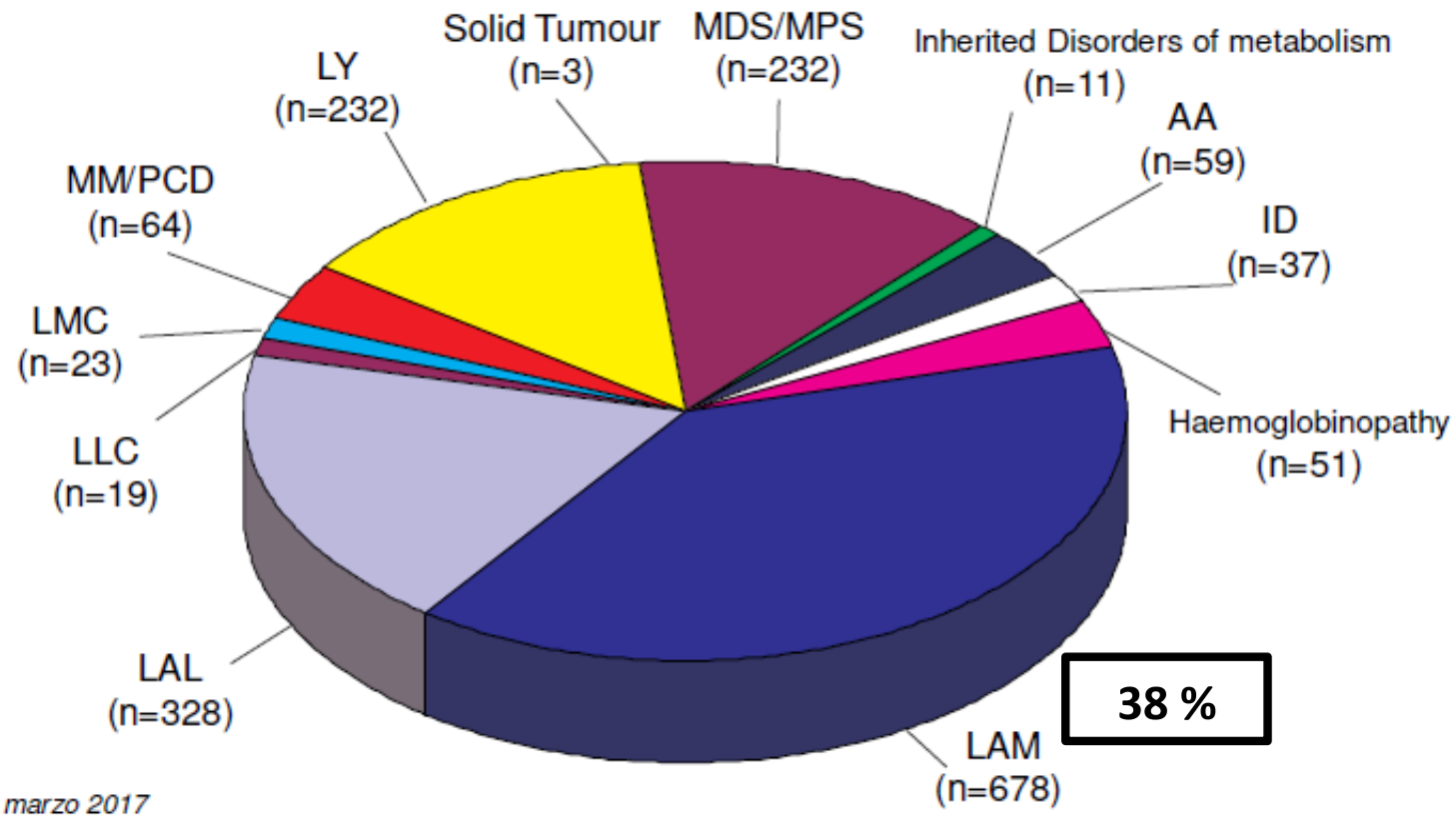
Il trapianto nella leucemia acuta mieloide a rischio intermedio

Domenico Pastore
UOC Ematologia Brindisi

GITMO Trapianto Allogenico

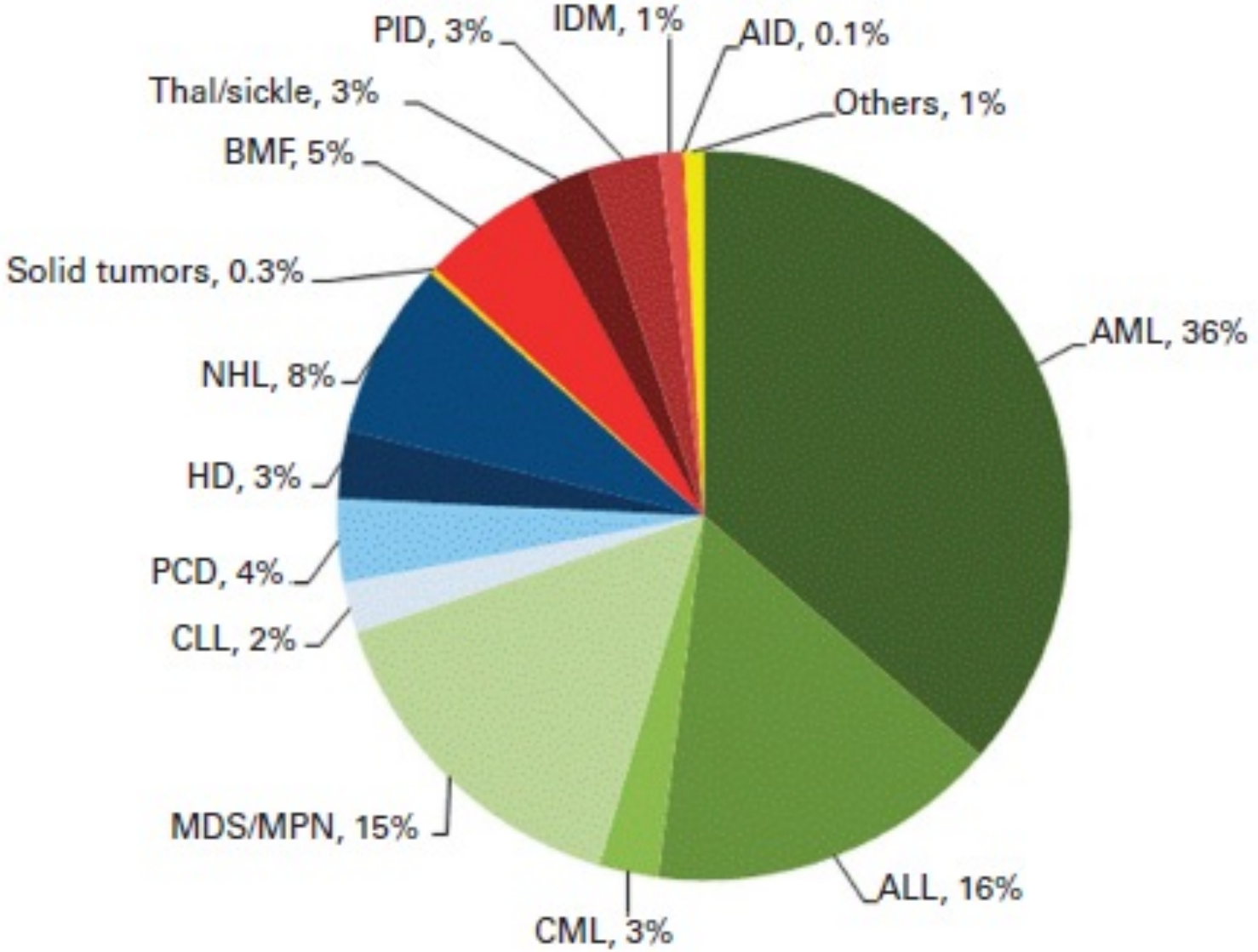
Numero Trapianti per principali Patologie

Attività 2016 **1796**



al 22 marzo 2017

Proportion of disease indications for allo SCT in Europe in 2014



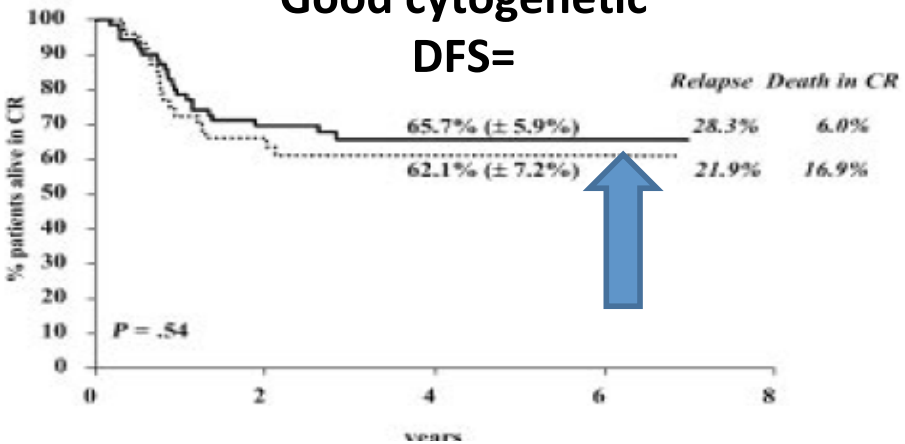
Passweg JR et al Bone Marrow Transplant 2016;51:786-792

Allo SCT in AML in CR1: an intention-to-treat analysis

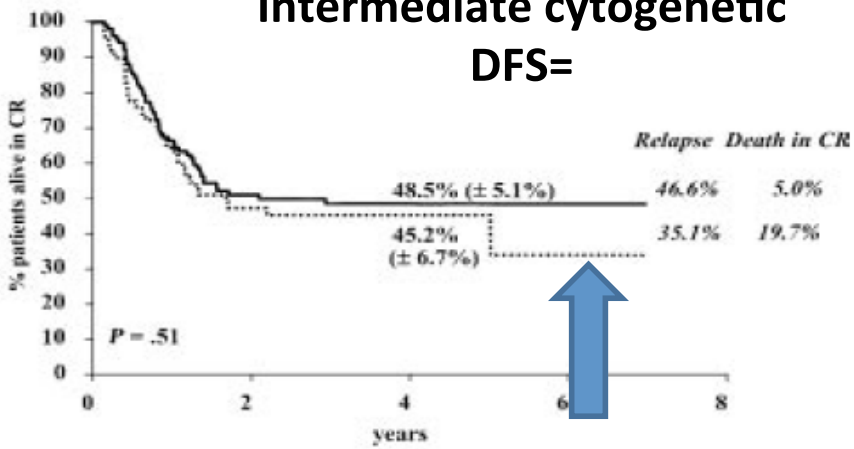
Donor vs no donor (HLA-identical sibling donor)

EORTC/GIMEMA AML-10 trial

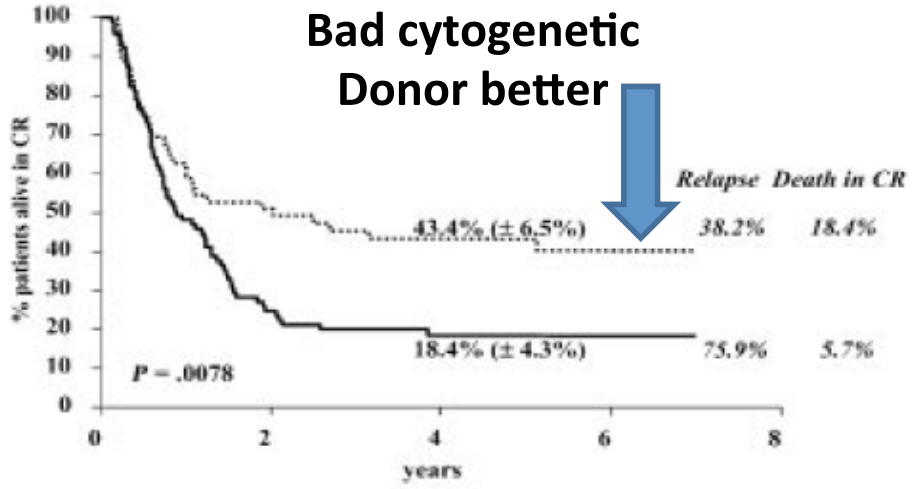
Good cytogenetic
DFS=



Intermediate cytogenetic
DFS=



Bad cytogenetic
Donor better



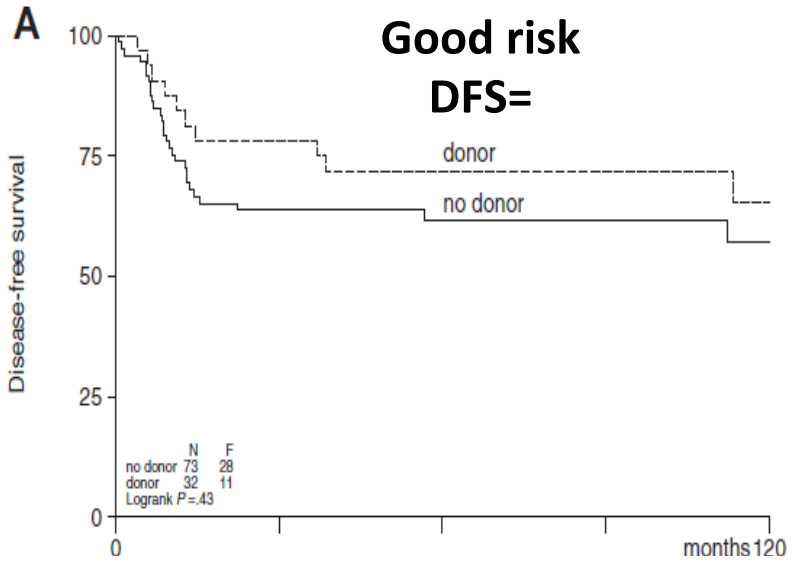
➢**Intermediate risk→Hazard Ratio 1**

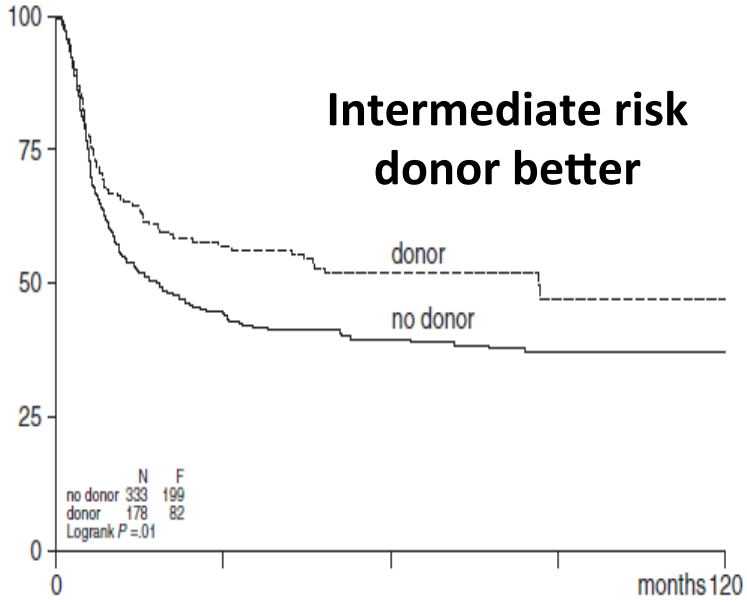
Suciu et al Blood 2003;102:1232-1240

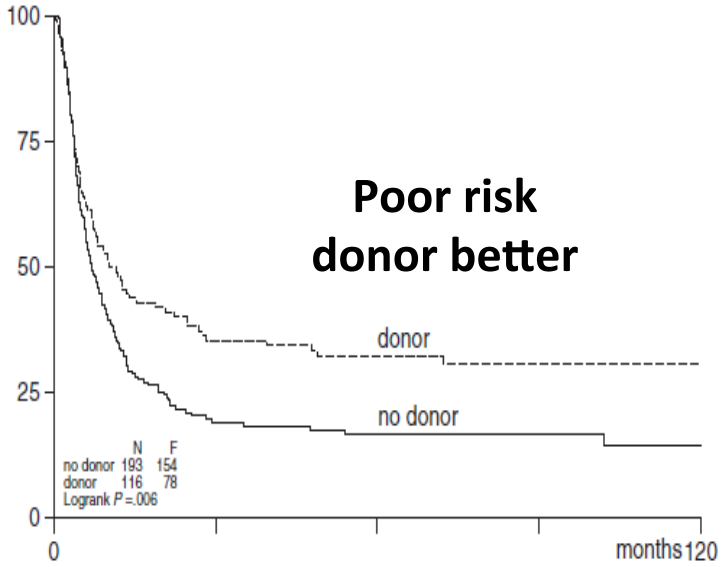
Donor vs no donor analysis

HLA-identical sibling donor

HOVON/SAKK study







Patients were classified as good, intermediate, and poor risk on the basis of cytogenetic abnormalities, the white blood cell(WBC) count at diagnosis, and whether CR was reached after cycle I or after cycle II

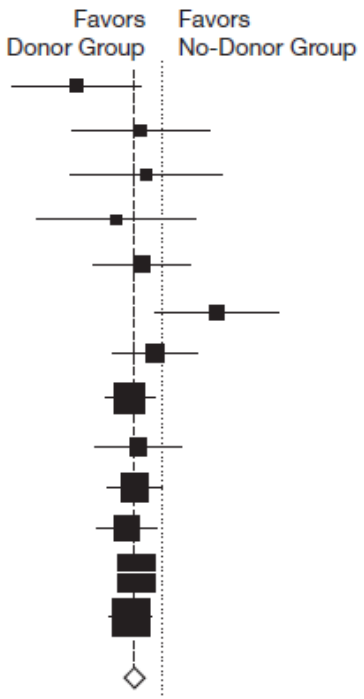
Cornelissen J et al Blood 2007;109:3658-3666

Meta-analysis of 18 clinical trials

Patients with or without matched sibling donor

Relapse-Free Survival (RFS) Benefit of Allogeneic SCT for AML in First Complete Remission

Source	No. of Patients: Donor Group	No. of Patients: No-Donor Group	No. of Trials	HR (95% CI)
Ferrant et al,[9] 1991[a]	24	72		0.50 (0.30-0.85)
Cassileth et al,[10] 1992[a]	54	29		0.84 (0.48-1.49)
Schiller et al,[11] 1992	28	54		0.88 (0.48-1.64)
Archimbaud et al,[12] 1994	27	31		0.69 (0.36-1.32)
Hewlett et al,[13] 1995	53	110		0.85 (0.58-1.27)
Sierra et al,[14] 1996	47	68		1.56 (0.95-2.57)
Haroussean et al,[15] 1997[a]	88	134		0.94 (0.67-1.33)
Keating et al,[16] 1998	279	355		0.77 (0.63-0.94)
Slovak et al,[17] 2000	89	174		0.83 (0.58-1.19)
Suciu et al,[18] 2003	293	441		0.80 (0.64-1.00)
Jourdan et al,[20] 2005	182	290		0.75 (0.59-0.96)
Burnett et al,[21] 2006	419	868		0.81 (0.70-0.95)
Cornelissen et al,[22] 2007	326	599		0.77 (0.64-0.91)
Overall RFS benefit (fixed effects)	1909	3225	18	0.80 (0.74-0.86)



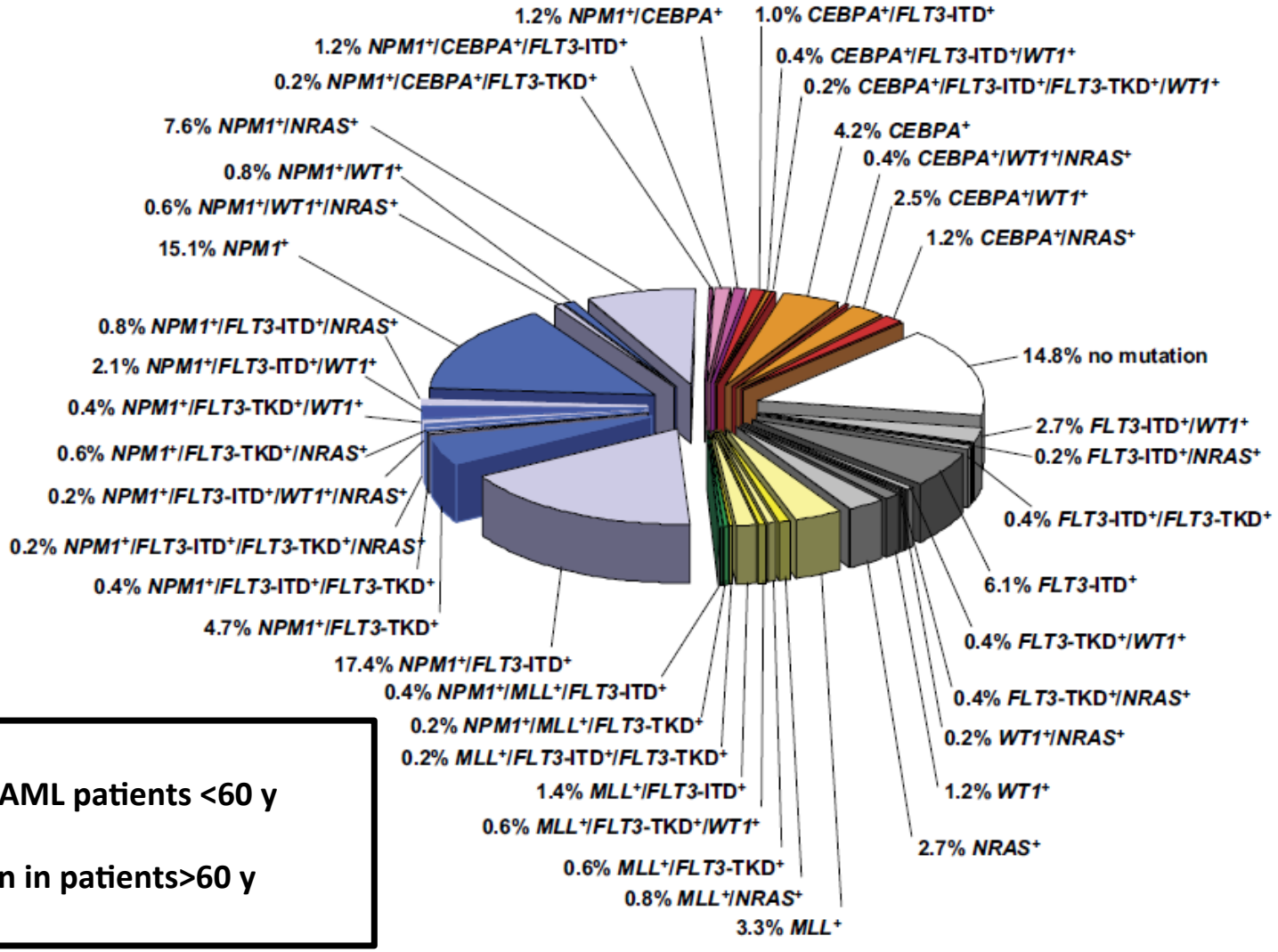
Cytogenetic risk	Patients in Donor group		Patients in No donor group	RFS	OS
Favorable	188	66%	359	1.06 (0.80–1.42	1.07 (0.83–1.38)
Intermediate	864		1635	0.76 (0.68–0.85)	0.83 (0.74–0.93)
Unfavorable	226		366	0.69 (0.57–0.84)	0.73 (0.59–0.90)

Koreth J et al JAMA 2009;310:2349-2361

Recurrent molecular abnormalities in AML

Gene	Overall prevalence	Common in	Overall impact on prognosis
NMP1	30-35%	CN(50%)	↑
FLT3/ITD	25%	CN(40%);t(6;9)(80%)	↓
FLT3/TDK	7%		→
CEBPA	6%	CN(10-15%)	↑ double mutation
KIT	3%	CBF-leukemias(5%)	↓
DNMT3A	15-25%	CN(25-35%)	↓
IDH1-2	7-15%	CN(8-25%)	IDH1 ↓
TET2	8-12%	sAML	↓

The molecular heterogeneity of cytogenetically normal AML



- 40%-50% of AML patients <60 y
- Less common in patients>60 y

European Leukemia Network

Dohner H et al Blood 2010;115:453-472

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

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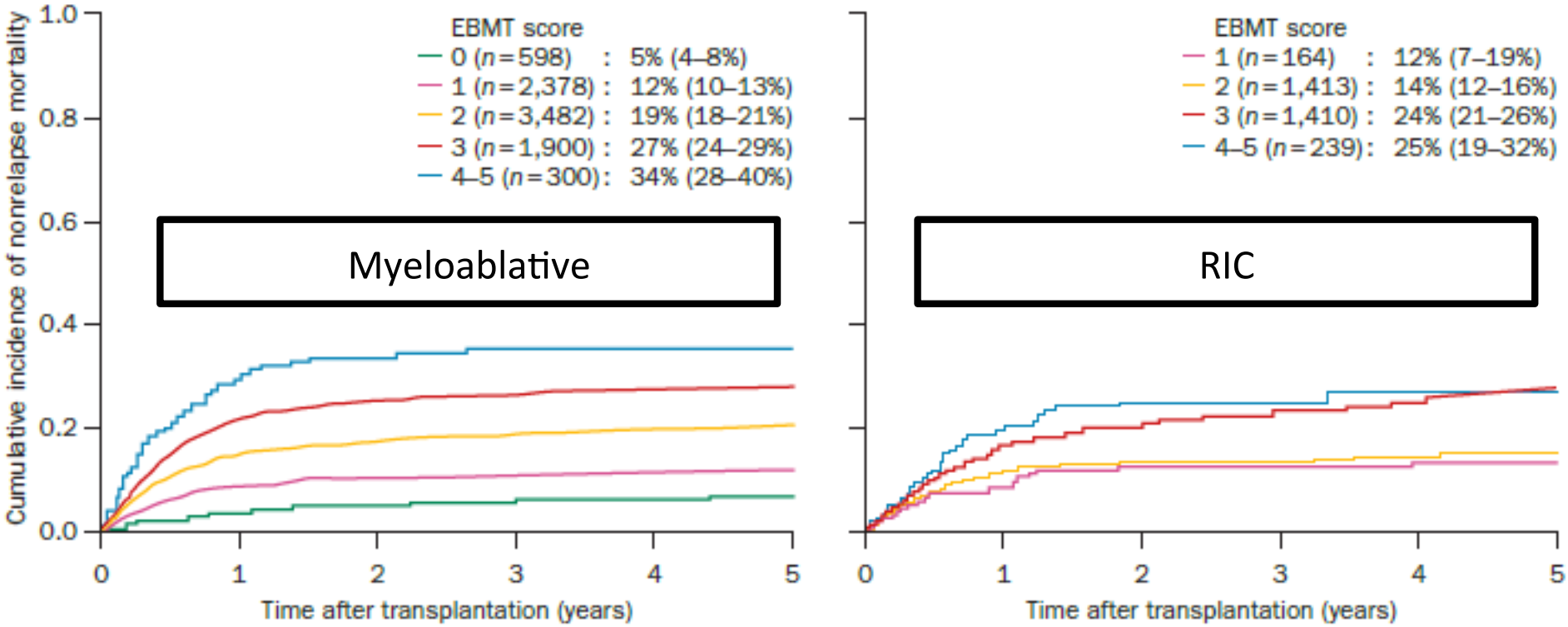
Dohner H et al Blood 2010;115:453-472

2017 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 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} *(whitout 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); *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)(21.3;q26.2);GATA2 MECOM(EVi1) -5 or del(5q);-7; -17/abn(17p) Complex karyotype;monosomal karyotype Wild-type NPM and FLT3-ITD^{high}

Dohner H et al Blood 2017;129:424-447

EBMT risk score



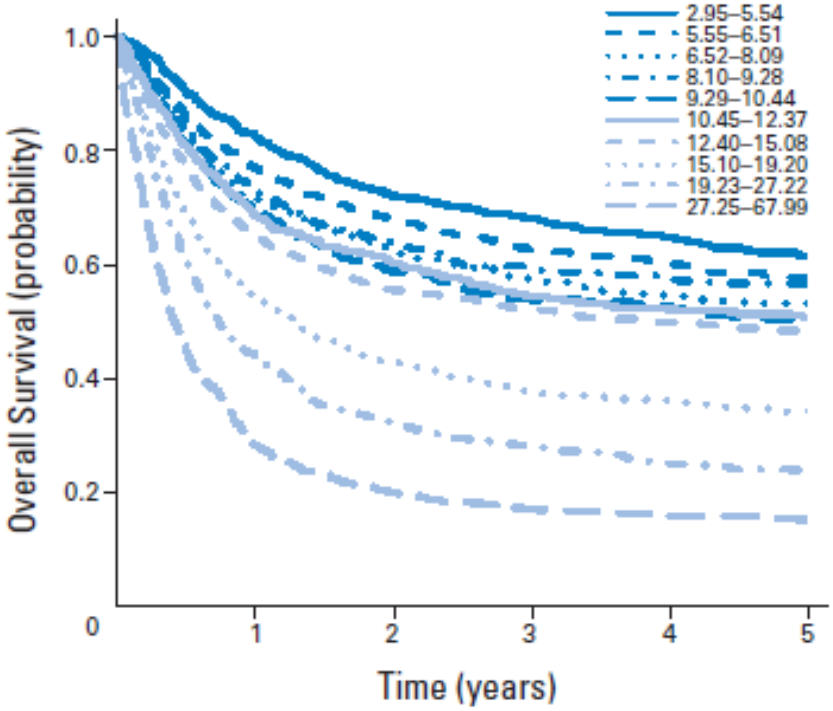
- Disease stage
- Patient age
- Donor type
- Time interval from diagnosis
- Donor-recipient gender combination

Gratwohl A . Bone Marrow Transplant 2012;47:749- 756

European Society for Blood and Marrow Transplantation - Alternating Decision Tree (EBMT-ADT)

The primary objective was
prediction of overall mortality at 100 days after HSCT

- ❑ Age of recipient
- ❑ Karnofsky performance status
- ❑ Diagnosis
- ❑ Disease stage
- ❑ Interval (days) from diagnosis to transplant
- ❑ Donor recipient CMV serostatus combination
- ❑ Donor type
- ❑ Conditioning
- ❑ Annual number of allo-HSCTs performed in the transplant medical center



Shouval R et al J Clin Oncol 2015;33:3144-3151

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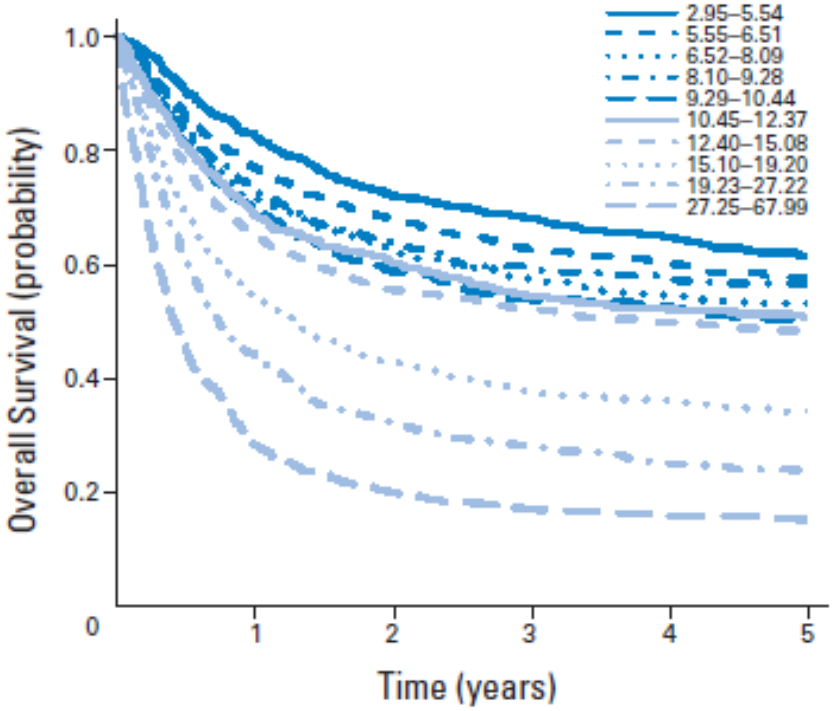


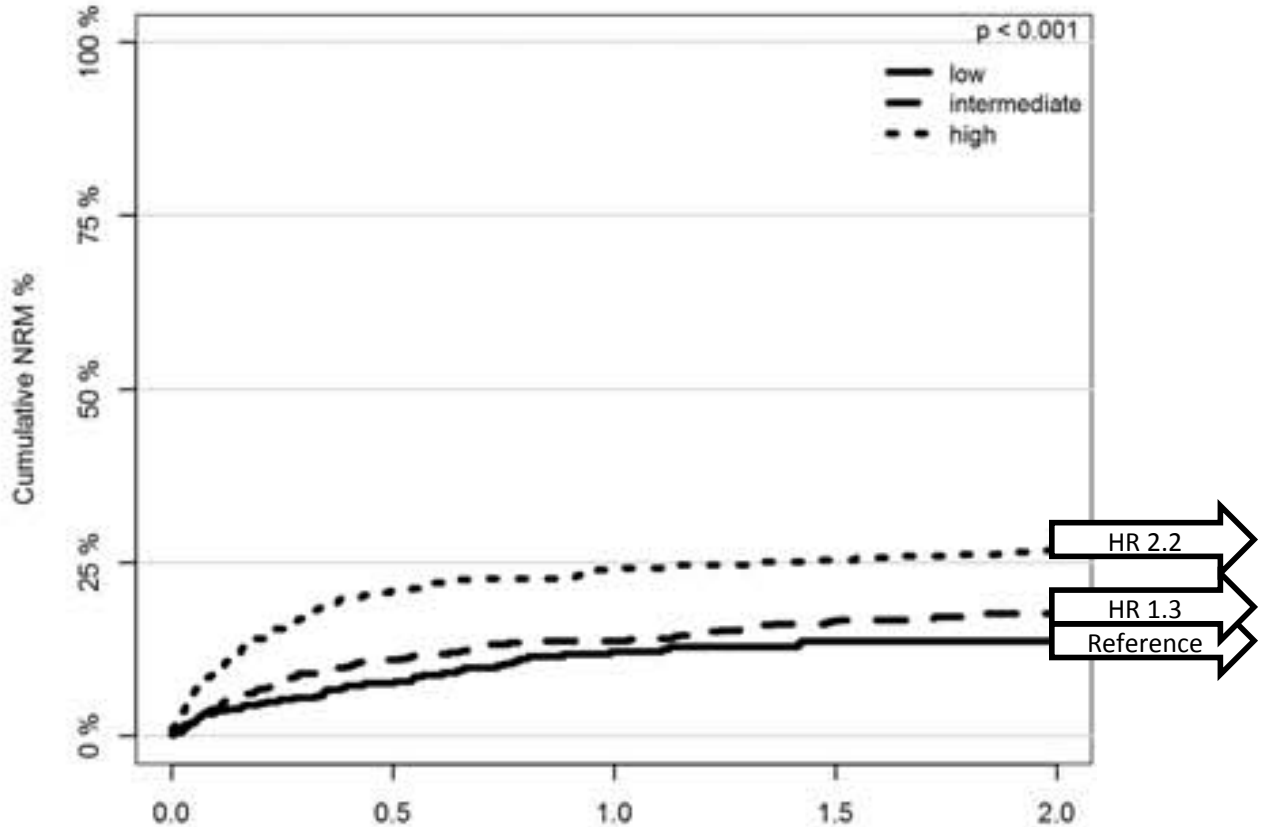
http://bioinfo.lnx.biu.ac.il/~bondi/web1.html

Shouval R et al J Clin Oncol 2015;33:3144-3151

Validation of the acute leukemia-EBMT score for prediction of mortality following allogeneic stem cell transplantation in a multi-center GITMO cohort

The primary objective was
prediction of overall mortality at 100 days after HSCT

- **Low<8.5**
- **Intermediate 8.6-10**
- **High>10**



Shouval R et al Am J Hematol 2017;92:429-434

ELN AML: an integrated risk-adapted approach

Prognostic factors for allogeneic-HSCT-related nonrelapse mortality

Pretransplantation	Peritransplantation	Post-transplantation
Favourable prognostic factors		
Sibling donor (HLA-matched) Shorter time from diagnosis to transplant* White ethnicity	Nonmyeloablative conditioning Stem-cell source (bone marrow or peripheral blood) T-cell depletion of the graft	Early immune recovery
Adverse prognostic factors		
Increased recipient age* Recipient and donor sex* Comorbidities (assessed using HCT–CI) Cytomegalovirus serostatus Cytokine polymorphism Unrelated donor HLA-mismatched Performance score Refractory leukaemia Therapy-related AML	Myeloablative conditioning regimen Alternative stem-cell source (umbilical cord blood)	Severe acute grade III–IV GVHD Persistent chronic extensive GVHD

Cornelissen JJ et al Nat Rev Clin Onc 2012;9:579-590

ELN AML: an integrated risk-adapted approach

Recommendations for allogeneic HSCT in patients with AML in their first complete remission based on integrated-risk profiles*

AML risk group‡	AML risk assessment§	Risk of relapse following consolidation approach		Prognostic scores for nonrelapse mortality that would indicate allogeneic HSCT as preferred consolidation		
		Chemotherapy or autologous HSCT (%)	Allogeneic HSCT (%)	EBMT score	HCT–CI score	Nonrelapse mortality risk (%)
Good	t(8;21) with WBC ≤20 Inv(16)/t(16;16) Mutated *CEBPA* (double allelic) Mutated NPM1 (No *FLT3*–ITD mutation) Early first complete remission and no MRD	35–40	15–20	NA (≤1)	NA (<1)	10–15
Intermediate	T(8;21) with WBC >20 Cytogenetically normal (or with loss of X and Y chromosomes), WBC count ≤100 and early first complete remission (after first cycle of chemotherapy)	50–55	20–25	≤2	≤2	<20–25
Poor	Otherwise good or intermediate, but no complete remission after first cycle of chemotherapy Cytogenetically normal and WBC >100 Cytogenetically abnormal	70–80	30–40	≤3–4	≤3–4	<30
Very poor	Monosomal karyotype Abn3q26 Enhanced Evi-1 expression	>90	40–50	≤5	≤5	<40

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Intermediate	T(8;21) with WBC >20 Cytogenetically normal (or with loss of X and Y chromosomes), WBC count ≤100 and early first complete remission (after first cycle of chemotherapy)	50–55 MRD negative after cycle 2	20–25	≤2	≤2	<20–25
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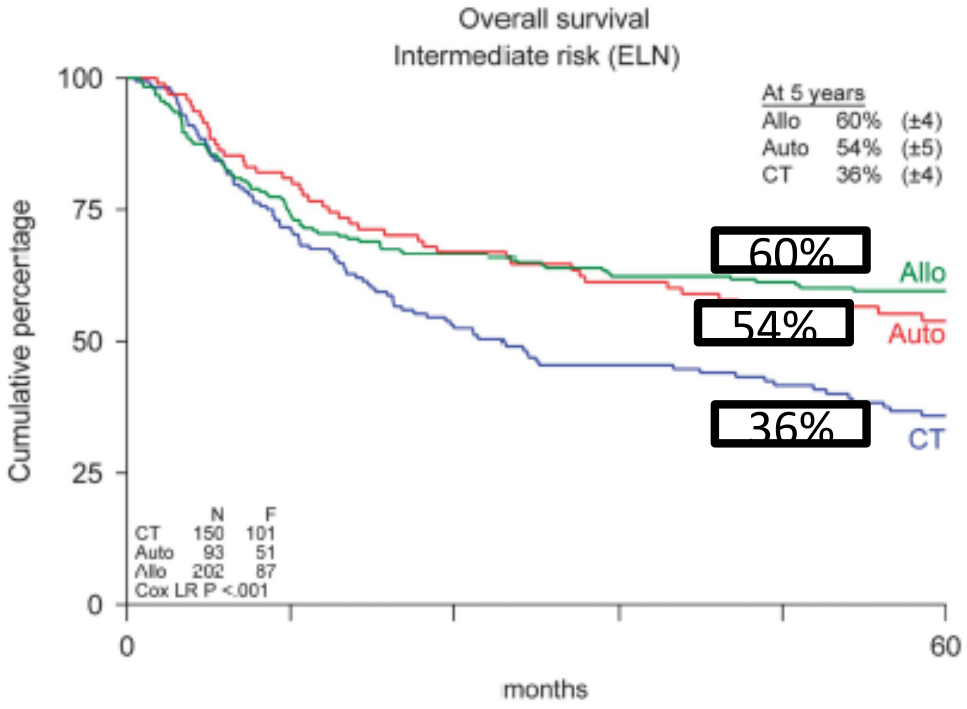
Very poor	Monosomal karyotype Abn3q26 Enhanced Evi-1 expression	>90	40–50	≤5	≤5	<40

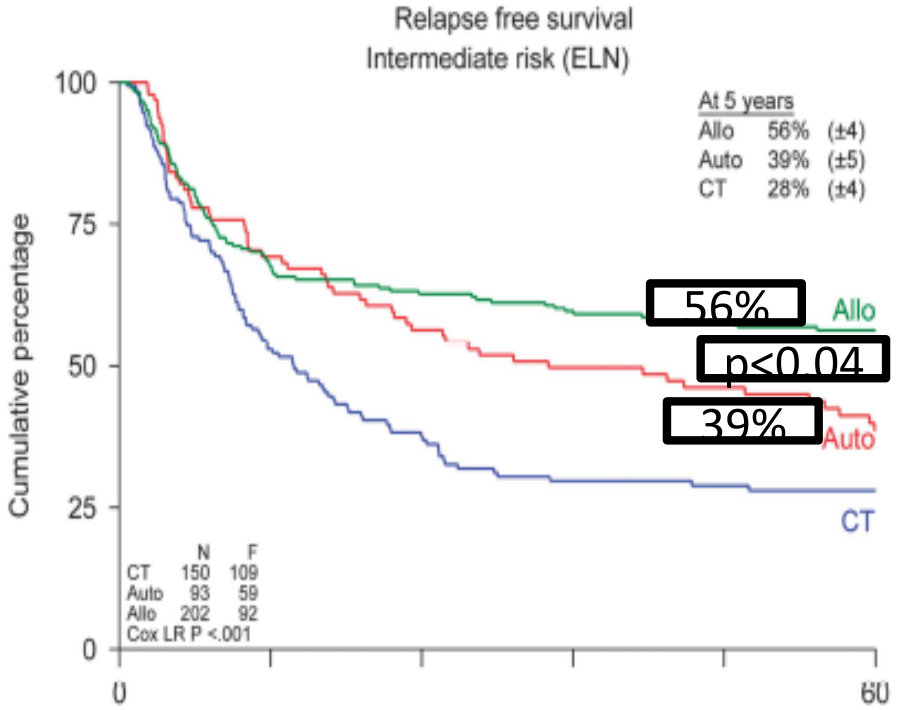
Allogeneic SCT might be favoured if the projected DFS is expected by at least 10% based on an individual's risk assessment

Cornelissen JJ et al Blood 2016;127:62-70

Post-remission approaches in patients with acute myeloid leukemia aged 40–60 years

- ❑ 760 pts
- ❑ Intermediate-I + Intermediate-II risk→55%
- ❑ MAC/RIT 70% sibling EBMT risk score 35% 3





NRM HR Allo vs Auto 3.2 p>0.001

Cornelissen JJ et al Leukemia 2015;29:1041-1050

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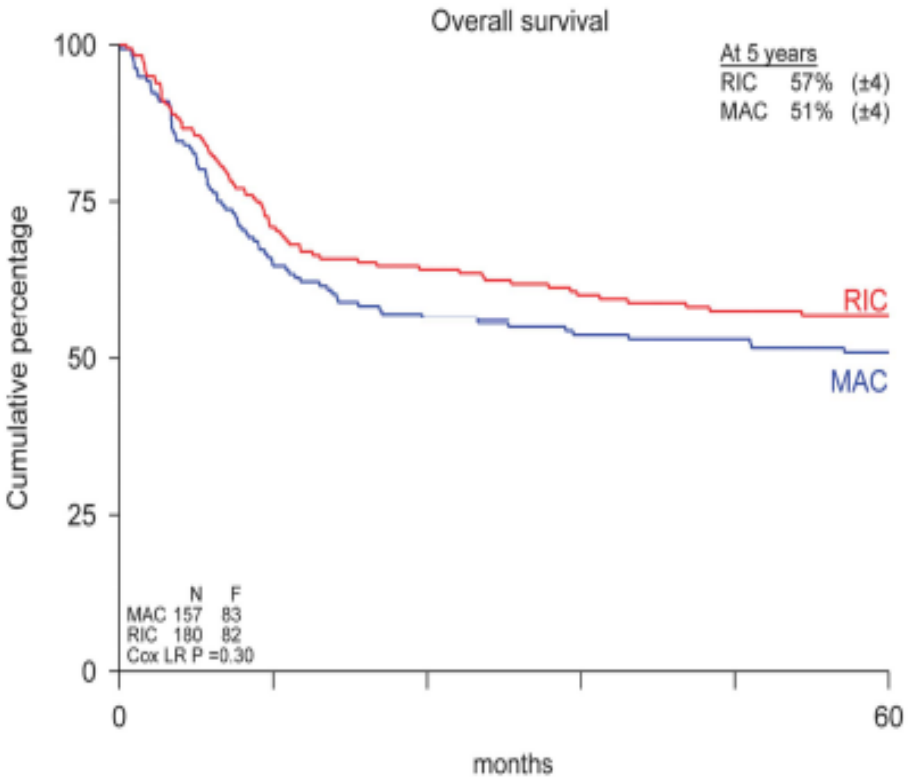

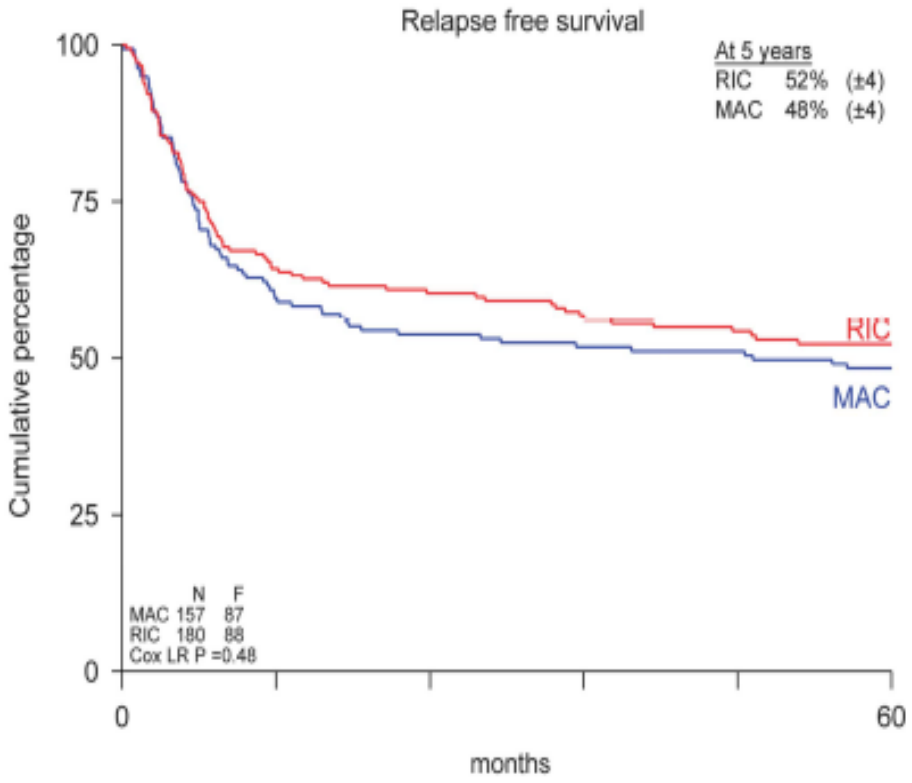

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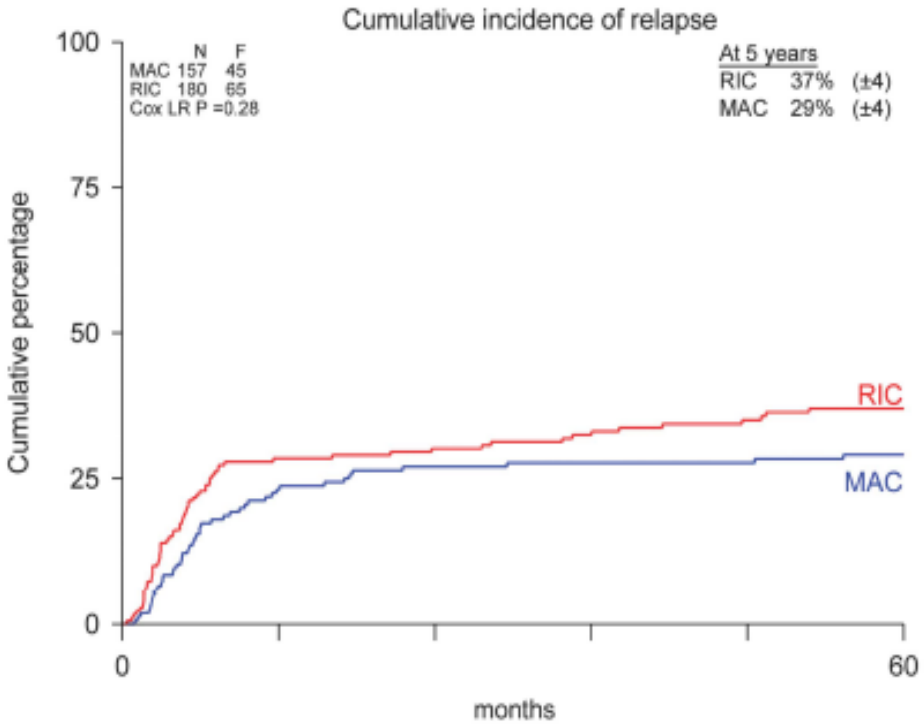
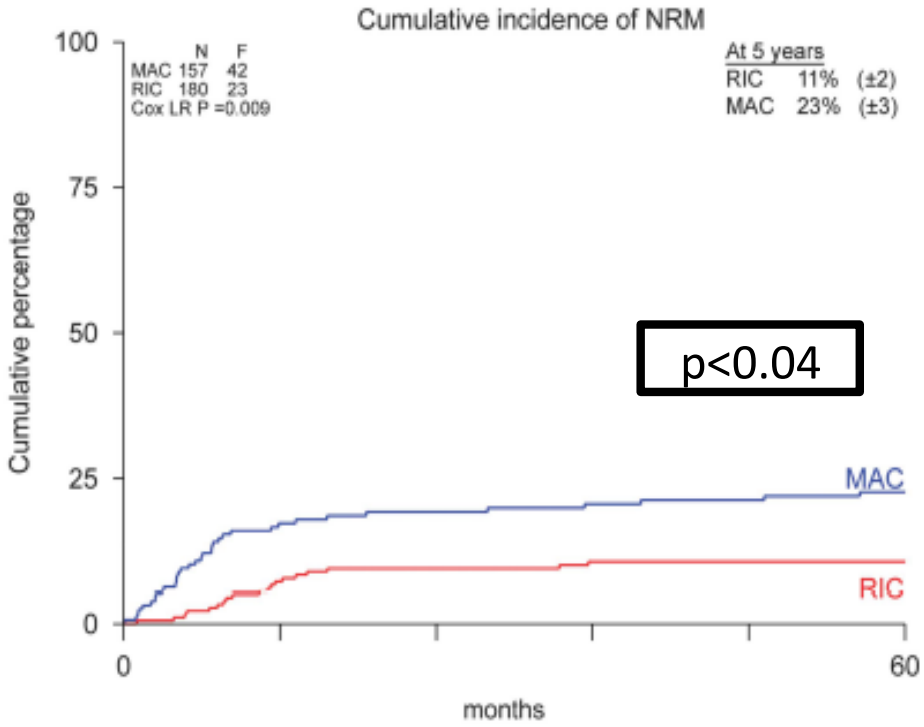


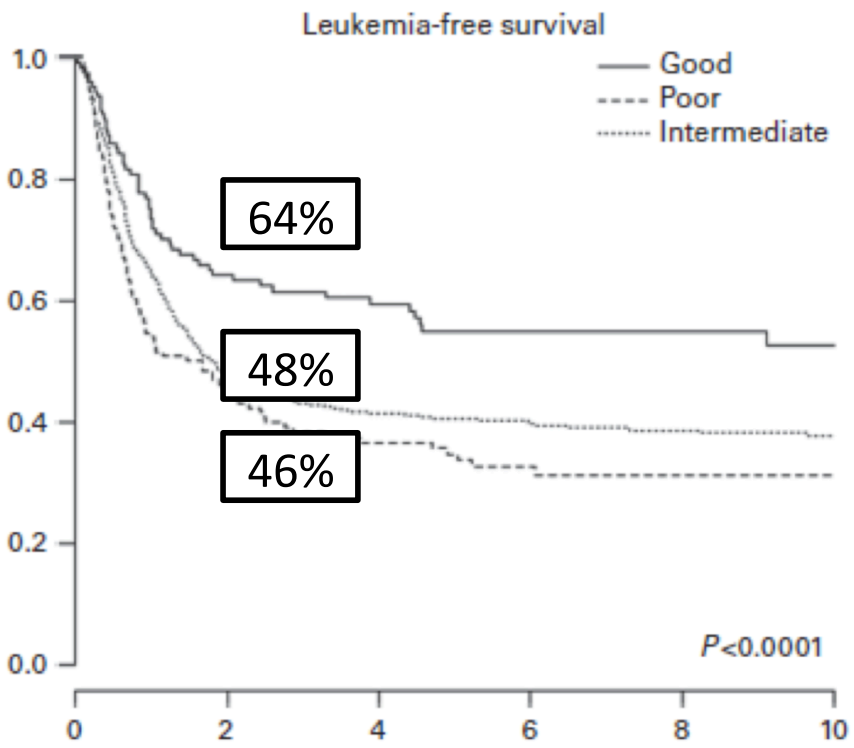


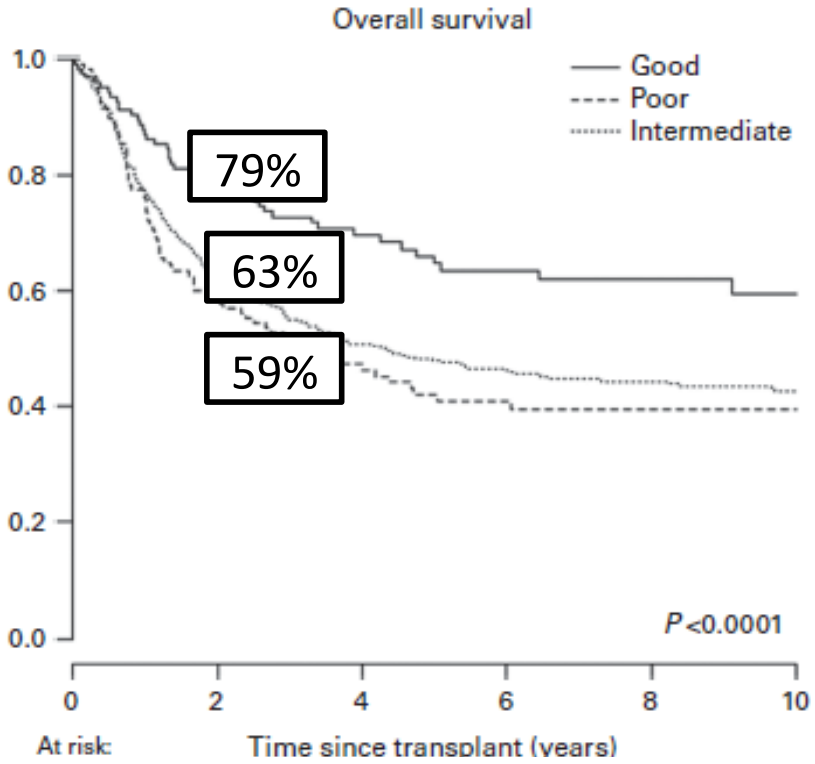
Cornelissen JJ et al Leukemia 2015;29:1041-1050

Autologous stem cell transplantation is still a valid option in good and intermediate-risk AML: a GITMO survey

Saraceni F et al Bone Marrow Transplant 2017;52:163-166

- 809 pts
- 67% Intermediate risk
- Median interval diagnosis-transplant 171 days. Median age years 47
- 68% PBSC





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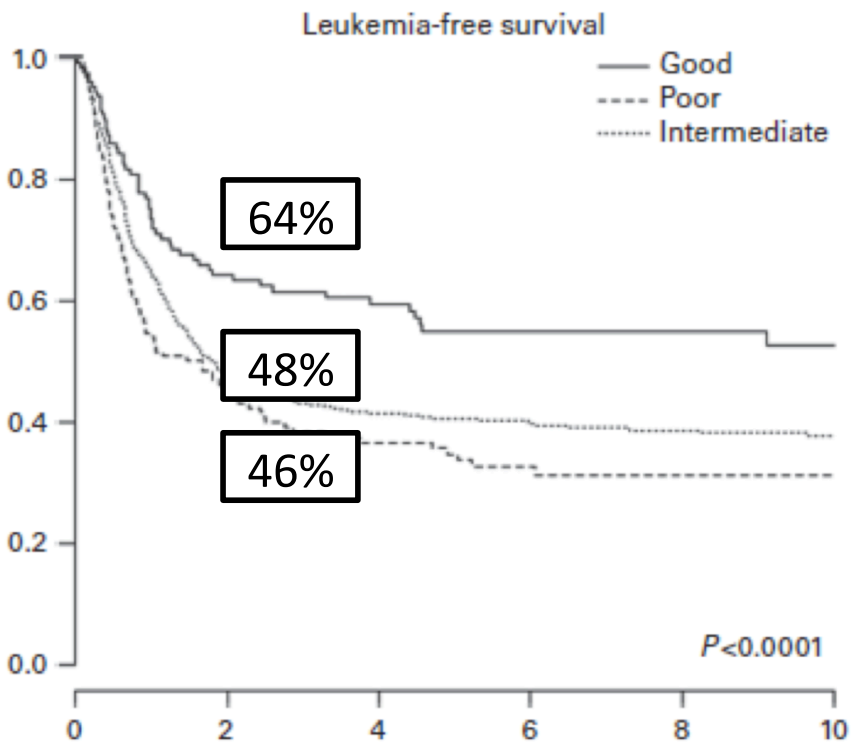
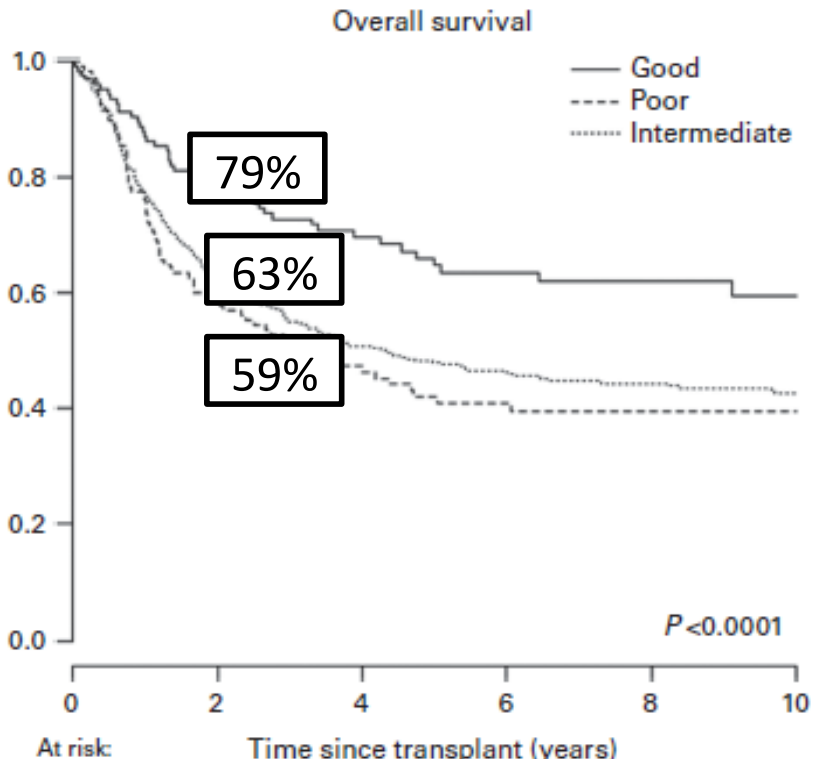
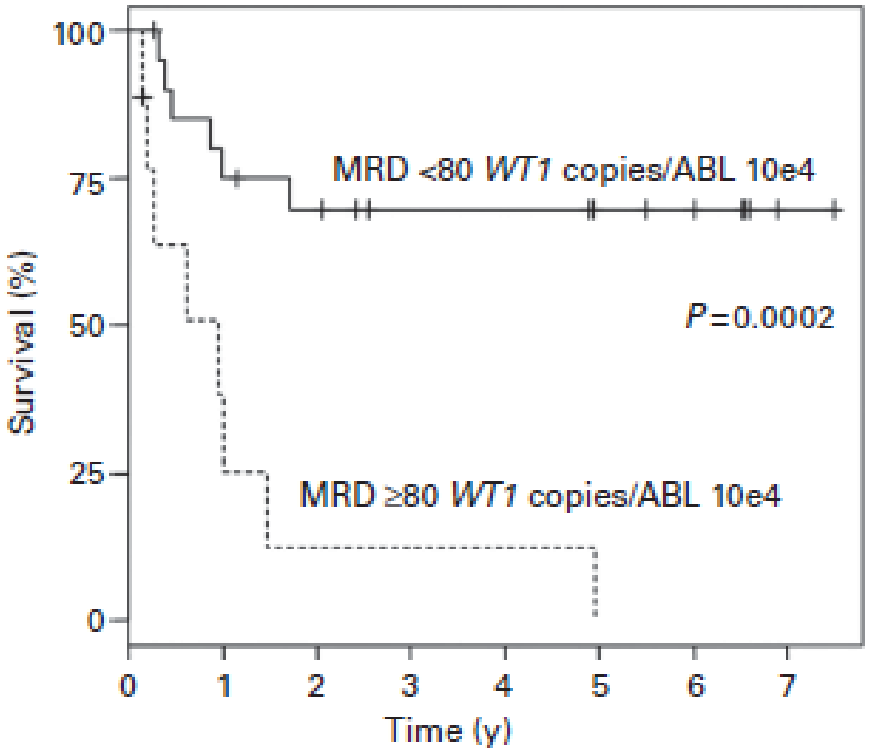


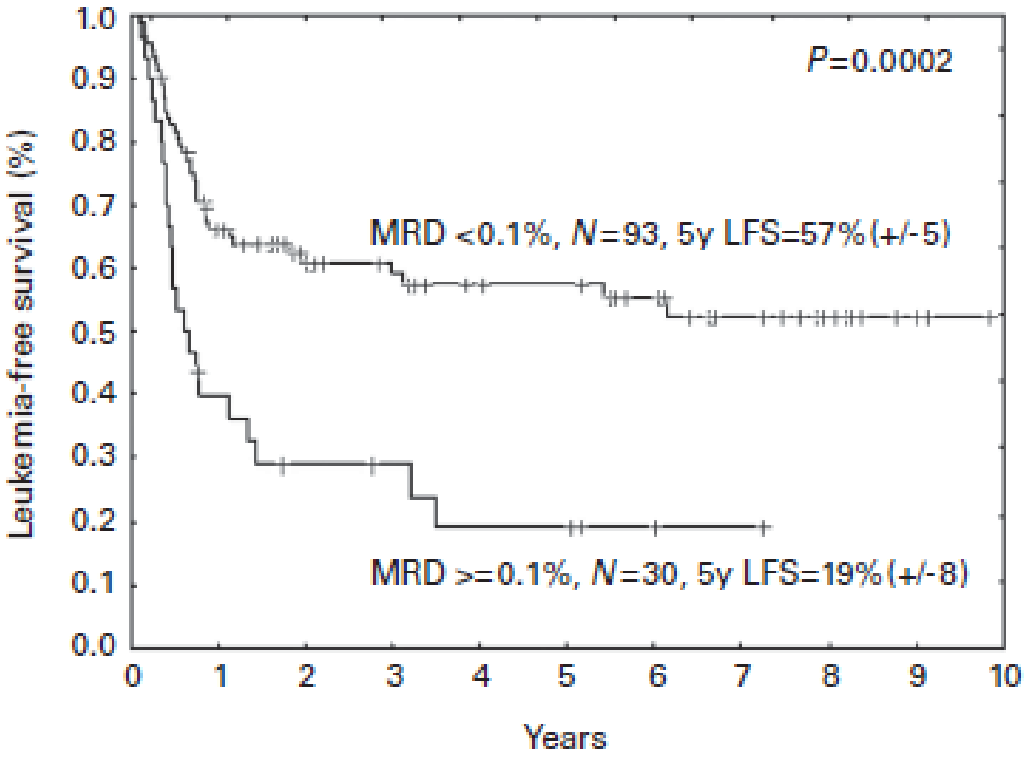


Auto-SCT should be considered as a possible alternative to allo-SCT in intermediate risk AML

Autologous stem cell transplantation for adult acute leukemia in 2015: time to rethink?

The impact of MRD status of autologous SCT



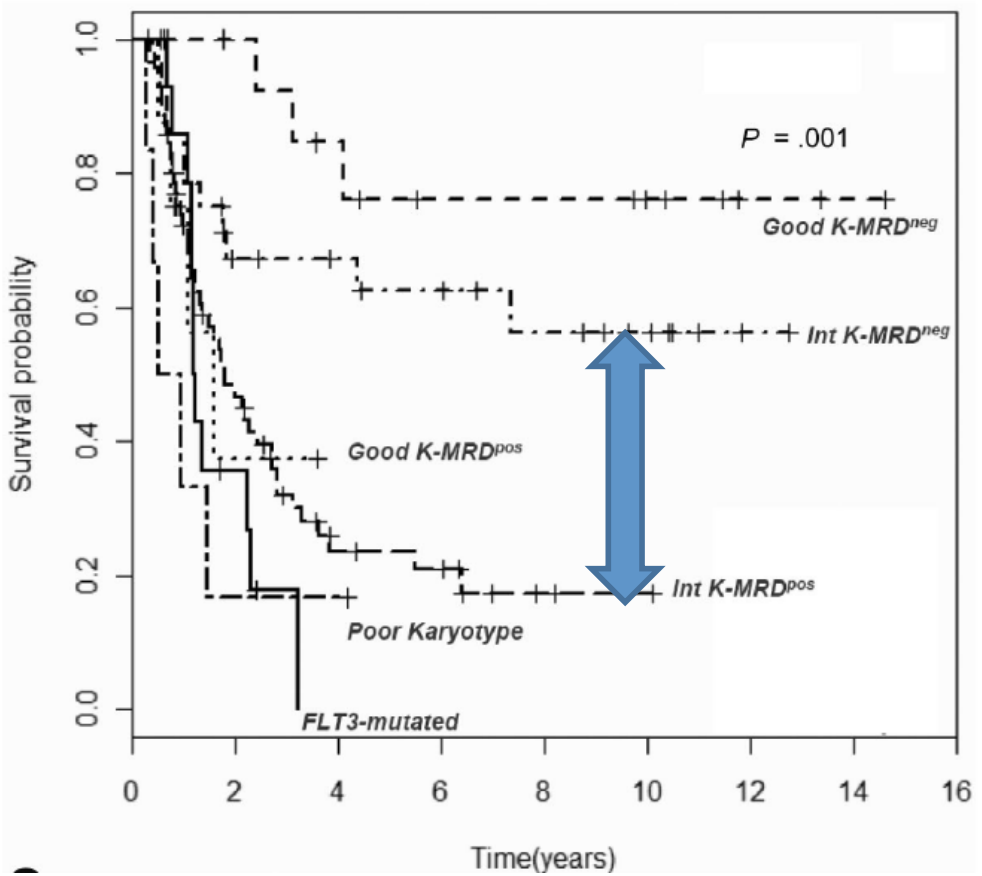


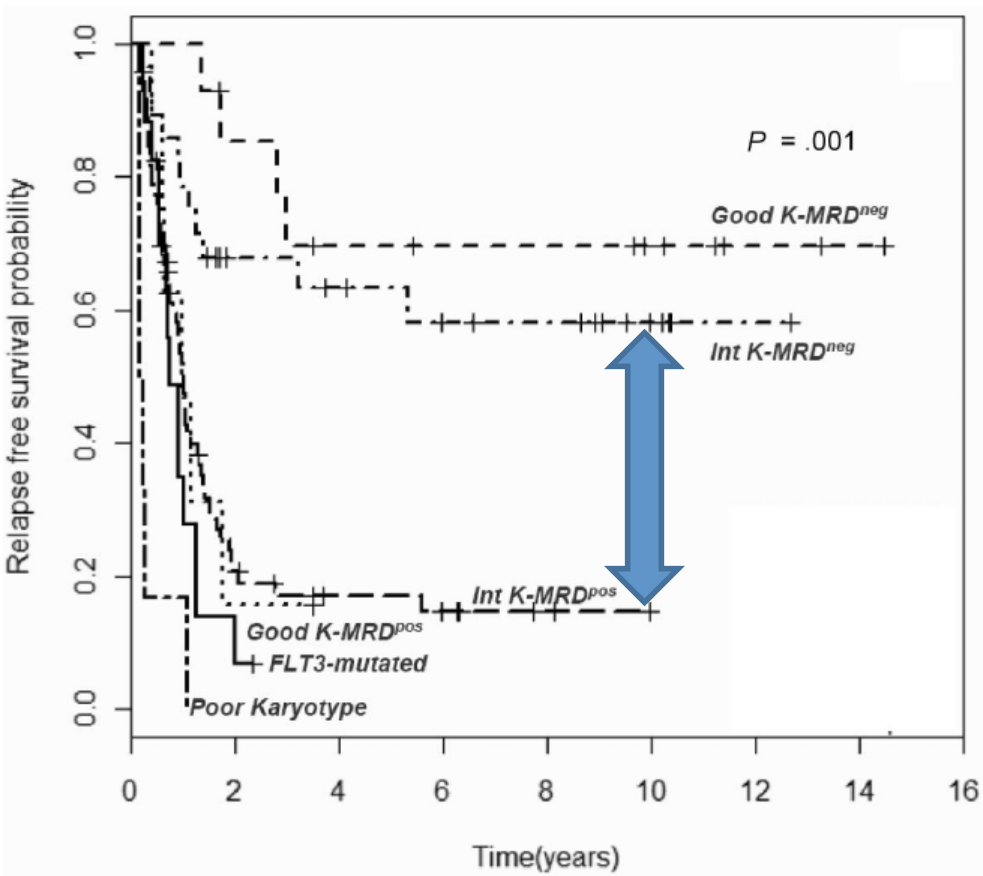
Gorin NC et al Bone Marrow Transplant 2015;50:1495-1502

Improving risk stratification in intermediate risk AML

- Post-consolidation MRD assessment by flow cytometry (LAIP)
- Cytogenetic +
- Molecular diagnostic characterization

Threshold of 3.5 x10^{-4} residual leukemic cells





Buccisano F et al Blood 2010;116:2295-2303

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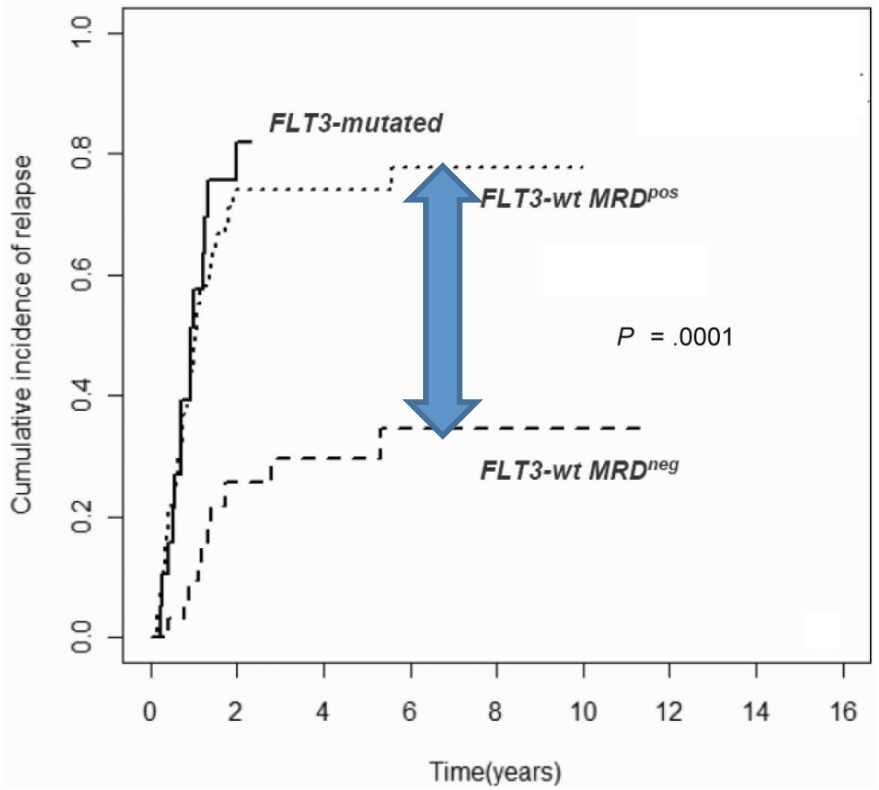
- Cytogenetic +
- Molecular diagnostic characterization



- **Adverse K**
- **FLT3+**
- **Good K / MRD+**
- **Int K / MRD+**

ALLO SCT CR1

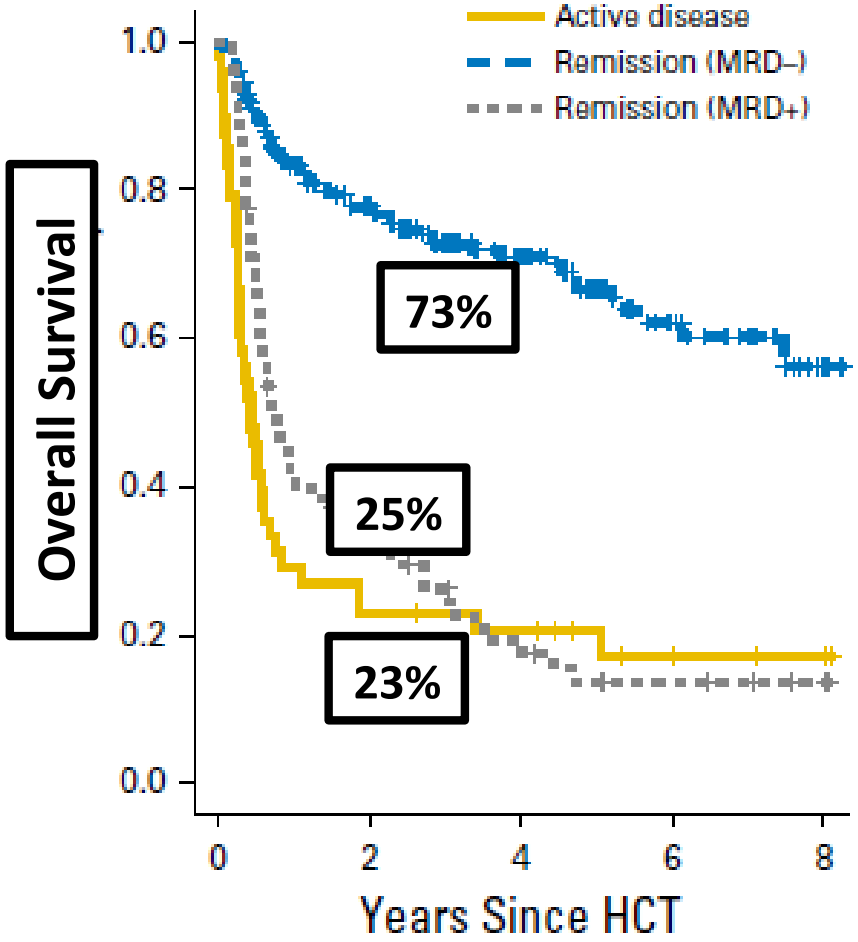
- **Good K / MRD-**
- **Int K / MRD-**

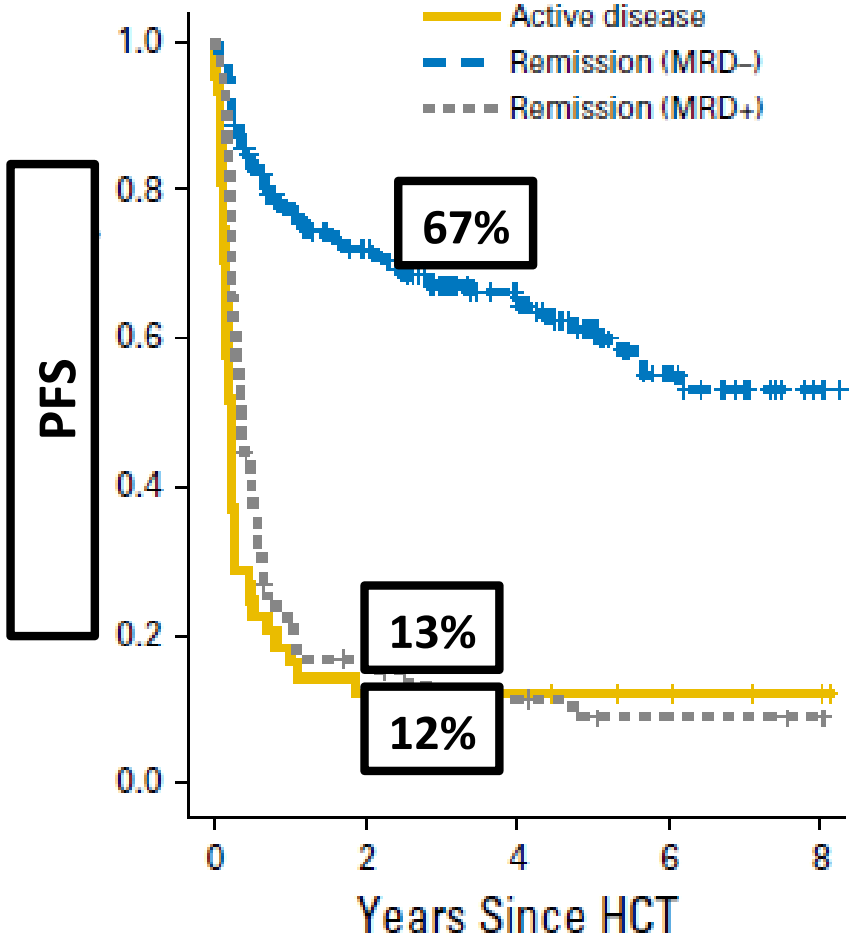
The integrated evaluation of baseline prognosticators and MRD improves risk-assessment and optimizes postremission therapy

Buccisano F et al Blood 2010;116:2295-2303

MRD pre allogeneic SCT

- 359 pts (60% intermediate risk)→myeloablative SCT
- Pre-HCT MRD evaluation (10-color MFC)





Araki D et al J Clin Oncol 2015;34:329-336

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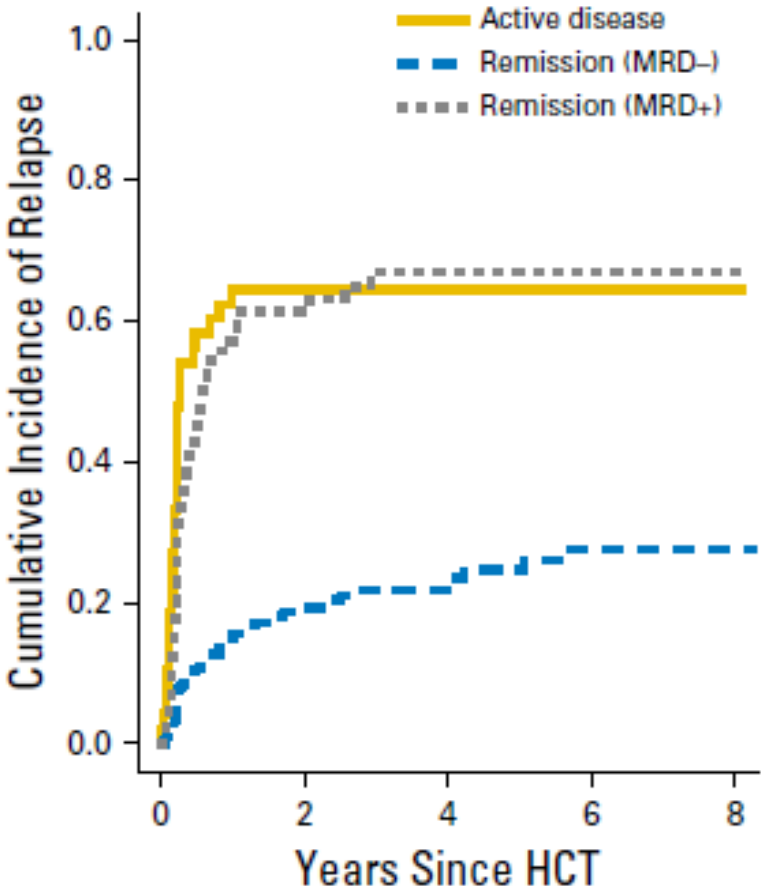
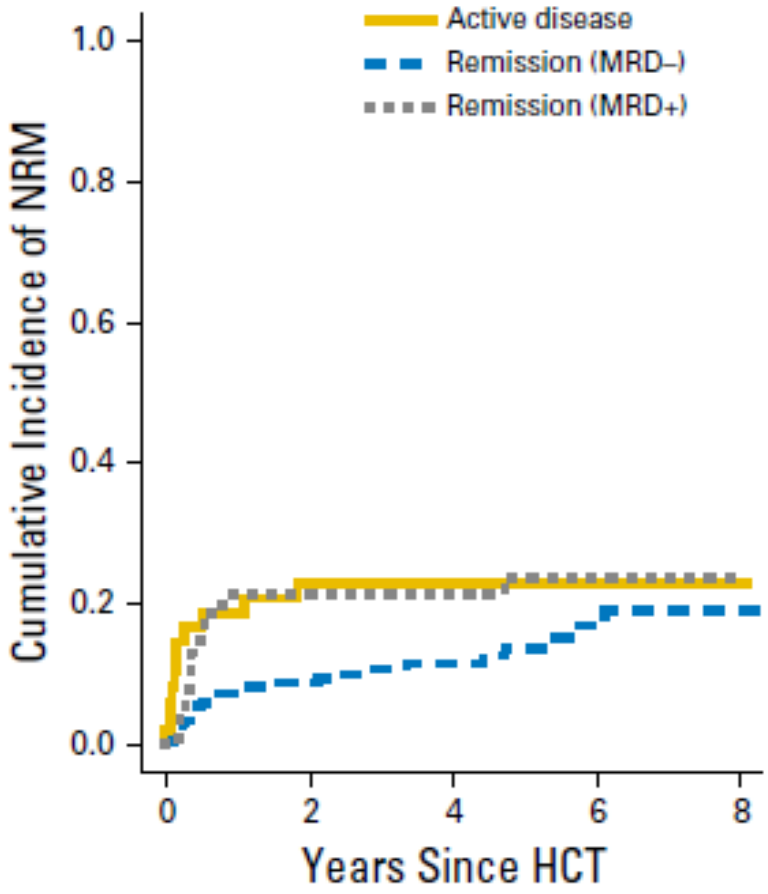
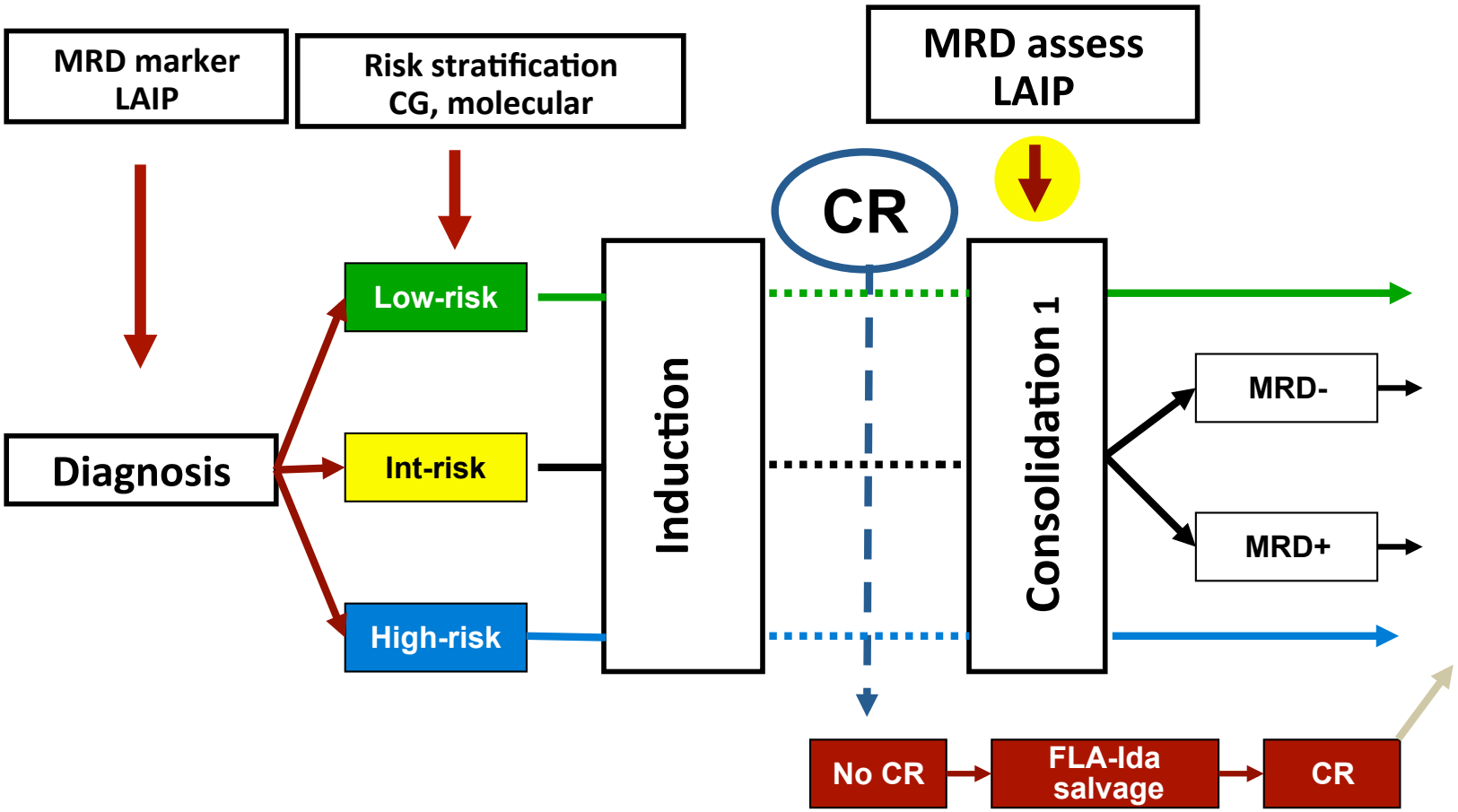




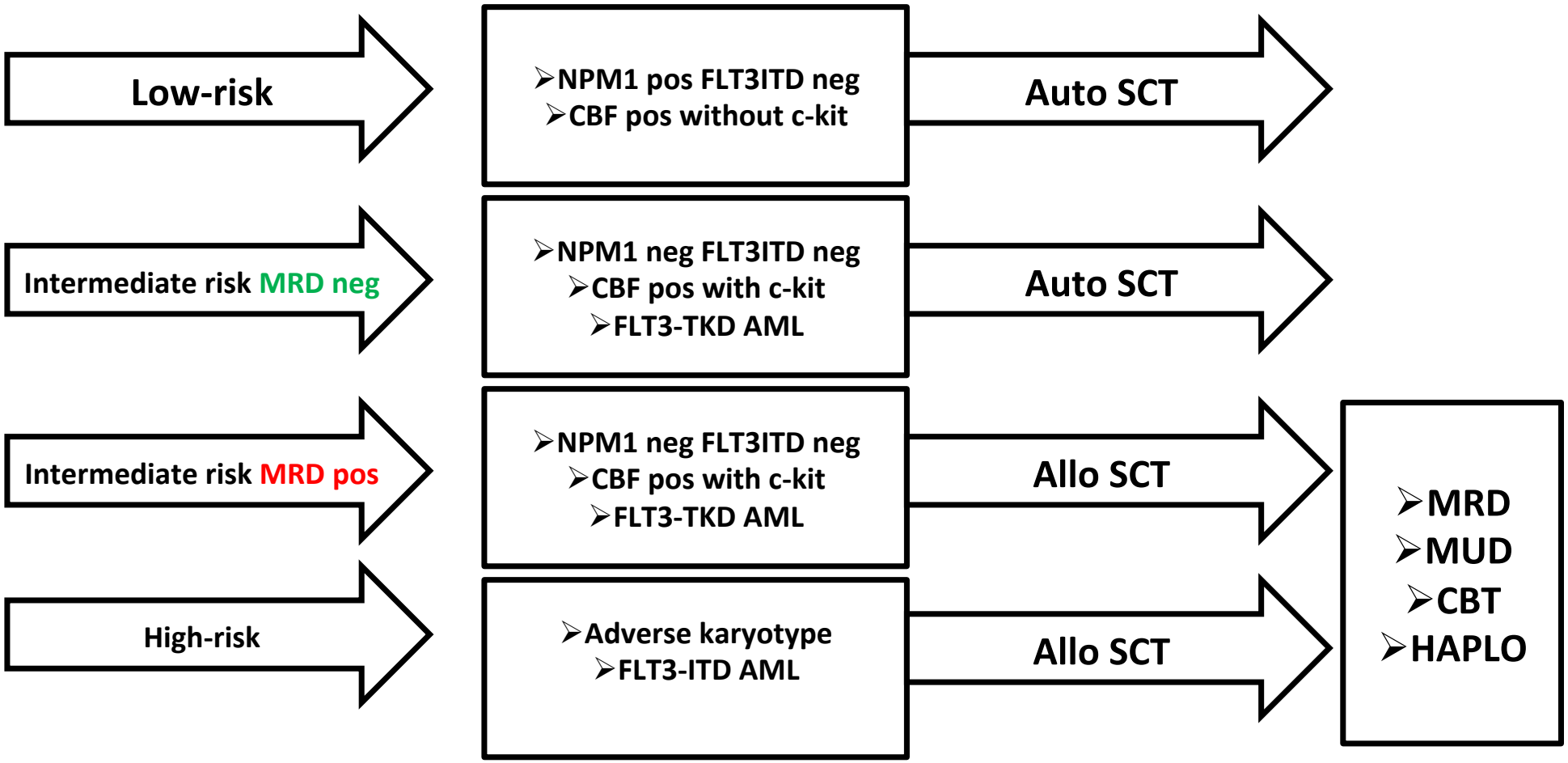
Araki D et al J Clin Oncol 2015;34:329-336

GIMEMA AML1310: a study of risk-adapted and MRD-directed therapy for adult AML



- Low-risk:CBF+, NPM+,FLT3/ITD-,c-Kit-
- Intermediate risk: all others
- High risk: adverse K, FLT3-ITD+

GIMEMA AML1310: a study of risk-adapted and MRD-directed therapy for adult AML



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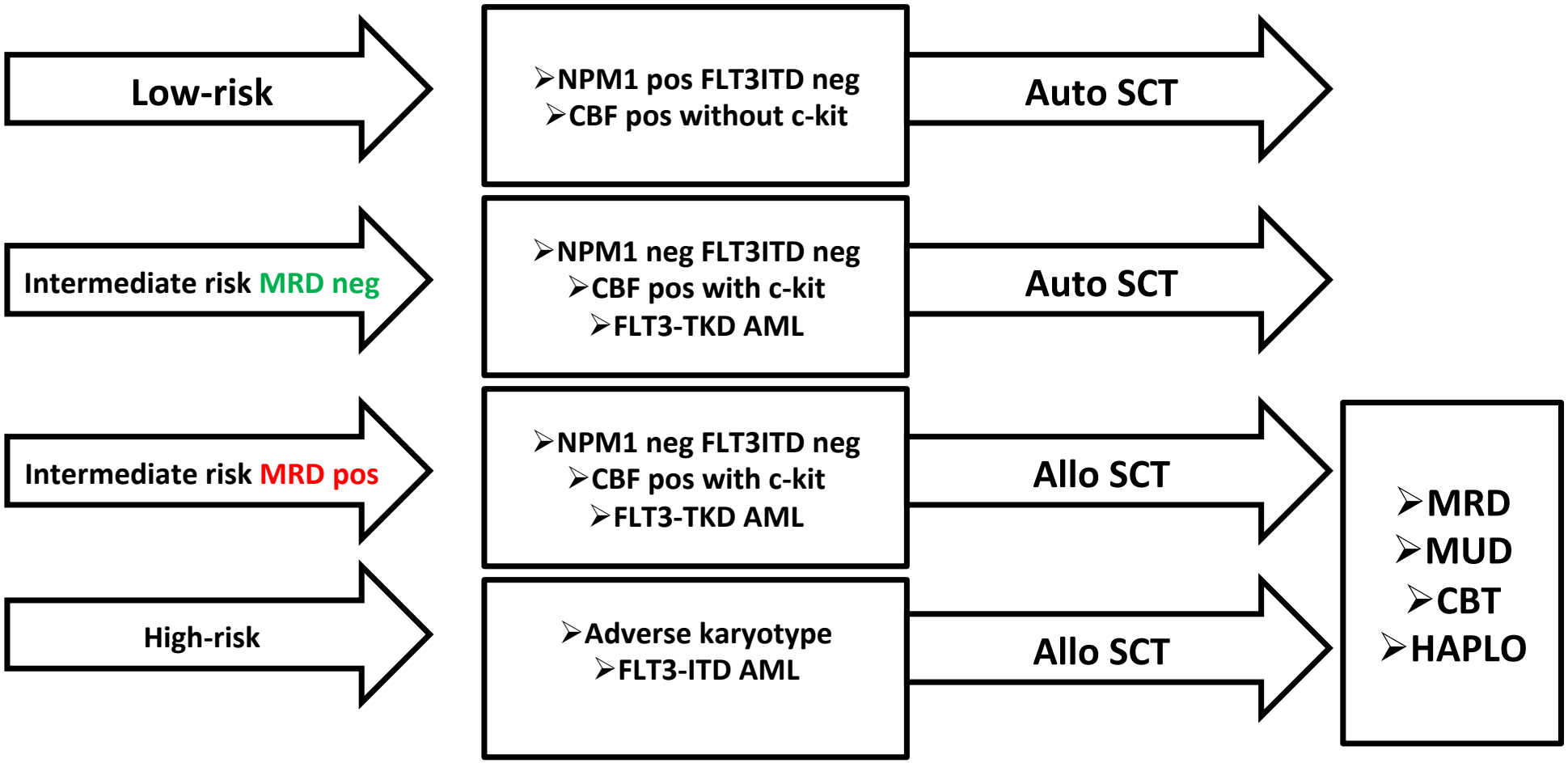
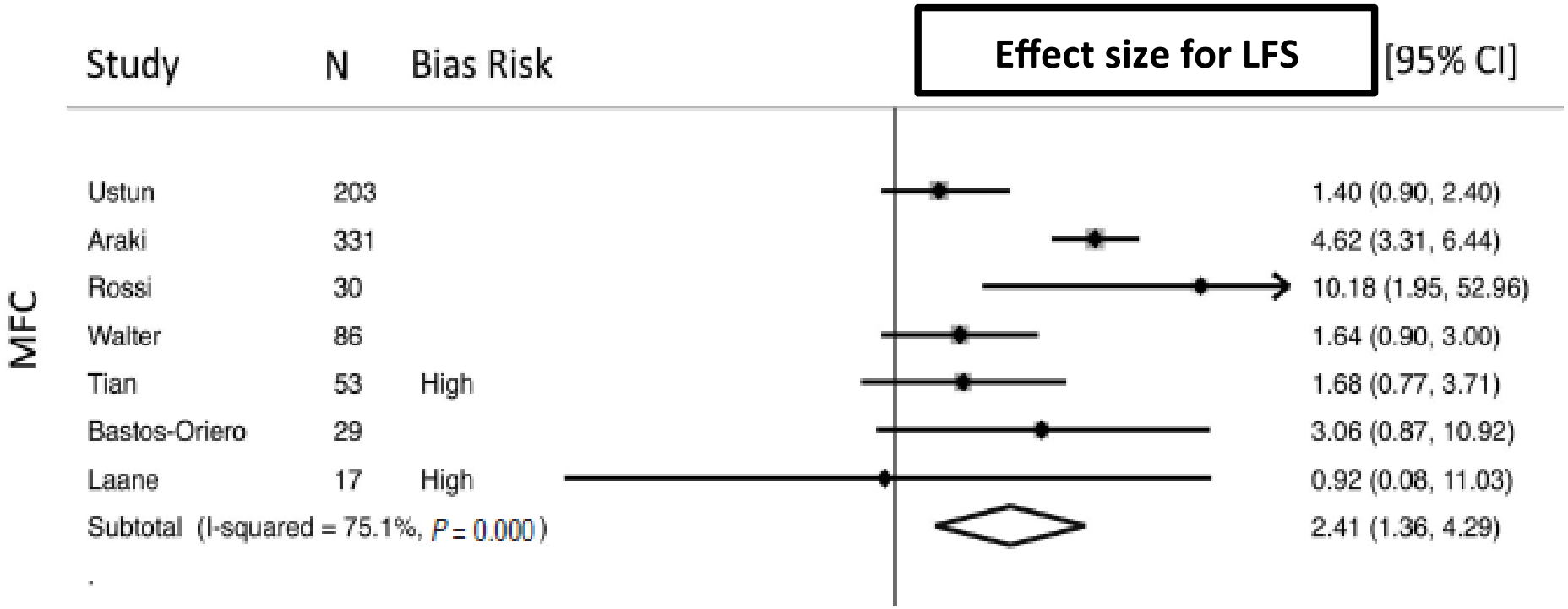


In the intermediate-risk category, ASCT can be avoided if MRD is not detectable

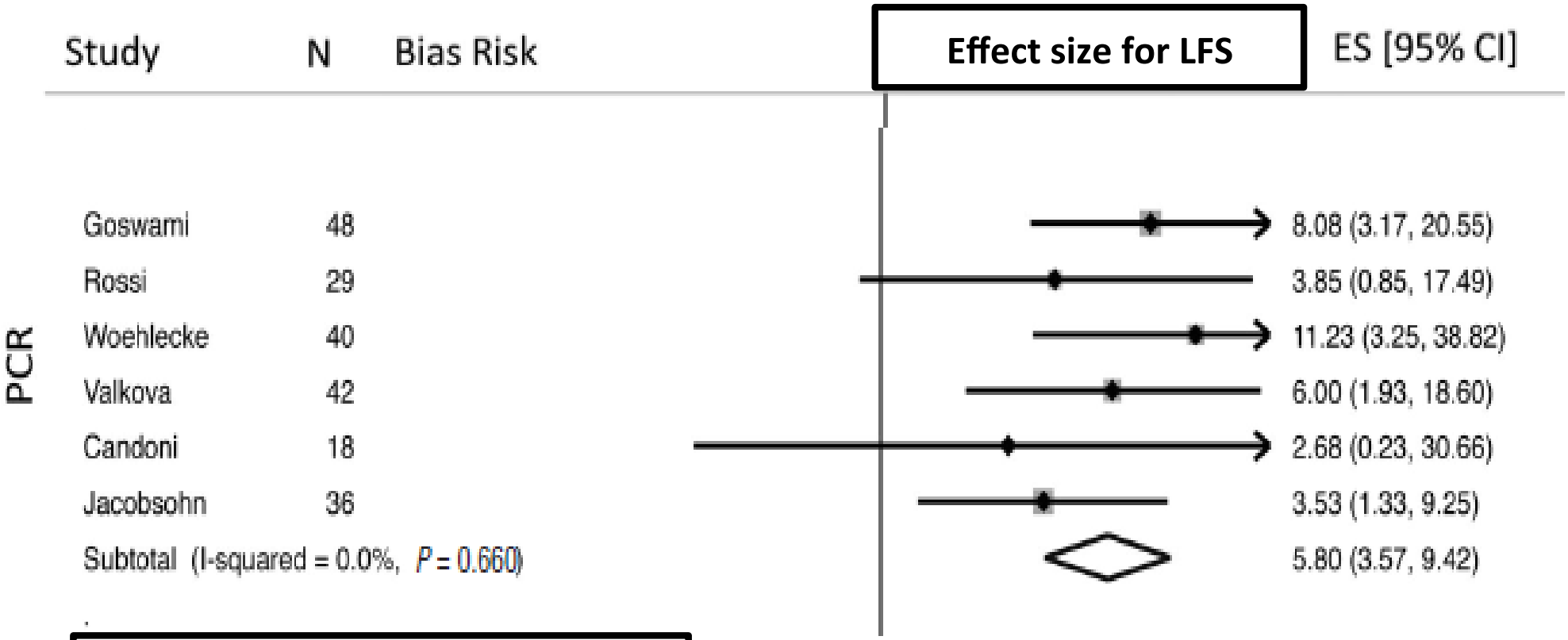
Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis



LAIP 3-10 colors

Buckley S et al Haematologica 2017;102:865-873

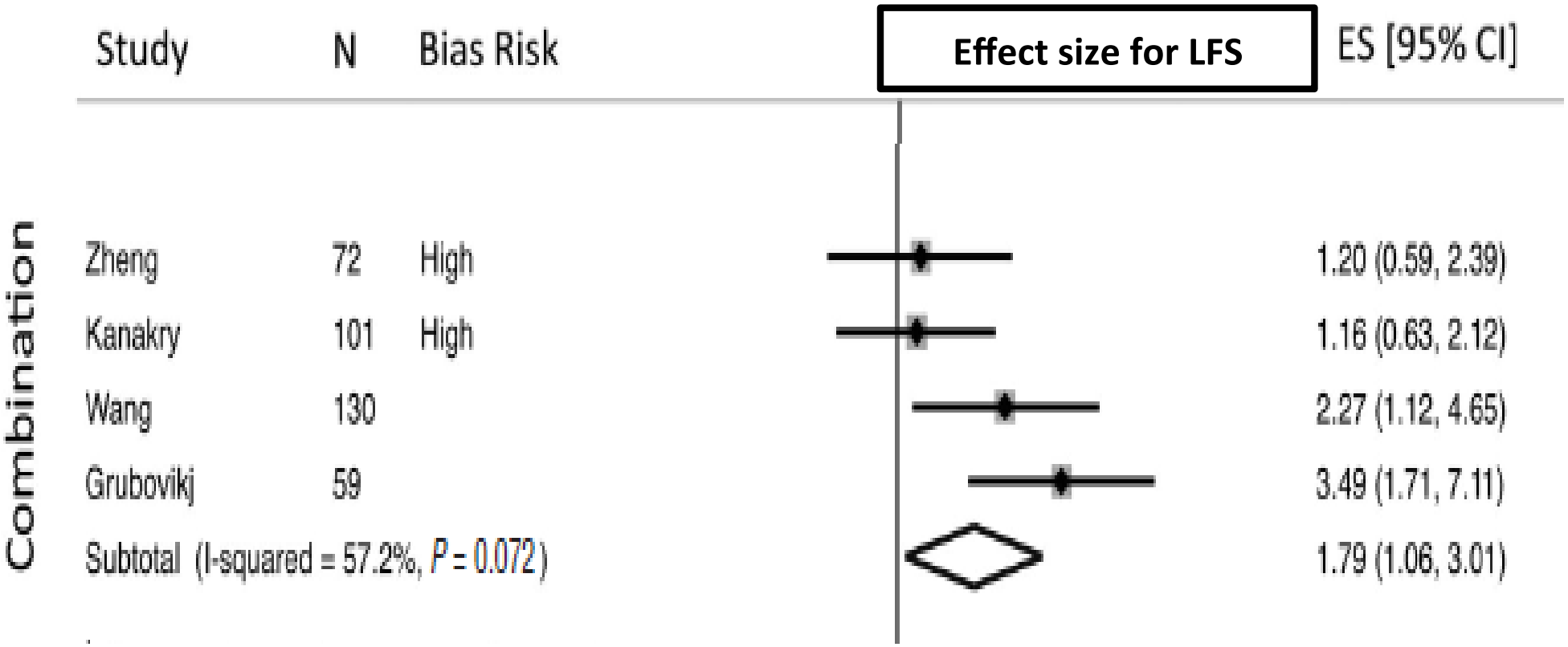
Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis



***WT1* polymerase chain reaction-based detection**

Buckley S et al Haematologica 2017;102:865-873

Minimal residual disease prior to allogeneic hematopoietic cell transplantation in acute myeloid leukemia: a meta-analysis



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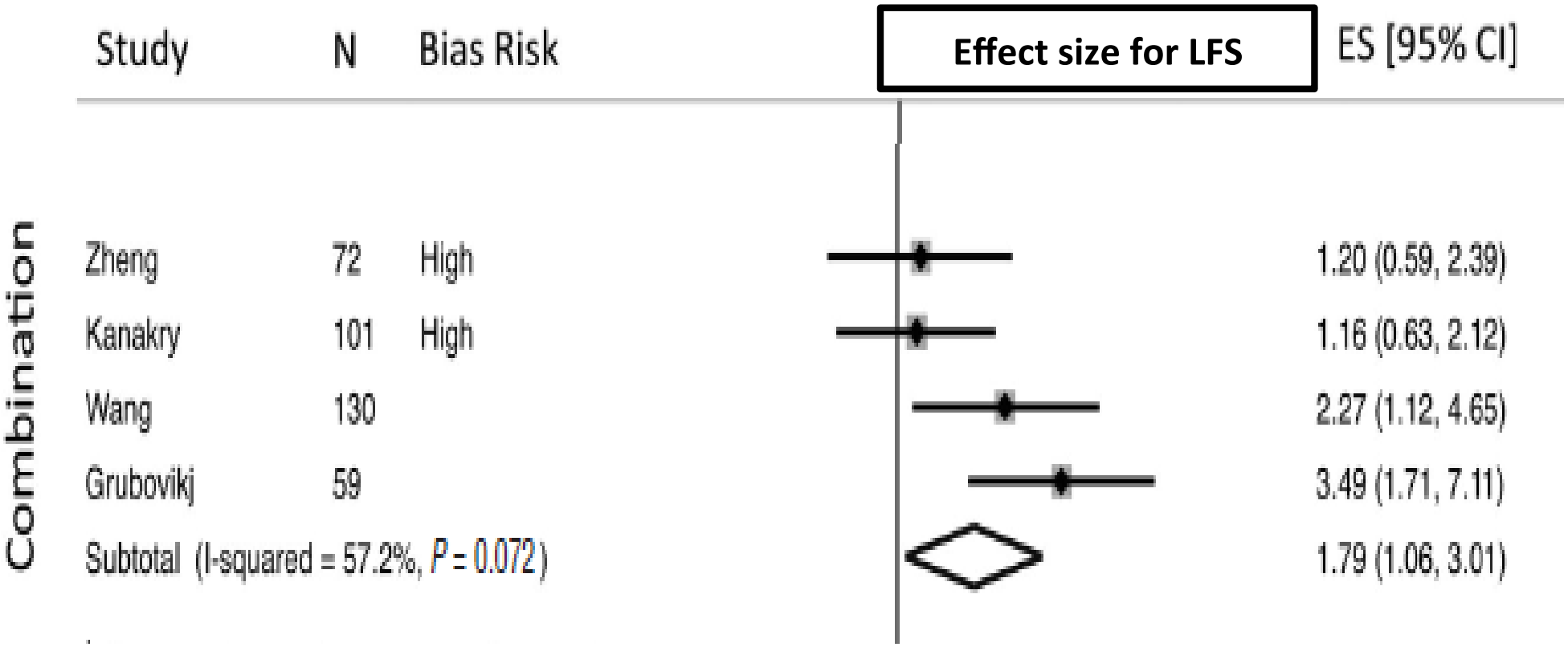

- A strong relationship between pre-HCT MRD status and post-HCT relapse
- MRD status should guide therapeutic decisions, either through treatment intensification for MRD pos patients

Buckley S et al Haematologica 2017;102:865-873

Suggested indications for allo-HSCT among young adults with AML in first complete remission

Risk factor	HLA-matched sibling	MUD/haplo/cord
Favorable	No	No
Favorable with c-KIT	**Yes**	Possible
Intermediate	**Yes**	Possible
Intermediate NPM $^{+}$/FLT3 $^{-}$	Possible	No
Intermediate Biallelic *CEBPA/ FLT3-ITD*$^{-}$	Possible	No
FLT3 ITD+	**Yes**	**Yes**
Unfavorable	**Yes**	**Yes**

Rowe J et al Blood 2010;116:3147-3156

HSCT in AML
ASBMT

Disease Status	Allo HCT	Auto HCT
CR1, low risk	**N**	**C**
CR1, intermediate risk	**S**	**C**
CR1, high risk	**S**	**C**
CR2	**S**	**C**

- S (Standard of Care)
- C : indication for wich large clinical trials are not available

Majhail N et al Biol Blood Marrow Transplant 2015;21:1863-1869

HSCT in AML
EBMT

Disease Status	Sibling donor	Well matched URD	Alternative donor	ASCT
CR1, low risk	**CO/II**	**D/II**	**GNR/II**	**CO/I**
CR1, intermediate risk	**S/II**	**CO/II**	**D/II**	**S/I**
CR1, high risk	**S/II**	**S/II**	**CO/II**	**CO/I**
CR2	**S/II**	**S/II**	**CO/II**	**CO/II**

- ❑ S (Standard of Care)
- ❑ CO (Clinical option)
- ❑ D (Developmental)
- ❑ GNR (Generally not recommended)

Categories are based mainly on number of WBCs, cytogenetics at diagnosis and molecular markers

Sureda A et al Bone Marrow Transplant 2015;50:1037-1056

Allo SCT in intermediate-risk AML

- Sorror/EBMT risk-score/EBMT ADT
- MRD evaluation (auto??)

Genomic Classification and Prognosis in Acute Myeloid Leukemia