Allogene Stammzelltransplantation bei akuten Leukämien: **AML**

Matthias Stelljes / Münster

06.10.23, 14:00 – 14:30

Potential conflict of interest

1. Employment or Leadership Position: -

2. Advisory Role or Speaker Honoraria: Pfizer, Jazz, Amgen, Novartis, BMS, MSD, medac

3. Stock Ownership: -

4. Patent, Copyright, Licensing: -

5. Financing of Scientific Research: Pfizer

Leitlinien Onkopedia // DAG-HSZT

Onkopedia (https://www.onkopedia.com/de)

AML (08/23)
Christoph Röllig, Francis Ayuketang Ayuk, Jan Braess, Michael Heuser, Markus G. Manz, Jakob Passweg, Dirk Reinhardt, Richard F. Schlenk, Armin Zebisch

ALL (05/22)
Nicola Gökbuget, Claudia Baldus, Monika Brüggemann, Alexander W. Hauswirth, Urs Schanz, Sigrid Machherndl-Spandl, Matthias Stelljes, Max Topp

Indikation zur allogenen Stammzelltransplantation (05/16)
Peter Dreger, Dietrich Beelen, Martin Bornhäuser, Hermann Einsele, Nicolaus Kröger, Jakob Passweg, Robert Zeiser für die DAG-HSZT

Veraltet !

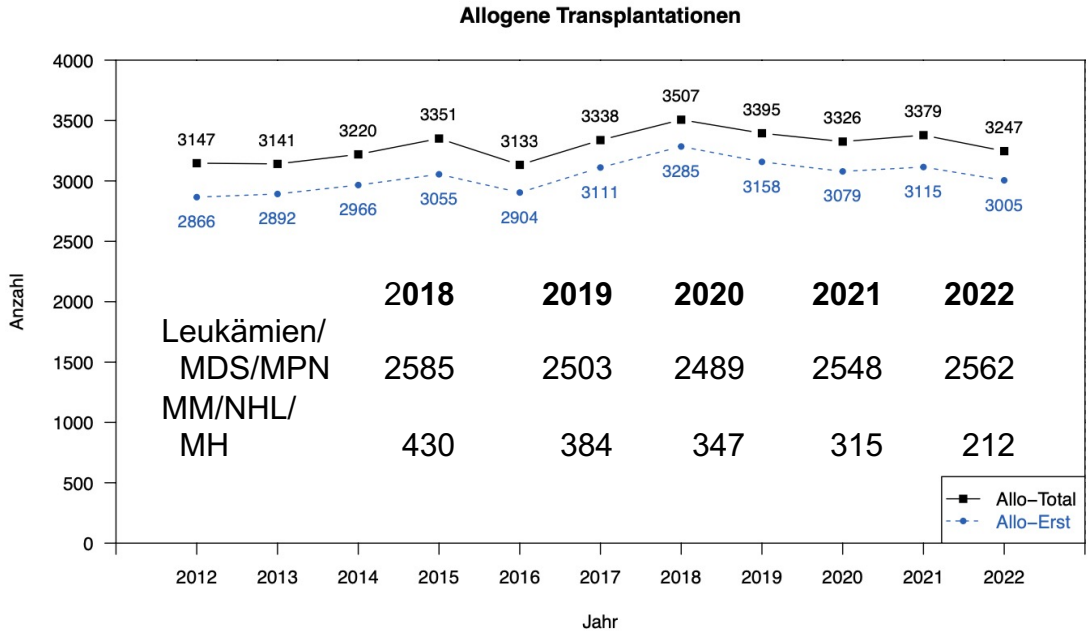
Veraltet !

DAG-HSZT (https://dag-hszt.de/LeitlinienallogeneSCT.html)

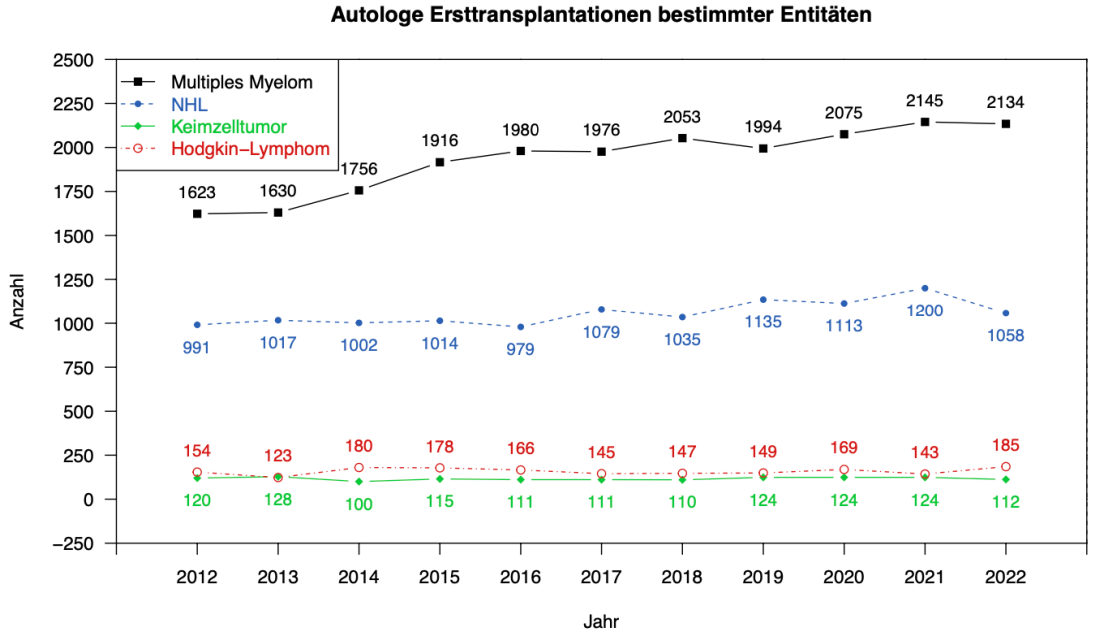
Leitlinie zur Stammzelltransplantation und CAR-T- Zelltherapie: Indikationen in der Behandlung hämatologischer Erkrankungen bei Erwachsenen (06/22).
Peter Dreger, Martin Bornhäuser, Gesine Bug, Hermann Einsele, Nicolaus Kröger, Eva-Maria Wagner-Drouet, Robert Zeiser, Matthias Stelljes

Deutscher Konsensus 2021 zur Spenderauswahl für die allogene Stammzelltransplantation
DGI - K Fleischhauer, E Arrieta-Bolanos, F Ayuk, D Fürst, M Füssel, P Horn, J Mytilineos, H Tran; PAS&ZT – M Eyrich, P Lang, R Meisel; DAG-HSZT – W Bethge, M Bornhäuser, P Dreger, G Kobbe, H Ottinger, J Schetelig, M Stelljes, E Wagner, R Zeiser, N Kröger

Zelltherapien in Deutschland



	2018	2019	2020	2021	2022
Leukämien/ MDS/MPN	2585	2503	2489	2548	2562
MM/NHL/ MH	430	384	347	315	212



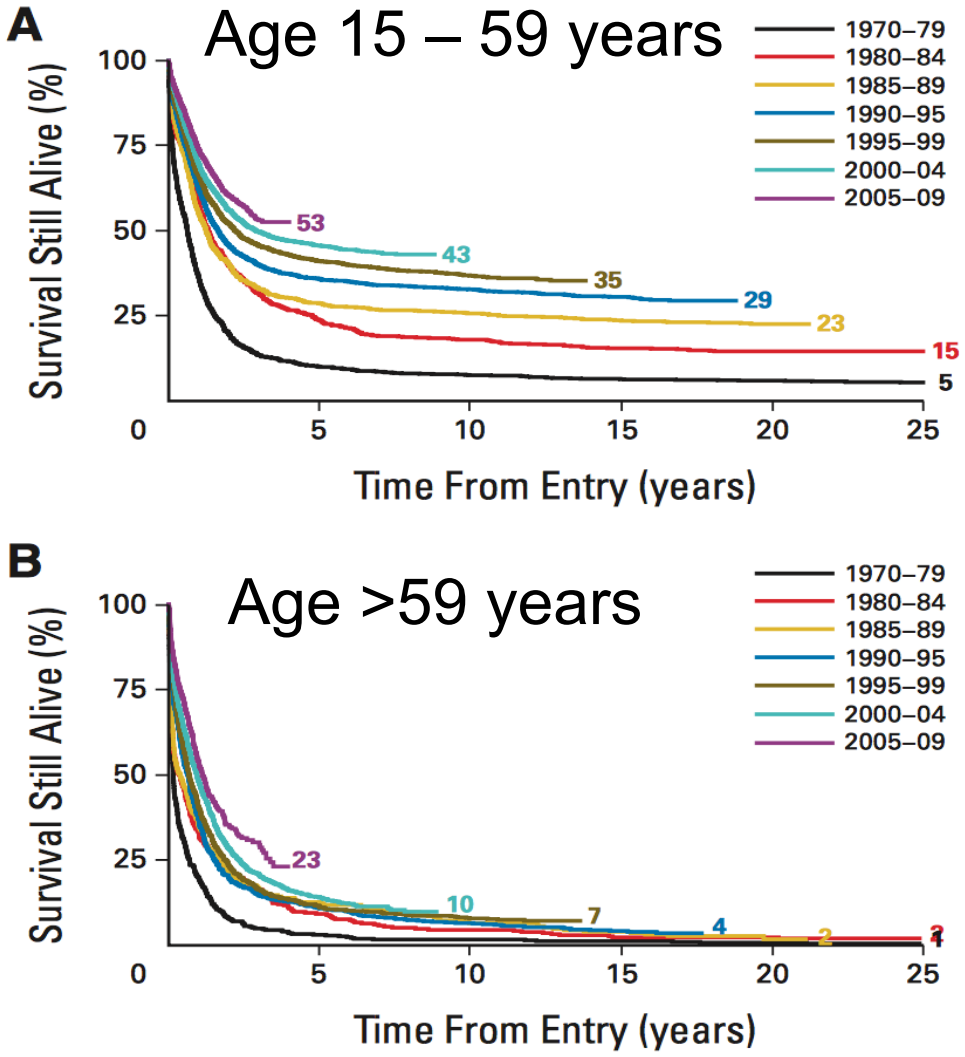
CAR-T-Zell-Therapien in Deutschland

Diagnose	2018		2019		2020		2021		2022	
	autolog	allogen	autolog	allogen	autolog	allogen	autolog	allogen	autolog	allogen
Autoimmunerkrankung	0	0	0	0	0	0	4	0	8	0
Malignom	46	1	0	0	0	0	0	0	0	0
Malignom: ALL	0	0	47	0	39	0	46	3	39	1
Malignom: Lymphom	0	0	201	0	318	1	335	1	382	1
Malignom: Myelom	0	0	0	0	0	0	0	0	199	0
Malignom: anderes	0	0	4	0	18	0	48	0	0	0
andere Indikation	0	0	0	0	0	0	0	0	27	0
Gesamt	**46**	**1**	**252**	**0**	**375**	**1**	**433**	**4**	**655**	**2**

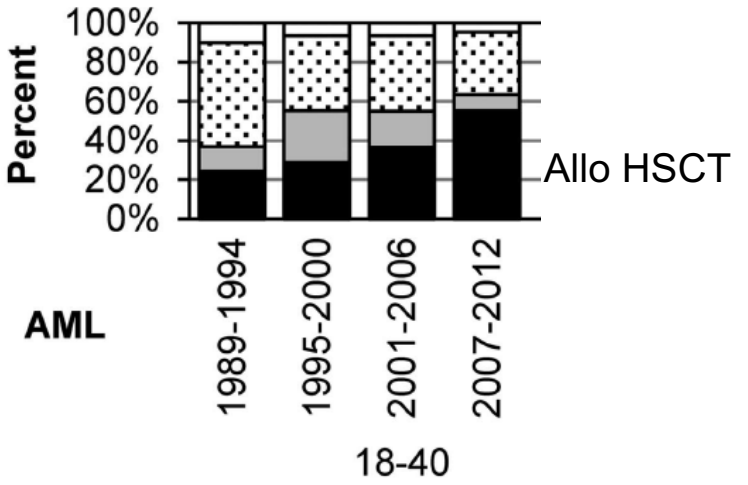
DRST, German Registry for Stem Cell Transpl.

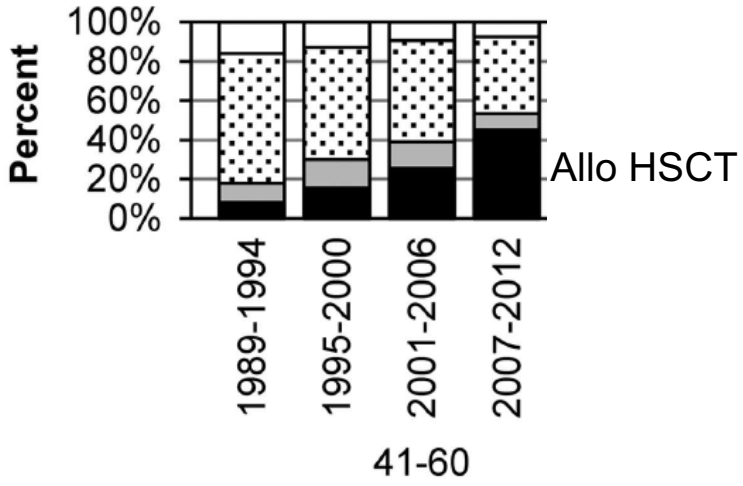
Survival of AML patients from 1970 – 2009

2023: 49 years of „7 + 3“ (Yates et al. 1974)



Burnett et al, JCO 2011





Dinmohamed et al. Leukemia 2016

Allogeneic SCT in AML

Estimates for Germany:

- 3.600 newly diagnosed adult patients with AML/year

  approx. 2.500 patients aged 18-75 year

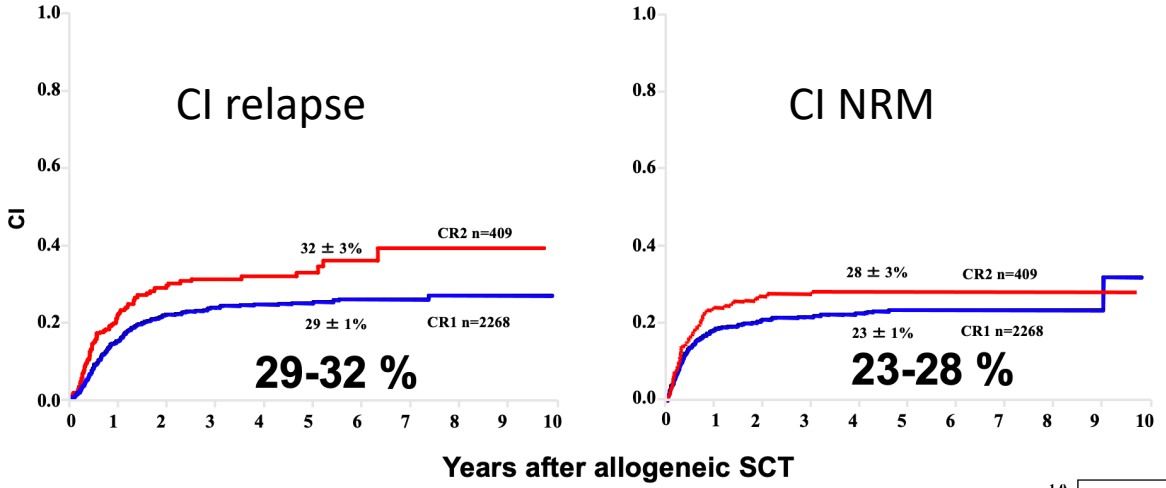
- 1400 allo HSCT in **adult AML (18-75 years)** patients/year

More than half of adult patients with newly diagnosed AML received / will receive an allo SCT

DRST registry (2022) and national government registry

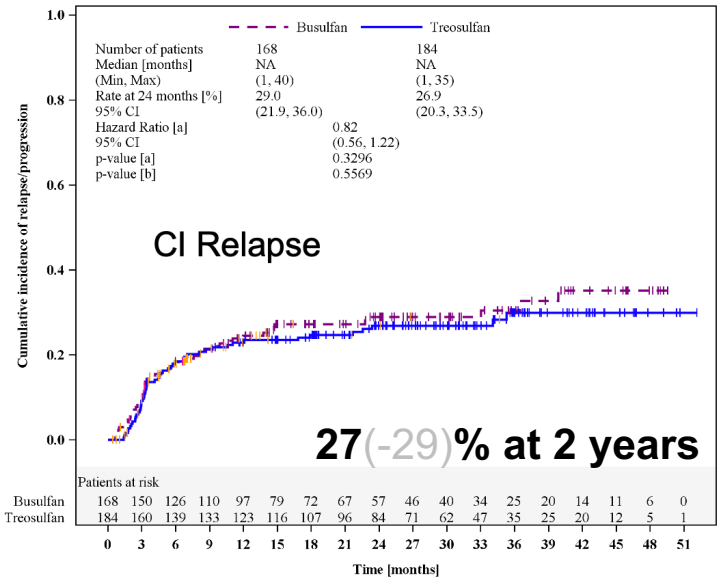
Transplant results of the last 3 decards: Reduced incidences of NRM

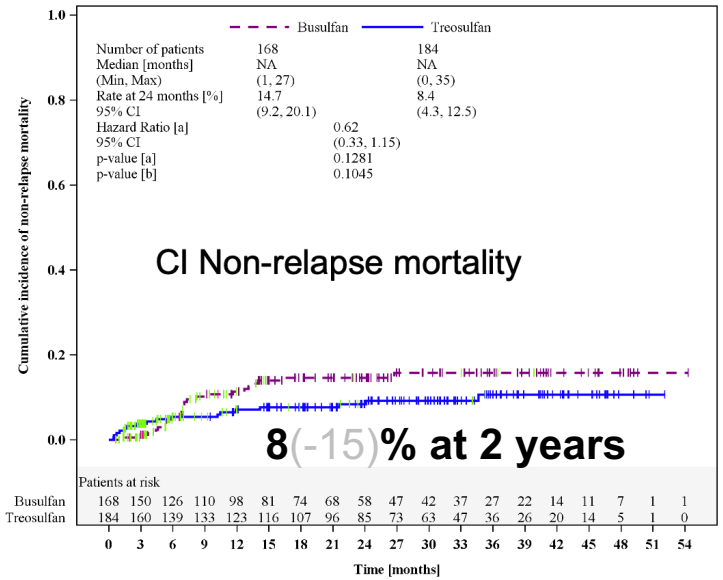
AML in CR: EBMT data 1993-2003



Frassoni et al., EBMT-ALWP 2003

AML in CR: Treo/Flu vs. BU/Flu 2013-2016

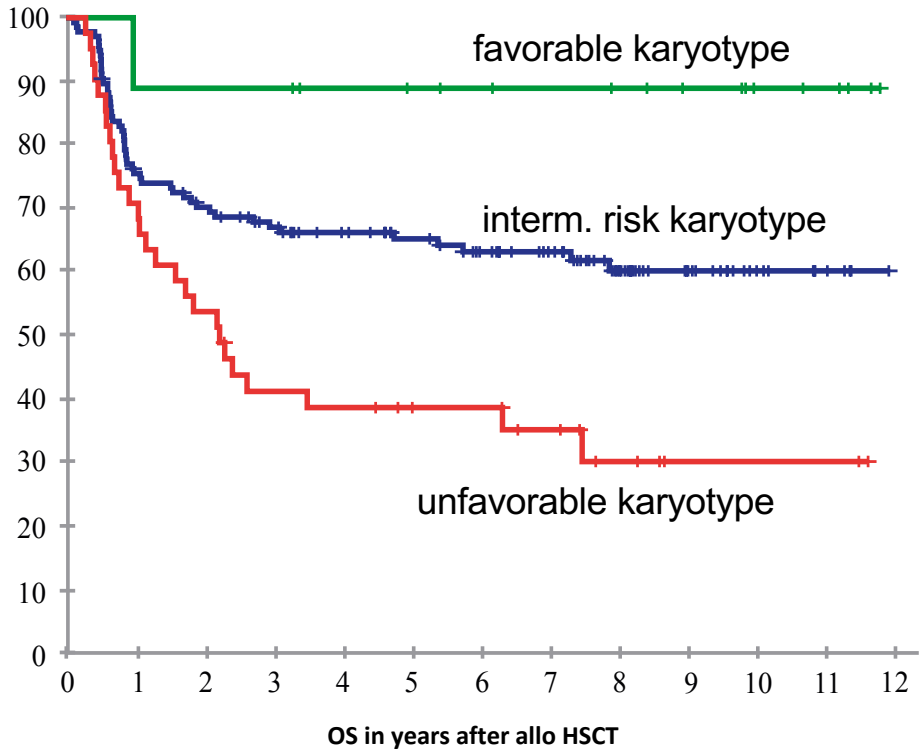




Stölzel et al., EBMT 2022

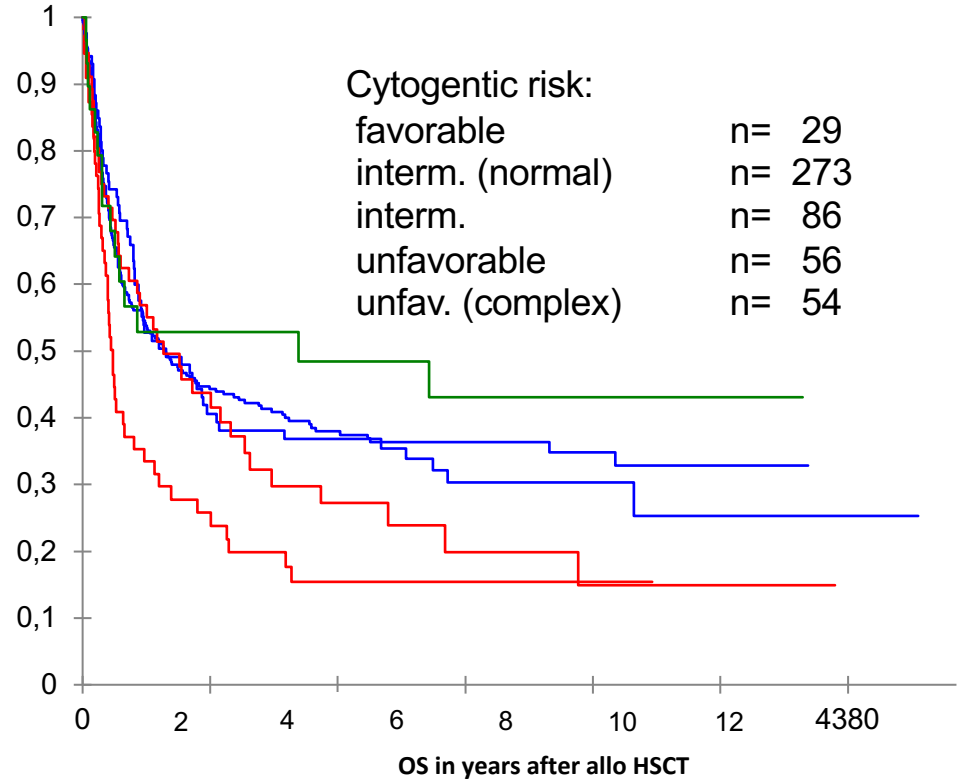
Preventing relapse: Allogeneic HSCT in CR1 versus >CR1

Allo. HSCT for AML in CR1



Stelljes et al., JCO 2014

Allo. HSCT for AML >CR1

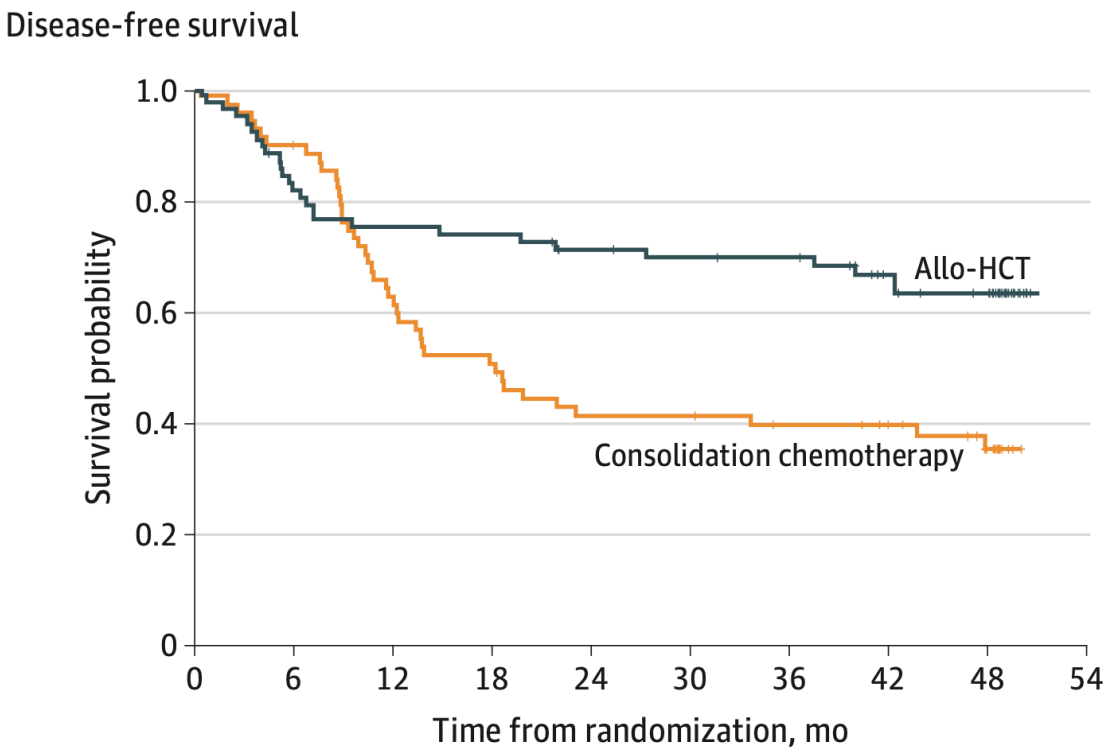


Evers… Stelljes; ASH 2018

AML-CG

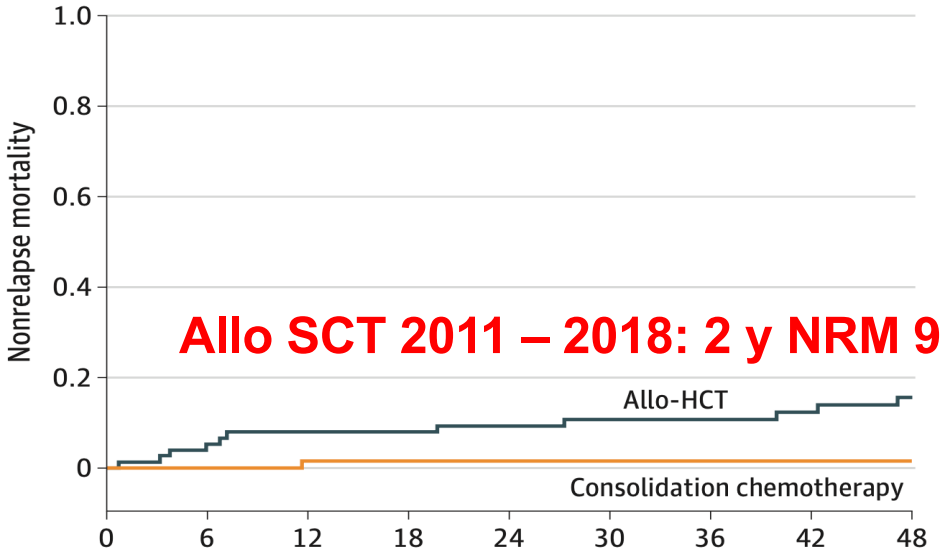
For Most Patients with standard-risk AML, allo SCT remains the most effective treatment option

A prospective randomized trial (ETAL-1)

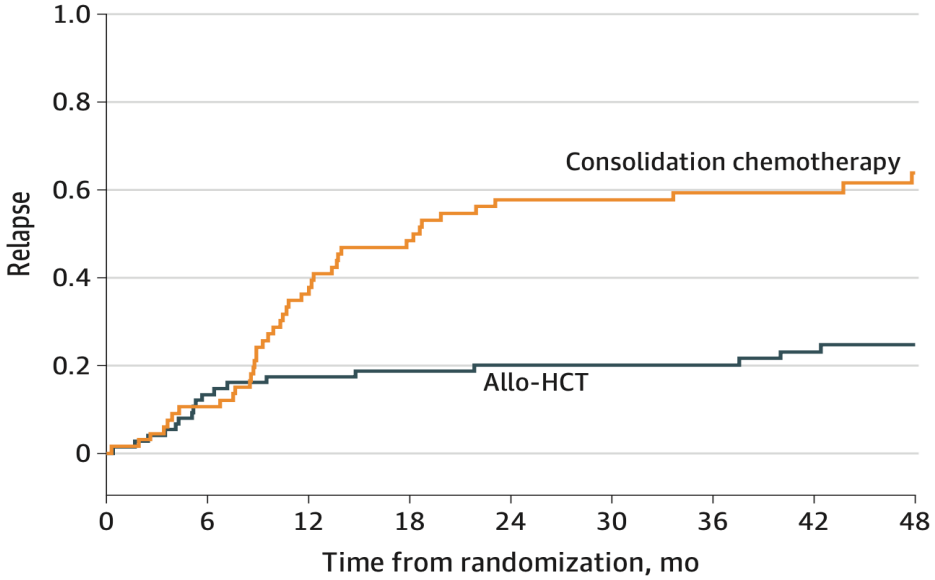


No. at risk

Consolidation chemotherapy	67	59	41	33	26	26	23	20	12
Allo-HCT	76	61	56	55	50	48	47	39	34



Allo SCT 2011 – 2018: 2 y NRM 9 %

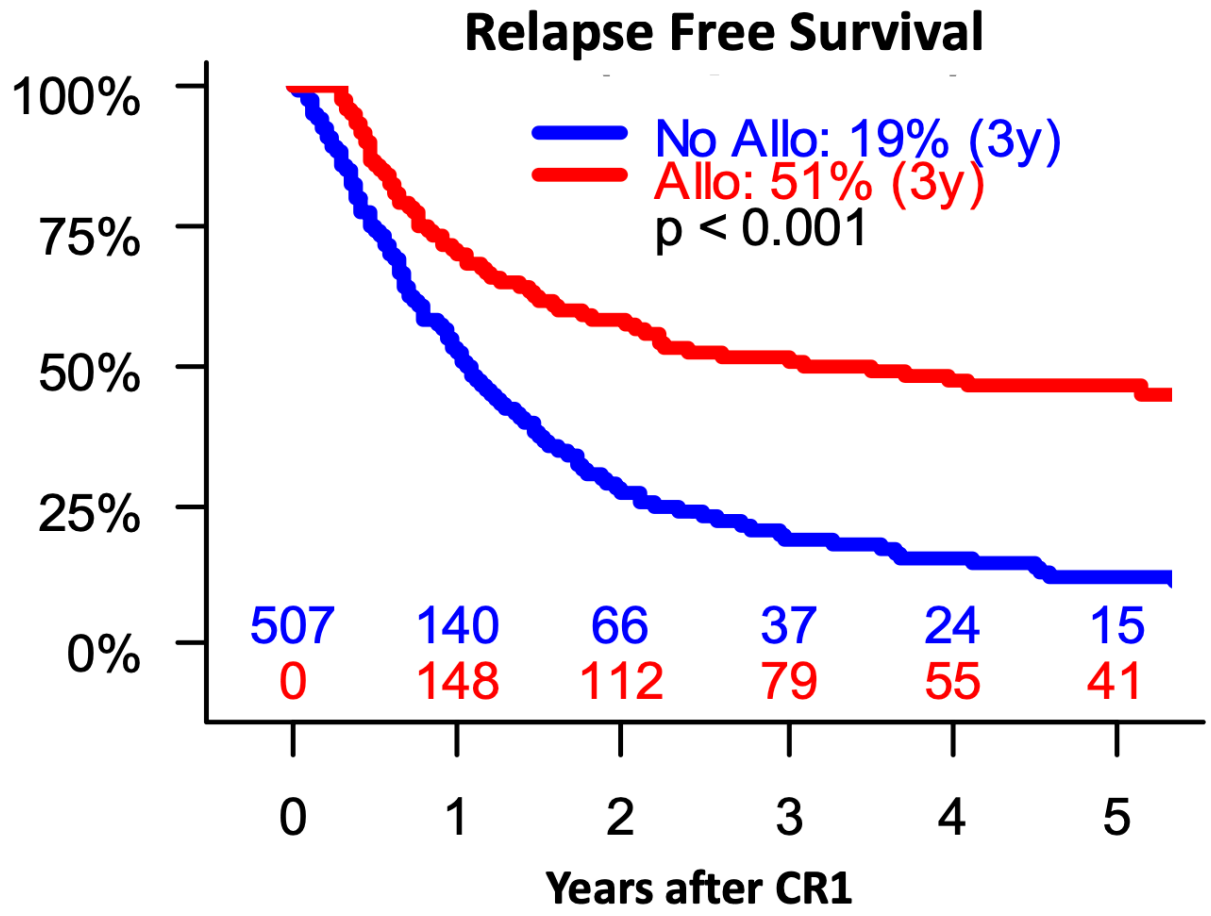


Bornhäuser …. Stelljes; JAMA Oncol. 2023

Allogeneic SCT improves outcome of older patients with AML in CR1

Real Life Study of 507 patients

- Age: 60-70 y
- AML in CR1
- ELN int or unfav
- Intensive chemo
- 2007-2017
- 7 FILO Centers



Devillier Blood Advances 2021

Allogeneic SCT improves outcome of older patients with AML in CR1

Real Life Study of 507 patients

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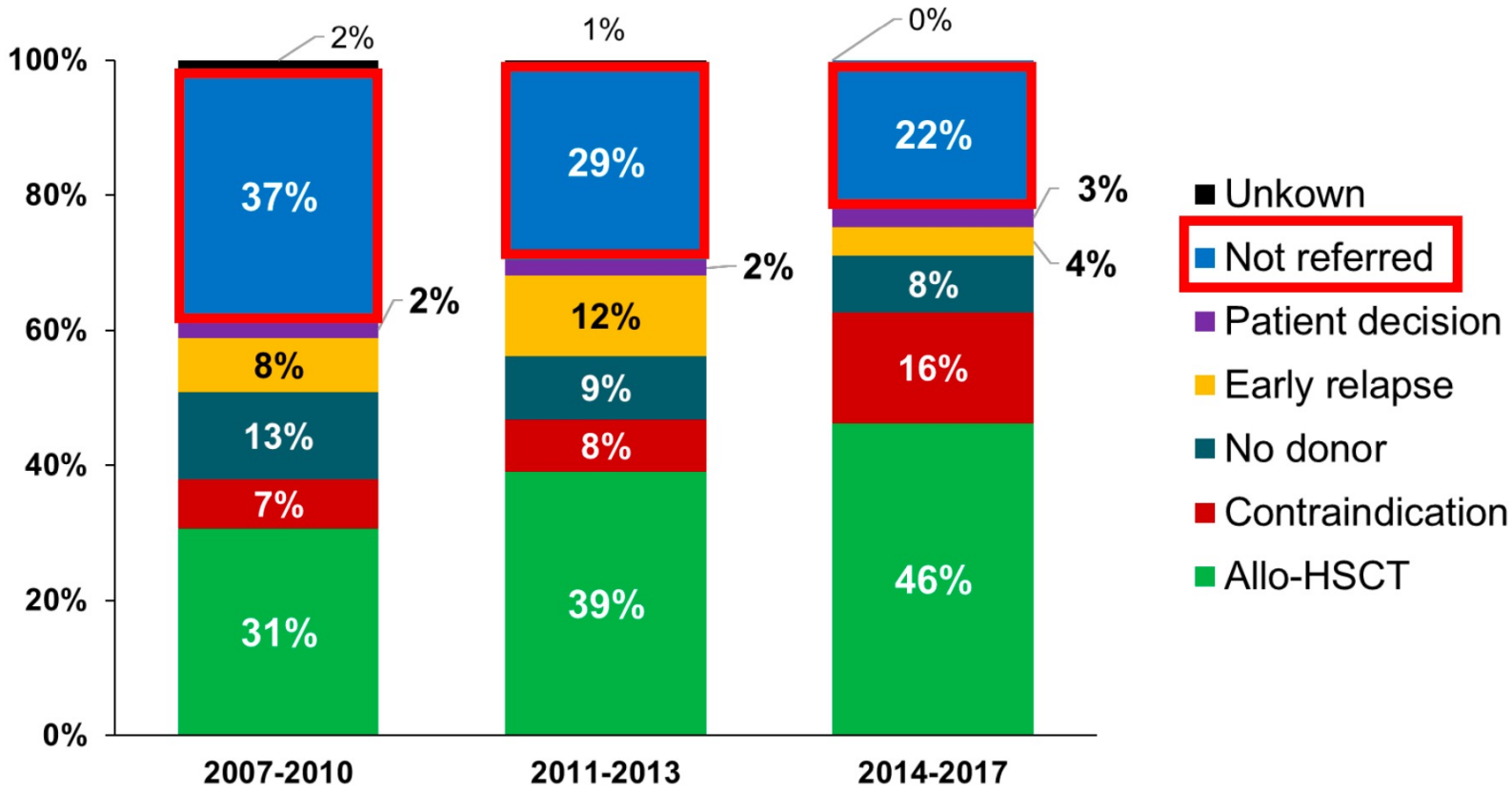
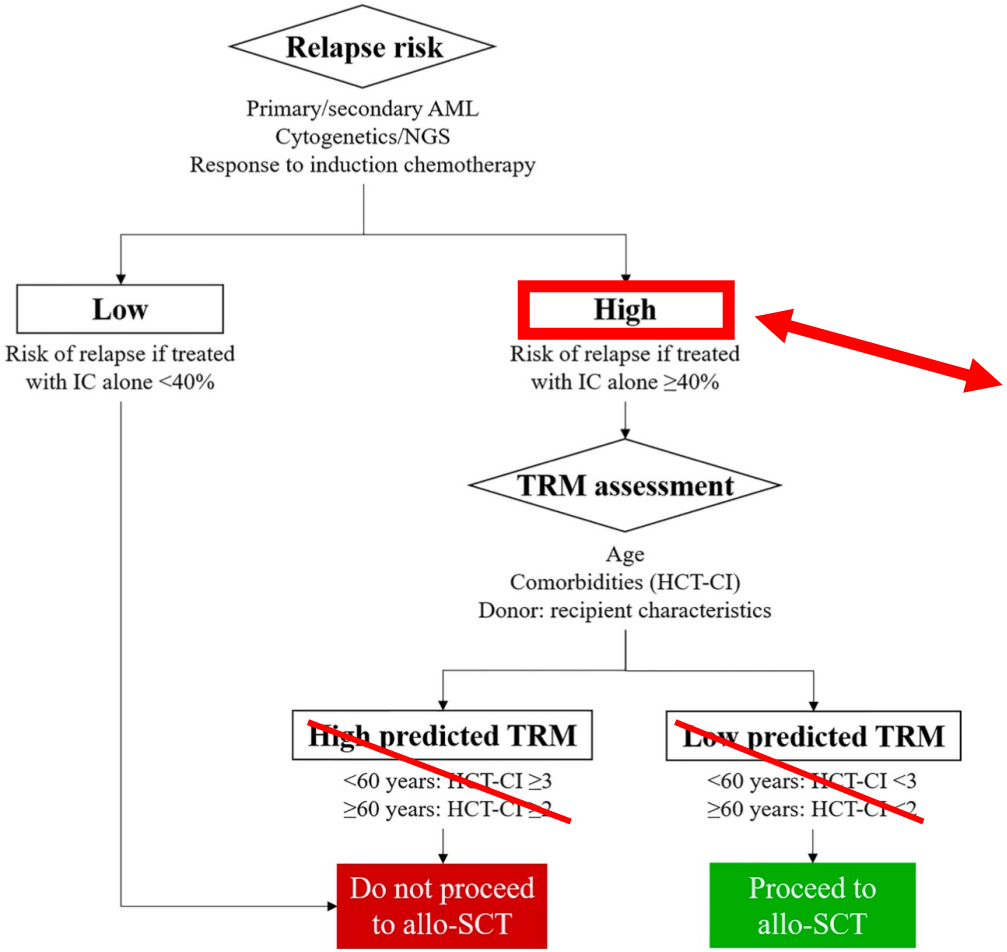


Devillier Blood Advances 2021

AML in CR1: Indication for allogeneic HSCT



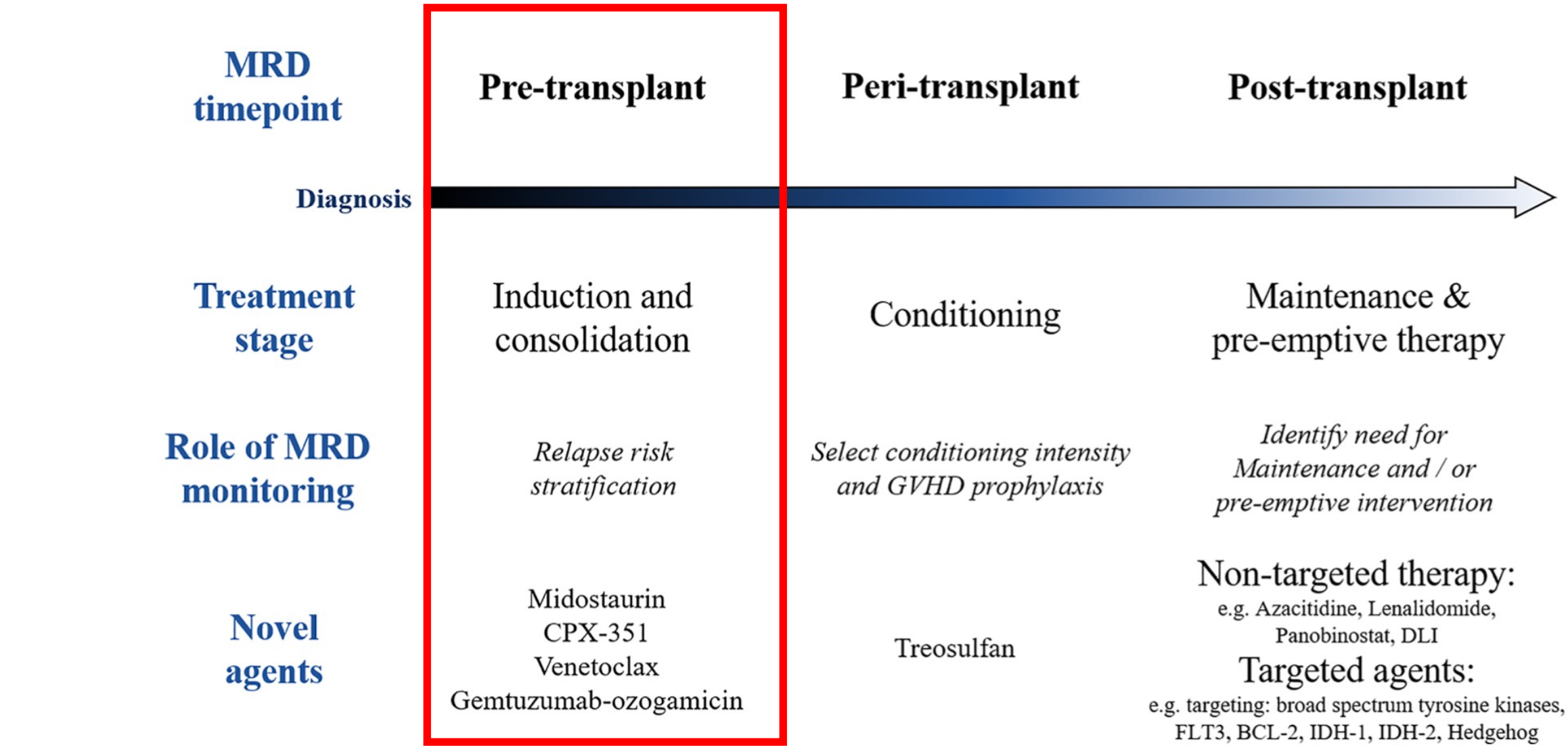
ELN 2022

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*[a] without *FLT3*-ITD • bZIP in-frame mutated *CEBPA*
Intermediate	• Mutated *NPM1*[a] with *FLT3*-ITD • Wild-type *NPM1* with *FLT3*-ITD • 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;q34.1)/*DEK*::*NUP214* • t(v;11q23.3)/*KMT2A*-rearranged • t(9;22)(q34.1;q11.2)/*BCR*::*ABL1* • t(8;16)(p11;p13)/*KAT6A*::*CREBBP* • inv(3)(q21.3q26.2) 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*, or *ZRSR2* • Mutated *TP53*

Loke et al., Frontiers in Immunology 2022

Döhner et al., BLOOD 2022

Preventing relapse: Role of measurable residual disease (MRD) and novel agents at different stages of the treatment pathway in AML



Adapeted from Loke et al., Frontiers in Immunology 2021

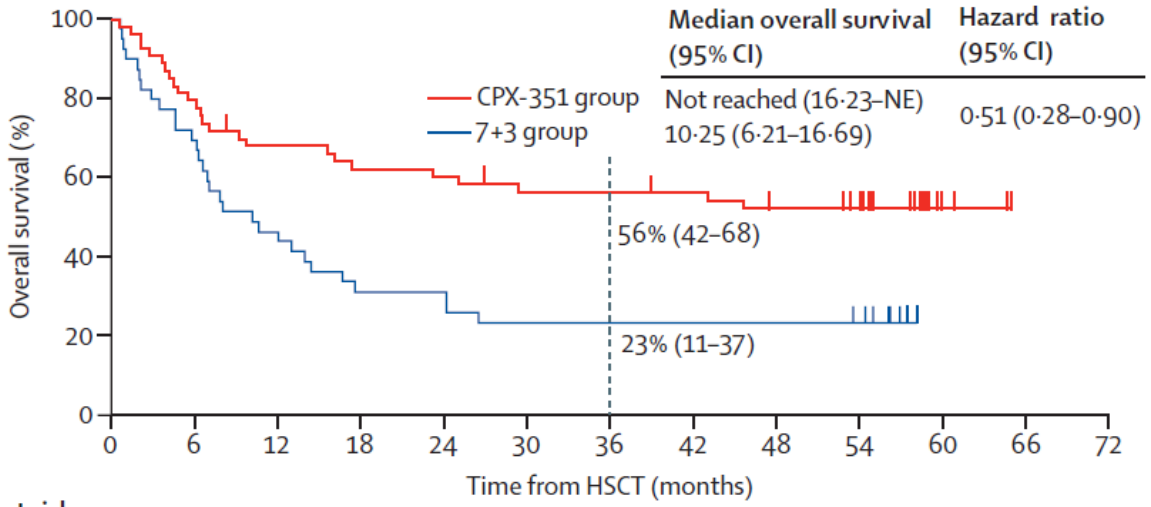
No impact of high-dose cytarabine on the outcome of patients transplanted for AML in first remission

Dose Ara-C	Patients	LFS (means ± SE)	RI (means ± SE)	TRM (means ± SE)
Induction				
No	17	76 ± 10	13 ± 8	13 ± 8
SD	726	55 ± 2	23 ± 2	28 ± 2
ID	24	50 ± 10	21 ± 9	47 ± 11
HD	44	45 ± 8	42 ± 9	21 ± 7
P-value		0·14	0·02*	0·98
Consolidation				
No	154	51 ± 4	27 ± 4	29 ± 4
SD	393	56 ± 3	24 ± 3	26 ± 3
ID	68	54 ± 6	21 ± 6	28 ± 6
HD	193	56 ± 4	23 ± 4	27 ± 3
P-value		0·88	0·72	0·92
Induction and/or consolidation				
SD	493	55 ± 2	24 ± 2	27 ± 2
ID	87	51 ± 6	22 ± 5	34 ± 6
HD	222	55 ± 3	26 ± 3	25 ± 3
P-value		0·72	0·41	0·81

Cahn et al. 2000, British Journal of Haematology

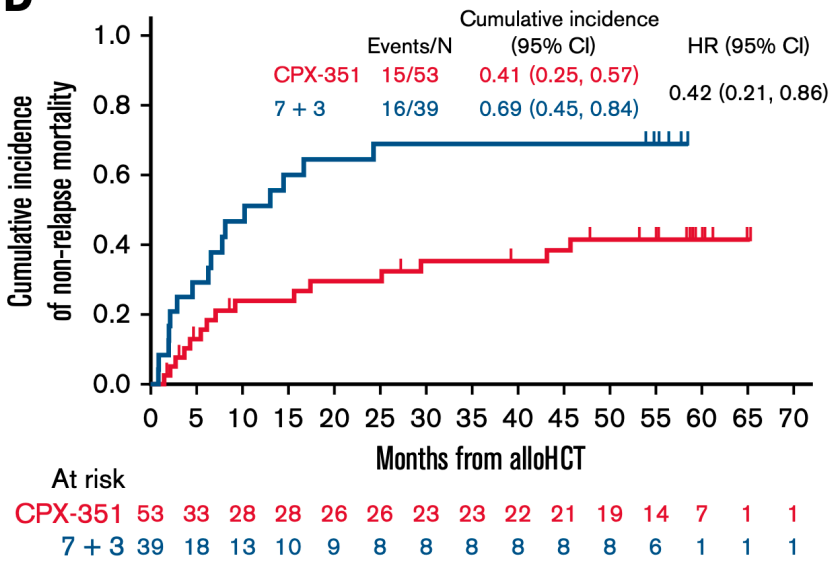
CPX-351 (cytarabine and daunorubicin) Liposome for Injection Versus Conventional Cytarabine Plus Daunorubicin in Older Patients With Newly Diagnosed Secondary AML

OS after allogeneic SCT



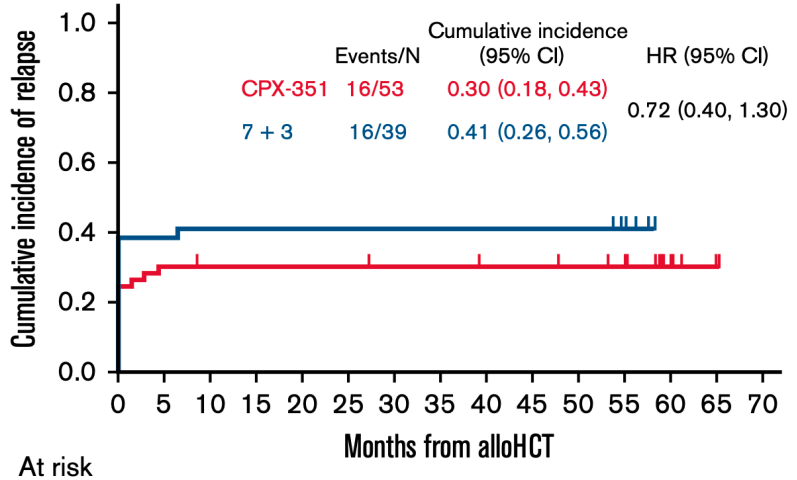
Number at risk (number censored)													
CPX-351 group	53	42	35	32	31	28	28	27	24	21	6	0	0
	(0)	(0)	(1)	(1)	(1)	(2)	(2)	(3)	(4)	(7)	(22)	(28)	(28)
7+3 group	39	27	18	12	12	9	9	9	9	8	0	0	0
	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(0)	(1)	(9)	(9)	(9)

D



At risk														
CPX-351	53	33	28	28	26	26	23	23	22	21	19	14	7	1	1
7 + 3	39	18	13	10	9	8	8	8	8	8	8	6	1	1	1

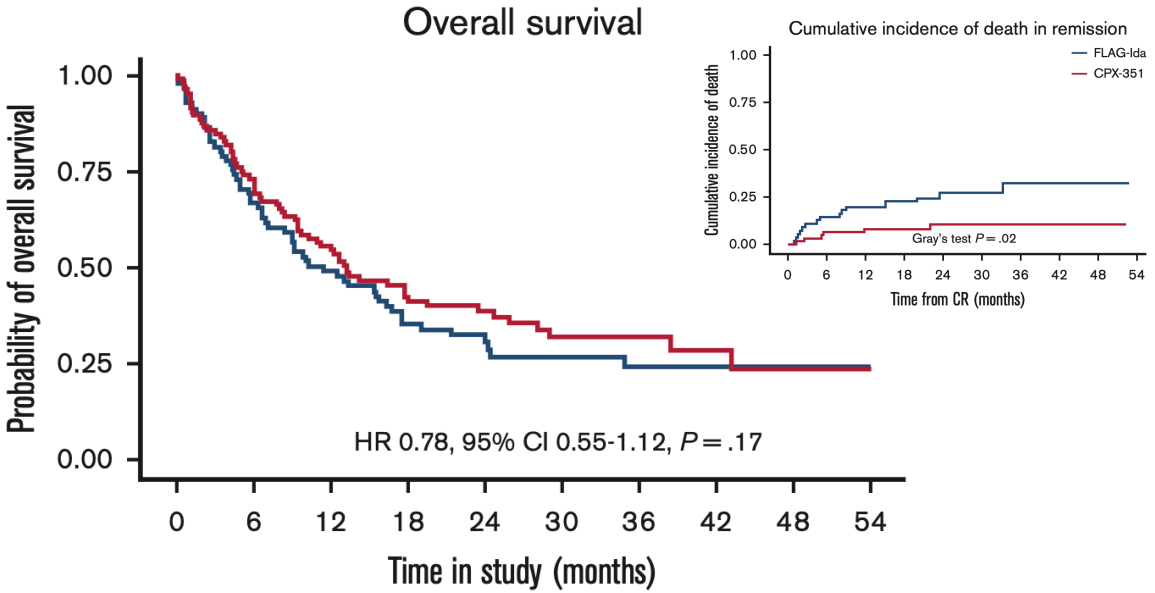
C



At risk														
CPX-351	53	33	28	28	26	26	23	23	22	21	19	14	7	1	1
7 + 3	39	18	13	10	9	8	8	8	8	8	8	6	1	1	1

Lancet et al., Lancet Hematol 2021; Geoffrey et al. Blood adv. 2022

A RANDOMISED COMPARISON OF CPX-351 AND FLAG-IDA IN HIGH RISK AML. RESULTS FROM THE NCRI AML19 TRIAL

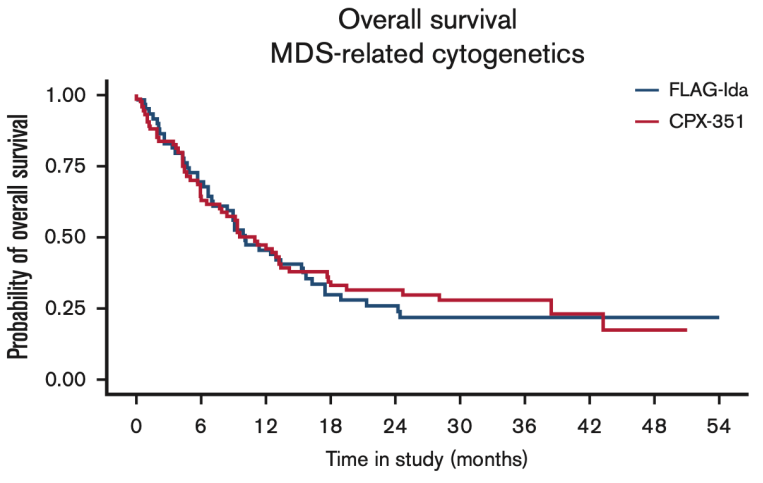


Number at risk

FLAG-Ida	81	53	39	24	17	10	9	2	2	1
CPX-351	105	75	57	39	27	16	12	7	3	1

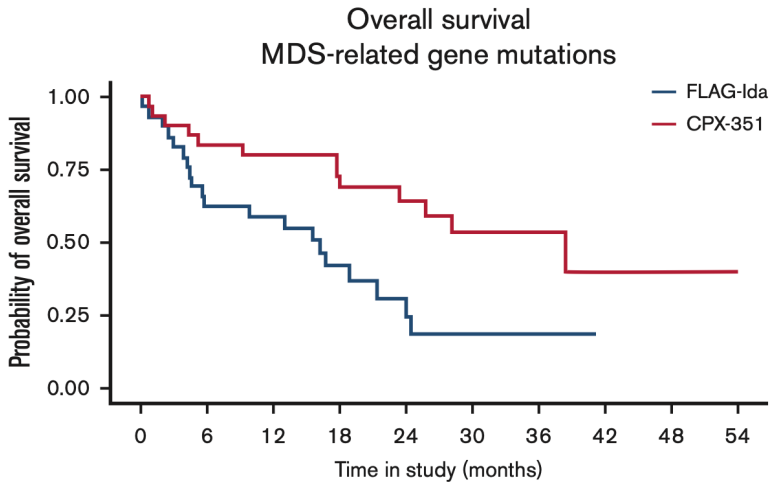
	CPX-351	FLAG-Ida	P-value
Med. age, y (range)	57 (23-70)	55 (18-67)	
CR/CRi. %	51	65	0.15
Transplant rate, %	64	50	

Othmann et al., Blood Advances 2023



Number at risk

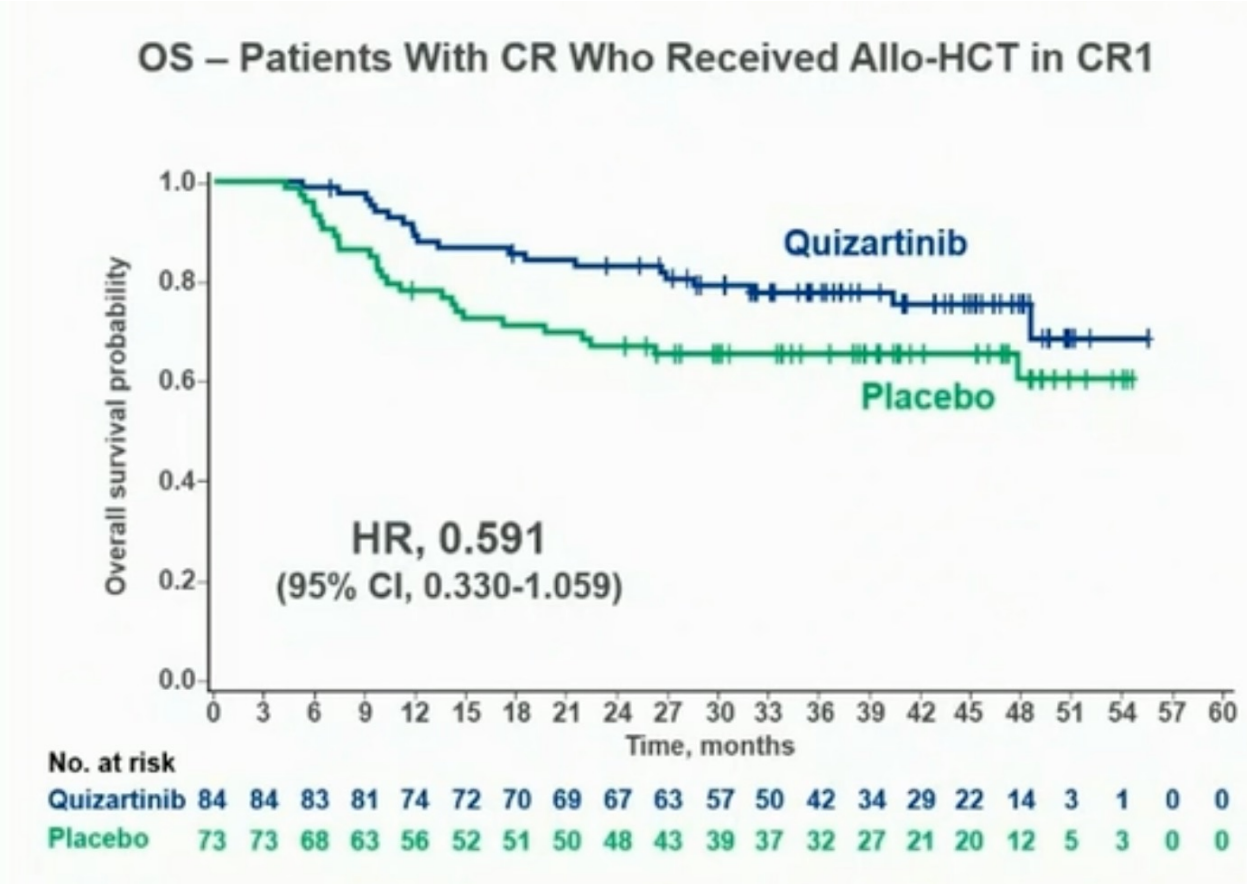
FLAG-Ida	59	41	27	16	13	7	7	2	2	1
CPX-351	74	49	34	23	19	13	9	4	1	0

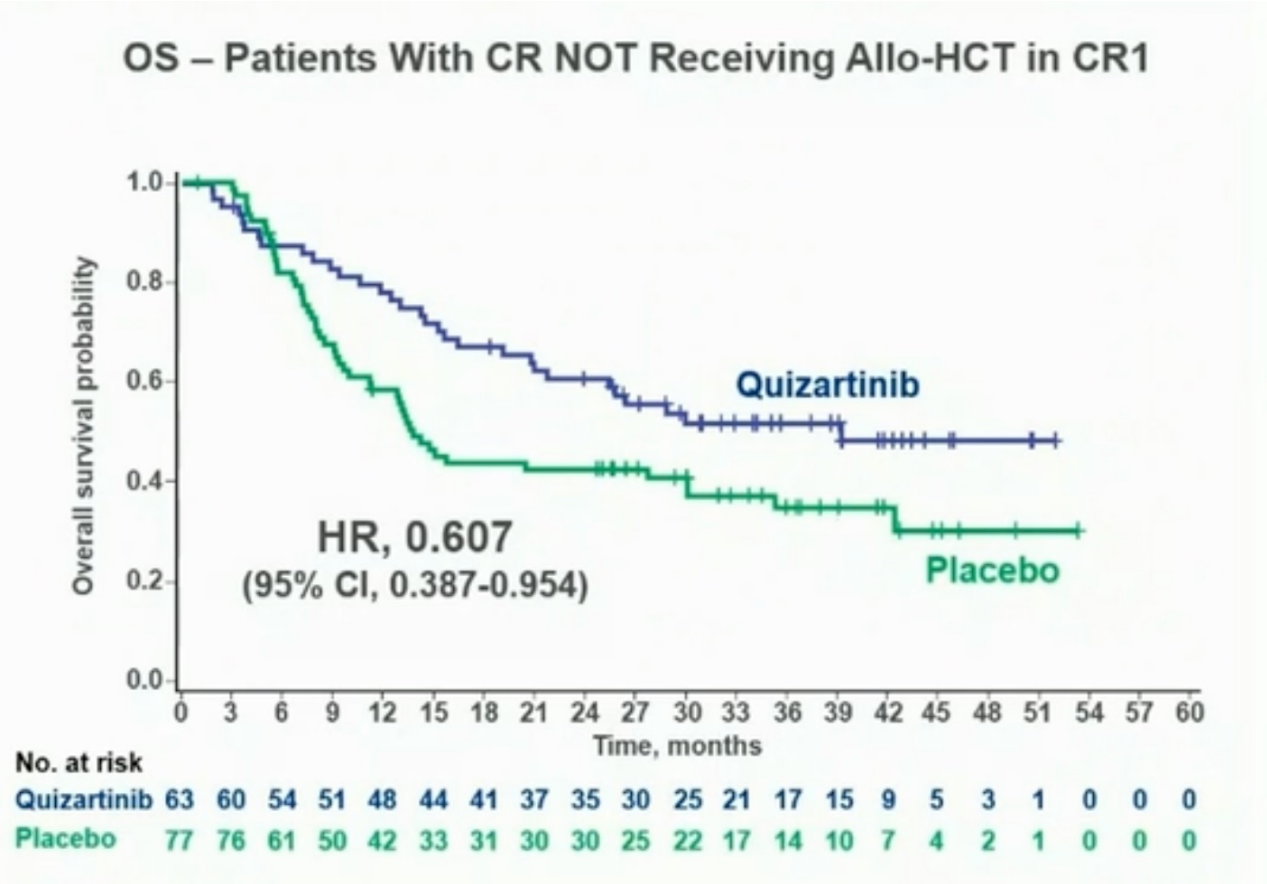


Number at risk

FLAG-Ida	29	17	16	9	4	2	2	0	0	0
CPX-351	30	25	24	20	15	7	5	2	1	1

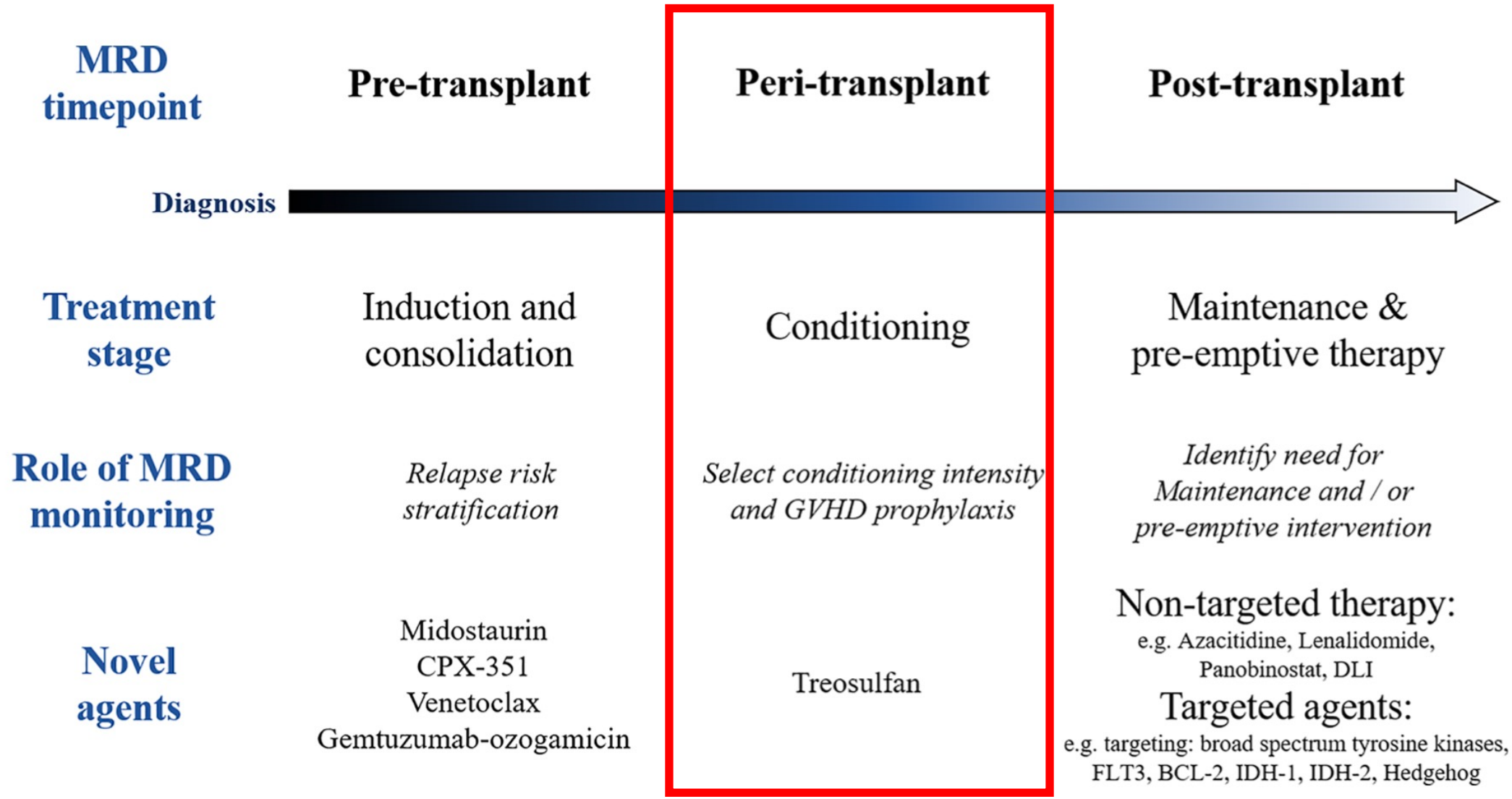
QUIZARTINIB PROLONGED SURVIVAL VS PLACEBO PLUS INTENSIVE INDUCTION AND CONSOLIDATION THERAPY FOLLOWED BY SINGLE-AGENT CONTINUATION IN PATIENTS AGED 18-75 YEARS WITH NEWLY DIAGNOSED FLT3-ITD+ AML





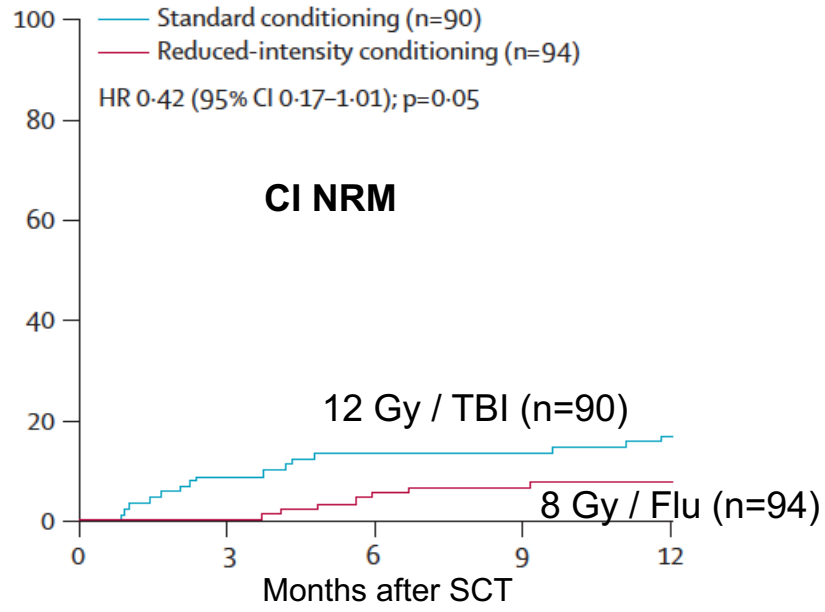
Erba et al., EHA 2022; Lancet 2023

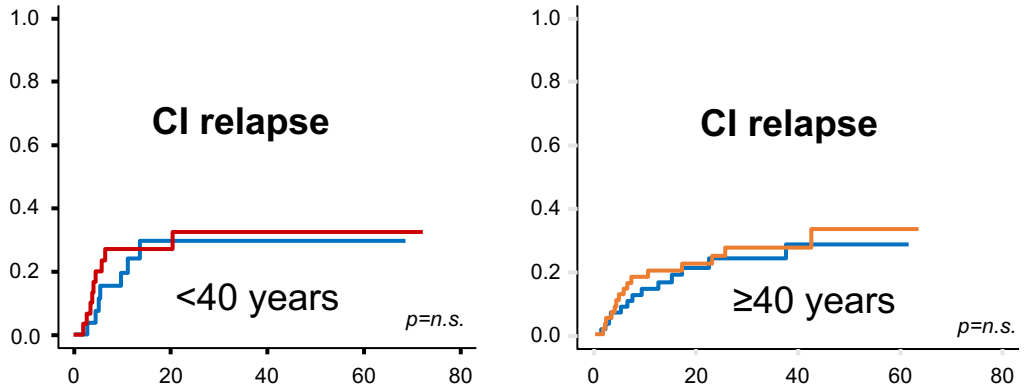
Preventing relapse: Role of measurable residual disease (MRD) and novel agents at different stages of the treatment pathway in AML



Adapeted from Loke et al., Frontiers in Immunology 2021

TBI 8 Gy / Fludarabine vs. TBI 12 Gy / Cy (Phase III Study), 2004 - 2009



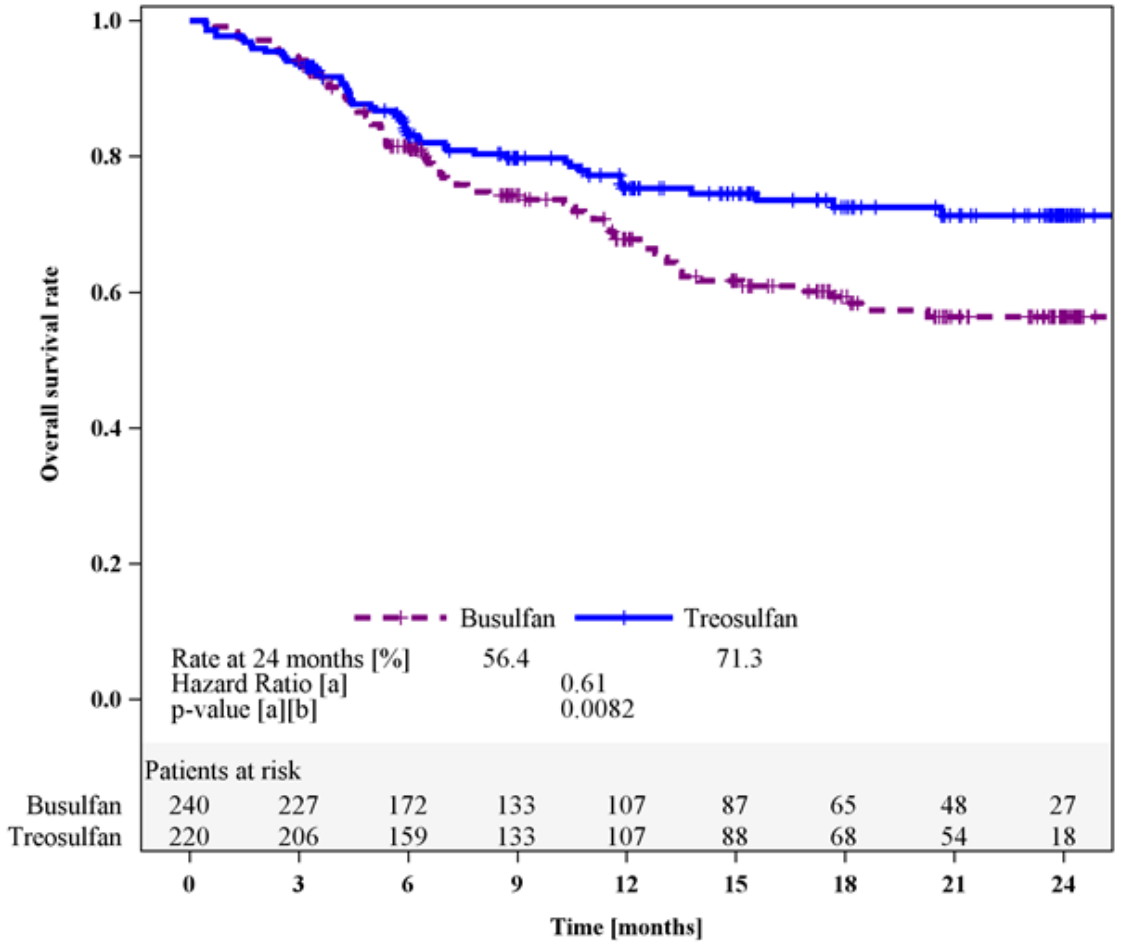


	Standard conditioning (n=96)	Reduced-intensity conditioning (n=99)
Median age	45 (18–60)	44 (18–60)
Age group		
18–40 years	31 (32%)	35 (35%)
41–60 years	65 (68%)	64 (65%)
Sex		
Female	49 (51%)	56 (57%)
Male	47 (49%)	43 (43%)
Cytogenetic risk		
Intermediate*		
Normal karyotype	54 (56%)	65 (66%)
Other intermediate abnormalities	16 (17%)	12 (12%)
High		
+8	12 (13%)	5 (5%)
Complex (≥3 aberrations)	8 (8%)	9 (9%)
–5, –7, del(5q)	3 (3%)	3 (3%)
Inv(3), t(3;3)	0 (0%)	1 (1%)
t(6;11), t(11;19)	3 (3%)	3 (3%)
t(6;9)	0 (0%)	1 (1%)
Donor		
Matched sibling	58 (60%)	59 (60%)
All alleles matched, unrelated	24 (25%)	28 (28%)
One allele mismatched, unrelated	14 (15%)	12 (12%)

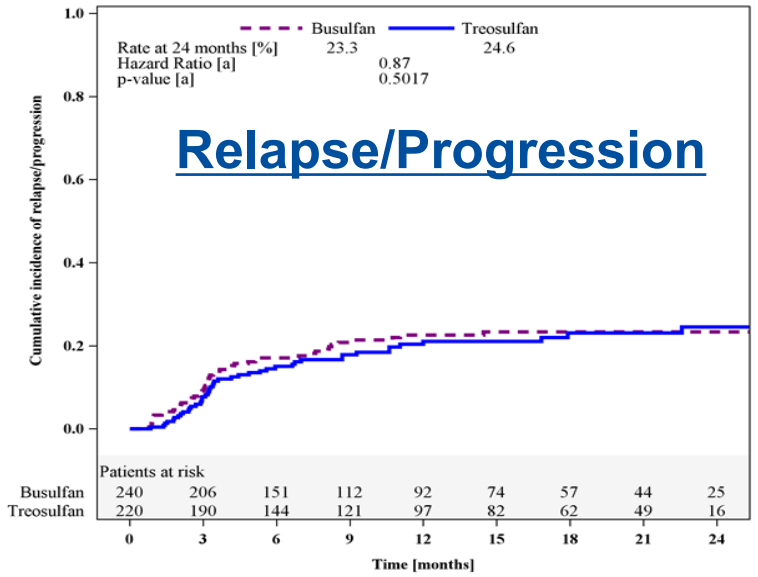
Bornhäuser, …,Stelljes; Lancet Oncol. 2012

Treosulfan/Fludarabine vs. Busulfan/Fludarabine Prior to Allogeneic SCT in Elderly or Comorbid Patients with AML or MDS

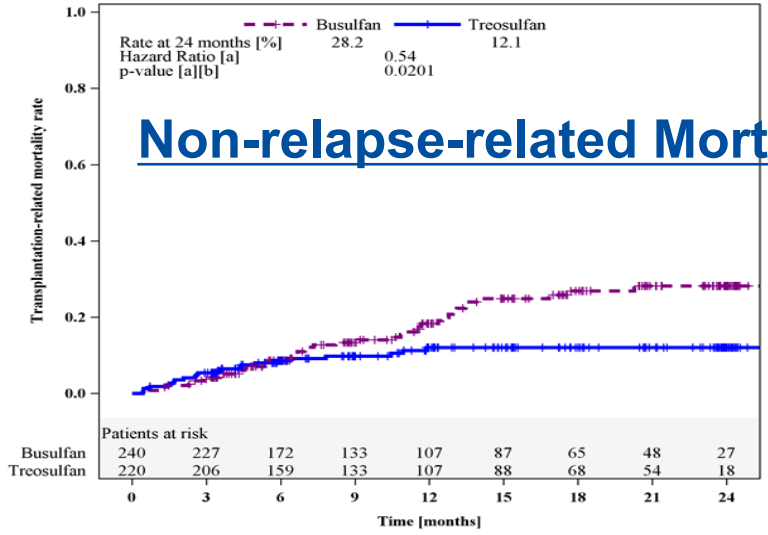
Overall Survival



Relapse/Progression



Non-relapse-related Mortality



Beelen, Trenschel, Stelljes et al., Lancet haem. 2020; Beelen, Stelljes et al., American Journal of Hematology 2022

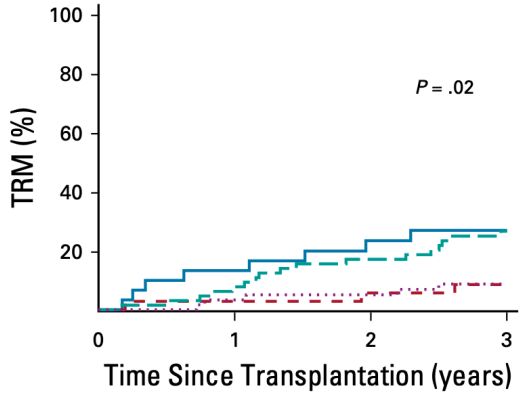
Impact of Conditioning Intensity of Allogeneic Transplantation for AML With Genomic Evidence of Residual Disease

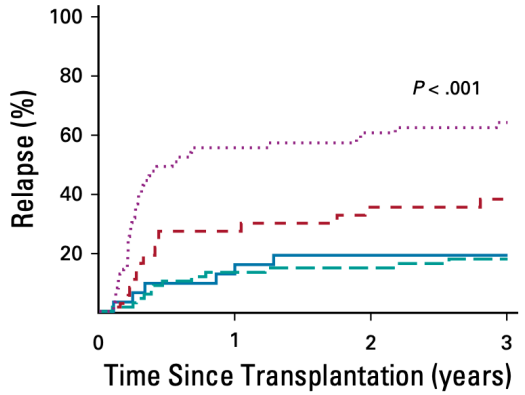
Characteristic	MAC, No. (%)	RIC, No. (%)	Total, No.
No. of patients	95	95	190
Age			
Median (range)	54.9 (21.9-66)	54.7 (21.9-65.9)	
≤ 50	28 (29.5)	27 (28.4)	55
> 50	67 (70.5)	68 (71.6)	135
Cytogenetics			
Favorable	5 (5.3)	11 (11.6)	16
Intermediate	59 (62.1)	52 (54.7)	111
Poor	26 (27.4)	28 (29.5)	54
Not tested	3 (3.2)	1 (1.1)	4
Unknown	2 (2.1)	3 (3.2)	5
Disease risk			
Standard	51 (53.7)	45 (47.4)	96
High	42 (44.2)	47 (49.5)	89
Unknown	2 (2.1)	3 (3.2)	5

Characteristic	MAC, No. (%)	RIC, No. (%)	Total, No.
Donor type			
Related	41 (43.2)	45 (47.4)	86
Unrelated	54 (56.8)	50 (52.6)	104
Donor match			
Mismatched	9 (9.5)	12 (12.6)	21
Matched	86 (90.5)	83 (87.4)	169
Graft type			
PB	89 (93.7)	85 (89.5)	174
BM	6 (6.3)	10 (10.5)	16
Conditioning regimen			
Flu/Bu4	54 (56.8)	NA	54
Bu/Cy	37 (39.0)	NA	37
Cy/TBI	4 (4.2)	NA	4
Flu/Mel	NA	17 (17.9)	17
Flu/Bu2	NA	78 (82.1)	78
ATG			
ATG	13 (13.7)	16 (16.8)	29
No ATG	82 (86.3)	79 (83.2)	161

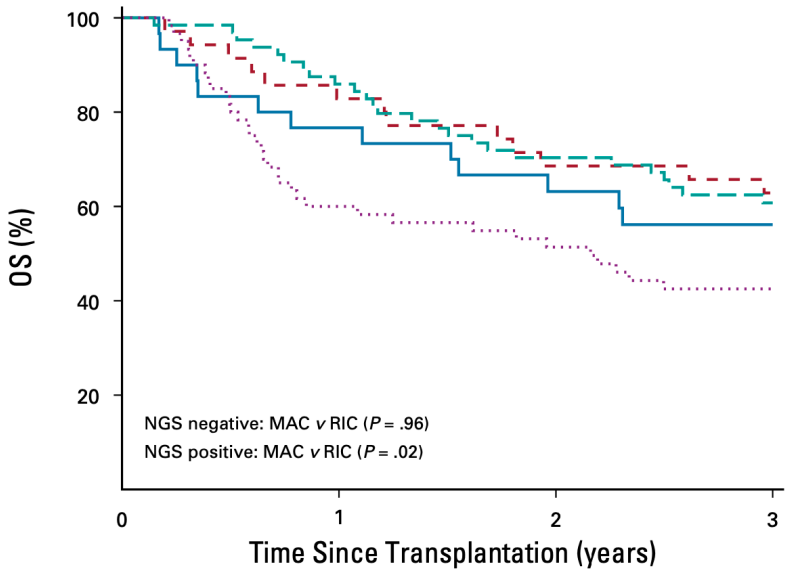
Hourigan et al., JCO 2021

Impact of Conditioning Intensity of Allogeneic Transplantation for AML With Genomic Evidence of Residual Disease



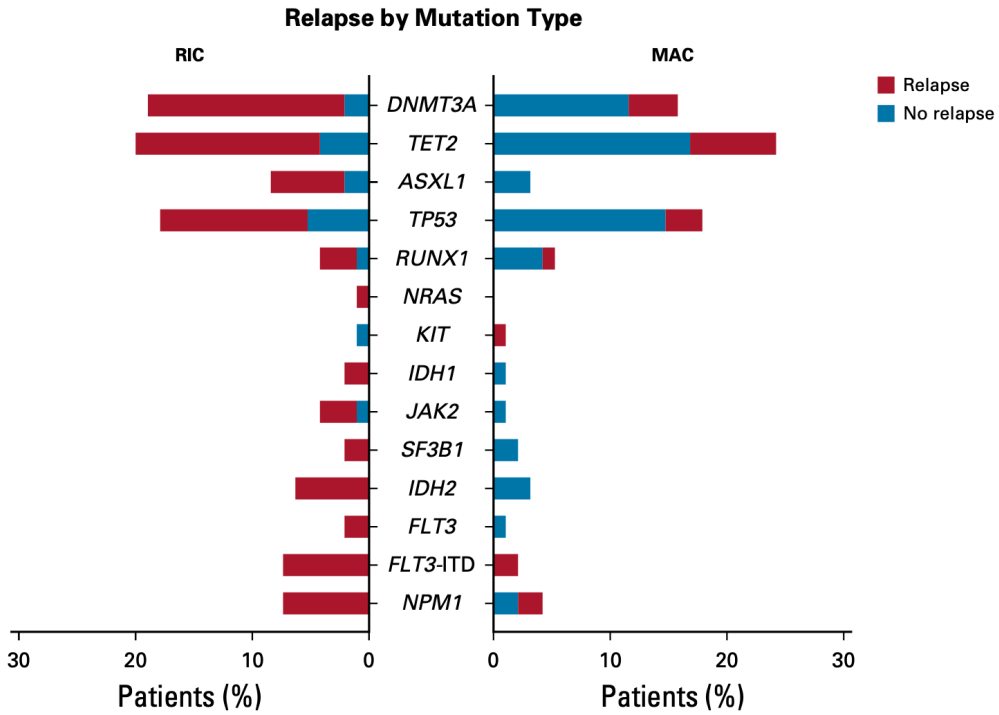


No. at risk				
NGS negative				
MAC	30	21	16	15
RIC	35	24	20	18
NGS positive				
MAC	65	50	43	32
RIC	60	23	17	13



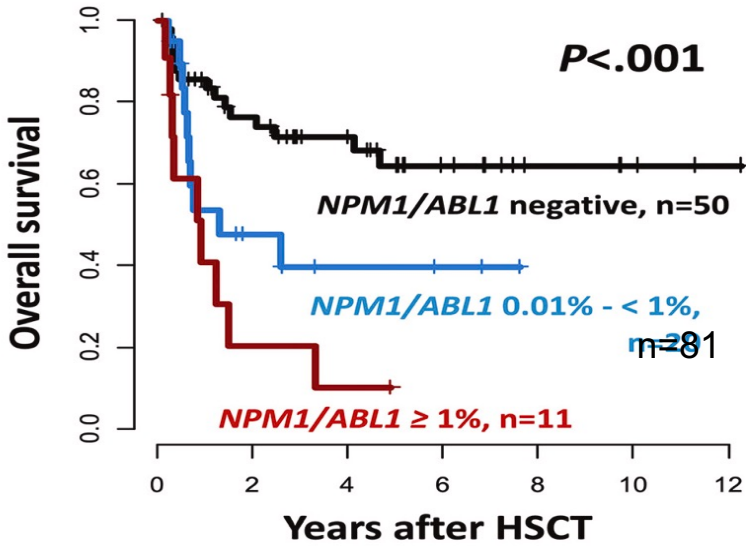
No. at risk				
NGS negative				
MAC	30	23	18	16
RIC	35	29	24	22
NGS positive				
MAC	65	55	45	35
RIC	60	36	29	24

NGS negative, MAC
NGS negative, RIC
NGS positive, MAC
NGS positive, RIC

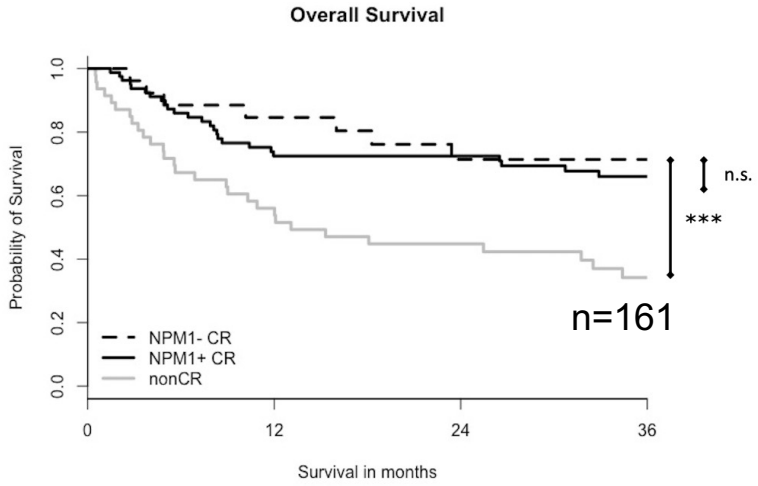


Hourigan et al., JCO 2020

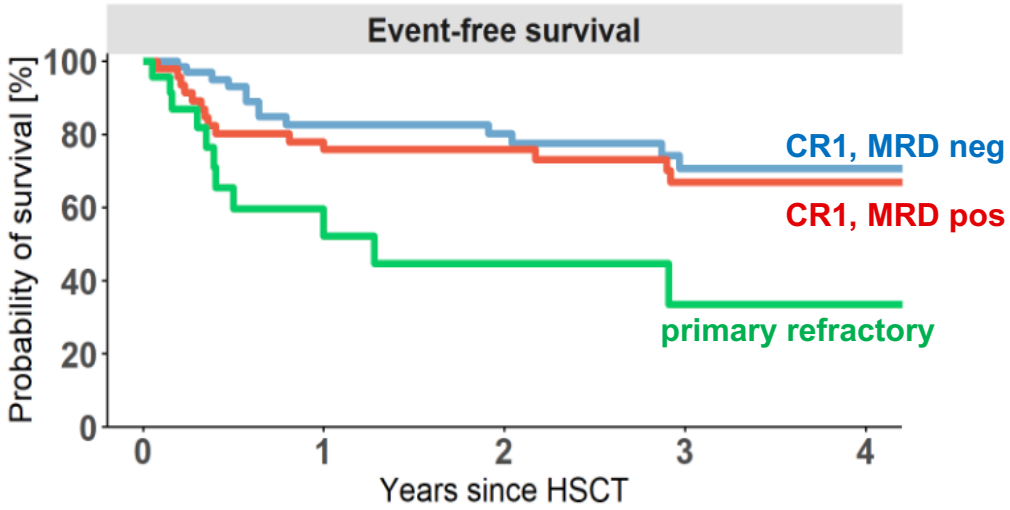
Impact of Mutated NPM1 MRD in Patients with AML Undergoing HCT

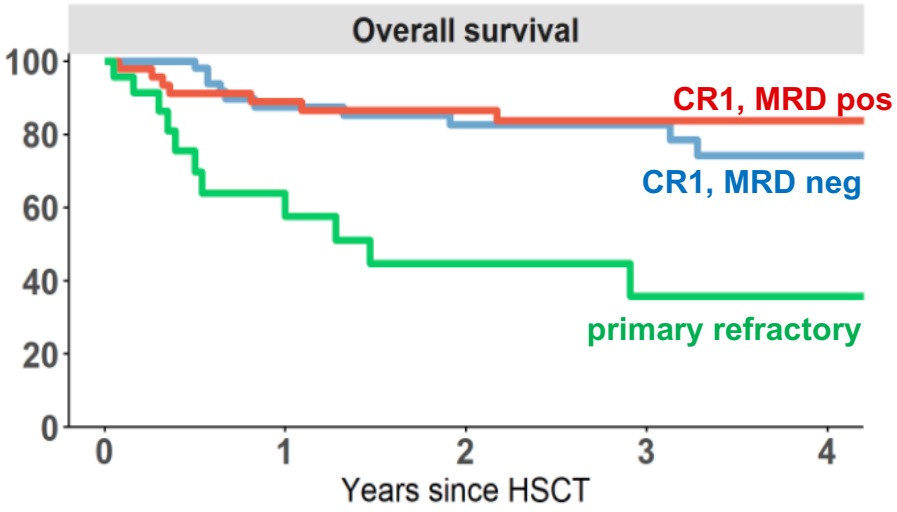


Schwind et al. ASH 2022



Fraccaroli et al. ASH 2022

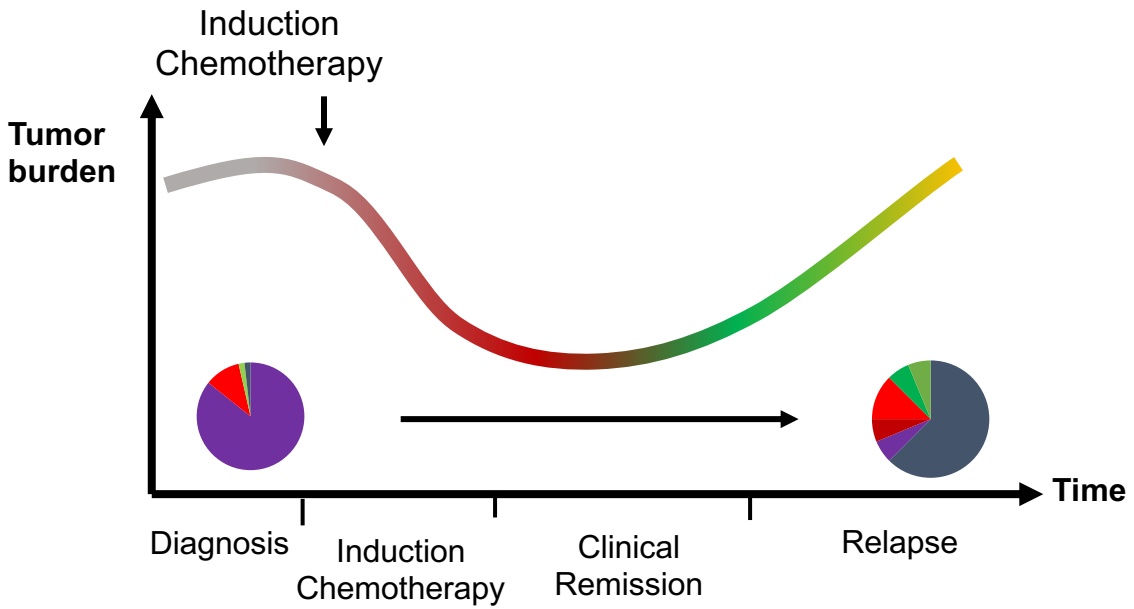


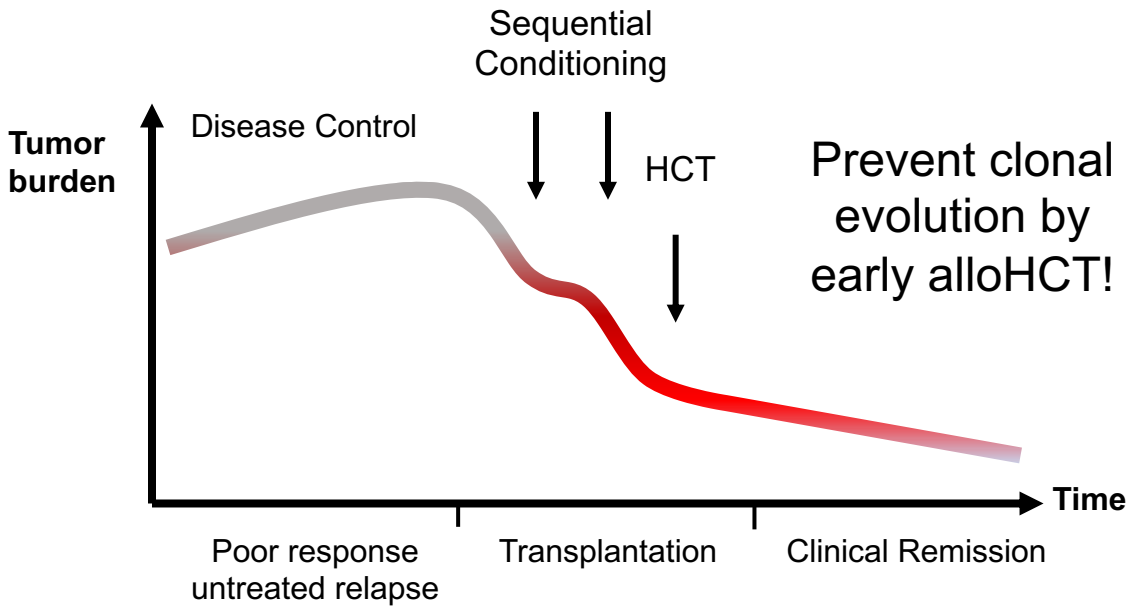


Münster, Dresden, Nürnberg & Frankfurt 2023

In patients with R/R AML sequential conditioning and immediate alloHCT results in similar OS and LFS compared to intensive remission induction chemotherapy followed by alloHCT: Results from the randomized Phase III ETAL3-ASAP

- Current intensive salvage chemotherapy regimens lead to CR-rates of 35 to 50% in high/intermediate risk AML.
- Relapsed and/or refractory AML is characterized by increased clonal complexity and chemotherapy resistance
- Sequential conditioning based on high-dose cytarabine or -melphalan plus RIC alloHCT resulted in long-term disease control for r/r AML (Schmid JCO 2005, Steckel BJH 2018).





Stelljes et al., ASH 2022

In patients with R/R AML sequential conditioning and immediate alloHCT results in similar OS and LFS compared to intensive remission induction chemotherapy followed by alloHCT: Results from the randomized Phase III ETAL3-ASAP

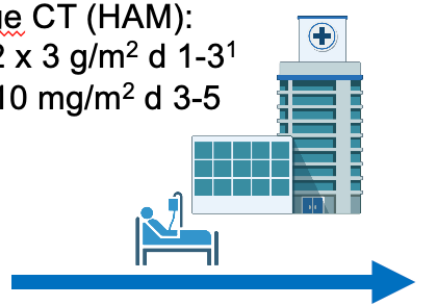
- Age 18 – 75 years
- poor response after first induction[2] of non-favorable AML OR first untreated relapse
- HLA compatible donor
- Fit for salvage CT and alloHCT[3]

R

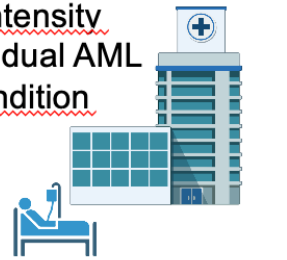
1:1, stratified for disease status, AML biology and age

RIST

Salvage CT (HAM):
AraC 2 x 3 g/m² d 1-3[1]
Mitox 10 mg/m² d 3-5



Conditioning Intensity adapted to residual AML and patient condition



DisC

watchful waiting
or
low-dose AraC
or
Mitoxantron 10 mg/m²

Sequential Conditioning:
- FLAMSA-RIC
- HD-Melphalan +Flu/TBI

Primary Endpoint:
DFS@d56 after HCT
OS from Rando

[1] Cytarabine 2 x 1 g/m² for patients >60 yrs
[2] poor response was defined as ≥5% marrow blasts after 1st induction; (see also Röllig *et al*, abstract 217, ASH 2022)
[3] Patients with WBC≥50 GPT/L, CNS manifestations, prior alloHCT, LVEF <50%, O_2 supplementation., bilirubin >1.5xULN, GFR <50 ml/min were not eligible

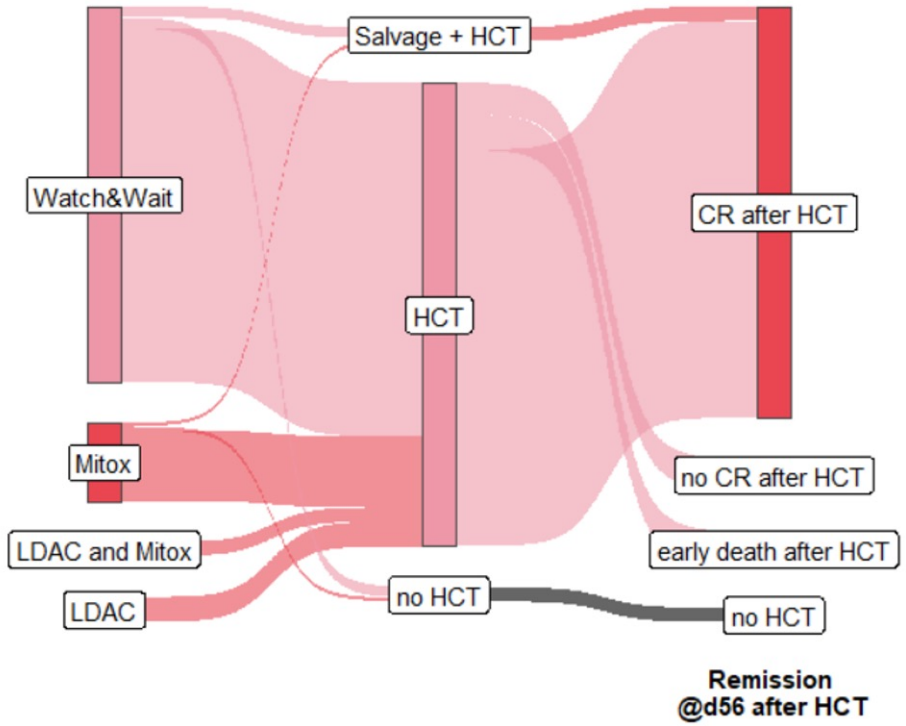
Stelljes et al., ASH 2022

In patients with R/R AML sequential conditioning and immediate alloHCT results in similar OS and LFS compared to intensive remission induction chemotherapy followed by alloHCT: Results from the randomized Phase III ETAL3-ASAP

Disease Control arm

76% of patients bridged by watchful waiting

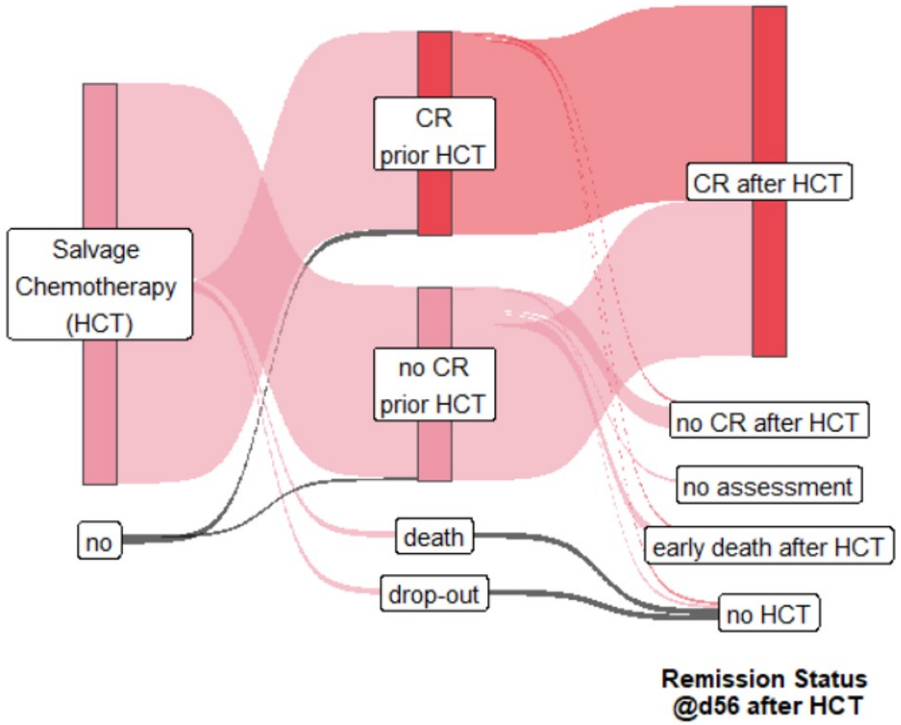
Median time to HCT 4 weeks; @16weeks 97% HCT



Remission Induction arm

Every second patient achieved a CR

Median time to HCT 8 weeks; @16weeks 93% HCT



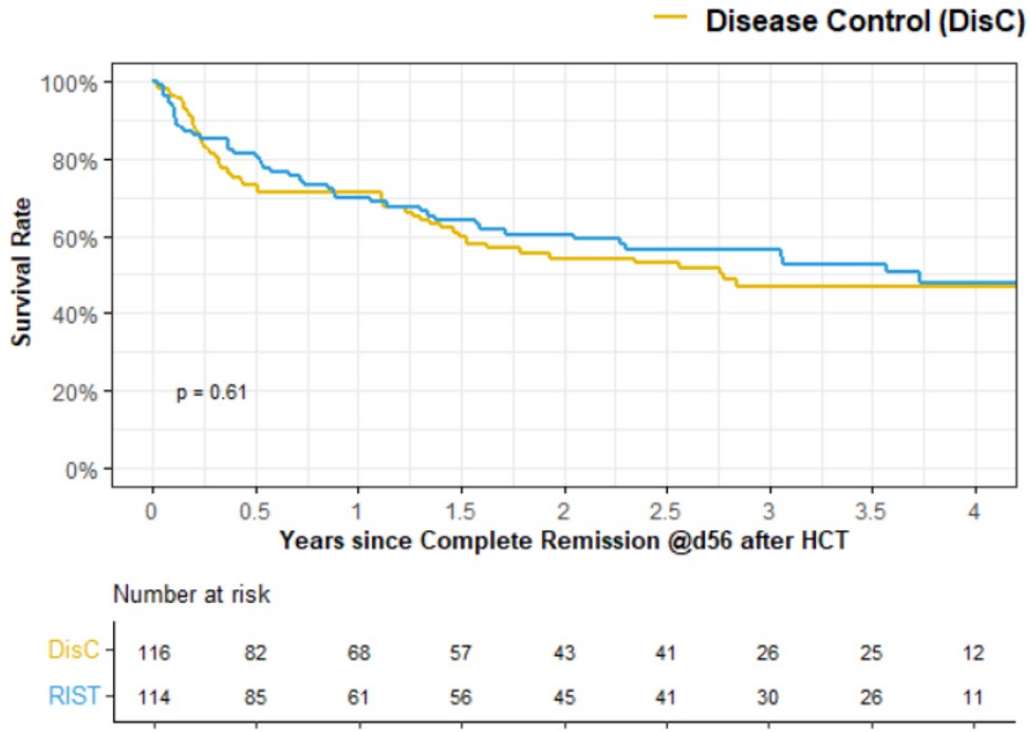
ITT populations, data lock 2022-07-19, analysis as of 2022-11-04

Stelljes et al., ASH 2022

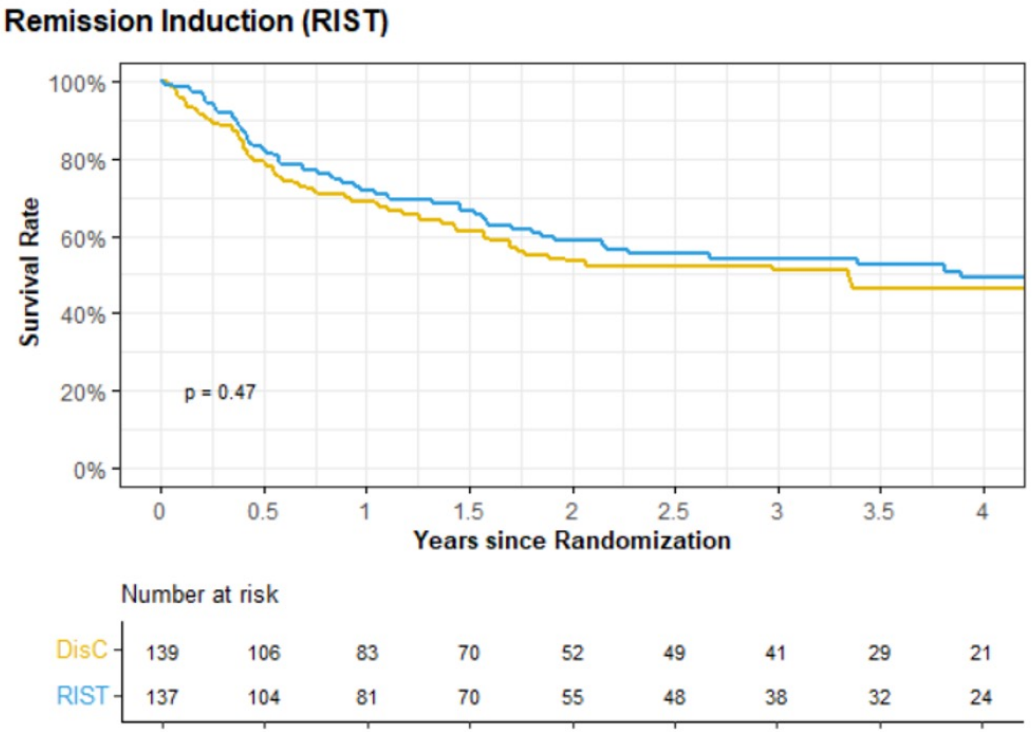
In patients with R/R AML sequential conditioning and immediate alloHCT results in similar OS and LFS compared to intensive remission induction chemotherapy followed by alloHCT: Results from the randomized Phase III ETAL3-ASAP

No Difference in Leukemia-free from DFS@d56 and Survival from randomization!

Leukemia-free Survival from d56



Overall Survival from Rando



Median follow-up from Randomization: 37 months

Stelljes et al., ASH 2022

High Dose-Melphalan Conditioning for Allogeneic SCT in R/R AML

d-11	d-10	d-9	d-8	d-7	d-6	d-5	d-4	d-3	d-2	d-1	d0
Mel 140	Pause					Flu 30	Flu 30	Flu 30	Flu 30	TBI	TBI Allo Tx
Mel 100-140					Flu 30	Flu 30	Flu 30 Bu	Flu 30 Bu	Flu 30		
Mel 100-140	Pause				Flu 30	Flu 30	Flu 30 Treo10	Flu 30 Treo10	Flu 30 Treo10		Allo Tx

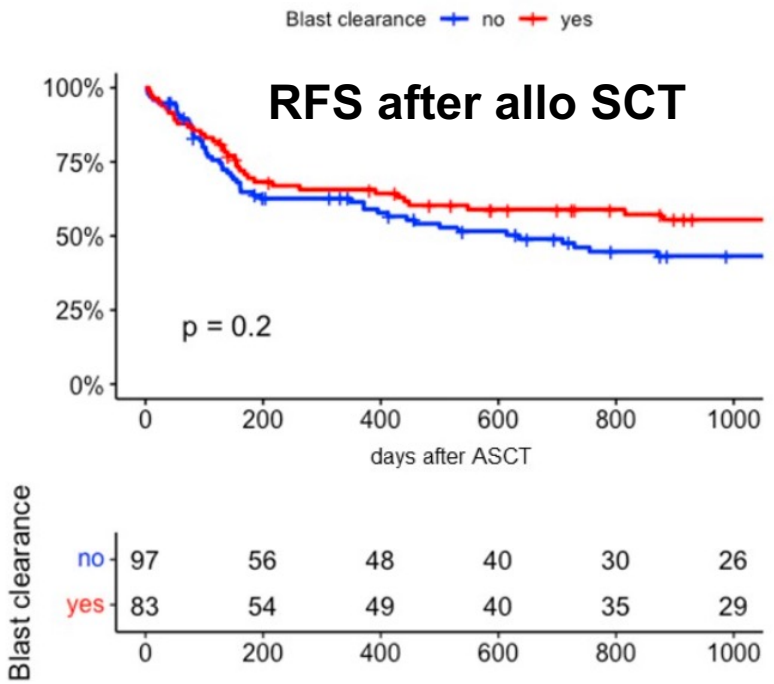
180 patients
med. age 67 years (range 45-76 y)

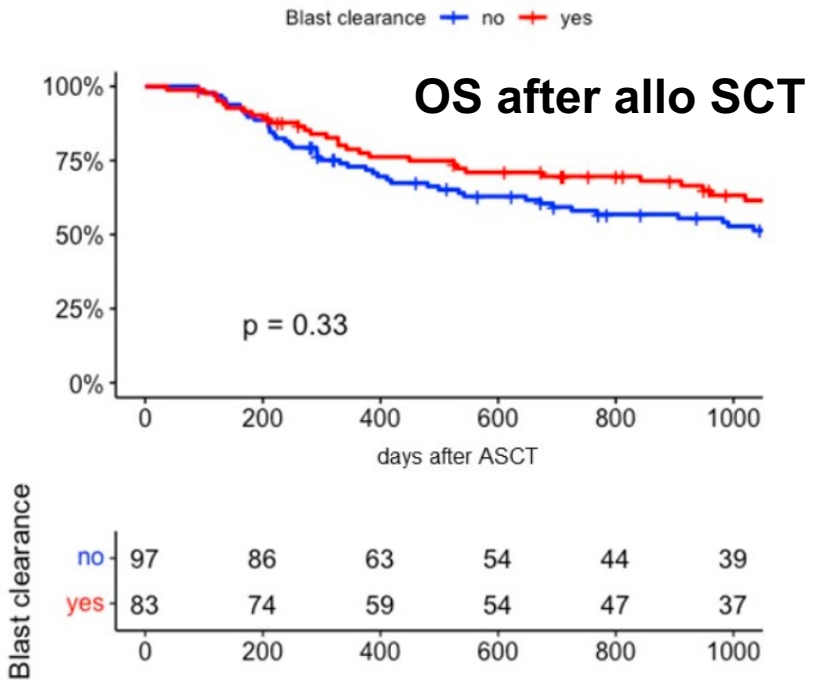
allo SCT 2014-2023 in Münster

71 HD-Mel// 8 Gy TBI, Flu
101 HD-Mel// Bu, Flu
14 HD-Mel// Treo, Flu

Median initial blast count 70% (5-90%)

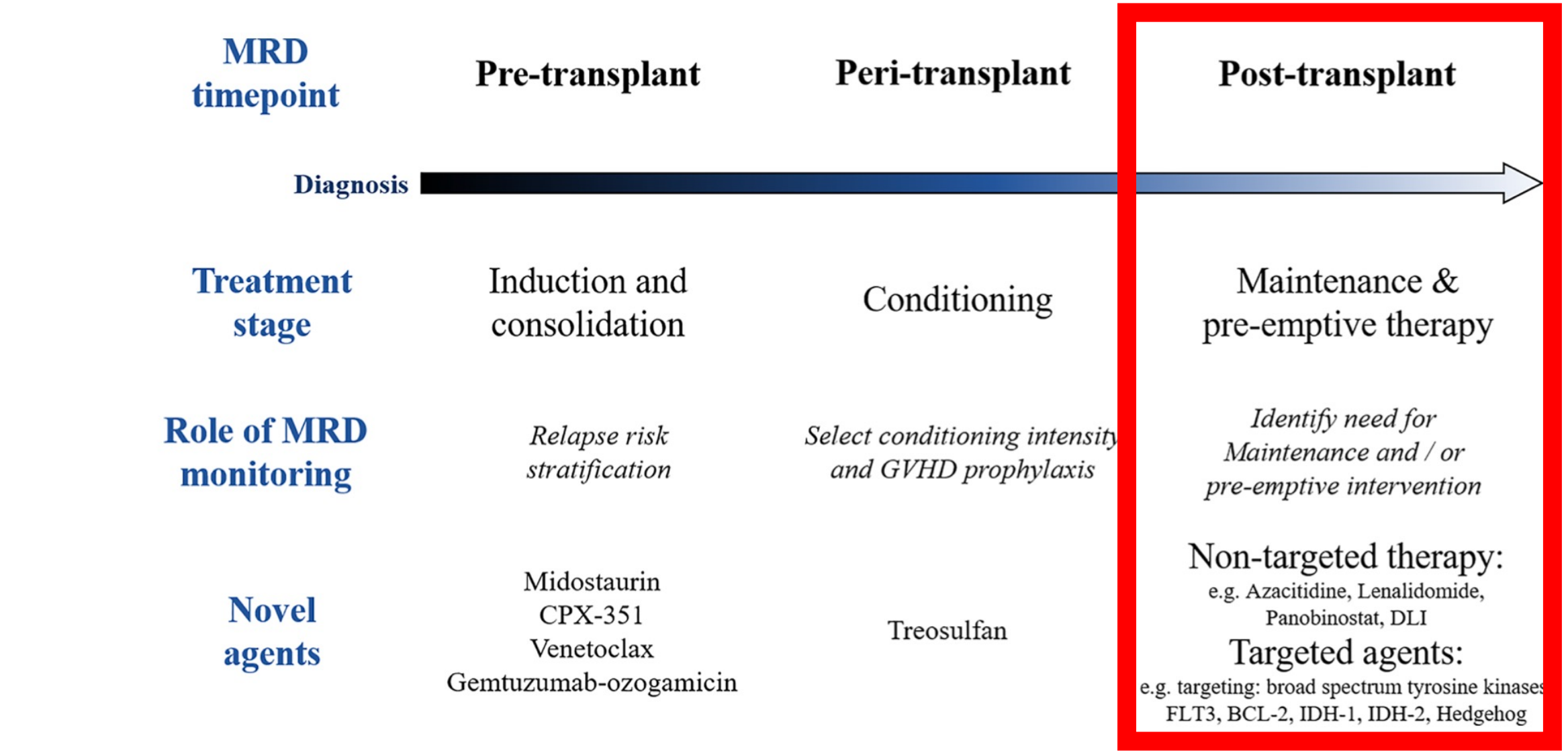
Median blast count d-7: 20% (0-90%)





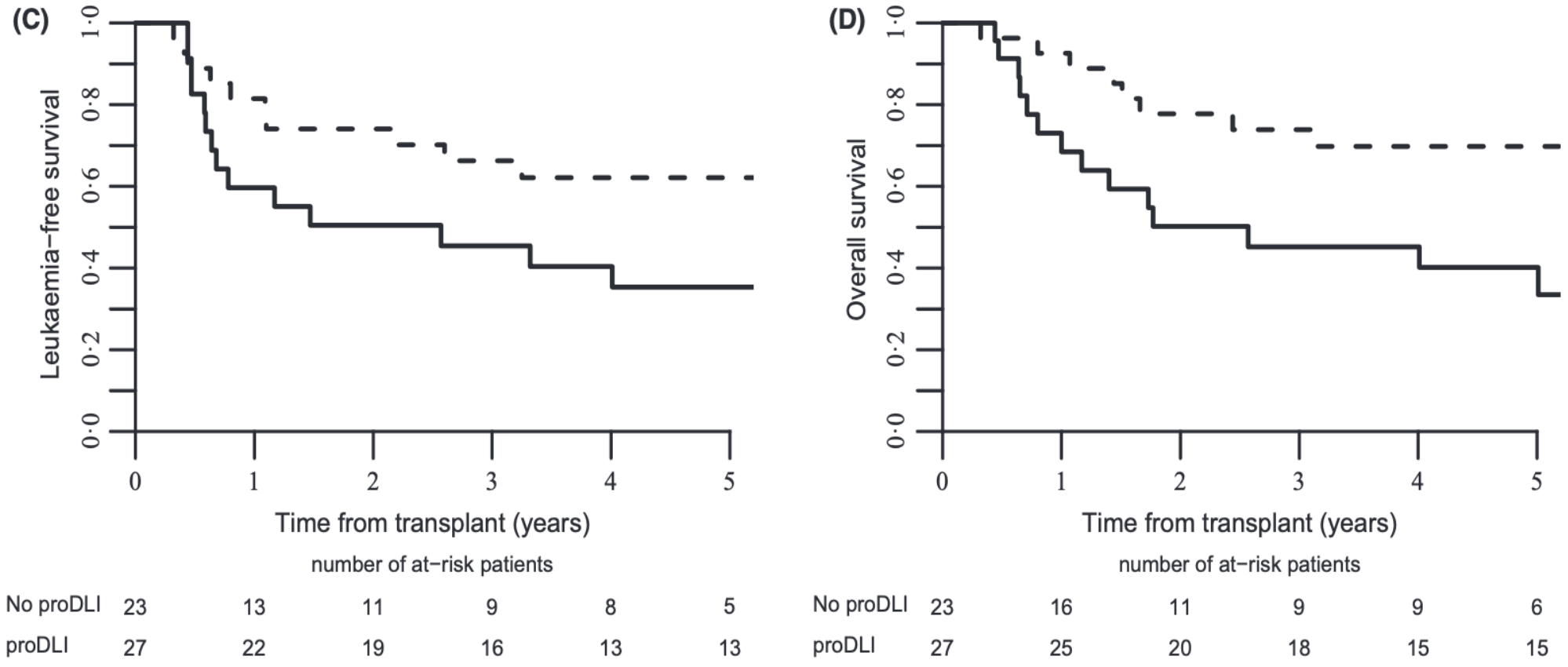
Ronnacker et al., ASH 2023, submitted

Preventing relapse: Role of measurable residual disease (MRD) and novel agents at different stages of the treatment pathway in AML



Adapeted from Loke et al., Frontiers in Immunology 2021

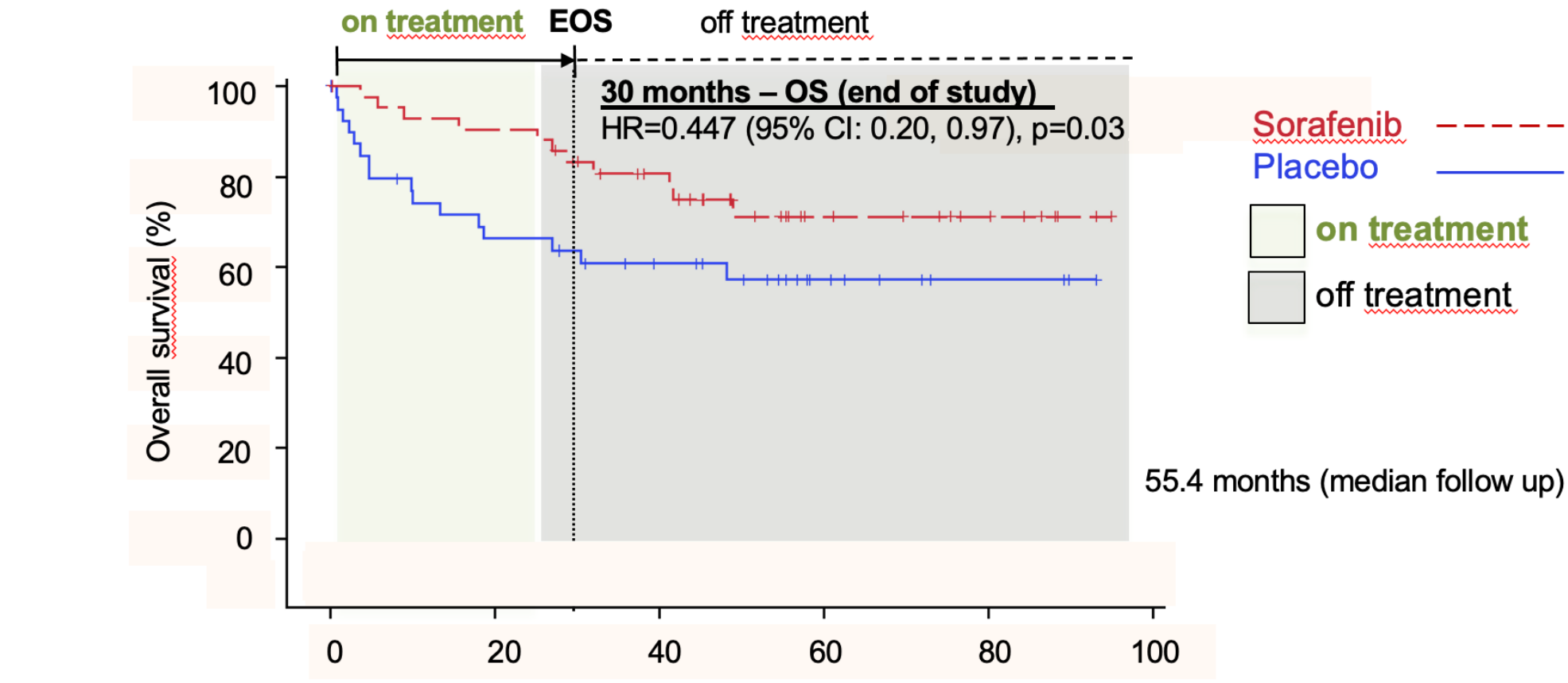
Prophylactic donor lymphocyte infusion after allogeneic HSCT in acute leukaemia - a matched pair analysis



Schmid et al., BJH 2019

Sorafenib Maintenance After Allo. HSCT for AML With *FLT3*–Internal Tandem Duplication Mutation

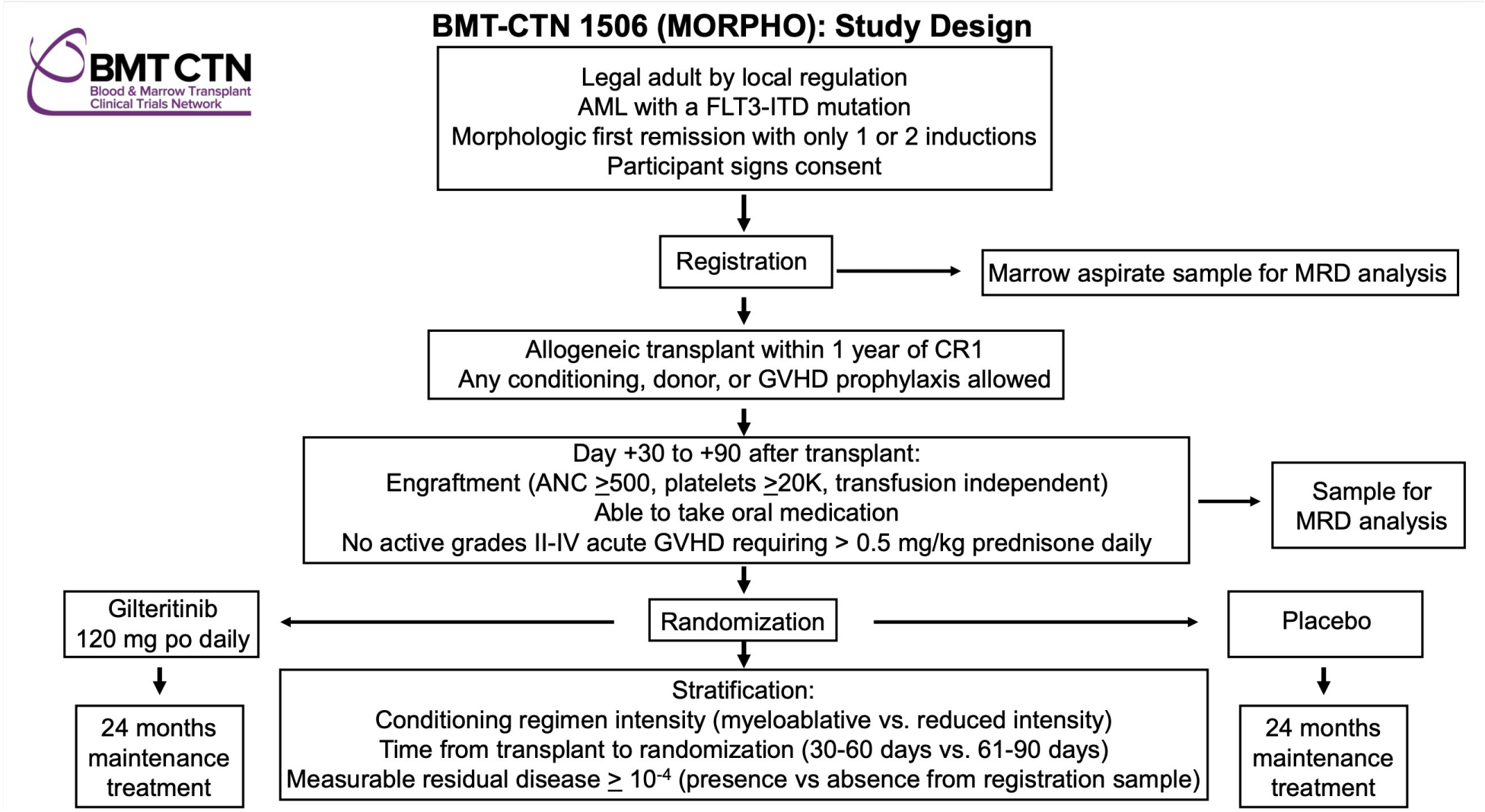
Overall survival



Abbreviations: CI, confidence interval; HR, hazard ratio; EOS,end of study

Burchert et al., JCO 2020

BMT-CTN 1506 (MORPHO): A randomized trial of the FLT3 inhibitor gilteritinib as post-transplant maintenance for FLT3-ITD AML



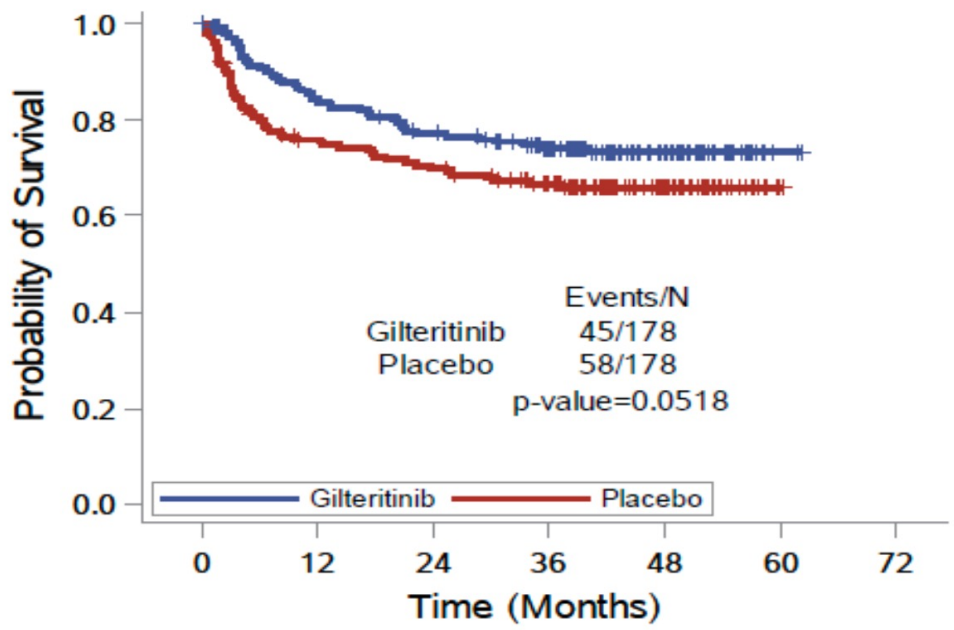
Lewis et al., EHA 2023

BMT-CTN 1506 (MORPHO): A randomized trial of the FLT3 inhibitor gilteritinib as post-transplant maintenance for FLT3-ITD AML

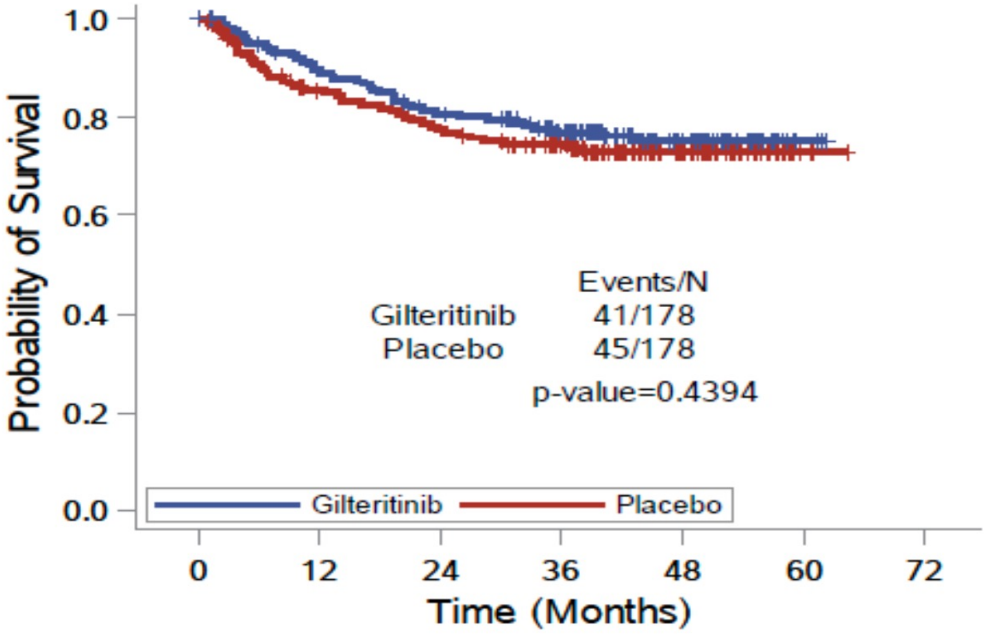
BMT CTN
Blood & Marrow Transplant Clinical Trials Network

BMT-CTN 1506 (MORPHO): Efficacy Outcome

Primary objective:
Relapse-free survival
HR = 0.679 (0.459-1.005)
P = 0.0518



Key secondary objective:
Overall survival
HR = 0.846 (0.554-1.293)
P = 0.4394



Lewis et al., EHA 2023

BMT-CTN 1506 (MORPHO): A randomized trial of the FLT3 inhibitor gilteritinib as post-transplant maintenance for FLT3-ITD AML

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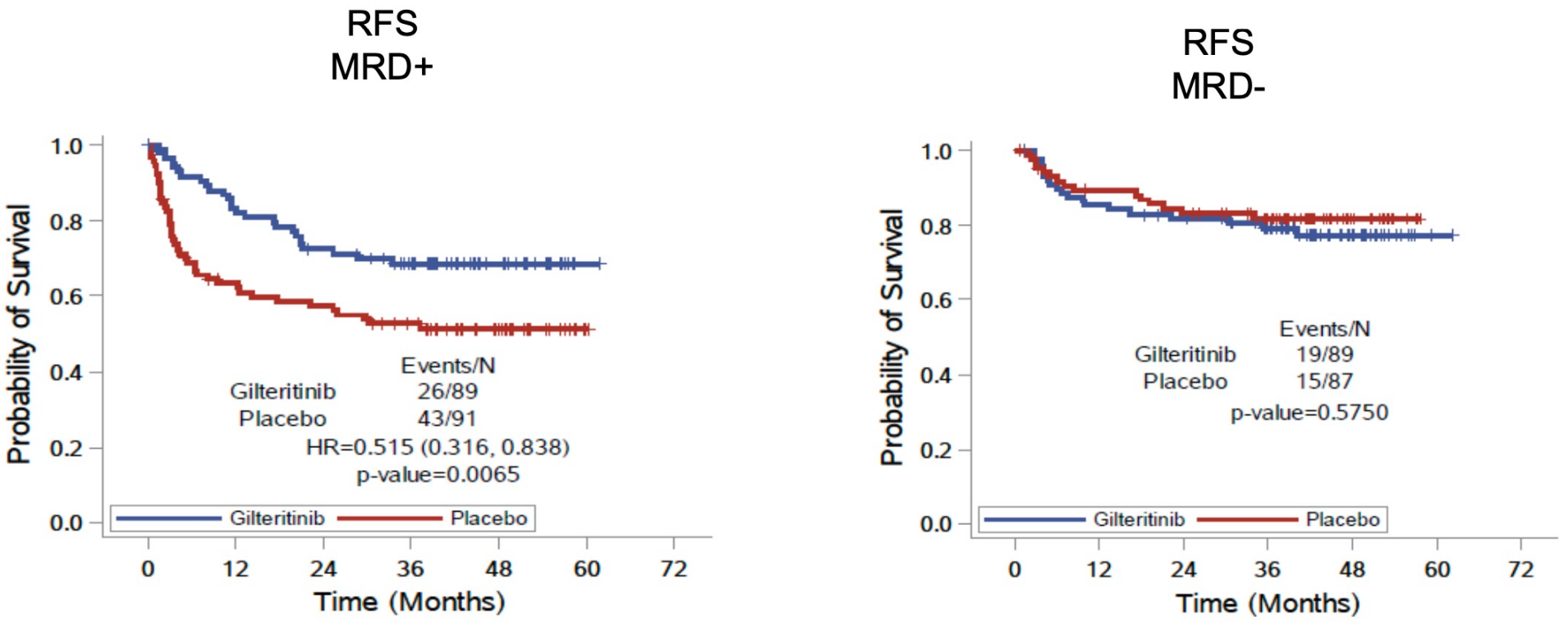
Effect of detectable MRD6 on RFS by study arm



Lewis et al., EHA 2023

BMT-CTN 1506 (MORPHO): A randomized trial of the FLT3 inhibitor gilteritinib as post-transplant maintenance for FLT3-ITD AML

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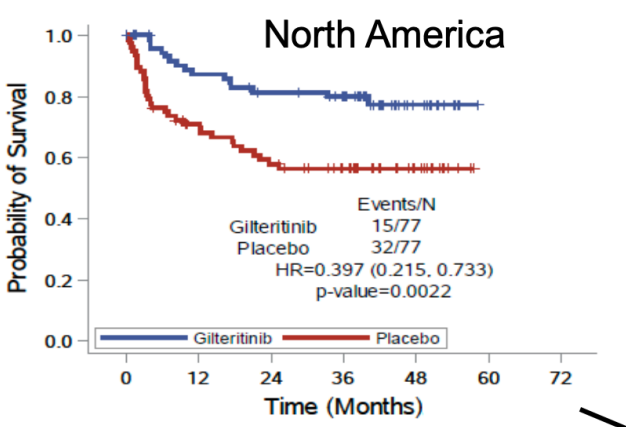
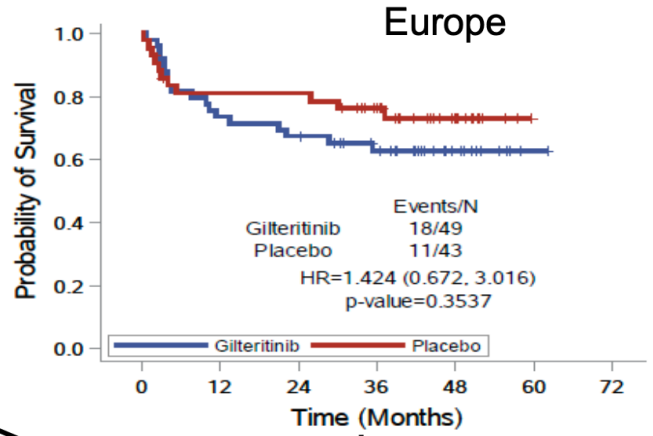
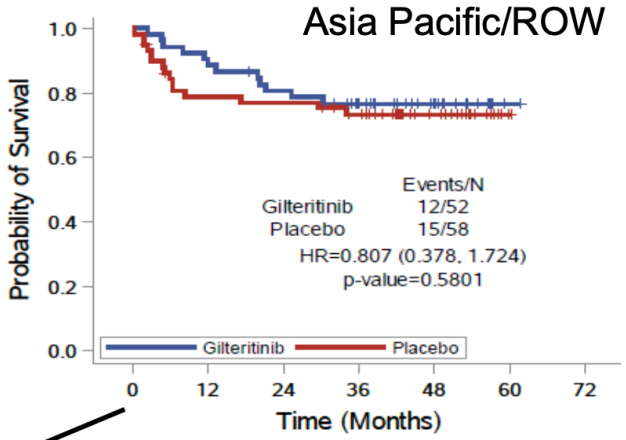
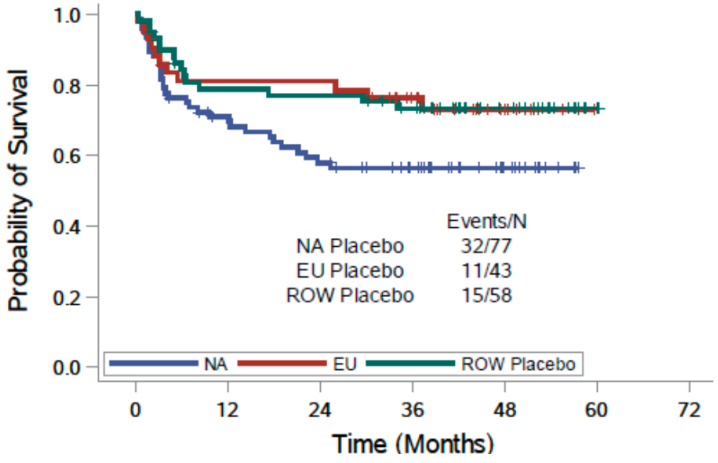
Blood & Marrow Transplant Clinical Trials Network

RFS by region









- Compared with Europe and Asia/ROW, pts in North America:
  - Went to HCT a mean of 26 days sooner
  - Received fewer courses of chemotherapy pre-HCT
  - Were more likely to be treated with a FLT3 inhibitor pre-HCT (93.5% vs 36.6%)

Lewis et al., EHA 2023

Take home message

Allo SCT USA ≠ Allo SCT Europe ≠ Allo SCT Germany

Tx center[a] ≠ Tx center[b]

Conditioning MAC/RIC[a] ≠ Conditioning MAC/RIC[b]

Indikationen (DAG-HSZT 06/22):

Entität	Krankheitsspezifisches Risiko	AlloHCT			Auto
		MSD	MUD	AD	
Akute Leukämien					
AML [9-11]	CR1 (ELN niedrig, MRD–)	-	-	-	E
	CR1 (ELN niedrig, MRD+)	S	S	S	-
	CR1 (ELN intermediär)	S	S	S	E
	CR1 (adverse risk)	S	S	S	-
	CR >1	S	S	S	E
	R/R	S	S	S	-
APL [12]	APL CR2, MRD-	-	-	-	O
	APL CR2, MRD+	S	S	O	-

S=Standard, E=unter Evaluation, MSD=HLA-identer Geschwisterspender, MUD=HLA-matched unverwandter Spender, AD=alternativer Spender (haplo oder MMUD)