XIX Congresso della Società GITMO

RIUNIONE NAZIONALE GITMO

TORINO, CENTRO CONGRESSI LINGOTTO, 5 - 6 MAGGIO 2025

Pro e contro il trapianto allogenico nelle malattie onco-ematologiche refrattarie
PRO

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Nulla da dichiarare

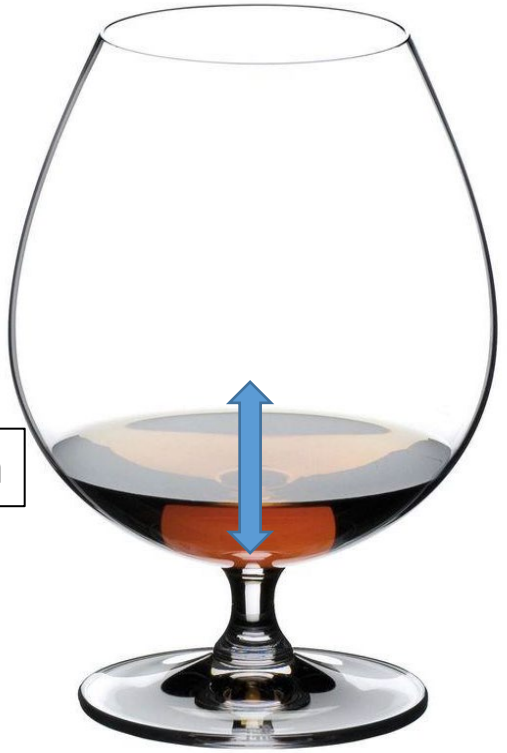
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other

ALLO in refractory AML

Giovanni

ALLO futile

Luca



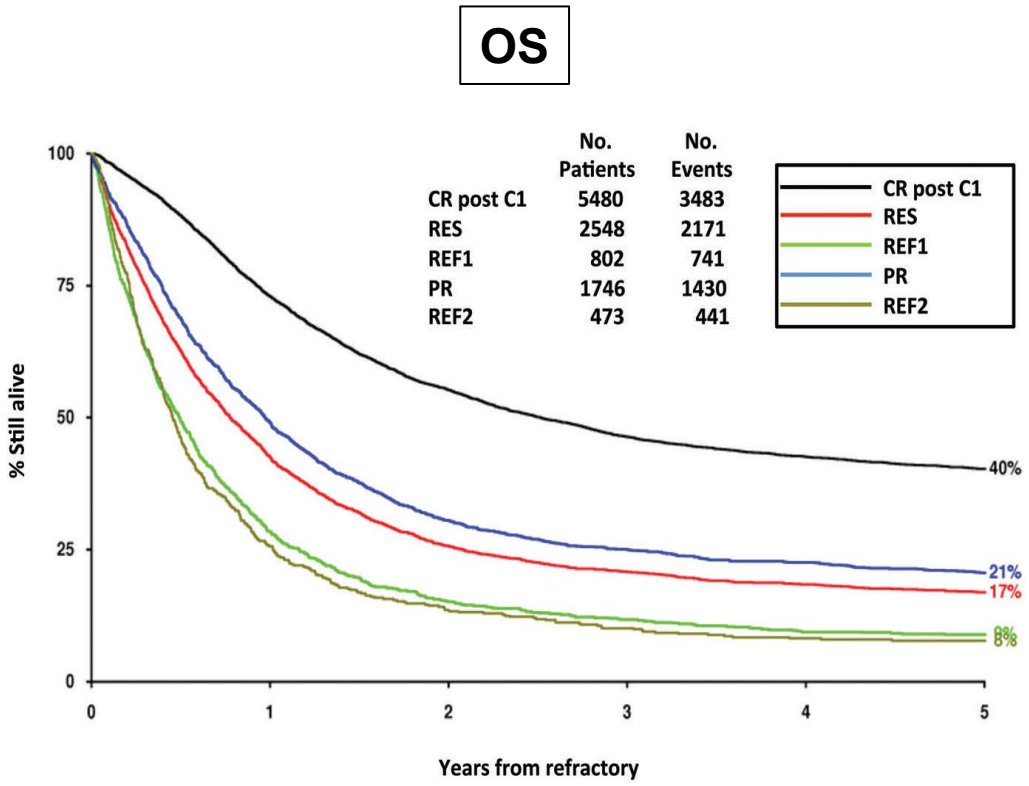
ALLO utile

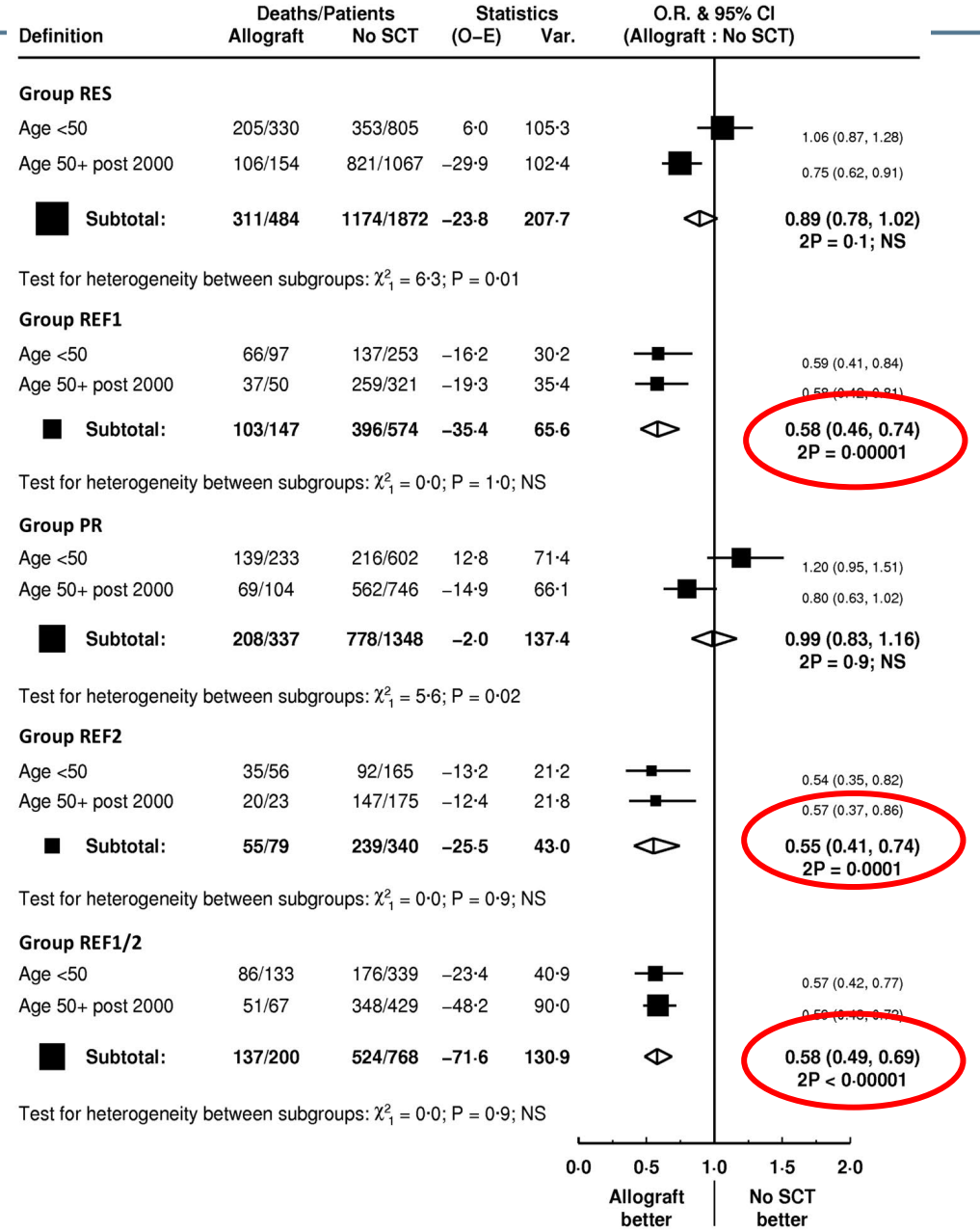
Refractory AML: definition

	Resistant (RES)	Partial remission (PR)	Refractory1 (REF1)	Refractory2 (REF2)
Definition	failure to achieve complete remission (CR) after C1	after first IC with fewer than 15% blasts or a greater than 50% reduction in blast percentage	after **first IC** with more than 15% blasts and a less than 50% proportional reduction in blast percentage	after **second IC** with more than 15% blasts and a less than 50% proportional reduction in blast percentage

Ferguson, Haematologica 2016

Refractory AML: definition





Ferguson, Haematologica 2016

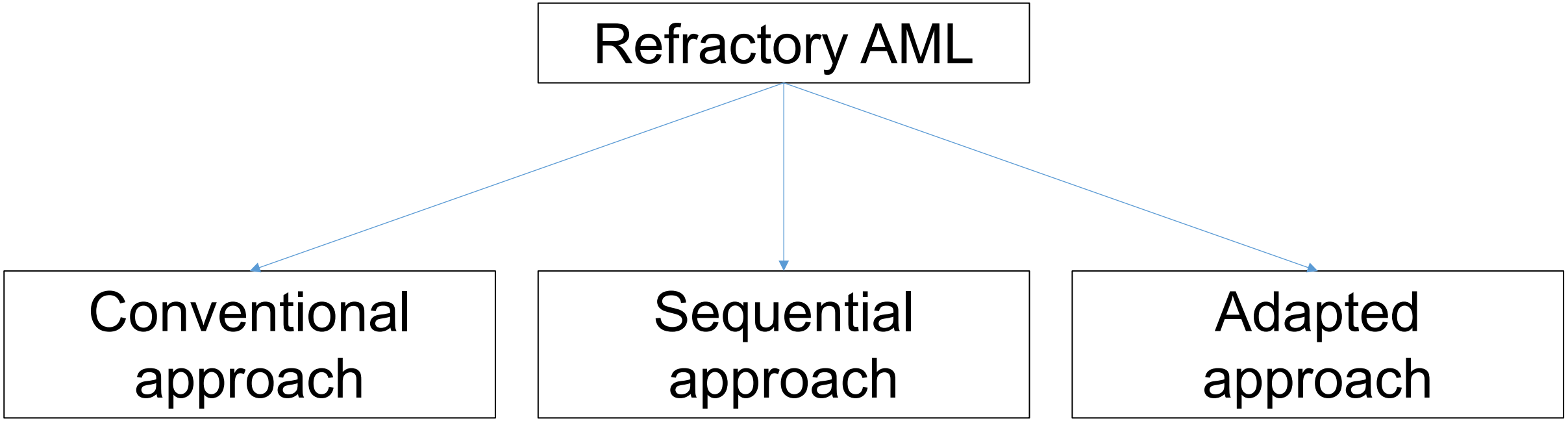
Refractory AML: definition

- ELN definition

	Definition
Refractory disease	No CR, CRh or CRi at the response landmark **after 2 courses** of intensive induction treatment or a defined landmark, 180 d after commencing less intensive therapy
Relapsed disease	Bone marrow blasts ≥5%; or reappearance of blasts in the blood in at least 2 peripheral blood samples at least one week apart; or development of extramedullary disease
MRD relapse **(after CR, CRh or CRi without MRD)**	1. Conversion from MRD negativity to MRD positivity, independent of method 2. Increase of MRD copy numbers ≥ 1 log10 between any 2 positive samples in patients with CR_{MRD-LL}, CRh_{MRD-LL} or CRi_{MRD-LL} by qPCR

Dohner, Blood 2022

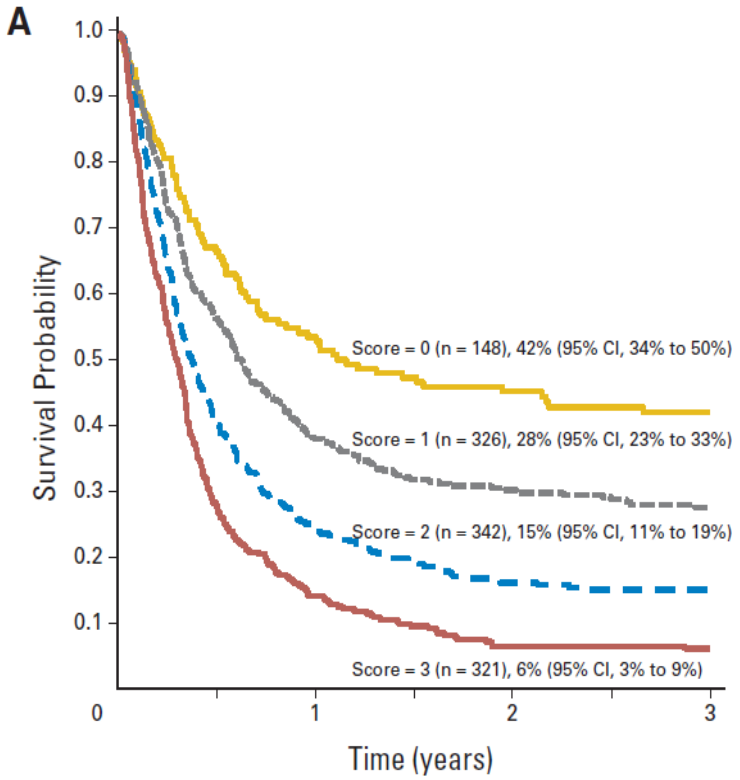
How to approach refractory AML



Conventional approach

Inclusion period	1995-2004 N= 1673
Median age	38 y
Donor	MRD/MUD
CTX	MAC TBI or BU-based
Stem cell	BM 65%
GVHD prophylaxis	CNI+MTX/MMF 85%
AML refractory to 2 IC	**REF2 38%**

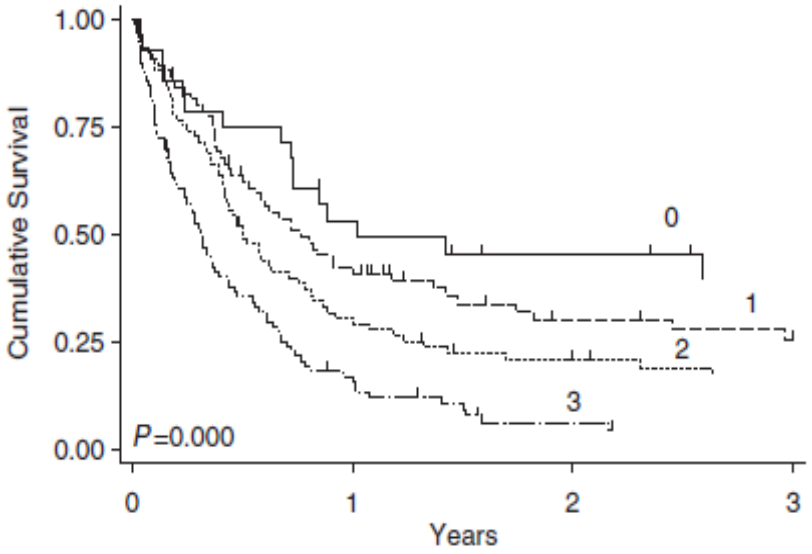
AML	
Disease group	
PIF or duration of first CR > 6 months	0
Duration of first CR < 6 months	1
Cytogenetics prior to HSCT	
Good or intermediate	0
Poor	1
HLA match group	
HLA identical sibling or well matched or partially matched unrelated	0
Mismatched unrelated	1
Related other than HLA identical sibling	2
Circulating blasts	
Absent	0
Present	1
Karnofsky or Lansky score	
90-100	0
< 90	1

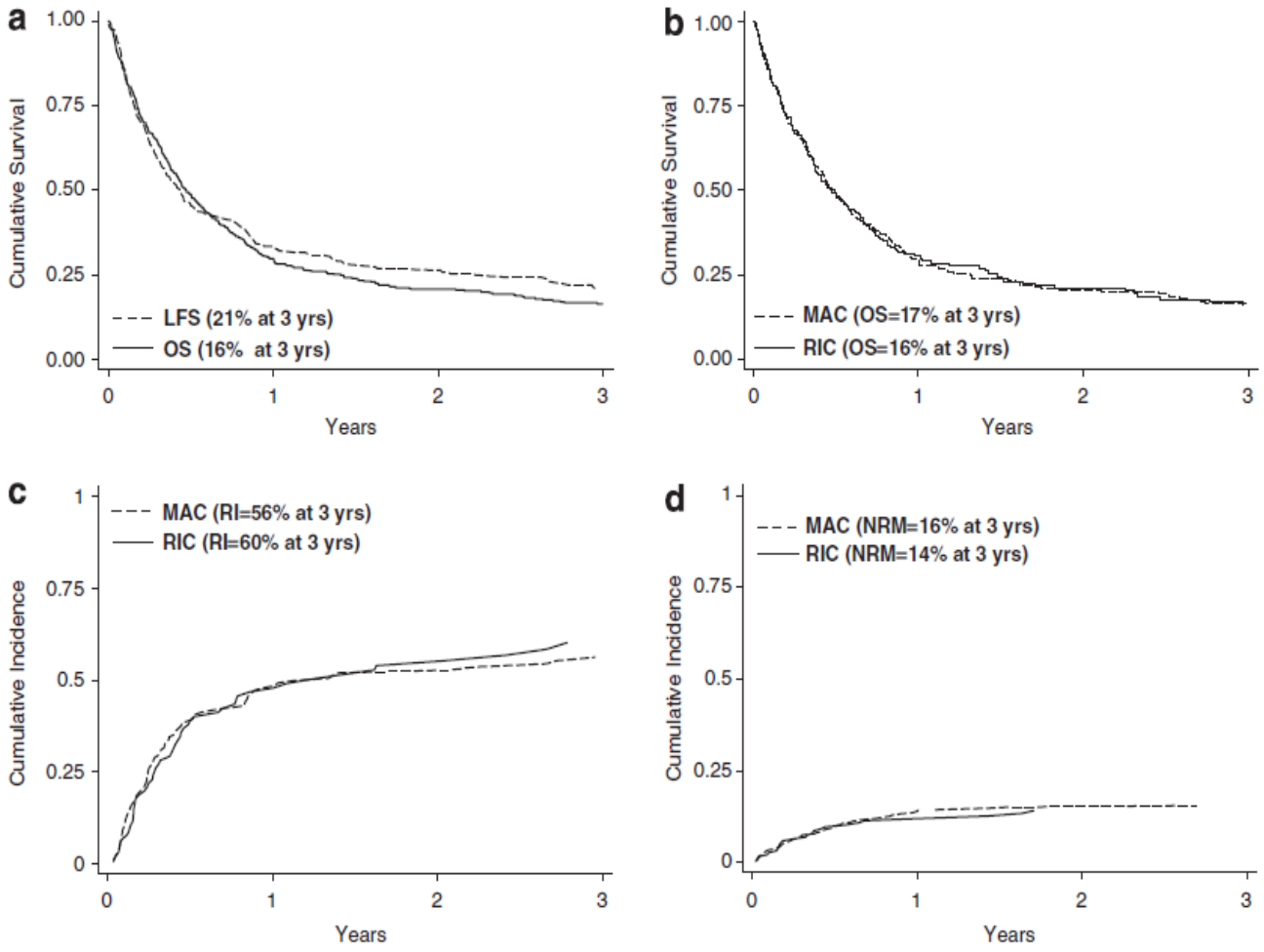


Duval, JCO 2010

Conventional approach

Inclusion period	1999-2009
Median age	47y
Donor	MRD/MUD/Haplo/CB
CTX	MAC and RIC (40%)
Stem cell	PBSC 65%
T-cell depletion	ATG 40%
AML refractory to 2 IC	**REF2 32%**

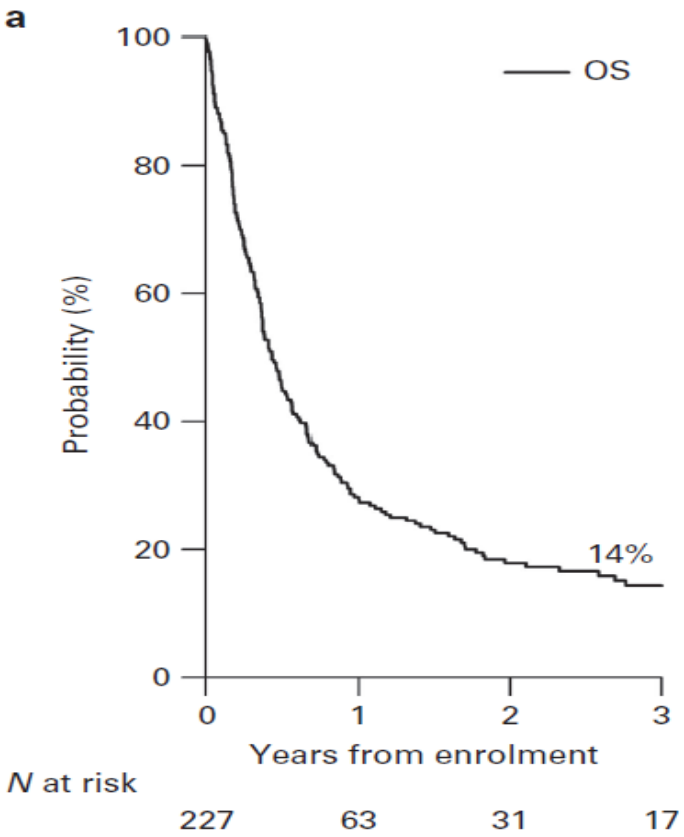


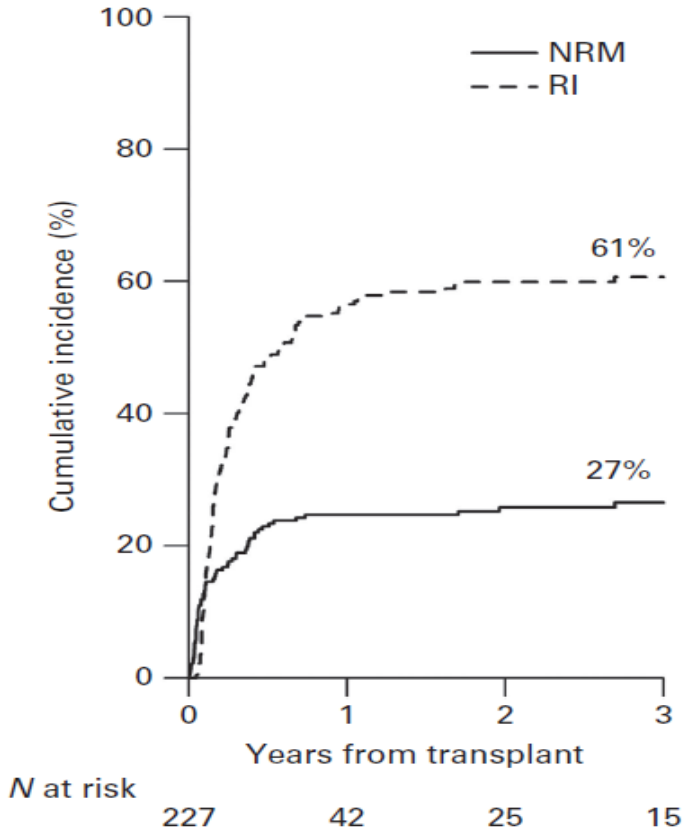


Todisco, Leukemia 2013

Conventional approach

Inclusion period	1999-2012
Median age	49y
Donor	MRD/MUD/Haplo/CB
CTX	MAC and RIC (31%)
Stem cell	PBSC 65%
T-cell depletion	ATG 50%
AML refractory to 2 IC	**REF2 100%**

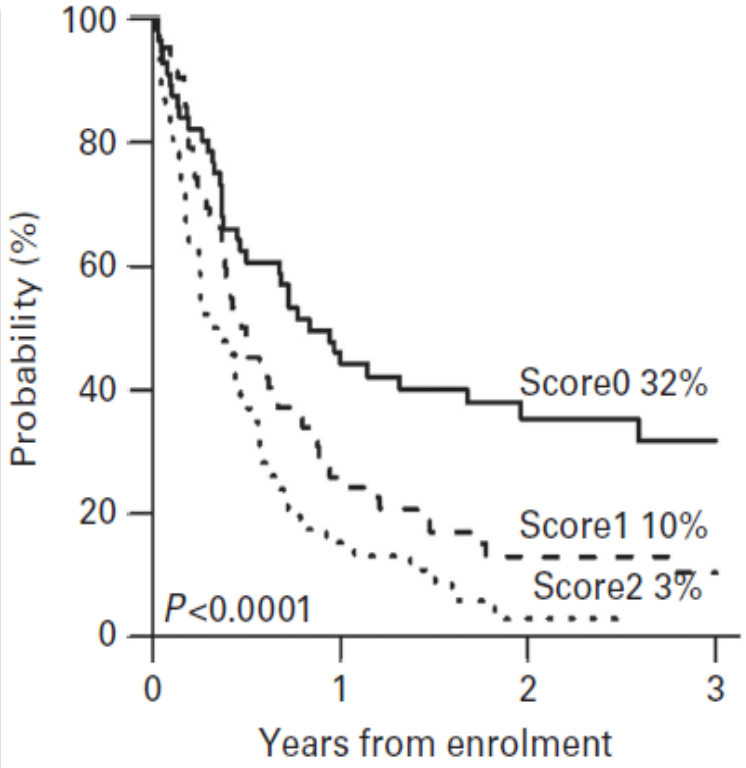




Todisco, BMT 2017

Conventional approach

Score variables	Score	Data available	*N* (%)
Chemotherapy cycles		220	
≤2	0		122 (55)
>2	1		98 (45)
Blast infiltration		197	
BM<25% or no PB	0		78 (40)
BM≥25% or any PB	1		119 (60)
Age		227	
≤60	0		187 (82)
>60	1		40 (18)
Cytogenetics/ Molecular biology		191	
Favorable/Intermediate I	0		81 (42)
Intermediate II /Adverse	1		110 (58)

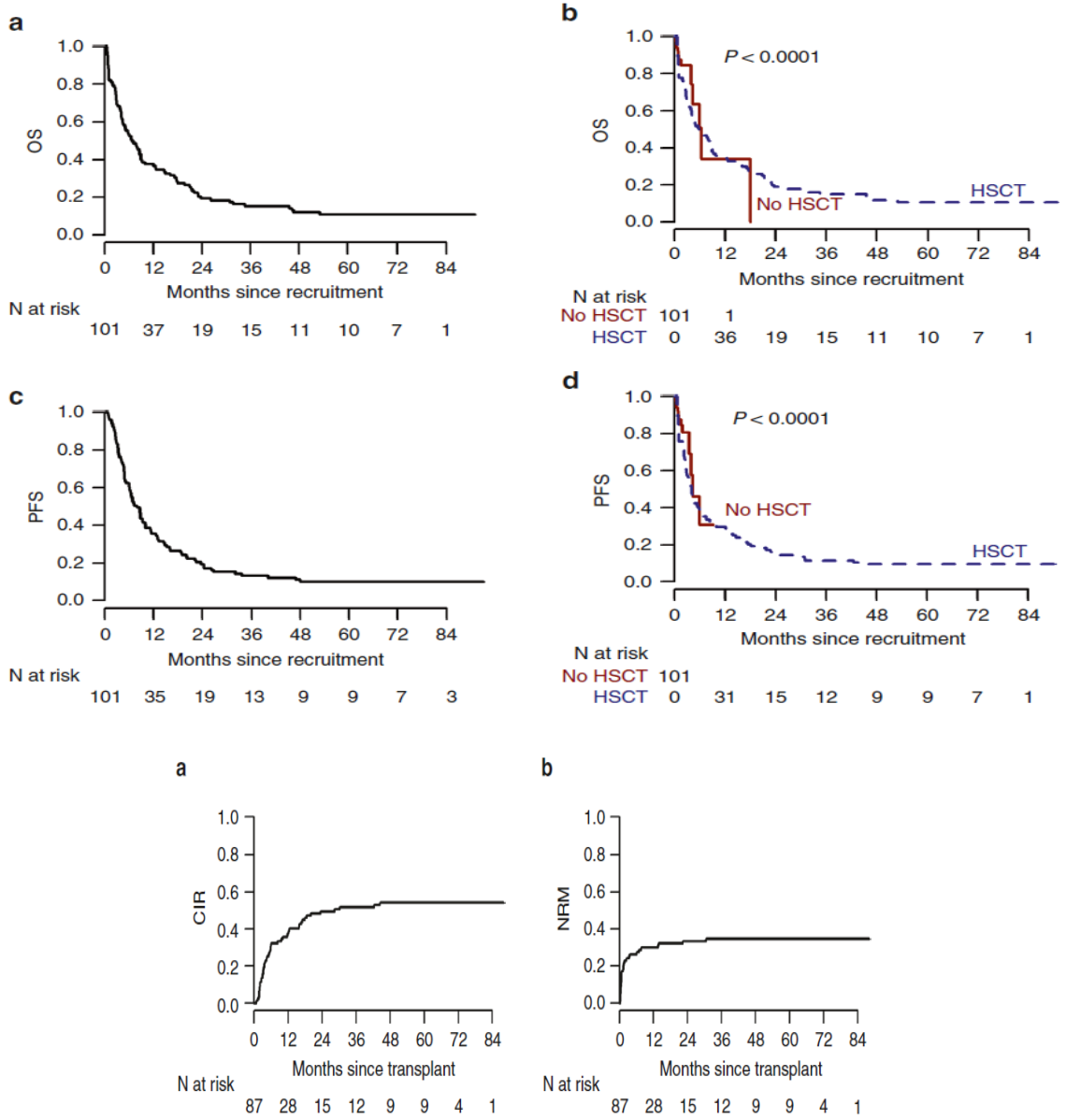


Score	Risk factor	*N*=165	HR (95% CI)	*P*	OS at 3 years
0	0-1	56 (34)			32%
1	2	63 (38)	1.73 (1.13-2.63)	0.0112	10%
2	3-4	46 (28)	2.62 (1.68-4.10)	<0.0001	3% 2 Yrs

Todisco, BMT 2017

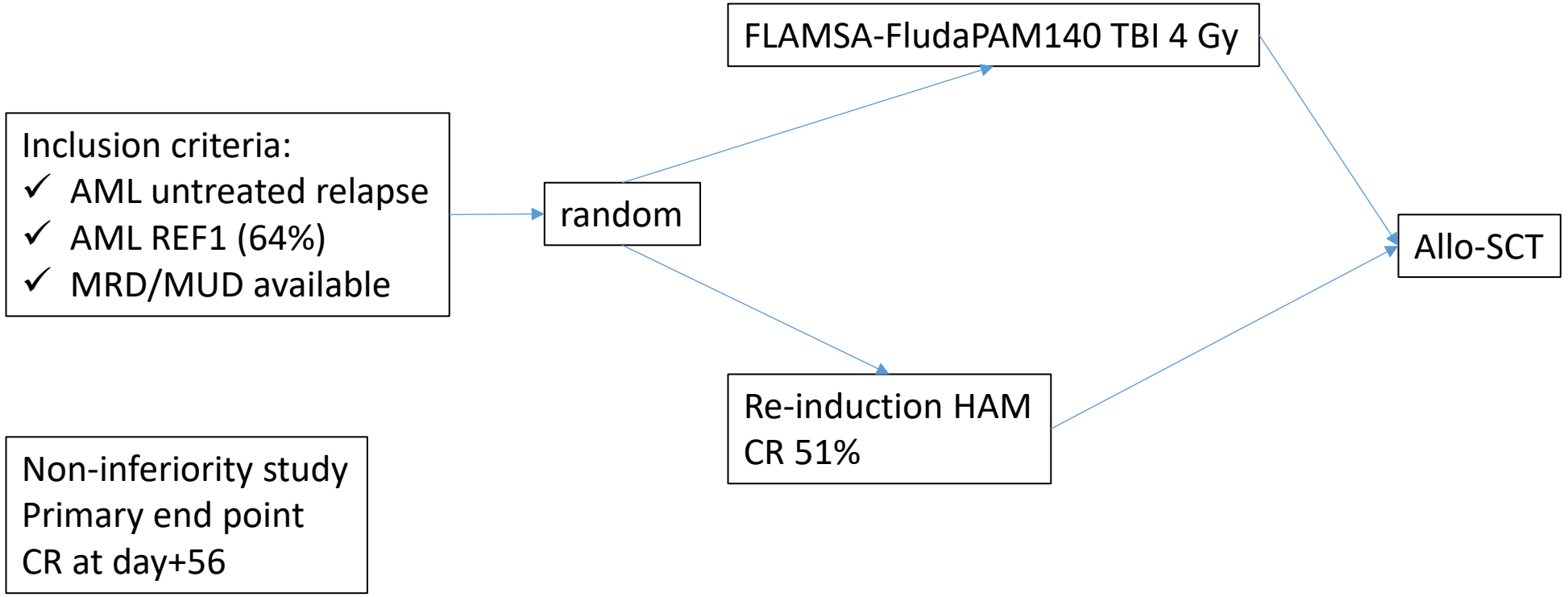
Conventional approach

Inclusion period	2013 N= 101
Median age	54y
Donor	MUD/Haplo/CB
CTX	MAC (TBF MAC 94%)
Stem cell	PBSC 50%
T-cell depletion	ATG 62%
AML refractory to 2 IC	**REF2 47%**



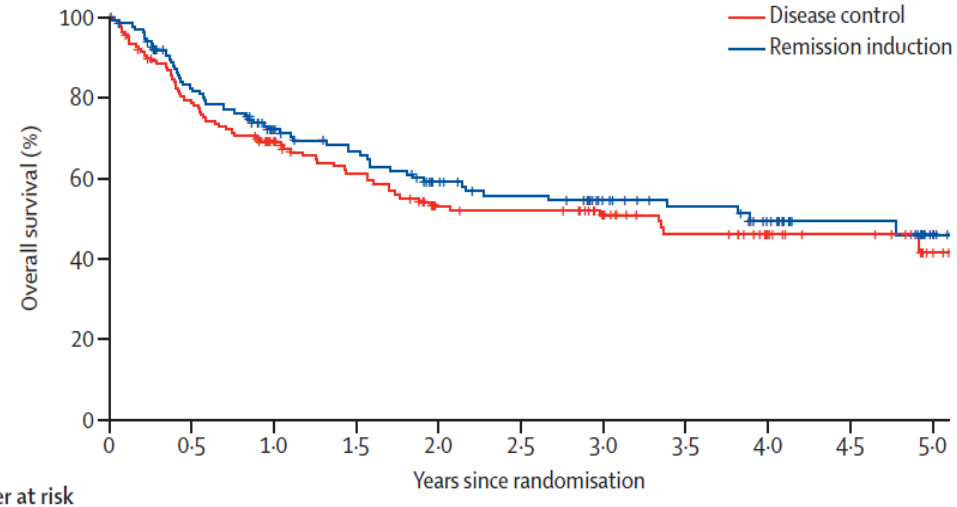
Bonifazi, BMT 2022

ALLO in refractory AML: ASAP trial

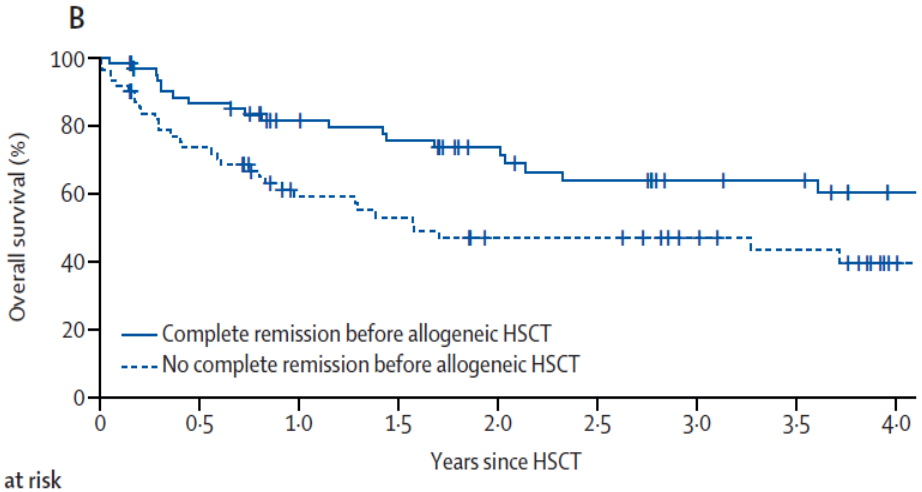


Stelljes, Lancet Haematol 2024

ALLO in refractory AML: ASAP trial



Number at risk (number censored)											
Disease control	140	106	83	69	51	49	41	29	21	14	5
	(0)	(5)	(15)	(20)	(29)	(30)	(37)	(46)	(54)	(61)	(69)
Remission induction	141	105	82	71	56	49	39	32	24	14	6
	(1)	(13)	(23)	(28)	(35)	(39)	(48)	(54)	(60)	(70)	(77)



Number at risk (number censored)									
Complete remission	65	52	42	38	31	26	20	19	11
	(0)	(5)	(12)	(13)	(19)	(20)	(26)	(27)	(34)
No complete remission	63	44	29	26	20	20	15	12	4
	(0)	(3)	(10)	(10)	(13)	(13)	(18)	(20)	(27)

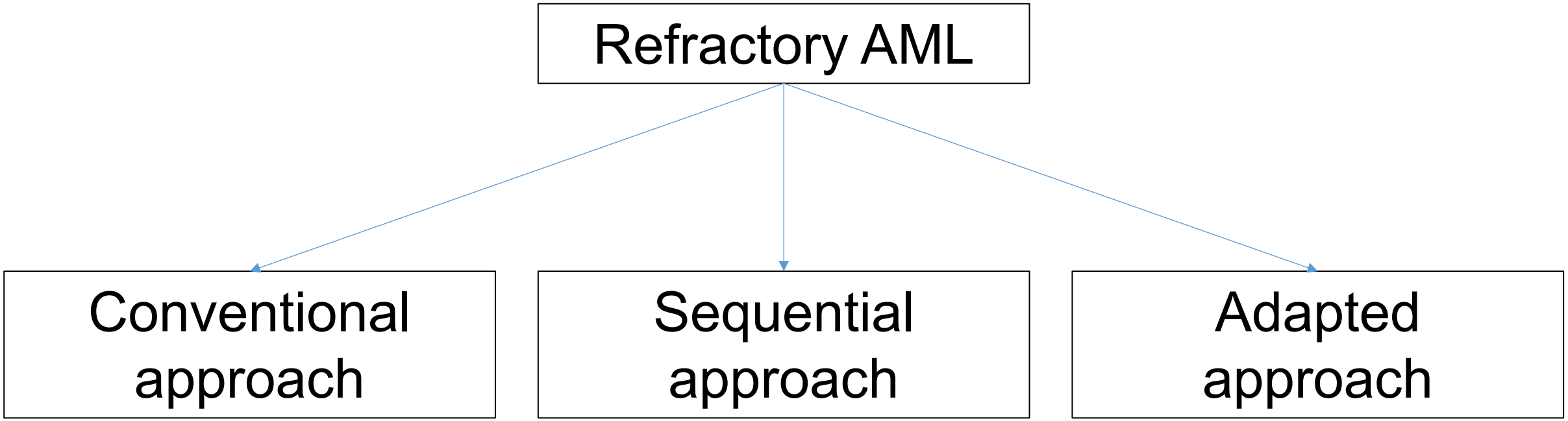
Stelljes, Lancet Haematol 2024

Conventional approach

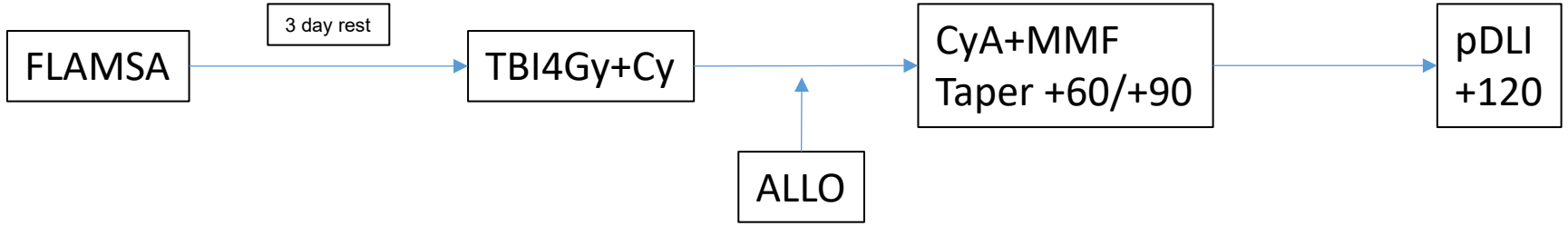
	N	Age	Inclusion criteria	% blasts (median)	Donor type	Conditioning	pDLI	CIR	LFS	OS	NRM
Duval 2010	1673	38	PIF, untreated, Refractory, relapse	21%	MRD/MUD	MAC	No	NR	NR	19%	38%
Craddock 2011	168	40	PIF	38%	MUD	MAC/RIC	No	NR	20%@5y	22%@5y	NR
Hemmati 2014	131	52	PIF and relapse	22%	MRD/MUD	MAC/RIC FLAMSA-RIC (21%)	Yes	48%@5y	25%@5y	/	26%@3y
Liu 2015	133	40, 30 21	PIF and relapse	26%	MRD/MUD Haplo	MAC	No	NR	36%@3y	40%@3y	19%@3y
Nagler 2015	852	43 39	PIF and relapse	20% 16%	MRD/MUD	BUCY TBICY	No	53%@2y 54%@2y	25%@2y 28%@2y	31%@2y 33%@2y	21%@2y 17%@2y
Todisco 2017	227	49	PIF	>25%	MRD/MUD Haplo CB	MAC 69% RIC 31%	No	61%@3y	23%@y	14%@3y	27%@3y
Nagler 2022	3430	55	PIF and relapse	NR	MRD/MUDHaplo	MAC 54% RIC 46% FLAMSA-RIC 13%	no	48%@2y	28%@2y	36%@2y	24%@2y
Baron 2022	219	56	PIF and relapse	NR	mMUD Haplo	MAC/RIC	no	40%@2y 50%@2y	42%@2y 26%@2y	46%@2y 28%@2y	18%@2y 24%@2y
Yanada 2023	6927	53	PIF and relapse	NR	MRD/MUD CB	MAC 67% RIC 33%	no	53%@5y	NR	23%@5y	27%@5y

Bono, Cells 2024

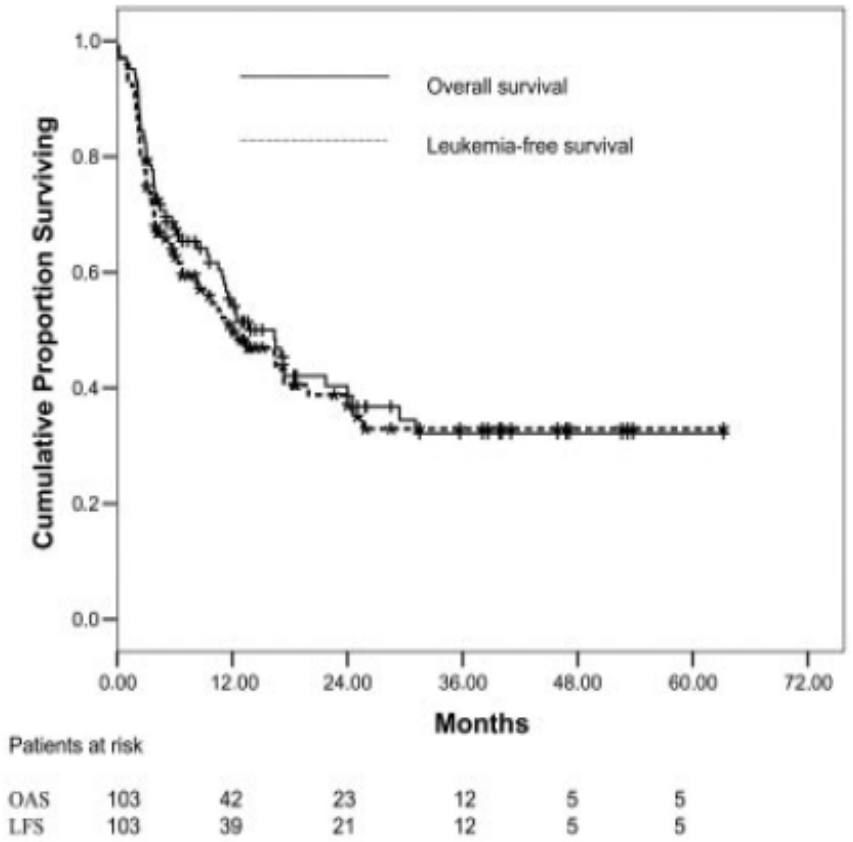
How to approach refractory AML

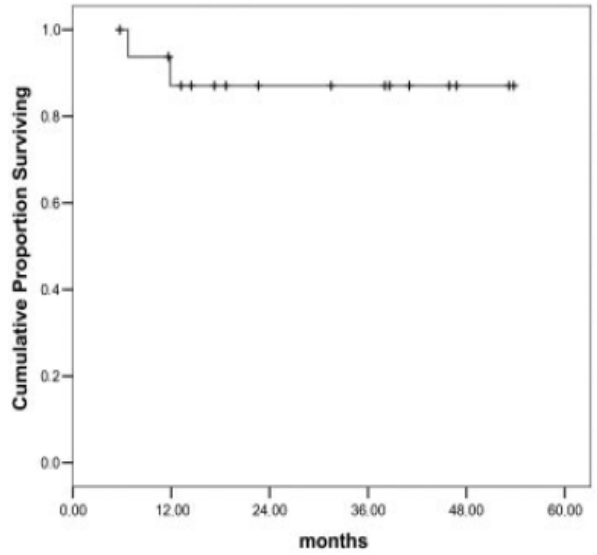


Sequential approach



	2005	2006
N	75	103
Median age	52y	51y
Donor	MRD/MUD	MRD/MUD
Stem cell	PBSC	PBSC
T-cell depletion	ATG MUD	ATG MUD
Inclusion criteria	**REF1 REL <3M REL >2 AREB2**	**REF1/2 REL <6M REL >2**
Typing HLA I	Serologic	serologic

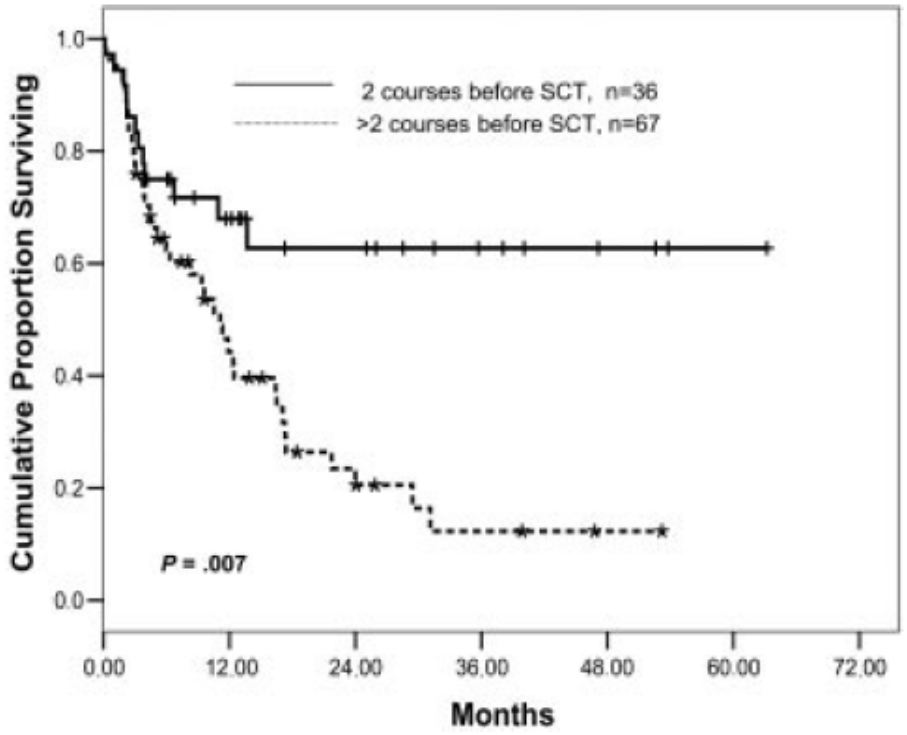




Schmid, JCO 2005, Blood 2026

Sequential approach

	Overall survival		Leukemia-free survival	
	Univariate	Multivariate (HR)	Univariate	Multivariate (HR)
Stage at SCT, PIF vs other	.017	NS	.006	NS
No. of chemotherapy cycles before SCT, 2 vs more than 2	.008	.007 (3.01)	.008	.002 (3.25)
BM infiltration by leukemic blasts at SCT, less than or greater than 50%	.07	NS	.09	NS
Time from diagnosis to SCT, less than or greater than median	.011	NS	.008	NS
$CD34^+$ cell counts in the graft, less than or greater than median	.028	.047 (2.00)	.02	.05 (1.8)



Schmid, Blood 2026

Sequential approach: retrospective studies

	N	Age	Inclusion criteria	% blasts (median)	Donor	Sequential CT	Rest	Conditioning	pDLI	CIR	OS	LFS	NRM
Ringden 2017	267	51	PIF and relapse	NR	MRD/MUD	FLAMSA	3d	TBI4Gy, Cy BU-based PAM	no	48%@3y	30%@3y	26%@3y	26%@3y
Dulery 2018	72	54	PIF, first/second relapse	NR	MRD/MUD haplo	TEC	3d	BU6.4FLU	**yes**	38%@2y	57%@2y	NR	24%@2y
Steckel 2018	292	56	Primary refractory Untreated relapse	32%	MRD/MUD	PAM140	5d	TBI8Gy/FLU TREO/FLU	no	34%@1y	34%@3y	31%@3y	36%@1y
Saraceni 2019	856	51-58	PIF and relapse	NR	MRD/MUD	FLAMSA / /	NR	BU/TBI-based TREO/FLU TBF	no	53%@2y 46%@2y 54%@2y	34%@2y 37%@2y 24%@2y	27%@2y 22%@2y 29%@2y	20%@2y 26%@2y 24%@2y
Rodrìguez-Arbolì, 2020	1018	39	PIF and relapse	NR	MRD/MUD	FLAMSA	NR	TBI-based CT-based MAC	no	55%@2y 53%@2y 51%@2y	36%@2y 50%@2y 33%@2y	27%@2y 40%@2y 30%@2y	18%@2y 7%@2y 19%@2y
Le Bourgeois 2020	131	52	PIF and relapse	NR	MRD	ClofaARAC	3d	BU9.6CY	no	45%@2y	38%@2y	29%@2y	35%@2y
Sockel 2022	173	56	Relapse (36%) first line	10%	MRD/MUD haplo	ClofaARAC	/	FLU-PAM Clofa-PAM	no	30%@4y	43%@4y	NR	36%@4y
Guijarro 2022	140	55	PIF or relapse	20%	MRD/MUD haplo	FLAG-IDA	3d	PAM140 mg/m^2	no	30%@5y	25%@5y	NR	45%@5y
Weller 2022	114	60	PIF or relapse	17%	MRD/MUD haplo	FLAMSA	3d	RIC	**yes**	41%@2y	45%@2y	46%@2y (no DLI) 70%@2y (DLI)	27%@2y

Bono, Cells 2024

Sequential approach: prospective studies

	N	Median age	Inclusion criteria	% blasts at ALLO	CR	Sequential	Rest	CTX	Donor	GVHD prophylaxis	IS tapering	Prophylactic DLI	CIR	OS	LFS	NRM
Schmid 2005	75	52y (18-65)	No response to HD ARAC Relapse 3 M after CR Second relapse Delayed response to IC Relapse after auto Secondary AML/MDS	NR	11%	FLAMSA-RIC*	3 days	TBI4Gy, Cy	MRD 49% MUD 51%	CSA day -1 MMF Day 0 ATG	CSA day +60 to 90 MMF day +50	Yes 24% Day +120 Median day +160	20%	42%@2y	40%@2y	33%@1y
Schmid 2006	103	51y (18-68)	PIF after ≥2 IC Relapse 6 M after CR Refractory to salvage IC ≥2nd relapse	30% (0-90%)	4%	FLAMSA-RIC*	3 days	TBI4Gy, Cy	MRD 40% MUD 60%	CSA day -1 MMF Day 0 ATG	CSA day +60 to 90 MMF day +50	Yes 24% Day +120 Median day +159	37%	40@2y	39%@2y	17%@1y
Middeke 2016	84	61y (40-75)	PIF after ≥2 IC Relapsed	54% (5-92%)	None	ClofaARAC	ALLO in aplasia	ClofaPAM	MRD 18% MUD 54% mMUD29%	CSA day -1 MMF Day 0 ATG	Not reported	No	26%@2y	43@2y	DFS 52%	23%@2y
Jaiswal 2016	41	26y (2-65)	PIF after ≥2 IC Relapsed refractory	14-16% (5-65%)	None	no	/	BUFLUPAM	Haplo	PTCY CSA day +5 MMF day +5	CSA day +60 MMF from +14 to +21	Yes 90% Day +21, +35, +60	43% 21% with DLI	53%@18 M 70% with DLI 35% w/out	44%@18 M 62% with DLI 25% w/out	19%@1y
Mohty 2017	24	47y (20-57)	PIF after 2 IC Persisting hypoplasia	20% (6-82%)	None	ClofaARAC-RIC§	3 days	BUCY	MRD 63% UD 37%	CSA day -1 MMF Day 0 ATG	CSA day +90 MMF +62 to 90	Yes 25% Day +120	54%@2y	38%@2y	29%@2y	12%@2y
Davies 2018	47	53y (23-68)	PIF after 1 IC Relapse 6 M after CR	NR	None	DaunoARAC-RIC	3 days	FLUCY	MRD 49% MUD 51%	CSA day -1 Short MTX	CSA day +90	No	30%@3y	39%@2y	39%@2y	35%@1y

*RIC consisted of TBI4 Gy, ATG, and cyclophosphamide

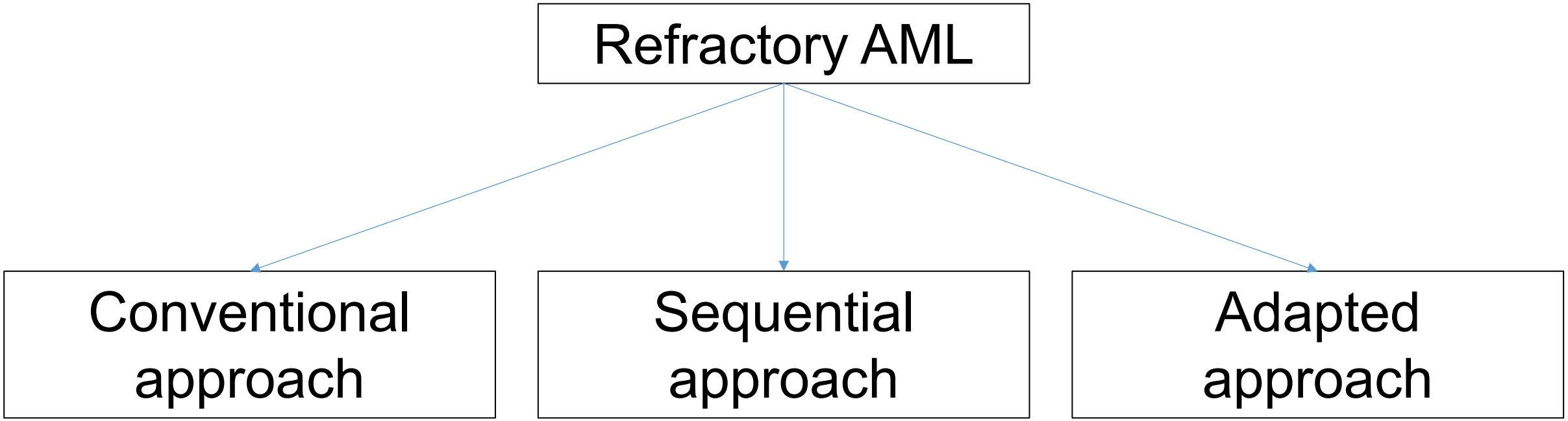
§ RIC consisted of busulfan 6.4 mg/kg + cyclophosphamide 60 mg/kg

^excluding 10 patients treated with a nonmyeloablative conditioning regimen. The MAC consisted of fludarabine 150 mg/m^2, busulfan 9.6 mg/kg, and malphalan 140 mg/m^2.

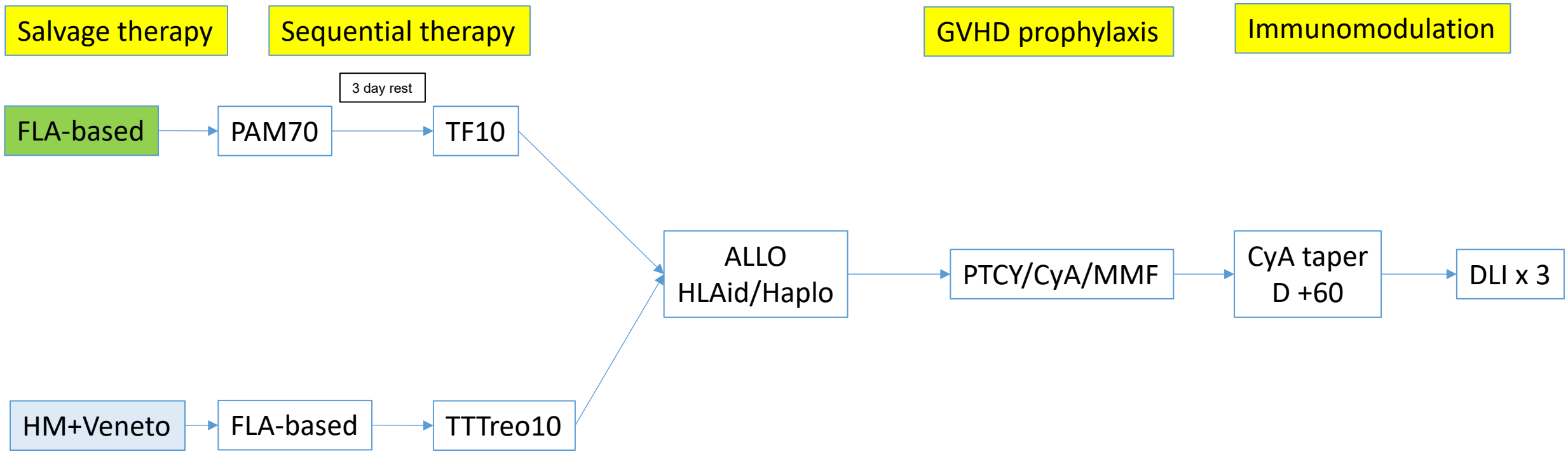
°MAC consisted of TBF (thiotepa 10 mg/kg, busulfan 9.6 mg/kg, and fludarabine 150 mg/m2)

Bono, Cells 2024

How to approach refractory AML



Adapted approach in refractory AML



Adapted approach in refractory AML

	Disease	Age	N CT lines	Last CT	Disease status at ALLO	Sequential	CTX	Donor	GVHD prophy	Taper CyA	aGVHD	Status
#1	AML FLT3ITD+, NPM1+	29	2	Aza-Veneto	Hematological CR2, MRD+	FLA-Ida	BUFLU65	HLAid sib	PTCY-based	ongoing	no	Day +90 Alive, CR, MRD-
#2	AML t(8;21)	41	2	Aza-Veneto	Active disease, blasts 25%	FLA-Ida	TTFLU65	MUD	PTCY-based	Day +93	Day +106 G3, GI No DLI	Day +338 Alive, CR, MRD- Severe cGVHD
#3	AML monosomal	60	3	FLA-Ida Aza-Veneto	Active disease, blasts 15%	PAM70	BUFLU65	Haplo	PTCY-based	NE	NE	Day +17 Dead, VOD

ALLO in refractory AML