Global Leukemia Academy

GLOBAL LEUKEMIA ACADEMY

Bridging Science and Practice: From Newest Clinical Approaches to Real-World Clinical Cases – Day 2

16–17 November 2023 – Europe

Meeting sponsors AMGEN astellas

APTITUDE HEALTH

Global Leukemia Academy

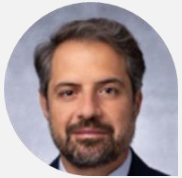
Welcome again and meeting overview

Naval Daver

APTITUDE HEALTH

Meet the Faculty

CHAIR



Elias Jabbour, MD
MD Anderson Cancer Center,
Houston, TX, USA

CO-CHAIR

Naval Daver, MD
MD Anderson Cancer Center,
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FACULTY

Nicola Gökbuget, MD
University Hospital Frankfurt
Frankfurt, Germany

Stephane De Botton, MD, PhD
Gustave Roussy Cancer Center
Paris, France

Josep-Maria Ribera, MD, PhD
Catalan Institute of Oncology
Hospital Germans Trias i Pujol
Badalona, Spain

Charles Craddock, CBE, FRCP (UK), FRCPath, DPhil
University of Birmingham
Queen Elizabeth Hospital
Birmingham, UK

Objectives of the program

Learn about the latest clinical advances and sequencing considerations for ALL and AML

Understand the role of risk stratification and the clinical usage of MRD on treatment

Gain insight on the management of ALL and AML, including AYA ALL and *FLT3*+ AML

Engage in patient case-based panel discussions

Discuss sequencing strategies for acute leukemias

Explore regional challenges in the treatment of acute leukemias across Europe

Day 2: Virtual Plenary Sessions

Time (CET)	Title	Speaker
18.00 – 18.10	Welcome to Day 2	Naval Daver
18.10 – 18.25	Frontline approaches and the role of genetic variants in ALL – Ph+ and Ph-like	Elias Jabbour
18.25 – 18.45	Current treatment options for relapsed ALL in adult and elderly patients	Josep-Maria Ribera
18.45 – 19.05	Current treatment options for relapsed AML in adult and elderly patients	Charles Craddock
19.05 – 19.35	AML case-based panel discussion • Case AML: young, high risk – Vitor Botafogo • Case AML: elderly – Justin Loke • Discussion – panelists: all faculty	Naval Daver and all faculty
19.35 – 19.45	Break	
19.45 – 20.05	Long-term safety considerations for AML and ALL	Stephane De Botton
20.05 – 20.35	Current and future role of transplantation in acute leukemias (including regional insights) • AML – Charles Craddock • ALL – Nicola Gökbuget • Discussion	Charles Craddock and Nicola Gökbuget
20.35 – 21.05	Panel discussion: How treatment in first line influences further treatment approaches in ALL and AML • Will CAR T and bispecifics change the landscape? • Role of HSCT – is it still confirmed? • What does the future look like?	Elias Jabbour and all faculty
21.05 – 21.15	Session close	Elias Jabbour and Naval Daver

Question 1

What age group is considered elderly for AML patients?

A. ≥50 years
B. ≥55 years
C. ≥60 years
D. ≥65 years
E. ≥70 years

Question 2

How do you assess for minimal residual disease (MRD) for ALL?

A. Multicolor flow
B. Molecular PCR
C. Next-generation sequencing platform
D. We do not check for MRD

Question 3

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. ALK inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. CAR T approaches are active beyond second line in Ph– ALL

Question 4

The prognosis of R/R AML patients depends on:

A. Age
B. Prior therapy (eg, HSCT)
C. Timing of relapse
D. The mutational and cytogenetic profile of the disease
E. All of the above
F. A and D

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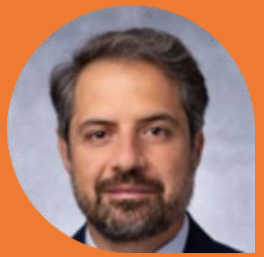
Frontline approaches and the role of genetic variants in ALL – Ph+ and Ph-like

Elias Jabbour



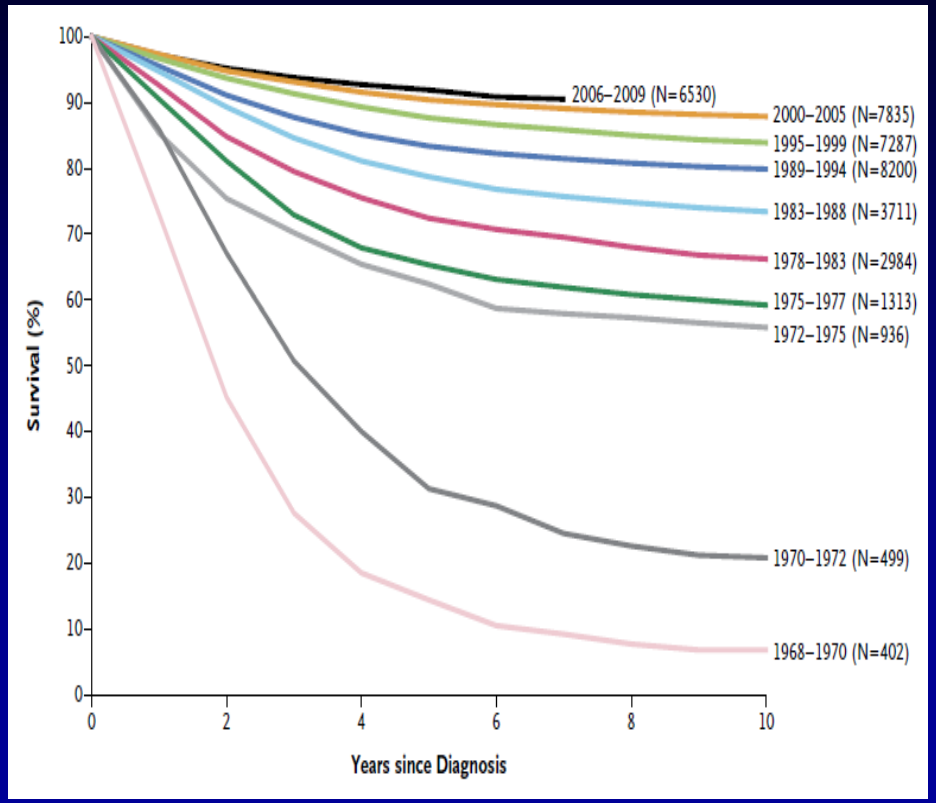
APTITUDE HEALTH

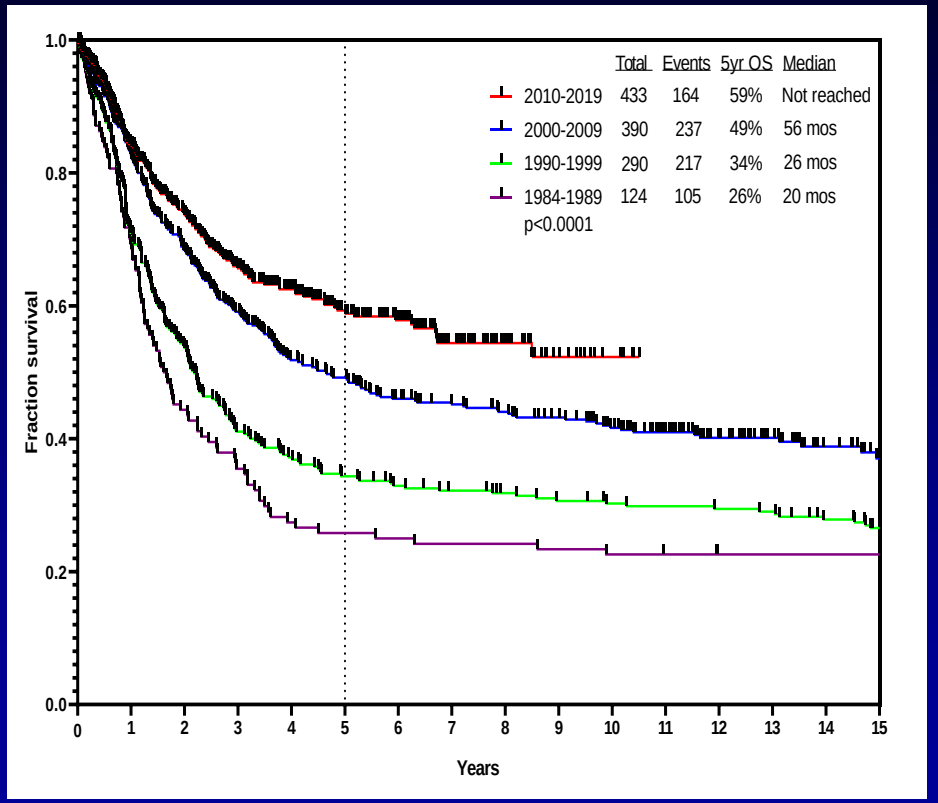
Integration of Immunotherapy in the Management of Frontline Acute Lymphocytic Leukemia: Ph+ and Ph-Like Variants

Elias Jabbour, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, TX

GLA 2023

Survival in Pediatric and Adult ALL With Classical Intensive ChemoRx Regimens





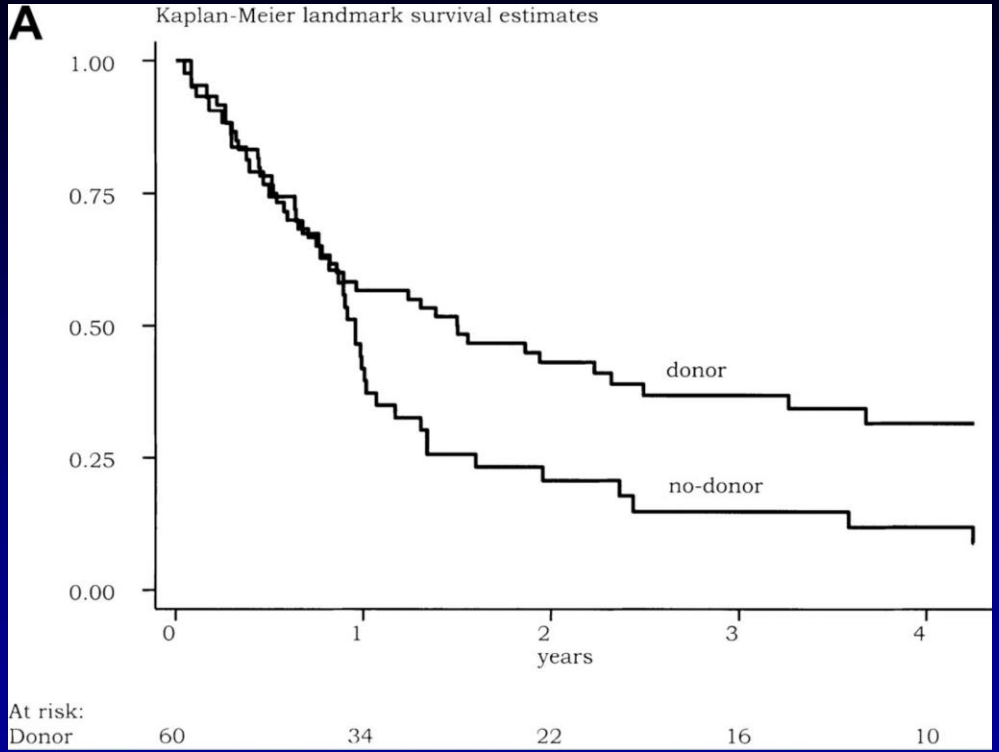
Hunger et al. *N Engl J Med.* 2015;373(16):1541-1552.

Kantarjian H, et al. *Cancer.* 2022;128:240-259.

Reasons for Recent Success in Adult ALL

- Addition of TKIs (ponatinib) ± blinatumomab to chemoRx in Ph+ ALL
- Addition of rituximab to chemoRx in Burkitt and pre-B ALL
- Addition of CD19 bispecific T-cell engager (BiTE) antibody blinatumomab, and of CD22 monoclonal antibody drug conjugate (ADC) inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR T-cell therapy
- Importance of MRD in CR (at CR vs 3 mos; NGS)

SCT for Ph+ ALL: Pre-TKI



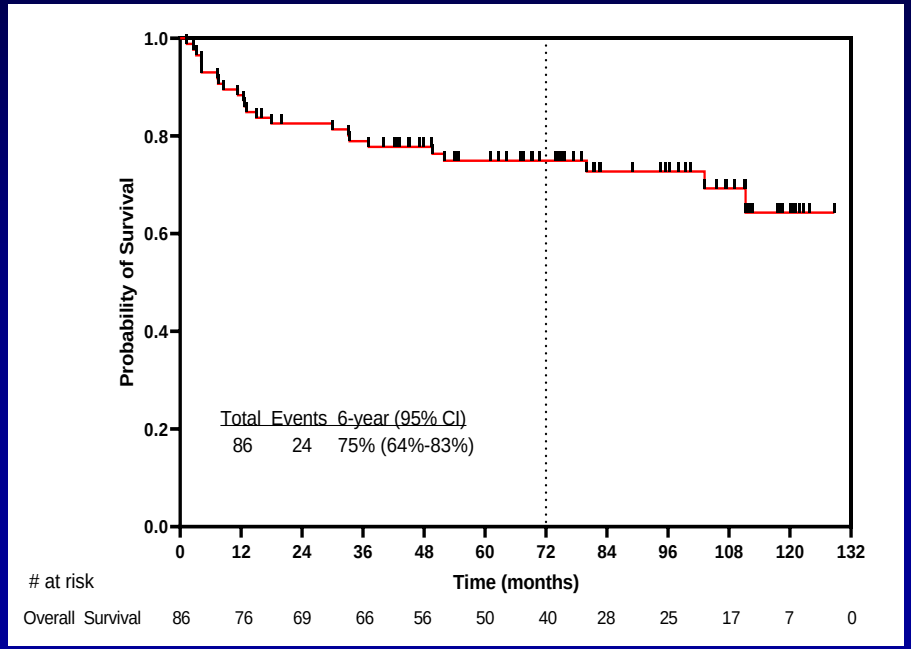
- Donor (n = 60) – 3-year OS: 37%
- No donor (n = 43) – 3-year OS: 12%

Dombret H, et al. *Blood.* 2002;100(7):2357-2366.

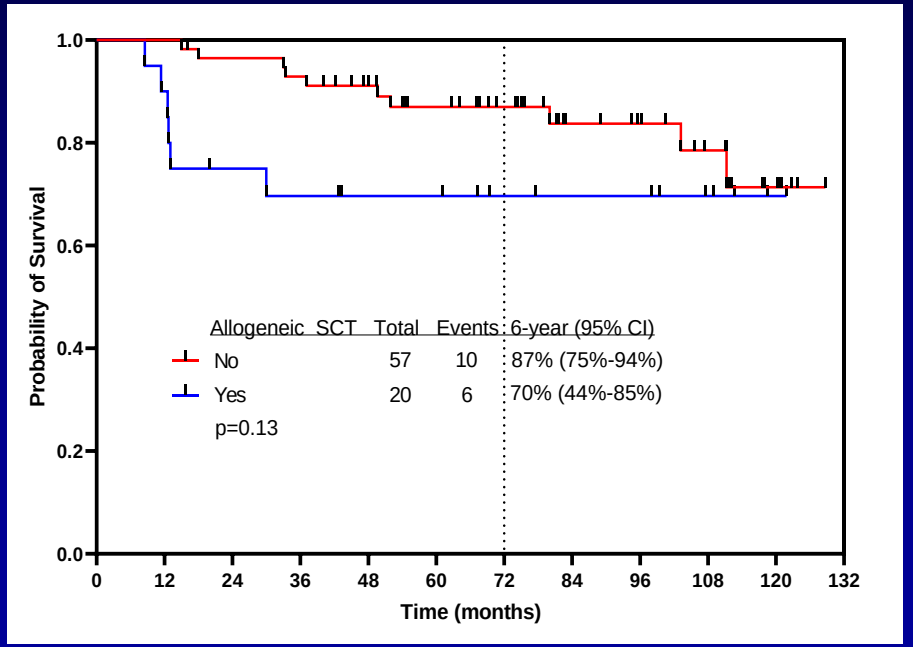
Hyper-CVAD + Ponatinib in Ph+ ALL: Long-Term FU of More Than 6 Years

- 86 pts Rx; median age 47 yr (39–61); median FU 80 mo (61–109)
- CR 68/68 (100%); FCM MRD negative 85/86 (99%); CMR 84%; 6-yr OS 75%, EFS 65%

OS

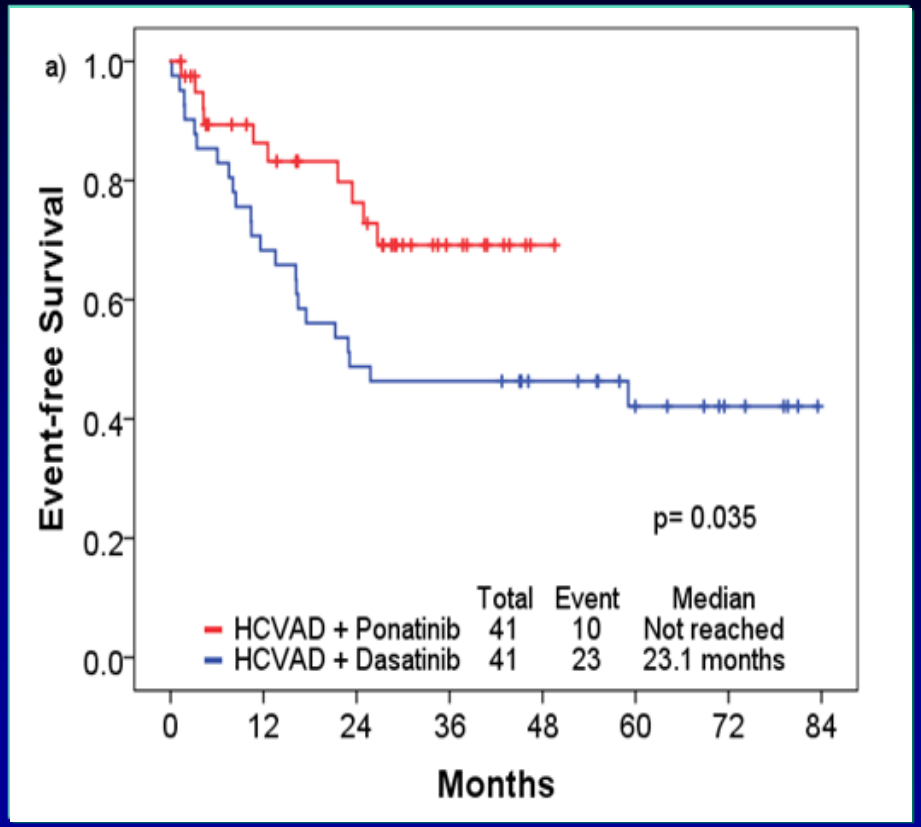


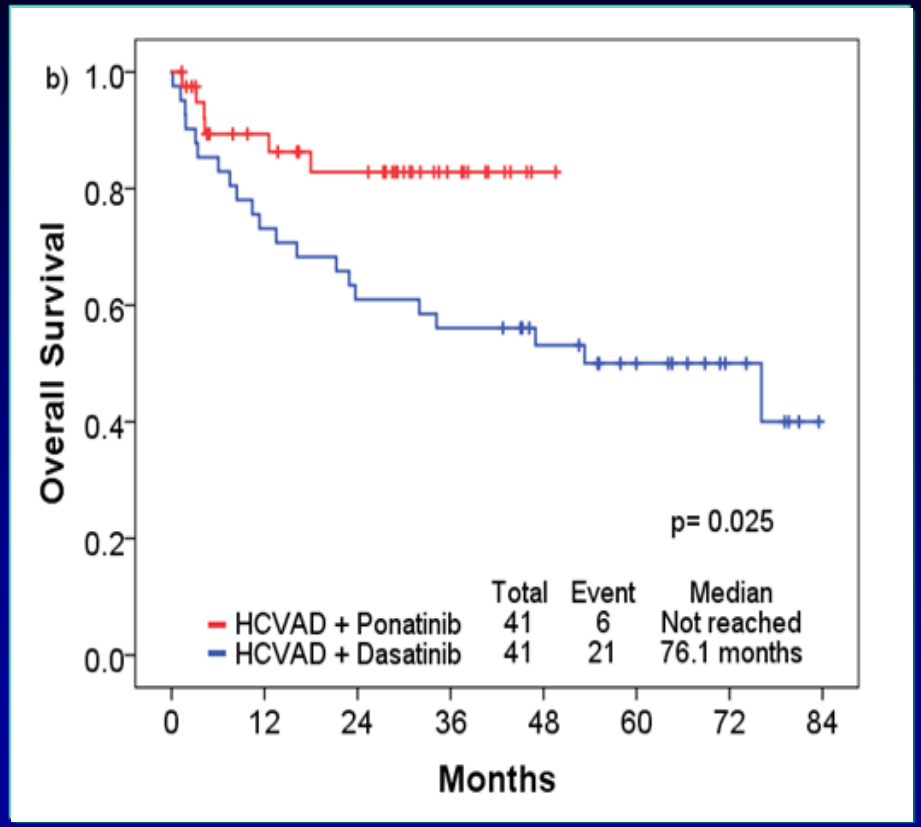
6-Mos Landmark



Kantarjian H, et al. *Am J Hematol.* 2023;98(3):493-501.

Propensity Score Analysis: HCVAD + Ponatinib vs HCVAD + Dasatinib in Ph+ ALL

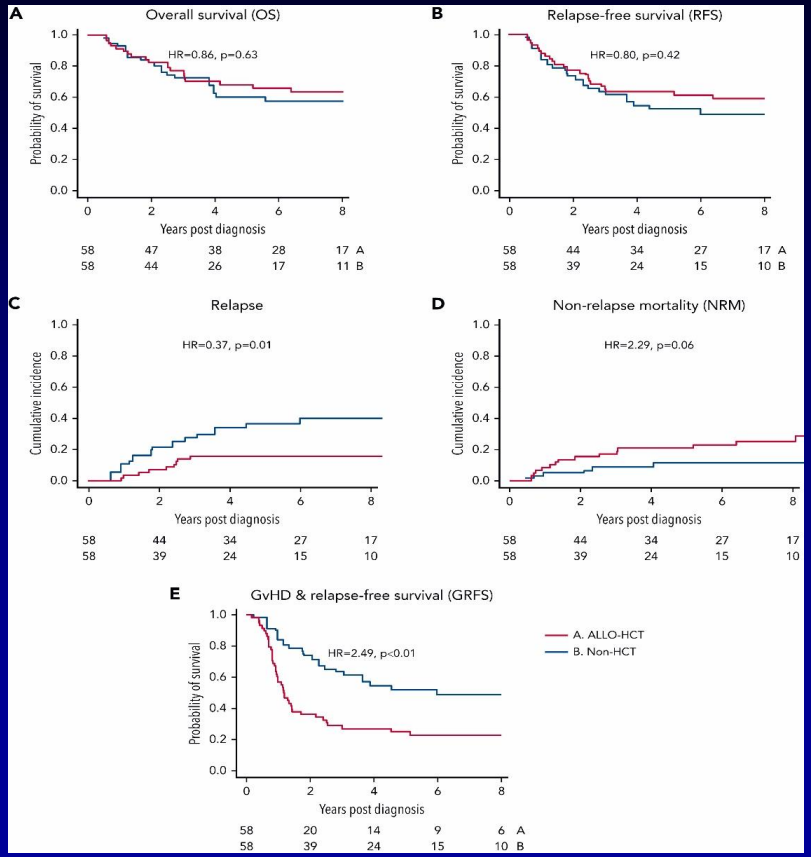




Sasaki et al. *Cancer.* 2016;122(23):3650-3656.

No Benefit of Allogeneic SCT in Patients With Ph+ ALL Who Achieve CMR

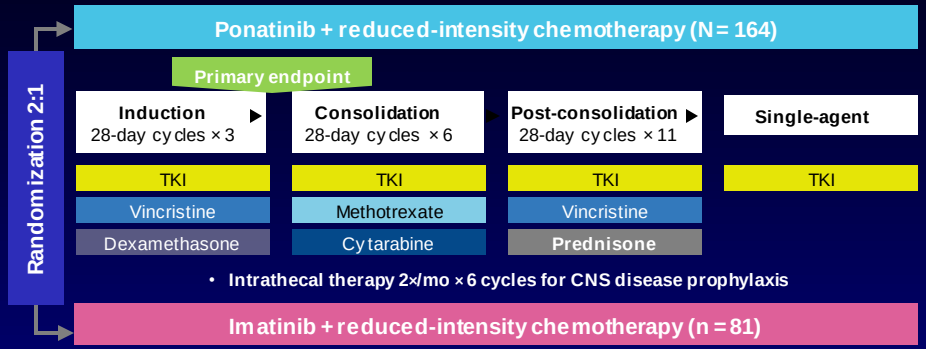
- Propensity score analysis of patients who achieved CMR within 3 months
- Allogeneic SCT → lower risk of relapse but higher NRM
- No impact of SCT on OS or RFS



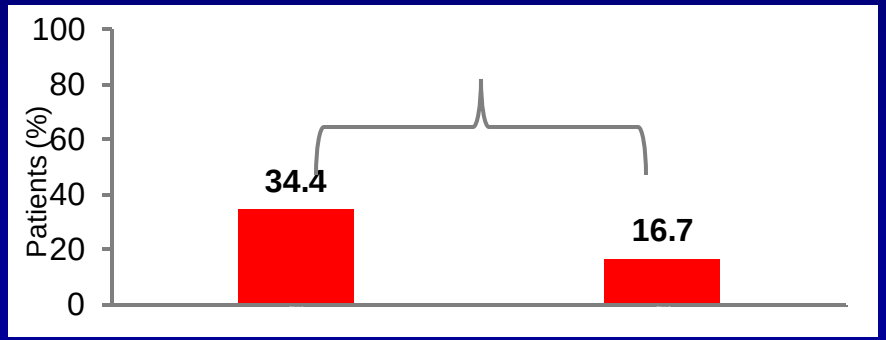
Ghobadi A, et al. *Blood.* 2022;140(20):2101-2112.

Ponatinib vs Imatinib With Low-Dose ChemoRx in Ph+ ALL: PhALLCON

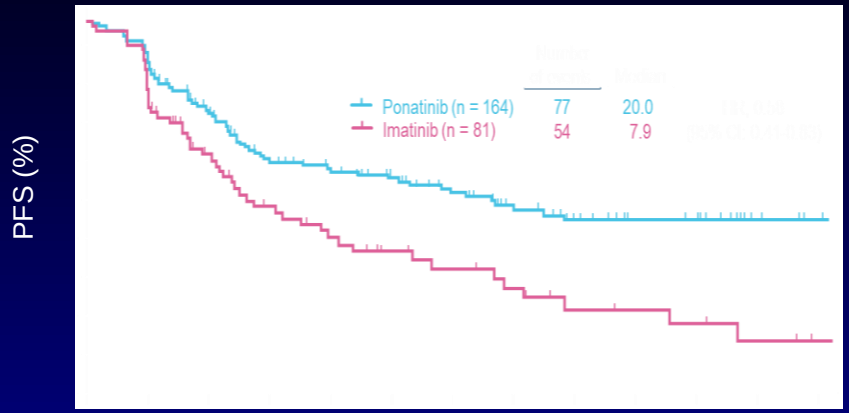
Study design



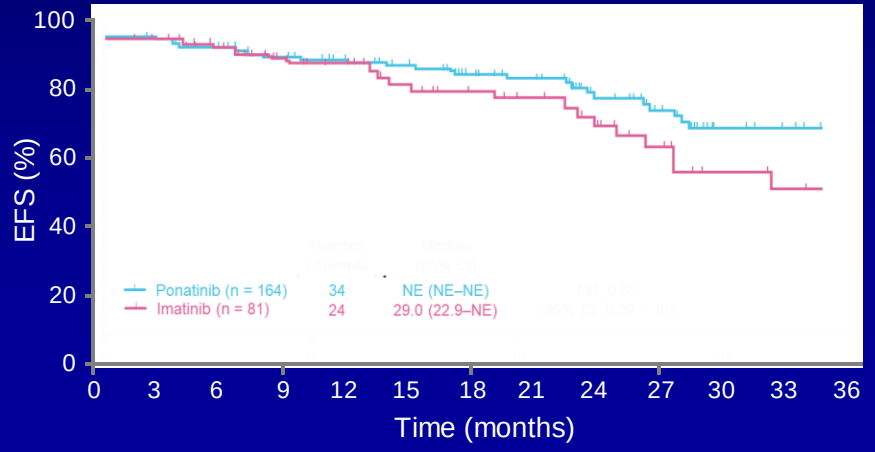
Primary endpoint:
MRD– (MR4) CR at end of induction
RR: 2.06 (95% CI = 1.19–3.56); *P* = .0021



PFS



EFS

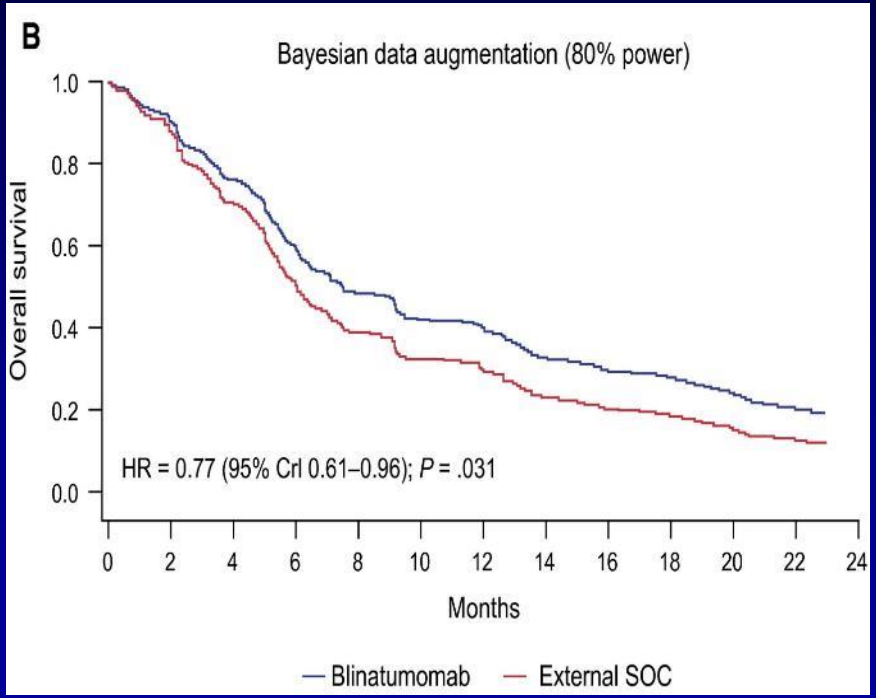


Jabbour E, et al. *HemaSphere*. 2023;7:abstract S110.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

Blina vs SOC

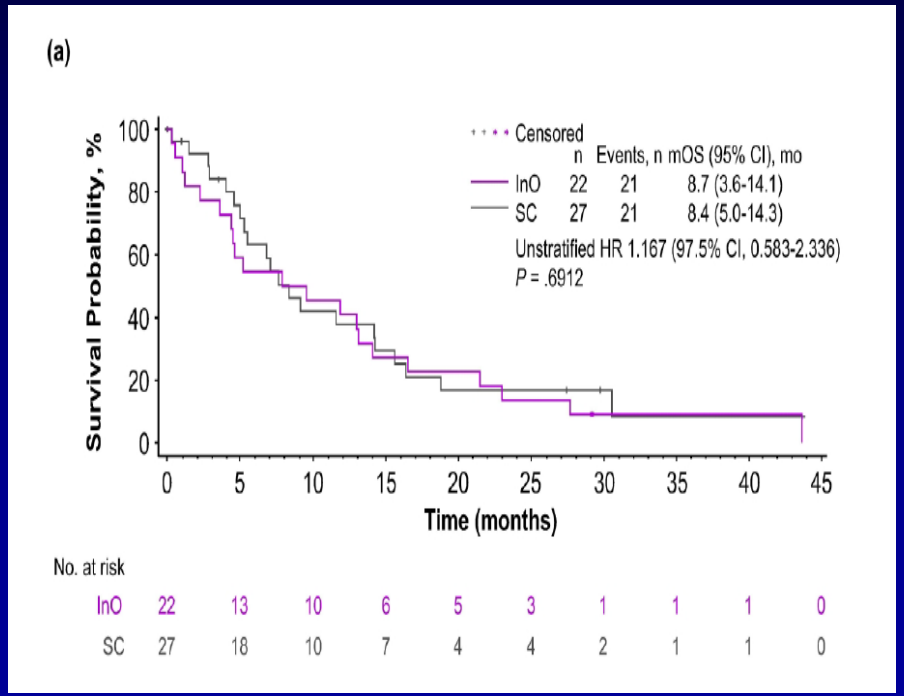
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



Rambaldi et al. *Cancer.* 2019;126:304-310.

Ino vs SOC

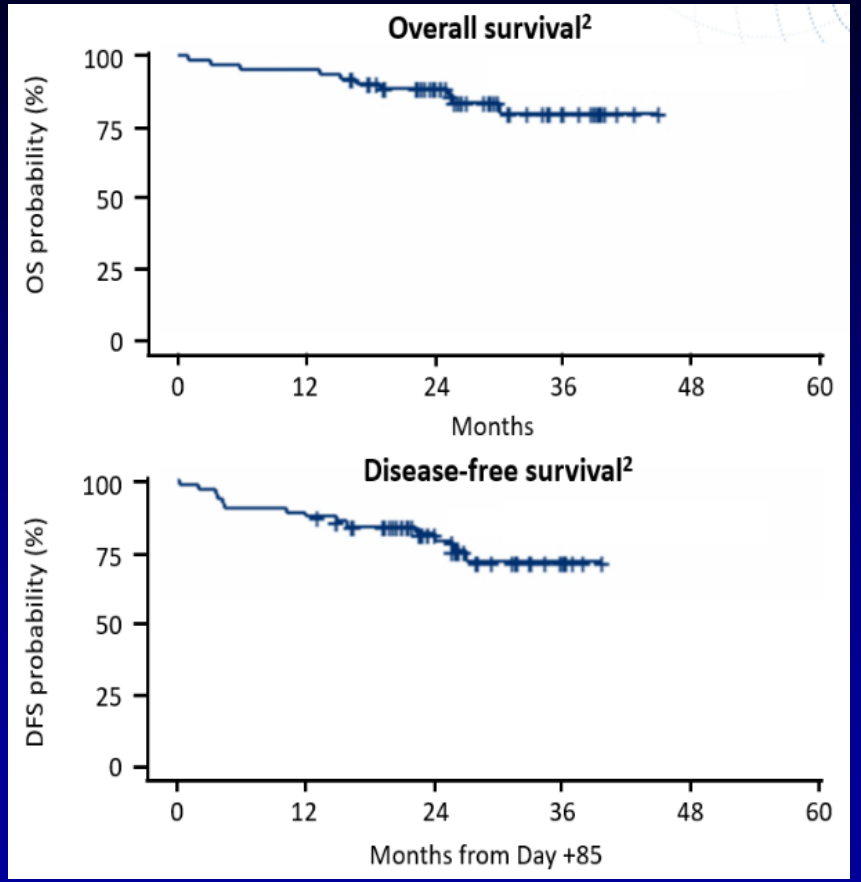
- CR/CRi 73% vs 56%
- 1-yr PFS 20% vs 4.8%



Stock W, et al. *Cancer.* 2020;127(6):905-913.

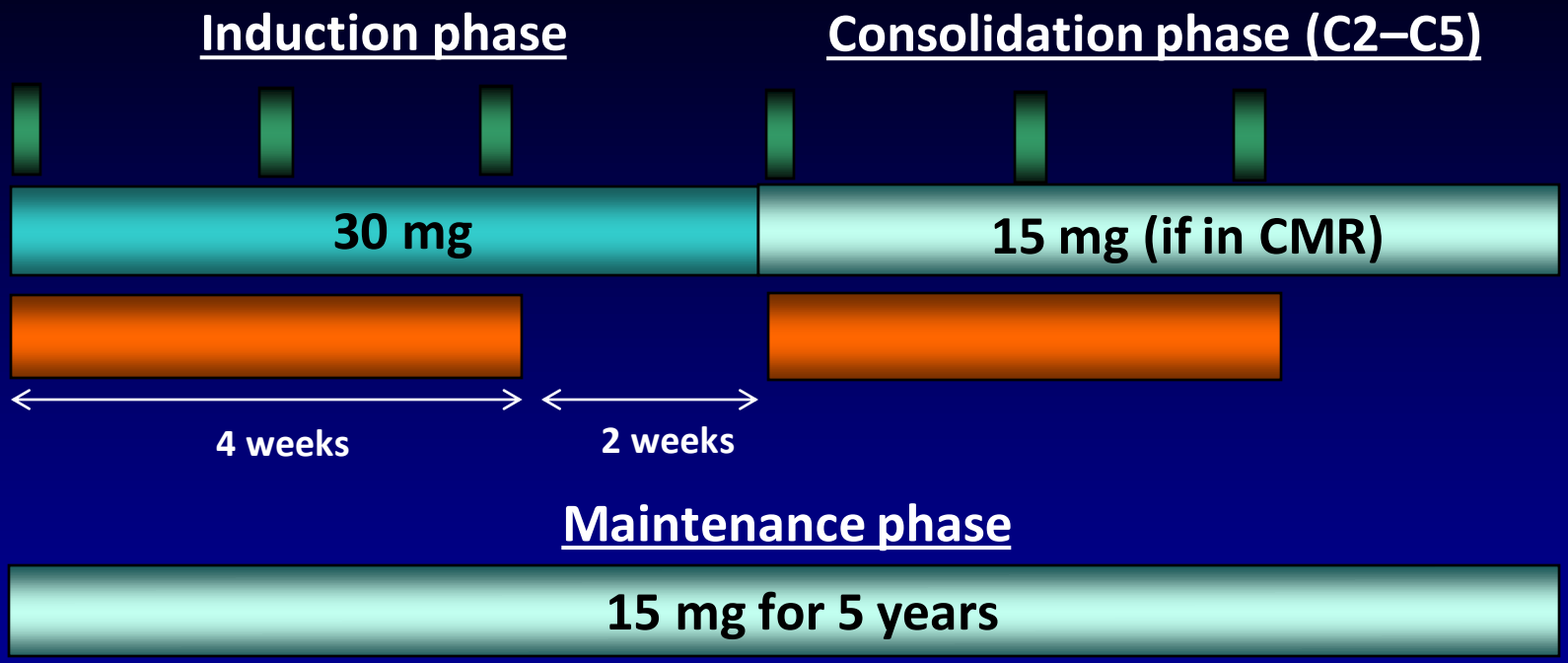
Dasatinib + Blinatumomab (D-ALBA) in Newly Dx Ph+ ALL: Update

- 63 pts Rx; median age 54 yr (24–82). Median FU 40 mo
- Molecular response (32/53 = 60%)
  - 22 CMR (41%)
- 29/58 (50%) who started Blina had SCT – 6 in CR2
- SCT did not impact OS or DFS – but SCT "enriched" by 23 pts who did not have molecular response
- 9 relapses: 4 hematologic, 4 CNS, 1 nodal
- 40-mo OS 78%, DFS 75%
- Outcome better if MR: DFS 100% vs 80% (*P* = .028)
- Outcome worse if *IKZF1* positive: 2-yr OS 84% vs 54% (*P* = .026)



Chiaretti S, et al. EHA 2022. Abstract P353.

Ponatinib + Blinatumomab in Ph+ ALL: Regimen

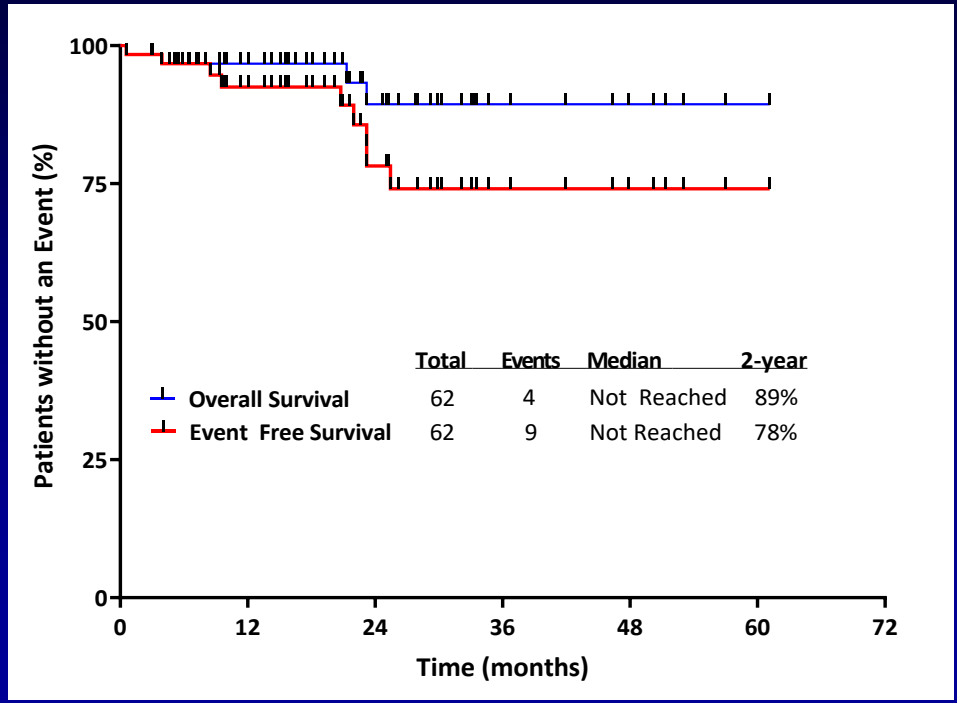


Jabbour E, et al. *Lancet Haematol*. 2023;10(1):e24-e34.

Ponatinib and Blinatumomab in Newly Dx Ph+ ALL

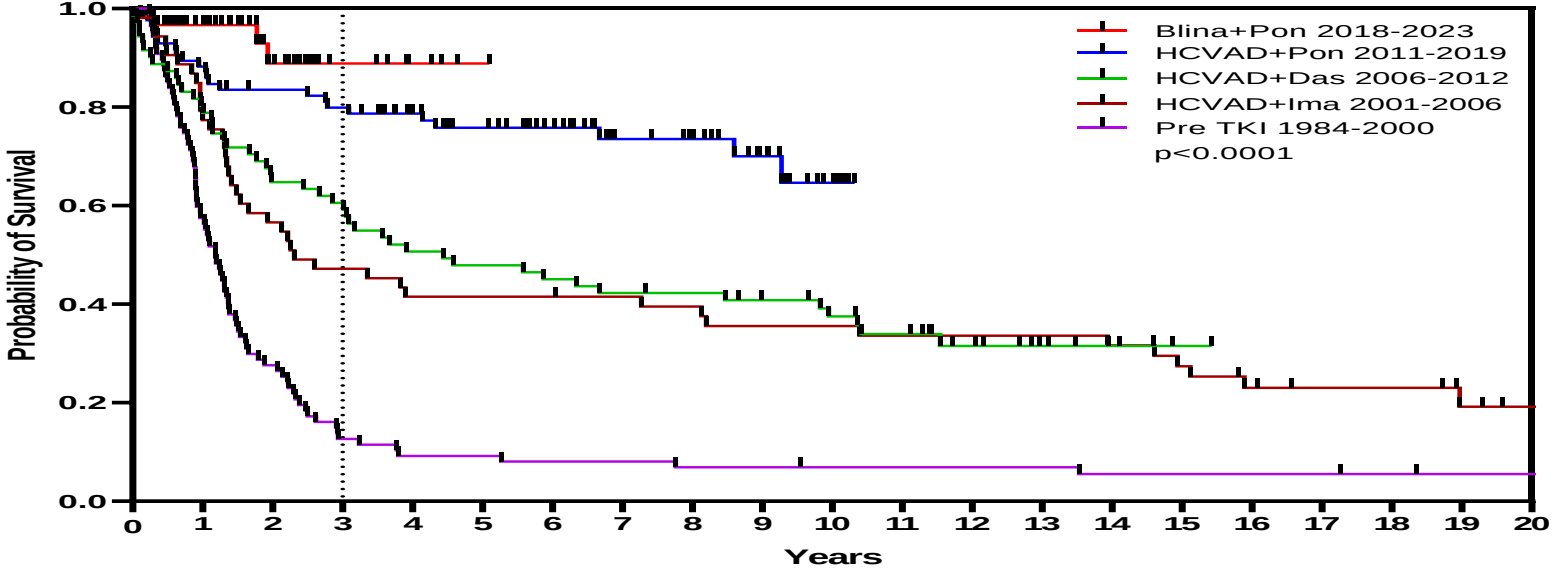
- 62 pts Rx with simultaneous ponatinib 30–15 mg/D and blinatumomab ×5 courses. 12–15 ITs
- Only 1 pt had SCT (2%)
- Median F/U 19 months. 2-yr EFS 78%, OS 89%
- 6 relapses (all p190): 3 CNS, 1 CRLF2+ (Ph–), 2 systemic

Parameter	%
CR-CRi	98
% CMR	84
% NGS-MRD negative	91
% 2-yr OS	89



Short N, et al. *HemaSphere.* 2023;7:abstract S118 (updated August 2023).

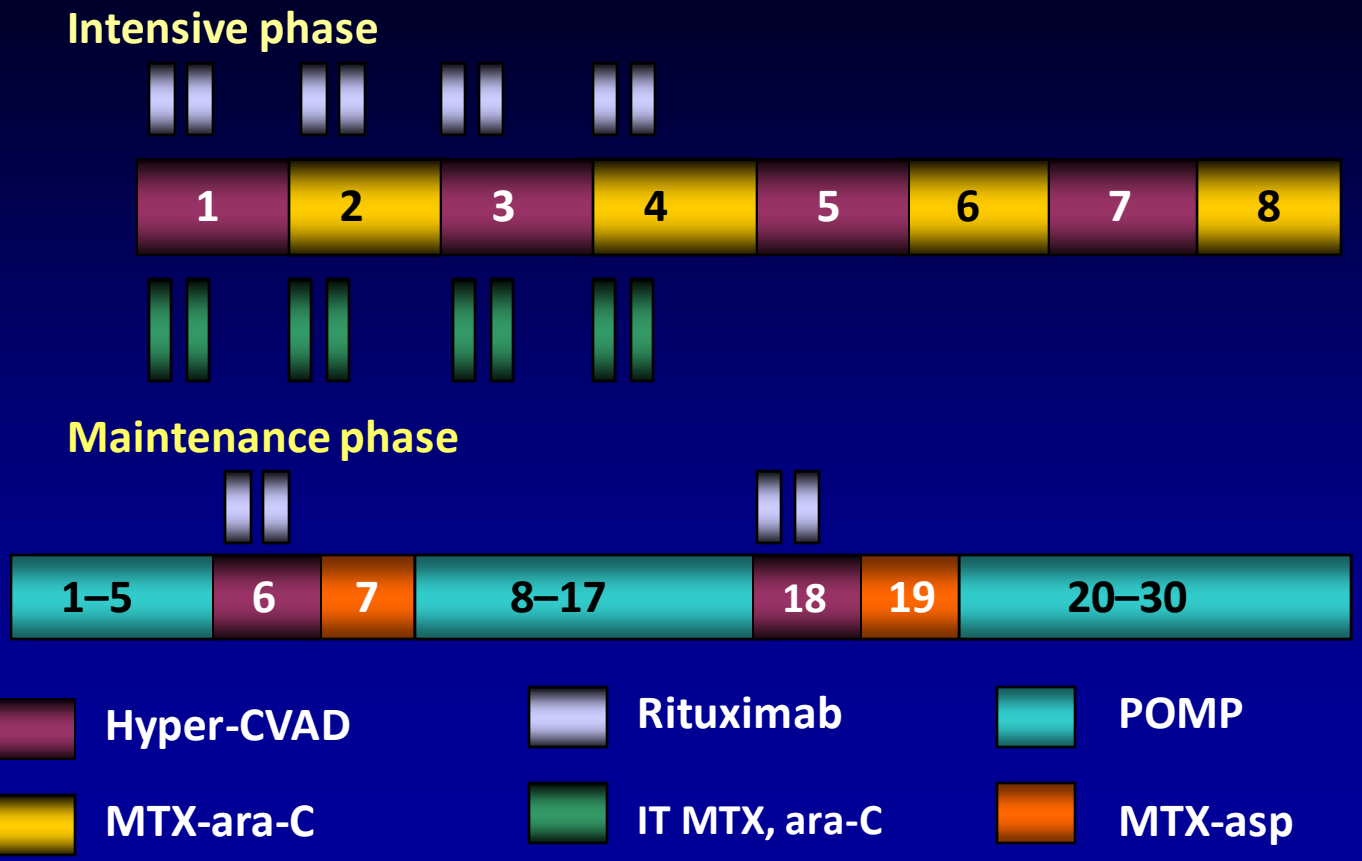
Ph+ ALL: Survival by Decade (MDACC 1984–2023)



	Total	Events	3yr OS	5yr OS	Median
Blina+Pon 2018-2022	62	4	89%	—	Not reached
HCVAD+Pon 2011-2019	85	23	80%	76%	Not reached
HCVAD+Das 2006-2012	71	47	61%	48%	53 mos
HCVAD+Ima 2001-2006	53	41	47%	42%	28 mos
Pre TKI 1984-2000	87	83	13%	9%	14 mos

p<0.0001

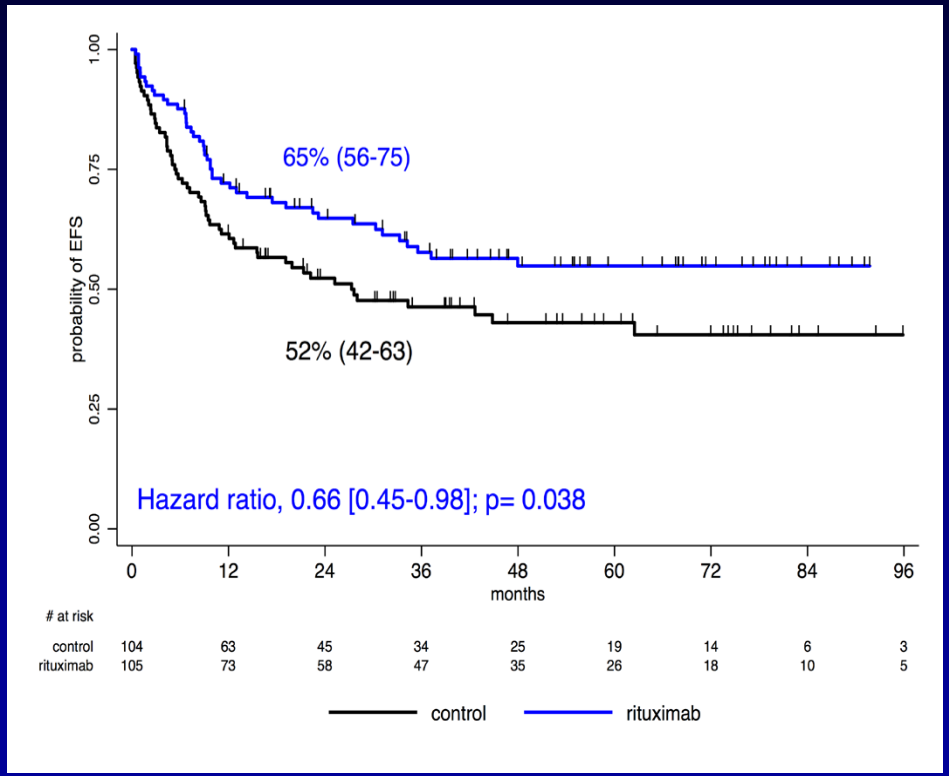
Hyper-CVAD + Rituximab in Precursor B-ALL

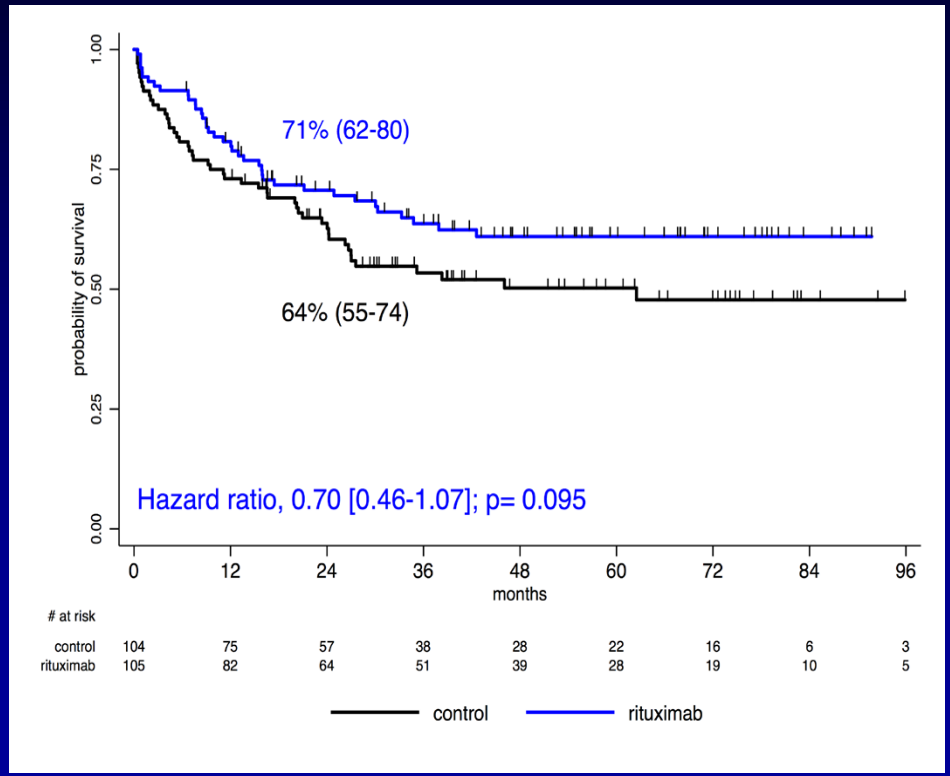


Thomas. *J Clin Oncol.* 2010;28:3880-3889.

Chemo Rx ± Rituximab: Results of the Randomized GRAALL-R 2005 Trial in Pre B-ALL

Median follow-up 30 months



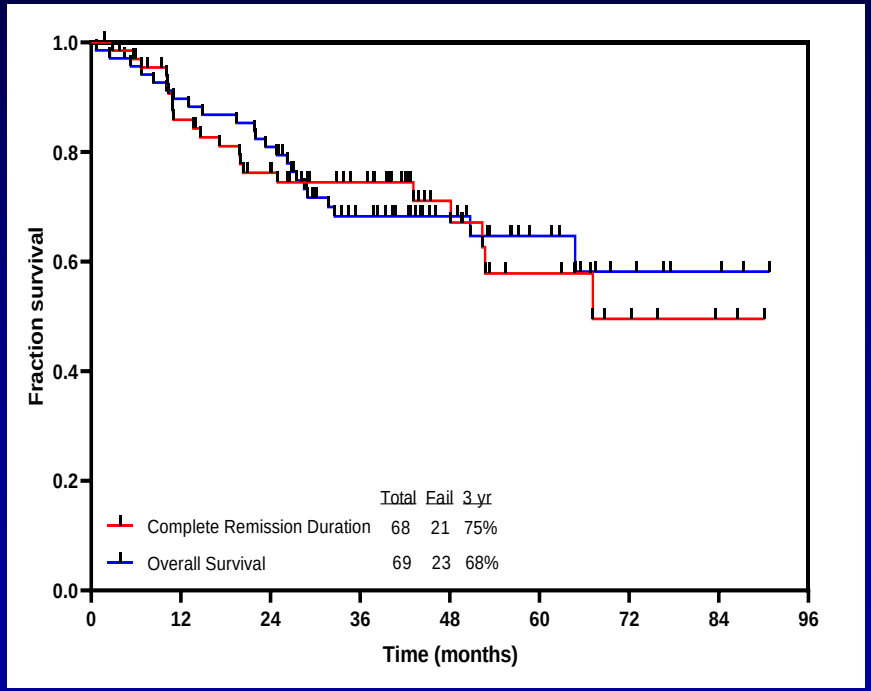


Maury. *N Engl J Med.* 2016;375:1044-1053.

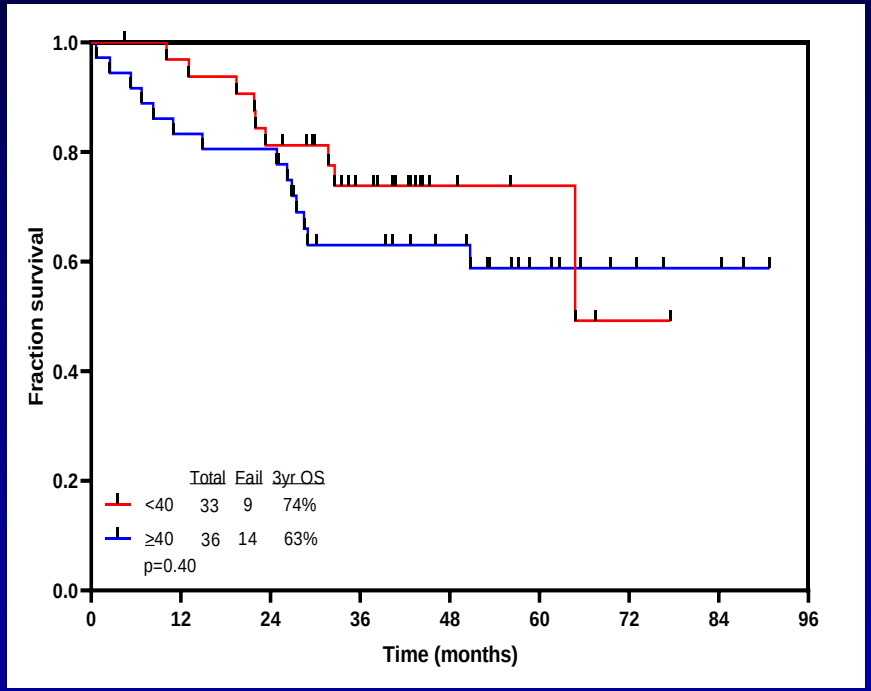
HCVAD + Ofatumumab: Outcome (N = 69)

- Median follow up of 44 months (4–91)
- CR 98%, MRD negativity 93% (at CR 63%), early death 2%

CRD and OS Overall

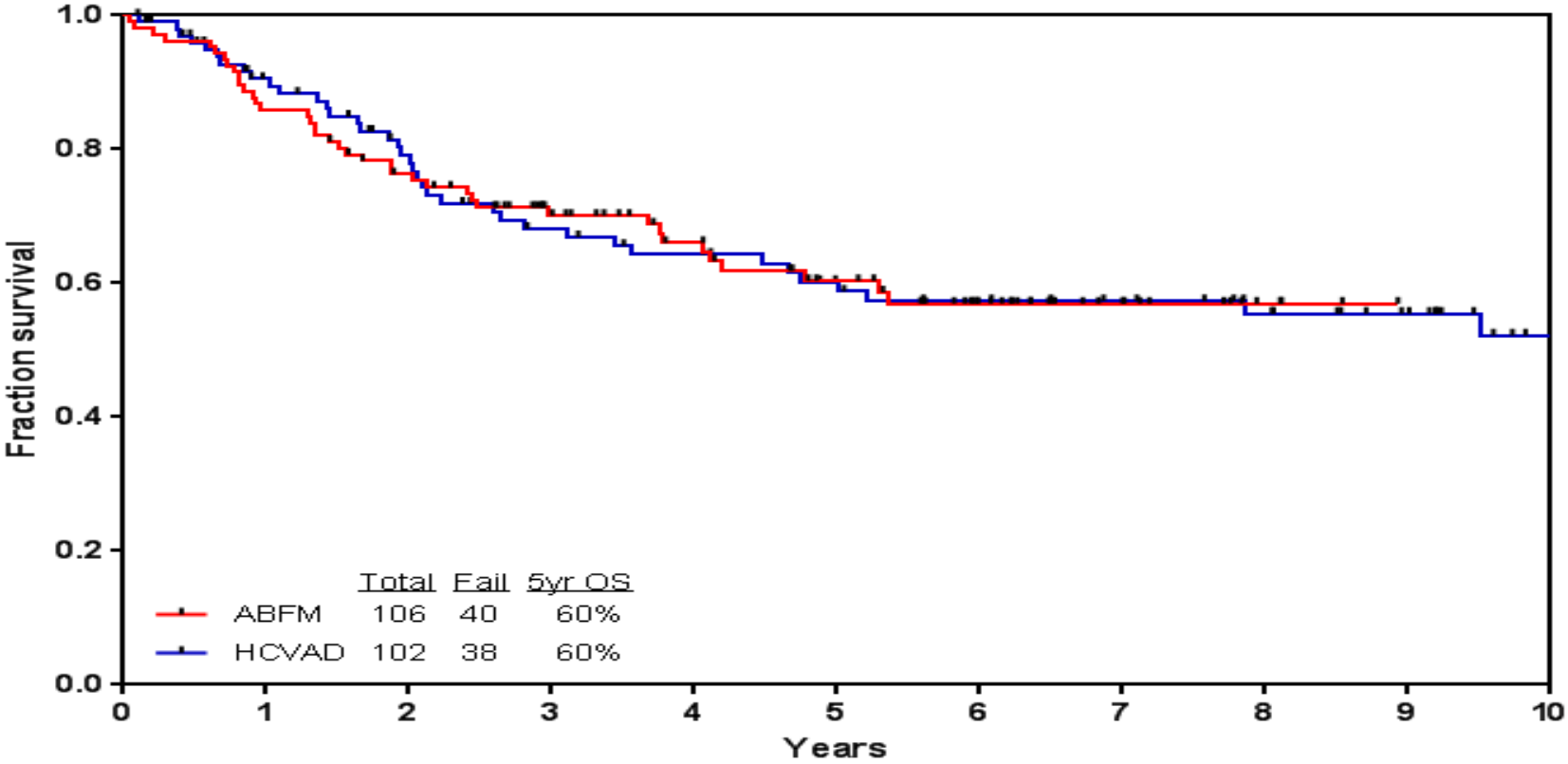


OS by Age



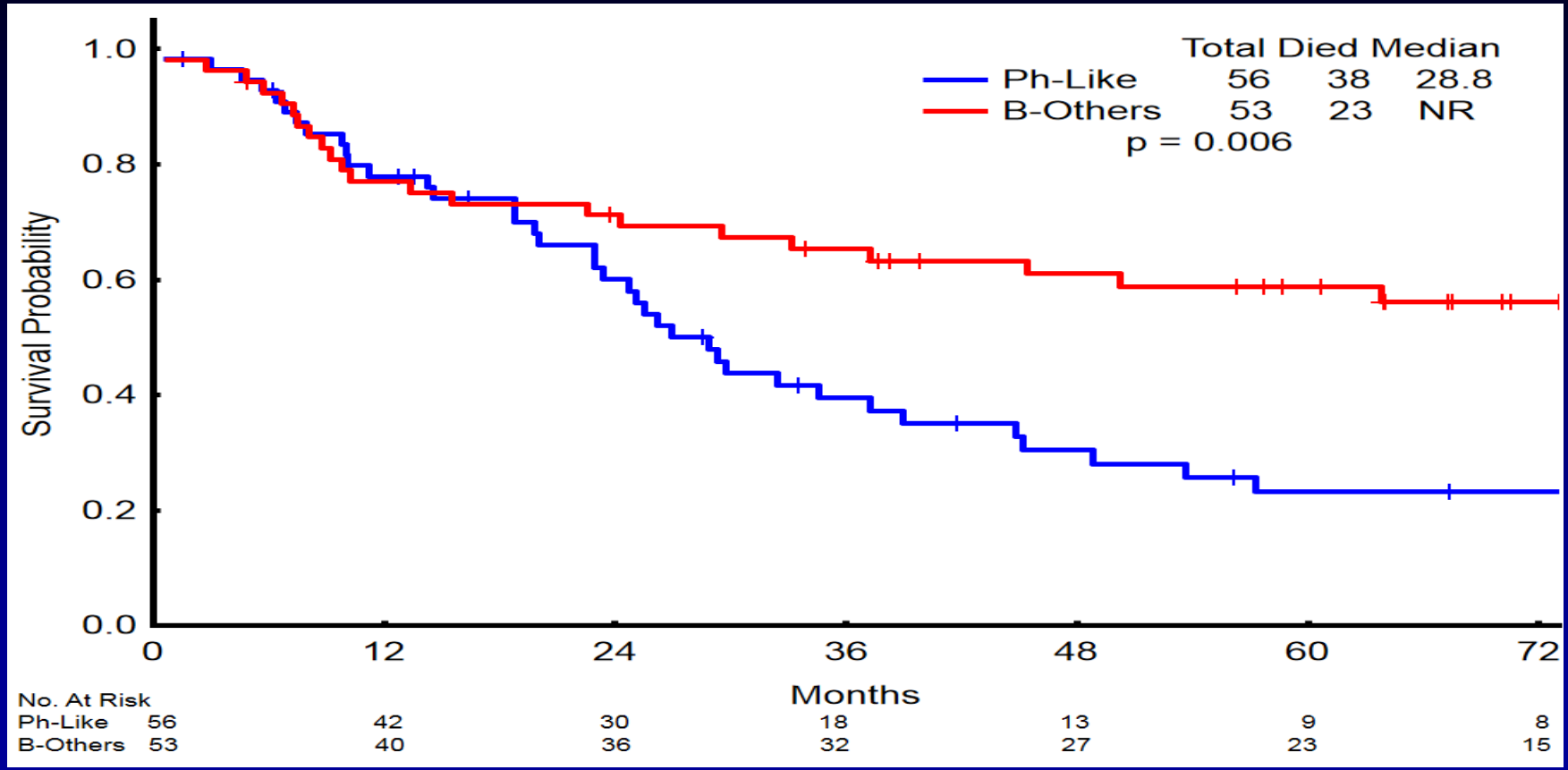
Jabbour E, et al. *Lancet Haematol.* 2020;7:e523-e533.

Hyper-CVAD vs ABFM: Overall Survival



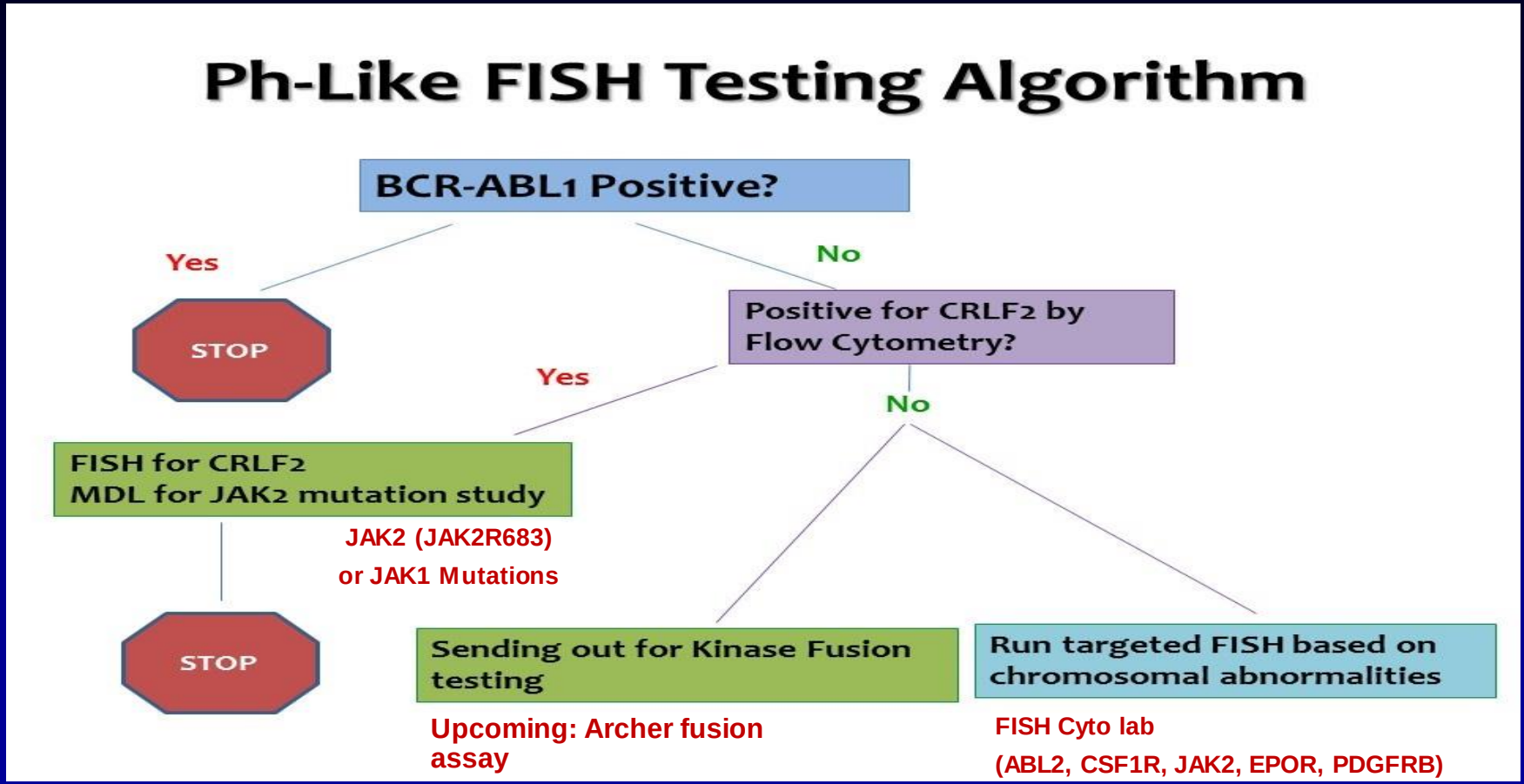
Rytting. *Cancer.* 2014;120:3660-3668; Rytting. *Am J Hematol.* 2016;91:819.

Ph-Like ALL – Worse Survival

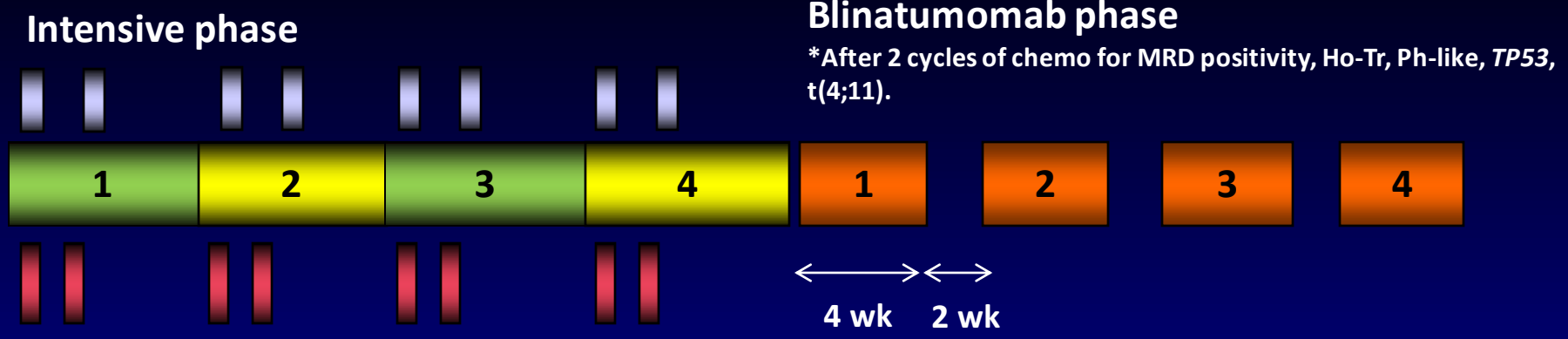


Jain N, et al. *Blood.* 2017;129:572-581.

Ph-Like ALL Testing Algorithm MDACC



Hyper-CVAD + Blina in B-ALL: Regimen (first cohort; N = 38)



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

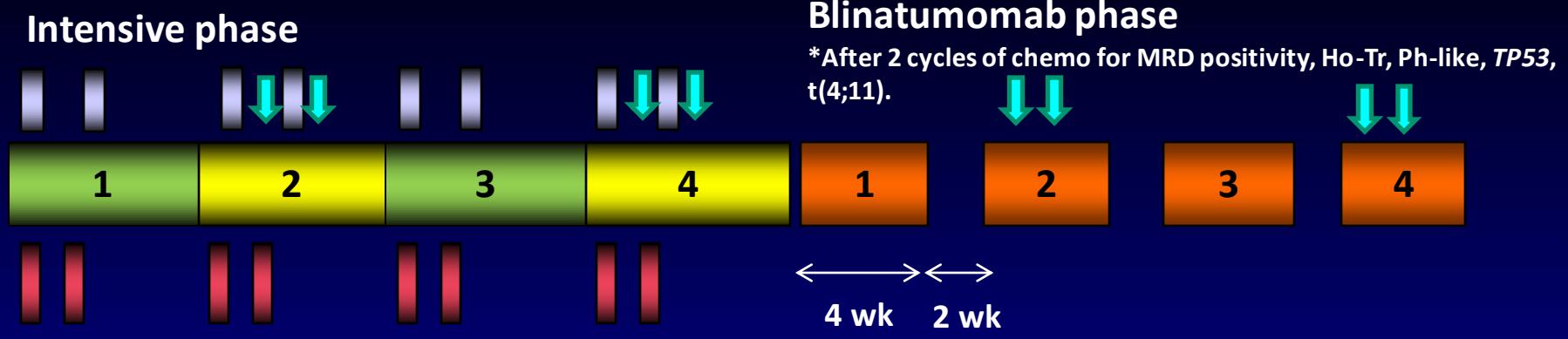
MTX + Ara-C

IT MTX + Ara-C × 8

POMP

Short N, et al. *HemaSphere.* 2023;7:abstract P358.

Hyper-CVAD + Blina + Ino in B-ALL: Regimen (second cohort)



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

MTX (500 mg/m^2) + Ara-C (1 g/m^2)

IT MTX + Ara-C × 8

POMP

Inotuzumab 0.3 mg/m^2 on D1 and D8

Short N, et al. *Blood*. 2022;140(suppl 1):8966-8968. Abstract 4043.

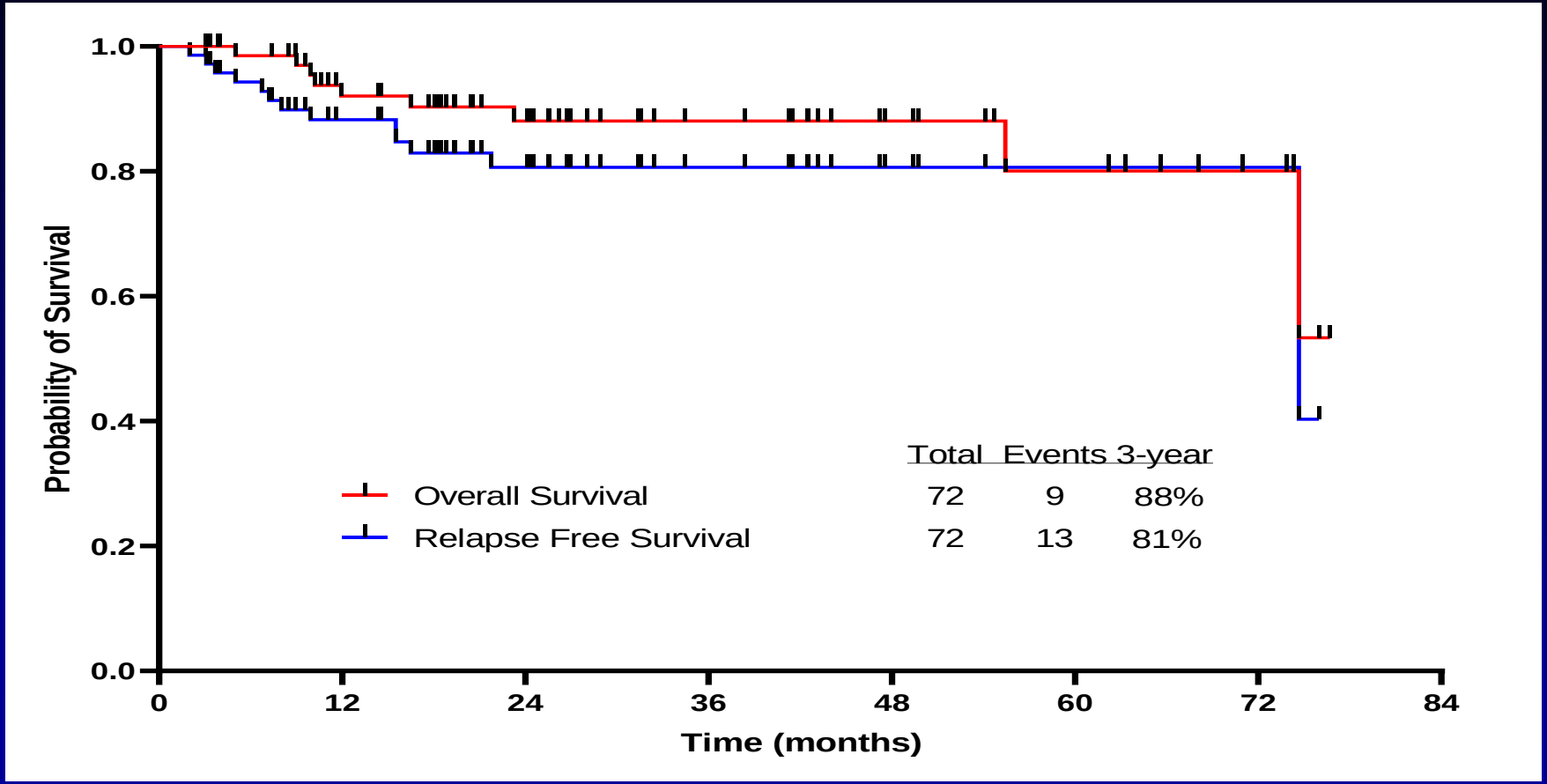
Hyper-CVAD + Blina + Ino in B-ALL: Response Rates

Response Assessment	Overall N (%) (= 72)	Cohort 1 (n = 38)	Cohort 2 (n = 34)
CR after induction	47/56 (84)	26/32 (81)	21/24 (88)
CR at any time	56/56 (100)	32/32 (100)	24/24 (100)
MRD negativity after induction	43/62 (69)	25/33 (76)	18/29 (62)
MRD negativity at any time	59/62 (95)	32/33 (97)	27/29 (93)
NGS neg at any time	25/34 (74)	2/4 (50)	23/30 (77)
Early death (30-day)	0	0	0

- 6 are CR at start (cohort 1); 10 are CR at start (cohort 2)
- Median time to MRD negativity: 21 days (14–151)

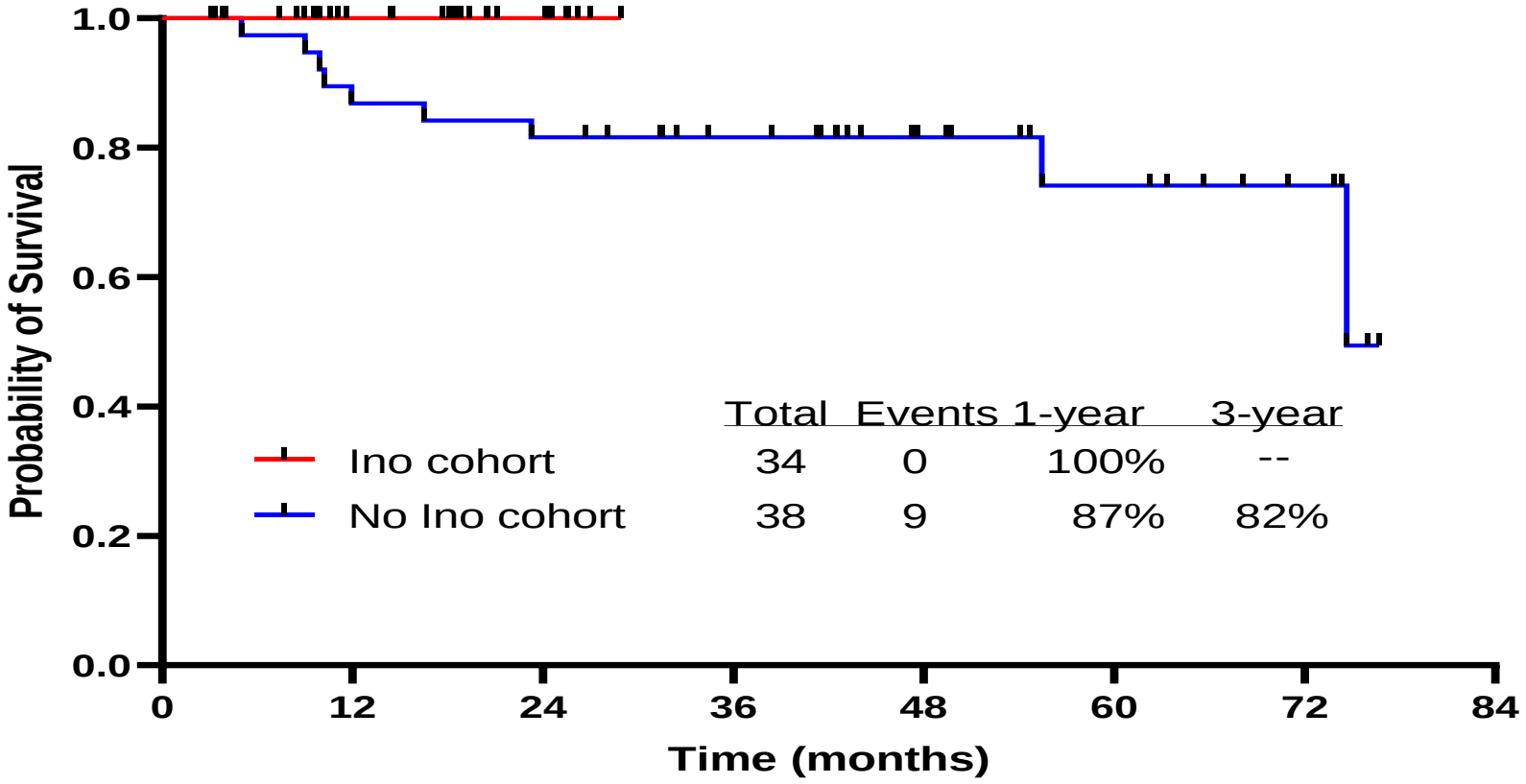
Short N, et al. *HemaSphere.* 2023;7:abstract P358.

Hyper-CVAD + Blinatumomab + InO in B-ALL: Outcome



Short N, et al. *HemaSphere.* 2023;7:abstract P358.

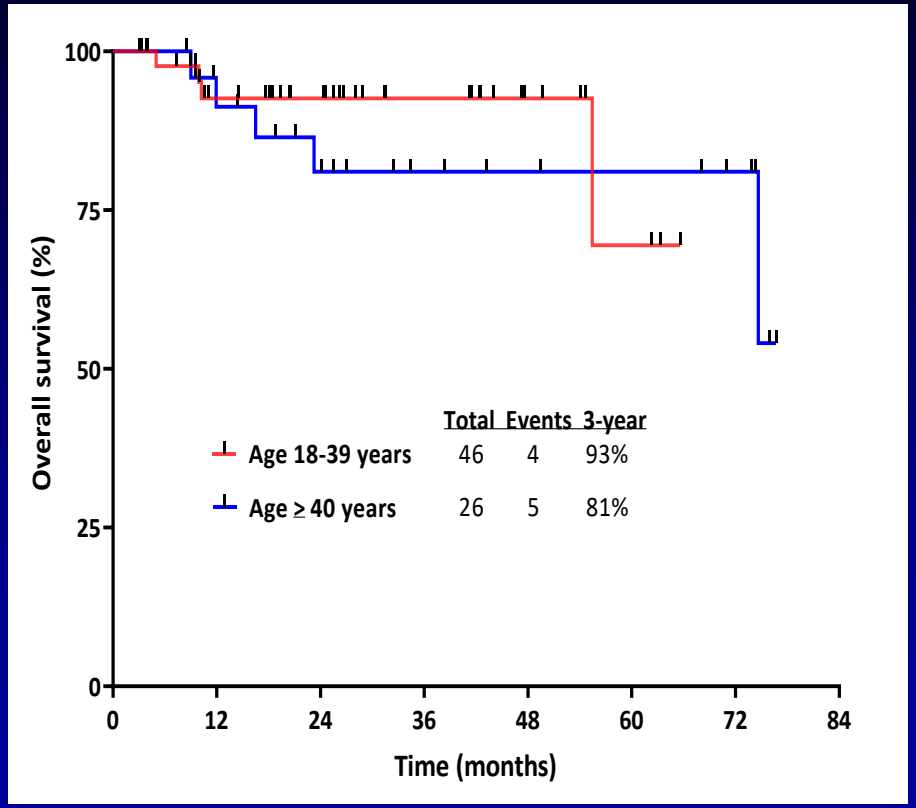
Hyper-CVAD + Blinatumomab + InO in B-ALL: Outcome



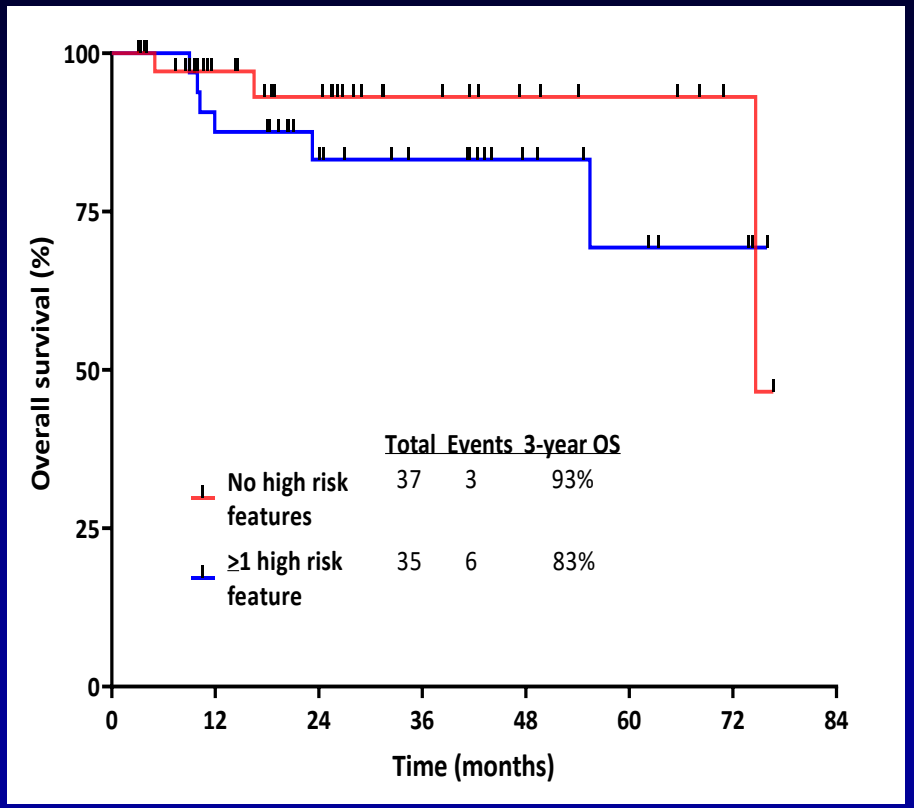
Short N, et al. *HemaSphere.* 2023;7:abstract P358.

Hyper-CVAD + Blinatumomab + InO in B-ALL

Outcome by Age

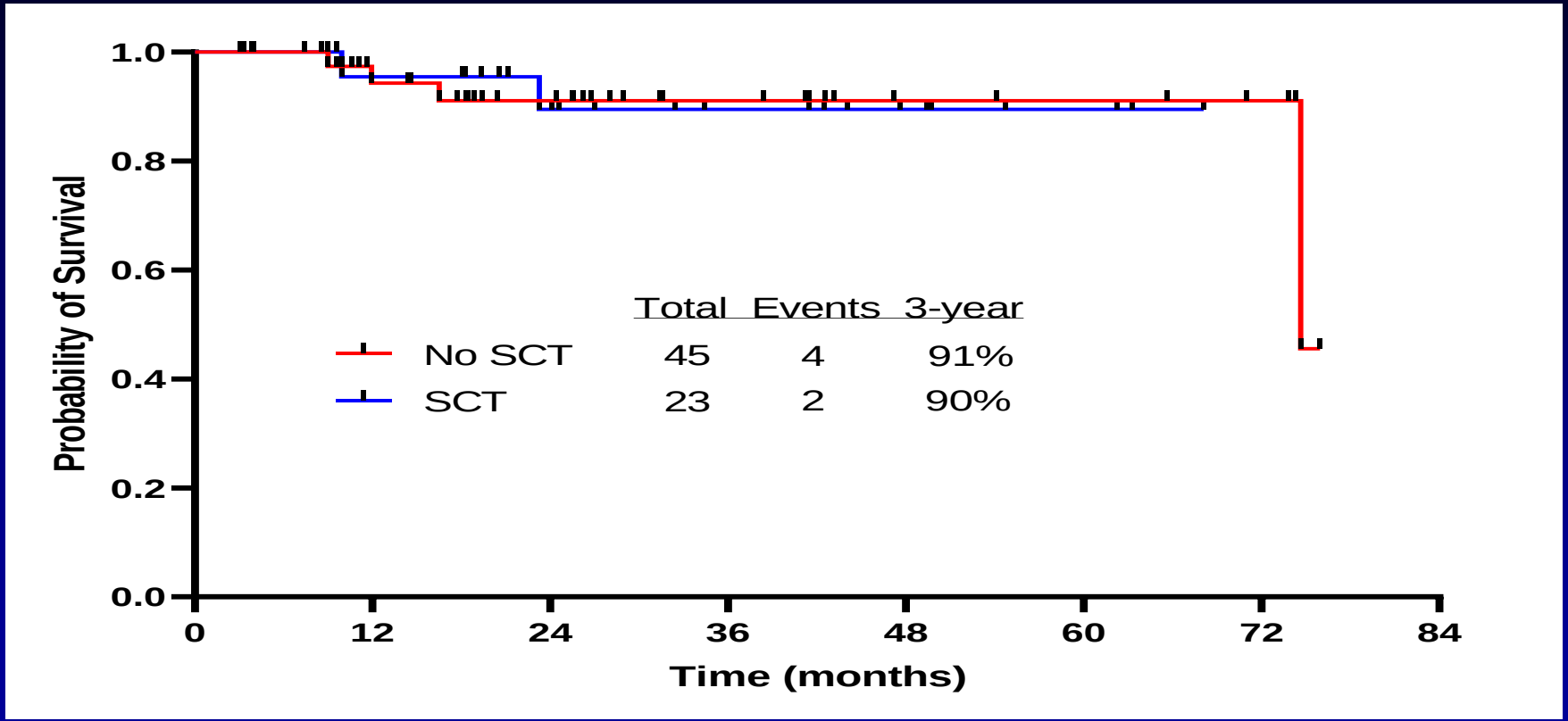


Outcome by Risk Features



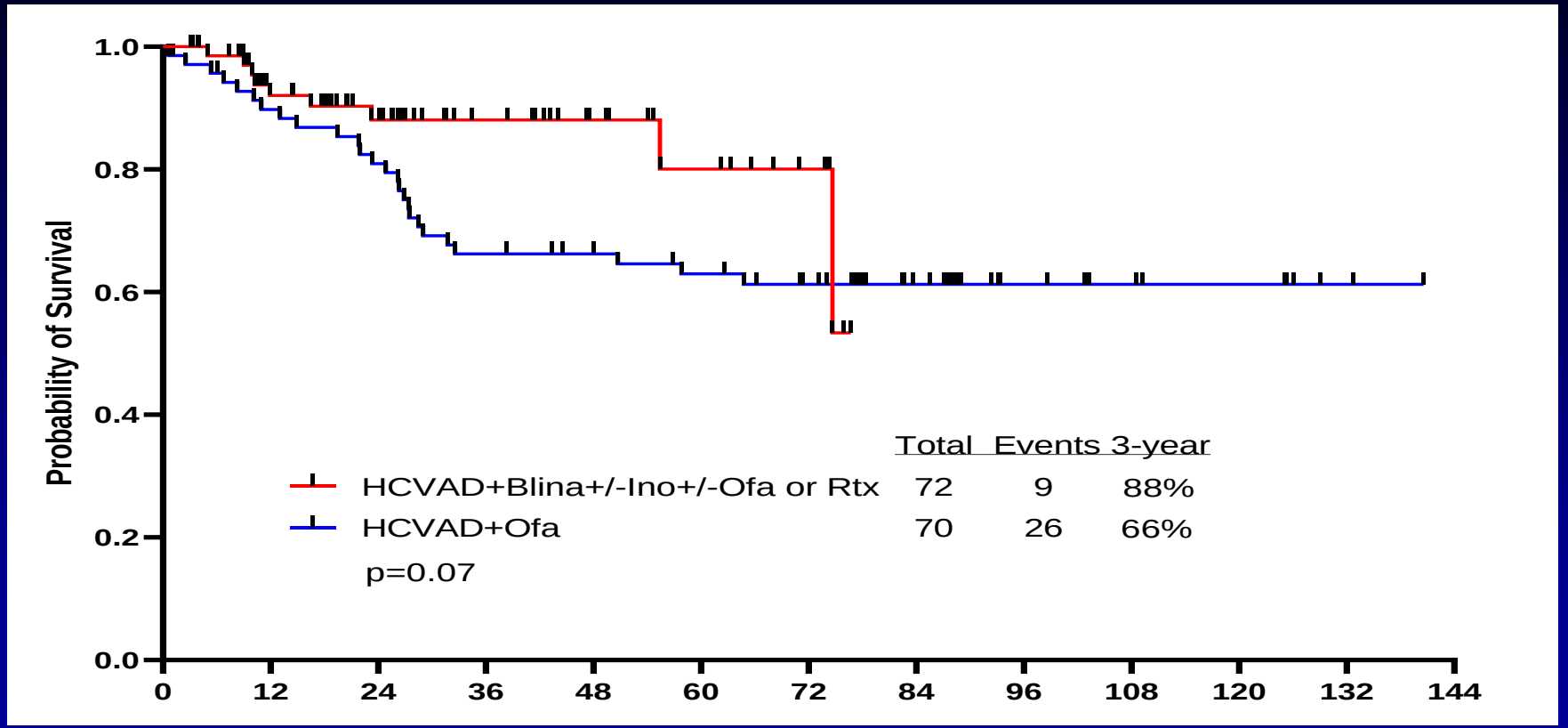
Short N, et al. *HemaSphere.* 2023;7:abstract P358.

Hyper-CVAD + Blinatumomab + InO in B-ALL: 5-Month Landmark – Impact of ASCT



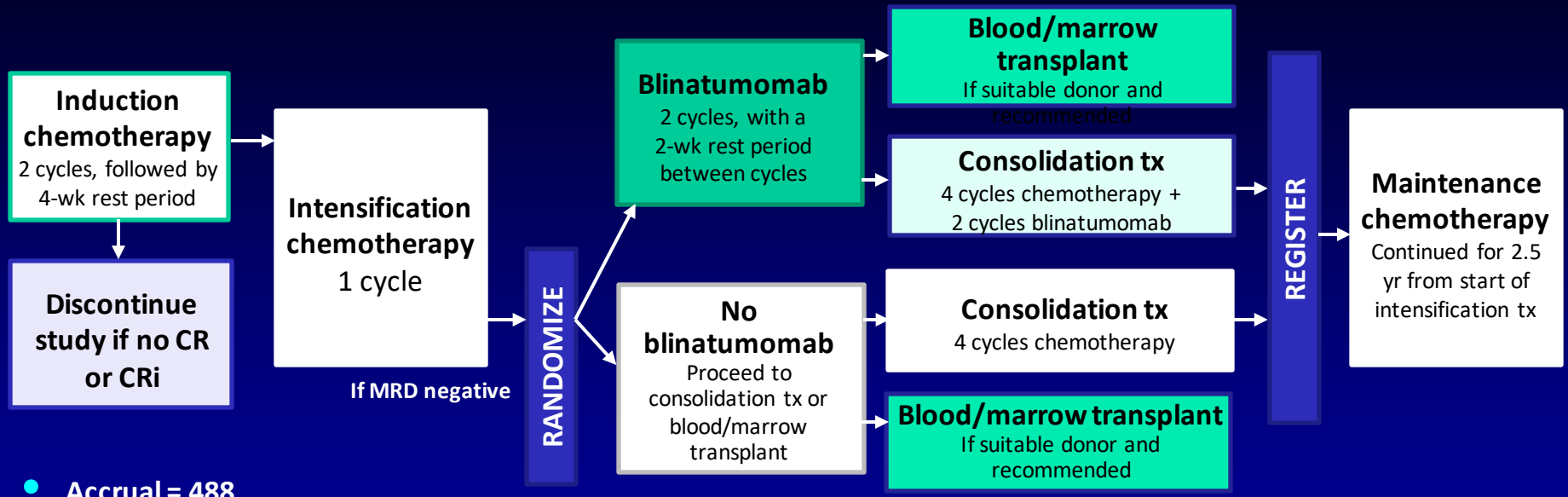
Short N, et al. *HemaSphere.* 2023;7:abstract P358.

Hyper-CVAD + Blinatumomab in B-ALL: Historical Comparison



Short N, et al. *HemaSphere.* 2023;7:abstract P358.

E1910 Randomized Phase III Trial: Blina vs SOC as Consolidation in MRD-Negative CR

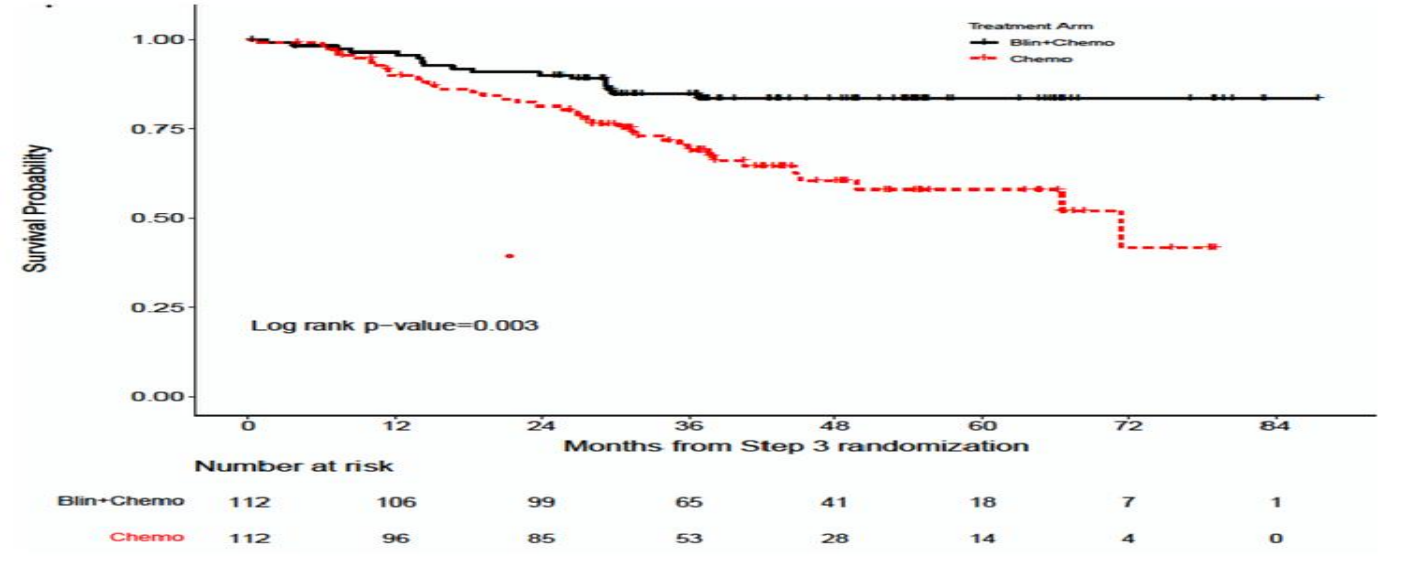


- Accrual = 488
- US intergroup study
- n = 265/360 (509) patients
- USA, Canada, Israel
- 1:1 randomization

Litzow MR, et al. *Blood.* 2022;140(suppl 2): abstract LBA-1.

E1910 Randomized Phase III Trial: Blina vs SOC as Consolidation in MRD-Negative Remission

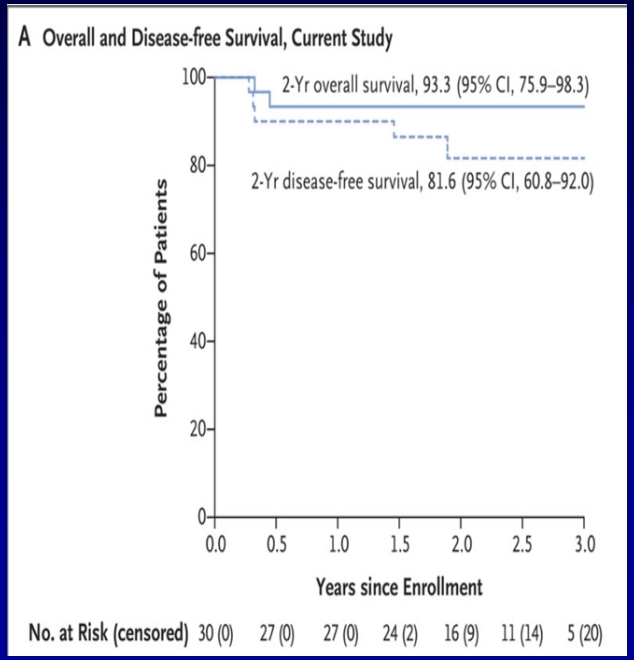
- 488 pts median age 51 yr (30–70)
- 224 MRD-negative CR randomized 1:1
- 22 pts (20%) Rx ASCT in each arm
- Median FU 43 months; median OS NR vs 71.4 mo (HR = 0.42; *P* = .003)

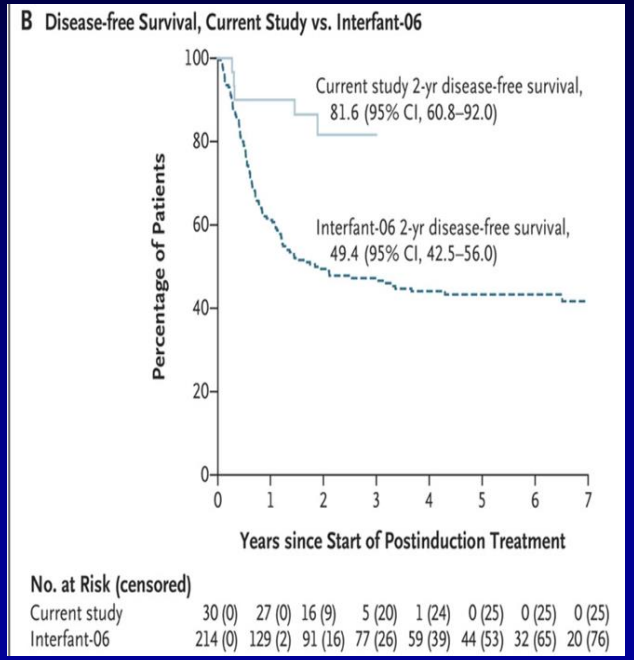


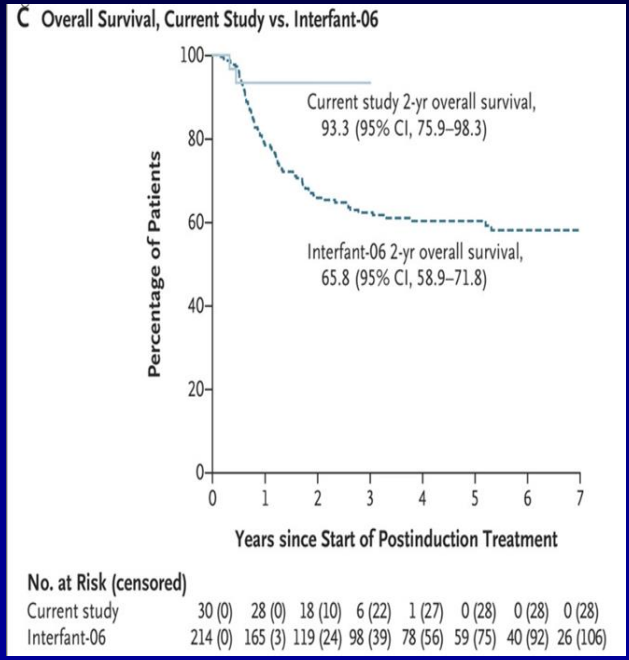
Litzow MR, et al. *Blood.* 2022;140(suppl 2): abstract LBA-1.

ChemoRx + Blinatumomab in Newly Dx KMT2A – Rearranged ALL

- **30 infants age <1 yr Rx with chemoRx induction, then 1 course blina consolidation (15 mcg/m² × 28), then chemoRx continuation**



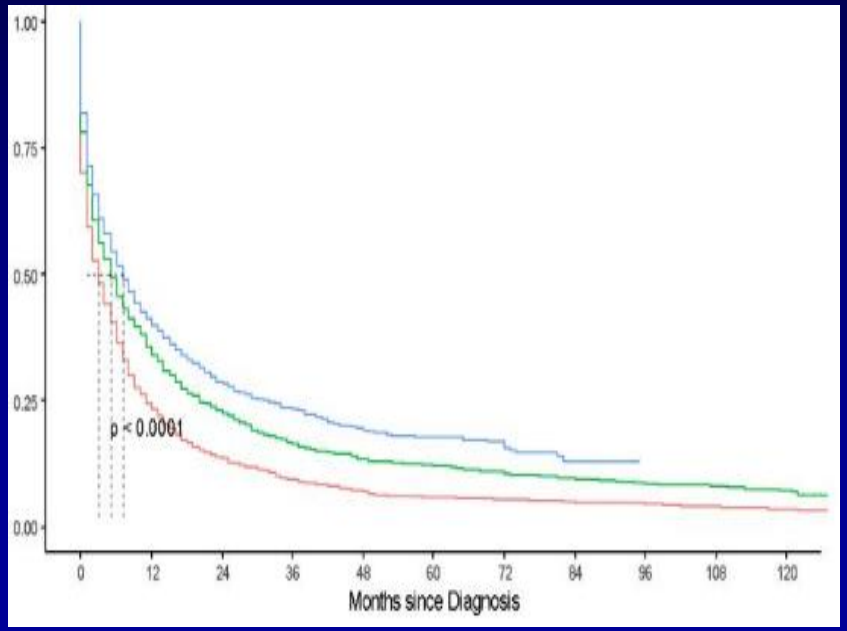


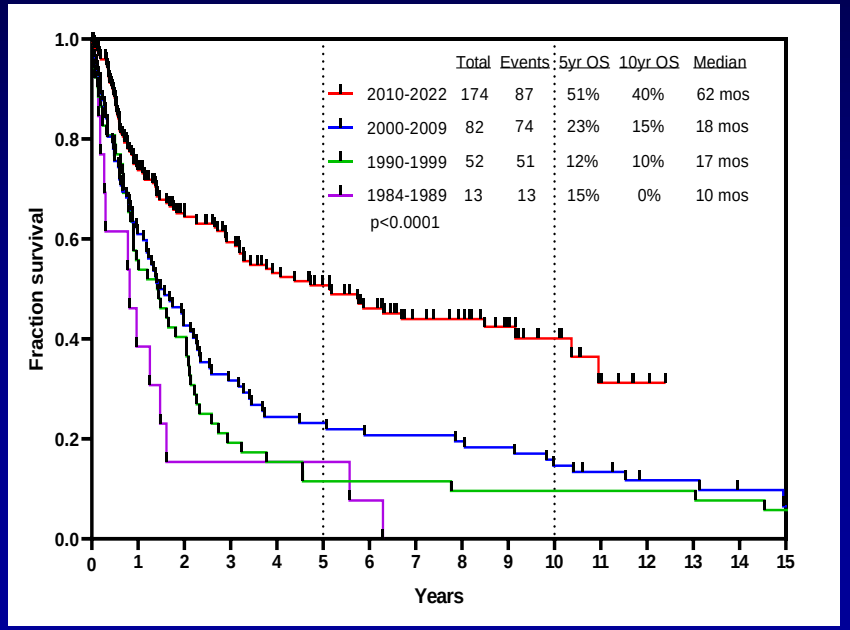


Vam der Sluis, et al. *N Engl J Med.* 2023;388:1572-1581.

MDACC vs SEER ALL: Survival by Decades for ≥60 Years

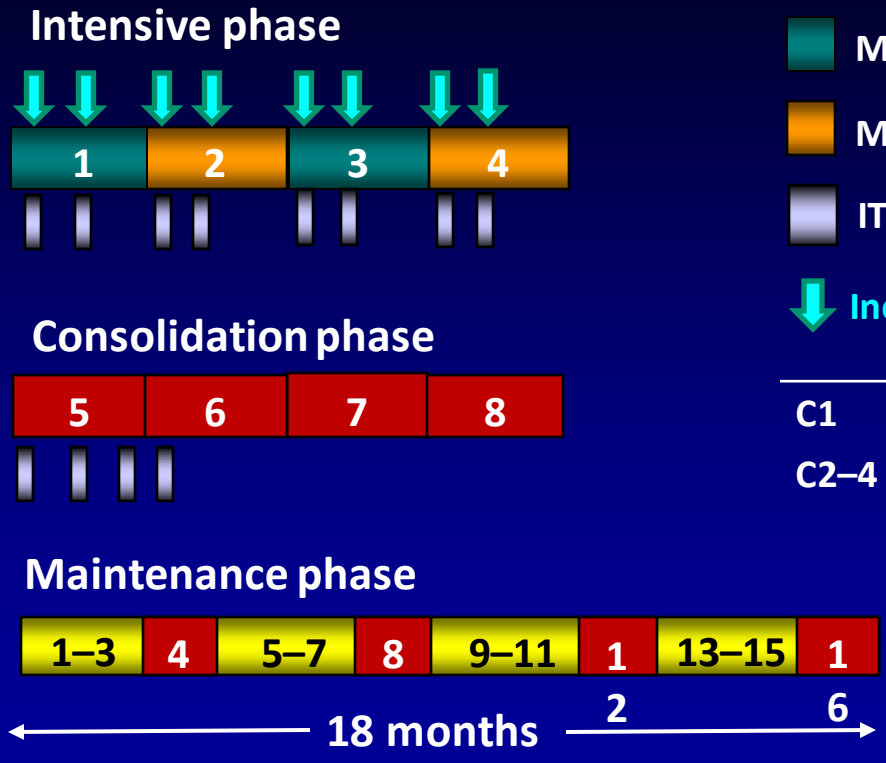
- 26,801 pts age ≥65 yr B-ALL 91%
- OS better in Ph+ (HR 0.68) and 2012–2018 (HR 0.64); worse in secondary ALL (HR 1.15), AA (HR 1.19), and Hispanic (HR 1.1)
- 5-yr OS <20%





Gupta V, et al. *Blood*. 2022;140(suppl 1):3185-3186. Abstract 1379.

Mini-HCVD + Ino ± Blina in Older ALL: Modified Design



Mini-HCVD

Mini-MTX + cytarabine

Blinatumomab

IT MTX + Ara-C

POMP

Ino*	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2–4	0.6	0.3 D2 and D8

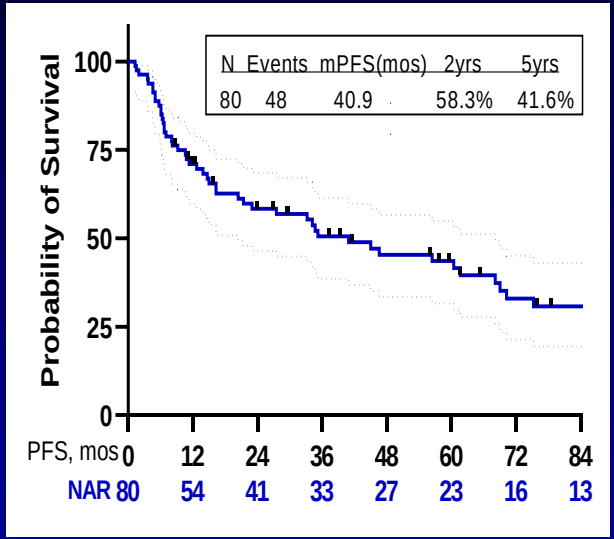
Total Ino dose = 2.7 mg/m^2

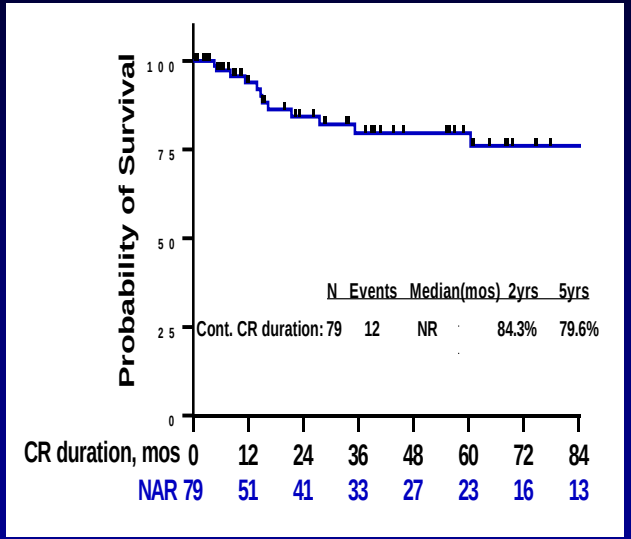
*Ursodiol 300 mg tid for VOD prophylaxis.

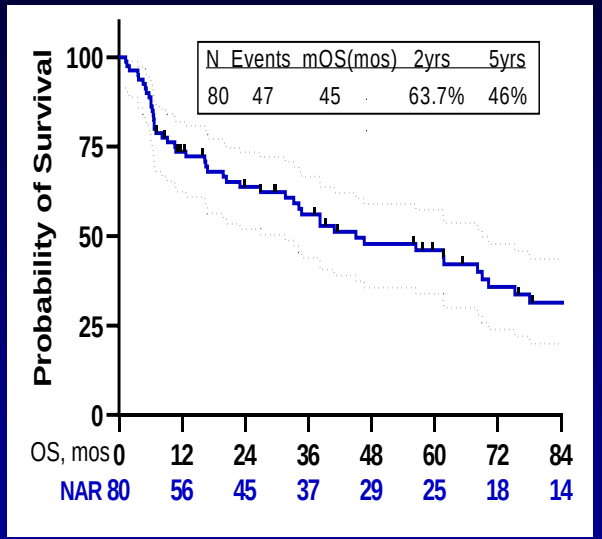
Haddad F, et al. EHA 2022. Abstract P355.

Hyper CVD + Inotuzumab + Blinatumomab in Older ALL

- 80 pts; median age 68 yrs (60–87). 38% ≥70 yrs. Rx with mini-HCVD × 6–8; Blina ×4 → POMP 1 yr with blina Q3 mos; Ino 0.6 mg/m² D1 and 0.3 mg/m² D8 and 0.3 mg/m² D1 and D8 C2,4,6,8 (2.7 mg/m²)
- ORR rate 99% (89% CR); MRD negative 94% (80% at CR); F/U 93 mos





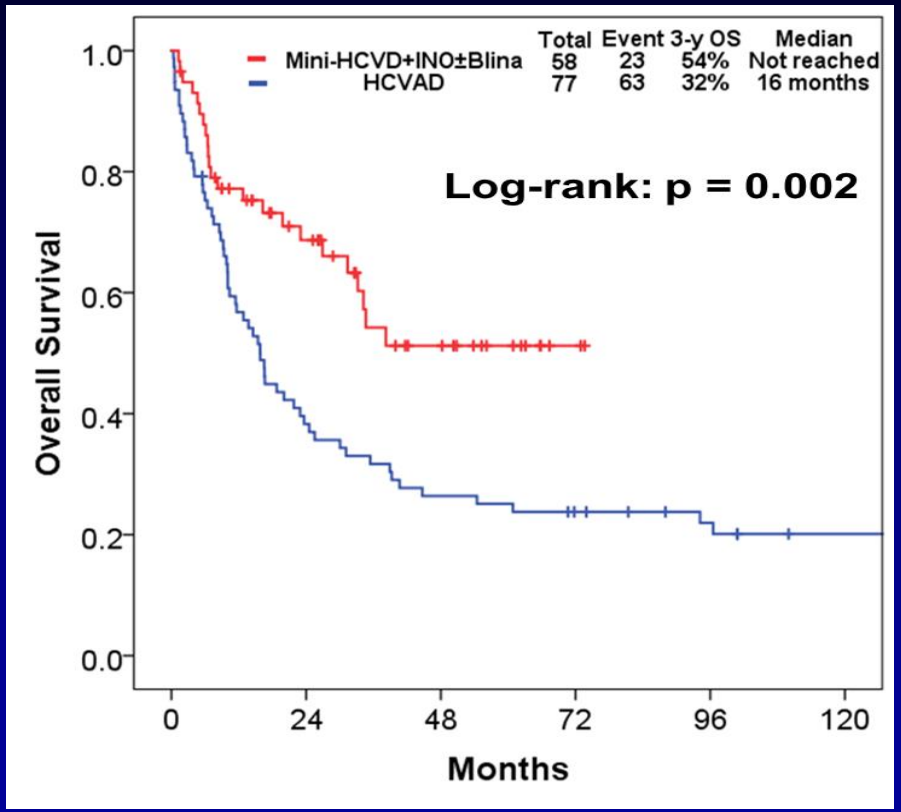


- 5/12 pts with relapse (42%) had EMD (1 concurrent BM relapse), all with CNS involvement (5/80; 6%)
- Death due PD/NR: 12/80 (15%); median 23 mos (2–78); median age 64 yrs (60–79)
- Death due to AML/MDS: 9/80 (11%); median 34 mos (7–75); median age 71 yrs (64–87)
- Death in CR: 26/80 (33%); 13/30 (43%) in pts ≥70 yrs
- 12/26 deaths (46%) Rx related (9 sepsis, 3 VOD, 2 ASCT)

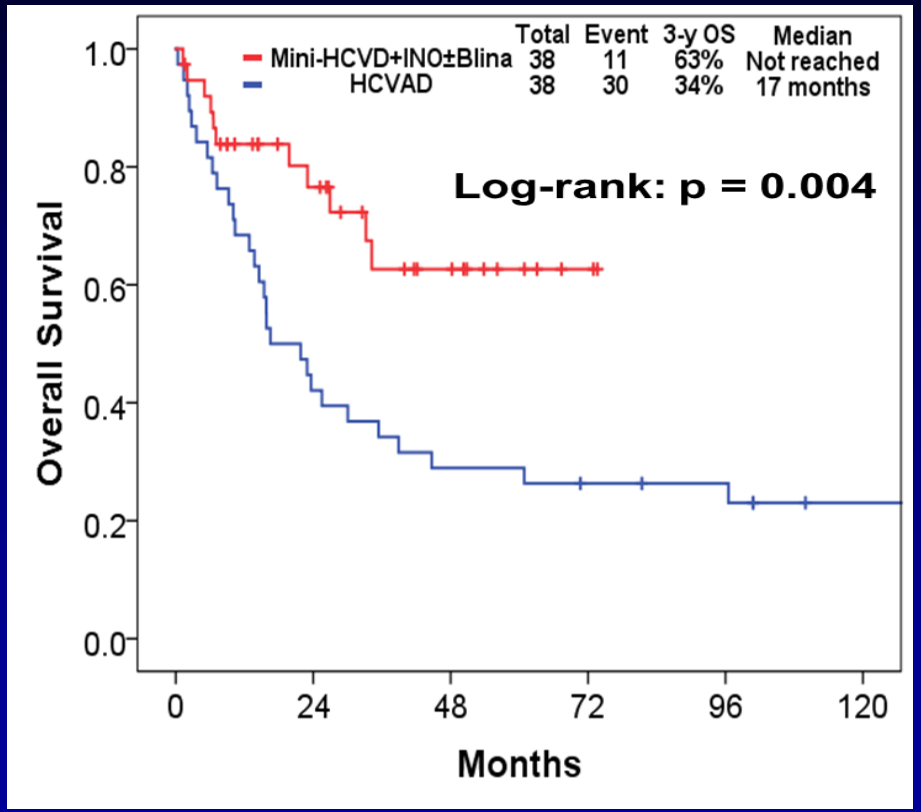
Kantarjian H, et al. *Lancet Oncol.* 2018;19(2):240-248;. Jabbour E, et al. *Lancet Hematol.* May 12, 2023.

Mini-HCVD + INO ± Blina vs HCVAD in Older ALL: Overall Survival

Pre-matched

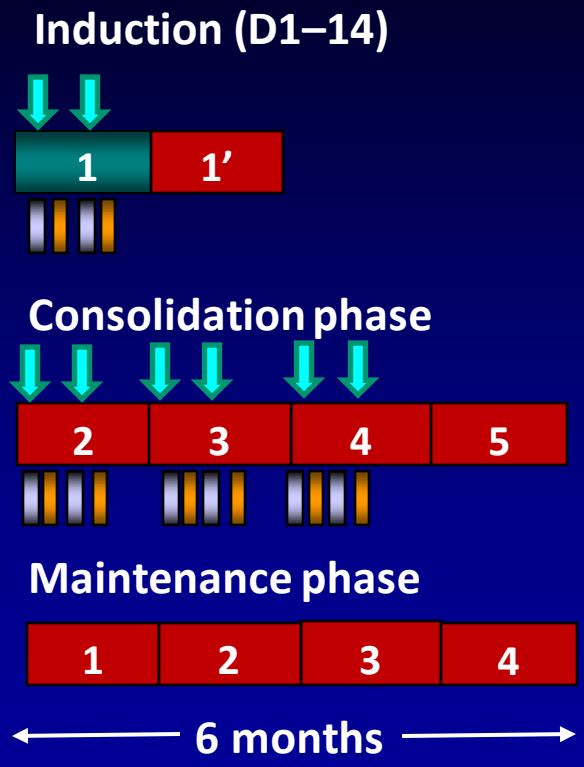


Matched



Jabbour E, et al. *Cancer.* 2019;125(15):2579-2586.

Ino + Blina in Older ALL: Amended Design (pts ≥70 yr)



Dex 20 mg D1–4 and VCR 1 mg D4

Blinatumomab

IT MTX + Ara-C

Rituximab if CD20 positive

1' Blinatumomab for 2 weeks

Ino*	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D1, 0.3 D8
C2–C4	0.6	0.3 D1 and D8

Total Ino dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis.

ChemoRx-Free Inotuzumab + Blinatumomab in Pre–B-ALL (Alliance A041703)

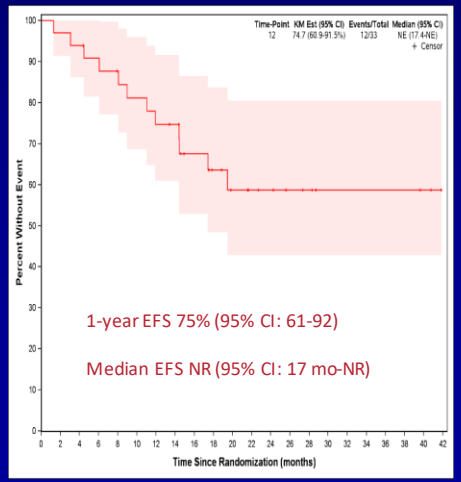
- 33 pts; median age 71 yr (60–84). Median CD22 92%. F/U 22 mo
- Induction: InO 0.8 mg/m^2 D1, 0.5 mg/m^2 D8 and 15 (1.8 mg/m^2)
- Maintenance: If CR-CRi, InO 0.5 mg/m^2 D1, 8, 15 (1.5 mg/m^2) × 2 then BLINA × 2
- If no CR-CRi, BLINA 28 mcg/D × 21 then × 28 × 3
- IT × 8
- CR 85% post-InO × 3; cumulative CR 97%
- 1-yr EFS 75%; 1-yr OS 84%
- 9 relapses; 2 deaths in CR. 9 deaths, 6 post-relapse. ?1 SOS

N=33	Induction InO I A/B/C	Blinatumomab Course II
Composite CR*	28 (85%)	32 (97%)
CR	15 (45%)	19 (58%)
CRh	11 (33%)	12 (36%)
CRi	2 (6%)	1 (3%)
Refractory	3 (9%)•	-
Survival		
1-yr EFS	75% (95% CI 61-92%)	
1-yr OS	84% (95% CI 72-92%)	

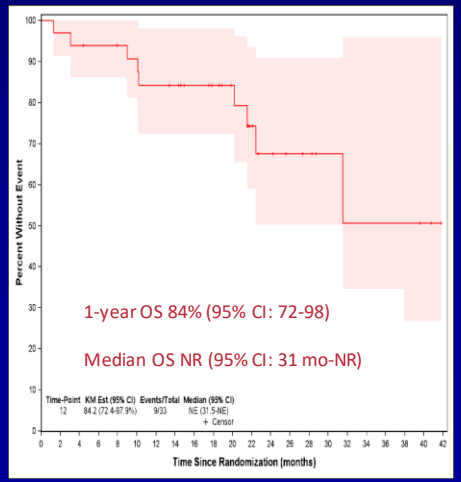
*CR+CRh+CRi

• 1 completed IA only, 2 proceeded to course II

EFS

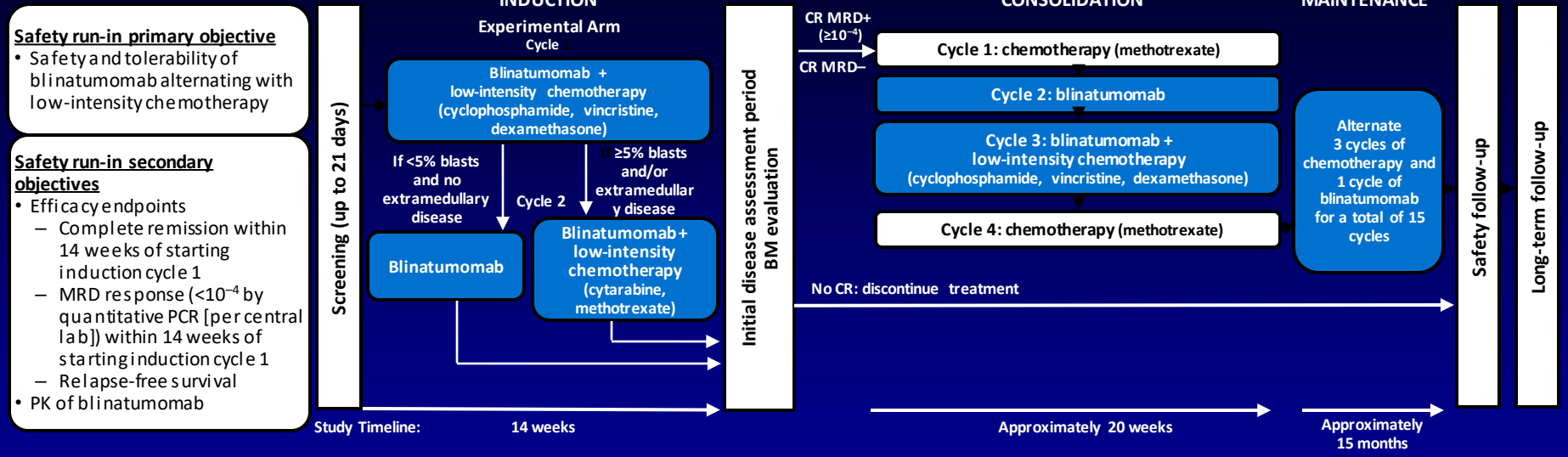


OS



Wieduwilt M, et al. *HemaSphere*. 2023;7(S3):p e08838b7. Abstract S117.

Blina + Low-Intensity ChemoRx in Older Pre-B ALL: Golden Gate SaFety Run-In Results of Phase III



- 10 pts; median age 69 yrs (57–77); 40% ≥70 yrs
- 9/10 had molecular response after C1; 7/10 MRD-negative CR
- No grade ≥3 CRS or ICAN

Jabbour E, et al. *Blood.* 2022;140:abstract 2732.

ALL 2023: Conclusions

- Significant improvements across all ALL categories
- Incorporation of Blina-Ino in FL therapy highly effective and improves survival
- Early eradication of MRD predicts best overall survival
- Antibody-based Rxs and CAR Ts both outstanding; not mutually exclusive/competitive (vs); rather, complementary (together)
- Future of ALL Rx
  1) Less chemotherapy and shorter durations
  2) Combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22
  3) SQ blinatumomab
  4) CAR Ts CD19 and CD19 allo and auto in sequence in CR1 for MRD and replacing ASCT

Thank You

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Global Leukemia Academy

Q&A

APTITUDE HEALTH

Instituto de Investigación CONTRA LA LEUCEMIA Josep Carreras

FUNDACIÓN PETHEMA Para el tratamiento de la Leucemia y el Linfoma

ICO Institut Català d'Oncologia Hospital Germans Trias i Pujol

Global Leukemia Academy

Current treatment options for relapsed ALL in adult and elderly patients

Josep-Maria Ribera

APTITUDE HEALTH

Disclosures

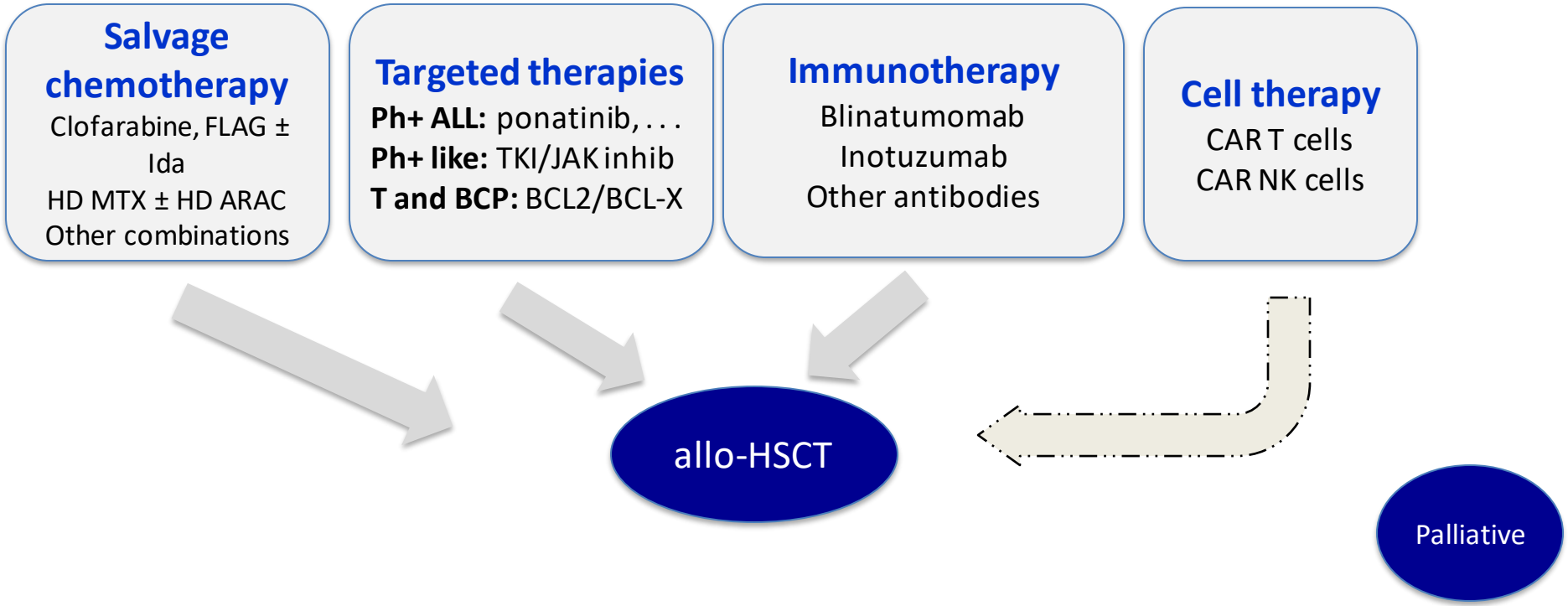
- Pfizer: speaker and advisory boards honoraria, clinical trials
- AMGEN: speaker and advisory boards honoraria, research support, clinical trials
- Shire: speaker and advisory boards honoraria
- Ariad: speaker and advisory boards honoraria, clinical trials
- Takeda: speaker and advisory boards honoraria, clinical trials
- Novartis: speaker and advisory boards honoraria

Current Results of Treatment in Adult ALL

Subset	Overall Survival Rates
Burkitt-like ALL	75%–85%
Ph-negative, standard-risk, B-lineage ALL	60%–70%
Ph-negative, high-risk, B-lineage ALL	40%–50%
Ph-positive ALL	50%–80%
Ph-like ALL	30%–40%
T-ALL, thymic	60%–70%
T-ALL, mature	40%–50%
T-ALL, early	30%–40%

40%–50% of adult ALL patients experience relapse

Treatment Options in Patients With R/R ALL

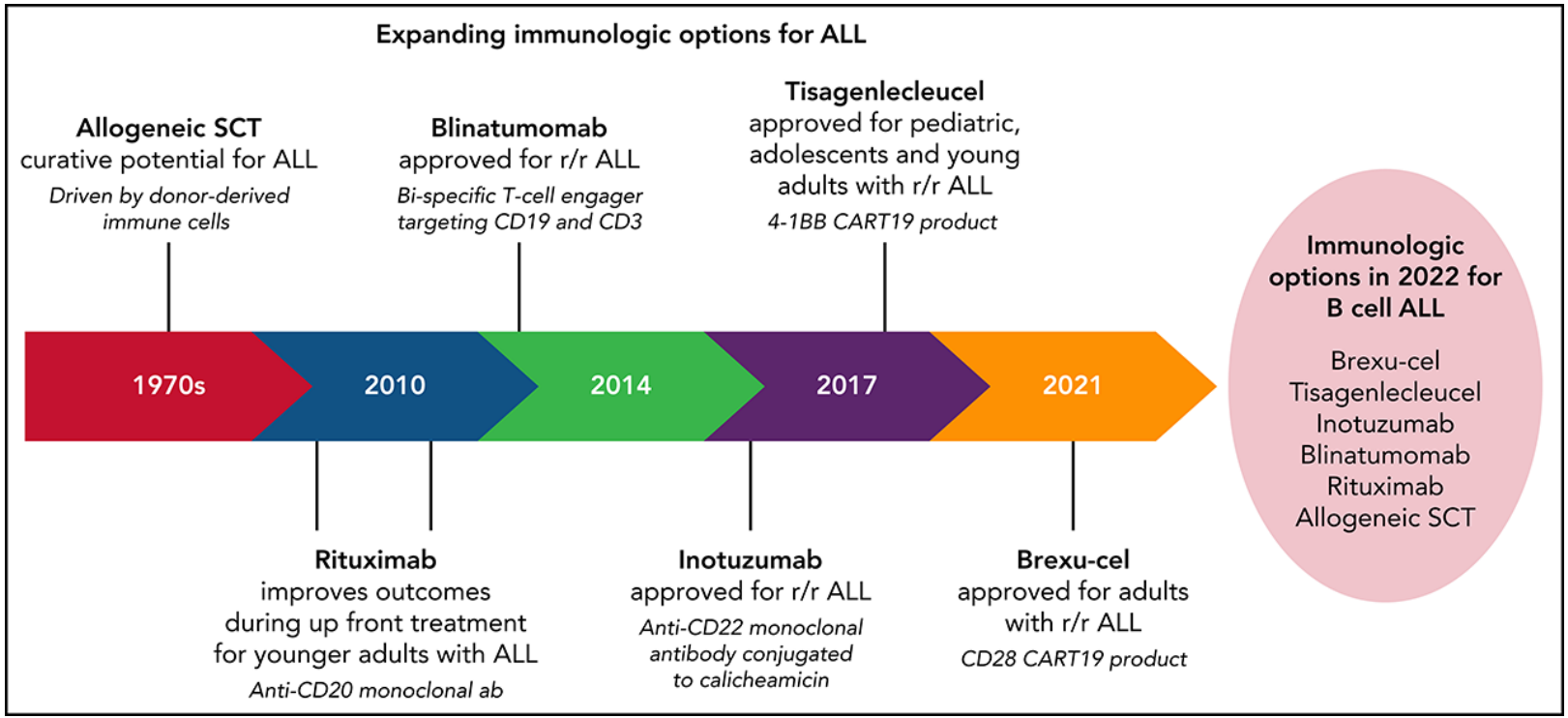


Advances in R/R ALL

- Attenuated chemotherapy + MoAb
- TKI + MoAb (Ph+ ALL)
- Combination of apoptosis inhibitors
- Attenuated chemotherapy + apoptosis inhibitors
- Improvements in CAR T (BCP ALL and T-ALL)
- Precision medicine

Best in combination

Current Immunotherapies for ALL



Frey NV. *Blood.* 2022;140:11-15.

Targeted Therapies and Immunotherapy in ALL

Target	Subtype of ALL	Precision Medicine/Immunotherapy
BCR::ABL1	Mainly B-lineage ALL	ABL TKI such as imatinib, dasatinib, and ponatinib
ABL-class abnormalities: *ABL1*, *ABL2*, *PDGFRB*, *CSF1R*	Ph-like ALL with *ABL*-class abnormalities	ABL TKI such as imatinib, dasatinib, and ponatinib
NTRK3 rearrangement	Ph-like ALL	Larotrectinib
JAK-STAT signaling	Ph-like ALL	*JAK* inhibitors such as ruxolitinib
FLT3	*KMT2A*-rearranged ALL	*FLT3* inhibitors such as lestaurtinib and midostaurin
Epigenetic abnormalities	*KMT2A*-rearranged ALL	Demethylating agents such as azacytidine; HDAC inhibitors such as panobinostat
Components of the aberrant *KMT2A* complex such as menin and DOT1L	*KMT2A*-rearranged ALL	Menin inhibitors, DOT1L inhibitors
BCL2	*KMT2A*-rearranged ALL, *TCF3::HLF*-rearranged ALL, immature T-ALL	Venetoclax
BCL-XL	T-ALL	Navitoclax
Purine nucleoside pathway	*KMT2A* rearranged ALL, T-ALL	Clofarabine in *KMT2A*-rearranged ALL, nelarabine in T-ALL
Proteasome	T-ALL	Proteasome inhibitor such as bortezomib
LCK	Mature T-ALL	Dasatinib
CD19	B-lineage ALL	Blinatumomab
CD19	B-lineage ALL	CD19-directed CAR T cells
CD22	B-lineage ALL	Inotuzumab
CD22	B-lineage ALL	CD22-directed CAR T cells
CD7	T-ALL	CD7-directed CAR T cells
CD38	T-ALL	Daratumumab

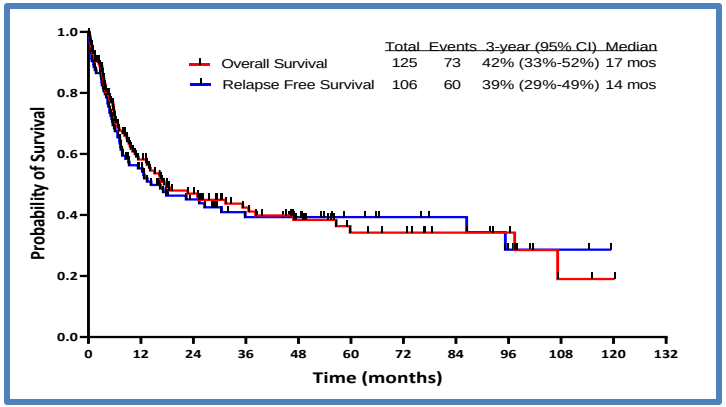
Pieters R, et al. *J Clin Oncol.* 2023.

Therapies for R/R ALL

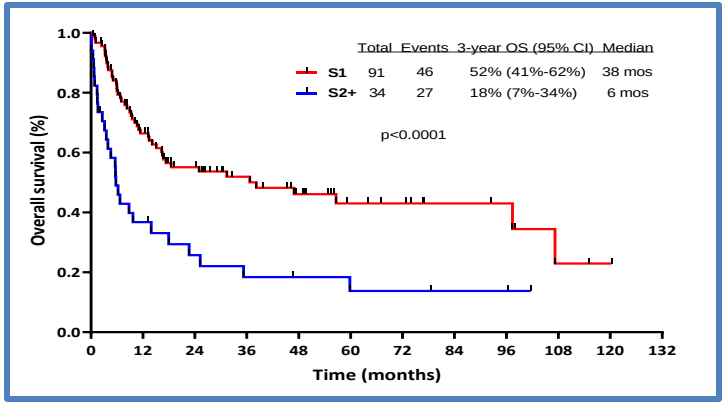
- **BCP ALL**
  - **Proven efficacy**
    - Blinatumomab and inotuzumab (isolated or sequentially), ideally combined with low-dose CHT, and followed by allo-HSCT
    - CD19 CAR T trispecific MoAb (approved after 2 Tx lines or in pts with relapse after HDSCT)
    - Blinatumomab (and also InO) in MRD+ relapses
    - TKI (ponatinib) and immunotherapy in Ph+ ALL
  - **Under research**
    - Menin inhibitors, FLT3 inhibitors, DOT1L inhibitor, demethylating agents (*KMT2A*r ALL)
    - Blinatumomab/InO for Ph-like ALL
    - SC blinatumomab
    - CD22-directed MoAb conjugated to SG3199, trispecific MoAb . . .
    - BCL-2/BCL-XL inhibitors
    - CD22 CAR T, CD19/22 CAR T
- **T-ALL**
  - **Approved:** Nelarabine, clofarabine . . .
  - **Under research:** BCL-2/BCL-XL inhibitors, proteasome inhibitors, anti-CD38 MoAb,
    Combinations of the above ± CHT
    CAR T (CD7, CD5 . . .)

Mini-HCVD + INO ± Blina in R/R B-ALL

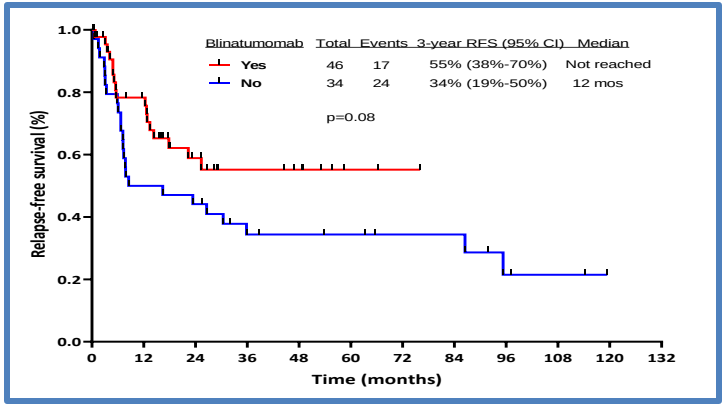
Entire cohort



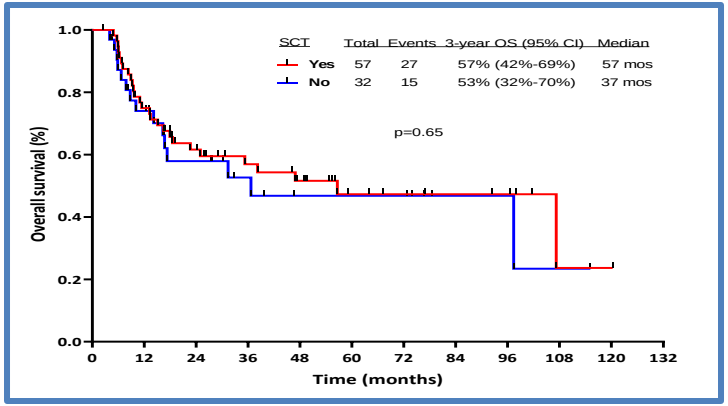
By line of therapy



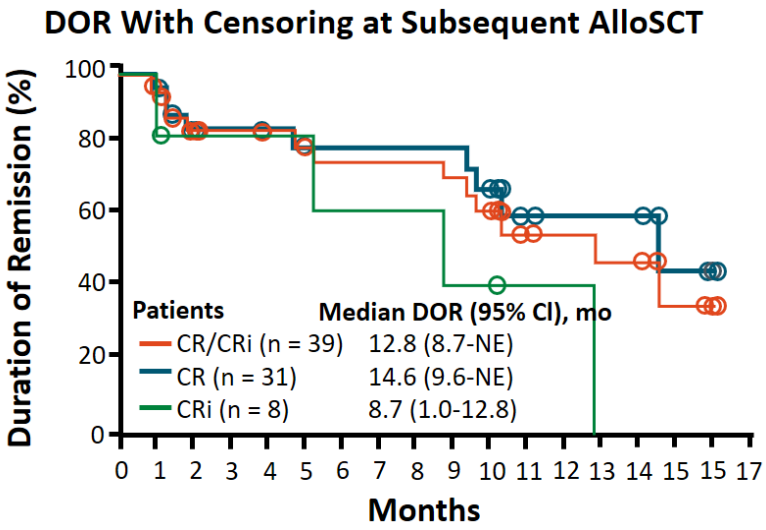
By receipt of blinatumomab

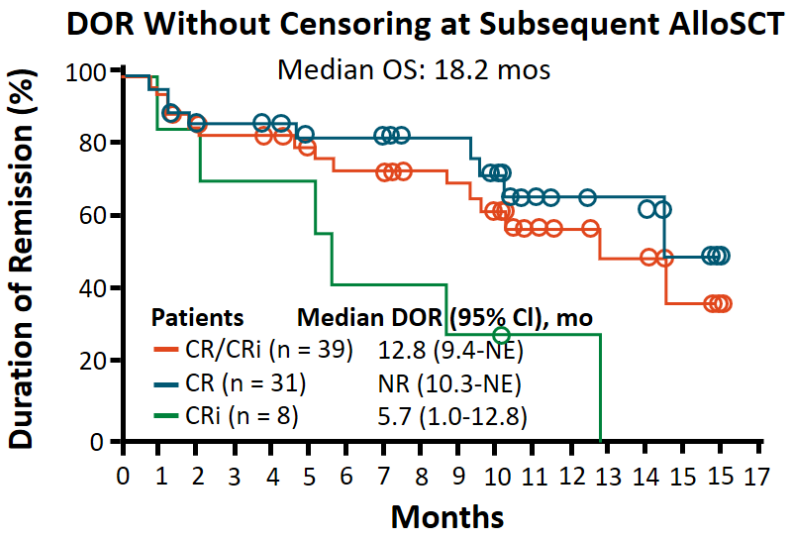


By subsequent allo-HSCT



Brexu-Cel



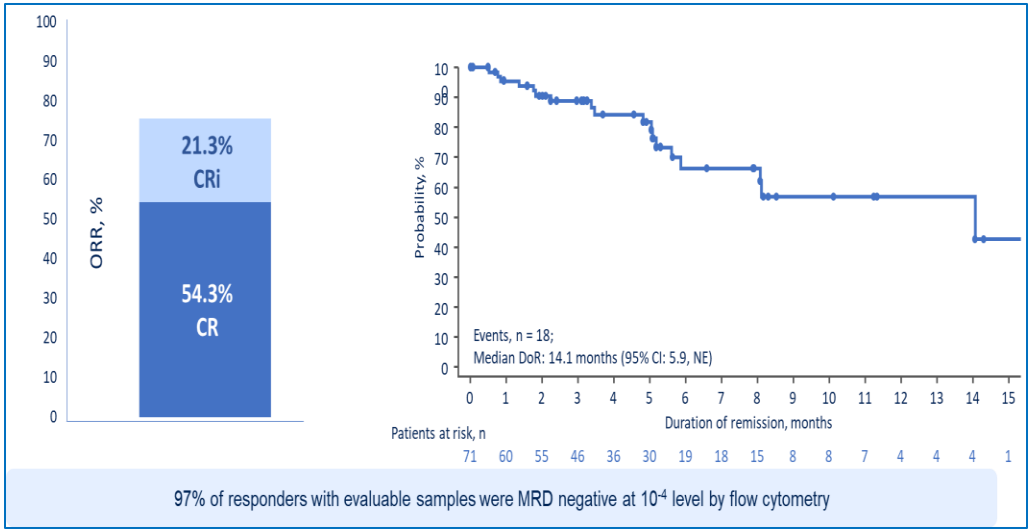


- 10 patients (18%), including 9 with CR/CRi and 1 with BFBM, received allo-SCT at a median of 98 days (range, 60-207) post-infusion
- As of the data cutoff, 12 of 39 patients who achieved CR/CRi (31%) were in ongoing remission without allo-SCT

Shah et al. *Lancet.* 2021;398:491; Sha et al. EHA 2021. Abstract S117.

Obe-cel in R/R ALL

- 112 pts enrolled, 94 infused
- BM ≤20%: 100 × 10^6 CAR T cells on D1, and 310 × 10^6 CAR T cells on D10
- BM >20%: 10 × 10^6 CAR T cells on D1, and 400 × 10^6 CAR T cells on D10 31% S3+
- ORR = 76% (CR = 54%); ITT = 63% (CR = 46%)
- MRD negativity 97%; DOR 14.1 mo
- G3 CRS 3.2% and ICANS 7.4%

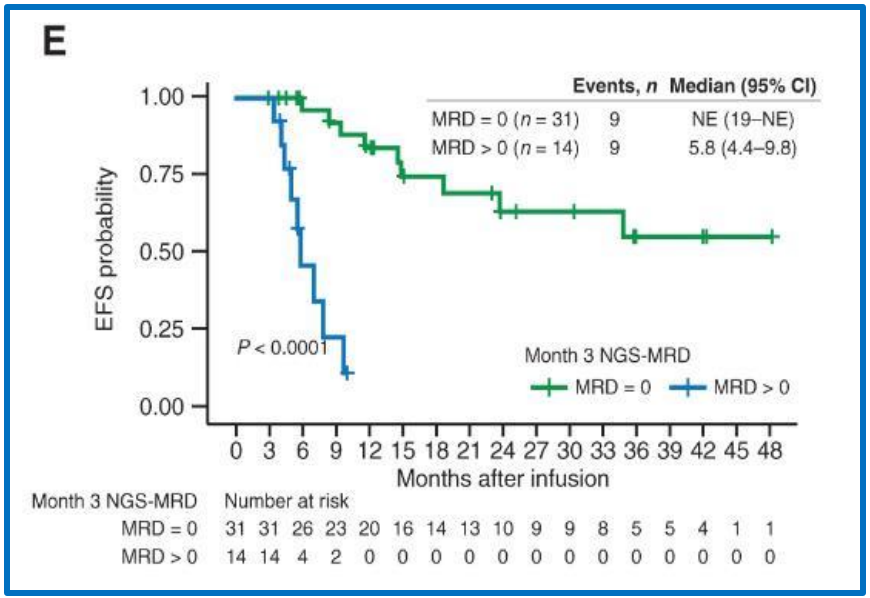


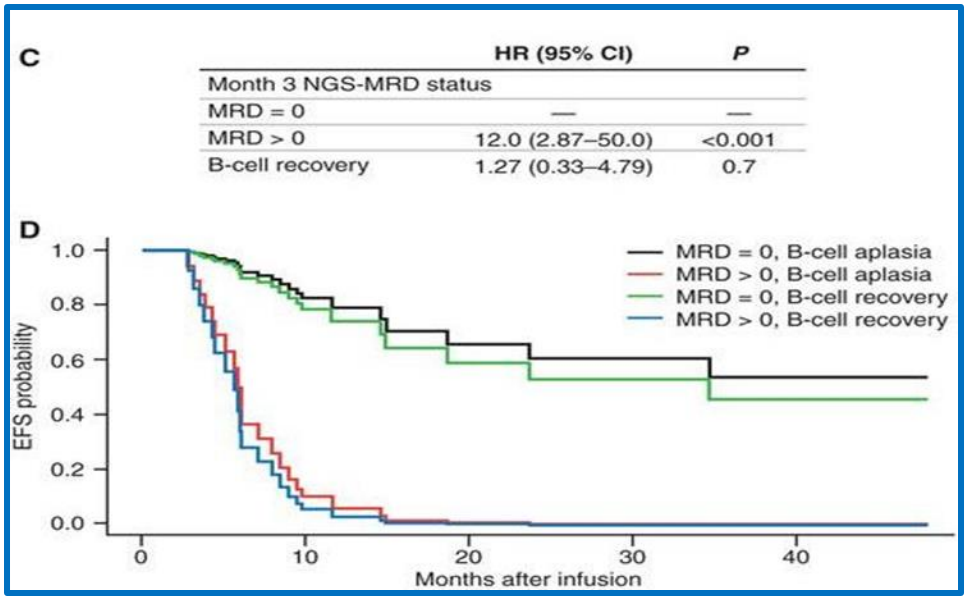
	BM blasts ≤20% at pre-conditioning (N = 37)	BM blasts >20% at pre-conditioning (N = 57)	All infused patients (N = 94)
CRS			
Any grade, n (%)	24 (64.9)	47 (82.5)	71 (75.5)
Grade ≥3, n (%)	1 (2.7)	2 (3.5)	3 (3.2)
ICANS			
Any grade, n (%)	5 (13.5)	19 (33.3)	24 (25.5)
Grade ≥3, n (%)	1 (2.7)	6 (10.5)	7 (7.4)

Roddie C, et al. EHA 2023.

NGS MRD Negativity After CAR T-Cell Therapy for ALL

- Detectable MRD after tisa-cel by NGS independently predicted for EFS and OS
- NGS MRD status at 3 months was superior to B-cell aplasia/recovery at predicting relapse/survival



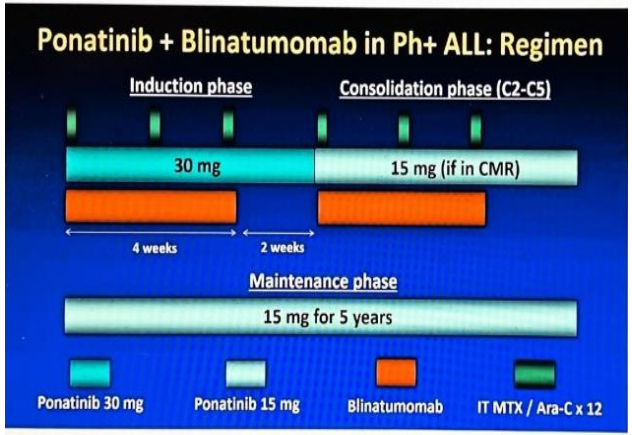


Pulsipher MA, et al. *Blood Cancer Discov.* 2022;3(1):66-81.

Ponatinib and Blinatumomab for Patients With R/R Ph+ ALL

Phase II study: newly diagnosed (ND) Ph+ ALL, R/R Ph+ ALL, or CML-LBP

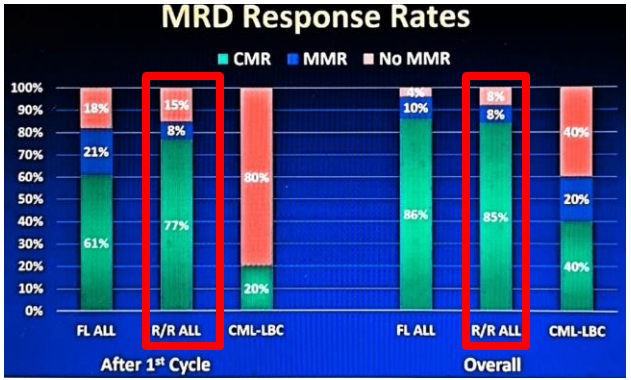
Treatment: Up to 5 cycles of blina. Ponatinib 30 mg/d during cycle 1, 15 mg/d once CMR. Ponatinib at least 5 y. IT × 12 cycles

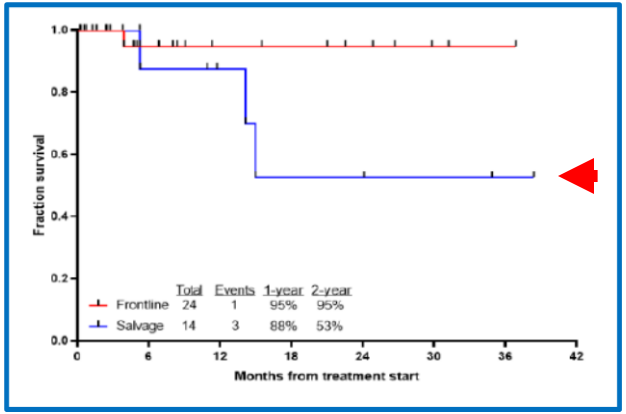


Response Rates

Response, n/N (%)	All N = 50	Frontline Ph+ ALL N = 30	R/R Ph+ ALL N = 14	CML-LBC N=6
CR/CRp/CRi*	36/39 (92)	19/20 (95)	12/13 (92)	5/6 (83)
CR	33 (85)	18 (94)	11 (85)	4 (67)
CRp	2 (5)	1 (6)	0	1 (17)
CRi	1 (3)	0	1 (8)	0
PR	1 (3)	0	0	1 (17)
MMR	43/47 (91)	28/29 (97)	12/13 (92)	3/5 (60)
CMR	38/47 (81)	25/29 (86)	11/13 (85)	2/5 (40)
Early death	1 (3)	1 (6)	0	0

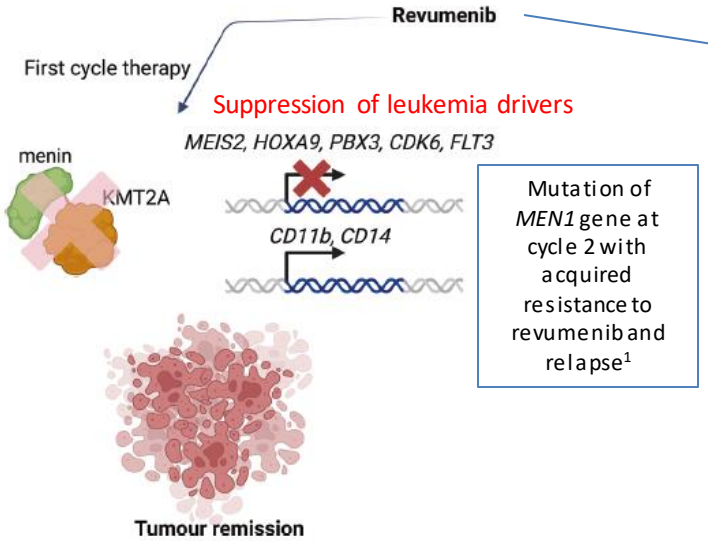
* 10 frontline pts and 1 salvage pt in MRD+ CR at start





Short N, et al. ASH 2021. Abstract 2298.

Phase Ib trial: Menin Inhibitor (revumenib)



Mutation of *MEN1* gene at cycle 2 with acquired resistance to revumenib and relapse[1]

Clinical trial (R/R *KMT2A*r and *NPM1*mut ALs)[2]

Median age = 42.5; prior lines 1-12 (4)

Efficacy population (response %)

		ORR	CR	CRh	MRDneg*
N	60	53	**30**	**10**	78
***KMT2A*r**	46	59	**20**	**13**	73
ALL subset	10		**40**		

*CR/CRh patients.

Revumenib doses of 226 mg q12h and 276 mg q12h in Arm A, and 113 mg q12h and 163 mg q12h in Arm B* met the prespecified criteria for RP2D.

*Pts on strong cytochrome P450 inhibitors.

RP2D, recommended phase II dose.

1. Di Fazio P, et al. *Signal Transd Targ Ther.* 2023:8;384; 2. Issa GC, et al. *Nature*. 2023;615:920.

BCL-2/BCL-X_L inhibitors: Venetoclax and Navitoclax for R/R ALL

Phase I open-label dose escalation, multi-center study

- ✓ Venetoclax 400 mg/day
- ✓ Navitoclax dose escalation
- ✓ Chemotherapy

N = 47 R/R ALL enrolled

N = 19 R/R T-ALL

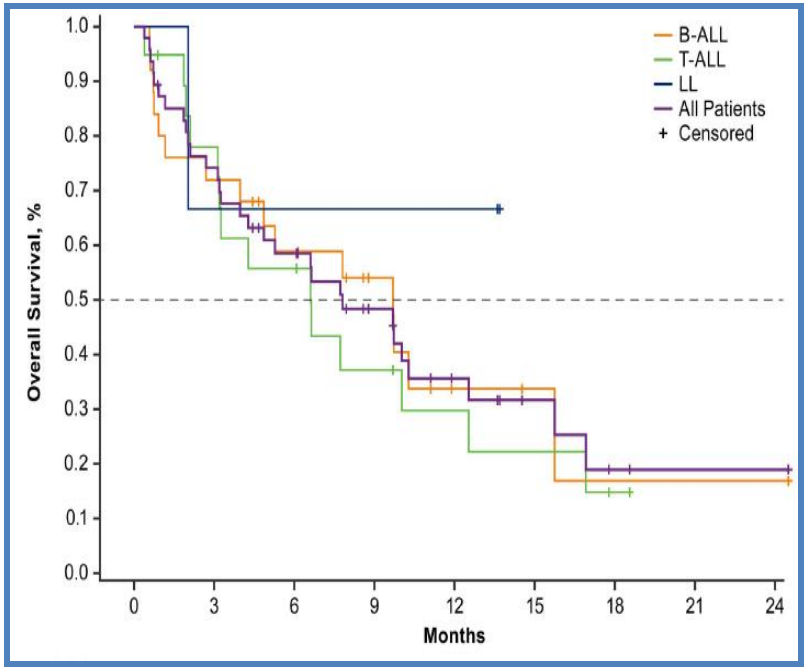
T-ALL (CR/CRi/CRp): 55.6%

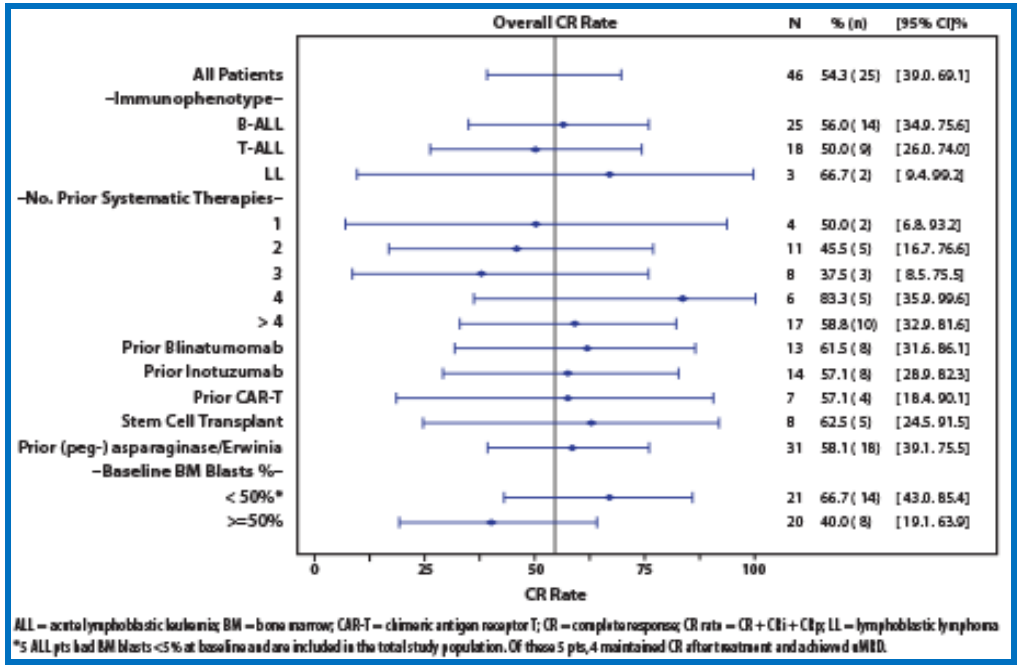
- ETP (8/12): **66.7%**
- Non-ETP (2/6): 33%

Parameter	B-ALL (*n* = 25)	T-ALL (*n* = 19)	LL (*n* = 3)	All patients[a] (N = 47)
Response[b], *n* (%)				
CR rate (CR/CR_i/CR_p)	16 (64.0)	10 (52.6)	2 (66.7)	28 (59.6)
PR	3 (12.0)	0	0	3 (6.4)
SD	2 (8.0)	6 (31.6)	0	8 (17.0)
PD	4 (16.0)	3 (15.8)	1 (33.3)	8 (17.0)
Patients with ALL and morphologic CR at baseline, *n*	*n* = 1	*n* = 4	NA	*n* = 5
Response, *n* (%)				
CR rate (CR/CR_i/CR_p)	0	3 (75.0)		3 (60.0)
SD	0	1 (25.0)		1 (20.0)
NE[c]	1 (100)	0		1 (20.0)
DOR[d] in all responders				
n	19	10	2	31
Median (95% CI), mo	9.1 (1.4–14.6)	4.2 (0.8–12.3)	NE (NE–NE)	4.2 (2.3–11.5)
OS				
Median (95% CI), mo	9.7 (4.0–15.7)	6.6 (3.2–12.5)	NE (2.0–NE)	7.8 (4.0–12.5)
12-month (95% CI), %	33.8 (13.7–55.2)	29.7 (10.4–52.2)	66.7 (5.4–94.5)	35.6 (20.9–50.7)
Bone marrow MRD, *n* (%)				
MRD negative ($<10^{-4}$)	9 (36.0)	6 (31.6)	1 (33.3)	16 (34.0)
MRD positive	10 (40.0)	3 (15.8)	1 (33.3)	14 (29.8)
Other[e]	6 (24.0)	10 (52.6)	1 (33.3)	17 (36.2)

Pullarkat VA, et al. *Cancer Discov.* 2021;11:1440-1453.

Venetoclax and Navitoclax in R/R ALL and LBL





B-ALL: 25, T-ALL: 19, LL: 3

CR: 60%

Recommended dose for phase II: 400 mg Ven + 50 mg Nav (25 for <45 kg)

Pullarkat VA, et al. *Cancer Discov.* 2021;11:1440-1453.

Daratumumab+ VCR-DNR-PDN-ASP in children and AYA (n = 29) with R/R T-ALL (DELPHINUS trial, NCT03384654)

Patients: 24 child (age 1-17 y), 5 YA (age 18-30 y) ALL pts, and 10 LL pts (age 1-30 y)
Median (range) age: 10.0 (2-25) y (ALL) and 14.5 (5-22) y (LL); Initial
Median (range) cycles received: 2 (1-3)
Safety

- All pediatric ALL pts had a grade 3/4 TEAE
- No pediatric ALL pt discontinued DARA due to AEs
- 1 (4.2%) died due to TEAEs (brain edema and hepatic failure) unrelated to DARA

Conclusions: The addition of DARA to VPLD showed improved response rates compared with those achieved with backbone therapy alone, with a manageable safety profile

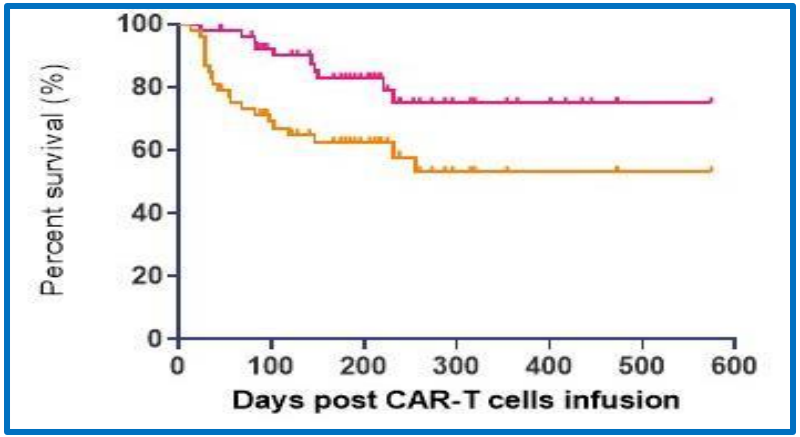
Group	CR	ORR
Pediatric (ALL) (N = 24)	10 (42%)*	CR: 13, CRi 7. ORR 20 (83%)
YA (ALL) (n = 5)	3 (60%)	3(60%)
LyL (n = 10)	4 (40%)	4 (40%)

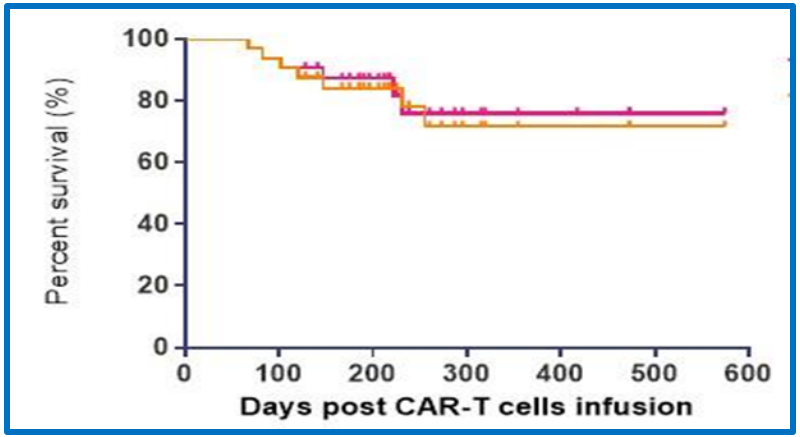
*10 (41.7%) pediatric ALL pts achieved MRD negativity.

Hgan LE, et al. ASCO 2022. Abstract 10001.

R/R T-ALL and T-LBL Rx With CD7-Targeted CAR T Cell

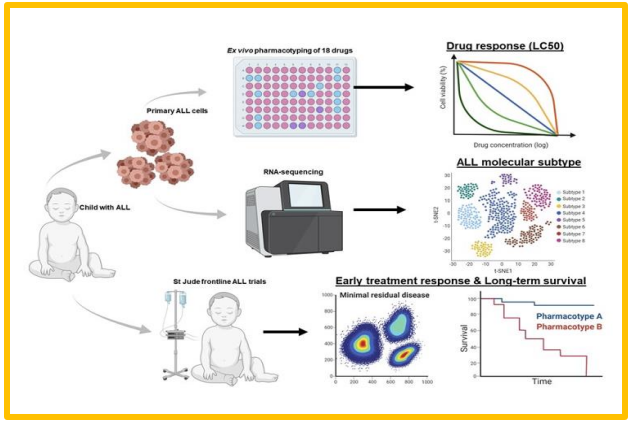
- Novel fratricide-resistant naturally selected 7CAR-T cells (NS7CAR) from bulk T cells without additional genetic selection
- 52 pts with R/R T-ALL (n = 34) and T-LBL (n = 18); median age 22 yr (2–47)
- Median prior lines of Rx 5 (2–15)
- Median FU 206 days
- MRD-negative CR 96%
- 5 pts had G3 CRS, and 1 had G4 CRS
- 18-mo OS 75%; EFS 53%
- 32 pts (61%) had allo-SCT
- 18-mo OS 76% and EFS 71.5%





Zhang X, et al. *Blood.* 2022;140(suppl 1):2369-2370. Abstract 980.

Pharmacotypes Across the Genomic Landscape of Pediatric ALL: Impact on Tx



- 805 children with ND ALL from SJCRH
- Pharmacotyping of 8 drugs and 23 ALL subtypes
- 6 functional clusters based on pharmacotypes
- Drug sensitivity cluster significantly associated with EFS, even after adjusting for MRD

- **B-ALL**
  - ***ETV6-RUNX1* and hyperdiploidy:** ↑ sensitivity to ASP and GLUC
  - ***KMT2A, BCR-ABL1, BCR-ABL1*-like:** resistant to ASP and GLUC
  - ***DUX4* and *ETV6-RUNX1*-like:** resistance to many cytotoxic drugs
  - ***BCR-ABL1, BCR-ABL1*-like, *CRLF2*:** distinctive drug sensitivity profiles
  - Sensitivities to ASP, GLUC, cytarabine, and thiopurines positively correlated with MRD
- **T-ALL**
  - **ETP-ALL:** resistant to most cytotoxic drugs compared with T-ALL
  - Sensitivities to ASP, GLUC, cytarabine, and thiopurines not correlated with MRD

Lee S, et al. ASH 2022. Abstract 719.

Conclusions on Tx of R/R ALL

- Single-agent (immuno) therapy insufficient
- **Combinations improve results**: chemo + immunotherapy, chemo + BCL2/BCLx inhibitors, BCL2/BCLx inhibitors + immunotherapy . . .
- **Cellular therapy necessary**: allo-HSCT, CAR T, CAR T → allo-HSCT
- **Pharmacotyping**: Possibility of selection of therapy according to genetic background


Thank you
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Global Leukemia Academy

Q&A

APTITUDE HEALTH

Global Leukemia Academy

Current treatment options for relapsed AML in adult and elderly patients

Charles Craddock

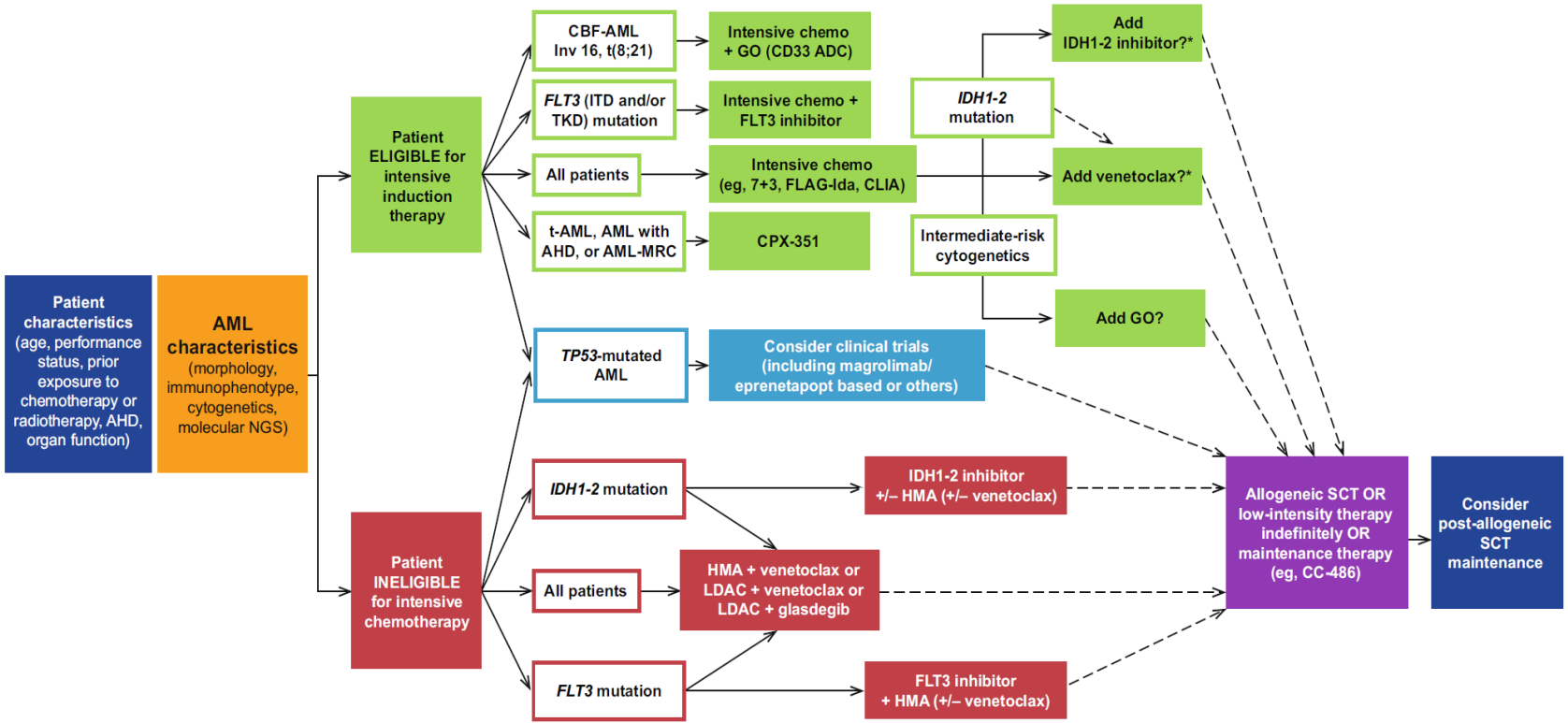
APTITUDE HEALTH

Current treatment options for relapsed AML in adult and elderly patients

Charles Craddock, CBE, MD, PhD, FMedSci

University of Warwick,
Centre for Clinical Haematology,
Queen Elizabeth Hospital Birmingham

Evolving diagnostic and treatment paradigm for newly diagnosed AML

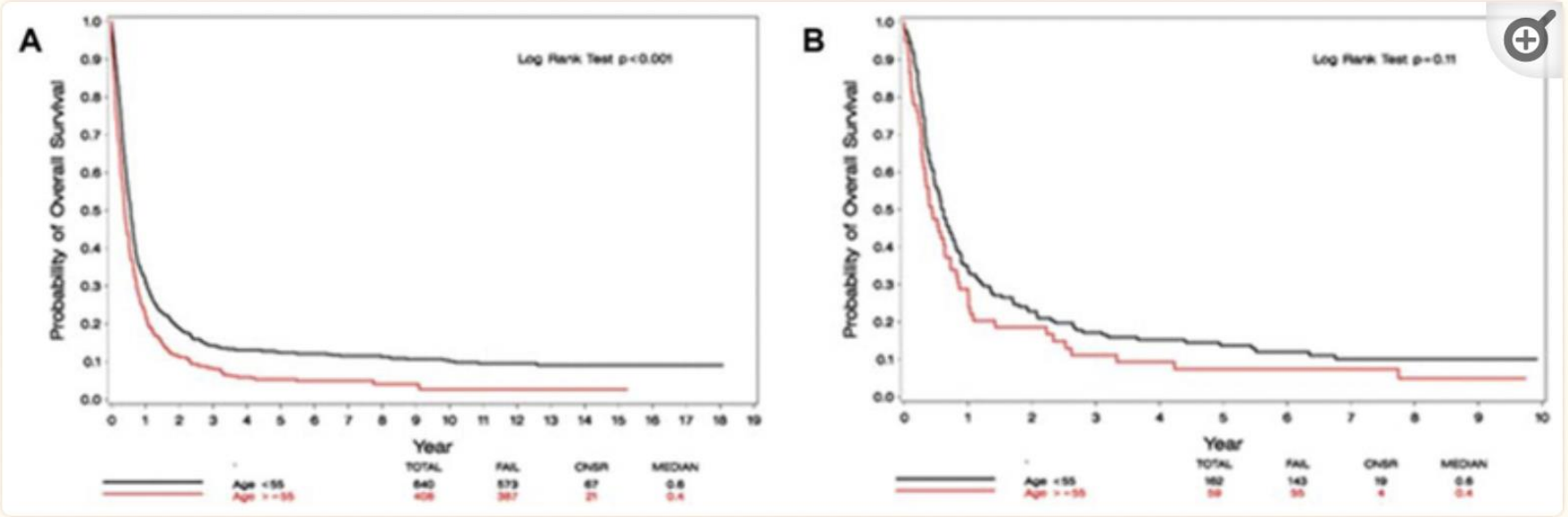


Disease relapse is the major barrier to long-term survival in adult AML

- Disease relapse remains the major cause of treatment failure in adults with AML treated with curative intent using either IC or allo-SCT
- Outcome after relapse is poor and strategies with the potential to reduce disease recurrence are urgently required
- Key to the effective implementation of strategies to reduce the risk of relapse is characterization of relapse biology

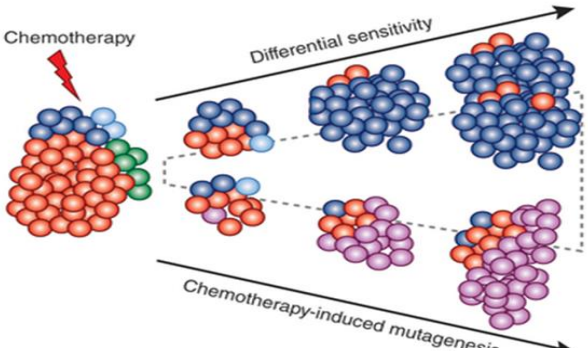
Loke J, et al. *Br J Haematol.* 2020

Outcome in relapsed AML: Age, cytogenetics, duration of CR1, allograft exposure predict survival



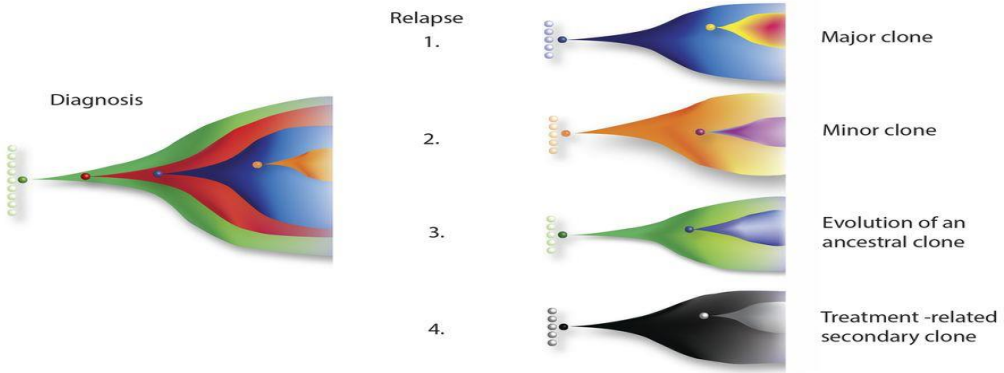
Ganzel et al. 2019.

Clonal evolution and importance of repeat genomic testing at time of AML recurrence



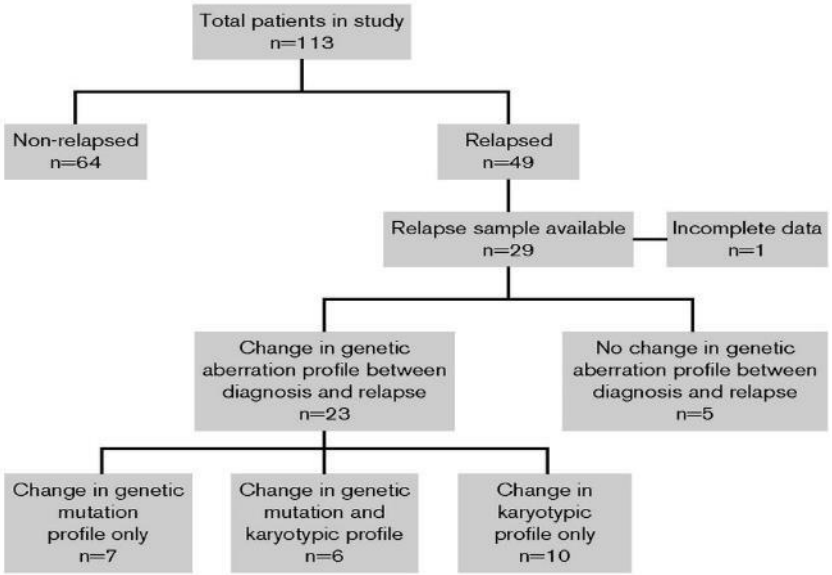
Leukemia is not a static condition

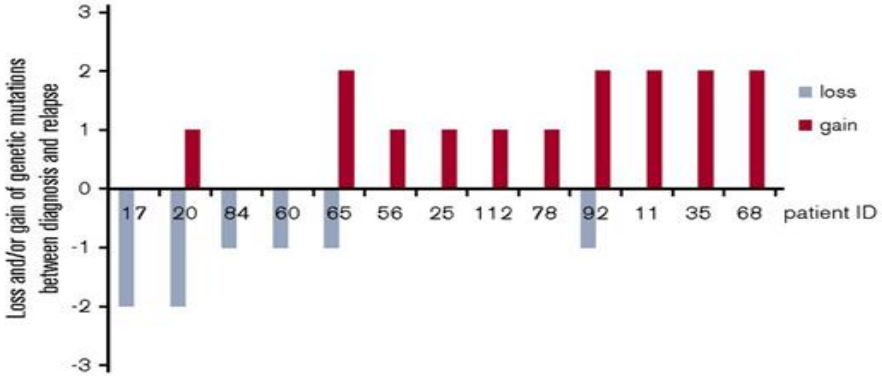
Repeat genomic analysis at relapse is necessary



Kleppe M, et al. *Nat Med.* 2014; Grimwade D, et al. *Blood.* 2016

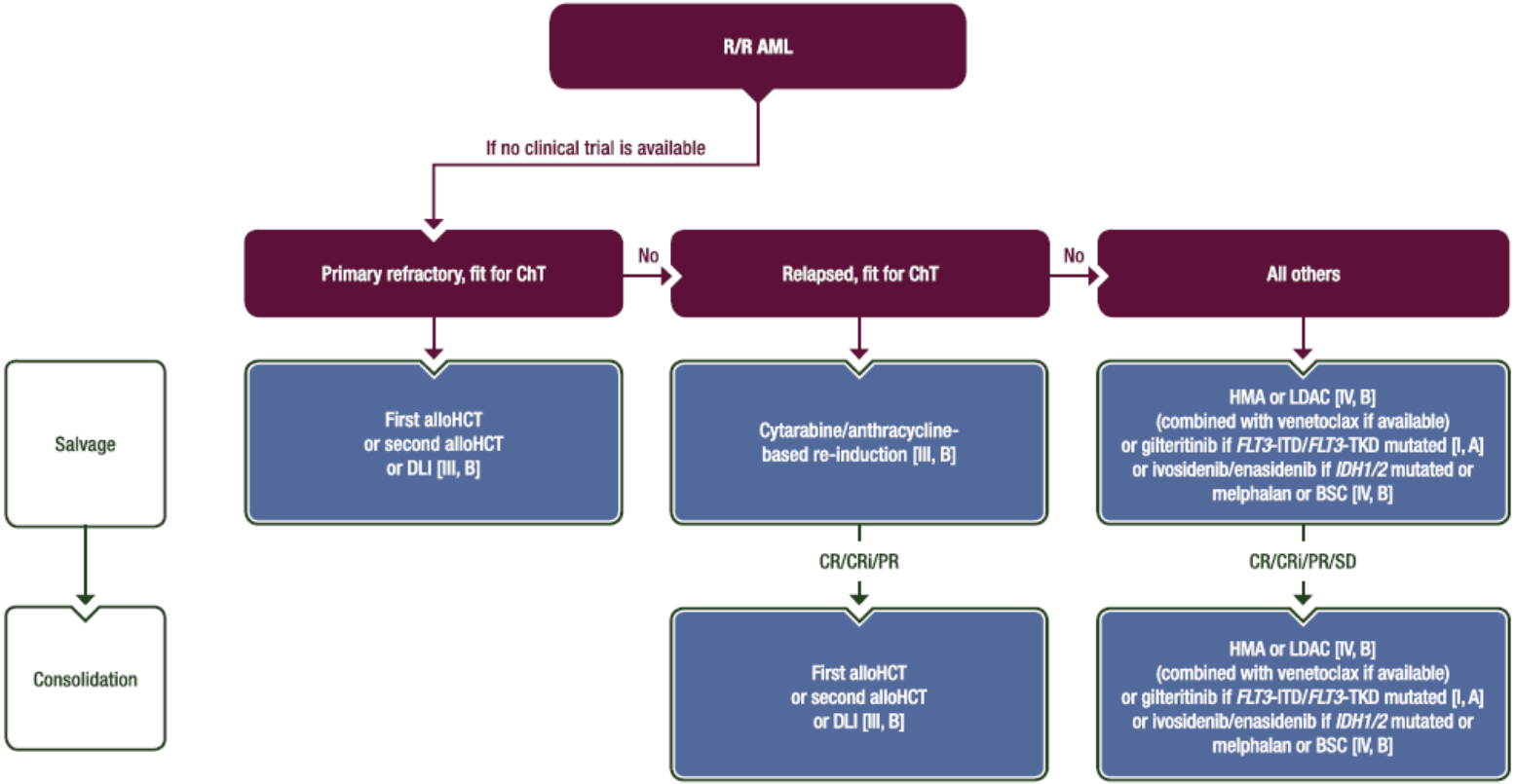
Mutational instability at disease relapse informs the choice of relapse therapies





Quek L, et al. *Blood Adv.* 2016.

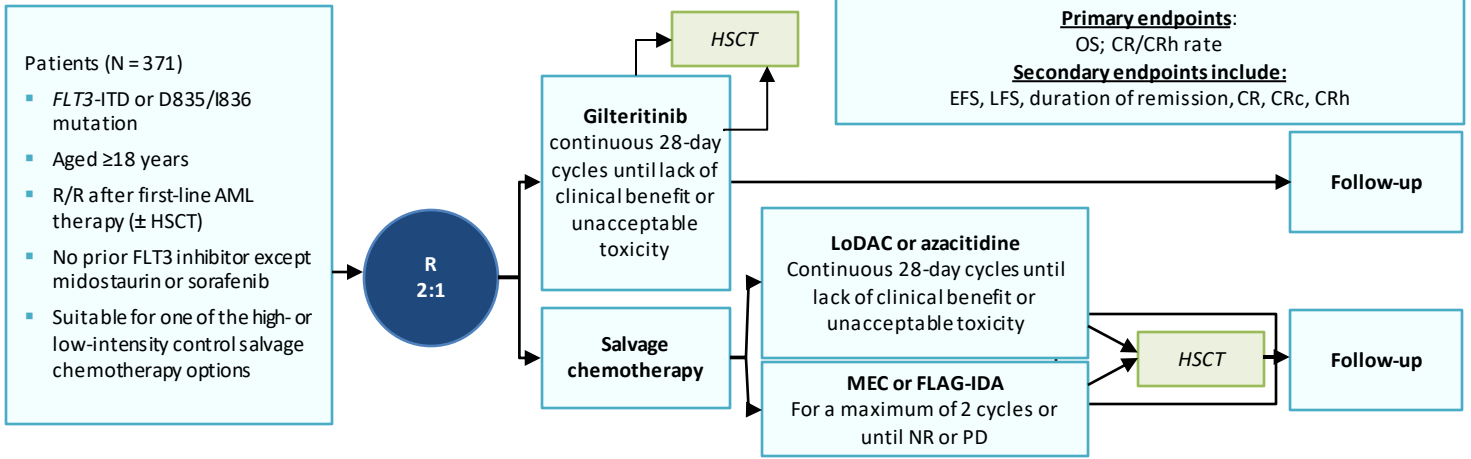
ESMO guidelines for R/R AML



Heuser M, et al. *Ann Oncol.* 2020.

Gilteritinib: Phase III ADMIRAL trial

MONOTHERAPY VS SALVAGE CHEMOTHERAPY (ADMIRAL; NCT02421939)



- ADMIRAL addresses gilteritinib efficacy in the R/R disease setting compared with salvage chemotherapy; the study includes patients who are and are not fit for high-intensity chemotherapy
- On the basis of data from the ADMIRAL study, gilteritinib is approved in over 40 other countries for treatment of adults with *FLT3*-mutated R/R AML

Perl et al. *NEJM.* 2019.

ADMIRAL: Baseline demographics

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).*

Characteristic	All Patients (N=371)	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)
Age — yr			
Median	62.0	62.0	61.5
Range	19.0–85.0	20.0–84.0	19.0–85.0
Female sex — no. (%)	201 (54.2)	131 (53.0)	70 (56.5)
Cytogenetic risk status — no. (%)			
Favorable	5 (1.3)	4 (1.6)	1 (0.8)
Intermediate	271 (73.0)	182 (73.7)	89 (71.8)
Unfavorable	37 (10.0)	26 (10.5)	11 (8.9)
Unknown	58 (15.6)	35 (14.2)	23 (18.5)
Previous therapy for AML — no. (%)			
Anthracycline	311 (83.8)	205 (83.0)	106 (85.5)
FLT3 inhibitor	46 (12.4)	32 (13.0)	14 (11.3)
HSCT	74 (19.9)	48 (19.4)	26 (21.0)
Response to first-line therapy before enrollment — no. (%)†			
Relapse	225 (60.6)	149 (60.3)	76 (61.3)
Primary refractory disease without HSCT	146 (39.4)	98 (39.7)	48 (38.7)
Preselected salvage chemotherapy per IRT — no. (%)			
High-intensity chemotherapy	224 (60.4)	149 (60.3)	75 (60.5)
Low-intensity chemotherapy	147 (39.6)	98 (39.7)	49 (39.5)
FLT3 mutation subtype — no. (%)‡			
ITD only	328 (88.4)	215 (87.0)	113 (91.1)
TKD only	31 (8.4)	21 (8.5)	10 (8.1)
ITD and TKD	7 (1.9)	7 (2.8)	0

* The intention-to-treat population included all the patients who underwent randomization. Percentages may not total 100 because of rounding. AML denotes acute myeloid leukemia, HSCT hematopoietic stem-cell transplantation, ITD internal tandem duplication, and TKD tyrosine kinase domain.
† Response was based on findings from interactive response technology (IRT).
‡ Central laboratory confirmed the *FLT3* mutation status. Five patients (1.3%) had unconfirmed *FLT3* mutations; four patients (1.6%) were assigned to the gilteritinib group and one (0.8%) to the chemotherapy group.

Perl et al. *NEJM.* 2019.

ADMIRAL: Adverse event profile

Table 3. Incidence of Adverse Events during Treatment That Occurred in at Least 20% of the Patients in Either Treatment Group (Safety Analysis Population).*

Event	Gilteritinib (N=246)			Salvage Chemotherapy (N=109)		
	Adverse Event of Any Grade	Grade ≥3 Adverse Event	Serious Adverse Event	Adverse Event of Any Grade	Grade ≥3 Adverse Event	Serious Adverse Event
	number of patients (percent)					
Febrile neutropenia	115 (46.7)	113 (45.9)	76 (30.9)	40 (36.7)	40 (36.7)	9 (8.3)
Anemia	116 (47.2)	100 (40.7)	8 (3.3)	38 (34.9)	33 (30.3)	0
Pyrexia	105 (42.7)	8 (3.3)	32 (13.0)	32 (29.4)	4 (3.7)	1 (0.9)
Alanine aminotransferase increased	103 (41.9)	34 (13.8)	13 (5.3)	10 (9.2)	5 (4.6)	0
Diarrhea	81 (32.9)	9 (3.7)	10 (4.1)	32 (29.4)	3 (2.8)	0
Aspartate aminotransferase increased	99 (40.2)	36 (14.6)	10 (4.1)	13 (11.9)	2 (1.8)	0
Hypokalemia	71 (28.9)	32 (13.0)	0	34 (31.2)	12 (11.0)	1 (0.9)
Constipation	76 (30.9)	2 (0.8)	0	16 (14.7)	0	0
Fatigue	70 (28.5)	6 (2.4)	4 (1.6)	14 (12.8)	2 (1.8)	1 (0.9)
Platelet count decreased	56 (22.8)	54 (22.0)	5 (2.0)	28 (25.7)	27 (24.8)	0
Cough	72 (29.3)	1 (0.4)	2 (0.8)	11 (10.1)	0	0
Thrombocytopenia	63 (25.6)	56 (22.8)	4 (1.6)	18 (16.5)	18 (16.5)	1 (0.9)
Headache	64 (26.0)	3 (1.2)	5 (2.0)	16 (14.7)	0	0
Peripheral edema	59 (24.0)	1 (0.4)	0	13 (11.9)	0	0
Vomiting	53 (21.5)	1 (0.4)	1 (0.4)	15 (13.8)	0	0
Dyspnea	58 (23.6)	10 (4.1)	10 (4.1)	7 (6.4)	3 (2.8)	2 (1.8)
Blood alkaline phosphatase increased	56 (22.8)	7 (2.8)	1 (0.4)	2 (1.8)	0	0

* The events shown are limited to adverse events that had a difference in incidence of more than 2 percentage points between the treatment groups. The safety population comprised all the patients who had received at least one dose of trial treatment.

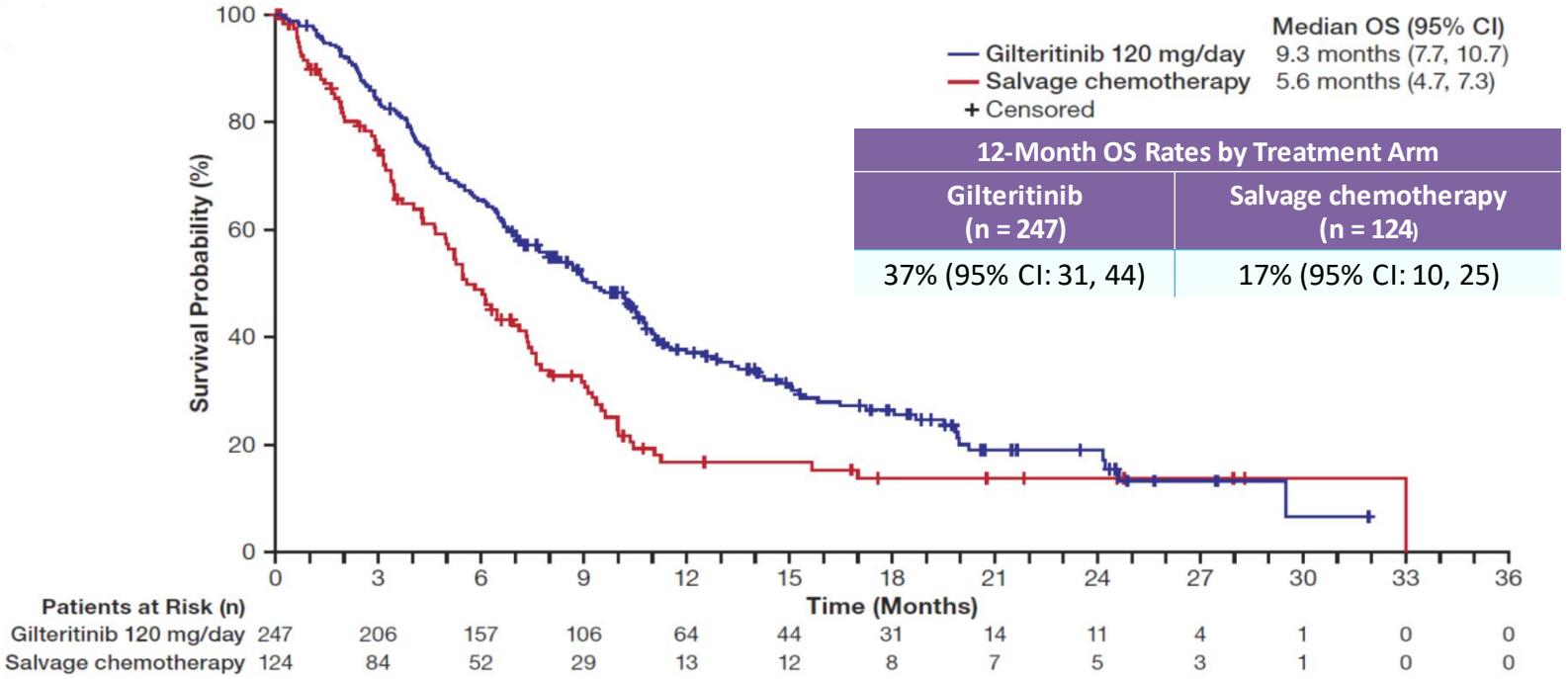
- Incidence of exposure-adjusted AE of grade ≥3 was 19.4 events/PY in gilteritinib group vs 42.44 in chemotherapy group
- Mortality at 30/60 days of ITT in gilteritinib group was 2.0%/7.7% and 10.2%/19.0% in chemotherapy group
- Drug-related fatal AEs occurred in 7 patients in gilteritinib group vs 4 in chemotherapy group

Perl et al. *NEJM.* 2019.

ADMIRAL: Response outcomes (ITT population: N = 371)

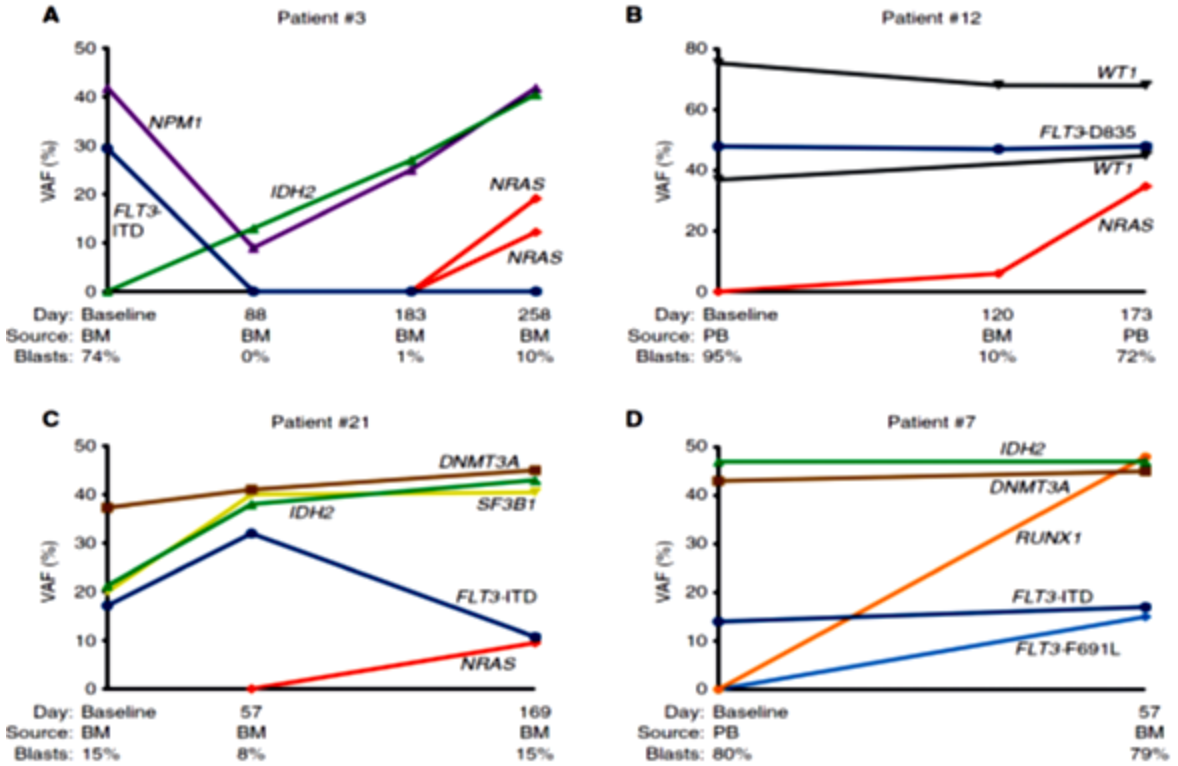
RESPONSE PARAMETER	GILTERITINIB (n = 247)	SALVAGE CHEMOTHERAPY (n = 124)
CR, n (%)	52 (21)	13 (11)
CRh, n (%)	32 (13)	6 (5)
CRi, n (%)	63 (26)	14 (11)
CRp, n (%)	19 (8)	0 (0)
CRc, n (%)	134 (54)	27 (22)
CR/CRh, n (%)	84 (34)	19 (15)
PR, n (%)	33 (13)	5 (4)
ORR, n (%)	167 (68)	32 (26)
NR, n (%)	66 (27)	43 (35)
Mean time to achieve CRc (SD), months	2.3 (1.9)	1.3 (0.5)
Median DOR (95% CI), months	11.0 (4.6, NE)	1.8 (NE, NE)
Allogeneic HSCT, n (%)	63 (26)	19 (15)

ADMIRAL: Overall survival (ITT population: N = 371)



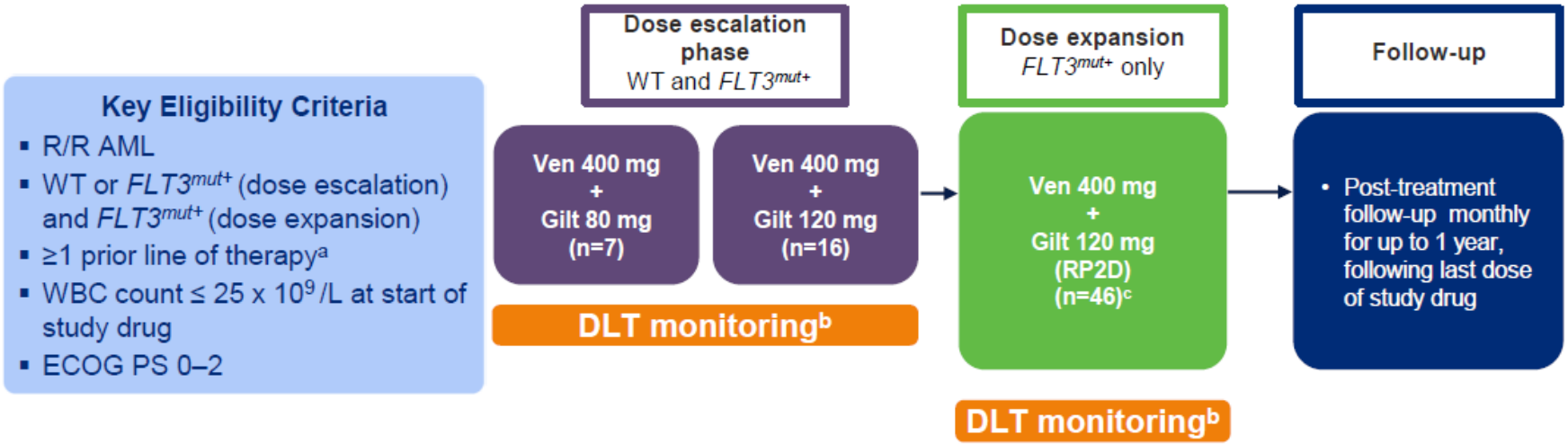
12-Month OS Rates by Treatment Arm	
Gilteritinib (n = 247)	Salvage chemotherapy (n = 124)
37% (95% CI: 31, 44)	17% (95% CI: 10, 25)

Multiple mechanisms of gilteritinib resistance

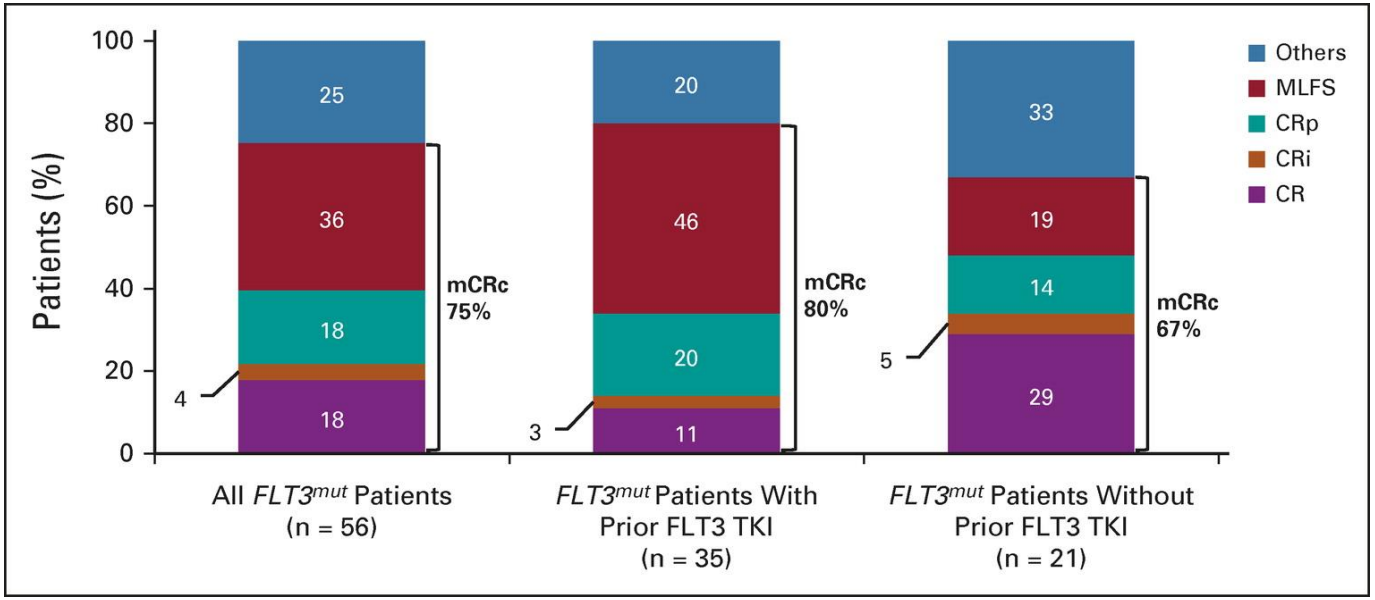


McMahon CM, et al. *Cancer Discov.* 2019.

Gilteritinib and venetoclax: Phase Ib study for *FLT3*+ R/R AML



Gilteritinib-venetoclax is an effective salvage therapy in relapsed *FLT3*+ AML

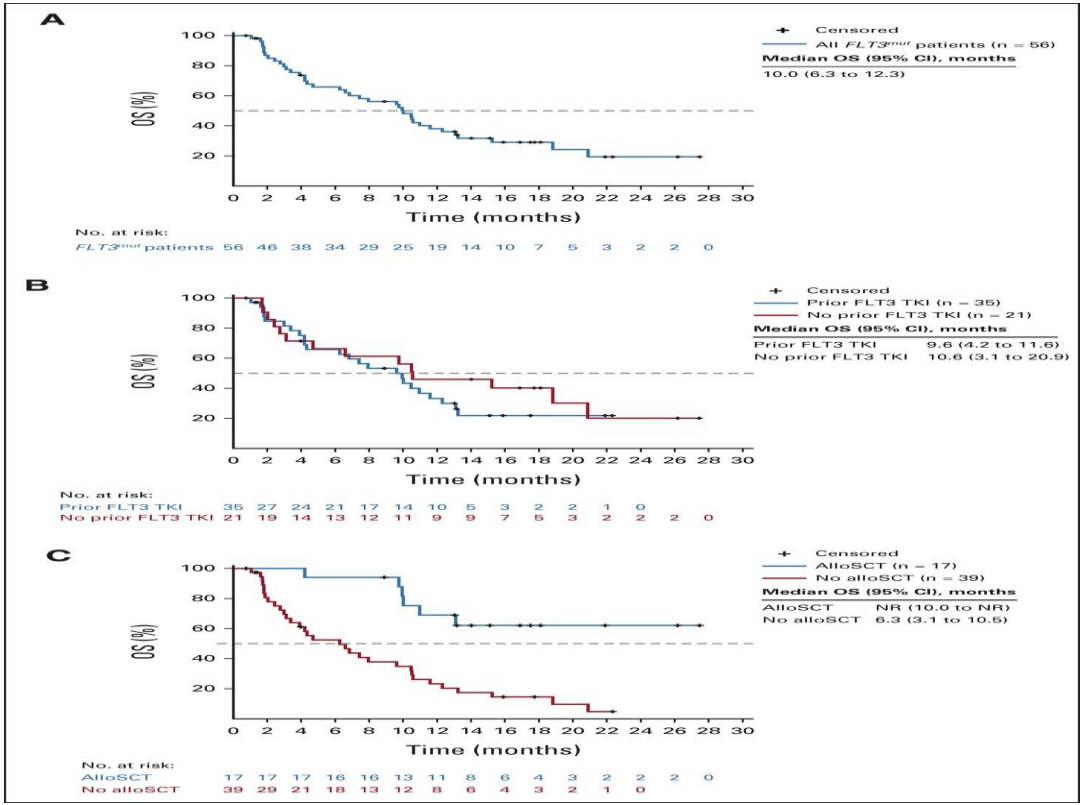


Daver N, et al *J Clin Oncol.* 2022.

Overall survival in relapsed *FLT3*+ AML: Impact of

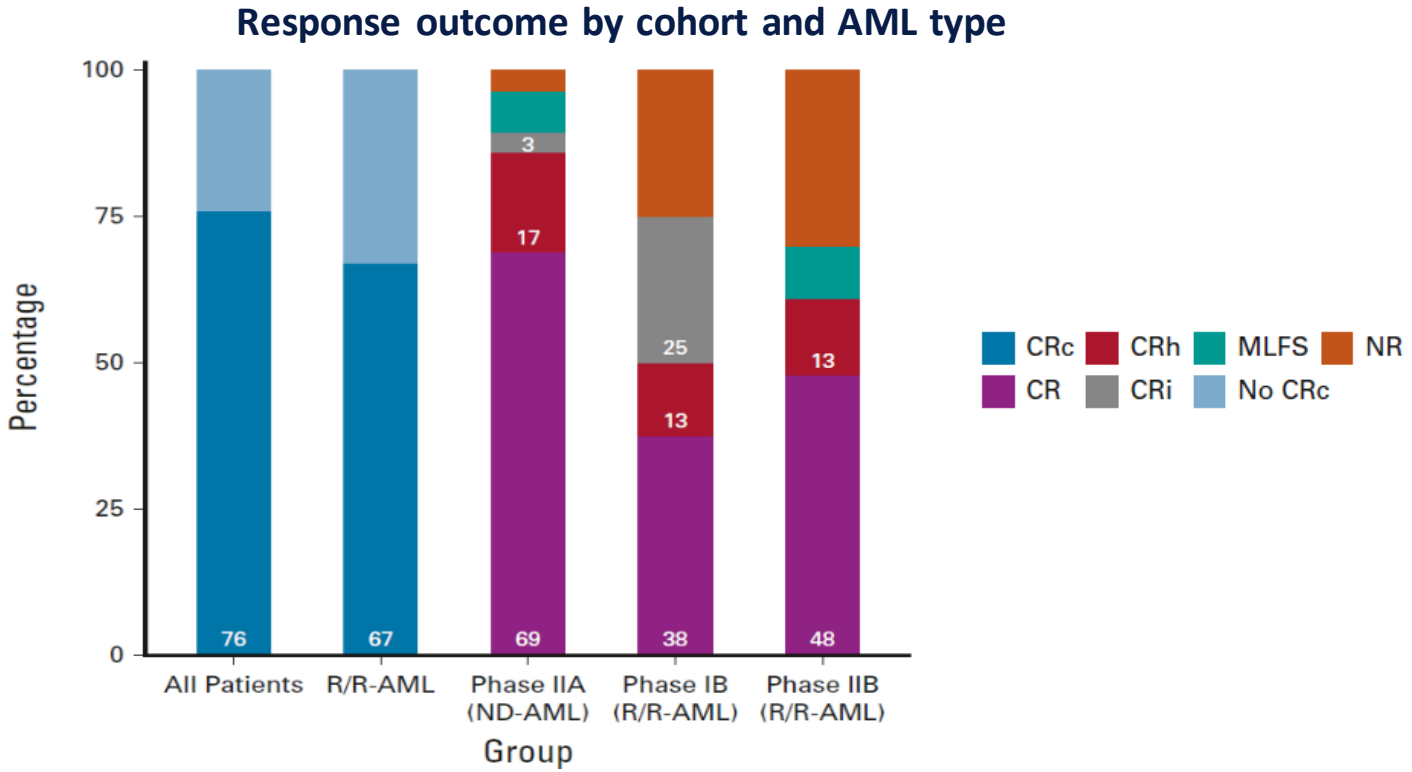
i. Prior FLT3 inhibitor exposure

ii. Stem cell transplantation



Daver N, et al *J Clin Oncol.* 2022.

Venetoclax + FLAG-IDA: Response outcomes
Phase Ib/II study of venetoclax + FLAG-IDA in ND and R/R AML

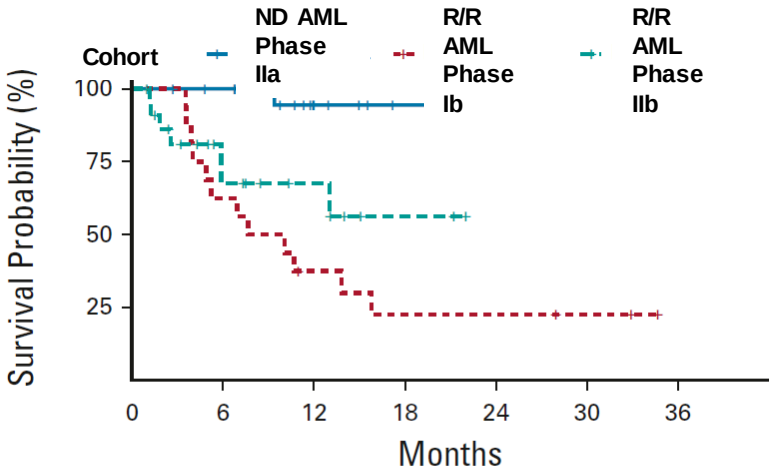


DiNardo CD, et al. *J Clin Oncol.* 2021.

Venetoclax + FLAG-IDA: OS

Phase Ib/II study of venetoclax + FLAG-IDA in ND and R/R AML

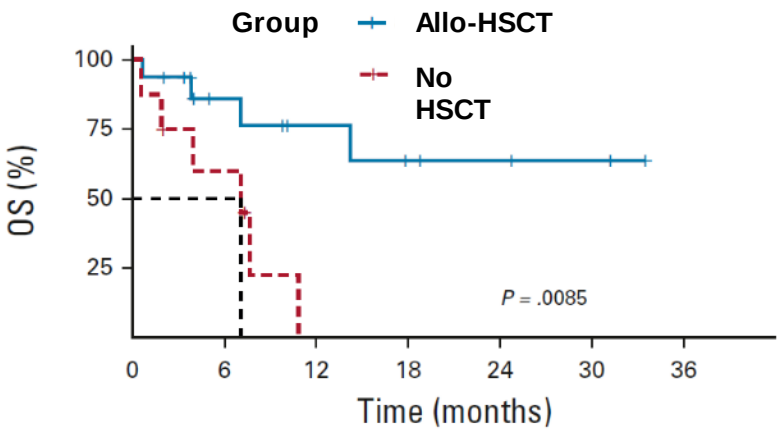
OS by cohort



No. at risk:

PIIA: ND-AML	29	26	12	7	0	0	0
PIB: R/R-AML	16	10	5	3	3	2	0
PIIB: R/R-AML	23	10	6	2	0	0	0

3-month landmark analysis of HSCT in patients attaining CRc



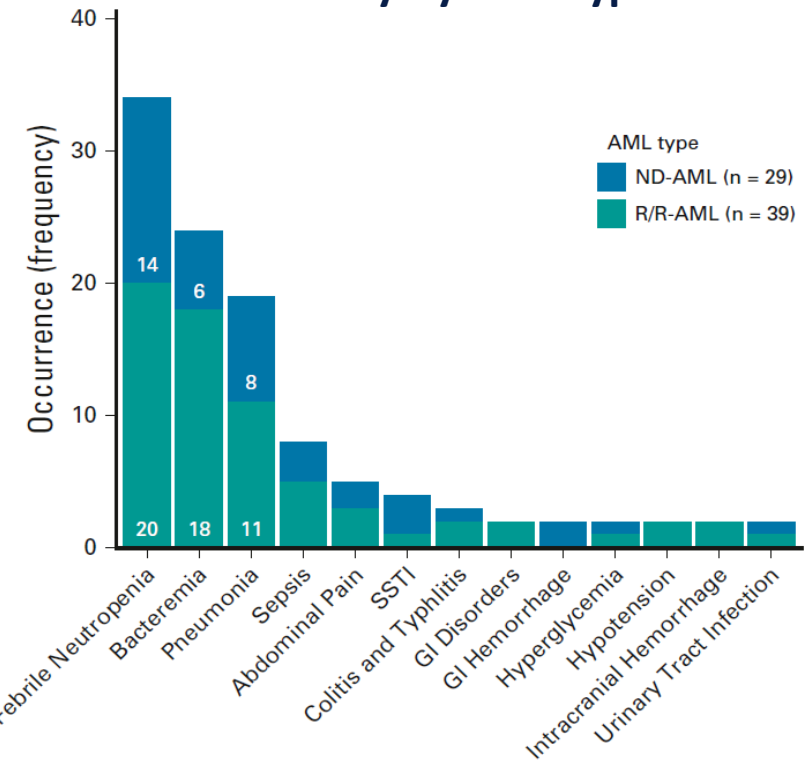
No. at risk:

alloHSCT	16	9	6	4	3	2	0
No HSCT	8	4	0	0	0	0	0

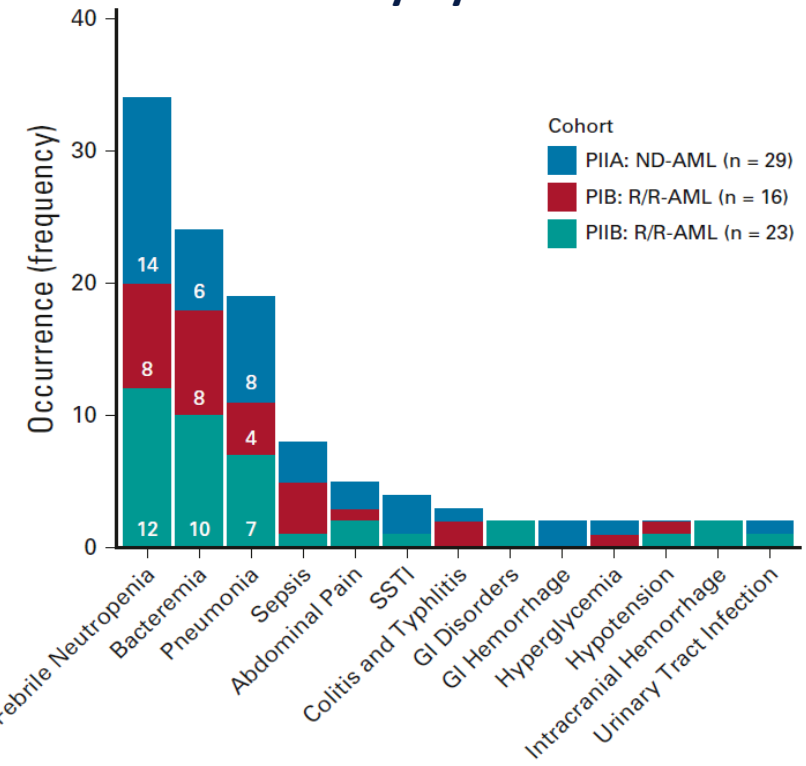
DiNardo CD, et al. *J Clin Oncol.* 2021.

Venetoclax + FLAG-IDA: Safety
Phase Ib/II study of venetoclax + FLAG-IDA in ND and R/R AML

Safety by AML type

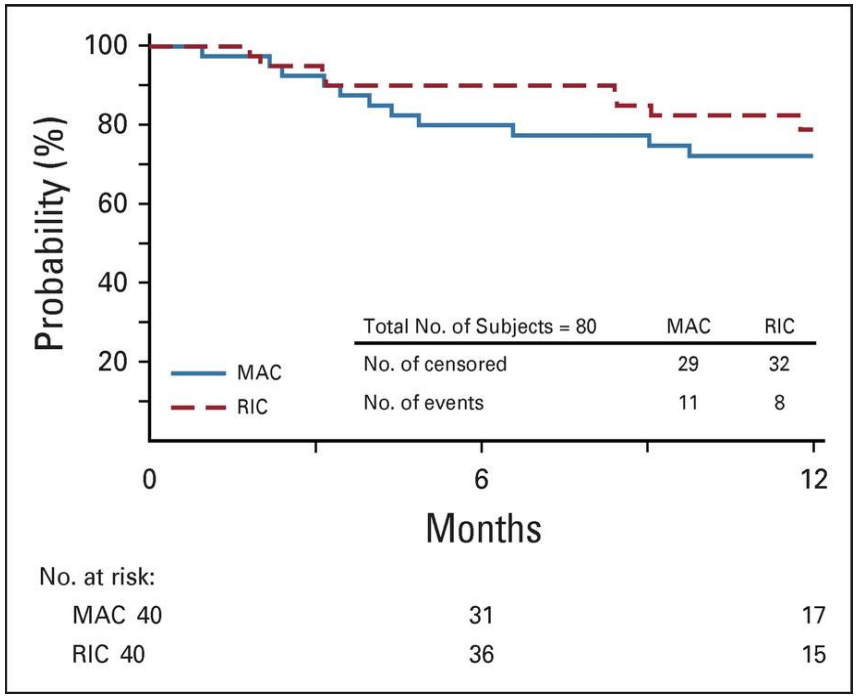


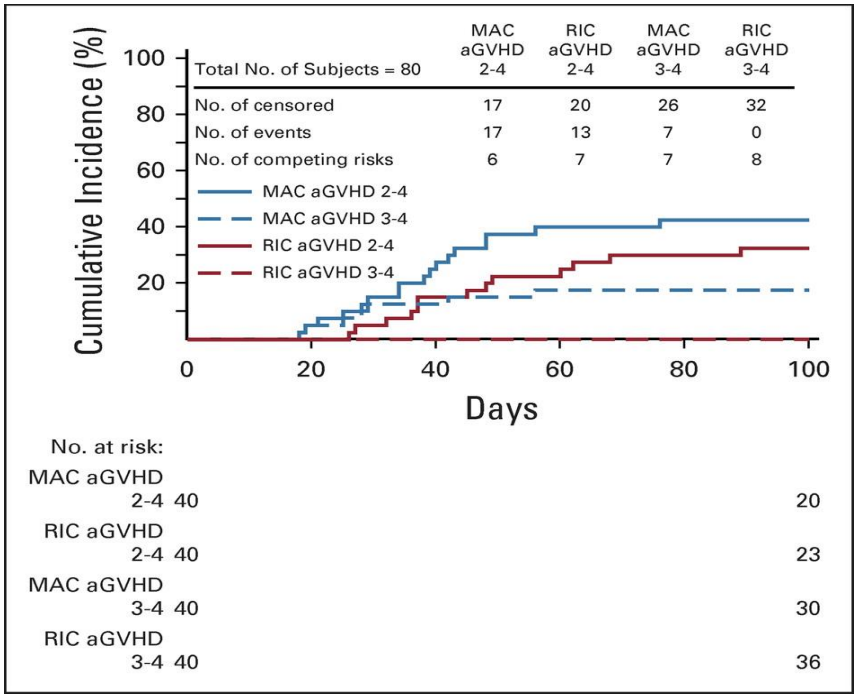
Safety by cohort



DiNardo CD, et al. *J Clin Oncol.* 2021.

Post-transplant Cy improves outcomes in adults transplanted using mismatched unrelated donors

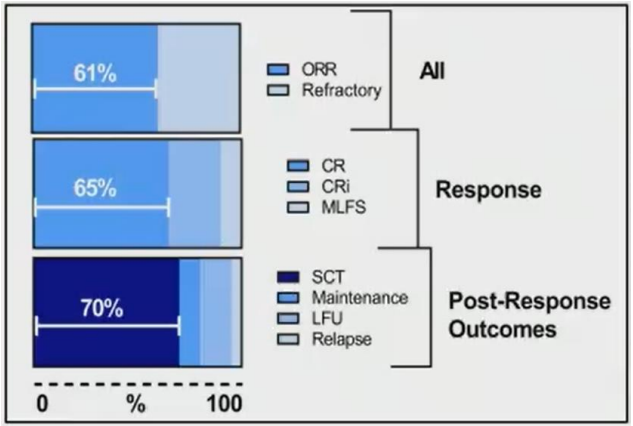




Shaw et al. *J Clin Oncol.* 2021.

Updated results from a phase IIb study of venetoclax and FLAG-IDA in R/R AML: Response rates

Response	N = 33; n (%)
ORR	20 (61)
Composite response	18 (55)
CR	13 (40)
CRi	5 (15)
MRD negative	13 (40)
MLFS	2 (6)
Follow-up	
ASCT	14 (42)
Maintenance	2 (6)
LFU after response	3 (9)
Relapse on-trial	1 (3)
Refractory	13 (40)



13/18 CRc patients (72%) were MRD negative

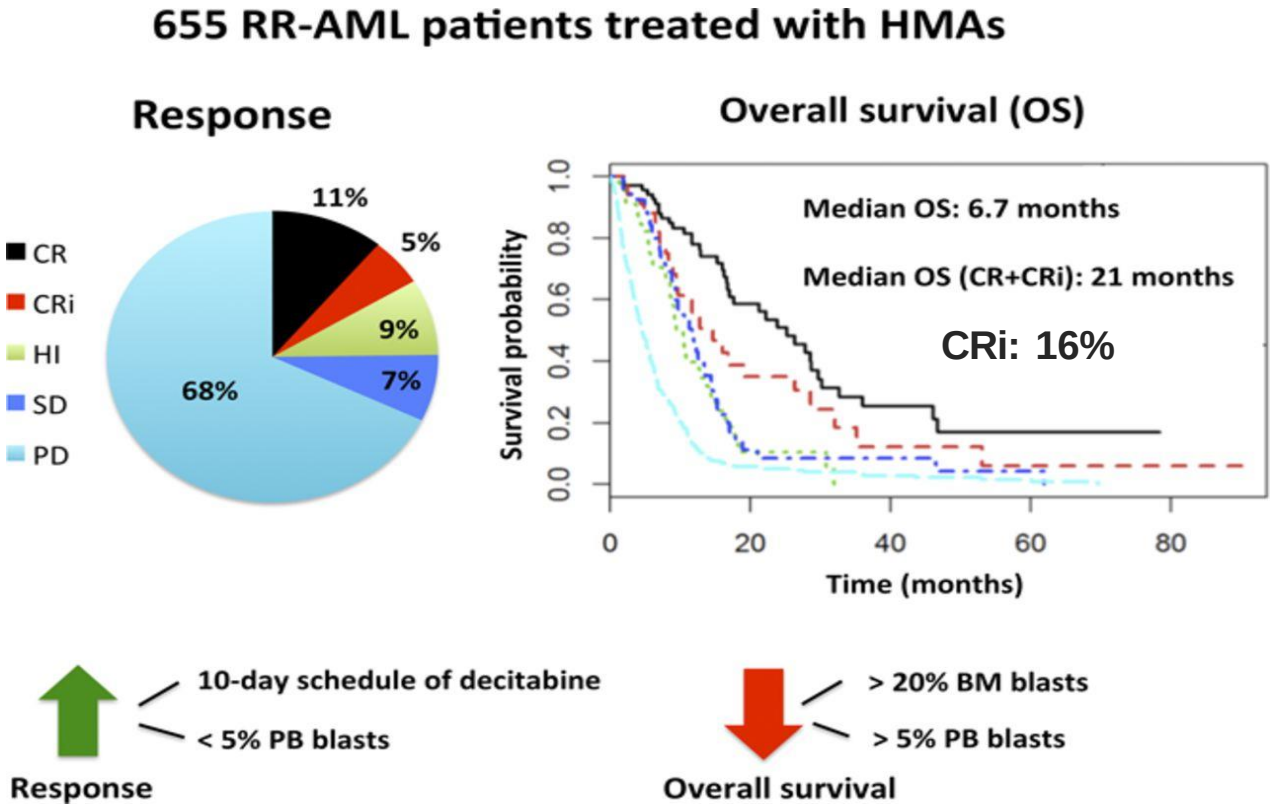
ELN Risk	N	CRc
Favorable	7/33 (21%)	6/7 (85%)
Intermediate	4/33 (12%)	3/4 (75%)
Adverse	22/33 (67%)	9/22 (41%)

Mutation	N	CRc
NPM1	5/33 (15%)	4/5 (80%)
RUNX1	7/33 (21%)	4/7 (57%)
ASXL1	6/33 (18%)	2/6 (33%)
TP53	7/33 (21%)	1/7 (14%)

AML, acute myeloid leukemia; ASCT, allogeneic SCT; CR, complete remission; CRc, composite remission rate; CRi, CR with incomplete count recovery; ELN, European LeukemiaNet; LFU, lost to follow-up; MLFS, morphological leukemia-free state; MRD, minimal residual disease; ORR, objective response rate; R/R, relapsed/refractory; SCT, stem cell transplant.

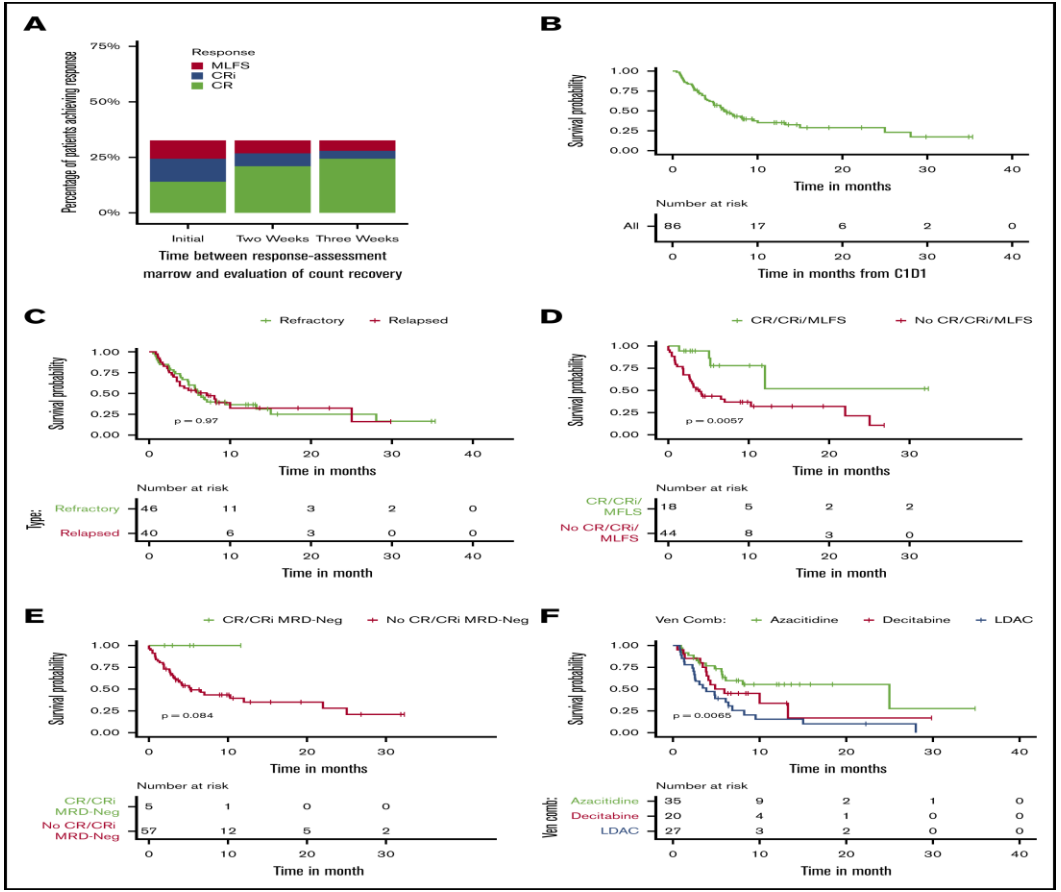
Desikan SP, et al. ASH 2022. Abstract 221.

Hypomethylating agents in relapsed/refractory AML



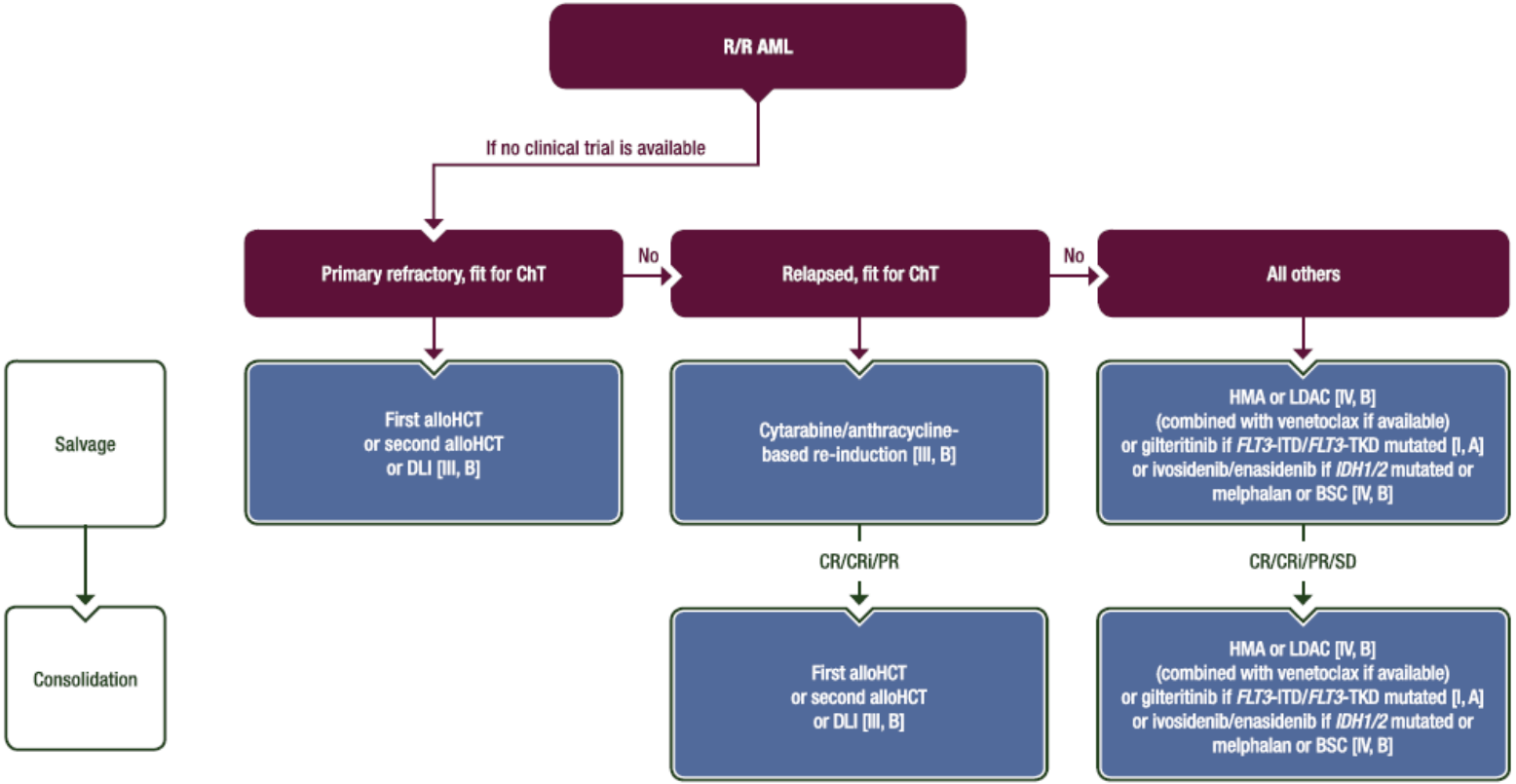
Stahl M, et al. *Blood Adv*. 2021.

Venetoclax combination therapy for R/R AML: Response



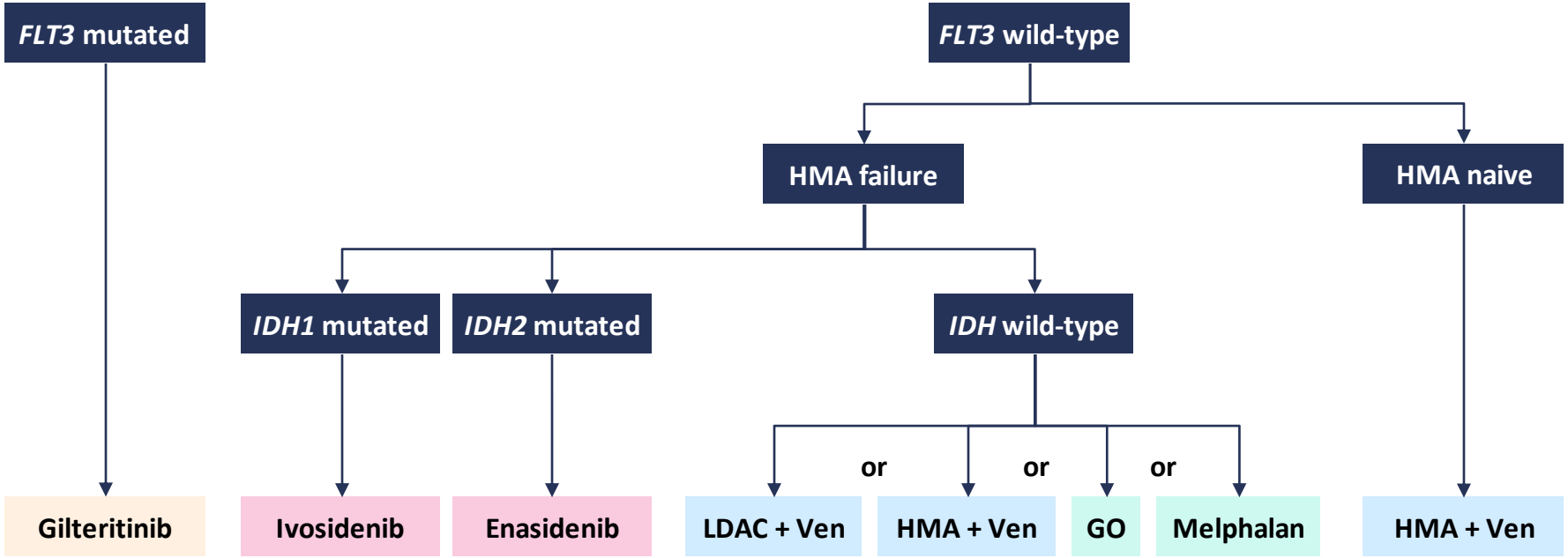
Stahl M, et al. *Blood Adv*. 2021.

ESMO guidelines for R/R AML



Heuser M, et al. *Ann Oncol.* 2020.

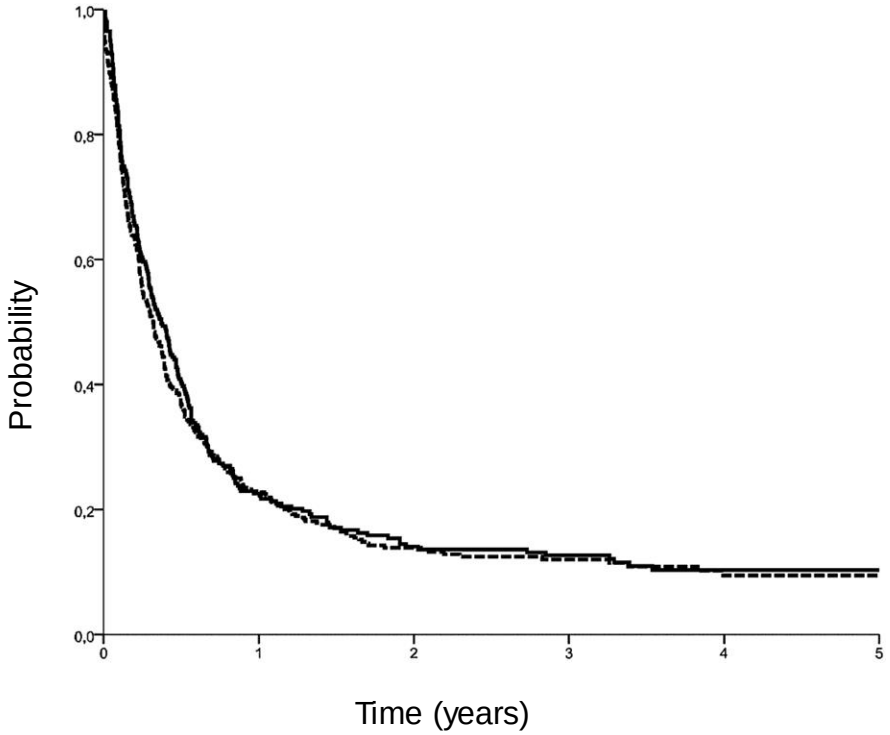
Onkopedia updates to guidelines for patients with R/R AML ineligible for allogeneic stem cell transplant



Management of disease relapse posttransplant

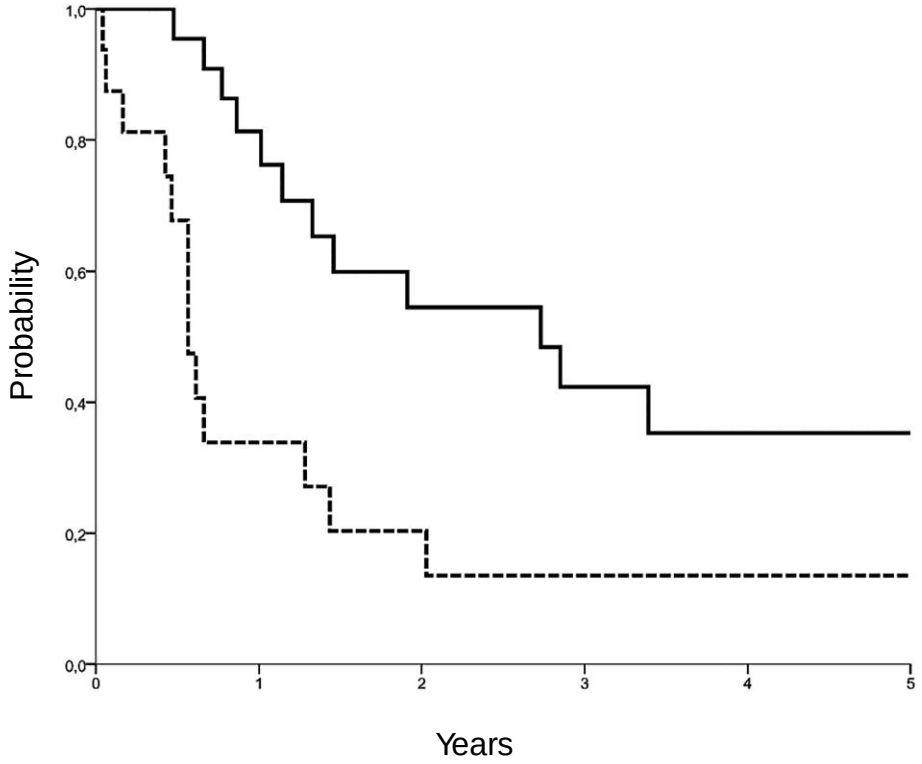
- In patients relapsing post-allograft, acquisition of CR is a prerequisite of long-term survival
- Approximately 20-30% of patients treated with salvage chemotherapy have a second CR, but toxicity is significant
- Alternative salvage strategies include
  - Immunosuppression taper
  - Salvage azacitidine
  - Lenalidomide-azacitidine combination therapy

Long-term survival in patients who experience relapse after allogeneic SCT for AML



Schmid C, et al. *Blood.* 2012.

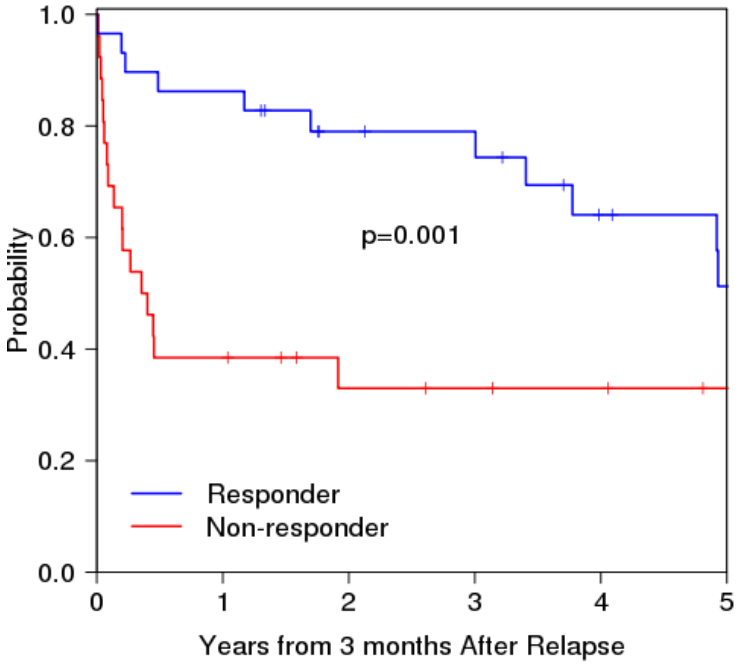
Acquisition of CR after salvage therapy is a prerequisite of long-term survival in patients experiencing relapse post-allograft



Schmid C, et al. *Blood.* 2012.

Immunosuppression taper as sole therapy for relapse post-allograft

- 535 patients whose disease relapsed after HCT at DFCI between 2004 and 2012 were identified
- 123 received immunosuppression taper as primary treatment of disease relapse
- 34 out of 123 responded to IS taper alone
- 1/22 MA (2.5%) and 33/101 RIC (32.7%) responded to IS taper alone (*P* =.0073)

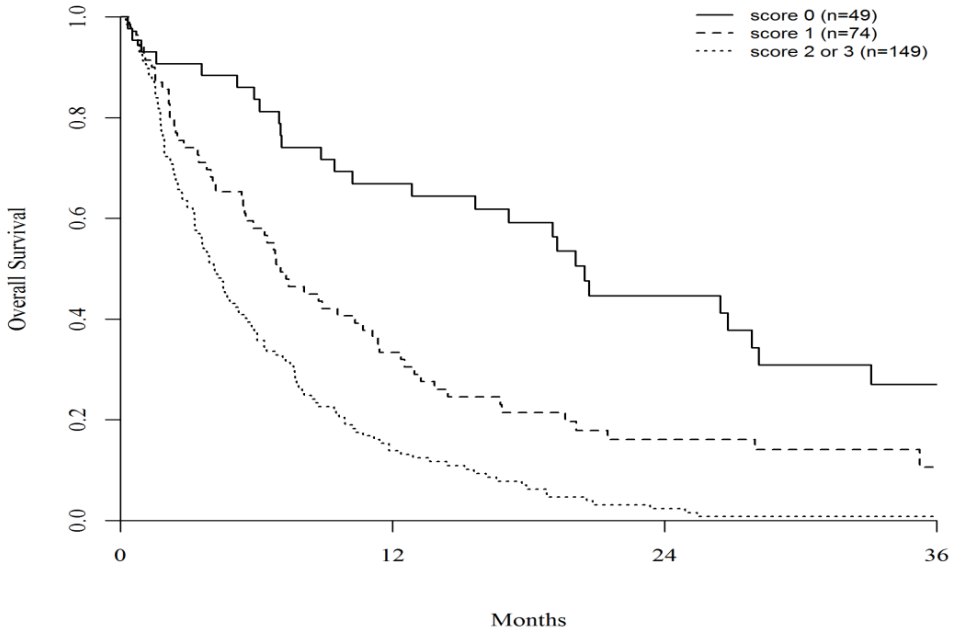


Kekere et al. ASH 2014.

Salvage azacitidine in patients whose disease relapsed after allogeneic SCT for AML/MDS

- 272 patients on EBMT ALWP database with relapsed AML/MDS who received salvage AZA
- Outpatient therapy
- Response rate 15% CR; 24% CR + PR
- Multivariable analysis of predictors of CR:
  - Interval time transplant to relapse >12 months (P = .04)
  - Good-risk cytogenetics (P = .02)
- Multivariable analysis of predictors of OS at 2 years:
  - Blasts in BM at relapse <median (P = .02)
- Interval time transplant to relapse
  - 6–12 vs <6 months (P =.0006)

Overall survival after salvage azacitidine in patients experiencing relapse after an allograft for AML/MDS

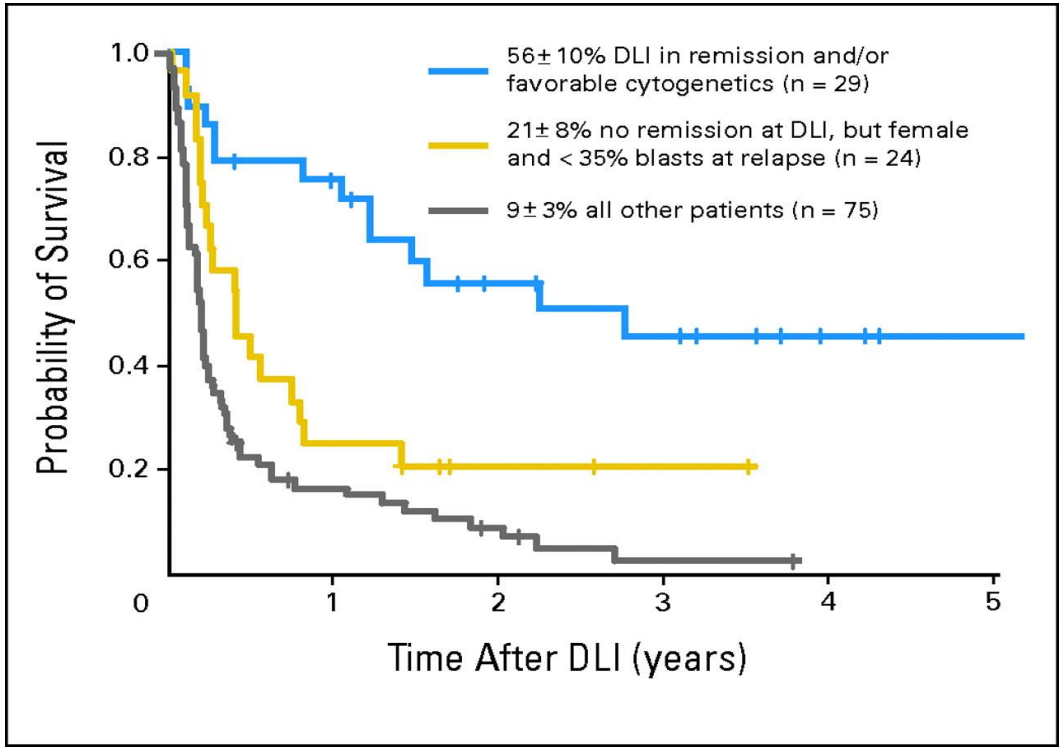


Craddock C, et al. ASH 2014.

Emergent salvage strategies in patients experiencing relapse post-allograft

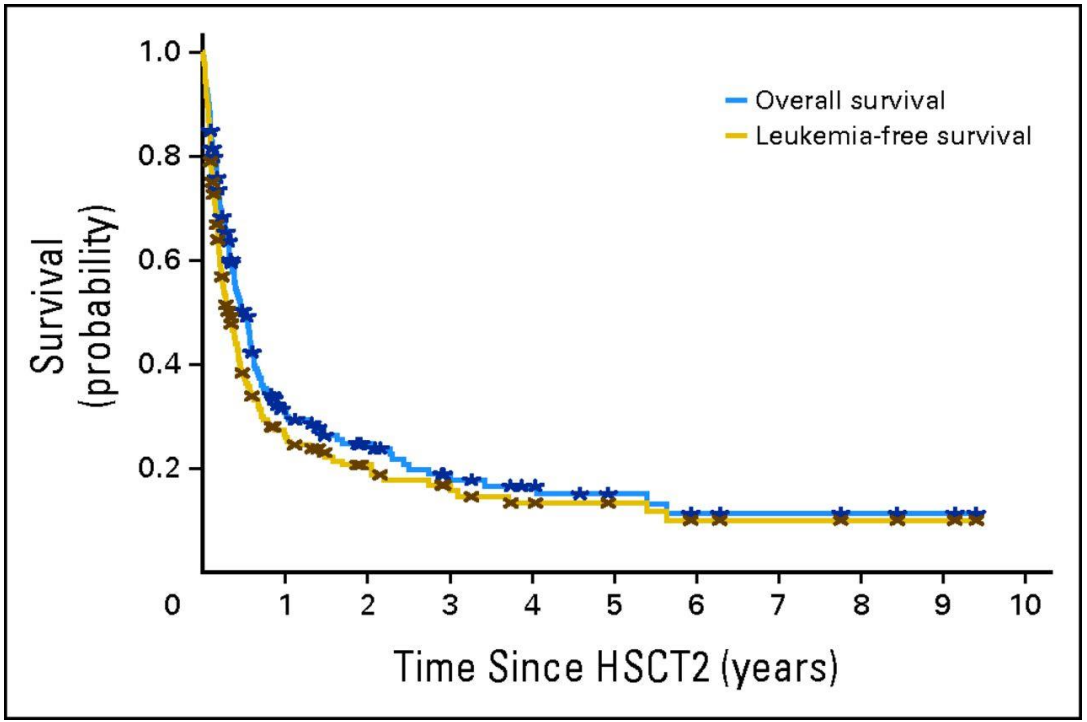
- Gilteritinib-VEN in *FLT3*+ AML
- FLAG-IDA–VEN
- VEN-AZA
- CAR T cells

Outcome after DLI is determined by cytogenetics, disease status at time of DLI, and duration of CR posttransplant



Schmid C, et al. *J Clin Oncol*. 2007.

Outcome after second allograft is determined by duration of CR posttransplant and disease status at transplant, but not by changing donor



Christopeit et al. *J Clin Oncol.* 2013.

Conclusions

- Biological characterization of the cellular origin of disease relapse posttransplant is required
- A personalized approach to defining both relapse risk and kinetics is required
- Improved strategies to induce a second CR in patients who experience relapse post-allograft are required
- Second transplant and DLI represent potentially curative options in the minority of patients who have a CR

Global Leukemia Academy

Q&A

APTITUDE HEALTH

Global Leukemia Academy

AML case-based panel discussion

Case 1: Vitor Botafogo

Case 2: Justin Loke

Moderator: Naval Daver

APTITUDE HEALTH

Global Leukemia Academy

High-risk AML with *TP53* mutation

Vitor Botafogo Gonçalves

Clinical Hematology Department

Institut Català d´Oncologia – Hospital Germans Trias i Pujol

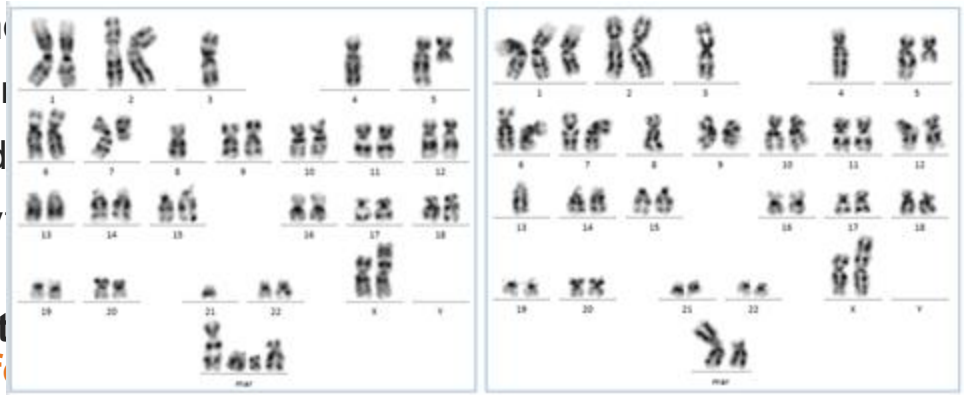
Badalona, Spain

16–17 November 2023 – Europe

APTITUDE HEALTH

Case presentation

- 51-year-old woman, n
- No past medical histo
- July 2023: fatigue and
- **Blood count**: leukocy 9.2 g/dL, 193 × 10^9/L platelets
- **Bone marrow aspirat** ble with AML with some monocytic diff



- **Karyotype:** complex and monosomyc
  - 45-47,X,der(X)t(X;3)(p22.1;q21),+1,add(1)(q32),-3, -4, del(5)(q12q33),del(6)(p22),del(7)(q11.2q32),-8,-13,-21, +4mar[cp20]
- **NGS:** pathogenic mutation in *TP53* (VAF 37%), probably pathogenic mutations in *DNMT3A* (VAF 2%) and *SMC3* (VAF 19%)
- **Final diagnosis**: AML with mutated *TP53* (ELN22/WHO/ICC)
- Cultured skin fibroblasts analysis: no germline mutation

Which treatment would you chose for this patient?

A. Azacitidine monotherapy
B. 3+7 schedule (anthracycline + Ara-C)
C. Clinical trial
D. Azacitidine + venetoclax

TP53 mutation is commonly associated with chemotherapy resistance

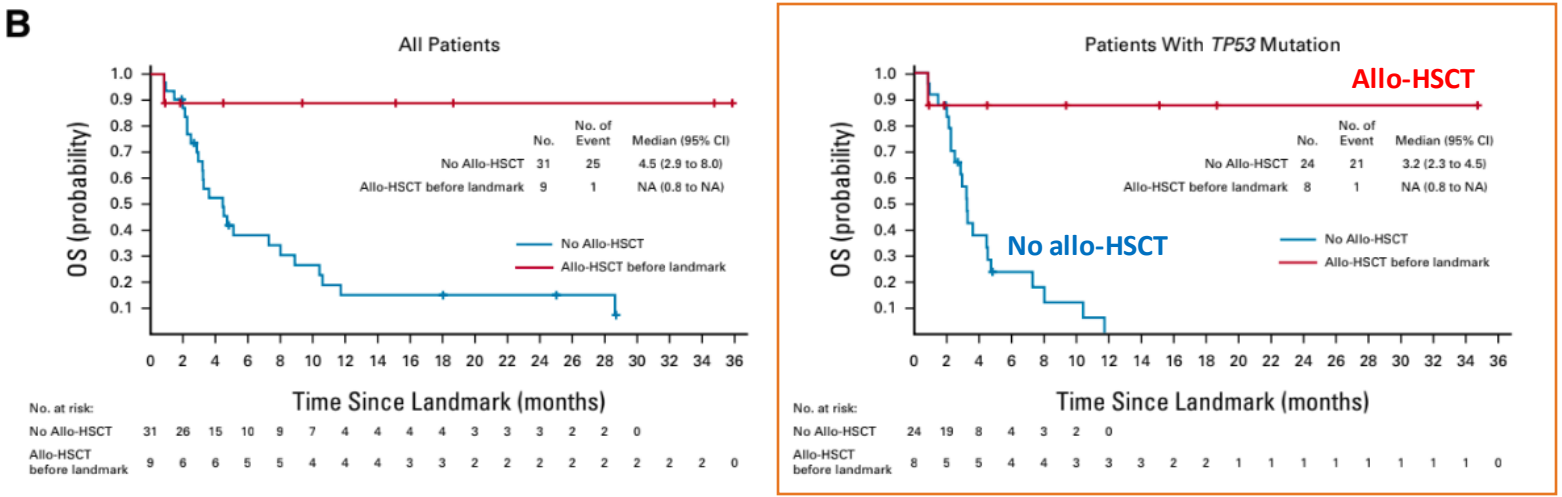
Trials for AML with mutated *TP53* (phase II and III only)

Trial	Phase	Population	Intervention	Published	Results
NCT03931291 (**APR-246**; Eprenetapopt)	II	*TP53*-mut AML or MDS post-HSCT (n = 33)	Maintenance AZA + APR-246 after HSCT	Mishra A, et al. *J Clin Oncol*. 2022;40:3985-3993	1-year RFS probability 59.9%; 1-year OS probability 78.8%
NCT03063203 (**Decitabine**)	II	*TP53*-mut AML R/R to cytarabine-based induction (n = 17)	Decitabine after induction	Ferraro F, et al. *Haematologica*. 2022;107:1709-1713	1-year OS 29% (median 244 days); 7/17 patients HSCT (median survival 354 d)
NCT03080766 (**Decitabine**)	II	De novo AML with complex/monosomal karyotype	Decitabine monotherapy for induction	Not published yet	No data
NCT04542057 ENHANCE-2 (**Magrolimab**)	III	De novo AML with *TP53* mut	AZA + Magro **vs** AZA + VEN or intensive chemo	Not published yet	Currently closed (no clear benefit of magrolimab)

Source: Clinical Trials.gov.

Magrolimab + azacitidine combination (phase Ib prior to ENHANCE-2)

N = 87 (n = 72, mut*TP53*)
CR mut*TP53* = 31.9%
8 patients w/ mutTP53 received allo-HSCT
Median OS w/ allo-HSCT: not reached
Media OS no allo-HSCT: 3.2 months



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Daver N, et al. *J Clin Oncol.* 2023;41:4893-4904.

Back to our case: Initial treatment response

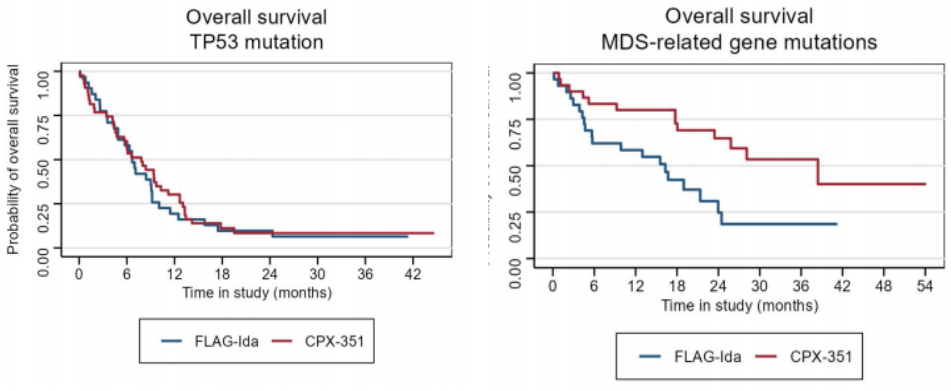
- Our patient was included in **ENHANCE-2** trial
- Randomized to **AZA + magrolimab** arm
- Completed 2 treatment cycles
- Refractory to treatment: **persistence of peripheral blood blast cells** (around 17%)

Gilead Sciences has stopped its ENHANCE-2 study. Based on an ad hoc analysis/independent data monitoring committee: magrolimab is unlikely to demonstrate a survival benefit in AML with *TP53* mutations compared with standard of care.

Which salvage therapy would you propose?

A. CPX-351 (bridge to HSCT)
B. 3+7
C. FLAG-IDA + venetoclax (bridge to HSCT)
D. Azacitidine + venetoclax

A randomized comparison of CPX-351 and FLAG-IDA in adverse-karyotype AML and high-risk MDS: the UK NCRI AML19 trial



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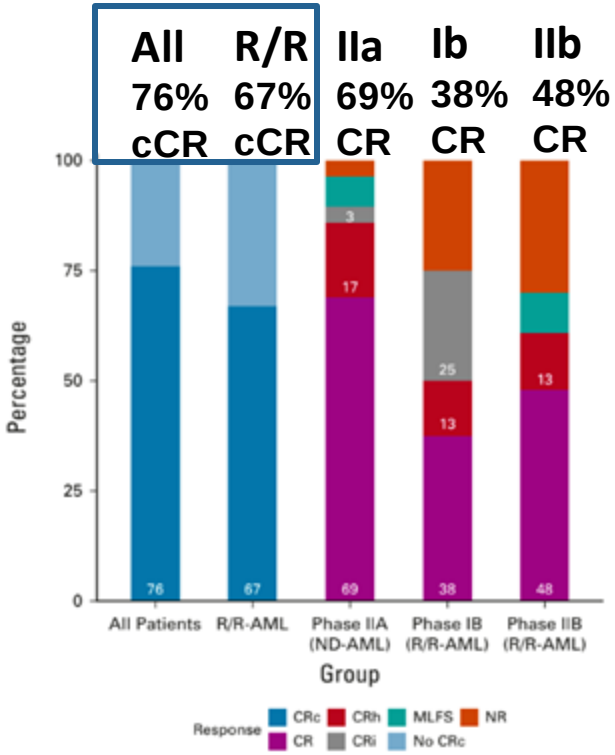
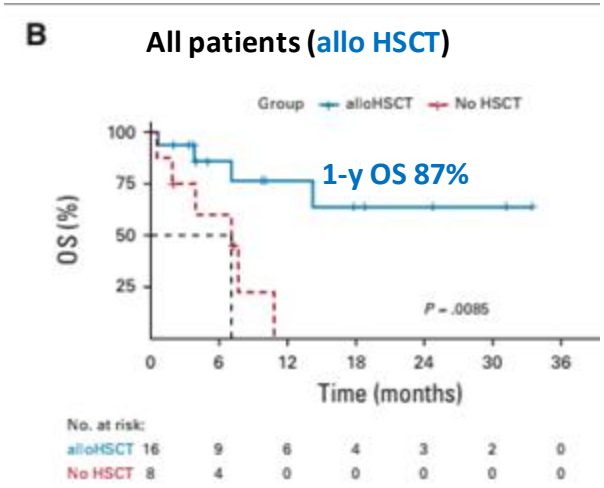
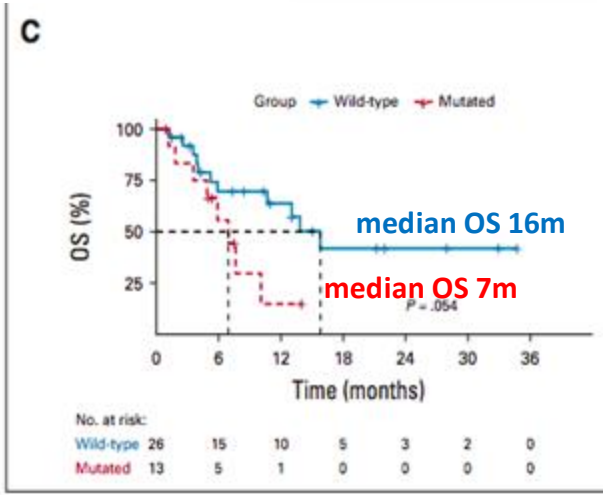
Othman J, et al. *Blood Adv*. 2023;7:4539-4549.

FLAG-IDA + venetoclax (phase Ib, IIa, and IIb)

Phase Ib (R/R AML, n = 16); (n = 2 w/*TP53* mut)
Phase IIa (de novo AML, n = 29); (n = 3 w/ *P53* mut)
Phase IIb (R/R AML, n = 23); (n = 5 w/*TP53* mut)







DiNardo CD, et al. *J Clin Oncol*. 2021;39:2768-2778.

Back to our case: Salvage therapy

> **Started treatment with FLAG-IDA + venetoclax** (October 2023)
> Currently at **day 27** of treatment – starting hematologic recovery
> **Complication:** febrile neutropenia. Good response to antibiotics
> Prophylaxis: cotrimoxazole, acyclovir, posaconazole
> Pegfilgrastim

> HSC donor: **brother; HLA compatibility 9/10**

Treatment of newly-diagnosed *TP53*mut AML

Systematic review and meta-analysis

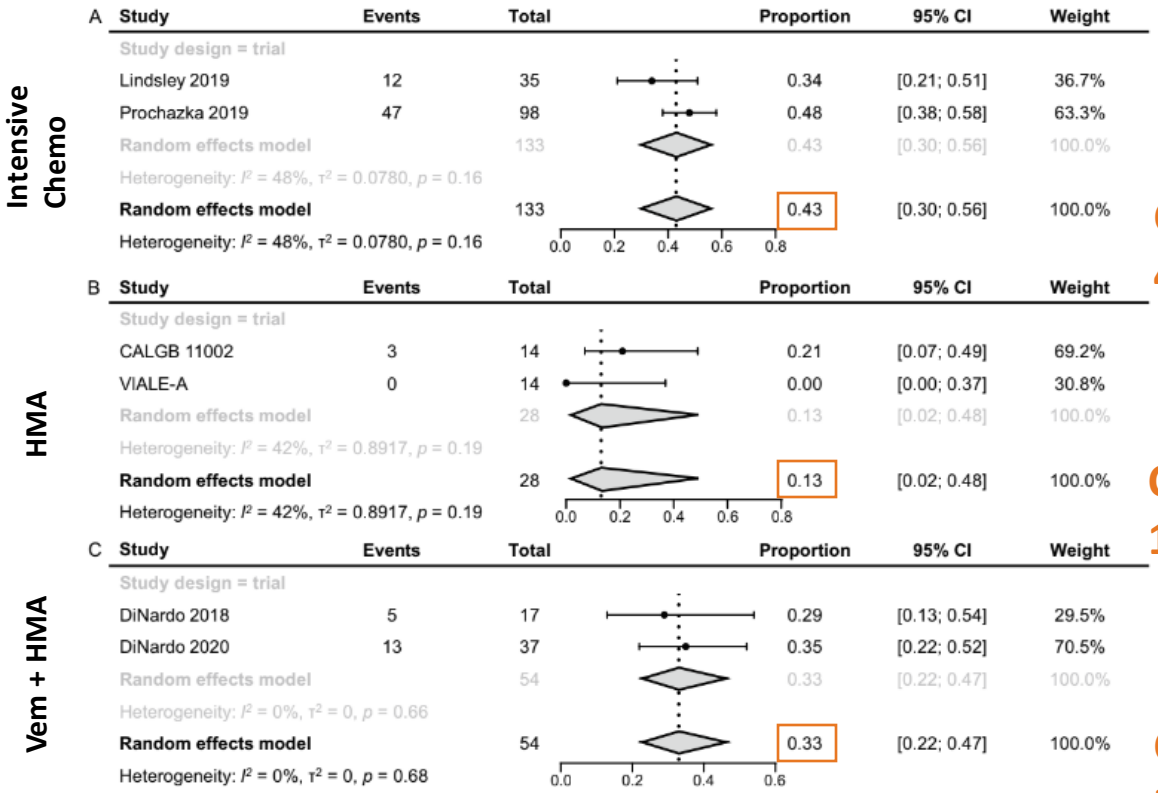


Fig. 2 CR in patients with *TP53*m AML treated with IC (**A**), HMA (**B**), and VEN + HMA (**C**). AML, acute myeloid leukemia; CI confidence interval; CR, complete remission; HMA, hypomethylating agent; IC, intensive chemotherapy; *TP53*m, *TP53*-mutated; VEN, venetoclax

OS was poor for all 3 treatment strategies:

IC – 6.5 months

Vem + HMA – 6.2 months

HMA – 6.1 months

Daver N, et al. *J Hematol Oncol*. 2023;16:19.

Take-home messages

- *TP53*-mutated AML is associated with treatment resistance and poor outcomes
- HSCT may increase OS of patients, but relapses are frequent, mainly when *TP53* mutation is associated with complex karyotype or other genetic abnormalities
- There is still a significant need for improvement in treatment strategies for patients with *TP53*-mutated AML

Daver N, et al. *J Hematol Oncol*. 2023;16:19; Loke J, et al. *Cancer*. 2022;128:2922-2931.

THANK YOU VERY MUCH

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Alba Mesa Tudel
Rebeca Jurado Tapiador
Isabel Granada Font
Lurdes Zamora Plana

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Global Leukemia Academy

Discussion
High-risk AML with *TP53* mutation

Vitor Botafogo Gonçalves

APTITUDE HEALTH

Global Leukemia Academy

Case presentation

Justin Loke
AACR-CRUK Transatlantic Fellow
Birmingham, UK, and Boston, USA

APTITUDE HEALTH

67-year-old female patient

- AML, diagnosed – significantly dysplastic features on morphology
- No significant past medical history
- Lives independently with partner, ECOG PS 1

- CPX-351 × 2 cycles – uneventful, morphological CR

- Normal karyotype, *DNMT3A, TET2, RAD21, NPMI, FLT3*-ITD, *CEBPA* mutations

Question 1

What is your choice for consolidation?

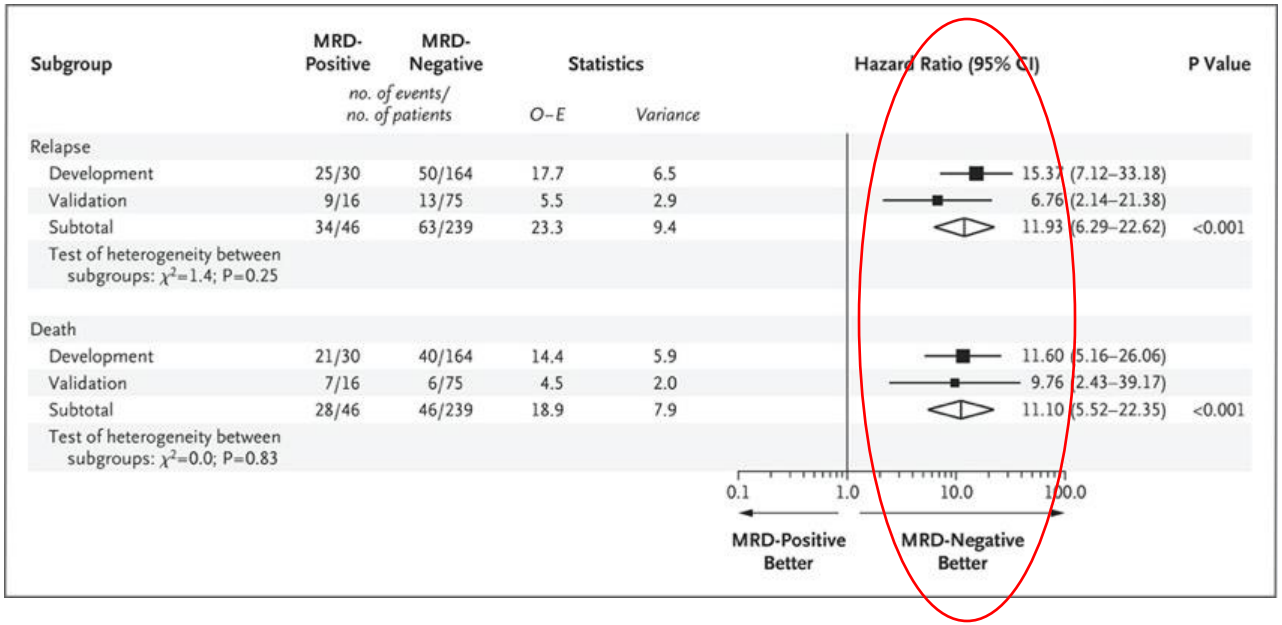
A. Further cycle of CPX-351 alone

B. Switch to midostaurin combination consolidation and maintenance

C. RIC allograft only if *NPM1* MRD results are high

D. RIC allograft regardless of *NPM1* MRD results

Presence of MRD predicts for relapse after second course of chemotherapy for AML with *NPM1* mutation



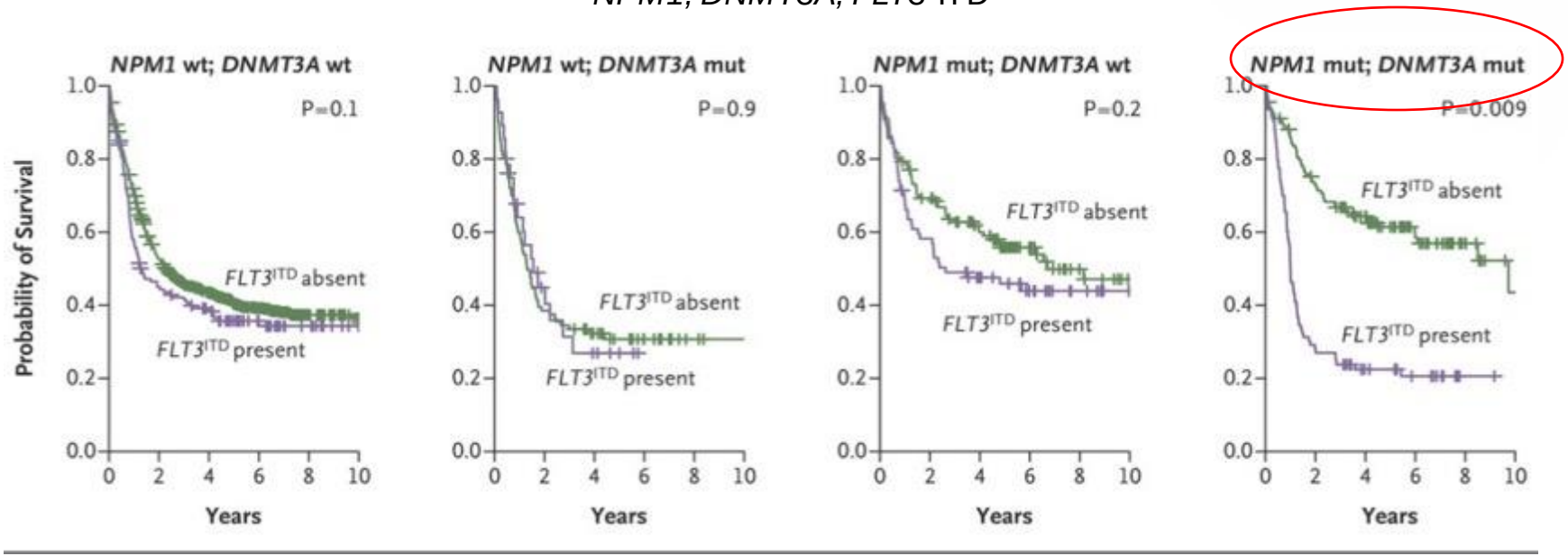
Subgroup	MRD-Positive	MRD-Negative	Statistics		Hazard Ratio (95% CI)	P Value
	no. of events/ no. of patients		O–E	Variance		
Relapse						
Development	25/30	50/164	17.7	6.5	15.37 (7.12–33.18)	
Validation	9/16	13/75	5.5	2.9	6.76 (2.14–21.38)	
Subtotal	34/46	63/239	23.3	9.4	11.93 (6.29–22.62)	<0.001
Test of heterogeneity between subgroups: χ^2=1.4; P=0.25						
Death						
Development	21/30	40/164	14.4	5.9	11.60 (5.16–26.06)	
Validation	7/16	6/75	4.5	2.0	9.76 (2.43–39.17)	
Subtotal	28/46	46/239	18.9	7.9	11.10 (5.52–22.35)	<0.001
Test of heterogeneity between subgroups: χ^2=0.0; P=0.83						

Irrespective of co-occurring mutation or *FLT3*-ITD ratio?
Study of younger patients; numbers small in subgroups

Ivey A, et al. *N Engl J Med.* 2016;374:422-433.

Influence of gene-gene interactions on overall survival

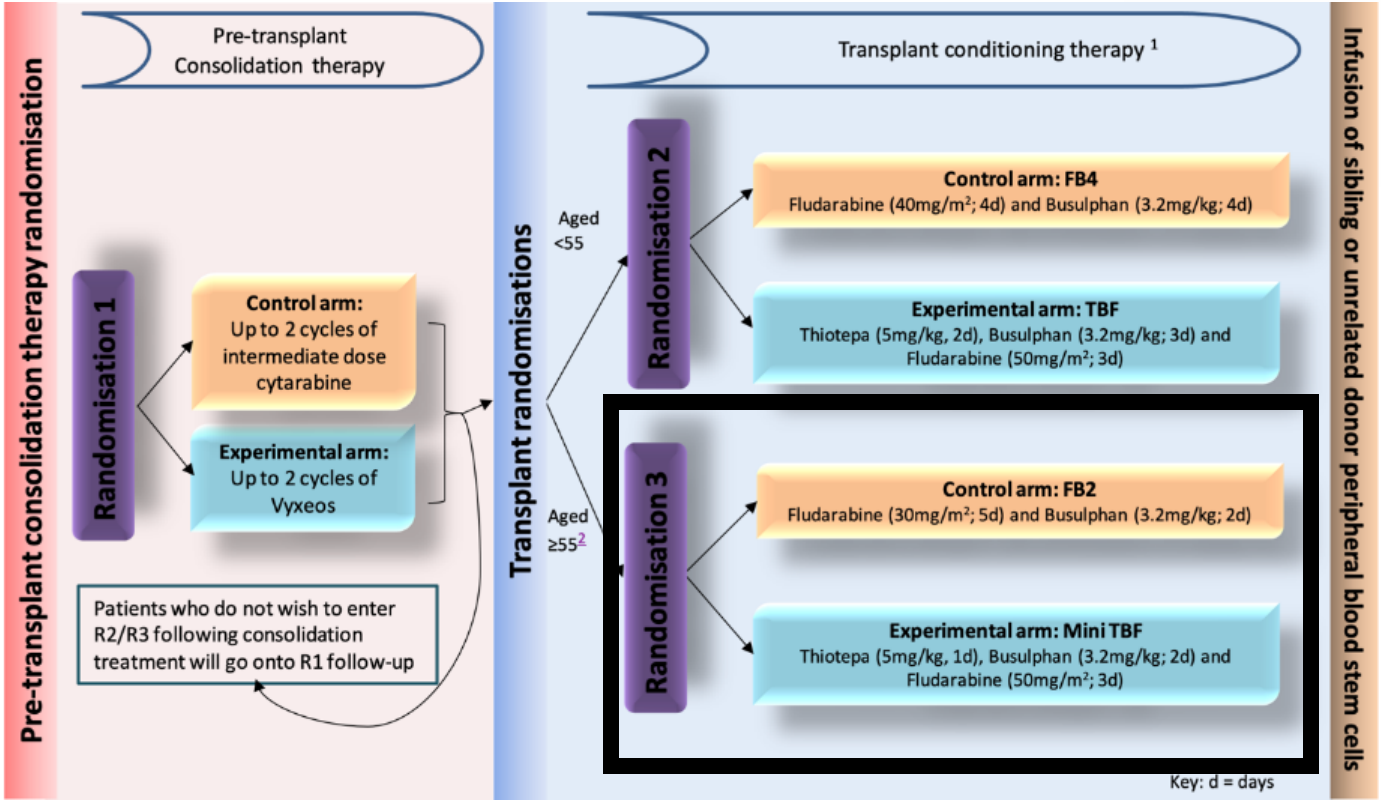
NPM1, *DNMT3A*, *FLT3*-ITD



Papaemmanuil E, et al. *N Engl J Med.* 2016;374:2209-2221.

NPM1 MRD post-course 2 positive in peripheral blood

TRANSPLANT DETAILS: UK IMPACT-COSI trial, reduced-intensity mini–TBF-conditioned allograft from sibling donor



Question 2

- Relapsed AML with *NPM1* mutation post-allograft (+4 months)
  - 12% blasts, 87% donor chimerism, 60 bp *FLT3*-ITD (8%), TET2 (6%), *RAD21* (4%), *NPM1* positive

What is your treatment choice?

A. Intermediate dose/intensive chemotherapy (eg, Ara-C)
B. Venetoclax + Aza or LDAC
C. Straight to donor lymphocyte infusion
D. Gilteritinib

Case (cont.)

- Relapsed AML with *NPM1* mutation post-allograft (+4 months)
  - 12% blasts, 87% donor chimerism, 60 bp *FLT3*-ITD (8%), *TET2* (6%), *RAD21* (4%), *NPM1* positive

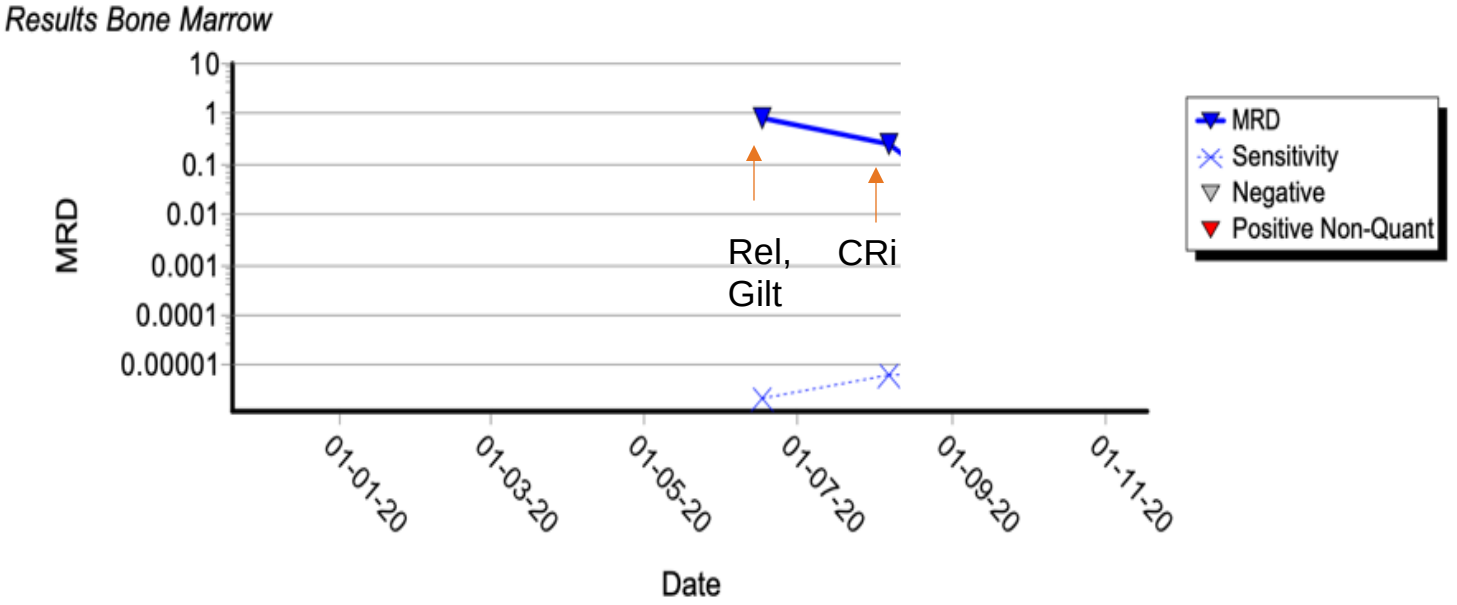
- Gilteritinib 120 mg od
  - Complications: cytopenias (especially thrombocytopenia); normal QTc
  - Post-cycle 1: hypoplastic complete remission (5% cellularity)

Interpreting response to gilteritinib

Table 2. Antileukemic Responses (Intention-to-Treat Population).*

Variable	Gilteritinib (N=247)	Salvage Chemotherapy (N=124)	Hazard Ratio or Risk Difference (95% CI)†
Median overall survival (95% CI) — mo	9.3 (7.7–10.7)	5.6 (4.7–7.3)	0.64 (0.49–0.83)
Median event-free survival (95% CI) — mo	2.8 (1.4–3.7)	0.7 (0.2–NE)	0.79 (0.58–1.09)
Response — no. (%)			
Complete remission	52 (21.1)	13 (10.5)	10.6 (2.8–18.4)
Complete remission or complete remission with partial hematologic recovery	84 (34.0)	19 (15.3)	18.6 (9.8–27.4)
Complete remission with partial hematologic recovery	32 (13.0)	6 (4.8)	ND
Complete remission with incomplete hematologic recovery	63 (25.5)	14 (11.3)	ND
Complete remission with incomplete platelet recovery	19 (7.7)	0	ND
Partial remission	33 (13.4)	5 (4.0)	ND
No response	66 (26.7)	43 (34.7)	ND
Composite complete remission‡	134 (54.3)	27 (21.8)	32.5 (22.3–42.6)
Overall response	167 (67.6)	32 (25.8)	
Median duration of remission (95% CI) — mo§	11.0 (4.6–NE)	NE (NE–NE)	NE
Time to composite complete remission — mo	2.3±1.9	1.3±0.5	NA
Median leukemia-free survival (95% CI) — mo	4.4 (3.6–5.2)	6.7 (2.1–8.5)	NE

Perl A, et al. *N Engl J Med.* 2019;381:1728-1740.


Results Bone Marrow
MRD
10
1
0.1
0.01
0.001
0.0001
0.00001
Rel, Gilt
CRi
01-01-20
01-03-20
01-05-20
01-07-20
01-09-20
01-11-20
Date
MRD
Sensitivity
Negative
Positive Non-Quant

Question 3

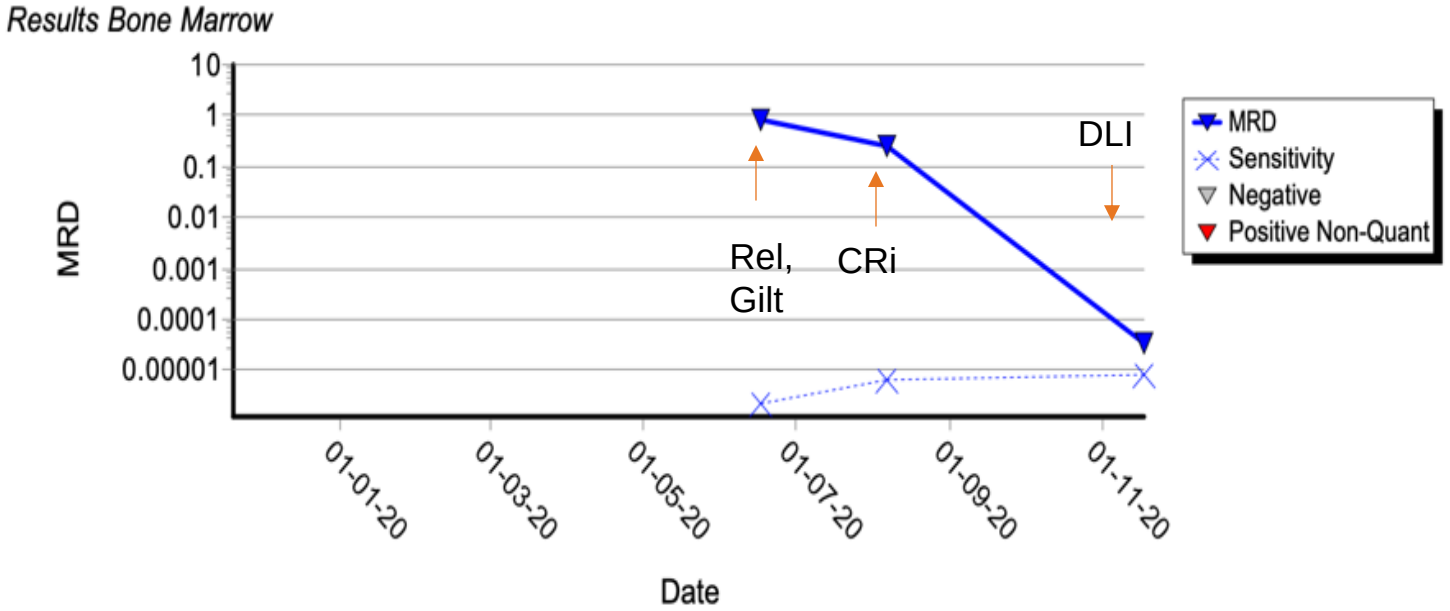
- Relapsed AML with *NPM1* mutation (4%) post-allograft (+4 months)
- Gilteritinib 120 mg od
  - Complications: cytopenias (especially thrombocytopenia); normal QTc
  - Post-cycle 1: hypoplastic complete remission (5% cellularity)

How would you treat this patient?

A. Donor lymphocyte infusion/CD34 top-up
B. Continue current dose of gilteritinib
C. Increase dose of gilteritinib
D. Switch to alternative FLT3i

Case (cont.)

- Relapsed AML with *NPM1* mutation (4%) post-allograft (+4 months)
  - 12% blasts, 87% donor chimerism, 60 bp *FLT3*-ITD (8%), *TET2* (6%), *RAD21* (4%)
- Gilteritinib 120 mg od
  - Complications: cytopenias (especially thrombocytopenia); normal QTc
  - Post-cycle 1: hypoplastic complete remission (5% cellularity)
- CD34-positive selected top-up and DLI
- T-cell chimerism 100% donor, 1% blasts


Results Bone Marrow
MRD
10
1
0.1
0.01
0.001
0.0001
0.00001
01-01-20
01-03-20
01-05-20
01-07-20
01-09-20
01-11-20
Date
Rel, Gilt
CRi
DLI
MRD
Sensitivity
Negative
Positive Non-Quant

Summary

- Combined diagnostics and molecular monitoring allow accurate prognostication of patients with AML
- Decision to proceed to allograft reliant on accurate prediction of relapse risk and TRM
- Novel targeted therapies may provide treatment options that may be better for QOL
- Importance of consolidating responses and dealing with new treatment toxicities

Global Leukemia Academy

Discussion
Case presentation

Justin Loke

APTITUDE HEALTH

Global Leukemia Academy

BREAK

APTITUDE HEALTH

Global Leukemia Academy

Long-term safety considerations for AML and ALL

Stephane De Botton

APTITUDE HEALTH

ALFA
Acute Leukemia French Association

UNIVERSITÉ PARIS SUD
université PARIS-SACLAY

GUSTAVE ROUSSY

Long-term safety considerations for AML and ALL

Stéphane
De BOTTON

Long-term safety considerations

Acute leukemias are not chronic diseases

Recognition of long-term complications = substantial improvements in OS

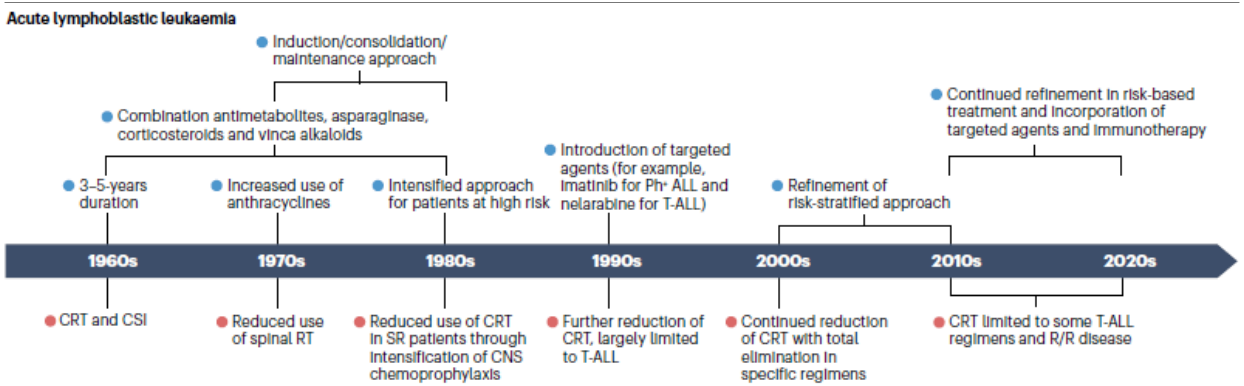
1. 90% of children with ALL will become long-term survivors

   Best model to study the burden of chronic disease and the excess of risk of early and late death
2. Survival of HCT has increased

   Burden of chronic disease even more complex
3. Significance of long term?

   Does the low cure rate in the elderly AML population preclude “long-term” safety considerations?

Pediatric ALL

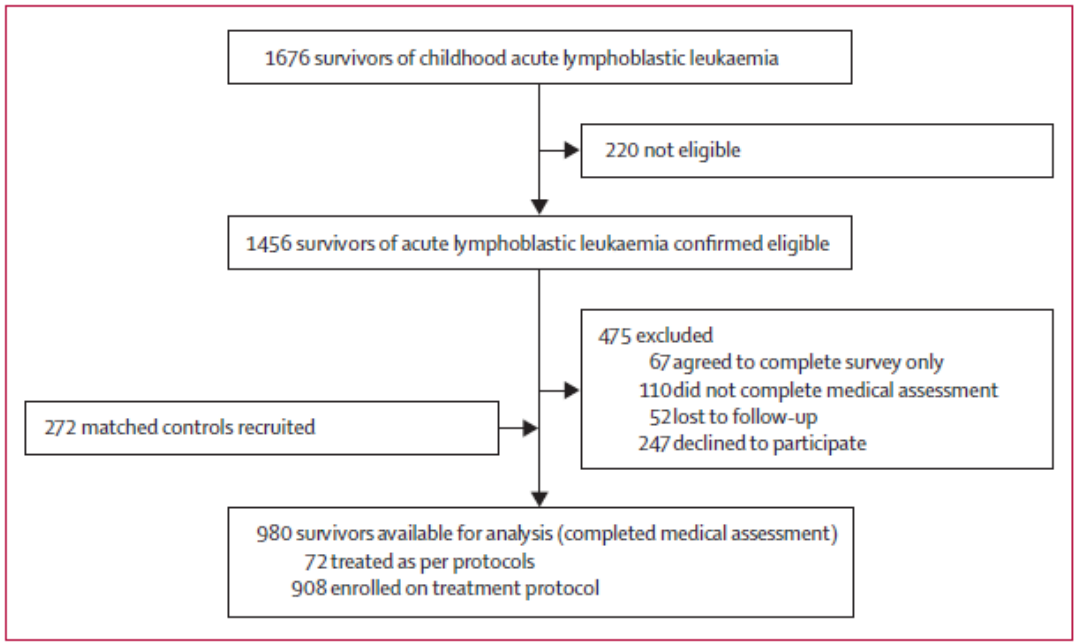


- Very high cure rate
- Treatment protocols adapted over time according to the risk stratification and incorporation of new therapies (TKI) and immunotherapies (bispecific Abs/CAR T)
- CNS chemoprophylaxis replaced CRT
- Overall: Treatment-related morbidity has not declined but rather evolved to include a higher prevalence of chemotherapy-related toxicities

Ehrhardt MJ, et al. *Nat Rev Clin Oncol.* 2023 Oct;20(10):678–696.

Pediatric ALL

The St Jude Lifetime (SJLIFE) Cohort is a retrospective cohort study with prospective follow-up



Median time from diagnosis of 30.0 years (22.7–36.3)

Mulrooney DA, et al. *Lancet Haematol.* 2019;6:e306-e316.

Pediatric ALL

The St Jude Lifetime (SJLIFE) Cohort is a retrospective cohort study with prospective follow-up

	Acute lymphoblastic leukaemia survivors (N=980)					Matched controls (N=272)					p value
	Normal*	Grade 1	Grade 2	Grade 3	Grade 4	Normal*	Grade 1	Grade 2	Grade 3	Grade 4	
Cardiovascular											
Cardiomyopathy	953 (97%)	..	16 (2%)	11 (1%)	0	270 (99%)	..	1 (<1%)	1 (<1%)	0	0·34
Hypertension	435 (46%)	347 (35%)	133 (14%)	47 (5%)	0	153 (56%)	79 (29%)	31 (11%)	9 (3%)	0	0·084
High cholesterol	649 (66%)	243 (25%)	83 (9%)	5 (1%)	0	191 (70%)	64 (24%)	17 (6%)	0	0	0·58
Hypertriglyceridaemia	730 (75%)	200 (20%)	37 (4%)	12 (1%)	1 (<1%)	219 (81%)	42 (15%)	10 (4%)	1 (<1%)	0	0·46
Endocrine or reproductive											
Growth hormone deficiency	743 (76%)	229 (23%)	8 (1%)	..	..	266 (98%)	6 (2%)	0	..	..	<0·0001
Adrenal insufficiency	960 (98%)	12 (1%)	8 (1%)	0	0	272 (100%)	0	0	0	0	0·26
Hypothyroidism	964 (98%)	0	16 (2%)	0	0	259 (95%)	0	13 (5%)	0	0	0·0035
Central hypogonadism	915 (93%)	27 (3%)	38 (4%)	..	..	272 (11%)	0	0	..	..	0·016
Primary hypogonadism (men)	426 (86%)	17 (3%)	52 (11%)	0	..	125 (96%)	0	0	5 (4%)	..	<0·00043
Primary hypogonadism (women)	445 (92%)	..	..	40 (8%)	..	139 (98%)	..	..	3 (2%)	..	0·022
Oligospermia or azoospermia†	76 (32%)	..	55 (23%)	104 (44%)	..	NA	NA	NA	NA	NA	NA

Median time from diagnosis of 30.0 years (22.7–36.3)

Mulrooney DA, et al. *Lancet Haematol.* 2019;6:e306-e316.

Pediatric ALL

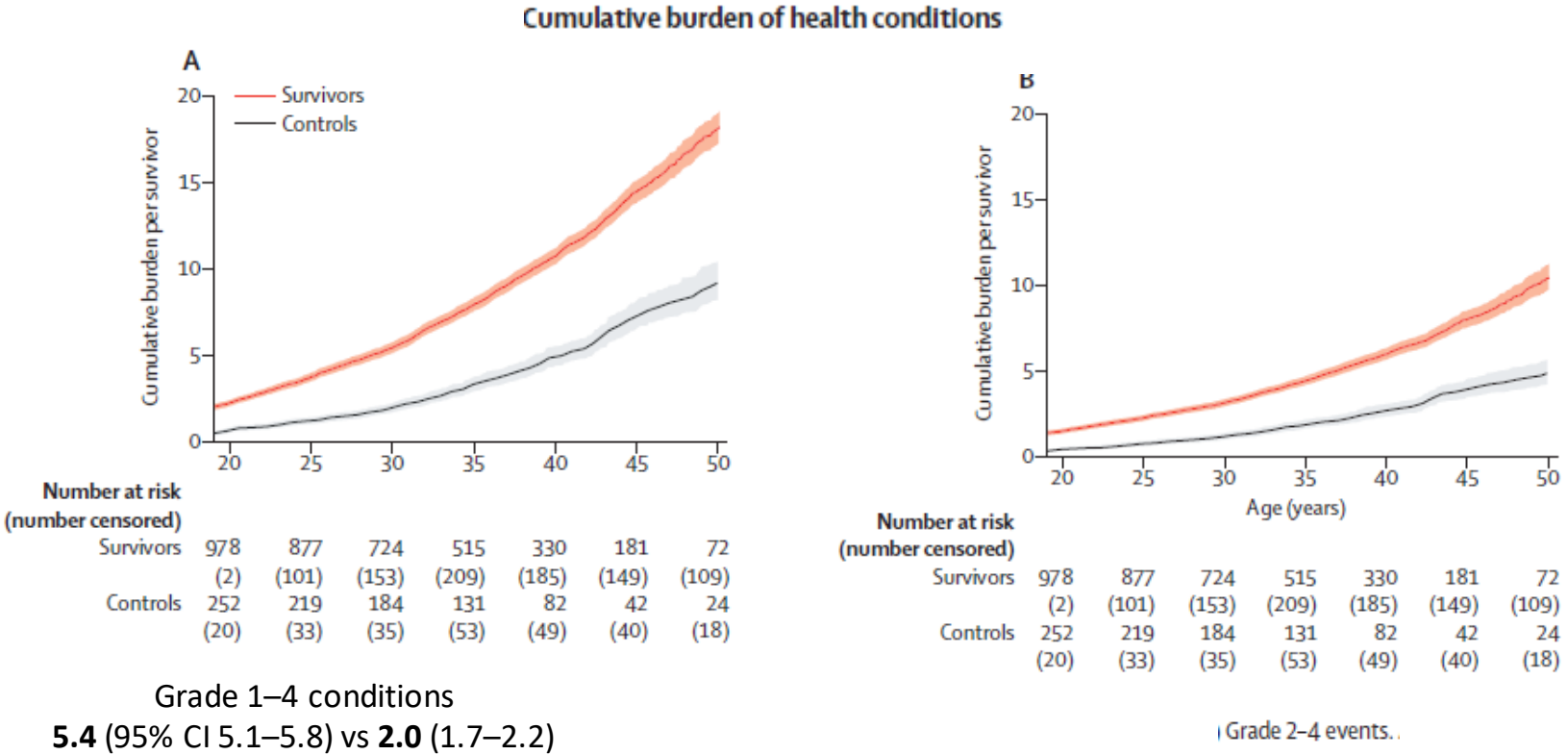
The St Jude Lifetime (SJLIFE) Cohort is a retrospective cohort study with prospective follow-up

	Acute lymphoblastic leukaemia survivors (N=980)					Matched controls (N=272)					p value
	Normal*	Grade 1	Grade 2	Grade 3	Grade 4	Normal*	Grade 1	Grade 2	Grade 3	Grade 4	
Bone health											
Lone bone mineral density	471 (48%)	394 (40%)	115 (12%)	0	..	NA	NA	NA	NA	NA	NA
Osteonecrosis	861 (88%)	91 (9%)	25 (3%)	3 (<1%)	..	NA	NA	NA	NA	NA	NA
Metabolic											
Impaired fasting glucose	790 (81%)	128 (13%)	44 (5%)	18 (2%)	0	218 (80%)	43 (16%)	10 (4%)	1 (<1%)	0	0·26
Overweight or obesity	276 (28%)	..	269 (27%)	330 (34%)	105 (11%)	100 (37%)	..	69 (25%)	78 (29%)	25 (9%)	0·13
Neurological											
Peripheral sensory neuropathy	684 (70%)	221 (23%)	52 (5%)	23 (2%)	..	237 (87%)	30 (11%)	5 (2%)	0	..	<0·0001
Peripheral motor neuropathy	891 (91%)	19 (2%)	50 (5%)	20 (2%)	..	272 (100%)	0	0	0	..	<0·0095
Stroke	927 (95%)	6 (1%)	8 (1%)	18 (2%)	21 (2%)	271 (100%)	0	0	1 (<1%)	0	0·16
Cataract	829 (85%)	134 (14%)	12 (1%)	4 (<1%)	1 (<1%)	250 (92%)	19 (7%)	2 (1%)	1 (<1%)	0	0·056

Median time from diagnosis of 30.0 years (22.7–36.3)

Mulrooney DA, et al. *Lancet Haematol.* 2019;6:e306-e316.

Pediatric ALL

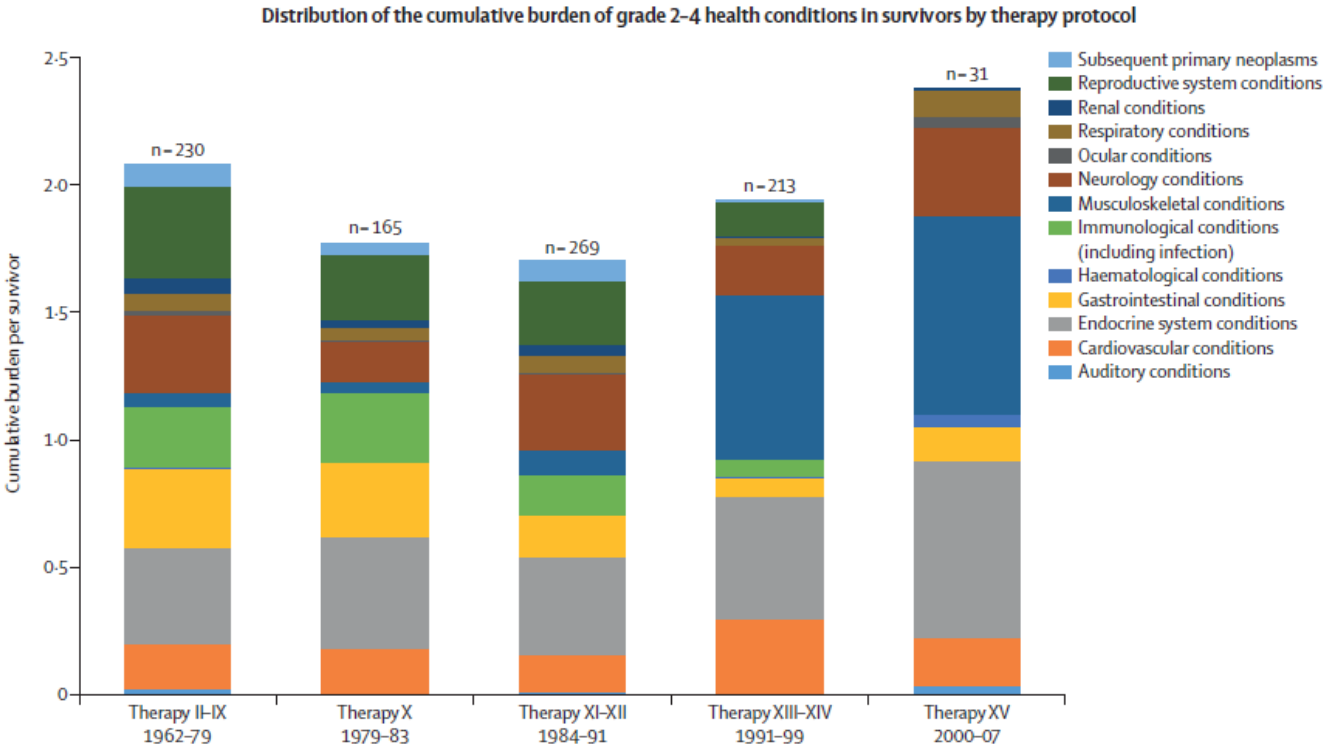


Grade 1–4 conditions

5.4 (95% CI 5.1–5.8) vs **2.0** (1.7–2.2)

Mulrooney DA, et al. *Lancet Haematol.* 2019;6:e306-e316.

Pediatric ALL



The organ systems affected changed substantially over time

Mulrooney DA, et al. *Lancet Haematol.* 2019;6:e306-e316.

Pediatric ALL

As treatment evolved, with the increased use of CNS-active systemic therapy (dexamethasone and asparaginase) and intensified intrathecal chemotherapy, the type of organ dysfunction changed

Survivors treated between 1962–1991

- Subsequent malignancies
- Neurologic sequelae
  - Stroke and seizures
- Endocrinopathies
  - Adrenal insufficiency and growth hormone deficiency (chemoradiotherapy-induced hypothalamic pituitary dysfunction)
  - Hypothyroidism
- Infectious complications
  - Including transfusion related

Survivors treated after 1991

- Neurologic sequelae
  - Peripheral neuropathies, both motor and sensory
- Endocrinopathies
  - Impaired glucose metabolism
  - Obesity
- Musculoskeletal
  - Decreased bone mineral density
  - Osteonecrosis (intensified use of asparaginase and the replacement of prednisone with dexamethasone)

Mulrooney DA, et al. *Lancet Haematol.* 2019;6:e306-e316.

Pediatric AML

Considerable risk of late AEs associated with

- High-dose anthracyclines
- Allogeneic HSCT required for sustained remission

Ehrhardt MJ, et al. *Nat Rev Clin Oncol.* 2023 Oct;20(10):678-696.

Late effects in adults after HCT

NEW/RECURRENT CANCER

- Periodic morphological and minimal residual disease measurement
- Secondary cancers

FINANCIAL BURDEN

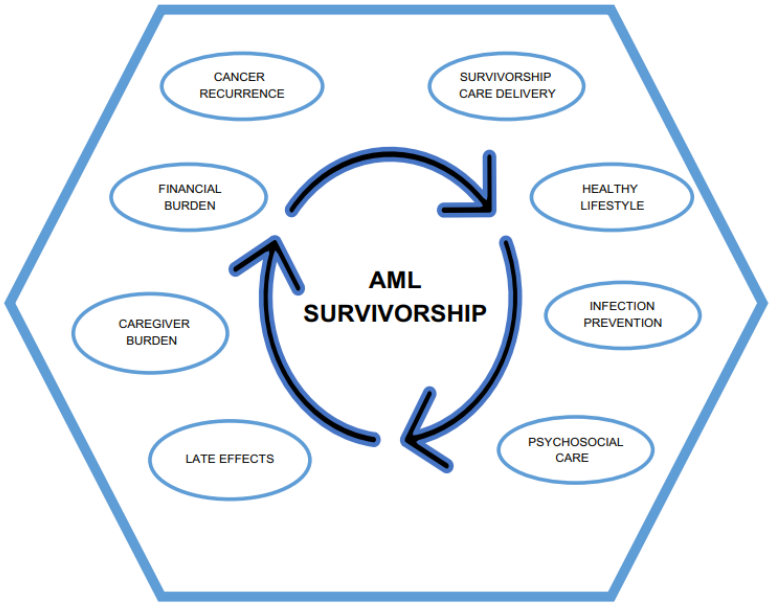
- Loss of household income
- Loss of employment
- Insurance problems
- Medical and non medical costs

CAREGIVER BURDEN

- Caregiver burnout
- Anxiety/Depression
- Poor self-care
- Increase in chronic illness
- Reduced quality of life

LATE EFFECTS

- Infections
- Organ dysfunction
- Bone Health
- Cancer related fatigue
- Mental health problems
- Reproductive adverse effects
- Chronic graft-vs-host disease



SURVIVORSHIP CARE DELIVERY

- Monitoring for side effects
- Routine health screening
- Age and gender appropriate cancer screening
- Coordinated care between providers
- Leverage telemedicine for survivorship care

HEALTHY LIFESTYLE

- Diet
- Supplements
- Exercise
- Weight management
- Lifestyle behaviors

INFECTION PREVENTION

- Vaccinations
- Preventive antibiotics
- Safe food and water
- Hand hygiene

PSYCHOSOCIAL CARE

- Address psychosocial needs
- Screen for and manage financial hardship
- Care for caregiver

Granroth G, et al. *Curr Hematol Malig Rep.* 2022;17(6):243-253.

Late effects in adults after HCT

Organ system	Late Effect*,**	Time Range of Onset After HCT	Cumulative Incidence	References
Cardiovascular	Arterial events	NR	1.5% at 5 years, 4.1% at 10 years, 12.8% at 20 years, 22.1% at 25 years; 22% at 5 years	Tichelli, Blood 2007; Auberle, Cardio-Oncology 2023
	LVEF < 45%	NR	9% at 5 years	Auberle, Cardio-Oncology 2023
	Atrial Arrhythmia	NR	7% at 5 years	Auberle, Cardio-Oncology 2023
	Ischemic Stroke	4-10 years	1-5%	DeFilipp, BBMT 2017
Gastrointestinal	GVHD causing late GI symptoms	Within 6 months of HCT	~18% of HCT patients	Sung, BBMT 2017; Flowers Blood 2015
	Liver cirrhosis	Median of 10 years after HCT, although cirrhosis has been reported to occur as early as a year post HCT	4-24% at 20 years	Inamoto, Hematologica 2017; Strasser Blood 1999
	Cancer	Mouth/pharyngeal cancer onset ~1-4 years Oral cavity cancer onset ~5 years Esophageal cancer onset ~1-4 years	32-92 per 100,000 person years[¥] 14-100 per 100,000 person years 4-59 per 100,000 person years	Inamoto, BMT 2016

Kelkar A, et al. *Front Oncol.* 2023;13:1175794.

Late effects in adults after HCT

Organ system	Late Effect*,**	Time Range of Onset After HCT	Cumulative Incidence	References
Endocrine	Diabetes	1-3 years	8-41%	Inamoto, Hematologica 2017; Shaw BBMT 2017
	Thyroid dysfunction	Subclinical compensated hypothyroidism occurs in up to 15% of patients in the first year	30% by 25 years after BMT	Inamoto, Hematologica 2017; Majhail BBMT 2012
	Osteoporosis	Bone loss occurs 6-12 months post HCT	Up to 50% of patients post BMT	Inamoto, Hematologica 2017
	Avascular necrosis	Median of 12 months post HCT	Cumulative incidence of 3-15% post BMT	Inamoto, Hematologica 2017; Bhatia Exp Rev Hem 2011; Enright H AJM 1990; Socie BJH 2003
	Gonadal dysfunction	Most onset early after conditioning, but subset develop late dysfunction after the first year	3-15% of long-term survivors	Phelan et al, TCT 2021; Buchbinder et al, BBMT 2013
Dermatologic	GVHD causing late skin symptoms	Median onset 4-6 months after HCT	~70% of all patients who develop GVHD	Lee, ASHed 2008; Majhail, BBMT 2012
	Skin cancer	May onset as early as 1 year, but most onset > 10 years post transplant	3-6% at 20 years	Inamoto, BMT 2016; Majhail BBMT 2012

Kelkar A, et al. *Front Oncol.* 2023;13:1175794.

Late effects in adults after HCT

Organ system	Late Effect*,**	Time Range of Onset After HCT	Cumulative Incidence	References
Neurologic	Muscle Cramping	Median of 6 months in those who developed chronic GVHD	33-66% of patients with chronic GVHD	Kraus, PLOS ONE 2012; Bilic, BMT 2016; Lehky, TCT 2022
	Altered sensation	Median onset 6 months post HCT	~20% of patients with neuromuscular complications	Bilic, BMT 2016
	Other neuropathy	Median onset 6 months post HCT	Up to 65% at 14 months post HCT	Sostak, Neurology 2003
Psychiatric	Fear of Progression	<6 months	29% at ~2 years	Hefner, BMT 2014
	PTSD	<6 months	15% at ~2 years	Hefner, BMT 2014
	Depression	<6 months	27% at ~2 years; 7.7% at 10+ years	Hefner, BMT 2014; Sun, BBMT 2013
	Anxiety	<6 months	27% at ~2 years; 3.4% at 10+ years	Hefner, BMT 2014; Sun, BBMT 2013
	Sleep Disturbance	<6 months	43% at ~6 years	Bishop, JCO 2007

Kelkar A, et al. *Front Oncol.* 2023;13:1175794.

Late effects in adults after HCT

Organ system	Late Effect*,**	Time Range of Onset After HCT	Cumulative Incidence	References
Ophthalmologic	Dry eyes	Majority within 3 months of onset of chronic GVHD, ~20% develop 3 months - 2 years of onset of chronic GVHD	40-60% in those with cGVHD	Mohty, ASH Ed 2010; Sun Y-C BBMT 2015
	Cataracts	3-4 years	> 80% at 6-10 years post BMT	Mohty, ASH Ed 2010; Inamoto BBMT 2019
	Ischemic microvascular retinopathy	Onset within 6 months post HCT	Up to 10%	Inamoto BBMT 2019
	CMV retinitis	Onset dependent on timing of CMV reactivation	5-23% in patients with CMV viremia	Inamoto BBMT 2019
Late Infectious	NR	NR	6.4% at 12 years; 10% at 12 years (if still on IS at 2-years)	Norkin, BBMT 2019
Hematologic	VTE	NR	2.4% at 5 years; 4.9% at 10 years; 7.1% at 20 years	Gangaraju, BA 2021
Autoimmune	Cytopenias	Early-onset: 2-8 months; Late-onset: 6-18 months	Early-onset: 1%; Late-onset: 2%	Chen, BMT 1997

Kelkar A, et al. *Front Oncol.* 2023;13:1175794.

Late effects in adults after HCT

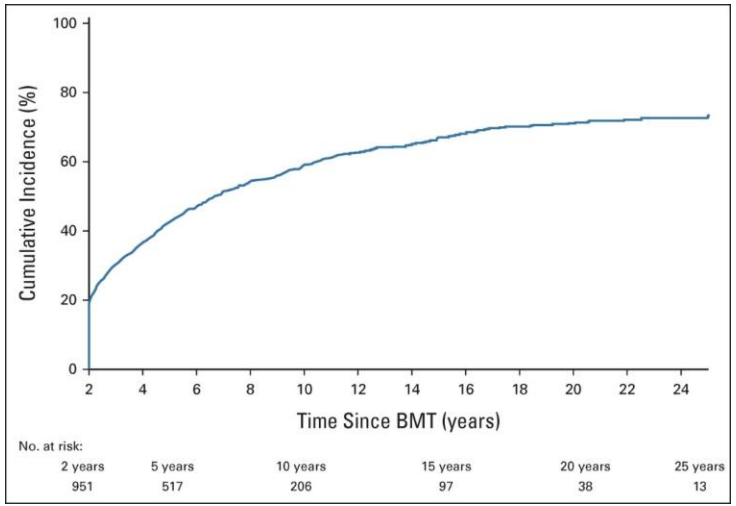
TABLE 2. Prevalence and Risk of Poor Health Status Among Blood or Marrow Transplantation Survivors and Sibling Controls

Outcome	Survivors (n = 840), No. (%)	Siblings (n = 1,310), No. (%)	P[a]	Multivariable Regression (Model 1), OR (95% CI)	P[b]	Multivariable Regression (Model 2), OR (95% CI)	P[b]
Poor general health	167 (22.5)	84 (6.6)	< .001	3.8 (2.8 to 5.1)	< .001	2.9 (2.0 to 2.4)	< .001
Functional impairment	260 (34.3)	214 (16.4)	< .001	2.9 (2.3 to 3.6)	< .001	2.5 (2.0 to 3.2)	< .001
Activity limitation	355 (47.0)	258 (19.7)	< .001	3.7 (3.0 to 4.5)	< .001	3.1 (2.5 to 3.8)	< .001
Pain	205 (30.3)	197 (16.1)	< .001	2.2 (1.7 to 2.7)	< .001	1.9 (1.5 to 2.5)	< .001
Anxiety/fears	127 (18.9)	112 (9.3)	< .001	2.4 (1.8 to 3.1)	< .001	2.2 (1.7 to 3.0)	< .001

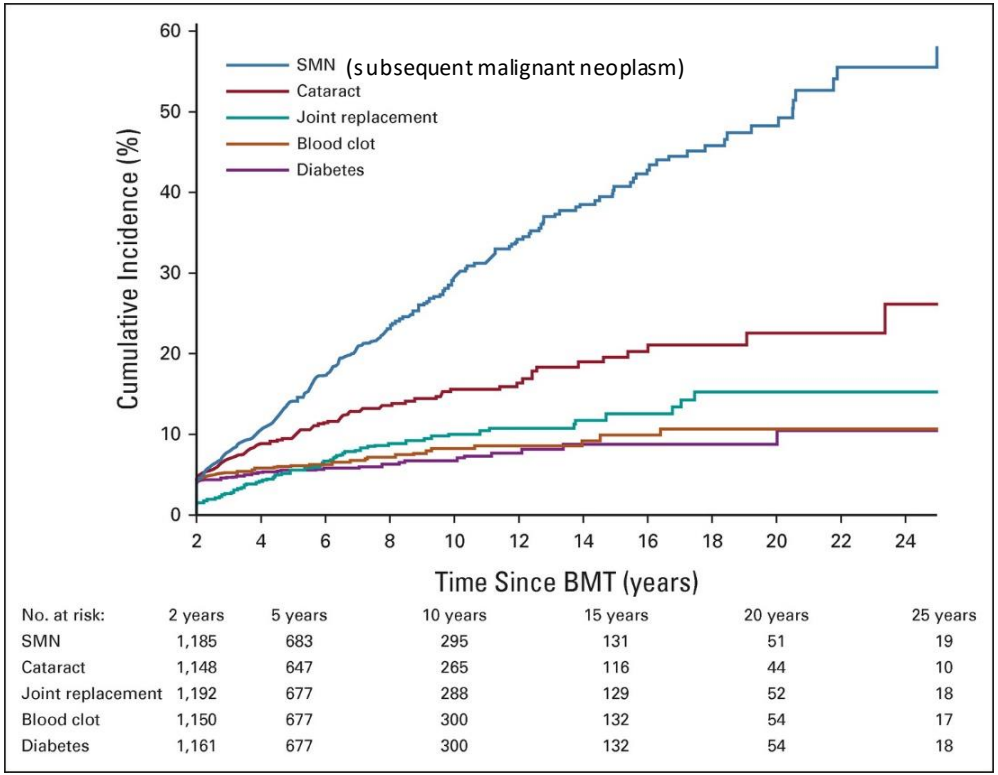
NOTE. Model 2: adjusted for all the variables included in each outcome of interest for model 1 plus the presence of any (yes/no) grades 3 or 4 chronic health conditions.
Abbreviation: OR, odds ratio.
[a]Chi-squared test.
[b]Logistic regression.

Armenian et al. *J Clin Oncol.* 2022;40(28):3278-3288.

Late effects in adults after HCT



Cumulative incidence of grade 3-5 conditions among BMT survivors

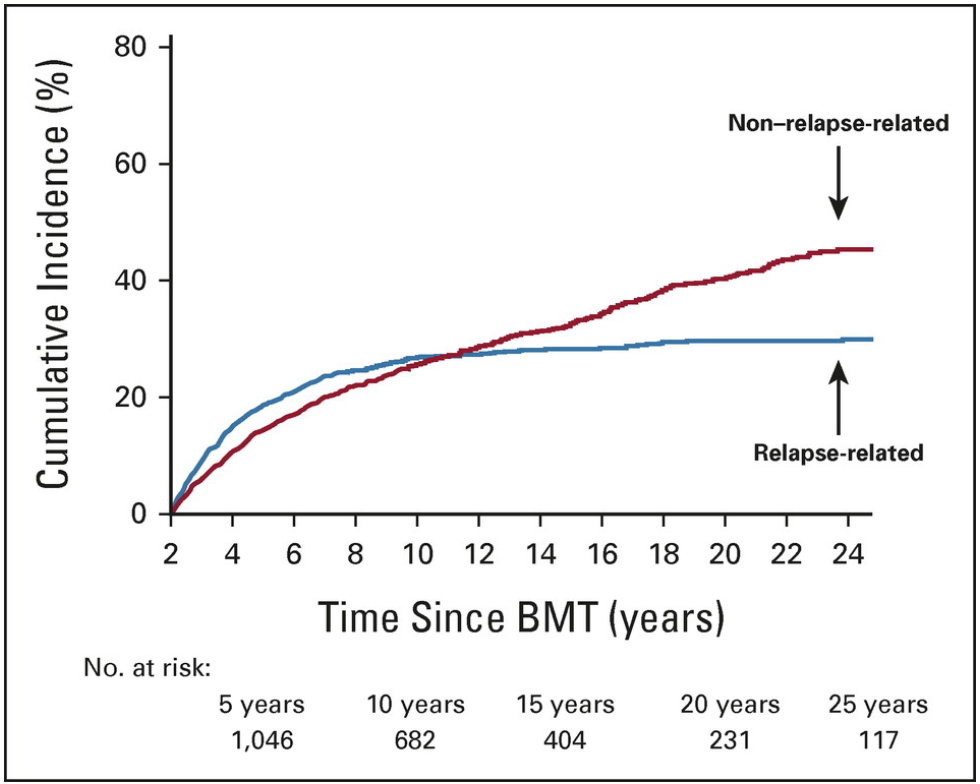


No. at risk:	2 years	5 years	10 years	15 years	20 years	25 years
SMN	1,185	683	295	131	51	19
Cataract	1,148	647	265	116	44	10
Joint replacement	1,192	677	288	129	52	18
Blood clot	1,150	677	300	132	54	17
Diabetes	1,161	677	300	132	54	18

Cumulative incidence of select grade 3-5 conditions among BMT survivors

Armenian et al. *J Clin Oncol.* 2022;40(28):3278-3288.

Late effects in adults after HCT



Among 2-year survivors
Primary disease (43.8%)
Infection (21.3%)

Among 15-year and 20-year survivors

- SMN
  16.5% at 15 years/21.4% at 20 years

- Cardiovascular disease
  16.5% at 15 years/16.7% at 20 years

Armenian et al. *J Clin Oncol.* 2022;40(28):3278-3288.

In clinical practice?

Survivorship – Acute Myelogenous Leukemia (AML)

ELIGIBILITY

AML patients 4 years post diagnosis and in remission

CONCURRENT COMPONENTS OF VISIT

SURVEILLANCE

Year 4, every 6 months. Then starting year 5, annually:

- History and physical examination
- CBC with differential
- Chemistries (glucose, calcium, creatinine, sodium, potassium, bilirubin, ALT, LDH, uric acid)
- Coagulation profile
- Bone marrow aspiration if peripheral smear is abnormal or cytopenias develop

New primary or relapsed disease?

- Yes → Return to primary treating physician
- No → Continue survivorship monitoring

MONITORING FOR LATE EFFECTS

Consider:

- Cardiovascular screening[1] annually and monitor cardiac function if patient is symptomatic
- Lipid panel annually
- Bone Health (see Breast Cancer Survivorship: Bone Health algorithm)

→ Refer or consult as indicated

RISK REDUCTION/ EARLY DETECTION

PSYCHOSOCIAL FUNCTIONING

→ See Page 2

DISPOSITION

ALT = alanine aminotransferase
LDH = lactate dehydrogenase

[1] Consider use of Vanderbilt's ABCDE's approach to cardiovascular health

Survivorship – Acute Myelogenous Leukemia (AML)

ELIGIBILITY

AML patients 4 years post diagnosis and in remission

CONCURRENT COMPONENTS OF VISIT

RISK REDUCTION/ EARLY DETECTION

Patient education, counseling and screening:

- Lifestyle risk assessment[1]
- Cancer screening[2]
- HPV vaccination as clinically indicated (see HPV Vaccination algorithm)
- Screening for Hepatitis B and C as clinically indicated (see Hepatitis B Virus (HBV) Screening and Management algorithm)
- Vaccinations[3] as appropriate
  - Pneumococcus vaccines PCV13 followed by PPSV23 at least 8 weeks apart. Thereafter, only PPSV23 every 5 years.
  - Influenza vaccination yearly
  - Consider one dose of tetanus-diphtheria-pertussis (Tdap) vaccine as an adult if patient has not received Tdap previously and there are no contraindications. Thereafter tetanus-diphtheria (Td) vaccination every 10 years.
  - Zoster Vaccine Recombinant, Adjuvanted (Shingrix) can be considered for patients whose last chemotherapy treatment is greater than 6 months, has a shared patient-provider conversation regarding the vaccine, and meets ACIP criteria[4]
  - Recommendations for vaccination of household members
  - Patients should inform their providers about plans to travel outside of the US at least one month in advance for appropriate counseling and vaccinations

PSYCHOSOCIAL FUNCTIONING

Assess for the following as clinically indicated:

- Distress management (see Distress Screening and Psychosocial Management algorithm)
- Relationship issues
- Infertility
- Fatigue
- Access to primary health care
- Cognitive testing
- Financial stressors

DISPOSITION

Refer or consult as indicated

ACIP = Advisory Committee on Immunization Practices

[1] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[2] Includes breast, cervical (if appropriate), colorectal, liver, lung, pancreatic, prostate and skin cancer screening
[3] Based on Centers for Disease Control and Prevention (CDC) guidelines
[4] Adults age 50 years and older with a history of chickenpox or shingles

Survivorship – Acute Lymphoblastic Leukemia (ALL)

ELIGIBILITY

ALL patients 5 years post diagnosis and in remission

CONCURRENT COMPONENTS OF VISIT

SURVEILLANCE

Year 5-9, every 6 months. Then starting year 10, annually:
- History and physical examination
- CBC with differential
- Chemistries (CMP, LDH, and uric acid)

New primary or relapsed disease?

- Yes → Return to primary treating physician
- No → Continue survivorship monitoring

MONITORING FOR LATE EFFECTS

Consider:
- Pulmonary toxicity and monitor pulmonary function tests (PFT) if patient is symptomatic
- Cardiovascular screening[1] annually
- Lipid panel annually
- Immunoglobulin levels annually
- CD4 count annually if not recovered
- Bone Health (see Breast Cancer Survivorship: Bone Health algorithm)
- Neuropathy screening
- Avascular necrosis as clinically indicated
- Assess for diabetes and glucose intolerance if indicated (late onset)

→ Refer or consult as indicated

RISK REDUCTION/ EARLY DETECTION

PSYCHOSOCIAL FUNCTIONING

→ See Page 2

DISPOSITION

CMP = complete metabolic panel
LDH = lactate dehydrogenase

[1] Consider use of Vanderbilt's ABCDE's approach to cardiovascular health

Survivorship – Acute Lymphoblastic Leukemia (ALL)

ELIGIBILITY

ALL patients 5 years post diagnosis and in remission

CONCURRENT COMPONENTS OF VISIT

RISK REDUCTION/ EARLY DETECTION

Patient education, counseling and screening:
- Lifestyle risk assessment[1]
- Cancer screening[2]
- HPV vaccination as clinically indicated (see HPV Vaccination algorithm)
- Screening for Hepatitis B and C as clinically indicated (see Hepatitis B Virus (HBV) Screening and Management algorithm)
- Vaccinations[3] as appropriate
  - Pneumococcal vaccines PCV13 followed by PPSV23 at least 8 weeks apart. Thereafter, only PPSV23 every 5 years.
  - Influenza vaccination yearly
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  - Patients should inform their providers about plans to travel outside of the US at least one month in advance for appropriate counseling and vaccinations
  - Recommendations for vaccination of household members

PSYCHOSOCIAL FUNCTIONING

Assess for the following as clinically indicated:
- Distress management (see Distress Screening and Psychosocial Management algorithm)
- Access to primary health care
- Vision/cataract screening (see Cataract Screening algorithm)
- Financial stressors
- Relationship issues
- Infertility

DISPOSITION

Refer or consult as indicated

ACIP = Advisory Committee on Immunization Practices

[1] See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
[2] Includes breast, cervical (if appropriate), colorectal, liver, lung, pancreatic, prostate and skin cancer screening
[3] Based on Centers for Disease Control and Prevention (CDC) guidelines
[4] Adults age 50 years and older with a history of chickenpox or shingles

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Q&A

APTITUDE HEALTH

Global Leukemia Academy

Current and future role of transplantation in acute leukemias

Charles Craddock (AML)

Nicola Gökbuget (ALL)

APTITUDE HEALTH

Global Leukemia Academy

Transplantation in AML

Charles Craddock

APTITUDE HEALTH

Current and future role of transplantation in AML

Charles Craddock, CBE, FRCP (UK), FRCPath, DPhil, FMedSci
Queen Elizabeth Hospital Birmingham and University of Warwick
UK

Disclosures

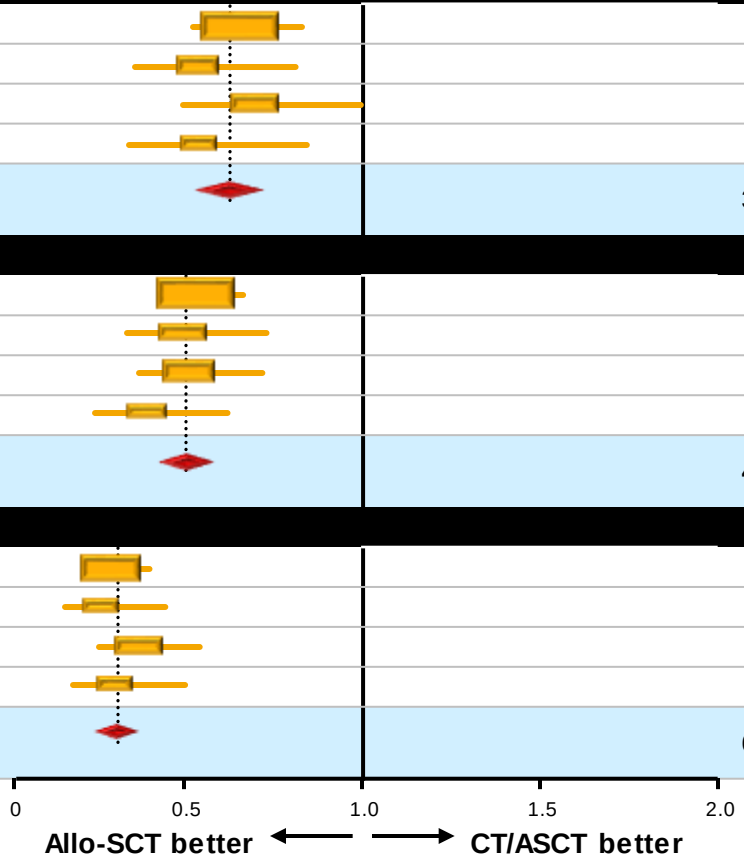
Company Name	Research Support	Employee	Consultant	Stockholder	Speaker Bureau	Advisory Capacity	Other
Abbvie	No	No	Yes	No	Yes	Yes	No
Janssen	No	No	Yes	No	Yes	Yes	No
KITE	Yes	No	Yes	No	No	No	No
Novartis	No	No	Yes	No	Yes	Yes	No
Roche	No	No	Yes	No	Yes	No	No
Jazz	Yes	No	Yes	No	No	No	No
BMS	No	No	Yes	No	Yes	Yes	No
Pfizer	No	No	Yes	No	Yes	Yes	No
Astellas	No	No	Yes	No	Yes	Yes	No
Daiichi Sankyo	No	No	Yes	No	Yes	Yes	No
Eurocept	No	No	Yes	No	Yes	Yes	No

The central role of allografting in the management of high-risk AML

- Allografting delivers maximal antileukemic activity in AML – a potent and manipulable antitumor effect across all cytogenetic groups
- The toxicity of allo-SCT has steadily declined, with 2-year NRM estimated at 15-20% in fit adults with a well-matched donor
- Increased donor availability and decreased transplant toxicity have resulted in allo-SCT becoming a centrally important treatment modality in most fit adults with AML in CR1
- Allografting exerts a potent and broadly equivalent antitumor effect across all cytogenetic groups

Allo-SCT reduces relapse risk in AML, independent of karyotype

Cytogenic Group	Events/Patients CT/ASCT	Events/Patients Allo-SCT	HR and 95% CI (CT/ASCT : allo-SCT)	Reduction SD	*P* Value
OVERALL SURVIVAL					
CN	389/688	129/306			
CA	111/168	34/87			
CA unfav	84/115	63/117			
CA MK	58/62	36/45			
Total	**642/1033** (62%)	**262/555** (47%)		**35%** (5%) **reduction**	**2P <.001**
RELAPSE-FREE SURVIVAL					
CN	448/688	136/306			
CA	119/168	38/87			
CA unfav	99/115	68/117			
CA MK	59/62	36/45			
Total	**725/1033** (70%)	**278/555** (50%)		**48%** (4%) **reduction**	**2P <.001**
RELAPSE					
CN	412/688	73/306			
CA	115/168	21/87			
CA unfav	95/115	49/117			
CA MK	57/62	28/45			
Total	**679/1033** (66%)	**117/555** (31%)		**67%** (3%) **reduction**	**2P <.001**



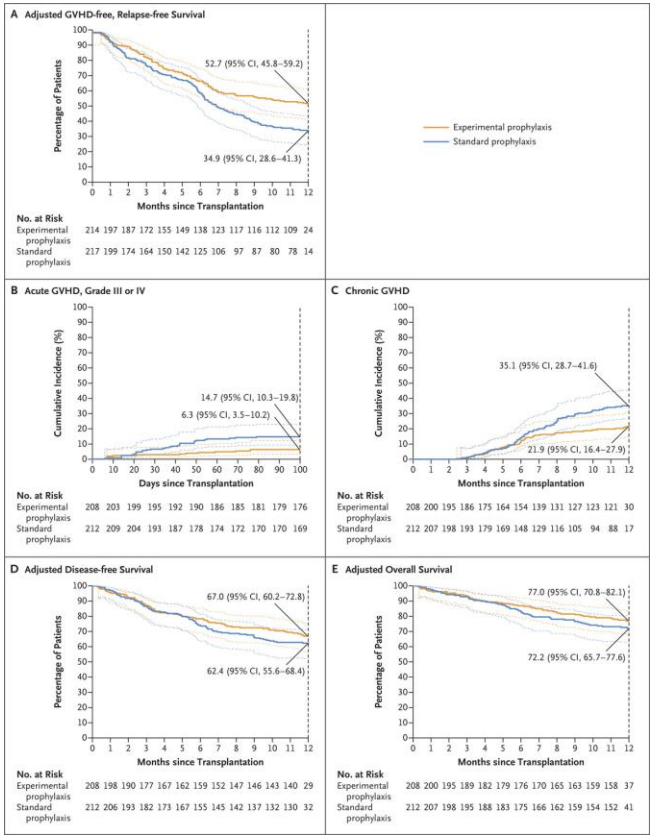
Cornelissen J, et al. *J Clin Oncol.* 2012.

Transplant indications in AML CR1 in 2023

2017 ELN Risk Stratification by Genetics	MRD After Cycle 2 Chemotherapy	Estimated Risk of Relapse Based on Consolidation With:		Maximal Tolerated NRM Prognostic Scores for Allo-SCT to Be Beneficial	
		Chemotherapy alone (%)	Allo-SCT (%)	HCT-CI score	NRM risk (%)
Favorable	Negative	25–35	15–20	N/A (<1)	5
	Positive	70–80	30–40	≤3–4	<30
Intermediate	Negative	50–60	25–30	≤2	<20
	Positive	70–80	30–40	≤3–4	<30
Adverse	N/A	>90	45–55	<5	<35

Loke J, et al. *Br J Haematol.* 2020.

Posttransplant Cy reduces acute and chronic GVHD after RIC allo-SCT



Bolanos-Meade et al. *NEJM.* 2023.

Posttransplant Cy reduces GVHD-related death without a concomitant increase in relapse

Table 3. Causes of Death in Patients in the Intention-to-Treat Population.

Cause of Death	Experimental-Prophylaxis Group (N=214)	Standard-Prophylaxis Group (N=217)
	number/total number (percent)	
Recurrence or persistence of disease	19/48 (40)	24/56 (43)
Primary graft failure	2/48 (4)	0
Acute GVHD	2/48 (4)	8/56 (14)
Chronic GVHD	0	1/56 (2)
Infection	8/48 (17)	10/56 (18)
Organ failure	11/48 (23)	6/56 (11)
Hemorrhage	3/48 (6)	1/56 (2)
Acute respiratory distress syndrome	0	1/56 (2)
Other*	3/48 (6)	5/56 (9)

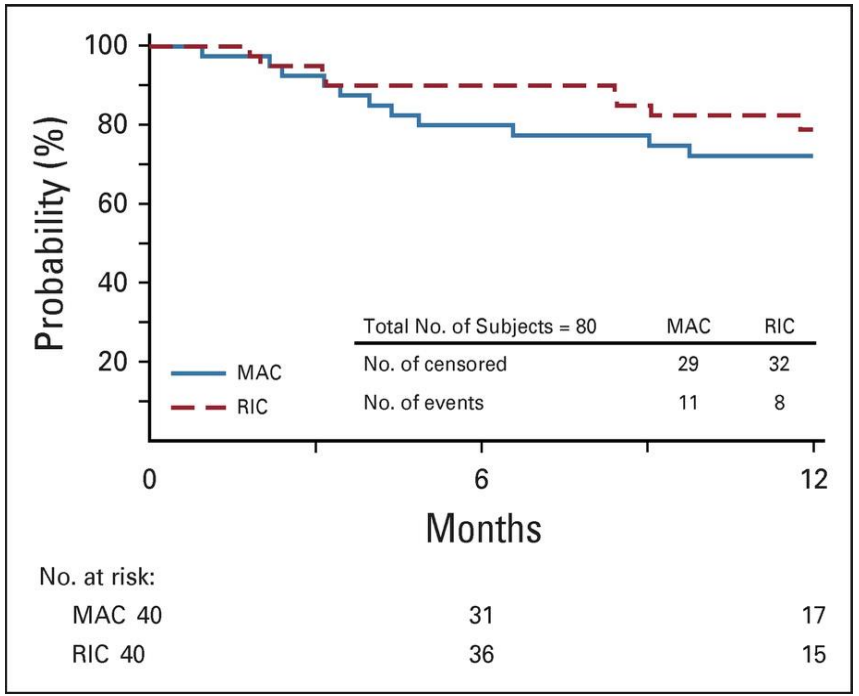
* The "other" category includes accident, septic shock, thrombotic microangiopathy, and unknown.

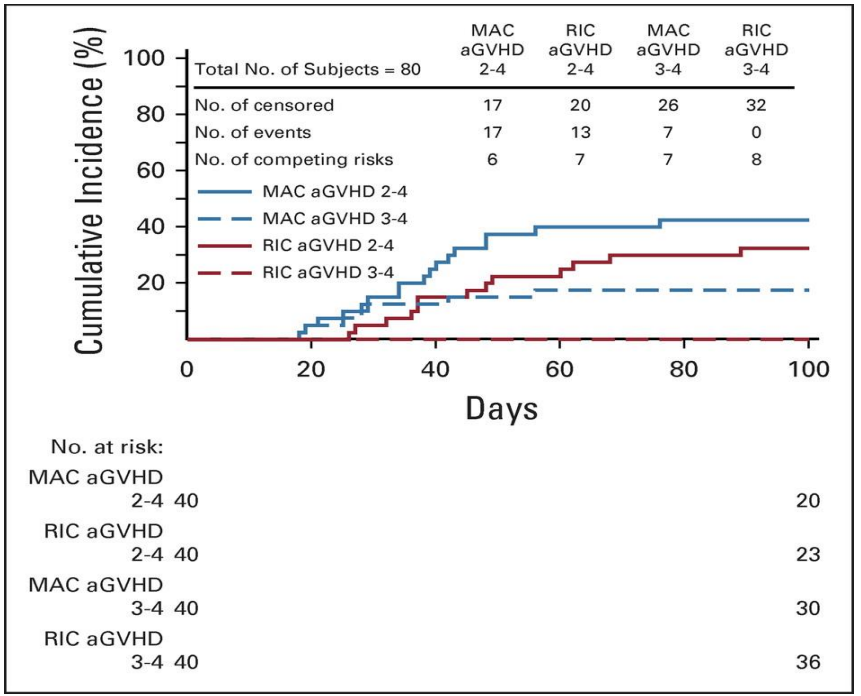
Bolanos-Meade et al. *NEJM.* 2023.

BMT CTN 1703: Conclusions

- In well-matched RIC PBSCT, PTCy/Tac/MMF produces
  - Superior GRFS, owing to reduced severe acute and chronic GVHD
  - No increase in relapse/progression
  - Slightly delayed hematopoietic recovery
  - More grade 2 but not grade 3 infections, mostly in first month
- Data support emerging role of PTCy GVHD prophylaxis regimens
- Awaiting results of IMPACT MoTD trial that incorporates ATG in control arm

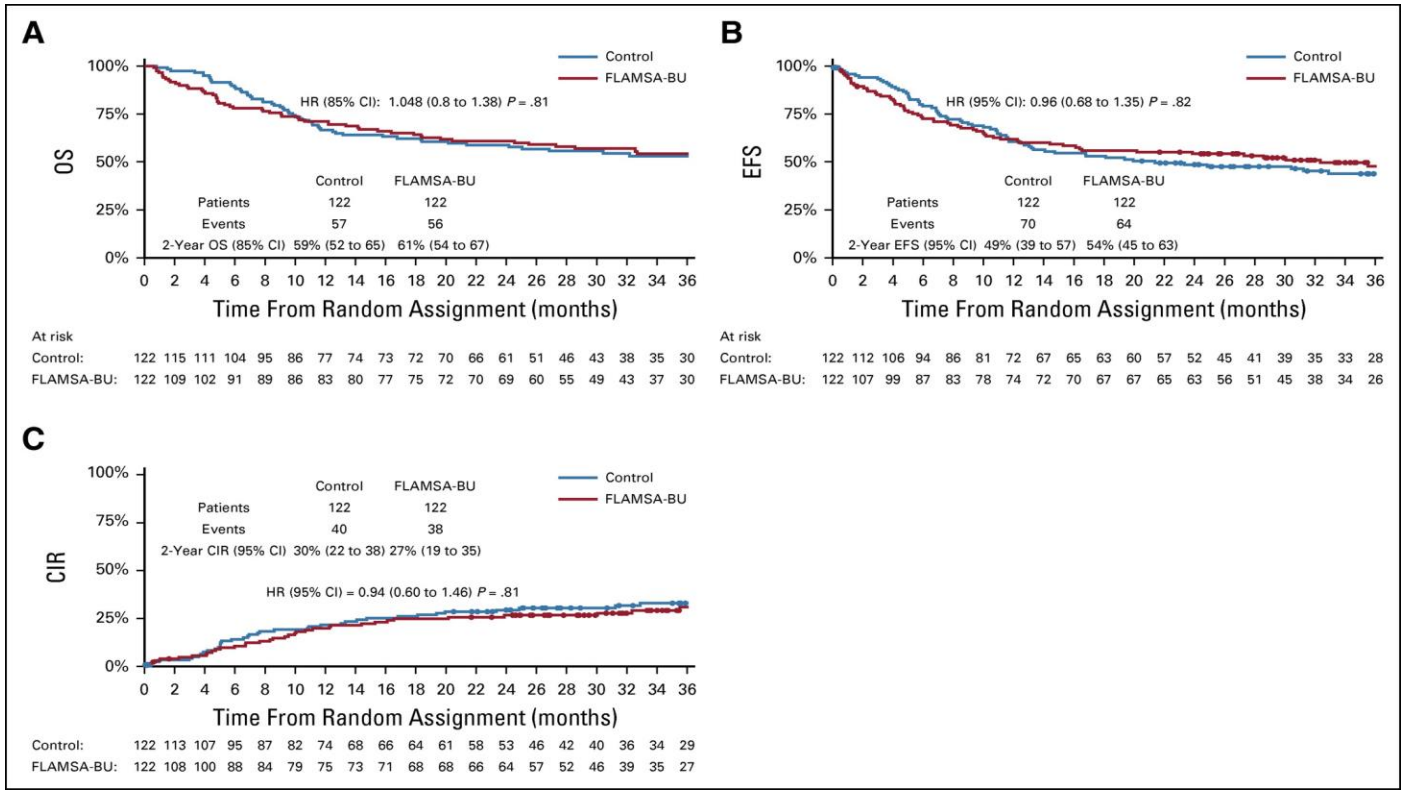
Posttransplant Cy improves outcomes in adults transplanted using mismatched unrelated donors





Shaw et al. *J Clin Oncol.* 2021.

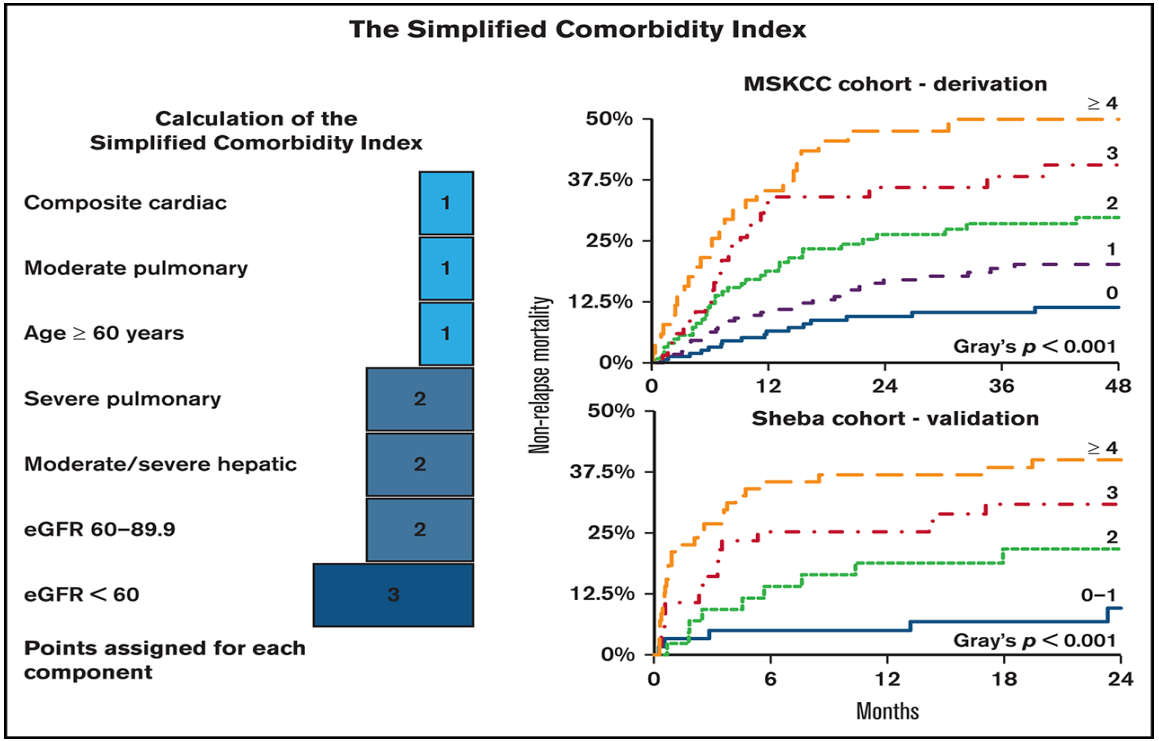
Kinetics of transplant Co after RIC allo-SCT in AML: FIGARO analysis



Craddock C, et al. *J Clin Oncol.* 2020.

The Simplified Comorbidity Index: A new tool for prediction of nonrelapse mortality in allo-HCT

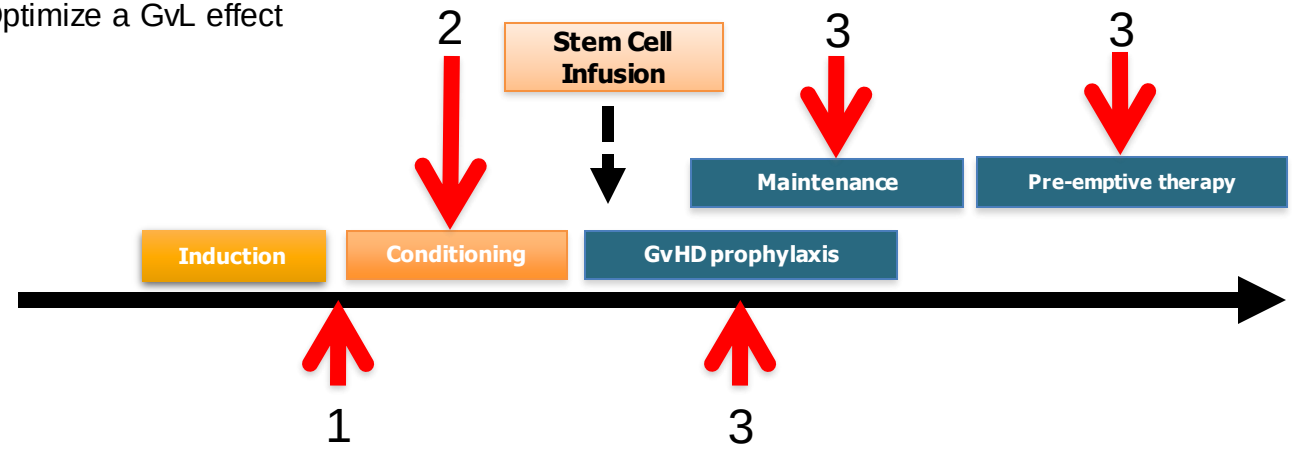
Specific challenge is late GVHD-related toxicity in over 60s



Shouval et al. *Blood Adv.* 2022.

Strategies to reduce relapse in patients allografted for AML: Choosing the best conditioning regimen

1) Minimize pretransplant disease burden
2) Optimize cytotoxic properties of the conditioning regimen
3) Maintenance drug or cellular therapies that
   - Target residual leukemic stem/progenitors
   - Optimize a GvL effect

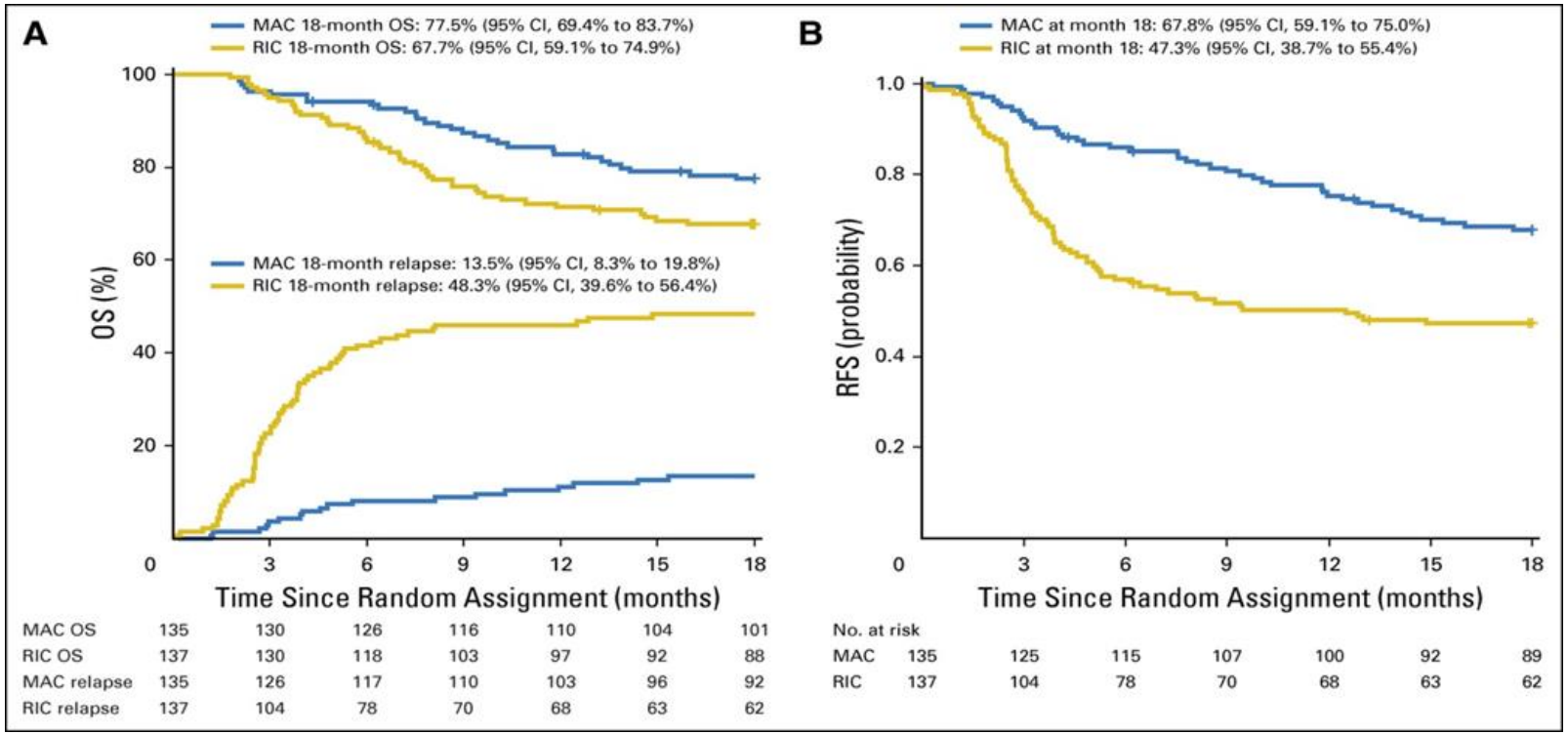


Craddock C, et al. *Bone Marrow Transpl.* 2019.

Prospective comparison of RIC and MAC in AML and MDS: US-CTN 0901 study

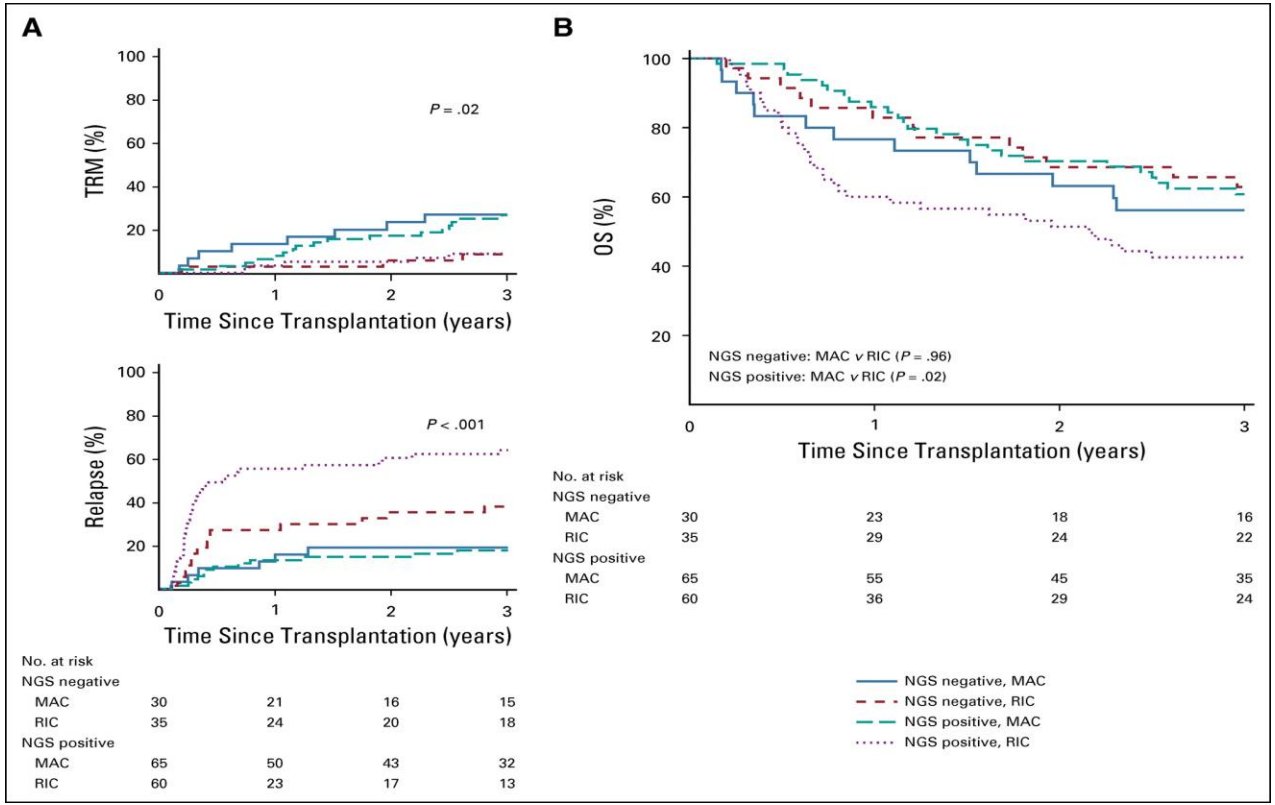
- 272 patients with AML and MDS (<5% blasts pretransplant)
- Age 18-65
- MAC- Bu/Cy or Cy/TBI
- RIC- Flu/Bu_2 or Flu/Mel
- GVHD prophylaxis CsA/MTX. CsA levels and taper not specified
- Reduced risk NRM (4% vs 16%; *P* = .002) of grade 2-4 acute GVHD in RIC arm (31% vs 44%; *P* = .02) and chronic GVHD (47% vs 64%; *P* = .19)
- Increased relapse in patients with AML, but not MDS
- Equivalent OS

US-CTN 0901 outcome after MAC or RIC allograft: US CTN study



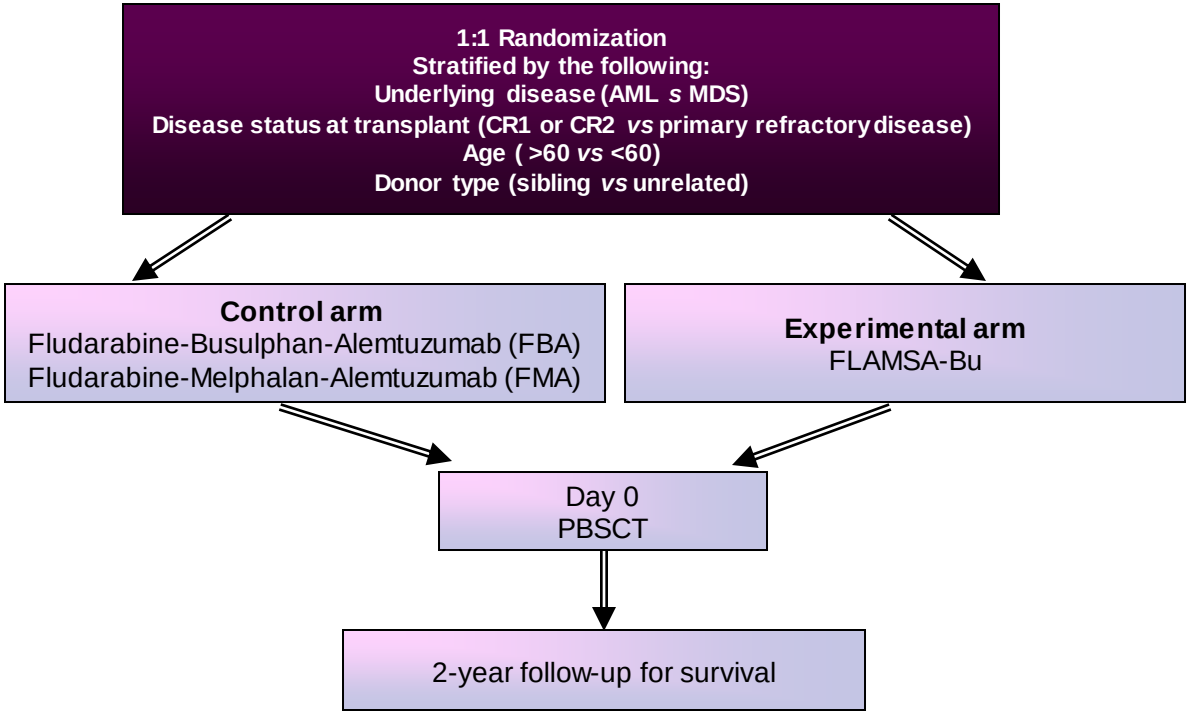
Scott et al. *J Clin Oncol.* 2017.

Outcome according to conditioning regimen intensity and pretransplant NGS MRD status



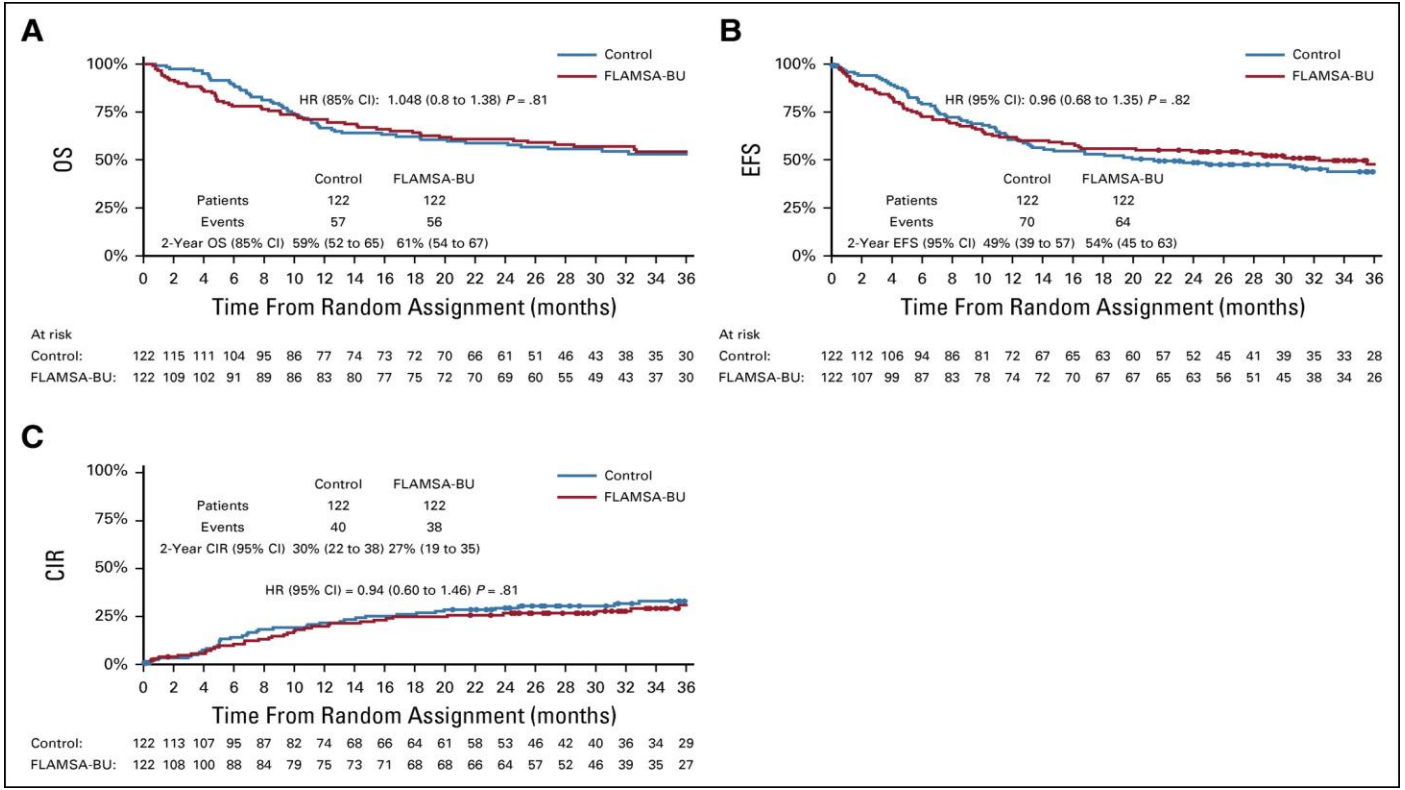
Hourigan et al. *J Clin Oncol.* 2019.

FIGARO: Randomized trial of a FLAMSA-Bu intensified RIC regimen in high-risk AML and MDS



Pretransplant and posttransplant flow MRD prospectively evaluated in all FIGARO patients

Impact of FLAMSA-Bu Regimen on transplant outcome in high-risk AML: FIGARO

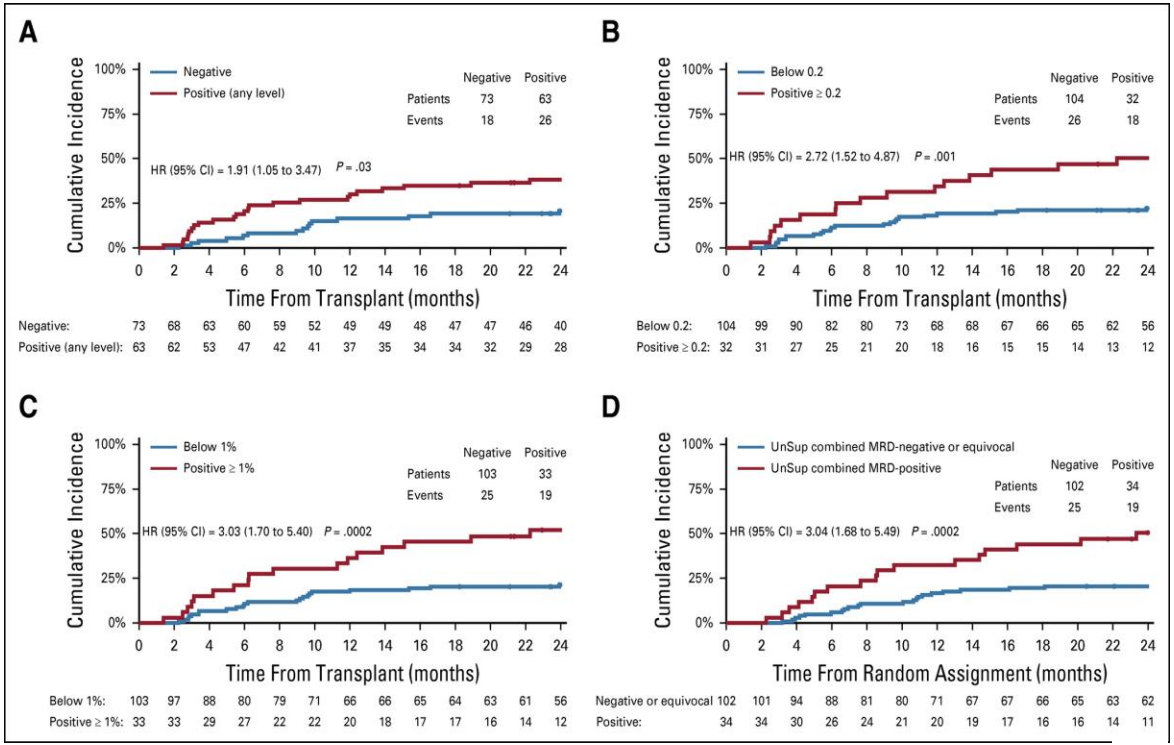


Craddock C, et al. *J Clin Oncol.* 2020.

Impact of pretransplant MRD on the incidence of relapse in patients allografted on FIGARO trial

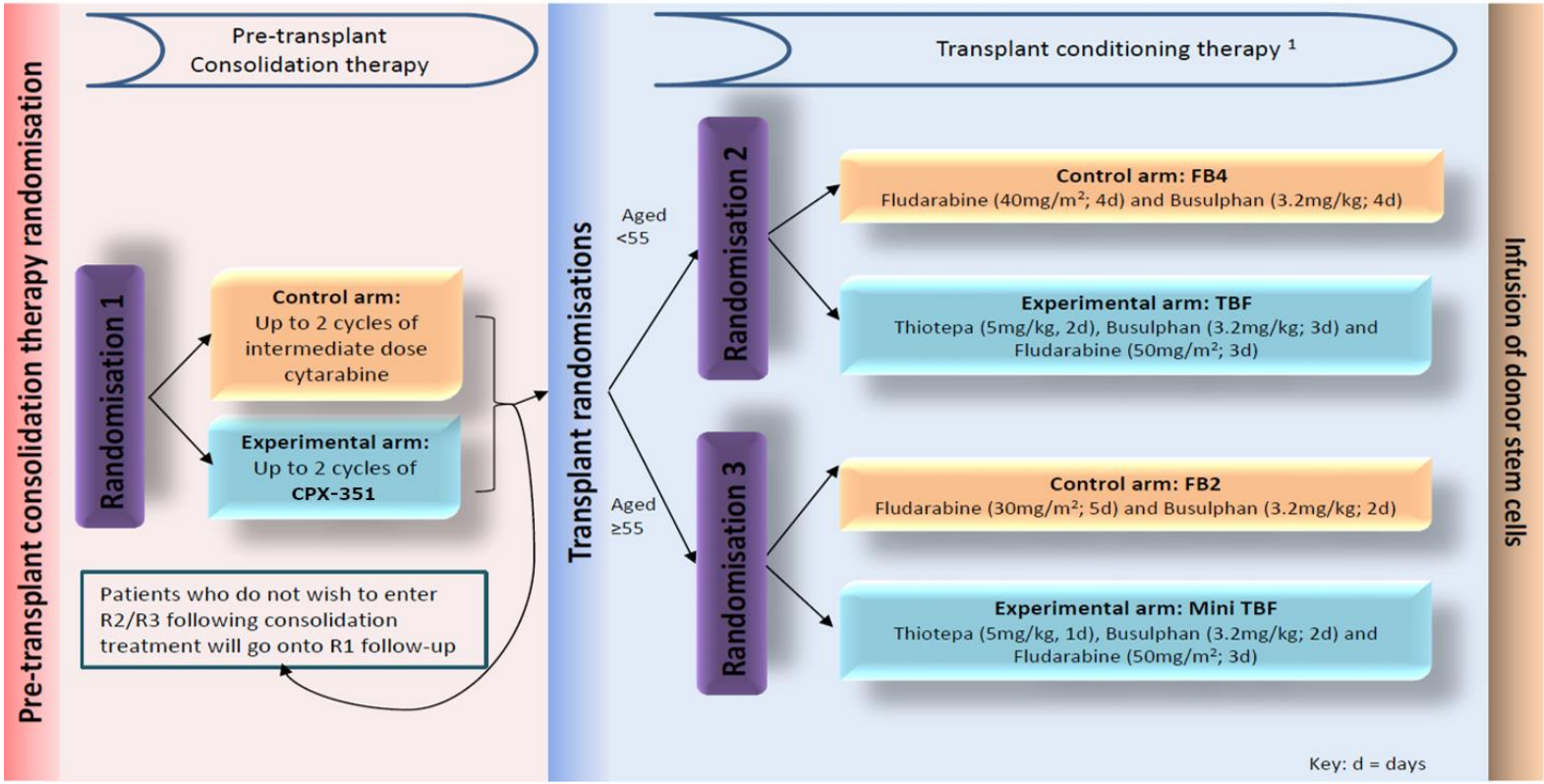
No interaction between MRD status and conditioning regimen

- CIR MRD– 20%
  CIR MRD+ 41%
  P = .01
- 2-yr MRD– 70%
  OS MRD+ 51%
  P = .05



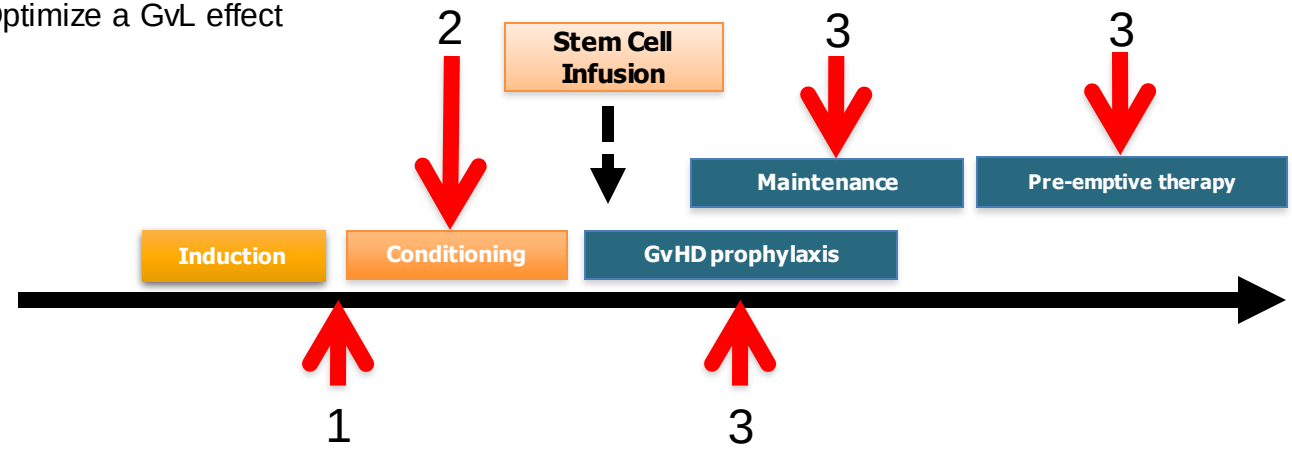
Craddock C, et al. *J Clin Oncol.* 2020.

COSI trial schema: Randomization 2 and 3



Strategies to reduce relapse risk in patients allografted for AML

1) Minimize pretransplant disease burden
2) Optimize cytotoxic properties of the conditioning regimen
3) Maintenance drug or cellular therapies that
   - Target residual leukemic stem/progenitors
   - Optimize a GvL effect



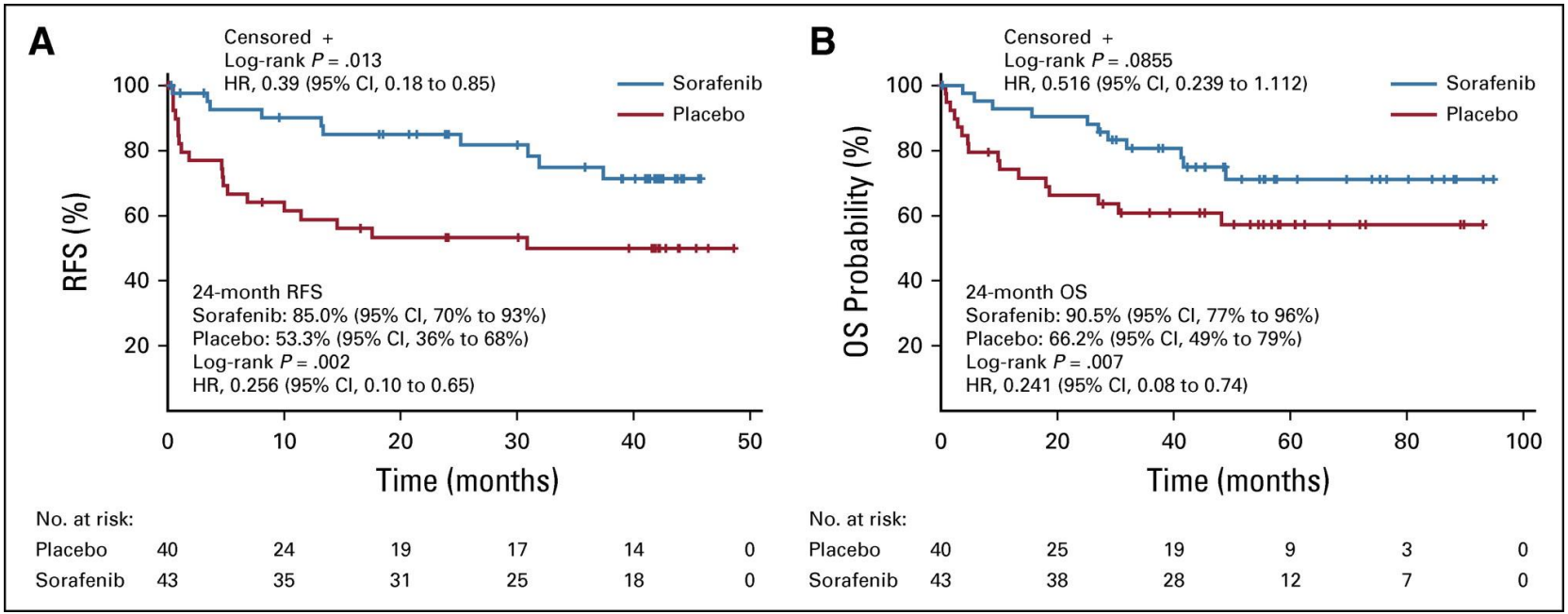
Craddock C, et al. *Bone Marrow Transpl.* 2019.

Agents under investigation in posttransplant maintenance

Agent	Study	Population	Reference
Sorafenib	Randomized prospective phase II trials	*FLT3*-ITD AML who received HCT in first CR	Burchert A, et al. J Clin Oncol 2020: 38:2993-3002
Gilteritinib	Phase III, multicenter, randomized	*FLT3*-ITD AML who received HCT in first CR	Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02997202 (accessed Sep 2020)
CC486	AMADEUS, phase III, randomized	Patients with AML or MDS post-allograft	Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04173533 (accessed Sep 2020)

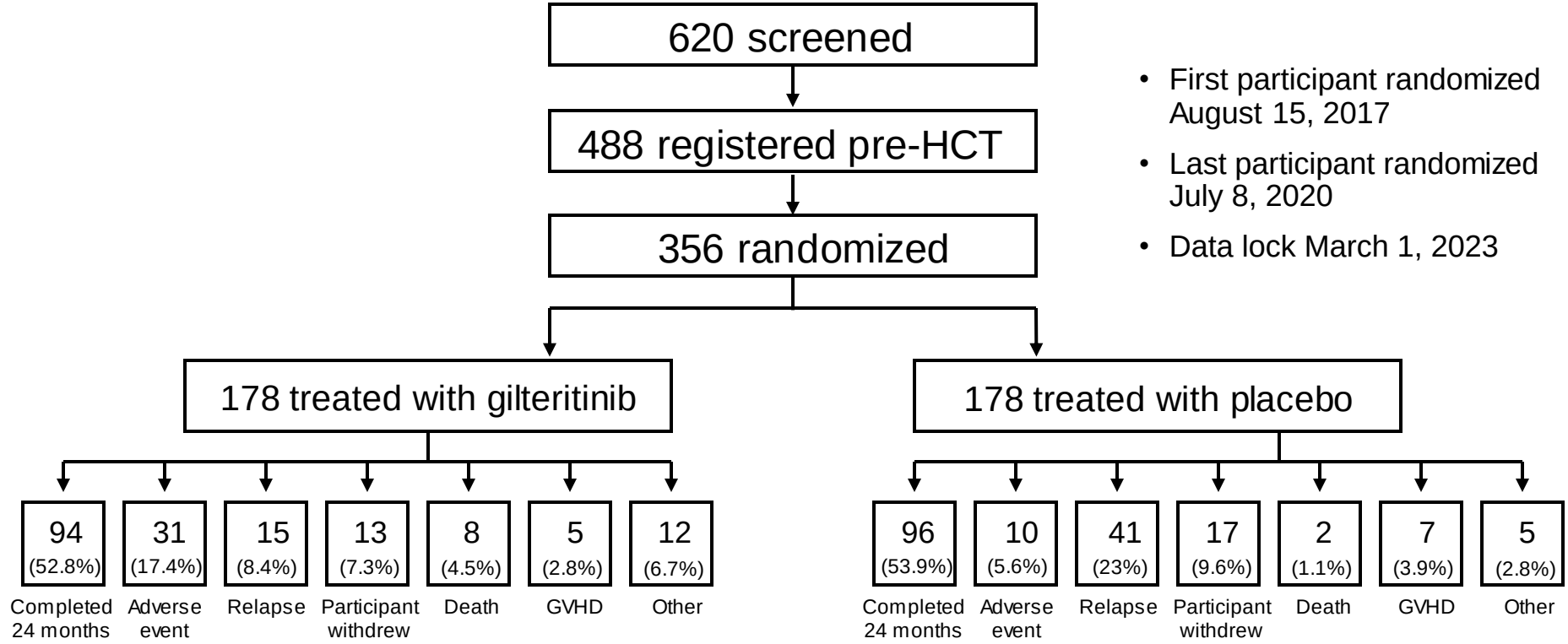
CR, complete remission; mCR, morphologic CR.

Posttransplant sorafenib maintenance improves outcome after allo-SCT in patients allografted for *FLT3*-ITD+ AML



Burchert et al. *J Clin Oncol.* 2020.

BMT-CTN 1506 (MORPHO): Patient disposition



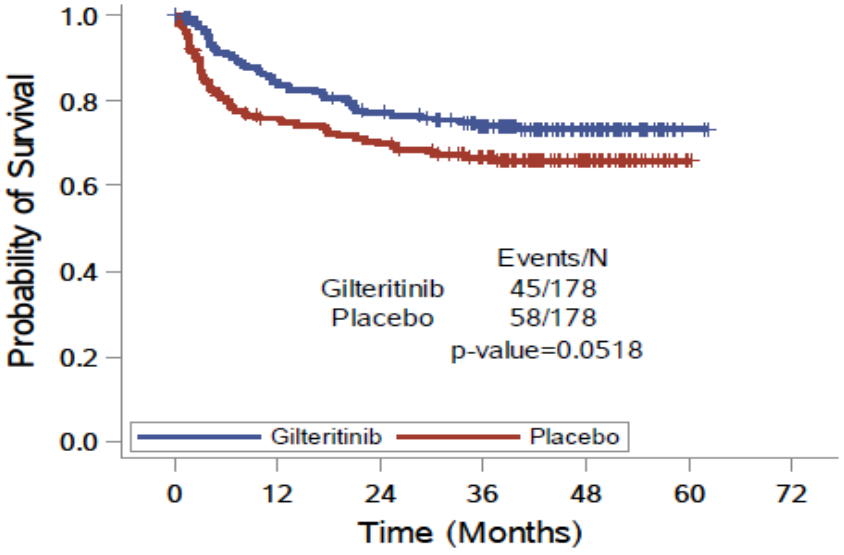
- First participant randomized August 15, 2017
- Last participant randomized July 8, 2020
- Data lock March 1, 2023

Reason for discontinuation

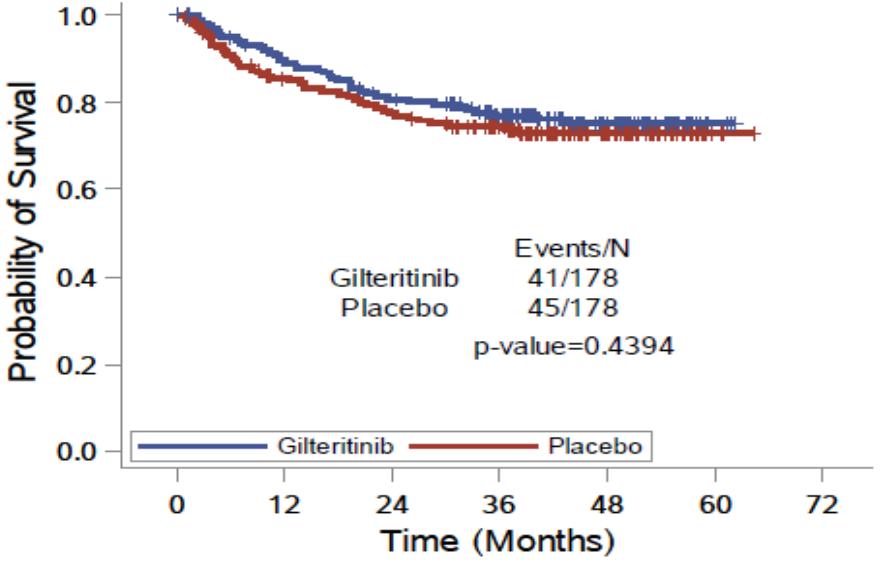
Reason for discontinuation

BMT-CTN 1506 (MORPHO): Efficacy outcome

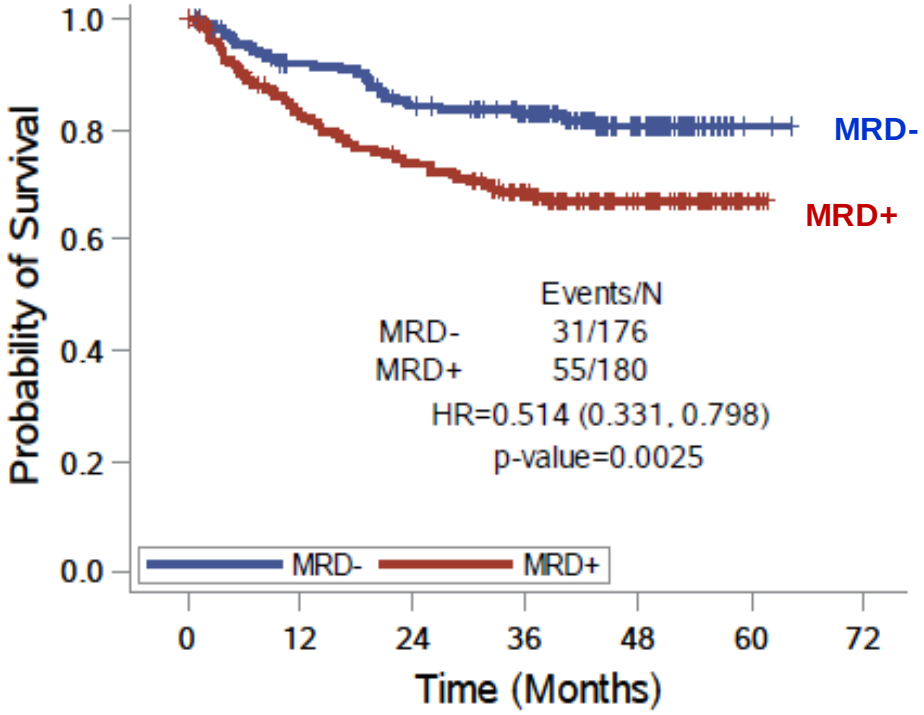
Primary objective:
Relapse-free survival
HR = 0.679 (0.459-1.005)
P = .0518



Key secondary objective:
Overall survival
HR = 0.846 (0.554-1.293)
P = .4394

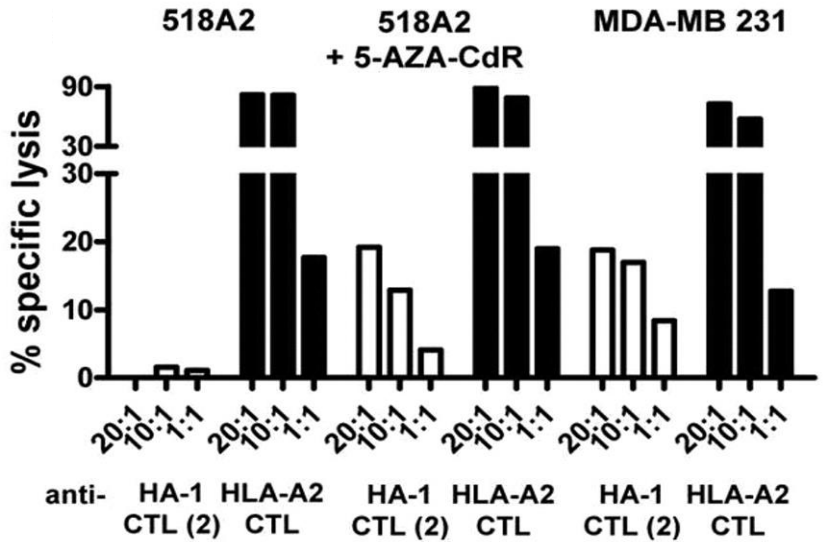


Effect of MRD6 on OS overall, irrespective of treatment arm
MRD6 at registration (pre-HCT) or randomization (post-HCT)



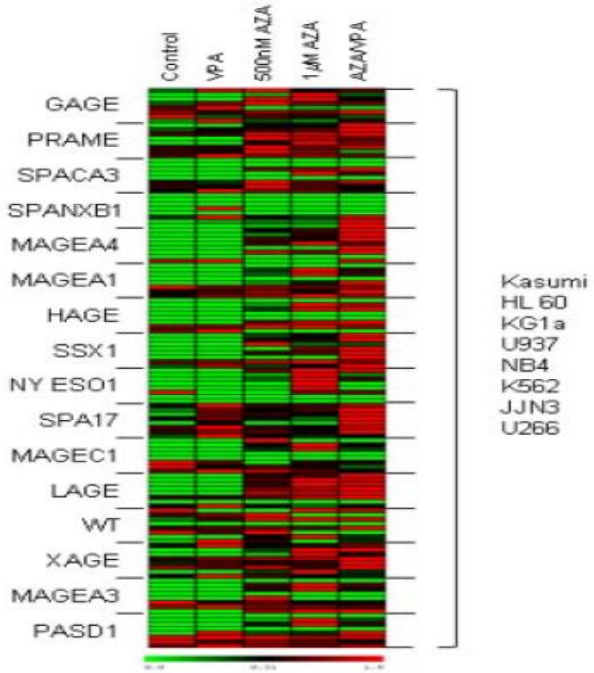
AZA upregulates the expression of epigenetically silenced putative GVL targets

AZA upregulates mHAg expression on AML blasts



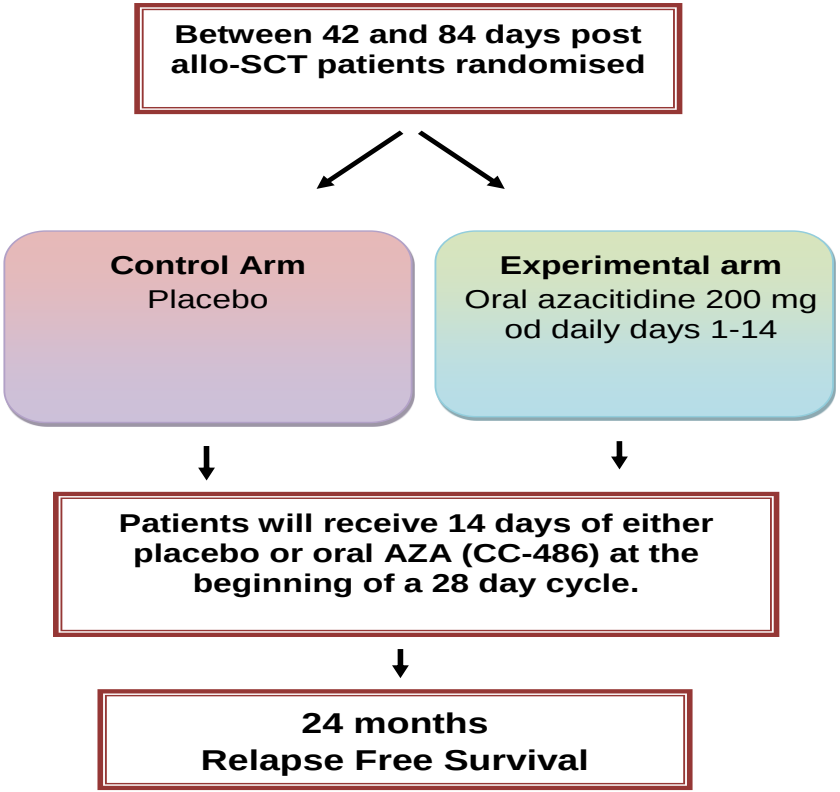
Hambeach et al. *Blood.* 2009.

AZA upregulates MAGE-A1 expression on AML blasts



Goodyear et al. *Blood.* 2010.

AMADEUS: Randomized trial of CC486 maintenance in patients allografted for AML



What is the optimal allograft strategy in high-risk AML?

- In fit adults under 55, a MAC regimen is preferred – especially in patients who are MRD+
- Older adults who are MRD+ can still achieve good posttransplant outcomes with a RIC regimen, but novel conditioning/posttransplant strategies are required
- There is no evidence that transplant should be deferred in CR1 patients who are MRD+
- No benefit of FLAMSA-Bu in AML CR1
- Importance of identifying patients at high risk of relapse
- Strategies to accelerate early acquisition of full donor T-cell chimerism are required
  - ✓ Early taper of immunosuppression
  - ✓ Prophylactic DLI
- Prospective trials are urgently required if we are to optimize transplant outcome

Global Leukemia Academy

Transplantation in ALL

Nicola Gökbuget

APTITUDE HEALTH

Current and Future Role of SCT in Adult ALL

Nicola Gökbuget

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GMALL Study Coordinator

UNIVERSITÄTS KLINIKUM FRANKFURT
GOETHE-UNIVERSITÄT

GMALL
German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia

uct Universitäres Centrum für Tumorerkrankungen Frankfurt
University Cancer Center

DKTK Deutsches Konsortium für Translationale Krebsforschung

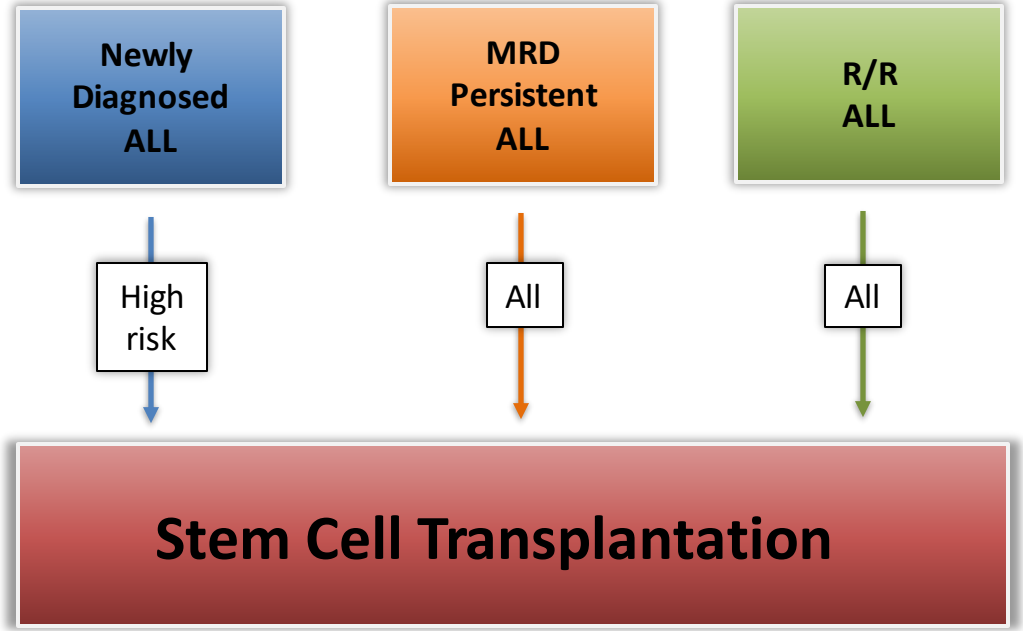
Goals of allo-HSCT in adult ALL

1. **Maximize antileukemic effect by**
   - TBI
   - High-dose chemotherapy

2. **Utilize graft-vs-leukemia effect**

3. **Utilize these SCT effects in specific subgroups, particularly those with high-risk features**
   - Eg, immature subtypes (pro-B/MLL, early T)
   - Ph+ ALL

Place of allo-HSCT in adult ALL (classical)



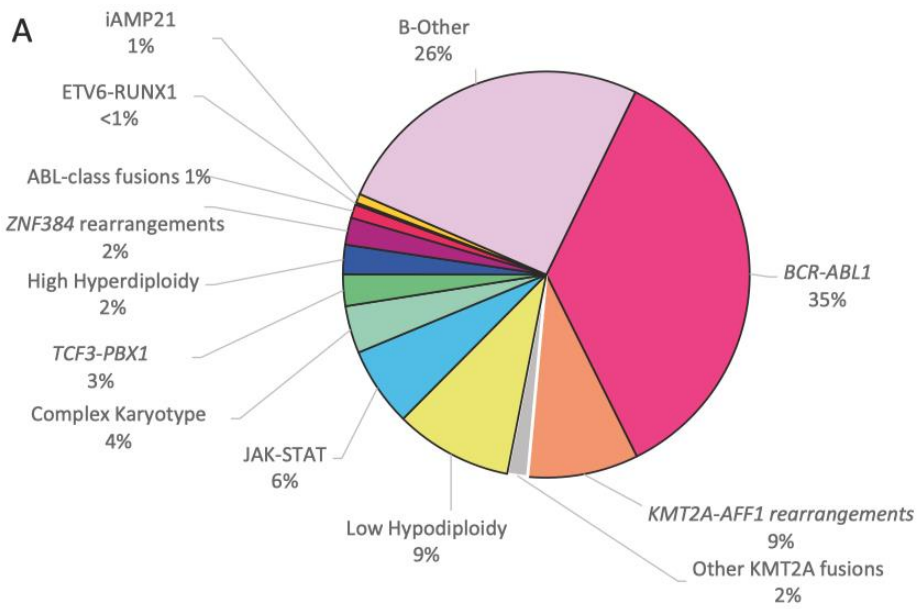
Place of allo-HSCT in adult ALL:
Current considerations

1. Conventional prognostic factors vs molecular factors vs MRD
2. New compounds for the treatment of ALL
3. Mortality of SCT
4. Methodological challenges to evaluate the impact of SCT
5. SCT as nonstandardized/nonstandardizable modality

Cytogenetic classification in adult B-precursor ALL (N = 652)

Moorman et al, Leukemia 2022

De novo ALL 25-65 yr (UKALL14)



CNA affecting IKZF1, CDKN2A/B, PAX5, BTG1, ETV6, EBF1, RB1, and PAR1 were assessed in 436 patients. None of the individual deletions or profiles were associated with survival, either in the cohort overall or within key subgroups.

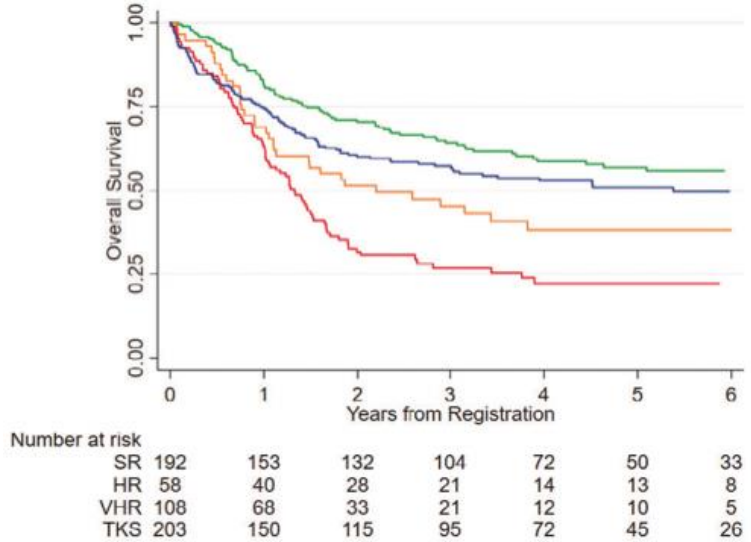
Subgroup	N	%	RR	OS
B-Other	148	26%	25%	63%
ZNF384	12	2%	0%	100%
High hyper	13	2%	26%	54%
TCF3-PBX1	14	3%	38%	54%
KMT2A-AFF1	49	9%	50%	46%
KMT2a-other	9	2%	50%	44%
Low hypo	52	9%	52%	22%
JAK-STAT	35	6%	56%	36%
Complex	21	4%	60%	24%
BCR-ABL	197	35%	31%	57%
ABL-class	6	1%	0%	67%

Cytogenetic classification in adult B-precursor ALL

Moorman et al, Leukemia 2022

Genetic Risk Group	Definition	Freq
Standard risk (SR)	BCP-ALL with *ZNF384*-r, HeH and other abnormalities	34%
High risk (HR)	*KMT2A*-r	10%
Very High Risk (VHR)	Low hypodiploid, complex karyotype, JAK-STAT abnormalities	19%
Tyrosine kinase activating (TKA) fusions	*BCR-ABL1*, ABL-class fusions	36%

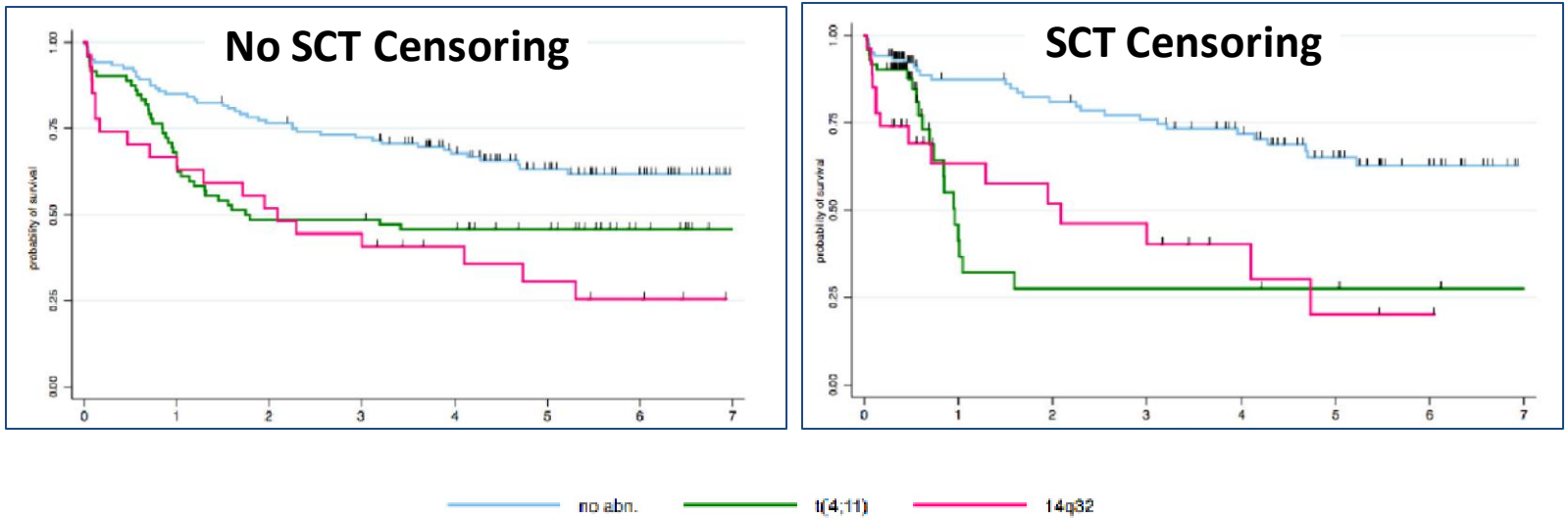
Overall Survival
De novo ALL 25-65 yr (UKALL14)



Cytogenetic aberrations in adult ALL (GRAALL trials)

Lafage-Pochitaloff et al, Blood 2017

Overall Survival



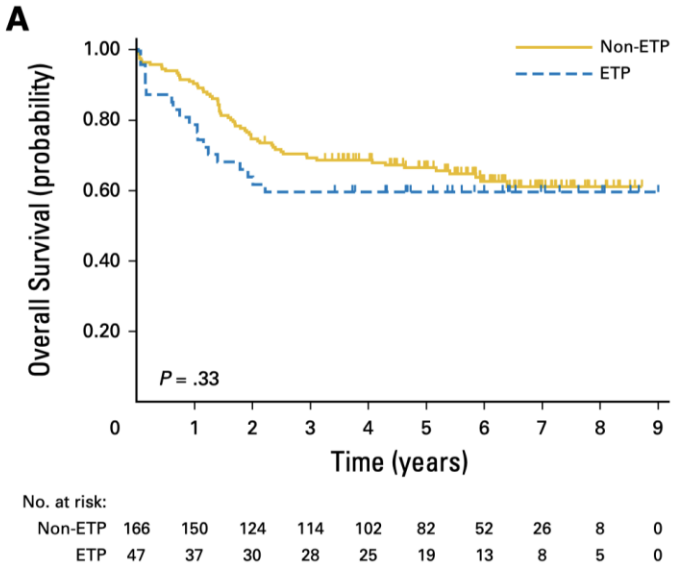
t(4;11) and 14q23 aberrations were the relevant cytogenetic high-risk groups

Outcome of T-ALL according to allo-SCT in CR1

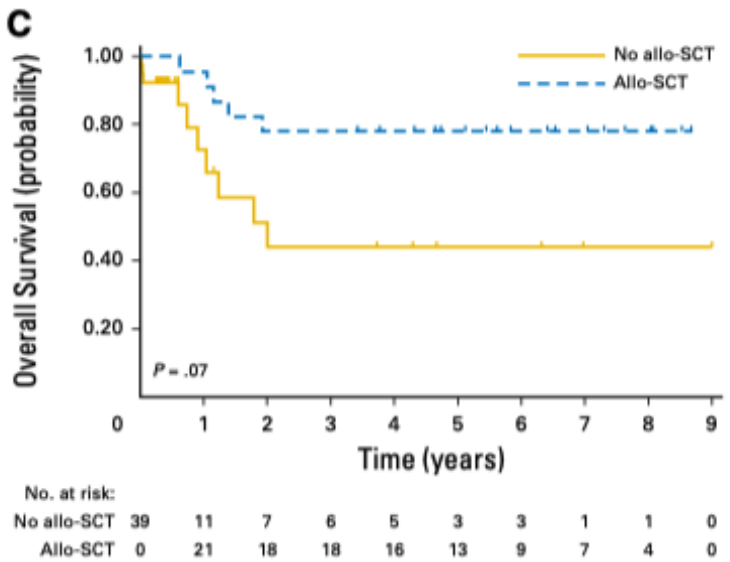
Bond et al, JCO 2017

Overall Survival

Non-ETP vs ETP ALL



SCT in ETP ALL



Treatment outcome in adult Ph+ ALL

Chalandon et al, Blood 2014

Age: 47 (15-59) y
N = 268

R

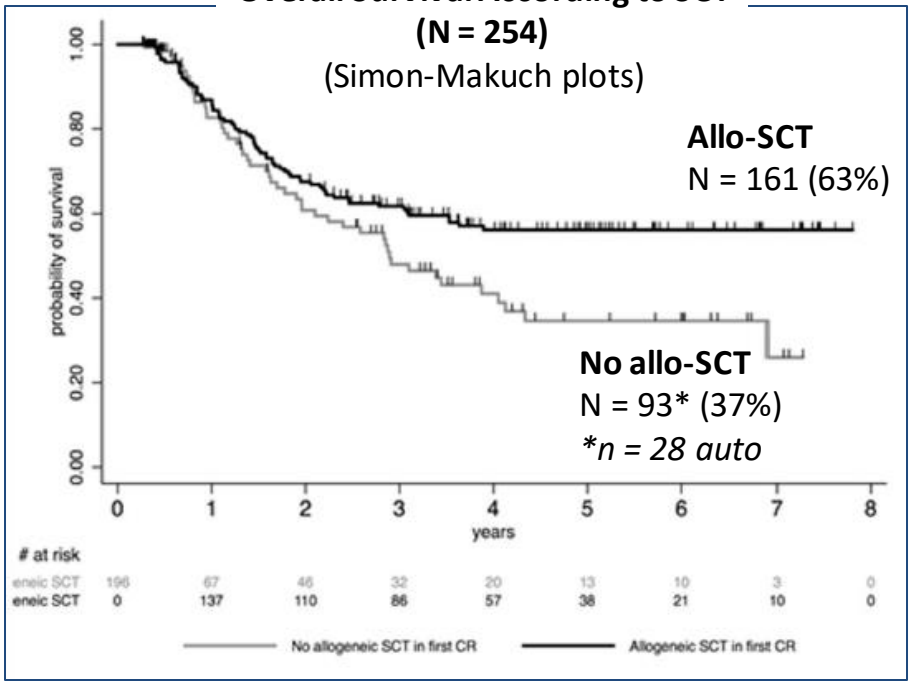
1: IM + VCR-Dexa (28 d)

2: IM + Hyper-CVAD 1 (14 d)
(VCR, DNR, Dexa, Cyclo)

IM + HDAC/HDMTX

SCT

Overall Survival According to SCT
(N = 254)
(Simon-Makuch plots)



Allo-SCT
N = 161 (63%)

No allo-SCT
N = 93* (37%)
**n = 28 auto*

Potential adverse cytogenetic/molecular prognostic factors in ALL at diagnosis

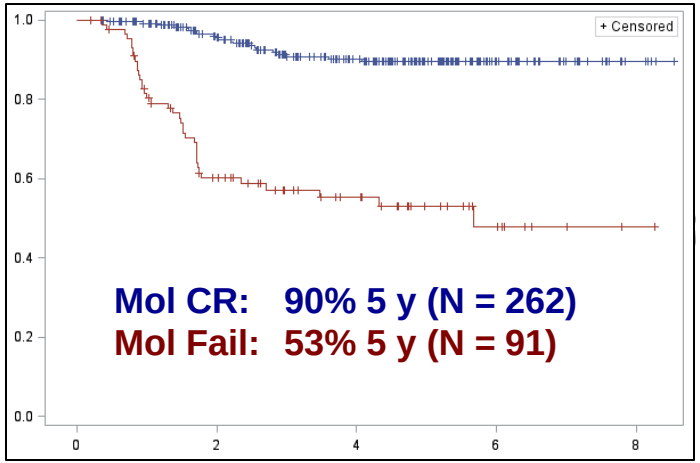
1. **Unclear whether applicable for modern regimens**
2. **High heterogeneity and small patient groups: Prognostic impact on weak basis**
3. **Unclear whether additional information in pts with MRD**
4. **Unclear whether SCT benefit**

Prognostic impact of MRD after induction/consolidation in pediatric and adult ALL

Overall Survival, Adult

GMALL 07/2003

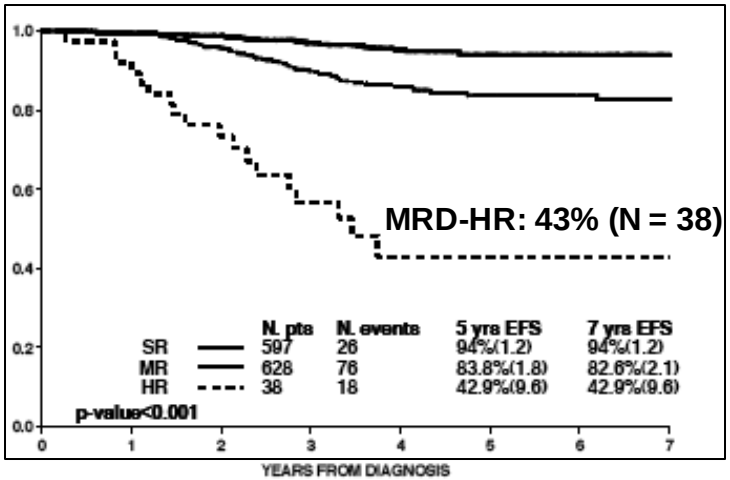
Gökbuget et al, Blood 2012



Event-Free Survival, Pediatric

AIEOP-BFM ALL 2000

Conter et al, Blood 2010



Incidence of MRD-HR: 26%

Incidence of MRD-HR: 3%

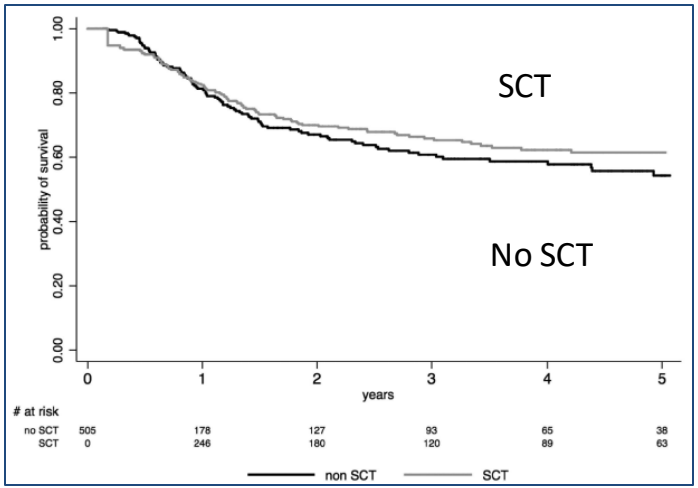
Therapeutic action based on MRD is one central challenge in management of ALL in all age groups

Impact of SCT in Ph– HR-ALL in first CR

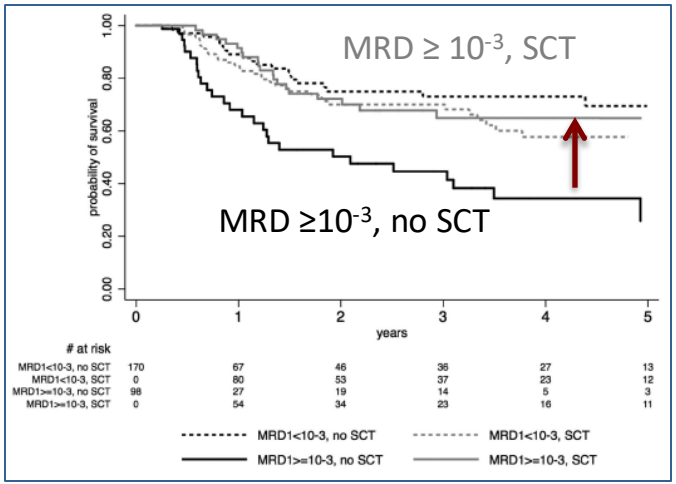
Dhedin et al, Blood 2014

GRAALL studies 2003/2005
15-55 yr; Ph–
Conventional and MRD-based risk stratification
N = 522 HR ➔ SCT in 282 (54%)

Overall Survival*



Overall Survival in MRD+/– Patients*



*Simon-Makuch plots with SCT as time-dependent covariate.

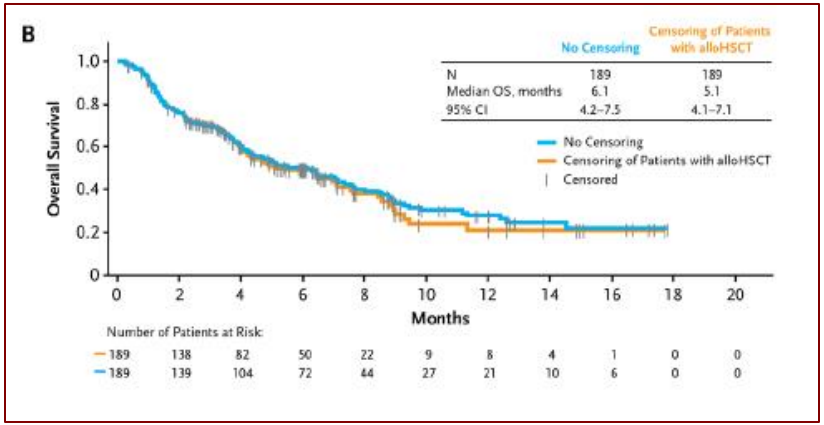
Place of allo-HSCT in adult ALL:
Current situation

1. Conventional prognostic factors vs molecular factors vs MRD
   - ► **Most study groups rely on MRD only**
     Giebel et al, Bone Marrow Transplant 2018
   - ► Immediate SCT is probably not the optimal approach for high MRD
2. **New compounds for the treatment of ALL**
3. Mortality of SCT
4. Methodological challenges to evaluate the impact of SCT
5. SCT as nonstandardized/nonstandardizable modality

Impact of SCT post-blinatumomab/inotuzumab

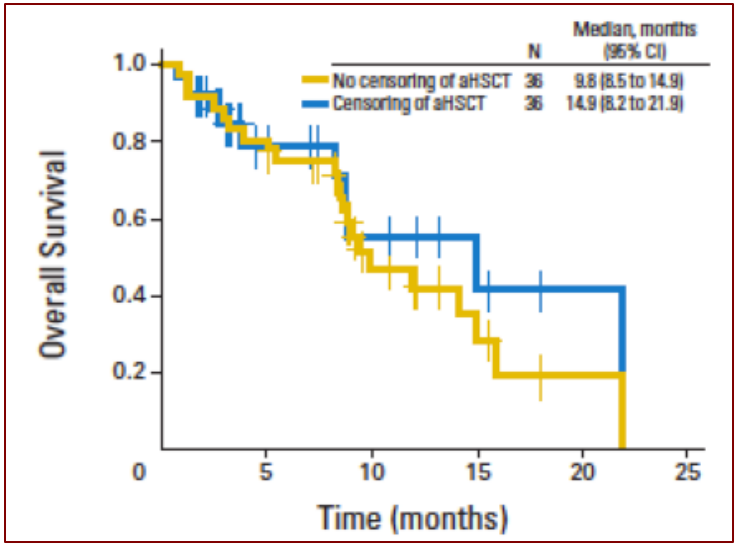
Blinatumomab (211 trial)

Topp & Gökbuget et al, Lancet Oncol 2015



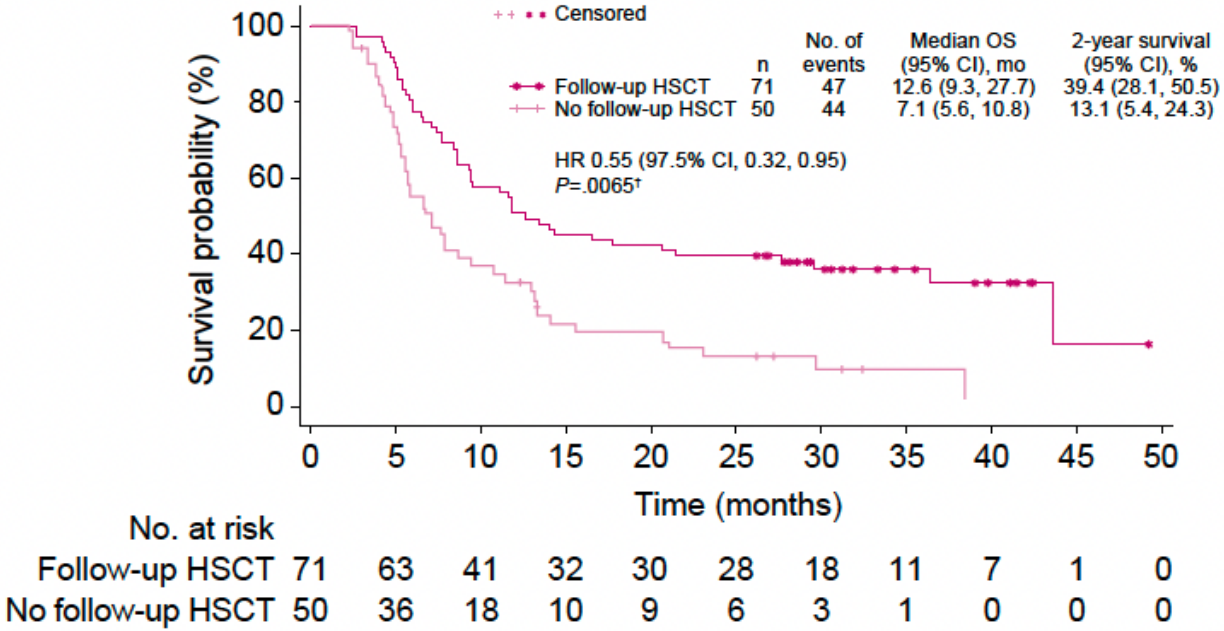
Blinatumomab (206 trial)

Topp & Gökbuget et al, JCO 2014



Impact of SCT post-blinatumomab/inotuzumab

Kantarjian et al. Cancer 2019

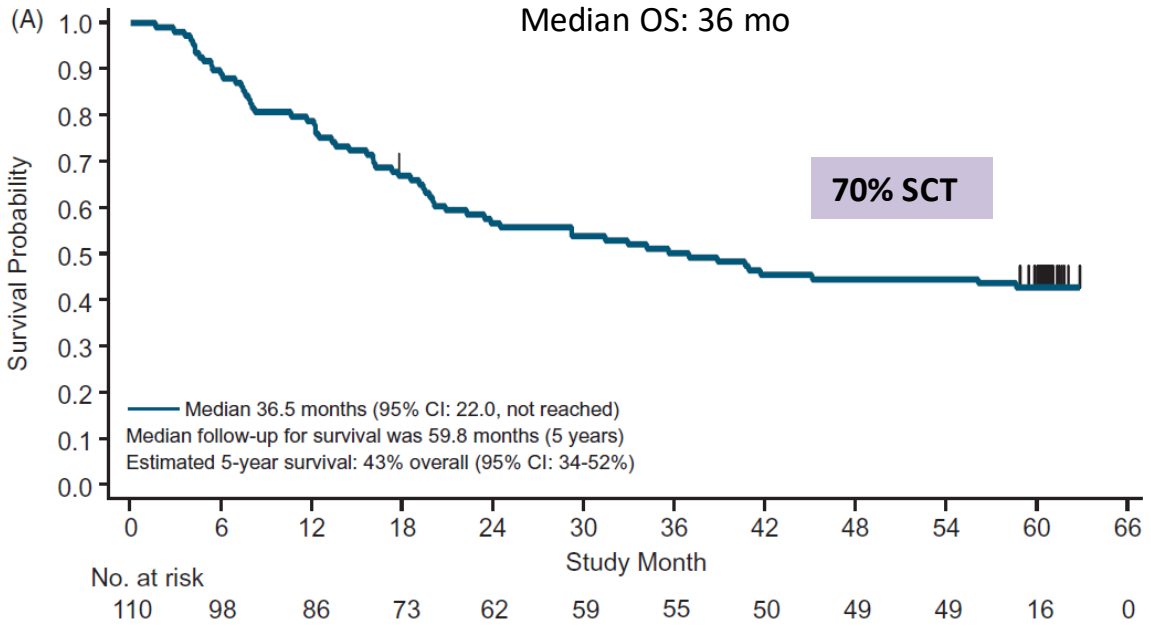


Impact of SCT?
Relevant mortality (>30%) of SCT
No long-term survivors without SCT

Blinatumomab in MRD+ ALL

Gökbuget et al. Leuk Lymphoma 2020

Overall Survival:
Ph– Patients With BCP-ALL and MRD



Blinatumomab in MRD+, Ph– B-precursor ALL

Gökbuget et al. Leuk Lymphoma 2020

SCT in Continuous CR: 67%

Characteristics of SCT Patients

Total:	74
Median age:	**42 (18-67)**
>55 yr:	26%
>CR1:	26%
Incomplete MRD response:	15%
Unrelated donor:	66%
Mismatch:	**40%***
Myeloablative:	80%*

*Refers to those with available data.

Outcome of SCT vs No SCT

	SCT in CCR	No HSCT
All patients		
Total	**74**	**36**
Alive w/o relapse	**40%**	**19%**
Died w/o relapse	**36%**	**8%**
Relapse	**23%**	**72%**
Median OS	**NR**	**56 mo**

SCT after relapse: 12 (46%)

Place of allo-HSCT in adult ALL: Current situation

1. Conventional prognostic factors vs molecular factors vs MRD
2. **New compounds for the treatment of ALL**
   - **SCT is still standard in R/R ALL after new compounds**
   - **Nontransplant follow-up procedures important**
3. **Mortality and morbidity of SCT**
4. Methodological challenges to evaluate the impact of SCT
5. SCT as nonstandardized/nonstandardizable modality

Impact of age on outcome of allo MAC HSCT in CR1

Giebel et al, Haematologica 2017

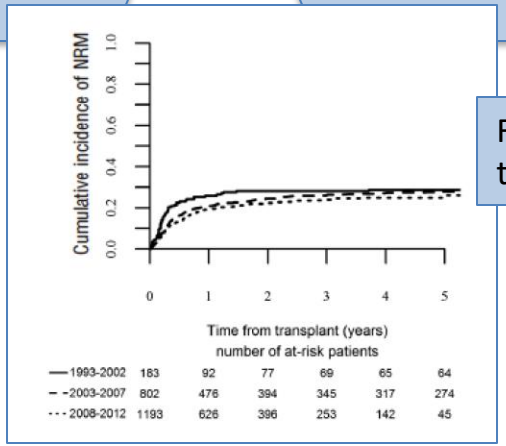
NRM at 2 Years

SIB SCT

Age	03-2007	08-2012
18-25 yr	11%	12%
26-35 yr	17%	11%
36-45 yr	23%	15%
46-55 yr	31%	23%
Total	20%	15%

MUD SCT

Age	03-2007	08-2012
18-25 yr	16%	18%
26-35 yr	20%	18%
36-45 yr	29%	26%
46-55 yr	38%	28%
Total	22%	24%

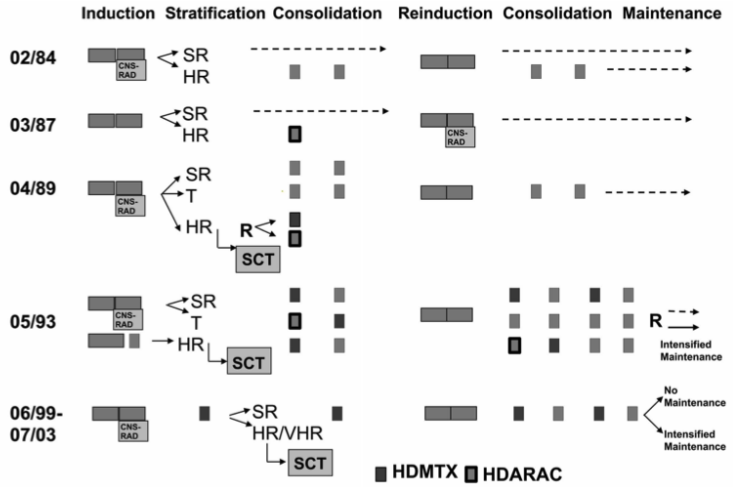


Further increase up to 5 yr

Health condition of long-term (>5 yr) survivors of adult ALL

Gökbuget et al, Haematologica 2023

Patients:	538
Age (at diagnosis):	29 (15-64)
Age (at evaluation):	39 (19-74)
FU time:	7 (3-24) yr



Comorbidities*		**SCT**
No	44%	↓
Skin	18%	↑
Cardiac	13%	↑
Neurologic	27%	↑
Eyes	12%	↑
Endocrine (f/m)	24%/17%	↑
Syndromes*		
Infections	12%	↑
Fatigue	13%	↑
GvHD	15%	↑

*Incidence >10%.

Place of allo-HSCT in adult ALL: Current situation

1. Conventional prognostic factors vs molecular factors vs MRD
2. New compounds for the treatment of ALL
3. **Mortality of SCT**
   - **Standards should be established**
   - **No high-risk procedures in MRD– patients**
4. **Methodological challenges to evaluate the impact of SCT**
5. SCT as nonstandardized/nonstandardizable modality

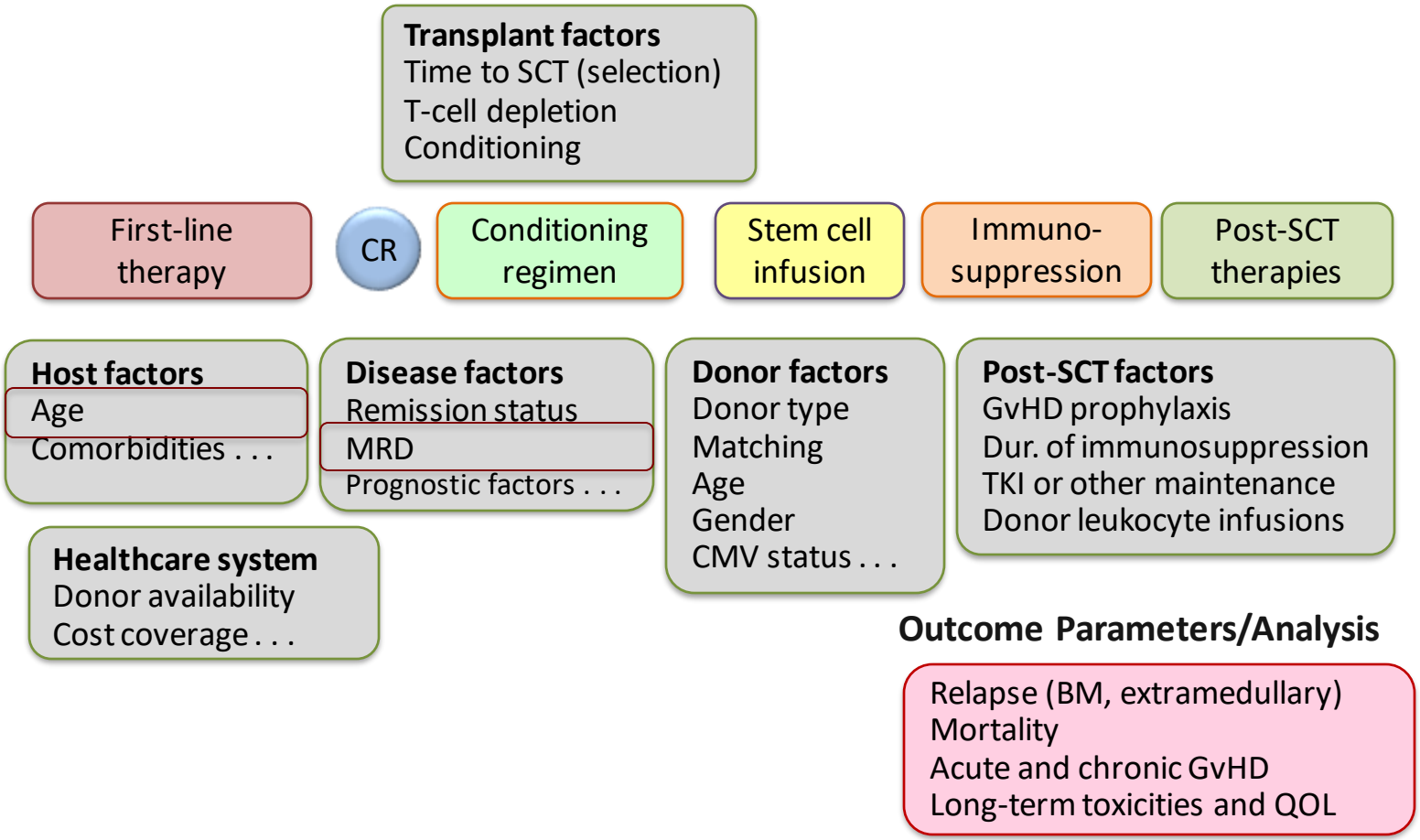
Challenges with regard to statistical comparison of SCT vs chemotherapy

1. **Only possible in prospective trials**
2. **How to account for potential bias**
   - CR patients only
   - Donor availability
   - Insurance status
   - Age, general condition, comorbidities
   - Early relapse
   - Transplant realization rate
3. **How to account for time to SCT (“immortal person-time”)**
   - Censoring vs non-censoring of SCT
   - Landmark analysis
   - Mantel-Byar analysis
   - Simon-Makuch plot

Place of allo-HSCT in adult ALL: Current situation

1. Conventional prognostic factors vs molecular factors vs MRD
2. New compounds for the treatment of ALL
3. Mortality of SCT
4. Methodological challenges to evaluate the impact of SCT
5. **SCT as nonstandardized/nonstandardizable modality**

Stem cell transplantation in ALL: Not 1 approach



Place of allo-HSCT in adult ALL: Current considerations

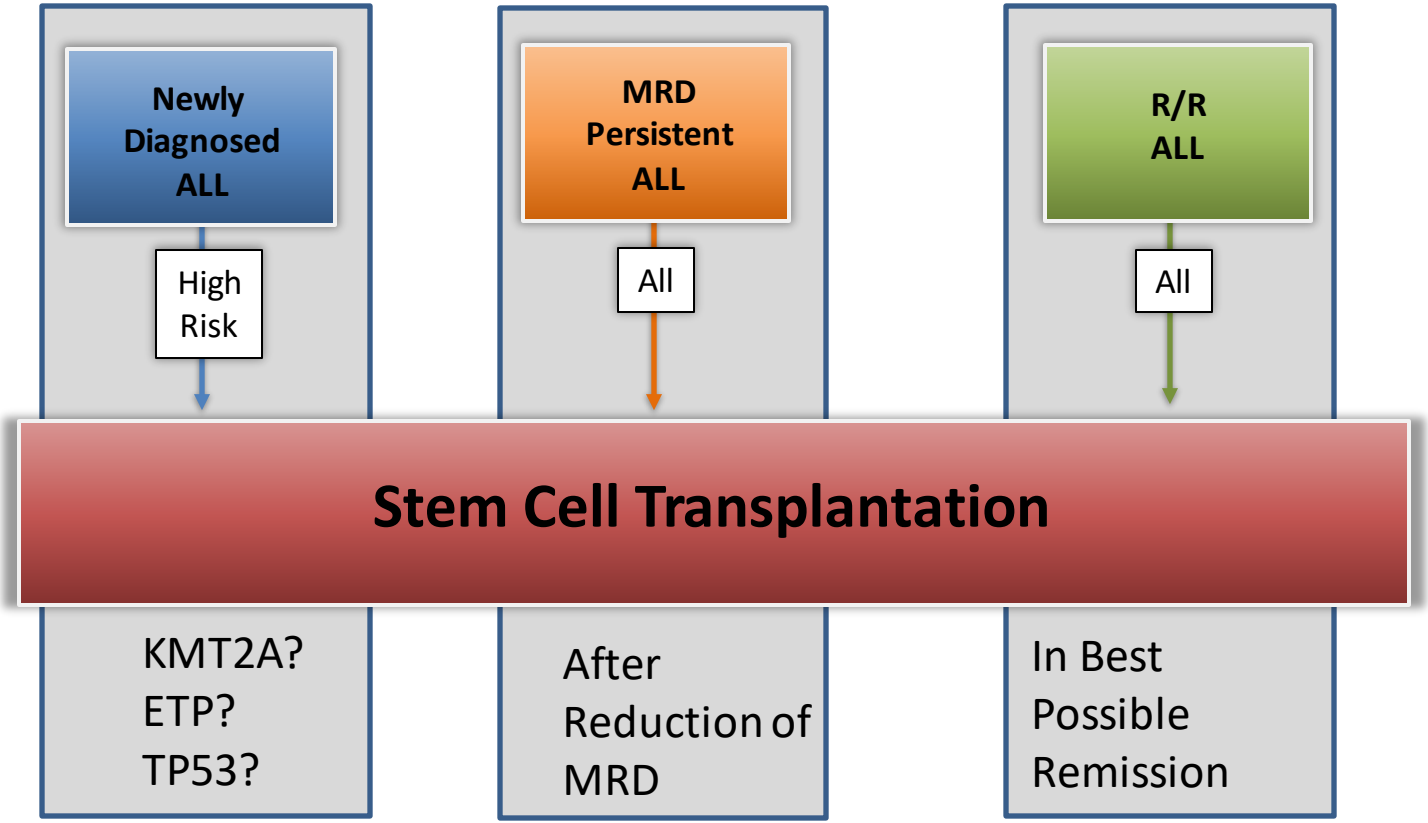
High risk definition
- Risk of relapse
- Risk of mortality

Time point of risk
- At diagnosis
- Later

Age

Type of chemo
Type of SCT

New compounds
- Antibodies
- BiTEs
- CARs



Stem cell transplantation in adult ALL:

Future indications

1. Is a solely MRD-based SCT indication the right way?
2. Can we abrogate the SCT indication in MRD poor responders by the use of new compounds?
3. Can we improve SCT outcome and reduce TRM?
4. Will the rate of SCT indications be reduced with more molecular remissions in first line and fewer relapses?
5. Which role for alternative donors/dose-reduced conditioning?
6. Are CAR T cells an alternative to SCT?

We can only move forward with prospective clinical trials including standardized SCT indications and SCT procedures

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Q&A

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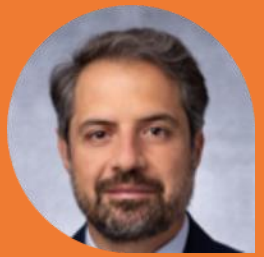
Panel discussion: How treatment in first line influences further treatment approaches in ALL and AML

Moderator: Elias Jabbour



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Interactive discussion

1. Will CAR T and bispecifics change the landscape?
2. Role of HSCT – is it still confirmed?
3. What does the future look like?

We encourage our audience to ask questions using the Q&A box

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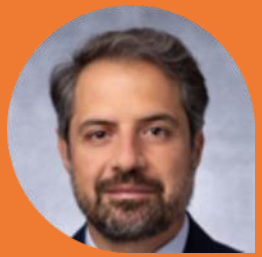
ARS questions

Elias Jabbour



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Question 3 [REPEATED]

Which of the following is NOT true for ALL?

A. Inotuzumab and blinatumomab plus chemotherapy is active in both front line and salvage for ALL

B. ALK inhibitors can be combined with other therapy modalities in Ph+ ALL

C. MRD is highly prognostic for relapse and survival in Ph– ALL

D. CAR T approaches are active beyond second line in Ph– ALL

Question 4 [REPEATED]

The prognosis of R/R AML patients depends on:

A. Age
B. Prior therapy (eg, HSCT)
C. Timing of relapse
D. The mutational and cytogenetic profile of the disease
E. All of the above
F. A and D

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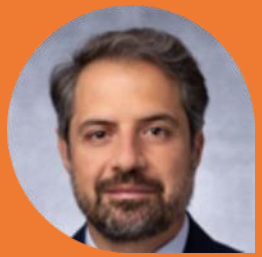
Session close

Elias Jabbour and Naval Daver



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Thank you!

- Thank you to our sponsors, expert presenters, and to you for your participation
- Please complete the **evaluation link** that will be sent to you via chat
- The meeting recording and slides presented today will be shared on the globalleukemiaacademy.com website within a few weeks
- If you have a question for any of our experts that was not answered today, you can submit it through the GLA website in our Ask the Experts section

THANK YOU!

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