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Emerging and Practical Concepts and Controversies in Leukemias

15 May 2021

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

Elias Jabbour

APTITUDE HEALTH

Meet the Faculty

Elias Jabbour, MD
Professor of Medicine
Department of Leukemia
University of Texas
MD Anderson Cancer Center
USA

Patrick A. Brown, MD
Johns Hopkins University
School of Medicine, USA

Naval Daver, MD
Associate Professor
Department of Leukemia
University of Texas
MD Anderson Cancer Center
USA

Lia Gore, MD
Professor and Chief of Pediatric Hematology/
Oncology/Bone Marrow Transplant
Children's Hospital Colorado and the University
of Colorado School of Medicine
USA

Aaron Logan, MD, PhD
UCSF, Helen Diller Family
Comprehensive Cancer Care, USA

José-Maria Ribera, MD
Chief of the Stem Cell Transplantation at University
Hospital "Germans Trias I Pujol"
Head of the Clinical Hematology Department for the
Catalan Institute of Oncology
Spain

JPAC Faculty

- **Shaun Fleming, MBBS(Hons), FRACP, FRCPA**
  Alfred Hospital, Australia
- **Bhavna Padhye, MD**
  The Children's Hospital at Westmead, Australia

Objectives of the Program

- Understand current treatment patterns for leukemia including incorporation of new technologies in ALL and AML
- Uncover when genomic testing is being done and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring leukemias
- Gain insights into antibodies and bispecifics in ALL: what are they? When and how should they be used? Where is the science going?
- Discuss the evolving role of ADC therapies
- Review promising novel and emerging therapies in ALL and AML

Virtual Plenary Sessions (Day 1)

TIME (UTC +9)	TITLE	SPEAKER
9.00 – 9.10	Welcome and meeting overview; introduction to the voting system	Elias Jabbour
9.10 – 9.50	Recent developments in acute leukemias	Elias Jabbour
9.50 – 10.15	Review of prognostic value of MRD in acute leukemias	Aaron Logan
10.15 – 10.30	Genetic variants in ALL – Ph+ and Ph-like	José-Maria Ribera
10.30 – 10.45	AYA ALL patients – what is the current treatment approach for this diverse patient population?	Lia Gore
10.45 – 10.55	Break	
10.55 – 11.10	Bispecifics as post-reinduction therapy improve survival in high-risk first-relapse pediatric and AYA B-ALL	Patrick Brown
11.10 – 11.35	Therapeutic approaches in high-risk and older AML patients	Naval Daver
11.35 – 12.20	Leukemia board discussion • Regional challenges in times of COVID-19 – Shaun Fleming (20 min) • Case discussion – Bhavna Padhye (15 min) • Discussion (10 min)	Moderator: Elias Jabbour All faculty
12.20 – 12.50	Debate on sequencing CD19-targeted approaches • Monoclonal antibodies and bispecifics first (10 min) • CAR T first (10 min) • Discussion and voting (10 min)	Moderator: Aaron Logan Elias Jabbour José-Maria Ribera All faculty
12.50 – 13.00	Session close	Elias Jabbour

Virtual Breakout – Adult Leukemia Patients (Day 2)

Chair: Elias Jabbour

TIME (UTC +9)	TITLE	SPEAKER
11.00 – 11.15	Session open • Educational ARS questions for the audience	Elias Jabbour
11.15 – 11.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation (15 min) • Q&A (5 min)	Aaron Logan
11.35 – 11.55	Current treatment options for relapsed ALL in adult and elderly patients (including COVID-19 and vaccination strategy) • Presentation (15 min) • Q&A (5 min)	José-Maria Ribera
11.55 – 12.30	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in adult and elderly patients Panelists: Elias Jabbour, José-Maria Ribera, Aaron Logan	Shaun Fleming
12.30 – 12.45	Break	
12.45 – 13.05	Personalized induction and maintenance approaches for AML • Presentation (15 min) • Q&A (5 min)	Naval Daver
13.05 – 13.25	Optimizing management of relapsed/refractory AML • Presentation (15 min) • Q&A (5 min)	Eunice Wang
13.25 – 14.15	Case-based panel discussion or questions on regional challenges in AML care	Case 1: Chyn Chua Case 2: Sun Loo
14.15 – 14.30	Session close	Elias Jabbour

Virtual Breakout – Pediatric ALL Patients (Day 2)

Chair: Patrick Brown

TIME (UTC +9)	TITLE	SPEAKER
11.00 – 11.15	Session open • Educational ARS questions for the audience	Patrick Brown
11.15 – 11.35	First-line treatment of pediatric ALL • Presentation (15 min) • Q&A (5 min)	Bhavna Padhye
11.35 – 11.55	Current treatment options for relapsed ALL in children including HSCT; COVID-19 considerations and vaccinations • Presentation (15 min) • Q&A (5 min)	Michael Osborn
11.55 – 12.15	Bispecifics for pediatric ALL, focus on frontline therapy • Presentation (15 min) • Q&A (5 min)	Patrick Brown
12.15 – 12.45	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in pediatric patients Panelists: All faculty	Case 1: Bhavna Padhye (10 min) Case 2: Michael Osborn (10 min) Discussion (10 min)
12.45 – 13.30	Interactive Q&A and session close • Educational ARS questions for the audience	Patrick Brown

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Introduction to the Voting System

Elias Jabbour

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Q

Question 1

Where are you from?

a) Australia
b) Malaysia
c) South Korea
d) Taiwan
e) China
f) Hong Kong
g) Singapore
h) Japan
i) Other

Q

Question 2

Which patients do you treat?

a) Adults only
b) Children only
c) Adults and children
d) Other

Q

Question 3

Which of the following is NOT true?

a) Inotuzumab and blinatumomab + chemotherapy is active in both frontline 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-negative ALL

d) CAR T approaches are not active beyond 2L in Ph-negative ALL

Q

Question 4

In AML the MRD assessment by RT-qPCR is especially useful for

a) FLT3 ITD

b) *NPM1* mutation

c) Biallelic *CEBPA* mutation

d) *SF3B1* mutation

e) *ASXL1* mutation

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Recent developments in ALL and AML

Elias Jabbour

APTITUDE HEALTH

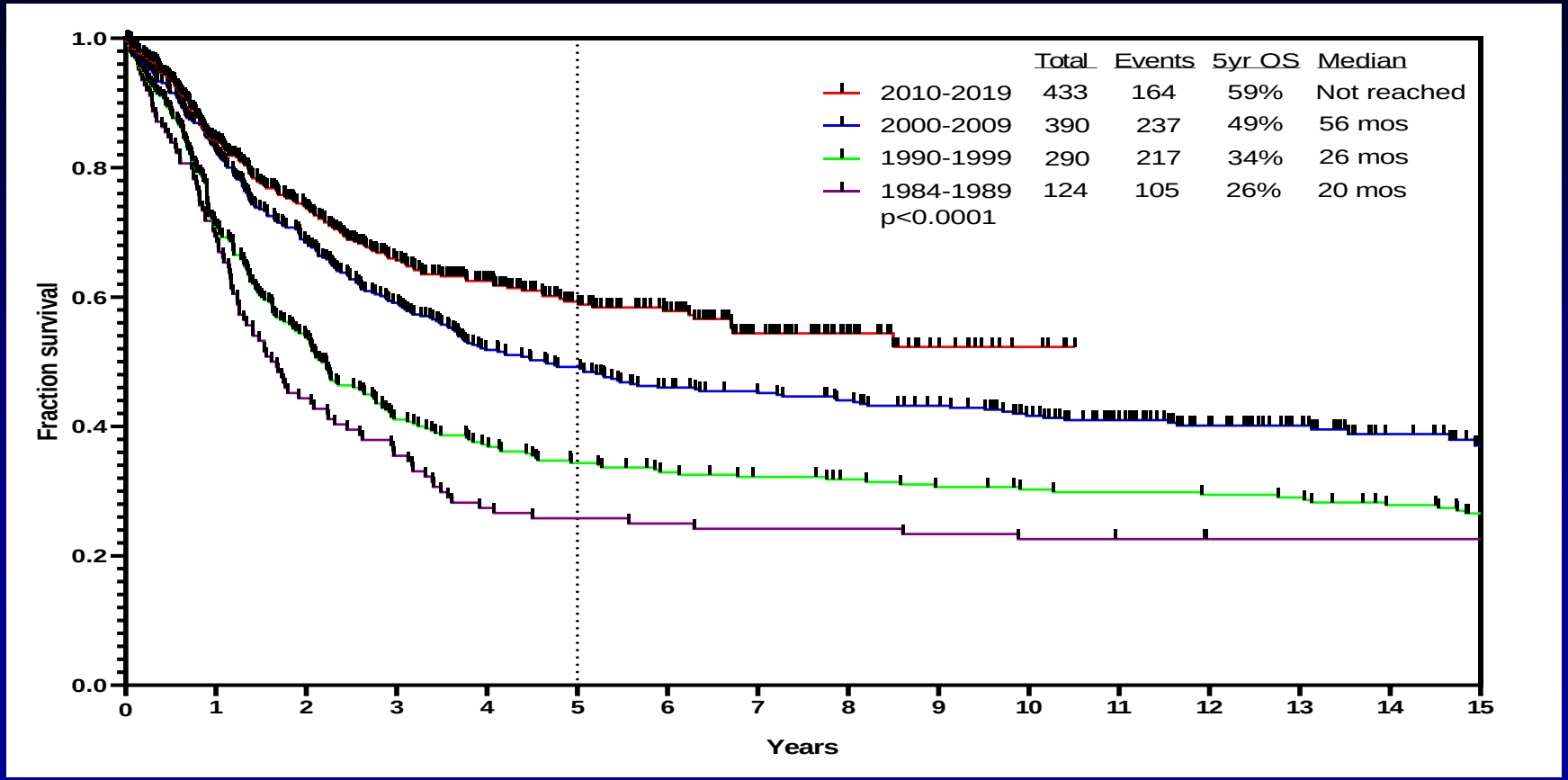
Recent Developments in Acute Leukemia

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

2021

ALL

ALL: Survival by Decade (MDACC 1985–2020)



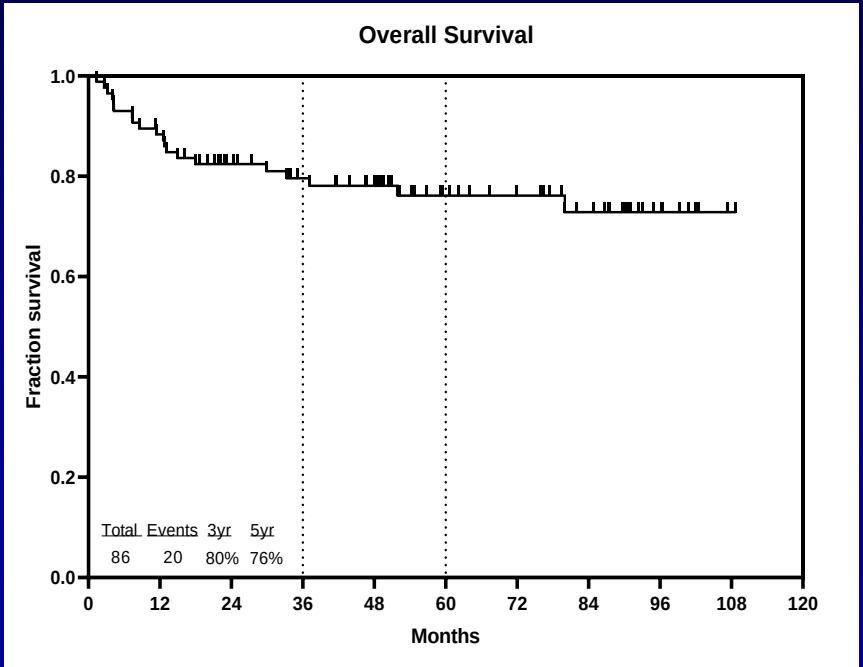
Reasons for Recent Success in Adult ALL

- Addition of TKIs (ponatinib) +/- blinatumomab to chemoRx in Ph+ ALL
- Addition of rituximab to chemoRx in Burkitt and pre–B-ALL
- Potential benefit of addition of CD19 antibody construct blinatumomab, and of CD22 monoclonal antibody inotuzumab to chemoRx in salvage and frontline ALL Rx
- CAR T therapy
- Importance of MRD in CR (at CR vs 3 mos; NGS)

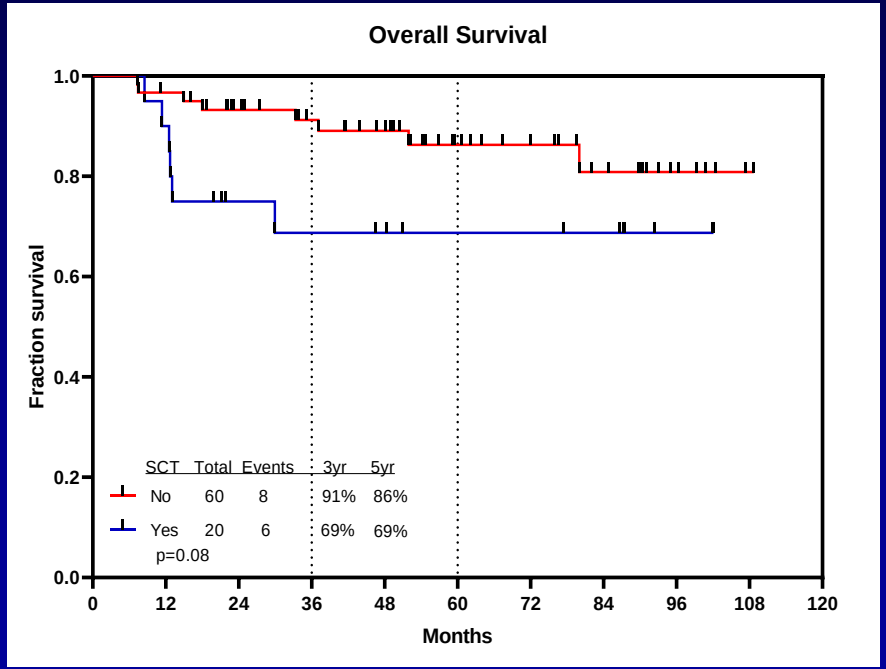
HyperCVAD + Ponatinib in Ph+ ALL

- 86 pts Rx; median age 47 yrs (39–61); median FU 48 mos (10–100)
- CR 68/68 (100%); FCM-MRD negative 85/86 (99%); CMR 84%; 3/5-yr OS 80/76%, EFS 76/71%

Overall Survival



6-Month Landmark

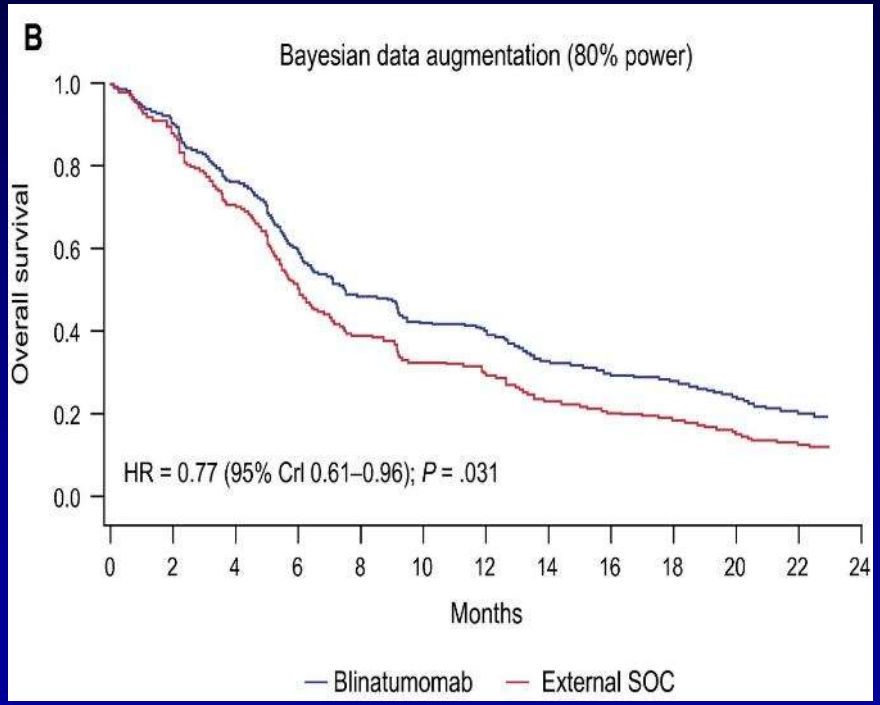


Jabbour E, et al. *Lancet Hematol.* 2018;618:(and update December 2020); Short et al. *Blood.* 2019;134:Abstract 283.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

Blina vs SOC

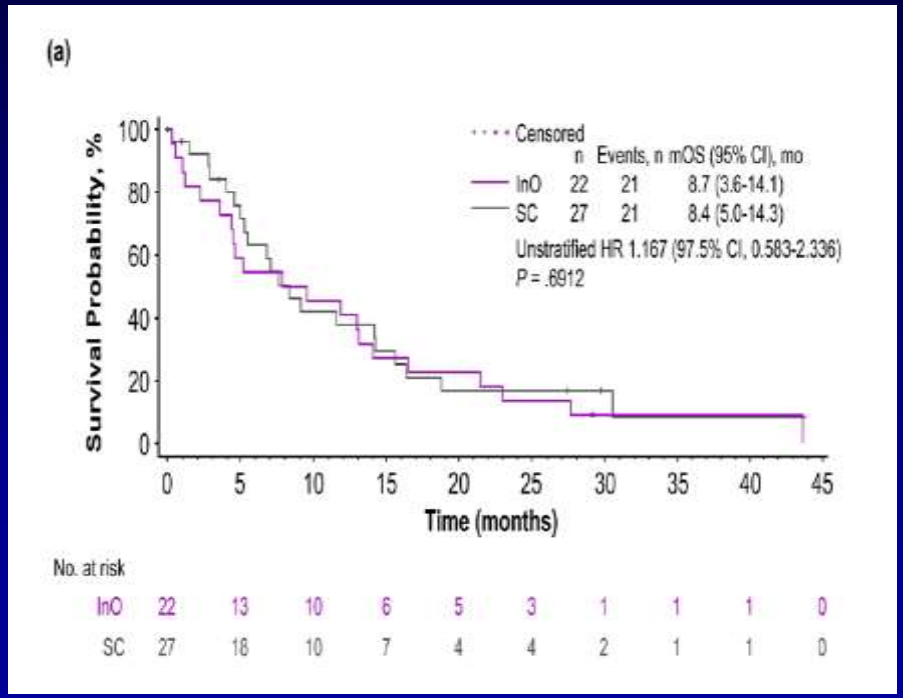
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



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

Ino vs SOC

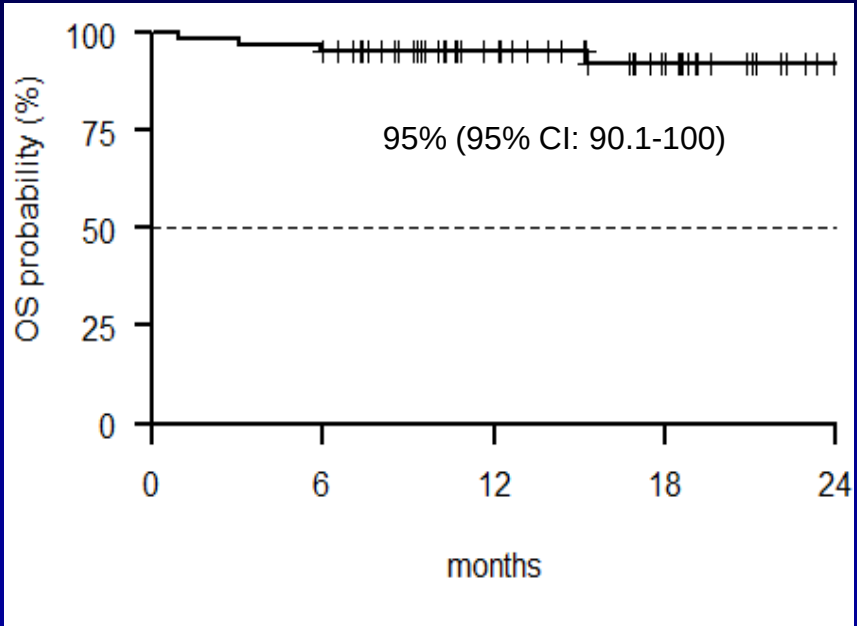
- CR/CRi 73% vs 56%
- 1-yr PFS 20% vs 4.8%

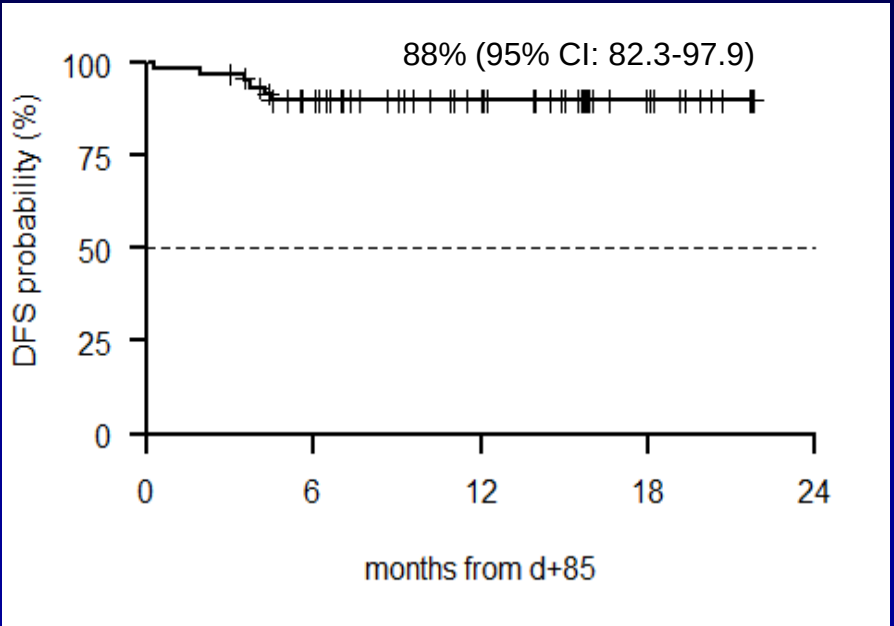


Stock W, et al. *Cancer.* 2020;127(6):905-913.

Dasatinib-Blinatumomab in Ph+ ALL

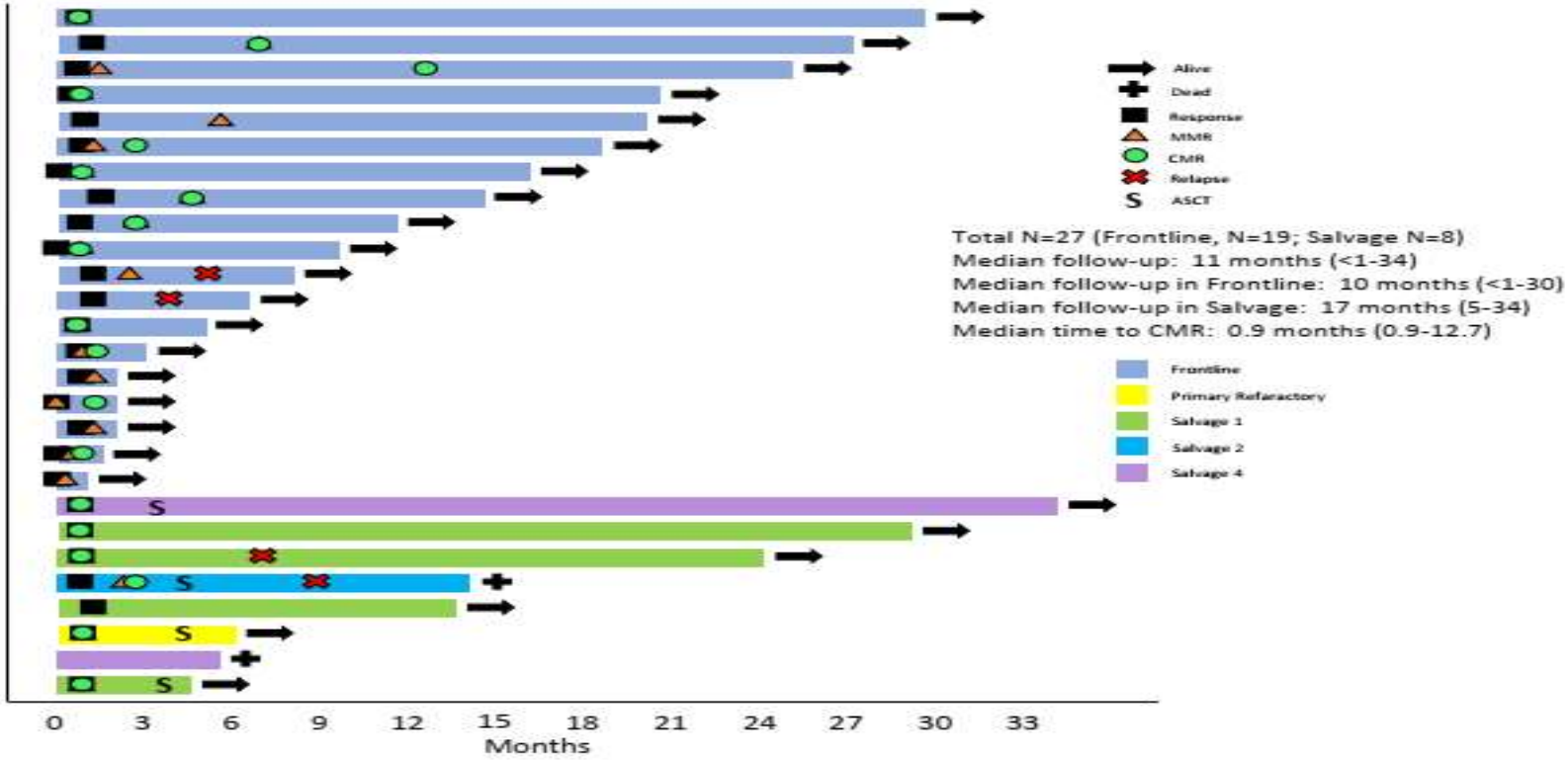
- 63 pts, median age 54 yr (24–82); Dasatinib 140 mg/D × 3 mo; add blinatumomab × 2–5
- 53 post–dasa-blina × 2 – molecular response 32/53 (60%), 22 CMR (41%); MRD ↑ in 15, 6 *T315I*; 12-mo OS 95%; DFS 88%





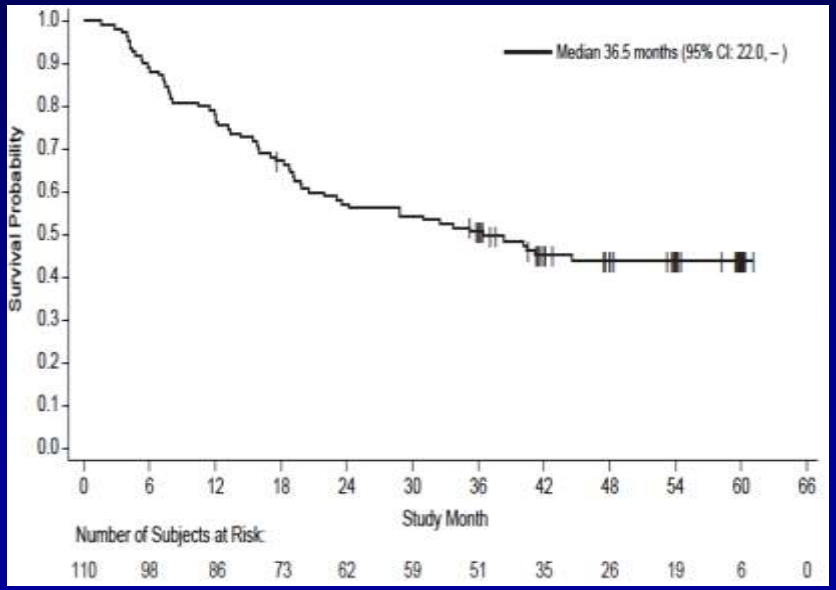
Foa et al. *N Engl J Med.* 2020;383:1613.

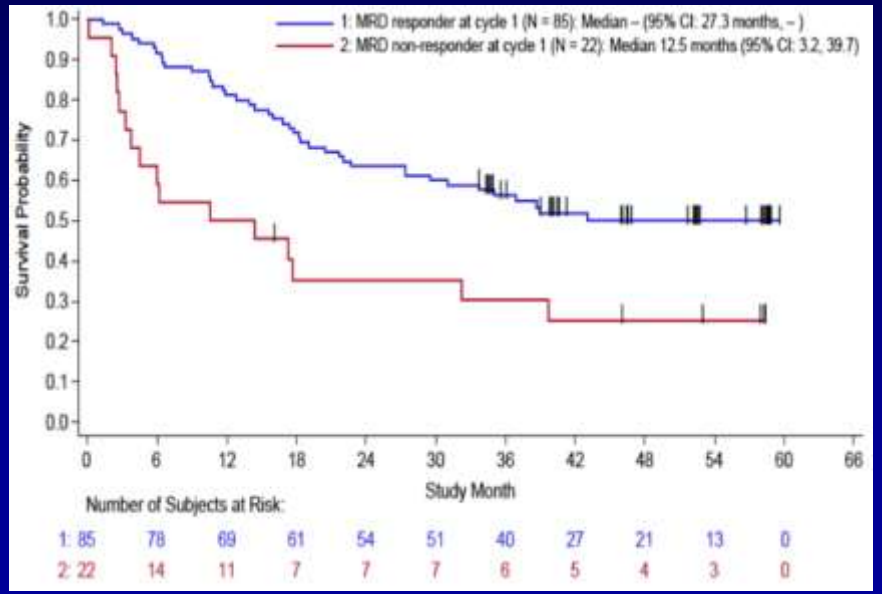
Blinatumomab + Ponatinib Swimmer Plot (N = 27)



Blinatumomab for MRD+ ALL in CR1/CR2

- 113 pts Rx. Post-blina MRD– 88/113 = 78%
- 110 evaluated (blasts <5%, MRD+); 74 received alloSCT. Median FU 53 mo
- Median OS 36.5 mo; 4-yr OS 45%; 4-yr OS if MRD– 52%
- Continuous CR 30/74 post-alloSCT (40%); 12/36 without SCT (33%)

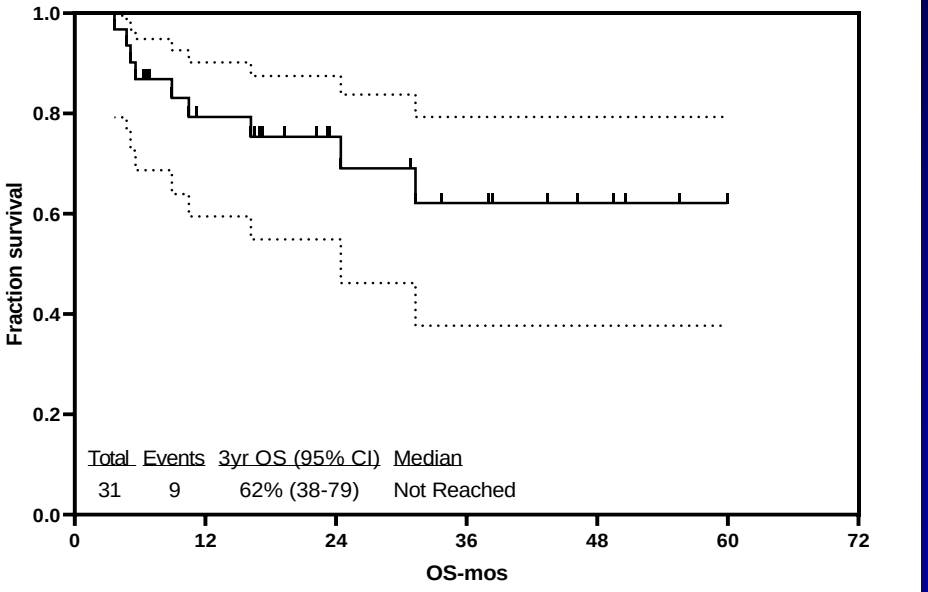


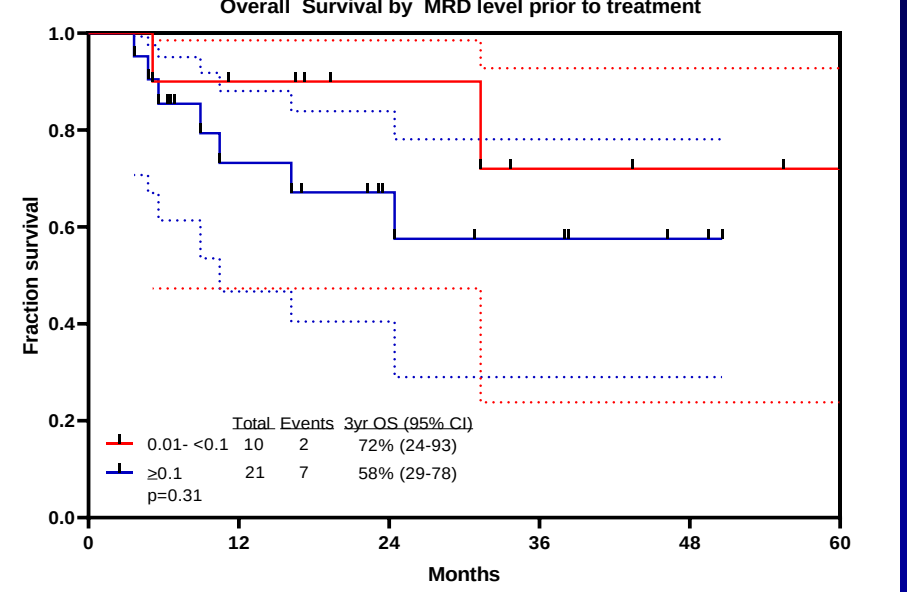


Goekbuget N, et al. *Blood.* 2018;132:abstract 554.

Blinatumomab for MRD+ ALL in CR1/CR2+

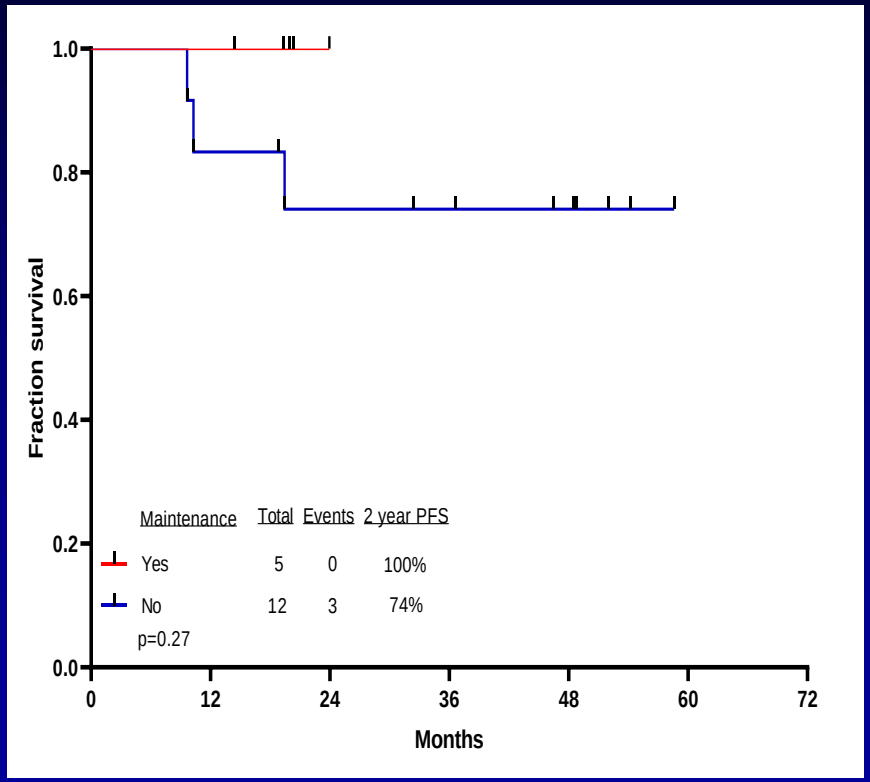
- 31 pts Rx. Post blina MRD-negative 23/31 = 74%
- 10 pts 0.01 to <0.1% RR = 90%; 21 pts ≥0.1% RR = 67%
- Median OS not reached; **3-yr OS 62%; 3-yr OS if MRD-negative 72%**
- Continuous CR 6/8 post alloSCT (75%); 9/15 without SCT (60%)



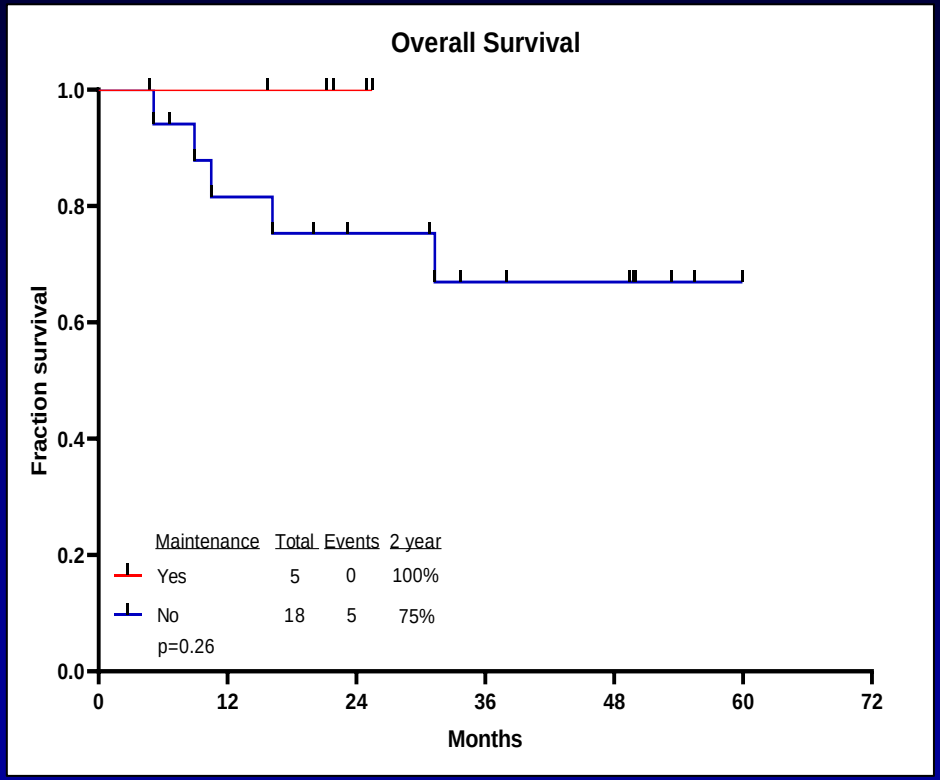


Blinatumomab for MRD+ ALL in CR1/CR2+: Impact of Maintenance

PFS

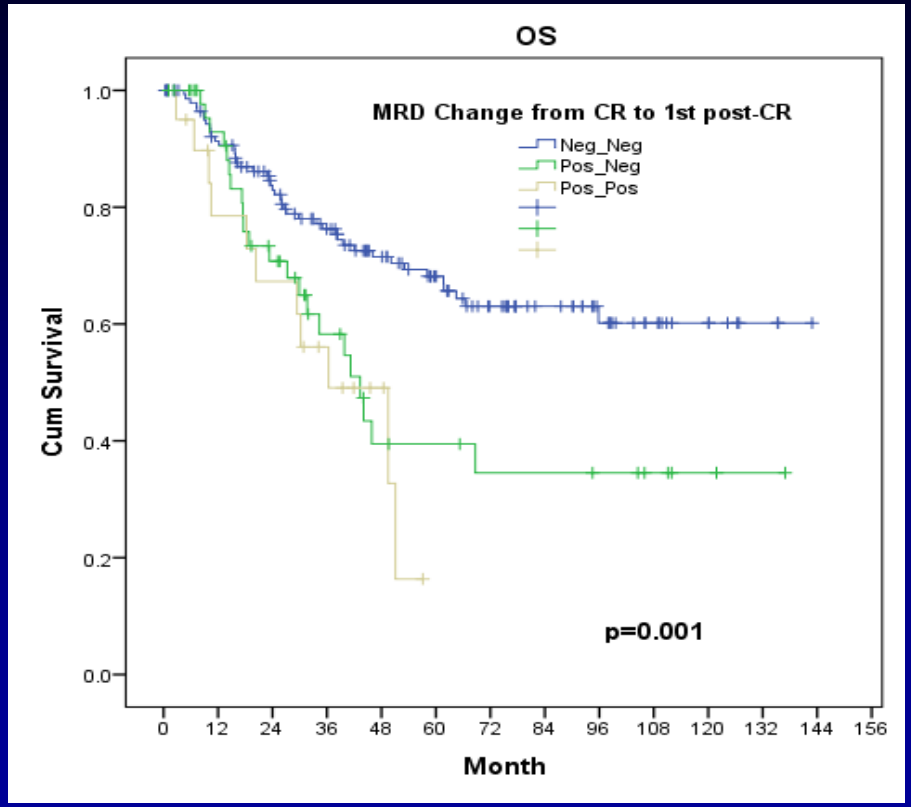


OS



Dynamics of MRD: Outcome

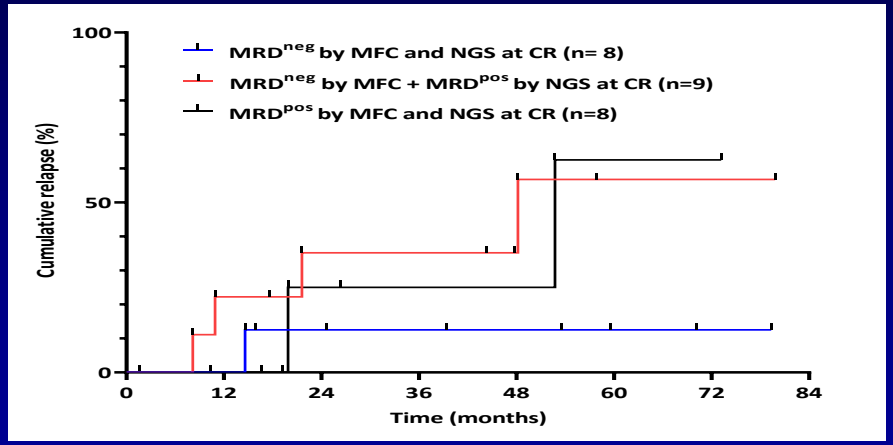
MRD Status		Patients (%) n = 214	5-yr EFS, %	5-yr OS, %
@CR	@ First post-CR			
Negative	**Negative**	**147 (69)**	**56**	**68**
≤0.1%	Negative	14 (7)	31	46
>0.1%	Negative	33 (15)	32	38
Positive	Positive	20 (9)	NA	NA

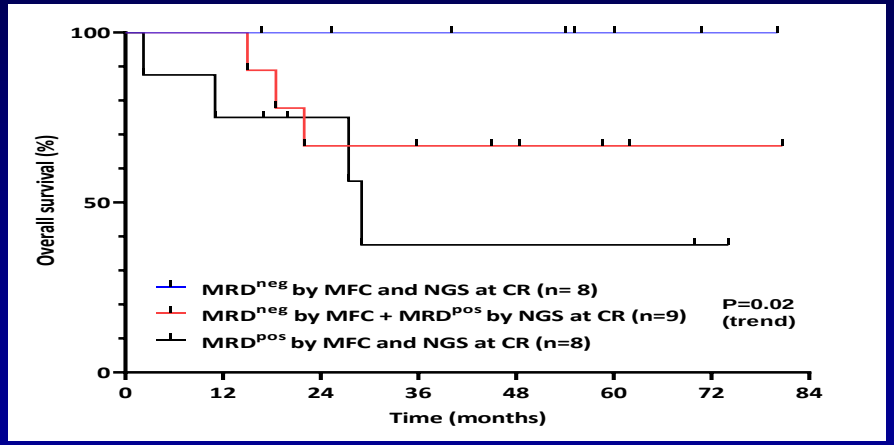


Yilmaz et al. *Am J Hematol.* 2020;95(2):144-150.

MRD in ALL: NGS vs FCM

- 67 pts Rx (66% HCVAD; 34% mini-HCVD)
- 32/84 (38%) discordant (ie, MRDneg by MFC but MRDpos by NGS)
  - 48% at CR and 30% at mid-consolidation
- MRDneg by NGS highly predictive at CR with HCVAD





5-year CIR rates

MRD^{neg} by MFC and NGS: 13%

MRD^{neg} by MFC + MRD^{pos} by NGS: 57%

MRD^{pos} by MFC and NGS: 63%

5-year OS rates

MRD^{neg} by MFC and NGS: 100%

MRD^{neg} by MFC + MRD^{pos} by NGS: 67%

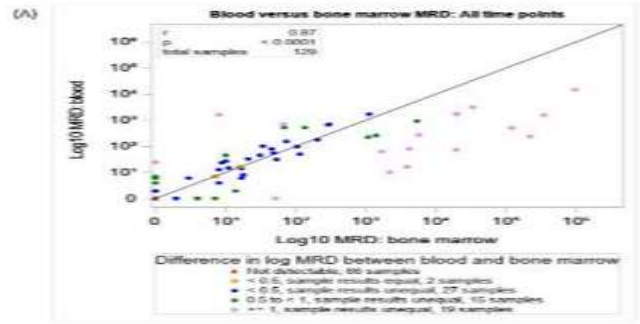
MRD^{pos} by MFC and NGS: 38%

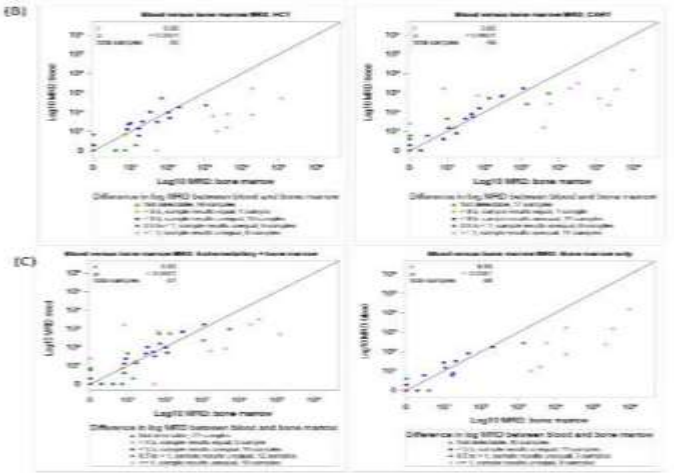
Short et al. *Blood.* 2020;136:abstract 583.

NGS MRD in R/R ALL: PB vs BM

- 62 pts (42 ASCT; 17 CAR T; 3 both); median age 42 yrs (30–53); 87% B-ALL; F/U 341 days
- Evaluation D = +28, D = +90, Q3–6 mos
- 126 paired samples; concordance 88%; r = 0.87– *P* <.0001; 14 discordant samples
- 100% and 85% of relapse post ASCT and CAR T had PB MRD+ within 90 and 60 days, respectively

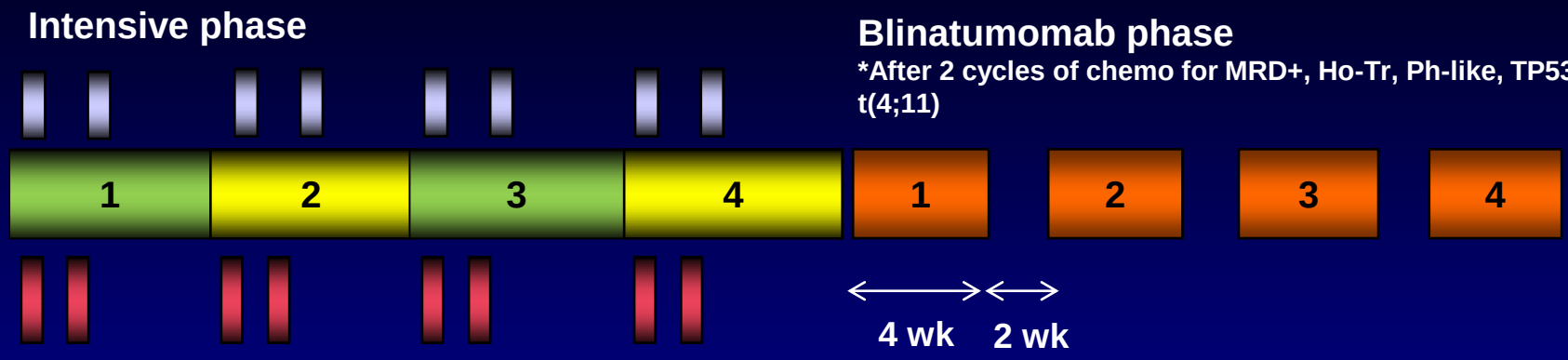
Figure 1. Peripheral Blood Vs. Bone Marrow MRD by NGS, (A) Total Study Cohort (B) HCT and CART (C) Extramedullary +/- Marrow and Marrow Only

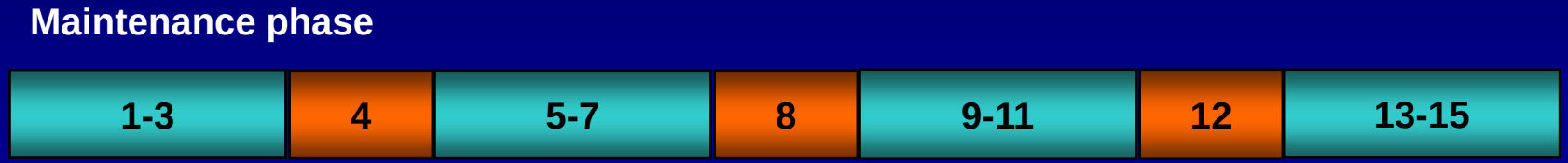




Muffly et al. *Blood*. 2020;136:abstract 975.

Hyper-CVAD + Blinatumomab in B-ALL: Regimen





Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

MTX + Ara-C

IT MTX/Ara-C × 8

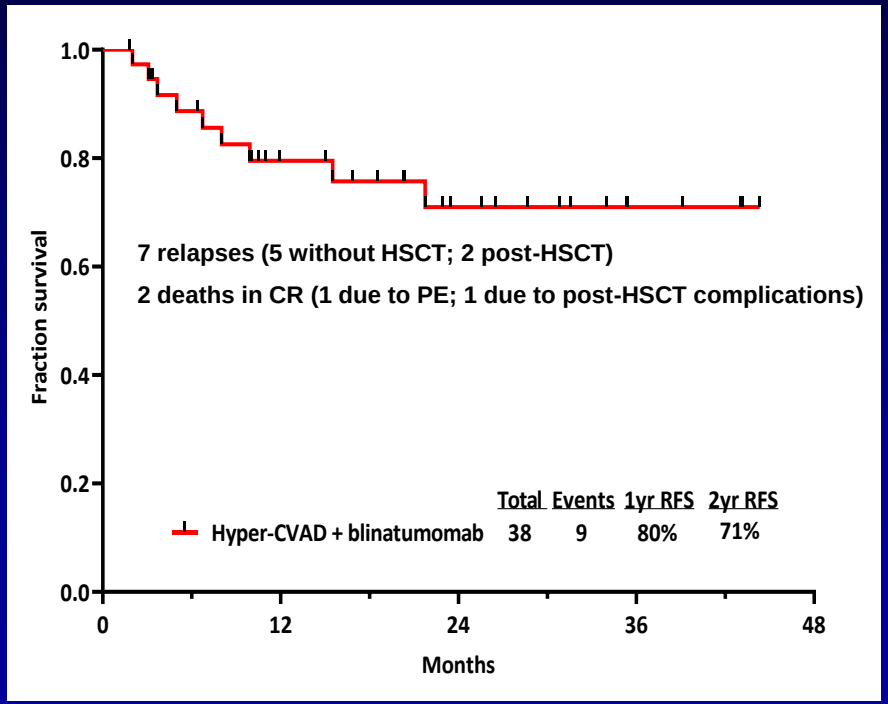
POMP

Short et al. *Blood.* 2020;136:abstract 464.

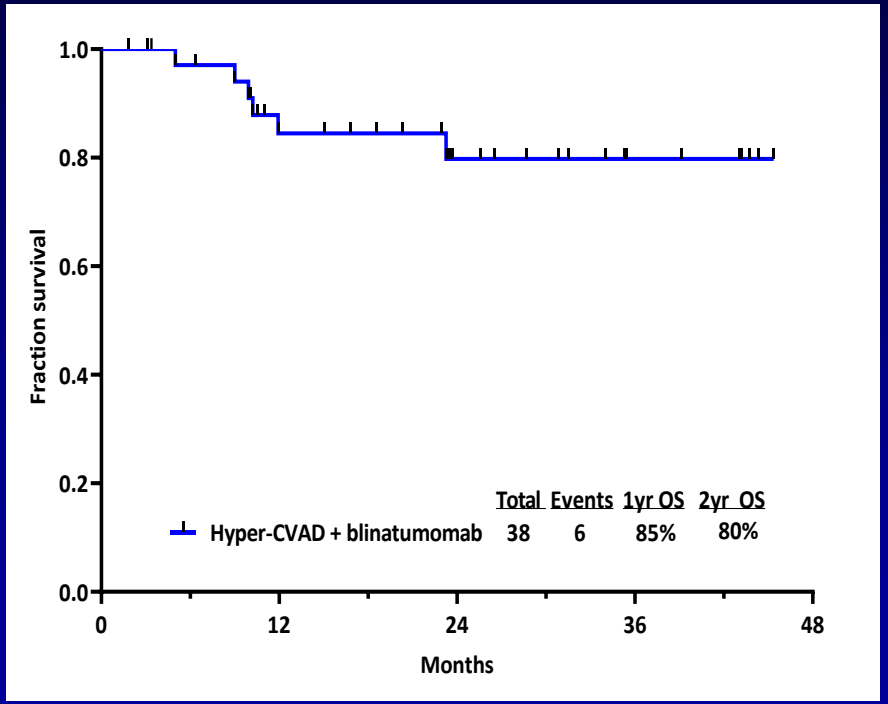
Hyper CVAD→Blinatumomab in Newly Dx Adult ALL

- 38 pts; median age 36 yrs (17–59 yrs). Rx with O-HCVAD × 4→POMP 1 yr with blina Q3 mos
- CR rate 100%; MRD negative 97% (71% at CR); 60-day mortality 0%; 12 (32%) allo-SCT; F/U 24 mos

RFS

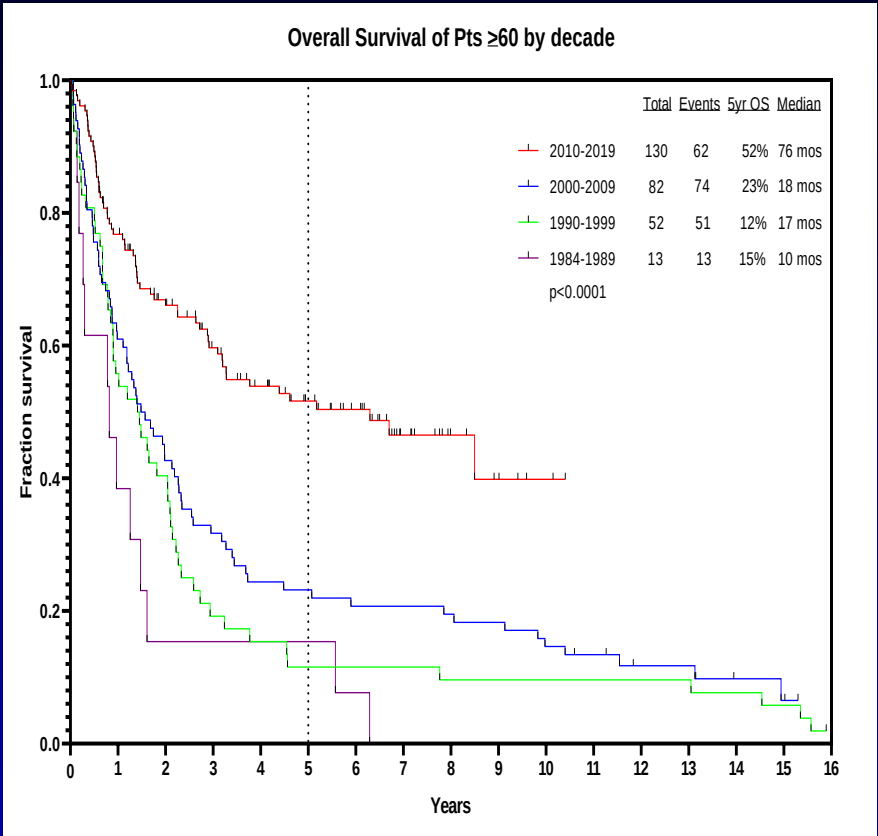


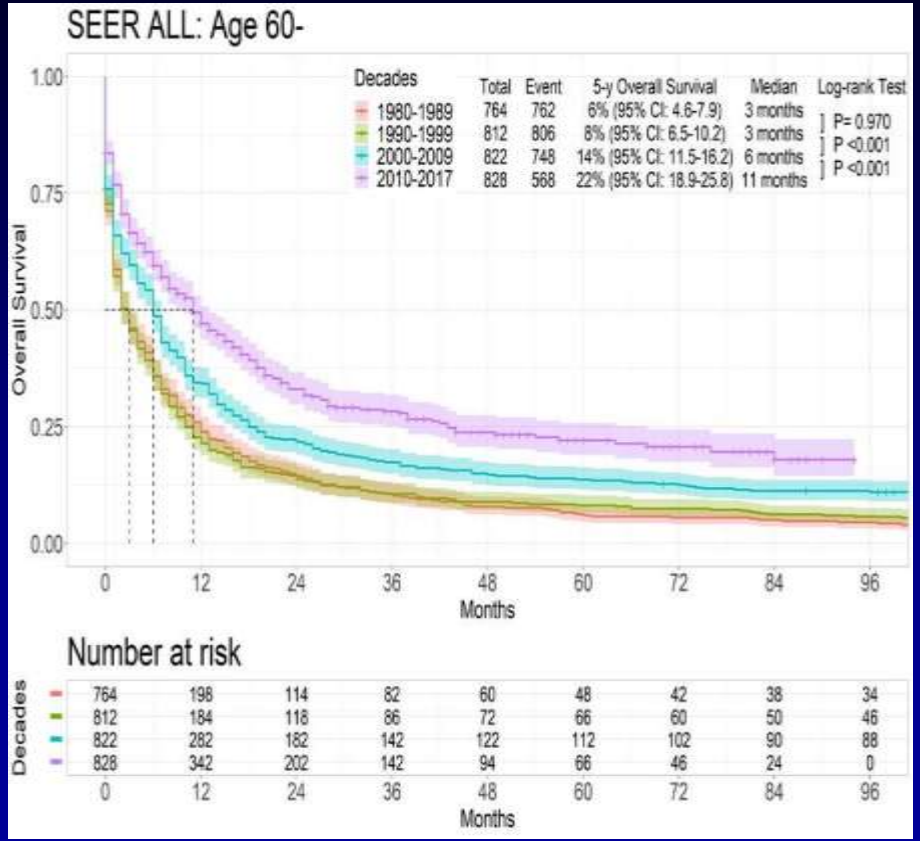
OS



Short et al. *Blood.* 2020;136:abstract 464.

MDACC ALL: Survival by Decades for ≥60 Years





Mini-HCVD + Ino ± Blina in Older ALL (N = 70)

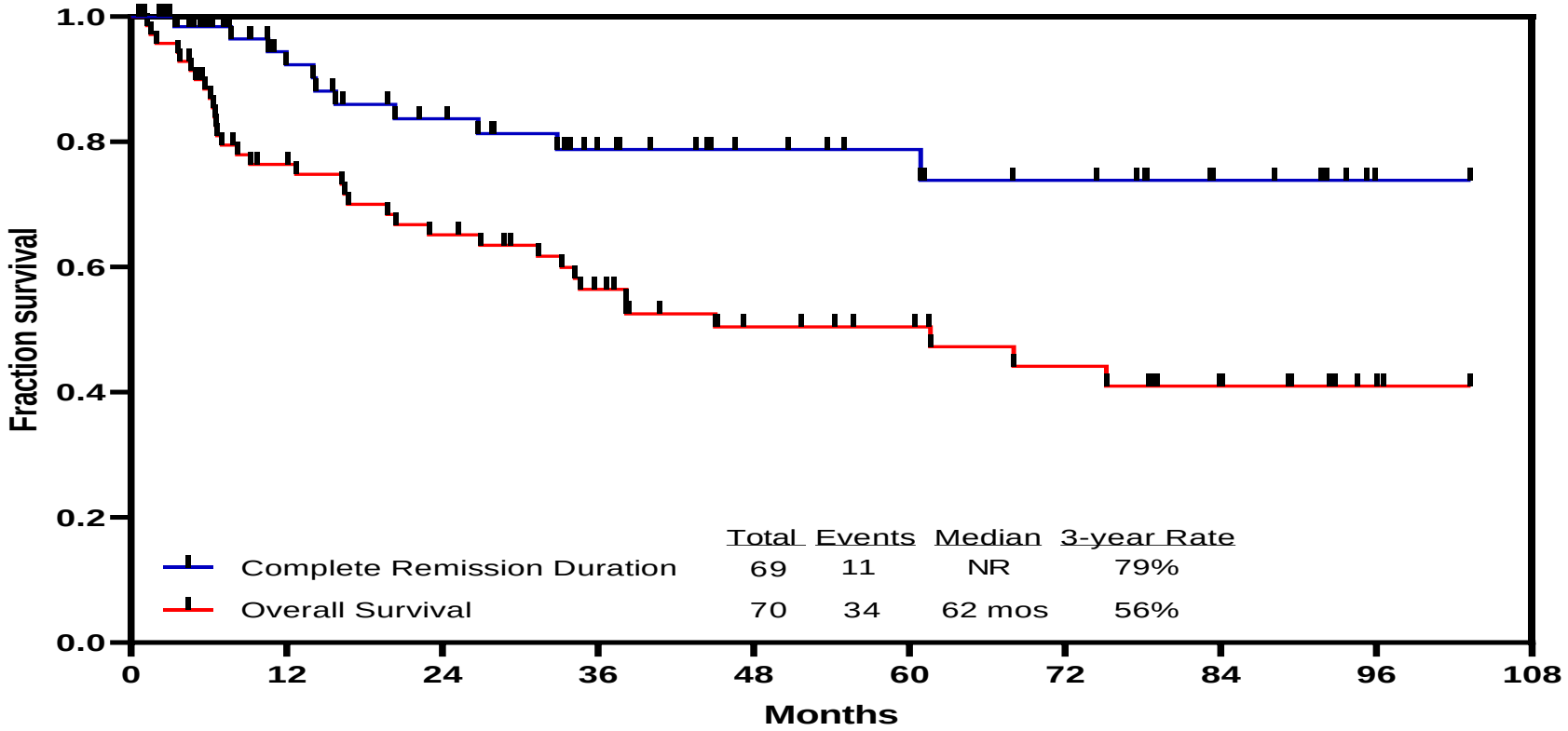
Characteristic	Category	N (%)/Median [range]
Age (years)	**≥70**	**68 [60–81]** **29 (41)**
Performance status	≥2	10 (14)
WBC ($\times 10^9$/L)		3.1 [0.6–111.0]
Karyotype	Diploid HeH **Ho-Tr** **Tetraploidy** **Complex** **t(4;11)** Misc IM/ND	23 (33) 5 (7) **12 (17)** **3 (4)** **3 (4)** **1 (1)** 10 (14) 13 (19)
CNS disease at diagnosis		4 (6)
CD19 expression, %		99.6 [30–100]
CD22 expression, %		96.7 [27–100]
CD20 expression	≥20%	38/64 (59)
***CRLF2*+ by flow**		**7/38 (18)**
***TP53* mutation**		**21/51 (41)**

Response (N = 64)	N (%)
ORR	**63 (98)**
CR	56 (88)
CRp	6 (9)
CRi	1 (2)
No response	1 (2)
Early death	**0**

Flow MRD response	N (%)
D21	53/66 (80)
Overall	**65/68 (96)**

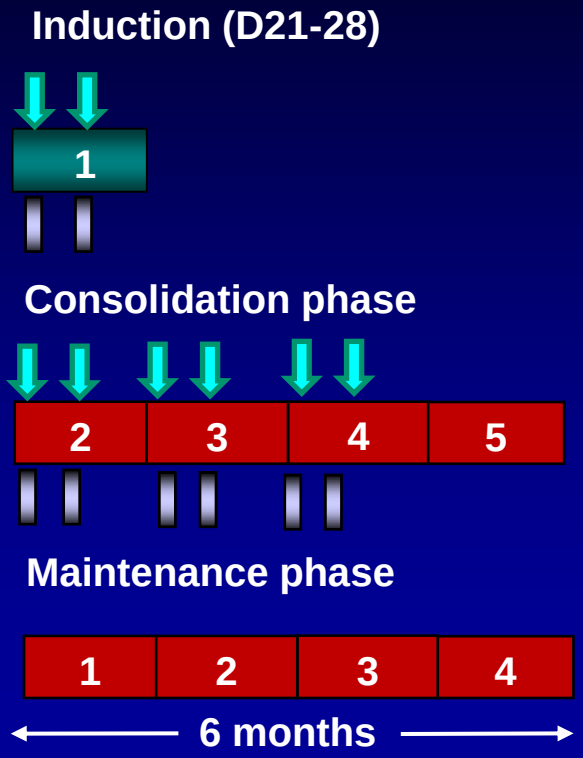
Short et al. *Blood.* 2020;136:abstract 1014.

Mini-HCVD + INO ± Blina in Older ALL: CRD and OS (Entire Cohort)



Short et al. *Blood.* 2020;136:abstract 1014.

INO + Blina in Older ALL: Amended Design (pts ≥70 years)



Dexa 20 mg D1-4 and VCR 1 mg D4

Blinatumomab

IT MTX, Ara-C

INO*	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2–C4	0.6	0.3 D2 and D8

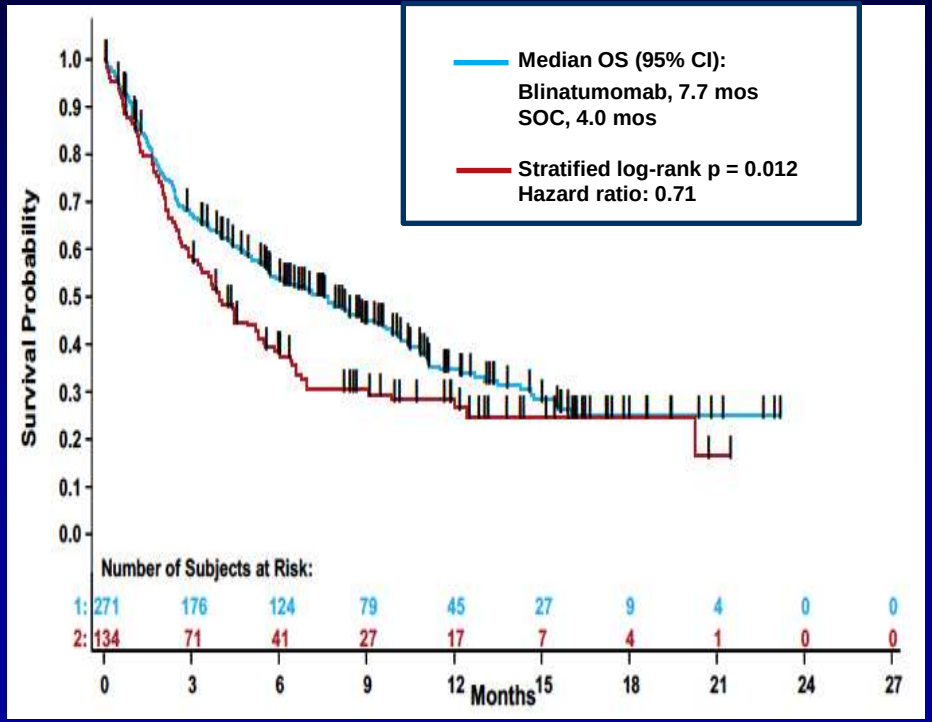
Total INO dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis

Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

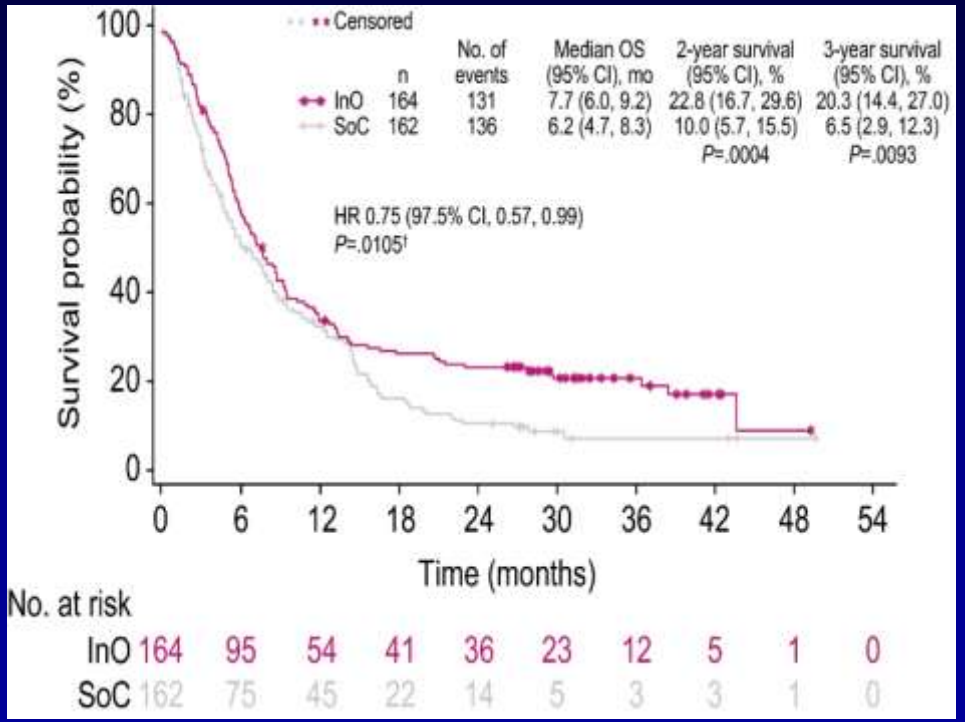
- **Marrow CR**

Blina vs SOC: 44% vs 25%



Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

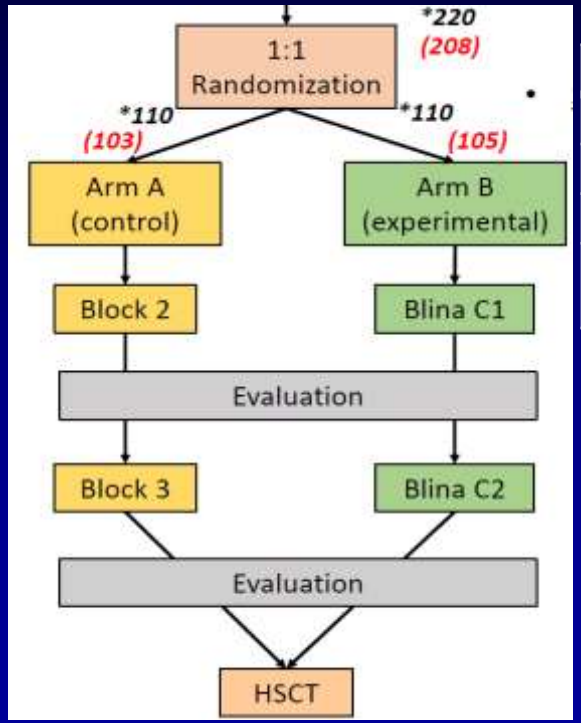
Ino vs SOC: 74% vs 31%



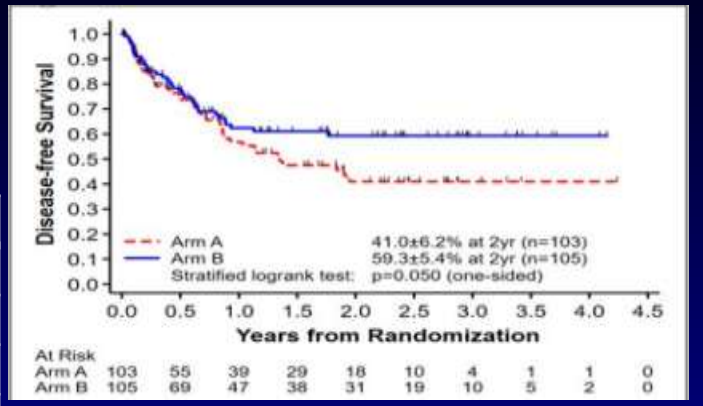
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

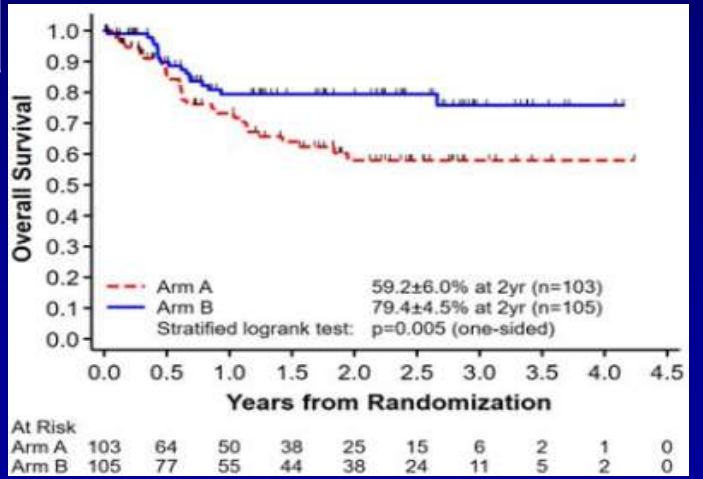
Phase III Study of Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

- 208 pts HR/IR randomized 1:1 to blina (n = 105) vs chemo Rx (n = 103) post Block 1 reinduction



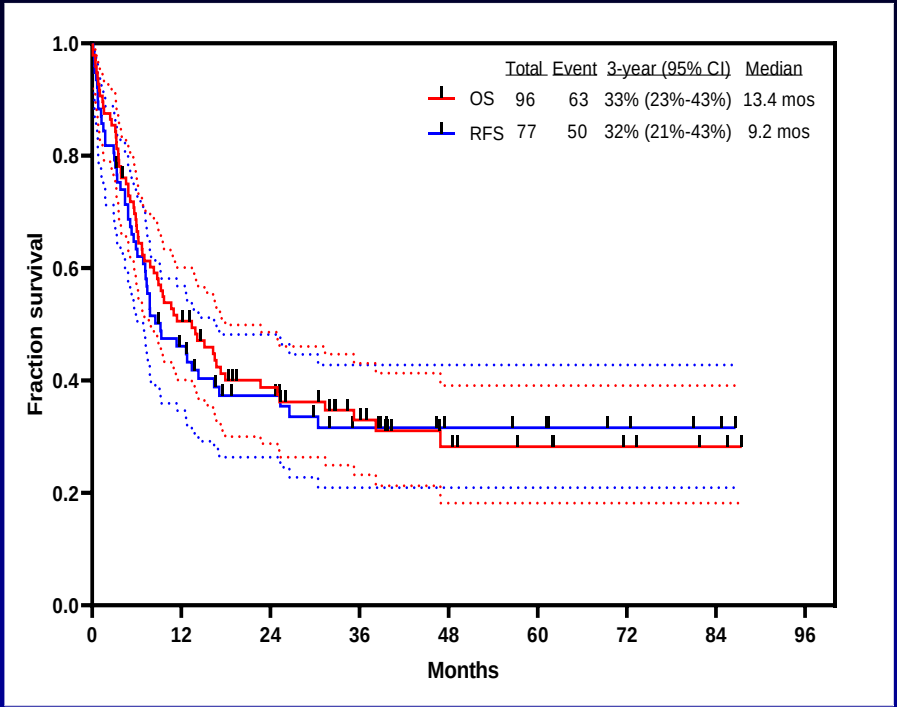
Parameter	Blina	Chemo	*P*
% 2-yr DFS	59	41	.05
% 2-yr OS	79	59	.005
% SCT	73	49	<.001
% MRD clearance	79	21	<.001

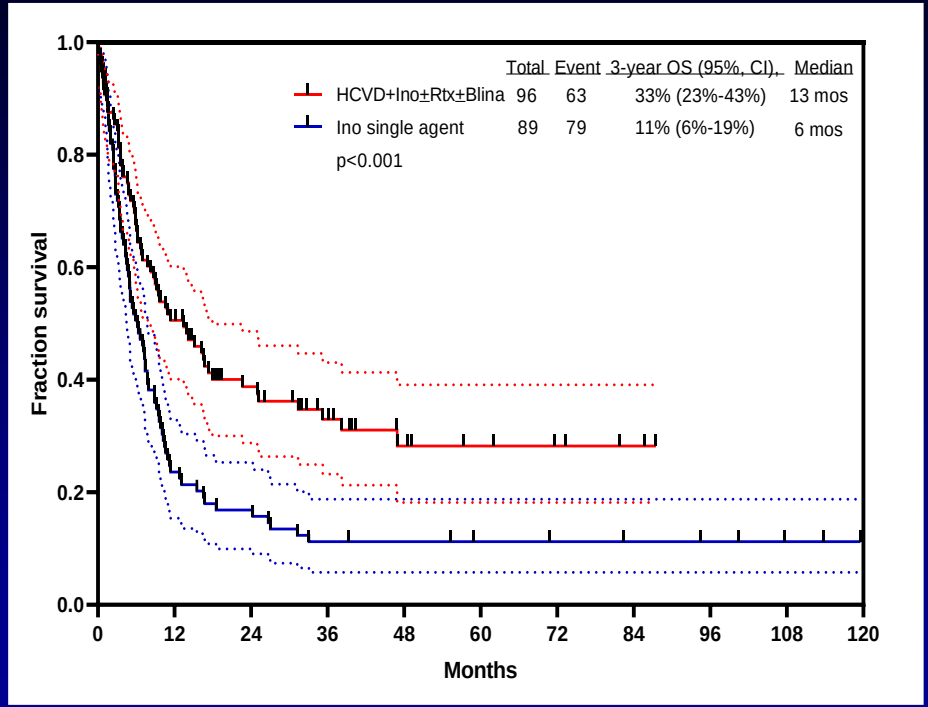




Brown et al. *JAMA*. 2021:325(9):833-842.

Mini-HCVD + INO ± Blina in R/R ALL: Outcome





	Single dose (n = 67)	Fractionated lower dose followed by blina (n = 29)
VOD (%)	9 (13)	1 (3)

Sasaki et al. *Blood.* 2020;136: abstract 1895.

Antibodies vs CAR T in ALL: Comparing Apples to Apples

Age Group	Salvage	Rx	% CR	% OS (× yr)
Pedi	S1	Blinatumomab	79	79 (2)
	S2	Inotuzumab	62	40 (1)
	S2	CAR T	67 (82% of infused)	66 (2)
Adult	S1	Mini-CVD-ino-blina	91	40(3)
	S2-S3	Mini-CVD-ino-blina	57–61	20–40 (2)
	S2+	CAR T (active ALL)	65	10–20 (2)

ALL 2021: Conclusions

- Ino and blina + chemoRx in salvage and frontline
  - S1 – mini-CVD-ino-blina CR 90%; 3-y OS 42%
  - Older frontline – CR 90%; 3-yr OS 56%
  - Moving younger adults (HCVAD-blina-ino)
- Great outcome in Ph+ ALL
  - 5-yr OS 76%
  - Chemotherapy-free regimens: Blinatumomab and ponatinib
- Bcl2-Bclxl inhibitors
  - Venetoclax-navitoclax combo in R/R ALL RR 50%
  - Mini CVD + ven in older frontline CR 90+%
- MRD eradication
  - NGS > FCM and PCR; NGS PB = NGS BM
  - MRD-negative CR best predictor for outcome
- CAR T cells; Strategies redefining their role in early savage and frontline
  - Dual CD19-22; Fast-off CD19; allo CAR T cells (CD19, CD22, CD20?)
- Incorporate new strategies
  - Blinatumomab SQ TIW, blinatumomab + checkpoint inhibitors

AML

AML in 2017–2020, 10 Agents FDA Approved

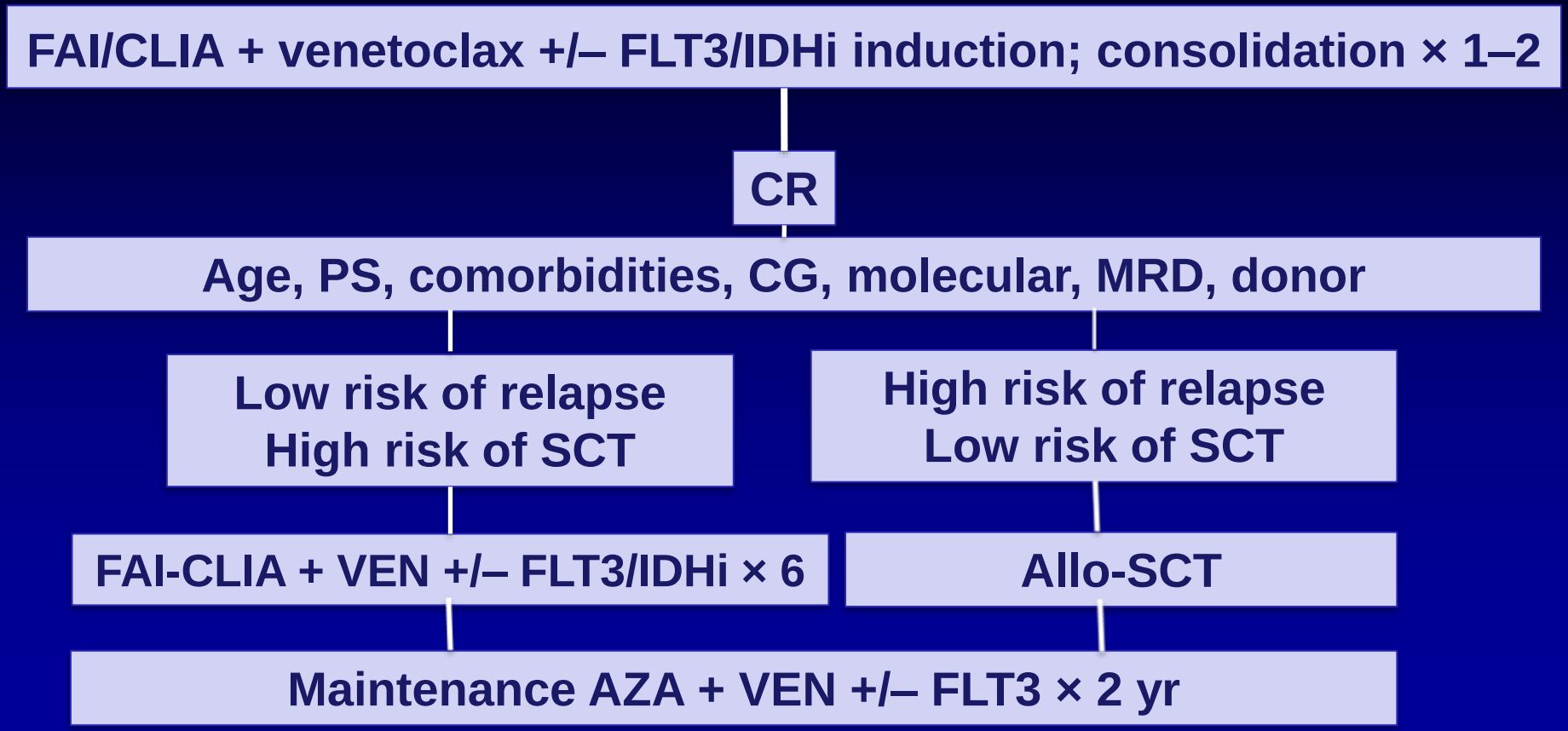
- **Midostaurin** (RYDAPT) for de novo younger AML (≤60 yr), *FLT3* mutation – April 2017
- **Gilteritinib** (*FLT3* inhibitor) for *FLT3*+ R/R AML
- **Enasidenib** (AG-221; IDHIFA) for R/R AML and *IDH2* mutation – August 2017
- **Ivosidenib** (AG-221) for R/R AML – August 2018
- **CPX-351** (Vyxeos) for newly Dx Rx-related AML and post-MDS AML – August 2017
- **Gemtuzumab ozogamicin** revival for frontline AML Rx – August 2017
- **Venetoclax** for newly Dx older/unfit for intensive chemo, with AZA/DAC, ara-C
- **Glasdegib** for newly Dx older/unfit, with ara-C
- **Oral decitabine** – **HMA Rx for MDS and CMML** – August 2020
- **Oral azacitidine** in AML maintenance – Sept 2020

Clinical Applications of Molecular Studies in AML

- ***FLT3*-ITD mutations – add FLT3 inhibitor (midostaurin, sorafenib, gilteritinib), consider allo-SCT and post SCT FLT3i**
- ***IDH1–2* mutations – add *IDH* inhibitor: enasidenib (AG-221/IDH2 inhibitor), ivosidenib (AG-120/IDH1 inhibitor)**
- ***NPM1* mutation in diploid CG – ara-C sensitivity**
- ***TP53* mutation – consider decitabine 10 days ± others (GO, venetoclax); refer to allo-SCT; role of CD47 Ab (magrolimab)**
- **MLL-AML; t(11q23;---) – Menin inhibitors**

NCCN guidelines. Acute Myeloid Leukemia; v2.2018

Therapy of Younger AML at MD Anderson in 2021+

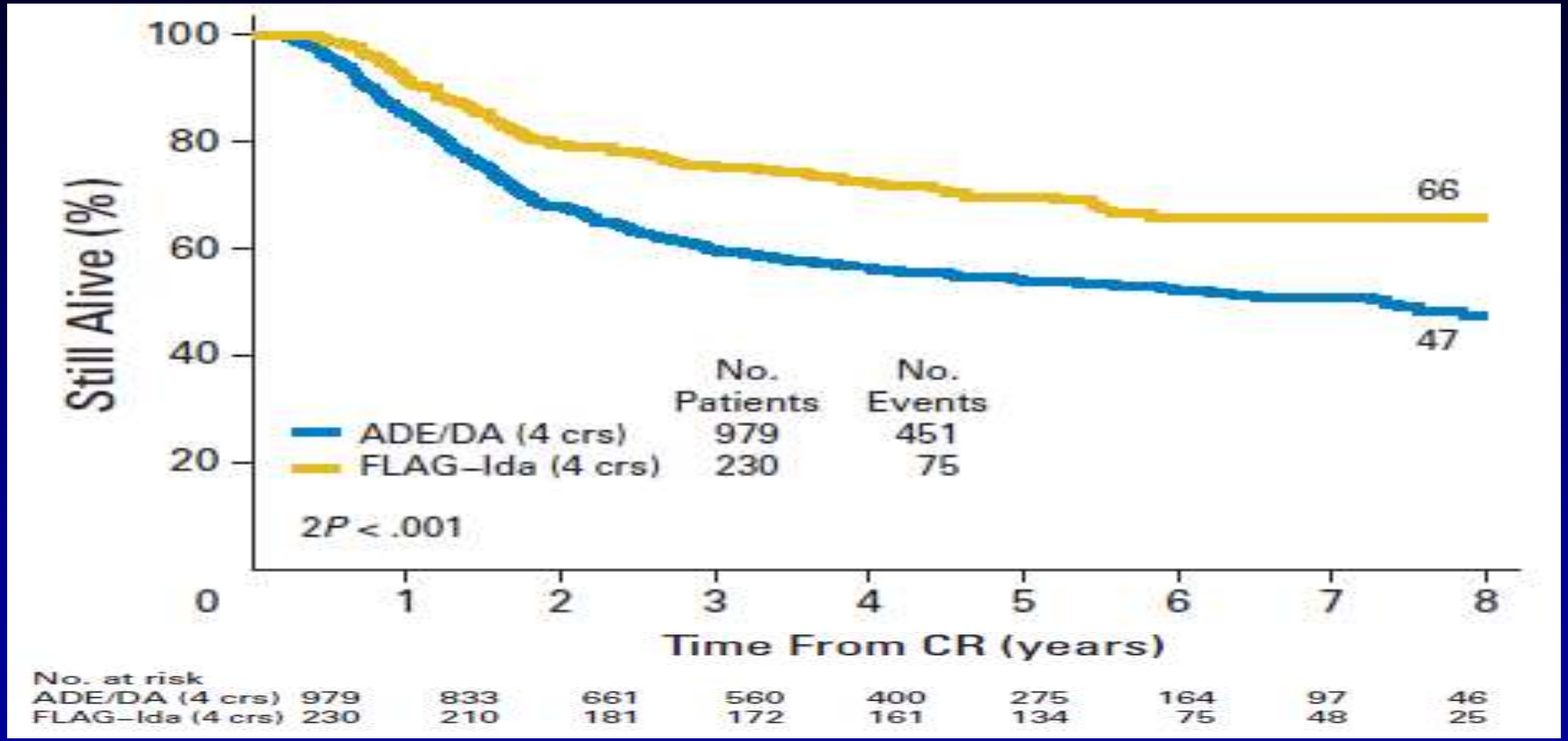


High-Dose Ara-C Induction Improves Outcomes in AML

- Meta-analysis of 3 randomized trials
- EORTC-GIMEMA: survival benefit in age ≤45 yr
- Chinese study
- MRC AML 15
- Italian study

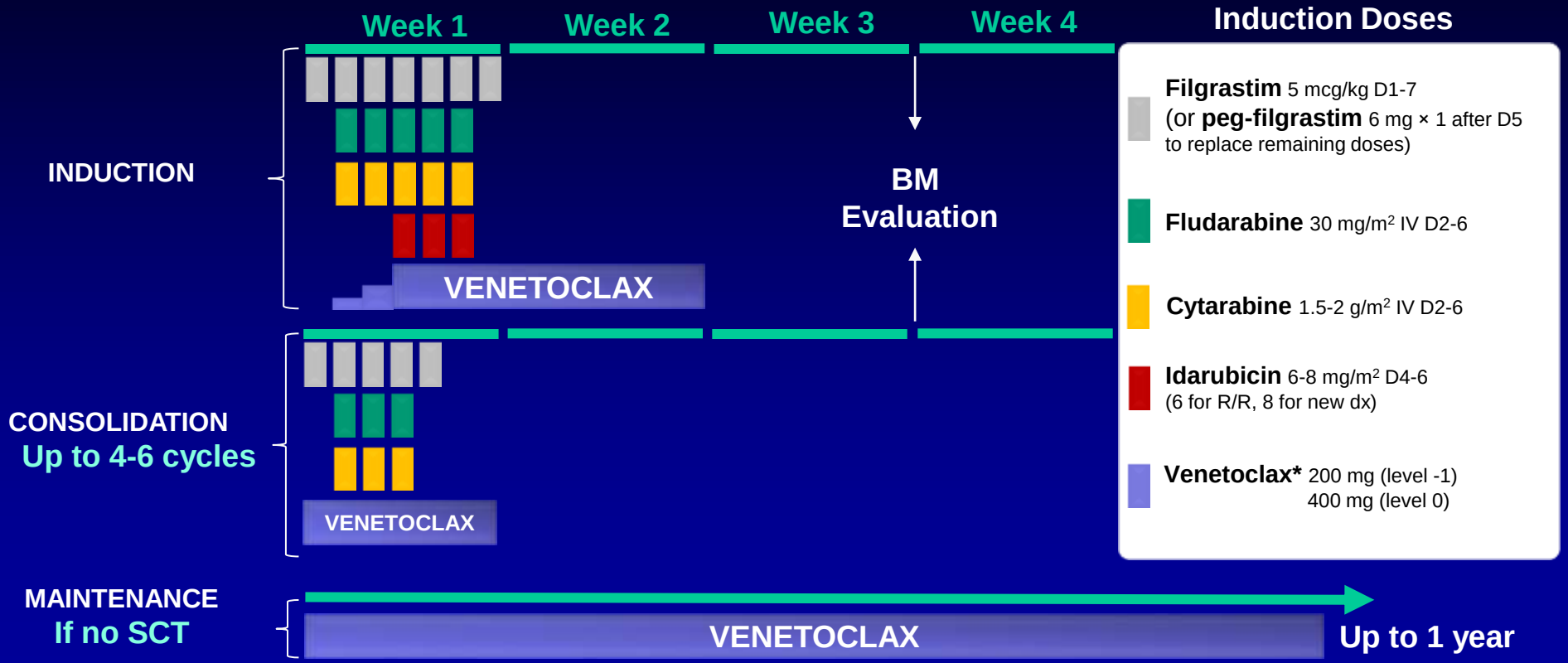
Kern W, Estey EH. *Cancer.* 2006;107(1):116-124; Willemze R, et al. *J Clin Oncol.* 2014;32(3):219-228; Wei H, et al. *Blood.* 2017;130:abstract 146; Burnett AK, et al. *J Clin Oncol*. 2013;31:3360-3368; Bassan R, et al. *Blood Adv.* 2019;3(7):1103-1117.

MRC AML 15: ADE/DA vs FLAG-Ida – 4 Courses



Burnett AK, et al. *J Clin Oncol*. 2013;31:3360-3368.

FLAG-IDA-VEN Treatment Plan



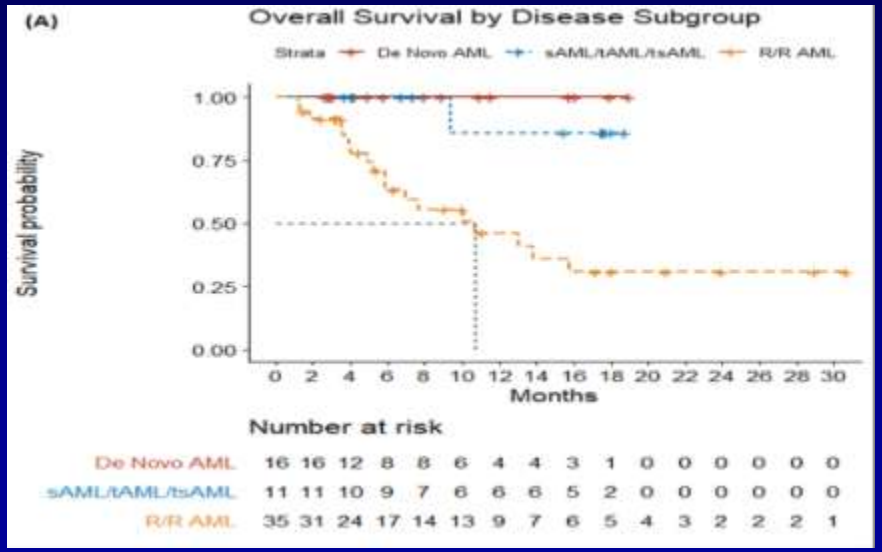
Abou Dalle, et al. *Blood.* 2019;134:abstract 176.

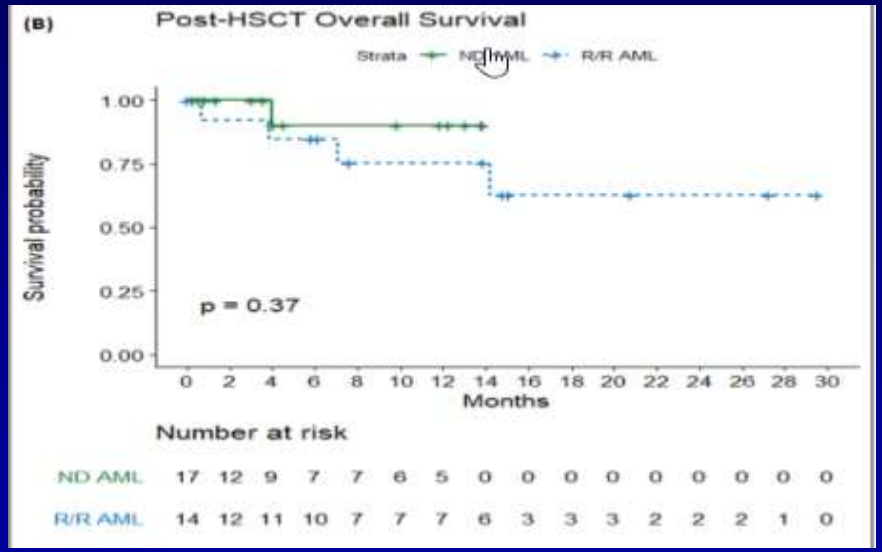
*Concomitant azole permitted with adequate dose reduction.

FLAG-IDA + Venetoclax in AML

- FLAG-IDA + VEN evaluated in R/R AML, then newly Dx AML
- 62 pts Rx: ND AML 27; R/R AML 35

Parameter	ND AML	R/R AML
% ORR	96	75
% CR + CRh + CRi	89	65
% MRD-negative	96	70
% 12-mos OS	85+	60

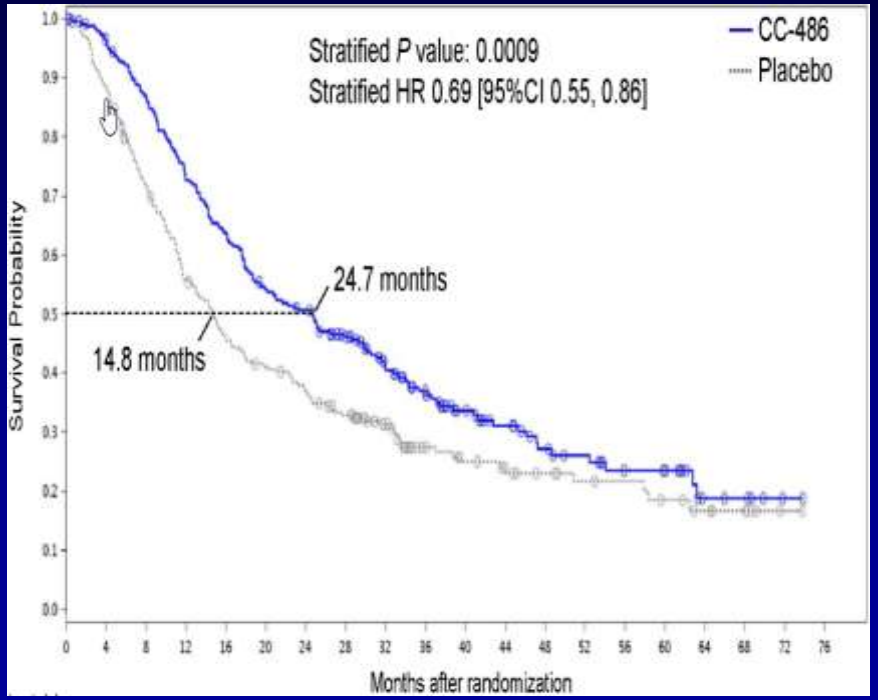


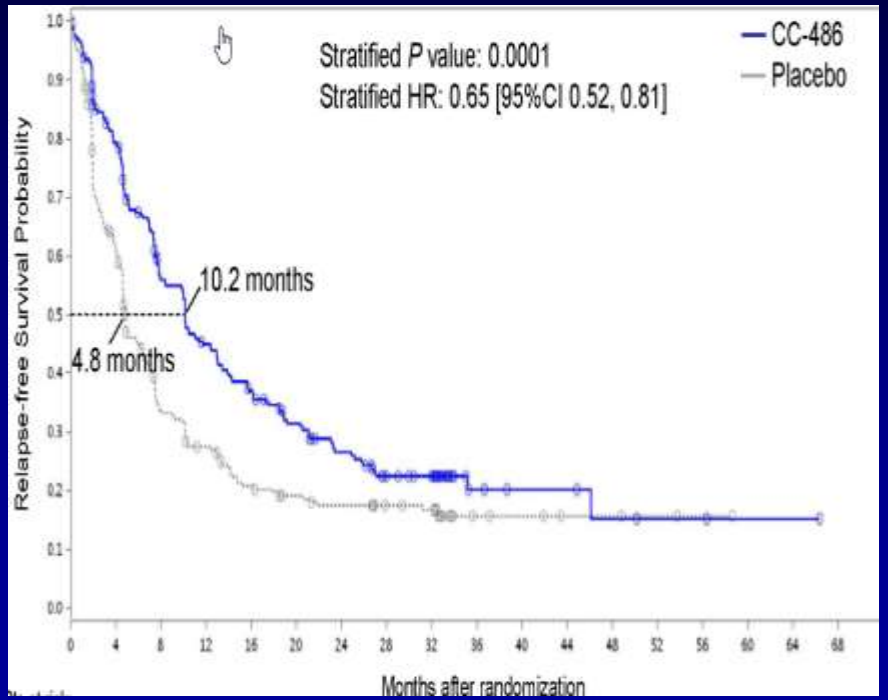


Lachowiez et al. *Blood*. 2020;136:abstract 332.

Phase III Study of Oral Azacitidine vs Placebo as Maintenance in AML (QUAZAR AML-001)

- 472 pts 55+ yr (median age 68 yr) with AML in CR-CRi <4 mo randomized to CC-486 300 mg/daily × 14 Q mo (n = 238) or PBO (n = 234)





Wei H, et al. *Blood.* 2019;134:LBA 3.

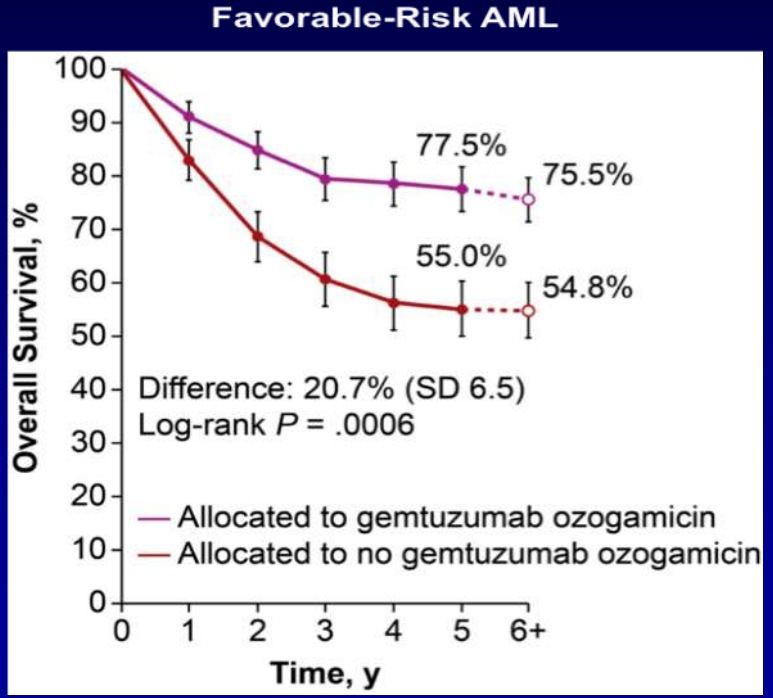
AML: What Definitely Works

- FLT3 inhibitors
- IDH1–2 inhibitors
- CD33 and CD123 antibodies
- Venetoclax
- Maintenance with oral azacitidine
- ? Oral decitabine-cedazuridine + venetoclax in older/unfit AML

Gemtuzumab Ozogamicin Meta-Analysis of 5 AML Randomized Trials

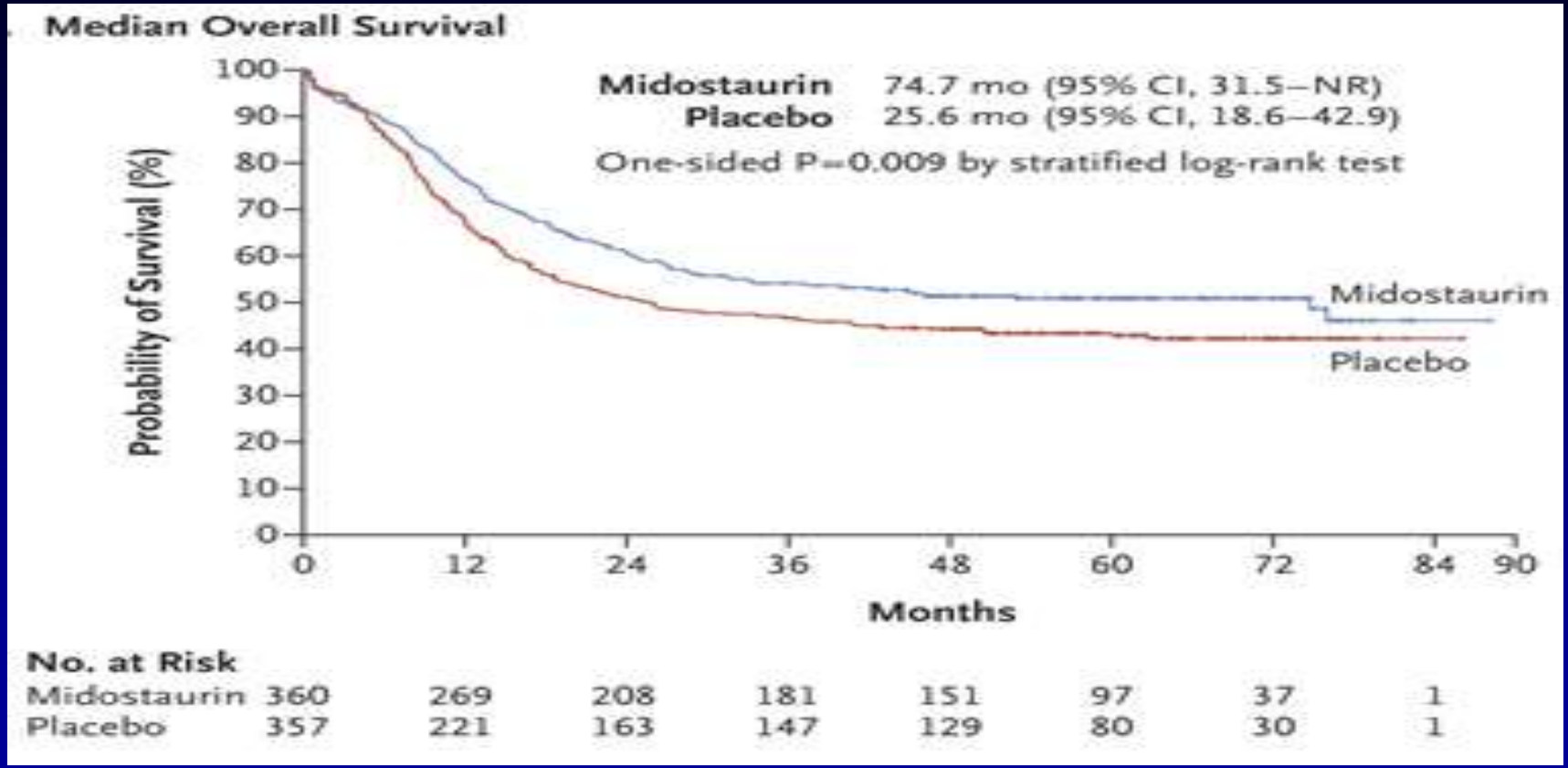
5 randomized trials of 3,325 pts: SWOG, ALFA, UK-MRC AML15 and 16, GOELAMS

Addition of GO
❑ No ↑ CR rate: OR, 0.91; *P* = .3
❑ Did not increase mortality: OR, 1.13; *P* = .4
❑ Improved survival: OR, 0.89; *P* = .01
❑ Reduced relapse: OR, 0.81; *P* = .001
❑ Highly significant survival benefit for favorable risk (OR, 0.47; P = .006) and intermediate risk (OR, 0.84; *P* = .005)



Hills RK. *Lancet Oncol*. 2014;15:986.

Chemo Rx ± Midostaurin in AML (RATIFY)

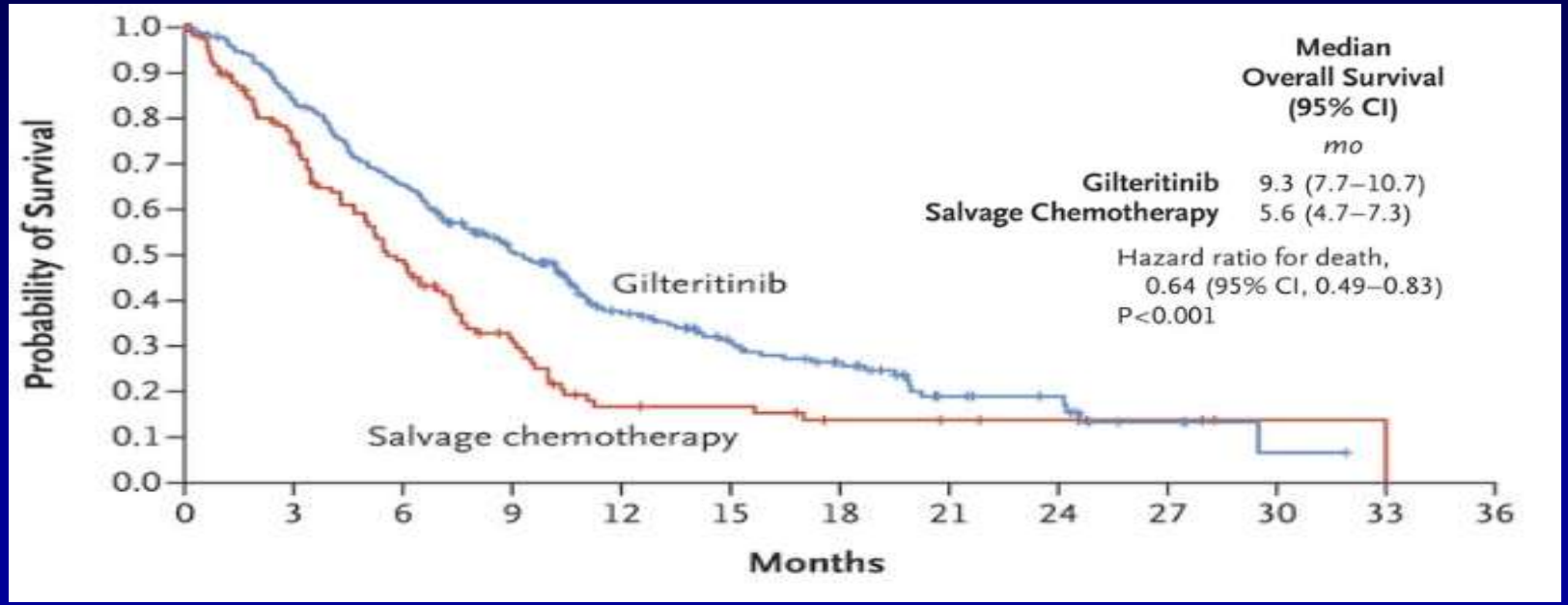


Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

Gilteritinib vs Chemo Rx in R/R *FLT3*-Positive AML

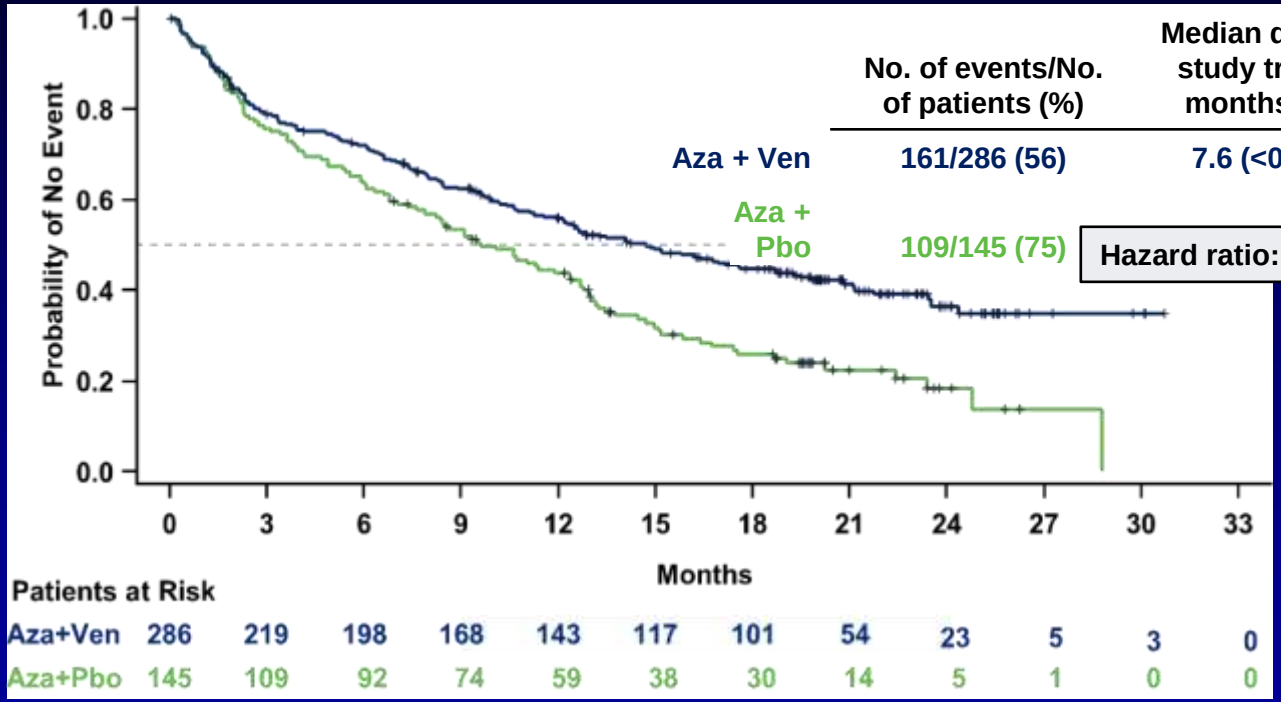
- 371 pts randomized 2:1 to gilteritinib 120/D vs chemo Rx (n = 127)

Parameter	Gilt	Chemo Rx
% CR	21	10
% CR + CRi	34	15
Median OS (mos)	9.3	5.6



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

AZA +/- VEN in AML – Overall Survival



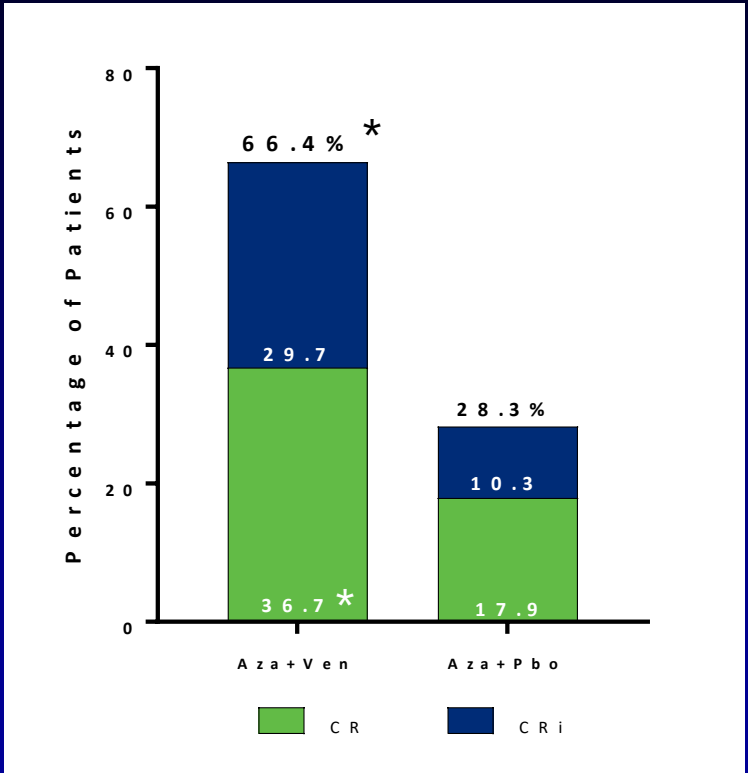
	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza + Ven	161/286 (56)	7.6 (<0.1–30.7)	14.7 (11.9–18.7)
Aza + Pbo	109/145 (75)		

Hazard ratio: 0.66 (95% CI: 0.52–0.85), *P* <.001

Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

AZA +/- VEN in AML – Composite Response Rate (CR + CRi)



	No. of treatment cycles, median (range)	Median time to CR/CRi, months (range)	*CR + CRi by initiation of cycle 2, n (%)
Aza + Ven (n = 286)	7.0 (1.0 – 30.0)	1.3 (0.6 – 9.9)	124 (43.4)
Aza + Pbo (n = 145)	4.5 (1.0 –26.0)	2.8 (0.8 – 13.2)	11 (7.6)

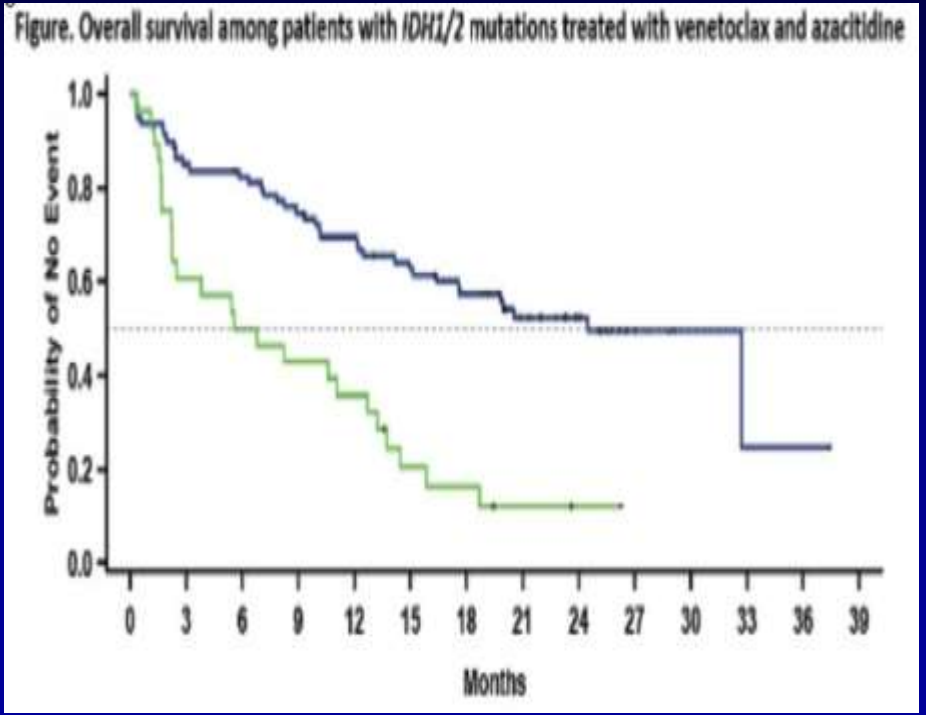
*CR + CRi rate, CR rate, and CR + CRi by initiation of cycle 2 are statistically significant with *P* <.001 by CMH test.

DiNardo C, et al. *N Engl J Med*. 2020;383:617-629.

Azacitidine +/- Venetoclax in Newly Dx *IDH2*-Mutated AML

- AZA +/- ven given to 107 pts with older/unfit
- AML: 79 AZA + VEN; 28 AZA

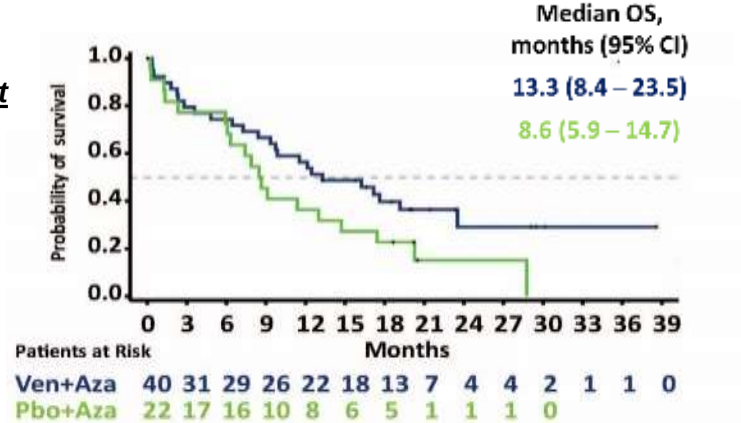
No (%) Parameter	AZA-VEN (n = 79)	AZA (n = 28)
CR + CRi	62 (79)	3 (11)
CR + CRh	57 (72)	2 (7)
CR	35 (44)	1 (4)
Median DOR (mos)	29.5	17.5
Median OS (mos)	24.5	12.3



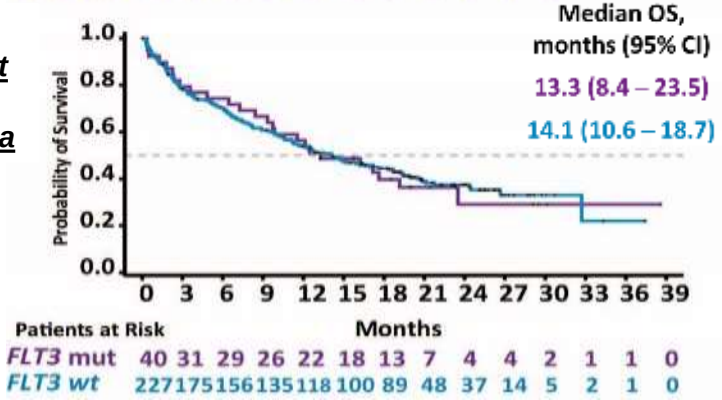
Pollyea D, et al. *Blood.* 2020;136:abstract 461.

AZA +/- VEN in Older FLT3-Mutated AML: Survival Benefit With VEN Only in *FLT3-TKD*, Not *FLT3-ITD*

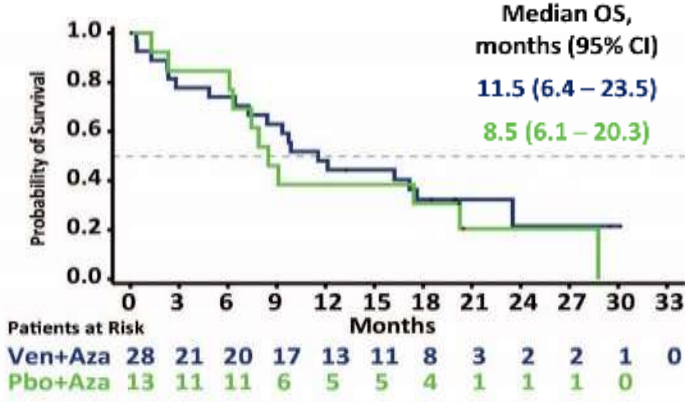
A. FLT3mut



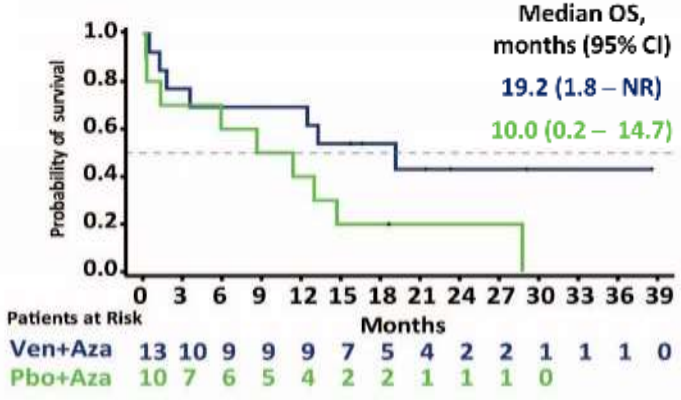
B. FLT3mut vs wt in Ven + Aza



C. FLT3-ITD



D. FLT3-TKD

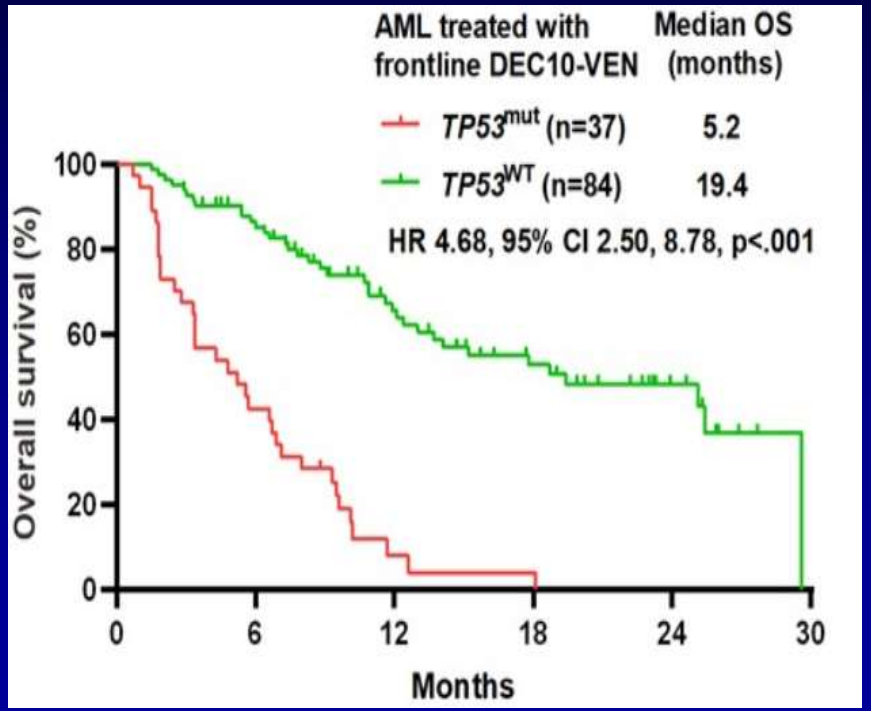


Konopleva M, et al. *Blood*. 2020;136:abstract 1904.

DAC + Venetoclax in *TP53* AML

- 121 pts with newly Dx AML Rx with DAC10 + VEN. Median age 72 yrs (49–89); 37 (31%) with *TP53*-AML

Parameter	TP53 (n = 37)	Other (n = 84)	*P*
% ORR	65	88	.003
% CR	35	57	.02
% CR-CRi	54	76	.015
% MRD-negative	19	52	.001
% 30/60 D mortality	5/27	0/2	<.001
Median OS (mos)	5.2	19.4	<.001



Kim et al. *Blood.* 2020;136:abstract 693.

Magrolimab (5F9; Anti-CD47 Ab) and Azacitidine in MDS and AML

- 68 pts (39 MDS, 29 AML). Median age 73 yrs. 58 evaluable
- AZA 75 mg/m^2/D×7; magrolimab 1–30 mg/kg weekly, then Q2 weeks
- MDS — ORR 30/33 = 91%; 14 CR (42%)
- AML — ORR 16/25 = 64%; 10 CR (40%)
- CG CR in 9/26 MDS (35%) and 6/12 AML (50%)
- 12/16 (75%) *p53*-mutant pts responded (9/12 AML = 75%; 3/4 MDS)

Sallman. ASCO 2020.

Leukemia Research – Promising Combination Strategies in 2021

- FLT3 inhibitors
- IDH 1/2 inhibitors
- Gemtuzumab; other CD33 and CD123 MoAbs, Ab constructs; CAR T targeting CD33/123
- Venetoclax
- Oral azacitidine; oral decitabine
- CD47 Ab (macrophage stimulation)

Leukemia Questions?

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- **Office: 713-792-4764**

Global Leukemia Academy

Review of prognostic value of MRD in ALL

Aaron Logan

APTITUDE HEALTH

UCSF Helen Diller Family Comprehensive Cancer Center

Prognostic Value of MRD in Acute Leukemias

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Blood and Marrow Transplantation

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Question 1

In acute lymphoblastic leukemia, at which of the following time points is MRD $>10^{-4}$ prognostic for survival?

(a) End of induction

(b) After consolidation

(c) Prior to transplant

(d) After transplant

(e) All of the above

Question 2

In AML, the presence of molecular MRD following consolidation chemotherapy is associated with decreased survival using which gene aberrations?

(a) *DNMT3A*

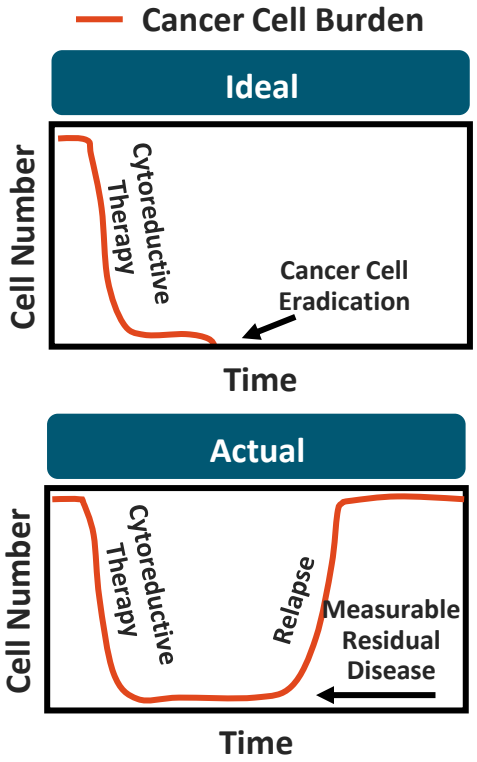
(b) *TET2*

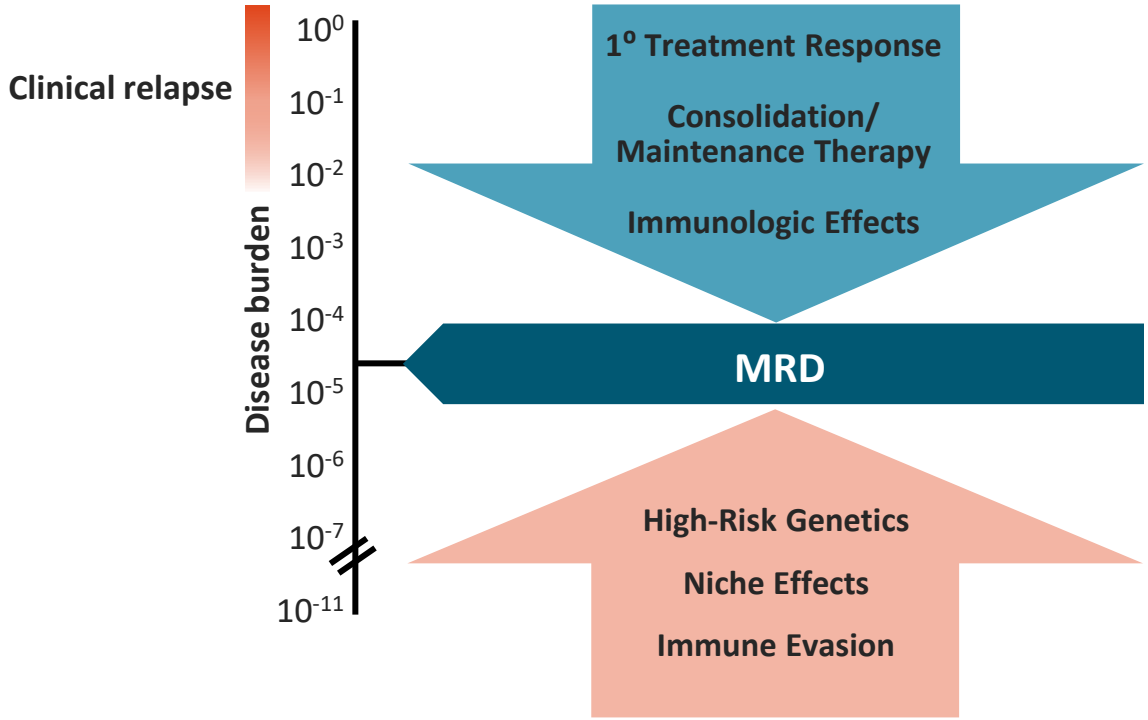
(c) *NPM1*

(d) *ASXL1*

(e) All of the above

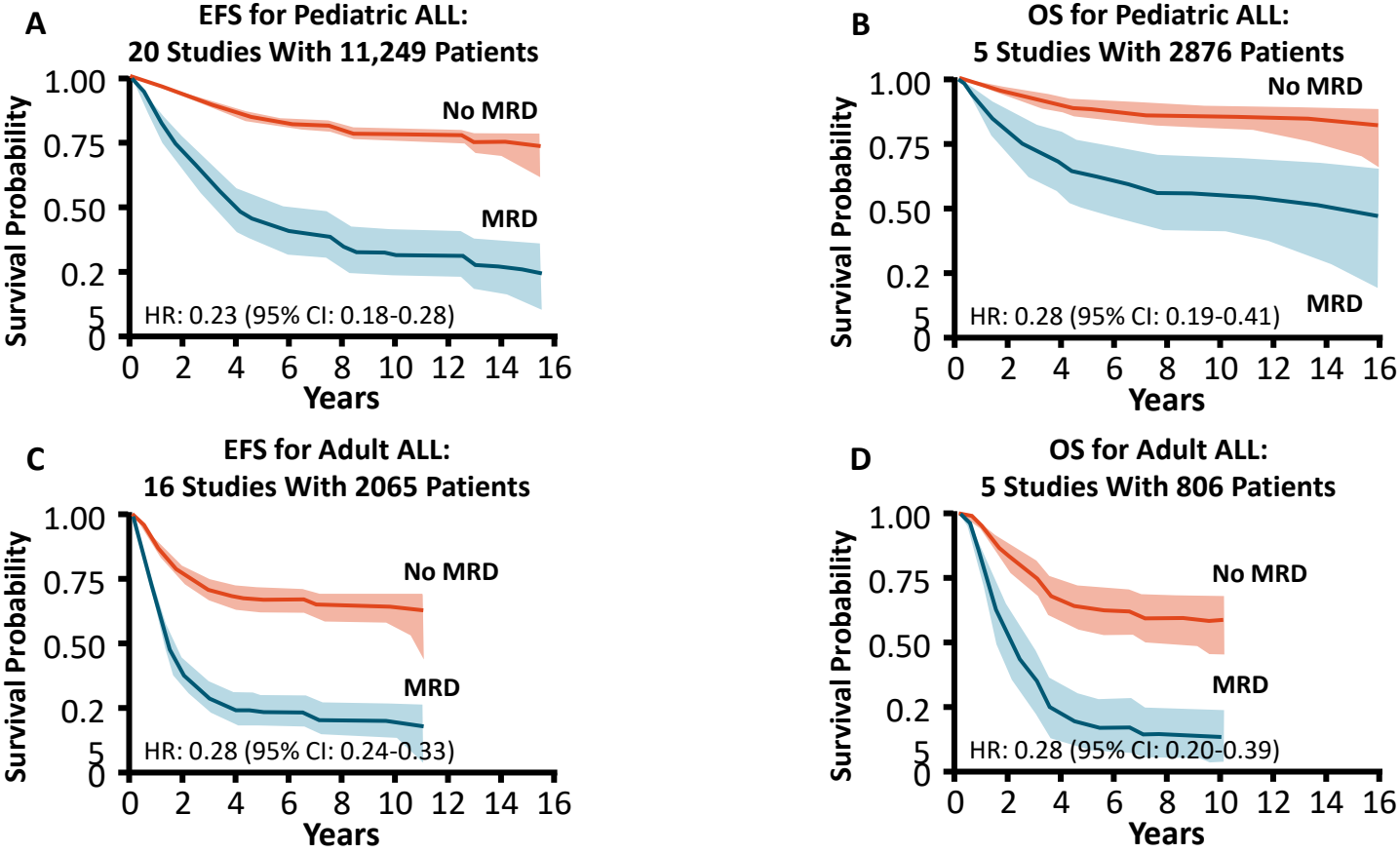
Measurable (Minimal) Residual Disease (MRD)





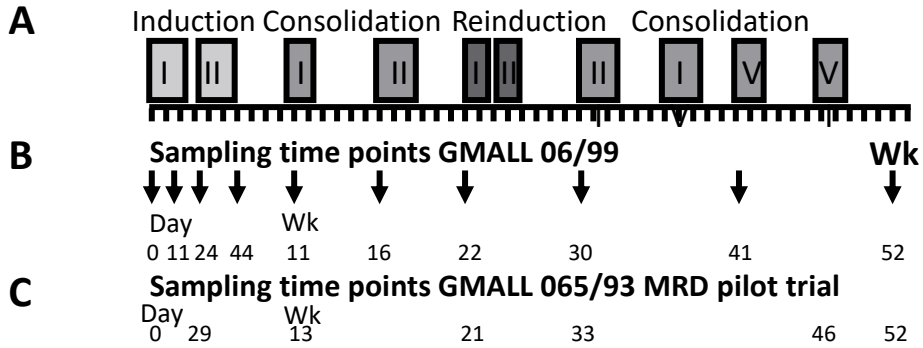
Akabane H, Logan A. *Clin Adv Hematol Oncol*. 2020;18(7):413-422.

MRD Strongly Predicts Outcome in Pediatric and Adult ALL



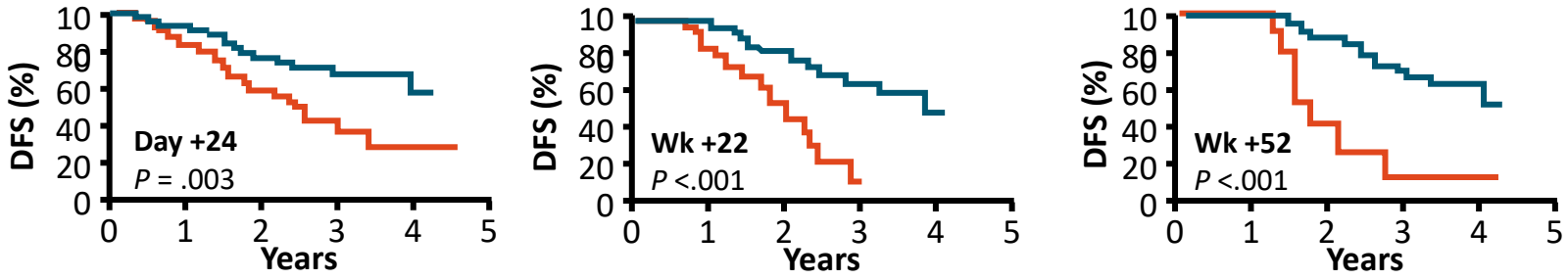
Berry DA, et al. *JAMA Oncol*. 2017;3:e170580.

MRD at Any Point in Therapy Predicts Outcome



MRD Quantified Using Quantitative PCR

Probability of DFS According to MRD



MRD	n	3-Yr DFS (95% CI)
Negative/<10^{-4}	75	68.6 (55.0-82.2)
>10^{-4}	82	37.8 (24.5-51.1)

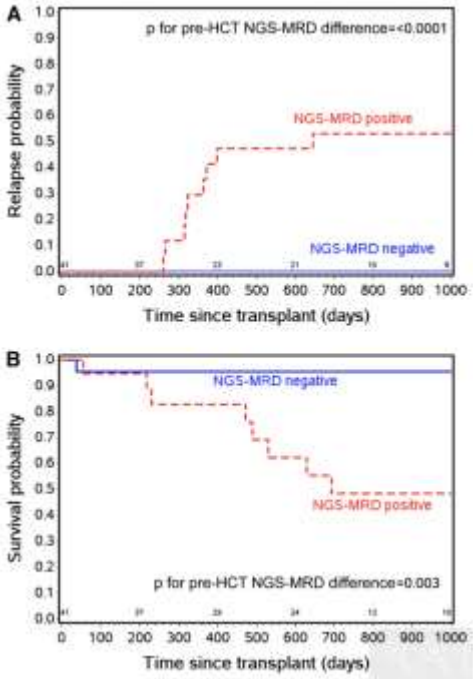
MRD	n	3-Yr DFS (95% CI)
Negative/<10^{-4}	10	65.4 (54.1-76.7)
>10^{-4}	1	11.8 (0-31.6)
	25	

MRD	n	3-Yr DFS (95% CI)
Negative/<10^{-4}	11	67.9 (56.9-80.6)
>10^{-4}	3	14.6 (0.0-40.0)
	11	

Brüggemann M, et al. *Blood*. 2006;107:1116-1123.

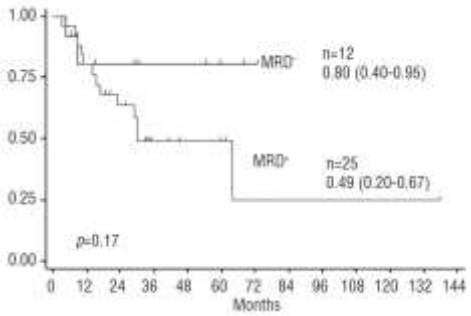
MRD Status Pre-HCT Predicts RFS and OS

- N = 56, age 1-21
- COG ASCT0431
- MRD Quant: NGS

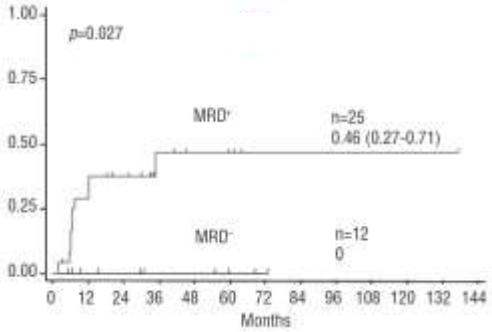


N = 43, age 18-63
MAC alloHCT in CR1
MRD quant:
TCR/Ig ASO-PCR or BCR/ABL Q-PCR or MLL/AF4 Q-PCR

MRD status pre-HCT: OS



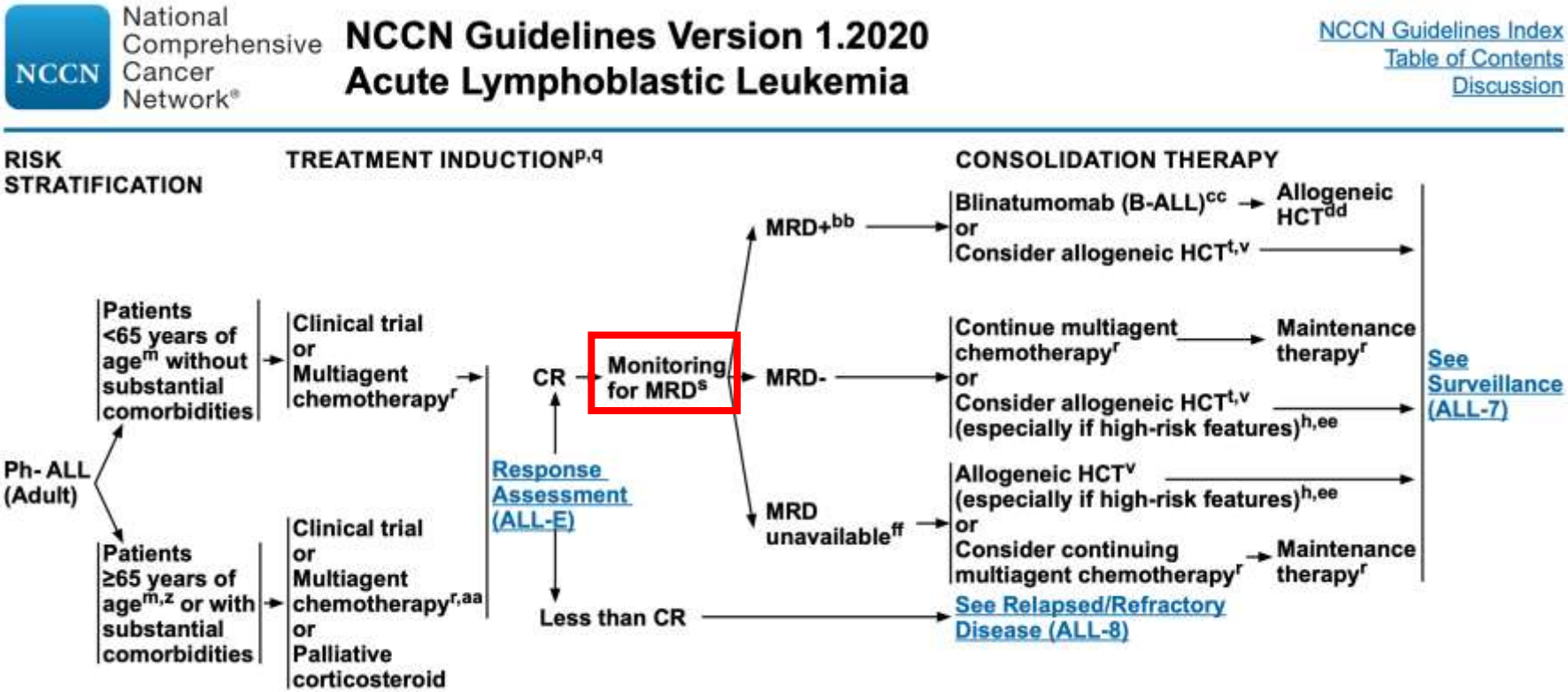
MRD status pre-HCT: CIR



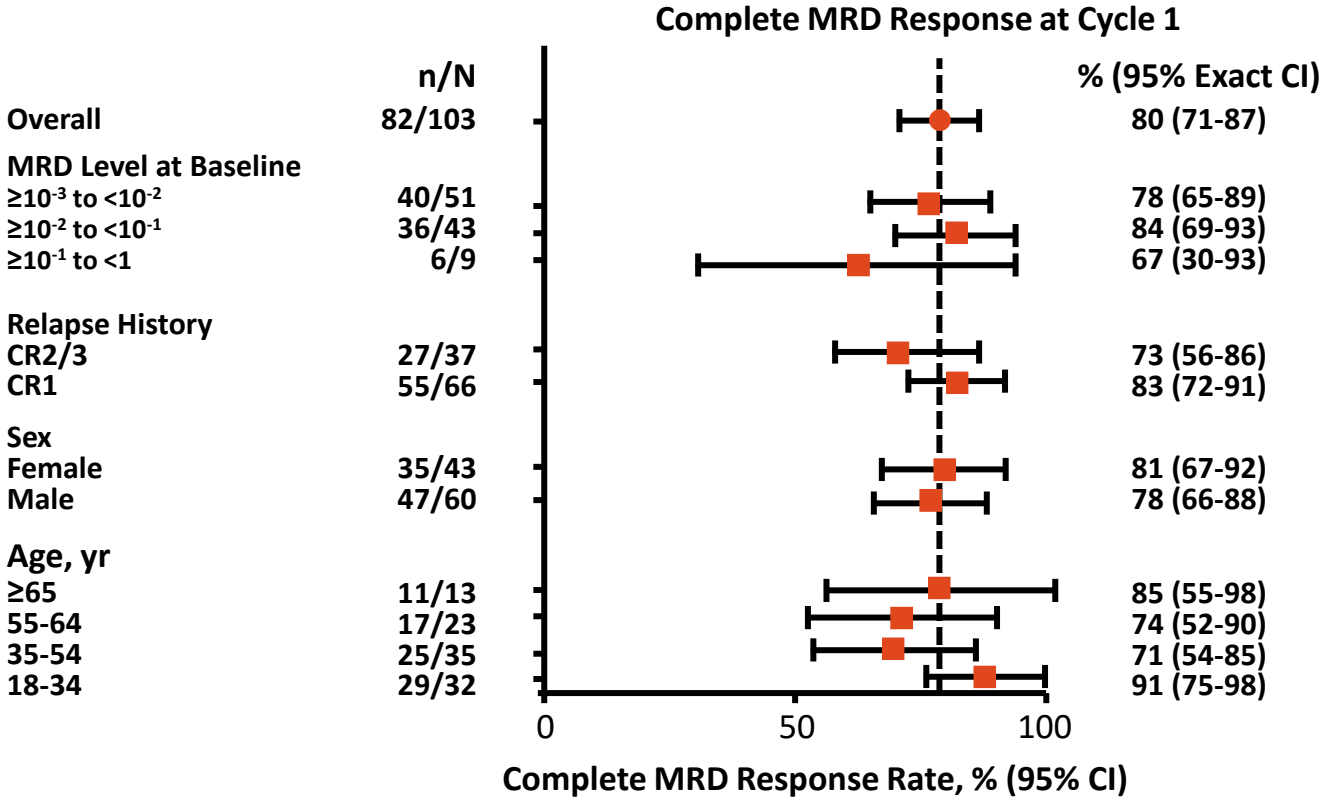
Pulsipher MA, et al. *Blood*. 2015;125:3501-3508.

Spinelli O, et al. *Haematologica*. 2007;92:612-618.

MRD Assessment in Remission Is Standard of Care

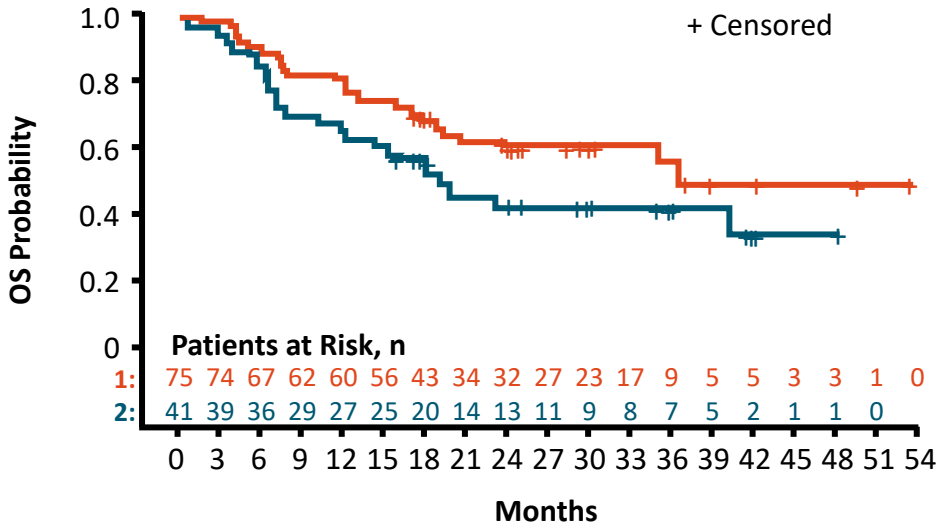


Blinatumomab BLAST Trial: Preemption of ALL Relapse Using MRD-Directed Treatment



Gökbuget N, et al. *Blood*. 2018;131:1522-1531.

Blinatumomab BLAST Trial: Preemption of B-ALL Relapse Using MRD-Directed Treatment

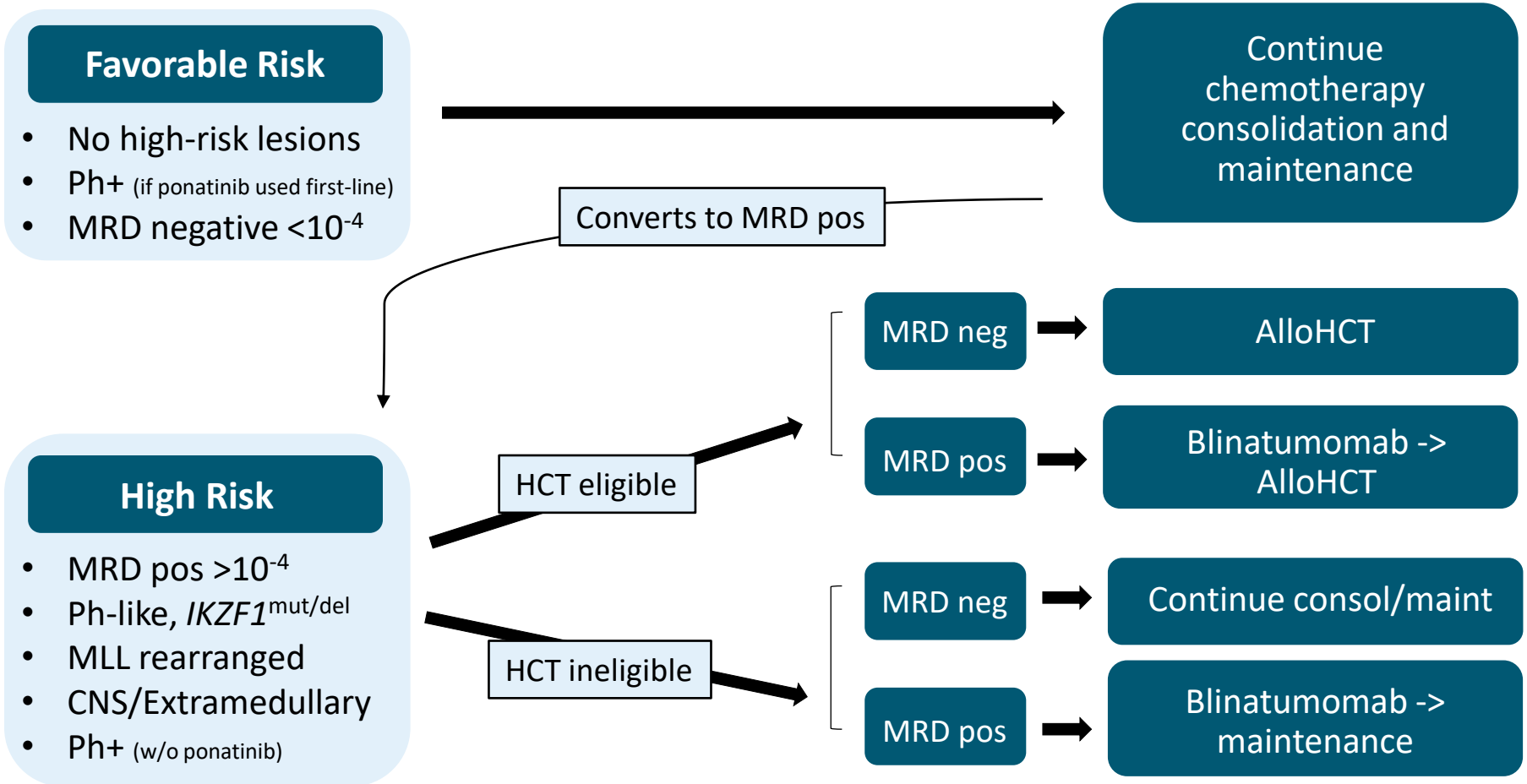


1: Patients in 1st CR (n = 75); median: 36.5 (95% CI: 20.6-NR)

2: Patients in 2nd or 3rd CR (n = 41); median: 19.1 (95% CI: 11.9-NR)

Gökbuget N, et al. *Blood*. 2018;131:1522-1531.

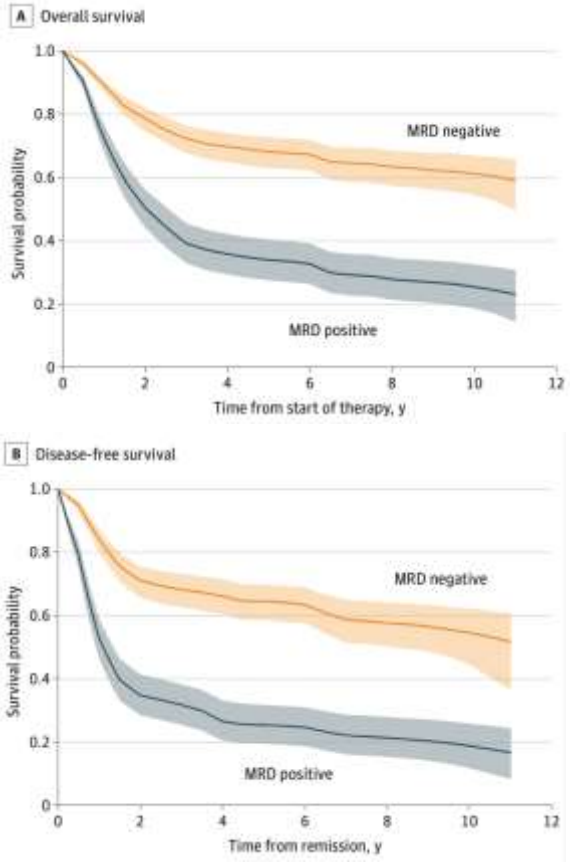
Management of ALL Patients in First Complete Remission



MRD Predicts Outcome in AML

Meta-analysis of 81 studies, n = 11,151

Subgroup	Studies included, No. (%)	
	In OS analysis	In DFS analysis
Age group	n = 61	n = 64
Adult	50 (82)	51 (80)
Pediatric	10 (16)	11 (17)
Mixed	1 (2)	2 (3)
MRD time point	n = 80	n = 85
Induction	53 (66)	54 (64)
During consolidation	11 (14)	15 (18)
After consolidation	16 (20)	16 (19)
MRD detection method	n = 63	n = 67
MFC	25 (40)	29 (43)
PCR (*WT1*)	7 (11)	8 (12)
PCR (gene/fusion)	22 (35)	21 (31)
NGS	4 (6)	4 (6)
Cytogenetics/FISH	2 (3)	2 (3)
Others	3 (5)	3 (5)
AML subtype	n = 61	n = 64
CBF	9 (15)	12 (19)
Non-CBF	52 (85)	52 (81)
Specimen source	n = 63	n = 67
Bone marrow	56 (89)	58 (87)
Peripheral blood	5 (8)	5 (7)
Mixed	2 (3)	4 (6)



Short NJ, et al. *JAMA Oncol*. 2020;6(12):1890-1899.

MRD Predicts Outcome in Core-Binding Factor AML

Meta-analysis of 13 studies, n = 694

Study or Subgroup	MRD negative Events	Total	MRD positive Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Leroy 2005	14	15	1	6	6.0%	70.00 [3.65, 1342.66]	2005
Narimatsu 2008	8	13	6	7	8.1%	0.27 [0.02, 2.92]	2008
Corbacioglu 2010	23	29	11	20	15.6%	3.14 [0.89, 11.04]	2010
Dohner 2012	17	20	6	13	12.5%	6.61 [1.28, 34.14]	2012
Zhang 2013	22	23	4	9	8.1%	27.50 [2.50, 302.17]	2013
Hoyos 2013	45	63	3	10	14.0%	5.83 [1.36, 25.09]	2013
Wang 2014	15	27	12	27	17.3%	1.56 [0.53, 4.57]	2014
Wei 2016	45	60	9	31	18.3%	7.33 [2.78, 19.36]	2016
Total (95% CI)		**250**		**123**	**100.0%**	**4.58 [1.98, 10.58]**	
Total events	189		52				

Heterogeneity: Tau² = 0.76; Chi² = 16.19, df = 7 (P = 0.02); I² = 57%
Test for overall effect: Z = 3.56 (P = 0.0004)

Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10 100
MRD positive better RFS MRD negative better RFS

Study or Subgroup	MRD negative Events	Total	MRD positive Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Liu Yin 2012	118	123	13	32	27.2%	34.49 [11.04, 107.80]	2012
Zhang 2013	22	23	2	9	19.2%	77.00 [6.03, 982.88]	2013
Willekens 2016	19	22	45	51	25.4%	0.84 [0.19, 3.73]	2016
Wei 2016	47	60	17	31	28.2%	2.98 [1.17, 7.60]	2016
Total (95% CI)		**228**		**123**	**100.0%**	**7.88 [1.25, 49.83]**	
Total events	206		77				

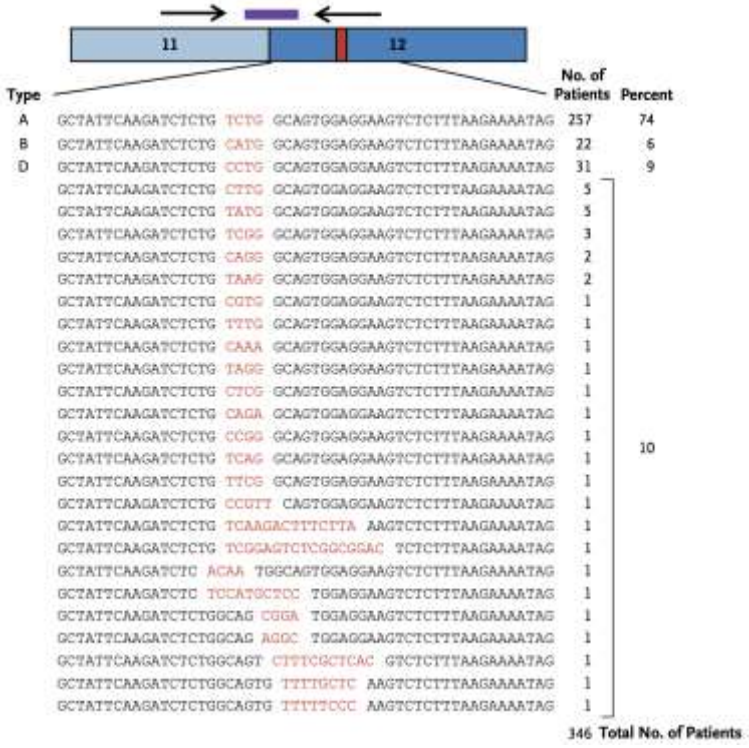
Heterogeneity: Tau² = 2.92; Chi² = 21.75, df = 3 (P < 0.0001); I² = 86%
Test for overall effect: Z = 2.19 (P = 0.03)

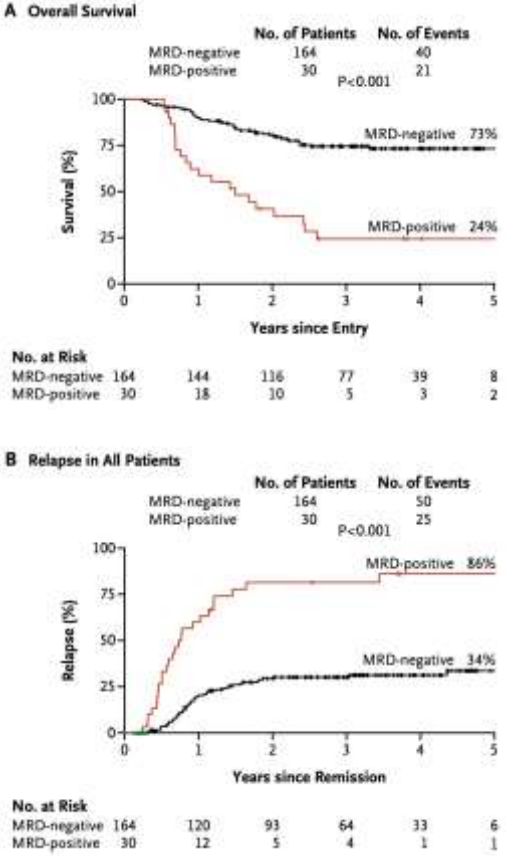
Odds Ratio M-H, Random, 95% CI

0.001 0.1 1 10 1000
MRD positive better OS MRD negative better OS

Rotchanapanya W, et al. *J Pers Med*. 2020;10(4):250.

MRD Predicts Outcome in *NPM1*+ AML





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

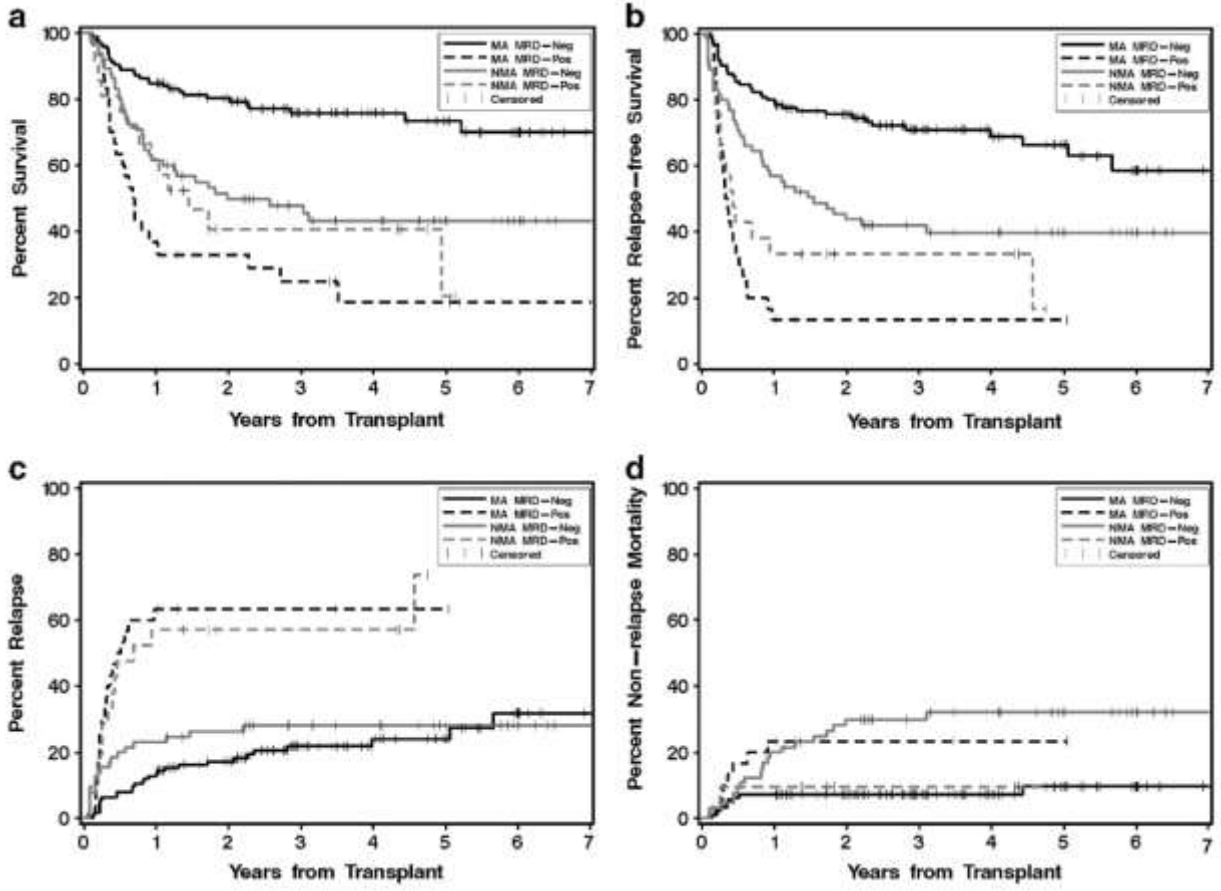
MRD Assessment by Genetic Aberrations in AML: Caveats

Genetic abnormality	Type	Techniques for detection	Usually cleared after successful therapy	Persistence after therapy associated with adverse outcome
RUNX1-RUNX1T1, CBFB-MYH11, PML-RARA	AML-related	qPCR	Yes	Yes
NPM1	AML-related	qPCR	Yes	Yes
KMT2A rearrangement, *DEK-NUP214, BCR-ABL1*	AML-related	qPCR	Unknown	Unknown
NRAS/KRAS	AML-related	NGS	Yes	Yes
FLT3-ITD/FLT3-TKD	AML-related	NGS PCR	Yes (but may be lost at relapse or acquired at relapse of previously *FLT3* wild-type AML)	Unknown
KIT	AML-related	NGS PCR	Yes	Yes
PTPN11	AML-related	NGS	Yes	Yes
GATA2	Likely AML-related	NGS	Yes	Unknown
CEBPA	Likely AML-related	NGS	Yes	Unknown
WT1	Likely AML-related	NGS	Yes	Unknown
RUNX1	CH (potentially AML-related)	NGS	Variable	Yes
IDH1/IDH2	CH (potentially AML-related)	NGS ddPCR	Variable	Yes
DNMT3A	CH	NGS	Usually not	No
ASXL1	CH	NGS	Variable	No
TET2	CH	NGS	Usually not	No
SRSF2	CH	NGS	Variable	No
BCOR	CH	NGS	Variable	No
TP53	CH	NGS	Variable	Yes

Persistent clonal hematopoiesis may not represent AML MRD

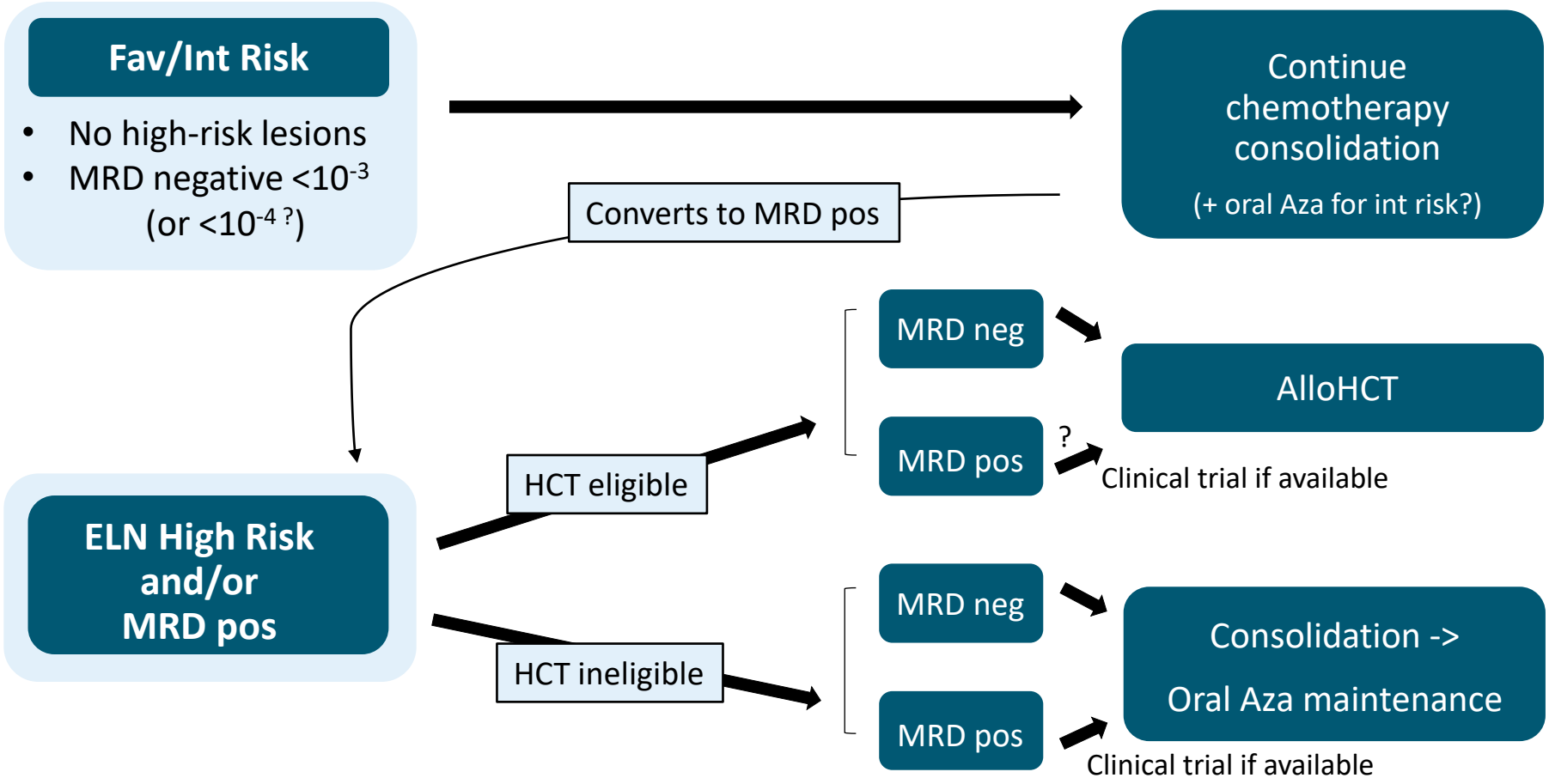
Hasserjian RP, et al. *Blood*. 2020;135(20):1729-1738.

Flow Cytometry MRD Pre-AlloHCT Predicts Outcome AML



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

Management of AML Patients in First Complete Remission



Measurable Residual Disease Summary

- MRD predicts RFS and OS in ALL and AML
- Robust data support making clinical decisions on the basis of presence of $>10^{-4}$ MRD in ALL
- In AML, the supported decision threshold varies between $>10^{-3}$ and $>10^{-4}$ on the basis of currently available data
- Pre-transplant MRD is associated with poor outcomes in ALL and AML
- Management of MRD-positive AML remains an unmet clinical need

Global Leukemia Academy

Genetic variants in ALL – Ph+ and Ph-like

José Maria Ribera

APTITUDE HEALTH

Global Leukemia Academy:
Emerging and Practical Concepts and Controversies in Leukemias
May 15, 2021

Genetic variants in ALL: Ph+ and Ph-like

J.M. Ribera

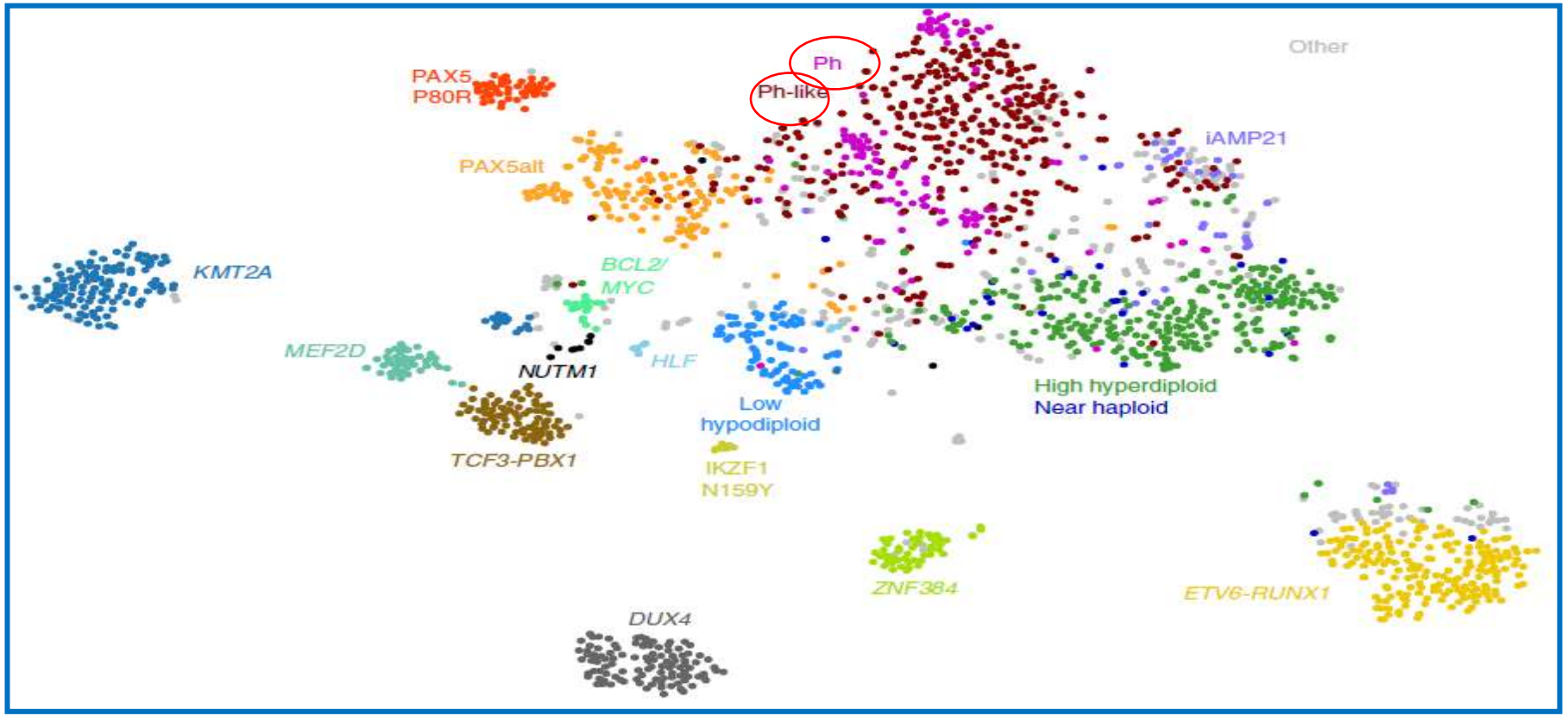
Clinical Hematology Department

ICO-Hospital Germans Trias i Pujol

Institut de Recerca contra la Leucèmia Josep Carreras

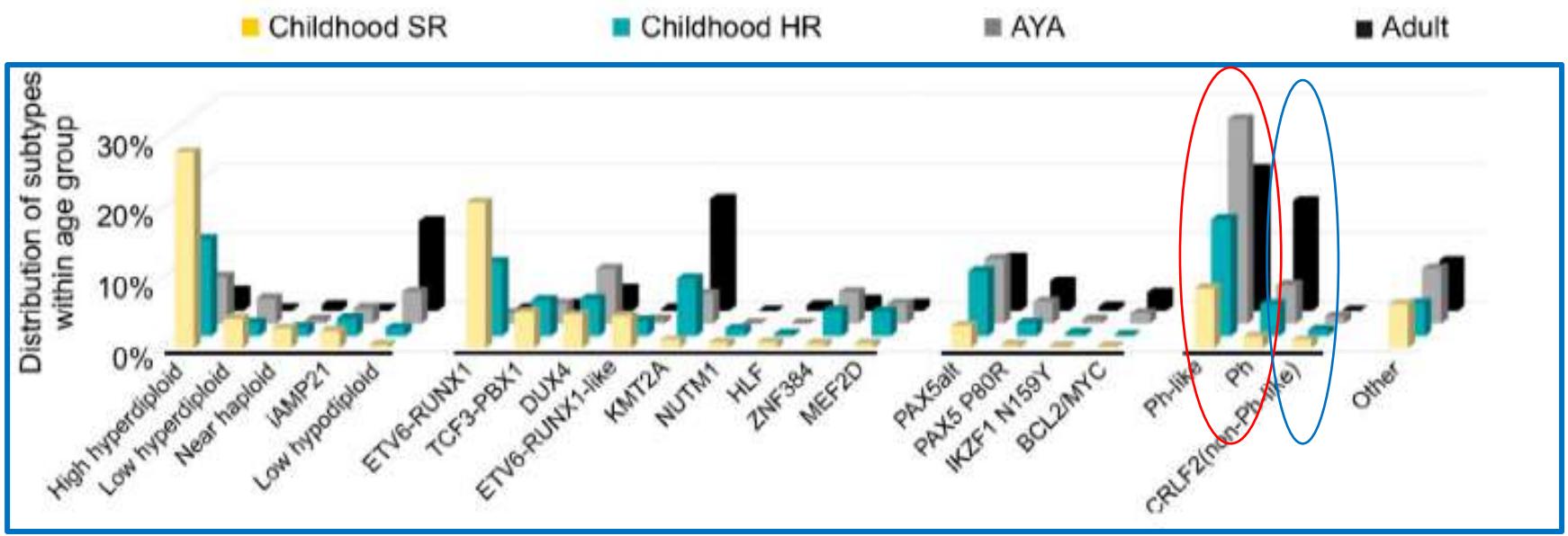
Universitat Autònoma de Barcelona, Spain

RNA seq in ALL: Gene-expression profiles



Gu Z, et al. *Nat Genet*. 2019;51:296-307.

Age differences in the distribution of genetic subtypes in ALL



Gu Z, et al. *Nat Genet*. 2019;51:296-307.

Ph+ ALL

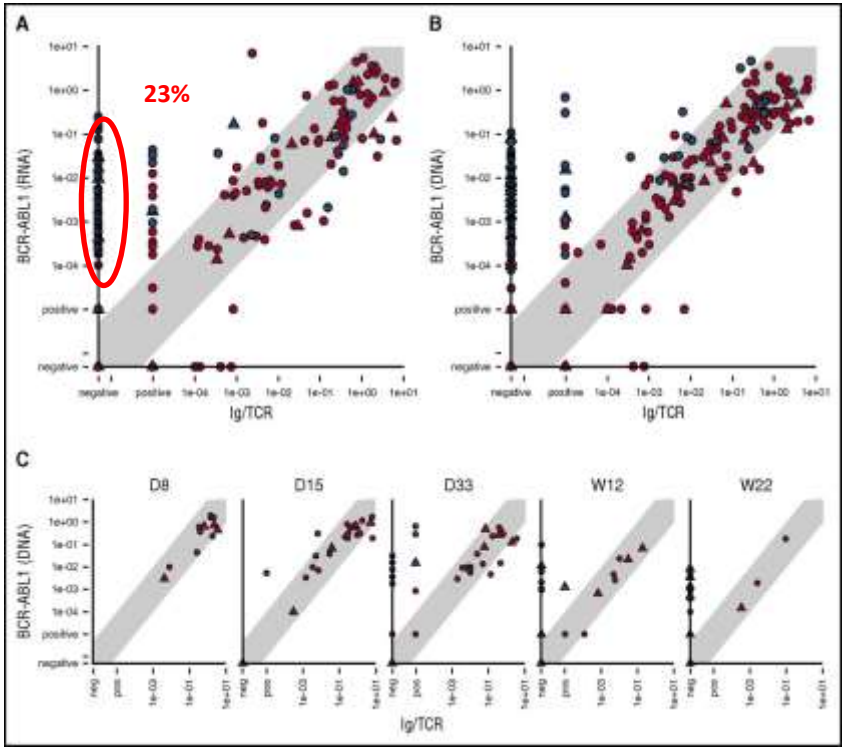
Ph+ ALL

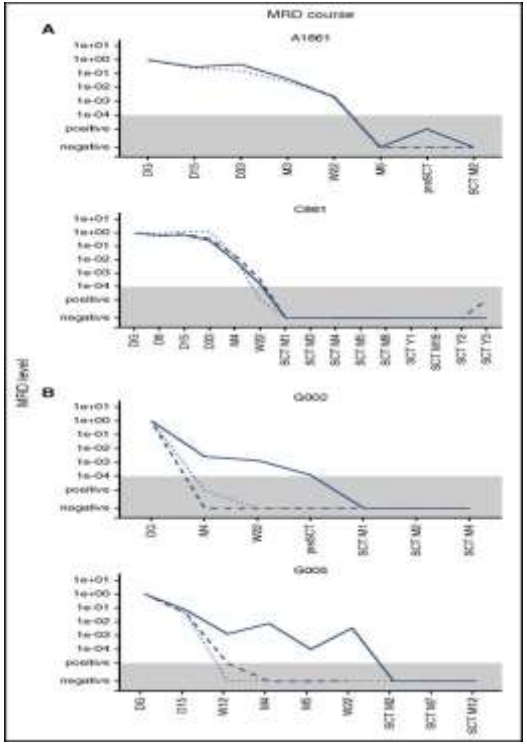
- 5% of ALL in children, 25%–30% in adults, and 40%–50% in elderly patients
- p190 BCR-ABL (m-BCR) fusion protein more frequent than p210 (M-BCR)
- TKIs have improved the prognosis in children and in adults, less in elderly patients
  - Currently 70%–80% of children and 45%–50% of adults are expected to be cured. Curability in elderly people is less prevalent
  - Need for HSCT questionable in children, standard approach in adults, recommendable (RIC) in fit elderly patients
- Novel nonchemotherapeutic approaches under investigation

Ph+ ALL: Open questions

- MRD assessment: RQ-PCR for BCR-ABL vs IG/TCR rearrangements
- Management of HR biologic features: IKZF1^{plus}, ACA . . .
- Use of third-generation TKI upfront
- Indication of HSCT in patients in molecular response
- Need and duration of TKI maintenance after HSCT
- Role of immunotherapy upfront

RQ-PCR for BCR-ABL vs IG/TCR rearrangements





Concordant

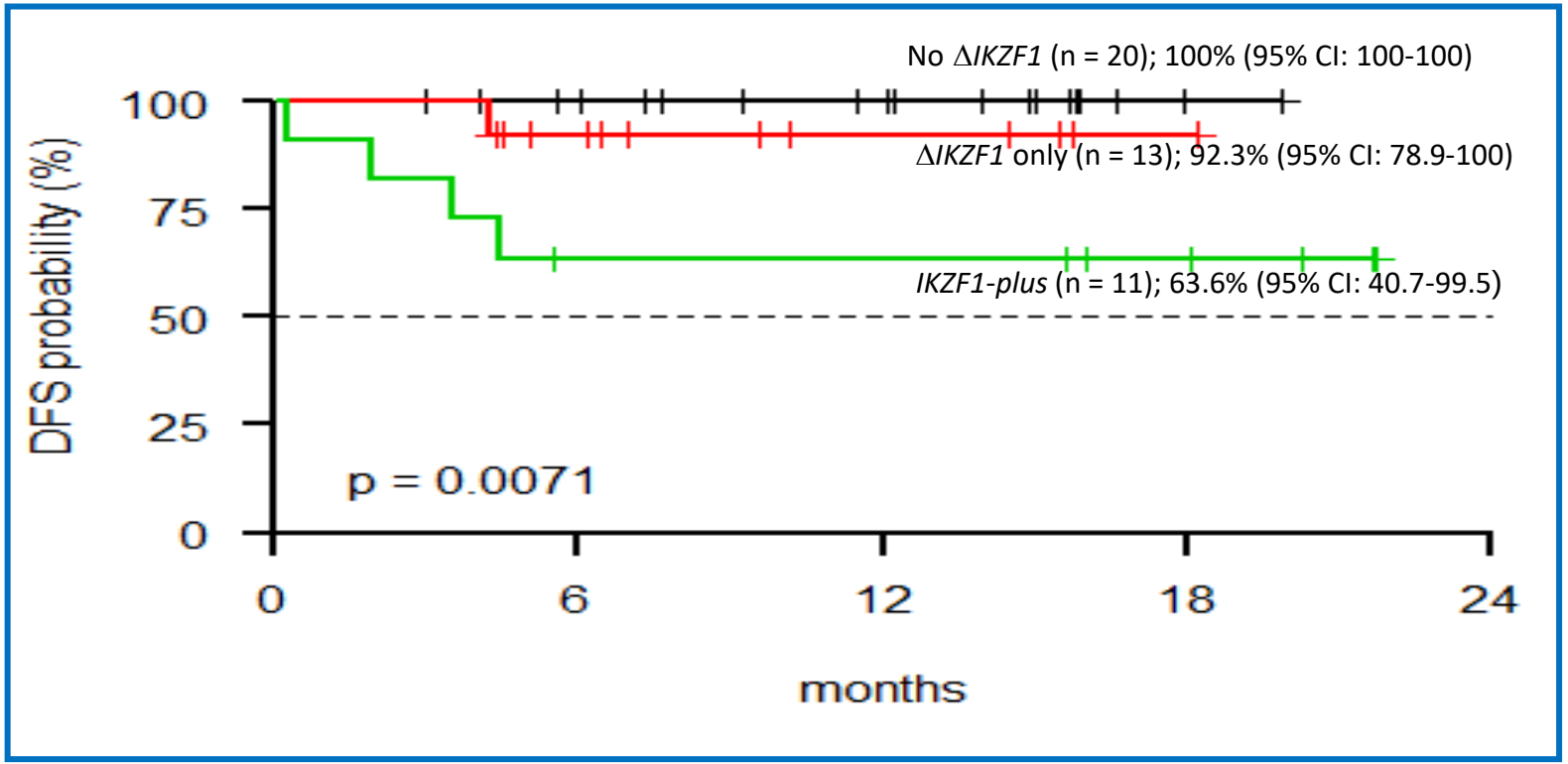
BCR-ABL1 = Ig = *IKZF1*

Discordant

BCR-ABL1 ≠ Ig = *IKZF1*

Hovorkova L, et al. *Blood*. 2017;129:2771-2781.

D-ALBA: Impact of additional genomic lesions on DFS



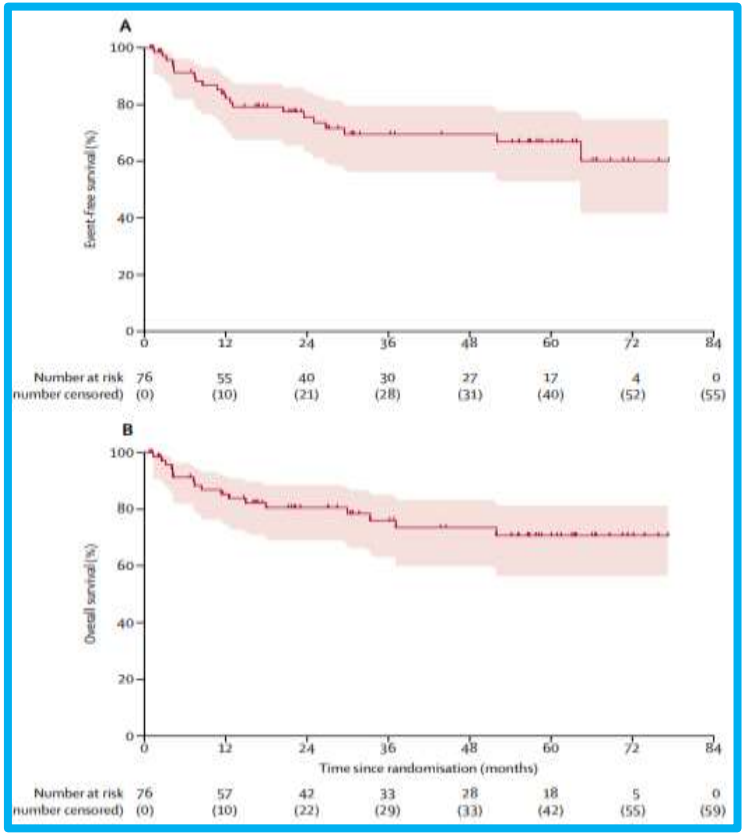
Among *IKZF1-plus* cases, 4 acquired *ABL1* mutation

Foa R, et al. *N Engl J Med*. 2020;383:1613-1623.

HyperCVAD + ponatinib in Ph+ ALL

Parameter	n/N (%)
CR*	65/65 (100)
MMR	74/76 (97)
CMR	63/76 (83)
MRD flow negativity†	74/75 (99)
Early death	0 (0)

*Eleven patients in CR at start;
†One patient with no sample.

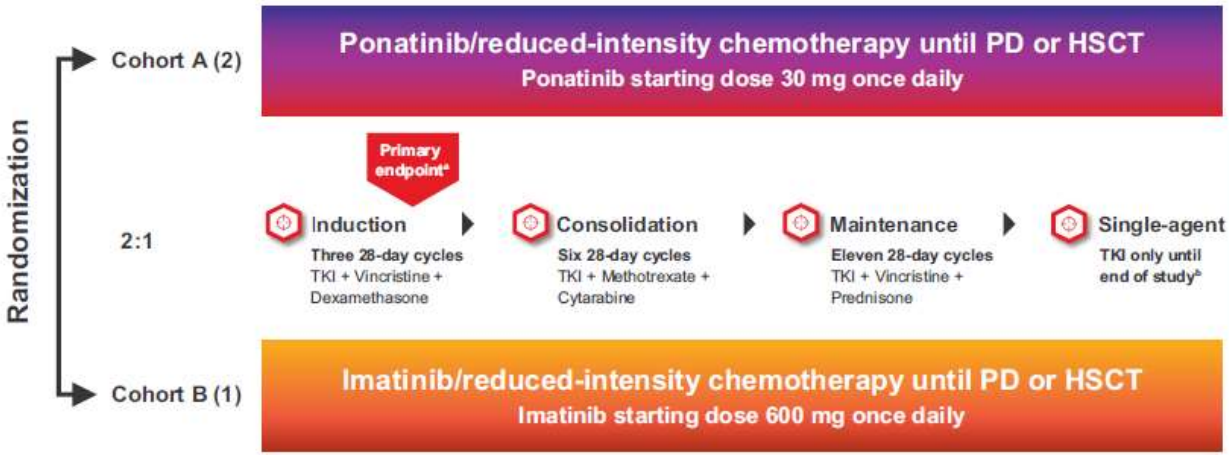


Ponatinib 45 mg is indicated for adult patients with Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the *T315I* mutation.

Jabbour E, et al. *Lancet Haematol*. 2018;5:e618-e627.

PhALLCON Phase III trial

Figure 1. Study Design



[a] Primary endpoint: Minimal residual disease–negative (BCR-ABL1/ABL1 ≤0.01%) CR at the end of induction

[b] Following 20 cycles of reduced-intensity chemotherapy regimen, single-agent TKI to be administered continuously until patients have completed the study, experienced relapse from CR or PD, have an unacceptable toxicity, withdraw consent, proceed to HSCT or alternative therapy, or sponsor terminates the study

- **Sample size:** 230 to 320 patients, aged ≥18 years

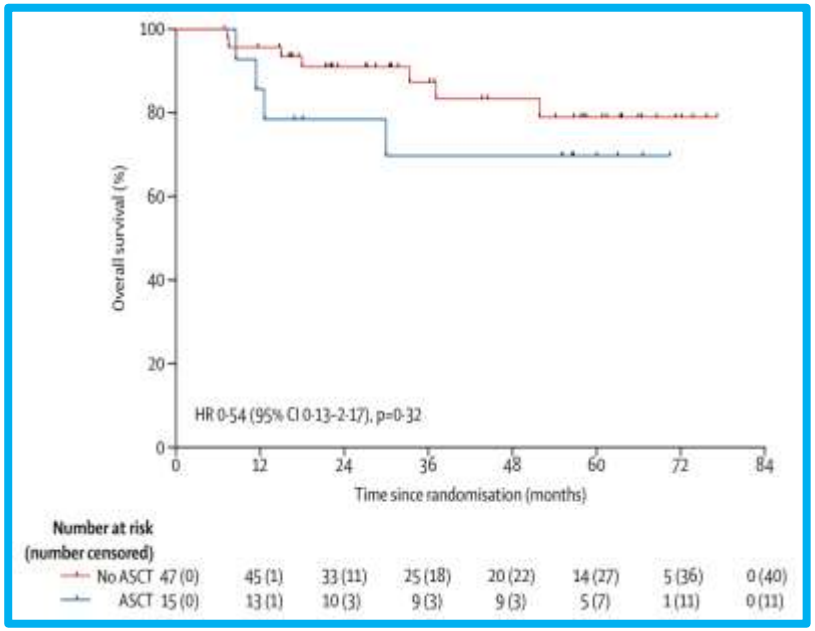
PD, progressive disease.

Ponatinib 45 mg is indicated for adult patients with Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the *T315I* mutation.

Jabbour E, et al. Poster presentation at ASH 2020. Abstract 1026.

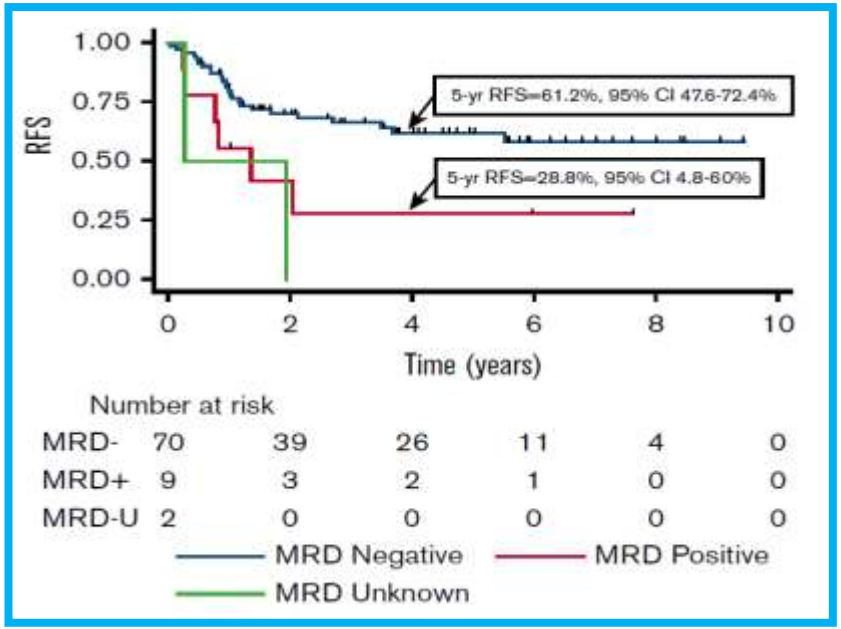
Indication of HSCT in patients in molecular response

No



Jabbour E, et al. *Lancet Haematol*. 2018;5:e618-e627.

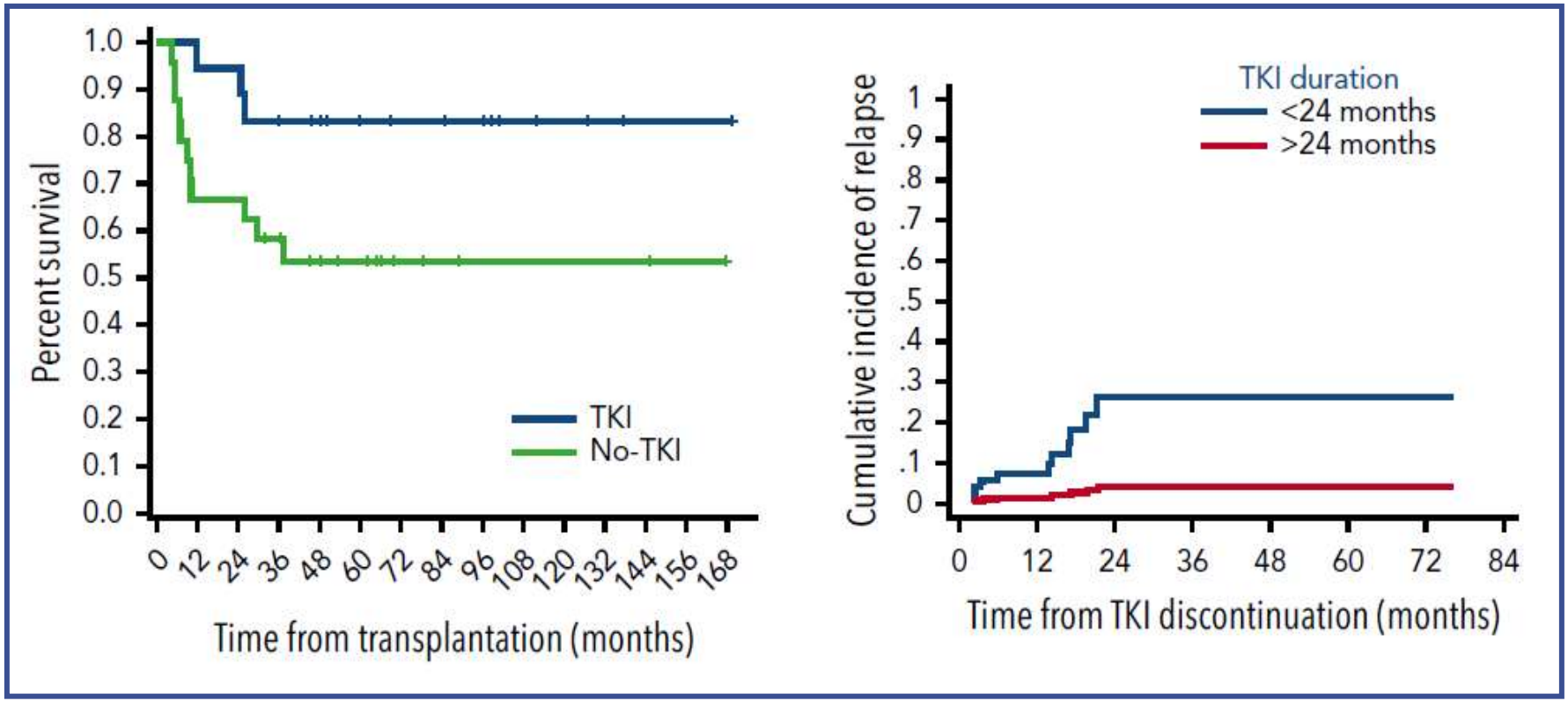
Yes



Webster JA, et al. *Blood Adv*. 2020;4:5078-5088.

GRAALL 2020: randomized study alloHSCT vs CHT in patients in CMR

Prophylactic TKI after alloHSCT: MDACC experience

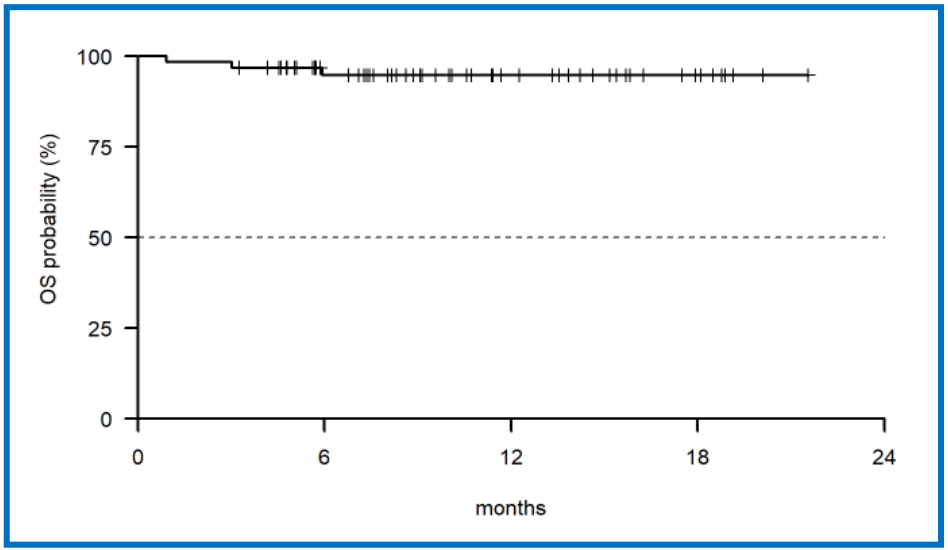


Saini N, et al. *Blood*. 2020;136:1786-1789.

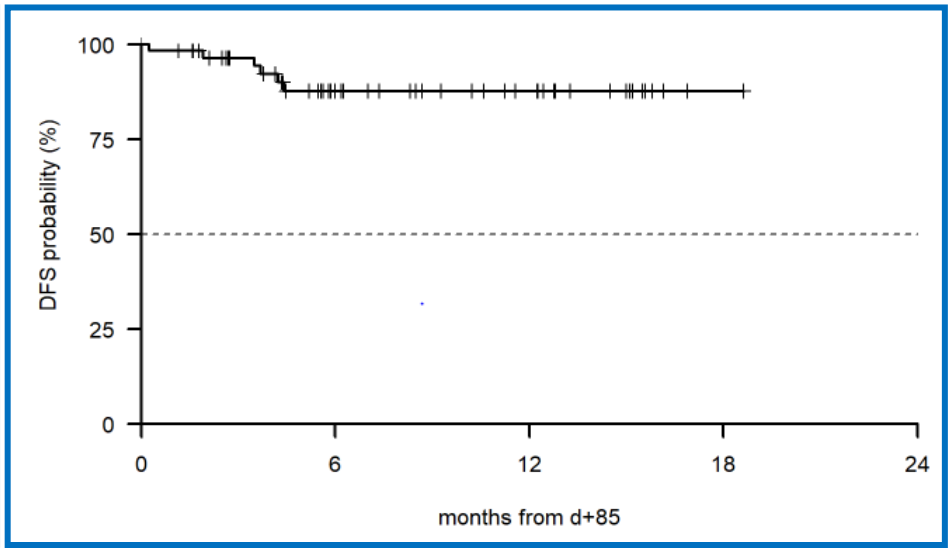
Dasatinib-blinatumomab in Ph+ ALL

- 63 pts, median age 54 yr (24–82)
- Dasatinib 140 mg/D × 3 mo; add blinatumomab × 2–5
- Overall molecular response at day 85 (**dasatinib** + steroids)**: 29%**
- Overall molecular response after cycle 2 of **blinatumomab**: **60%**

OS

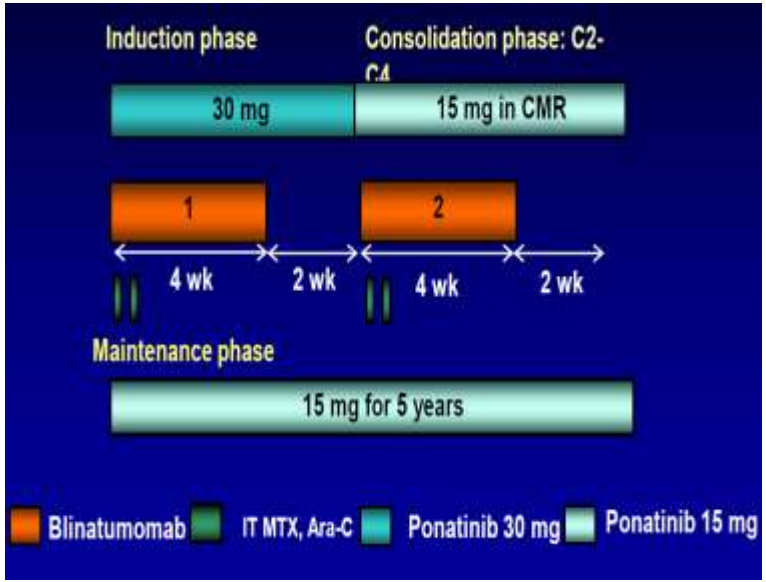


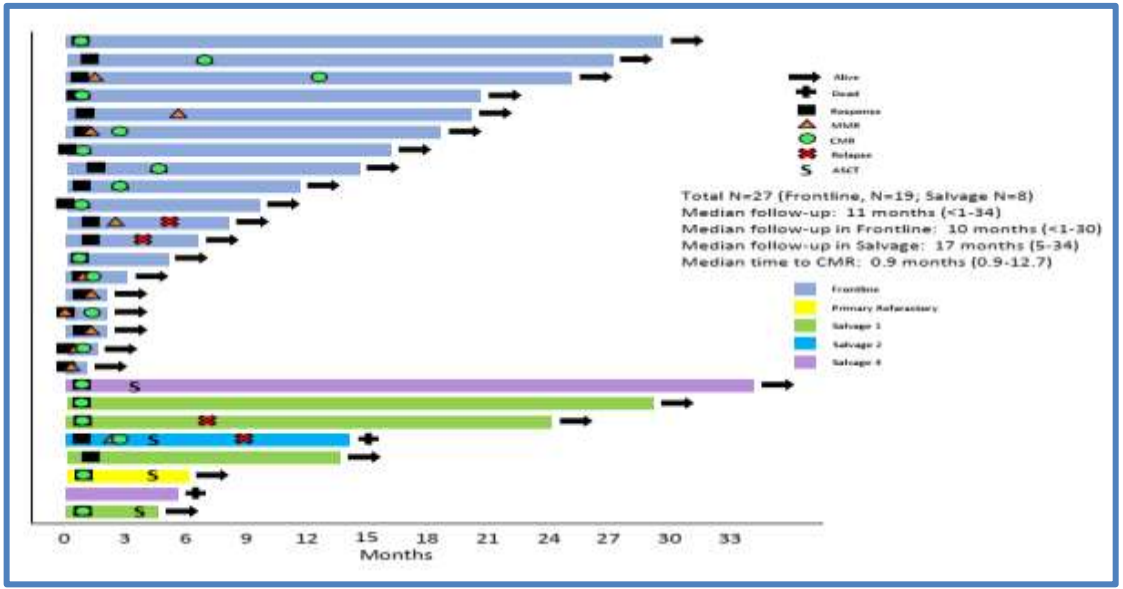
DFS



Foa R, et al. *N Engl J Med*. 2020;383:1613-1623.

Ponatinib + blinatumomab (N = 27; 19 in CR1)





IT MTX, intrathecal methotrexate; wk, week.

Clinical study data not approved by any HAs.

Ponatinib 45 mg is indicated for adult patients with Ph+ ALL who are resistant to dasatinib; who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate; or who have the *T315I* mutation.

Short N, et al. ASCO 2021. Abstract 7001.

Concluding remarks

- Imatinib or dasatinib concurrent with chemotherapy (intensive, attenuated, or minimal) from diagnosis: standard of care in Ph+ ALL. Promising results with ponatinib upfront
- Allogeneic HSCT generally indicated in fit patients. TKI after HSCT given to most patients. Caveats on the need of alloHSCT in CMR patients treated upfront with potent TKI ± immunotherapy
- Comparative studies with ponatinib vs first- or second-generation TKI underway or in preparation
- Combinations with TKI and immunotherapy with low/minimal chemotherapy show short-term promising results

Ph-like ALL

ALL BCR-ABL like/Ph like: Subtypes and age distribution

Spectrum of kinase alterations

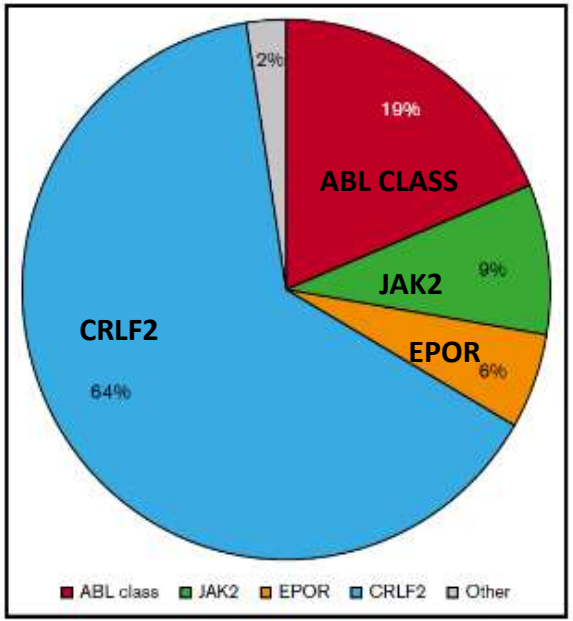
JAK/STAT pathway

- CRLF2 (±JAK point mut)
- JAK2
- EPOR
- Others

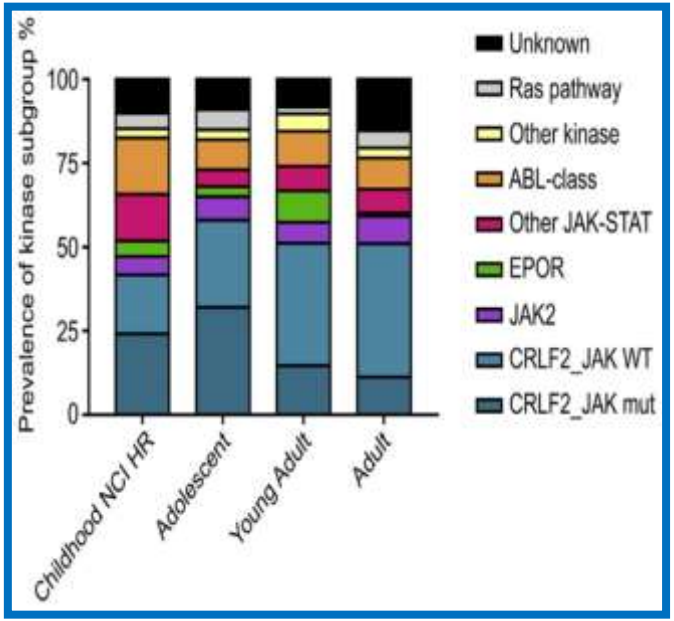
ABL class rearrangements

- PDGFRB
- ABL1
- ABL2
- CSF1R

N = 2506

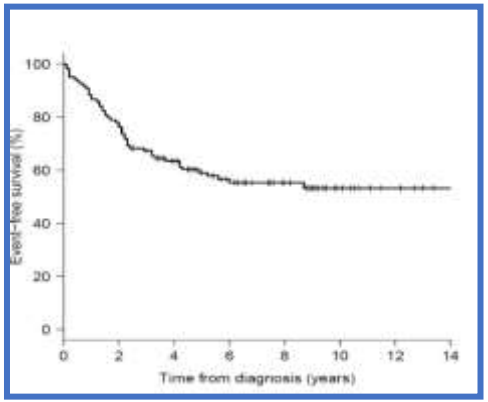


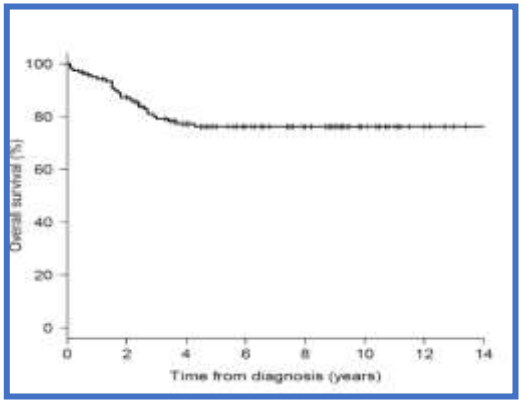
Harvey RC, Tasian SK. *Blood Adv*. 2020;4:218-228.

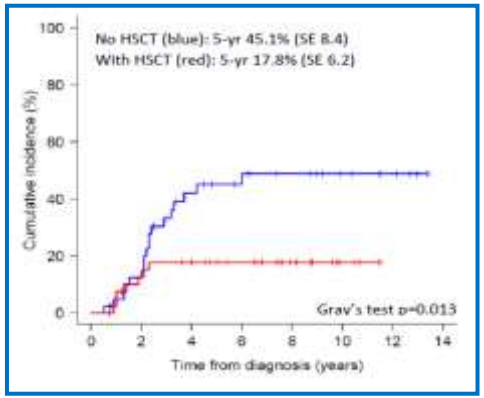


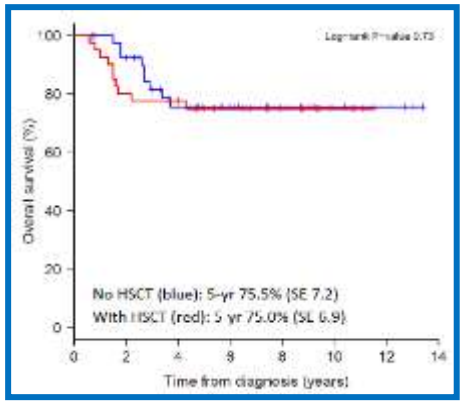
Roberts KG. *Best Pract Res Clin Haem.* 2017;30:212-221.

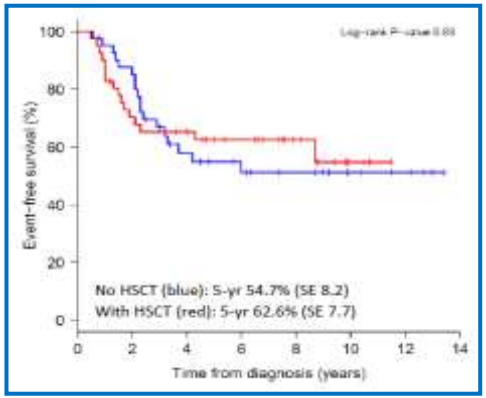
HSCT in Ph-like ALL with ABL class fusion in children in pre-TKI era:
International study of the Ponte di Legno Group





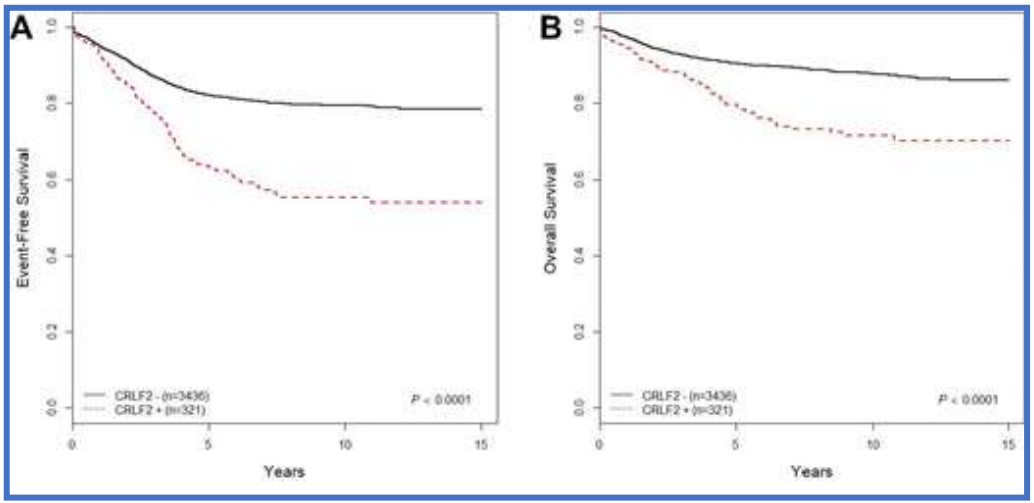


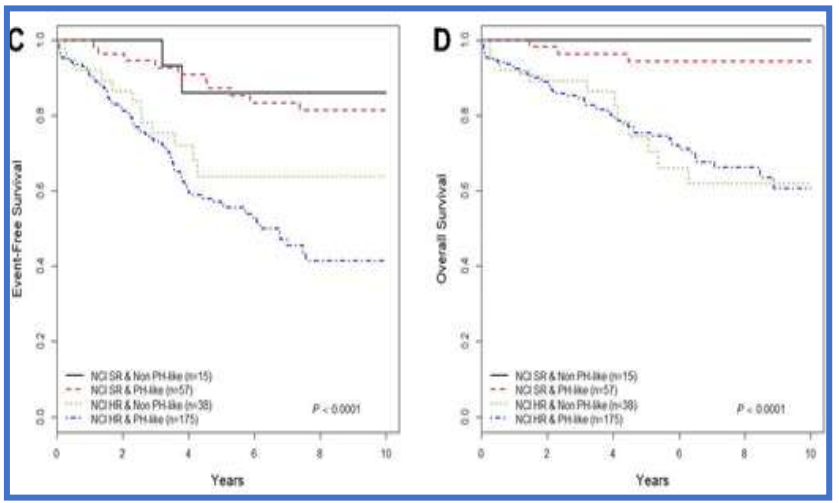




den Boer ML, et al. *Lancet Haematol*. 2021;8:e55-e66.

Outcomes of children/AYA with *CRLF2*+ Ph-like ALL treated with chemotherapy (COG data)





Tasian SK, et al. *Blood*. 2020;136(suppl 1): 45-46.

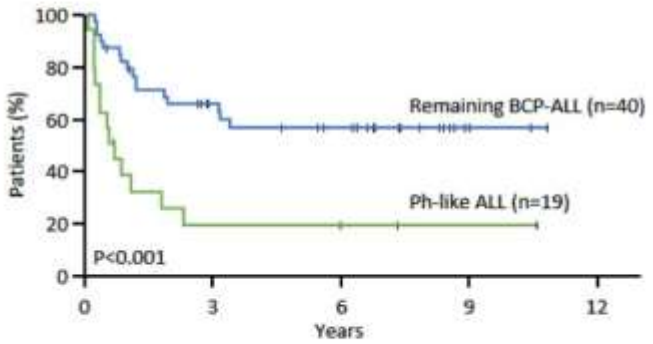
Results in adult Ph-like ALL

Author, year	Age group	Total patients and frequency of Ph-like ALL	5-year survival (EFS or OS)
Roberts et al 2014	16-20 21-39	77 (21%) 46 (27%)	EFS 41%, OS 66% EFS 24%, OS 26%
Herold et al 2014	16-20 21-39 40-55 55-84	5 (19%) 12 (18%) 4 (9%) 5 (7%)	DFS (all ages) 19% OS (all ages) 22%
Boer et al 2015	16-20 21-39 40-71	6 (25%) 9 (19%) 6 (11%)	EFS (all ages) 24% OS (all ages) 30%
Jain et al 2017	15-39 40-84	33 (42%) 16 (24%)	OS (all ages) 23%
Roberts et al 2017	21-39 40-59 60-86	96 (28%) 62 (20%) 36 (24%)	EFS 24% EFS 21% EFS 8%

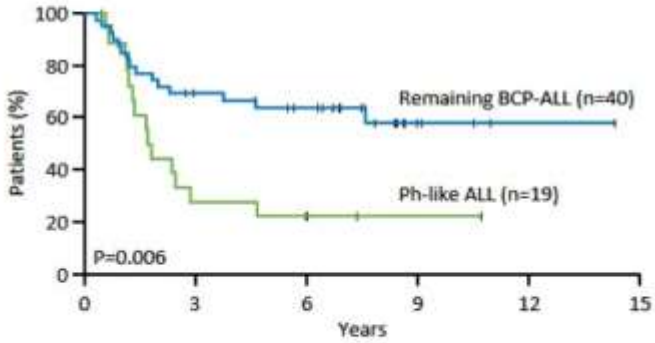
Ph-like ALL outcome in adults

GMALL: 06/99 & 07/03[1]

DFS

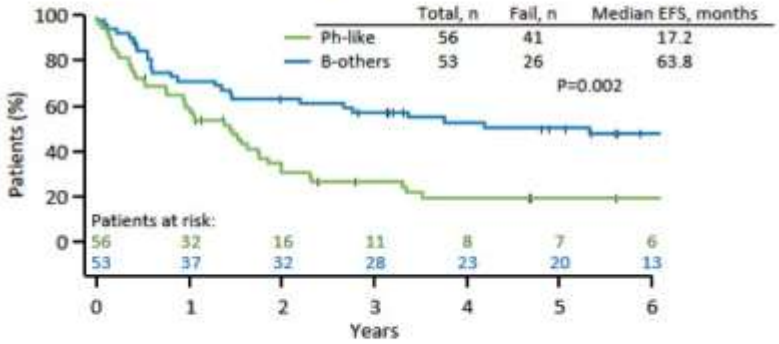


OS

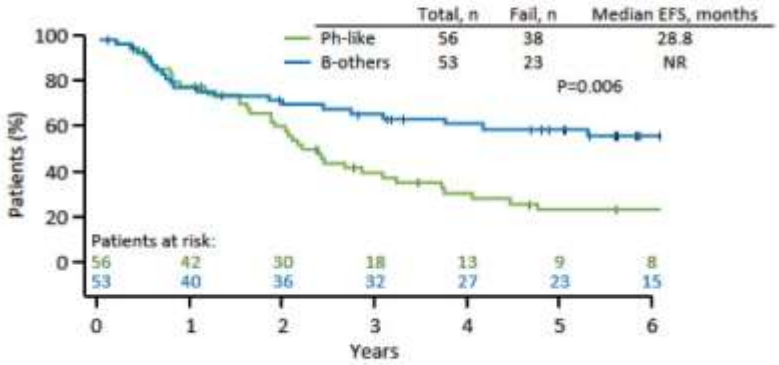


MDACC: HyperCVAD/A-BFM[2]

EFS



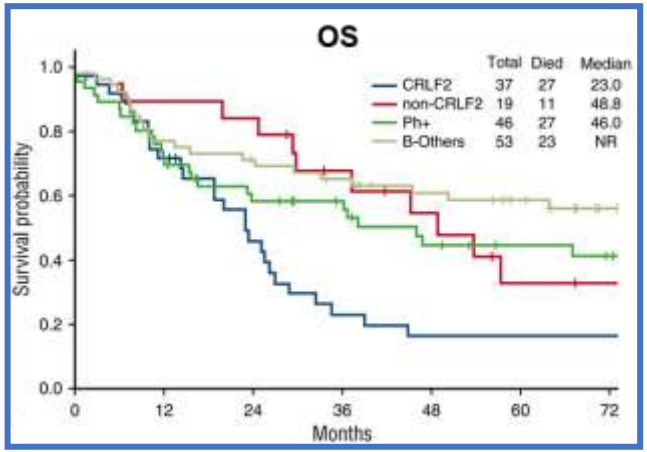
OS

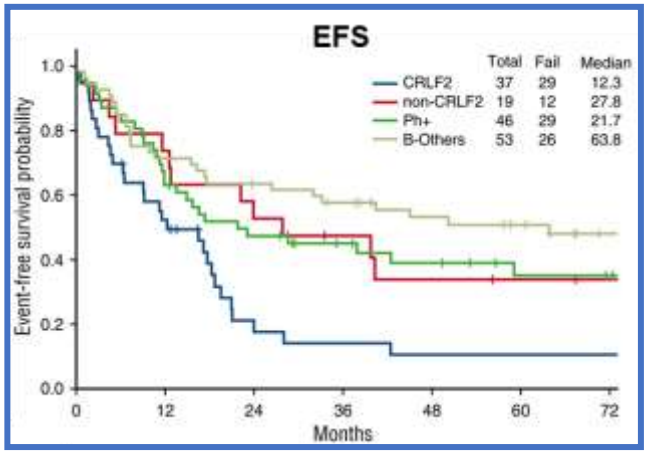


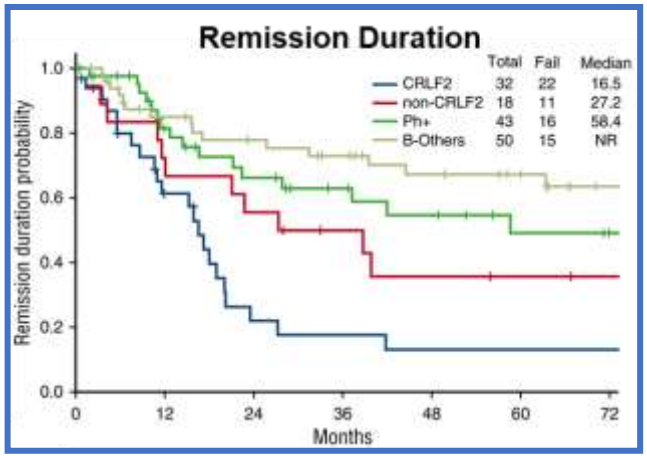
1. Herold T, et al. Haematologica 2017;102:130–8;
2. Jain N, et al. Blood 2017;129:572–81.

NR, not reached.

OS, EFS, and remission duration, *CRLF2*/non-*CRLF2* Ph-like vs others







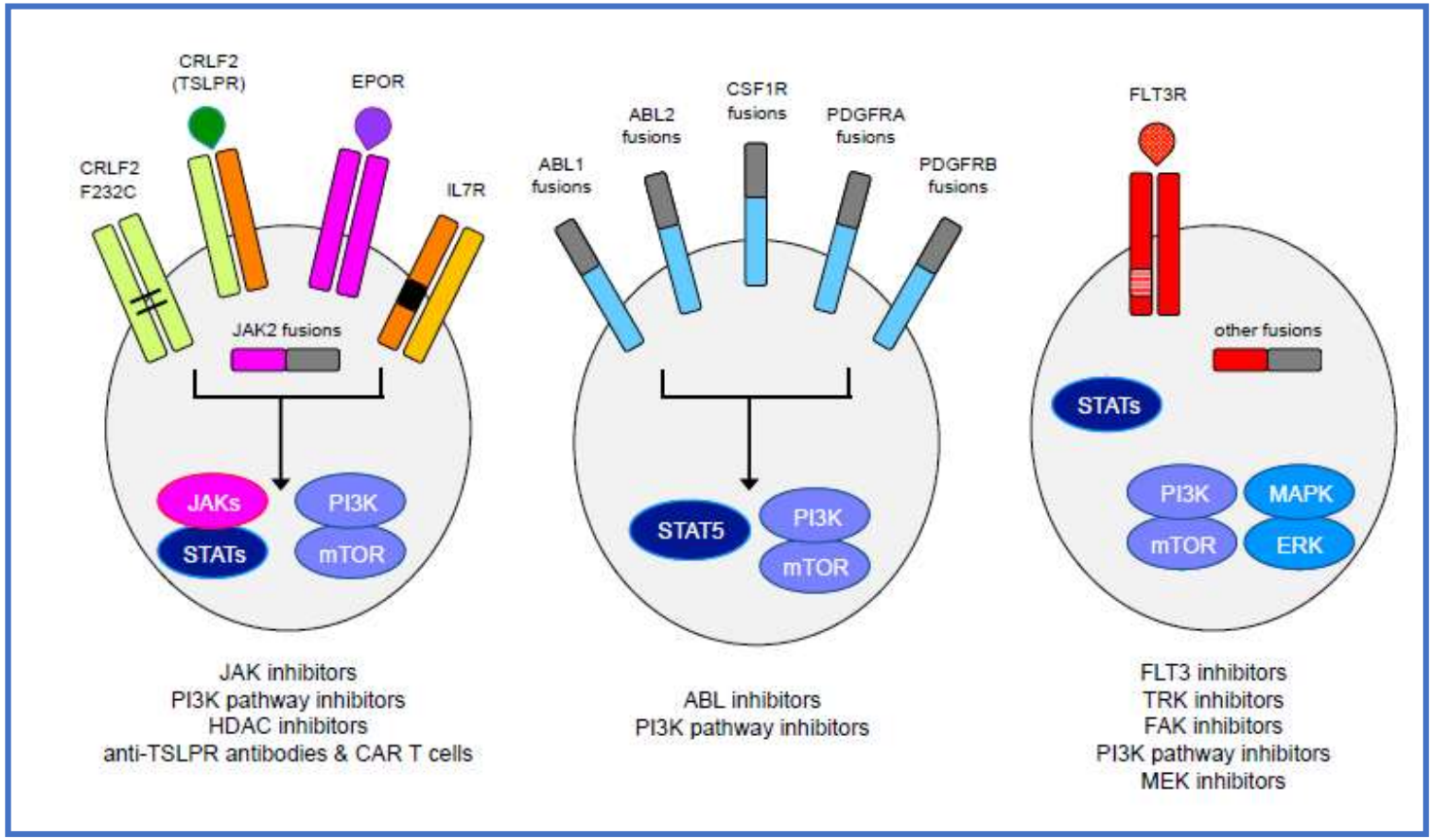
OS:
CRLF2 vs B-other, *P* =.001
CRLF2 vs non-*CRLF2*, *P* =.01

EFS:
CRLF2 vs B-other, *P* =.001
CRLF2 vs non-*CRLF2*, *P* =.01
CRLF2 vs Ph+, *P* =.02

Remission duration:
CRLF2 vs B-other, *P* <.001
CRLF2 vs Ph+, *P* =.001
Non-*CRLF2* vs B-other, *P* =.03

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

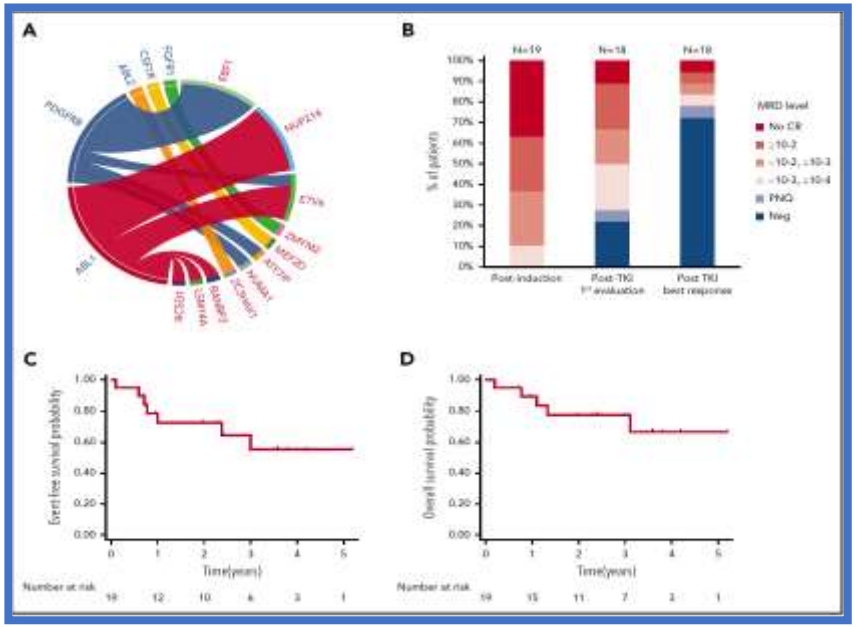
Therapeutic targets



Tasian SK, et al. *Blood*. 2017;130:2064-2072.

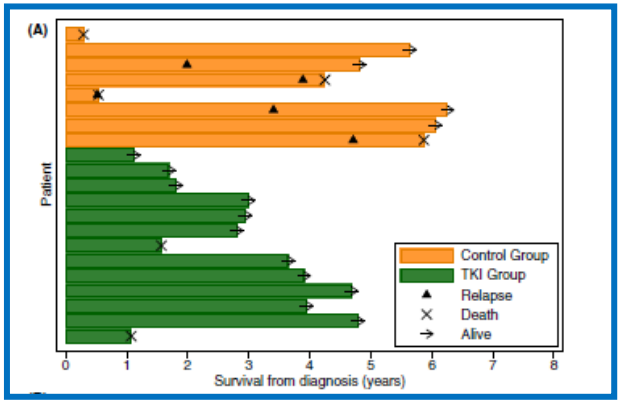
Adjuvant TKI in Ph-like ALL with ABL class fusion

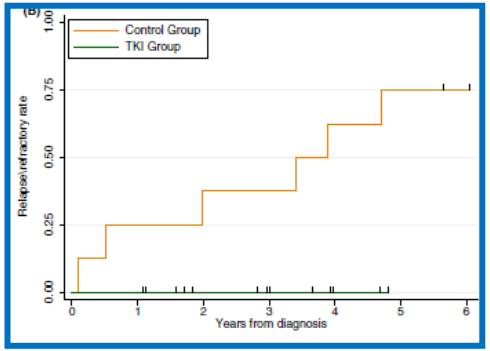
Adults

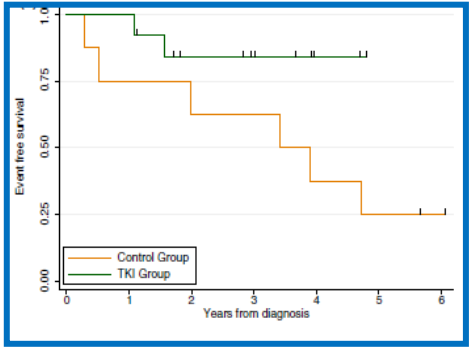


Tanasi I, et al. *Blood*. 2019;134:1351-1355.

Children and AYA







Moorman AV, et al. *Br J Haematol*. 2020;191:844-851.

Ongoing clinical trials in Ph-like ALL

NCT number	Group	Schedule	Phase	No. of pts	Age, yr	Status
02883049	COG	Dasatinib/Ruxolitinib	3	5956	1-30	Not recruiting
02723994	COG	Ruxolitinib	2	170	1-21	Recruiting
03117751	SJCRH	Dasatinib/Ruxolitinib	2/3	1000	1-18	Recruiting
02420717	MDACC	Dasatinib/Ruxolitinib	2	92	≥10	Not recruiting
03571321	Univ Chicago	Ruxolitinib	1	15	18-39	Recruiting
03643276	AIEOP/BFM	Bortezomib/Blina	3	5000	≤17	Recruiting
02716233	Hôpitaux de Paris	Imatinib	3	1578	1-18	Recruiting
03007147	COG/EsPhALL	Imatinib	3	700	2-21	Recruiting
03564470	Guangzhou	Chidamide/Dasatinib	2	120	14-55	Unknown

Expected to be opened soon

- Imatinib + CHT vs blinatumomab + CHT. International EsPhALL/COG AALL2131 phase 3 trial for ABL class pts
- Phase 1 CAR T for R/R *CRLF2*+ pts (NIH)

ClinicalTrials.gov. Accessed on November 28, 2020. Ribera JM. *Haematologica*. 2021 (in press).

Ph-like ALL: Concluding remarks

- Frequent in AYA and adults (15%–25%), especially in Latinos
- No universally accepted diagnostic tool
- Resistant to standard chemotherapy (CR 70%–80%, end-induction MRD+ ≥70%)
- Role of alloHSCT in CR1 unclear (only for MRD+ pts?)
- Some activity of TKI in cases with ABL class fusion in uncontrolled studies
- TKI, JAK inhibitors, proteasome inhibitors and immunotherapy are investigated in clinical trials

Q

Question #1

- What is the genetic lesion that confers poor prognosis in patients with Ph+ ALL treated with dasatinib and blinatumomab upfront?
  - Duplication of Ph chromosome
  - *IKZF1* plus
  - *CDKN2A/B* rearrangement
  - Monosomy 7 added to Ph chromosome
  - None of the above

Q

Question #2

- Which of the following drugs is not investigated in clinical trials in patients with Ph-like ALL?
  - Imatinib
  - Dasatinib
  - Ruxolitinib
  - Blinatumomab
  - Gilteritinib

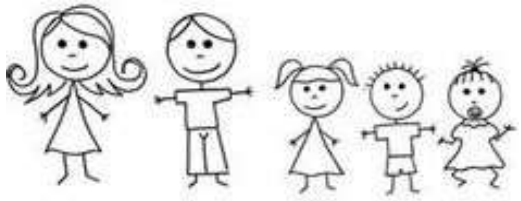
Global Leukemia Academy

AYA ALL Patients – What Is the Current Treatment Approach for This Diverse Patient Population?

Lia Gore

APTITUDE HEALTH

Adolescents and Young Adults With Acute Lymphoblastic Leukemia: Current Treatment Approaches



Prof Lia Gore, MD
Chief, Pediatric Hematology/Oncology/Bone Marrow Transplant-Cellular Therapeutics
University of Colorado School of Medicine and Children's Hospital Colorado

Success in Treating the Most Common Childhood Cancer

- 1948 – first case of temporary remission reported by Farber et al
- Successive generations of treatment show improved outcomes
- Current regimens offer survival of 90%–99% for most patients

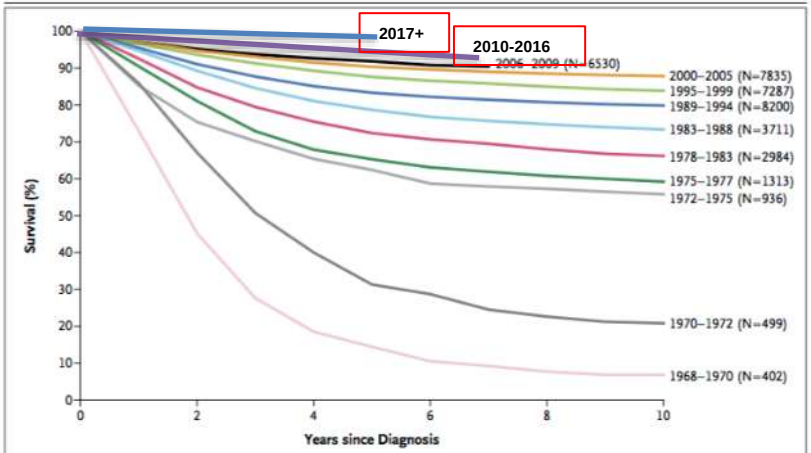
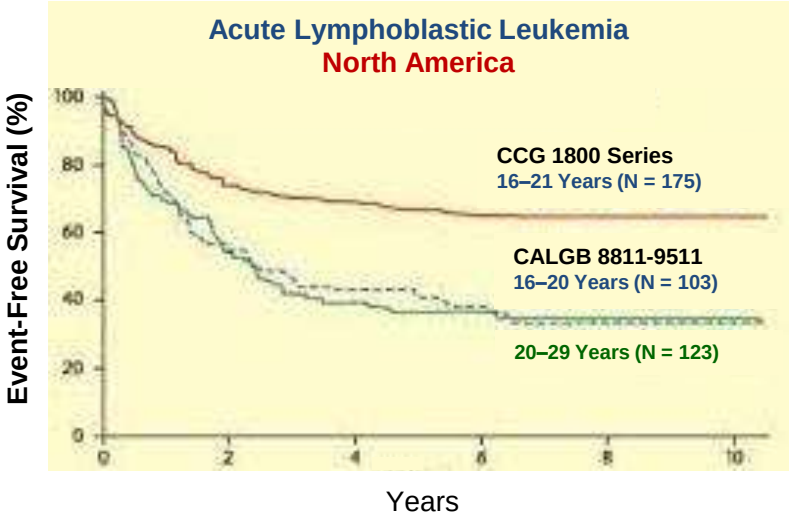


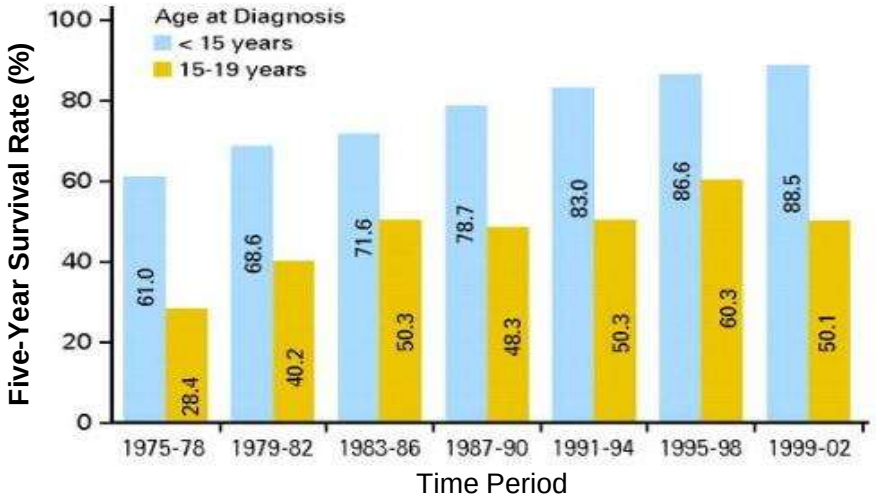
Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.

Hunger SP, Mullighan CG. *N Engl J Med.* 2015;373(16):1541-1552.

Outcomes Are Not as Good for Adolescents and Young Adults

- Older AYA patients do less well than younger AYA patients
- Outcomes depend on the site where a patient is treated





Stock W, et al. *Blood.* 2000;69:467a; Smith MA, et al. *J Clin Oncol.* 2010;28(15):2625-2634.

Outcomes for Patients With Favorable Genetics and CNS1 in Current COG Trials, Even for AYA Patients

NCI Risk	Day 8 MRD	Day 29 MRD	5-Year EFS	5-Year OS	n
Standard	<1%	<0.01%	95.7%	99.1%	1129
Standard	≥1%	<0.01%	91.7%	99.4%	170
Standard	Any	≥0.01%	88.1%	96.8%	369
High	<1%	<0.01%	94.9%	98.1%	243
High	≥1%	<0.01%	93.6%	95.5%	50
High	Any	≥0.01%	75.4%	90.4%	121

	Age <10 yr N = 107 (44%)	**Age ≥10 yr** N = 136 (56%)	***P* Value**
5-year EFS	98.0%	92.4%	.126
5-year OS	98.7%	97.8%	.411

CHILDREN'S ONCOLOGY GROUP

Raetz E, et al. ASH 2015. Abstract 807.

Observations on AYA Patients in Oncology

- Adolescence is a major developmental milestone with different needs and requirements
- AYAs have different needs compared with toddlers and young children and adults over the age of 40
- Many AYAs with leukemia are diagnosed at adult-focused facilities and referred to oncologists who primarily care for adult cancer patients
- ALL represents a small fraction of adult cancers, and thus providers generally are more focused on the more common solid tumor diagnoses
- Adult-focused providers are split into “hematology” and “oncology” and supportive services are much more limited compared with pediatric facilities (psychological, social, educational, financial, and insurance)

Issues Affecting AYA Patients

- Toxicity is increased and tolerability is decreased compared with children less than 10–12 years of age at diagnosis when treated on the same regimens

- Supportive care and psychosocial issues
  - School and work
  - Friends/social circles
    - Forced dependence in a time of evolving independence
  - Insurance status and financial stressors

- Late effects and survivorship
  - Endocrine – growth, thyroid, metabolic syndrome, sexual health and fertility
  - Cardiac – anthracycline exposure
  - Orthopedic – steroid choice/outcomes/joint toxicity
  - Neuropsychologic

Current/Recent COG Trials for AYA ALL Frontline and Relapse

	Trial	Disease	Primary Objective	Status
New Diagnosis	AALL1732*	Newly diagnosed HR B-ALL	Randomized trial of inotuzumab added to standard chemotherapy*	Age 1 to 31
	AALL1721	Newly diagnosed VHR B-ALL	Efficacy of CAR T in CR1	Age 1 to 25
	AALL1631	Newly diagnosed Ph+ ALL (to add Ph-like B-ALL with ABL1-class alterations)	Randomized trial of imatinib added to AALL0232 vs EsPhALL backbone	Age 1 to 21
	AALL1521	Newly diagnosed Ph-like B-ALL with JAK-STAT pathway alterations	Safety/efficacy of adding ruxolitinib to AALL1131 chemotherapy	Age 1 to 21
Relapse	AALL1331	First-relapse B-ALL	Randomized trial of blinatumomab vs chemotherapy	Complete/ Closed
	AALL1621	Second/greater-relapse B-ALL	Safety and efficacy of inotuzumab	Open up to age 21 at enrollment
	AINV18P1	First-relapse T-ALL/Lly and Second/greater-relapse B-ALL	Safety of palbociclib + chemotherapy	Open up to age 30 at enrollment
	AALL1821	First-relapse B-ALL	Safety and efficacy of blinatumomab + nivolumab	Open up to age 18 or 21 at enrollment

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*First study to include an embedded adherence study for chemo compliance.

Studies for AYA Patients in ALL

- **Study ACCL16N1:** Documentation and Delivery of Guideline-Consistent Treatment in AYA ALL
  - Cross-network study to evaluate quantitative and qualitative barriers and facilitators of documentation and delivery of treatment concordant with NCCN guidelines among AYAs diagnosed with ALL at an NCORP sites
- Collaboration between ALL and AYA committees to standardize the inclusion of patient-reported outcomes
- **Study ACCL1931:** Randomized study of L-carnitine for prevention of PEG-asparaginase–induced hepatopathy in AYAs treated for ALL
  - Co-developed with the Alliance for cross-group enrollment
- **Study E1Q11:** An NCTN-wide study that seeks to support AYAs in improving reproductive health after cancer treatment
- Stem Cell Transplantation Committee study assessed the frequency of developing acute and chronic GVHD in younger (age 2–12) vs older (age 13–30) patients following matched unrelated BMT in patients with ALL treated on 4 COG HSCT trials
  - **AYAs had a significantly increased risk of grade 2–4 GVHD compared with younger children**[1]

1. Andolina JR, et al. *Biol Blood Marrow Transplant.* 2020;26(3):S184.

Status of AYA Patients in ALL Trials: Late Effects

- **ALTE11C2:** Cross-sectional cohort approach to evaluate the late protective impact of dexrazoxane on left ventricular function
- **ALTE1621:** Randomized clinical trial evaluating secondary prevention of left ventricular dysfunction by carvedilol in at-risk survivors
- **ALTE11C1:** Longitudinal ovarian reserve after treatment with alkylators for lymphoma
  - Results are being used in developing an NCTN-wide study of a gonadotropin-releasing hormone agonist (GnRHa) to preserve fertility in at-risk females

COG AYA Toxicity Initiative

- Focus on identifying differential toxicities experienced by AYAs compared with younger children

- Key findings in ALL patients
  - Identified classic AYA toxicities along with emerging and potentially therapy-altering toxicities, including pancreatitis and thrombosis
  - 59 toxicities were common to either AYA (n = 51) or children (n = 8)
  - 4 unique toxicity signatures
  - Osteonecrosis was a standout late toxicity and was accompanied by a signature suggesting metabolic differences in older vs pediatric patients
  - Patients with osteonecrosis who were older than 10 years showed improved EFS compared with patients without ON (81% vs 65%; *P* <.0001)

- Created the analytic tools to develop unique AYA toxicity and response “signatures” across other malignancies (eg, CNS tumors, sarcomas) and examine therapies that may be responsible for health outcome disparities

Sarangdhar M, et al. *Blood.* 2017;130:2562.

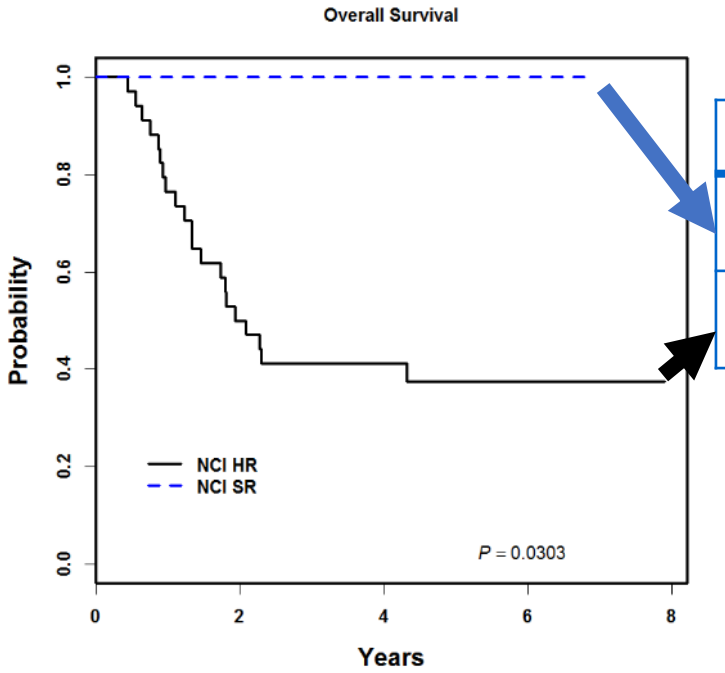
COG AYA Sexual Health Initiative

Accomplishments and current efforts include

- Completed a review, “Sexual health among adolescent and young adult cancer survivors: A scoping review from the Children’s Oncology Group Adolescent and Young Adult Oncology Discipline Committee”
- Completed data analysis for a COG-wide survey exploring clinician communication practices and education needs around sexual health
- Developing clinician education modules on sexual health issues relevant to the AYA cancer patient, including best practices in communication
  - Goal to conduct cognitive interviews on content and pilot study
- Identifying relevant sexual health data points that will be recommended for inclusion in future AYA-focused clinical trials

Cherven B, et al. *CA Cancer J Clin.* 2020;0:1-14.

Overall Survival After Induction Failure, by (M3) Marrow Status



	5-yr OS ± SE
AALL0331 (SR)	100%
AALL0232 (HR)	37.4% ± 10.5%

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AALL0232 PI: Eric Larsen, MD
AALL0331 PI: Kelly Maloney, MD

Will Immunotherapy for ALL Improve Outcomes and/or Decrease Toxicity for AYA Patients?

- Cooperative groups worldwide are now introducing various immunotherapy constructs into clinical trials
- Coordination of findings and development of future studies depend on cooperation among investigators and pharmaceutical sponsors globally
- Further implications for
  - Risk stratification
  - Biologic and genetic features of leukemia cells
  - Response kinetics
  - Surrogate and biomarkers of efficacy
  - Tolerability and reduction of toxicities known to be greater in AYAs

Increasing Focus on AYA Needs

- Increasing numbers of survivors of childhood and AYA malignancies are a success story
  - Better outcomes for AYA patients when treated at pediatric centers
- Continued need for studies and care guidelines that address the unique features and needs of AYA patients
- Implications for transition of care to adult and family medicine providers who have been educated in the care of pediatric cancer patients
- Multidisciplinary and cross-disciplinary work is essential

International Cooperation is Essential

Global Leukemia Academy

Break

APTITUDE HEALTH

Global Leukemia Academy

Bispecifics as post-reinduction therapy improve survival in high-risk first-relapse AYA B-ALL

Patrick Brown

APTITUDE HEALTH

A Randomized Phase 3 Trial of Blinatumomab Vs. Chemotherapy As Post-Reinduction Therapy in High and Intermediate Risk (HR/IR) First Relapse of B-ALL in Children and AYAs Demonstrates Superior Efficacy and Tolerability of Blinatumomab

A Report from Children's Oncology Group Study AALL1331

Patrick A. Brown, Lingyun Ji, Xinxin Xu, Meenakshi Devidas, Laura Hogan, Michael J. Borowitz, Elizabeth A. Raetz, Gerhard Zugmaier, Elad Sharon, Lia Gore, James A. Whitlock, Michael A. Pulsipher, Stephen P. Hunger, Mignon L. Loh

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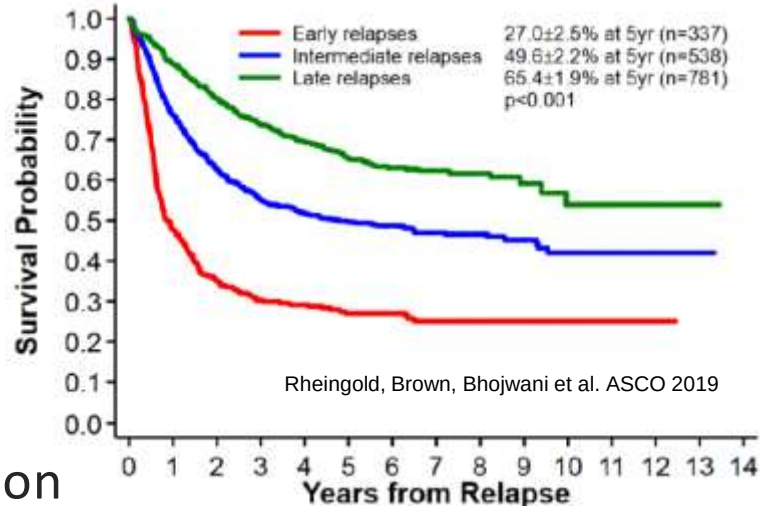
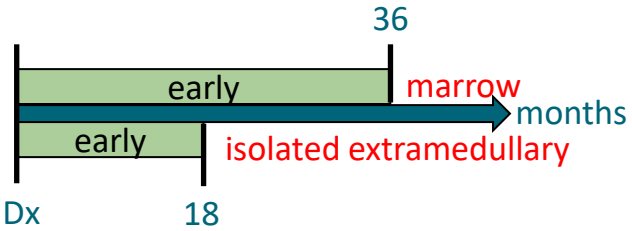
Background

- Poor survival for first relapse B-ALL in children, adolescents and young adults (AYA), especially early relapses



- Standard treatment approach
  - Reinduction chemotherapy -> 2nd remission
  - Consolidation
    - Early relapse: Intensive chemo -> HSCT
      - Goal: MRD-negativity prior to HSCT
    - Late relapse
      - "MRD high": same as early
      - "MRD low": Intensive chemo -> maintenance therapy



How can we improve on this "standard"?

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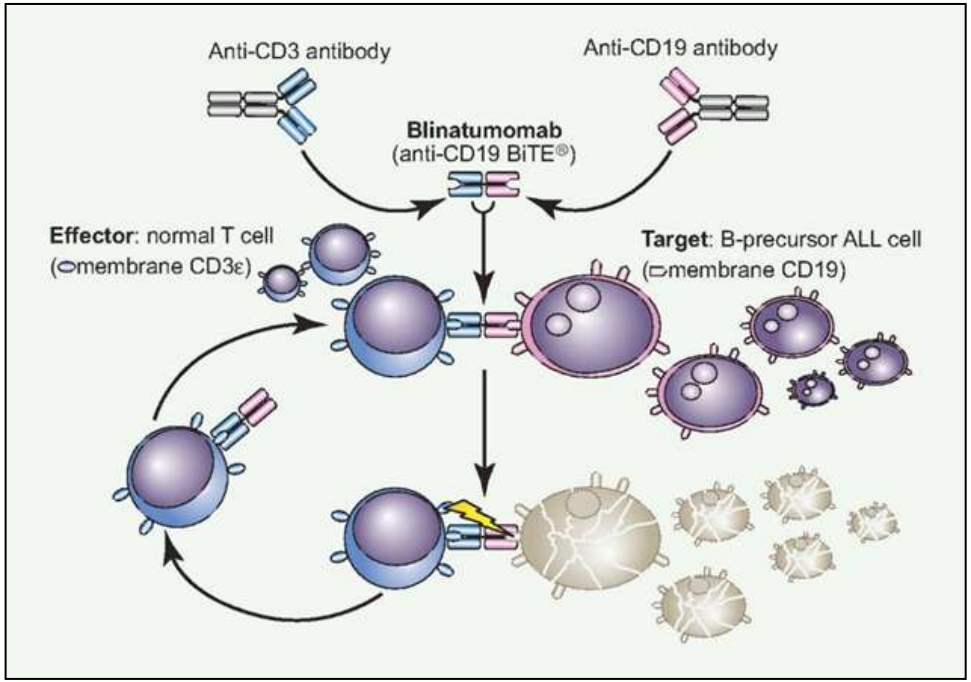
Blinatumomab (CD19 BiTE)



Adapted from Brown P. *Blood.* 2018;131:1497-1498

- In multiply relapsed/refractory setting (pediatrics)
  - CR 35%–40%
  - MRD-negative CR 20%–25%

von Stackelberg et al. JCO. 2016; 34:4381-4389

- In MRD+ setting (adults)
  - 80% MRD clearance
  - 60% subsequent DFS (bridge to HSCT)

Gokbuget N, et al. *Blood.* 2018;131:1522-1531

Objective of COG AALL1331:
To determine if substituting blinatumomab for intensive consolidation chemotherapy improves survival in 1st relapse of childhood/AYA B-ALL

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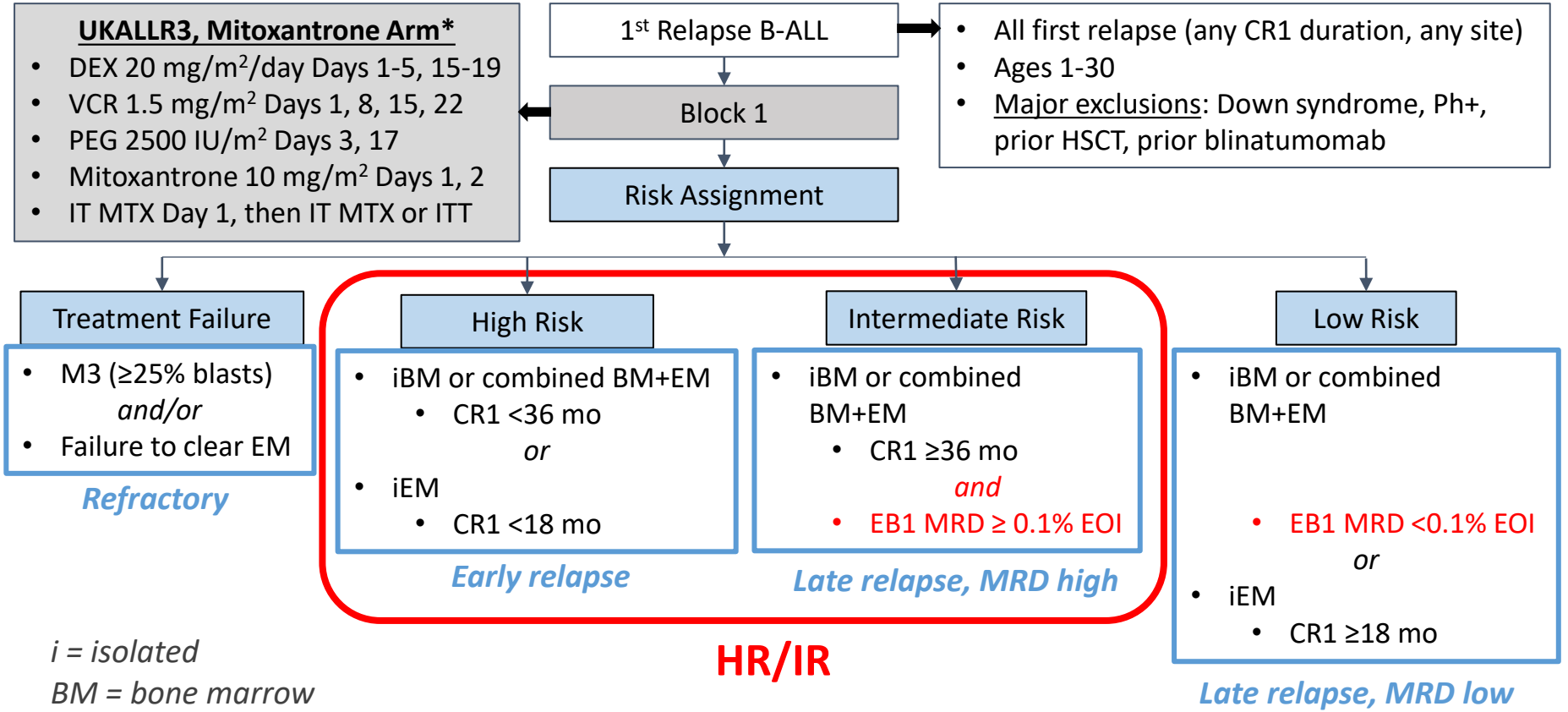


i = isolated
BM = bone marrow
EM = extramedullary (CNS, testes)
CR1 = duration of first remission
EB1 = end-Block 1

*UKALLR3 reference: Parker, et al. *Lancet.* 2010;376:2009-2017.

Brown P, et al. *JAMA*. 2021;325(9):833-842.

Stratifications

- Risk group (HR vs IR)
- For HR:
  - Site (BM vs iEM)
  - For BM: CR1 duration (<18 vs 18-36mo)

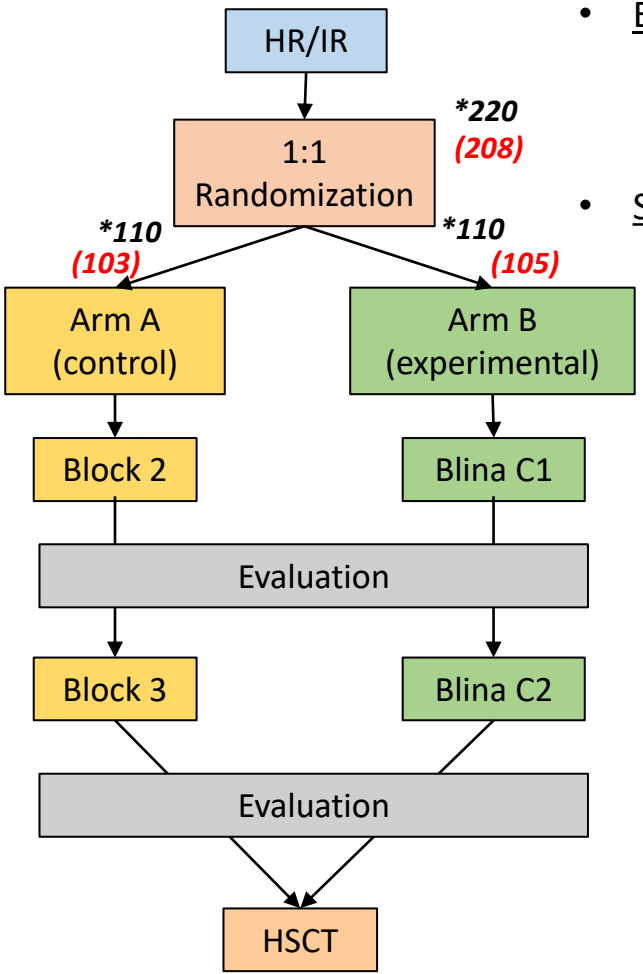
UKALLR3, Block 2*

- VCR, DEX week 1
- ID MTX, PEG week 2
- CPM/ETOP week 3
- IT MTX or ITT

UKALLR3, Block 3*

- VCR, DEX week 1
- HD ARAC, Erwinia Weeks 1-2
- ID MTX, Erwinia Week 4
- IT MTX or ITT

*UKALLR3 reference: Parker, et al. *Lancet*. 2010;376:2009-2017.



- Endpoints
  - Primary: DFS
  - Other: OS, MRD response, ability to proceed to HSCT
- Sample size n=220 (110 per arm)
  - Power 85% to detect HR 0.58 with 1-sided α=0.025
  - Increase 2 yr DFS from 45% to 63%

Blina C1 and Blina C2

- Blinatumomab 15 µg/m^2/day × 28 days, then 7 days off
- Dex 5 mg/m^2/dose × 1 premed (C1 only)

- ***First patient randomized Jan 2015***
- ***Randomization halted Sep 2019 (95% projected accrual)***

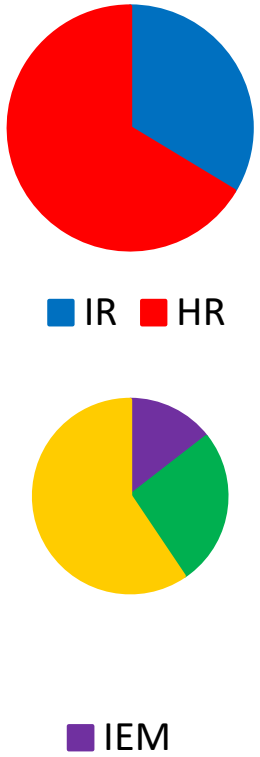
Brown P, et al. *JAMA*. 2021;325(9):833-842.

Early Closure Recommended by DSMC

- Scheduled review by DSMC Sep 2019 using data cut-off 6/30/2019 (~60% of projected events)
- Despite the monitoring threshold for DFS not being crossed, the DSMC recommended
  - Permanent closure of accrual to HR/IR randomization
  - Immediate cross-over to experimental Arm B for patients still receiving therapy
- DSMC recommendation based on
  - The difference in **DFS and OS** between arms
  - The profound difference in **toxicity** between arms
  - The highly significant difference in **MRD** clearance rates between arms

Randomization Stratification Factors

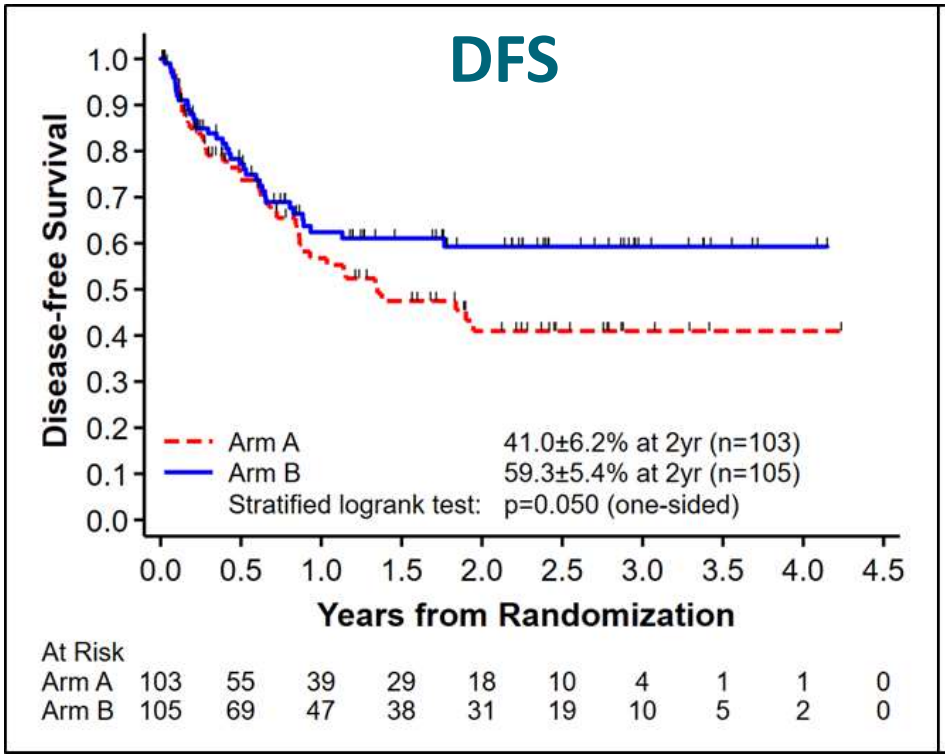
Stratification Factors	Arm A (n=103)	Arm B (n=105)
Risk Group Assignment after Block 1		
Intermediate Risk (late BM relapse, MRD high)	34 (33%)	36 (34%)
High Risk (early relapse)	69 (67%)	69 (66%)
High Risk Subsets		
• Marrow, CR1 <18 months (very early)	18 (26%)	18 (26%)
• Marrow, CR1 18-36 months (early)	41 (59%)	41 (59%)
• IEM, CR1 <18 months	10 (14%)	10 (14%)

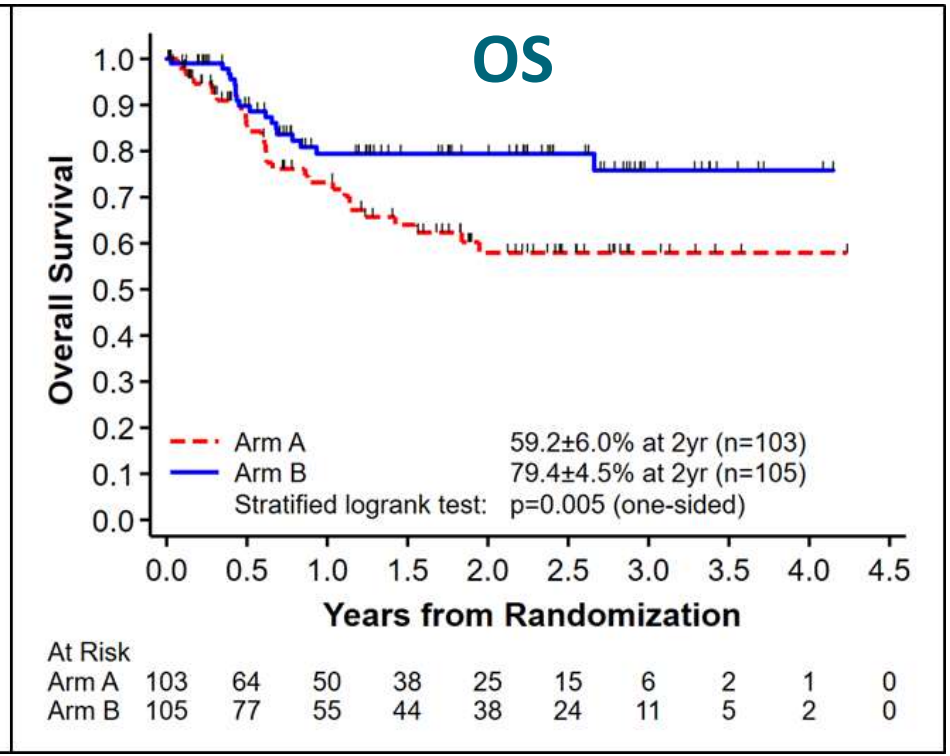


CHILDREN'S ONCOLOGY GROUP

Brown P, et al. *JAMA*. 2021;325(9):833-842.

Survival: Arm A (chemotherapy) vs Arm B (blinatumomab)



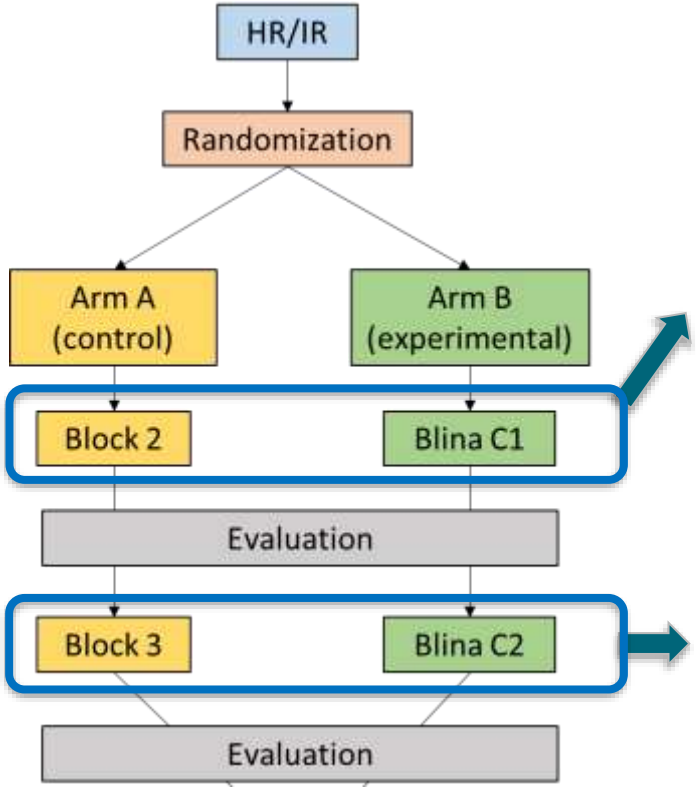


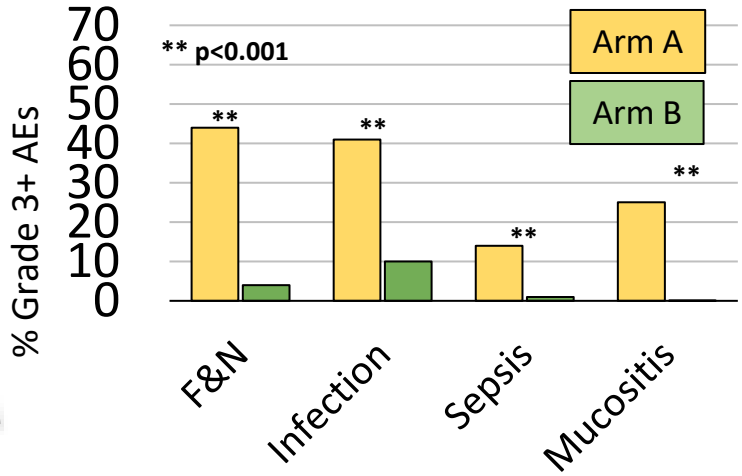
CHILDREN'S ONCOLOGY GROUP

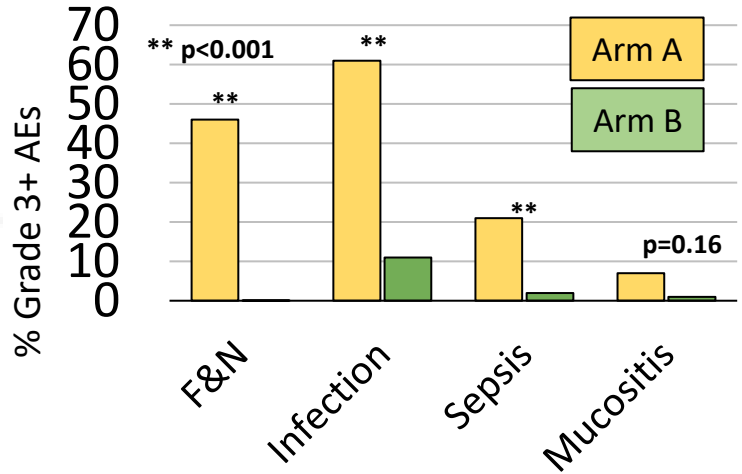
Median follow up 2.9 years

Brown P, et al. *JAMA*. 2021;325(9):833-842.

Adverse Events







- *N=4 post-induction Grade 5 AEs on Arm A (all infections)*
- *N=0 on Arm B*
- *Ages of Arm A deaths: 2, 17, 23, and 26 years old (AYA-skewed)*
- ***NOTE: AE rates significantly higher in AYA (Hogan, et al. ASH Abstract 2018)***

CHILDREN'S ONCOLOGY GROUP

Brown P, et al. *JAMA*. 2021;325(9):833-842.

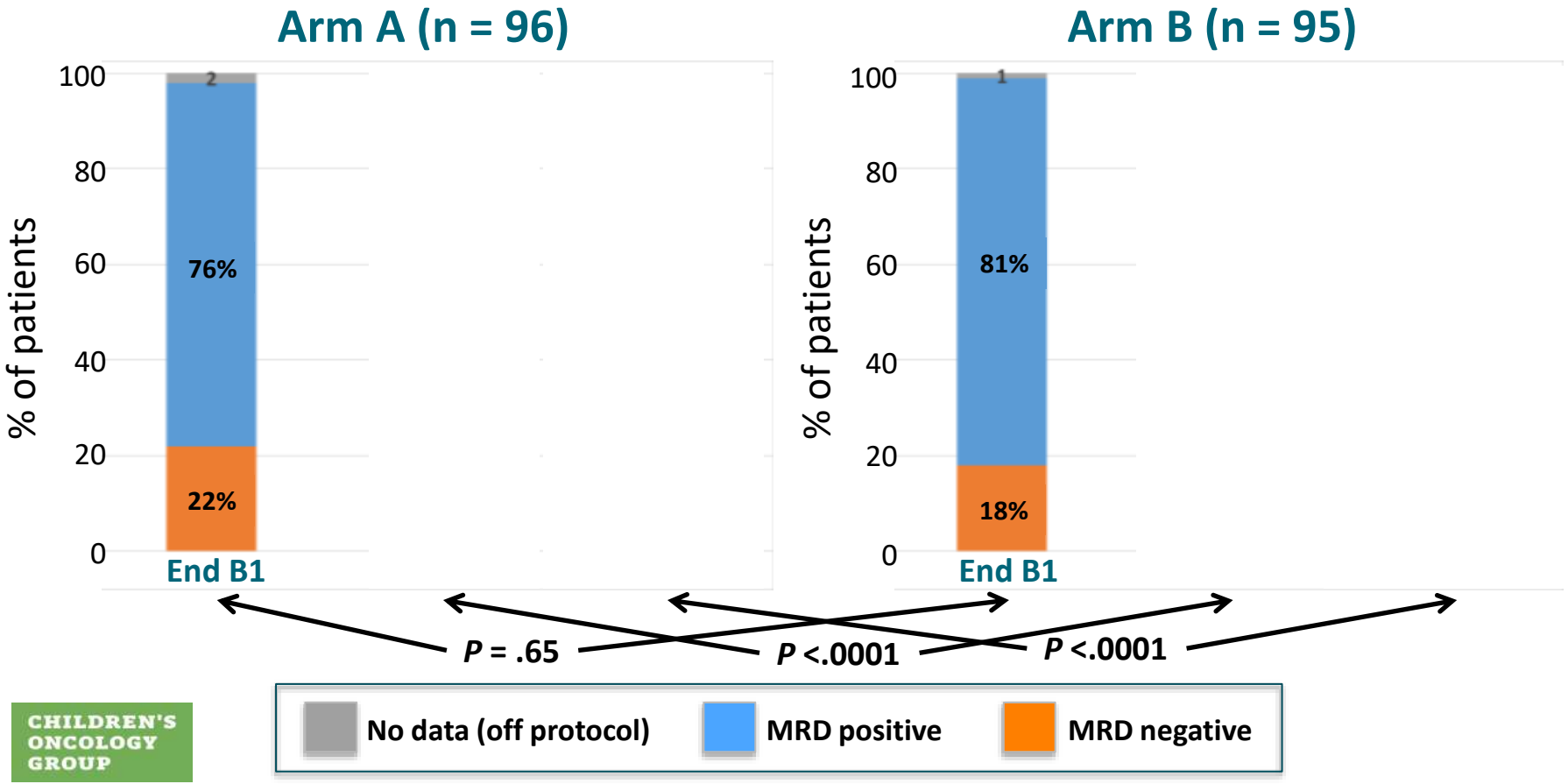
Blinatumomab-Related AEs on Arm B

	Blina C1 (n = 99)		Blina C2 (n = 83)	
Blinatumomab-related AEs	Any grade (%)	Grade 3-4 (%)	Any grade (%)	Grade 3-4 (%)
Cytokine Release Syndrome	22%	1%	1%	0%
Neurotoxicity	18%	3%	11%	2%
Seizure	4%	1%	0%	0%
Other (Encephalopathic)	14%	2%	11%	2%

CHILDREN'S ONCOLOGY GROUP

Brown P, et al. *JAMA*. 2021;325(9):833-842.

MRD Clearance (for iBM and BM+EM)



CHILDREN'S ONCOLOGY GROUP

Brown P, et al. *JAMA*. 2021;325(9):833-842.

Loss of MRD Response: CD19 + or –?

Supplemental Table S7. Arm B Patients Becoming MRD-positive after Blinatumomab Cycle 2

Patient	MRD %			
	End Block 1	End Blina Cycle 1	End Blina Cycle 2	CD19 Expression
1	0.3%	<0.01%	<0.1%*	No data*
2	0.12%	<0.01%	49%	+
3	0.22%	<0.01%	0.054%	+
4	0.25%	<0.01%	0.01%	+
5	0.024%	<0.01%	0.014%	-
6	0.61%	<0.01%	0.11%	+
7	0.026%	<0.01%	0.035%	-
8	5.4%	<0.01%	0.69%	-
9	<0.01%	<0.01%	0.2%	+
10	0.036%	<0.01%	54.3%	-

*MRD <0.1% with sensitivity 1 in 1000 (CD19 expression data not available due to lack of events)

+: CD19 expressed (no antigen loss); -: CD19 not expressed (antigen loss)

- ***There were 7 cases of MRD re-emergence, of which 3 were CD19-negative (antigen loss) and 4 were CD19-positive***
- ***There were 2 relapses, of which one was CD19-negative and one was CD19-positive***

CHILDREN'S ONCOLOGY GROUP

Brown P, et al. *JAMA*. 2021;325(9):833-842.

Outcomes for MRD+ After Blina

Supplemental Table S8. Outcomes of patients who were MRD positive after the second Blinatumomab cycle

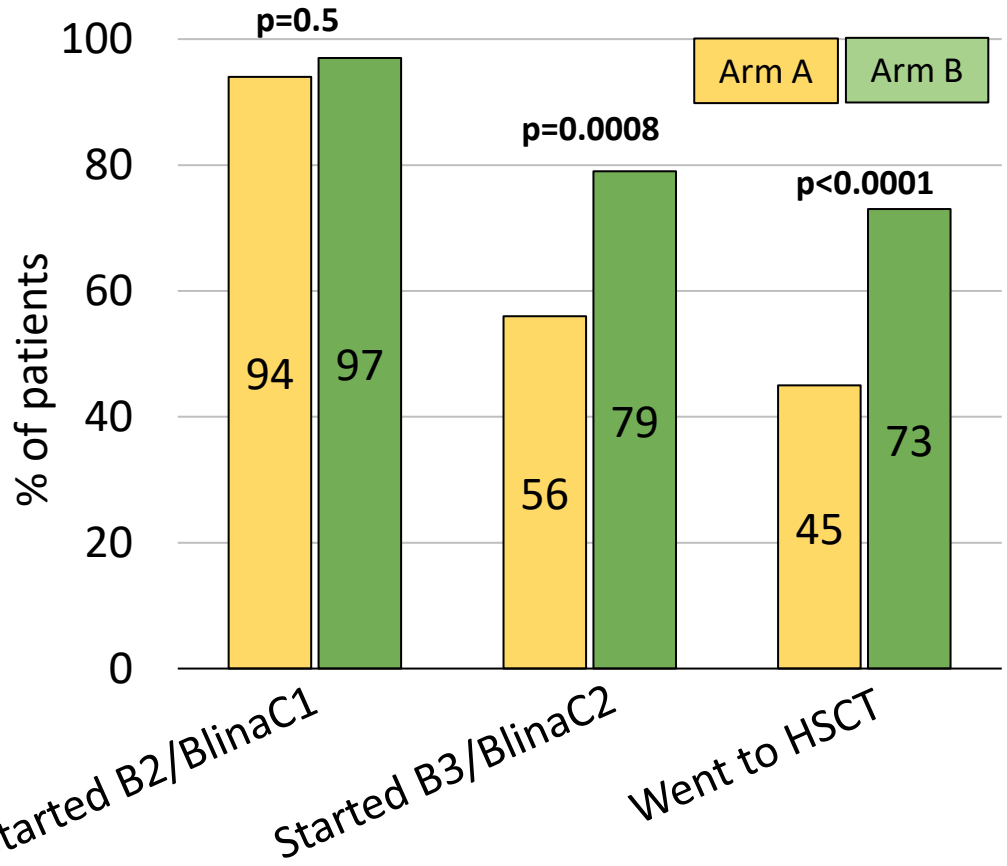
Patient	Risk Group	MRD Value at end of Blina Cycle 2	DFS Event	DFS days from randomization	Death	OS days from randomization
1	HR	0.1-0.99 %		1701		1701
2	HR	At least 1.0%	Relapse	63	Yes	972
3	HR	0.01-0.099 %	Relapse	194	Yes	286
4	HR	0.01-0.099 %		811		811
5	HR	0.01-0.099 %		440		440
6	HR	0.01-0.099 %	Relapse	302		453
7	HR	0.1-0.99 %		488		488
8	HR	0.1-0.99 %	Relapse	231	Yes	249
9	HR	0.1-0.99 %	Relapse	82		479
10	HR	At least 1.0%	Relapse	75		631
11	HR	Less than 0.1%(with sensitivity 1/1000)	Relapse	141	Yes	145
12	HR	0.1-0.99 %		437		437
13	HR	At least 1.0%	Relapse	67	Yes	150
14	HR	At least 1.0%	Relapse	71	Yes	152

Of the 14 patients, 9 (64%) have relapsed and 6 (43%) have died, confirming the strong negative prognostic impact of persistent MRD positivity.

CHILDREN'S ONCOLOGY GROUP

Brown P, et al. *JAMA*. 2021;325(9):833-842.

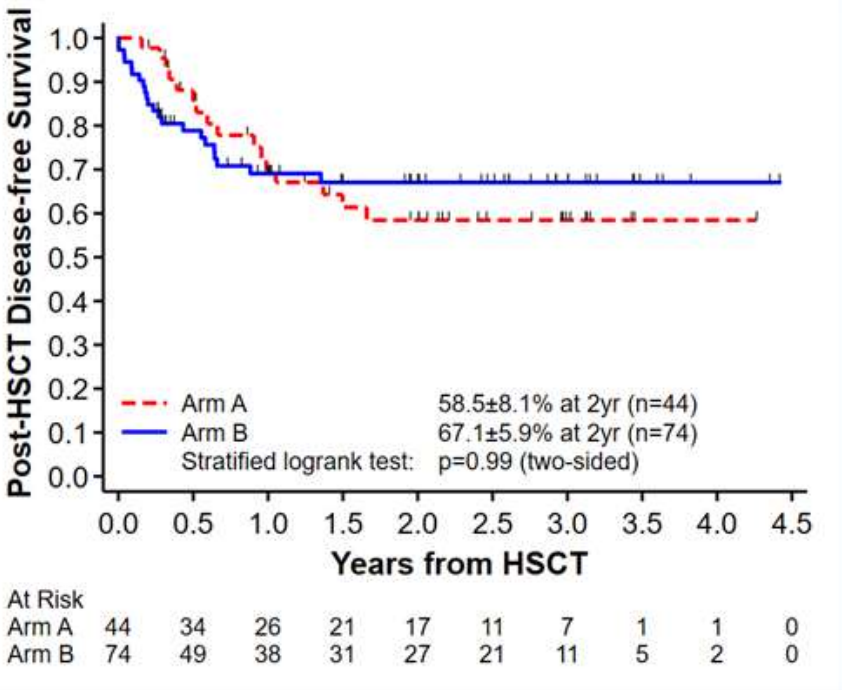
Proceeding to Transplant: Arm A vs Arm B

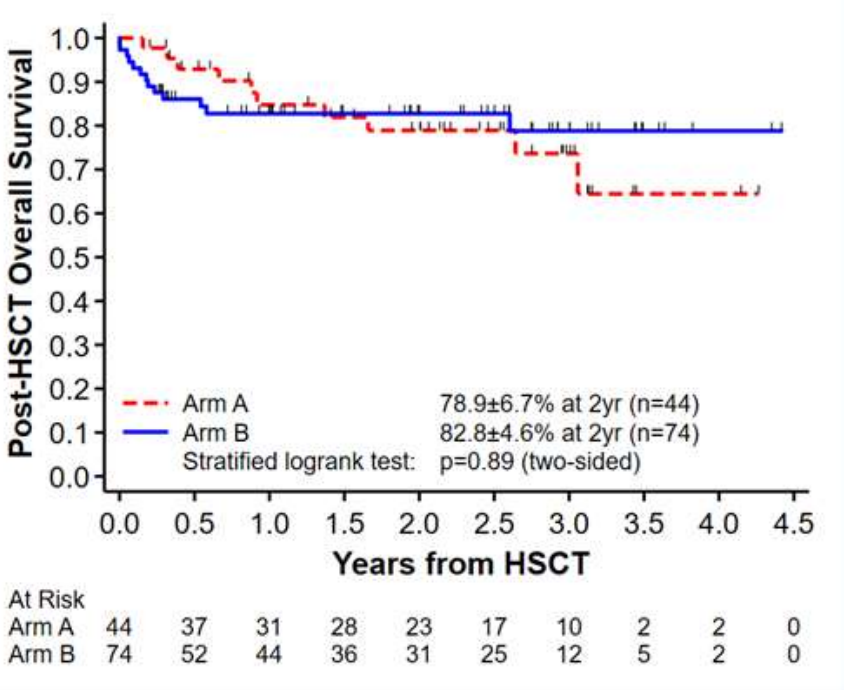


A significant contributor to the improved outcomes for Arm B (blina) vs Arm A (chemo) in HR/IR relapses may be the **ability of blinatumomab to successfully bridge to HSCT**

Brown P, et al. *JAMA*. 2021;325(9):833-842.

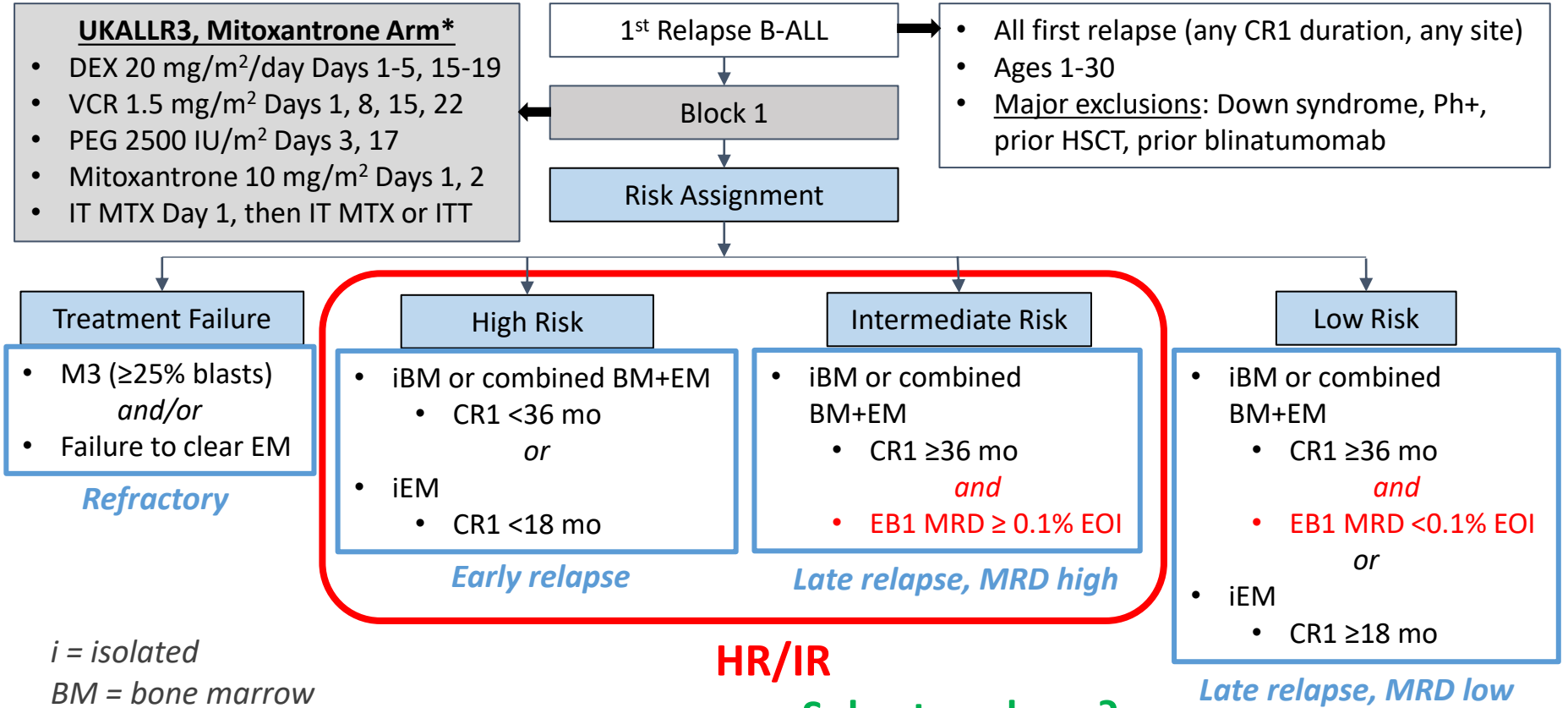
Post-HSCT Survival





CHILDREN'S ONCOLOGY GROUP

Brown P, et al. *JAMA*. 2021;325(9):833-842.



i = isolated
BM = bone marrow
EM = extramedullary (CNS, testes)
CR1 = duration of first remission
EB1 = end-Block 1

*UKALLR3 reference: Parker, et al. *Lancet.* 2010;376:2009-2017.

Brown P, et al. *JAMA*. 2021;325(9):833-842.

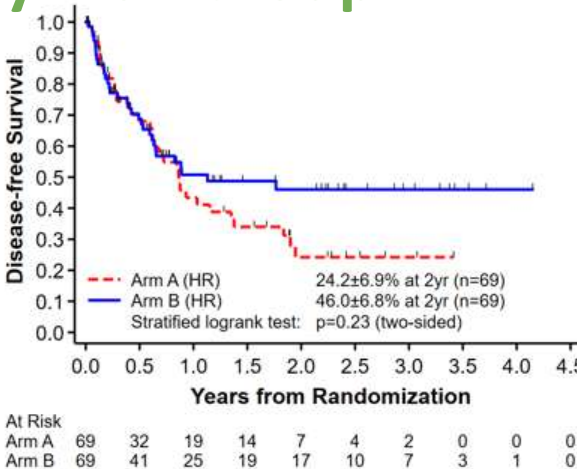
DFS and OS by Risk Group

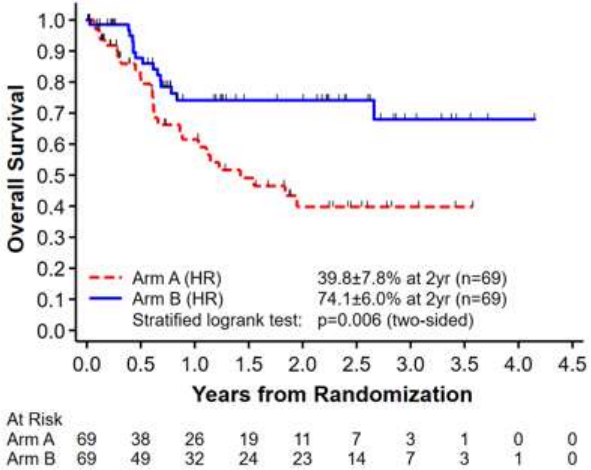
HR (n = 138)

iBM or combined BM+EM
- CR1 <36 mo

or

iEM
- CR1 <18 mo



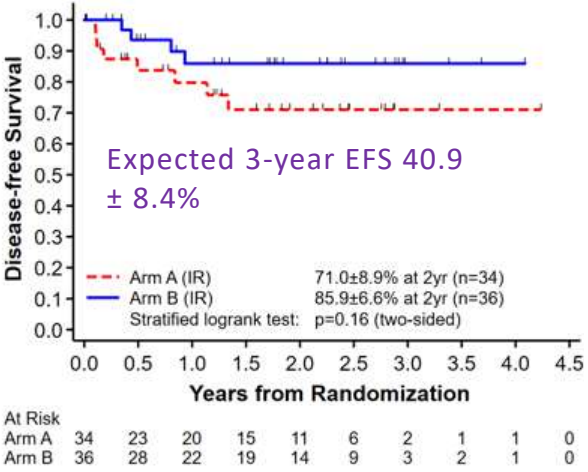


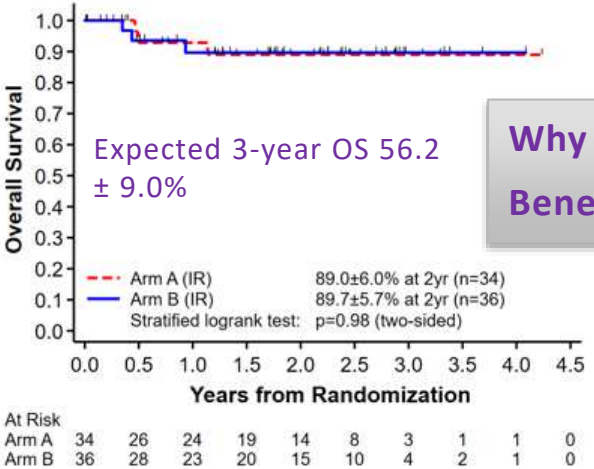
IR (n = 70)

iBM or combined BM+EM
- CR1 ≥ 36 mo

and

- EB1 MRD ≥0.1% EOI



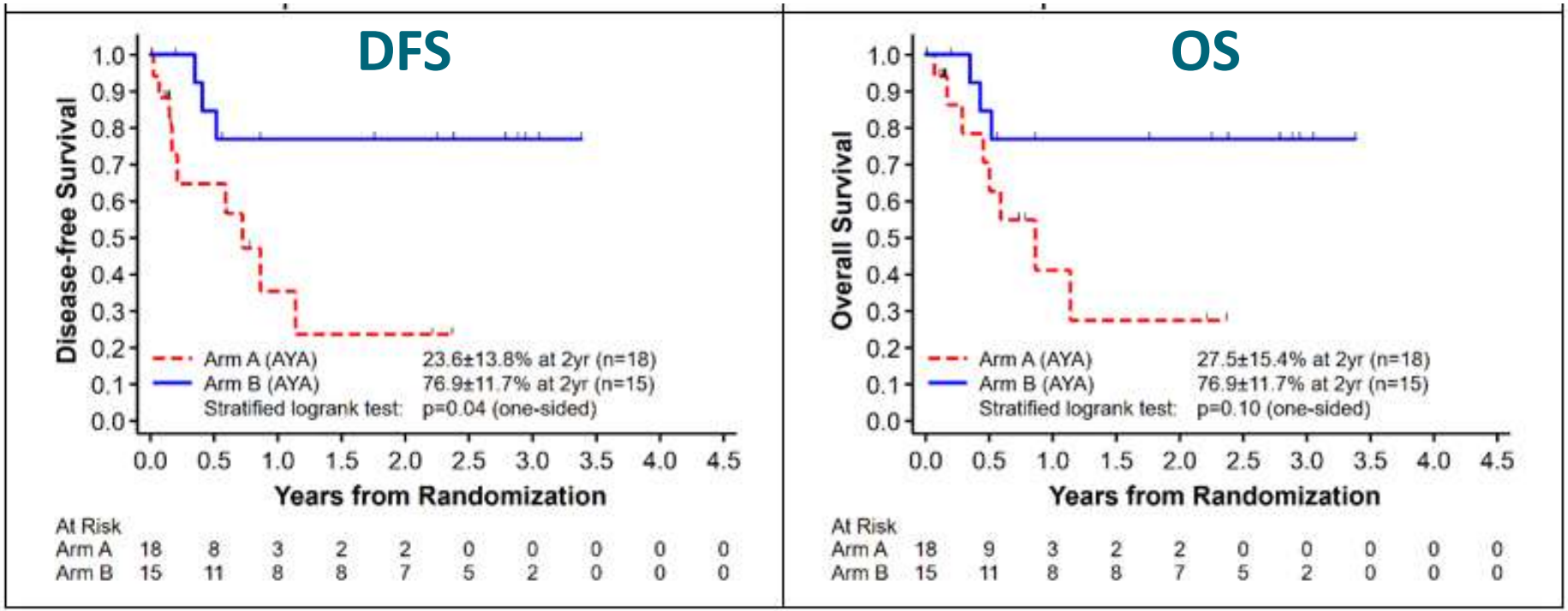


Why better?

Benefit of HSCT?

Brown P, et al. *JAMA*. 2021;325(9):833-842.

Results AYA Patients (Ages 18–30 at Relapse; N = 33/16%)

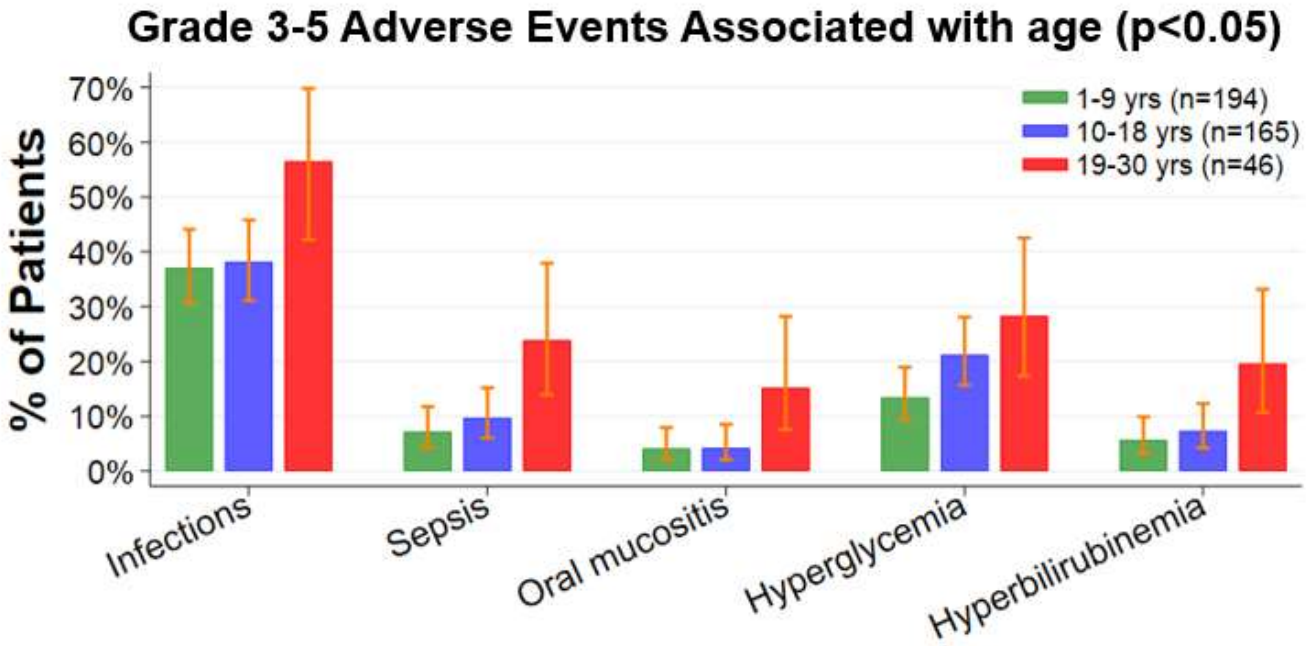


CHILDREN'S ONCOLOGY GROUP

Median follow up 2.9 years

Brown P, et al. *JAMA*. 2021;325(9):833-842.

Results AYA Patients (Ages 18–30 at Relapse)



CHILDREN'S ONCOLOGY GROUP

Hogan LB, et al. *Blood*. 2018;132(Suppl_1):1382.

Conclusions

- For children and AYA patients with HR/IR first relapse of B-ALL, blinatumomab is superior to standard chemotherapy as post-reinduction consolidation prior to HSCT, resulting in
  - Fewer and less-severe toxicities (especially AYA)
  - Higher rates of MRD response
  - Greater likelihood of proceeding to HSCT
  - Improved disease-free and overall survival
- Blinatumomab constitutes a new standard of care in this setting
- Future: Optimizing immunotherapy in relapsed ALL
  - Combination of blinatumomab and checkpoint inhibitors
  - Immunotherapy to replace or augment reinduction chemotherapy
  - CAR T cells to replace or augment HSCT

Q

Multiple Choice Question 1

Which of the following is NOT true of blinatumomab relative to chemotherapy as post-reinduction therapy for HR/IR first relapse of pediatric ALL?

a) Lower rate of clearance of residual disease
b) Lower rate of serious adverse events
c) Lower rate of relapse
d) Higher rate of proceeding to HSCT

AALL1331 Study Committee

- **Chair**: Pat Brown
- **Vice Chair**: Jim Whitlock
- **Stats**: Lingyun Ji, Mini Devidas
- **Heme/Onc**
  - Lia Gore
  - Laura Hogan
  - Terzah Horton
  - Stevie “Nix” Hunger
  - Kala Kamdar
  - Mignon Loh
  - Jen McNeer
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- **Lab/Path**
  - Mike Borowitz
  - Andrew Carroll
  - Fady Mikhail
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- **Rad Onc**: Stephanie Terezakis
- **Pharmacy**
  - Brooke Bernhardt
  - Olga Militano
- **CRA**: Christopher Henchen
- **Nursing**
  - Deb Schissel
  - Susan Zupanec
- **Research Coordinator**: Susan Conway, Don Sortillon, Naira Setrakian
- **Protocol Coordinator**: Rachel Vasquez

CHILDREN'S ONCOLOGY GROUP

Funding

- NCTN Operations Center Grant U10CA180886
- NCTN Statistics & Data Center Grant U10CA180899
- St. Baldrick's Foundation
- Blinatumomab provided by Amgen via Collaborative Research and Development Agreement (CRADA) with NCI/CTEP

Questions?

Global Leukemia Academy

Therapeutic approaches in high-risk and older AML patients

Naval Daver

APTITUDE HEALTH

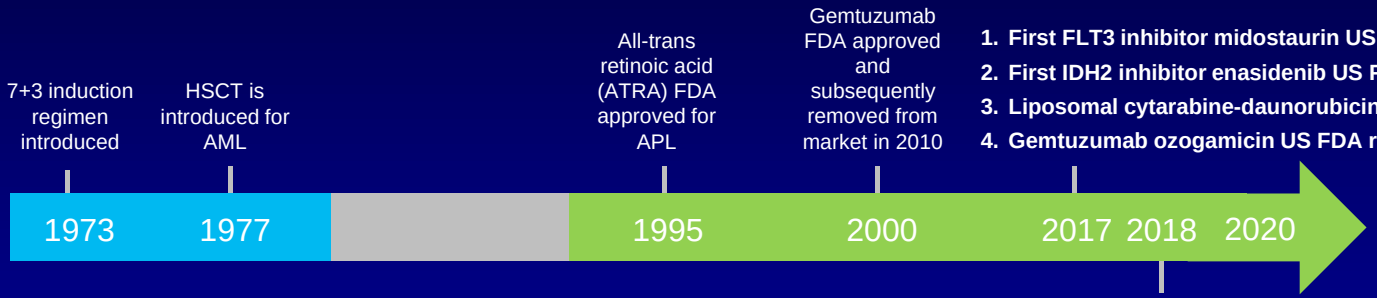
Therapeutic Approaches in High-Risk and Older AML Patients

Global Leukemia Academy

Naval Daver, MD
Director, Leukemia Research Alliance Program,
Associate Professor
Department of Leukemia
MD Anderson Cancer Center

Treatment of AML (accelerated progress 2017–2020): History

Since its introduction in the early 1970s, 7+3 therapy (cytarabine for 7 days + anthracycline for 3 days) has been the standard of care for AML

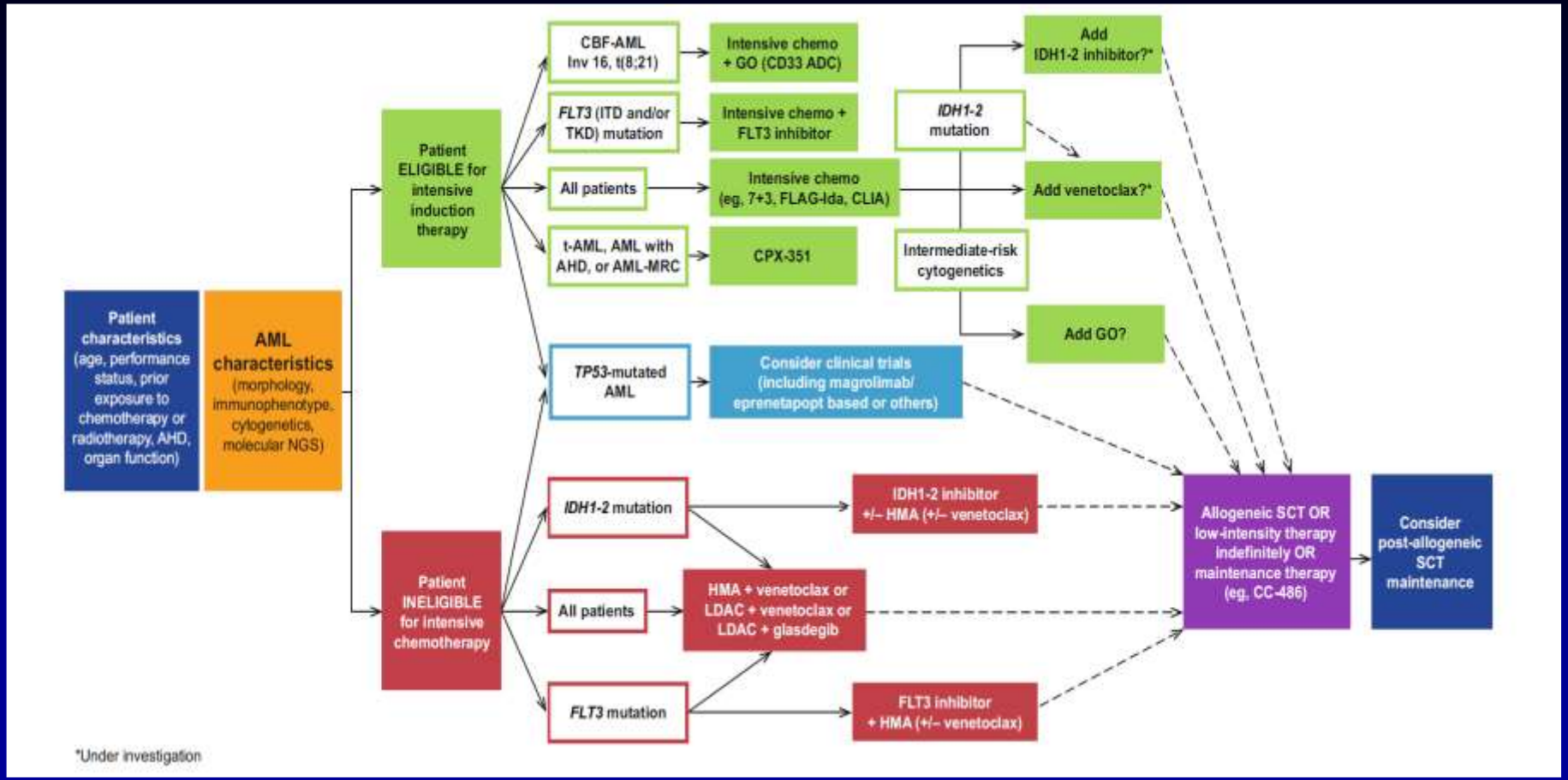


US FDA approvals

1. **First FLT3 inhibitor midostaurin US FDA approved**
2. **First IDH2 inhibitor enasidenib US FDA approved**
3. **Liposomal cytarabine-daunorubicin US FDA approved**
4. **Gemtuzumab ozogamicin US FDA re-approved**
5. **Ivosidenib is FDA approved in 2018 for relapsed or refractory AML with a susceptible *IDH1* mutation**
6. **AZA + VEN and LDAC + VEN approved for older AML (Nov 21, 2018)**
7. **LDAC + glasdegib approved for older AML (Nov 21, 2018)**
8. **Gilteritinib for relapsed *FLT3* AML (Dec 2018)**
9. **CC-486 maintenance post-induction/consolidation in AML (Aug 2020)**

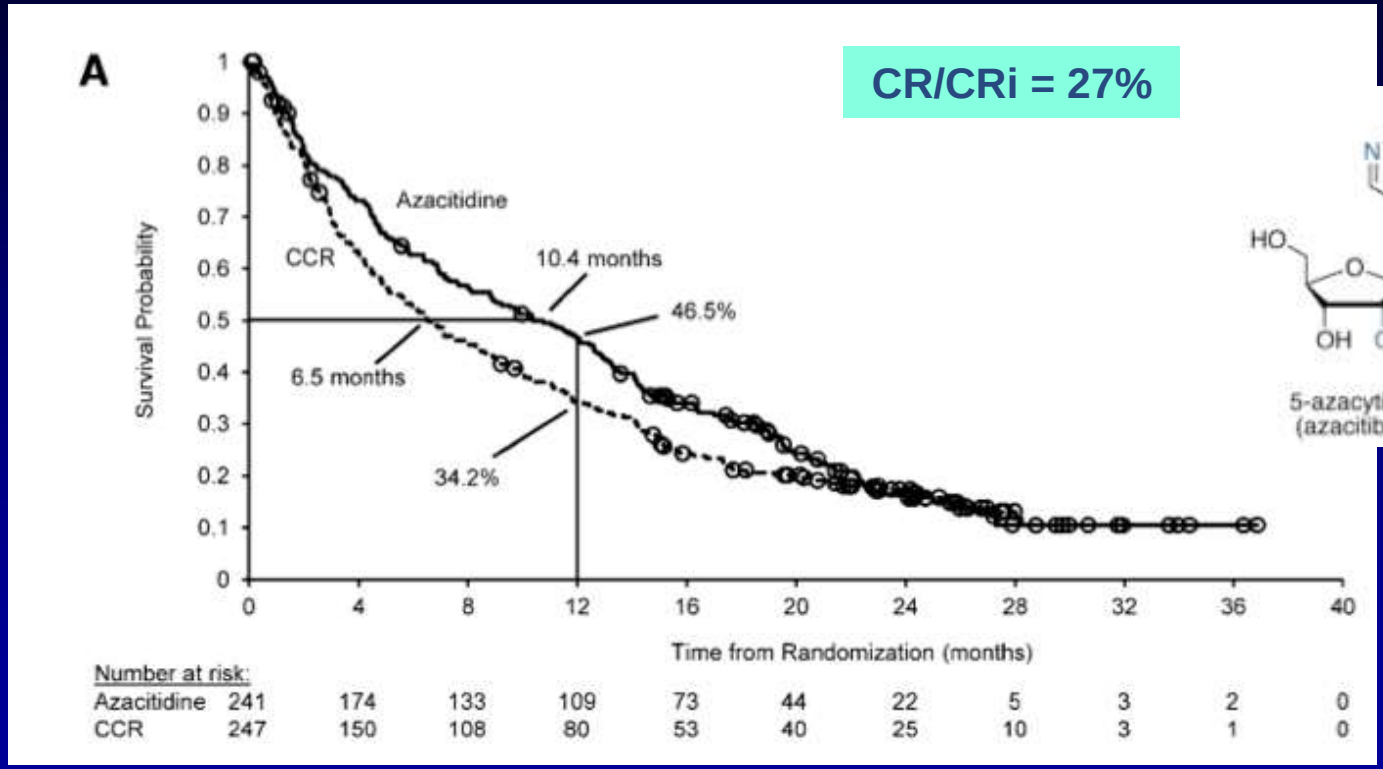
Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

Evolving Diagnostic and Treatment Paradigm for Newly Dx AML

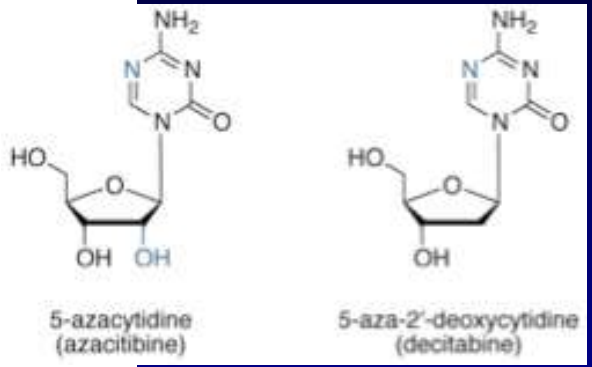


Daver N, et al. *Blood Cancer J.* 2020;10(10):107.

HMA-Based Therapies for Older AML: Hypomethylating Agents Are Well Tolerated and Safe in Older Patients, but Modest Single-Agent CR/CRi



CR/CRi = 27%



Dombret H, et al. *Blood.* 2015;36126(3):291-299.

Azacitidine +/– Venetoclax (VIALE-A) Study Design

Eligibility

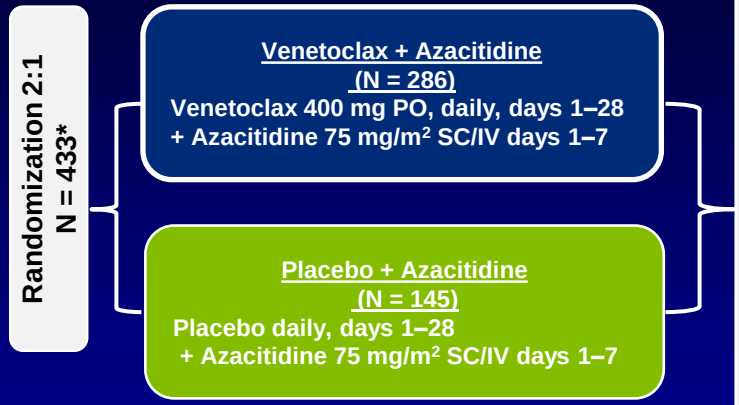
Inclusion

- Patients with newly diagnosed confirmed AML
- Ineligible for induction therapy defined as **either**
  - ❖ ≥75 years of age
  - ❖ 18 to 74 years of age with at least 1 of the comorbidities:
    - – CHF requiring treatment or ejection fraction ≤50%
    - – Chronic stable angina
    - – DLCO ≤65% or FEV1 ≤65%
    - – ECOG 2 or 3

Exclusion

- Prior receipt of any HMA, venetoclax, or chemotherapy for myelodysplastic syndrome
- Favorable-risk cytogenetics per NCCN
- Active CNS involvement

Treatment



Endpoints

Primary

- Overall survival

Secondary

- CR + CRi rate
- CR + CRh rate
- CR + CRi and CR + CRh rates by initiation of cycle 2
- CR rate
- Transfusion independence
- CR + CRi rates and OS in molecular subgroups
- Event-free survival

Randomization stratification factors	Age (<75 vs ≥75 years); cytogenetic risk (intermediate, poor); region
Venetoclax dosing ramp-up	**Cycle 1 ramp-up** Day 1: 100 mg, day 2: 200 mg, day 3–28: 400 mg **Cycle 2** → Day 1–28: 400 mg

DiNardo CD, et al. EHA 2020. Abstract LB2601.

Patient Baseline Characteristics

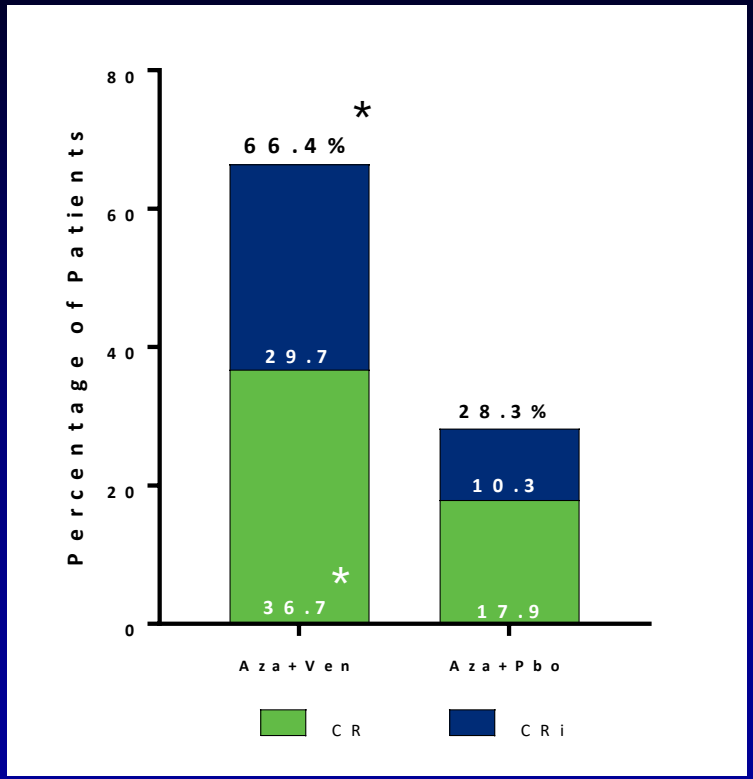
Characteristics	Ven + Aza (n = 286)	Pbo + Aza (n = 145)
Age		
Median (range) years	76 (49–91)	76 (60–90)
≥75 years, n (%)	174 (61)	87 (60)
Male, n (%)	172 (60)	87 (60)
AML type, n (%)		
De novo	214 (75)	110 (76)
Secondary	72 (25)	35 (24)
Secondary AML		
Post-MDS, CMML*	46 (64)	26 (74)
Therapy-related AML	26 (36)	9 (26)
ECOG PS, n (%)		
0–1	157 (55)	81 (56)
2–3	129 (45)	64 (44)
BM blast count, n (%)		
20 to <30%	85 (30)	41 (28)
≥30 to <50%	61 (21)	33 (23)
≥50%	140 (49)	71 (49)

Characteristics	Ven + Aza (n = 286)	Pbo + Aza (n = 145)
AML with myelodysplasia-related changes, n (%)	92 (32)	49 (34)
Cytogenetic risk, n (%)		
Intermediate	182 (64)	89 (61)
Poor	104 (36)	56 (39)
Somatic mutation, n/N (%)		
IDH1/2	61/245 (25)	28/127 (22)
FLT3	29/206 (14)	22/108 (20)
NPM1	27/163 (17)	17/86 (20)
TP53	38/163 (23)	14/86 (16)
Baseline hematologic status, n (%)		
Grade 3–4 neutropenia	206 (72)	90 (63)
Grade 3–4 anemia	88 (31)	52 (36)
Grade 3–4 thrombocytopenia	145 (51)	73 (50)
Transfusion dependent at baseline,† n(%)	155 (54)	81 (56)

*n = 7 patients in the Ven + Aza arm and n = 1 patient in the Pbo + Aza arm had antecedent CMML;
†Red blood cell or platelet transfusion within 8 weeks prior to the first dose of study drug or randomization.

DiNardo CD, et al. EHA 2020. Abstract LB2601.

Aza +/– Ven in AML: Composite Response Rate (CR + CRi)

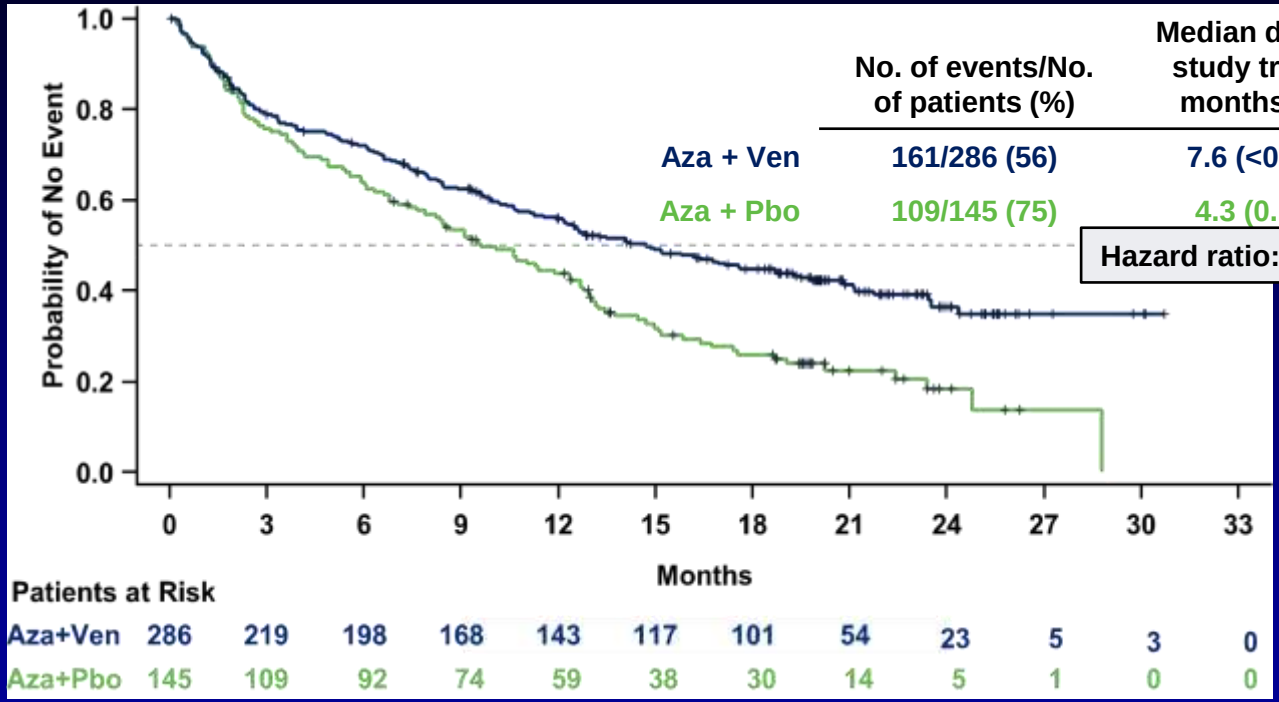


	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR + CRi by initiation of Cycle 2, n (%)
Aza + Ven (n = 286)	7.0 (1.0–30.0)	1.3 (0.6–9.9)	124 (43.4)
Aza + Pbo (n = 145)	4.5 (1.0–26.0)	2.8 (0.8–13.2)	11 (7.6)

*CR + CRi rate, CR rate, and CR + CRi by initiation of cycle 2 are statistically significant with *P* <.001 by CMH test.

DiNardo CD, et al. EHA 2020. Abstract LB2601.

AZA +/- VEN in AML: Overall Survival



	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza + Ven	161/286 (56)	7.6 (<0.1–30.7)	14.7 (11.9–18.7)
Aza + Pbo	109/145 (75)	4.3 (0.1–24.0)	9.6 (7.4–12.7)

Hazard ratio: 0.66 (95% CI: 0.52–0.85), *P* <.001

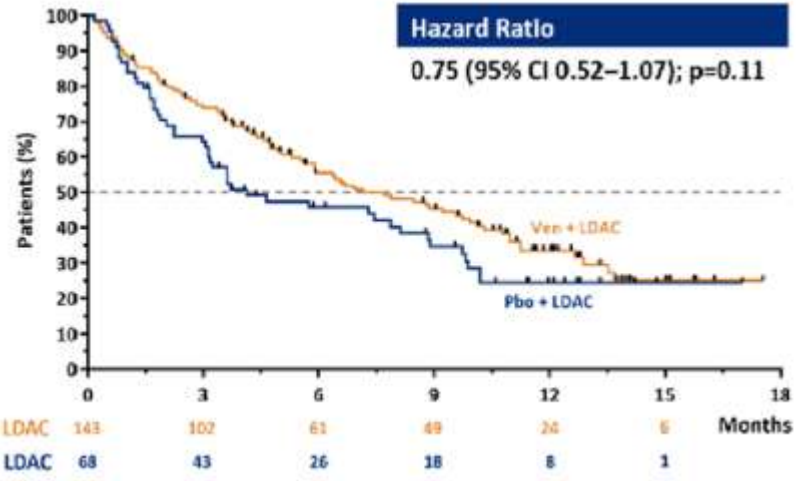
Median follow-up time: 20.5 months (range: <0.1 – 30.7)

DiNardo CD, et al. EHA 2020. Abstract LB2601.

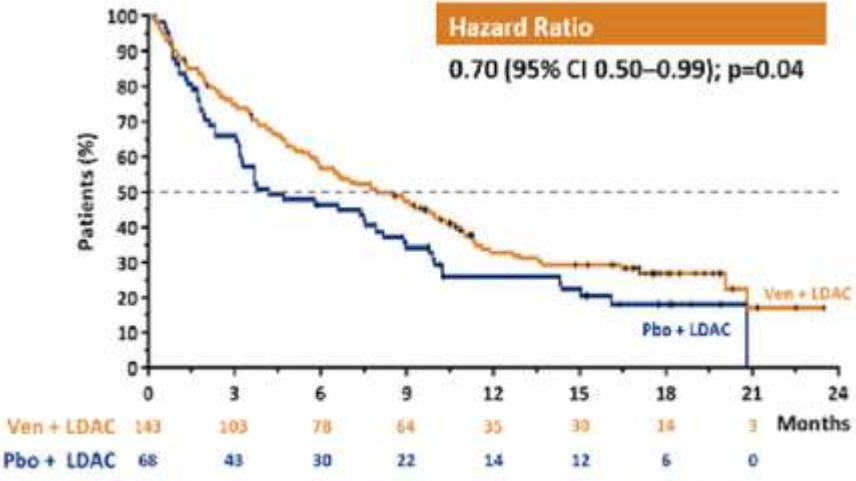
Low-Dose Cytarabine ± Venetoclax in AML: Results

	Response Rate	Median OS Mo. (95% CI)	Transfusion Independence	Quality of Life
Venetoclax + LDAC	48%	8.4 (5.9-10.1)	37%	↑
Placebo + LDAC	13%	4.1 (3.1-8.1)	16%	—

Overall Survival — Primary Endpoint



Overall Survival — +6 mo. Follow-up



Wei AH, et al. *Blood*. 2020;135:2137-2145.

Pratz 1944: Cytopenia Management in Patients With Newly Diagnosed Acute Myeloid Leukemia Treated With Venetoclax Plus Azacitidine in the VIALE-A Study

Protocol (VIALE-A – NCT02993523)

- Phase 3, double-blind, placebo controlled, 2:1 randomization of Ven + Aza vs Pbo + Aza
- Analysis of frequency and management of cytopenia in patients with CR or CRh

Population

- Patients with newly diagnosed AML ineligible for intensive chemotherapy due to age ≥75 years or comorbidities

Authors' conclusions

- Majority of Ven + Aza responders required dosing modifications to manage cytopenia, particularly delays between cycles or within-cycle reductions of Ven dosing days
- Post-remission cytopenia and dosing modifications were more frequent with Ven + Aza vs Pbo + Aza

CR/CRh rate: **66%** (Ven + Aza) vs **23%** (Pbo + Aza)

Cytopenia and dose adjustments in responders (CR/CRh)	Ven + Aza (n = 186)	Pbo + Aza (n = 33)
Post-remission grade 4 cytopenia lasting ≥1 week, %	**87**	**45**
1 episode	19	24
≥2 episodes	68	21
In-cycle dose interruptions for any reason, %	**26**	**24**
Median duration per cycle (range), days	2.0 (1–20)	1.0 (1–13)
Post-remission cycle delays due to cytopenia, %	**77**	**30**
Median duration per cycle delay (range), days	14.0 (1–129)	11.0 (3–63)
Post-remission reduction of Ven/Pbo dosing days and/or cycle delay totaling ≥7 days due to neutropenia, %	**75**	**27**
Median number of cycles (range)	2.0 (0–15)	0 (0–7)
Post-remission Ven/Pbo dosing ≤21-day cycles, %	69	30
Median time from remission to first ≤21-day cycle (range), days	92.0 (1–480)	74.0 (6–405)

AZA, azacitidine; CRh, CR with partial hematologic recovery; Pbo, placebo; Ven, venetoclax.

Pratz KW, et al. ASH 2020. Abstract 1944.

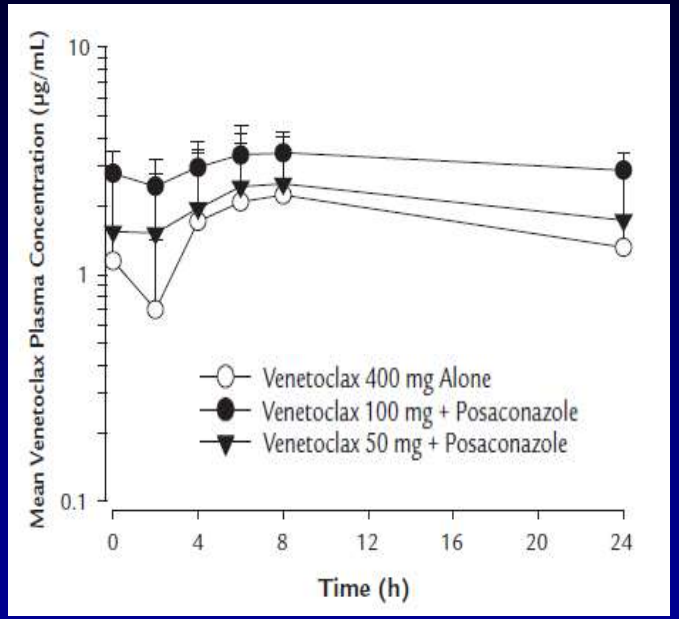
MDACC-Recommended Dosing Schema

- Ven D1–21 in cycle 1
- Bone marrow EOC1 (D21–D28) for all patients: if BM blasts <5% or <10% cellularity/acellular (majority of patients) – hold VEN 10–14 days for count recovery
- If needed, use G-CSF (usually if no spontaneous recovery after 14 days of Ven interruption)
- Cycle 2 onward: Ven D1–21 (or Ven D1–14) for most (subsequently may be further reduced to 7–10 days if cumulative myelosuppression observed)
- Cycles every 4–6 weeks on the basis of count recovery
- Continue second-generation azole prophylaxis, antibiotic, and antiviral until ANC >1.0 without fluctuations (usually after 4–5 cycles)

KEY: Reducing Ven duration does not seem to impact efficacy, but significantly improves neutropenia; more CR/CRh

Venetoclax and Azole Interaction Analysis

	Ven + Posa	Ven 400 mg	Comparison to Reference Point Estimate (90% CI)
Ven 100 mg + posaconazole (n = 6)			
C_{max} (µg/mL)	3.321	1.721	1.931 (1.201-3.104)
AUC_{0-24} (µg/mL)	67.739	26.545	2.552 (1.486-4.383)
Ven 50 mg + posaconazole (n = 5)			
C_{max} (µg/mL)	2.634	1.721	1.531 (0.927-2.528)
AUC_{0-24} (µg/mL)	46.625	26.545	1.756 (0.948-3.253)

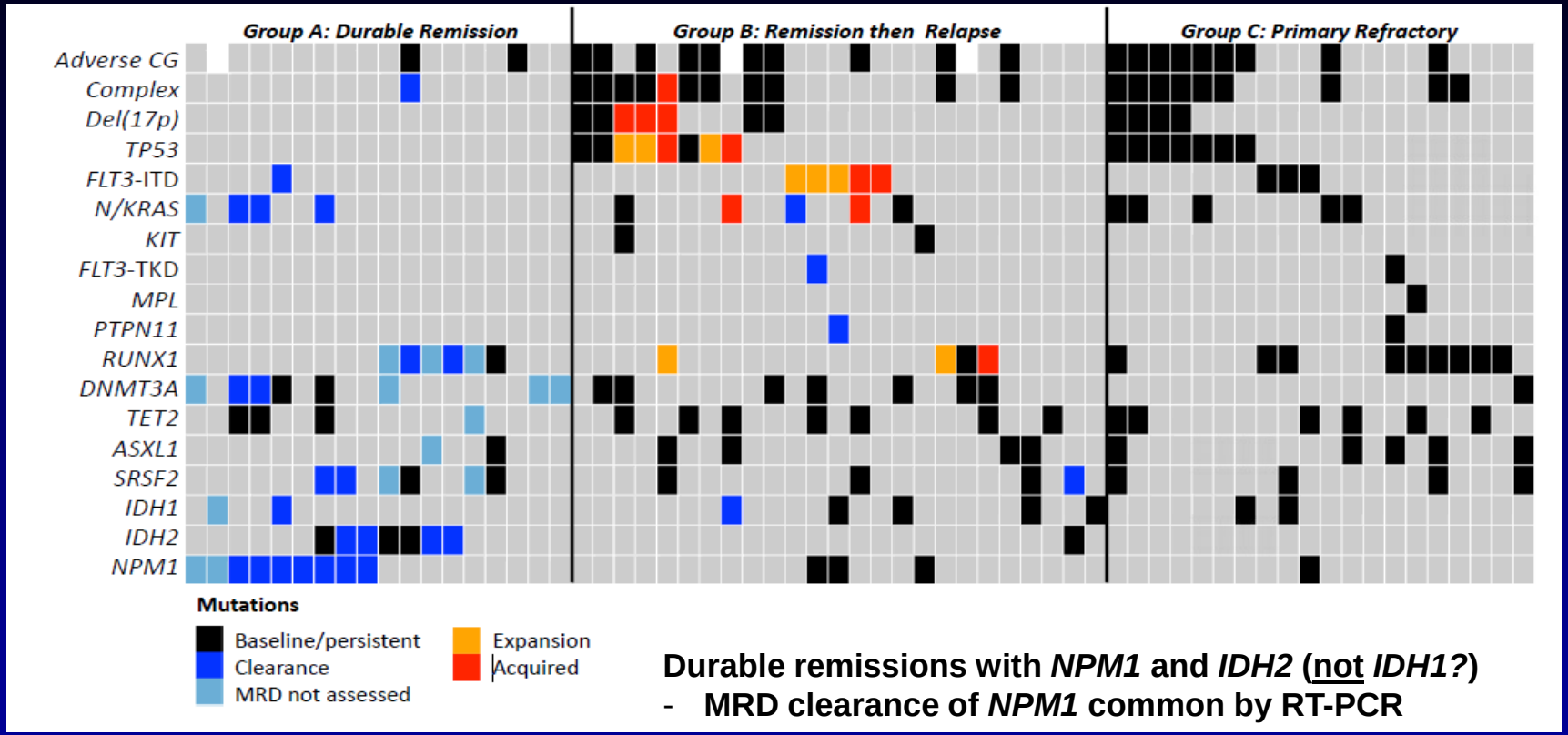


Agarwal SK, et al. *Clin Ther.* 2017;39:359-367.

Recommended Venetoclax Dose-Adjustments With Azoles

Antifungal	Package Insert Recommendation (Ven mg/d)	MDACC Dose Adjustment (Ven mg/d)
Posaconazole	70	50-100
Voriconazole	100	100
Isavuconazole	200	200
Caspofungin, echinocandins	400	400

Molecular Determinants of Outcome With Venetoclax Combos



Durable remissions with *NPM1* and *IDH2* (not *IDH1?*)
- **MRD clearance of *NPM1* common by RT-PCR**

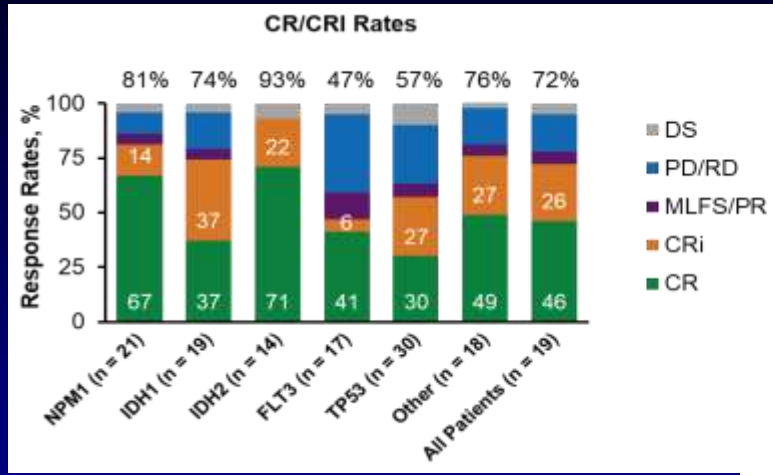
Patients treated at MDACC and The Alfred (n = 81)

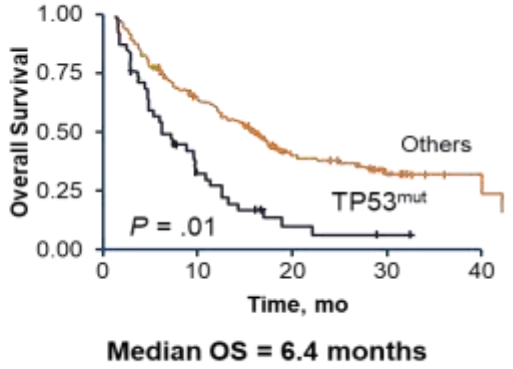
Resistance commonly associated with expansion or acquisition of *TP53* or signaling mutations including *K/NRAS* and *FLT3*-ITD

DiNardo CD, et al. *Blood*. 2020;135(11):791-803.

1. Poor Outcomes in *TP53*-Mutant AML, Even With Venetoclax-Based Treatment

Venetoclax + LDAC or HMA[1]

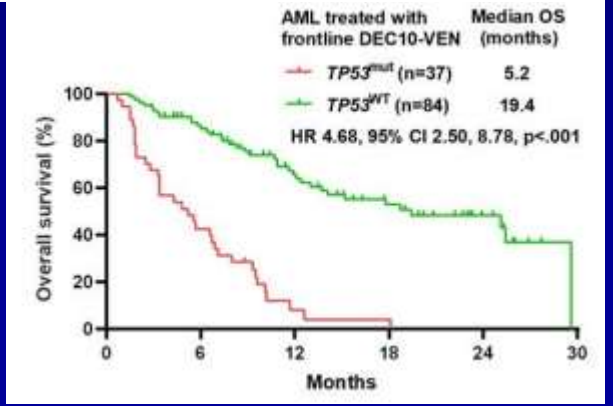




Median OS = 6.4 months

N = 121 patients with newly diagnosed AML receiving decitabine + venetoclax[2]

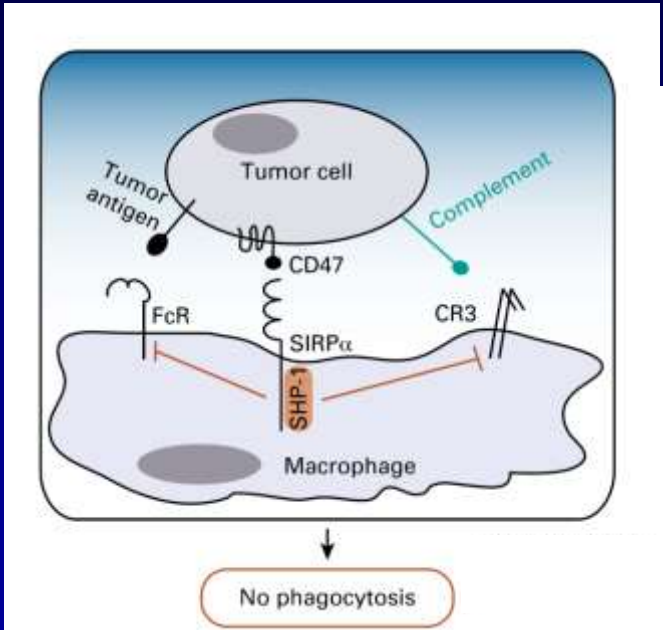
- **Those with *TP53*^{mut} had a lower rate of CR at 35% vs 57% in pts with *TP53*^{WT} (*P* = .026)**
- Lower rate of CR/CRi (54% vs 76%; *P* .015)



1. Chyla BJ, et al. ASH 2019. Abstract 546; 2. Kim K, et al. ASH 2020. Abstract 693.

CD47 Is a Major Macrophage Immune Checkpoint and "Do Not Eat Me" Signal in Myeloid Malignancies, Including AML

- CD47 is a "do not eat me" signal in cancers that enables macrophage immune evasion
- Increased CD47 expression predicts worse prognosis in AML patients



CD47 Expression in AML Patients

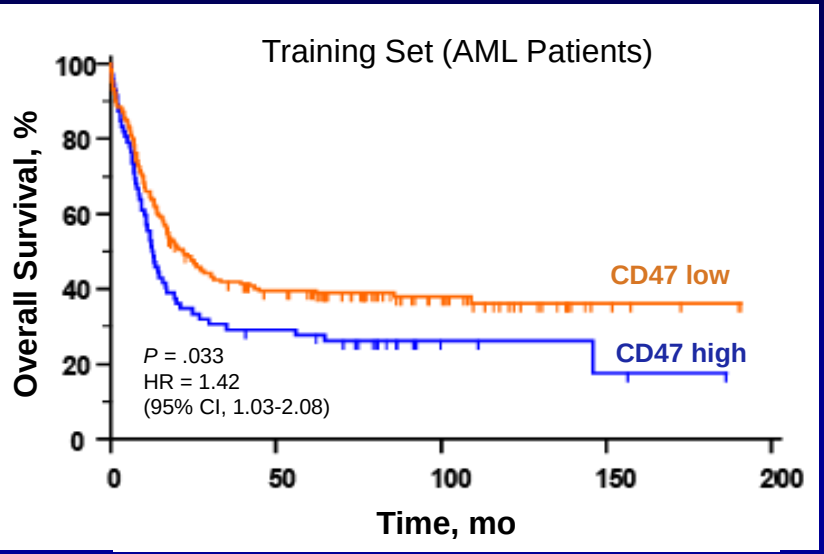
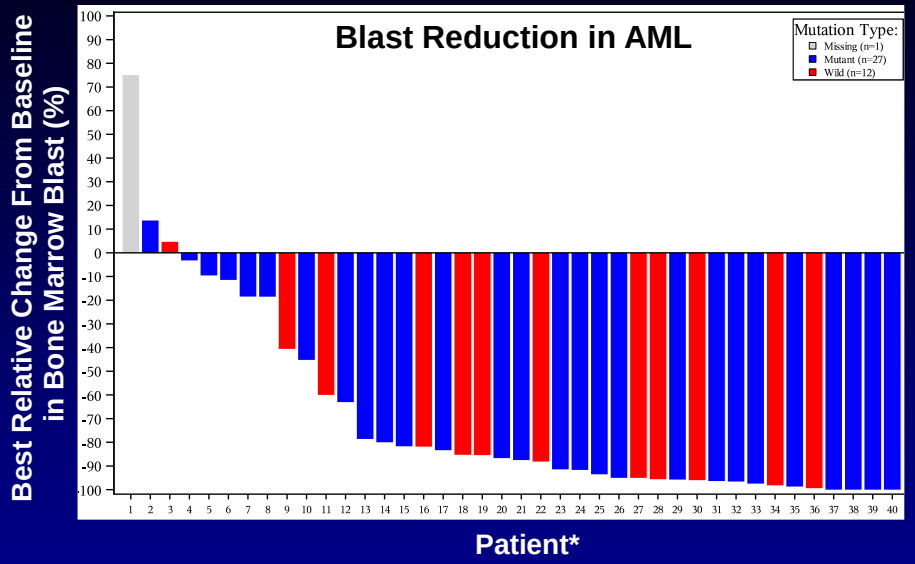


Figure at left adapted from Veillette A, Tang Z. *J Clin Oncol*. 2019;37:1012-1014 and Chao MP, et al. *Curr Opin Immunol*. 2012;24:225-232.
Figure at right adapted from Majeti R, et al. *Cell*. 2009;138:286-299.

Magrolimab + Aza Induces High Response Rates in AML

Best Overall Response	All AML (N = 43)	TP53-mutant AML (29)
ORR	**27 (63%)**	**20 (69%)**
CR	**18 (42%)**	**13 (45%)**
CRi	5 (12%)	4 (14%)
PR	1 (2%)	1 (3%)
MLFS	3 (7%)	2 (7%)
SD	14 (33%)	8 (28%)
PD	2 (5%)	1 (3%)



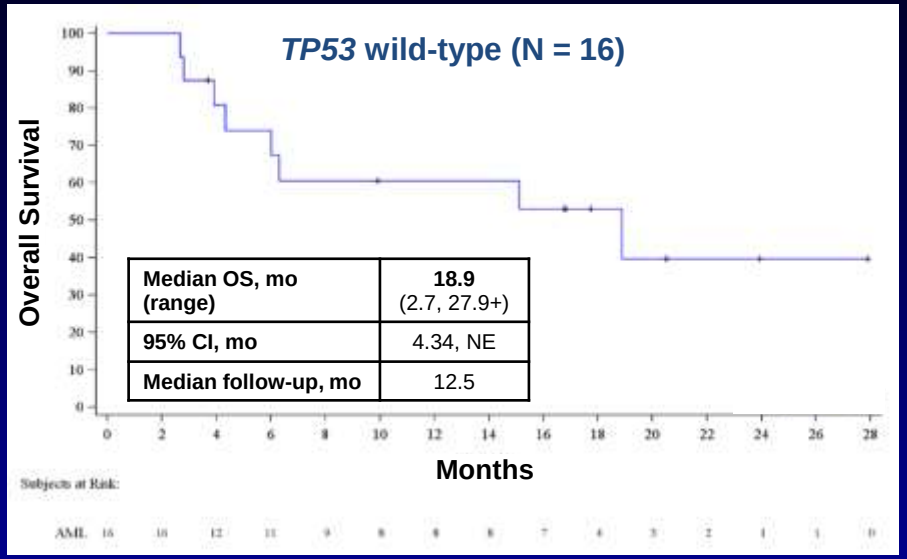
- **Magrolimab + Aza induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients**
- Median time to response is **1.95 months** (range 0.95 to 5.6 mo), more rapid than Aza monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab + Aza efficacy compares favorably with Aza monotherapy (CR rate 18%–20%)[1,2]

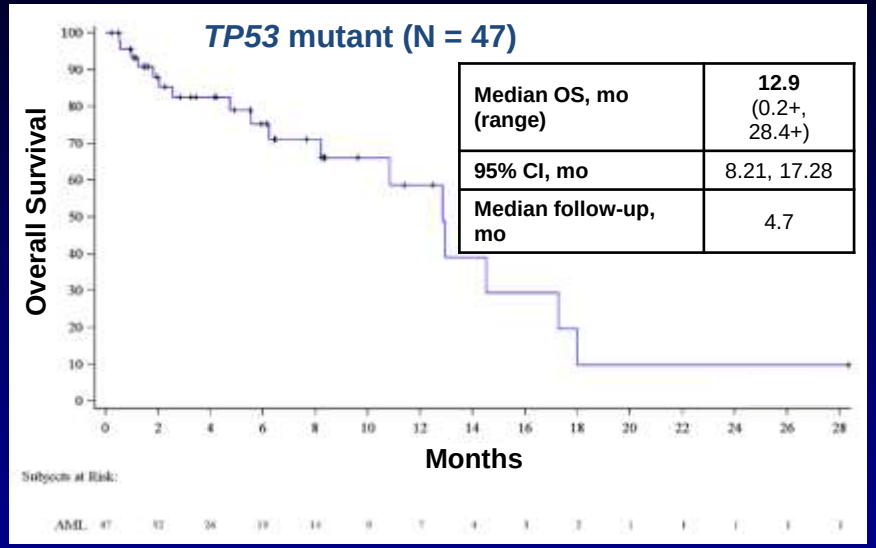
Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown. *Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

1. Fenaux P, et al. *J Clin Oncol*. 2010;28(4):562-569; 2. Dombret H, et al. *Blood*. 2015;126(3):291-299.

Sallman DA, et al. ASH 2020. Abstract 330.

Preliminary Median Overall Survival Is Encouraging in Both *TP53* Wild-Type and Mutant Patients





- Median OS is 18.9 months in *TP53* wild-type patients and 12.9 months in *TP53*-mutant patients
- This initial median OS data may compare favorably with venetoclax + hypomethylating agent combinations (**14.7–17.5 mo** in all-comers,[1,3] **5.2–7.2 mo** in patients who are *TP53* mutant[2,3])
- Additional patients and longer follow-up are needed to further characterize the survival benefit

NE, not evaluable.

1. DiNardo CD, et al. *N Engl J Med*. 2020;383(7):617-629; 2. Kim K, et al. Poster presented at: 62nd ASH Annual Meeting; December 5-8, 2020 (virtual); 3. DiNardo CD, et al. *Blood*. 2019;133(1):7-17.

Sallman DA, et al. ASH 2020. Abstract 330.

2. Older Adults With *FLT3*m AML: Poor Outcomes

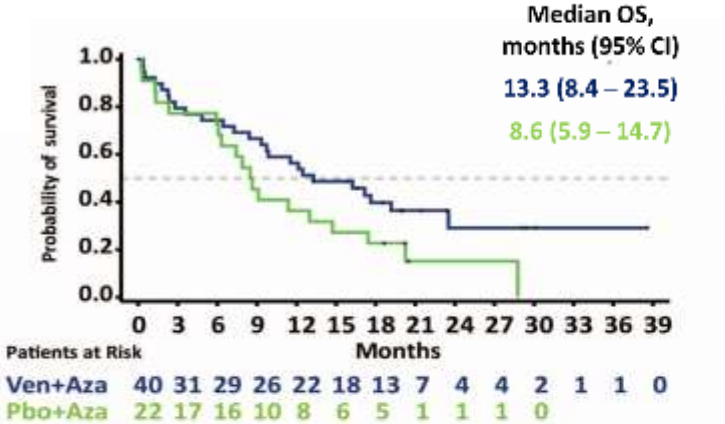
Frontline Therapy	N	Age, median	CRc (or CR/CRi)	OS, median	Ref.
Midostaurin + Aza	16	74 [59-85]	31%	8.7 mo	Gallogly, ASH 2017
Sorafenib + Aza	27	74 [61-86]	70%*	8.3 mo	Ohanian, Am J Hem 2018
Gilteritinib + Aza	15	75 [65-86]	67%	n/a	Esteve, ASH 2018
Quizartinib + Aza/LDAC	16	74 [62-83]	83%*	17.0 mo	Swaminathan, ASH 2017
Venetoclax + Aza (*FLT3*-ITD/TKD)	40	75 [49-91]	70%	13.3 mo	Konopleva, ASH 2020
Venetoclax + Aza (*FLT3*-ITD only)	28		68%	11.5 mo	

*CRc includes CR, CRi, and MLFS.

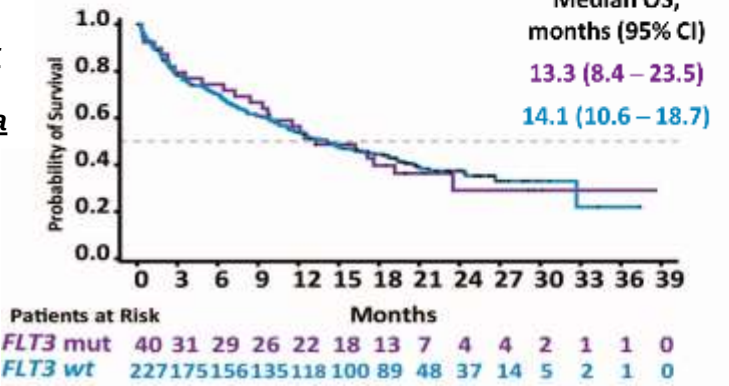
Yilmaz M, et al. ASH 2020. Abstract 26.

Overall Survival in Patients With FLT3 Mutation (Aza + Ven pooled analysis – FLT3)

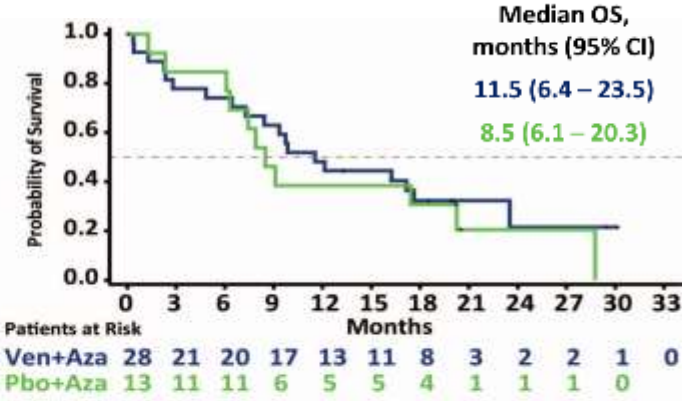
A. FLT3mut



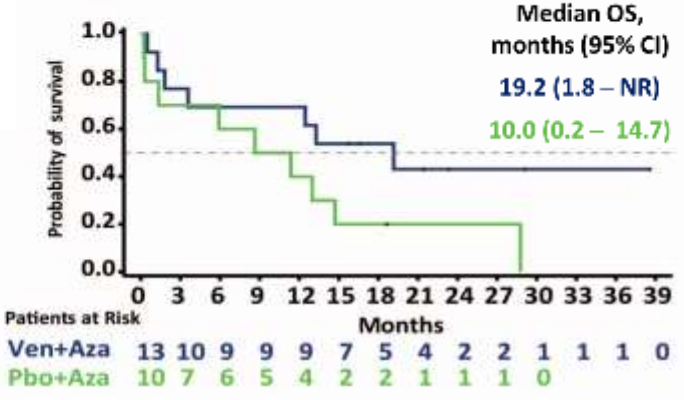
B. FLT3mut vs wt in Ven + Aza



C. FLT3-ITD



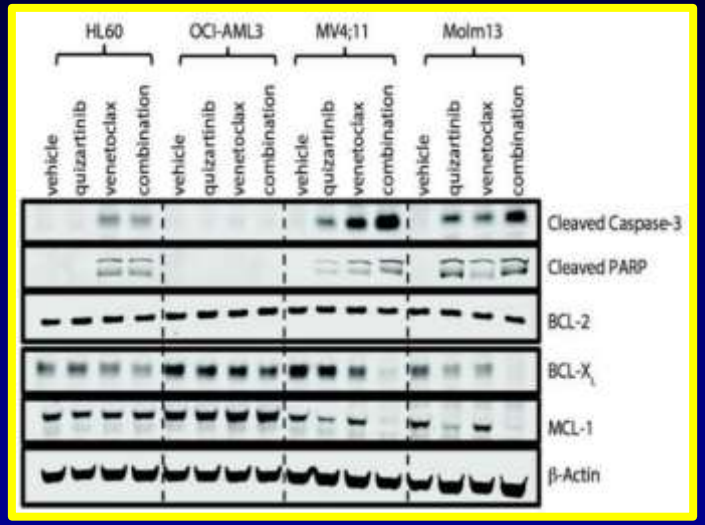
D. FLT3-TKD



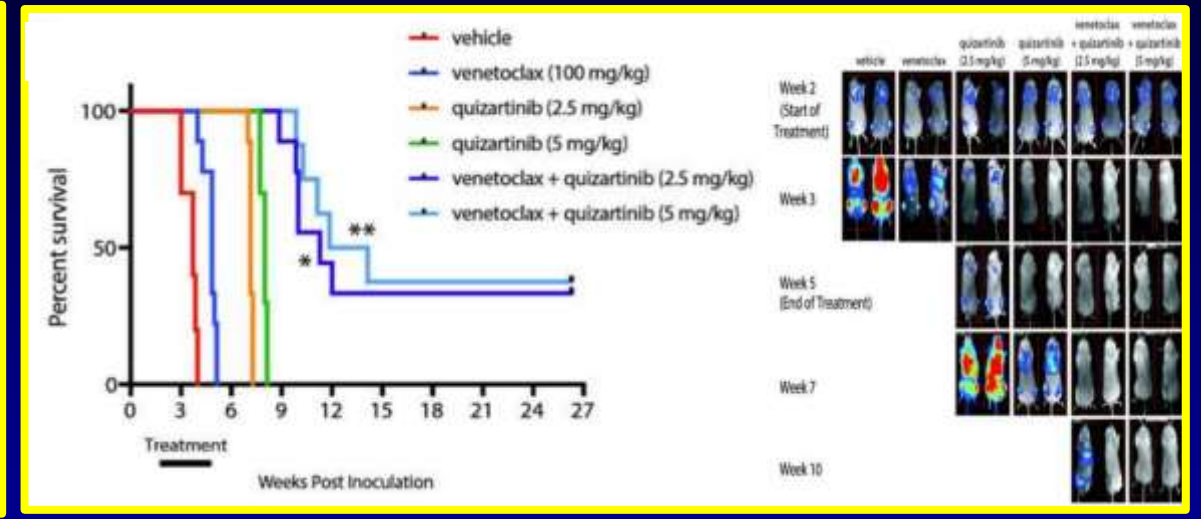
Konopleva M, et al. *Blood*. 2020;136:abstract 1904.

Overall survival (OS) was defined as the time from randomization to the date of death from any cause.

Venetoclax Combines Synergistically With Quizartinib



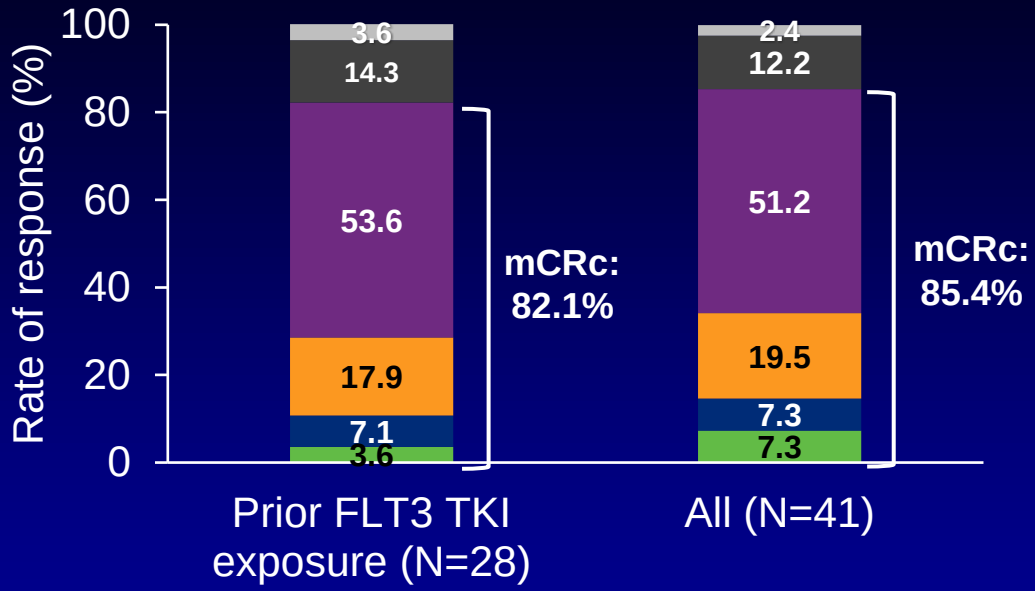
Cell lines were treated with combination – ↓ MCL-1, ↓ BCL-X_L



Venetoclax combined with quizartinib prolonged survival and reduced tumor burden in *FLT3*-ITD+ xenograft models

Mali RS, et al. *Haematologica*. 2021;106. doi:10.3324/haematol.2019.244020

Venetoclax + Gilteritinib in R/R *FLT3* AML: Summary of Best Responses



	All (N = 41)
mCRc, n (%)	35 (85.4%)
Time to best response (mCRc), median (range), months	0.9 (0.7–4.2)

The 85% mCRc rate compares favorably with the 52% CRc rate (using the same response parameters), with single-agent Gilt in the ADMIRAL phase 3 study[1]

Data cutoff: April 15, 2020. Analyses were conducted using data from all treated ITD and/or TKD patients irrespective of the availability of postbaseline disease assessment data prior to data cutoff date (ITT analysis), including patients who received non-RP2D dose during dose-expansion phase. Two on-treatment patients did not have their first disease assessment at the cutoff date and were not included in the efficacy analyses. No patients achieved partial remission. One patient (TKD only) discontinued with no response data.

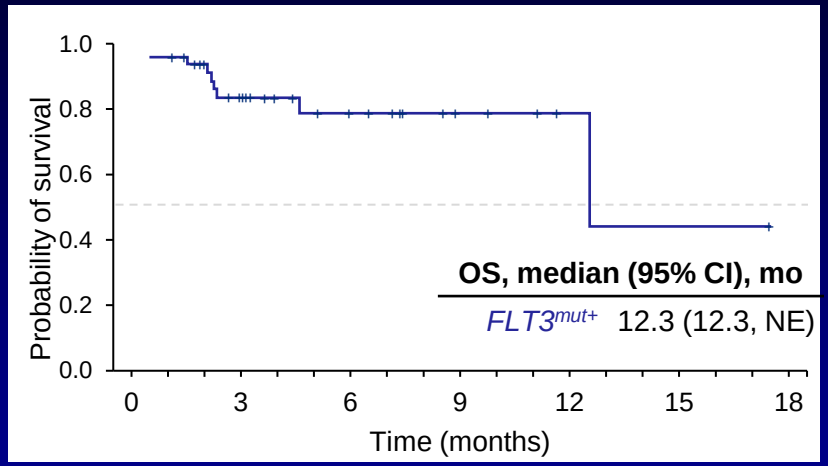
AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRi, CR with incomplete blood count recovery; CRp, CR with incomplete platelet recovery; FLT3, FMS-like tyrosine kinase 3; Gilt, gilteritinib; ITD, internal tandem duplications; ITT, intention to treat; mCRc, modified composite complete remission; MLFS, morphologic leukemia free state; NE, not estimable; PD, progressive disease; RD, resistant disease; TKI, tyrosine kinase inhibitor; TKD, tyrosine kinase domain.

1. Perl AE, et al. *N Engl J Med*. 2019;381(18):1728-1740.

Daver N, et al. ASH 2020. Abstract 333.

Venetoclax + Gilteritinib in R/R *FLT3* AML: OS in All *FLT3*$^{mut+}$ Patients and ITD Patients

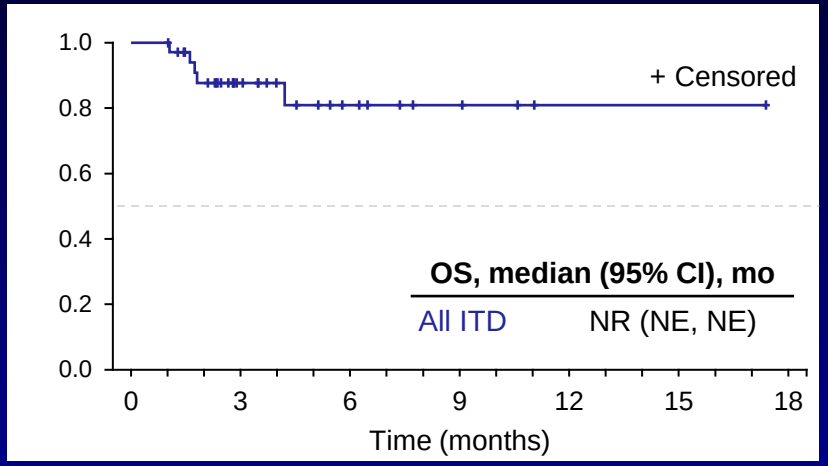
OS in all *FLT3*$^{mut+}$ patients (N = 41)



Patients at risk, n

***FLT3*$^{mut+}$**	41	40	30	20	15	13	10	7	5	5	4	3	2	1	1	1	1	1	0

OS in all ITD patients (N = 36)



Patients at risk, n

ITD ± TKD	36	36	28	18	13	11	8	6	4	4	3	2	1	1	1	1	1	1	0

Median (range) duration of follow-up: 3.5 months (0.8–17.4)

Data cut off: April 15, 2020.

FLT3^{mut+}, *FLT3* mutation; ITD, internal tandem duplications; mCRc, modified composite complete remission; MLFS, morphologic leukemia free state; NE, not estimable; NR, not reached; OS, overall survival; RP2D, recommended phase 2 dose; TKD, tyrosine kinase domain; TKI, tyrosine kinase inhibitor.

Daver N, et al. ASH 2020. Abstract 333.

Global Leukemia Academy

Leukemia board discussion

Moderator: Elias Jabbour

APTITUDE HEALTH

Global Leukemia Academy

Leukemia board discussion: Regional challenges in times of COVID-19

Shaun Fleming

APTITUDE HEALTH

Challenges of managing ALL in the era of COVID-19 – a perspective from "Down Under"

Dr Shaun Fleming, MBBS(Hons), FRACP, FRCPA

Clinical & Laboratory Haematologist

Alfred Health

Melbourne, Australia – the epicentre of COVID cases in Australia

- → While the majority of Australia has experienced only a brief first lockdown and small outbreaks, Melbourne spent 111 days in lockdown to combat COVID-19
- → The outbreak began in hotel quarantine workers and subsequently spread through the community undetected
- → At a peak of 750 cases per day, large outbreaks were seen in hospitals, aged care facilities, and other high-risk workplaces

Data from COVID-19 Data Repository by the Center for Systems Science and Engineering at Johns Hopkins University.

What are the challenges for managing ALL patients in the setting of COVID-19?

→ ALL-related challenges
- Should therapy be truncated? What are the impacts of therapy on patients?

→ Transplant challenges
- Access to overseas donors? Alternative donor sources?

→ COVID-19–specific challenges
- Morbidity and mortality in ALL patients who contract COVID

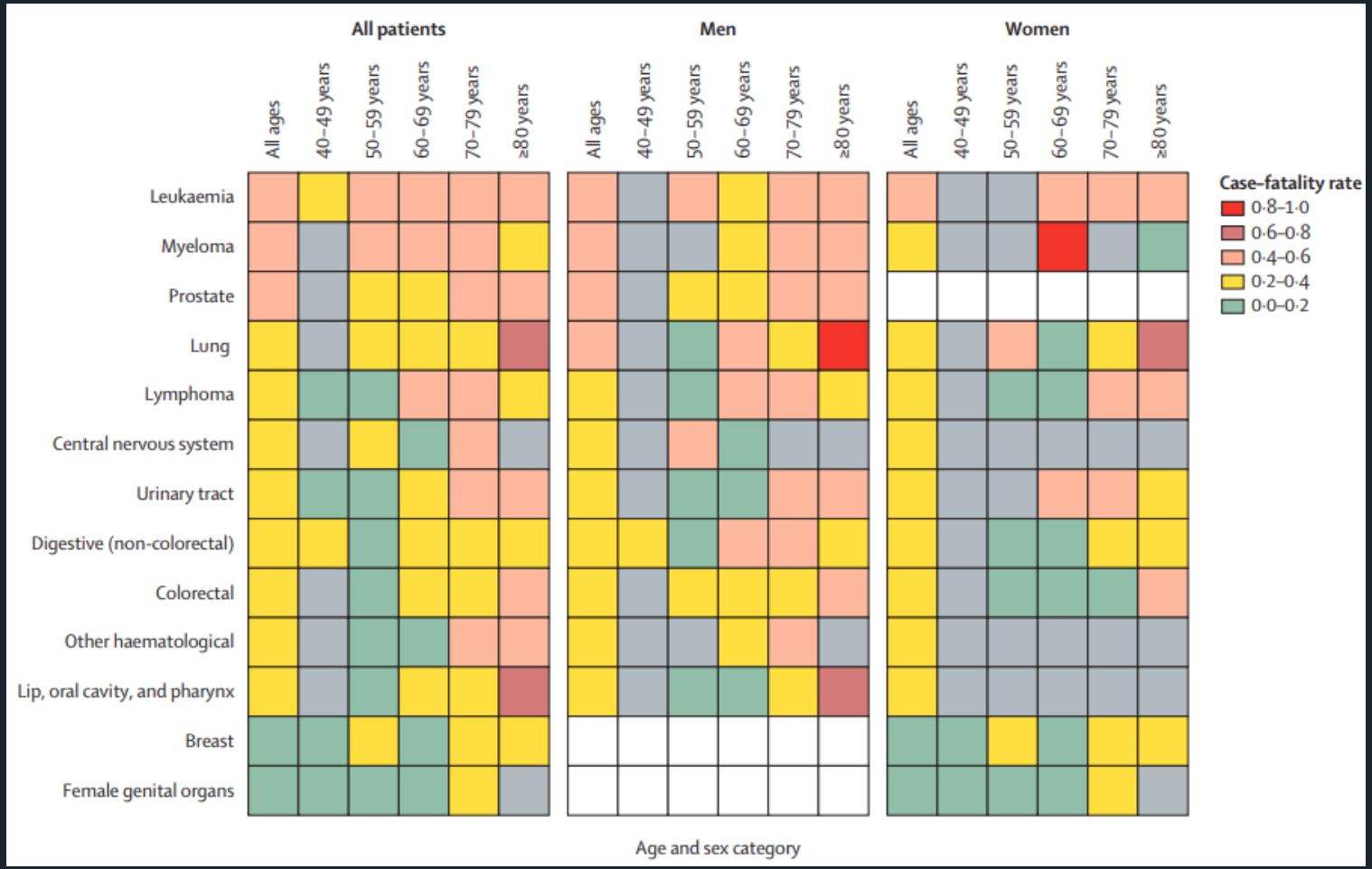
→ Vaccination challenges
- Where? When? With what? Will it work?

→ Psychosocial challenges
- Patients requiring prolonged therapy in hospitals where visitors are not allowed

What is known about the outcome of COVID-19 in ALL patients?

- → Patients with cancer have a higher risk of death and serious illness than the general population with COVID-19
  - In the UK Coronavirus Cancer Monitoring Project (UKCCMP) cohort of 1044 patients with cancer and COVID-19, 319 (30.6%) died, of whom 295 (92.5%) were recorded as death being due to COVID-19[1]
- → Patients with blood cancers appear to do particularly poorly relative to those with solid tumours
- → Younger adults overall had a lower risk of mortality than older adults
- → Patients with haematologic malignancies were generally overrepresented – perhaps suggesting an increased susceptibility to infection as well as poor outcomes
- → Specific outcome data for ALL are limited to case reports and short case series
- → Reactivation of COVID-19 has been reported in an ALL patient receiving therapy

Lee LYW, et al. *Lancet Oncol*. 2020;21(10):1309-1316.



Lee LYW, et al. *Lancet Oncol*. 2020;21(10):1309-1316.

General recommendations for treating ALL patients during the pandemic

→ Not a lot of evidence to guide us; however . . .

- Consider the risks and benefits of therapy, particularly if resources are constrained (especially applicable to patients on >2nd-line therapies)
- Induction therapy generally cannot be delayed; however, consideration should be given as to whether patients are COVID-19 positive, and monitoring for this
- It is generally recommended to deliver therapy as per protocol, in the absence of data to suggest that alterations would improve outcome
  - Consider testing patients prior to commencing intensive therapy blocks and delay 10–14 days if positive
  - May also consider testing prior to “reinduction” blocks during maintenance therapy
- Where possible, minimise presentations to hospital, providing home-based care, shipping medications

Butt A, Ali N. *Haematol Transfus Cell Ther*. 2021; Zeiden AM, et al. *Lancet Haematol*. 2020;7:e601-612; Baruchel A, et al. *Bull Cancer.* 2020;107:629-632.

Febrile neutropenia

→ Patients presenting with febrile neutropenia should be tested for COVID-19 on presentation and managed with appropriate respiratory precautions pending results

→ In patients with COVID-19 there is a theoretical risk of exacerbating inflammatory symptoms with G-CSF → consider cessation in active COVID-19 infection

- On the other hand, routine use of G-CSF to minimise febrile neutropenia and the need for hospitalisation should be considered in uninfected patients

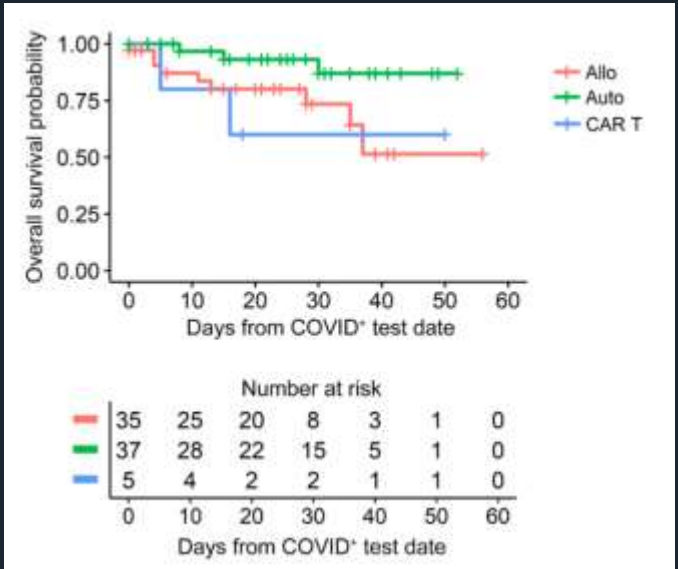
→ Empiric treatment for febrile neutropenia is still required

→ Re-evaluation for possible nosocomial infection with COVID-19 should be considered

NIH COVID treatment guidelines.

Transplantation during COVID-19

→ Should I offer a transplant to high-risk ALL patients during the pandemic?



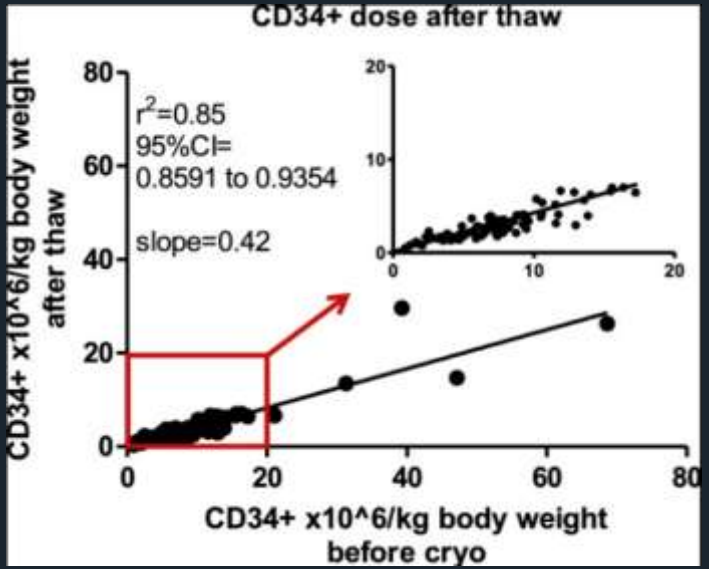
- Risk of mortality following transplantation if diagnosed with COVID-19 is relatively high
  - Risk factors for death are presence of 2 or more comorbidities or active disease
  - Death rate in patients without active malignancy was similar to the background hospitalised COVID population (21%)
- Discussion with patients about risks and benefits of transplantation and other cellular therapies (eg, CAR T) is warranted

Shah GL, et al. *J Clin Invest*. 2020;130:6656-6667.

Getting cells

→ With the border closures and delays in transport of cells, unrelated donor transplants have been more difficult

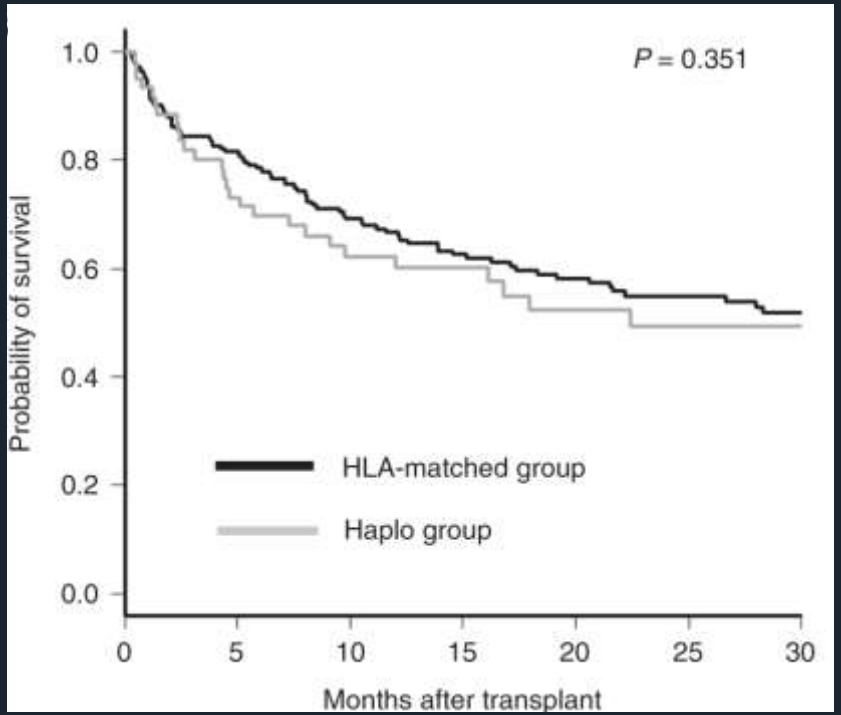
- Approximately 50% of the viable CD34+ cells are lost
- This did not appear to adversely affect engraftment, however
- Thus, transplant from unrelated donors is feasible during the pandemic
- May lead to delays, however, in cell procurement
  - Early in pandemic, 8 weeks; now approx 6 weeks for overseas donors (cf 3–4 weeks pre-pandemic)



Wiercinska E, et al. *J Transl Med*. 2021;19:145.

Alternative donor transplants

- → Haploidentical transplant may offer a faster turnaround time than unrelated donors
- → No need to freeze/thaw cells
- → Outcomes are not dissimilar to those seen with conventional donor transplants
  - EBMT data showed that in ALL patients in CR1, outcomes were not worse than either MUD or MMUD donors (Shem-Tov et al, *Leukemia* 2020)
- → Our approach has been to utilise haplo donors where delay would occur with unrelated donor transplants



Basquiera AL, et al. *Bone Marrow Transplant*. 2020;55:400-408.

Use of blinatumomab and other B-cell–depleting agents (eg, rituximab) during COVID-19 pandemic

→ Very limited data for blinatumomab

- Case report of patient developing COVID-19 while receiving therapy with blinatumomab amongst multiple other agents (outcome unknown)

→ Patients receiving agents such as rituximab or obinutuzumab appear to have poorer outcomes than those not receiving these agents[1]

- Data from a lymphoma cohort and confounded by effect of patient age and presence of active malignancy in the B-cell–depleted cohort
- Data in rheumatologic conditions suggest that patients do reasonably well[2]

→ Needs to be balance with the likely impact of poorer disease control if these agents are not used

1. Lamure S, et al. AACR 2021; 2. Baker D, et al. *Clin Exp Immunol*. 2020;202:149-161.

COVID vaccinations for patients with ALL

→ Vaccination should be offered to patients with haematologic malignancies
- Should be delayed until neutrophil recovery in patients receiving intensive therapies
- Following a transplant, a delay of 3 months is suggested for patients
  - No data currently to suggest increased GVHD post-vaccination
- Despite concerns regarding immune response, re-vaccination on immune recovery not currently recommended
- Consider vaccinating close contacts (“herd immunity”)

→ Special consideration in the ALL population
- The mRNA vaccines (Pfizer/BioNTech and Moderna) both contain PEG
  - In patients with a history of anaphylaxis to PEG-asparaginase, testing for PEG allergy may be suggested or use of an alternative agent

NIH COVID treatment guidelines.

Vaccine responses in patients with haematologic malignancies

→ Limited data on ALL patients – however, a study in CLL patients may shed some light

- Markedly lower rates of vaccine response in CLL patients compared with general population – 52% vs 100% (with Pfizer BNT162b2 vaccine)
  - Highest in patients in remission (79.2%)
  - Lowest in patients on active treatment (16%)
- No patients with anti-CD20 antibody exposure within the last 12 months responded
- Caveats to this study include the known effect of CLL on B-cell immune responses, and that this only considered antibody production as a surrogate for development of immunity

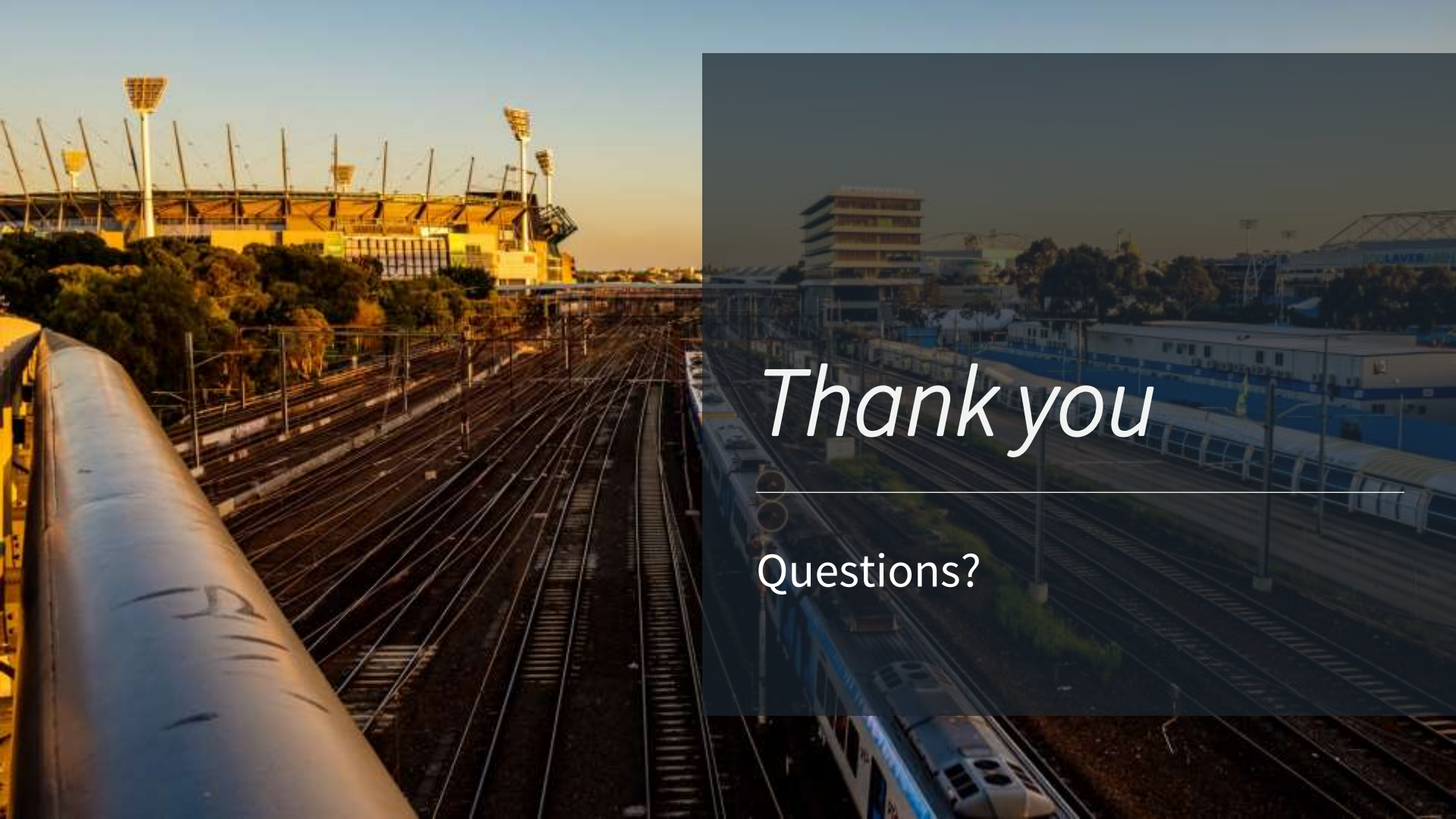
- A similarly poor response was seen in a further cohort, though highlighting CLL patients may be a particularly poor response group (Pre-print)

Herishanu Y, et al. *Blood*. 2021.

Summary

→ While data are limited, some general recommendations can be made

- Given the mortality associated with ALL if untreated or undertreated and the impact of active disease on COVID outcomes, patients should receive standard therapy for ALL
  - Any alteration to therapy should be weighed against the potential impact this may have on cure
- For patients receiving salvage therapies without curative intent, frank discussion about prognosis may be required
- Considerations for measures to minimise hospital presentations and exposure to the community are suggested, particularly during times of high prevalence
- Transplantation can still be considered in high-risk disease, with haploidentical donors being an option where unrelated donors are difficult to access
- Vaccination should be offered to patients with ALL despite uncertain efficacy in this population group
  - Given this uncertain efficacy, patients should be advised about NPI to reduce exposure risk, and vaccination of their “bubble” considered



Thank you

Questions?

Global Leukemia Academy

Leukemia board discussion: Patient case

Bhavna Padhye

APTITUDE HEALTH

Patient case

- 7 y/o female
- White cell count at diagnosis: 15.3×10^9/L
- Flow cytometry: CD7, cCD3, no features suggestive of ETP-ALL
- CNS: not involved
- Extramedullary involvement: nil

Patient case

- Started treatment as per AIEOP-BFM ALL 2017
  - Day 8: prednisolone response – poor (blast count 6.4)
  - Day 15: flow MRD 87% = persistent disease
  - Day 33 (end of induction): PCR MRD 6×10^{-1}
  - CNS remains negative

- What is the steroid of choice for patients with T-ALL?
- MRD-based risk stratification
- Indications for cranial RT
- Indications of BMT in CR-1
- Role of nelarabine

Steroid choice in induction

- Dexamethasone: greater potency and increased CNS penetration, but counterbalanced by increased infection

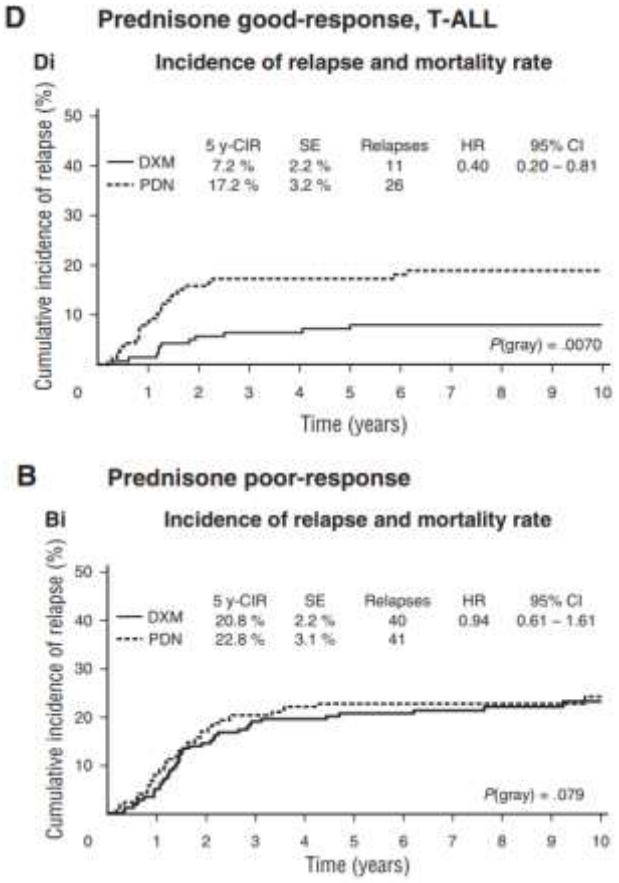
Study	Years of accrual	Population receiving CRT	Induction steroid	EFS or DFS; OS
COG AALL0434[6]	2007-2014 (n = 1895)	Intermediate and high-risk and CNS disease	Prednisone	89.3% DFS (4 y)
UKALL 2003[2,5]	2003-2011 (n = 388)	CNS disease only	Dexamethasone	81.2% EFS (5 y); 86.4% OS (5 y)
DFCI 05-001[3,4]	2005-2010 (n = 97)	All T-ALL patients	Prednisone	83% EFS (4 y); 89% OS (4 y)
AIEOP-BFM ALL 2000[1]	2000-2006 (n = 280 PGR)	All T-ALL patients*	Dexamethasone vs prednisone	87.8% EFS DEX (5 y); 91.4% OS DEX (5 y); 79.2% EFS PRED (5 y); 82.6% OS PRED (5 y)

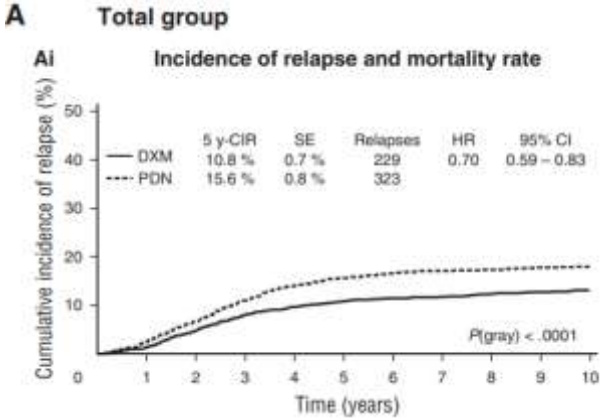
Raetz EA, et al. *Hematology Am Soc Hematol Educ Program*. 2016;1:580-588.

Pred vs Dex: BFM 2000

Key Points

- Dexamethasone vs prednisone in induction of pediatric ALL led to significant relapse reduction and increased treatment-related mortality.
- No overall survival benefit was achieved with dexamethasone except in the subset of patients with T-cell ALL and good early treatment response.





Möricke A, et al. *Blood*. 2015;127:2101-2112.

BFM 2000: MRD at TP1 and TP2

- Negativity of MRD at TP1 was the most favorable prognostic factor
- An excellent outcome was also obtained in patients turning MRD negative only at TP2, indicating that early (TP1) MRD levels were irrelevant if MRD at TP2 was negative
- MRD >10^{-3} atTP2 constitutes the most important predictive factor for relapse in childhood T-ALL

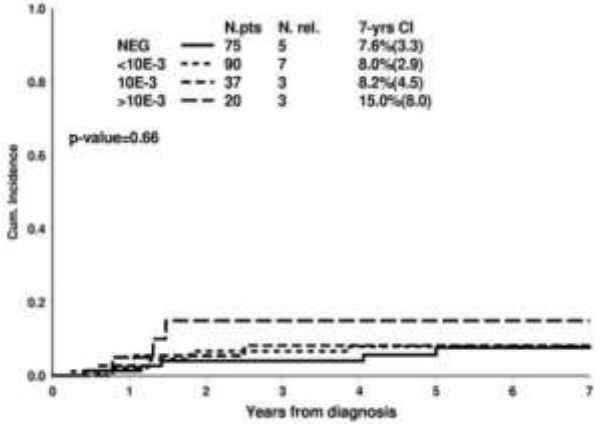


Figure 4. Cumulative incidence of relapse in 222 T-ALL patients with negative MRD at TP2 according to MRD results at TP1.

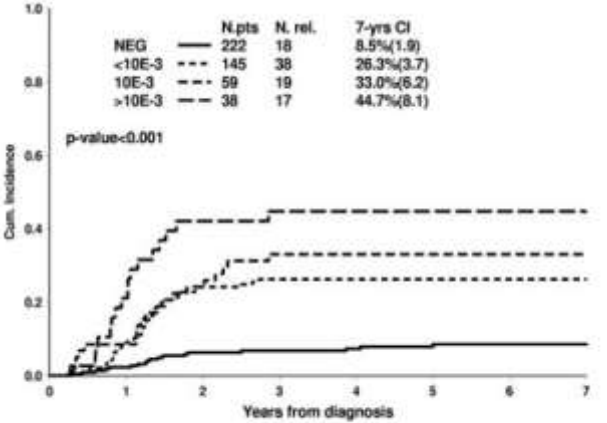


Figure 5. Cumulative incidence of relapse in 464 T-ALL patients by MRD levels at TP2.

Schrappe M, et al. *Blood*. 2011;118:2077-2084.

EFS and CI of relapse according to risk groups

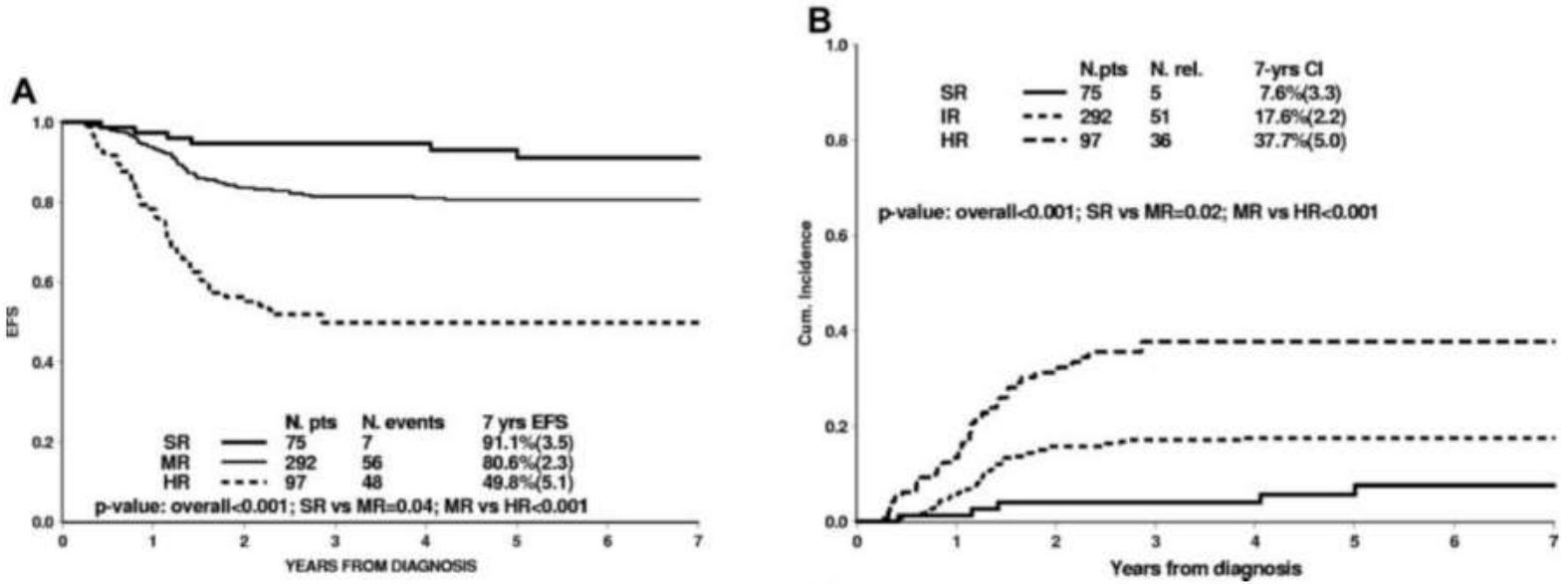


Figure 2. Treatment outcome in risk groups. EFS (A) and cumulative incidence of relapse (B) according to PCR-based MRD classification in 464 patients.

Schrappe M, et al. *Blood*. 2011;118:2077-2084.

Indications of BMT in CR-1

- Patients with high MRD at the end of consolidation
- Refractory ALL
- What about patients with M2/M3 marrow at the end of induction with low MRD at end of consolidation?

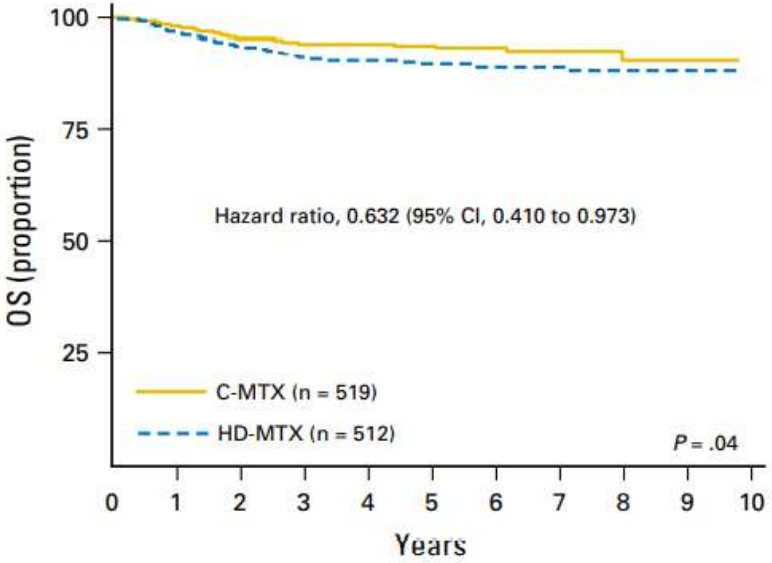
Nelarabine/AALL0434

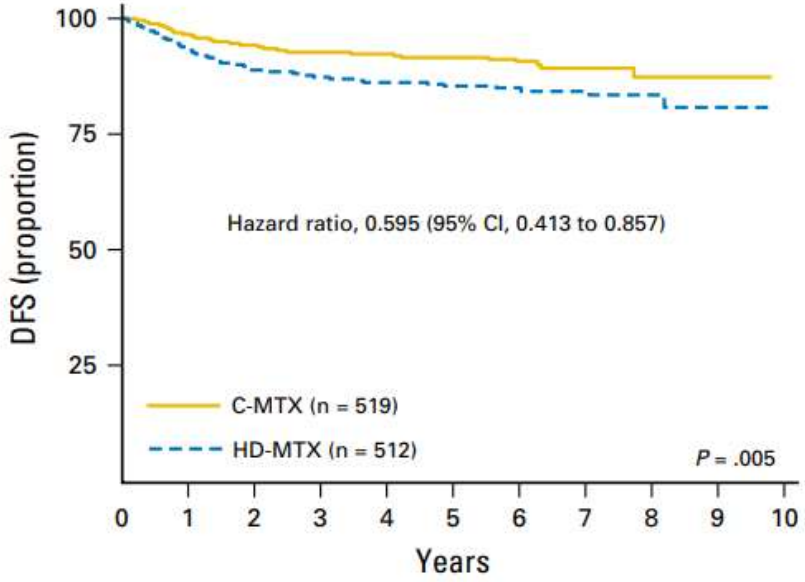
- 2 × 2 randomization
- Capizzi MTX vs HD MTX
- Nelarabine vs no nelarabine
- Prednisolone

- All HR and IR patients had prophylactic CRT

Winter SS, et al. *J Clin Oncol*. 2018;36:2926-2934; Dunsmore KP, et al. *J Clin Oncol*. 2020;38:3282-3293.

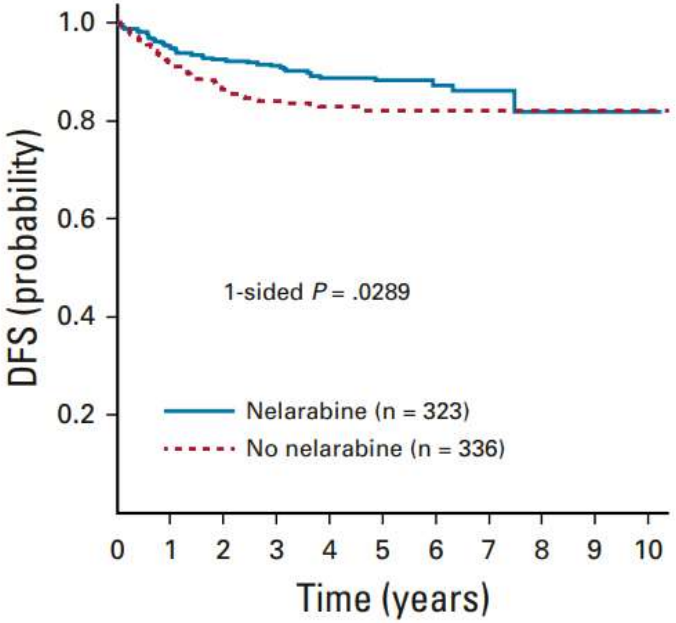
HD MTX vs Capizzi MTX

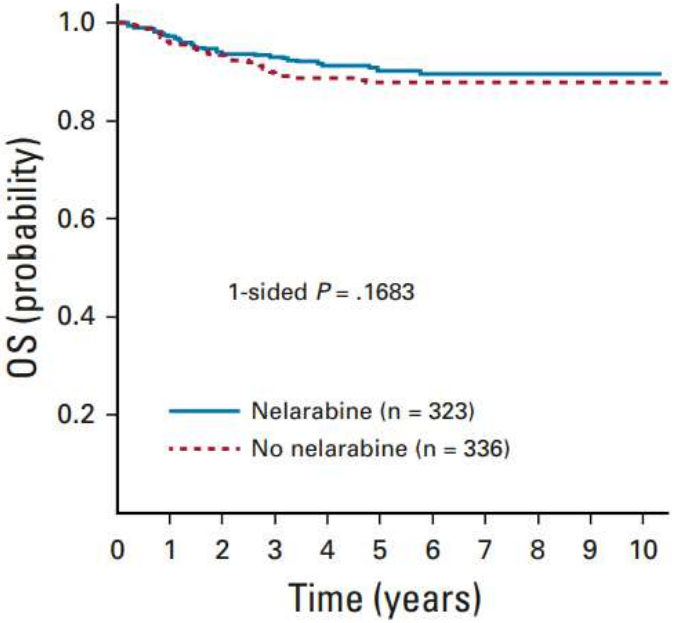




Winter SS, et al. *J Clin Oncol*. 2018;36:2926-2934.

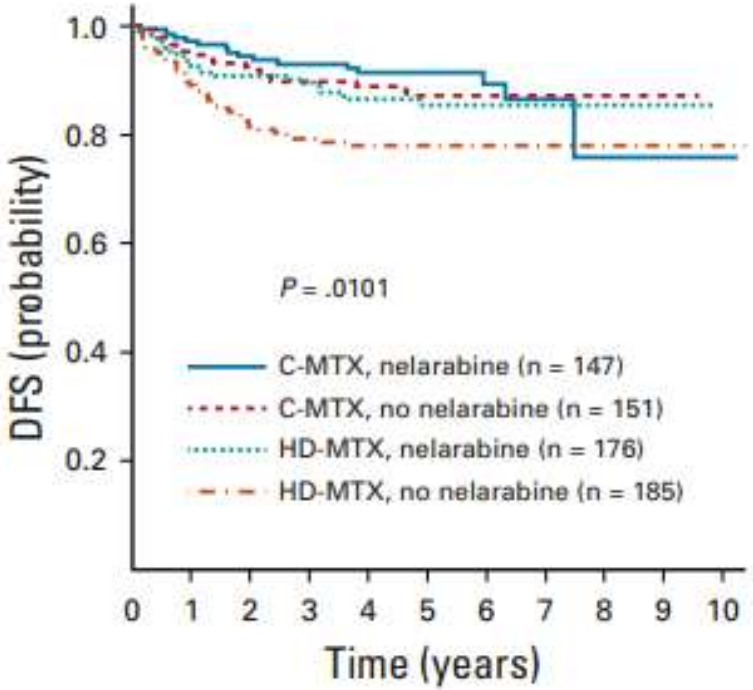
Nelarabine vs no nelarabine





Dunsmore KP, et al. *J Clin Oncol*. 2020;38:3282-3293.

Nelarabine and Capizzi MTX



Dunsmore KP, et al. *J Clin Oncol*. 2020;38:3282-3293.

Role of cranial RT

- CRT is effective at reducing CNS relapse, but the benefit is significantly offset by long-term morbidity, especially in young children
  - Endocrinopathies
  - Secondary cancers
  - Neurocognitive defects

- Most protocols avoid CRT except for patients with CNS-3
- Dex, asparaginase, HD MTX

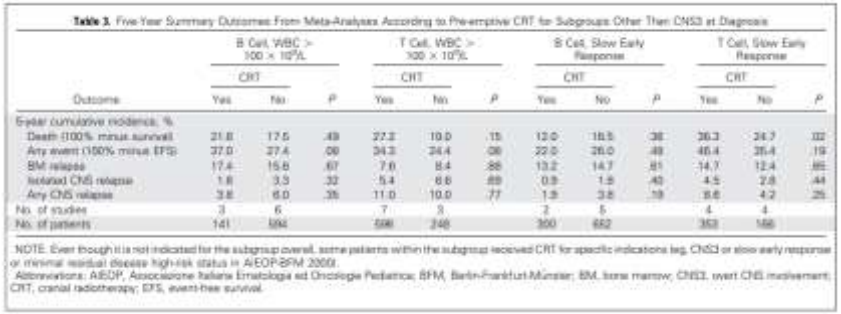


Table 3. Five-Year Summary Outcomes From Meta-Analyses According to Pre-emptive CRT for Subgroups Other Than CNS3 at Diagnosis

Outcome	B Cell, WBC > 100 × 10^9/L: CRT Yes	B Cell, WBC > 100 × 10^9/L: CRT No	B Cell, WBC > 100 × 10^9/L: P	T Cell, WBC > 100 × 10^9/L: CRT Yes	T Cell, WBC > 100 × 10^9/L: CRT No	T Cell, WBC > 100 × 10^9/L: P	B Cell, Slow Early Response: CRT Yes	B Cell, Slow Early Response: CRT No	B Cell, Slow Early Response: P	T Cell, Slow Early Response: CRT Yes	T Cell, Slow Early Response: CRT No	T Cell, Slow Early Response: P
5-year cumulative incidence, %												
Death (100% minus survival)	21.8	17.5	.49	27.2	19.0	.15	12.0	18.5	.36	36.3	24.7	.02
Any event (100% minus EFS)	37.0	27.4	.09	34.3	24.4	.06	22.0	26.0	.49	48.4	35.4	.19
BM relapse	17.4	15.6	.67	7.0	8.4	.88	13.2	14.7	.81	14.7	12.4	.66
Isolated CNS relapse	1.8	3.5	.32	5.4	6.6	.69	0.9	1.9	.40	4.5	2.8	.44
Any CNS relapse	3.8	6.0	.35	11.0	10.0	.77	1.9	3.8	.19	8.8	4.2	.25
No. of studies	3	6		7	3		2	5		4	4	
No. of patients	141	594		598	248		350	652		353	166	

NOTE. Even though it is not indicated for the subgroup overall, some patients within the subgroup received CRT for specific indications (eg, CNS3 or slow early response or minimal residual disease high-risk status in AIEOP-BFM 2009).
Abbreviations: AIEOP, Associazione Italiana Ematologia ed Oncologia Pediatrica; BFM, Berlin-Frankfurt-Münster; BM, bone marrow; CNS3, overt CNS involvement; CRT, cranial radiotherapy; EFS, event-free survival.

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Influence of Cranial Radiotherapy on Outcome in Children With Acute Lymphoblastic Leukemia Treated With Contemporary Therapy

Ajay Vora, Anita Andreano, Ching-Hon Pui, Stephen P. Hunger, Martin Schrappe, Anja Moericke, Andrea Biondi, Gabriele Escherich, Lewis B. Silverman, Nicholas Goulden, Mervi Taskinen, Rob Pieters, Keizo Horibe, Meenakshi Devidas, Franco Locatelli, and Maria Grazia Valsecchi

Vora A, et al. *J Clin Oncol*. 2016;34:919-926.

Coming back to the patient . . .

- After induction, went ahead with consolidation: IB
- PCR MRD at the end of consolidation: $<1 \times 10^{-4}$
- 3 high-risk blocks of therapy
- MRD before BMT: $<1 \times 10^{-4}$
- Underwent TBI-based conditioning and haploidentical BMT

Global Leukemia Academy

Leukemia Board Discussion

All faculty

APTITUDE HEALTH

Global Leukemia Academy

Debate on sequencing CD19-targeted approaches

Moderator: Aaron Logan

APTITUDE HEALTH

Q

Question

What is your preferred ALL treatment choice in salvage if all these therapies were available in your country?

a) CAR T therapies
b) Monoclonal antibodies or bispecifics

Global Leukemia Academy

Debate on sequencing CD19-targeted approaches: Monoclonal antibodies and bispecifics first

Elias Jabbour

APTITUDE HEALTH

Management of Patients With R/R Acute Lymphocytic Leukemia: Bispecifics and ADC

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

Conflict of Interest Disclosure

- **Research grants**
  - **Pfizer, Takeda, Amgen, AbbVie, Novartis**

- **Consultancy and advisory roles**
  - **Pfizer, Takeda, Amgen, AbbVie, BMS**

ALL Salvage Standards of Care in 2021

- Refer for investigational therapies – MoAb + ChemoRx; CAR T
- Ph+ ALL – TKIs + chemoRx; blinatumomab
- Pre–B-ALL
  - Blinatumomab (FDA approval 12/2014)
  - Inotuzumab (FDA approval 8/2017)
  - 2 CAR Ts (FDA approvals 8/2017 and 10/2017)
- T-ALL: nelarabine
- ChemoRx: FLAG IDA, Hyper CVAD, augmented HCVAD, MOAD

Historical Results in R/R ALL

- Poor prognosis in R/R ALL Rx with standard of care (SOC) chemotherapy

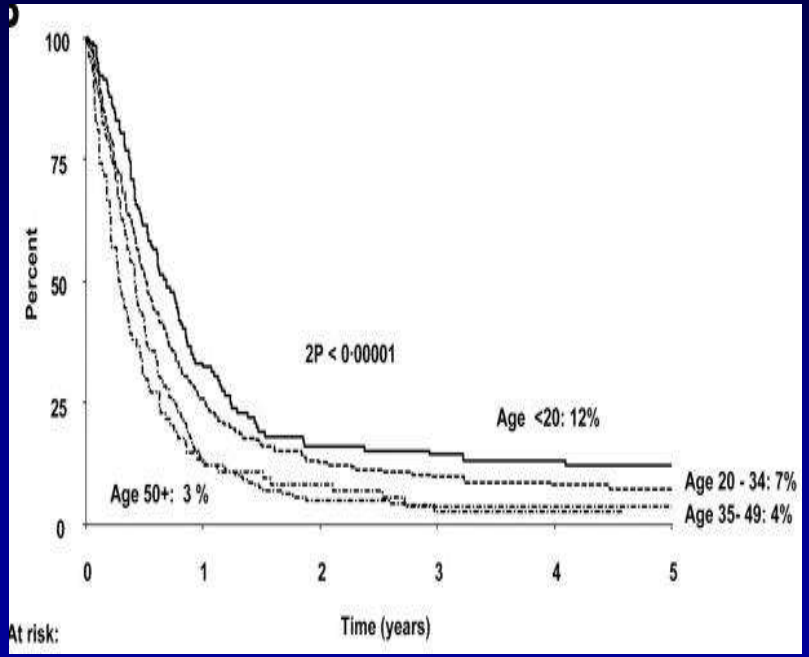
Rate (95% CI)	No prior salvage (S1)	One prior salvage (S2)	≥2 prior salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

Gökbuget N, et al. *Haematologica*. 2016;101:1524-1533.

ALL – Historical Survival Rates After First Relapse

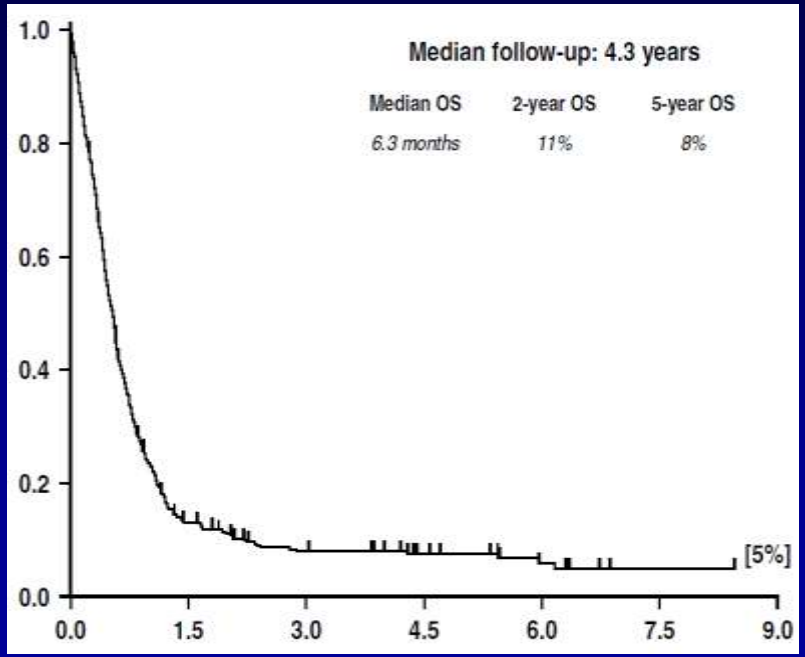
MRC UKALL2/ ECOG2993

Outcome of patients after 1st relapse
5-yr OS: 7%



LALA-94 Study (n = 421)

Outcome of patients after 1st relapse
2-yr OS: 11% and 5-yr OS: 8%

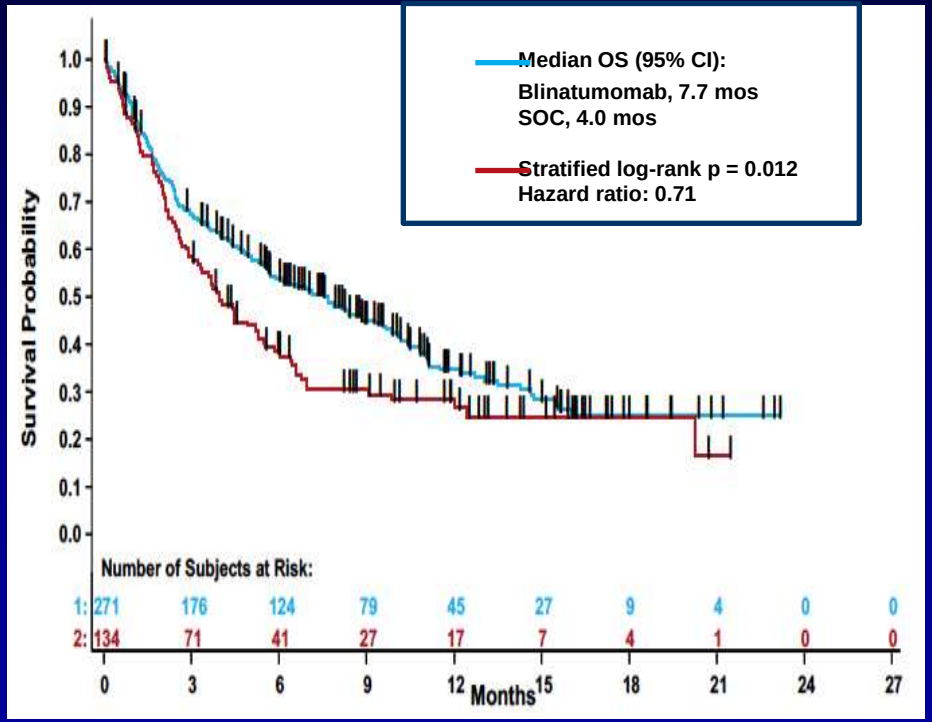


Fielding et al. *Blood*. 2007;109:944-950; Tavernier E, et al. *Leukemia*. 2007;21:1907-1914.

Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

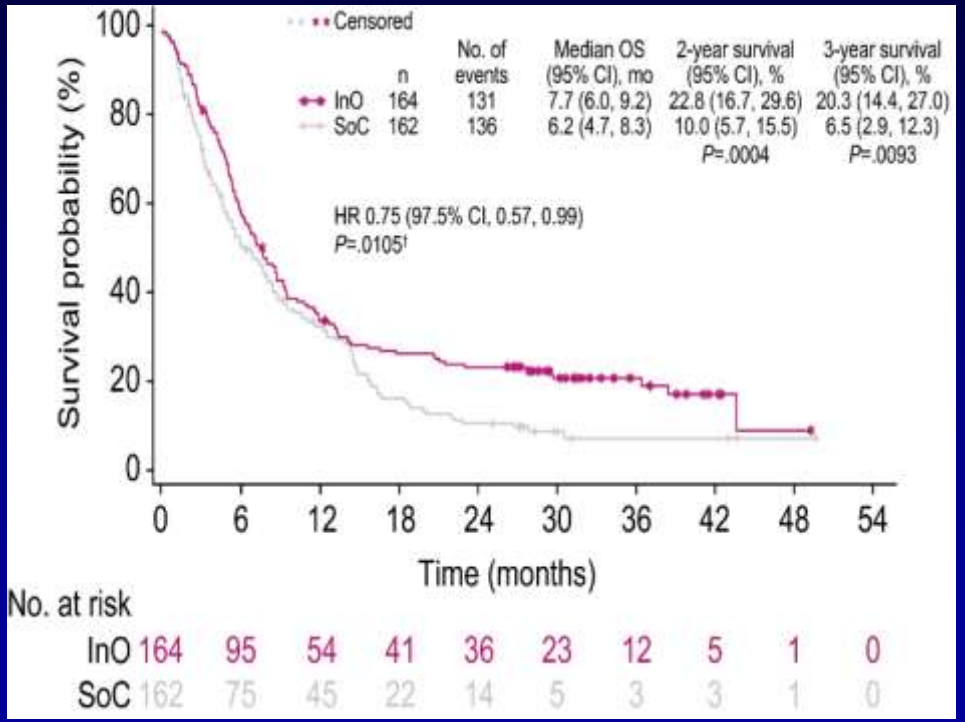
- **Marrow CR**

Blina vs SOC: 44% vs 25%



Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

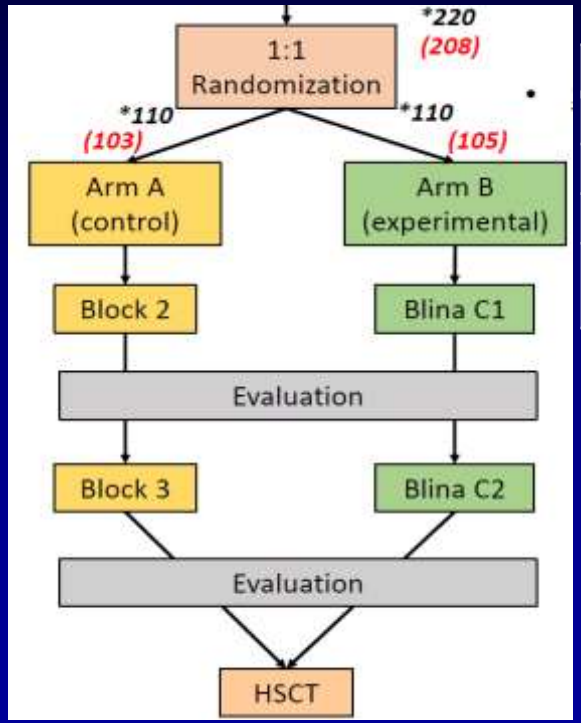
Ino vs SOC: 74% vs 31%



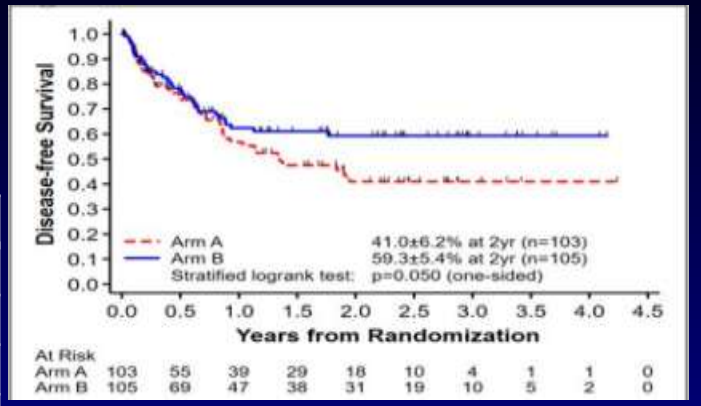
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

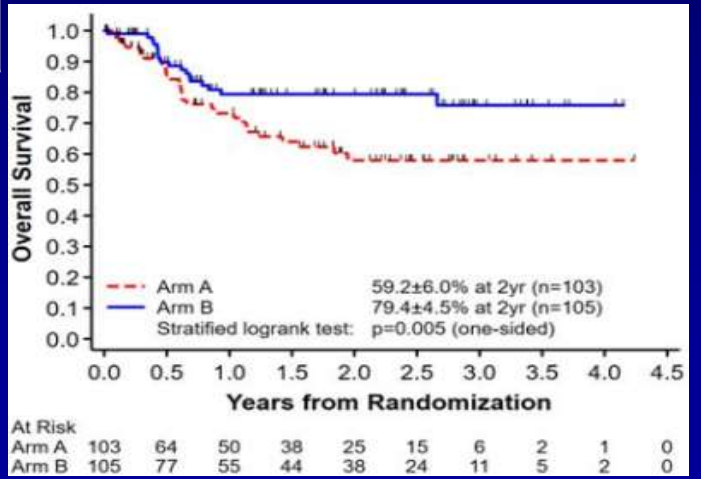
Phase III Study of Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

- 208 pts HR/IR randomized 1:1 to blina (n = 105) vs chemo Rx (n = 103) post Block 1 reinduction



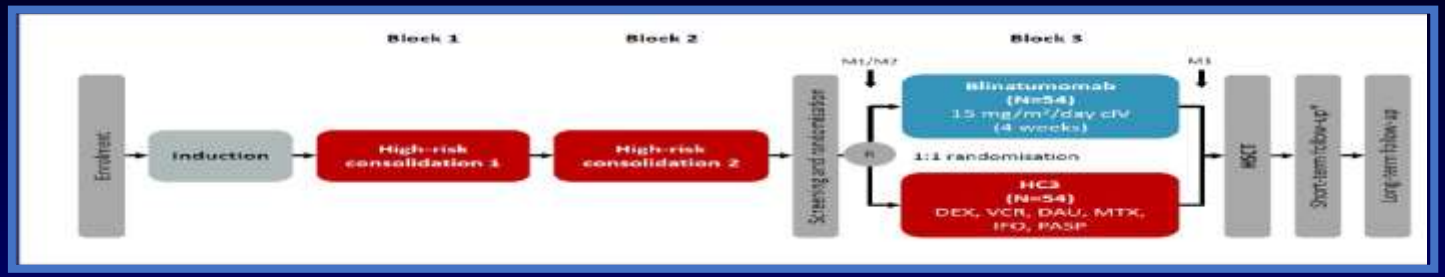
Parameter	Blina	Chemo	*P*
% 2-yr DFS	59	41	.05
% 2-yr OS	79	59	.005
% SCT	73	49	<.001
% MRD clearance	79	21	<.001





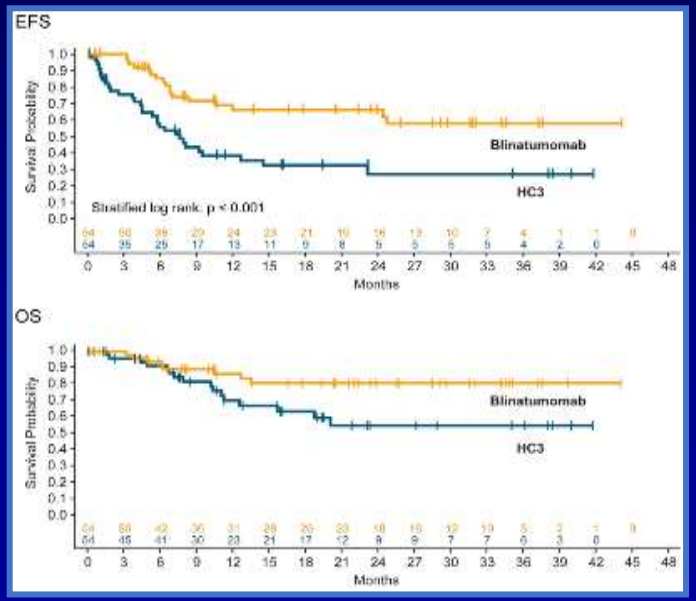
Brown et al. *JAMA*. 2021:325(9):833-842.

Blinatumomab vs Chemo Rx in Childhood ALL HR/First Relapse



Primary endpoint: EFS

	Blin (n = 54)	HC3 CHT (n = 54)
Events	18/54 (33%)	31/54 (57%)
EFS (median)	**Not reached**	**7.4 months**
MRD <10^{-4}	**43/46 (93%)**	**25/46 (54%)**
RR reduction (Blin vs HC3)	64% , HR 0.43, (95% CI 0.18–1.01)	
Grade ≥3 AEs	30/53 (57%)	41/51 (80%)



Locatelli F, et al. *JAMA*. 2021:325(9):843-854.

Phase II Study of Inotuzumab in R/R Pediatric ALL

- 32 pts enrolled, 28 Rx, 27 evaluable
- Median age 7.5 yrs (1.7–17). S2+ 57%. Prior blina 25%; prior ASCT 50%; prior CAR T Rx 11%
- Inotuzumab weekly × 3 up to 6 courses
  - RP2D 1.8 mg/m^2 (0.8-0.5-0.5)
- ORR = 81.5% (CR 50%); MRD neg 95% (82% after C1)
- 64% proceeded to ASCT and 14% to CAR T Rx
- 12-mos EFS 23%; 12-mos OS 46.5%
- 6 VOD (22%): 1 during InO; 5/14 post ASCT (36%)

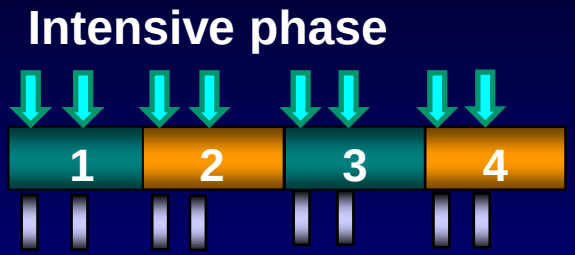
Brivio et al. *Blood*. 2020;136:abstract 164.

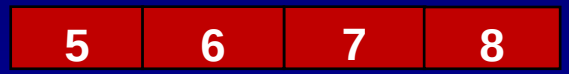
Mini-HCVD + INO + Blina in ALL: Design

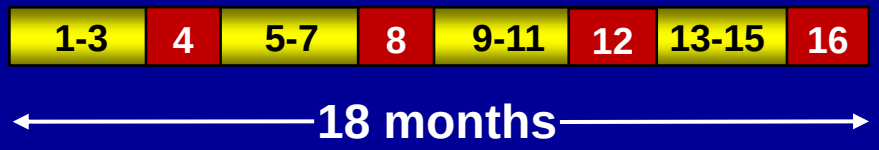
- Dose reduced HyperCVD for 4–8 courses
  - Cyclophosphamide (150 mg/m^2 ×6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 × 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - Modified to 0.9 mg/m^2 C1 (0.6 and 0.3 on D1&8) and 0.6 mg/m^2 C2-4 (0.3 and 0.3 on D1&8)
- Rituximab D2 and D8 (first 4 courses) for CD20+
- IT chemotherapy days 2 and 8 (first 4 courses)
- Blinatumomab 4 courses and 3 courses during maintenance
- POMP maintenance for 3 years, reduced to 1 year

Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055.

Mini-HCVD + INO ± Blina in R/R ALL: Long-Term Follow-Up







Mini-HCVD

Mini-MTX-cytarabine

IT MTX, Ara-C

Blinatumomab

POMP

INO	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D1, 0.3 D8
C2-4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m^2

Sasaki et al. *Blood.* 2020;136: abstract 1895.

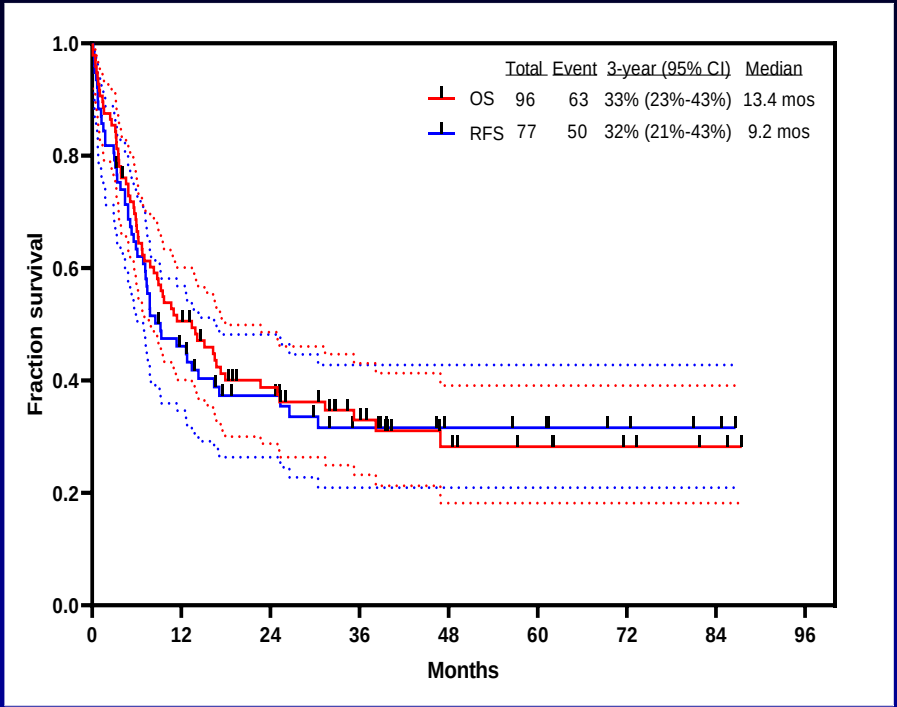
Mini-HCVD + INO ± Blina in R/R ALL (N = 96)

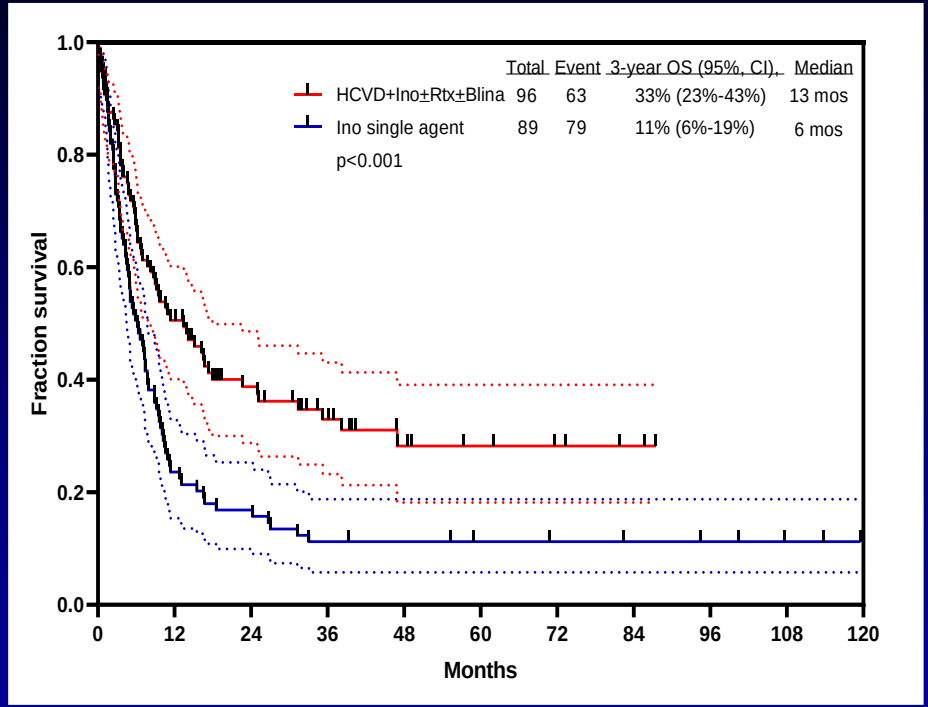
Characteristic	Category	No. (%)
Age (year)	Median [range]	37 [17–87]
Gender	Male	45 (47)
ECOG PS	2+	18 (19)
Salvage Status	S1 S1, Primary Refractory S1, CRD1 <12 months S1, CRD1 ≥12 months S2 ≥S3	64 (67) 8 (8) 25 (26) 31 (32) 18 (19) 14 (15)
Prior ASCT		19 (20)
Karyotype	Diploid T(4;11) Ho-Tr Complex Misc IM/ND	23 (24) 10 (10) 10 (10) 14 (16) 23 (24) 16 (17)
CD22	Median [range]	95 [14–100]
CD20	≥20%	23 (24)

Characteristic	No. (%)
Response, No. (%)	
Salvage 1	58/64 (91)
S1, Primary refractory	8/8 (100)
S1, CRD1 <12 mos	21 (84)
S1, CRD1 ≥12 mos	29 (94)
Salvage 2	11 (61)
≥ Salvage 3	8 (57)
Overall	77/96 (80)
MRD negativity	62/75 (83)
Salvage 1	50/56 (89)
≥ Salvage 2	12/19 (63)

Sasaki et al. *Blood.* 2020;136: abstract 1895.

Mini-HCVD + INO ± Blina in R/R ALL: Outcome

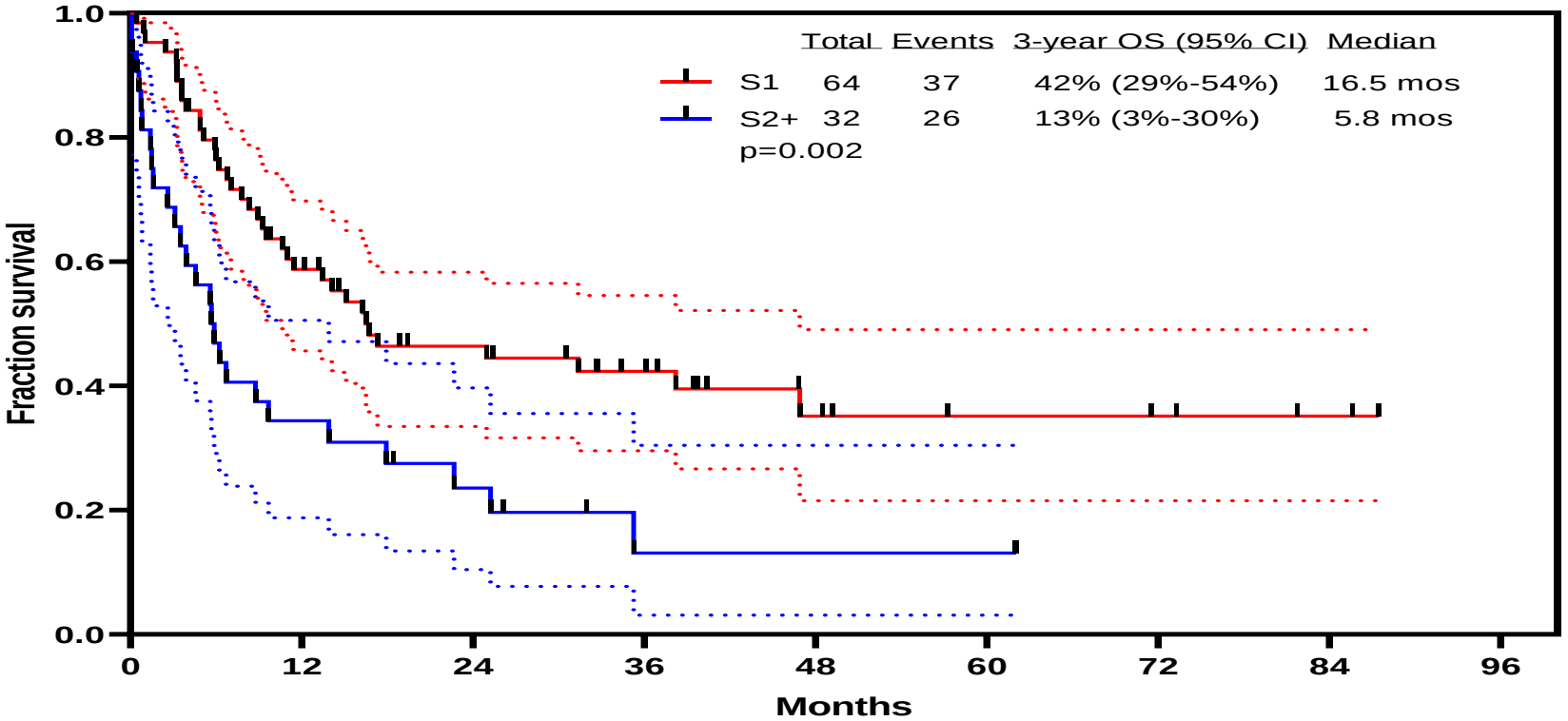




	Single dose (n = 67)	Fractionated lower dose followed by blina (n = 29)
VOD (%)	9 (13)	1 (3)

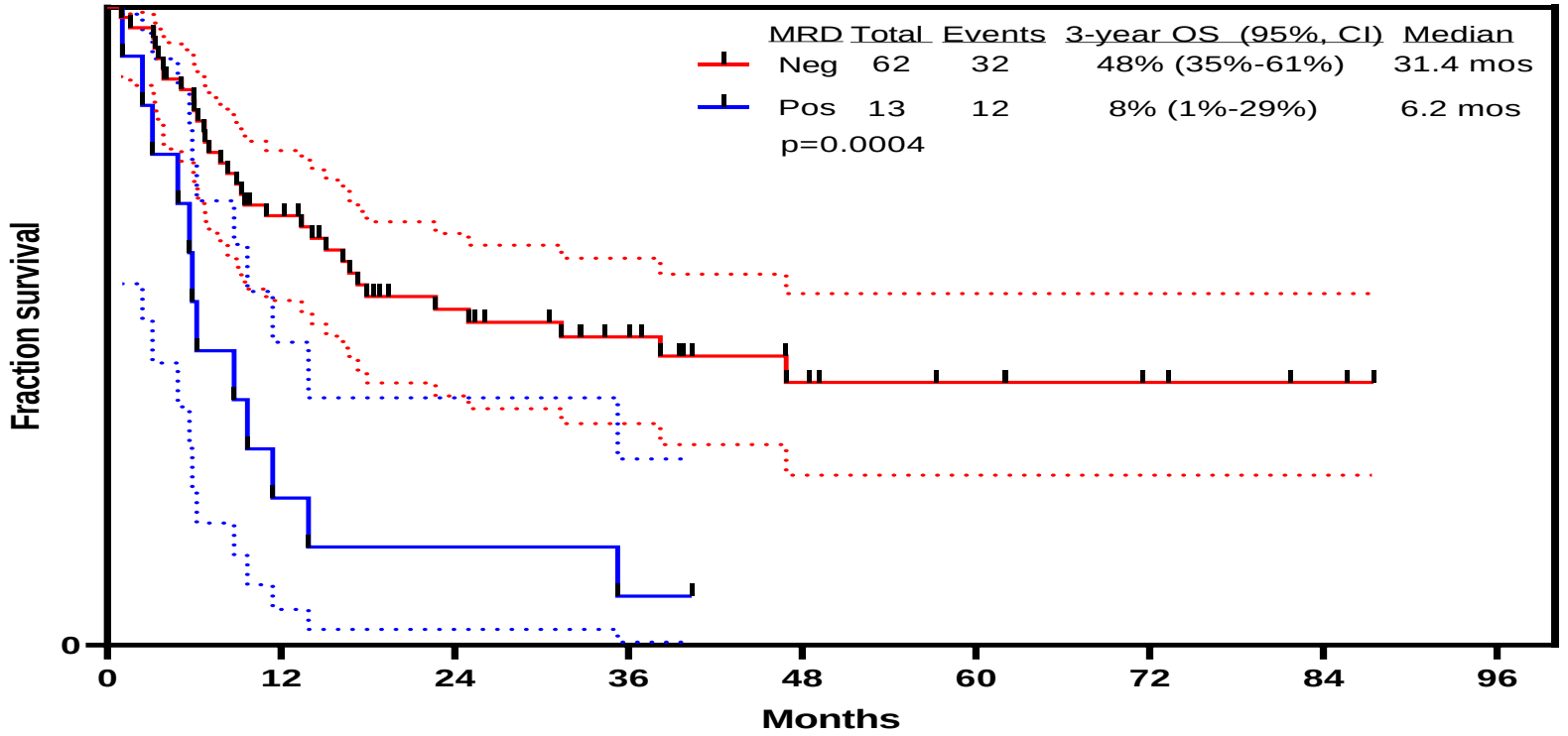
Sasaki et al. *Blood.* 2020;136: abstract 1895.

Mini-HCVD + INO ± Blinatumomab in R/R ALL
OS by Salvage Status



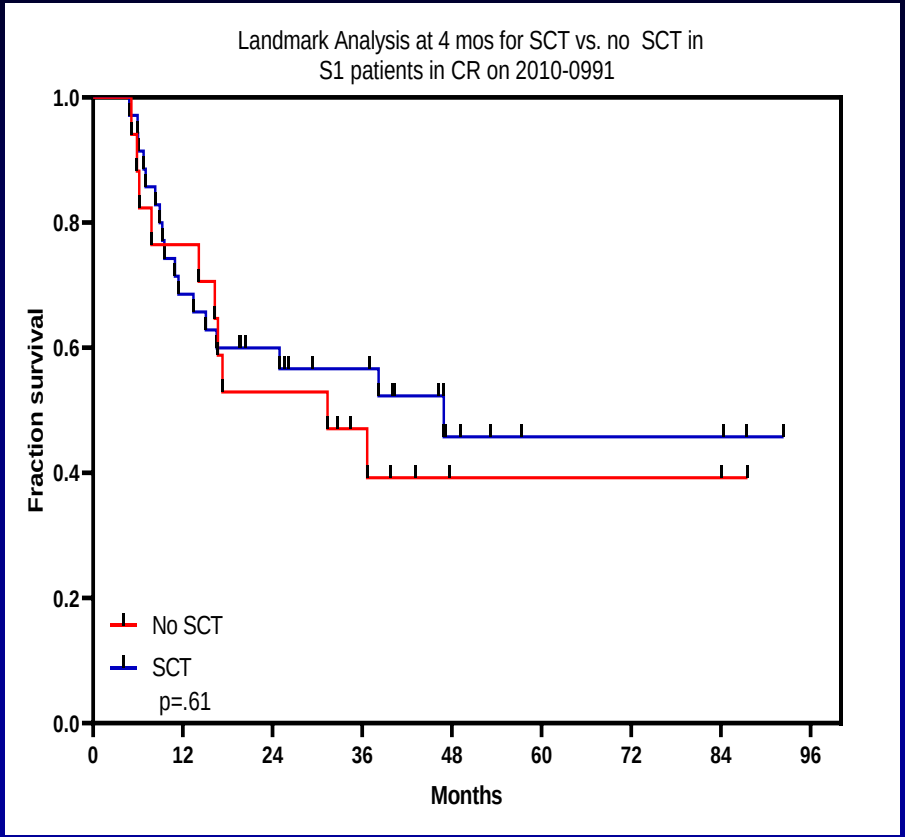
Rafei et al. *Blood.* 2020;134: abstract 1932.

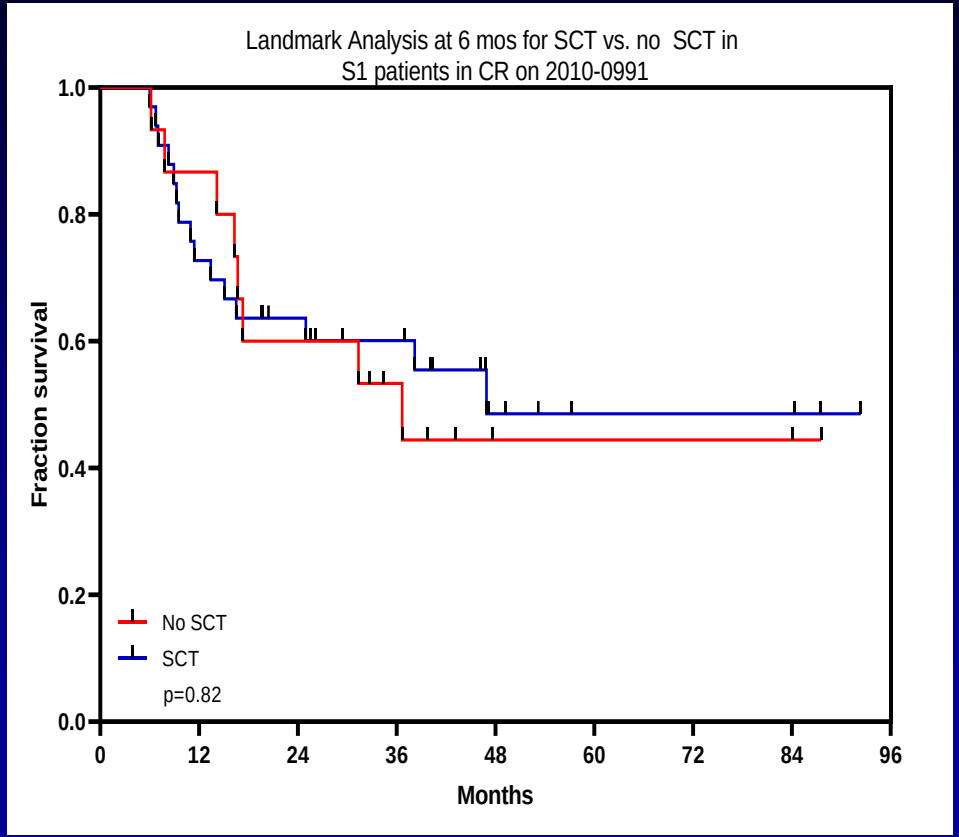
Mini-HCVD + INO ± Blinatumomab in R/R ALL
OS by MRD Status



Sasaki et al. *Blood.* 2020;136: abstract 1895.

Mini-HCVD + INO ± Blinatumomab in S1 ALL
OS by Subsequent ASCT

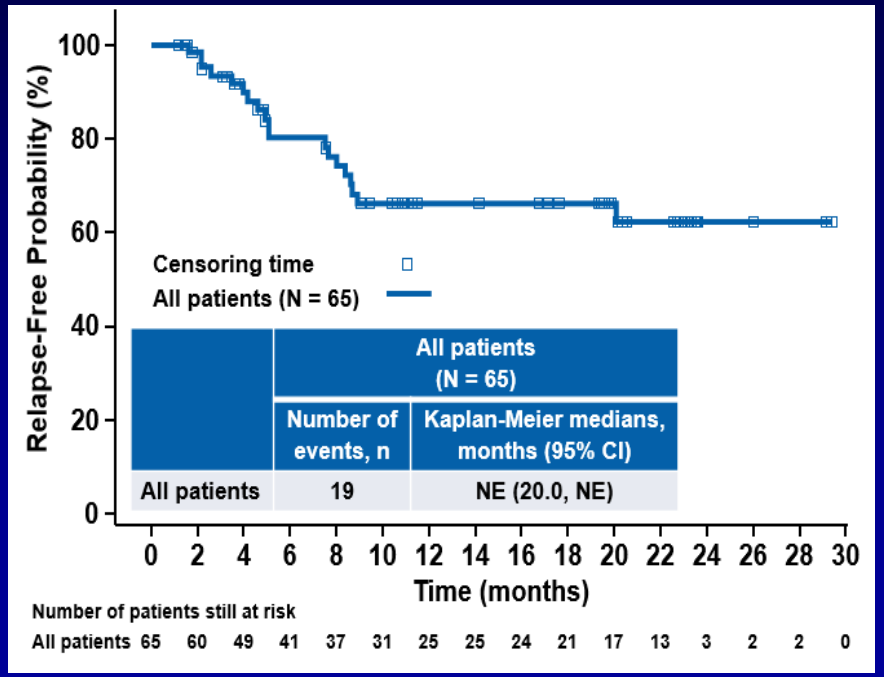


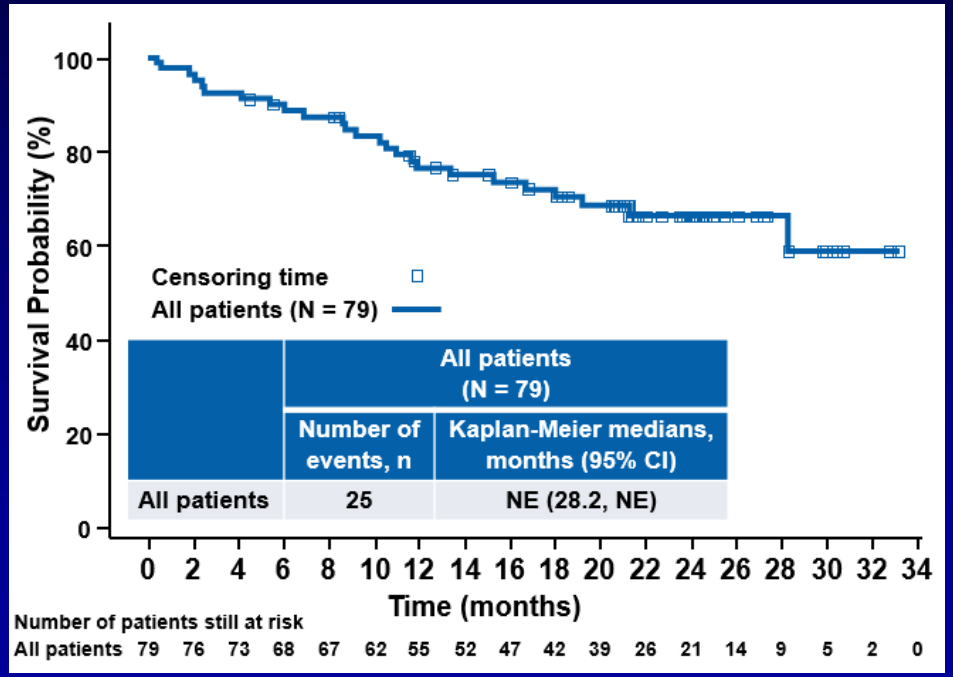


Rafei et al. *Blood*. 2020;134: abstract 1934.

ELIANA Trial Update

- 113 screened, 97 enrolled, 79 infused
- 3-mo CR 65/79 = 82%, or 65/97 = 67%
- 24-mos OS 66%; RFS 62%. Gr 3-4 CRS 49%. ICU 48%

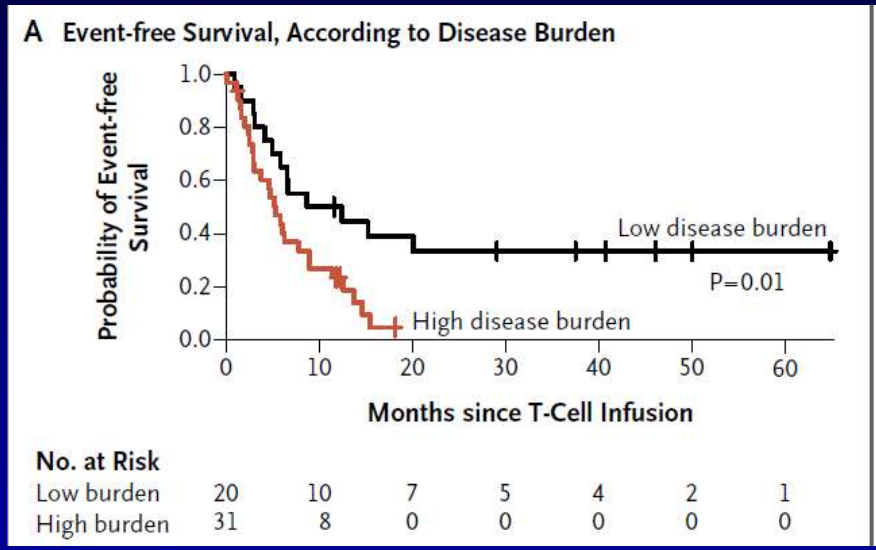


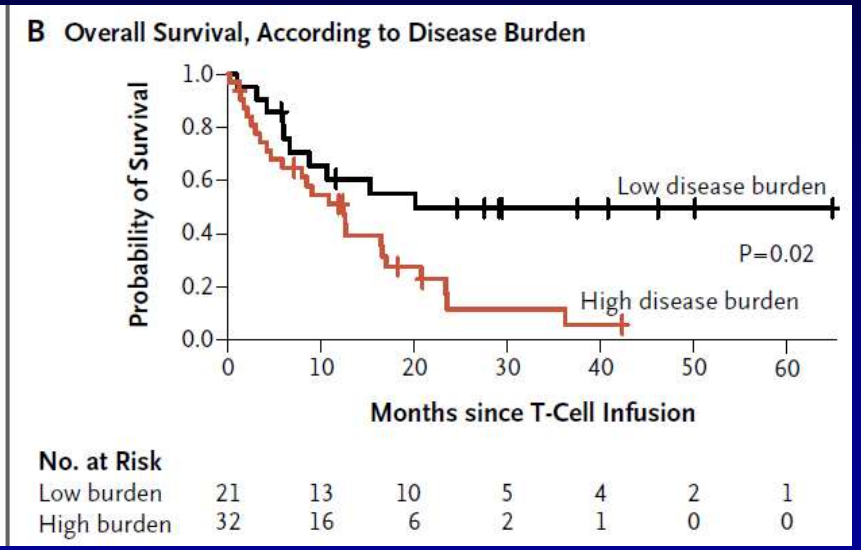


Grupp et al. EHA 2019. Abstract S1618.

CD19-CD28z CAR (MSKCC): Outcome by Tumor Burden

- **High tumor burden**
  - **Bone marrow blasts ≥5% (n = 27)**
  - **Bone marrow blasts <5% + extramedullary disease (n = 5)**
- **Low tumor burden (MRD+ disease) (n = 21)**





Median EFS
Low tumor burden (MRD+): 10.6 mos
High tumor burden: 5.3 mos

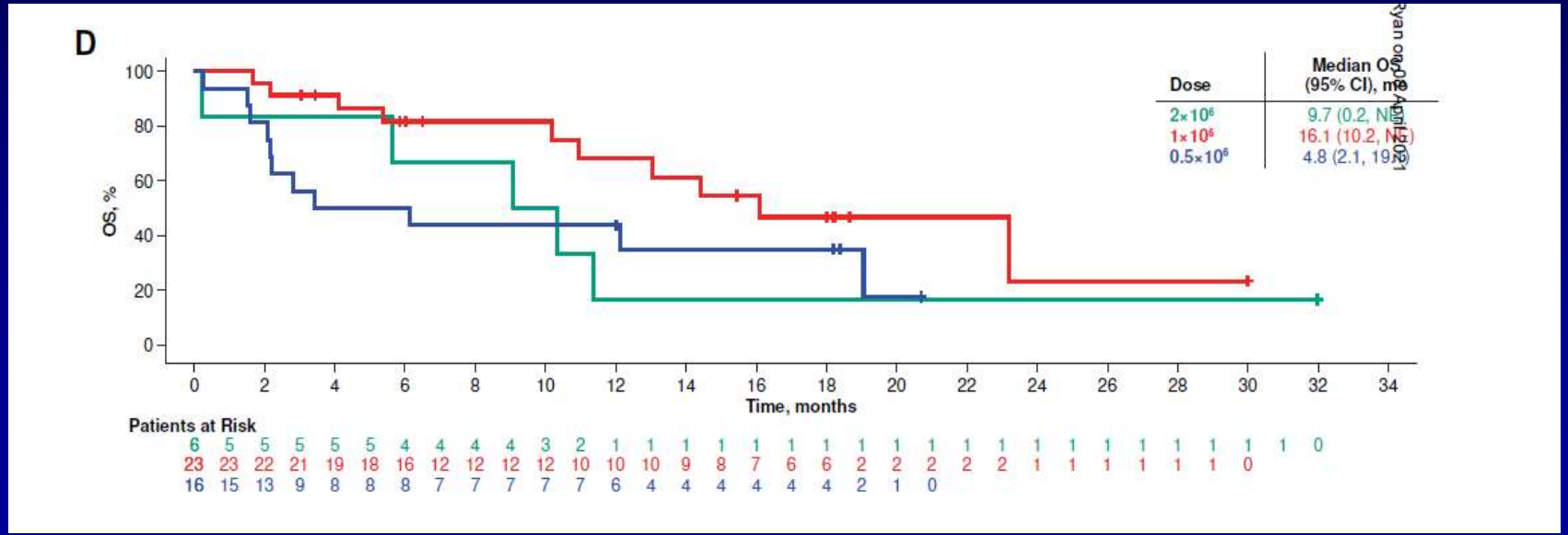
Median OS
Low tumor burden (MRD+): 20.1 mos
High tumor burden: 12.4 mos

Park et al. *N Engl J Med.* 2018;378:449.

MSKCC, Memorial Sloan Kettering Cancer Center

KTE-X19 Anti-CD19 CAR T-Cells RX (Kite) in R/R ALL: Phase I/II (ZUMA-3)

- 54 screened, 49 enrolled, 45 infused median age 46 yrs (18–77)
- ORR 83% (CR 65%); MRD– response 100%
- mDOR 17.6 mos; mRFS 7.7 mos; mOS 16.1 mos. Median F/U 22 mos; 6/19 (32%) ongoing response
- Grade ≥3: CRS 31%; NE 38%

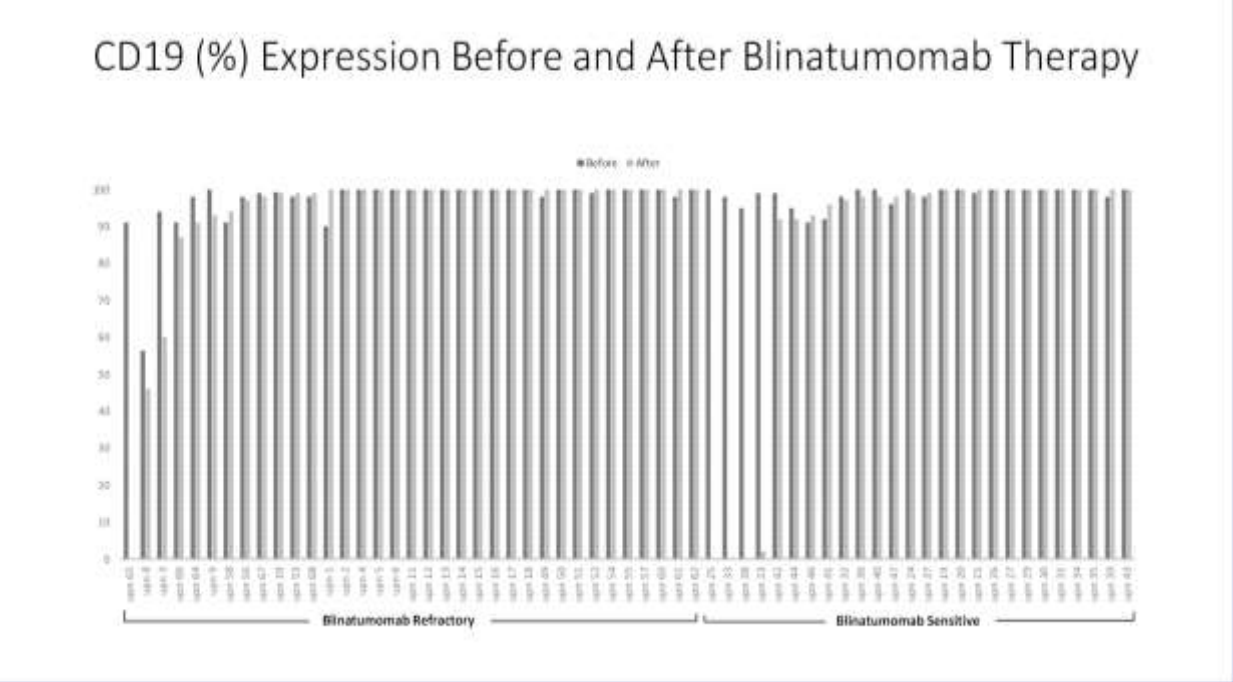


Shah et al. *Blood*. 2021, in press.

Antibodies vs CAR T in ALL: Comparing Apples to Apples

Age Group	Salvage	Rx	% CR	% OS (× yr)
Pedi	S1	Blinatumomab	79	79 (2)
	S2	Inotuzumab	62	40 (1)
	S2	CAR T	67 (82% of infused)	66 (2)
Adult	S1	Mini-CVD-ino-blina	91	40 (3)
	S2-S3	Mini-CVD-ino-blina	57–61	20–40 (2)
	S2+	CAR T (active ALL)	65	10–20 (2)

CD19 (%) Expression Before and After Blinatumomab Therapy



- 61 patients evaluated for immunophenotype, 56 (92%) had CD19-positive disease
  - 5 (8%) had ALL recurrence with CD19-negative disease
  - 2 patients progressed with lower CD19-positive disease

Jabbour et al. *Am J Hematol.* 2018;376:836-847.

Pre-CAR Blinatumomab = ↑ Relapse and ↓ EFS

- 412 pts ≤25 yrs (7 centers) Rx with 1 of 3 CAR T
- 375/412 achieved CR = 91%; 363 MRD negative (88%)
- 75 (18%) had prior blina; 57% CR
  - Prior blina KMT2A (15% vs 6%), EM disease (8% vs 4.6%)
- No difference in OS

Figure 1A. Relapse Free Survival

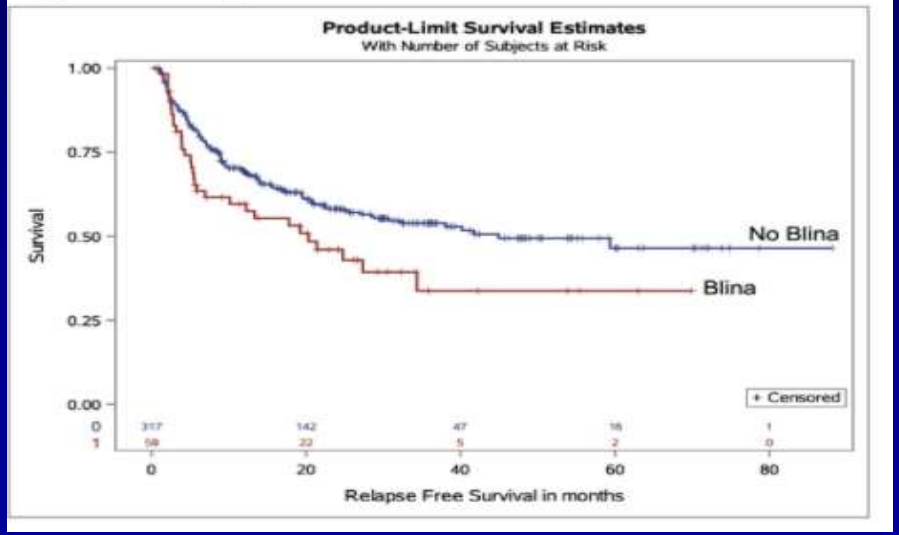
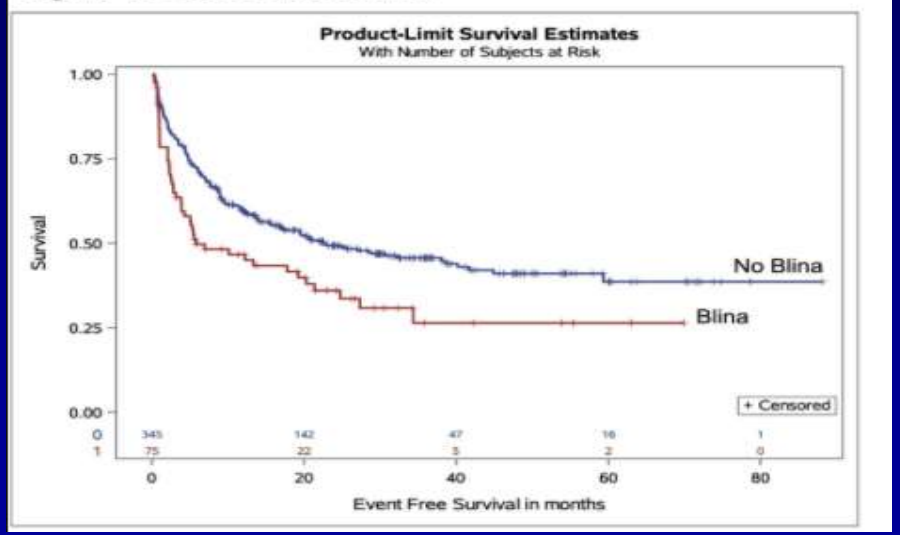


Figure 1B. Event Free Survival



Taraseviciute et al. *Blood*. 2020;136:abstract 269.

Salvage Therapies in ALL: Conclusions

- Very effective salvage therapy in R/R ALL
  - High MRD-negativity rate
  - Best outcome in Salvage 1
- Combination with low-dose chemotherapy
  - Safe and effective
  - Median survival 14 months
  - Salvage 1, 24 months (2-year OS rate >50%)
- AEs better controlled
- CRS: debulk with sequential chemotherapy
  - VOD lower doses explored
- CAR T-cell RX offered post blinatumomab and inotuzumab failure
  - Salvage 2 and high-risk Salvage 1 (eg, MLL)
  - Consolidation in high-risk patients (replacing allo-SCT)
- Better “blinatumomab” and “inotuzumab” needed
  - Better “Blina”: Long half-life; SQ; no neurotoxicities
  - Better “InO”: no VOD

Thank You

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Global Leukemia Academy

Debate on sequencing CD19-targeted approaches: CAR T first

José Maria Ribera

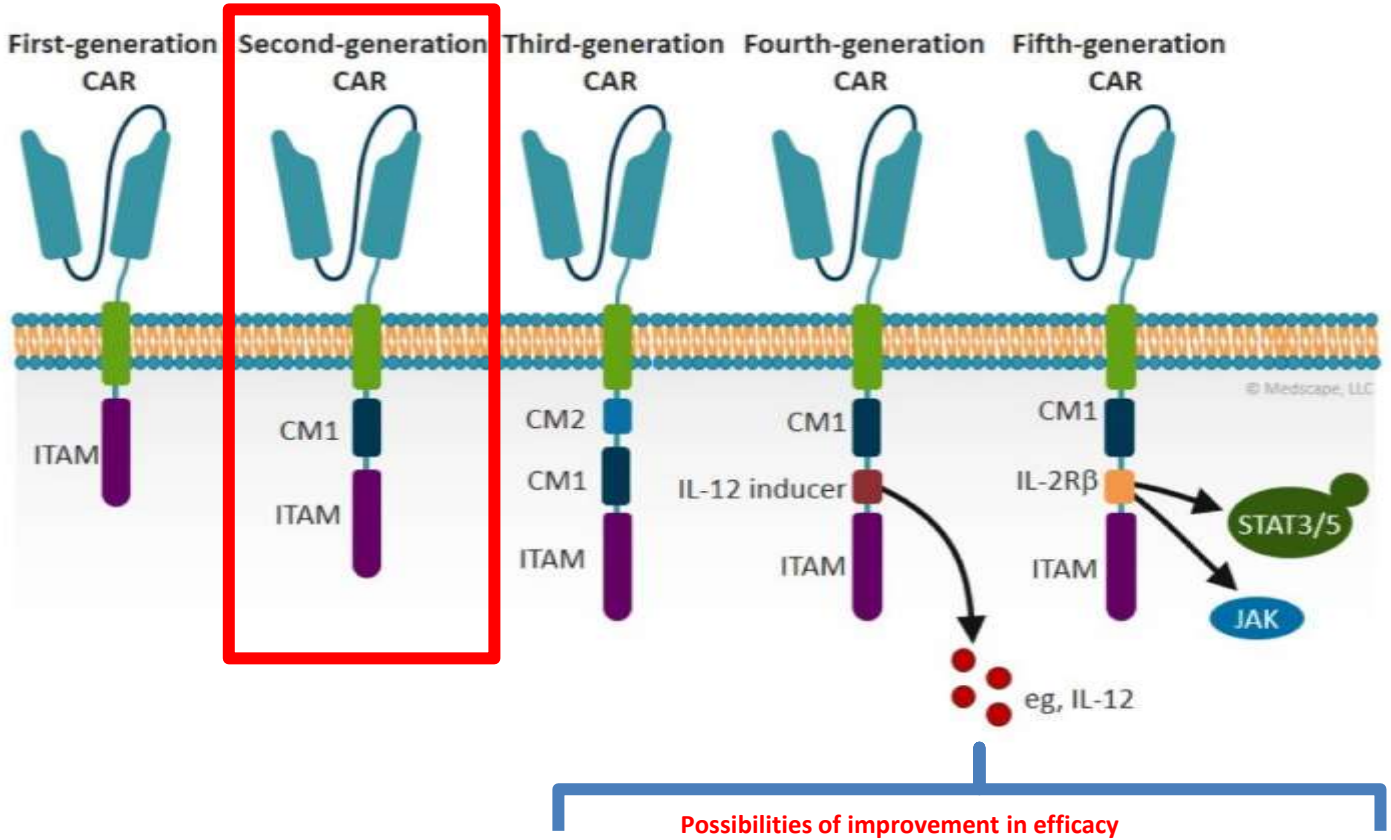
APTITUDE HEALTH

Global Leukemia Academy
Debate on Sequencing CD19-Targeted Approach
April 23, 2021

CAR T First

JM Ribera
Clinical Hematology Department
ICO-Hospital Germans Trias i Pujol
Institut de Recerca contra la Leucemia Josep Carreras
Badalona, Spain

Differences in CAR T-Cell Therapies



Tokarew N, et al. *Br J Cancer.* 2019;120:26-37.

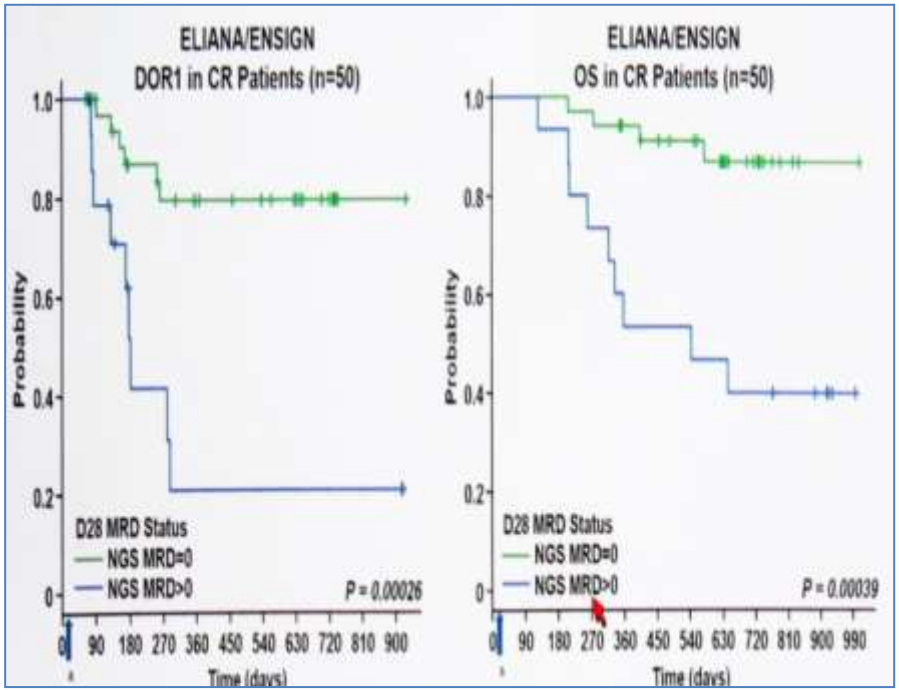
Second-Generation CD19 CAR T in R/R Adult ALL

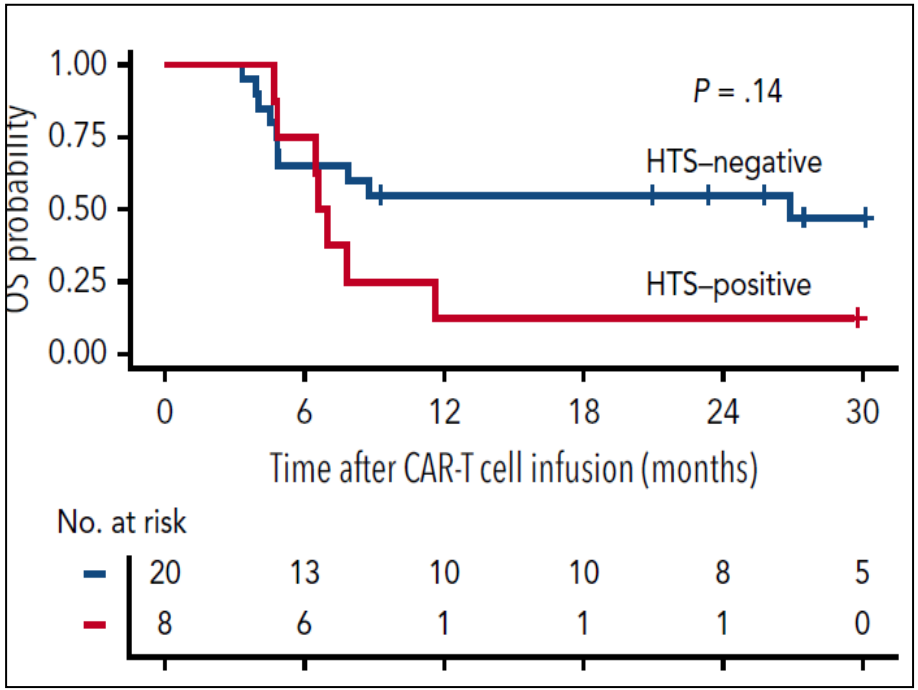
Study	N	Age, Median (range)	CR, %	MRD– in CR, %	Relapse (%)	PFS	OS
UPenn	35	33 (20-70) Single dose, low: 9 Single dose, high: 6 Fractionated dose, high: 20	33 50 90			0% 17% 49% (24 mo)	22% 17% 73% (24 mo)
MSKCC	53	44 (23-74)	83	67	57	Median: 6.1 mo	Median: 12.1 mo
FHCRC	53	39 (20-76)	85	85	49	Median: 7.6 mo	Median: 20 mo
City of Hope	13	33 (24-72)	100	91	NR	NR	NR
UCL	19	43 (18-72)	84	84	26	62% (6 mo)	NR
HCB-HSJD	27	35 (18-69)	85	85	15	Median: 9.4 mo	Median: 20.2 mo
KTE-X19	45	46 (18-77)	83	100		Median: 17.6 mo	Median: 16.1 mo

Second-Generation CD19 CAR T in R/R Adult ALL: Facts

- Limited experience, short-term results
- High CR rate (80%–90%), MRD– in 60%–80%
- Short duration of response (median 8–20 mo)
- Better results in pts with low tumor mass, promising in MRD+ pts
- Need for subsequent alloHSCT unclear, good results in some series
- Early MRD by high-throughput sequencing predicts outcome
- Prognostic factors in MRD– CR patients identified
- Major concerns: durability, CD19– relapses

Early Clearance of the Leukemic Clone by HTS Associated With Better Outcome





Median OS 26.9 vs 6.8 months

Pulsipher MA, et al. ASH 2018. Abstract 1551.

Hay K, et al. *Blood.* 2019;133:1652-1663.

CD19 CAR T Cells in Relapsed/Refractory Adult ALL

CAR: CD19 4-1BB

59 pts apheresis

53 infused

Patient characteristics

Median age: 39 (20–76) years

21% Ph+

43% prior SCT

26% bridging

Disease at lymphodepletion:

64% (N=34) morphological BM relapse (≥5%)

- 13 extramedullary

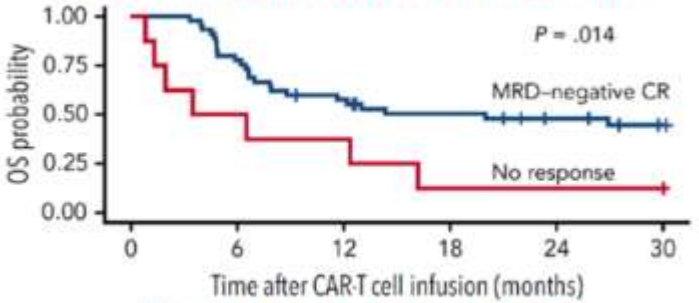
4% (N=2) extramedullary only

32% (N=17) MRD pos

- 3 extramedullary

85% in CR and MRD neg after infusion

Overall survival after infusion



Prognostic factors for EFS

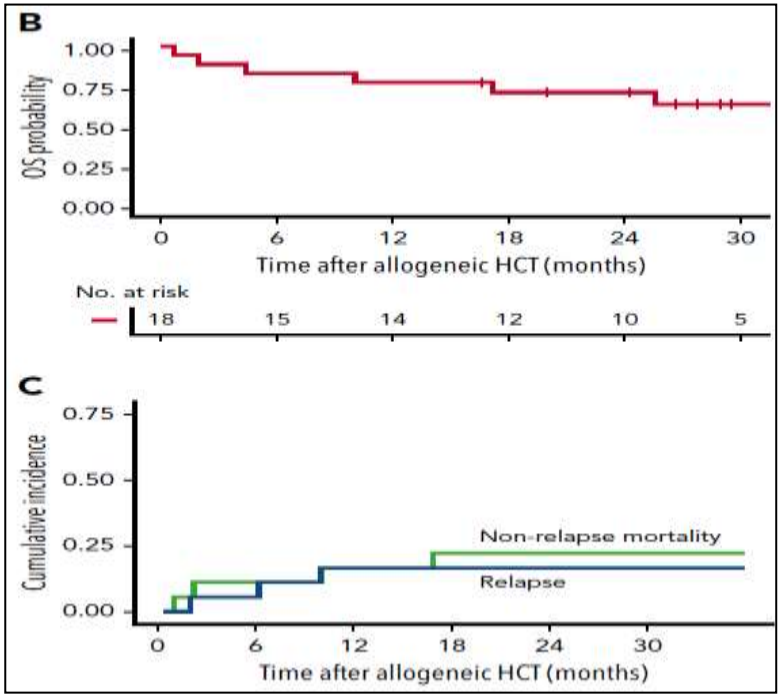
Variable	Multivariable analysis		
	HR	95% CI	P
LDH prelymphodepletion (per 100 U/L increment)	1.39	1.11-1.73	.004
Platelets prelymphodepletion (per 50 000/μL increment)	0.74	0.53-1.03	.069
Fludarabine added to lymphodepletion	0.25	0.15-0.78	.003
HCT after CAR T-cell therapy	0.39	0.13-1.15	.088

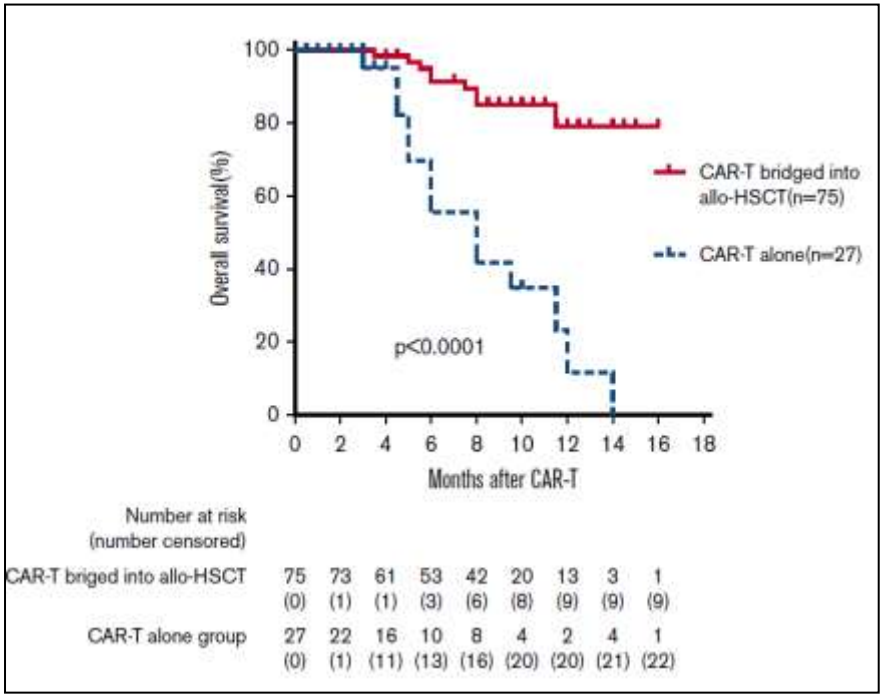
EFS, event-free survival.

Hay KA, et al. *Blood* 2019;133:1652-1663.

HSCT After CAR T

AlloHSCT in MRD– patients after CAR T





Hay K, et al. *Blood.* 2019;133:1652-1663.

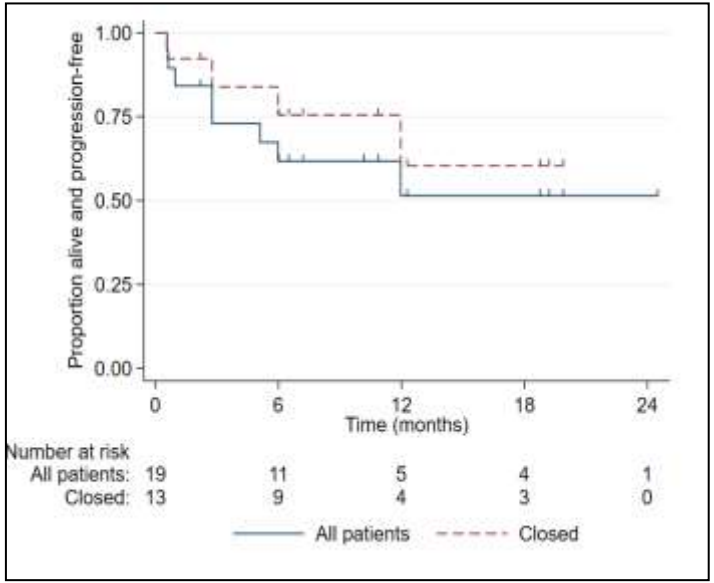
Zhang X, et al. *Blood Adv.* 2020;4:2325-2338.

Improvements in CAR T

1. Humanized CAR T
2. Fast-off rate, low-affinity CAR T 19
3. CAR T 22
4. Dual CAR T
5. CAR T for T-ALL
6. NK CAR

AUTO-1, a Novel Fast-Off Rate CD19 CAR in R/R BCP ALL

- Phase 1 of AUTO1 ALLCAR19 study in R/R BCP ALL
- **AUTO1**: Second-generation CD19 CAR T with lower affinity for CD19 and shorter target interaction time (more physiologic T-cell activation and reduced toxicity)
- **19 pts infused (additional 13 in a closed process)**
  - Median age 43 yr (18-62), 6/19 with Ph+ ALL
  - Prior tx with blinatumomab or inotuzumab: 73%
  - Prior HSCT: 63%
  - Refractory: 4; 1st rel: 8; 2nd rel: 5; 3rd rel: 2. >50% blasts: 42%
  - Median f/u: 11 mo (0.5-21)
- **Efficacy** (15 pts evaluable)
  - MRD– CR: 84%, 11/19 in continuous MRD– CR (median 12 mo)
  - 6-mo EFS: 62%
  - Subsequent alloHSCT: 1
- **Safety**
  - No grade ≥3 CRS
  - Grade ≥3 neurologic toxicity: 16%



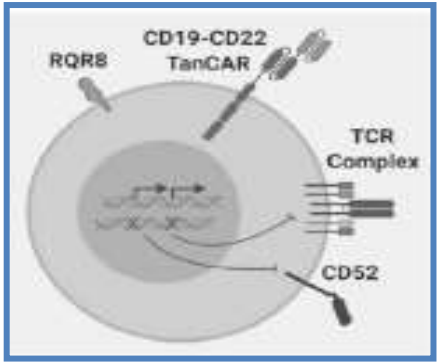
Roddie C, et al. EHA 2020. Abstract S119; SOHO 2020; ASH 2020. Abstract 160.

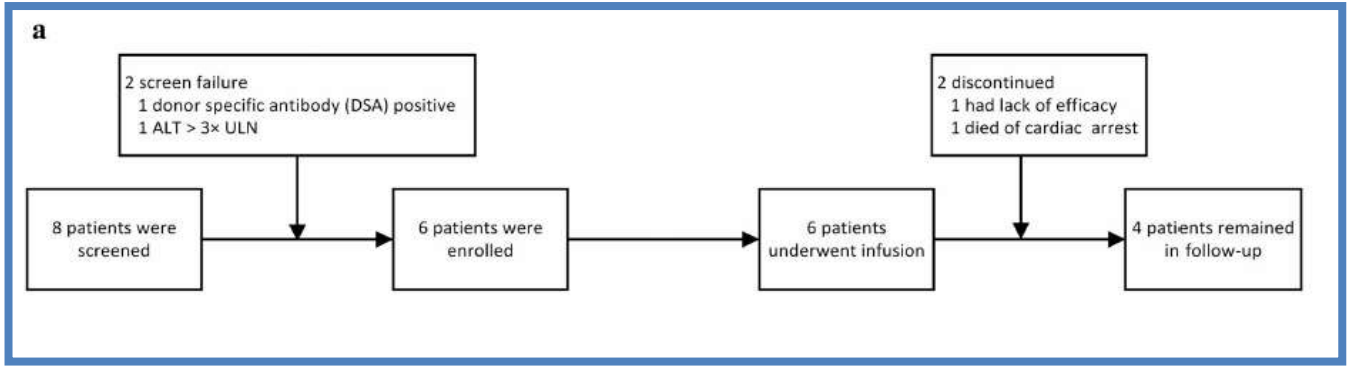
Autologous Dual CAR T 19/22

Author (yr)	Trial Phase	Pts, n Age (range)	CR	MRD– CR	Survival	Grade ≥3 CRS	Grade ≥3 ICANS
Dai H (2020)	I	6	6 (100%)	6 (100%)	5/6	0	0
Schultz LM (2019)	I	19 (2-68 yr)	11/12 (92%)	10/11 (91%)	92% (9 mo)	1/14	1/14
Yang J* (2020)	I	10 (3-48 yr)	10 (100%)	9 (90%)	9/10	0	0

*Fast CAR technology (24 h).

CRISPR/Cas9-Engineered Universal CD19/CD22 Dual-Targeted CAR T Cell





Patient	Age	Previous lines of therapy	Source of PBMC	Phenotype of tumor cell	BM blasts prior to pre-conditioning therapy, %	Gene fusion	Dose level	CRS grade	Initial response	follow-up （days）
1*	54	6	Donor 1	CD19⁺ and CD22⁺	82	BCR-ABL1 T315I	DL1	1	CR, MRD⁻	MRD negative, (228)
2	45	2	Donor 1	CD19⁺ and CD22⁺	50	-	DL1	1	CR, MRD⁻	Underwent haplo-HSCT in remission on D60 (182)
3*⁺	26	4	Donor 2	CD19⁺ and CD22⁺	54	-	DL1	2	CRi, MRD⁻	MRD negative, (128)
4*	56	3	Donor 2	CD19⁺ and CD22⁺	72	-	DL2	3	CRi, MRD⁻	received salvage chemotherapy due to primary disease recurrence (95)
5	40	8	Donor 2	CD19⁺ and CD22⁺	4	BCR-ABL1	DL2	1	NR	Received salvage chemotherapy on D35 (94)
6	53	6	Donor 1	CD19⁺ and CD22⁺	1	BCR-ABL1 T315I	DL2	2	CRi, MRD⁻	Death, (57)

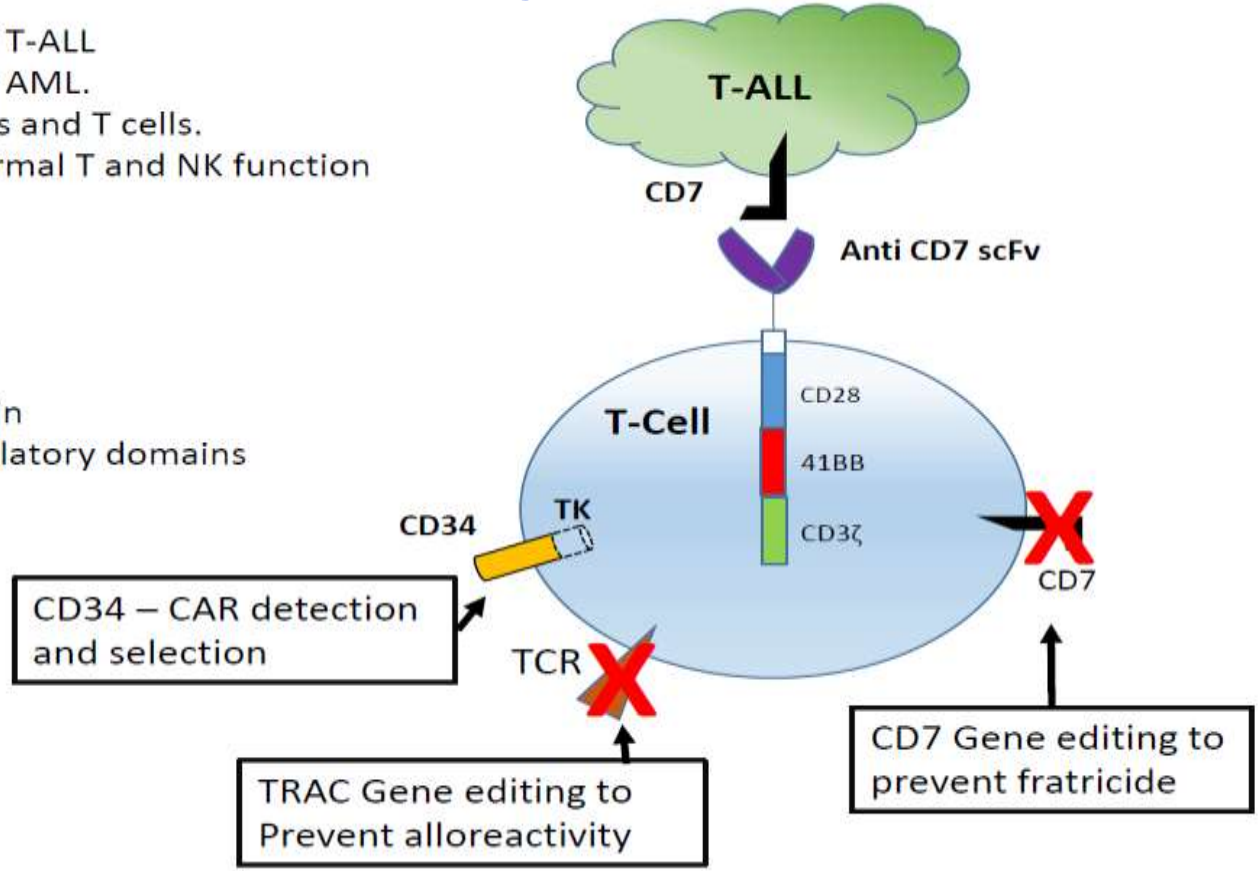
Hu Y. *Clin Cancer Res*. 2021. doi: 10.1158/1078-0432.CCR-20-3863.

CD7 CAR Design

- **CD7 as a target.**
  - Expressed on 98% of T-ALL
  - Expressed on 24% of AML.
  - Expressed on NK cells and T cells.
  - CD7-/- mice have normal T and NK function

- **CAR Design**
  - 3rd generation CAR
  - Anti CD7 scFv
  - CD3ζ signaling domain
  - 4-1BB, CD28 costimulatory domains
  - CD34

- **Gene editing**
  - CRISPR/Cas9



Courtesy of Dr Perales.

Clinical Trials of CAR T for T-ALL

T-Cell Antigen	CAR T	Trial Phase	ID/Location
CD5	CD5 CAR T	I	NCT03081910/Baylor College of Medicine
CD7	CD7 CAR T	I	NCT03690011/Baylor College of Medicine
CD7	UCART7	I	Washington University
TRBC1	TRBC1 CAR T	I	NCT03590574/UK

Baylor CART5, PEBL CD7, AutolusTRBC1, CART137, CART30, CART1a, WUGEN CD7 and CD2, and GracellCD7 are all moving forward.

Trials With CAR-NK in Leukemias

NCT	Start Year	Phase	Tumors	Target	NK Source	Sponsor Location	CAR Structure	Gene Transfer
Trials completed								
NCT00995137	2009	I	B-ALL	CD19	PB-NK	St. Jude Children's Research Hospital, US	ScFv-CD8αTM-CD137-CD3ζ	mRNA electroporation
Trials actively recruiting								
NCT01974479	2013	II	B-ALL	CD19	PB-NK	National University Health System, Singapore	ScFv-CD8αTM-CD137-CD3ζ	mRNA electroporation
NCT02742727	2016	I/II	Lymphoma, leukemia	CD7	NK92	PersonGen BioTherapeutics (Suzhou) Co., Ltd., China	ScFv-CD28-CD137-CD3ζ	Electroporation

Xie G, et al. *EBioMedicine*. 2020;59:102975. doi: 10.1016/j.ebiom.2020.102975.

CAR T in ALL

- At least as effective as mAb
- Methods to reduce toxicity (lower affinity, fractionated infusion)
- Increasingly short CAR T preparation
- Several targets, possible dual or triple simultaneous targeting
- Allogeneic production feasible and effective
- Also applicable to T-ALL/LBL
- Possible use of NK cells
- High possibility of improvement in design

Global Leukemia Academy

Debate on sequencing CD19-targeted approaches: Voting and Discussion

All faculty

APTITUDE HEALTH

Q

Question

What is your preferred ALL treatment choice in salvage if all these therapies were available in your country?

a) CAR T therapies
b) Monoclonal antibodies or bispecifics

Global Leukemia Academy

Session Close

Elias Jabbour

APTITUDE HEALTH

Q

Question

Which of the following is NOT true?

a) Inotuzumab and blinatumomab + chemotherapy is active in both frontline 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-negative ALL

d) CAR T approaches are not active beyond 2L in Ph-negative ALL

Q

Question 4

In AML the MRD assessment by RT-qPCR is especially useful for

a) FLT3 ITD

b) *NPM1* mutation

c) Biallelic *CEBPA* mutation

d) *SF3B1* mutation

e) *ASXL1* mutation

Virtual Breakout – Adult Leukemia Patients (Day 2)

Chair: Elias Jabbour

TIME (UTC +9)	TITLE	SPEAKER
11.00 – 11.15	Session open • Educational ARS questions for the audience	Elias Jabbour
11.15 – 11.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation (15 min) • Q&A (5 min)	Aaron Logan
11.35 – 11.55	Current treatment options for relapsed ALL in adult and elderly patients (including COVID-19 and vaccination strategy) • Presentation (15 min) • Q&A (5 min)	José-Maria Ribera
11.55 – 12.30	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in adult and elderly patients Panelists: Elias Jabbour, José-Maria Ribera, Aaron Logan	Shaun Fleming
12.30 – 12.45	Break	
12.45 – 13.05	Personalized induction and maintenance approaches for AML • Presentation (15 min) • Q&A (5 min)	Naval Daver
13.05 – 13.25	Optimizing management of relapsed/refractory AML • Presentation (15 min) • Q&A (5 min)	Eunice Wang
13.25 – 14.15	Case-based panel discussion or questions on regional challenges in AML care	Case 1: Chyn Chua Case 2: Sun Loo
14.15 – 14.30	Session close	Elias Jabbour

Virtual Breakout – Pediatric ALL Patients (Day 2)

Chair: Patrick Brown

TIME (UTC +9)	TITLE	SPEAKER
11.00 – 11.15	Session open • Educational ARS questions for the audience	Patrick Brown
11.15 – 11.35	First-line treatment of pediatric ALL • Presentation (15 min) • Q&A (5 min)	Bhavna Padhye
11.35 – 11.55	Current treatment options for relapsed ALL in children including HSCT; COVID-19 considerations and vaccinations • Presentation (15 min) • Q&A (5 min)	Michael Osborn
11.55 – 12.15	Bispecifics for pediatric ALL, focus on frontline therapy • Presentation (15 min) • Q&A (5 min)	Patrick Brown
12.15 – 12.45	Case-based panel discussion Management of long- and short-term toxicities and treatment selection in pediatric patients Panelists: All faculty	Case 1: Bhavna Padhye (10 min) Case 2: Michael Osborn (10 min) Discussion (10 min)
12.45 – 13.30	Interactive Q&A and session close • Educational ARS questions for the audience	Patrick Brown

Global Leukemia Academy

Closing Remarks

Elias Jabbour

APTITUDE HEALTH

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!

AMGEN

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Emerging and Practical Concepts and Controversies in Leukemias

SEE YOU TOMORROW!

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