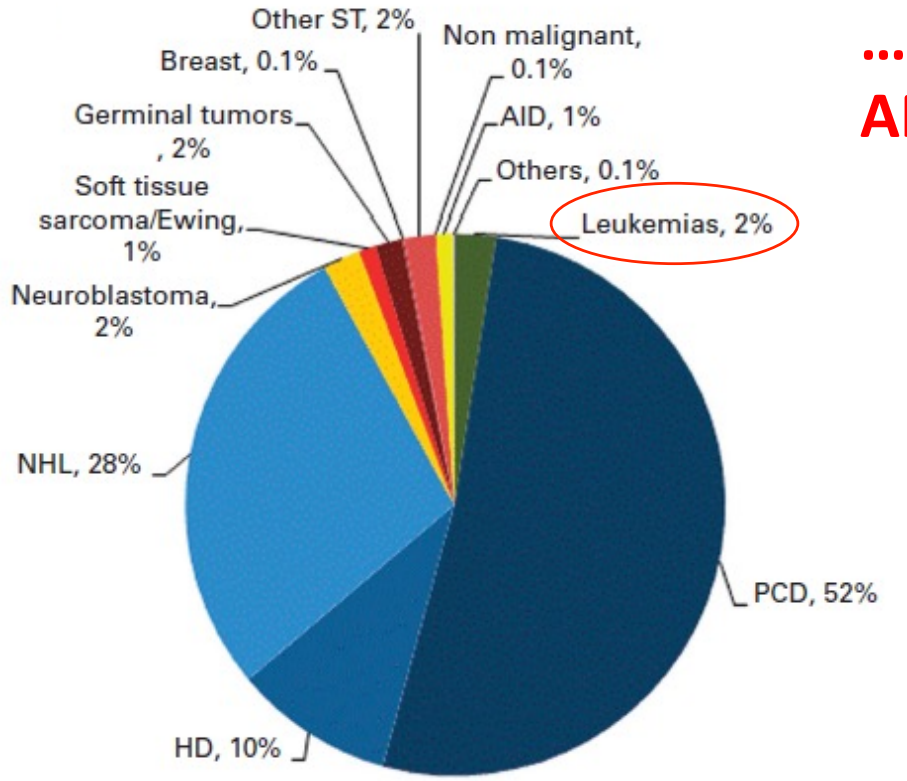
AUTOLOGOUS STEM CELL TRANSPLANT IN AML: THE CINDERELLA STORY

Ravenna, 27-Oct-2016

Francesco Saraceni
Hematology and SCT, Ravenna

Auto-SCT in AML

EBMT survey: Indications for auto-SCT in EUROPE - 2015



… and what about AML??

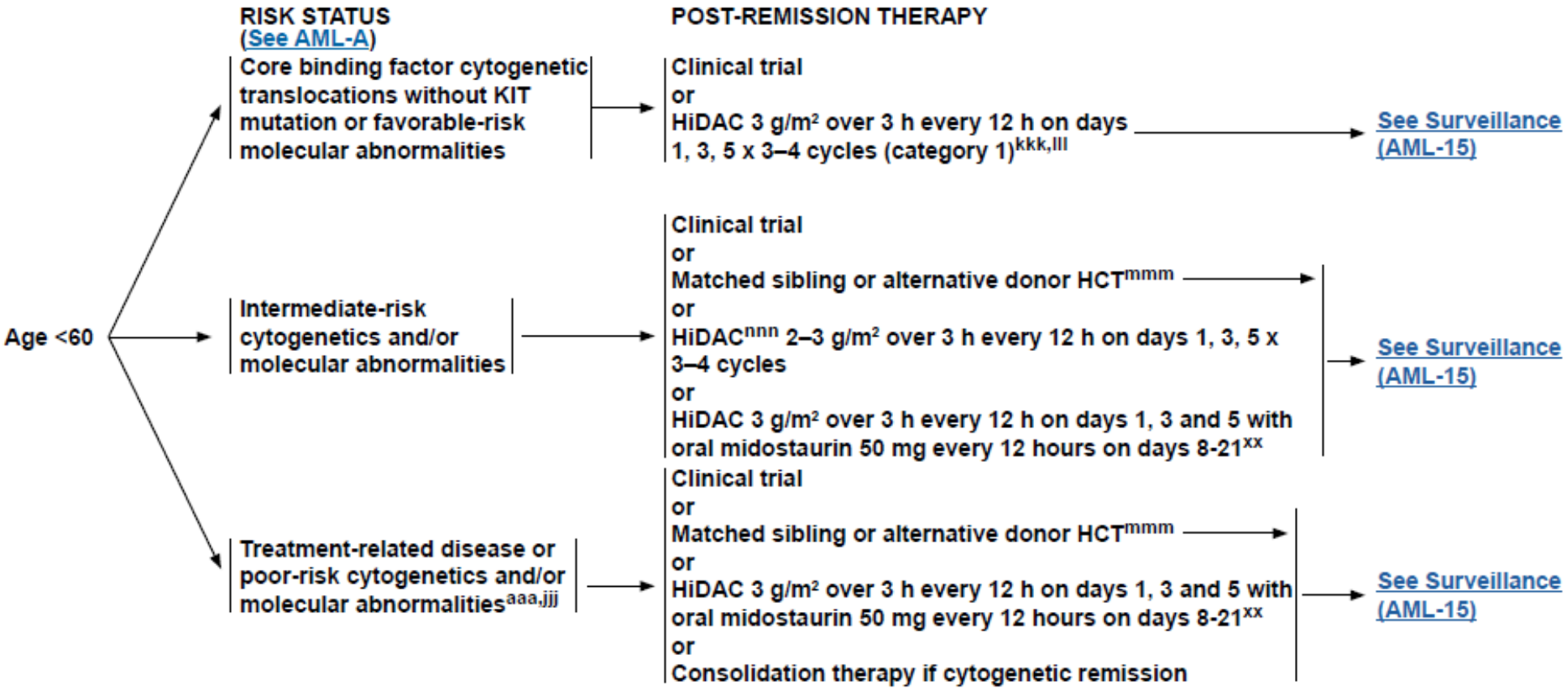
Passweg JR, Bone Marrow Transplantation 2017

Auto-SCT in AML

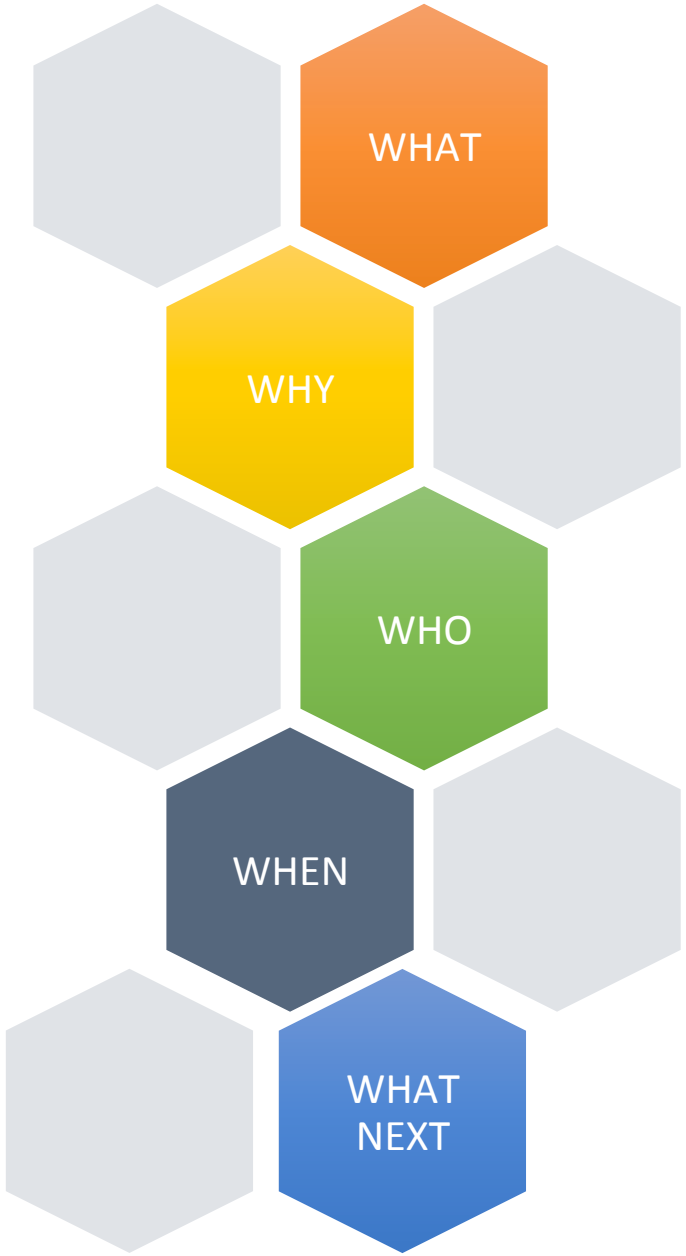
National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2017
Acute Myeloid Leukemia

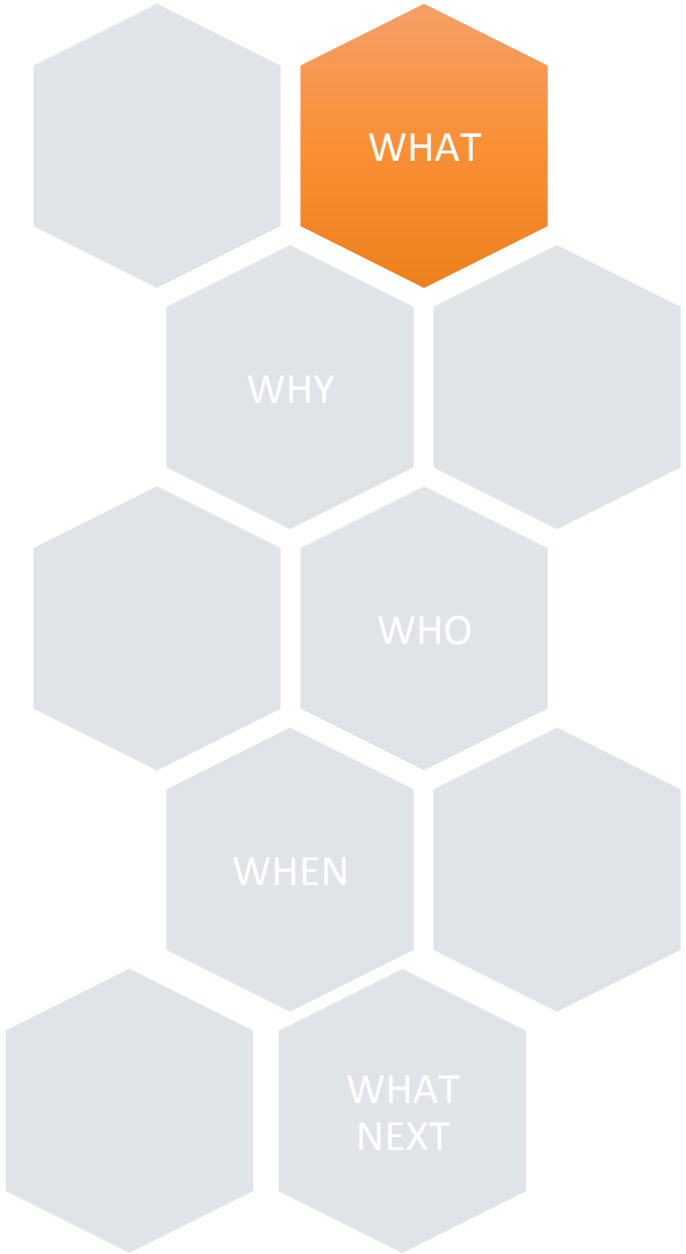
… and what about Auto-SCT??



Auto-SCT in AML: Overview



Auto-SCT in AML: Overview



Auto-SCT in AML: WHAT

1970

- Auto-SCT as backup for patients lacking a sibling donor

2000

- Developements in allo-SCT:
  - nMAC, RIC
  - Alternative donors

- Auto-SCT has fallen out of favour

2010

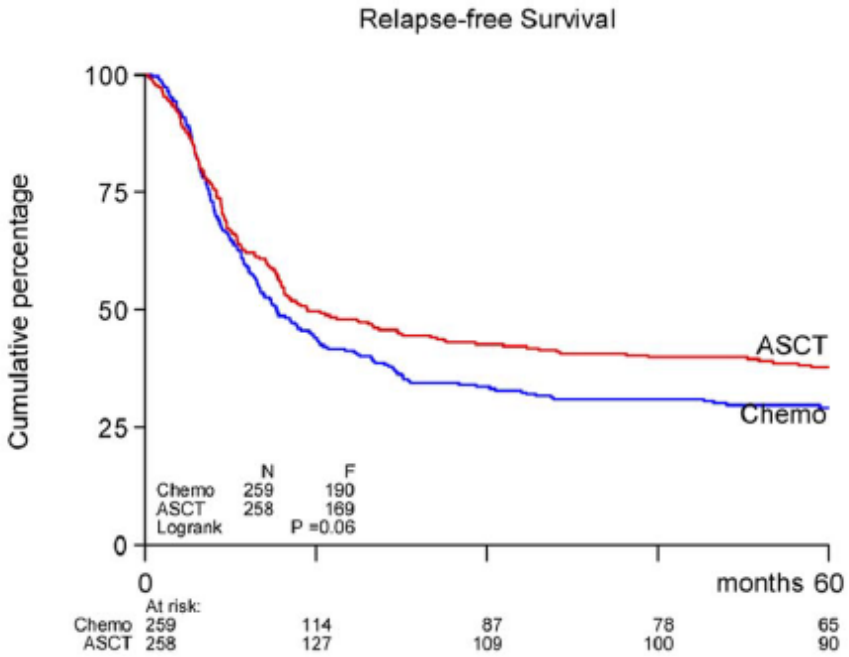
- Developements in auto-SCT practice: SC source, conditioning
- MRD

Re-discovery of auto-SCT in AML?

Auto-SCT in AML: WHAT

Randomized Auto-SCT vs CHT

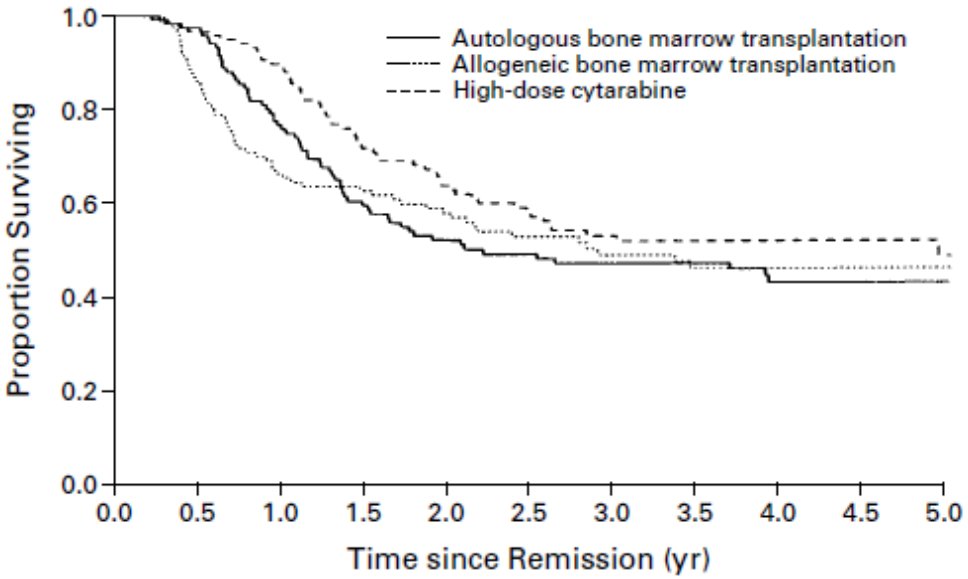
- Lower RI vs higher NRM
- Better LFS
- Similar OS



Vellenga E, Blood 2011

Randomized Auto-SCT vs Allo-SCT

- Higher RI vs lower NRM
- Inferior LFS
- Similar OS



Cassileth, N Eng J Med 1998

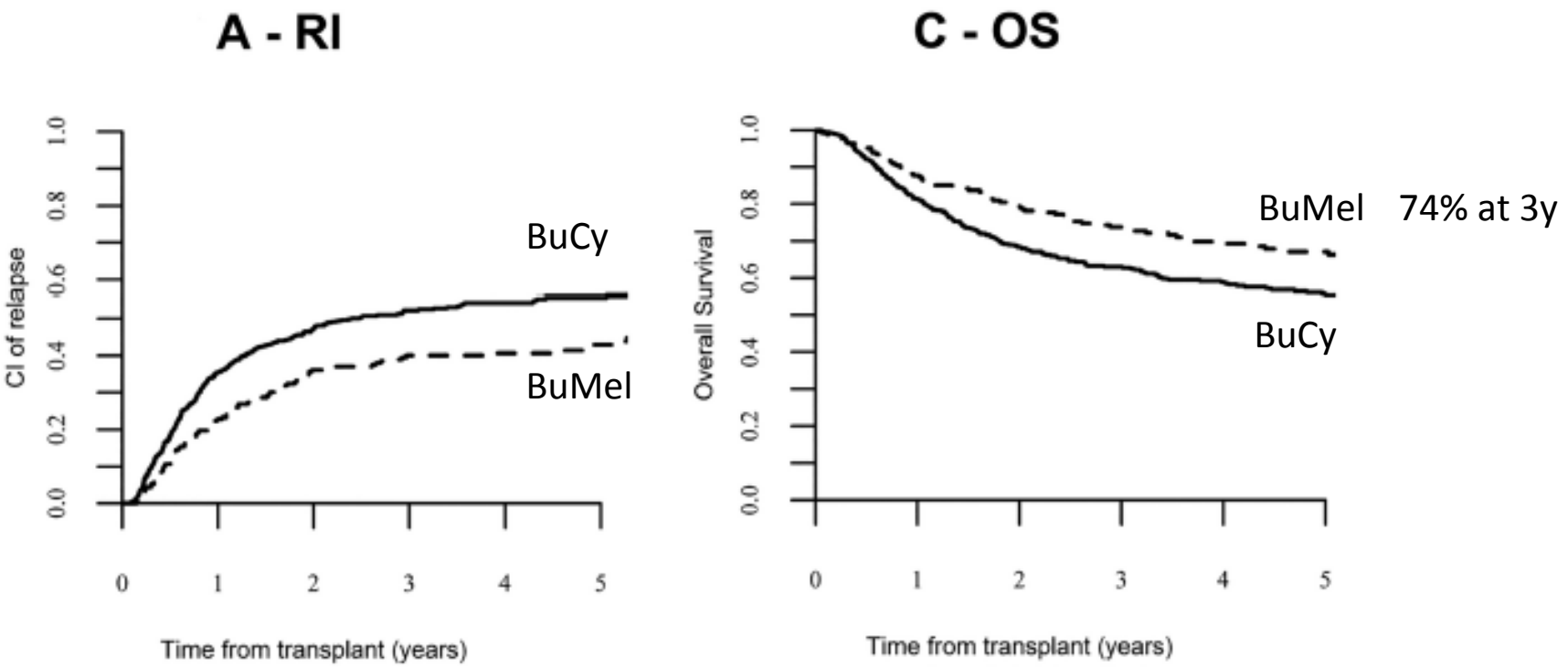
Koreth, JAMA 2009
Suciu, Blood 2003

Zittoun RA, N Eng J Med 1995
Harousseau JL, Blood 1997
Burnett AK, Lancet 1998
Slovak ML, Blood. 2000

Auto-SCT in AML: WHAT

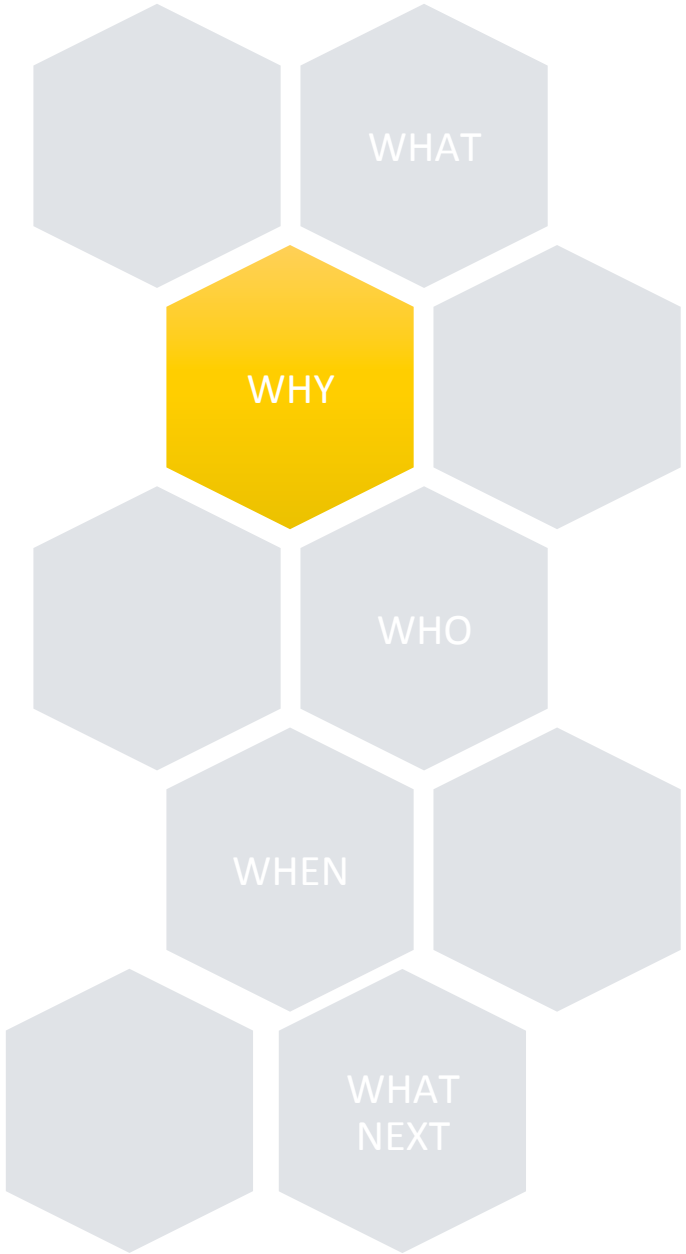
Improvements in auto-SCT

- Graft source: BM → PBSC
- Conditioning: TBI-based → BuCy → BuMel

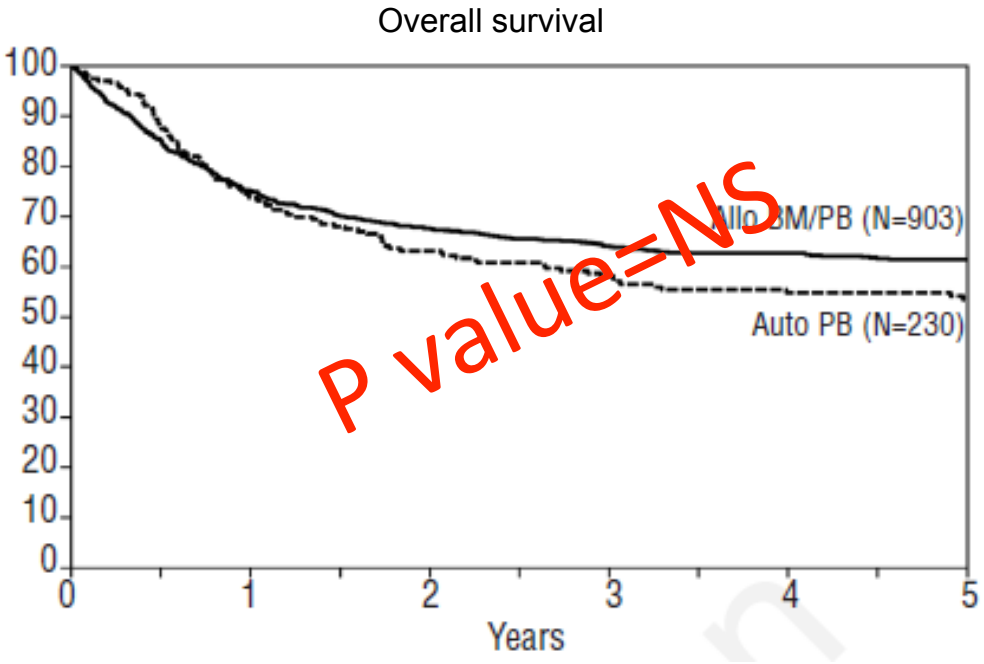


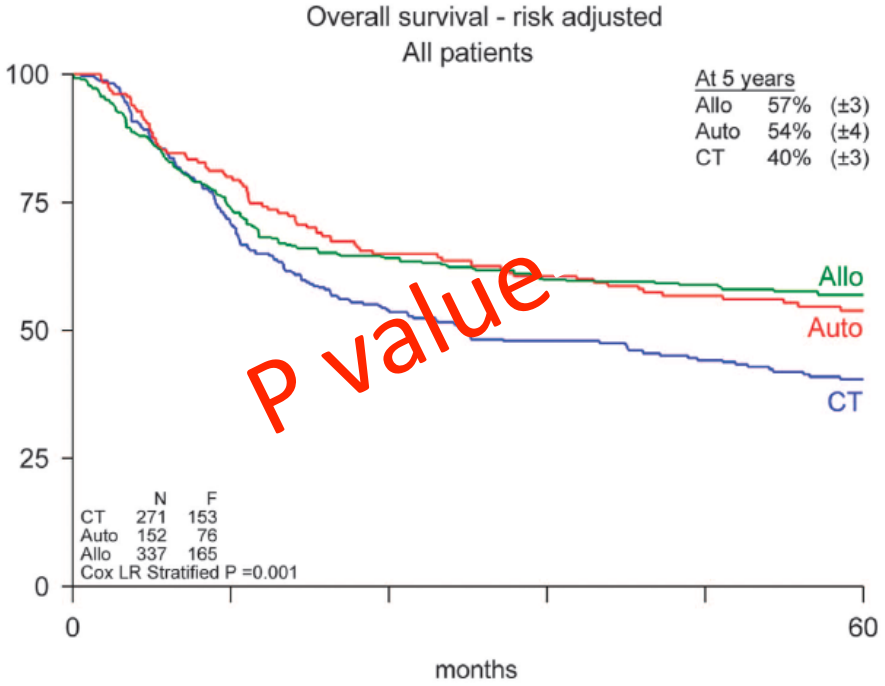
Gorin NC, Cancer 2017

Auto-SCT in AML: Overview



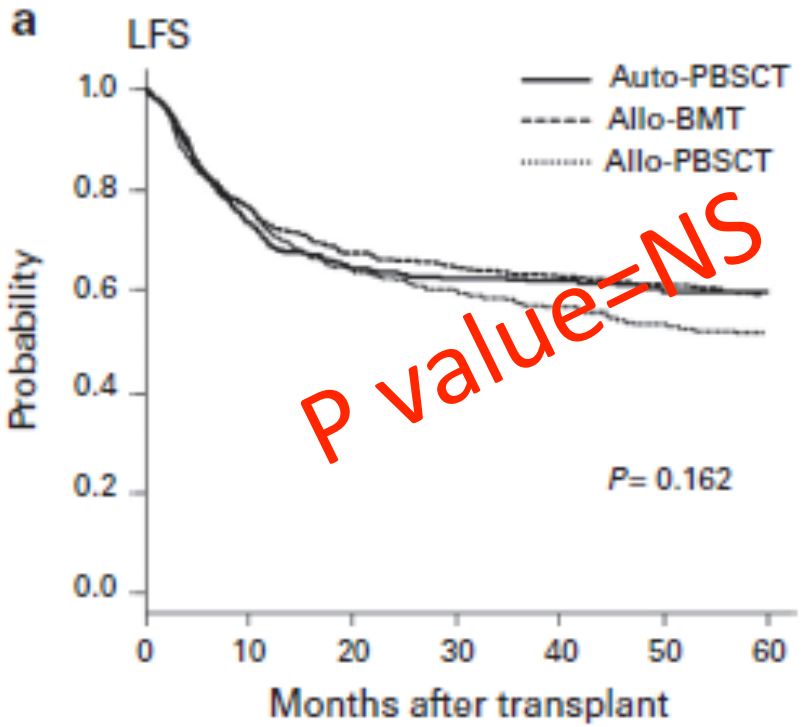
Auto-SCT in AML: WHY





Keating A, Haematologica 2013
Cornelissen J, Leukemia 2014

Auto-SCT in AML: WHY



1998=2016: Auto-SCT vs sibling allo-SCT: similar survival

Mizutani M, Bone marrow transplant 2016

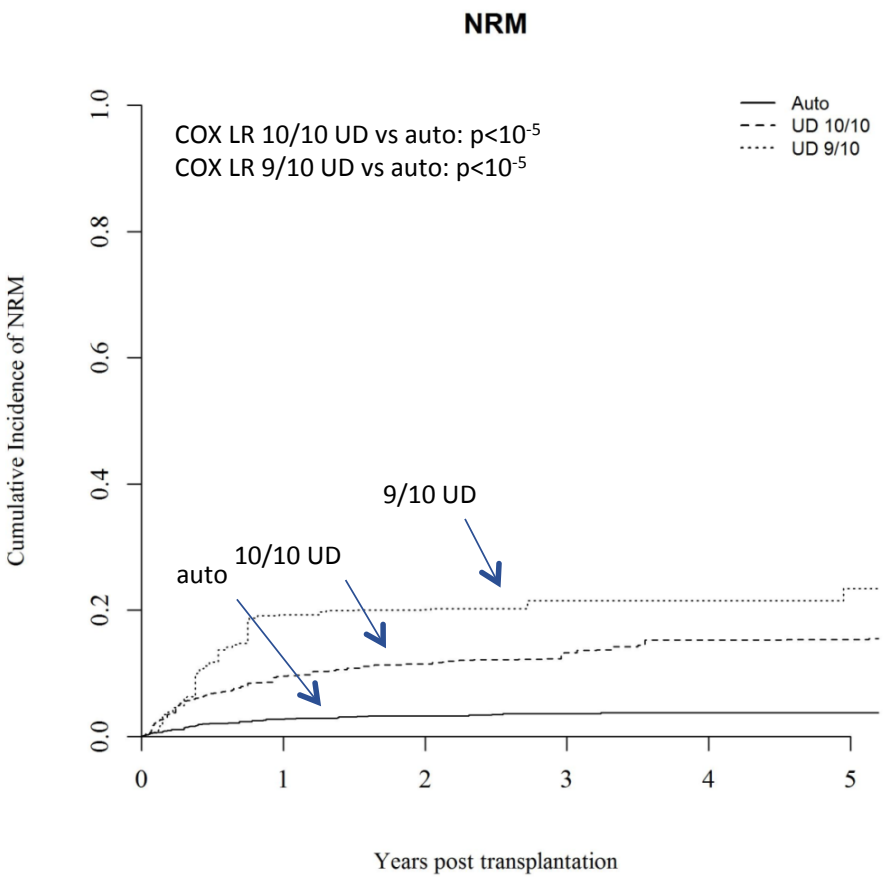
Auto-SCT vs 10/10 or 9/10 UD allo-SCT: ALWP-EBMT study

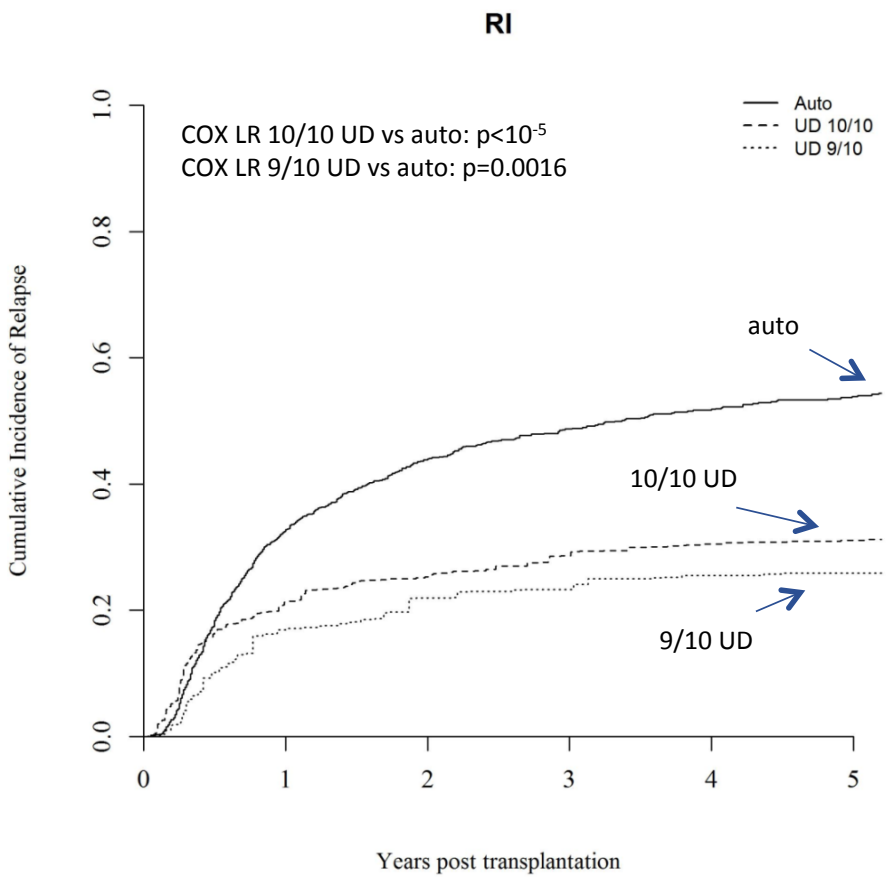
And what if compare auto-SCT vs MUD and MMUD?

Patient characteristics		auto-SCT	10/10 UD	9/10 UD
Total n. 2879		1202	1302	375
Cytogenetic risk, n (%)	good	518 (43)	608 (47)	187 (50)
	intermediate	624 (51)	550 (42)	165 (44)
	poor	186 (16)	615 (47)	184 (49)
Age		49 (18-78)	51 (18-76)	49 (18-69)
Stem cell source	BM	53 (4)	258 (20)	58 (16)
	PBSCs	1149 (96)	1044 (80)	317 (84)
Conditioning intensity	MAC	-	619 (48)	194 (52)
	RIC	-	677 (52)	180 (48)

Saraceni F, J Hematol Oncol 2016

Auto-SCT vs 10/10 or 9/10 UD allo-SCT: ALWP-EBMT study



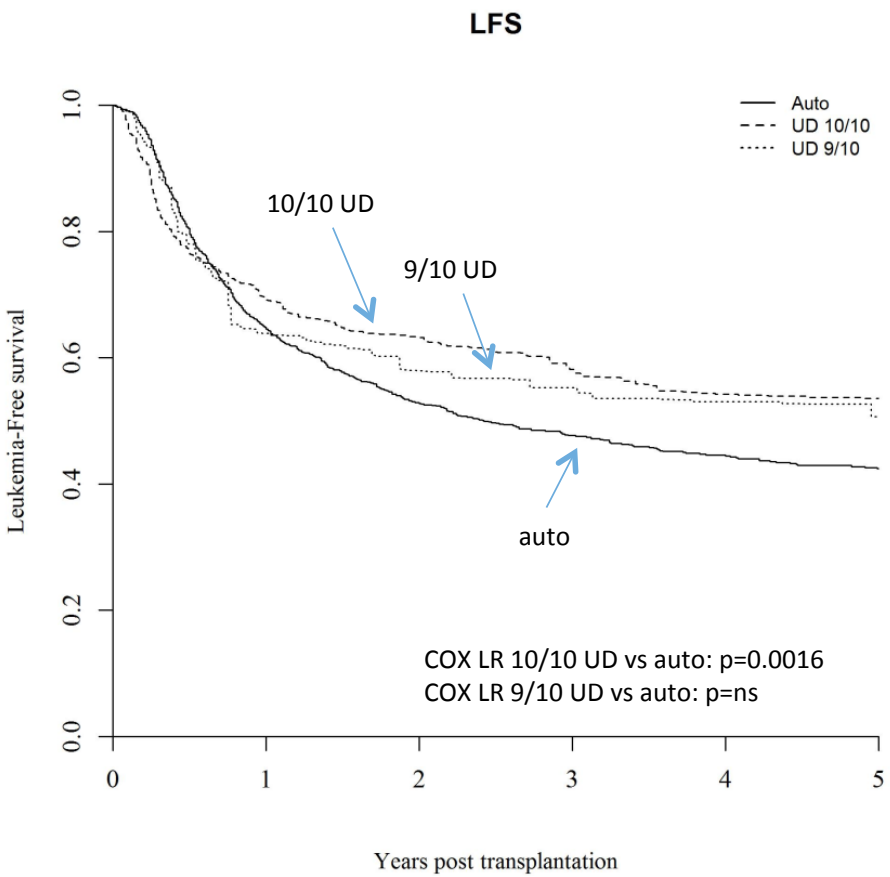


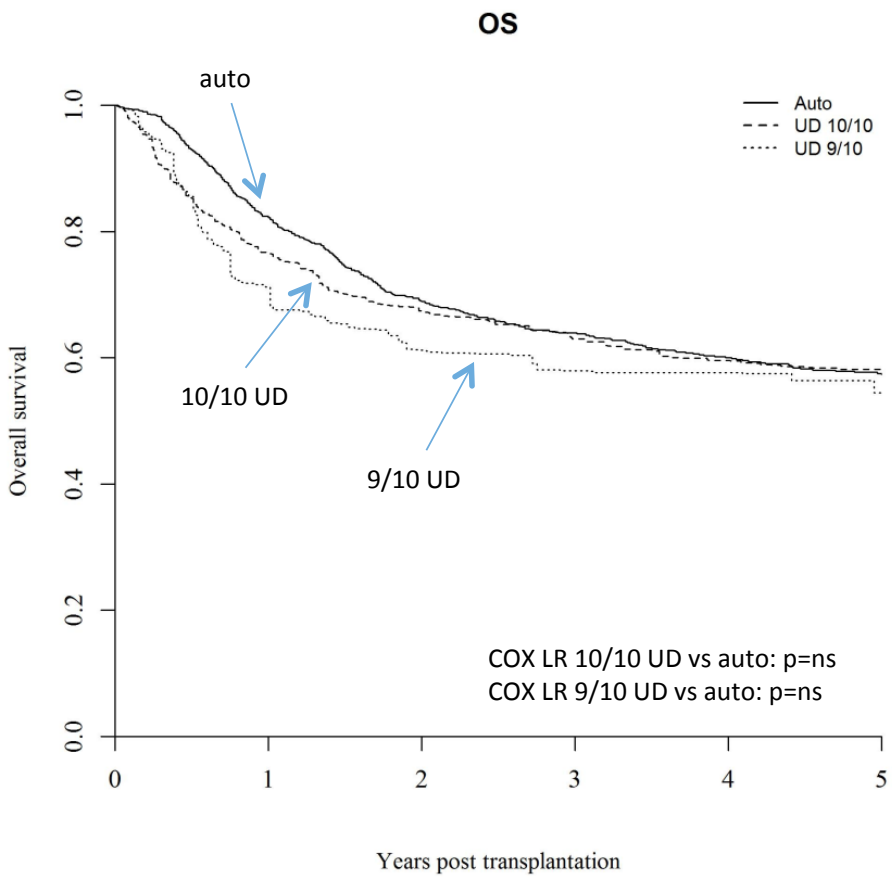
3-years PS-weighted NRM rates	
auto-SCT	4±2%
10/10 UD	13±2%
9/10 UD	21±2%

3-years PS-weighted RI rates	
auto-SCT	49±3%
10/10 UD	29±3%
9/10 UD	23±5%

Saraceni F, J Hematol Oncol 2016

Auto-SCT vs 10/10 or 9/10 UD allo-SCT: ALWP-EBMT study





3-years PS-weighted LFS rates	
auto-SCT	48±3%
10/10 UD	58±3%
9/10 UD	55±3%

3-years PS-weighted OS rates	
auto-SCT	64±3%
10/10 UD	63±3%
9/10 UD	58±4%

Saraceni F, J Hematol Oncol 2016

Auto-SCT in AML: WHY

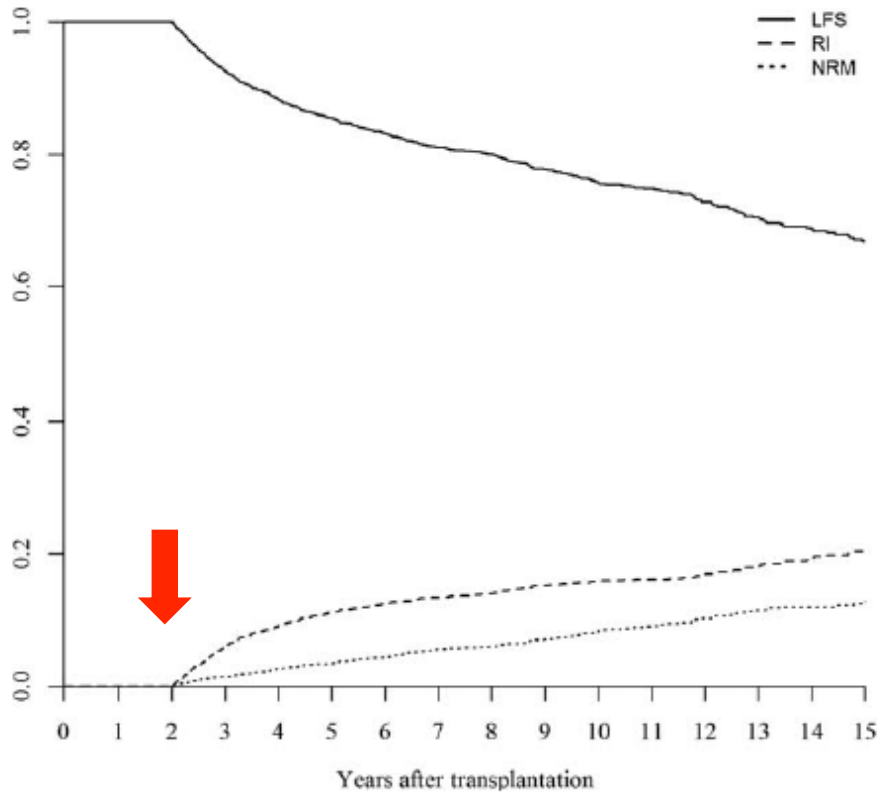


Figure 1. Outcomes of patients with acute myeloid leukemia who remained free of disease recurrence at least 2 years after autologous stem cell transplantation. LFS indicates leukemia-free survival; NRM, nonrecurrence mortality; RI, recurrence incidence.

Czerw T, Cancer 2016

Auto-SCT in AML: WHY

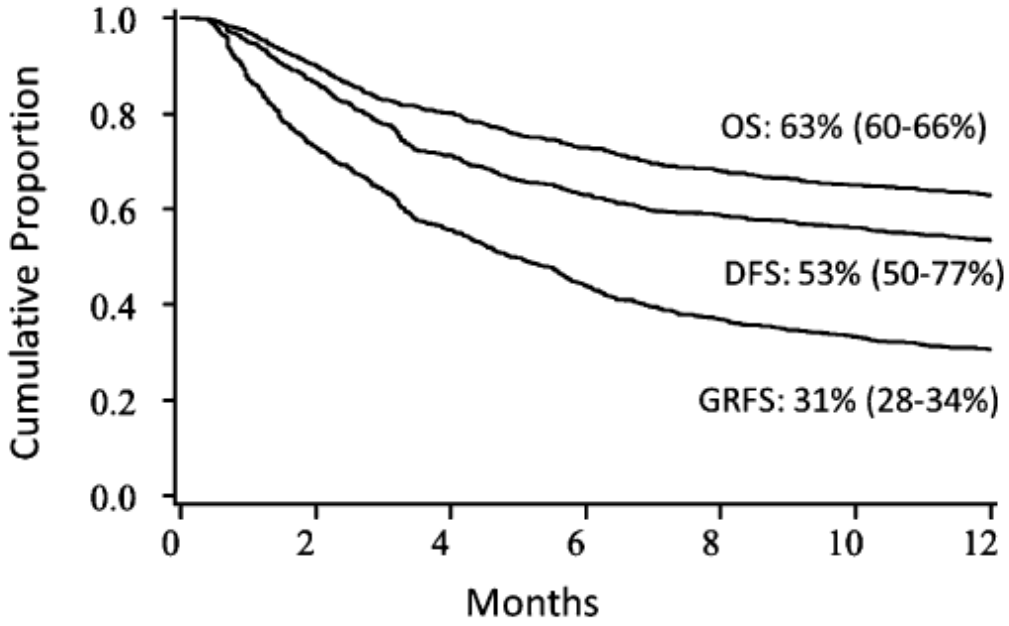


Figure 1. Kaplan-Meier estimates. OS, DFS, and GRFS.

Late effects following allo-SCT

- Immune deficiency, endocrine, ocular and salivary gland disfunction, skeletal disorders, respiratory tract, dental, liver, sexual disfunction, secondary cancers
- RR of grade 3–4 chronic health conditions x2.65 after ASCT, vs x4.5 after allo-HSCT compared with siblings of the survivors

Holtan SG, Blood 2015

Messerer D, Haematologica 2008

Auto-SCT in AML: WHY

PROs	CONs
OS above 60% long term	RI about 50% long term
Low NRM (3-4%)	LFS 40-50%
No GVHD	No GVL
Low incidence of late effects	Many pts fail to collect PBSCs
Better QoL vs allo	Theoretic possibility of graft contamination by blasts
Available in most centers	

Auto-SCT in AML: Overview

First designed for patients lacking an available donor, is now struggling to find an updated role in AML

Similar OS vs matched allo-SCT; maybe better than MMUD; lower incidence of late effects, better QoL

Auto-SCT in AML: Overview

Auto-SCT in AML: WHO

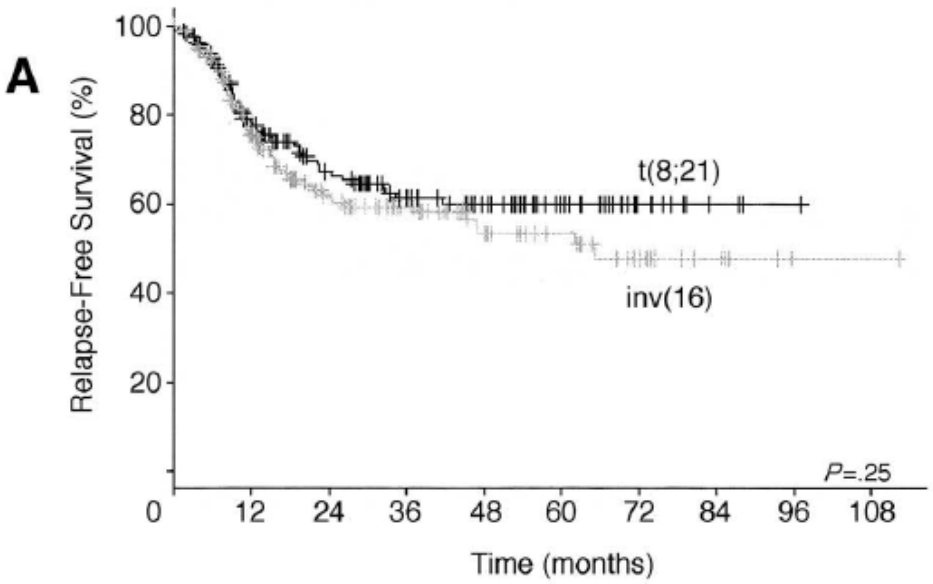
Table 5. 2017 ELN risk stratification by genetics

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*#

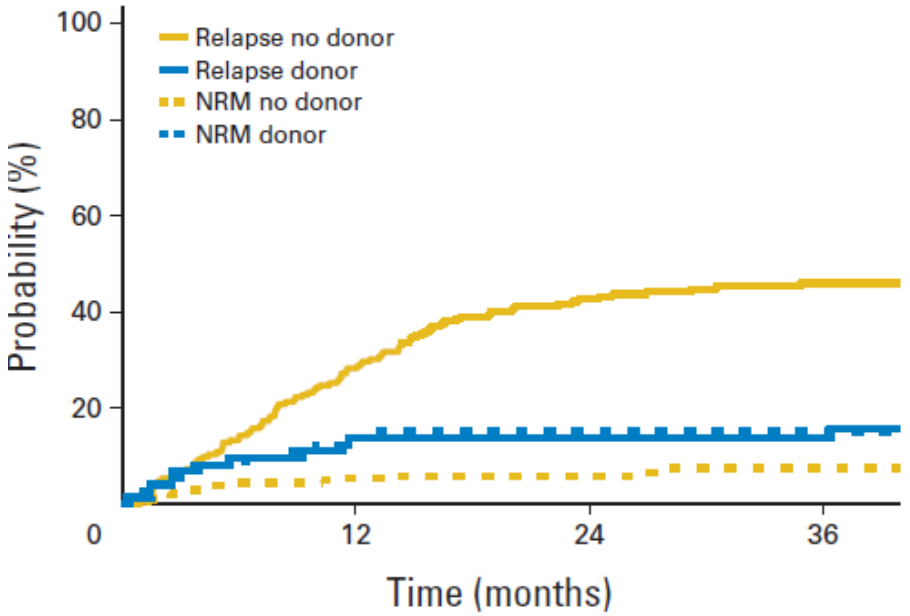
Dohner H, Blood 2017

Auto-SCT in AML: WHO: Good risk?

CBF-AML



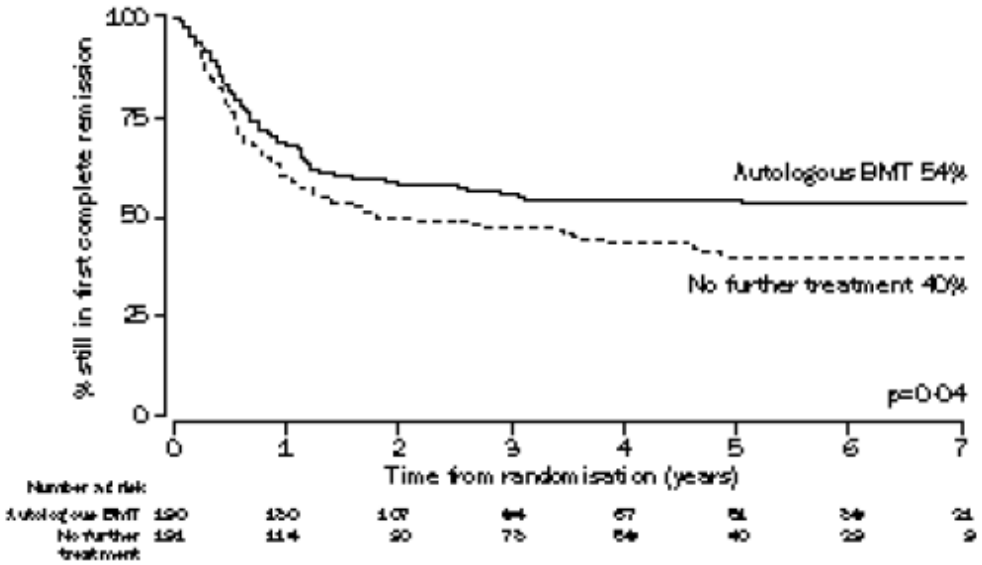
NPM1 mutated/FLT3wt

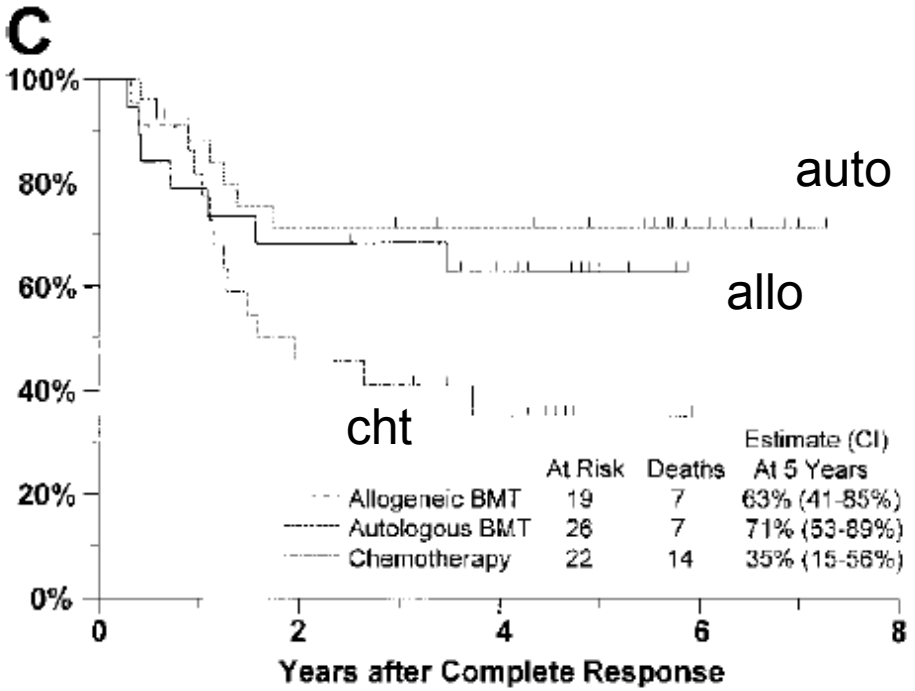


Schlenk RF, J Clin Oncol 2004
Rollig C, J Clin Oncol 2015

Auto-SCT in AML: WHO: Good risk – CBF AML?

CBF-AML





Burnett AK, Lancet 1998
Slovak ML, Blood 2000

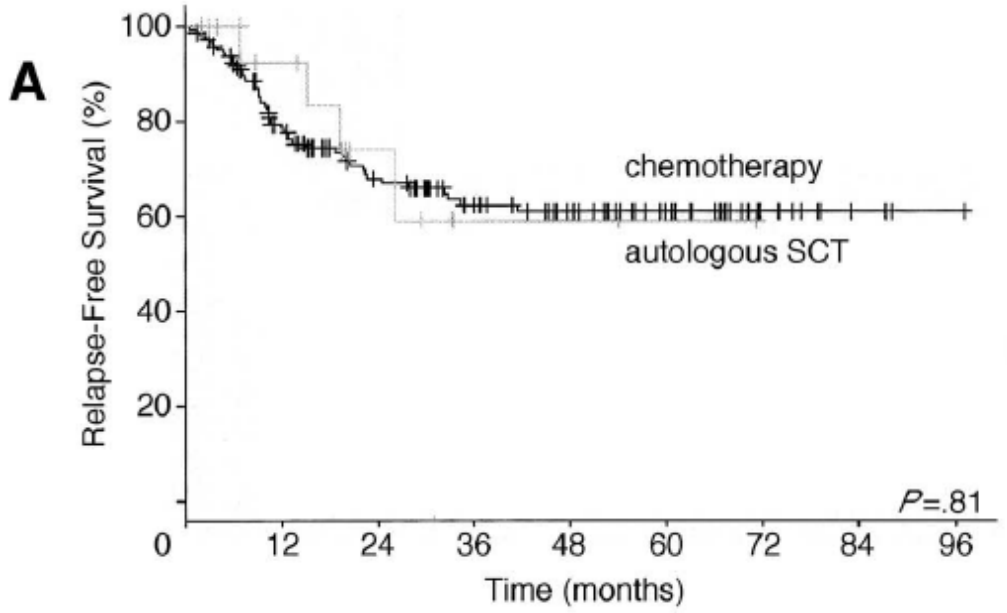
Auto-SCT in AML: WHO: Good risk – CBF AML?

Table 4. Prognostic factors and test for interaction with treatment arm

	No. of patients	No. of events	5-y RFS %			Cox regression, RFS B vs A			No. dead	5-y OS, %			Cox regression, OS B vs A		
			All	A	B	HR	95% CI	*P*		All	A	B	HR	95% CI	*P*
Total	517	359	33	29	38				317	42	41	44			
Age, y			$P = .010$					$P_{int} = .22$		$P < .001$					$P_{int} = .34$
≤ 40	177	114	37	29	47	0.65	0.44-0.95	.025	89	52	47	57	0.85	0.56-1.30	.46
41-50	117	72	38	30	46	0.73	0.46-1.16	.18	68	43	39	48	0.82	0.51-1.33	.43
> 50	223	173	28	29	27	0.98	0.73-1.32	.90	160	35	35	34	1.17	0.86-1.60	.33
Extramedullary disease			$P = .016$					$P_{int} = .25$		$P = .21$					$P_{int} = .85$
No	449	304	35	31	39	0.87	0.69-1.08	.21	272	43	41	45	1.03	0.81-1.31	.79
Yes	68	55	22	16	28	0.61	0.36-1.05	.076	45	37	35	38	0.98	0.54-1.76	.93
Cytogenetics			$P < .001$					$P_{int} = .13$		$P < .001$					$P_{int} = .20$
Favorable	39	20	49	33	67	0.39	0.15-1.02	.055	11	72	71	72	1.03	0.31-3.36	.97
Intermediate	393	271	35	32	38	0.87	0.69-1.11	.27	244	43	40	45	1.00	0.78-1.28	.99
Unfavorable	25	20	20	18	21	0.77	0.32-1.86	.56	18	28	27	29	0.99	0.39-2.52	.99
Very unfavorable	28	28	0	0	0	1.76	0.82-3.78	.15	27	4	6	0	2.49	1.15-5.41	.021
CR reached			$P < .001$					$P_{int} = .35$		$P < .001$					$P_{int} = .29$
Cycle 1	413	275	37	32	42	0.78	0.61-0.99	.037	241	45	43	48	0.95	0.74-1.23	.72
Cycle 2	104	84	20	18	21	0.97	0.63-1.49	.89	76	31	31	32	1.25	0.79-1.96	.34

Vellenga E, Blood 2011

Auto-SCT in AML: WHO: Good risk – CBF AML?

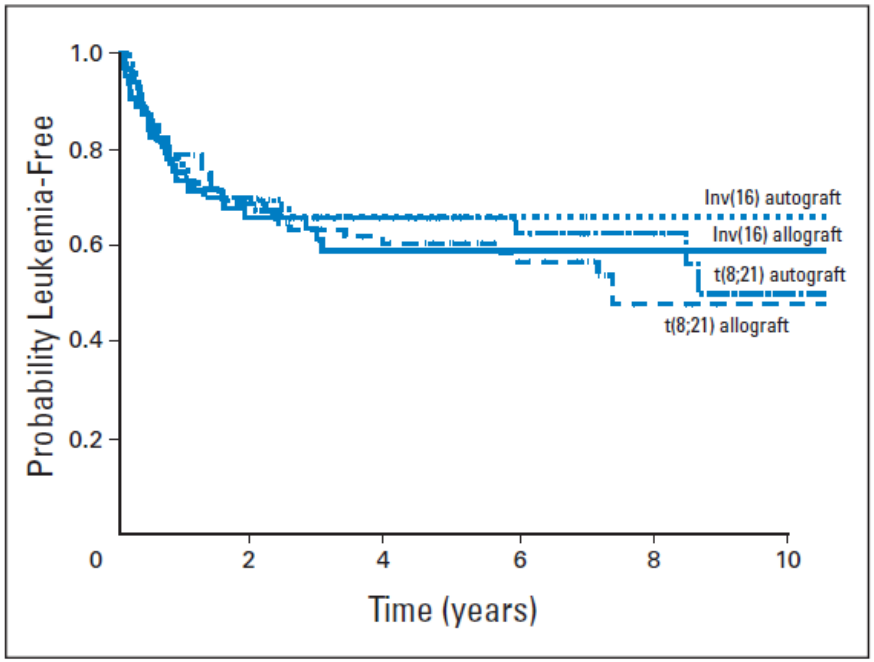


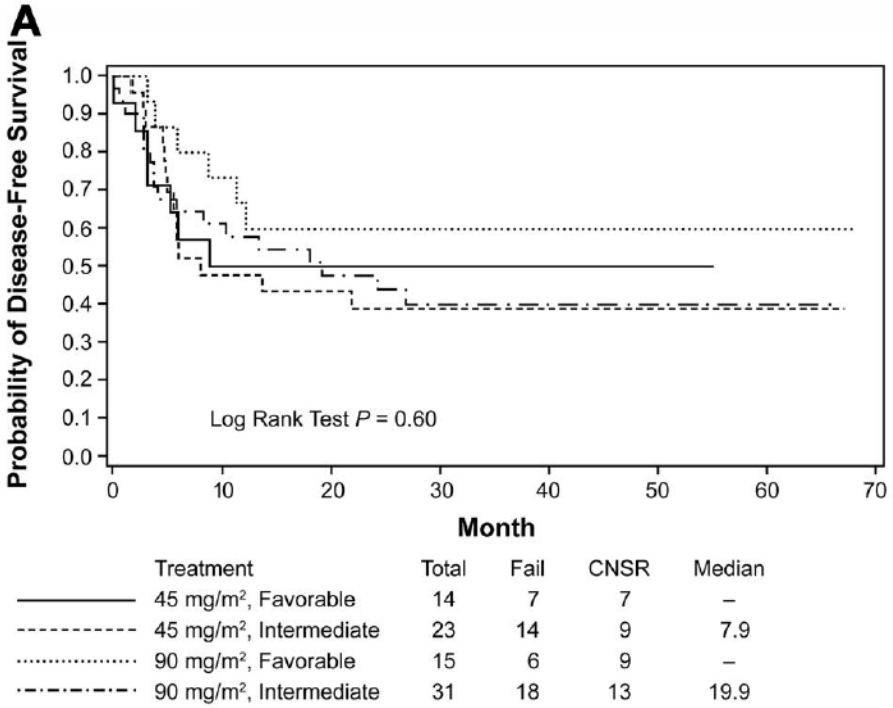
So, is auto-SCT better than just chemoterapy in CBF-AML?

Schlenk RF, J Clin Oncol 2004

Auto-SCT in AML: WHO: Good risk – CBF AML?

Surely we do not need allo-SCT in CBF AML

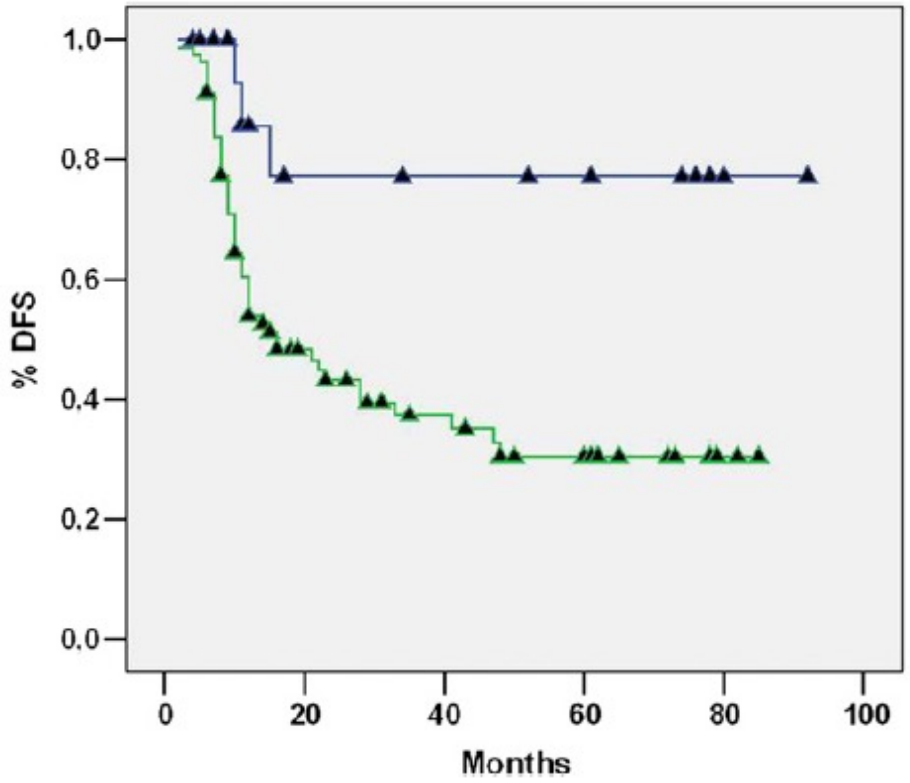




Gorin NC, J Clin Oncol 2008
Fernandez HF, Blood 2011

Auto-SCT in AML: WHO: Good risk – NPM1 mutated AML?

NPM1 mutated AML



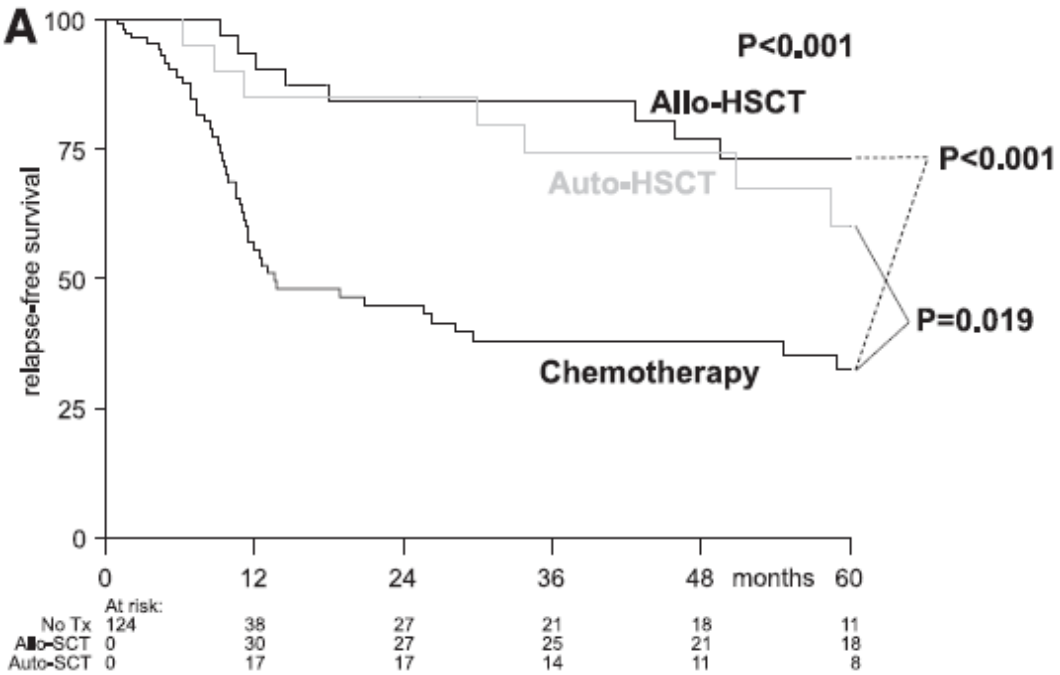
NPM1+/FLT3wt

All others

Ferrara F, Biol Blood Marrow Transplant 2010

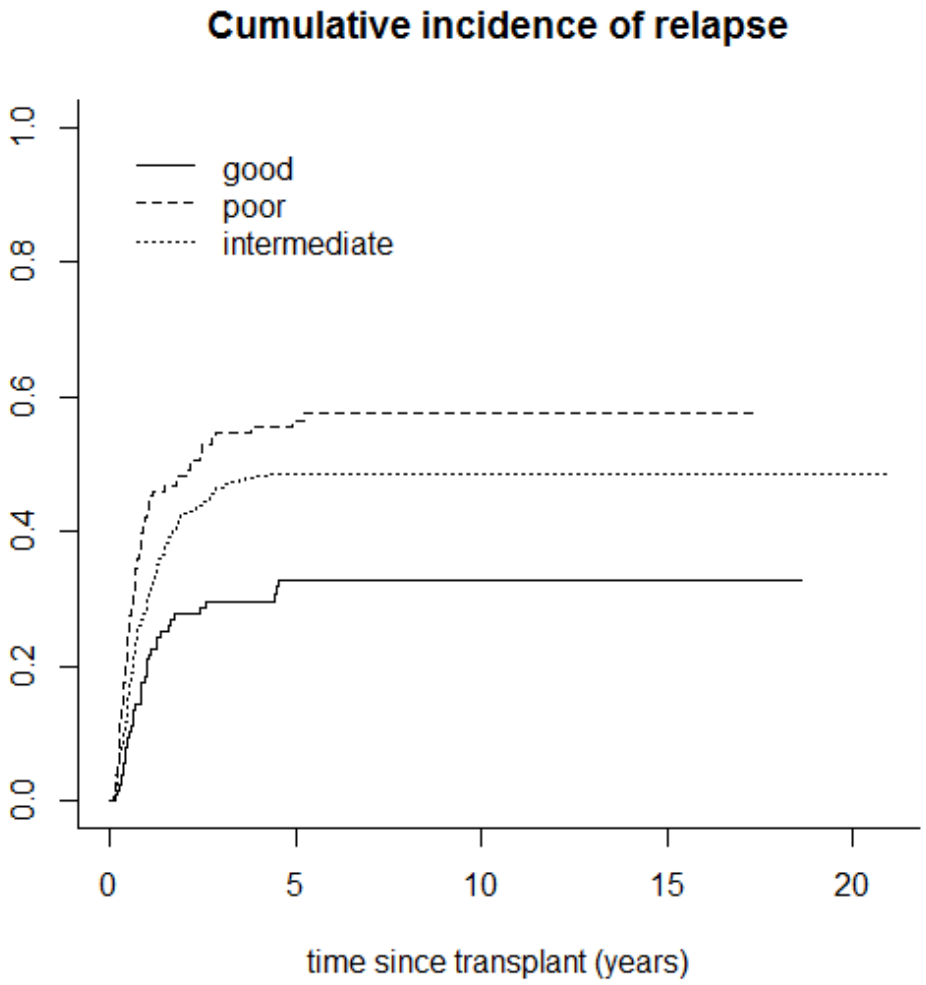
Auto-SCT in AML: WHO: Good risk – CEBPAdm AML?

CEBPAdm AML



Schlenk RF, Blood 2013

Auto-SCT in AML: GITMO AML CR1 auto-SCT study



Patients

n. 809 AML autografted in CR1

Cytogenetics available

RI

Good risk

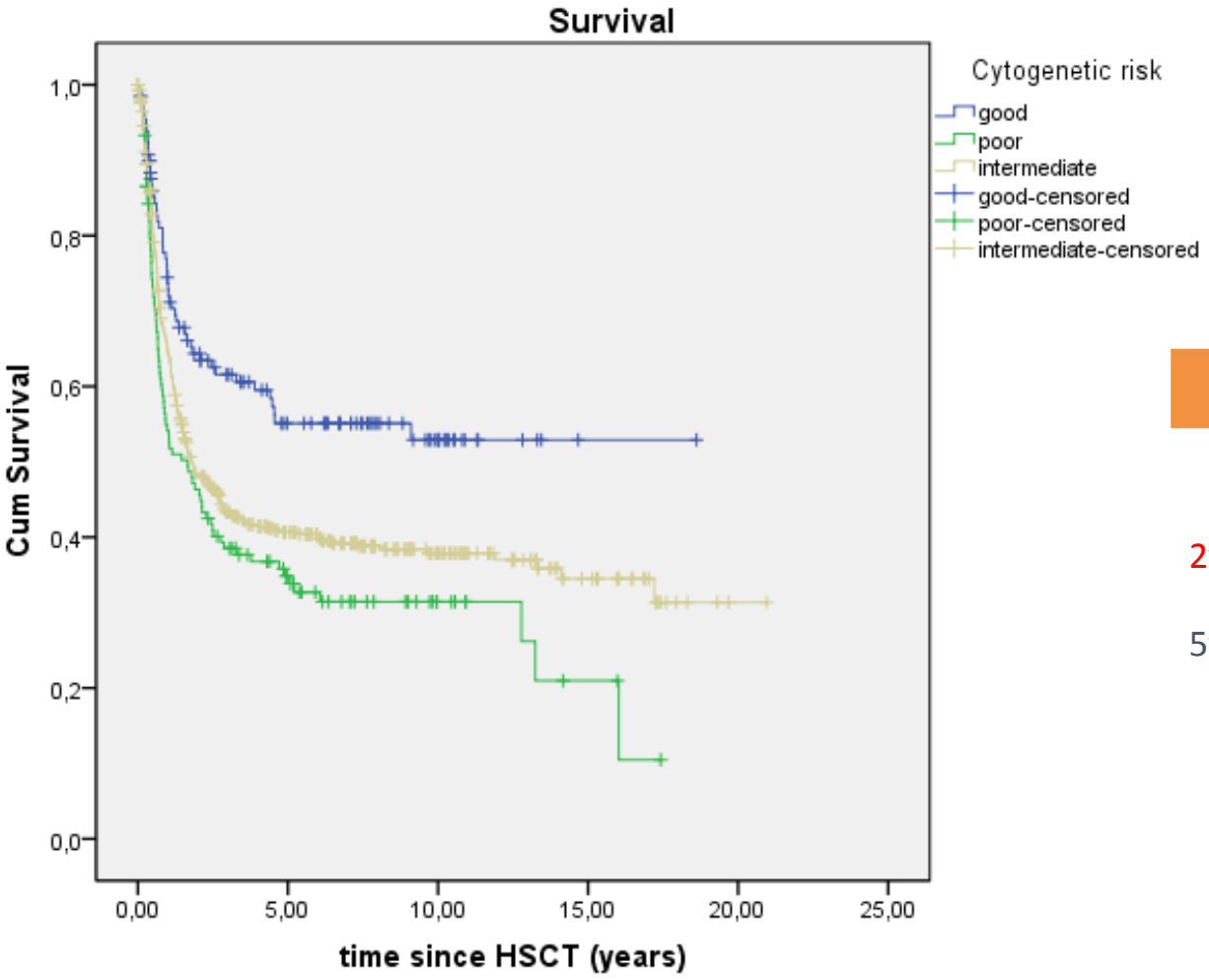
2y 27.7% (20.7-36.9)

5y 32.9% (25.3-42.7)

GITMO

Saraceni F, Bone Marrow Transplant 2017

Auto-SCT in AML: GITMO AML CR1 auto-SCT study



LFS

Good risk

2y 64.4 (56.4-73.4)

5y 55.1 (46.6-65.1)

GITMO

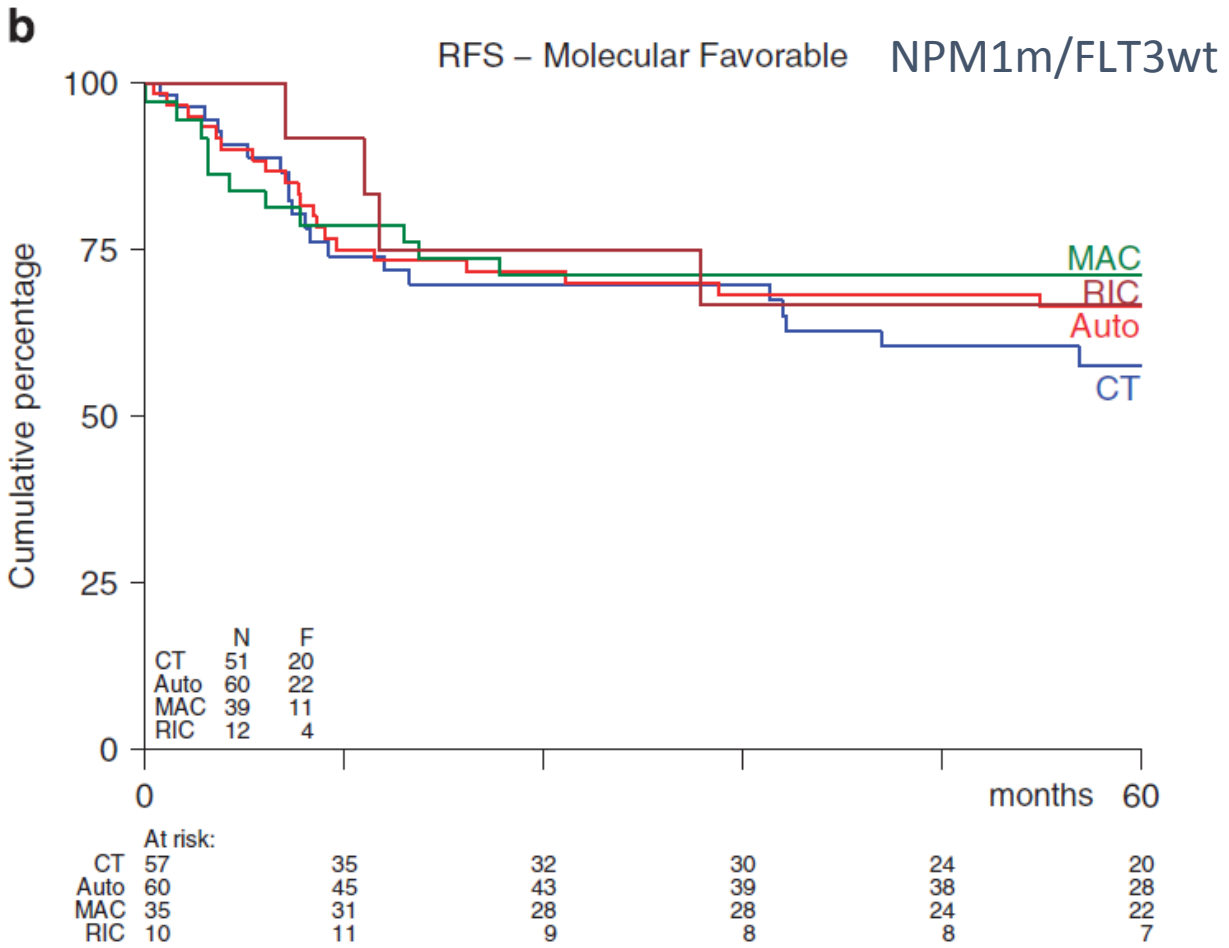
Saraceni F, Bone Marrow Transplant 2017

Auto-SCT in AML: ALWP-EBMT study-good risk subgroup

3-years PS-weighted Kaplan Meier				
	NRM	RI	LFS	OS
auto	4±2%	36±5%	59±5%	78±4%
10/10 UD	9±3%	19±5%	72±6%	77±5%

Saraceni F, J Hematol Oncol 2016

Auto-SCT in AML: WHO: Good risk



Versluis J, Leukemia 2017

Auto-SCT in AML: WHO

Table 5. 2017 ELN risk stratification by genetics

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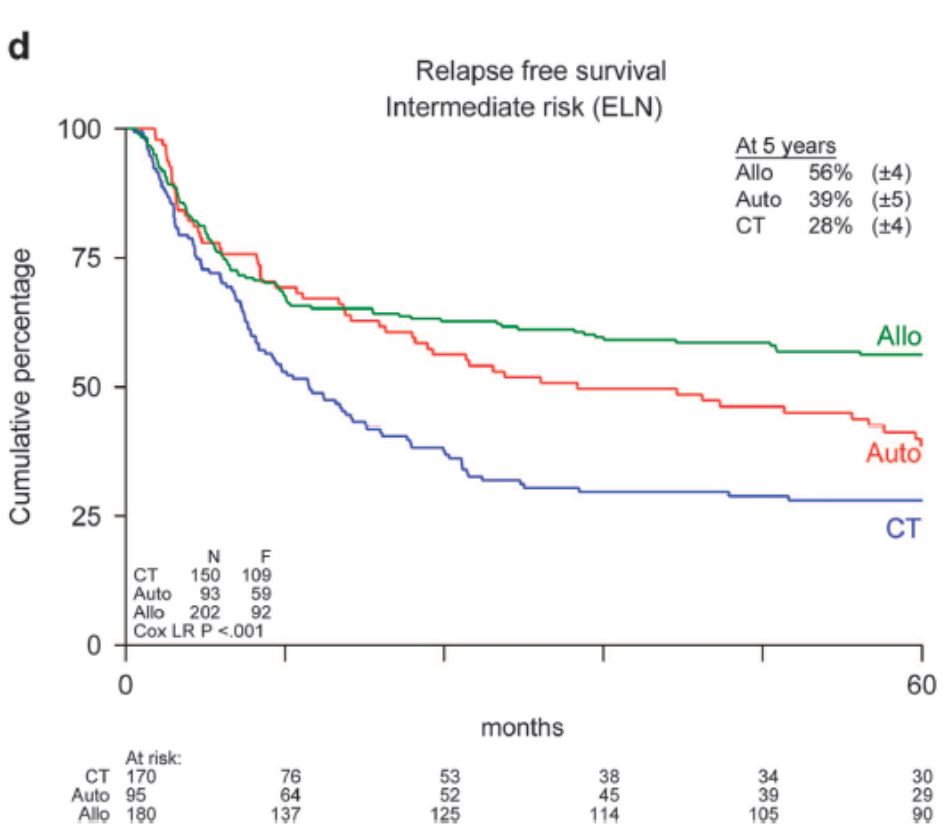
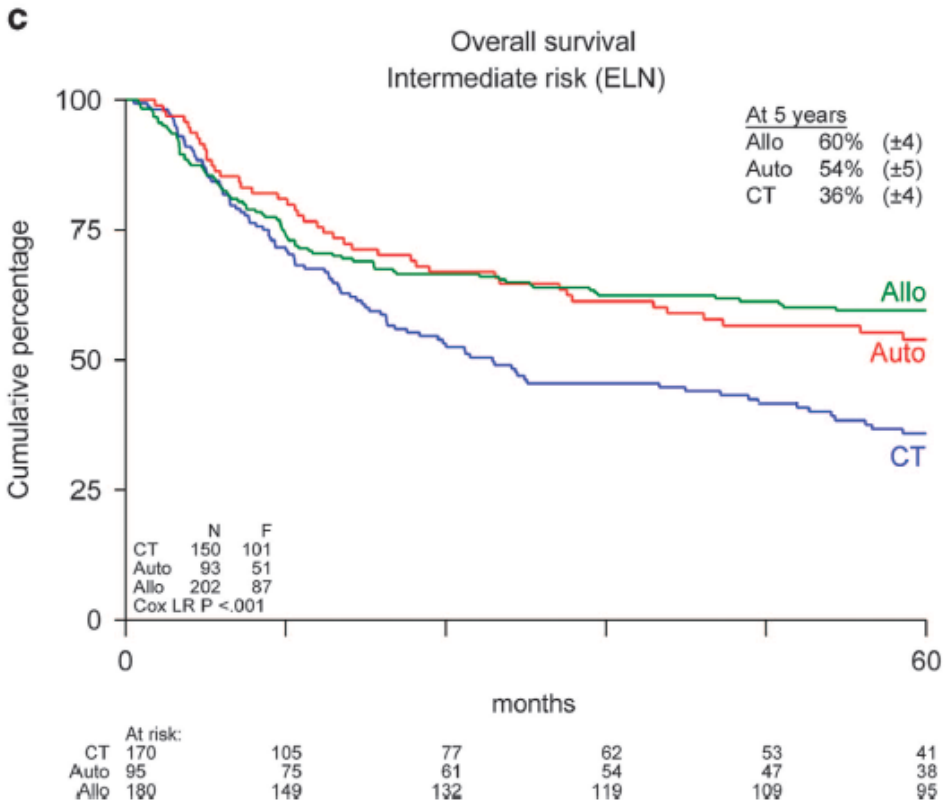
	inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}†
	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}†
	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}† (without adverse-risk genetic lesions)
	t(9;11)(p21.3;q23.3); *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*#

Dohner H, Blood 2017

Auto-SCT in AML: WHO: Intermediate risk

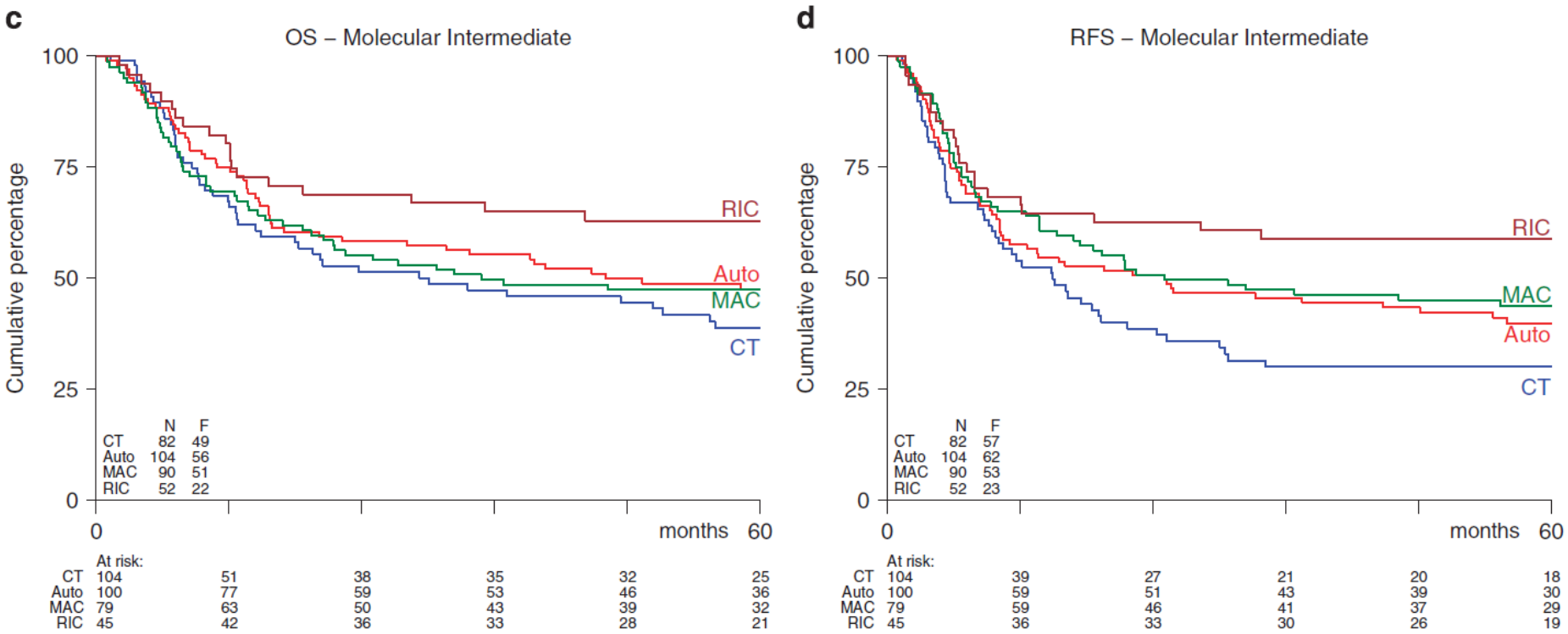




Cornelissen J, Leukemia 2014

Auto-SCT in AML: WHO: Intermediate risk

NPM1wt/FLT3wt

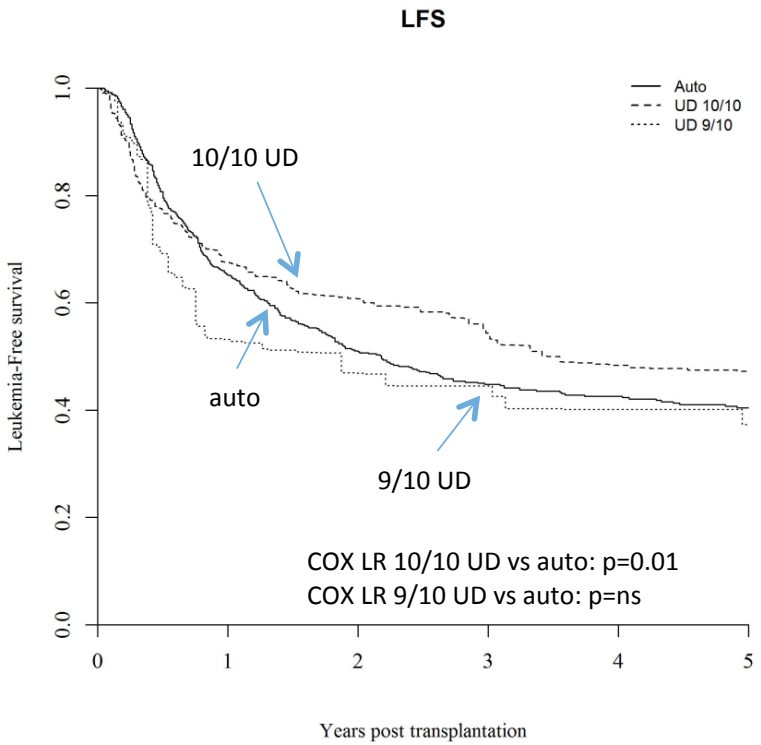


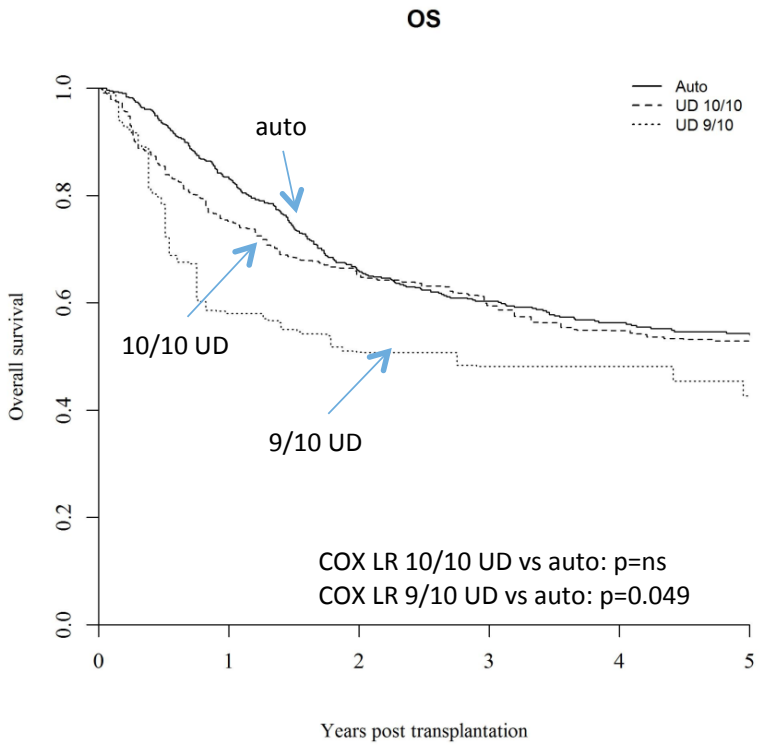
«[…] autologous is an option for patients lacking a matched donor»

Versluis J, Leukemia 2017

Auto-SCT in AML: ALWP-EBMT study-int risk subgroup

1339 intermediate risk AML





3-years PS –weighted Kaplan Meier

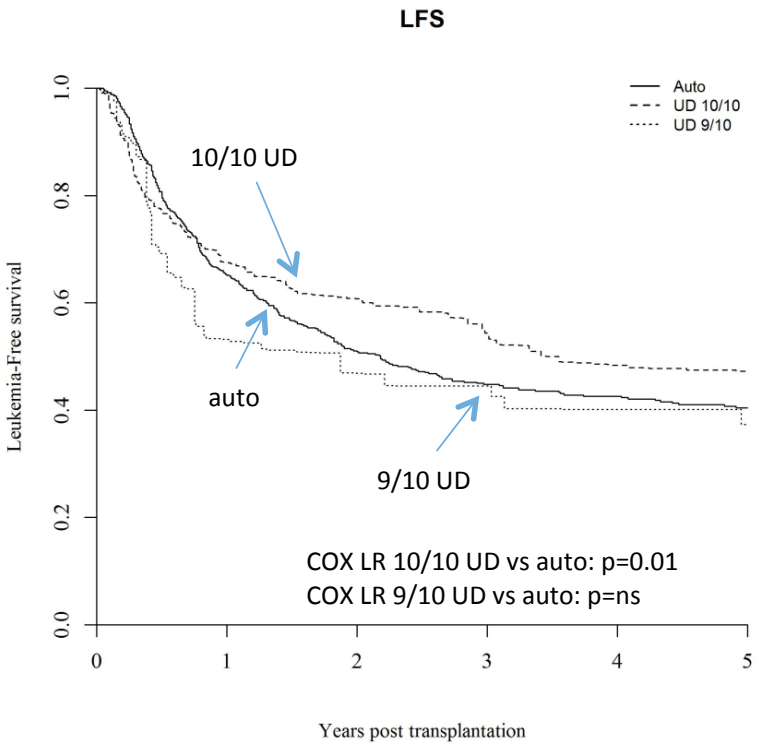
	NRM	RI	LFS	OS
auto	4±2%	51±4%	45±4%	60±4%
10/10 UD	16±3%	30±5%	54±4%	60±5%
9/10 UD	34±5%	21±4%	45±5%	48±4%

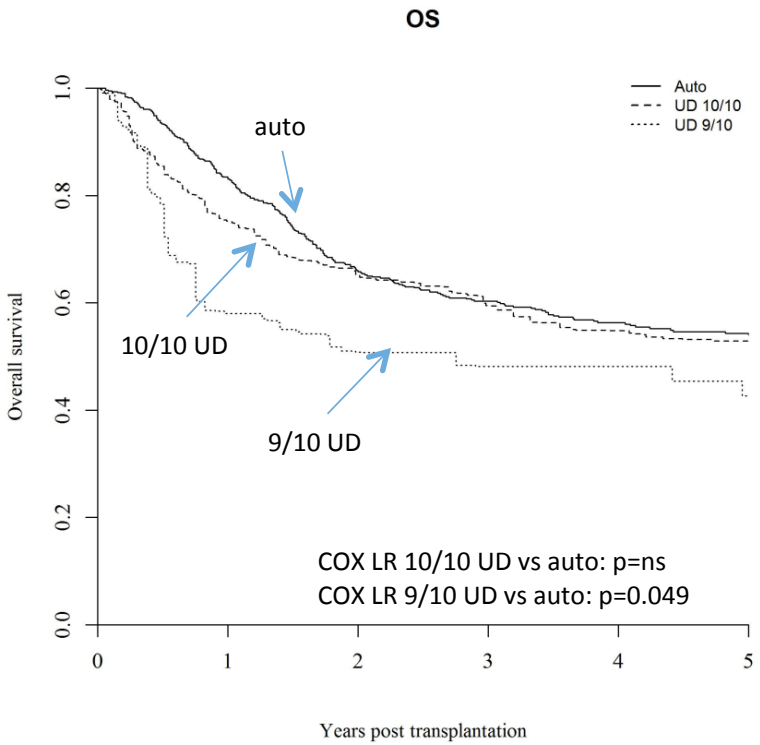
PS–weighted COX (auto as reference)

	HR	95% CI	p-value		HR	95% CI	p-value
NRM				**LFS**			
10/10	3,6	2-6,4	$<10^{-4}$	10/10	0,7	0,6-0,9	0,01
9/10	9,4	4.9-18	$<10^{-5}$	9/10	1,1	0,7-1,6	0,7
RI				**OS**			
10/10	0,5	0,4-0,7	$<10^{-5}$	10/10	0,98	0,7-1,3	0,9
9/10	0,4	0,3-0,8	0,004	9/10	1,6	1,001-2,5	0,049

Saraceni F, J Hematol Oncol 2016

Auto-SCT in AML: ALWP-EBMT study-int risk subgroup





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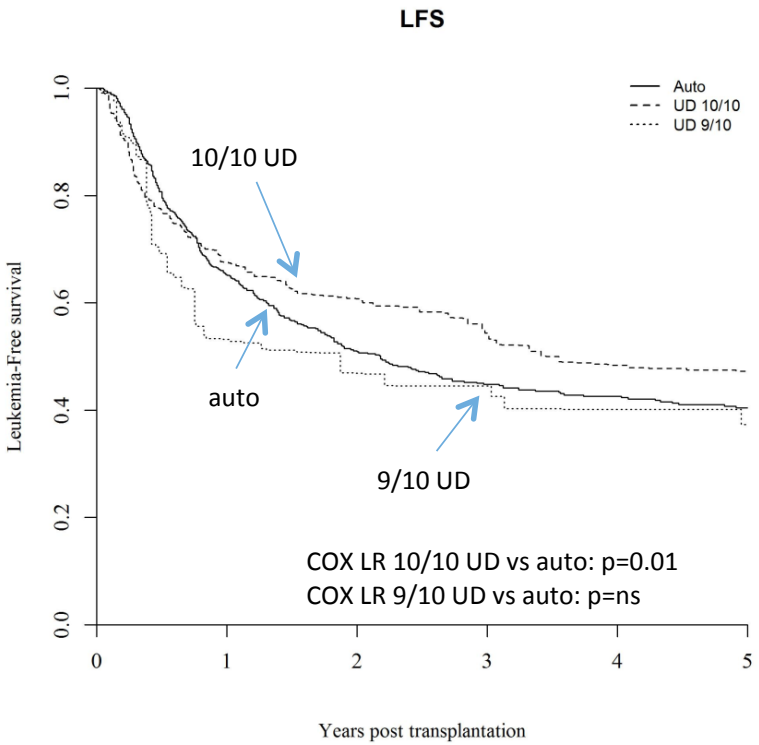

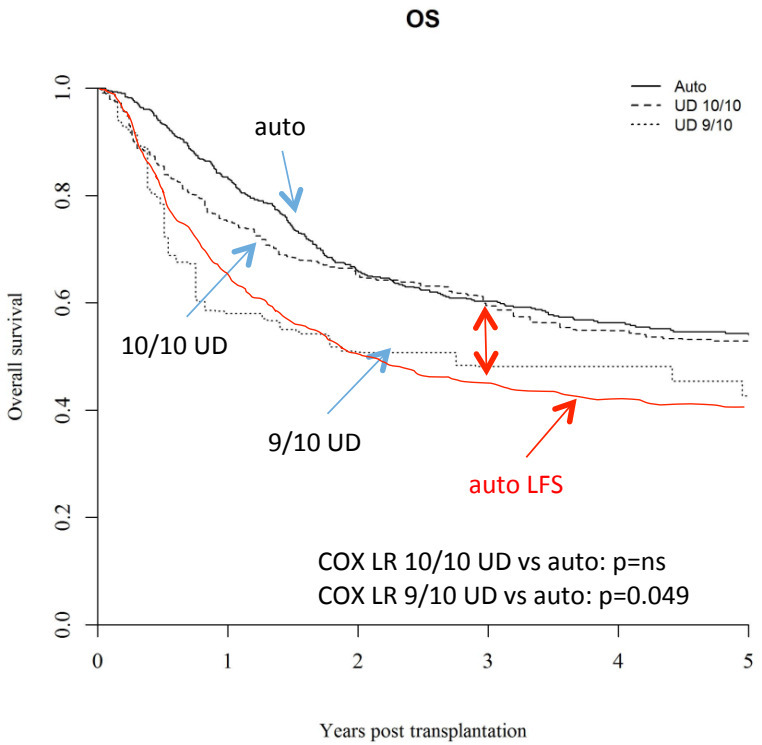

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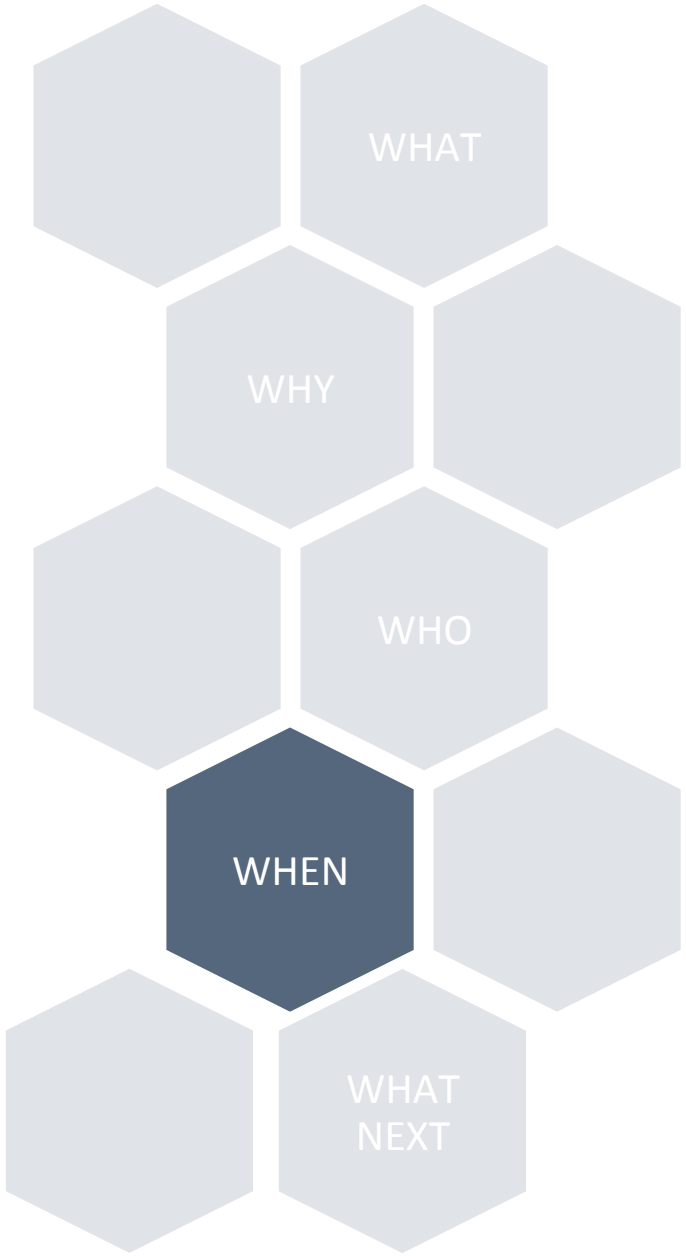
Auto-SCT in AML: Overview

First designed for patients lacking an available donor, is now struggling to find an updated role in AML

Similar OS vs matched allo-SCT; maybe better than MMUD; lower incidence of late effects, better QoL

Favourable risk.
Intermediate risk (??)

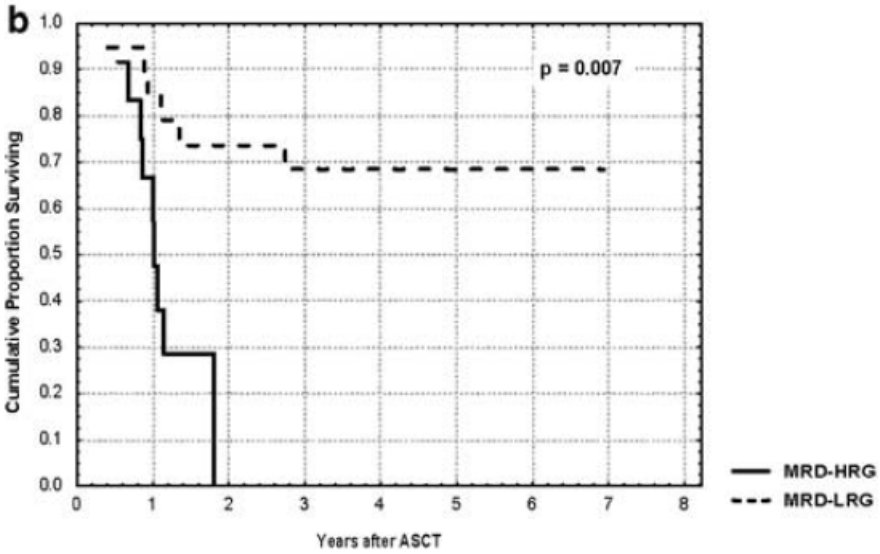
Auto-SCT in AML: Overview

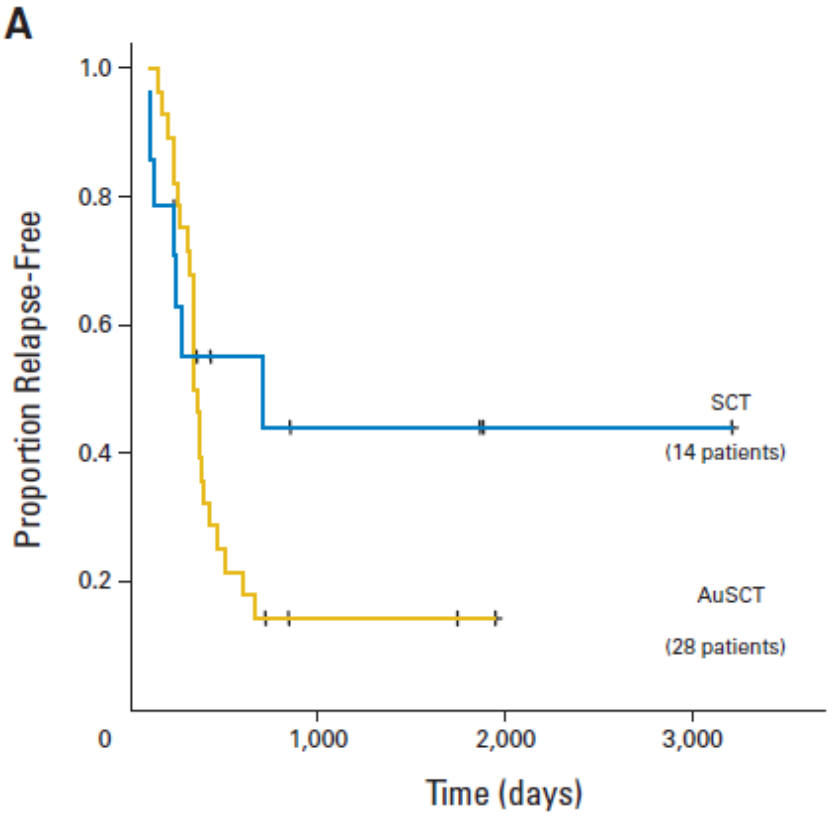


Auto-SCT in AML: WHEN

Gorin NC, Leukemia 1991. “Late autograft” better outcome as compared to “Early autograft”

MRD status!

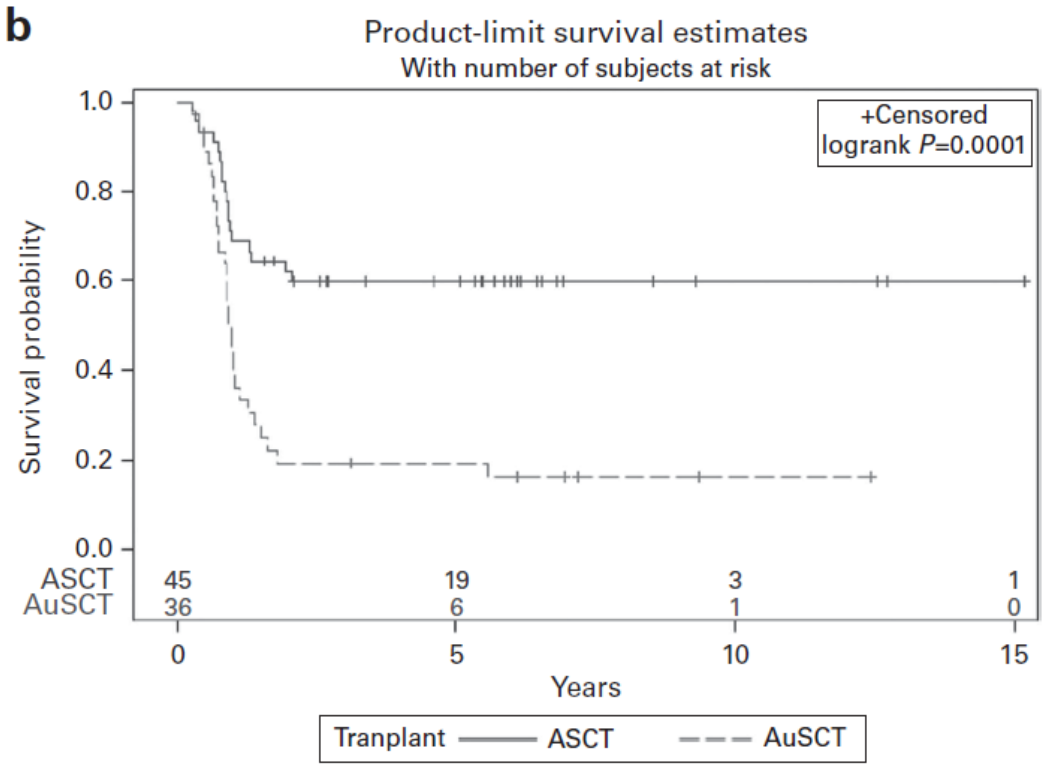




Venditti A, Leukemia 2003
Maurillo L, J Clin Oncol 2008

Auto-SCT in AML: WHEN

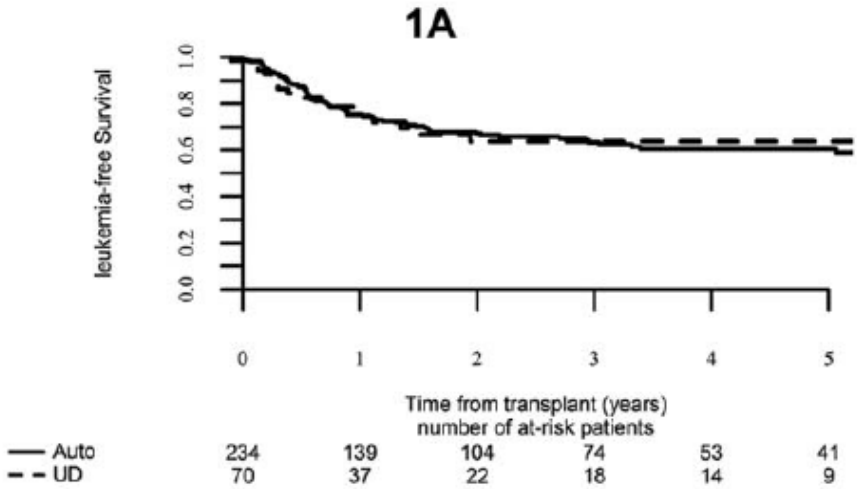
MRD+

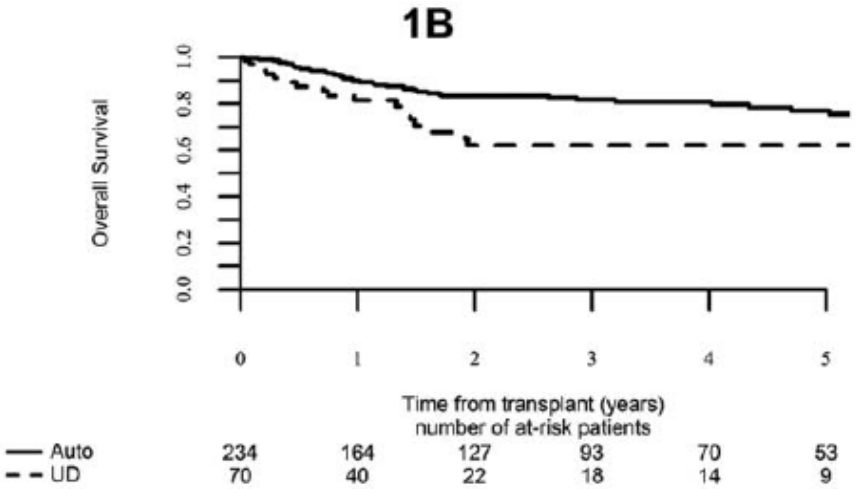


Buccisano, Bone Marrow Transplant 2017

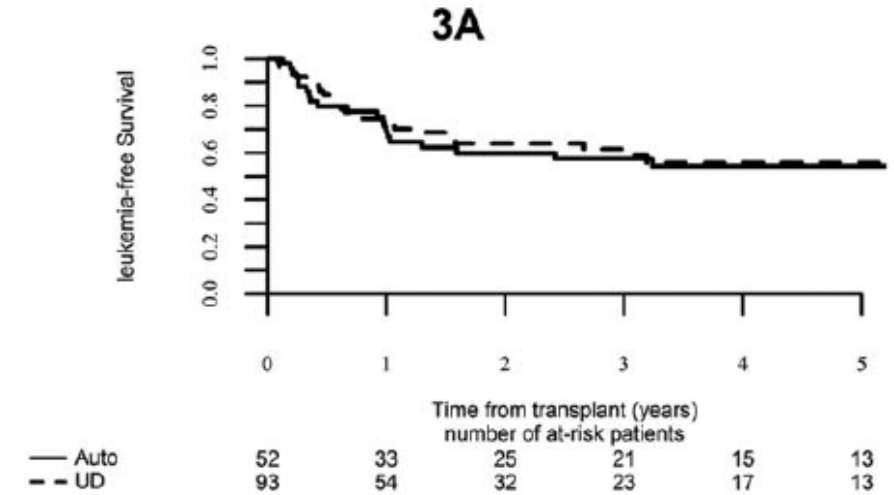
Auto-SCT in AML: WHEN

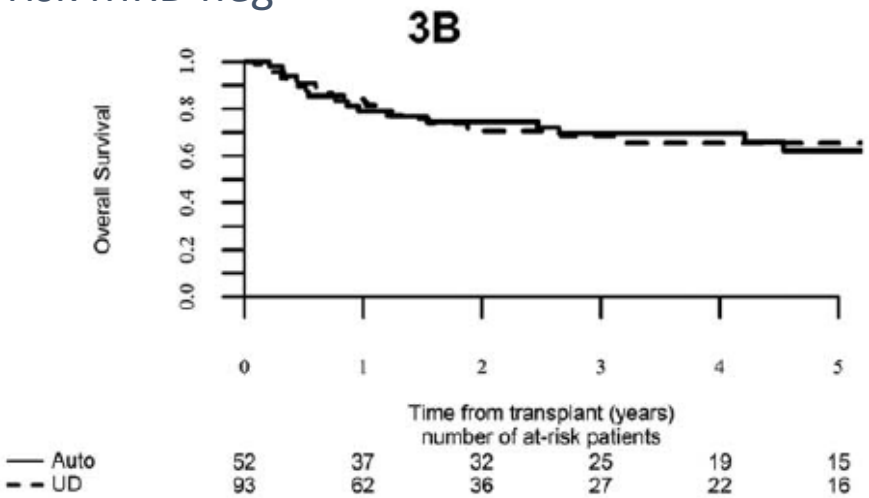
Favourable risk MRD neg





Intermediate-2 risk MRD neg

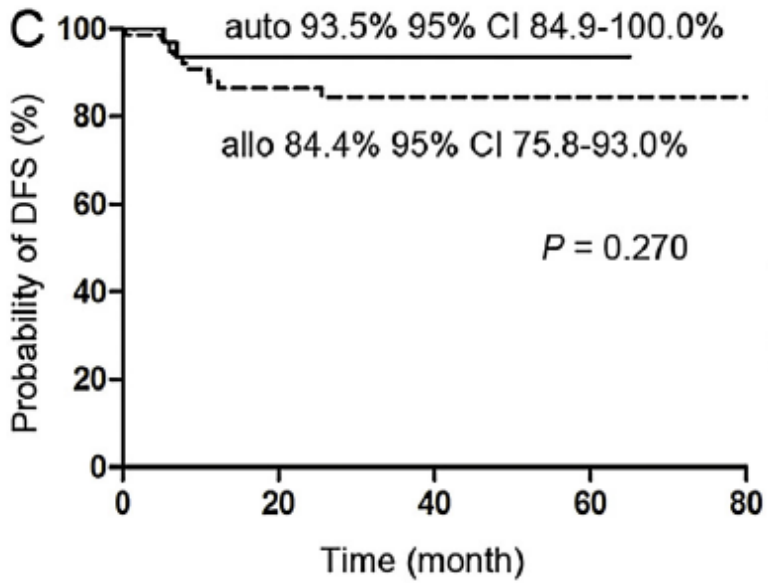




Gorin NC, Am J Hematol 2017

Auto-SCT in AML: WHEN

Favourable and intermediate risk AML, MRD neg



Yao J, Leuk Res 2017

Auto-SCT in AML: Overview

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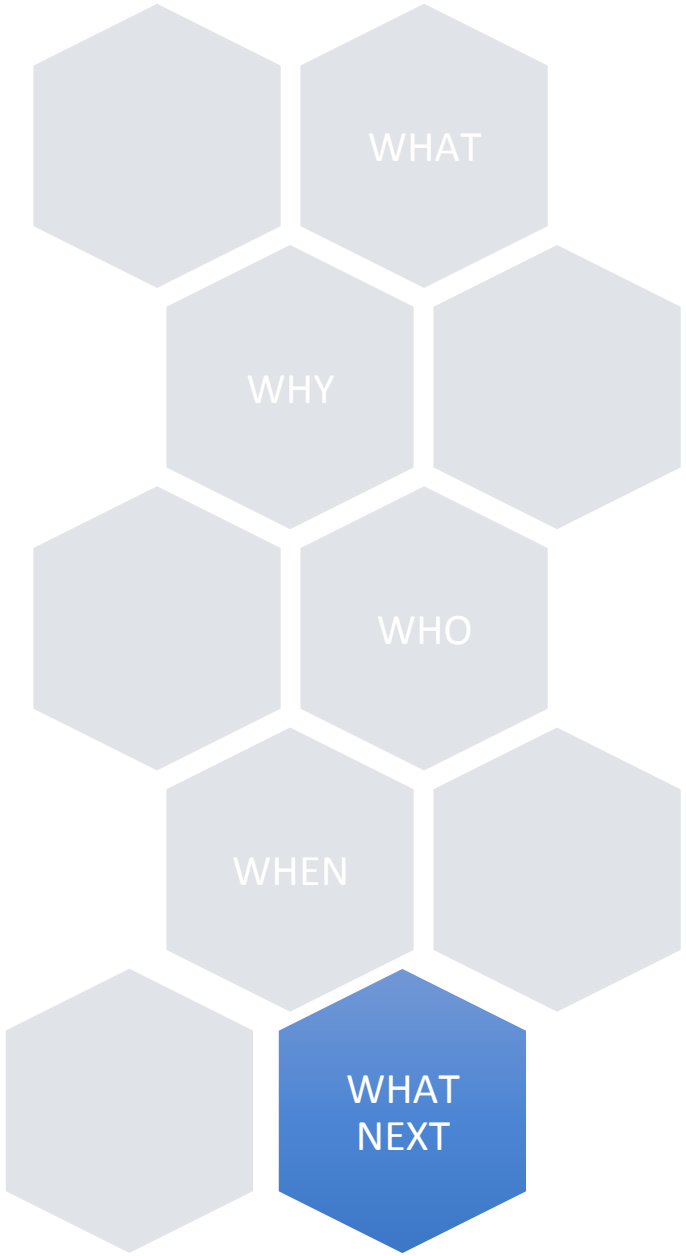
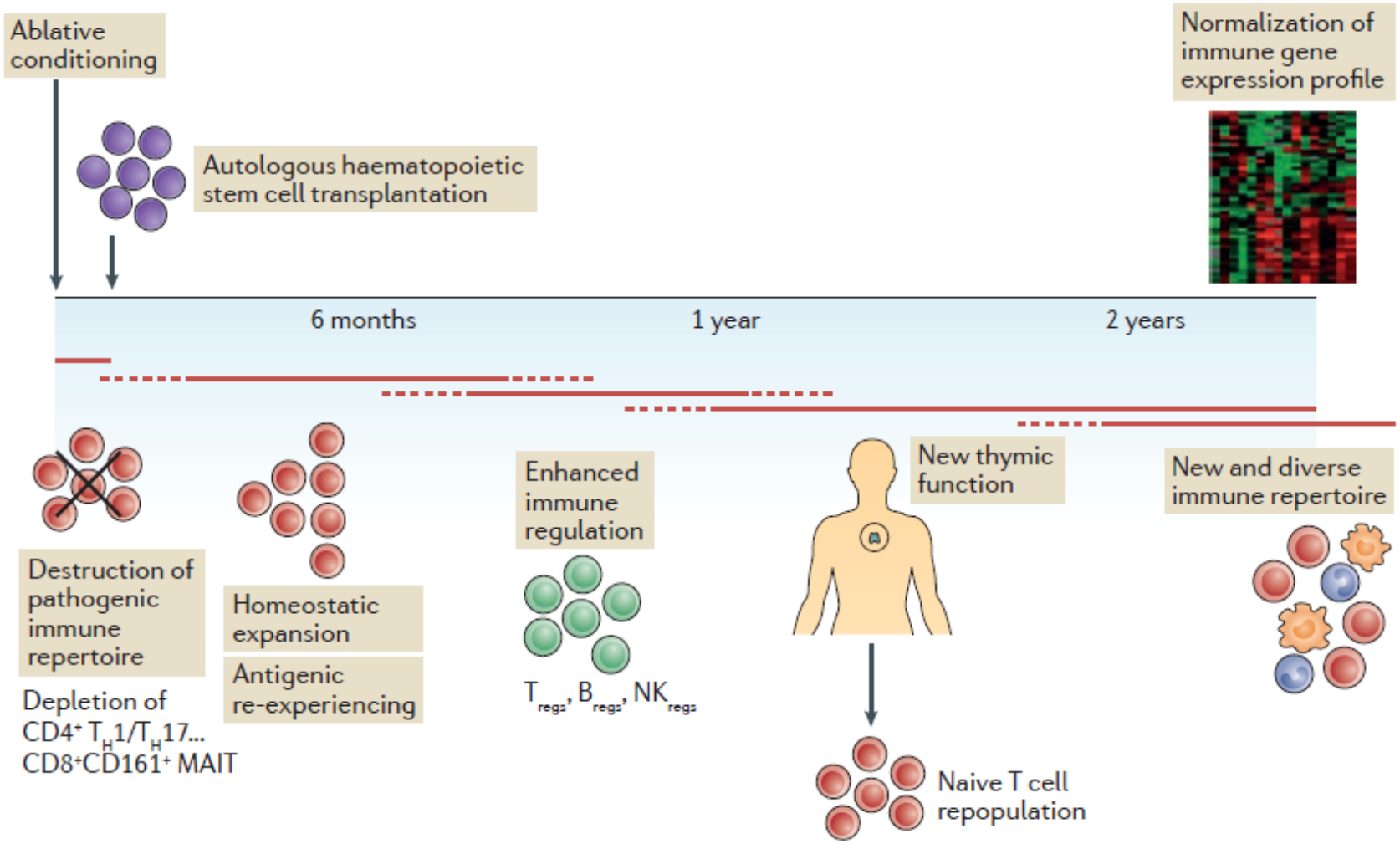
MRD negative

Auto-SCT in AML: Overview



Auto-SCT in AML: WHAT NEXT

The immune resetting following auto-SCT

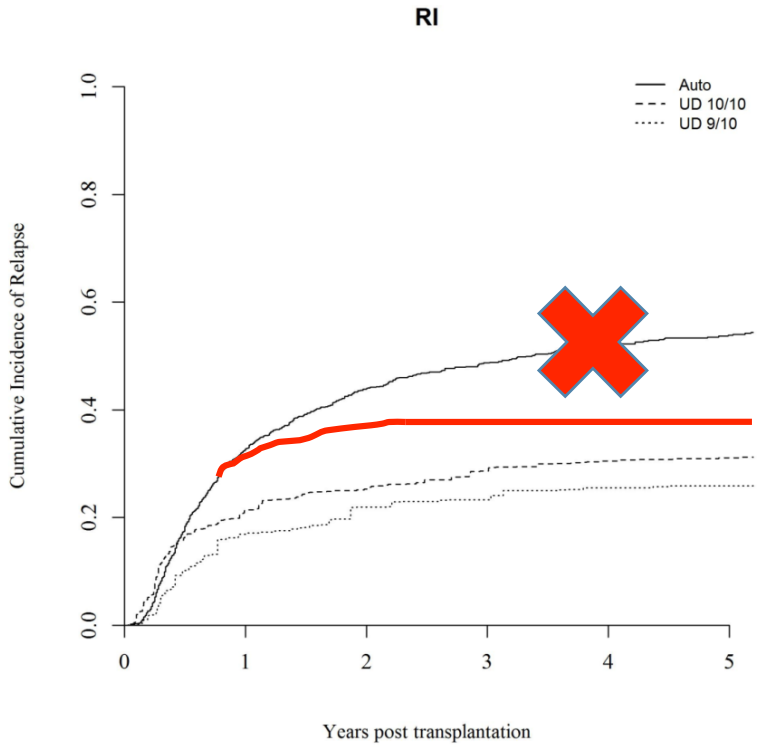


Muraro PA, Nat Rev Neur 2017

Auto-SCT in AML: WHAT NEXT

Strategies to prevent relapse following auto-SCT

- Maintenance (in ALL does work!)
  - Hypometylating agents
  - Deacetylase inhibitors
  - Targeted agents: FLT3-ITD inhibitors, IDH-1, IDH-2 inhibitors, BCL2-BCLX inhibitors
- Adoptive cell therapy
- Immunotherapy



Wetzler M, Haematologica 2013

Goodyear OC, Blood 2012

Bug G, Blood 2013

Chen YB, Blood 2014

Sandmaier B, Blood 2014

Stein EM, Blood 2017

Curti A, Blood 2011

Tettamanti S, Br J Haematol. 2013

Al-Hussaini, Blood 2016

Smith BD, Blood 2014

Auto-SCT in AML: Conclusion

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Favourable risk.
Intermediate risk (??)

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Post transplant strategies to prevent relapse

Aknowledgements

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