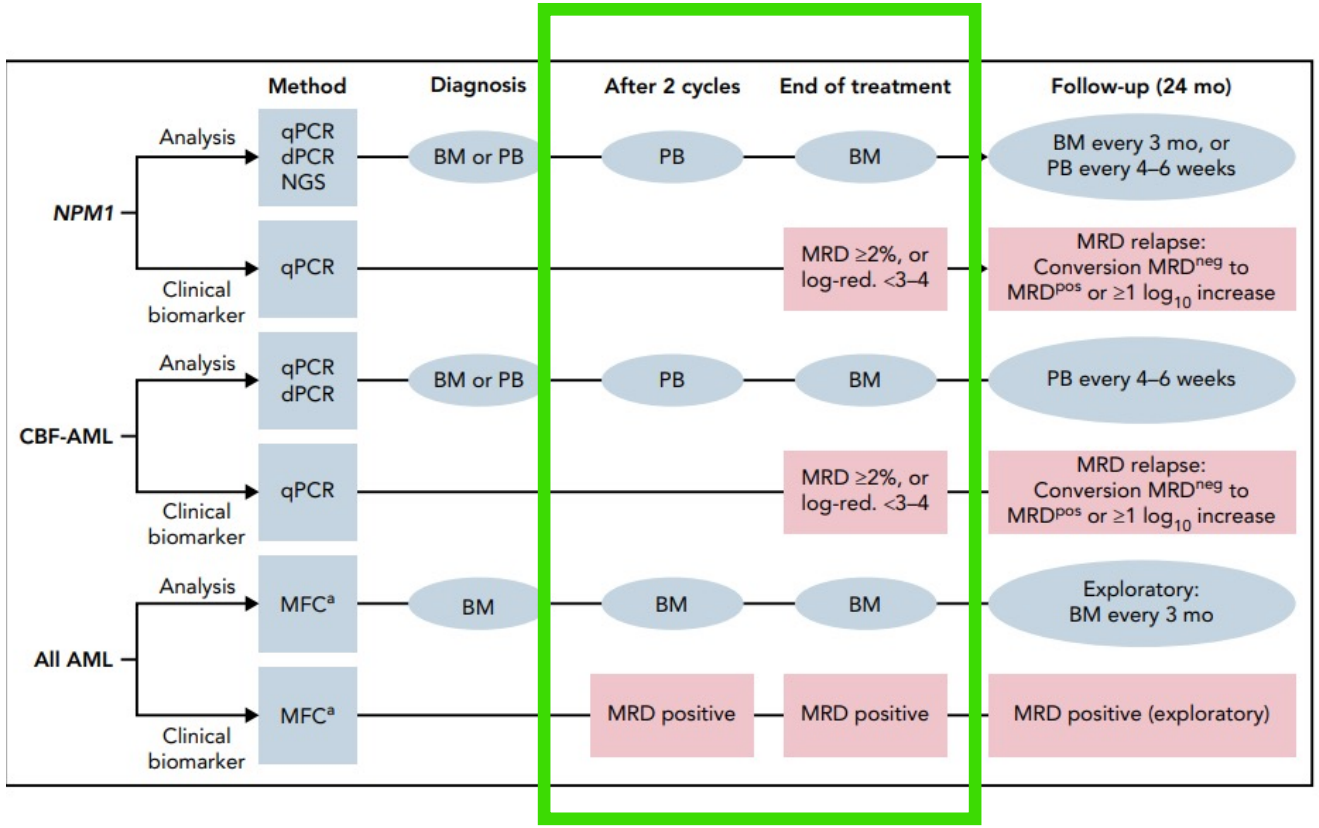
Impact of FLT3ITD mutant allele level on relapse risk in intermediate-risk acute myeloid leukemia



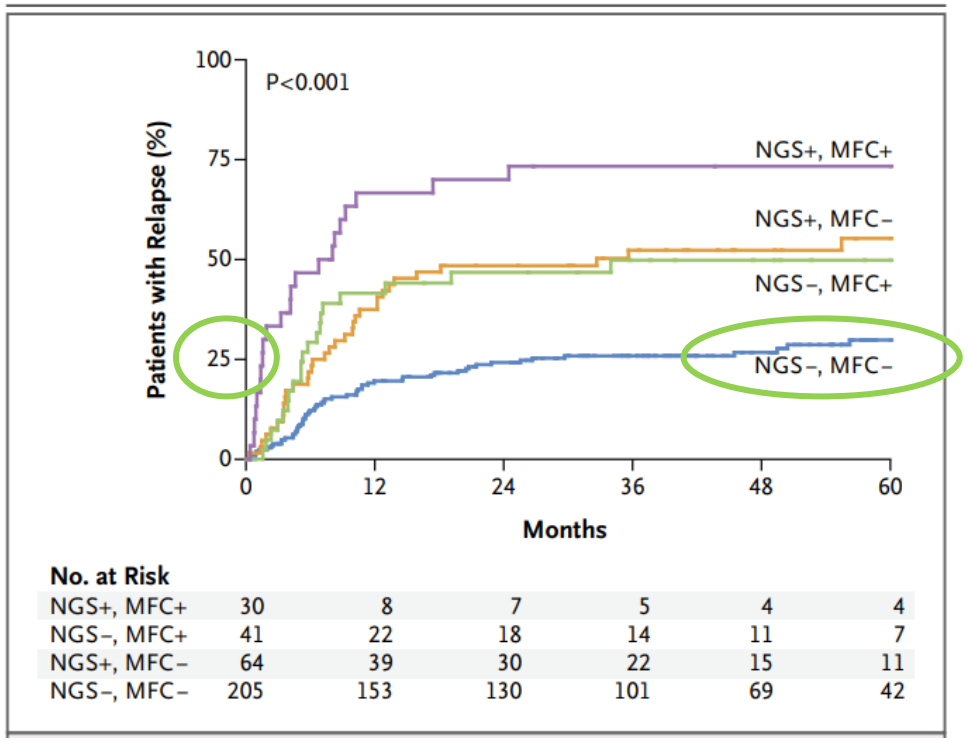


Linch et al. BLOOD, 10 JUL 2014;124

Algorithm of MRD assessment and time points at which MRD is considered a clinically relevant biomarker



Dohner H. et al. Blood, 2022 Sep 22; 140



Jongen-Lavrencic M et al. NEJM, 29 MAR 2018;378

Validation and refinement of the 2022 European LeukemiaNet genetic risk stratification of acute myeloid leukemia

ELN-2022 genetic subset	n	CR [%]	p	5y RFS [%], (95% CI)	p	5y OS [%], (95% CI)	p
Favorable							
inv(16)/t(16;16)	45	82	<0.0001	62 (48-80)	<0.0001	71 (58-85)	<0.0001
t(8;21)	36	58		52 (37-73)		50 (36-69)	
CEBPA bZIPinf	44	73		62 (44-87)		60 (46-77)	
*NPM1*mut without *FLT3*-ITD	238	74		49 (42-58)		51 (45-58)	
Intermediate							
*NPM1*wt without *FLT3*-ITD	40	58	<0.0001	4 (1-30)	<0.0001	23 (13-41)	<0.0001
*NPM1*mut with *FLT3*-ITD	164	68		38 (30-48)		36 (30-45)	
t(9;11)	22	59		39 (19-77)		21 (9-48)	
Other	76	66		29 (18-45)		39 (29-52)	
Adverse							
*ASXL1*mut or *RUNX1*mut	52	50	<0.0001	10 (3-34)	<0.0001	14 (7-29)	<0.0001
Mutations in *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1* or *ZRSR2*	79	65		25 (16-41)		26 (18-38)	
Complex karyotype, *TP53mut*	62	27		0		0	
Complex karyotype, *TP53wt*	38	42		19 (7-52)		18 (9-36)	
Multiple adverse characteristics	162	41		10 (6-21)		10 (6-16)	
Other adverse characteristics	60	42		27 (14-54)		27 (17-41)	

RFS OS

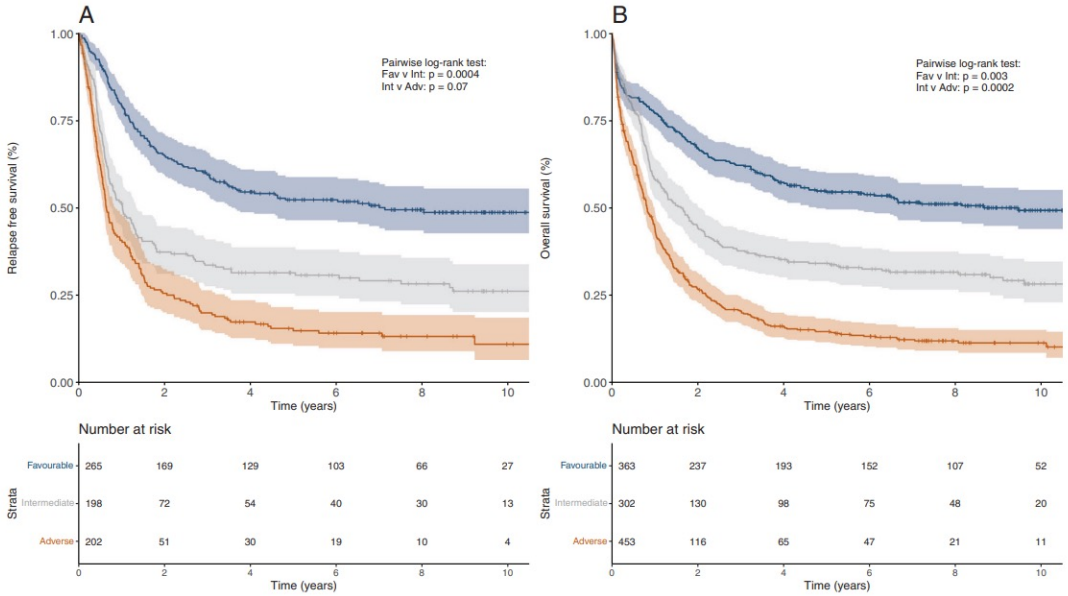
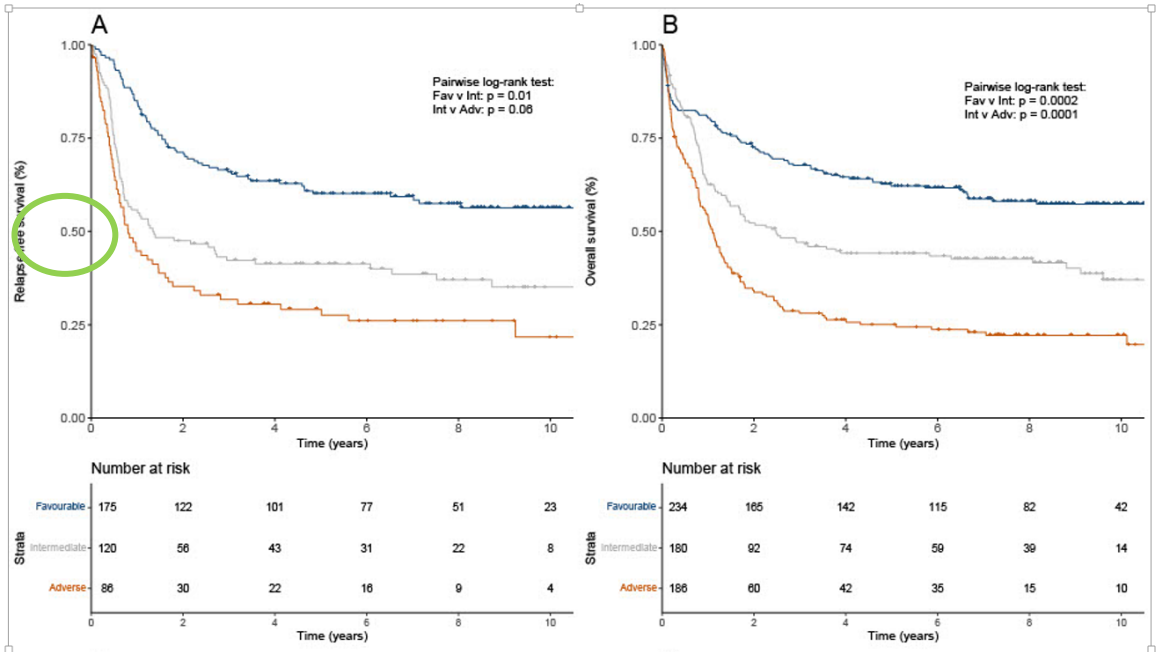


Fig. 2 Outcomes of patients according to the ELN-2022 risk groups. A Relapse-free survival and **B** overall survival in the entire cohort of 1118 patients. (age range: 18–86).

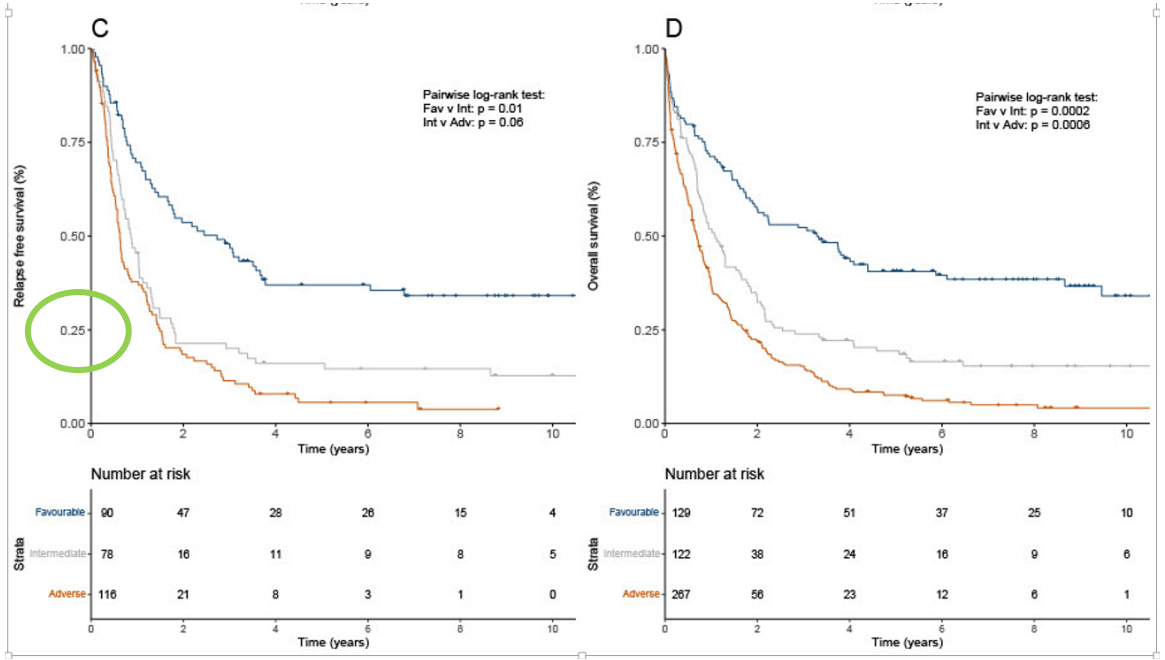
Raush C et al. Leukemia (2023) 37:1234 – 1244

Outcome of patients according to ELN-2022 risk groups stratified by Age

RFS and OS in patients < 60y



RFS and OS in patients ≥ 60y



Appendix. Raush C et al. Leukemia (2023) 37:1234 – 1244

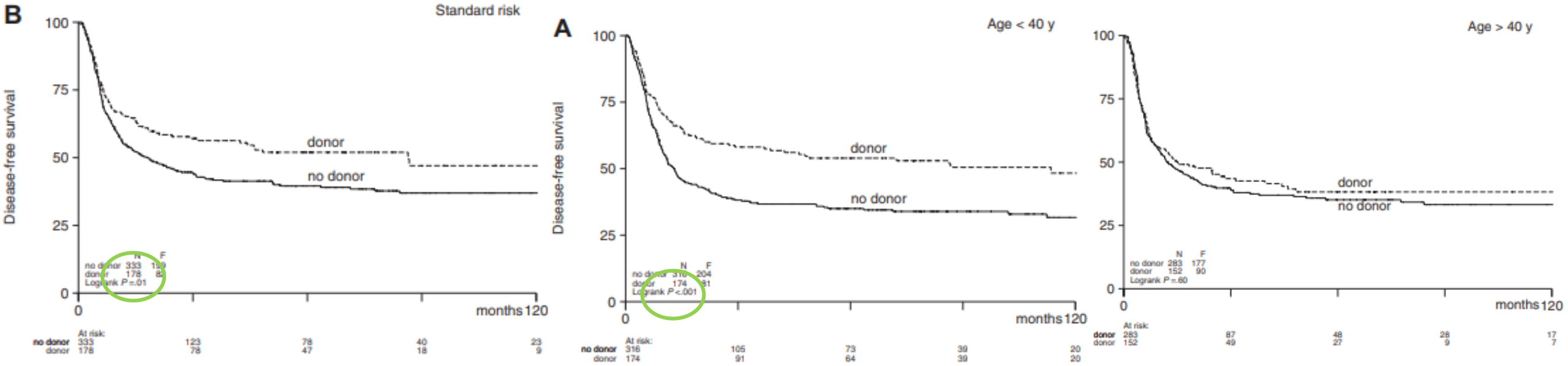
Cosa intendiamo per LMA a rischio intermedio?

- Diagnosi spesso di esclusione
- Incidenza di recidiva a 5 anni ~ 50%, se FLT3ITD+ > 60%
- Se MRD^{neg} post I consolidamento rischio di recidiva ~ 25% → andamento favorevole
- RFS a 5 anni ~ 30% (40% negli under 60, < 25% negli over 60)

Abbiamo studi che confrontano CT vs allo-SCT nelle LMA a rischio intermedio in RC1?

Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling SCT in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom?

1987 and 2004, 2287 pts, age 15-55y



Cornelissen et al. BLOOD, 1 MAY 2007;109

Results of a HOVON/SAKK donor versus no-donor analysis of myeloablative HLA-identical sibling SCT in first remission acute myeloid leukemia in young and middle-aged adults: benefits for whom?

Table 4. Effect of donor availability on outcome in AML in CR1

Outcome	Donor n	Donor No. of events	Donor Probability of outcome at 4 y ± SE, %	No donor n	No donor No. of events	No donor Probability of outcome at 4 y ± SE, %	P*	HR (95% CI)
All patients	326			599				
Survival		157	54 ± 3		326	46 ± 2	.09	0.85 (0.70–1.03)
DFS		171	48 ± 3		381	37 ± 2	< .001	0.71 (0.59–0.85)
Relapse		103	32 ± 3		354	59 ± 2	< .001	0.46 (0.37–0.57)
TRM		68	21 ± 2		27	4 ± 1	< .001	3.99 (2.55–6.25)
Good risk	32			73				
Survival		9	84 ± 6		17	78 ± 5	.99	1.01 (0.45–2.27)
DFS		11	72 ± 8		28	64 ± 6	.40	0.74 (0.37–1.50)
Relapse		7	22 ± 7		24	32 ± 6	.17	0.57 (0.24–1.31)
TRM		4	6 ± 4		4	4 ± 2	.42	1.80 (0.44–7.31)
Intermediate risk	178			333				
Survival		76	57 ± 4		172	48 ± 3	.23	0.85 (0.65–1.11)
DFS		82	53 ± 4		199	41 ± 3	.014	0.73 (0.56–0.94)
Relapse		50	28 ± 3		188	55 ± 3	< .001	0.47 (0.34–0.64)
TRM		32	19 ± 3		11	3 ± 1	< .001	5.13 (2.58–10.2)
Poor risk	116			193				
Survival		72	40 ± 5		137	30 ± 4	.17	0.82 (0.62–1.09)
DFS		78	33 ± 4		154	17 ± 3	.003	0.67 (0.51–0.88)
Relapse		46	39 ± 5		142	77 ± 3	< .001	0.43 (0.31–0.60)
TRM		32	28 ± 4		12	6 ± 2	< .001	3.47 (1.78–6.77)
Age younger than 40 y	174			316				
Survival		73	61 ± 4		164	49 ± 3	.015	0.71 (0.54–0.94)
DFS		81	55 ± 4		204	37 ± 3	< .001	0.59 (0.46–0.77)
Relapse		51	28 ± 3		187	58 ± 3	< .001	0.41 (0.30–0.56)
TRM		30	17 ± 3		17	5 ± 1	.002	2.6 (1.4–4.75)
Age older than 40 y	152			283				
Survival		84	44 ± 4		162	42 ± 3	.84	0.97 (0.75–1.27)
DFS		90	39 ± 4		177	36 ± 3	.15	0.83 (0.64–1.07)
Relapse		52	35 ± 4		167	60 ± 3	< .001	0.51 (0.37–0.70)
TRM		38	25 ± 4		10	4 ± 1	< .001	6.07 (3.0–12.24)

HR indicates hazard ratio for donor compared with no donor from multivariate Cox model adjusted for risk and age.
P from likelihood ratio test.

Table 5. Results of multivariate analysis in which donor availability, prognostic category, and age were considered

Parameter	Overall survival HR	Overall survival 95% CI	Overall survival P	Disease-free survival HR	Disease-free survival 95% CI	Disease-free survival P	Relapse HR	Relapse 95% CI	Relapse P
Donor availability*	0.85	(0.70–1.03)	.09	0.71	(0.59–0.85)	< .001	0.46	(0.37–0.57)	< .001
Prognostic category†			< .001			< .001			< .001
Intermediate	2.50	(1.67–3.76)		1.83	(1.30–2.56)		1.97	(1.35–2.87)	
Poor risk	4.53	(3.01–6.83)		3.49	(2.48–4.90)		3.67	(2.51–5.38)	
Age older than 40‡	1.39	(1.16–1.67)	< .001	1.23	(1.03–1.45)	.02	1.19	(0.98–1.43)	.07

Prognostic category according to cytogenetics, WBC count, and early or late attainment of CR (see "Patients, materials, and Methods").
HR indicates hazard ratio; CI, confidence interval.
*In comparison with no donor group.
†In comparison with good-risk group.
‡In comparison with age younger than 40 group.

Cornelissen et al. BLOOD, 1 MAY 2007;109

Allogeneic hematopoietic cell transplantation compared to chemotherapy consolidation in older acute myeloid leukemia (AML) patients 60-75 years in first complete remission (CR1): an alliance (A151509), SWOG, ECOG-ACRIN, and CIBMTR study

2008 and 2013, 431pts allo, 211pts CT, age 60-75y

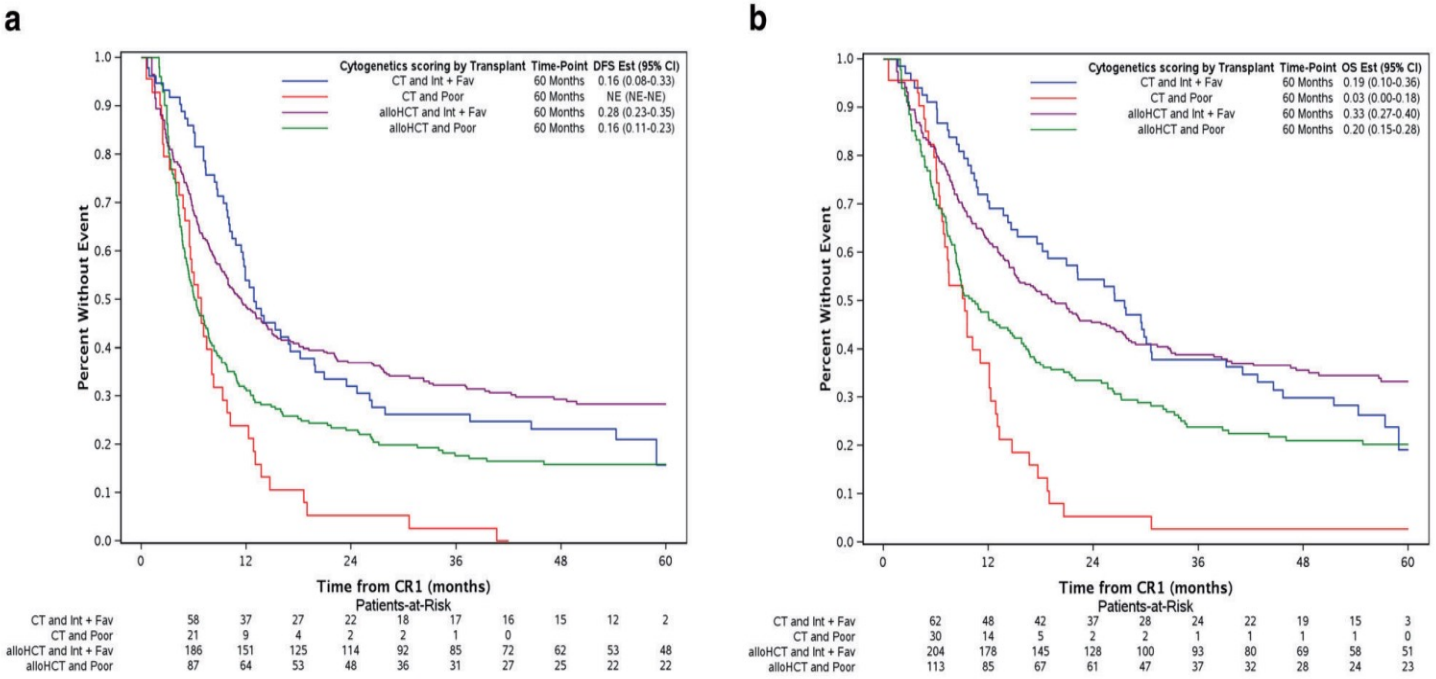


Fig. 2 Disease-free survival by alloHCT or CT stratified by intermediate or poor cytogenetic categories and 5-year point estimates (**2a**), overall survival by alloHCT or CT stratified by intermediate or poor cytogenetic categories and 5-year point estimates (**2b**)

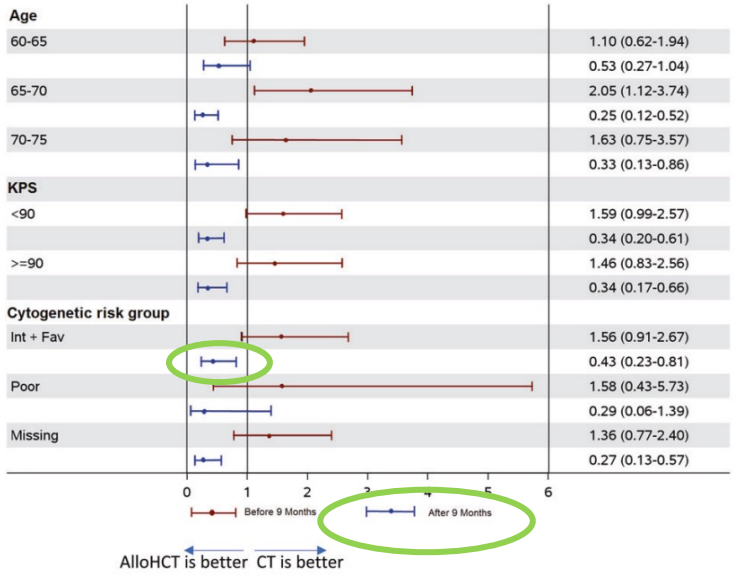


Fig. 3 The Forest plot represents the effect of each characteristic (age, Karnofsky Performance Status, and cytogenetic risk group) on overall survival per treatment before and after 9 months

Ustun C et al. Leukemia. 2019;33(11): 2599-2609

Outcomes of older patients aged 60 to 70 years undergoing reduced intensity transplant for acute myeloblastic leukemia: results of the NCRI acute myeloid leukemia 16 trial

2006 and 2012, 144pts allo, 788pts CT, age 60-70y

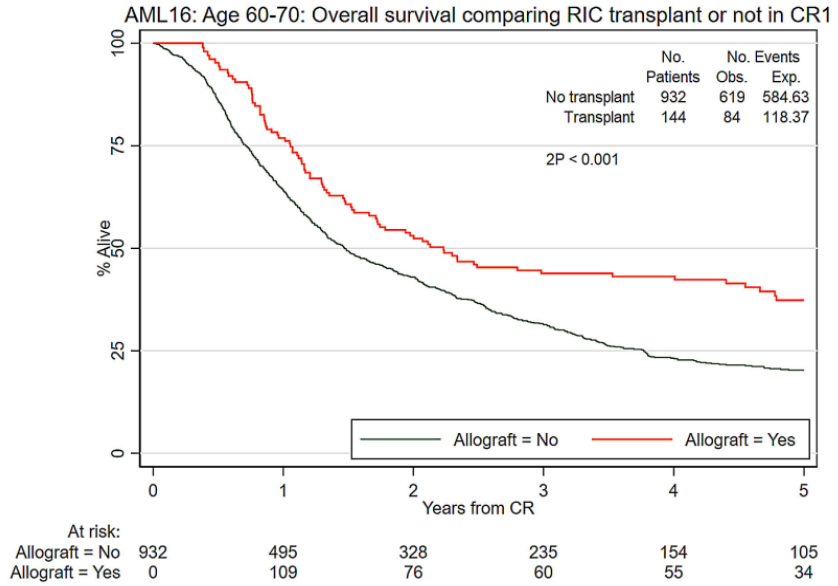


Figure 2. Overall survival comparing reduced intensity conditioning transplantation or not for acute myeloid leukemia in first complete remission. RIC: reduced intensity conditioning; CR1: first complete remission; Obs: observed; Exp: expected.

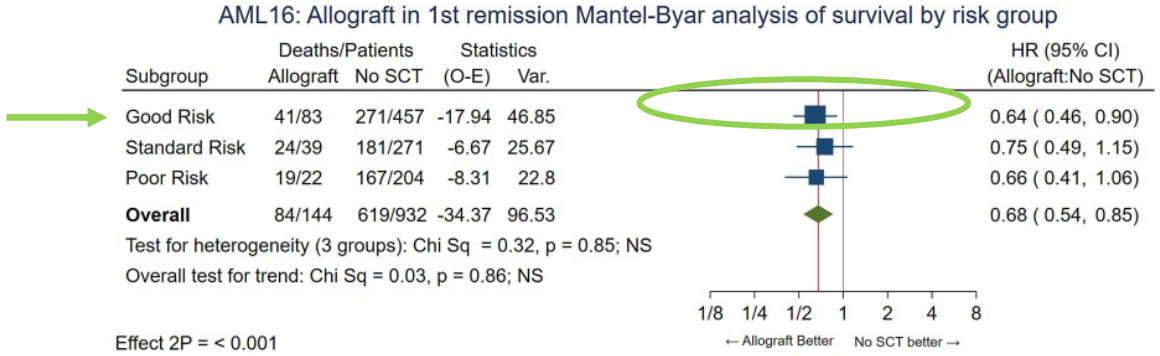


Figure 3. Mantel-Byar analysis of overall survival by Wheatley risk group. SCT: stem cell transplant; O-E: observed – expected; HR: hazard ratio; 95% CI: 95% confidence interval.

Table III. Simplified risk score.

Parameter	Score
Cytogenetic group	1 = favourable/intermediat[illegible]5 = adverse, 2 = unknown
WBC group	1 = <10·0, 2 = 10·0–49·9, 3 = 50–99·9, 4 = 100+ ($\times 10^9$/l)
Performance status	Performance status score: 0, 1, 2, 3, 4
Age group	1 = 60–64, 2 = 65–69, 3 = 70–74, 4 = 75+ (years)
AML type	1 = *de novo*, 3 = secondary
Total	Score (Cytogenetic group) + Score (WBC group) + Score (Performance status) + Score (Age group) + Score (AML type)
Risk Group	4–6 = Good, 7–8 = Standard, 9+ = Poor

Wheatley K et al. BJH. 2009; 145

Russel NH et al. Haematologica. 2021; 107

Cosa dicono gli studi che confrontano CT vs allo-SCT nelle LMA in RC1 a rischio intermedio?

- RFS a favore dell' allo-SCT, OS a favore dell'allo-SCT < 40aa
- RFS e OS a favore dell' allo-SCT a partire da 9 mesi post trapianto
- OS a favore dell'allo-SCT

Qual è l’outcome del trapianto allogenico nelle LMA in CR1?

Effectiveness of allogeneic hematopoietic cell transplantation for older (60-70y) patients with acute myeloid leukemia

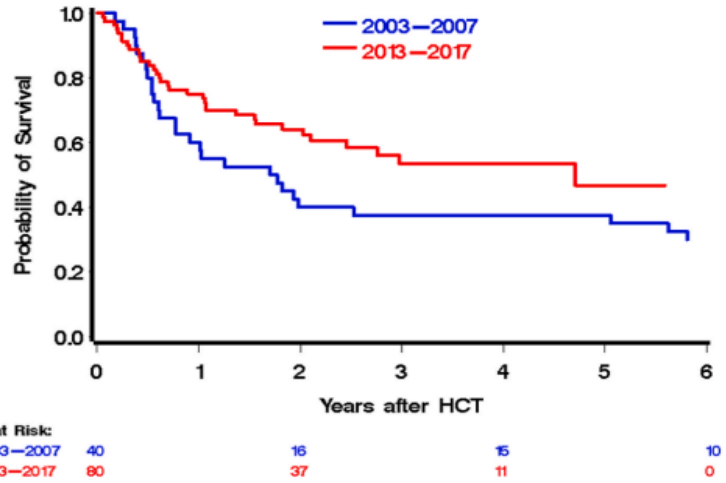


Fig. 3. Overall survival post-allogeneic hematopoietic cell transplantation for AML in CR1 over age 60.

an attempt by the Canadian/Australasian Group took 13 years to accrue 145 patients (fewer than 75 in each arm), and 27% of those assigned to transplantation never received the therapy [10].

Fig. 1. Incidence of hematopoietic cell transplantation for AML by age. The proportion of patients transplanted remains relatively constant at around 30% from birth until about age 65 and then precipitously declines.

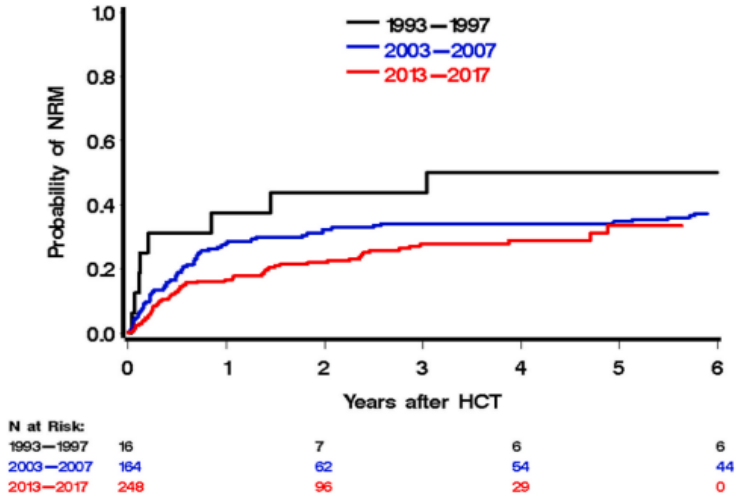


Fig. 2. Non-relapse mortality for patients aged 61–70 by era.

Appelbaum FR et al. Best Practice & Research Clinical Haematology 34 (2021) 101320

The European LeukemiaNet AML Working Party consensus statement on allogeneic HSCT for patients with AML in remission: an integrated-risk adapted approach

We suggest that allogeneic HSCT might be favoured if the projected disease-free survival is expected to improve by at least 10% based on an individual's risk assessment

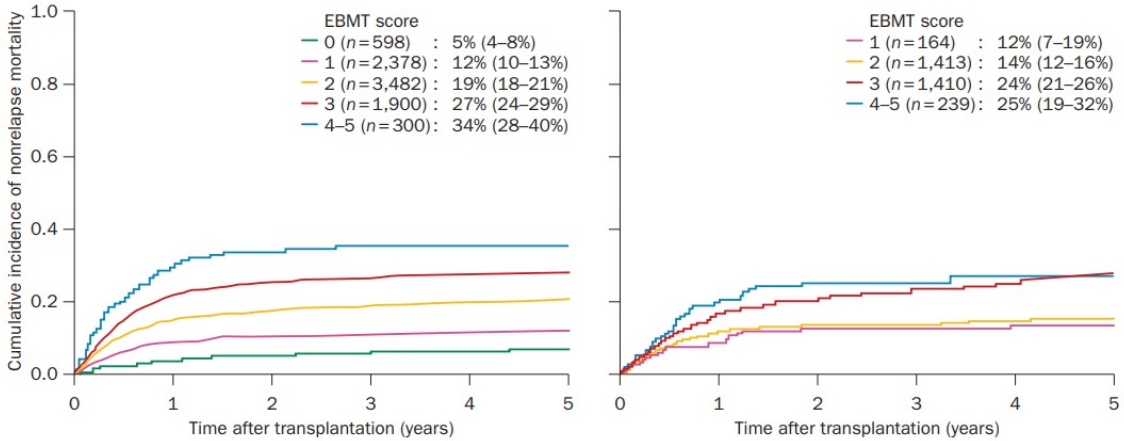


Figure 2 | Cumulative incidence of nonrelapse mortality, with relapse as a competing risk, in patients with AML in their first complete remission. Data for patients in Europe (2000–2010) were generated by the EBMT Acute Leukemia Working Party using the EBMT risk score, which includes the following parameters: patient age, donor type, time interval from diagnosis to transplantation and donor–recipient gender combination.[45] **a** | Patients who received myeloablative conditioning prior to allogenic HSCT. **b** | Patients who received RIC prior to allogeneic HSCT. Patients receiving RIC allogeneic HSCT were significantly older than patients receiving myeloablative allogeneic HSCT (median age 38 years [range 35–77] versus 56 years [range 54–77]; $P<0.0001$). Abbreviations: AML, acute myeloid leukaemia; EBMT, European Group for Blood and Marrow Transplantation; HSCT, haematopoietic stem cell transplantation; RIC, reduced-intensity conditioning.

Table 3 | Nonrelapse mortality (%) at 2 years after allogeneic HSCT*

Study	HCT–CI score			
	0	1–2	≥3	>5
Sorror *et al.*[69] Training set: *n*=708	9	14–27	41–43	Not reported
Sorror *et al.*[69] Validation set: *n*=346	14	19–22	40–41	Not reported
Sorror *et al.*[70] *n*=244‡	7	19–21	27–37	Not reported
Barba *et al.*[76] *n*=194	15	9–36	24–39	28–56

*The studies included recipients of both matched sibling or matched unrelated donor grafts following either myeloablative or nonmyeloablative conditioning. ‡177 patients from The Fred Hutchinson Cancer Research Center, Seattle, WA, USA and 67 patients from MD Anderson Cancer Center, Houston, TX, USA. Abbreviations: HCT–CI, haematopoietic cell transplantation comorbidity index; HSCT, haematopoietic stem cell transplantation.

Cornelissen, J. J. et al. Nat. Rev. Clin. Oncol. 9, 579–590 (2012)

Cornelissen 2012

Redefining and measuring transplant conditioning intensity in current era: a study in acute myeloid leukemia patients

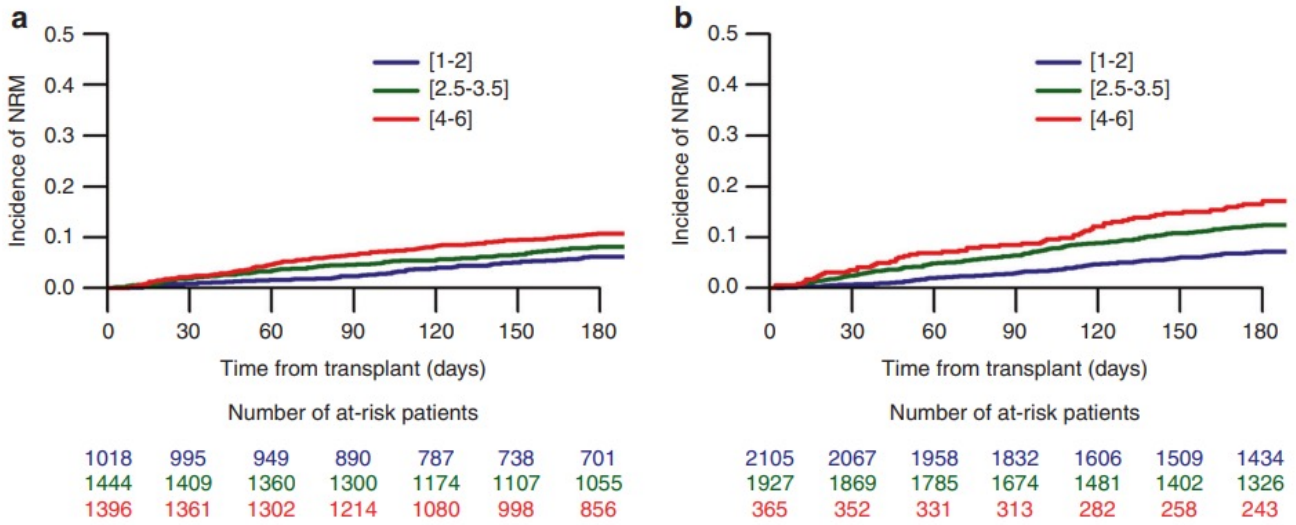


Fig. 2 Early nonrelapse mortality (NRM) according to TCI. **a** Early NRM in the subgroup of patients aged 45–55 years at transplant ($n = 3858$). **b** Early NRM in patients aged between 55 and 65 years ($n = 4397$).

Table 4 Multivariate analysis

Variable		NRM	Relapse
TCI	[1,2]	1	1
	[2.5–3.5]	1.27 (1.12–1.44), 0.0003	0.81 (0.73–0.89), <0.0001
	[4–6]	1.44 (1.22–1.69), <0.0001	0.7 (0.61–0.8), <0.0001

21% dei pazienti con HCT-CI ≥ 3

Spyridonidis A et al. Bone Marrow Transplantation (2020) 55:1114–1125

Uniform graft-versus-host disease prophylaxis with posttransplant cyclophosphamide, sirolimus, and mycophenolate mofetil following hematopoietic stem cell transplantation from haploidentical, matched sibling and unrelated donors

The cumulative incidence of NRM at 1-year was 14% (95% CI, 8–19%) (Fig. 4a).

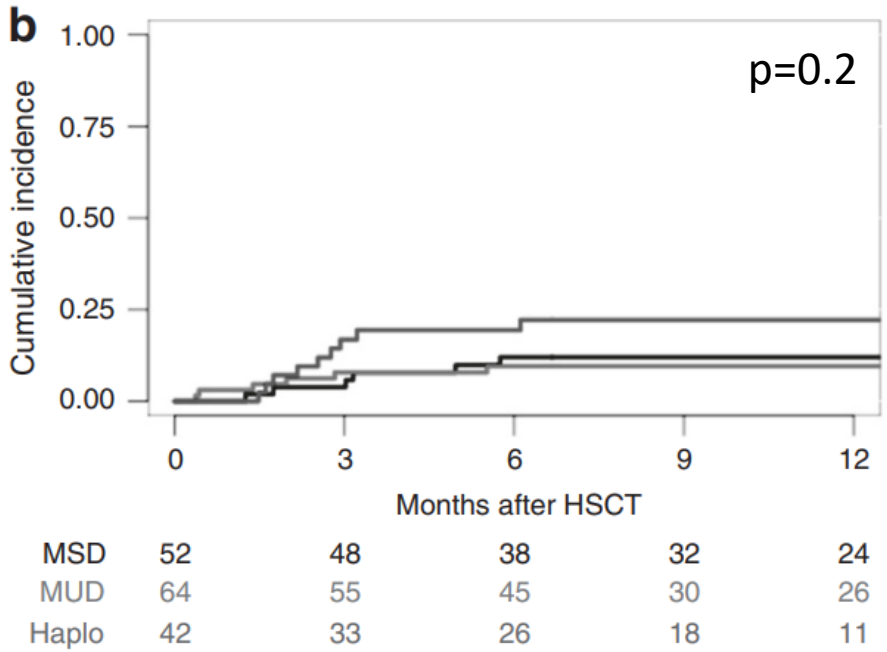


Fig. 4 Cumulative incidence of NRM. Cumulative incidence of overall non-relapse mortality (**a**) and according to donor type (**b**).

Montoro et al. Bone Marrow Transplant . 2020; 55(11):2147-2159

Qual è l'outcome del trapianto allogenico nelle LMA in CR1?

- La NRM si reduce in anni più recenti: attualmente è <20%
- Gli score trapiantologici sono utili per stimare la NRM ma vanno più che altro utilizzati per adeguare la procedura trapiantologica alle comorbidità del paziente
- TCI intermedi potrebbero permetterci di controllare meglio la malattia anche nei pazienti fragili
- Il tipo di donatore assume sempre meno un ruolo nell'algoritmo di scelta della terapia di consolidamento dei pazienti con LMA in RC

Acute myeloid leukemia: 2021 update on risk-stratification and management

TABLE 6 Deciding on allo HCT: ELN 2017 and MRD to assess risk of relapse and HCT-CI to asse post HCT

Pre-treatment ELN 2017 Risk	MRD detected by	MRD status after 1-2 cycles therapy	Risk relapse at 2 years without allo HCT	Risk of NRM justifying allo HCT (HCT-CI score associated with that risk)
Favorable (CBF)	PCR	Negative (70% of pts)	10%–20%	Too risky regardless of HCT-CI score
	PCR	Positive	50%	
Favorable (*NPM+/FLT3 -*)		Negative (90% of pts)	25%	≤20% (≤2)
		Positive	70%	≤10% (≤1)
				≤40% (≤3)
Intermediate	MFC	Negative (80% of pts)	25%	≤10% (≤1)
		Positive	80%	≤40% (≤3)
Adverse	MFC	Negative (66% of pts)	70-80%	≤40% (≤3)
		Positive	90-100%	CR ≤ 40% (≤3)

Estey EH. Am J Hematol. 2020;95:1368–1

Should intermediate risk fit patients undergo alloHSCT in CR1?

YES