Global Leukemia Academy

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Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

23 April 2021

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

Elias Jabbour

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Meet the Faculty

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

Franco Locatelli
Head of Department of Paediatric Haematology and Oncology, IRCCS Bambino Gesù Children's Hospital
Full Professor of Pediatrics at the Sapienza University
Rome, Italy

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
Aurora, CO, USA

Andre Schuh, MD
Associate Professor, University of Toronto
Staff Physician at Princess Margaret Cancer Center
Toronto, Ontario, Canada

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
Badalona, Barcelona, Spain

Roberta Demichelis, MD
Assistant Professor in the Department of Hematology/Oncology
INCMNSZ*
Mexico City, Mexico

*INCMNSZ, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán.

Objectives of the Program

- Understand current treatment patterns for acute leukemias including incorporation of new technologies
- Uncover when genomic testing is being done for acute leukemias, and how these tests are interpreted and utilized
- Understand the role of stem cell transplantation in acute leukemias as a consolidation in first remission
- Comprehensively discuss the role of MRD in managing and monitoring acute 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 in acute leukemias
- Review promising novel and emerging therapies in acute leukemias

Virtual Plenary Sessions (Day 1)

TIME (UTC-3)	TITLE	SPEAKER
18.00 – 18.10	Welcome and meeting overview; introduction to the voting system	Elias Jabbour
18.10 – 18.35	Recent developments in ALL and AML	Elias Jabbour
18.35 – 19.00	Review of prognostic value of MRD in ALL	José Maria Ribera
19.00 – 19.15	Genetic variants in ALL – Ph+ and Ph-like	Andre Schuh
19.15 – 19.30	AYA ALL patients – what is the current treatment approach for this diverse patient population? Special considerations for adolescents and young adults	Lia Gore
19.30 – 19.45	Break	
19.45 – 20.00	Bispecifics as post-reinduction therapy improve survival in high-risk first-relapse AYA B-ALL	Franco Locatelli
20.10 – 20.35	Therapeutic approaches in high-risk and older AML patients	Naval Daver
20.35 – 21.05	Debate on sequencing CD19-targeted approaches • Monoclonal antibodies and bispecifics first (10 min) • CAR T first (10 min) • Discussion and voting (10 min)	Moderator: Andre Schuh Elias Jabbour José Maria Ribera All faculty
21.05 – 21.50	Leukemia board discussion • Cases – Maria Sara Felice (15 min) • Regional challenges in times of COVID-19 – Roberta Demichelis (15 minutes) • Cases – Wellington Silva (15 min)	Moderator: Elias Jabbour All faculty
21.50 – 22.00	Session close	Elias Jabbour

Virtual Breakout: Adult Leukemia Patients (Day 2)

Chair: Elias Jabbour

TIME (UTC-3)	TITLE	SPEAKER
10.00 – 10.15	Session open • Educational ARS questions for the audience	Elias Jabbour
10.15 – 10.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation (15 min) • Q&A (5 min)	Elias Jabbour
10.35 – 10.55	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
10.55 – 11.45	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, Andre Schuh, local experts	Roberta Demichelis Wellington Silva
11.45 – 12.00	Break	
12.00 – 12.20	Personalized induction and maintenance approaches for AML • Presentation (15 min) • Q&A (5 min)	Naval Daver
12.20 – 12.40	Optimizing management of relapsed/refractory AML • Presentation (15 min) • Q&A (5 min)	Eunice Wang
12.40 – 13.15	Case-based panel discussion on regional challenges in AML care	Roberta Demichelis Wellington Silva
13.15 – 13.30	Session close • Educational ARS questions for the audience	Elias Jabbour

Virtual Breakout: Pediatric ALL Patients (Day 2)

Chair: Franco Locatelli

TIME (UTC-3)	TITLE	SPEAKER
10.00 – 10.15	Session open • Educational ARS questions for the audience	Franco Locatelli
10.15 – 10.35	First-line treatment of pediatric ALL • Presentation (15 min) • Q&A (5 min)	Lia Gore
10.35 – 10.55	Current treatment options for relapsed ALL in children including HSCT; COVID-19 considerations and vaccinations • Presentation (15 min) • Q&A (5 min)	Franco Locatelli
10.55 – 11.15	Bispecifics for pediatric ALL, focus on frontline therapy • Presentation (15 min) • Q&A (5 min)	Lia Gore
11.15 – 11.45	Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in pediatric patients Panelists: María Sara Felice (ARG), Oscar González Ramella (MEX), Adriana Seber (BRA), Carlos Andres Portilla (COL)	Luisina Peruzzo Jorge Ramirez Melo Gustavo Zamperlini
11.45 – 12.30	Interactive Q&A and session close • Educational ARS questions for the audience	Franco Locatelli

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Introduction to the Voting System

Elias Jabbour

APTITUDE HEALTH

Q

Question 1

Where are you from?

a) Argentina
b) Brazil
c) Canada
d) Colombia
e) Chile
f) Mexico
g) Peru
h) 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

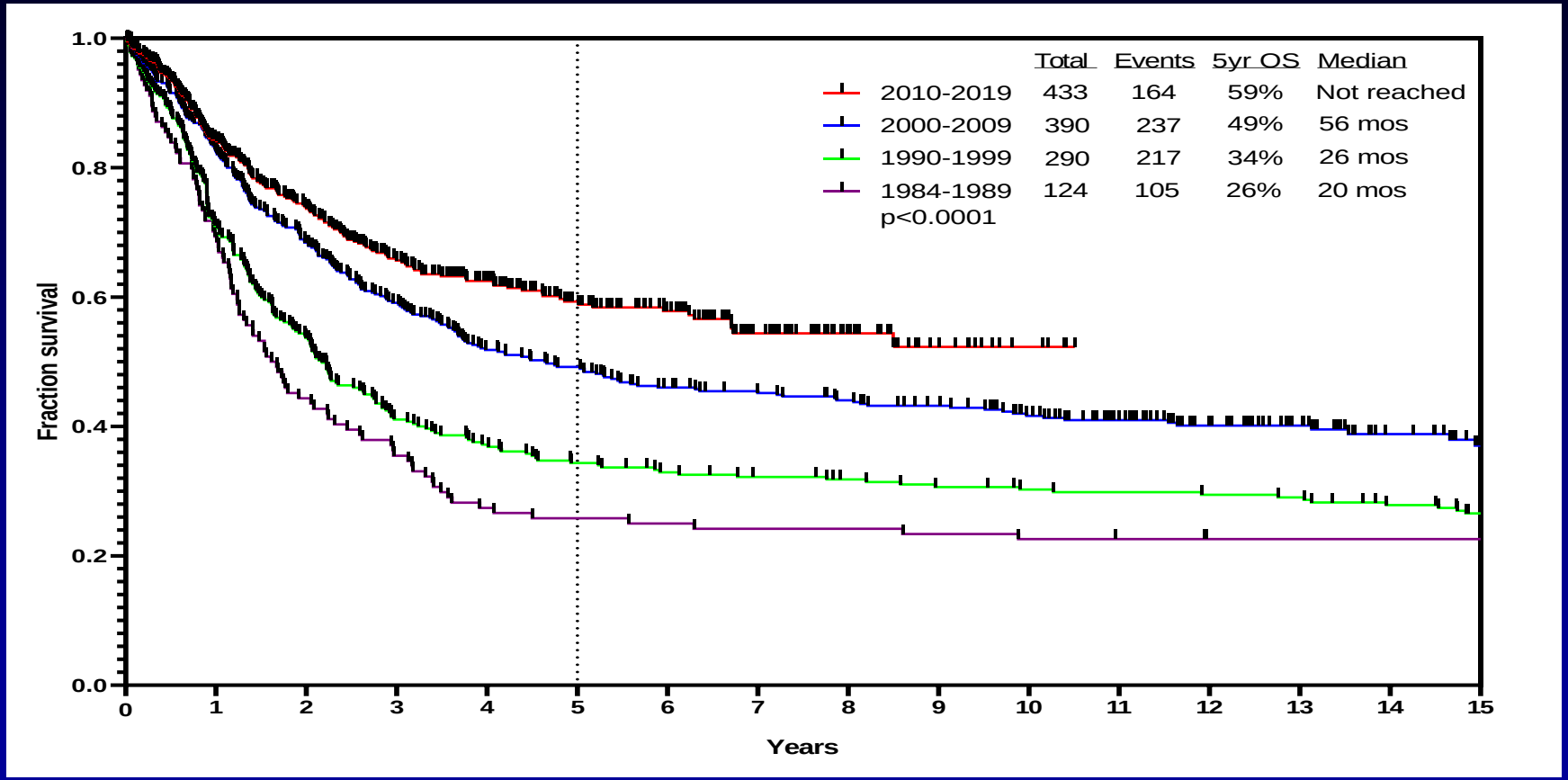
Recent Developments in Acute Leukemia

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)



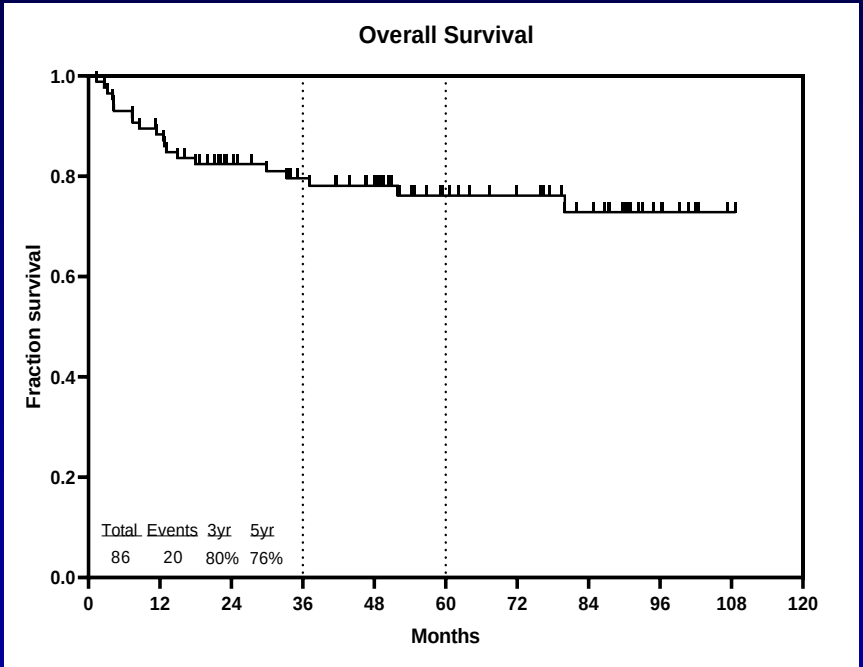
Reasons for Recent Success in Adult ALL

- 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)

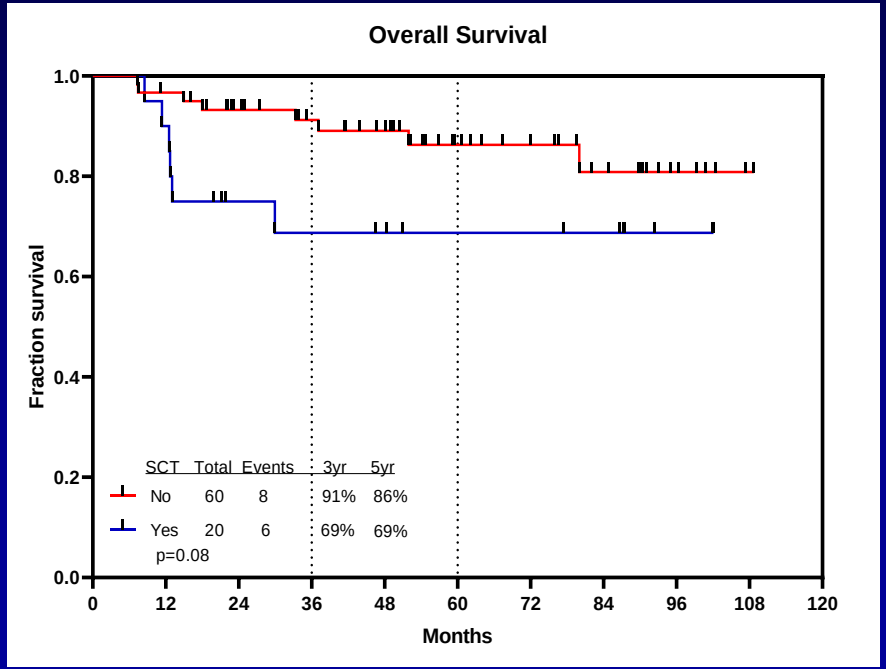
HyperCVAD + Ponatinib in Ph+ ALL

- 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

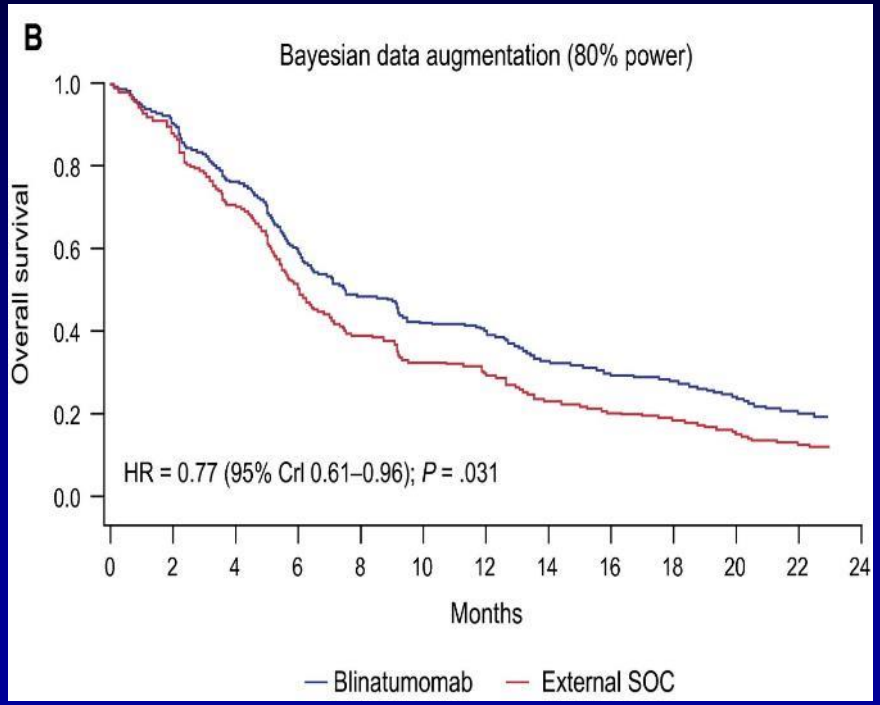


Jabbour E, et al. *Lancet Hematol.* 2018;618:(and update December 2020); Short et al. *Blood.* 2019;134:Abstract 283.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

Blina vs SOC

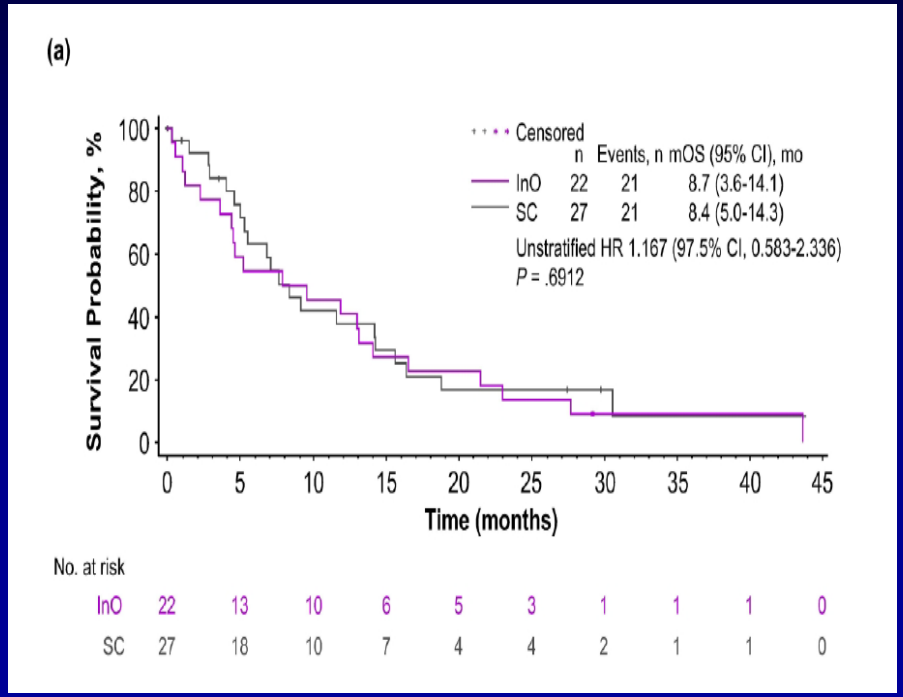
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



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

Ino vs SOC

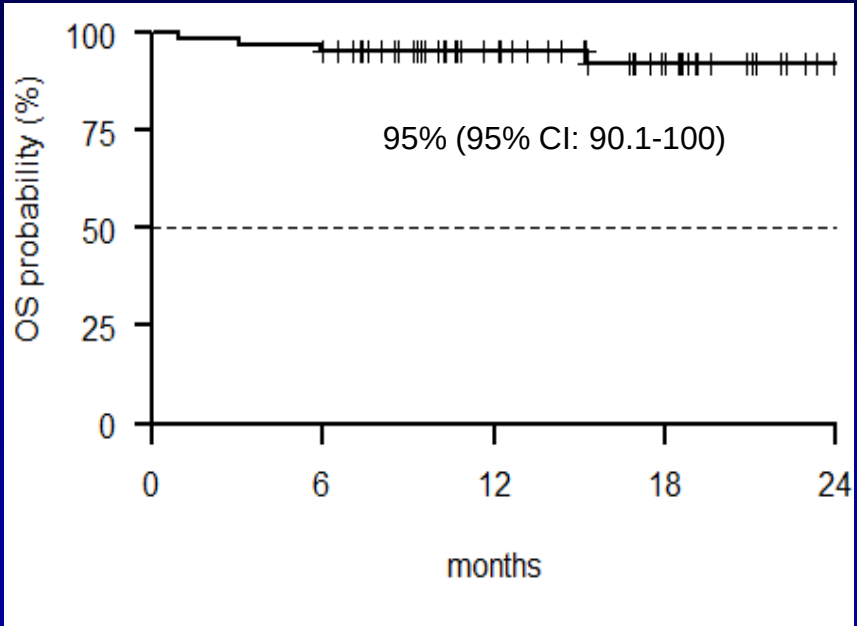
- CR/CRi 73% vs 56%
- 1-yr PFS 20% vs 4.8%

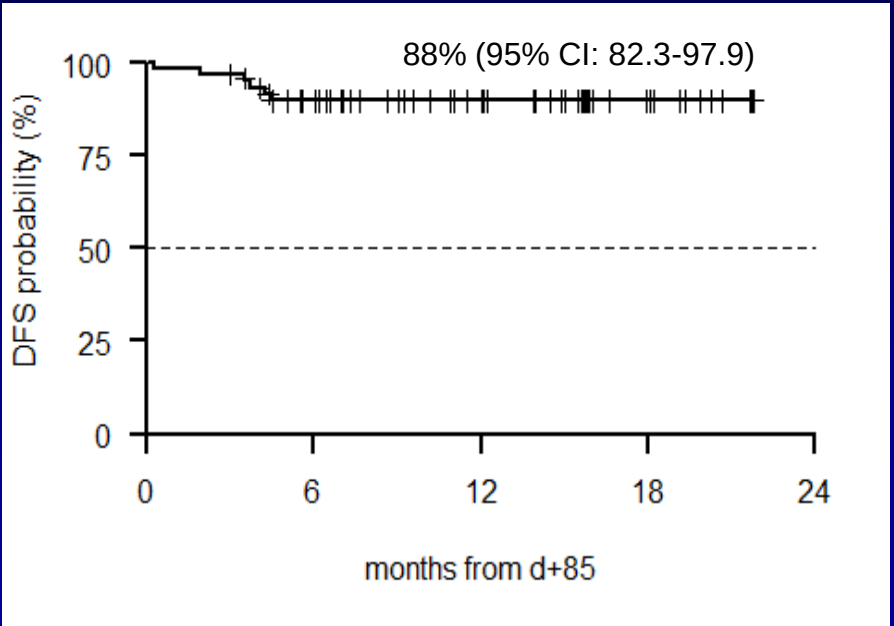


Stock W, et al. *Cancer.* 2020;127(6):905-913.

Dasatinib-Blinatumomab in Ph+ ALL

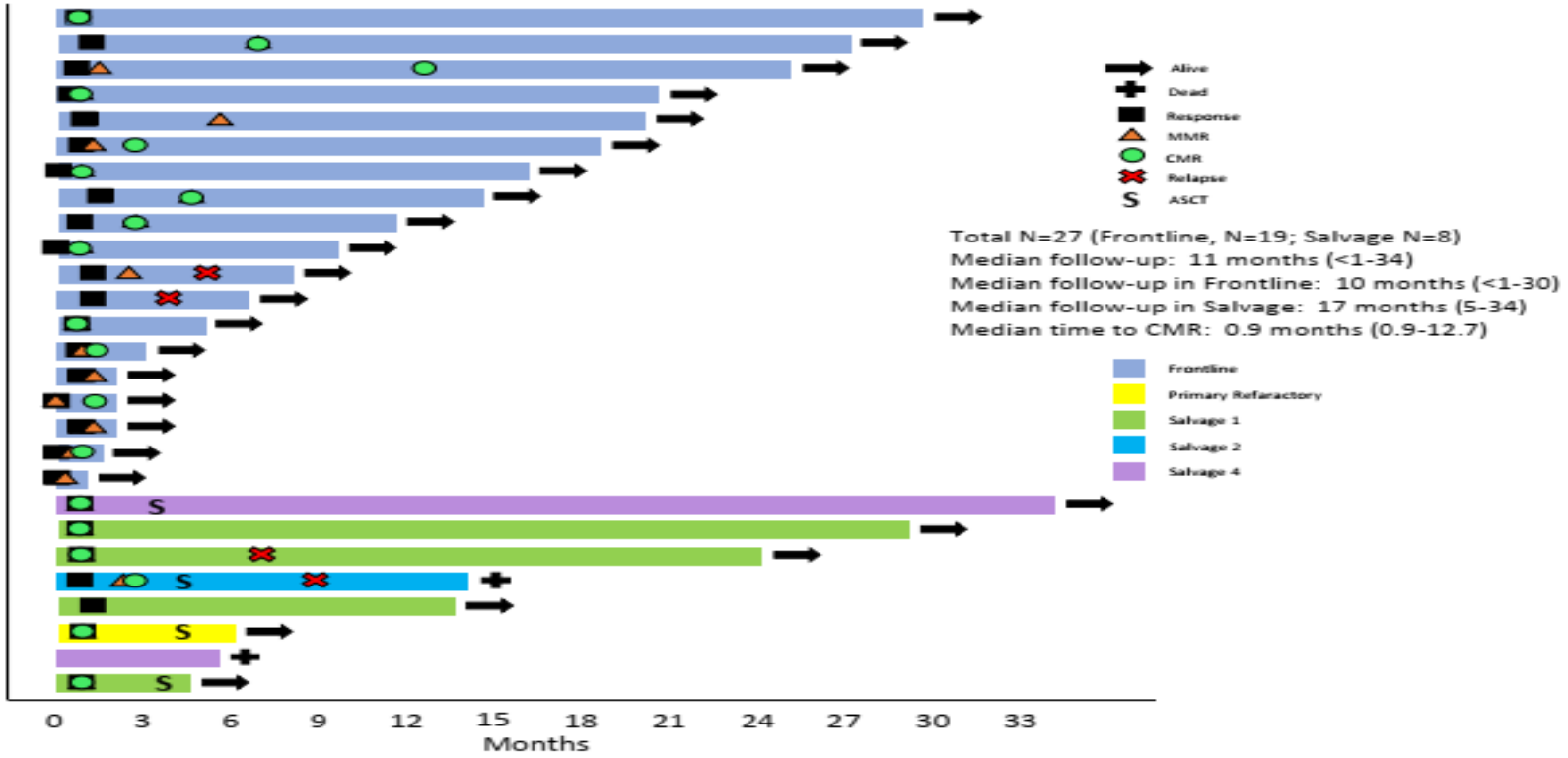
- 63 pts, median age 54 yr (24–82); Dasatinib 140 mg/D × 3 mo; add blinatumomab × 2–5
- 53 post–dasa-blina × 2 – molecular response 32/53 (60%), 22 CMR (41%); MRD ↑ in 15, 6 *T315I*; 12-mo OS 95%; DFS 88%





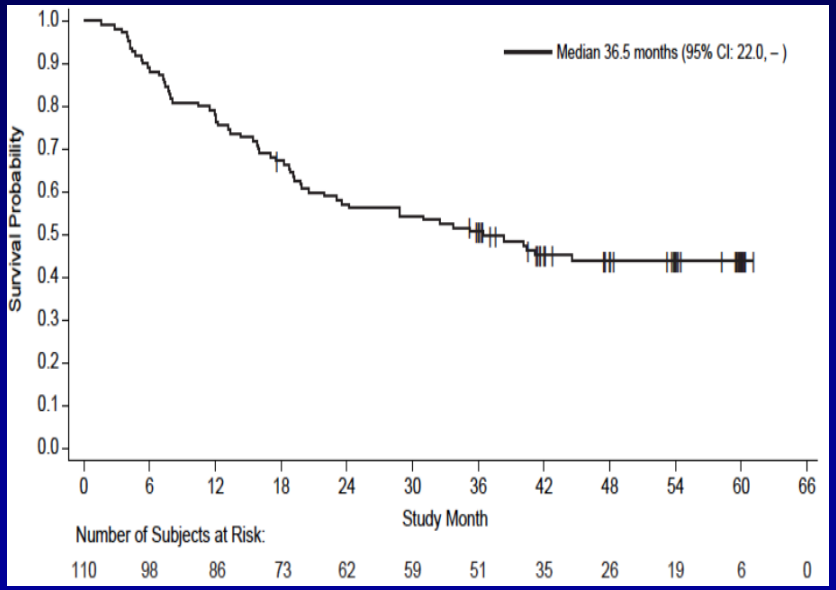
Foa et al. *N Engl J Med.* 2020;383:1613.

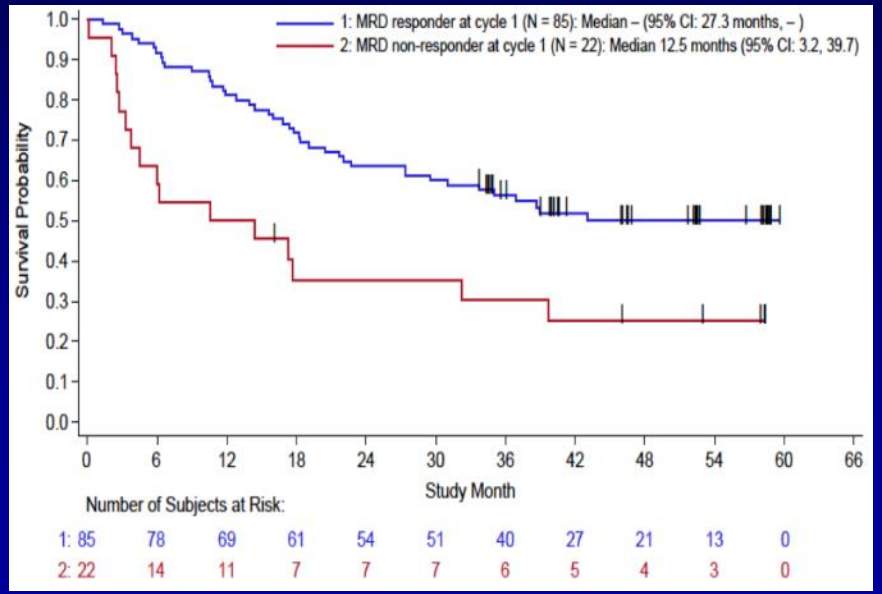
Blinatumomab + Ponatinib Swimmer Plot (N = 27)



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%)

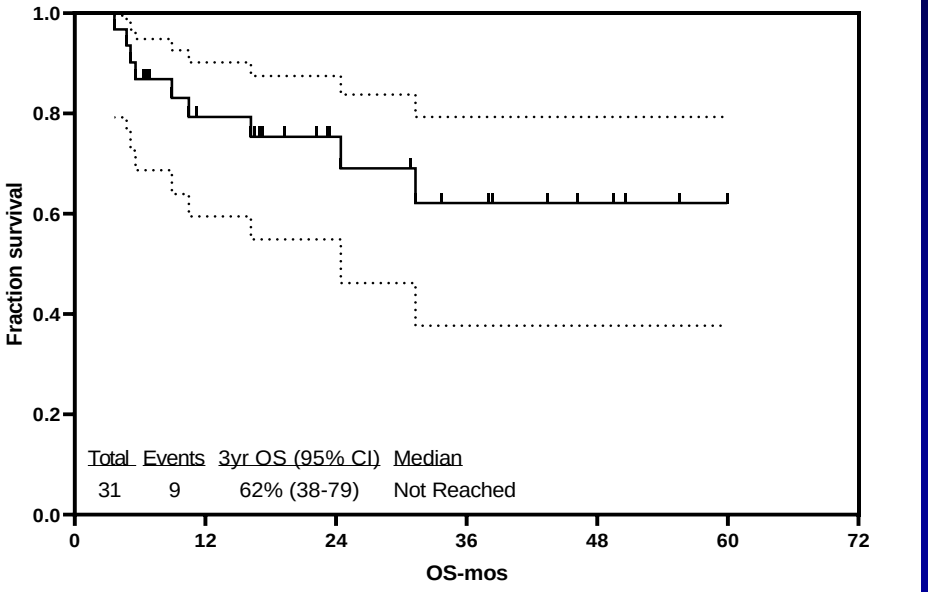


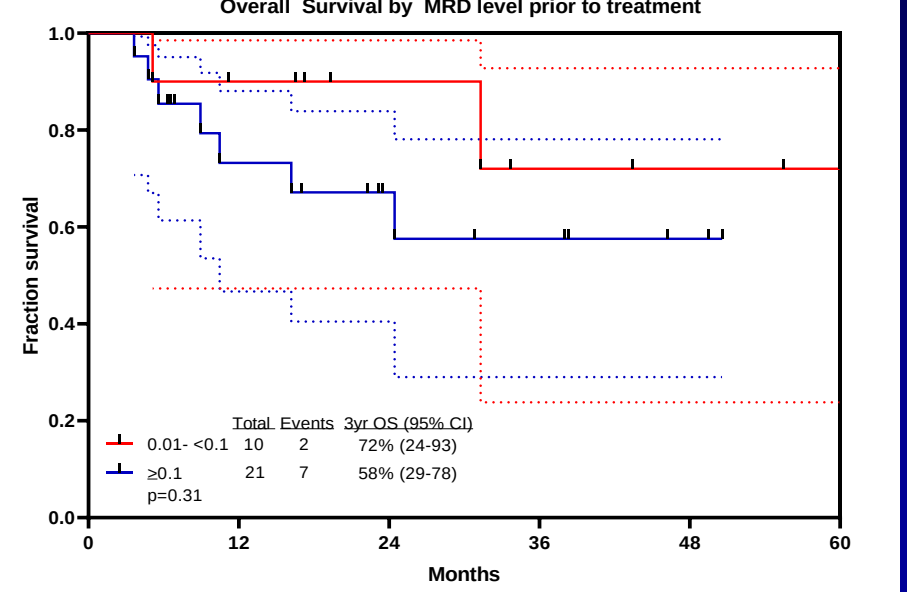


Goekbuget N, et al. *Blood.* 2018;132:abstract 554.

Blinatumomab for MRD+ ALL in CR1/CR2+

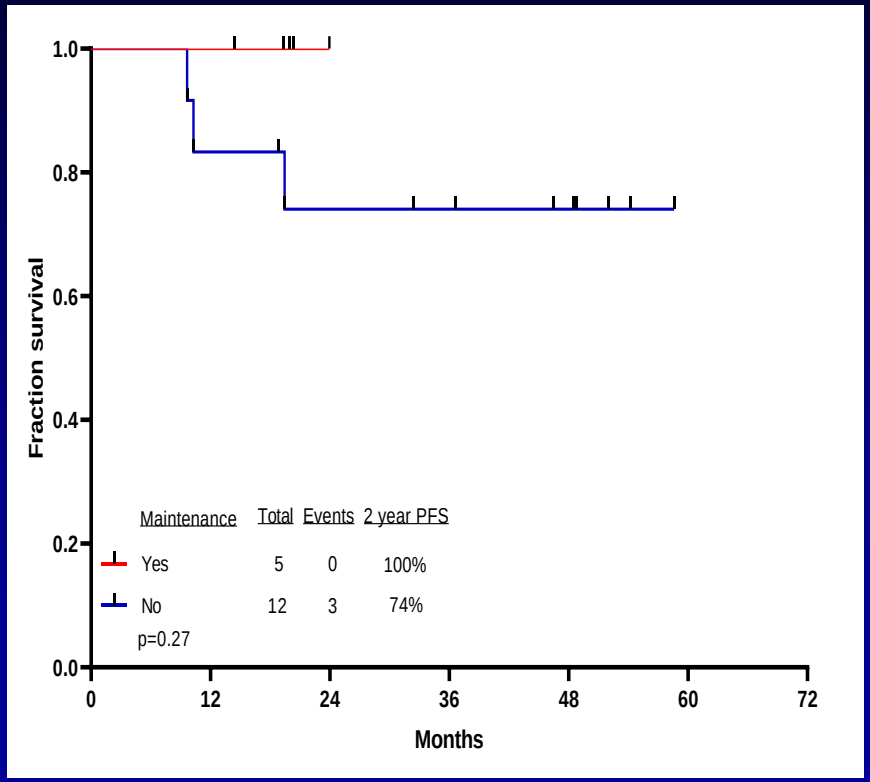
- 31 pts Rx. Post blina MRD-negative 23/31 = 74%
- 10 pts 0.01 to <0.1% RR = 90%; 21 pts ≥0.1% RR = 67%
- Median OS not reached; **3-yr OS 62%; 3-yr OS if MRD-negative 72%**
- Continuous CR 6/8 post alloSCT (75%); 9/15 without SCT (60%)



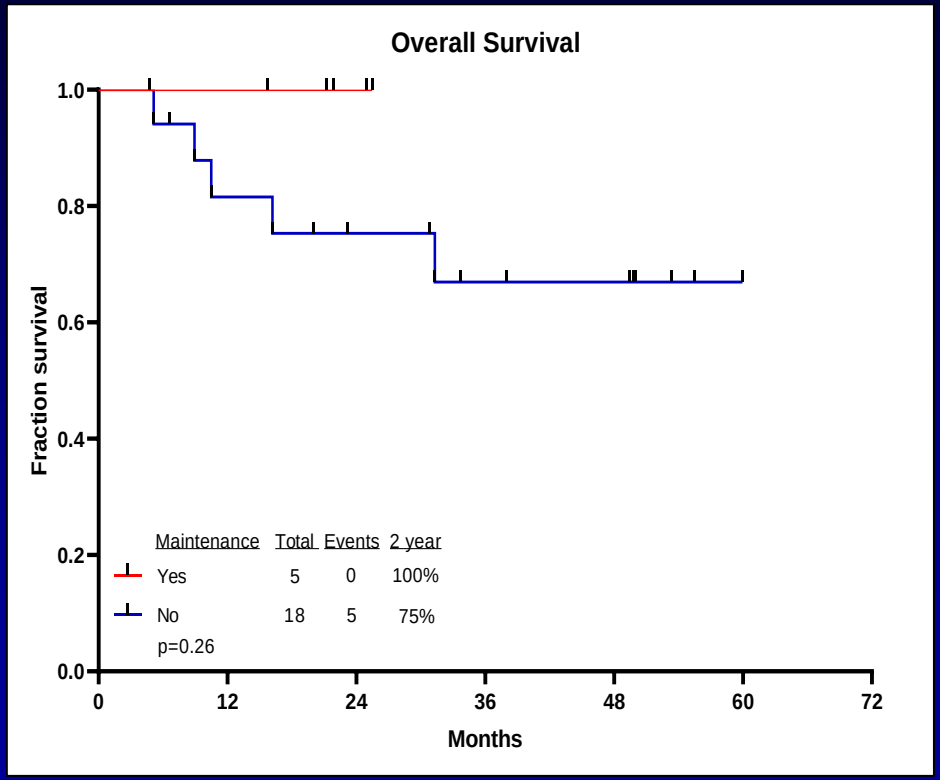


Blinatumomab for MRD+ ALL in CR1/CR2+: Impact of Maintenance

PFS

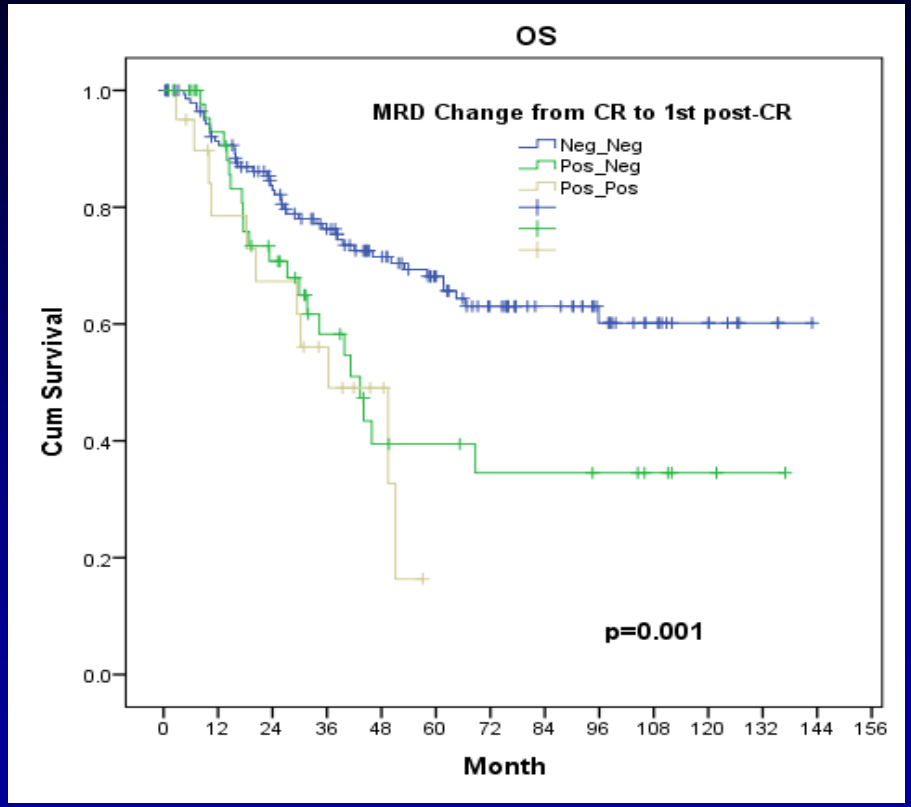


OS



Dynamics of MRD: Outcome

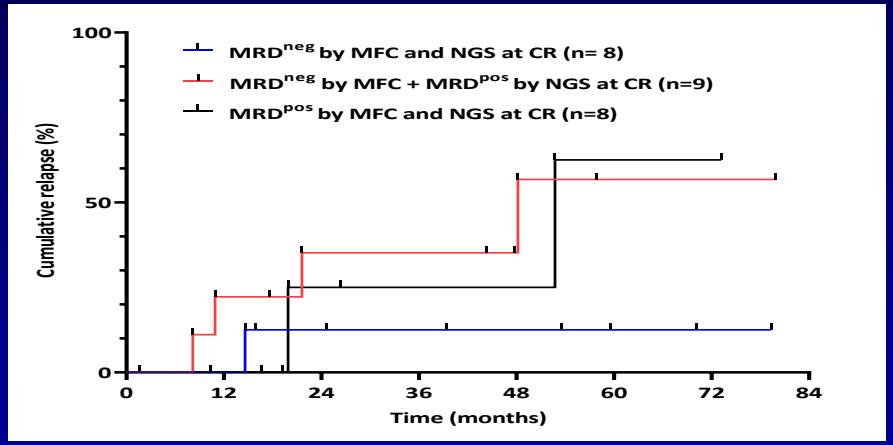
MRD Status		Patients (%) n = 214	5-yr EFS, %	5-yr OS, %
@CR	@ First post-CR			
Negative	**Negative**	**147 (69)**	**56**	**68**
≤0.1%	Negative	14 (7)	31	46
>0.1%	Negative	33 (15)	32	38
Positive	Positive	20 (9)	NA	NA

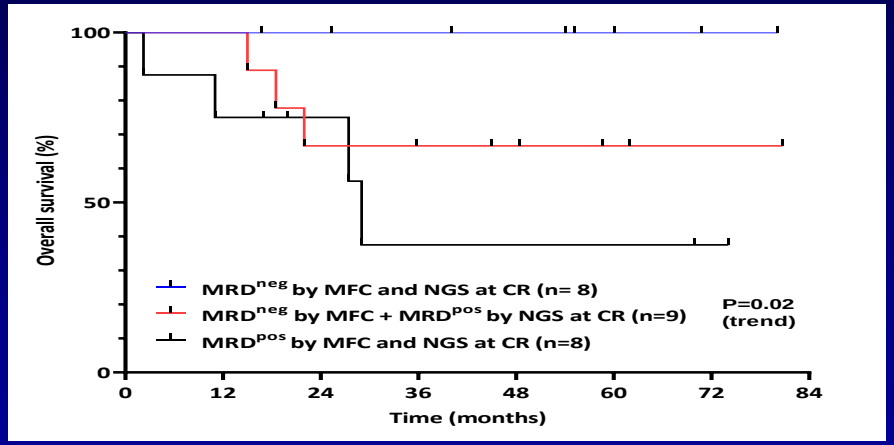


Yilmaz et al. *Am J Hematol.* 2020;95(2):144-150.

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%

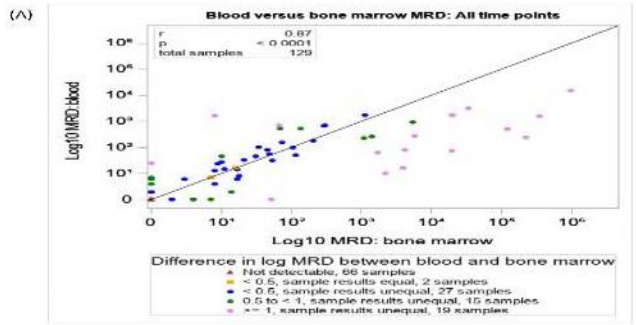
MRD^{pos} by MFC and NGS: 38%

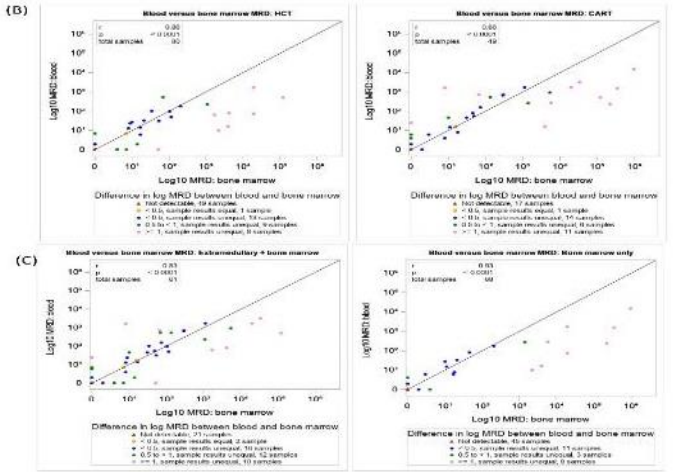
Short et al. *Blood.* 2020;136:abstract 583.

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

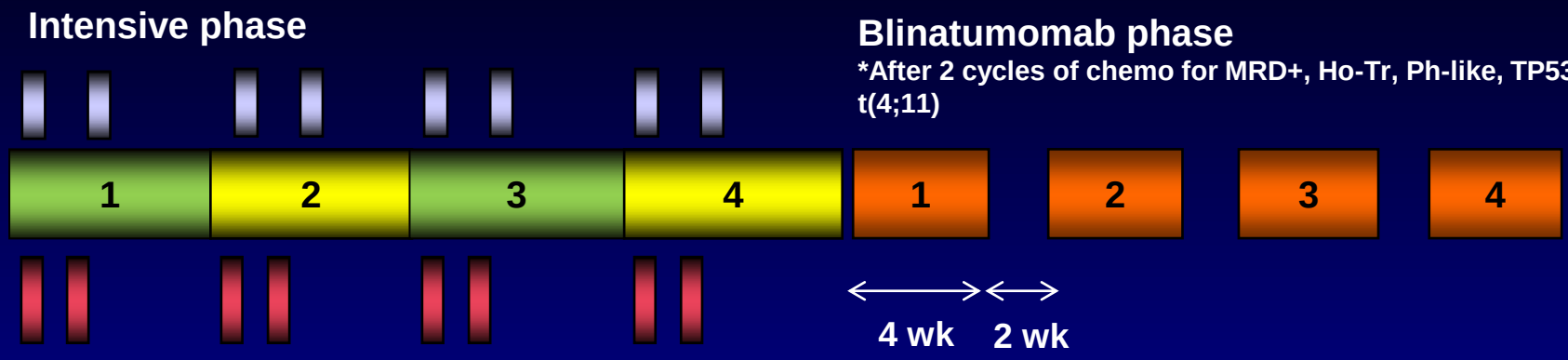
Figure 1. Peripheral Blood Vs. Bone Marrow MRD by NGS, (A) Total Study Cohort (B) HCT and CART (C) Extramedullary +/- Marrow and Marrow Only

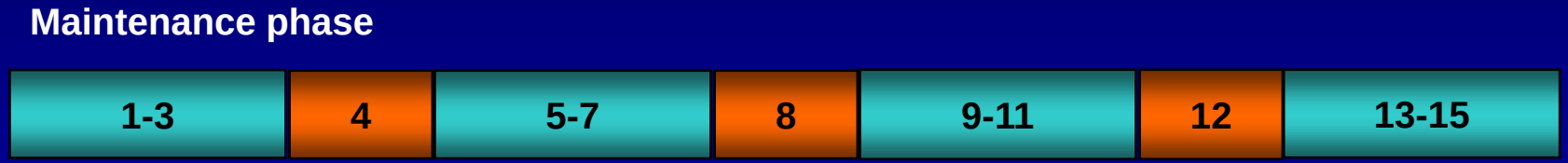




Muffly et al. *Blood*. 2020;136:abstract 975.

Hyper-CVAD + Blinatumomab in B-ALL: Regimen





Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

MTX + Ara-C

IT MTX/Ara-C × 8

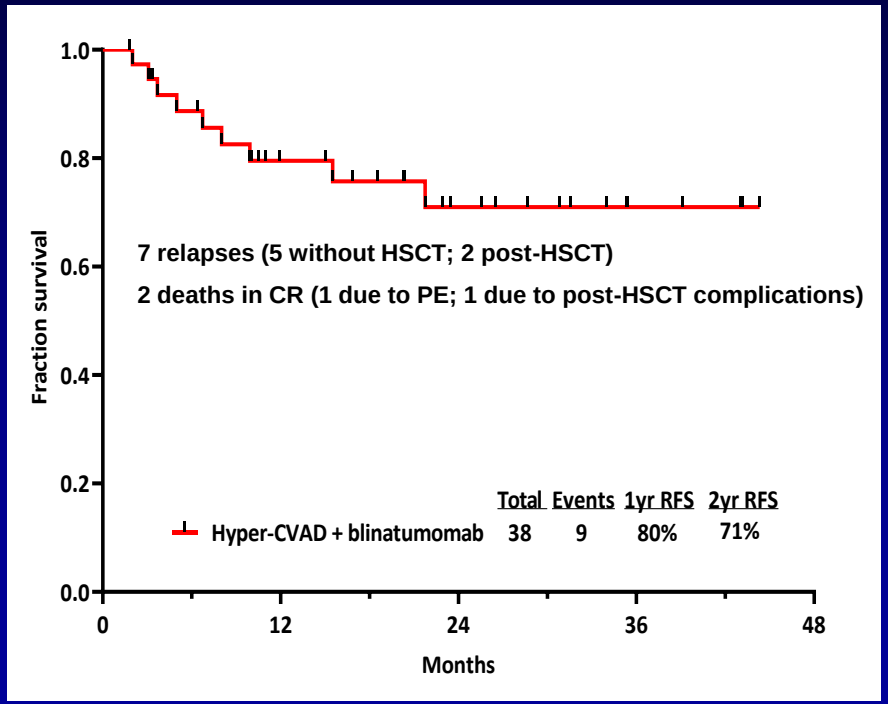
POMP

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

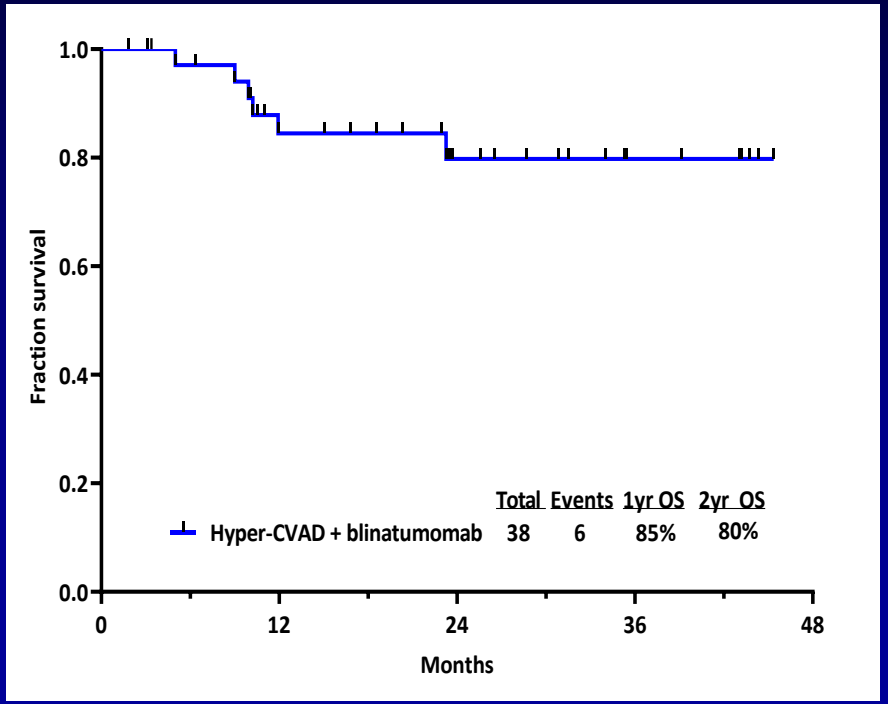
Hyper CVAD→Blinatumomab in Newly Dx Adult ALL

- 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

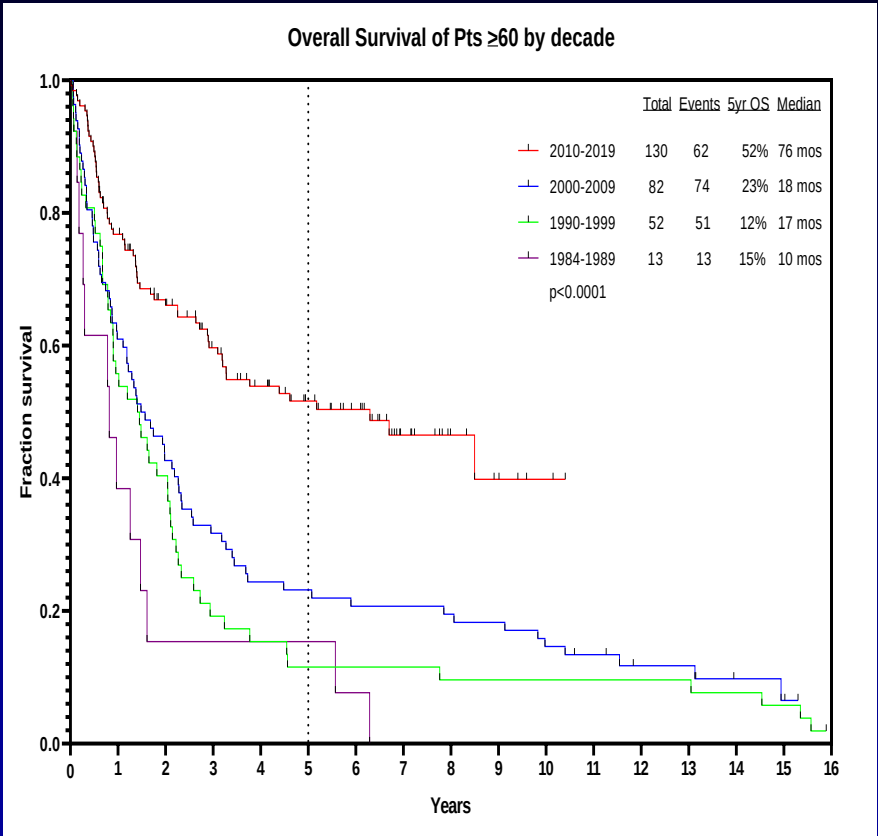


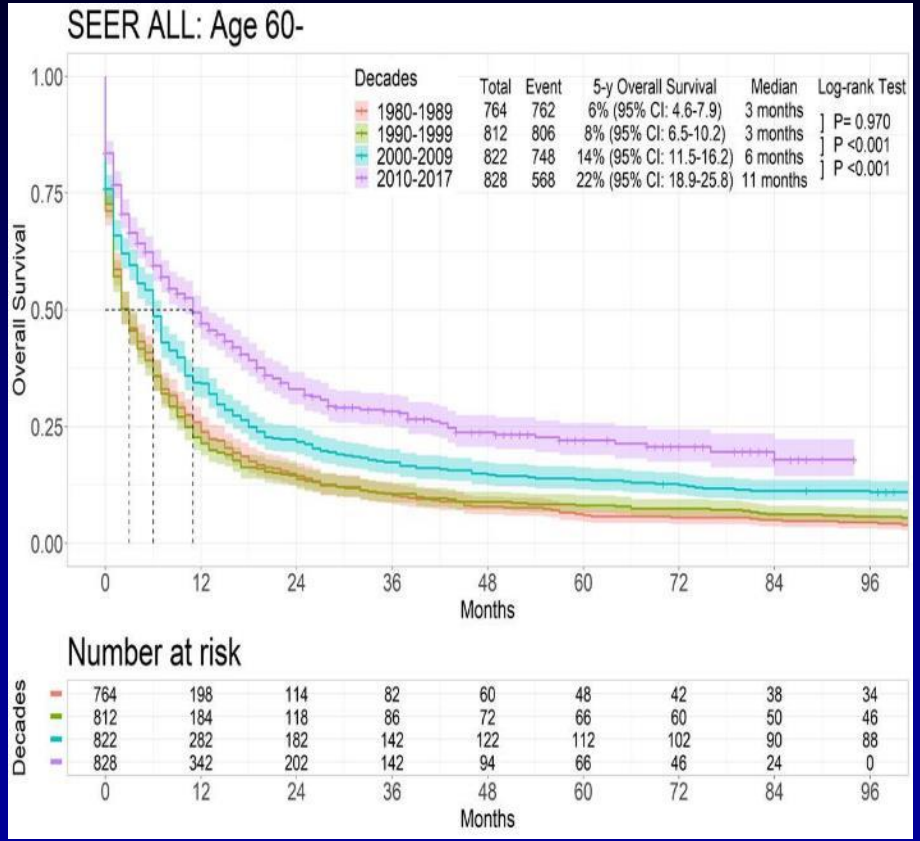
OS



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)

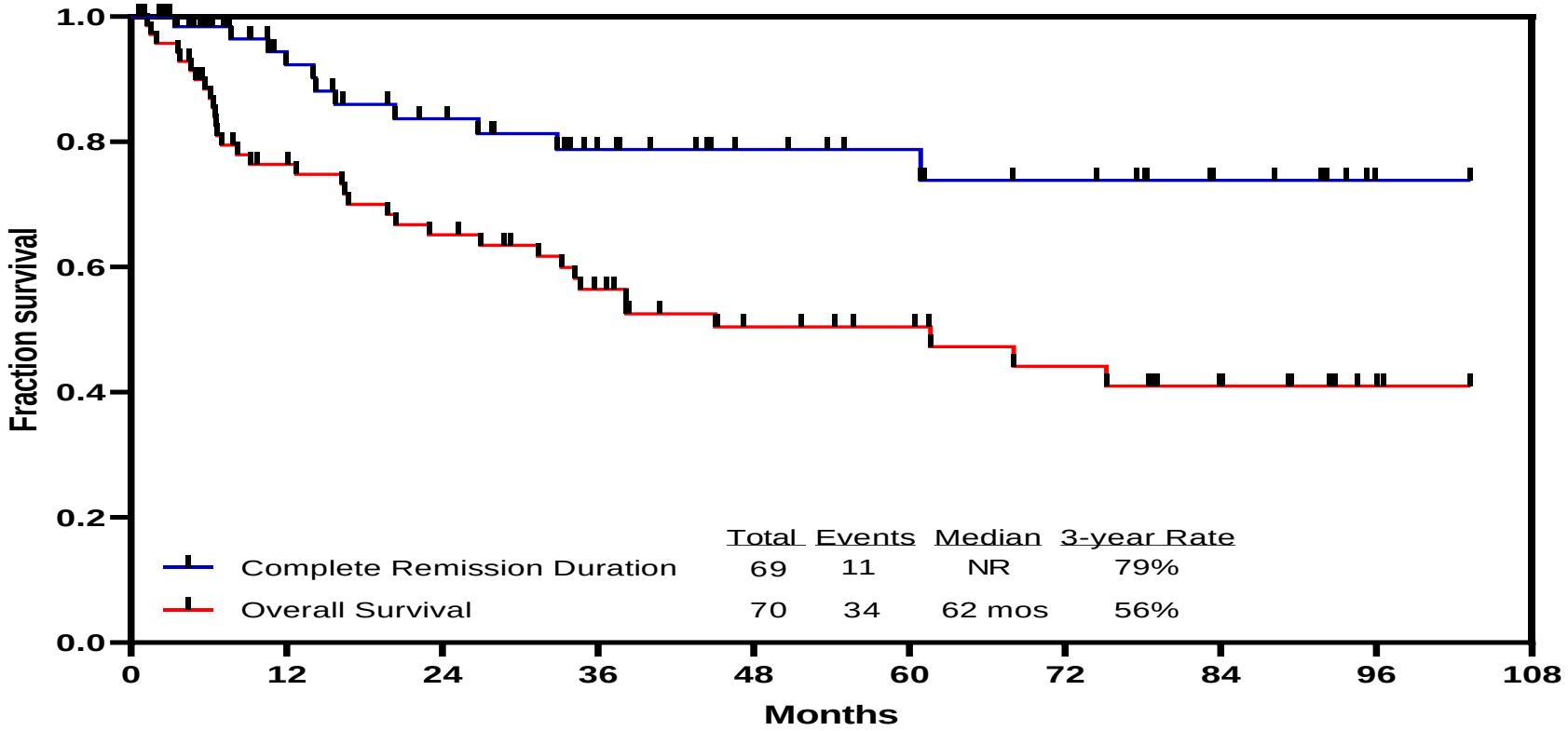
Characteristic	Category	N (%)/Median [range]
Age (years)	**≥70**	**68 [60–81]** **29 (41)**
Performance status	≥2	10 (14)
WBC ($\times 10^9$/L)		3.1 [0.6–111.0]
Karyotype	Diploid HeH **Ho-Tr** **Tetraploidy** **Complex** **t(4;11)** Misc IM/ND	23 (33) 5 (7) **12 (17)** **3 (4)** **3 (4)** **1 (1)** 10 (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)**

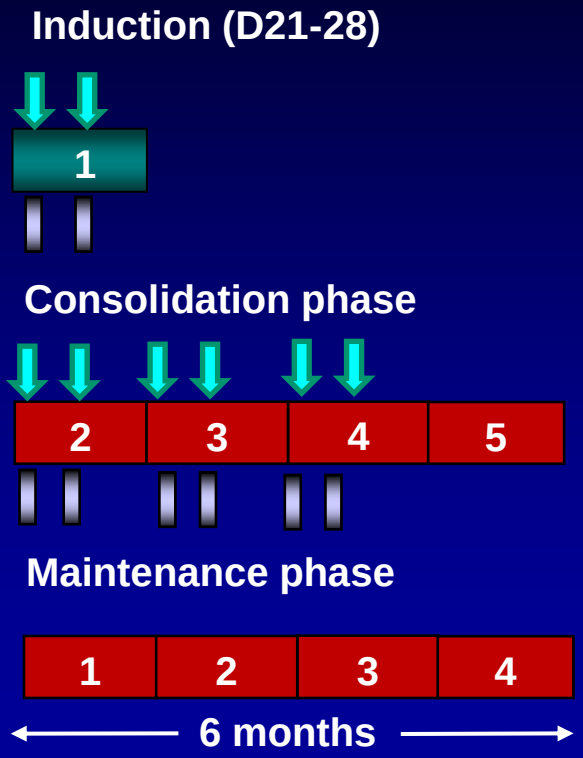
Short et al. *Blood.* 2020;136:abstract 1014.

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

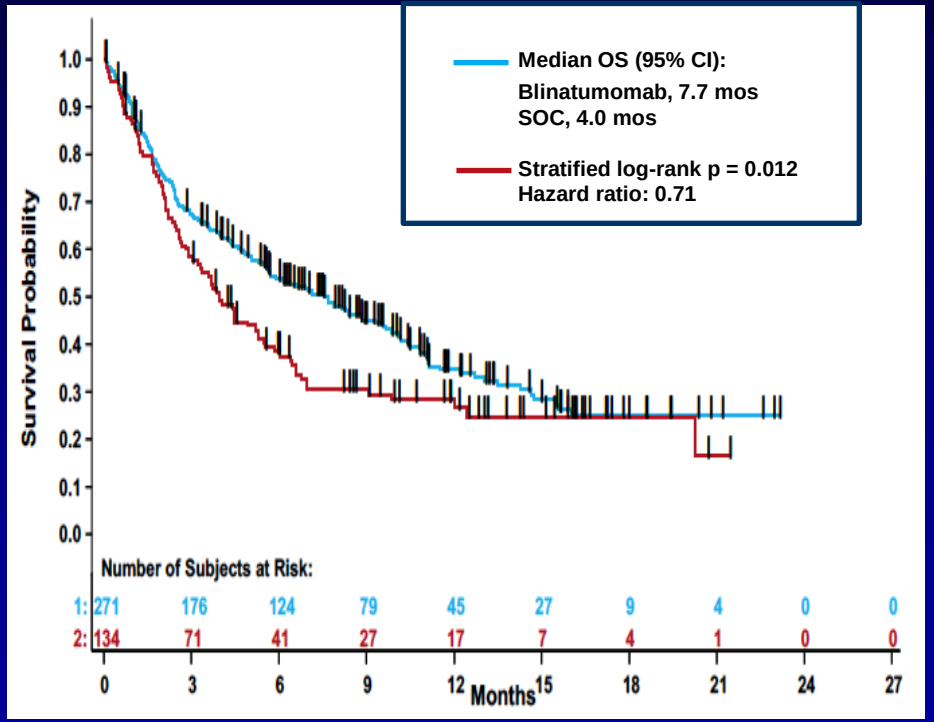
Total INO dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis

Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

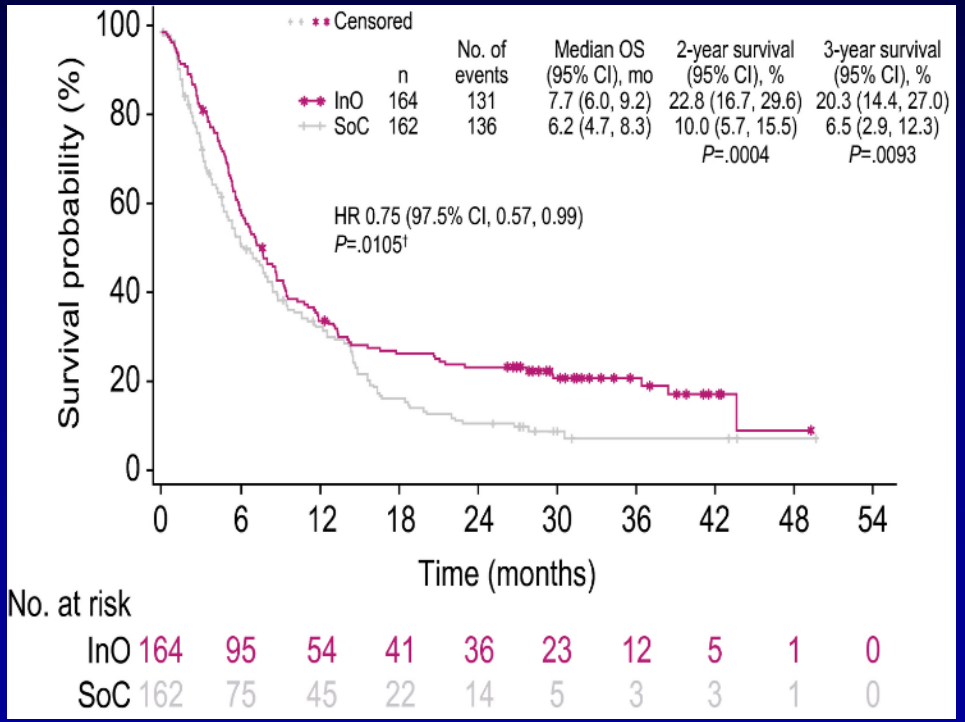
- **Marrow CR**

Blina vs SOC: 44% vs 25%



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

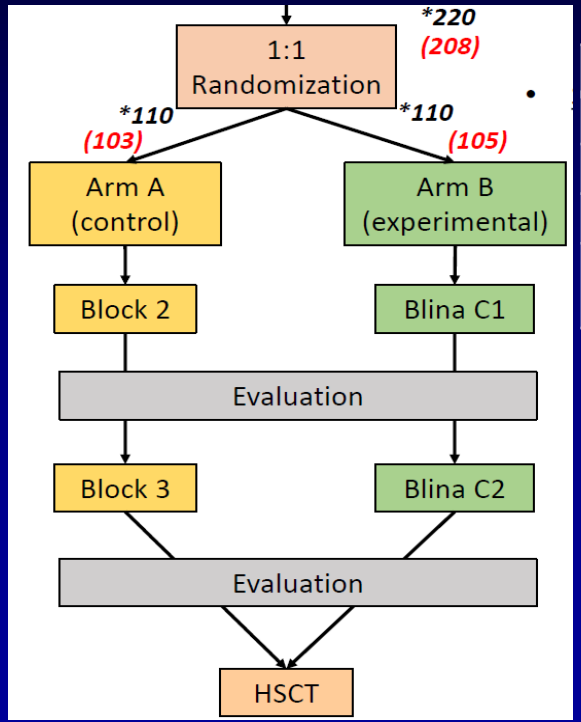
Ino vs SOC: 74% vs 31%



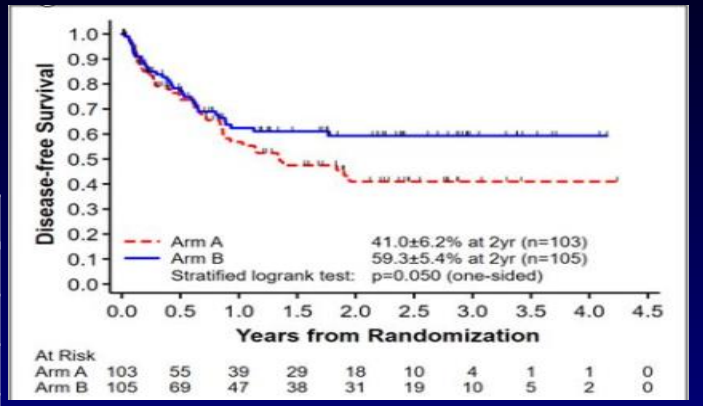
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

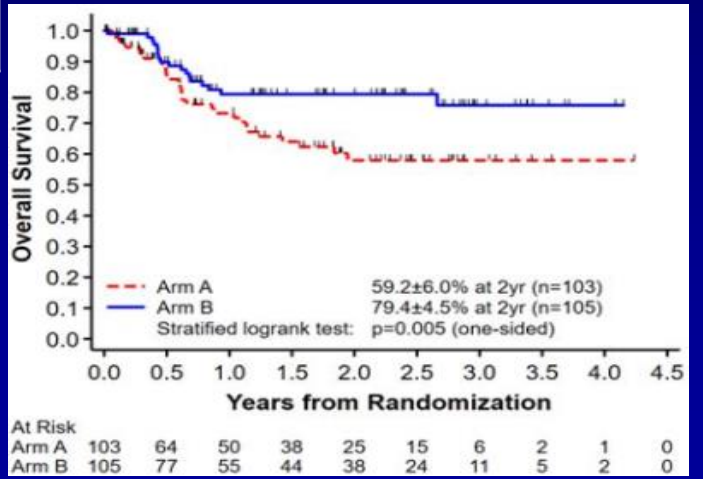
Phase III Study of Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

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



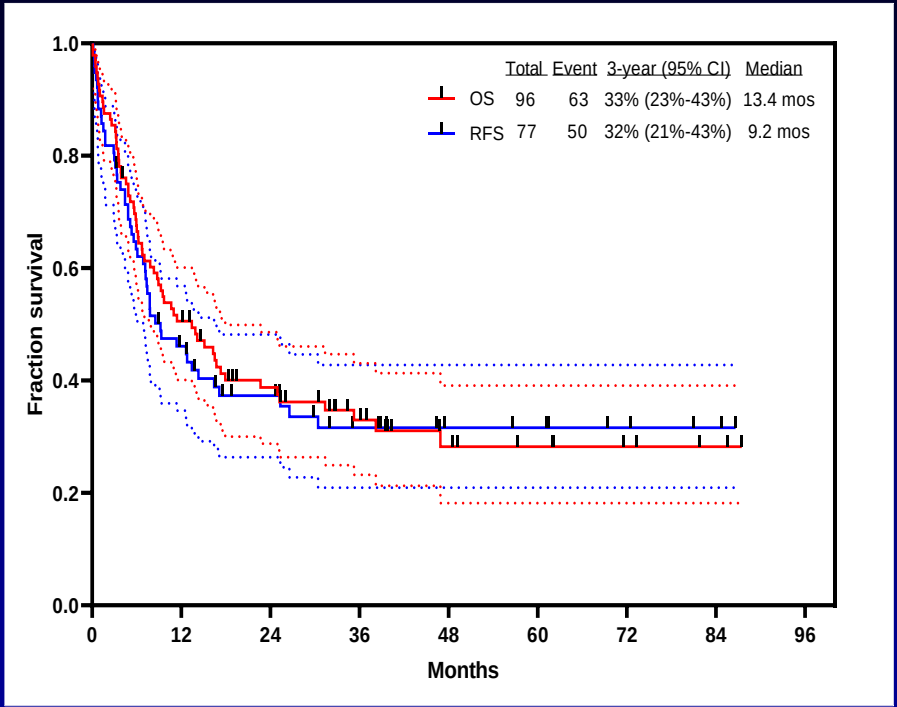
Parameter	Blina	Chemo	*P*
% 2-yr DFS	59	41	.05
% 2-yr OS	79	59	.005
% SCT	73	49	<.001
% MRD clearance	79	21	<.001

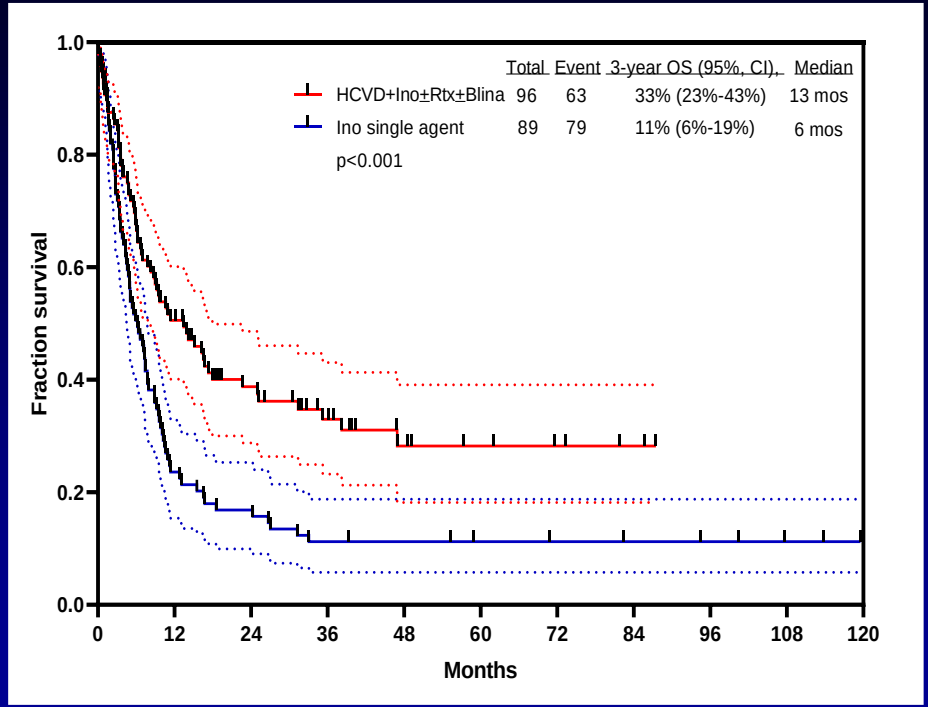




Brown et al. *JAMA*. 2021:325(9):833-842.

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

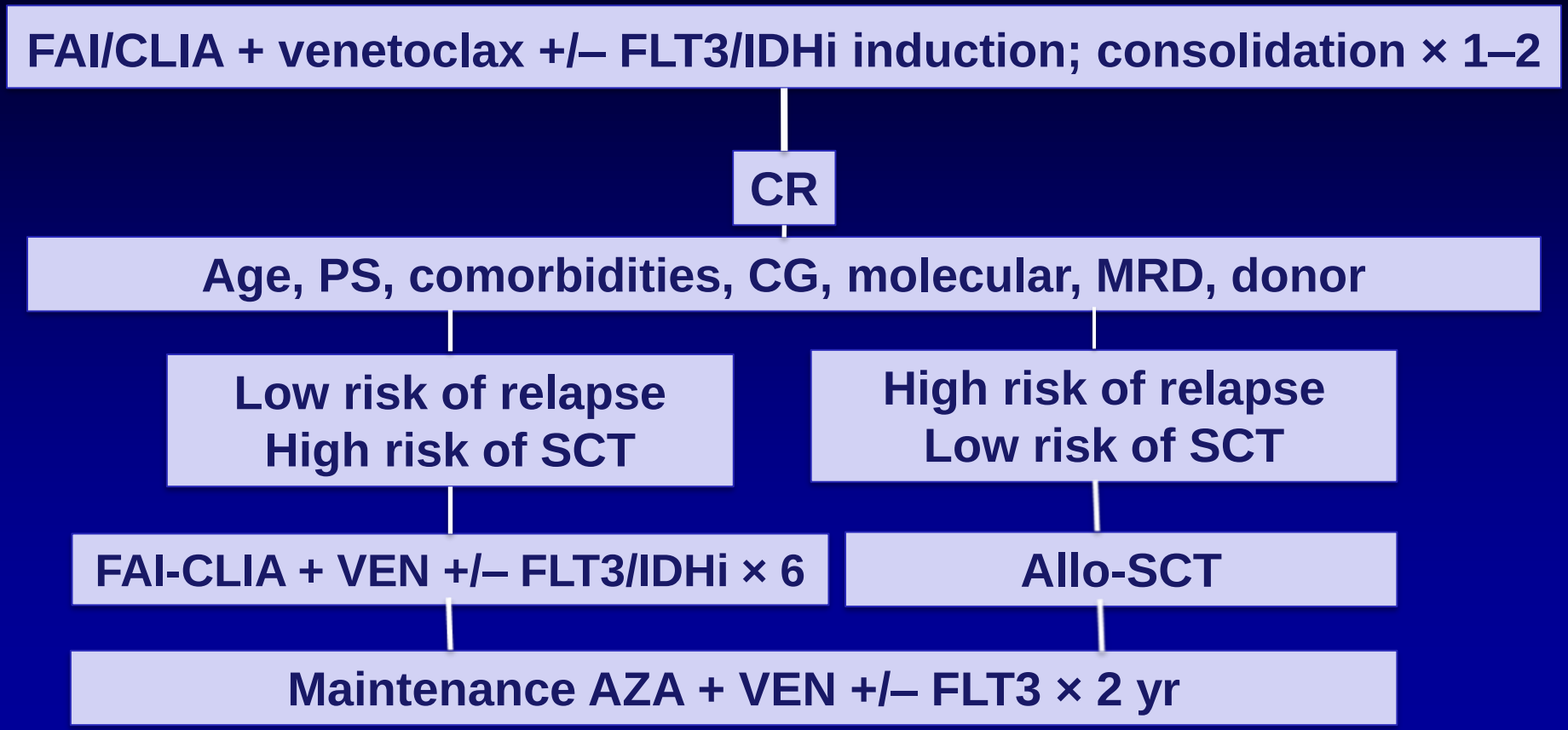
- **Midostaurin** (RYDAPT) for de novo younger AML (≤60 yr), *FLT3* mutation – April 2017
- **Gilteritinib** (*FLT3* inhibitor) for *FLT3*+ R/R AML
- **Enasidenib** (AG-221; IDHIFA) for R/R AML and *IDH2* mutation – August 2017
- **Ivosidenib** (AG-221) for R/R AML – August 2018
- **CPX-351** (Vyxeos) 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+

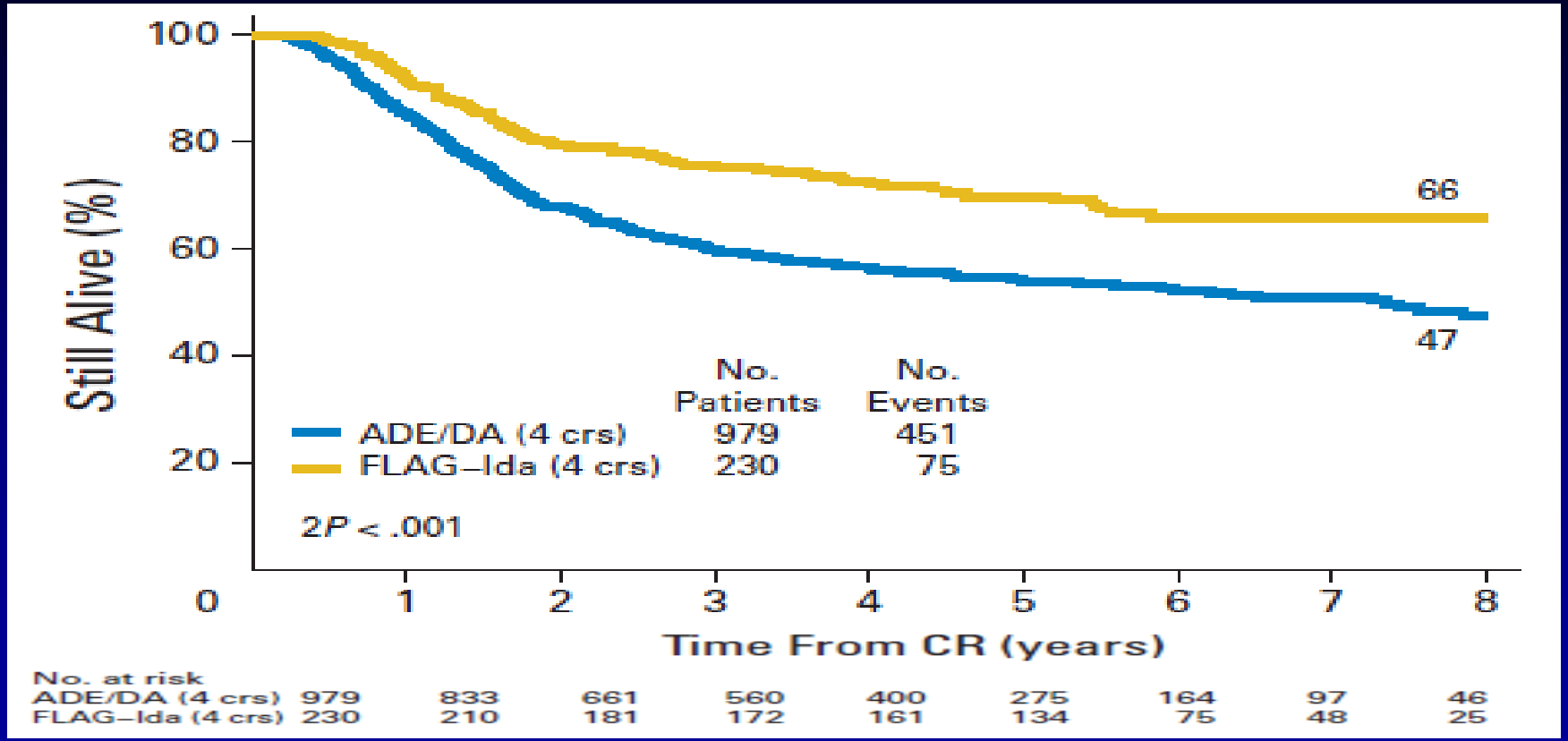


High-Dose Ara-C Induction Improves Outcomes in AML

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

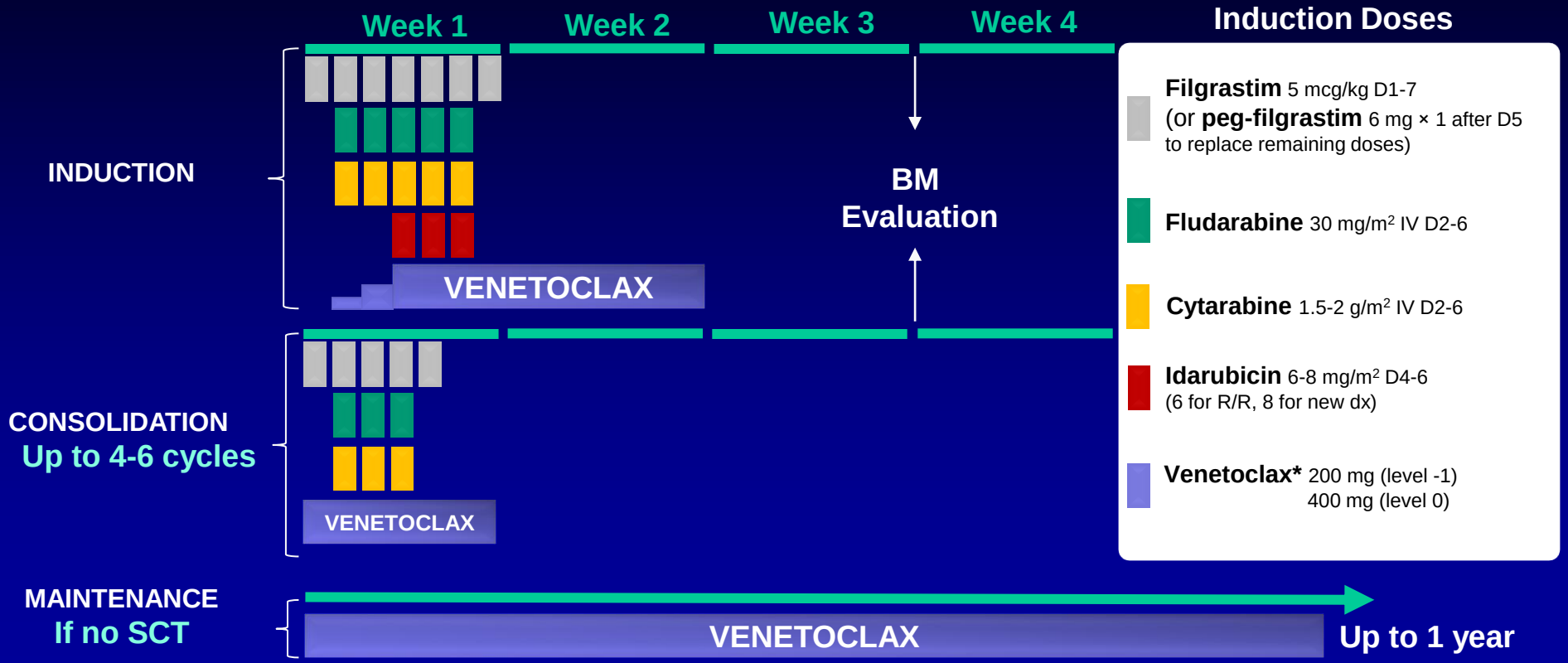
Kern W, Estey EH. *Cancer.* 2006;107(1):116-124; Willemze R, et al. *J Clin Oncol.* 2014;32(3):219-228; Wei H, et al. *Blood.* 2017;130:abstract 146; Burnett AK, et al. *J Clin Oncol*. 2013;31:3360-3368; Bassan R, et al. *Blood Adv.* 2019;3(7):1103-1117.

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



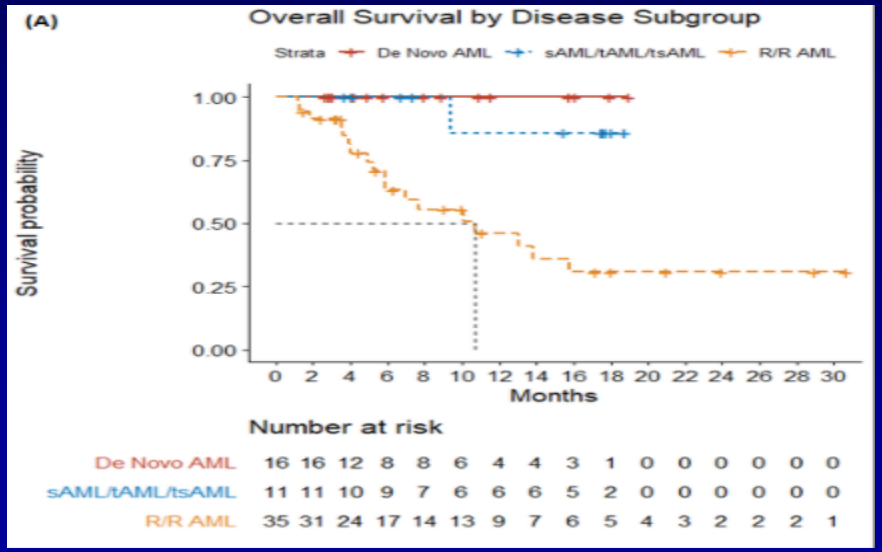
Abou Dalle, et al. *Blood.* 2019;134:abstract 176.

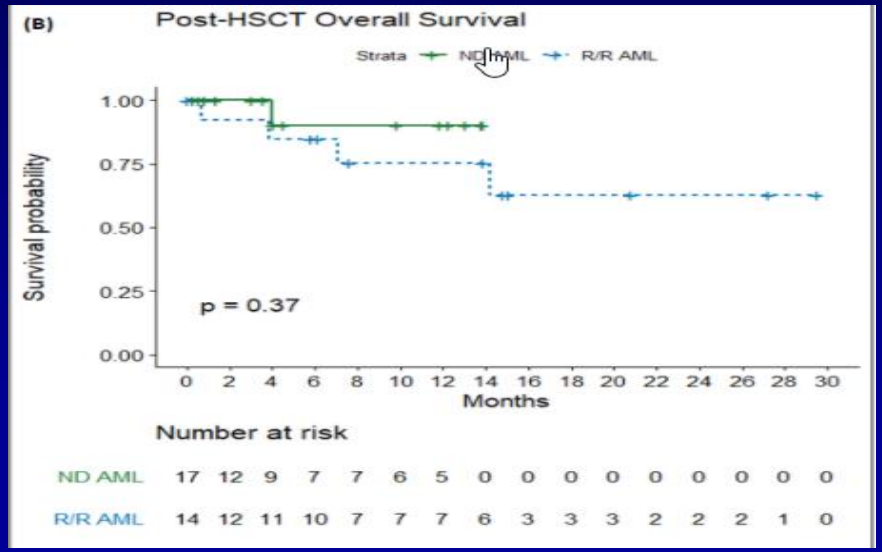
*Concomitant azole permitted with adequate dose reduction.

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

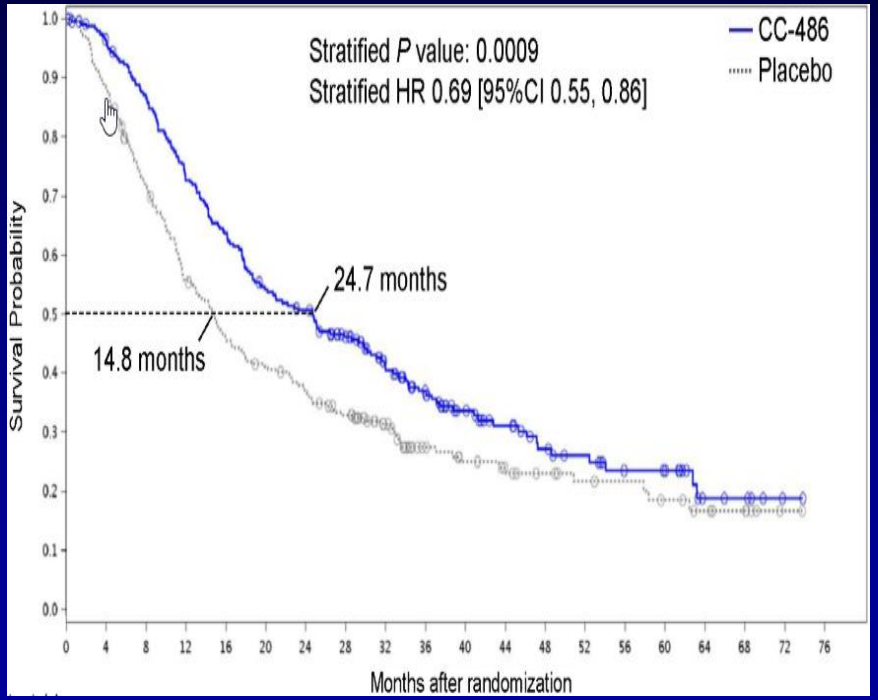


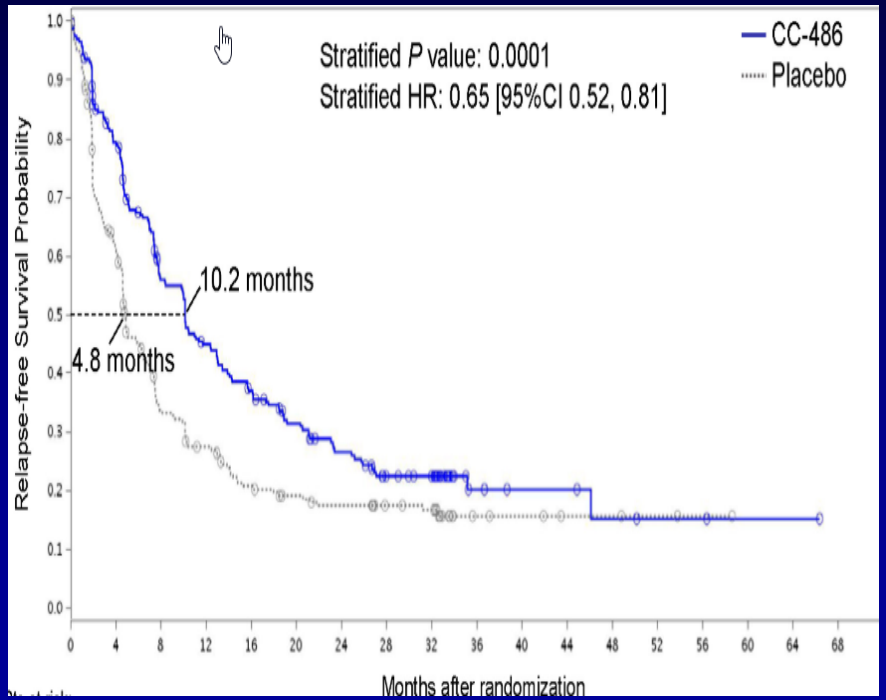


Lachowiez et al. *Blood*. 2020;136:abstract 332.

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.

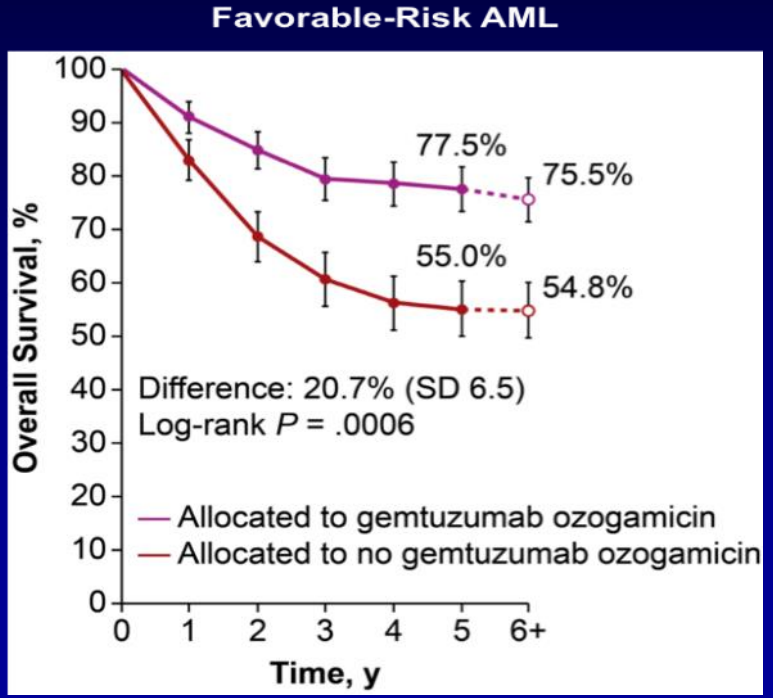
AML: What Definitely Works

- 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

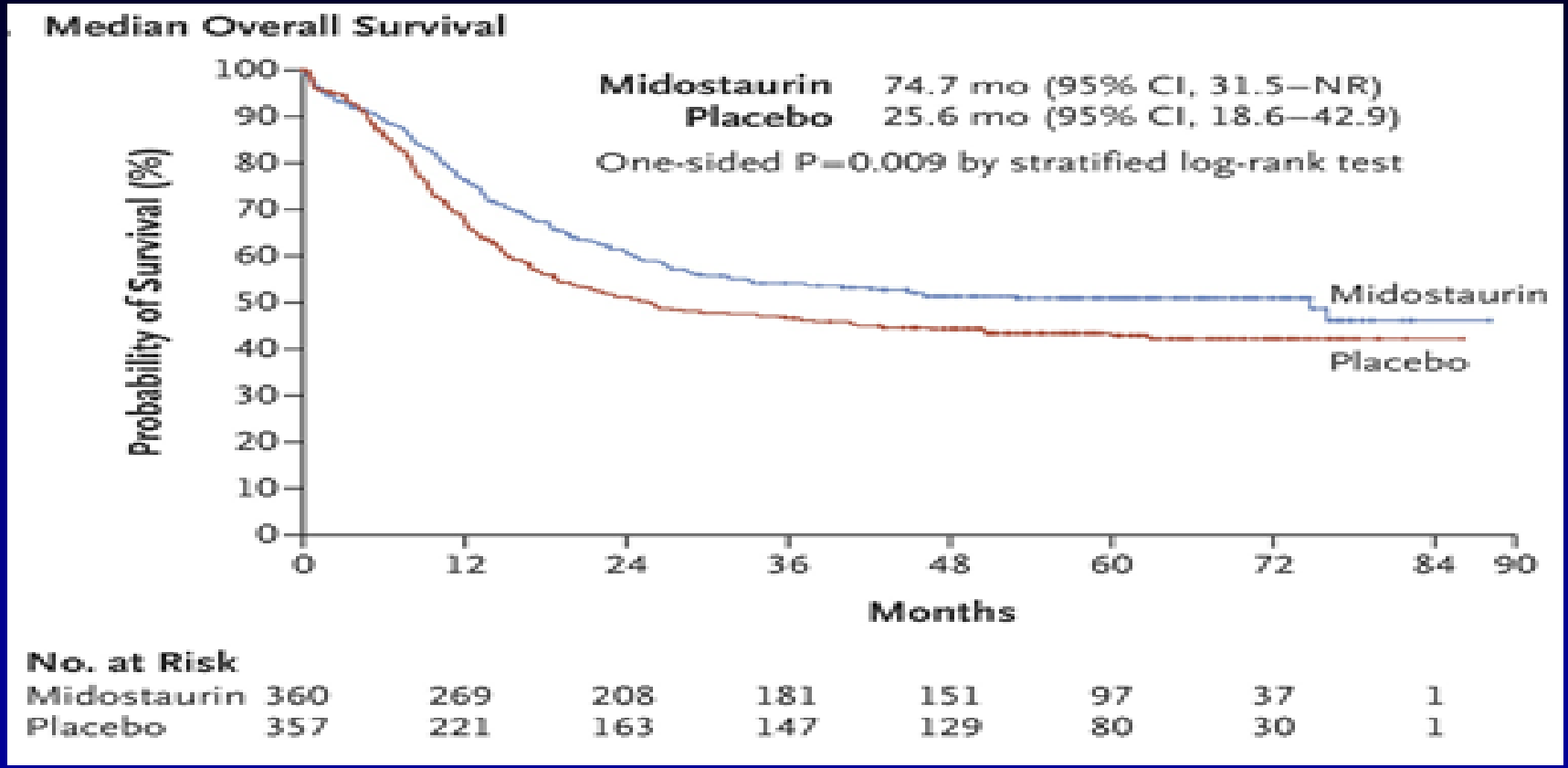
5 randomized trials of 3,325 pts: SWOG, ALFA, UK-MRC AML15 and 16, GOELAMS

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)

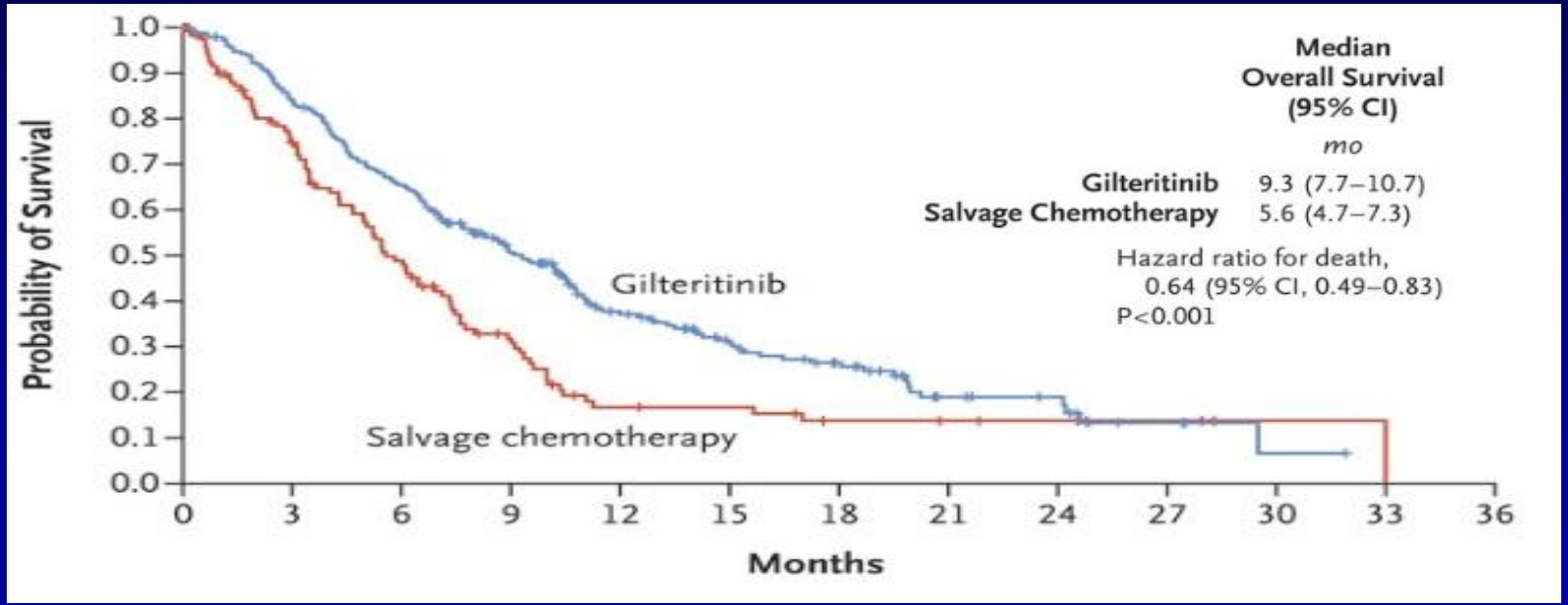


Stone RM, et al. *N Engl J Med*. 2017;377:454-464.

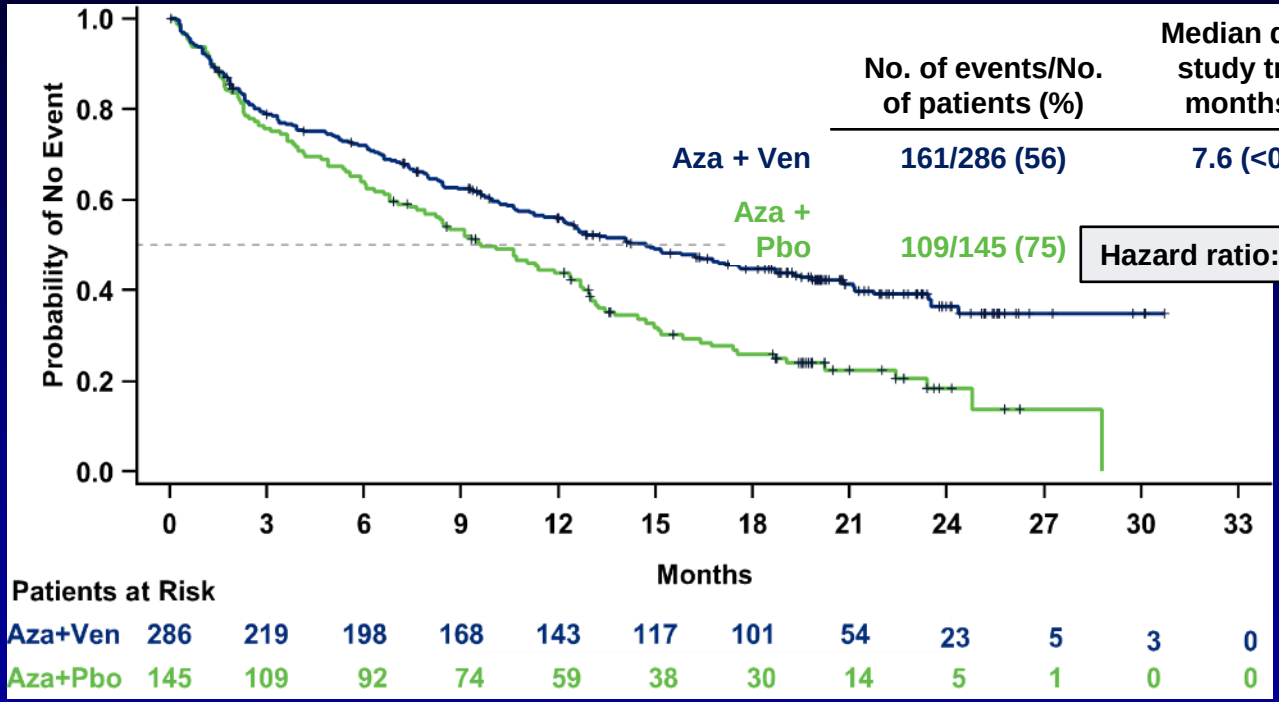
Gilteritinib vs Chemo Rx in R/R *FLT3*-Positive AML

- 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



AZA +/- VEN in AML – Overall Survival



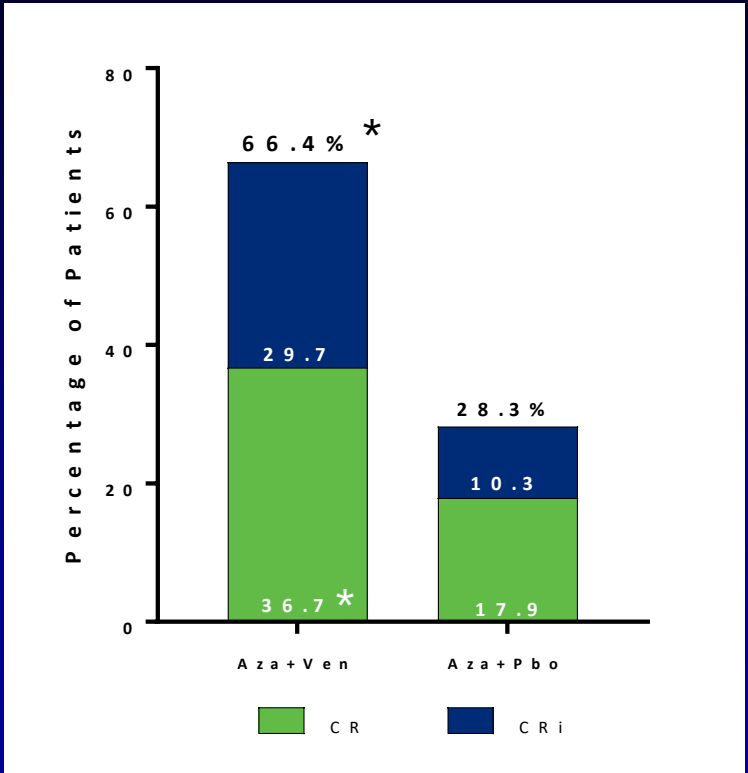
	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza + Ven	161/286 (56)	7.6 (<0.1–30.7)	14.7 (11.9–18.7)
Aza + Pbo	109/145 (75)		

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)

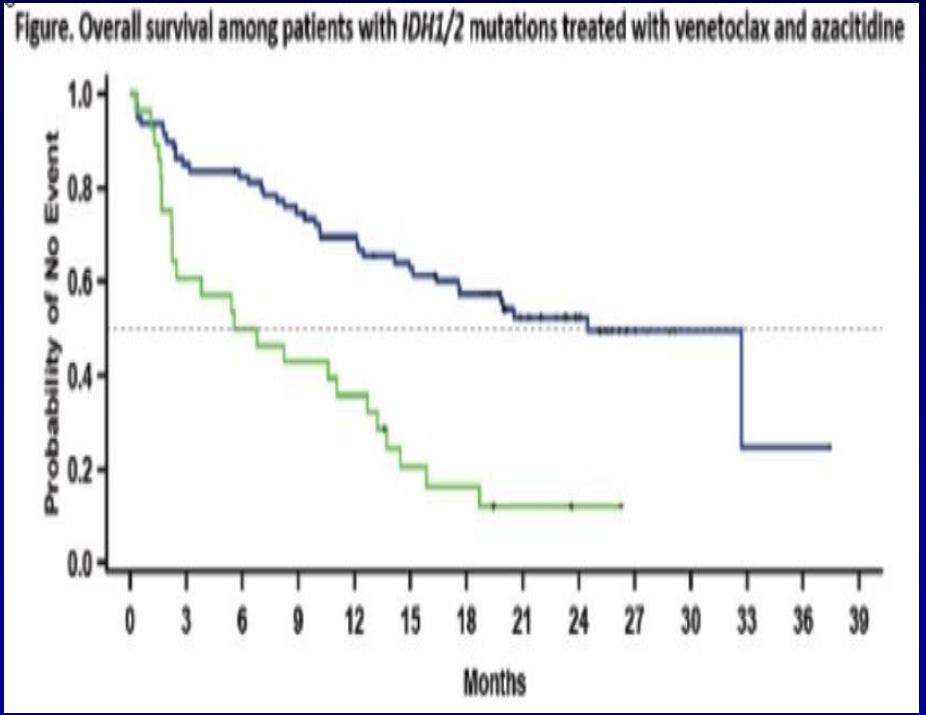
*CR + CRi rate, CR rate, and CR + CRi by initiation of cycle 2 are statistically significant with *P* <.001 by CMH test.

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

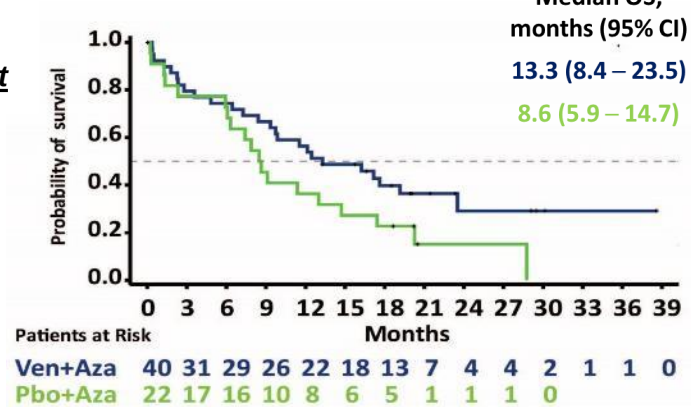
No (%) Parameter	AZA-VEN (n = 79)	AZA (n = 28)
CR + CRi	62 (79)	3 (11)
CR + CRh	57 (72)	2 (7)
CR	35 (44)	1 (4)
Median DOR (mos)	29.5	17.5
Median OS (mos)	24.5	12.3



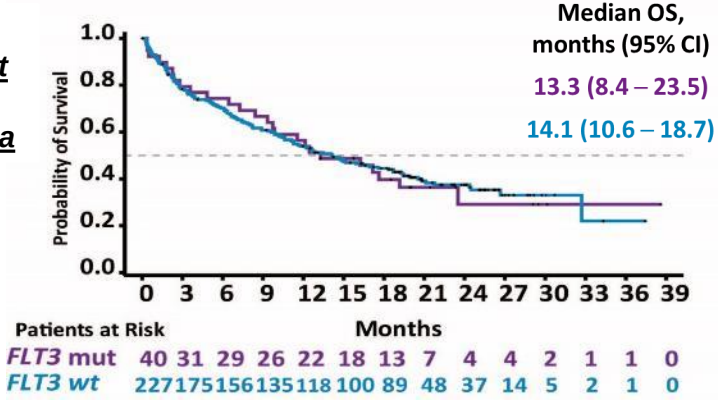
Pollyea D, et al. *Blood.* 2020;136:abstract 461.

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

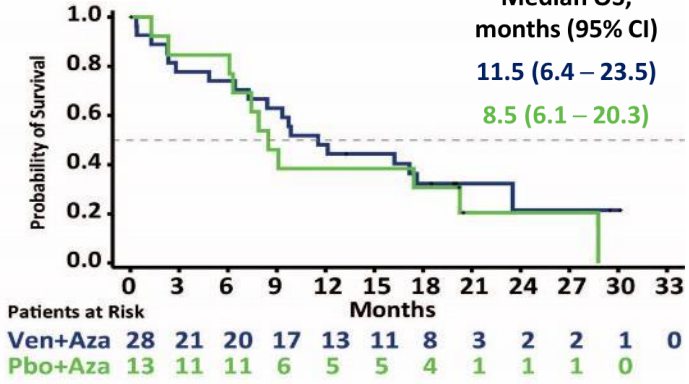
A. FLT3mut



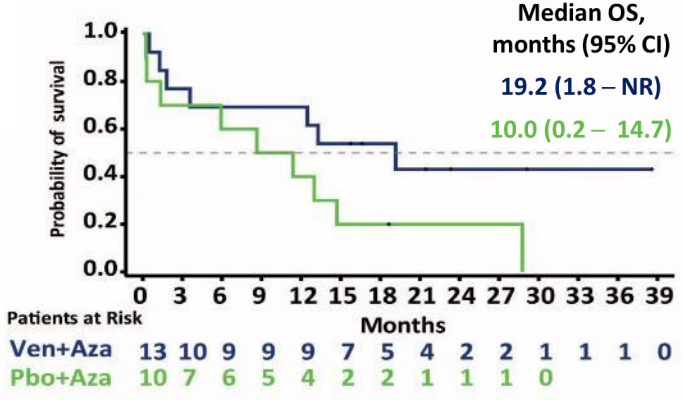
B. FLT3mut vs wt in Ven + Aza



C. FLT3-ITD



D. FLT3-TKD

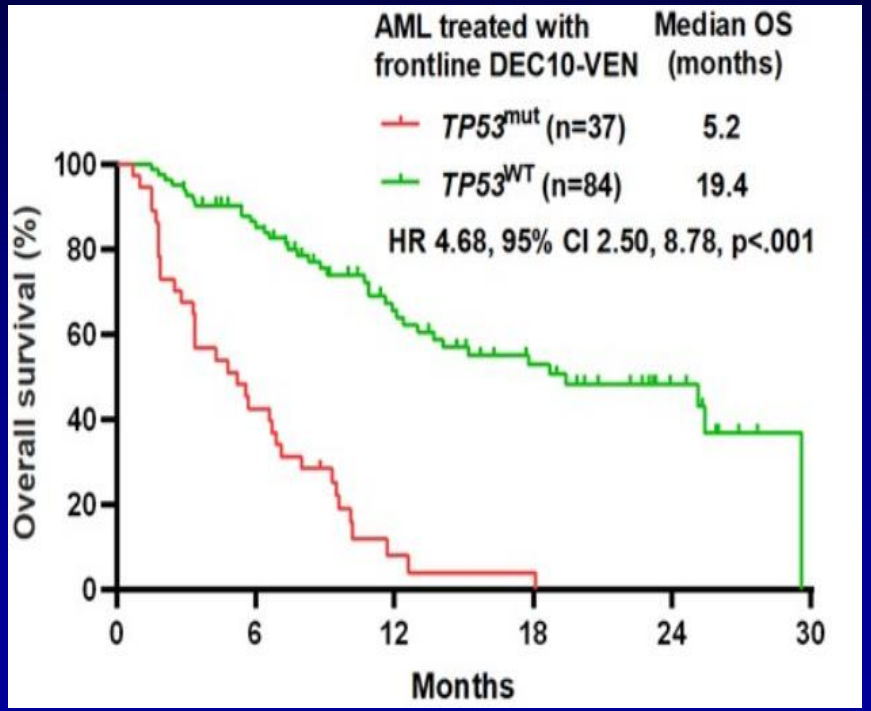


Konopleva M, et al. *Blood*. 2020;136:abstract 1904.

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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- **Cell: 713-498-2929**
- **Office: 713-792-4764**

Global Leukemia Academy

Review of prognostic value of MRD in ALL

José Maria Ribera

APTITUDE HEALTH

Global Leukemia Academy
Virtual Plenary Session
April 23, 2021

Review of the Prognostic Value of MRD in Acute Leukemias

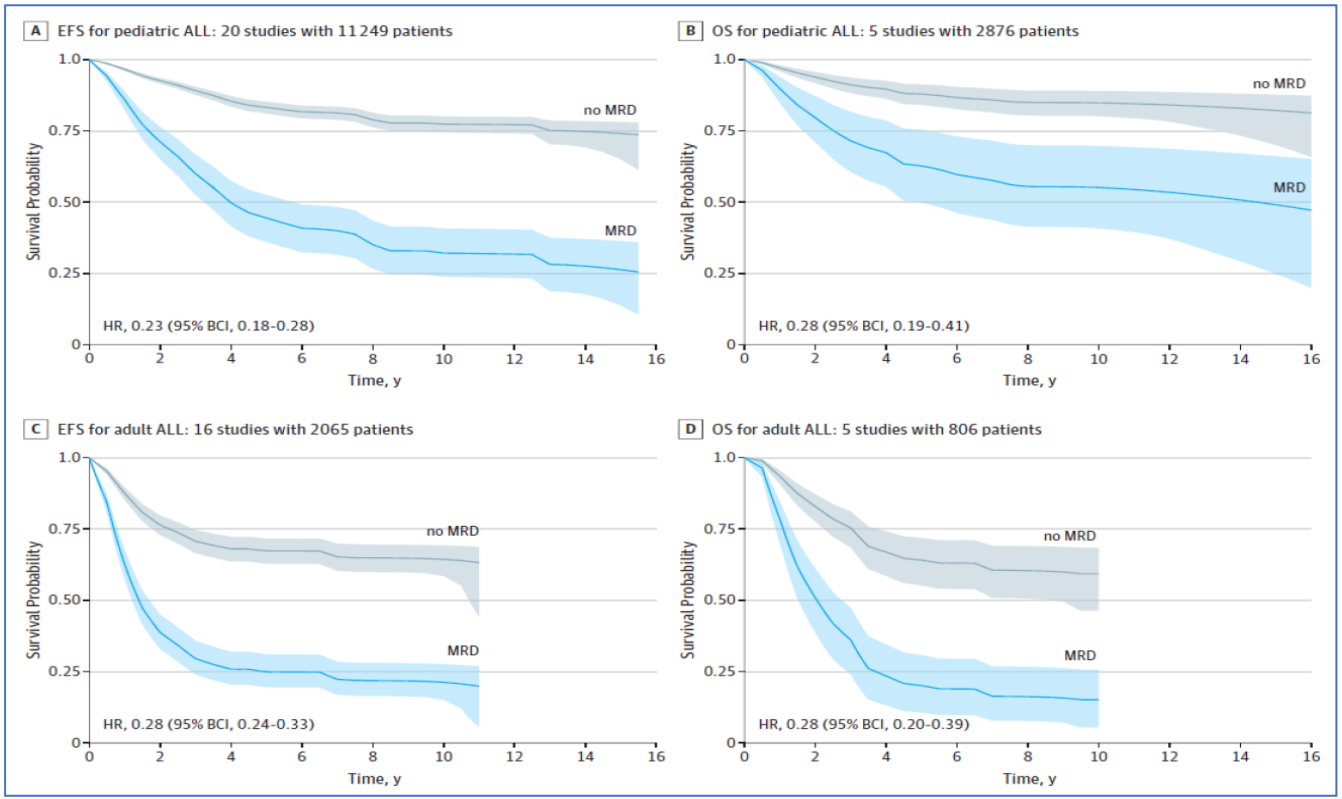
JM Ribera
Servicio de Hematologia Clinica
ICO-Hospital Germans Trias i Pujol
Institut de Recerca contra la Leucemia Josep Carreras
Badalona

Disclosures

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

Acute Lymphoblastic Leukemia

Negative MRD Is Associated With Longer EFS and OS in Pediatric and Adult ALL

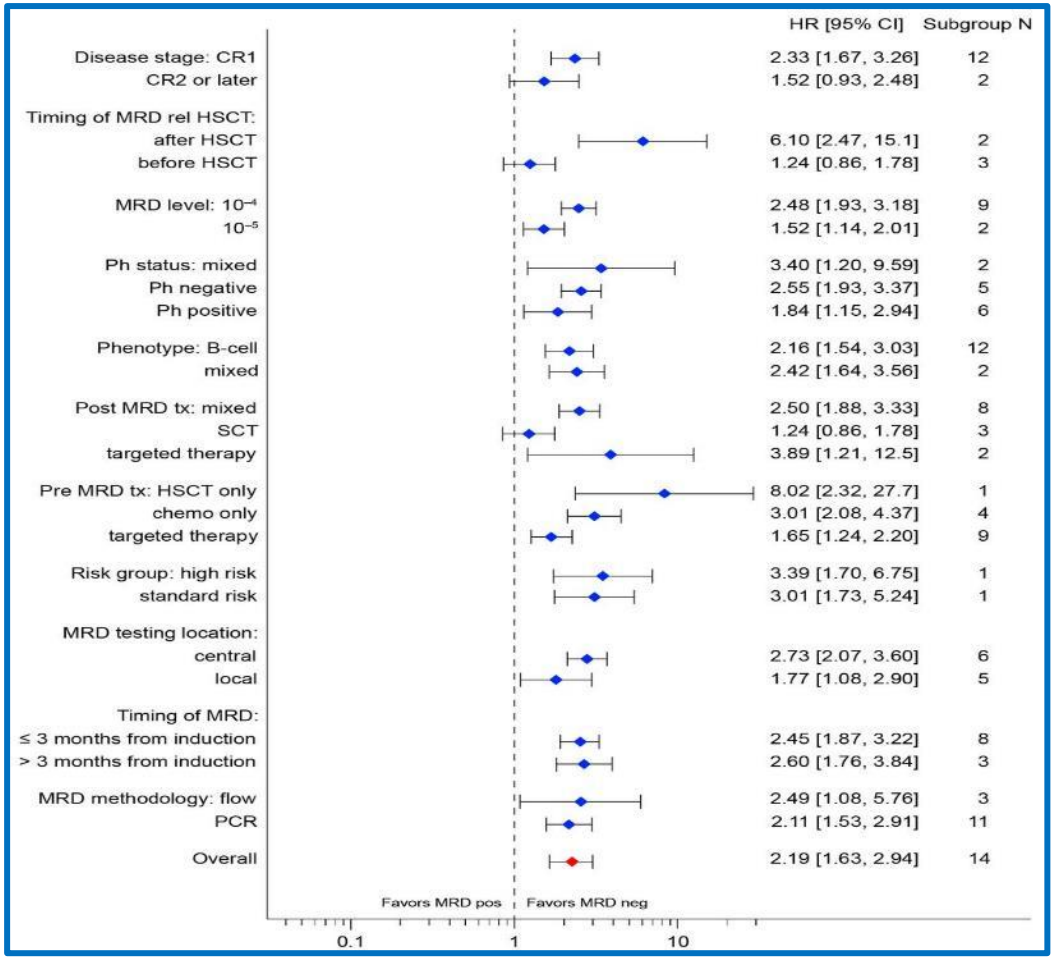


Meta-analysis of 20 pediatric ALL trials >11,000 patients

Meta-analysis of 16 adult ALL trials >2,000 patients

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

Prognostic Value of MRD in All Situations

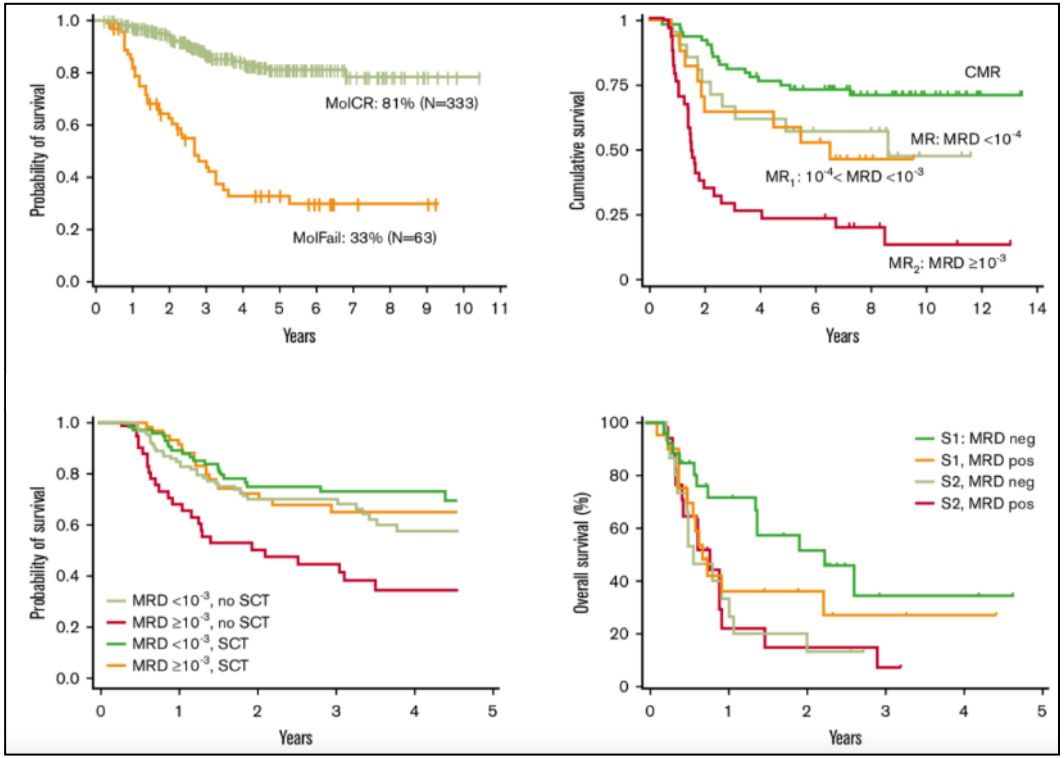


Bassan R, et al. *Haematologica*. 2019;104:2028-2039.

MRD Is a Strong Risk Factor in Adults With Ph– ALL

Persistent MRD predicts shorter survival

- Whatever the method (Ig-TCR PCR, MFC)
- Whatever the time points
- Whatever the thresholds
- Whatever the ALL status?
- Whatever the treatment?

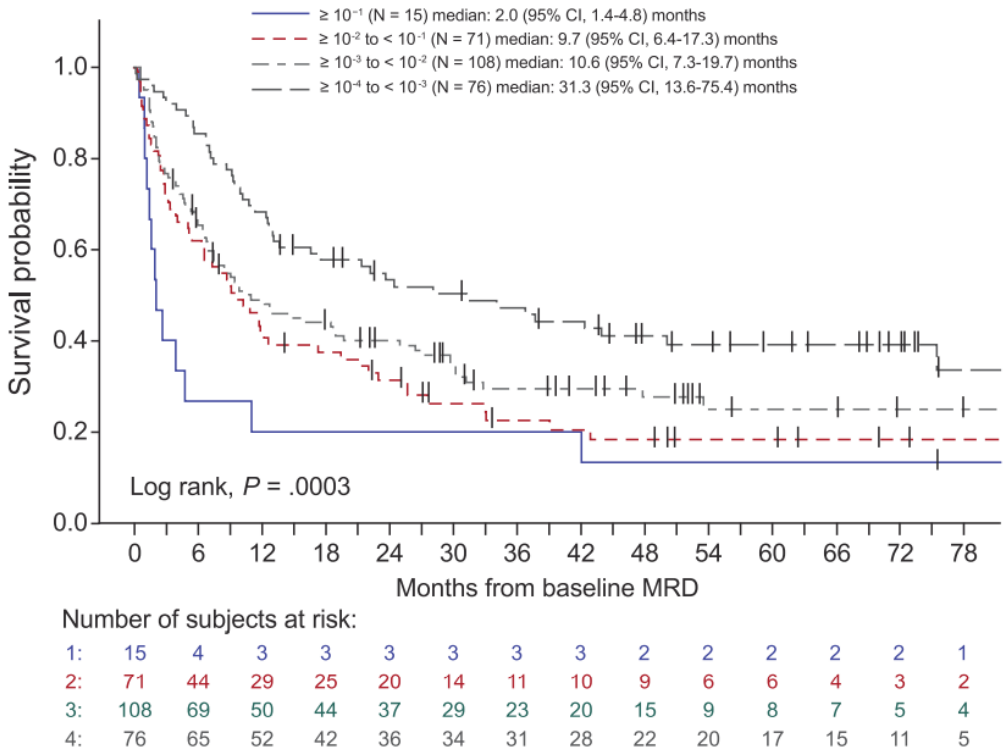


Brüggeman M, Kotrova M. *Blood Adv*. 2017;1:2456-2466.

Joint EU Survey on High MRD

Survey From 7 EU Cooperative Groups

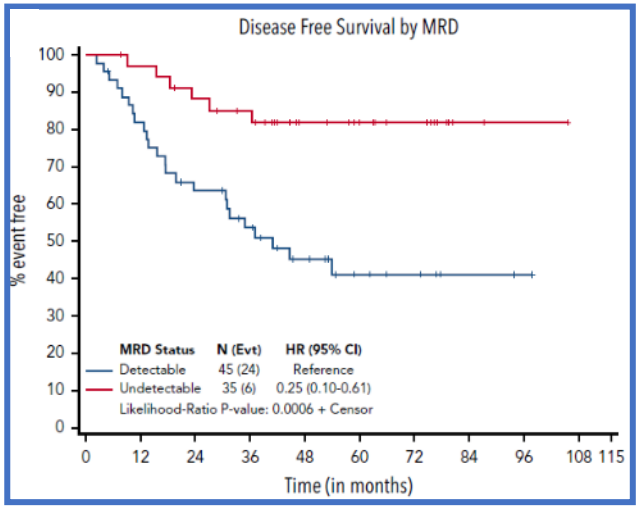
- N = 270 patients with measurable MRD during first remission
  - 80% molecular failure
  - 19% molecular relapse
- Median DOR, 18.5 months (95% CI: 11.9, 27.2)
- Median RFS, 12.4 months (95% CI: 10.0, 19.0)
- Median OS, 32.5 months (95% CI: 23.6, 48.0)



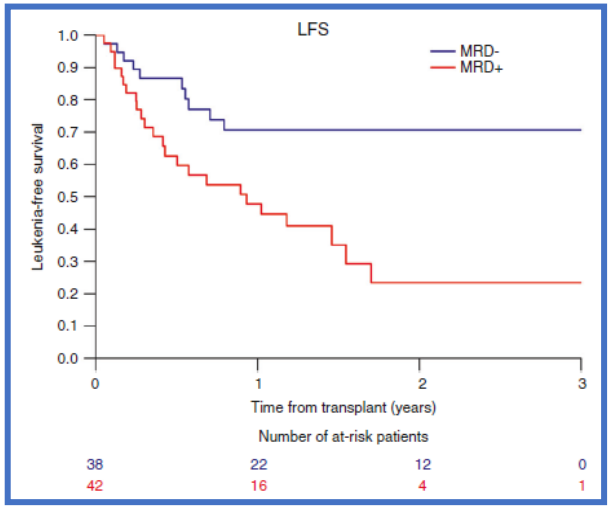
Gökbuget N, et al. *Hematology*. 2019;24:337-348.

Impact of MRD in Some ALL Subtypes

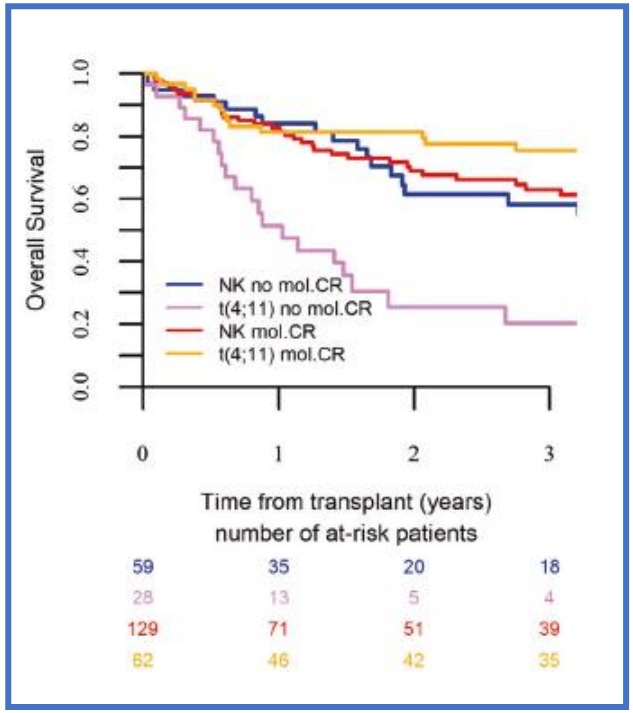
AYA[1]



IKZF1+[2]



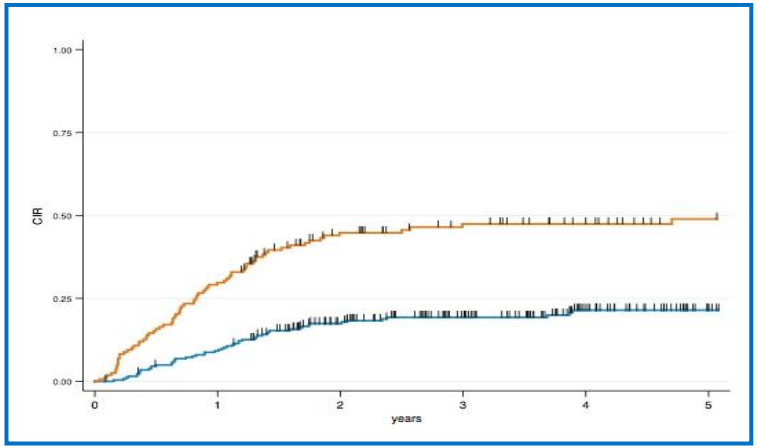
KMT2A+[3]

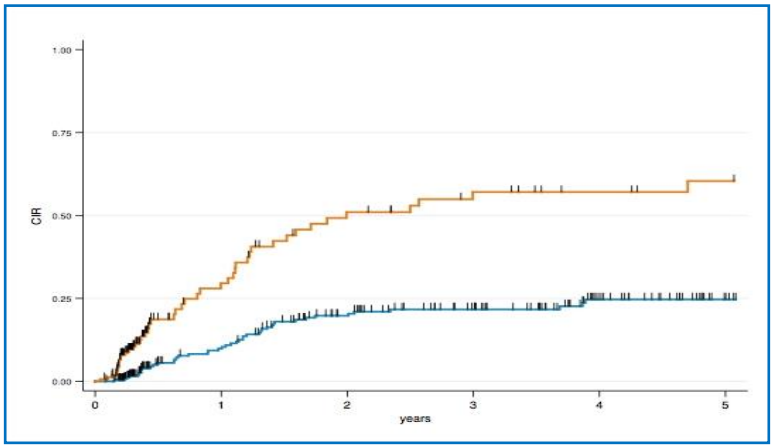


1. Stock W, et al. *Blood.* 2019;133:1548-1559; 2. Giebel S, et al. *Bone Marrow Transplant.* 2020. doi: 10.1038/s41409-020-01139-z;
3. Esteve J, et al. *Leukemia.* 2021. doi: 10.1038/s41375-021-01135-2.

MRD Is Not a Perfect Predictive Factor in Adult Ph– ALL

Post-induction Ig-TCR MRD
≥10^{-4}
<10^{-4}



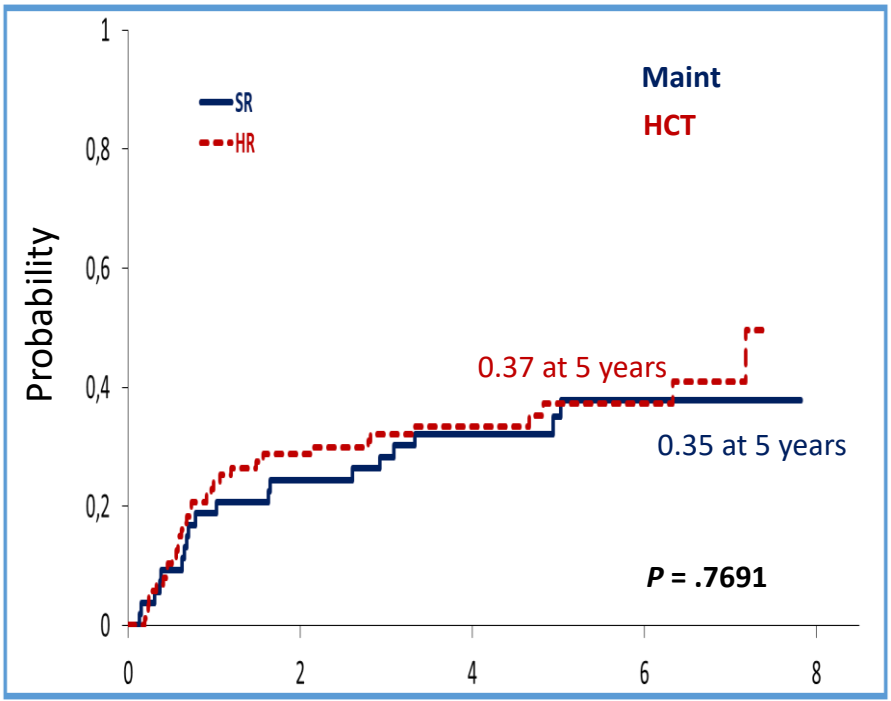


	Without AlloHSCT Censoring	With AlloHSCT Censoring
5-yr CCR in MRD+ pts	51.2%	39.6%
5-yr CIR in MRD– pts	21.2%	24.7%
Harrel's C-index	0.63	0.64

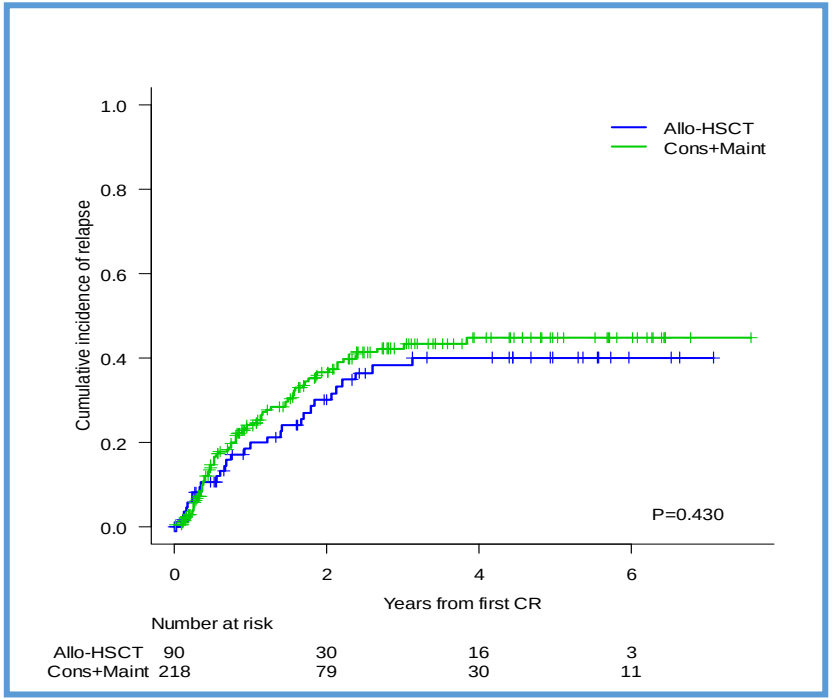
Courtesy of H. Dombret.

Beldjord K, et al. *Blood.* 2014;123:3739-3749; GRAALL data on file.

Cumulative Incidence of Relapse by Treatment Allocation (ITT analysis)

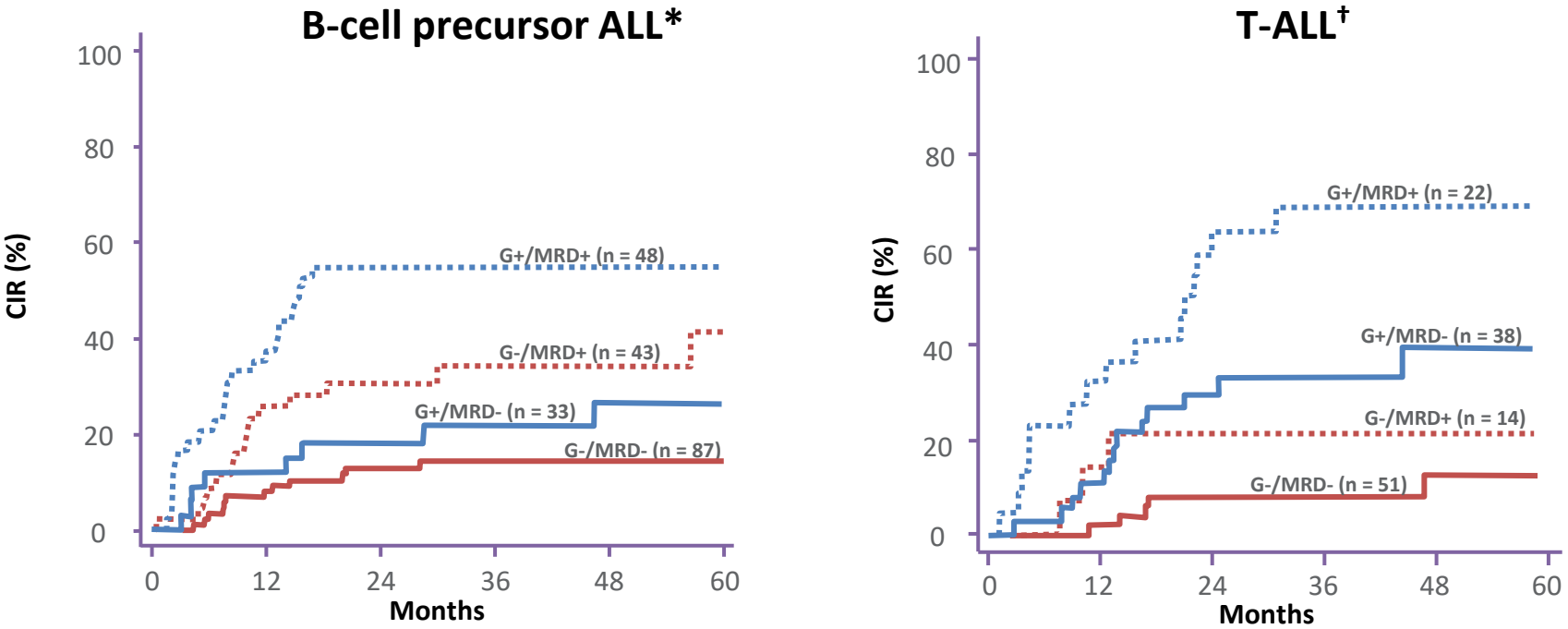


Bassan R, et al. *Blood Cancer J*. 2020;10(11):119.



Ribera JM, et al. *Blood*. 2021;137:1879-1894.

Independent Prognostic Impact of MRD and Oncogenetic Pattern on Relapse: GRAALL Data



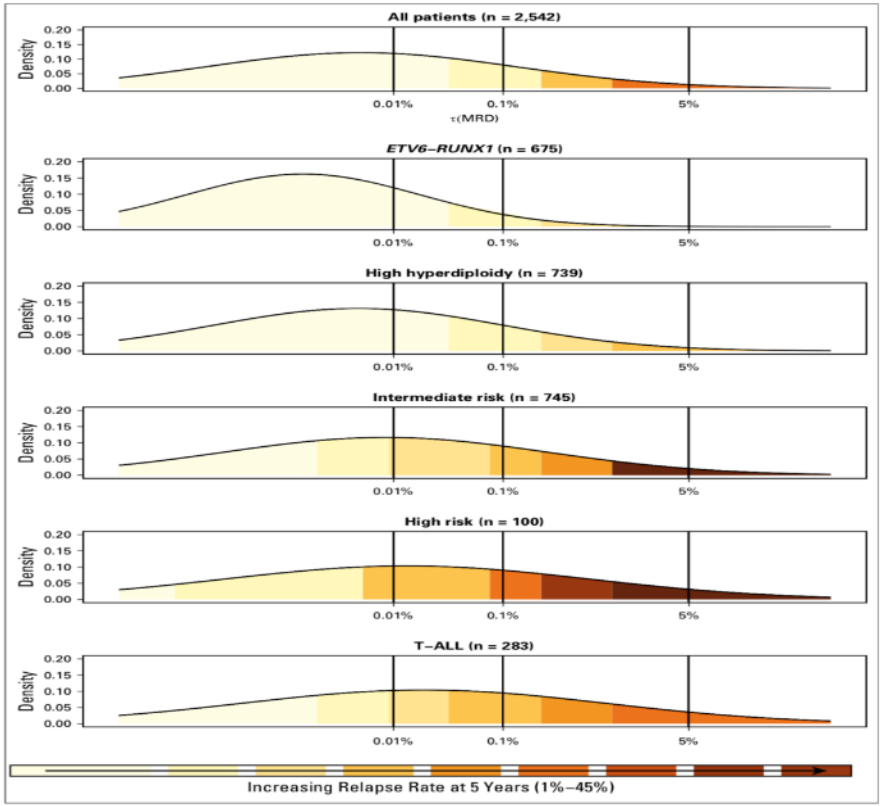
GENETIC RISK: ***B-cell precursor ALL** – MLL and/or *IKZF1* mutation; †**T-ALL** – no *NOTCH* and/or *RAS*/*PTEN* mutation
Adapted from Beldjord K, et al. *Blood*. 2014;123:3739-3749.

Value of MRD According to Genetic Subgroups

- **The value of MRD may depend on**
  - –Response kinetics
  - –Existence of resistant subclones

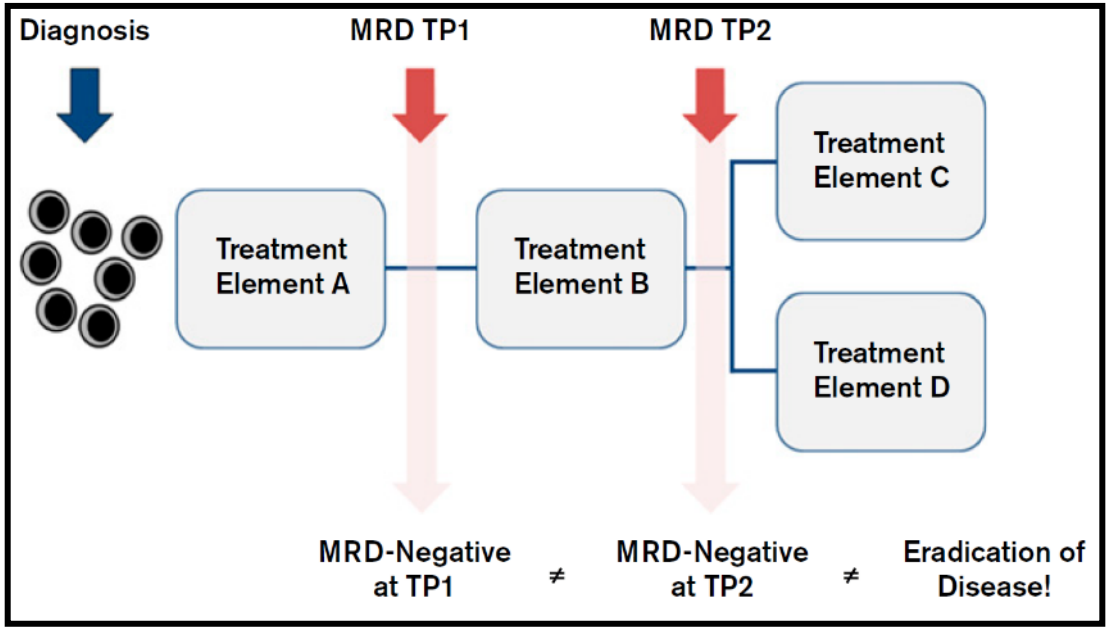
- Pediatric UKALL2003 study
  - –The risk of relapse was proportional to the MRD level within each genetic risk group
  - –However, absolute relapse rate that was associated with a specific MRD value varied significantly by genetic subtype

Integration of genetic subtype/subclone-specific MRD could allow a more refined risk stratification



O'Connor D, et al. *J Clin Oncol*. 2018;36:34-43.

Importance of Time Points in MRD Assessment



- **Negative** MRD at **TP1**: useful for recognizing patients with **low risk** of relapse
- **Positive** MRD at **TP2**: useful for recognizing patients with **high risk** of relapse

Brüggemann M, Kotrova M. *Blood Adv*. 2017;1:2456-2466.

Use of MRD for Therapeutic Decisions

1. Intensification

- Allogeneic HSCT in first hematologic remission

2. Antibody-based immunotherapy

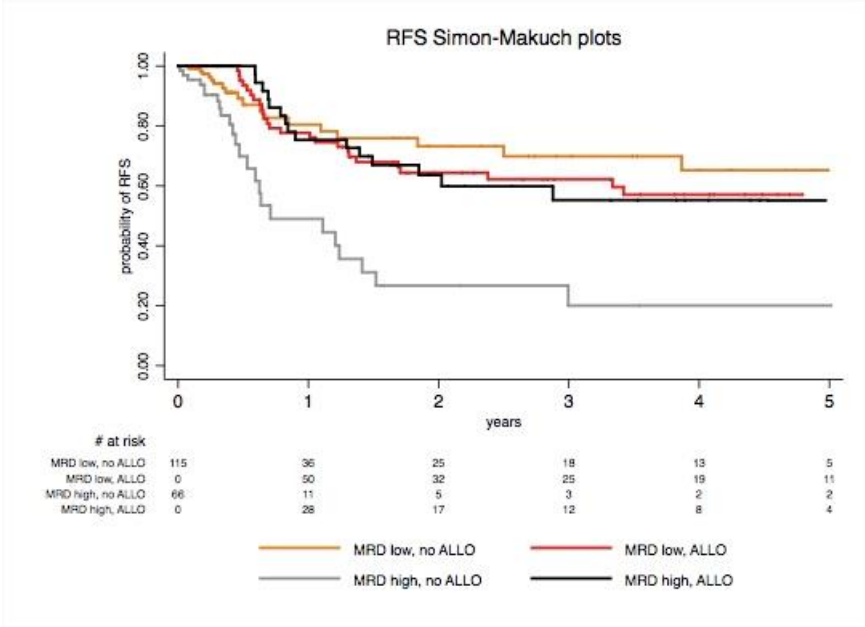
- Blinatumomab
- Inotuzumab ozogamicin
- CAR T cells

3. Targeted therapy

- TKI switch in Ph+ ALL
- Targeted therapy and immunotherapy

Allogeneic HSCT Benefits MRD+ Patients Only

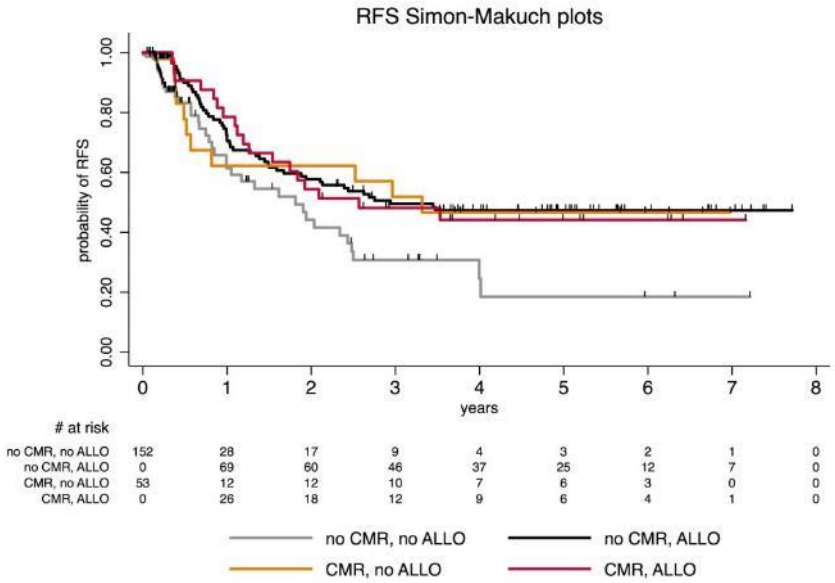
Ph– ALL



Test for interaction, *P* = .001

Dhedin N, et al. *Blood*. 2015;125(16):2486-2496.

Ph+ ALL



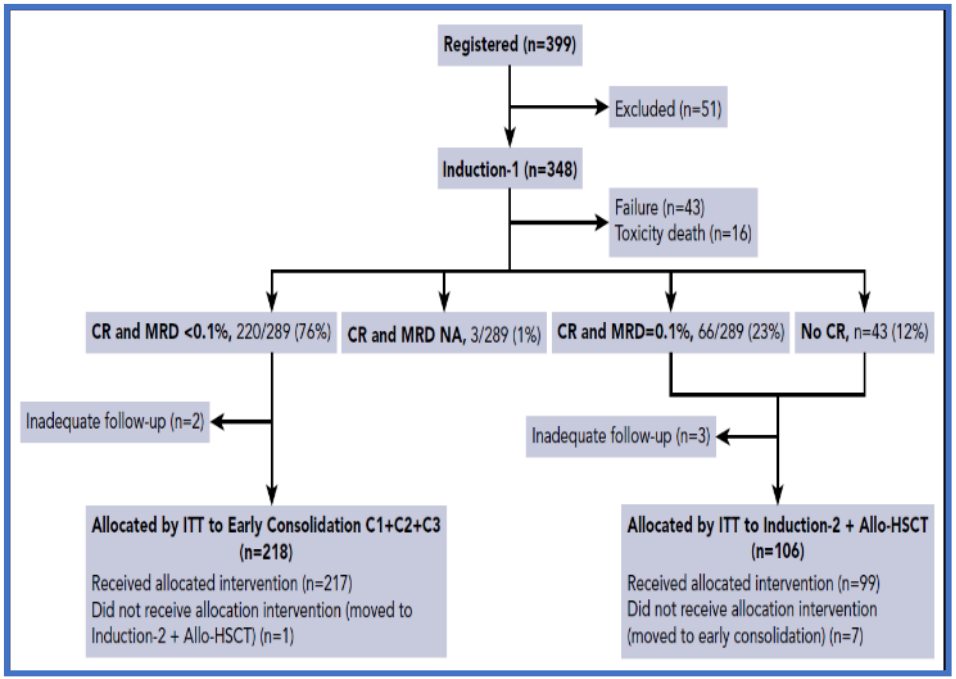
Test for interaction, *P* = .18

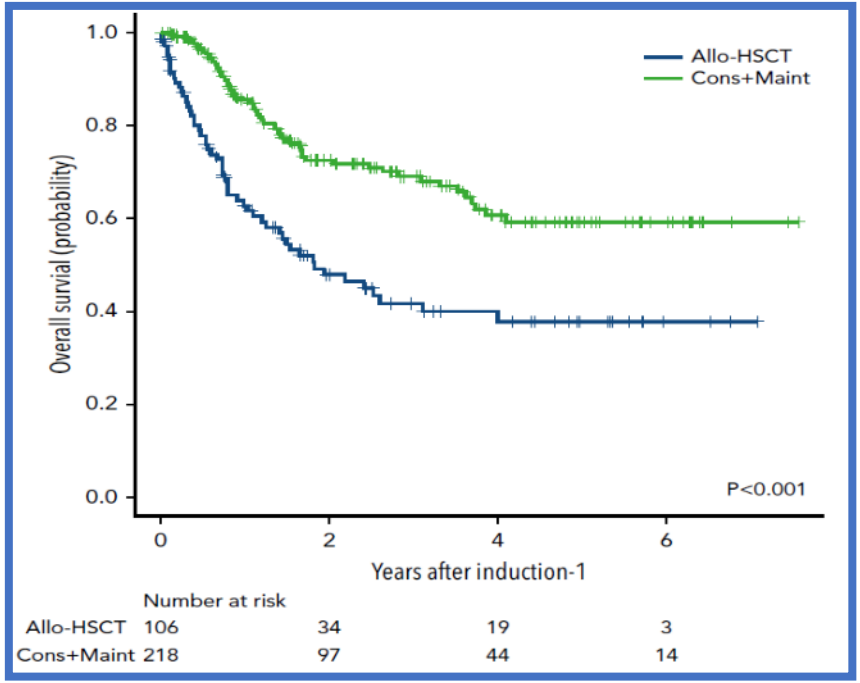
Chalandon Y, et al. *Blood*. 2015;125(24):3711-3719.

Prospective Studies With Indication for HSCT on the Basis of MRD Data (adult Ph– ALL)

Trial	Risk Groups	MRD Assessment	Randomization Assignment	References
NILG	SR & HR	PCR	• No • Allo(auto)HSCT in MRD+ pts	Bassan R. *Blood.* 2009;113:4153-4162
PETHEMA HR03	HR	4-color flow	• No • AlloHSCT in poor early cytologic responders or MRD+ pts	Ribera JM. *J Clin Oncol.* 2014;32:1595-1604
NILG 10/07	SR & HR	PCR	• No • Allo(auto)HSCT in MRD+ pts	Bassan R. *Blood Cancer J.* 2020;10:119
PETHEMA HR11	HR	8-color flow	• No • AlloHSCT in MRD+ pts	Ribera JM, et al. *Blood*. 2021;137:1879-1894
GMALL 08/2013	SR & HR	PCR	• Yes. AlloHSCT vs chemo in MRD– HR pts • AlloHSCT in MRD+ pts	Ongoing; NCT02881086

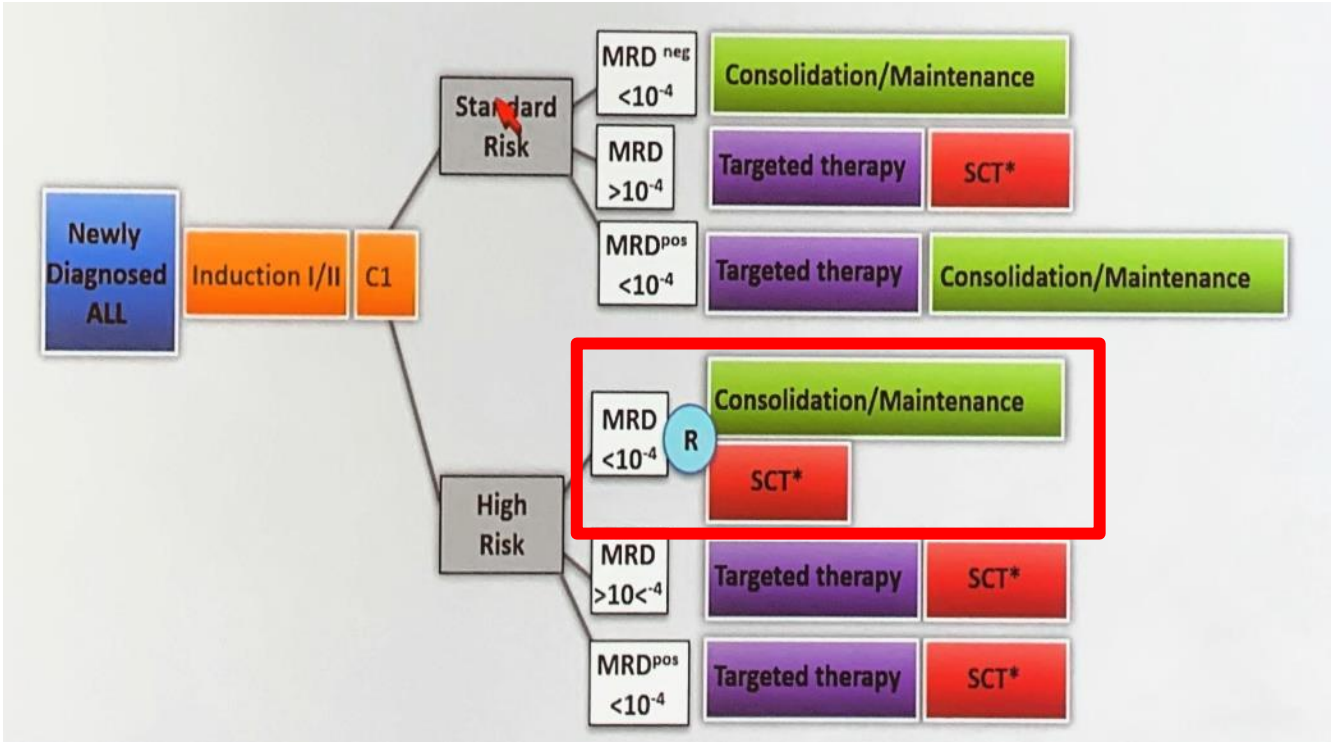
PETHEMA ALL HR11





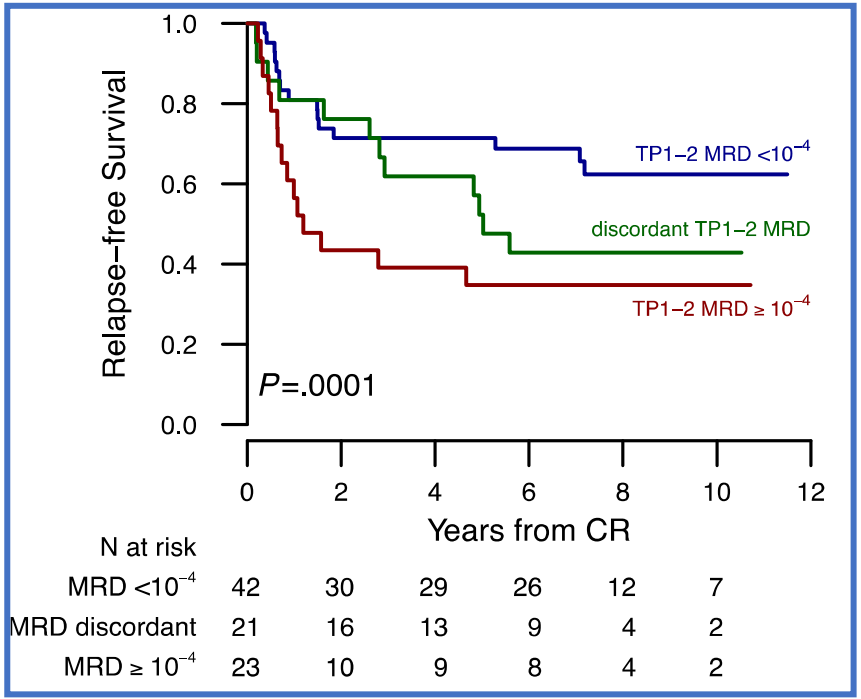
Ribera JM, et al. *Blood*. 2021;137:1879-1894.

Current GMALL Strategy De Novo <55 Years: GMALL Trial 08/2013 – Ph– ALL

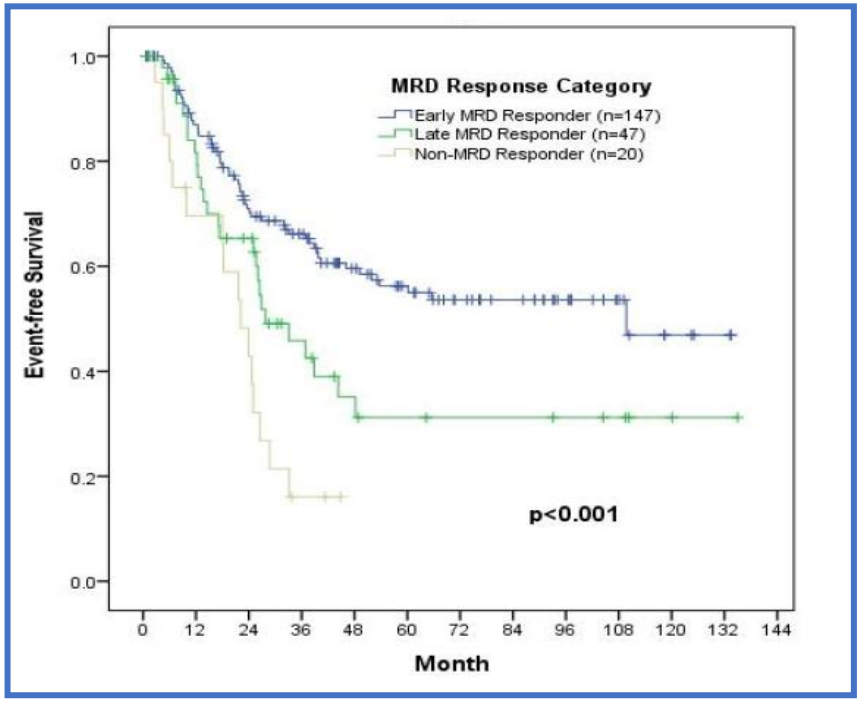


*Dose-reduced conditioning >45 yr.
Courtesy of N. Gokbuget.
NILG 10/07 Ph- ALL: Clinical Trials.gov NCT-00795756.

Prognostic Importance of Early MRD Response in Ph– ALL



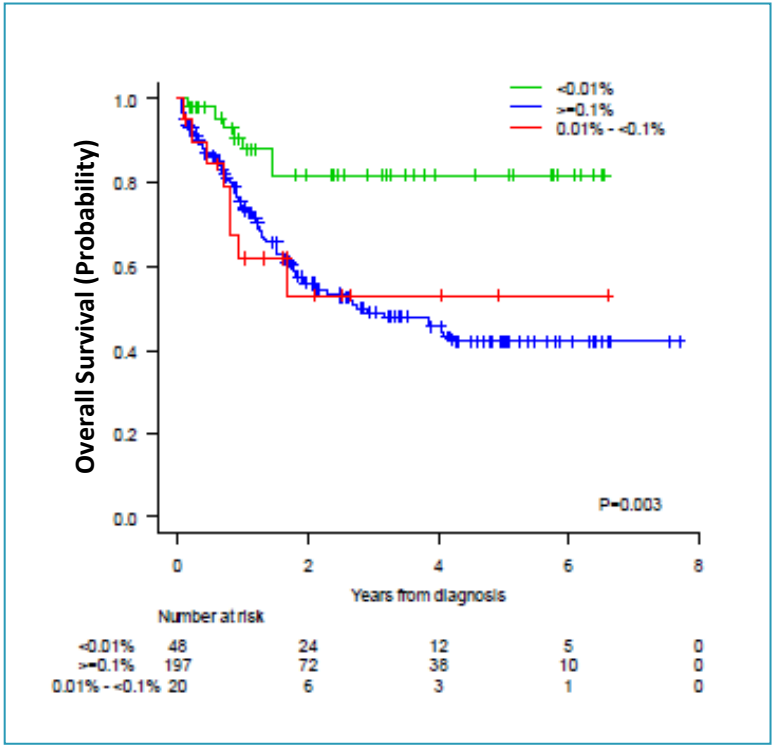
Bassan R, et al. *Blood Cancer J*. 2020;10:119.



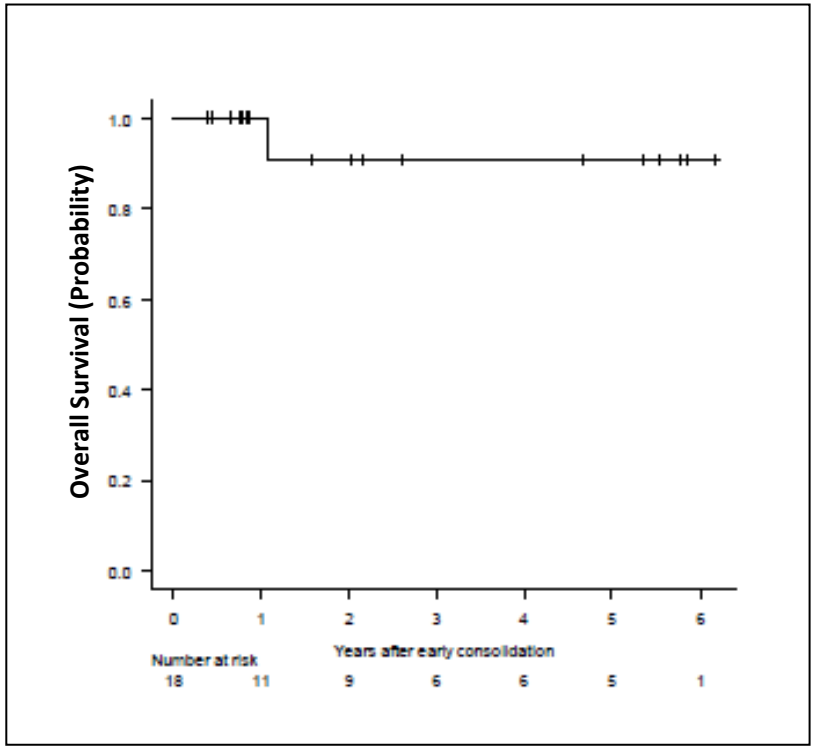
Yilmaz M, et al. *Am J Hematol*. 2020;95:144-150.

Overall Survival

According to post-induction MRD level

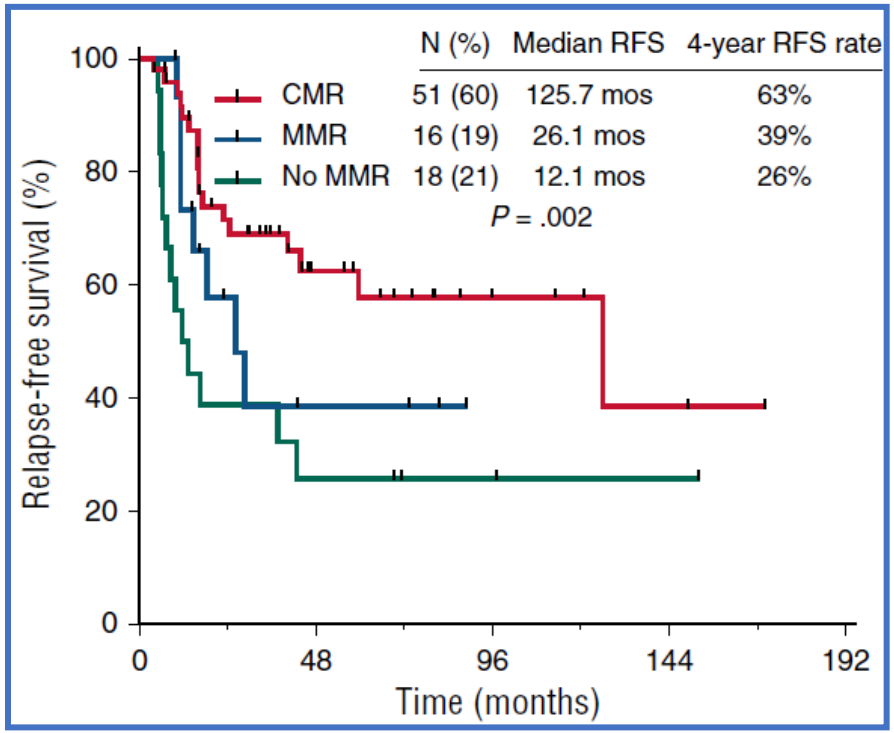


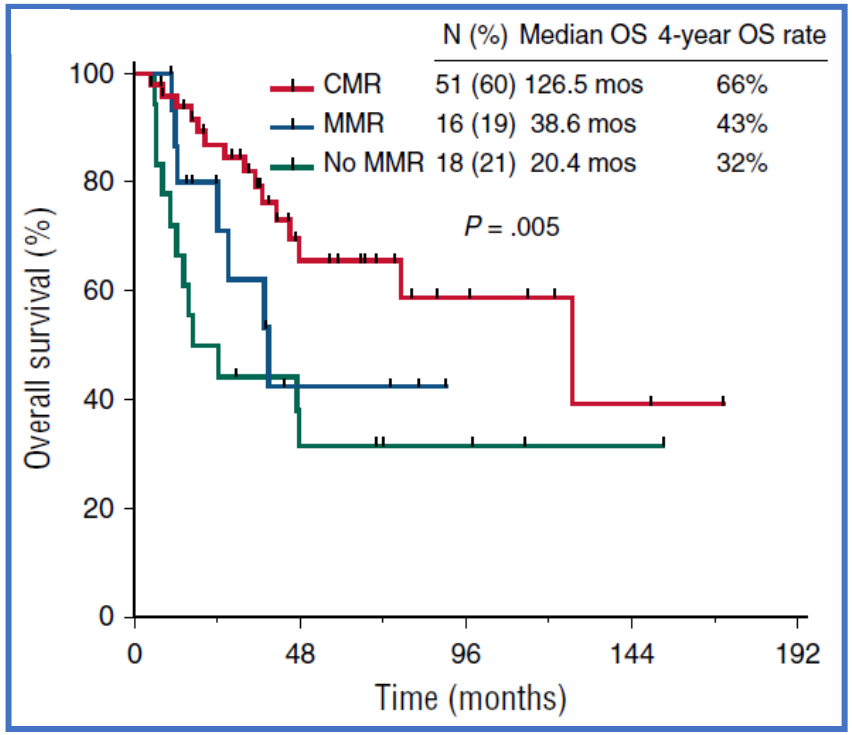
Patients with MRD <0.01% from d14



Ribera JM, et al. *Blood.* 2021;137(14):1879-1894.

CMR at 3 Months: The Best Prognostic Factor in Ph+ ALL





Short NJ, et al. *Blood*. 2016;128:504-507.

Use of MRD for Therapeutic Decisions

1. Intensification

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2. Antibody-based immunotherapy

- Blinatumomab
- Inotuzumab ozogamicin
- CAR T cells

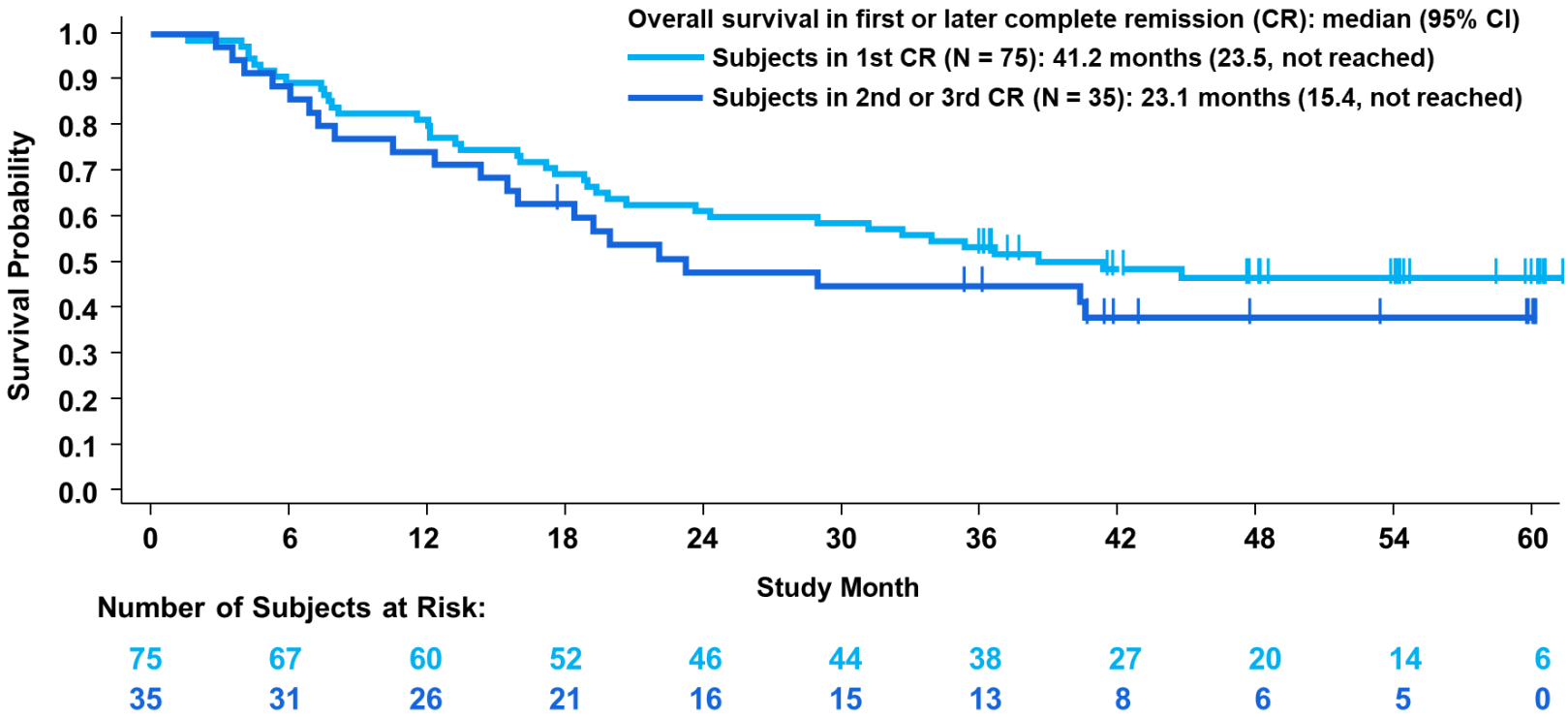
3. Targeted therapy

- TKI switch in Ph+ ALL
- Targeted therapy and immunotherapy

Overall Survival

By CR1 or CR2+

BLAST (MT103-203) STUDY



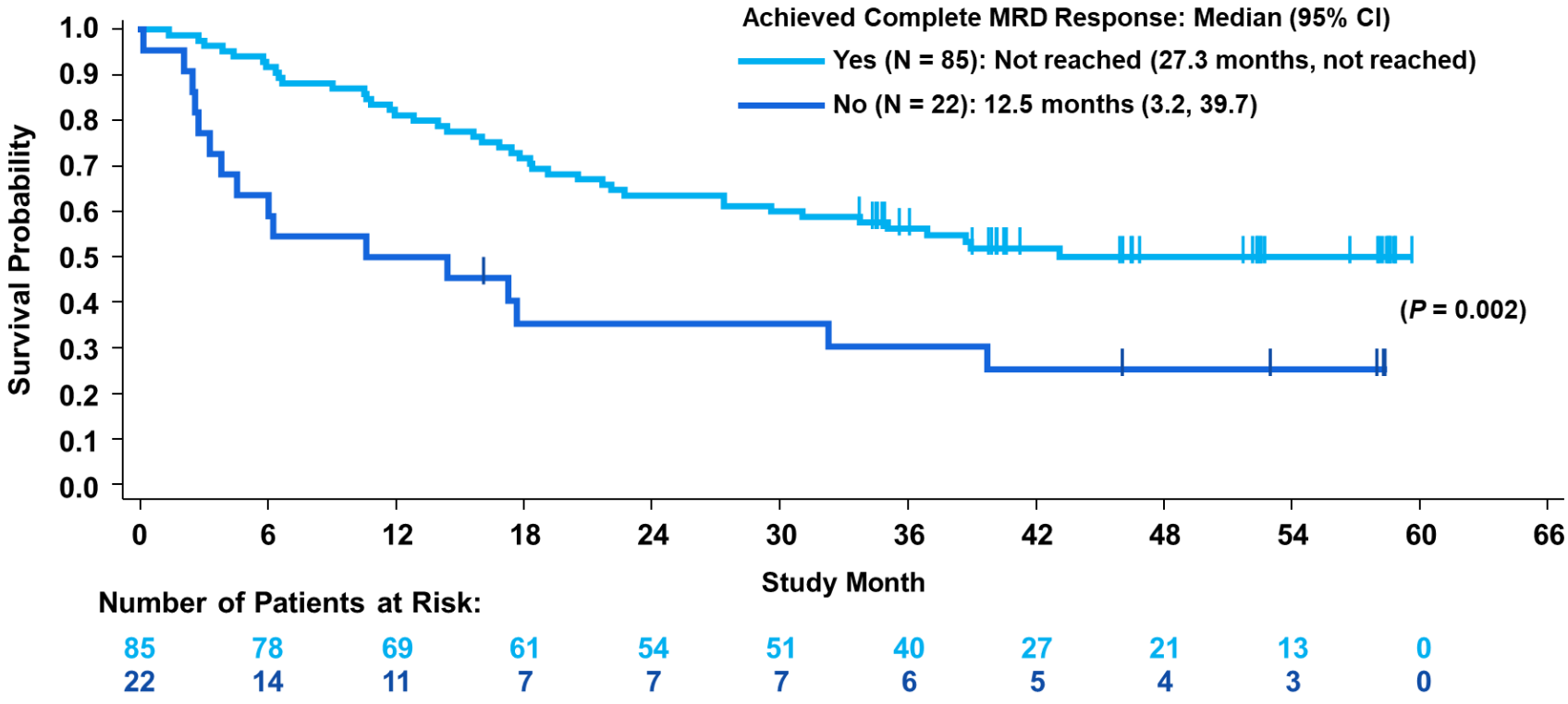
CR1, first complete remission; CR2+, second or later complete remission.

Gökbuget N, et al. ASH 2018. Presentation 554.

Overall Survival by Complete MRD Response

All Patients Analyzed

BLAST (MT103-203) STUDY



MRD, minimal residual disease.

Landmark analysis from day 45; complete MRD response was defined as no target amplification, with a minimum sensitivity of 10^{-4}.

Gökbuget N, et al. ASH 2018. Presentation 554.

Use of MRD for Therapeutic Decisions

1. Intensification

- Allogeneic HSCT in first hematologic remission

2. Antibody-based immunotherapy

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- Inotuzumab ozogamicin
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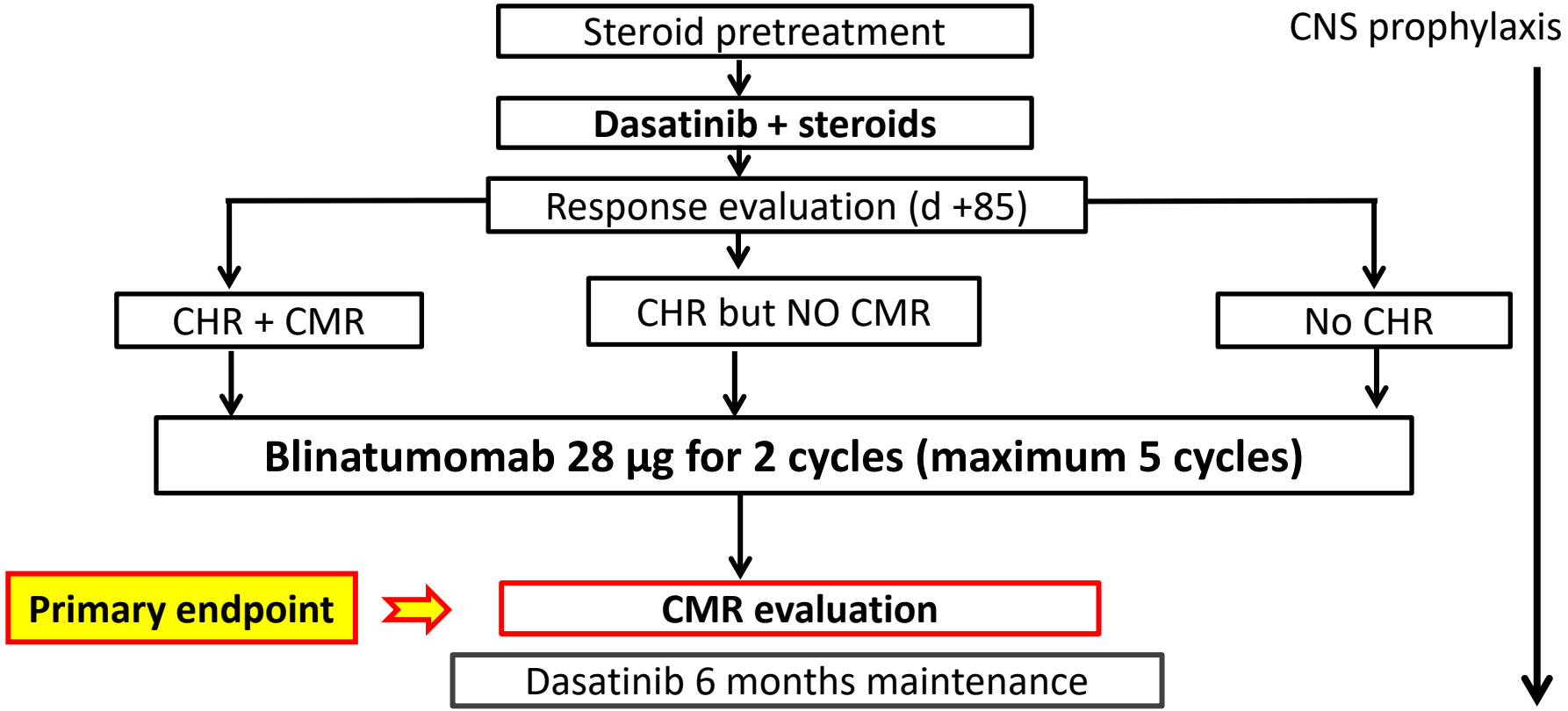
- TKI switch in Ph+ ALL
- Targeted therapy and immunotherapy

D-ALBA: Treatment Scheme



Chiaretti S, et al. *Blood*. 2019;134(suppl 1): abstract 740.

D-ALBA: Molecular Responses

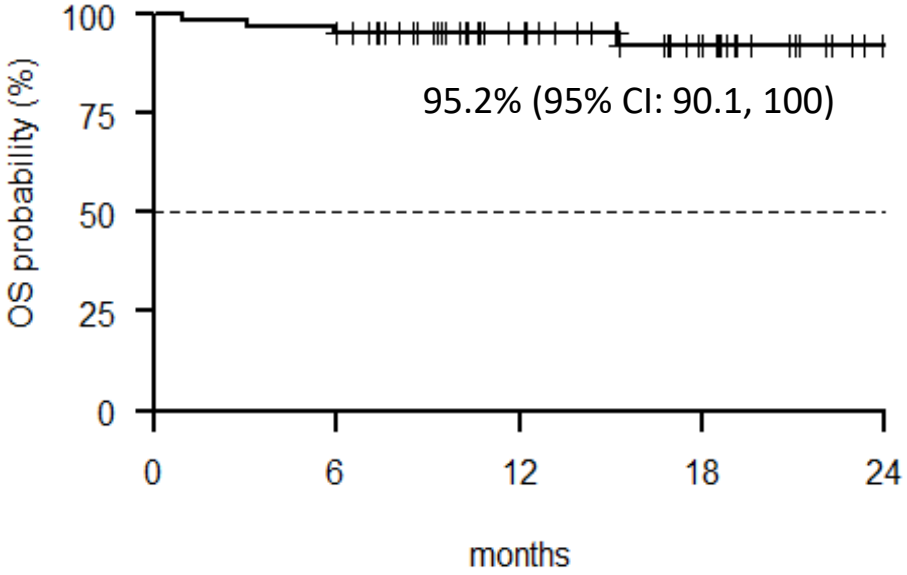
	CMR (%)	PNQ (%)	CMR and PNQ (%)
Day +22	3 (5.2)	7 (12.1)	10 (17.3)
Day +45	9 (15)	8 (13.3)	17 (28.3)
Day +57	11 (20.0)	7 (12.7)	18 (32.7)
Day +85	6 (10.3)	11 (19.0)	17 (29.3)
Post-cycle 1	19 (35.2)	16 (29.6)	35 (64.8)
Post-cycle 2	22 (41.5)	10 (18.9)	32 (60.4)
Post-cycle 3	19 (48.7)	8 (20.5)	21 (69.2)
Post-cycle 4	15 (44.1)	12 (35.3)	20 (79.4)
Post-cycle 5	12 (55.6)	5 (16.7)	17 (68.3)

Primary endpoint: 60.3% (95% CI: 46, 73.5)

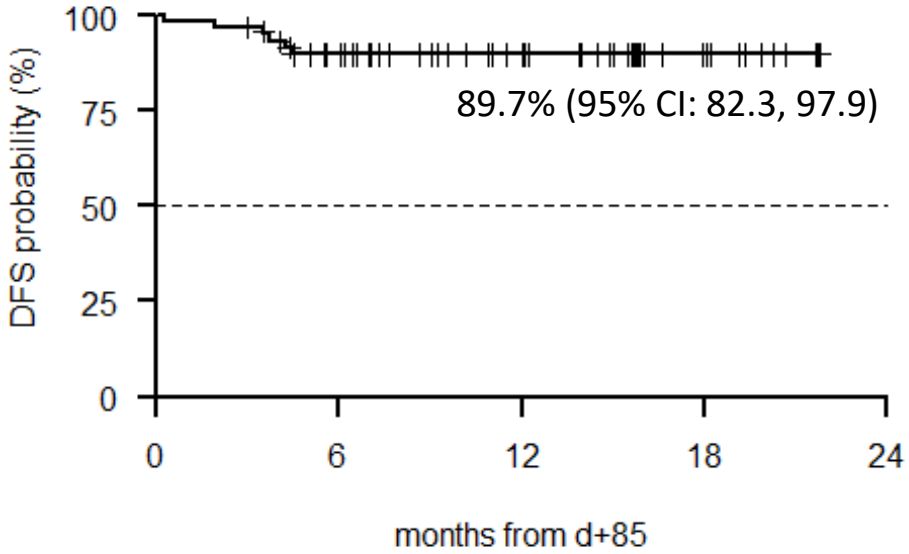
Chiaretti S, et al. *Blood*. 2019;134(suppl 1): abstract 740.

D-ALBA: OS and DFS

OS



DFS



Median follow-up: 14.3 months (0.9, 25)

Chiaretti S, et al. *Blood*. 2019;134(suppl 1): abstract 740.

Conclusions (ALL)

- MRD is the best prognostic factor in children and adults with ALL
- Prognostic significance at any time point (after induction, consolidation, before and after HSCT)
- Limited predictive value. Possible additional influence of oncogenetic factors
- MRD must de assessed within specific trials
- Possible early interventions to decrease the MRD level
  - Immunotherapy with mAb (blinatumomab, inotuzumab)
  - CAR T cells
- Combination with targeted therapy feasible (eg, Ph+ ALL) with promising preliminary results

Acute Myeloid Leukemia

MRD in AML: Techniques

Technique	Advantages	Disadvantages
Multiparameter flow cytometry	• Most commonly used method • Applicable to >90% of patients • Sensitivity 1×10^{-4} to 1×10^{-5} • Identification of leukemia-associated immunophenotypes (LAIP) and/or different from normal approach	• High level of expertise needed – Selection of right antibody panel – Standardization of analyses – Extensive knowledge about normal and regenerative BM expression of CD
Molecular measurable MRD	• Higher sensitivity of RT-qPCR • Novel developments of higher-sensitivity techniques – Digital droplet PCR – NGS (under investigation)	• Limited to specific stable genes during disease progression – *NPM1* – *RUNX1-RUNX1* – *CBF-MY11*

Where to Measure MRD in AML?

- **Standard approach**: bone marrow
- **Peripheral blood**
  - MFC: probably 1 log less sensitive
  - RT-qPCR: similar sensitivity?

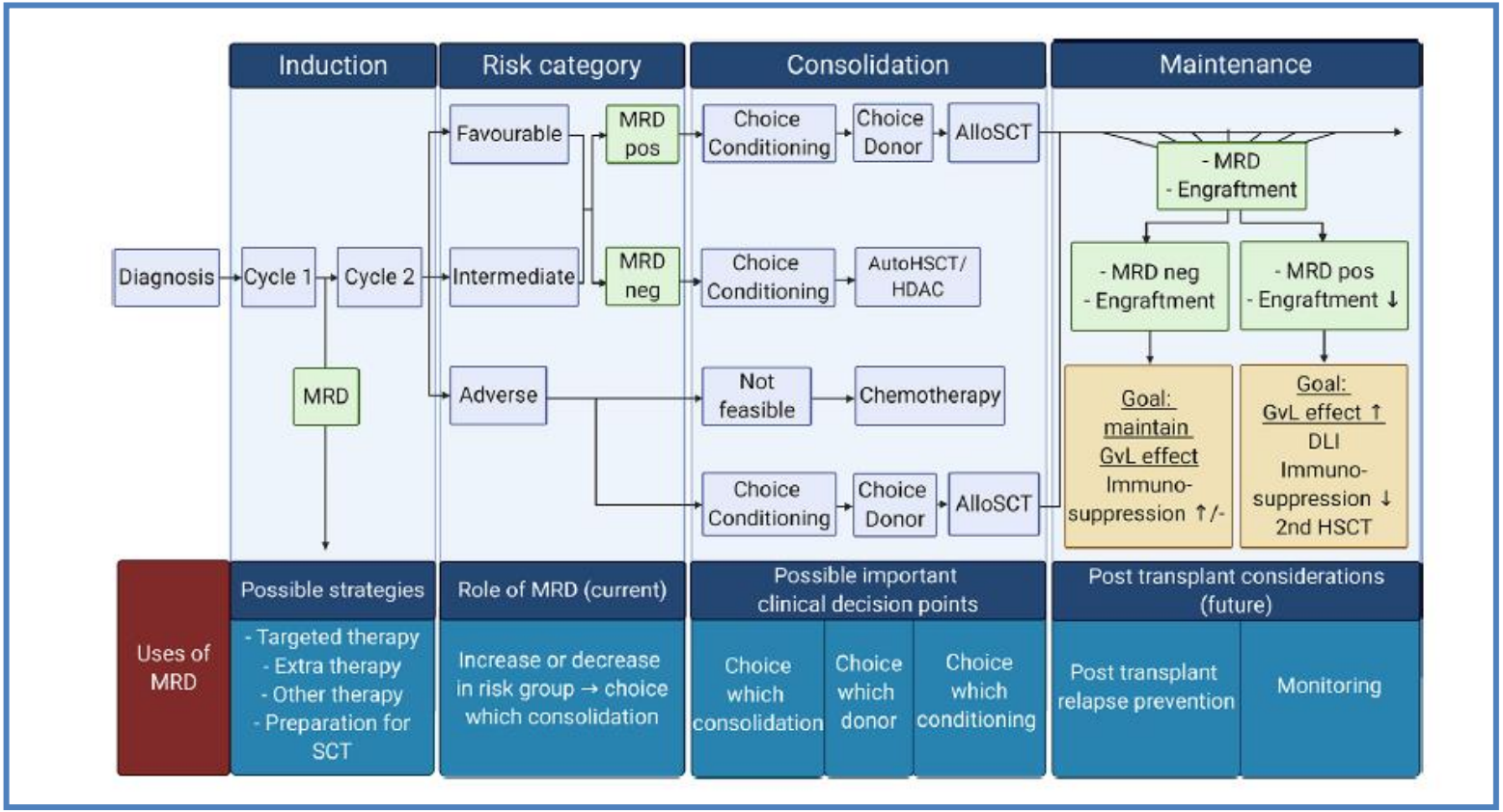
(Potential) Use of MRD in the Clinic

Potential Use	Comment
• ***Refine the CR status***	• MRD not officially recognized as surrogate endpoint
• ***Choose targeted therapy at induction***	• Under research
• ***Intensifying induction therapy in MRD+ pts***	• Several trials with new drugs and targeted therapies
• ***Choice of consolidation therapy***	• Incorporation of new drugs in this phase
• ***Defining the need and type of HSCT***	• Potentially useful for selecting allo/auto in intermediate-risk group
• ***Pre-emptive therapy before HSCT***	• Intensification of consolidation vs new drugs before HSCT
• ***Post-transplant interventions***	• Hypomethylating agents, DLI, immunotherapy, targeted therapy . . .

Prognostic and Predictive Value of MRD in AML

- **Growing evidence on the prognostic value** of MRD in
  - Post-remission
  - After consolidation
  - Before HSCT
- **Poor predictive value** (as in ALL)
  - 30% of MRD– patients relapse

Possible MRD Tailored Therapy in Different AML Phases



Ngai LL, et al. *Front Oncol.* 2021;10:603636.

Conclusions (AML)

- MRD has prognostic value in AML
- Techniques for MRD assessment less standardized than in ALL
- MRD still not officially recognized as surrogate endpoint
- MRD actively investigated as a decision tool for incorporation of new therapies and for selection of HSCT
- As in ALL, MRD has poor predictive value

Q

Question #1

The best moment of MRD assessment for prognosis in Ph+ ALL is:

A. At diagnosis
B. After induction (1 month from diagnosis)
C. After consolidation (3 months from diagnosis)
D. After autologous HSCT
E. After allogeneic HSCT

Question #1

The best moment of MRD assessment for prognosis in Ph+ ALL is:

A. At diagnosis
B. After induction (1 month from diagnosis)
C. After consolidation (3 months from diagnosis)
D. After autologous HSCT
E. After allogeneic HSCT

Q

Question #2

In AML, MRD assessment by RT-qPCR is especially useful in:

A. *FLT3*-ITD
B. *NPM1* mutation
C. Biallelic *CEBPA* mutation
D. *SF3B1* mutation
E. *ASXL1* mutation

Question #2

In AML, MRD assessment by RT-qPCR is especially useful in:

A. *FLT3*-ITD
B. *NPM1* mutation
C. Biallelic *CEBPA* mutation
D. *SF3B1* mutation
E. *ASXL1* mutation

Global Leukemia Academy

Genetic variants in ALL – Ph+ and Ph-like

Andre Schuh

APTITUDE HEALTH

Genetic Variants in ALL: Ph+ ALL and Ph-Like ALL

Andre Schuh
Princess Margaret Cancer Centre
Toronto

April 23, 2021

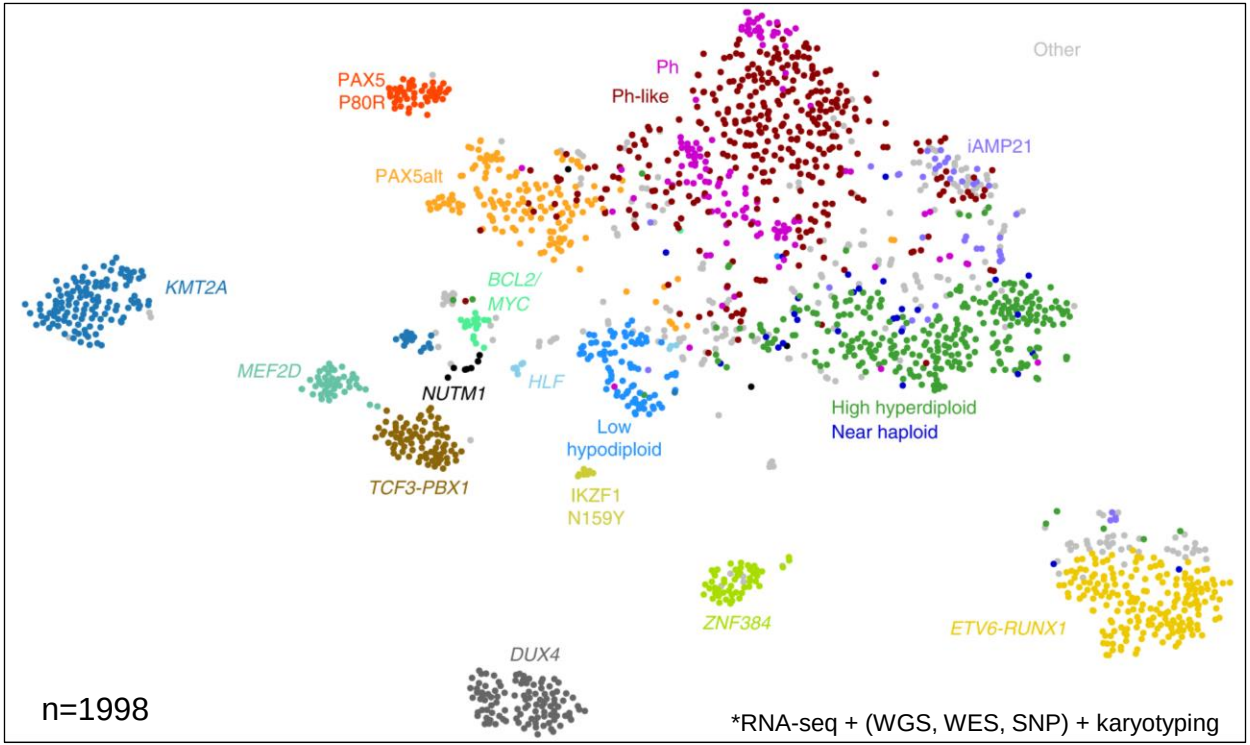
Disclosures:

Consultant -
AbbVie, Amgen, Astellas, Celgene/BMS, Phebra, Pfizer

Research Support/PI -
AbbVie, Agios, Amgen, Astellas, Celgene/BMS, GlycoMimetics, Kite, Pfizer

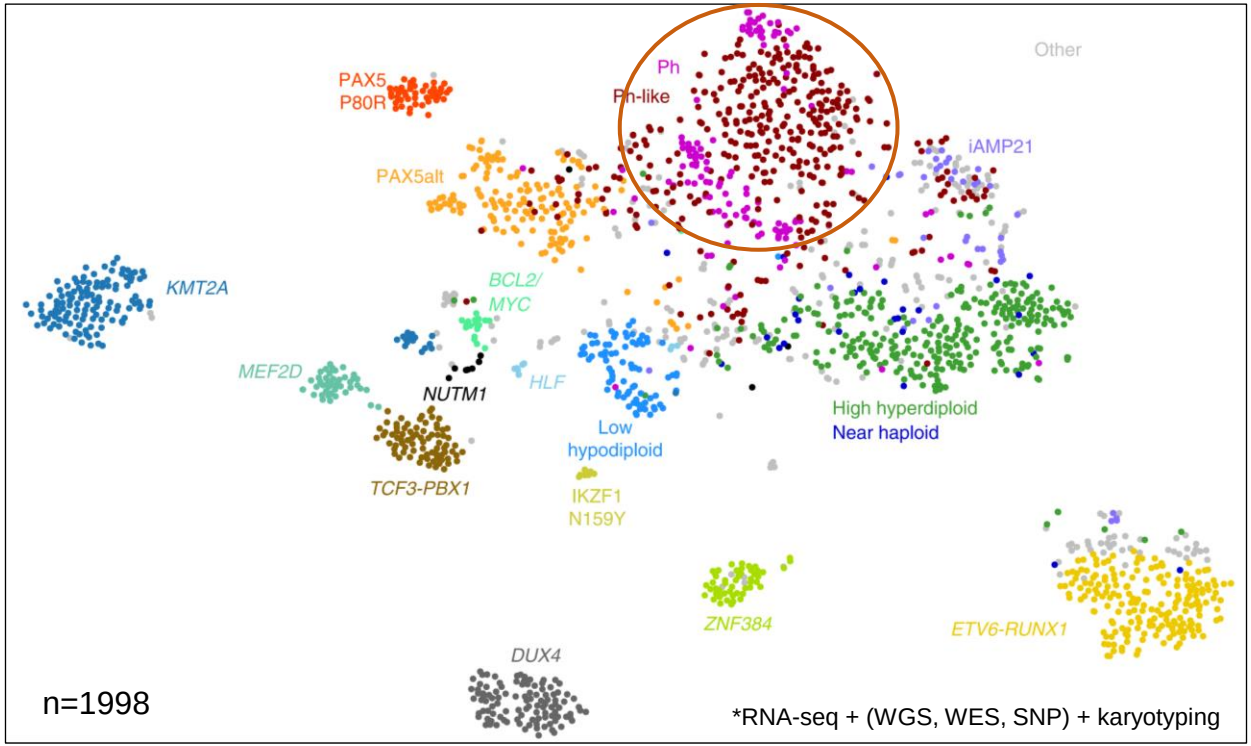
Scientific Advisory Board -
AbbVie, Agios, Amgen, Celgene/BMS, Jazz, Novartis, Phebra, Pfizer, Teva

Integrative Genetic Profiling* Defines 23 Subtypes of ALL



Gu Z. *et al., Nature Genetics* 2019; 51: 296-307

Integrative Genetic Profiling* Defines 23 Subtypes of ALL



- genetic subtype/phenocopy relationships
  e.g. Ph+ve and Ph-like

Gu Z. *et al., Nature Genetics* 2019; 51: 296-307

Ph+ ALL

- carries the Philadelphia (Ph) chromosome
- t(9;22)(q34.1; q11.2); *BCR-ABL1*
- dysregulated activation of ABL1 kinase
- known since 1970s
- confers higher risk

Ph-like ALL

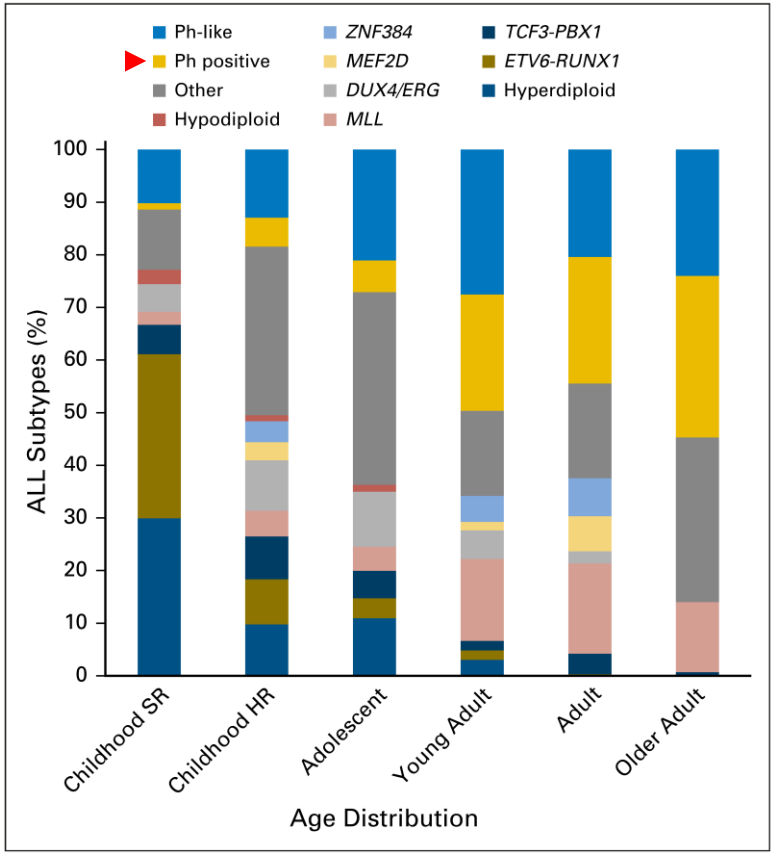
- Ph- ALL subtype with a gene expression profile similar to that of Ph+ ALL, but not carrying the Ph chromosome
- can carry a variety of alternative kinase-activating rearrangements and mutations, falling largely into ABL and JAK/STAT classes
- first described by 2 groups in 2009
- confers higher risk?

WHO Classification (2001, 2008, 2016)

B-lymphoblastic leukemia/lymphoma
B-lymphoblastic leukemia/lymphoma, NOS
B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2);*BCR-ABL1*
B-lymphoblastic leukemia/lymphoma with t(v;11q23.3);*KMT2A* rearranged
B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); *ETV6-RUNX1*
B-lymphoblastic leukemia/lymphoma with hyperdiploidy
B-lymphoblastic leukemia/lymphoma with hypodiploidy
B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3) *IL3-IGH*
B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3);*TCF3-PBX1*
Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1–like
Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukemia
Natural killer (NK) cell lymphoblastic leukemia/lymphoma

Ph+
ALL

Ph+ ALL Incidence Increases With Age



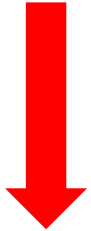
Iacobucci, I, and Mullighan, CG. *J Clin Oncol* 2017; 35:975-983

Treatment?

Pre-TKI Era

Longstanding "Truths"

- High risk
- Inferior outcomes with conventional ALL chemotherapy
- AlloSCT for all eligible patients



TKI Era

New Questions . . . New Trends

- Which TKI?
- Older patients
- Less intensive or chemo-free strategies, especially in the elderly
- Diminishing role of alloSCT
- Newer approaches to R/R disease
- Bring upfront the drugs that are effective in R/R disease

Pre-TKIs . . .

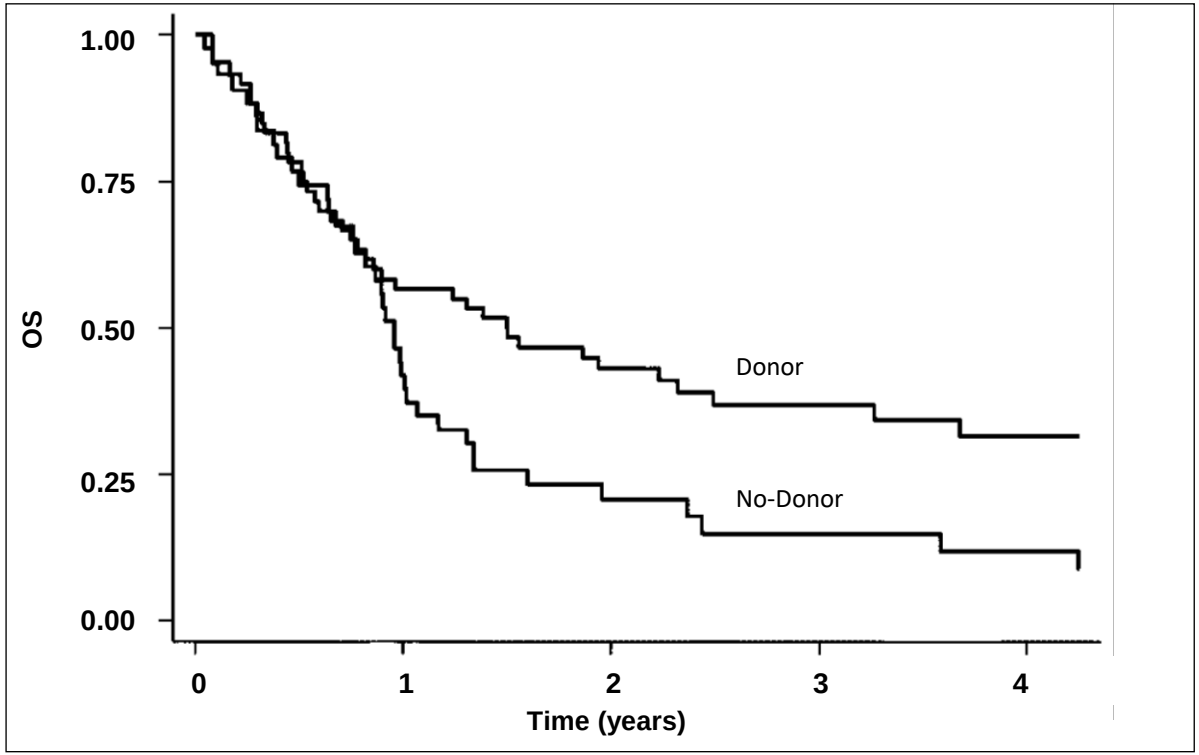
Ph+ ALL associated with an inferior outcome using conventional ALL chemotherapy

Outcomes of Patients With Newly Diagnosed Ph+ ALL Treated With Chemotherapy Only

Clinical Trial (year)	N	Median Age, [range]	Chemotherapy	CR, %	SCT in CR1, %	OS, %
Gotz (1992)[53]	25	44 [21-74]	BFM	76	8	6 at 40 mo
Larson (1995)[54]	30	32 [16-80]	CALGB	70	NA	16 at 36 mo
Thomas (2001)[6]	51	35 [14-89][a]	LALA	NA	16	10 at 60 mo
Gleissner (2002)[55]	175	45 [15-65]	GMALL	68	NA	15 at 36 mo
Takeuchi (2002)[3]	51	31 [15-59][a]	JALSG	51	NA	5 at 72 mo
Kantarjian (2004)[4]	48	40 [15-92][a]	HyperCVAD	92	23	12 at 60 mo
Pullarkat (2008)[5]	36	47 [17-64]	SWOG	67	NA	8 at 60 mo

Yilmaz, M. *et al. Clin Adv Hem Onc* 2018; 16:216-223

Role of AlloSCT, Ph+ ALL, Pre-TKI



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

TKI Era . . .

- Imatinib
- Dasatinib
- Ponatinib

Which TKI?

Outcomes of Patients With Newly Diagnosed Ph+ ALL Treated With Chemotherapy Plus Imatinib

Clinical Trial (year)	N	Median Age, [range]	Chemo-therapy	TKI, mg/d	CR, %	CMR, %	SCT in CR1, %	OS, %
Imatinib								
Yanada (2006)[56]	80	48 [15-63]	JALSG ALL202	IM 600	96	26 at CR	49	76 at 12 mo
Wassmann (2006)[9]	45	41 [19-63]	GMALL	IM 400	96	27 at CR	80	43 at 24 mo
Fielding (2014)[10]	175	42 [16-64]	UKALLXII/ ECOG2993	IM 400-600	92	NA	46	38 at 48 mo
Chalandon (2015)[13]	135	49 [18-59]	Low-int induction	IM 800	98	29 at ~3 mo	74	48 at 60 mo
	133	45 [21-59]	High-int induction	IM 800	91	23 at ~3 mo	79	43 at 60 mo
Bassan (2010)[57]	59	45 [20-66]	NILG	IM 600	92	40 at ~3 mo	72	38 at 60 mo
Daver (2015)[11]	54	51 [17-84]	HyperCVAD	IM 400-800	93	45 at ~3 mo	30	43 at 60 mo
De Labarthe (2007)[58]	45	45 [16-59]	GRAAPH 2003	IM 600-800	96	NA	49	51 at 18 mo
Lim (2015)[12]	87	41 [16-71]	Multiagent chemo	IM 600	94	NA	64	33 at 60 mo


Yilmaz, M. *et al. Clin Adv Hem Onc* 2018; 16:216-223

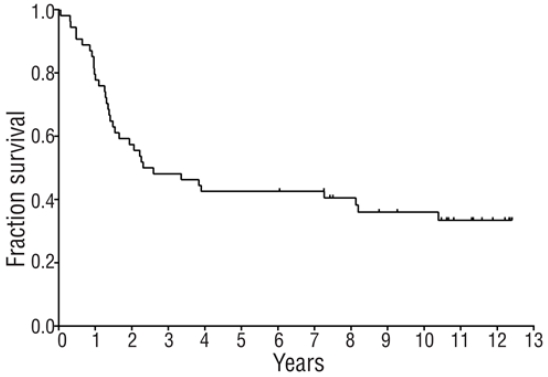
Outcomes of Patients With Newly Diagnosed Ph+ ALL Treated With Chemotherapy Plus Nilotinib, Dasatinib, or Ponatinib

Clinical Trial (year)	N	Median Age, [range]	Chemo-therapy	TKI, mg/d	CR, %	CMR, %	SCT in CR1, %	OS, %
Nilotinib								
Kim (2015)[23]	90	47 [17-71]	Multiagent chemo	NIL 800	91	77 at ~3 mo	63	72 at 24 mo
Dasatinib								
Foa (2011)[31]	53	54 [24-76]	Prednisone	DAS 100-140	93	22 at CR	NA	69 at 20 mo
Ravandi (2015)[30]	72	55 [21-80]	HyperCVAD	DAS 100	96	65 at ~3 mo	17	46 at 60 mo
Ravandi (2016)[59]	94	44 [20-60]	HyperCVAD	DAS 70-100	88	NA	47	69 at 36 mo
Ponatinib								
Jabbour (2015)[36,37]	64	48 [21-80]	HyperCVAD	PON 30-45	100	77 at ~3 mo	16	78 at 36 mo

Yilmaz, M. *et al. Clin Adv Hem Onc* 2018; 16:216-223

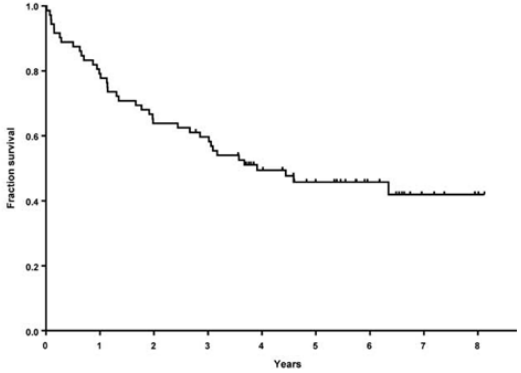
OS, HyperCVAD Plus Imatinib, Dasatinib, or Ponatinib

Imatinib: 5-yr OS, 43%



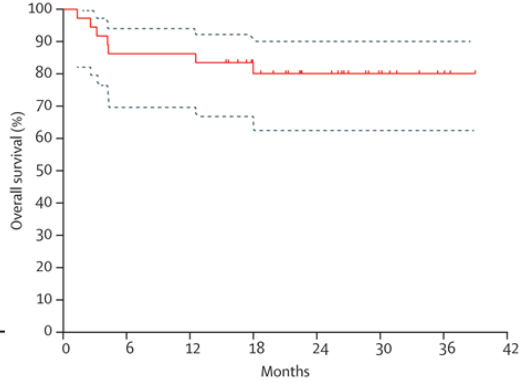
2001-2006
n=54
51 (17-84)

Dasatinib: 5-yr OS, 46%



2006-2012
n=72
55 (21-80)

Ponatinib: 3-yr OS, 79%*



2011-2013
n=53
54 (25-80)

***Estimated 5-yr OS, 71%**

Daver, N. *et al. Haemato*logica 2015; 100:653-61
Ravandi, F. *et al. Cancer* 2015; 121:4158-64
Jabbour, E. *et al. Lancet Hematology* 2015; 16:1547-55
Jabbour, E. *et al. Clin Lymph Myel Leuk* 2018; 18:257-65

Why Less Intensive Approaches?

Baseline facts

- Aging population and increasing incidence of Ph+ ALL
- Increasing toxicity of chemotherapy in the elderly (especially if “pediatric-inspired” protocols are used)
- Increased toxicity when TKIs added to conventional chemotherapy regimens

Taken together with

- Dramatically improved outcomes when TKIs added

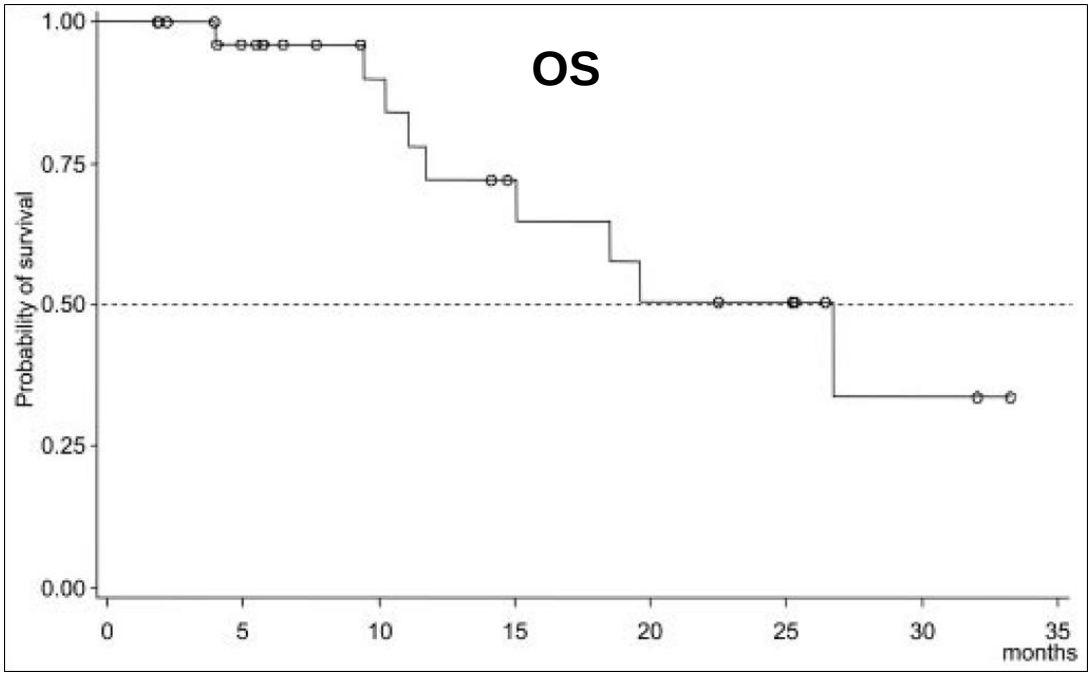
Opportunities for less-toxic, chemo- or steroid-sparing approaches?

Reduced-Intensity Approaches to Ph+ ALL: Low-Intensity Chemotherapy/Steroids Plus TKI

Clinical Trial (year)	N	Age, median [Range]	Chemotherapy	TKI, mg/d	CR, %	SCT in CR1, %	OS, %
Ottmann (2007)[15]	28	66 [54-79]	GMALL	IM 400	96	0	42 at 24 mo
Vignetti (2007)[14]	30	69 [61-83]	Prednisone	IM 800	100	0	50 at 24 mo
Delannoy (2006)[60]	29	66 [58-78]	GRALL-AFR09	IM 600	72	0	66 at 12 mo
Rousselot (2016)[32]	71	69 [59-83]	EWALL-Ph-01	DAS 100-140	96	10	36 at 60 mo
Ottmann (2014)[24]	47	65 [55-85]	EWALL-Ph-02	NIL 800	87	20	67 at 24 mo

Yilmaz, M. *et al. Clin Adv Hem Onc* 2018; 16:216-223

Imatinib Plus Prednisone Only



GIMEMA LAL0201-B Study: n=30, median age 69 (range 61-83)
Imatinib 800 mg/day plus prednisone 40 mg/m^2/day × 45 days
CR rate 97%; well tolerated; mostly done as OP; median OS ~20m

Vignetti, M. *et al. Blood* 2007; 109:3676-78

- less intensive induction regimens containing a TKI are feasible, less toxic, and associated with very high CR rates

- in absence of subsequent (or simultaneous) chemotherapy, however, molecular responses and OS are inferior

- simultaneous or subsequent chemotherapy results in better CMR rates and improved OS, similar to that obtained with more-intensive chemotherapy

Vignetti, M. *et al. Blood* 2007; 109:3676-78
Ottmann, O. *et al. Cancer* 2007; 109:2068-76
Chalandon, Y. *et al. Blood* 2015; 125:3711-3719

Relapsed Disease . . .

Ph+ ALL

- CR rates only moderate; outcomes post-relapse poor

Traditionally . . .

- Salvage chemotherapy
- Alternative TKI on the basis of *BCR-ABL1* KD mutation analysis
- AlloSCT

More recently . . .

- Blinatumomab, inotuzumab, CAR T cells
- Alternative TKI on the basis of *BCR-ABL1* KD mutation analysis
- AlloSCT

Going forward . . .

- Several studies evaluating upfront use of blinatumomab or inotuzumab +/– chemo plus TKIs . . .

Numerous questions remain

- Intensive chemotherapy, vs less-intensive chemo vs chemo-free approaches?
- Which TKI (dasatinib vs ponatinib)?
- Optimizing TKI plus blinatumomab etc for relapsed disease (we and others use both drugs simultaneously)
- Sequencing of blinatumomab and inotuzumab in the same patient?
- Role of blinatumomab in MRD+, Ph+ ALL in CR?
- Ongoing role of alloSCT in TKI/immunotherapy era?
- Optimized molecular monitoring strategy and when to switch TKIs
- Role of CAR T cells?

Ph-like (BCR-ABL like) ALL

Ph-like (BCR-ABL like) ALL

- Ph- subtype characterized by a gene expression profile similar to Ph+ ALL and a range of kinase-activating rearrangements and mutations, and associated with a poor outcome
- Frequently bear alterations of B-lymphoid transcription factor genes (most commonly *IKZF1*)
- ~1/2 are surface CRLF2+
- 10%–20% of standard- and high-risk childhood B-ALL, with an increasing prevalence with increasing age

Mullighan CG, *et al*., *NEJM*. 2009;360:470-480
Den Boer ML, *et al*., *Lancet Oncol*. 2009;10:125-134
Roberts KG, *et al*., *NEJM*. 2014; 371:1005–1015

Ph-Like (BCR-ABL like) ALL

Incidence

Prevalence and clinical outcomes of Ph-like ALL.

Clinical Trial	Age (yrs)	NCI Risk Group	Ph-like prediction	Ph-like ALL prevalence (%)	Total cases studied	Treatment Outcome
COG P9906	1–21	HR	PAM	20.5%	200	5 yr EFS 25.0%
COG AALL0232	1–30	HR	PAM	14.0%	572	5 yr EFS 62.6%
COG AALL0932	1–30	SR	LDA	17.0%	505	N/A
COG AALL1131	1–30	HR	LDA	22.4%	884	N/A
St. Jude Total XV	1–18	All	PAM	11.6%	344	5-yr EFS 90.0%
COALL 92/97	0–18	All	HC	19%	154	5 yr DFS 59.5%
DCOG ALL 8/9	0–18	All	HC	15%	92	5 yr DFS 57.1%
GMALL	16–84	All	PAM	12.6%	207	5-yr DFS 26%
HOVON	16–71	All	HC	16.5%	127	5-yr EFS ~25%
Multiple US	21–39	All	LDA	27.9%	344	5-yr EFS 24.1%
	40–59			20.4%	304	5-yr EFS 21.4%
	60–86			24.0%	150	3-yr EFS 8.0%
MDACC	15–49	All	PAM/LDA	42.0%	80	5-yr OS 23%
	40–84			24.0	68	
Multiple US	18–39	All	LDA	25.9%	27	N/A
	40–88			18.3%	60	

Roberts, K., *Best Pract & Res Clin Haem* 2017; 30:212-221

Baseline characteristics of Ph-like ALL, Ph+ ALL, and B-other ALL

	B-ALL categories, N = 155				
	Ph-like	Ph$^+$	B-other	*P* (all 3 groups)	*P* (Ph-like vs B-other)
N	56 (35%)	46 (32%)	53 (33%)		
Age, y median (range)	33.5 (15-71)	49 (22-84)	38 (15-79)	.001	.23
<40, n (%)	37 (66)	18 (39)	29 (55)		
≥40, n (%)	19 (34)	28 (61)	24 (45)		
Sex, n (%)					
Female	19 (34)	24 (52)	34 (64)	.006	.002
Male	37 (66)	22 (48)	19 (36)		
Ethnicity, n (%)					
White	13 (23)	20 (44)	27 (51)		
Hispanic	38 (68)	16 (35)	16 (30)	<.001	<.001
African American	2 (4)	8 (17)	6 (11)		
Asian	3 (5)	2 (4)	2 (4)		
Unclassified	—	—	2 (4)		

Jain, N *et al. Blood* 2017; 129:572-881

Baseline Characteristics of Ph-Like ALL, Categorized as *CRLF2*+ and Non-*CRLF2*

	Ph-like ALL, N = 56		
	CRLF2$^+$	Non-CRLF2	*P*
N	37	19	
Age, y, median (range)	35 (18-71)	26 (15-62)	.12
Sex, n (%)			
Female	10 (27)	9 (47)	.13
Male	27 (73)	10 (53)	
Ethnicity, n (%)			
White	8 (22)	5 (26)	
Hispanic	29 (78)	9 (48)	.008
African American	—	2 (10)	
Asian	—	3 (16)	
Cytogenetics, n = 49, n (%)			
Diploid	15 (45)	4 (25)	.49
Hyperdiploid	6 (18)	4 (25)	
Hypodiploid	3 (9)	1 (6)	
Miscellaneous	9 (28)	7 (44)	
Presenting features			
WBC, $\times 10^9$/L, median (range)	27.7 (1-603)	5.3 (1-81)	.001
Platelet count, $\times 10^9$/L, median (range)	36 (1-169)	41 (8-238)	.55
Hemoglobin, g/dL, median (range)	9.4 (6.5-13.7)	9.2 (5.7-15.1)	.19
Bone marrow blast %, median (range)	92 (62-98)	87 (17-99)	.17
CNS involvement at Dx, n (%)	5 (14)	3 (16)	.82
IKZF1 deleted, n = 41, n (%)	21/25 (84%)	7/16 (44%)	.014
Treatment received, n (%)			
Hyper-CVAD based	29 (78)	8 (42)	.007
Augmented BFM	8 (22)	11 (58)	

Jain, N *et al. Blood* 2017; 129:572-881

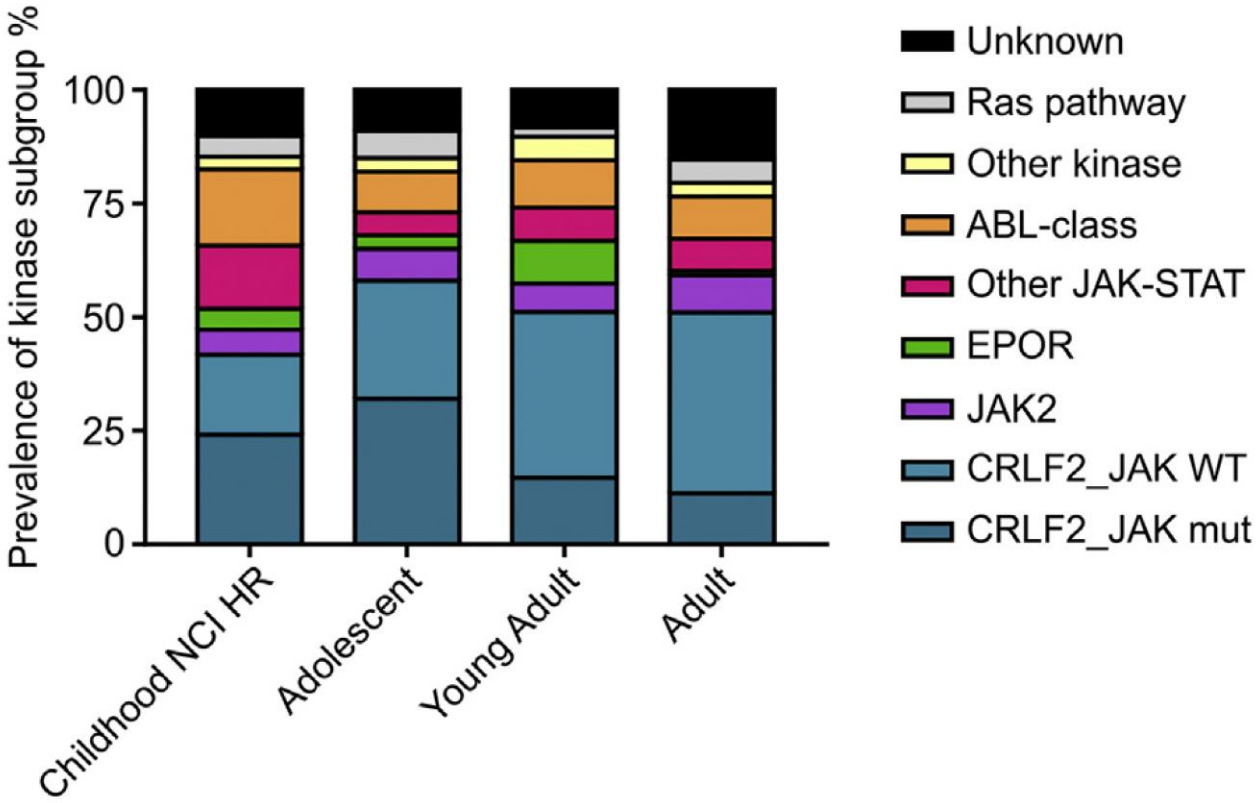
Kinase Alterations in Ph-like ALL

Class	Kinase gene	Number of fusion partners	Fusion partner genes	Potential TKI	Type of alteration	Method of identification
ABL	*ABL1*	12	*CENPC, ETV6, FOXP1, LSM14, NUP214, NUP153, RCSD1, RANBP2, SNX2, SFPQ, SPTAN1, ZMIZ1*	Dasatinib	In-frame fusion	FISH RT-PCR Transcriptome sequencing
	ABL2	3	*PAG1, RCSD1, ZC3HAV1*	Dasatinib	In-frame fusion	FISH RT-PCR Transcriptome sequencing
	CSF1R	3	*MEF2D, SSBP2, TBL1XR1*	Dasatinib	In-frame fusion	FISH RT-PCR Transcriptome sequencing
	LYN	2	*NCOR1, GATAD2A*	Dasatinib	In-frame fusion	RT-PCR Transcriptome sequencing
	PDGFRA	1	*FIP1L1*	Dasatinib	In-frame fusion	FISH RT-PCR Transcriptome sequencing
	PDGFRB	7	*ATF7IP, EBF1, ETV6, SSBP2, TNIP1, ZEB2, ZMYND8*	Dasatinib	In-frame fusion	FISH RT-PCR Transcriptome sequencing
JAK-STAT	*CRLF2*	2	*IGH, P2RY8*	JAK inhibitor PI3K/mTOR inhibitor	Translocation (*IGH*) Fusion to promoter (*P2RY8*)	FISH Flow cytometry
	JAK2	20	*ATF7IP, BCR, EBF1, ETV6, GOLGA5, HMBOX1, OFD1, PAX5, PCM1, PPFIBP1, RFX3, SMU1, SNX29, SSBP2, STRN3, TERF2, TPR, USP25, ZNF274,* ZBTB46,	JAK inhibitor PI3K/mTOR inhibitor	In-frame fusion	FISH RT-PCR Transcriptome sequencing
	EPOR	4	*IGH, IGK, LAIR1, THADA*	JAK inhibitor	Cryptic rearrangement	Transcriptome sequencing
	TYK2	3	*MYB, SMARCA4, ZNF340*	TYK2 inhibitor	In-frame fusion	RT-PCR Transcriptome sequencing
	IL2RB	1	*MYH9*	JAK inhibitor	Rearrangement	Transcriptome sequencing
	JAK1	0	N/A	JAK inhibitor	Sequence mutation	Sanger sequencing Exome sequencing
	JAK3	0	N/A	JAK inhibitor	Sequence mutation	Sanger sequencing Exome sequencing
	IL7R	0	N/A	JAK inhibitor	Indel mutation	Sanger sequencing Exome sequencing
	SH2B3	0	N/A	JAK inhibitor	Sequence mutation Focal deletions	Sanger sequencing Genome sequencing
Others	*NTRK3*	1	*ETV6*	TRK inhibitor	In-frame fusion	RT-PCR Transcriptome sequencing
	FLT3	1	*ZMYM2*	FLT3 inhibitor	In-frame fusion	RT-PCR Transcriptome sequencing
	FGFR1	1	*BCR*	FGFR inhibitor	In-frame fusion	RT-PCR Transcriptome sequencing
	BLNK	1	*DNTT*	Unknown	In-frame fusion	RT-PCR Transcriptome sequencing

FISH, fluorescence in situ hybridization; RT-PCR, reverse transcriptase polymerase chain reaction.

Roberts, K., *Best Pract & Res Clin Haem* 2017; 30:212-221

Rearrangements Vary with Age



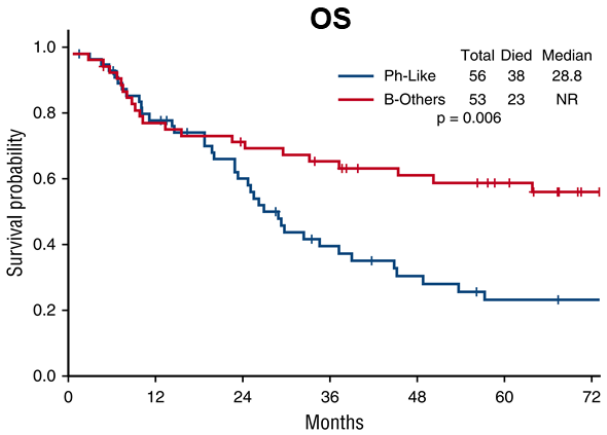
Roberts, K., *Best Pract & Res Clin Haem* 2017; 30:212-221

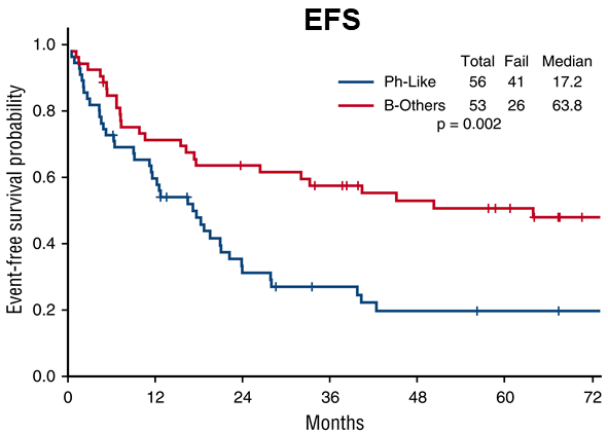
Responses in Ph-Like ALL, Ph+ ALL, and B-Other ALL

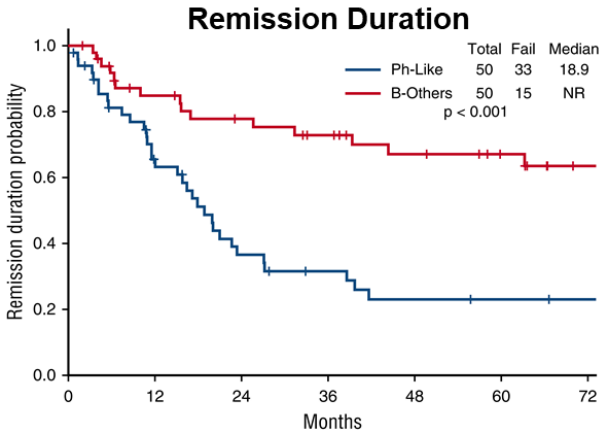
	B-ALL categories, N = 155				
	Ph-like	Ph$^+$	B-other	*P* (all 3 groups)	*P* (Ph-like vs B-other)
N	56 33.5 (15-71)	46 49 (22-84)	53 38 (15-79)		
CR/CRp, n (%)	50 (89)	43 (93)	50 (94)	.57	.34
MRD assessed at CR, n = 98, n (%)	33.5 (15-71)	49 (22-84)	38 (15-79)		
MRD$^+$	23 (70)	15 (44)	4 (13)	<.001	<.001
MRD$^-$	10 (30)	19 (56)	27 (87)		

Jain, N *et al. Blood* 2017; 129:572-881

OS, EFS, and Remission Duration, Ph-Like vs B-Other





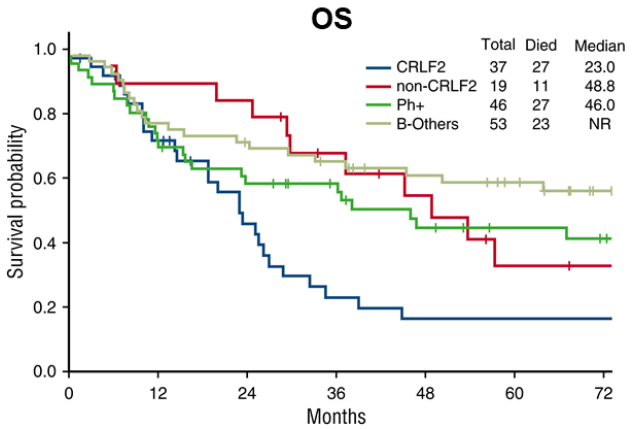


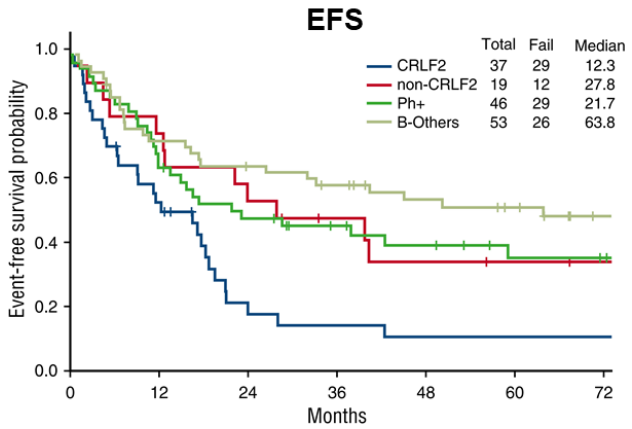
Ph-like
n=56; median age 33.5 (15-71)
HyperCVAD, 37 (66%)
Augmented BFM, 19 (34%)

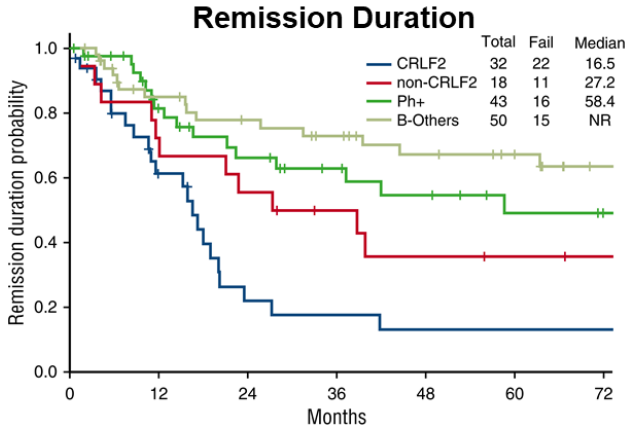
B-other
n=53; median age 38 (15-79)
HyperCVAD, 41 (77%)
Augmented BFM, 12 (23%)

Jain, N *et al. Blood* 2017; 129:572-881

OS, EFS, and Remission Duration, *CRLF2*/Non-*CRLF2* Ph-Like vs Others







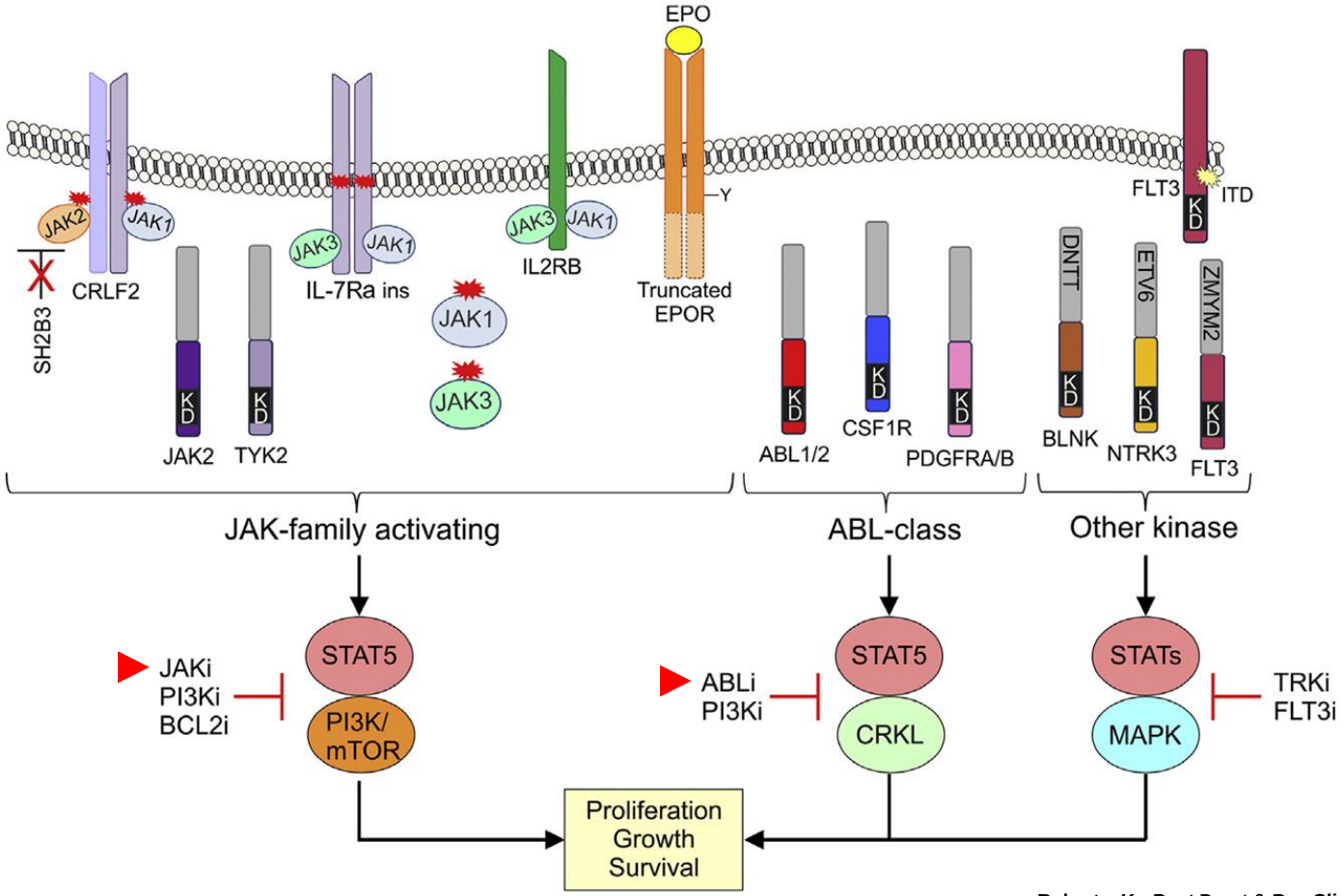
OS:
CRLF2 vs B-other, p=.001
CRLF2 vs non-*CRLF2*, p=.01

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; 129:572-881

Potential for Therapeutic Intervention



Roberts, K., *Best Pract & Res Clin Haem* 2017; 30:212-221

Does Intervention Change Outcomes?

- preclinical and isolated, retrospective, sometimes contradictory, anecdotal reports
    - actual data are very soft
        - more aggressive chemotherapy +/- alloSCT for Ph-like or for MRD+ve ALL?
        - TKI for ABL class Ph-like?
        - Ruxolitinib for JAK family?
        - role of alloSCT?
- numerous ongoing clinical trials
    - TKI
    - JAK inhibitor
    - blinatumomab/inotuzumab etc.

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Roberts KG *et al. J Clin Oncol* 2014; 32:3012-3020

- retrospective look at 422 pediatric patients with B-ALL treated in SJCRH Total Therapy XV study from 2000-2007
- study included risk-directed treatment escalation based on post-induction
- 344/422 patients had samples suitable for genetic analyses; 40/344 (11.6%) were Ph-like
- outcomes were then compared between patients with and without Ph-like ALL
    - EFS at 5 years, 90.0% vs. 88.4%; p=0.41
    - OS at 5 years, 92.5% vs. 95.1%; p=0.41
- but more Ph-like were MRD +ve, and thus were upgraded to more intensive treatment
- patients with Ph-like ALL with poor initial treatment response can be salvaged with MRD-based, risk-directed therapy

But…

Heatley, SL *et al. Haematologica* 2016; 102:e490-493

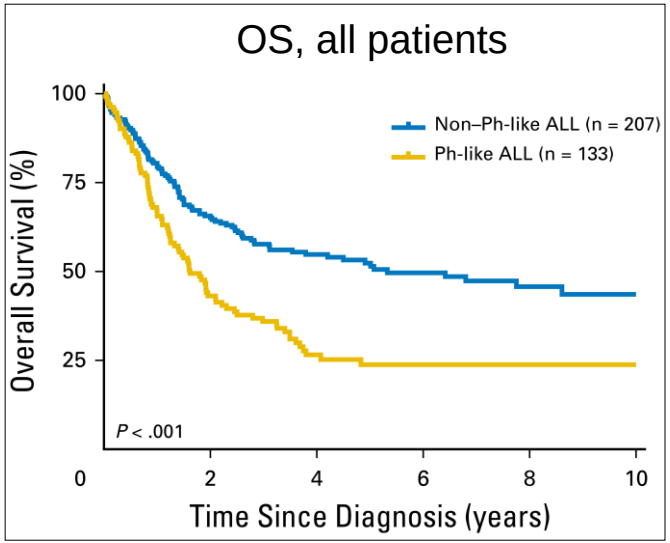
- in contrast, in the ANZCHOG ALL8 study, another pediatric, risk-directed study, Ph-like patients had significantly inferior EFS and OS, and increased treatment intensity did not prevent relapse

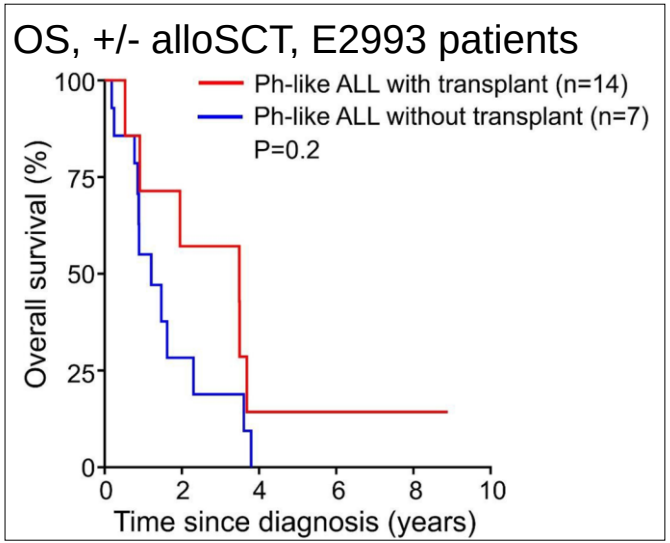
Jain, N *et al. Blood* 2017; 129:572-881

- and in contrast, in adult patients at MDACC, MRD-ve and MRD+ve patients had equally poor outcomes
- there was no treatment intensification for MRD positivity, and only 2 of 56 patients with Ph-like ALL underwent alloSCT
- achievement of MRD-ve status post induction had no effect on survival of Ph-like group

Roberts, KG *et al. J Clin Oncol* 2016; 35: 394-401

- description of 180 Ph-like adult patients gleaned from 8 NA clinical trials (n=909)
- outcomes poor as expected (n=133 Ph-like)
- alloSCT data known for 21 patients in study E2993





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        - ruxolitinib for JAK family?
- numerous ongoing clinical trials
    - TKI
    - JAK inhibitor
    - blinatumomab/inotuzumab etc.

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

- retrospective, ‘mixed-bag’ study of 24 French patients from pediatric and adult ALL studies, found to have various ‘ABL-class’ fusions
- 19 up-front chemo + TKI; 5 chemo + TKI at relapse
- anecdotally, some patients appear to have benefited from TKI

Cario, G *et al. Haematologica* 2020; 105: 1887-1894

- 46 ABL-class fusion +ve patients from AIEOP-BFM pediatric ALL 2000 and 2009 protocols
- Ph-like cases had poor initial response to therapy with MRD ≥ $5x10^{-4}$ in 71.4% post-induction and in 51.2% post-consolidation
- 13/46 cases received TKI (imatinib, 8; dasatinib, 5) starting at various times according to physician choice, including post-induction, during consolidation, post-consolidation, and post alloSCT
- 5-year EFS and 5-year-OS did not differ significantly between no-TKI and TKI groups; and alloSCT did not affect outcome

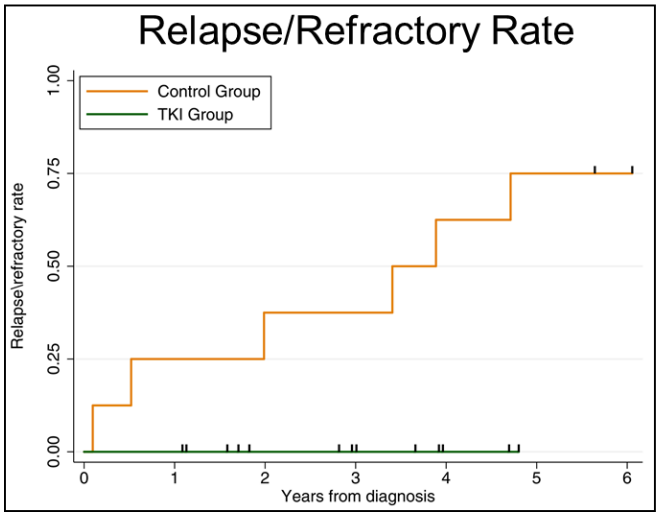
Moorman, AV *et al. BJH* 2020; 191: 844-851

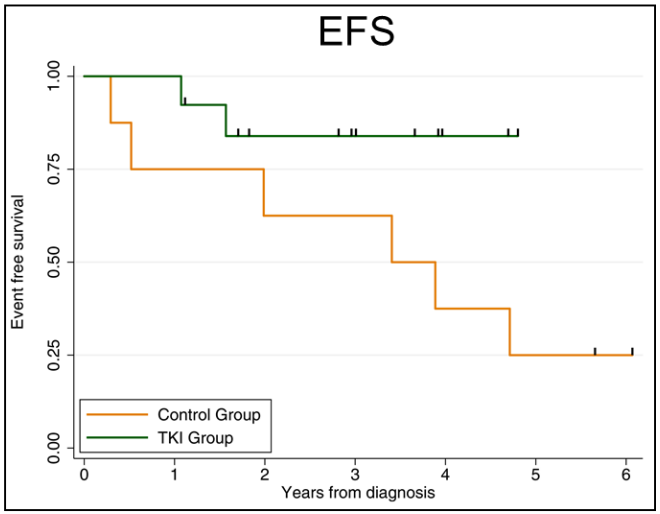
- during the course of pediatric UKALL2011 study, an intervention was introduced whereby slow responders (induction failures or MRD ≥ 1%), without other class-defining cytogenetic abnormalities, were screened for the presence of ABL-class fusions; when fusions were detected, imatinib (or dasatinib) was added to post-remission chemotherapy

- as the intervention was introduced during the course of the study, ABL-class fusion patients enrolled prior to the intervention, continued on study-defined post-remission chemotherapy without TKI, and served as a control

- 191 ‘slow responders’ ultimately yielded 21 ABL-class patients (median age 9 years)
  - 13/21 cases identified prospectively started on TKI
  - 8/21 cases identified retrospectively continued on standard study-defined post-remission chemotherapy

- during follow-up period (median 3.9 y), 0/13 TKI patients experienced a leukemia-related event, while 6/8 patients in the control group relapsed or died of primary disease





- 9/13 (69%) patients in the TKI group underwent alloSCT in CR1, compared with 3/8 (38%) in the control group (p=0.2)
- 4-year relapse rate, 0% vs 6.25% (p=0.009)
- <u>while not randomized, and only small numbers…highly suggestive</u>

Moorman, AV *et al. BJH* 2020; 191: 844-851

So, overall…

We don’t really know what to do

Ph-like Alteration	Drug	Disease Status	Age (y)	Study
ABL Class	Dasatinib	Newly Diagnosed	1-30	NCT01406746 (COG AALL1131)
	Dasatinib	Newly Diagnosed	1-18	NCT03117751 (SJCRH Total XVII)
	Dasatinib	Relapsed	≥10	NCT02420717 (MDACC)
	Dasatinib	Newly Diagnosed	1-30	NCT02883049
	Dasatinib + Chidamide	Newly Diagnosed	14-55	NCT03564470
CRLF2/JAK Pathway	Ruxolitinib	Newly Diagnosed	1-21	NCT02723994 (COG AALL1621)
	Ruxolitinib	Newly Diagnosed	1-18	NCT03117751 (SJCRH Total XVII)
	Ruxolitinib	Newly Diagnosed	18-39	NCT03571321
	Ruxolitinib	Relapsed	≥10	NCT02420717 (MDACC)
All B-ALL Ph-ve	Inotuzumab	Newly Diagnosed	18-39	NCT03150693
	Blinatumomab	Newly Diagnosed	30-70	NCT02003222

Conclusions:

1. Ph-like ALL remains inadequately diagnosed (and treated), especially in adults
2. Published outcomes data are largely anecdotal, retrospective, non-randomized, and highly contradictory
3. Optimal treatment algorithms remain largely undefined; the role of alloSCT remains unclear at present
4. Clinical trial data that will allow us to move out the era of Ph-like anecdotes are eagerly anticipated

Thank You!
Questions?
Comments?

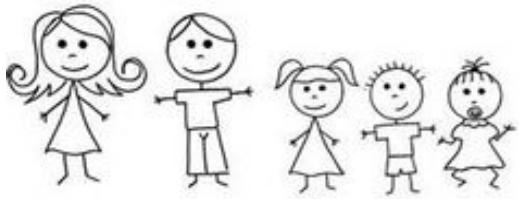
Global Leukemia Academy

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

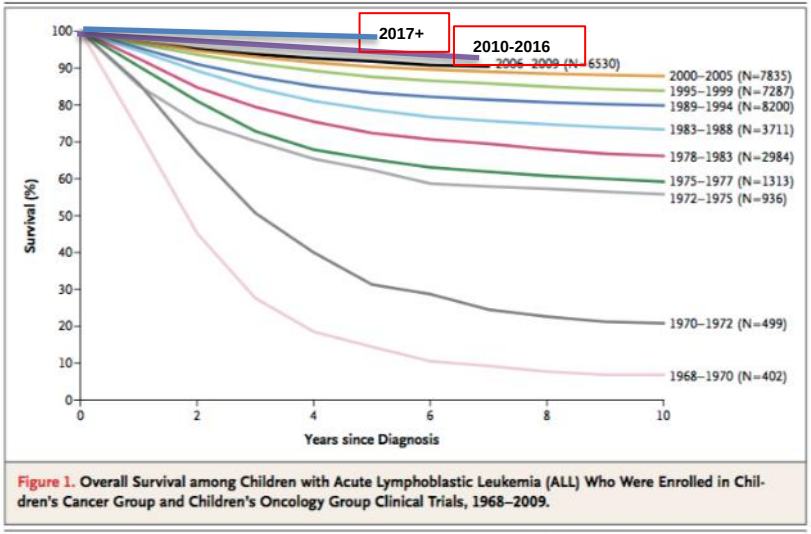
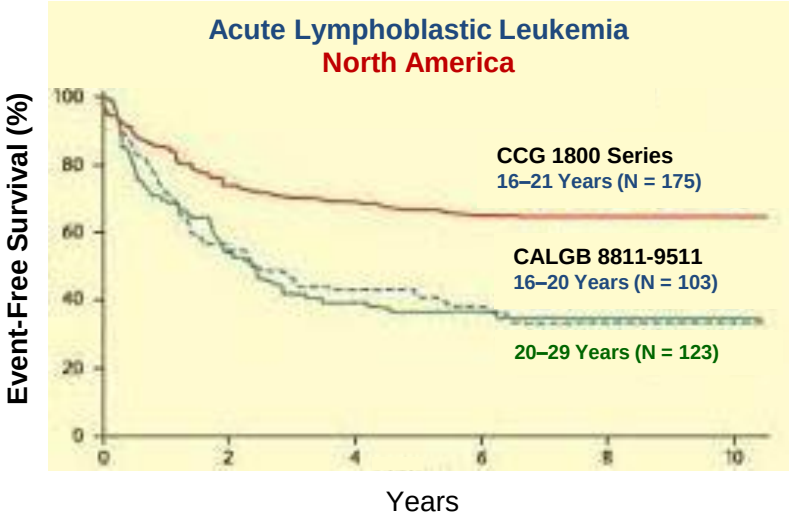


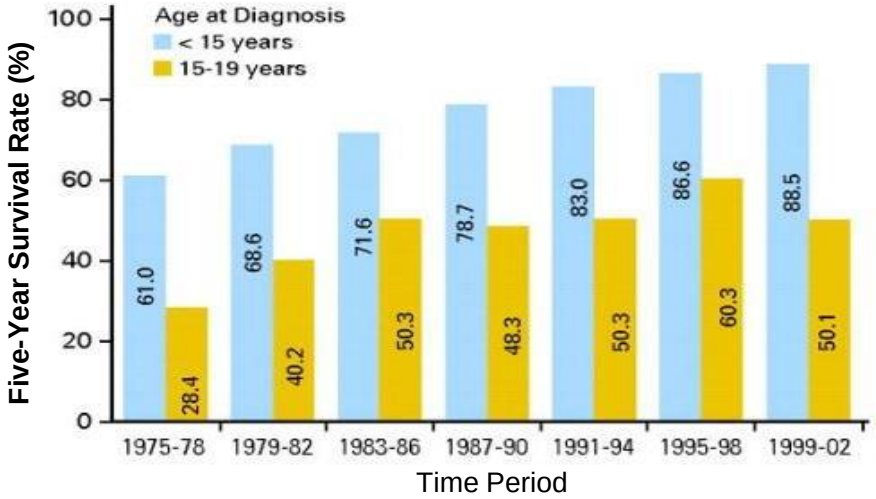
Figure 1. Overall Survival among Children with Acute Lymphoblastic Leukemia (ALL) Who Were Enrolled in Children's Cancer Group and Children's Oncology Group Clinical Trials, 1968–2009.

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.

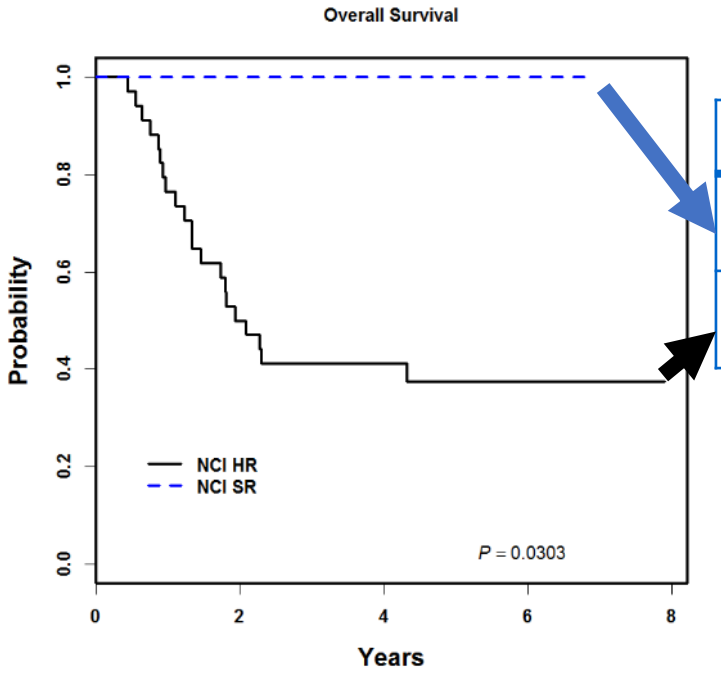
COG AYA Sexual Health Initiative

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%

CHILDREN'S ONCOLOGY GROUP

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

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Global Leukemia Academy

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

Franco Locatelli

APTITUDE HEALTH

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

Franco Locatelli, MD

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Dept. Pediatric Hematology/Oncology and Cell/Gene Therapy

IRCCS Ospedale Bambino Gesù, Roma, Italy

Disclosures

Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Bellicum	X				X	X	
Amgen					X	X	
Medac					X		
Neovii					X	X	
Novartis						X	
Sanofi						X	
Gilead					X		
bluebird bio					X		

Q

Learning question: What are the main factors influencing the outcome of pediatric and AYA patients with relapsed ALL?

1. Time between diagnosis and relapse
2. Immunophenotype
3. Site of relapse
4. All of the above

Relapsed ALL in Childhood:
Background

RELAPSE RATE:

Approximately 15%–20% of children with ALL relapse after standard treatment[1]

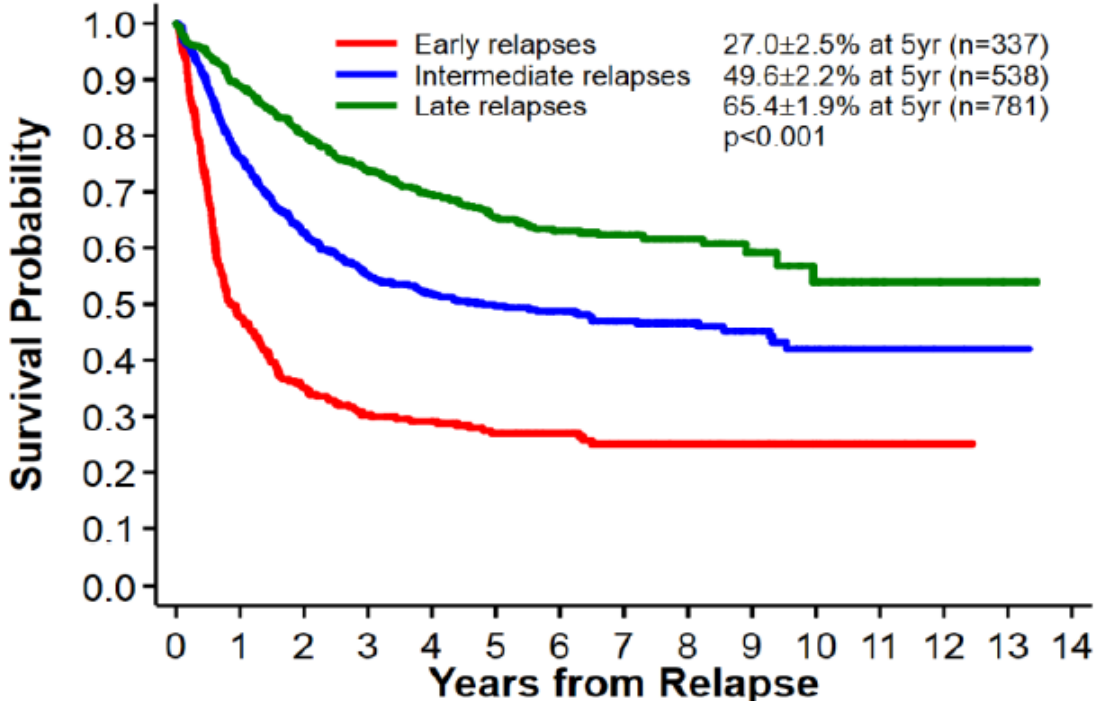
PROGNOSIS OF RELAPSED ALL LARGELY DEPENDS ON[2-6]

- ✓ Time from diagnosis to relapse
- ✓ Site of relapse
- ✓ Blast immune-phenotype

Almost all children with relapsed T-ALL and 2/3 of those with BCP-ALL are candidates for alloHSCT after a second morphologic complete remission (M1 marrow) is achieved[7-8]

BCP-ALL, B-cell precursor acute lymphoblastic leukemia; alloHSCT, allogeneic hematopoietic stem cell transplant.

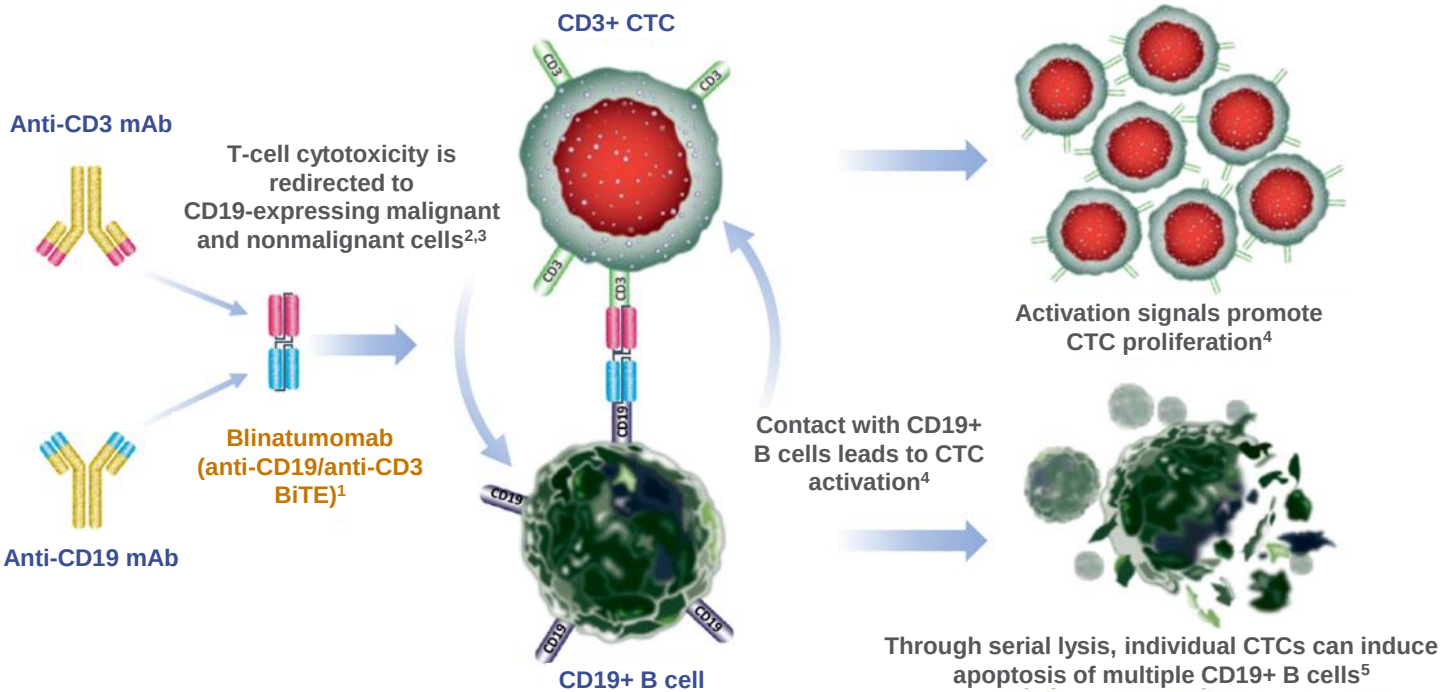
1. Hunger SP, Mullighan CG. *N Engl J Med.* 2015;373:1541-1552; 2. Chessells JM, et al. *Br J Haematol*. 2003;123:396-405; 3. Irving JA, et al. *Blood.* 2016;128:911-922; 4. Krentz S, et al. *Leukemia.* 2013;27:295-304; 5. Malempati S, et al. *J Clin Oncol.* 2007;25:5800-5807; 6. Schrappe M, et al. *N Engl J Med.* 2012;366:1371-1381; 7. Locatelli F, et al. *Blood.* 2012;120:2807-2816; 8. Peters C, et al. *J Clin Oncol.* 2015;33:1265-1274.



We need innovative therapies for improving the outcome of patients experiencing leukemia relapse

Rheingold SR, et al. ASCO 2019. Abstract 10008.

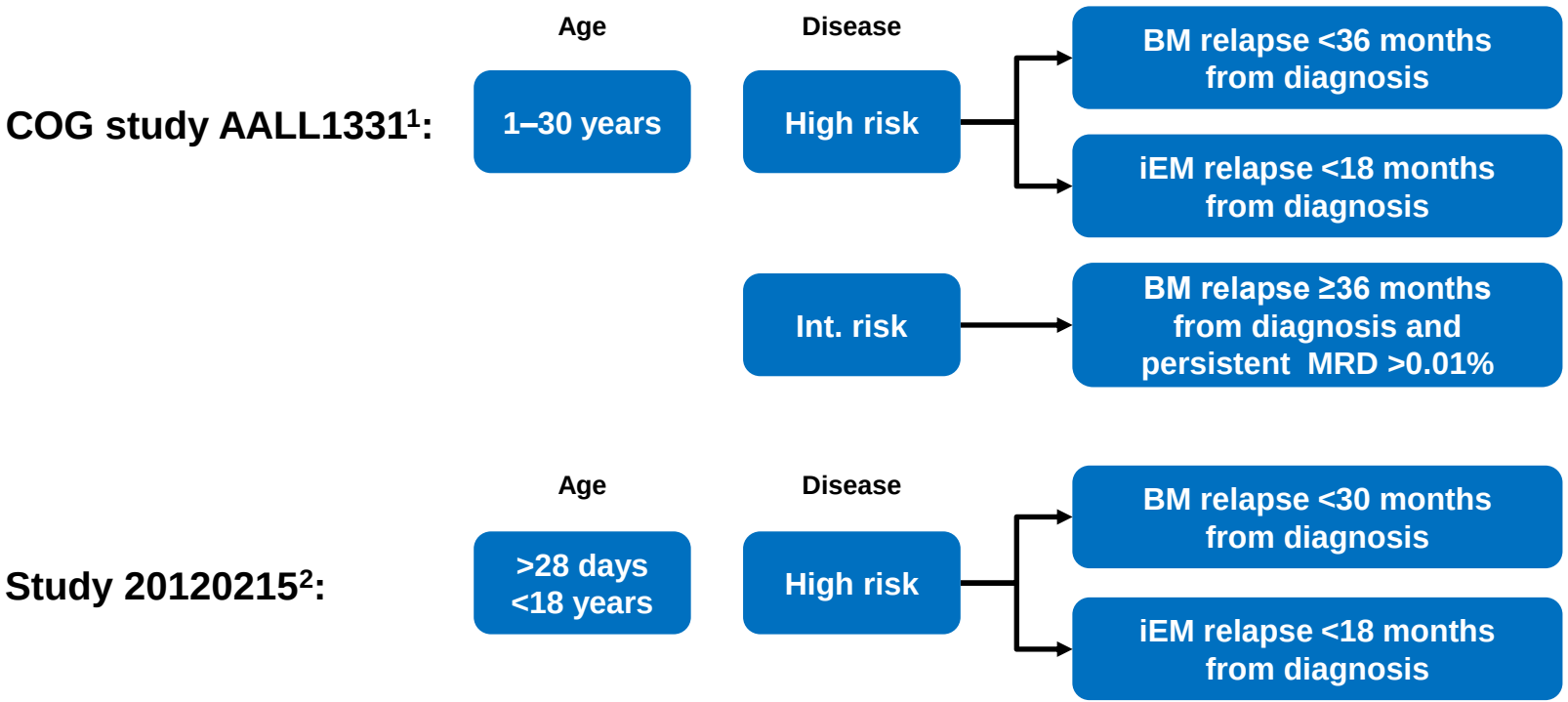
Blinatumomab (CD19 BiTE® molecule)



BiTE, bispecific T-cell engager; CD, cluster of differentiation; CTC, cytotoxic T cell; mAb, monoclonal antibody.

1. Baeuerle PA, et al. *Cancer Res*. 2009;69:4941-4944; 2. Bargou R, et al. *Science*. 2008;321:974-977; 3.Topp MS, et al. *Lancet Oncol*. 2015;16:57-66; 4. Klinger M, et al. *Blood*. 2012;119:6226-6233; 5. Hoffmann P, et al. *Int J Cancer*. 2005;115:98-104.

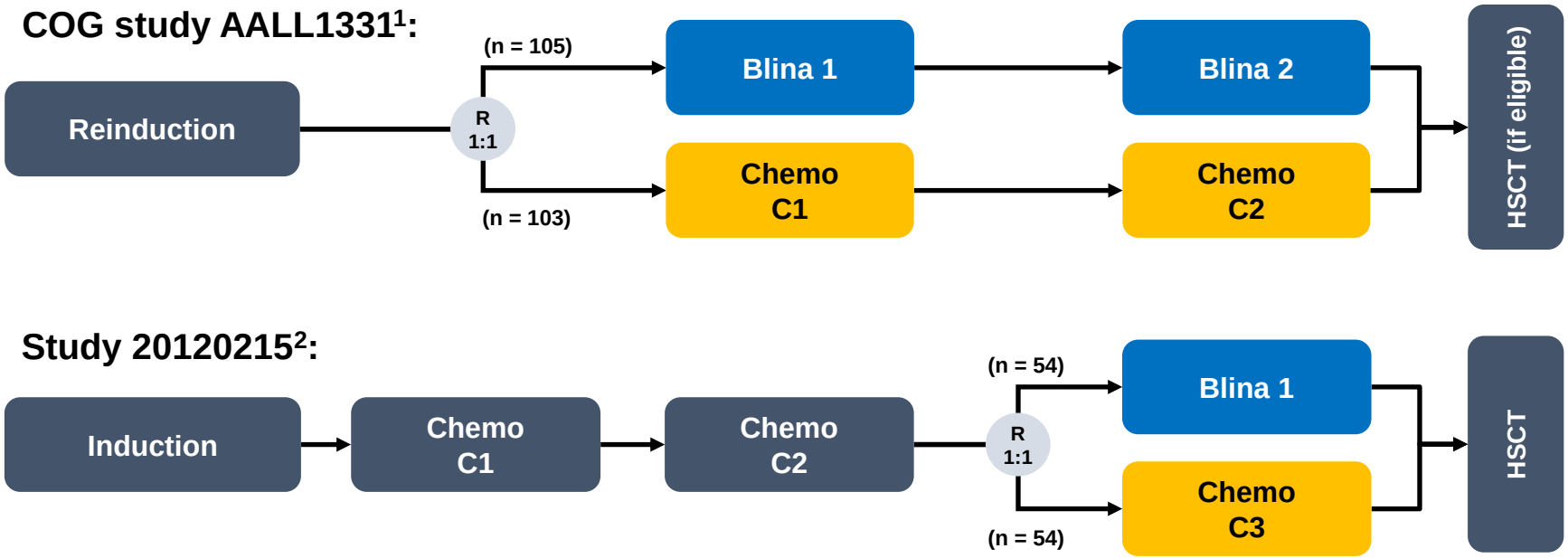
Phase III Studies: Key Enrollment Criteria



BM, bone marrow; iEM, isolated extramedullary; MRD, minimal residual disease.

1. Locatelli F, et al. *JAMA*. 2021;325:843-854; 2. Brown PA, et al. *JAMA*. 2021;325:833-842.

Design of the Phase III Studies

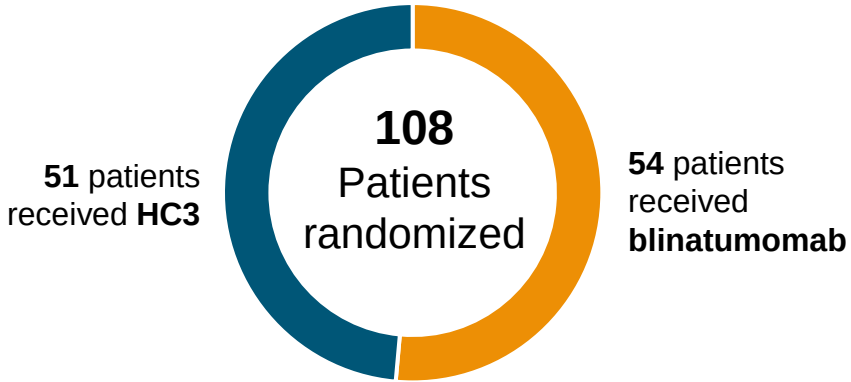


1. Locatelli F, et al. *JAMA*. 2021;325:843-854; 2. Brown PA, et al. *JAMA*. 2021;325:833-842.

Enrollment Terminated After First Interim Analysis due to Benefit Observed With Blinatumomab

- Patients enrolled from November 2015 to July 2019
- DMC recommended termination of enrollment after 50% of EFS events
- Study remains open for long-term follow-up of enrolled patients

- Target enrollment: ~202 patients



DMC, data monitoring committee; EFS, event-free survival.
Brown PA, et al. *JAMA*. 2021;325:833-842.

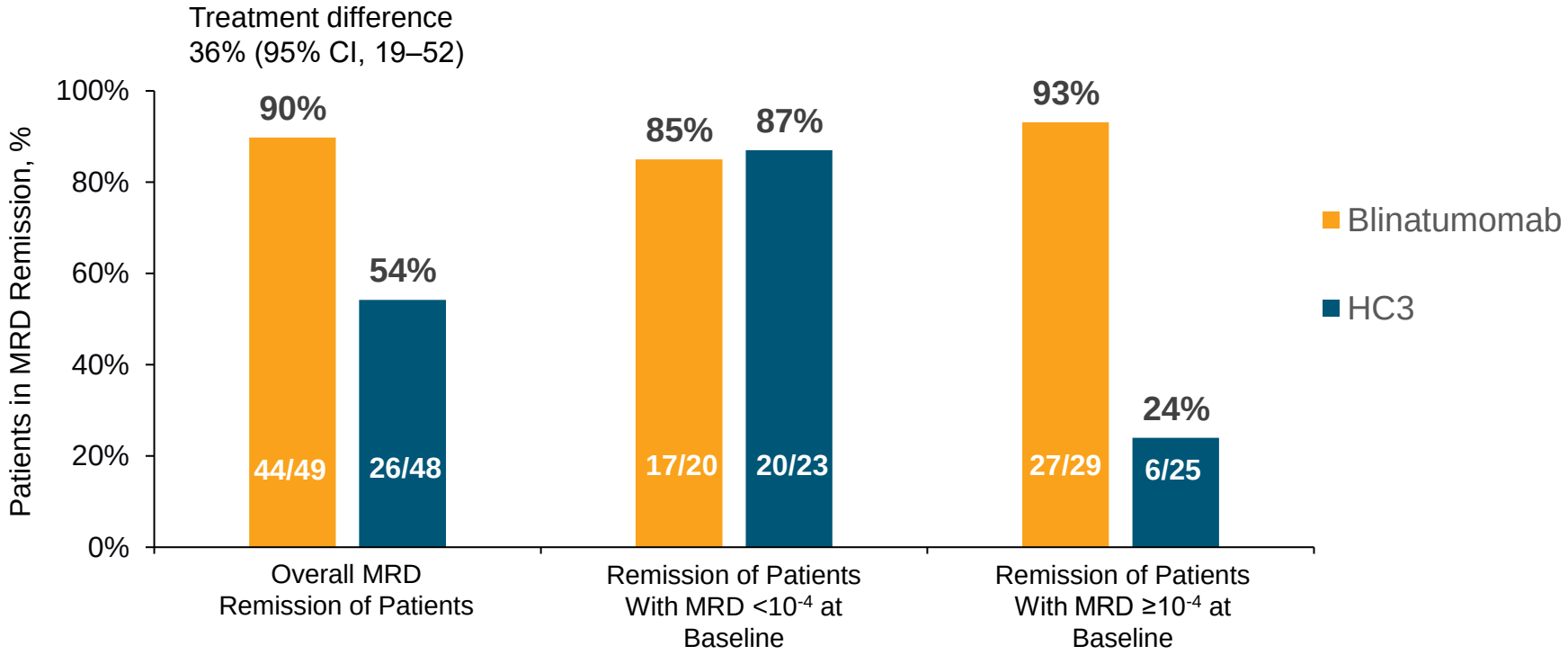
Demographic and Clinical Characteristics

	Blinatumomab (N = 54)	HC3 (N = 54)
Age		
Median (range), years	6 (1–17)	5 (1–17)
1–9 years, n (%)	39 (72)	38 (72)
≥10 years, n (%)	15 (28)	16 (30)
Sex, n (%)		
Male	30 (56)	22 (41)
Female	24 (44)	32 (59)
Genetic abnormalities, n (%)		
Hyperdiploidy[a]	6 (11)	6 (11)
t(12;21)(p13;q22)/TEL-AML1[a]	2 (4)	3 (6)
Hypodiploidy[b]	1 (2)	0 (0)
t(1;19)(q23;p13.3)/E2A-PBX1[b]	2 (4)	2 (4)
Other	8 (15)	9 (17)

	Blinatumomab (N = 54)	HC3 (N = 54)
EM disease, n (%)		
At relapse	10 (19)	14 (26)
BM assessment per central laboratory, n (%)		
M1	54 (100)	51 (94)
M2	0 (0)	2 (4)
MRD at screening, n (%)[c]		
$<10^{-4}$	25 (46)	26 (48)
$\geq 10^{-4}$	29 (54)	28 (52)
Mean (SD) time from first diagnosis to relapse, months	21.9 ± 8.0	22.8 ± 12.3

[a]Favorable prognosis. [b]Unfavorable prognosis. [c]MRD evaluated by PCR and/or flow cytometry.
EM, extramedullary; BM, bone marrow; MRD, minimal residual disease.
Brown PA, et al. *JAMA*. 2021;325:833-842.

Superior MRD Remission by PCR in the Blinatumomab Arm (overall and by baseline[a] MRD status, Study 20120215)

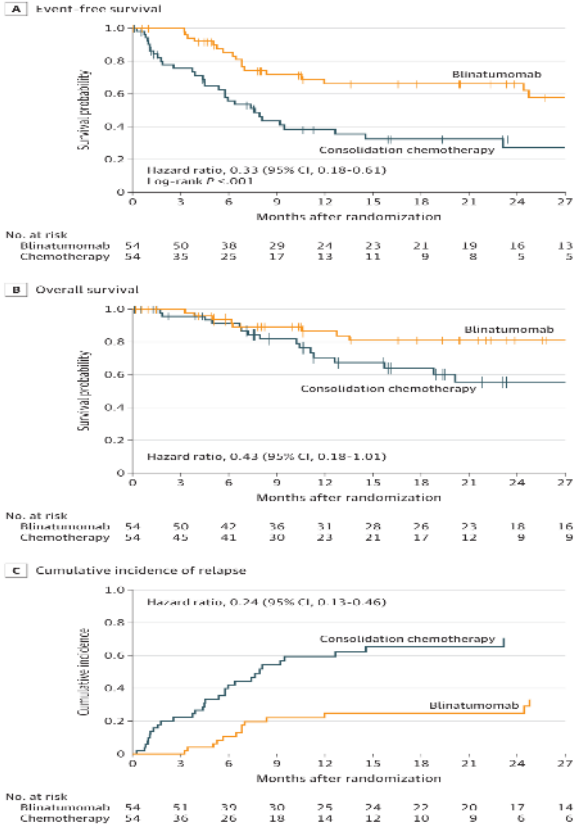


[a]Baseline: end of HC2 (screening sample before enrollment).
PCR, polymerase chain reaction.
Brown PA, et al. *JAMA*. 2021;325:833-842.

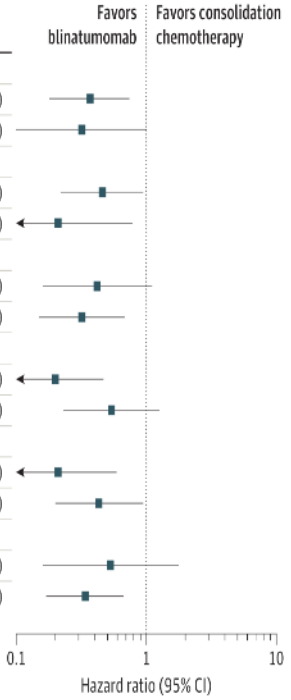
JAMA Network™

From: Locatelli F, et al. **Effect of Blinatumomab vs Chemotherapy on Event-Free Survival Among Children With High-risk First-Relapse B-Cell Acute Lymphoblastic Leukemia: A Randomized Clinical Trial**

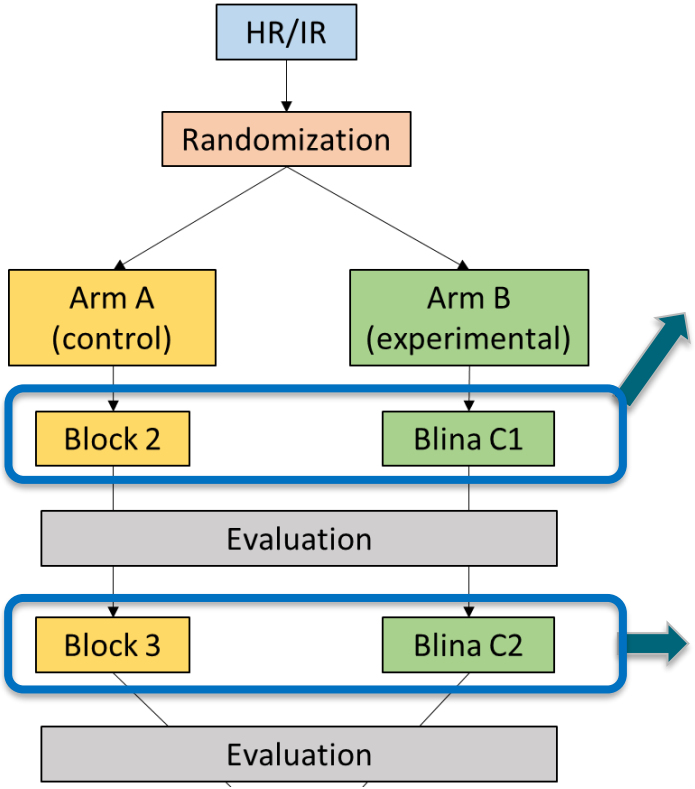
JAMA. 2021;325:843-854. doi:10.1001/jama.2021.0987

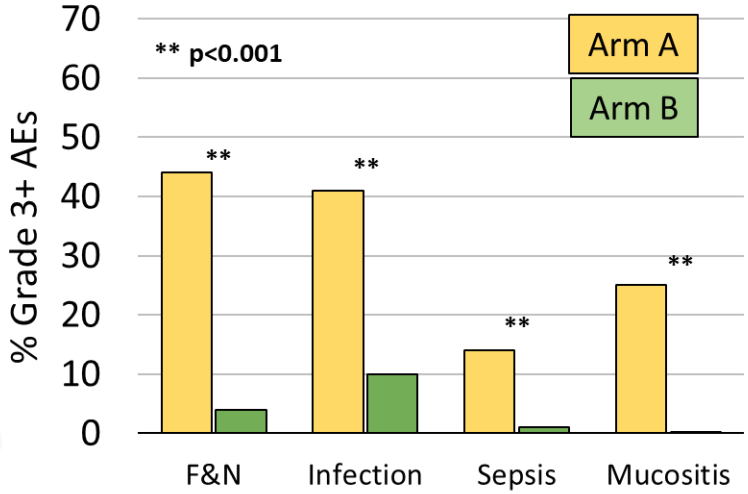


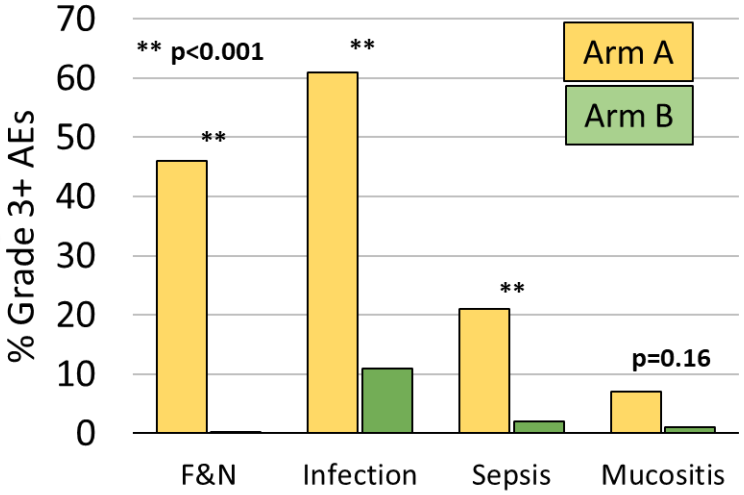
Subgroup	No. of events/No. treated (%) Blinatumomab	Consolidation chemotherapy	Hazard ratio (95% CI)
Age, y			
1-9	12/39 (30.8)	23/38 (60.5)	0.37 (0.18-0.74)
>9	5/15 (33.3)	8/16 (50.0)	0.32 (0.10-1.01)
Minimal residual disease at end of induction			
$<10^{-3}$ Blast cells	12/35 (34.3)	19/34 (55.9)	0.46 (0.22-0.95)
$\geq 10^{-3}$ Blast cells	3/15 (20.0)	9/16 (56.3)	0.21 (0.05-0.78)
Minimal residual disease before treatment start			
$<10^{-4}$ Blast cells	6/25 (24.0)	13/26 (50.0)	0.42 (0.16-1.11)
$\geq 10^{-4}$ Blast cells	11/29 (37.9)	18/28 (64.3)	0.32 (0.15-0.68)
Sex			
Male	9/30 (30.0)	14/22 (63.6)	0.20 (0.08-0.47)
Female	8/24 (33.3)	17/32 (53.1)	0.54 (0.23-1.26)
Time to relapse, mo			
<18	6/19 (31.6)	14/22 (63.6)	0.21 (0.07-0.59)
≥18 and ≤30	10/32 (31.3)	17/28 (60.7)	0.43 (0.20-0.95)
Extramedullary disease at relapse			
Yes	4/10 (40.0)	8/14 (57.1)	0.53 (0.16-1.78)
No	13/44 (29.5)	23/40 (57.5)	0.34 (0.17-0.67)



Adverse Events





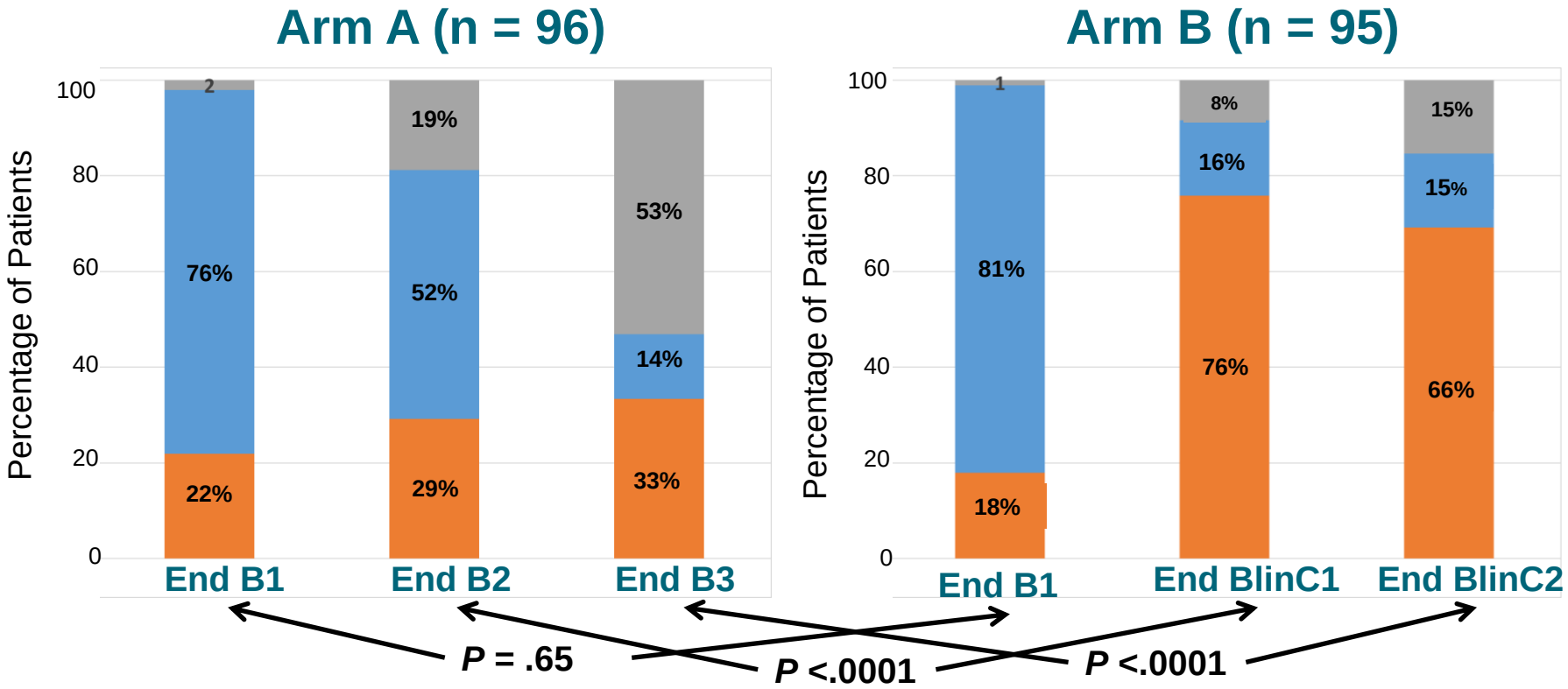


- *N = 4 post-induction grade 5 AEs on Arm A (all infections)*
- *N = 0 on Arm B*
- *Ages of Arm A deaths: 2, 17, 23, and 26 years old (AYA-skewed)*
- ***NOTE: AE rates significantly higher in AYA (Hogan, et al. ASH 2018 abstract)***

CHILDREN'S ONCOLOGY GROUP

Locatelli F, et al. *JAMA*. 2021;325:843-854.

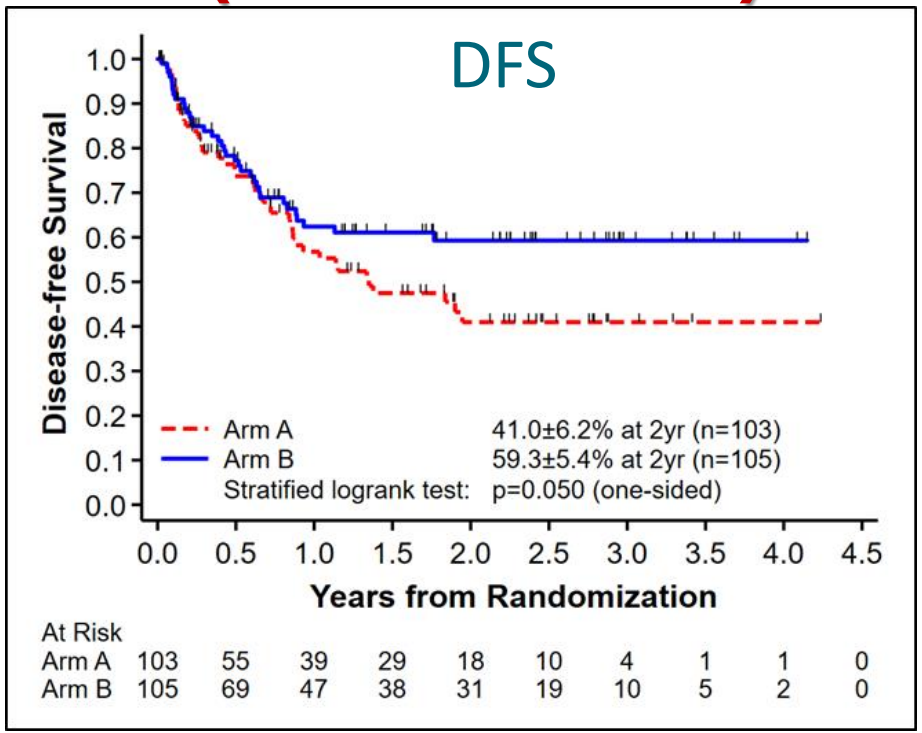
MRD Clearance (for iBM and BM + EM)

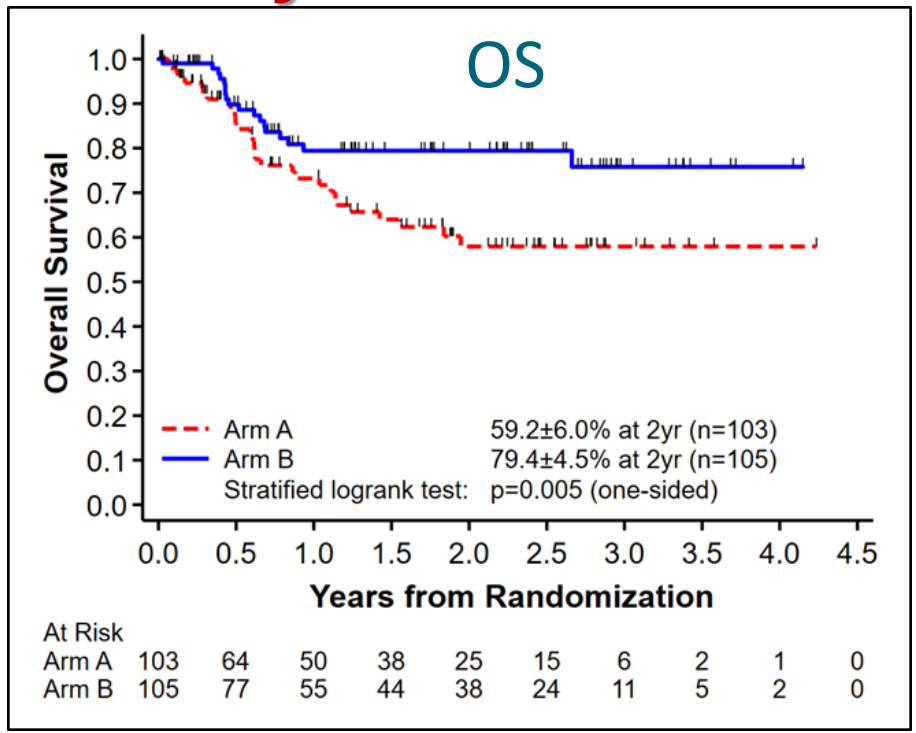


CHILDREN'S ONCOLOGY GROUP

Locatelli F, et al. *JAMA*. 2021;325:843-854.

Survival: Arm A (chemotherapy) vs Arm B (blinatumomab) – COG Study AALL1331





CHILDREN'S ONCOLOGY GROUP

Median follow-up 1.4 years

Locatelli F, et al. *JAMA*. 2021;325:843-854.

Final Considerations

- Immunotherapy is changing the therapeutic scenario of childhood B-ALL
- Blinatumomab is a monoclonal antibody characterized by a novel mechanism of action
- Blinatumomab has been shown to be superior to chemotherapy in the pre-transplant consolidation treatment of high-risk first-relapse patients
- Ongoing studies will define its role in standard-risk first-relapse patients and in newly diagnosed patients

Global Leukemia Academy

Therapeutic approaches in high-risk and older AML patients

Naval Daver

APTITUDE HEALTH

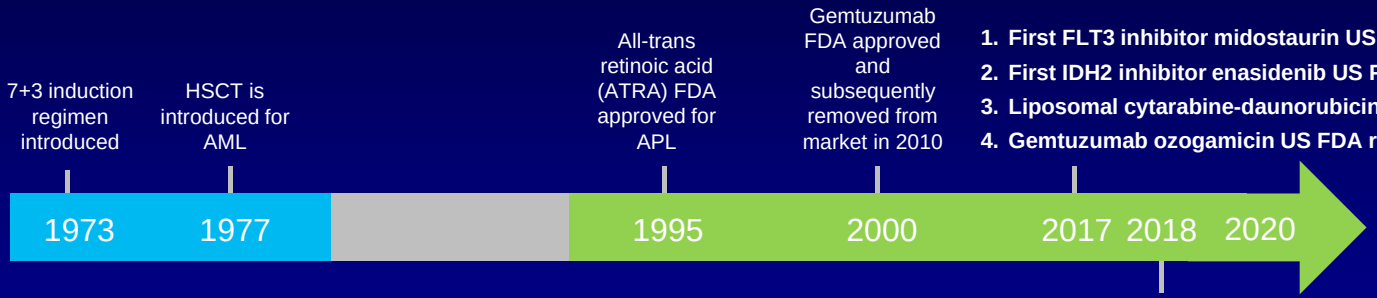
Therapeutic Approaches in High-Risk and Older AML Patients

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

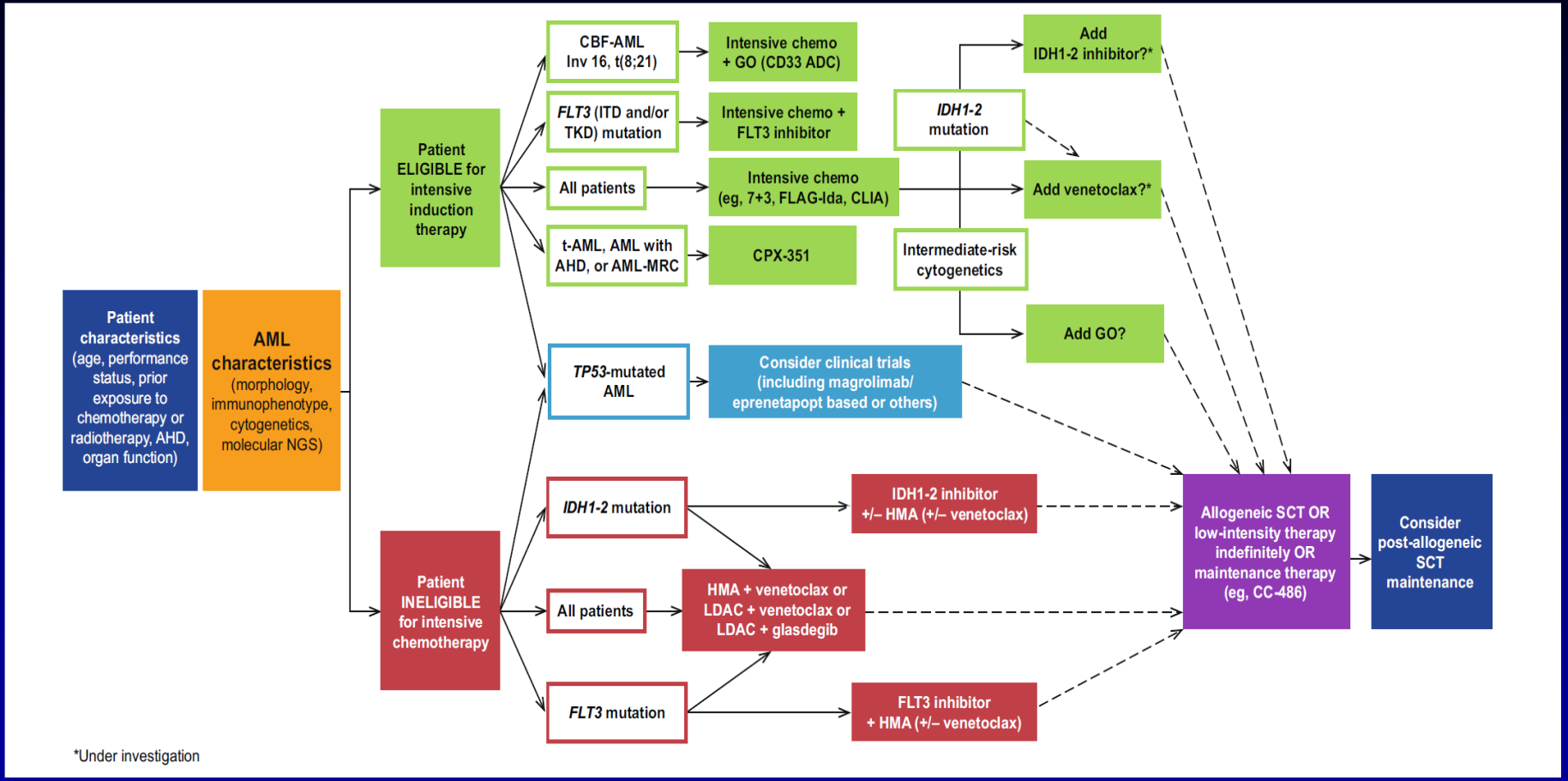


US FDA approvals

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)**

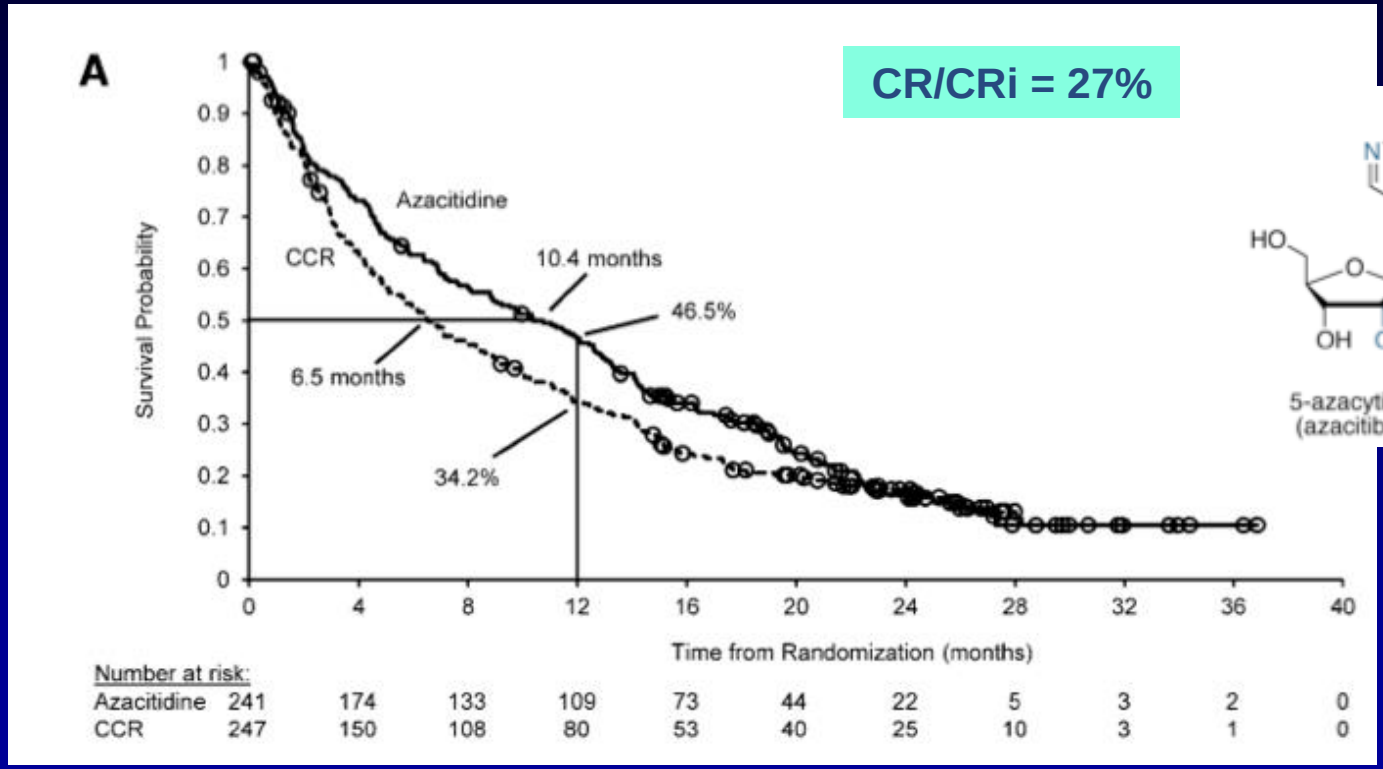
Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

Evolving Diagnostic and Treatment Paradigm for Newly Dx AML

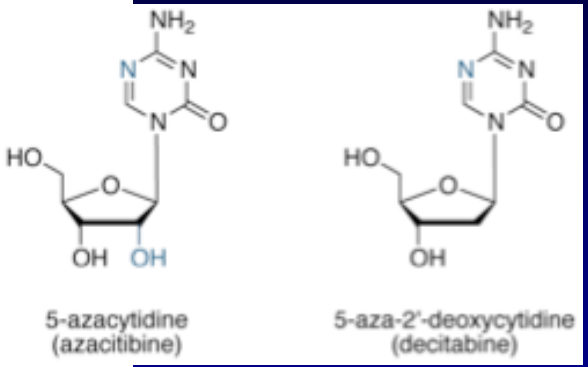


Daver N, et al. *Blood Cancer J.* 2020;10(10):107.

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

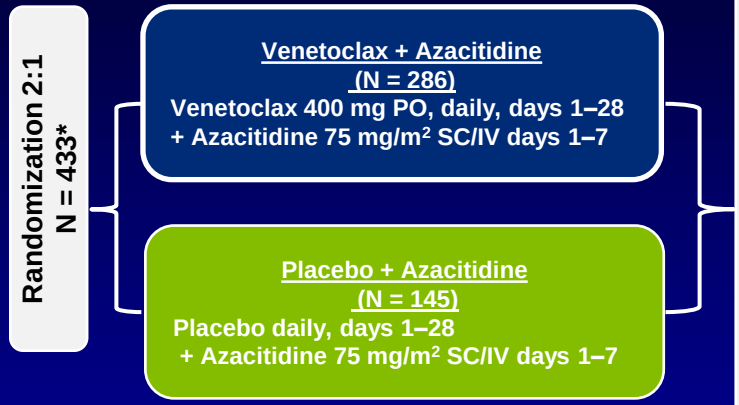
Inclusion

- 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



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

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

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

Patient Baseline Characteristics

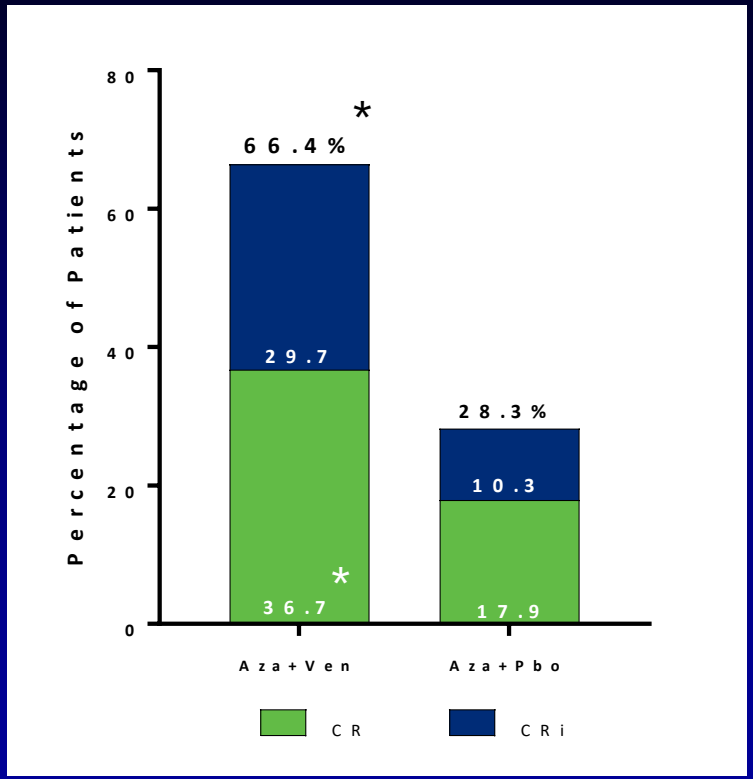
Characteristics	Ven + Aza (n = 286)	Pbo + Aza (n = 145)
Age		
Median (range) years	76 (49–91)	76 (60–90)
≥75 years, n (%)	174 (61)	87 (60)
Male, n (%)	172 (60)	87 (60)
AML type, n (%)		
De novo	214 (75)	110 (76)
Secondary	72 (25)	35 (24)
Secondary AML		
Post-MDS, CMML*	46 (64)	26 (74)
Therapy-related 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)

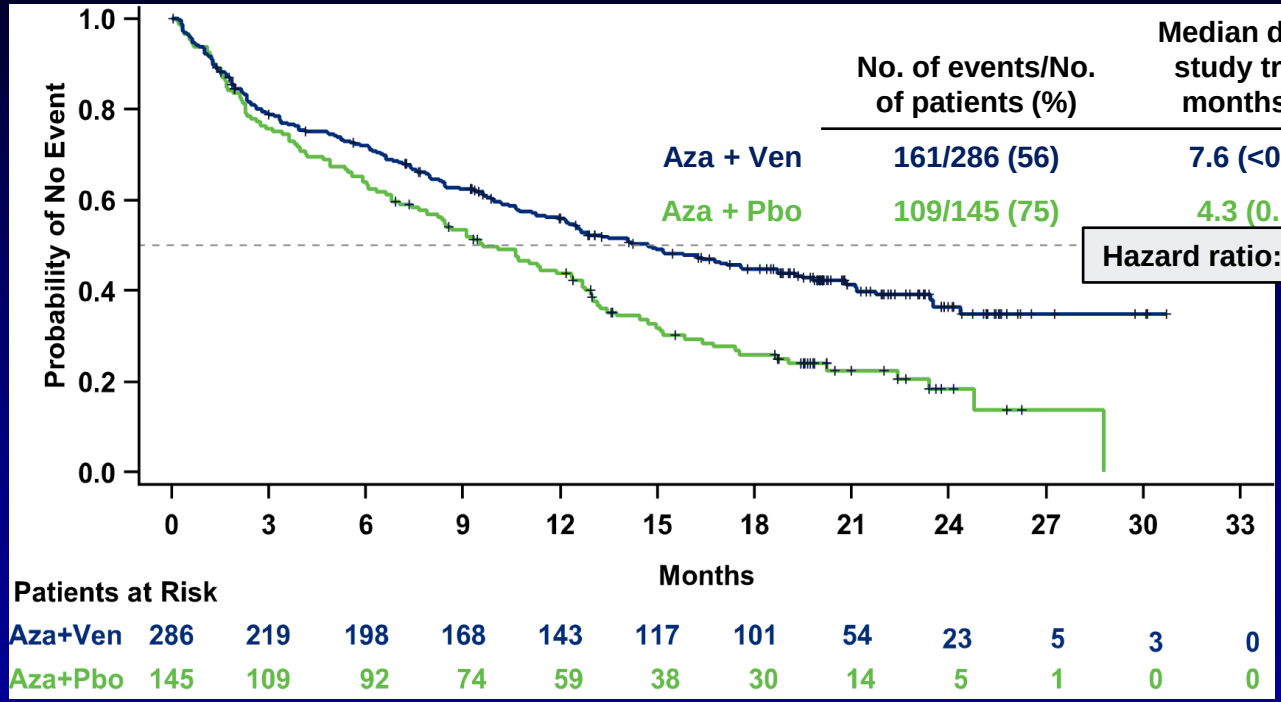


	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR + CRi by initiation of Cycle 2, n (%)
Aza + Ven (n = 286)	7.0 (1.0–30.0)	1.3 (0.6–9.9)	124 (43.4)
Aza + Pbo (n = 145)	4.5 (1.0–26.0)	2.8 (0.8–13.2)	11 (7.6)

*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

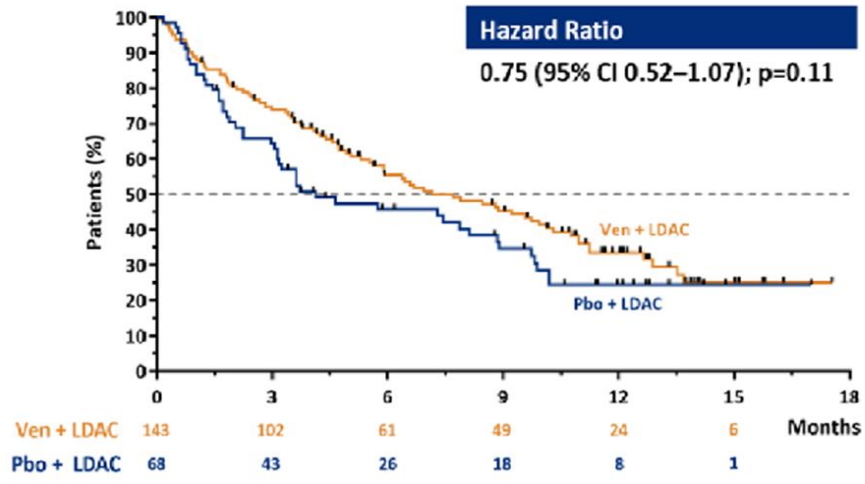
Median follow-up time: 20.5 months (range: <0.1 – 30.7)

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

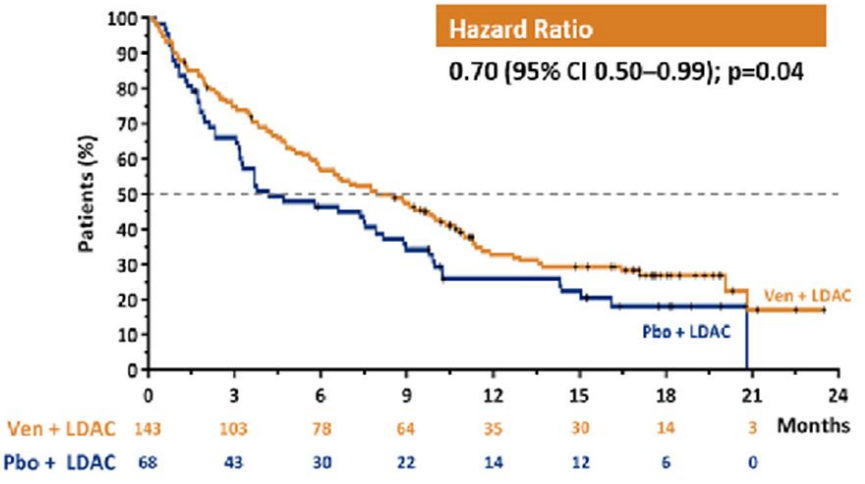
Low-Dose Cytarabine ± Venetoclax in AML: Results

	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.

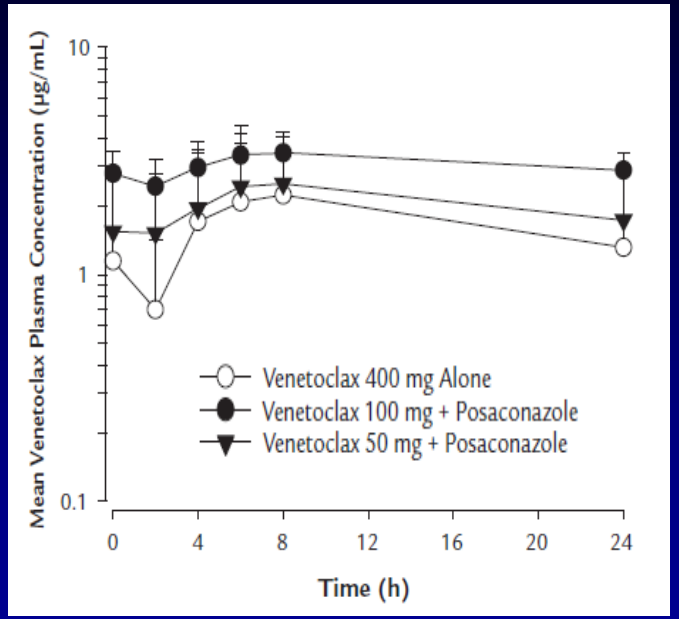
MDACC-Recommended Dosing Schema

- 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)

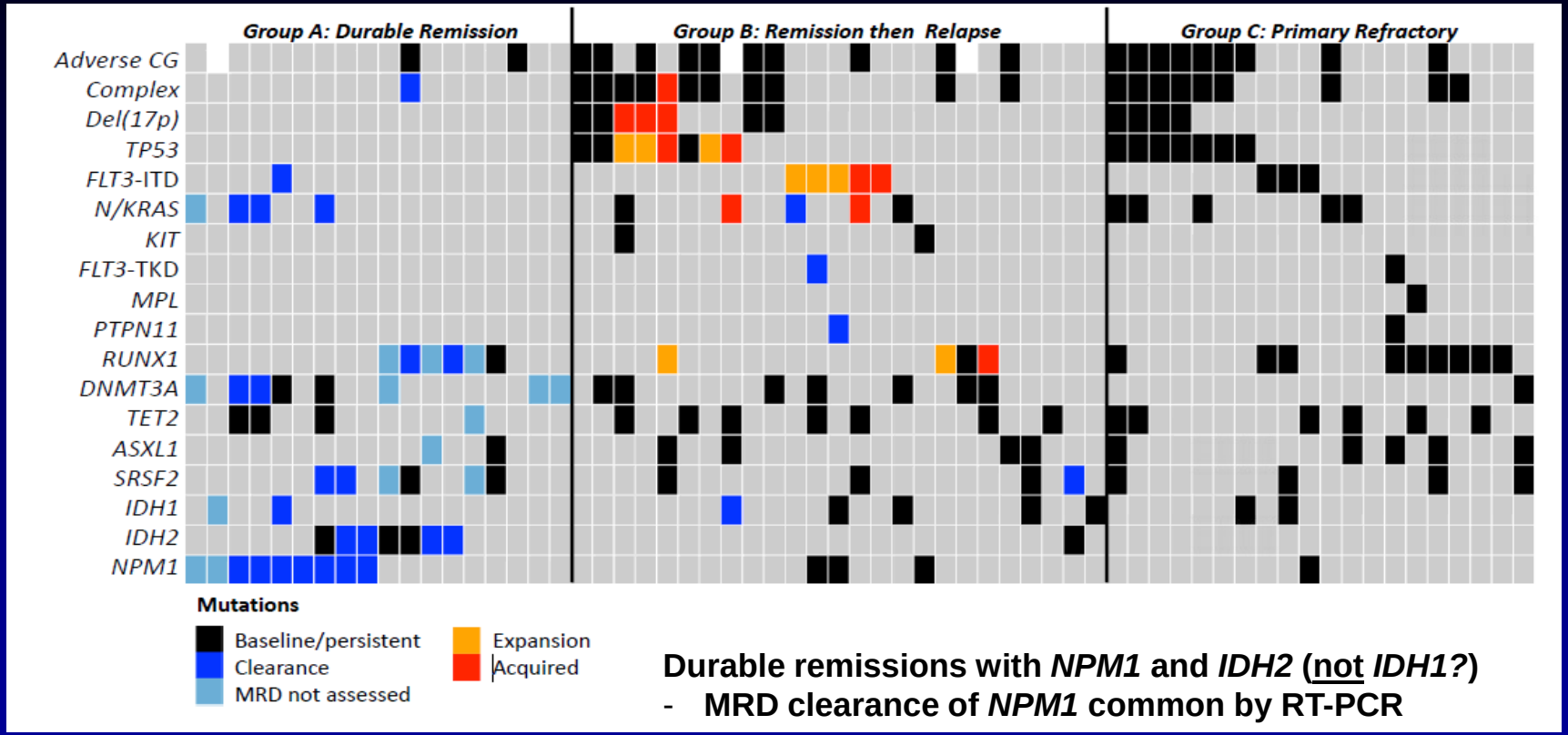


Agarwal SK, et al. *Clin Ther.* 2017;39:359-367.

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**

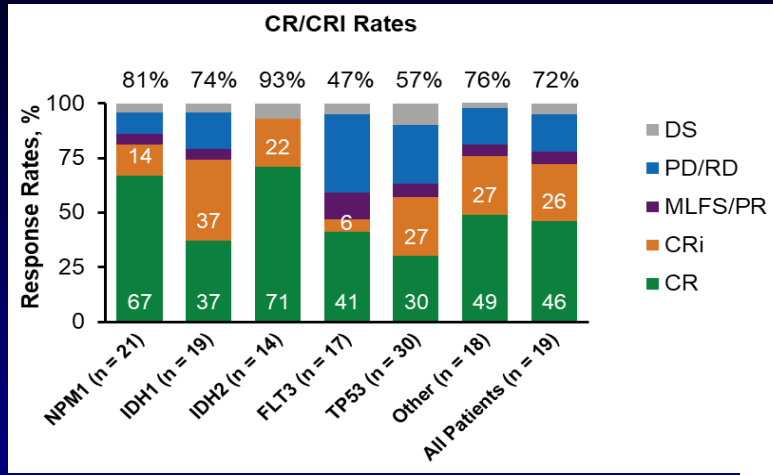
Patients treated at MDACC and The Alfred (n = 81)

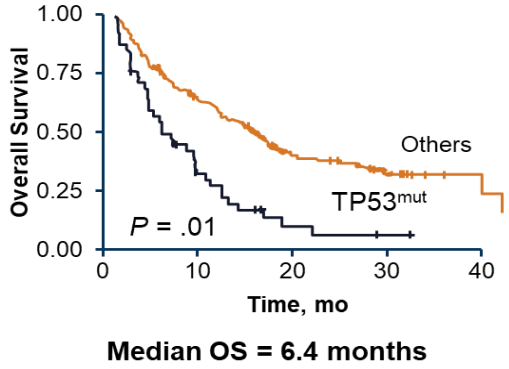
Resistance commonly associated with expansion or acquisition of *TP53* or signaling mutations including *K/NRAS* and *FLT3*-ITD

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]

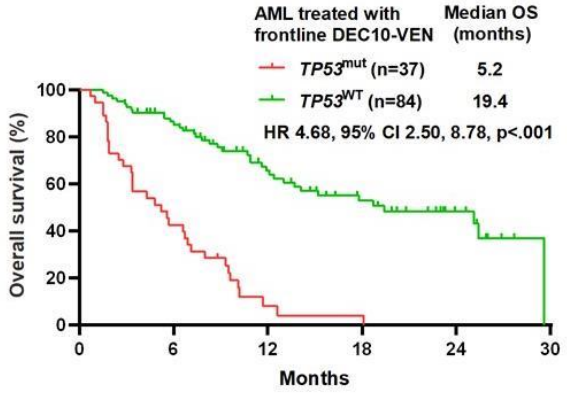




Median OS = 6.4 months

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

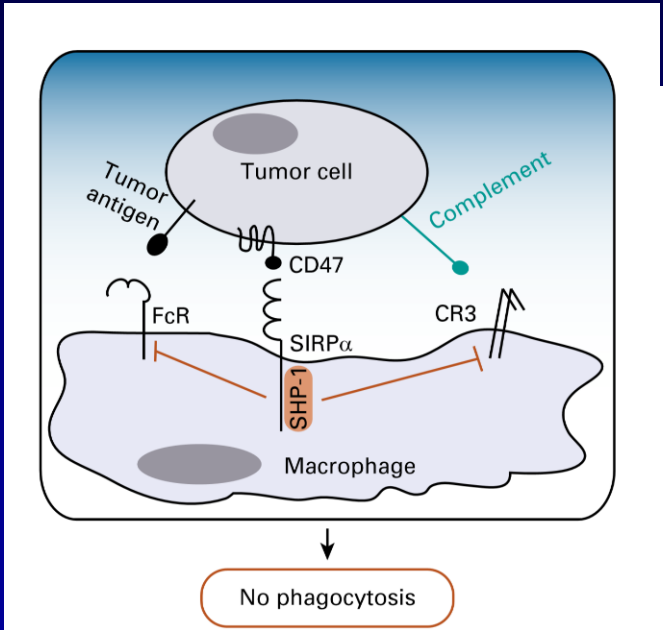
- **Those with *TP53*^{mut} had a lower rate of CR at 35% vs 57% in pts with *TP53*^{WT} (*P* = .026)**
- Lower rate of CR/CRi (54% vs 76%; *P* .015)



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

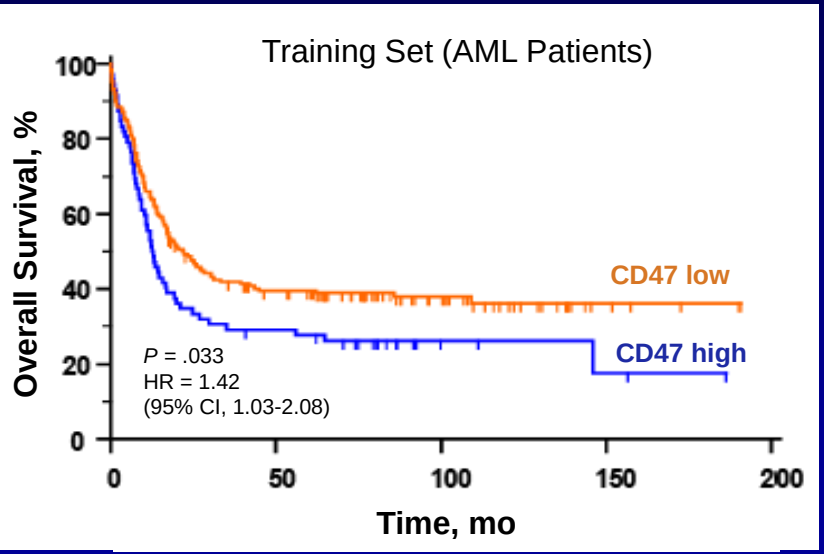
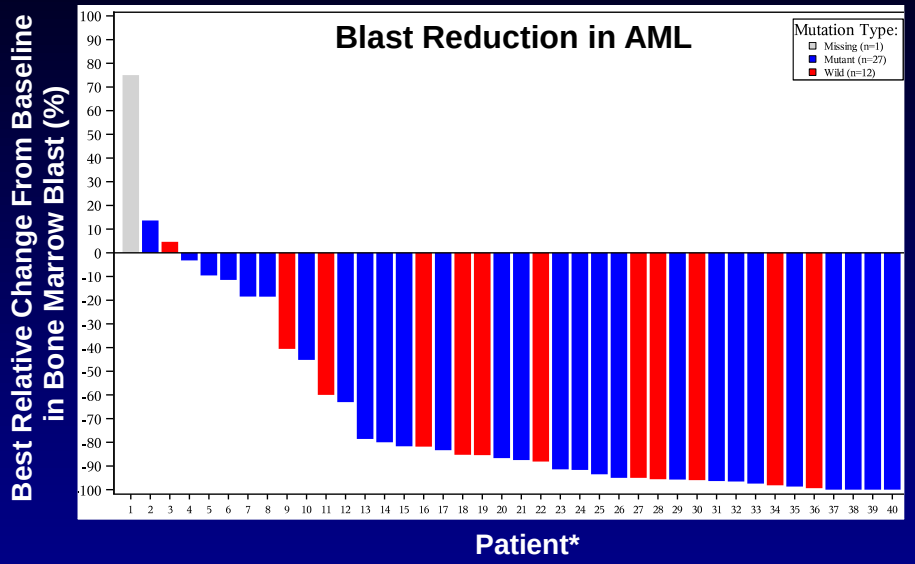


Figure at left adapted from Veillette A, Tang Z. *J Clin Oncol*. 2019;37:1012-1014 and Chao MP, et al. *Curr Opin Immunol*. 2012;24:225-232.
Figure at right adapted from Majeti R, et al. *Cell*. 2009;138:286-299.

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%)



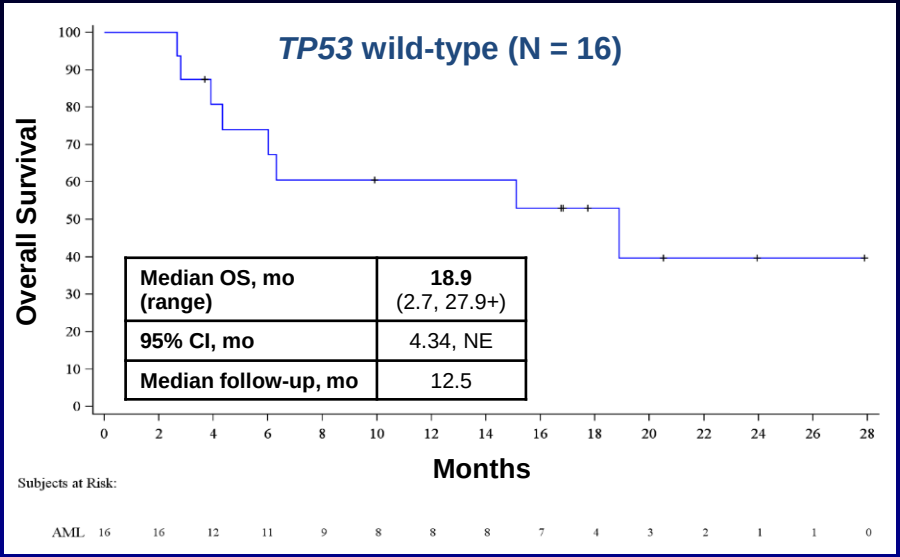
- **Magrolimab + Aza induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients**
- Median time to response is **1.95 months** (range 0.95 to 5.6 mo), more rapid than Aza monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab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

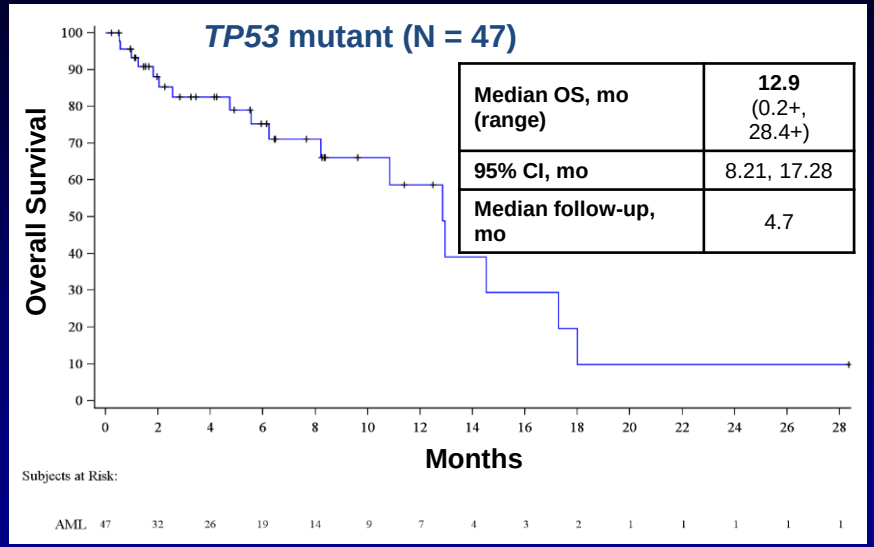
Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown. *Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

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

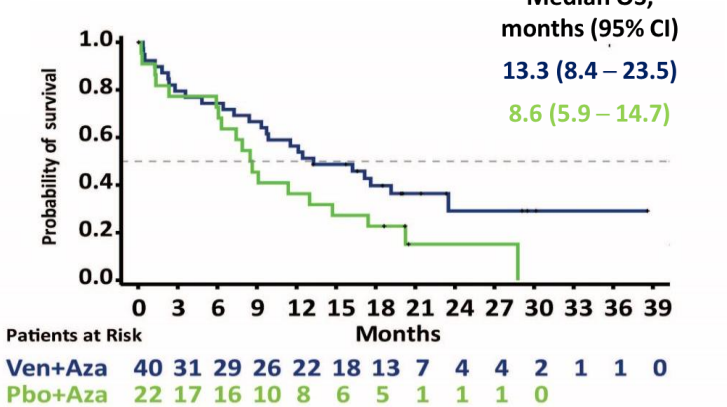
Frontline Therapy	N	Age, median	CRc (or CR/CRi)	OS, median	Ref.
Midostaurin + Aza	16	74 [59-85]	31%	8.7 mo	Gallogly, ASH 2017
Sorafenib + Aza	27	74 [61-86]	70%*	8.3 mo	Ohanian, Am J Hem 2018
Gilteritinib + Aza	15	75 [65-86]	67%	n/a	Esteve, ASH 2018
Quizartinib + Aza/LDAC	16	74 [62-83]	83%*	17.0 mo	Swaminathan,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

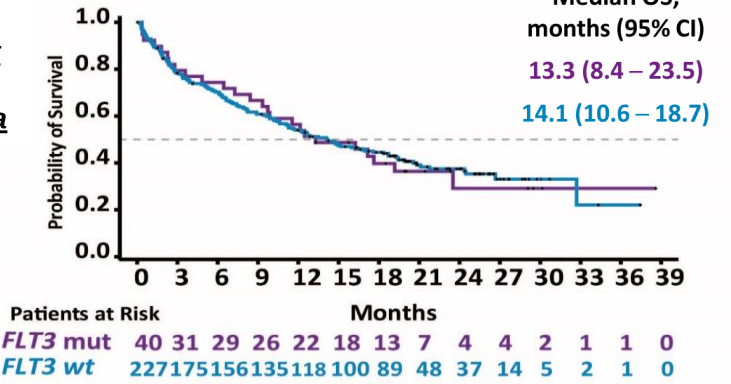
Yilmaz M, et al. ASH 2020. Abstract 26.

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

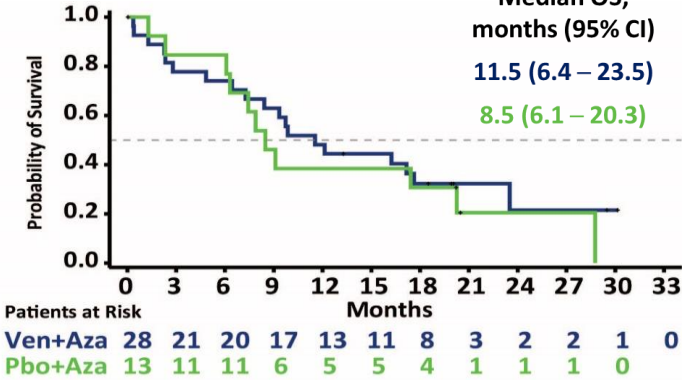
A. FLT3mut



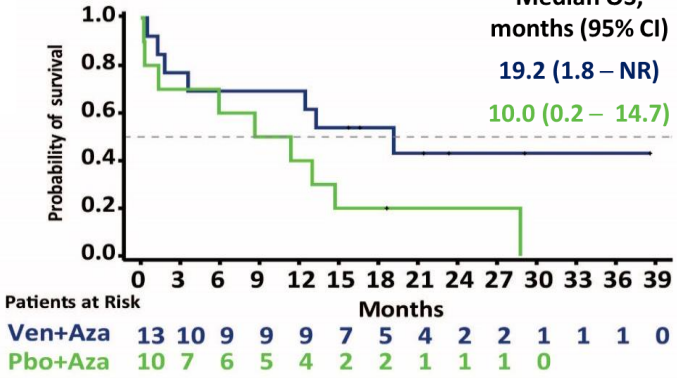
B. FLT3mut vs wt in Ven + Aza



C. FLT3-ITD



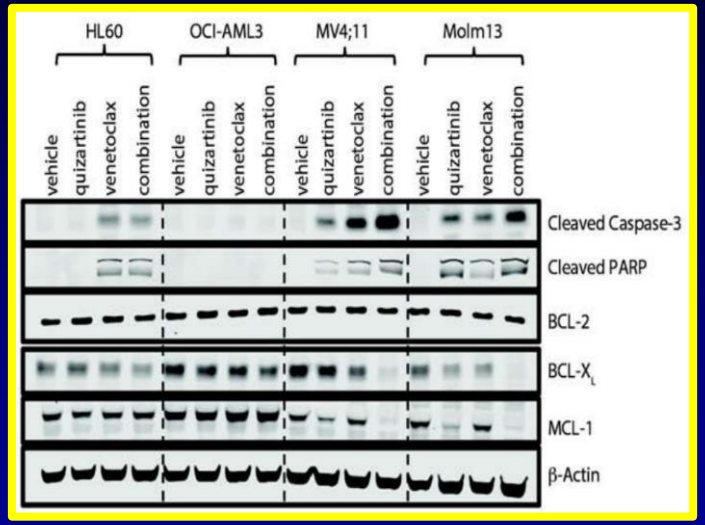
D. FLT3-TKD



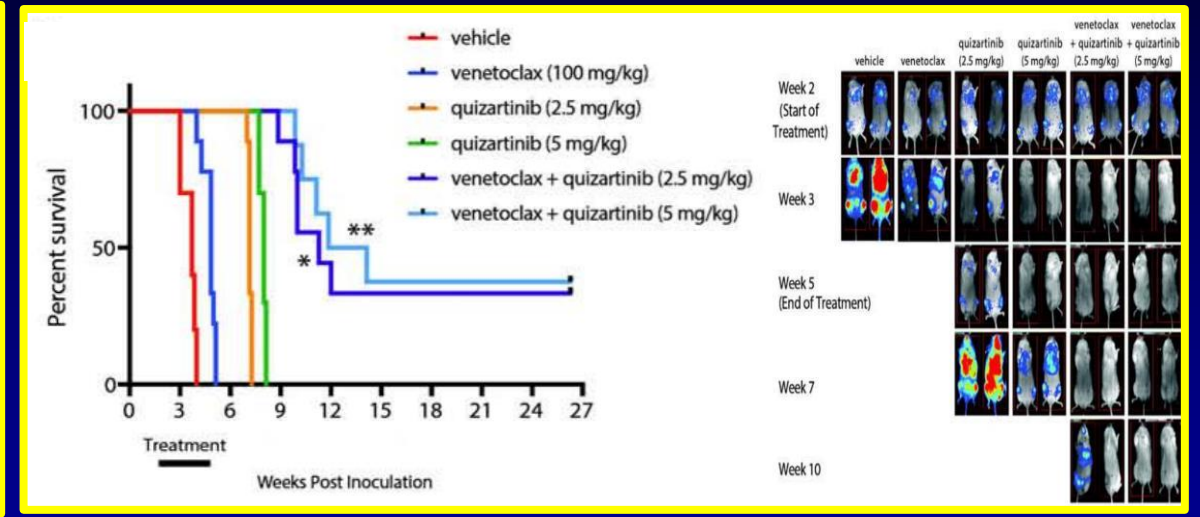
Konopleva M, et al. *Blood*. 2020;136:abstract 1904.

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

Venetoclax Combines Synergistically With Quizartinib



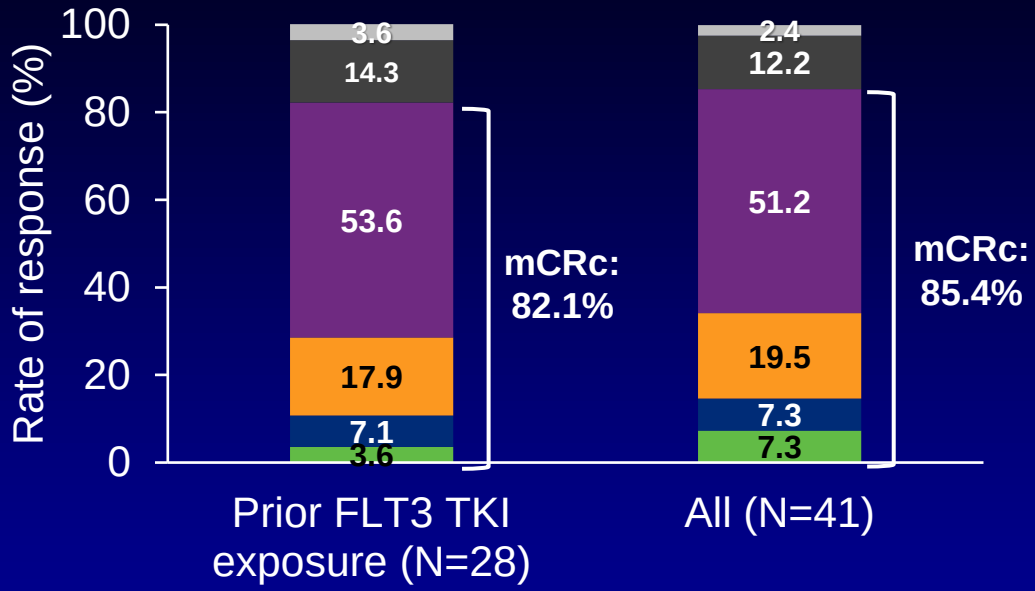
Cell lines were treated with combination – ↓ MCL-1, ↓ BCL-X_L



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.

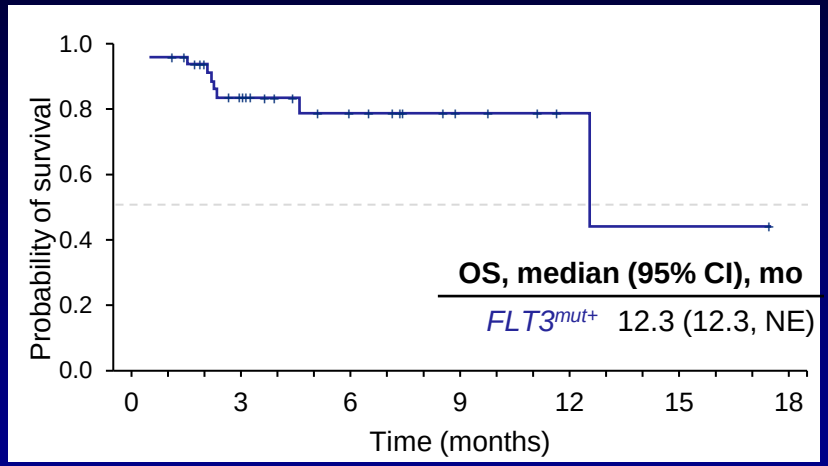
AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRi, CR with incomplete blood count recovery; CRp, CR with incomplete platelet recovery; FLT3, FMS-like tyrosine kinase 3; Gilt, gilteritinib; ITD, internal tandem duplications; ITT, intention to treat; mCRc, modified composite 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

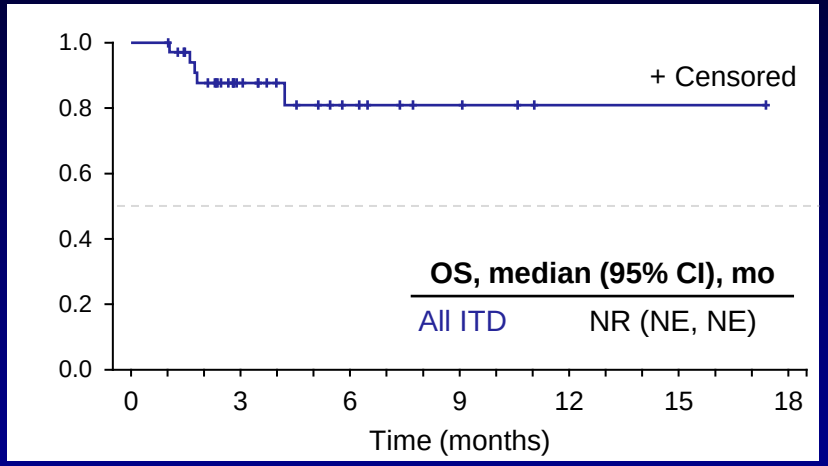
OS in all *FLT3*$^{mut+}$ patients (N = 41)



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

Debate on sequencing CD19-targeted approaches

Moderator: Andre Schuh

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

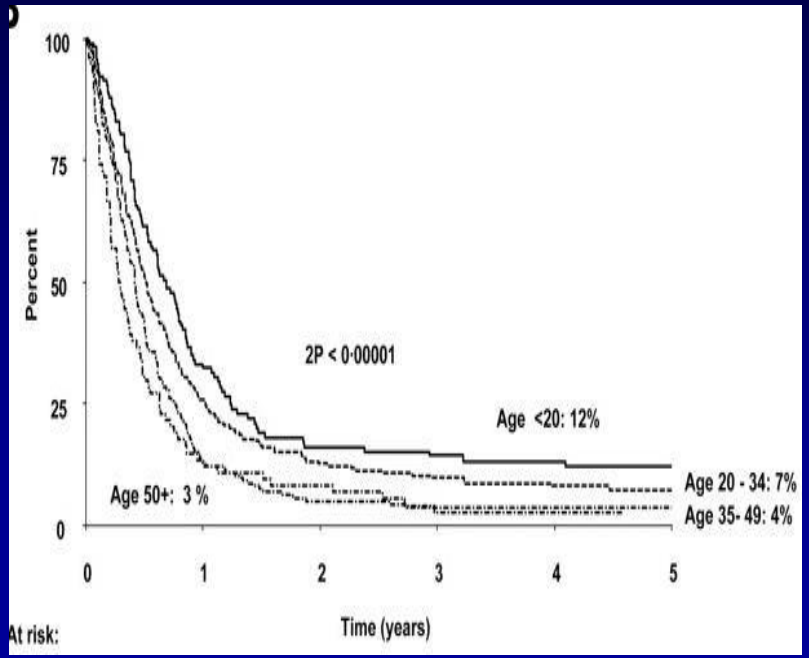
Rate (95% CI)	No prior salvage (S1)	One prior salvage (S2)	≥2 prior salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

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

ALL – Historical Survival Rates After First Relapse

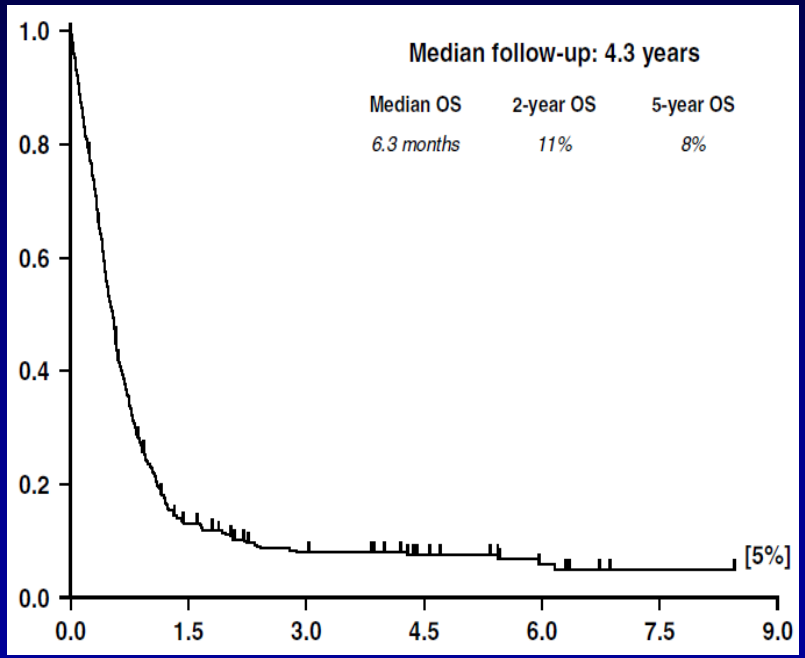
MRC UKALL2/ ECOG2993

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%

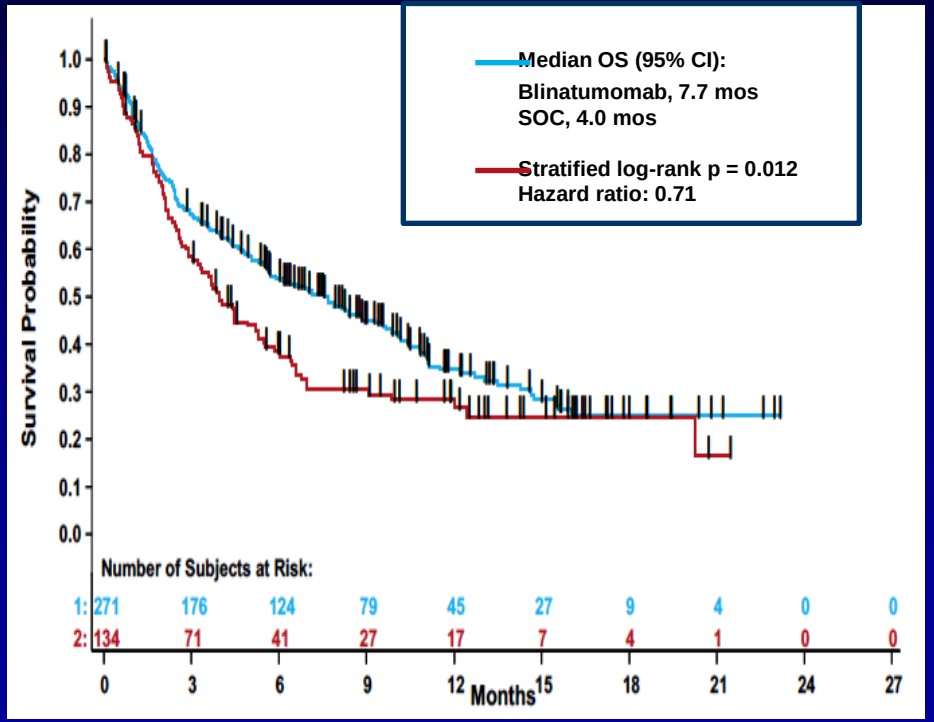


Fielding et al. *Blood*. 2007;109:944-950; Tavernier E, et al. *Leukemia*. 2007;21:1907-1914.

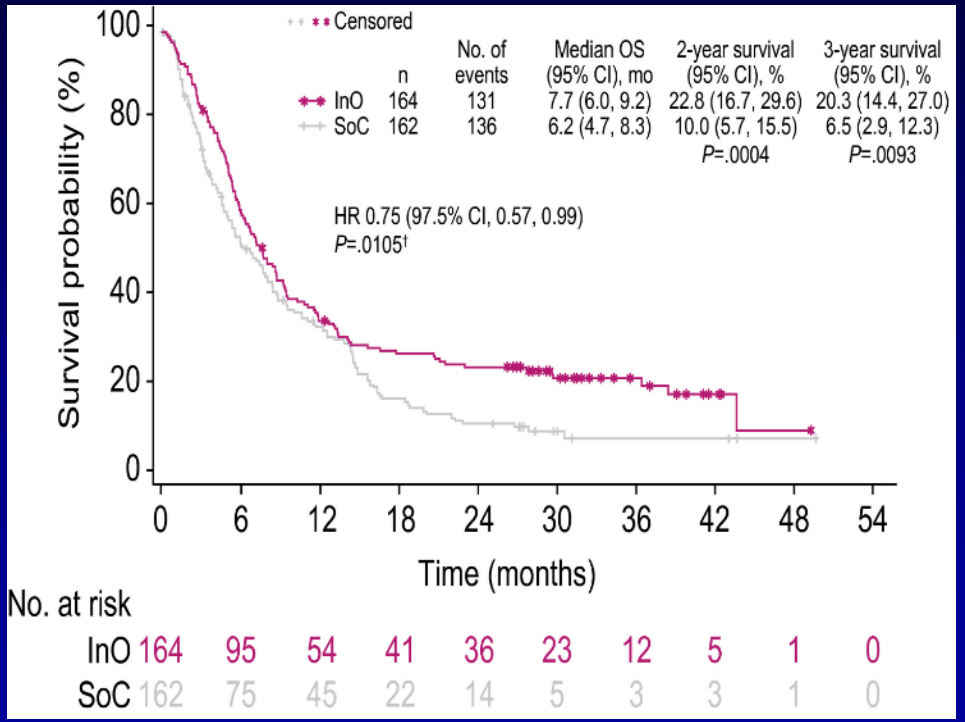
Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

- **Marrow CR**

Blina vs SOC: 44% vs 25%



Ino vs SOC: 74% vs 31%

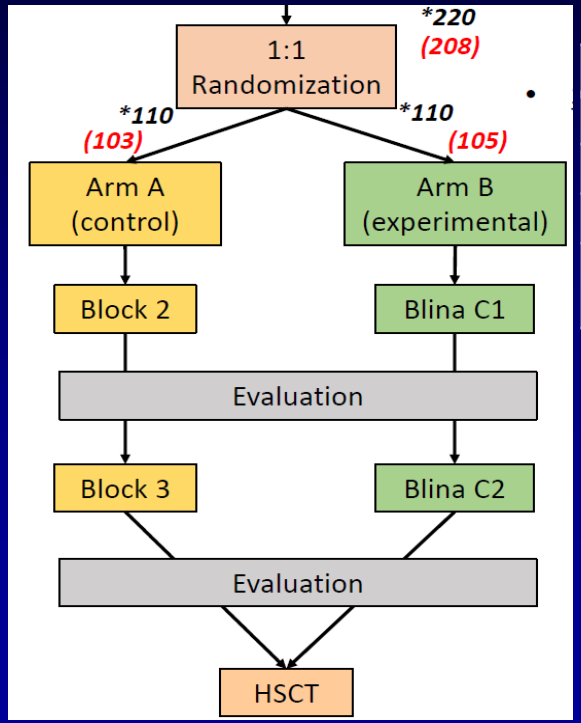


Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

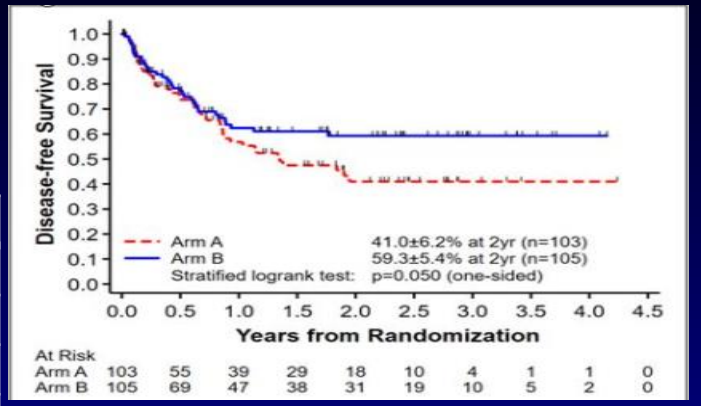
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

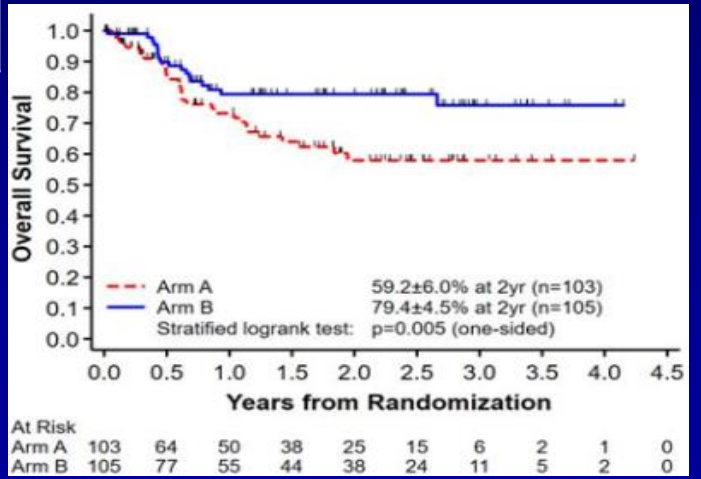
Phase III Study of Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

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



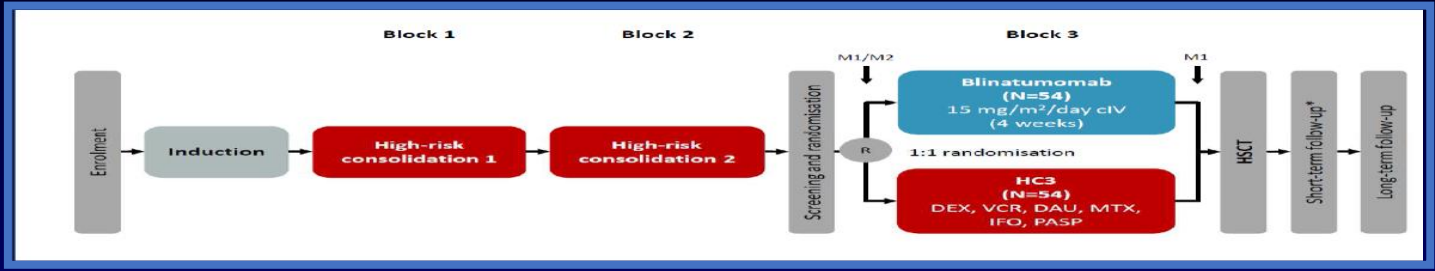
Parameter	Blina	Chemo	*P*
% 2-yr DFS	59	41	.05
% 2-yr OS	79	59	.005
% SCT	73	49	<.001
% MRD clearance	79	21	<.001





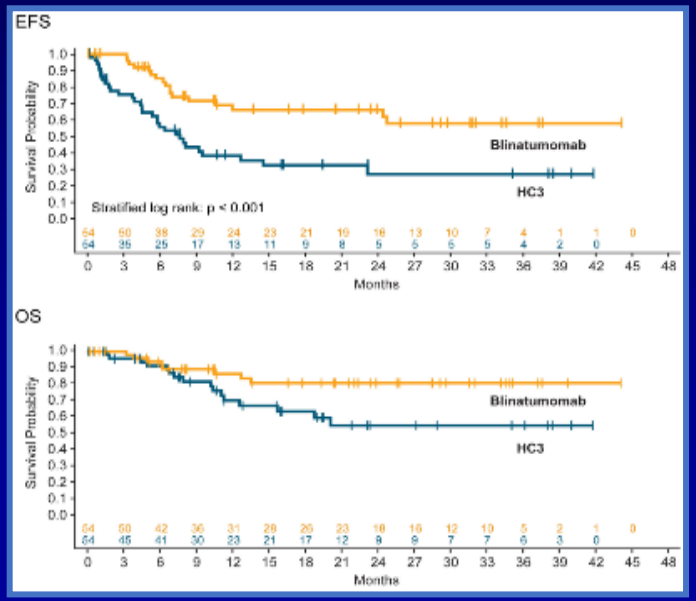
Brown et al. *JAMA*. 2021:325(9):833-842.

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%)

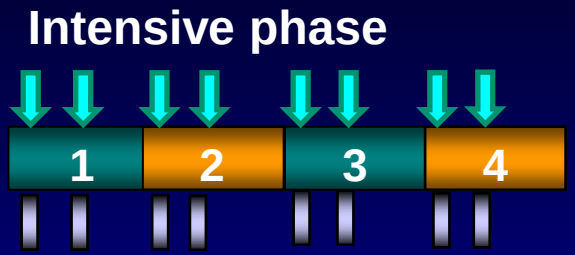
Brivio et al. *Blood*. 2020;136:abstract 164.

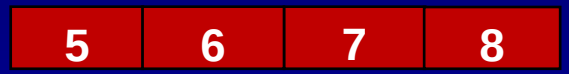
Mini-HCVD + INO + Blina in ALL: Design

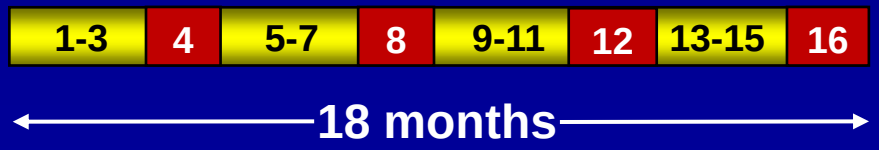
- Dose reduced HyperCVD for 4–8 courses
  - Cyclophosphamide (150 mg/m^2 ×6) 50% dose reduction
  - Dexamethasone (20 mg) 50% dose reduction
  - No anthracycline
  - Methotrexate (250 mg/m^2) 75% dose reduction
  - Cytarabine (0.5 g/m^2 × 4) 83% dose reduction
- Inotuzumab on D3 (first 4 courses)
  - 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.

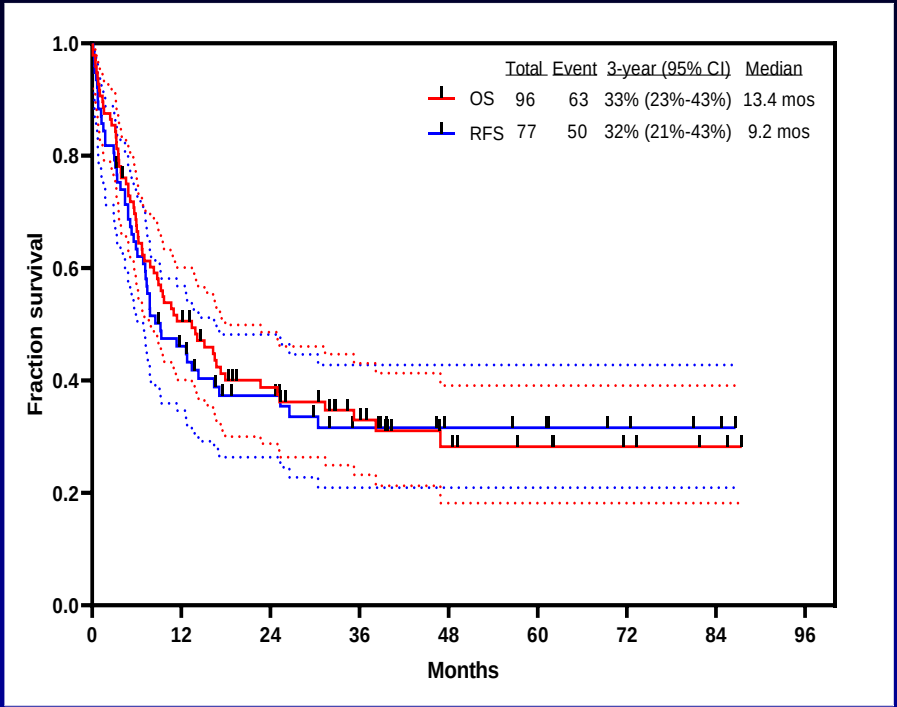
Mini-HCVD + INO ± Blina in R/R ALL (N = 96)

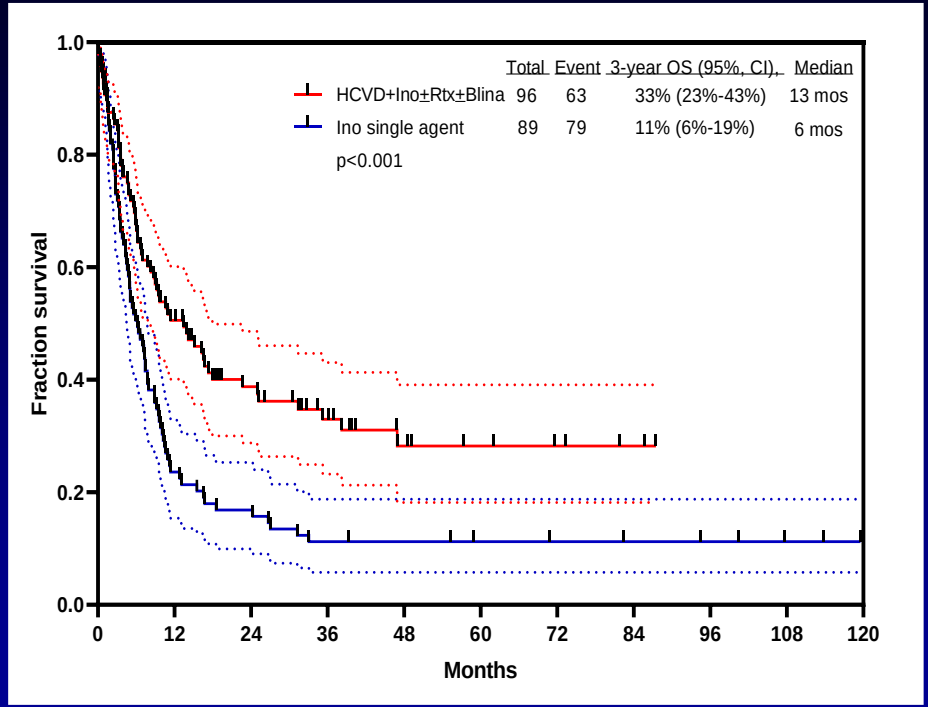
Characteristic	Category	No. (%)
Age (year)	Median [range]	37 [17–87]
Gender	Male	45 (47)
ECOG PS	2+	18 (19)
Salvage Status	S1 S1, Primary Refractory S1, CRD1 <12 months S1, CRD1 ≥12 months S2 ≥S3	64 (67) 8 (8) 25 (26) 31 (32) 18 (19) 14 (15)
Prior ASCT		19 (20)
Karyotype	Diploid T(4;11) Ho-Tr Complex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

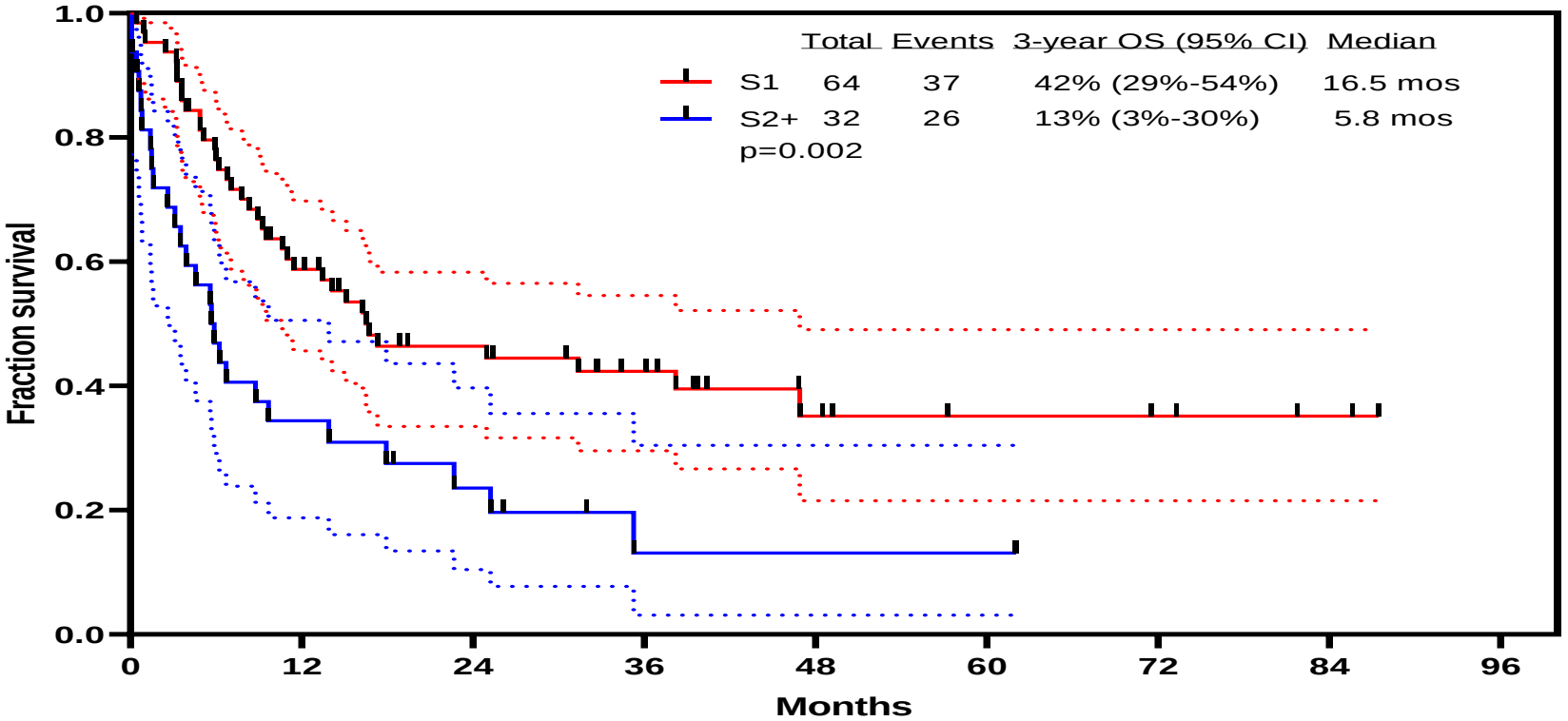




	Single dose (n = 67)	Fractionated lower dose followed by blina (n = 29)
VOD (%)	9 (13)	1 (3)

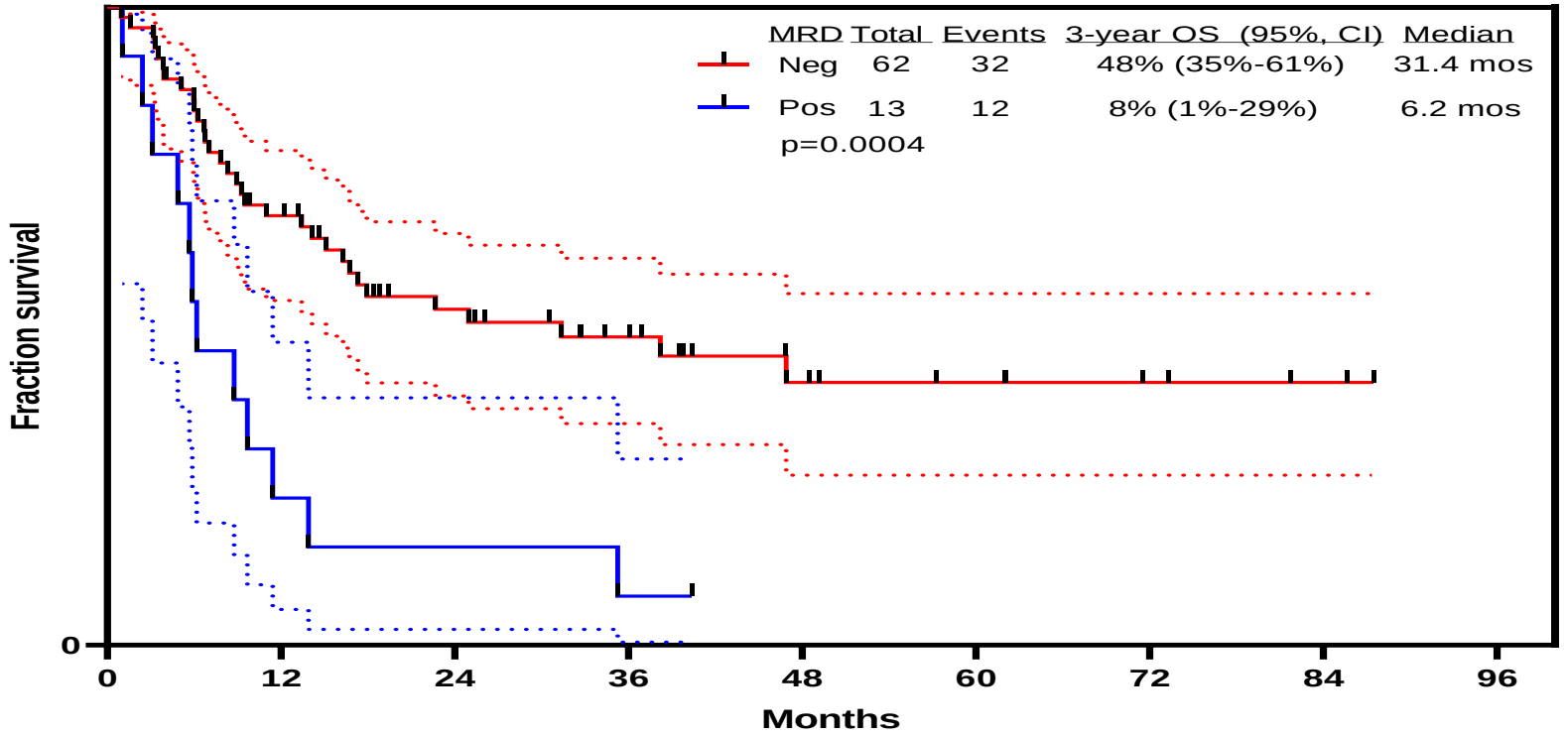
Sasaki et al. *Blood.* 2020;136: abstract 1895.

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



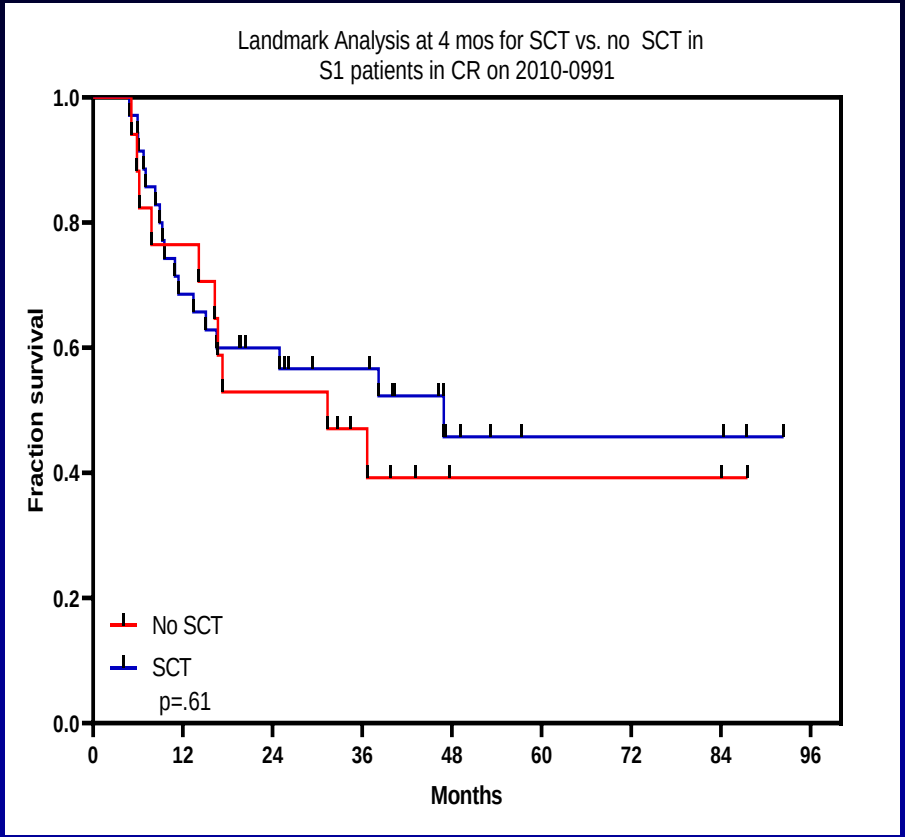
Rafei et al. *Blood.* 2020;134: abstract 1932.

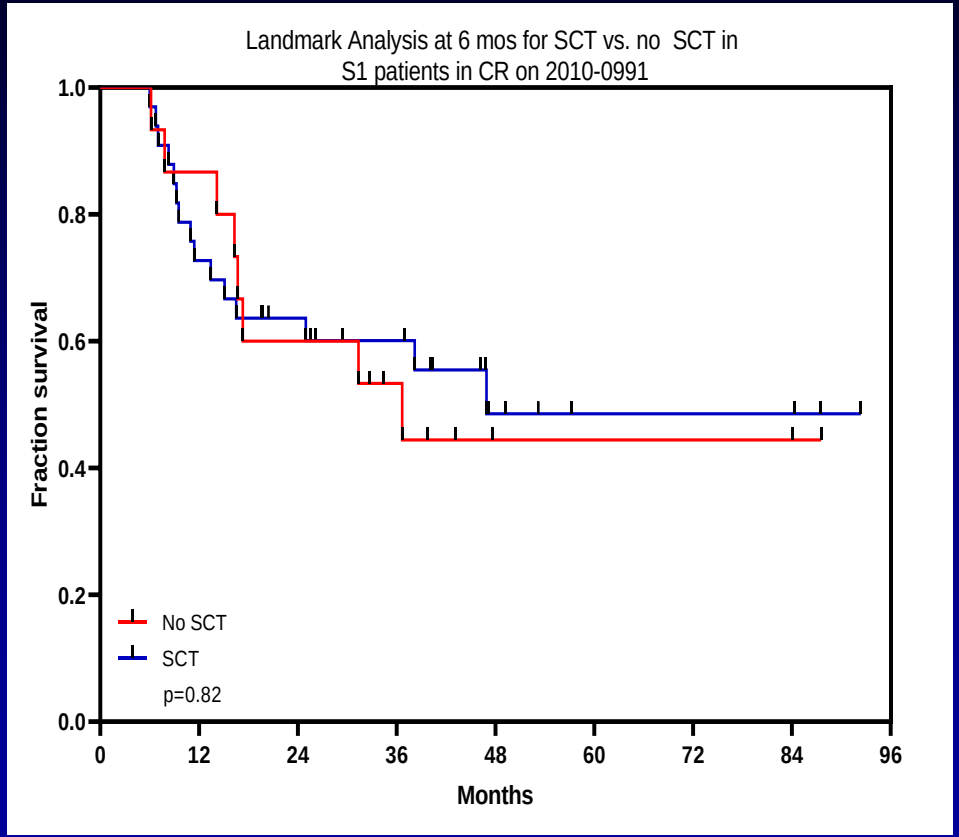
Mini-HCVD + INO ± Blinatumomab in R/R ALL
OS by MRD Status



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

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

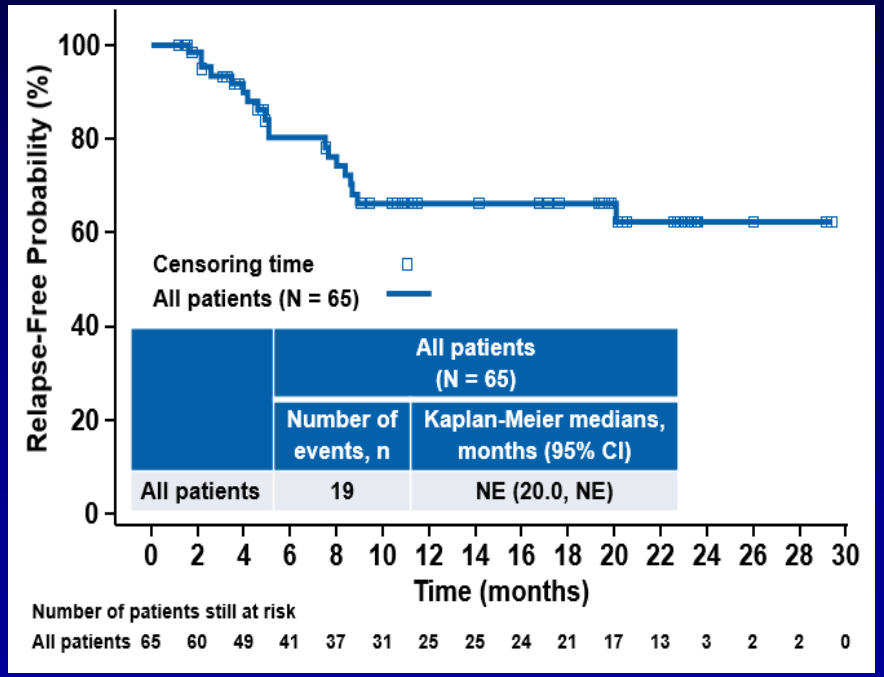


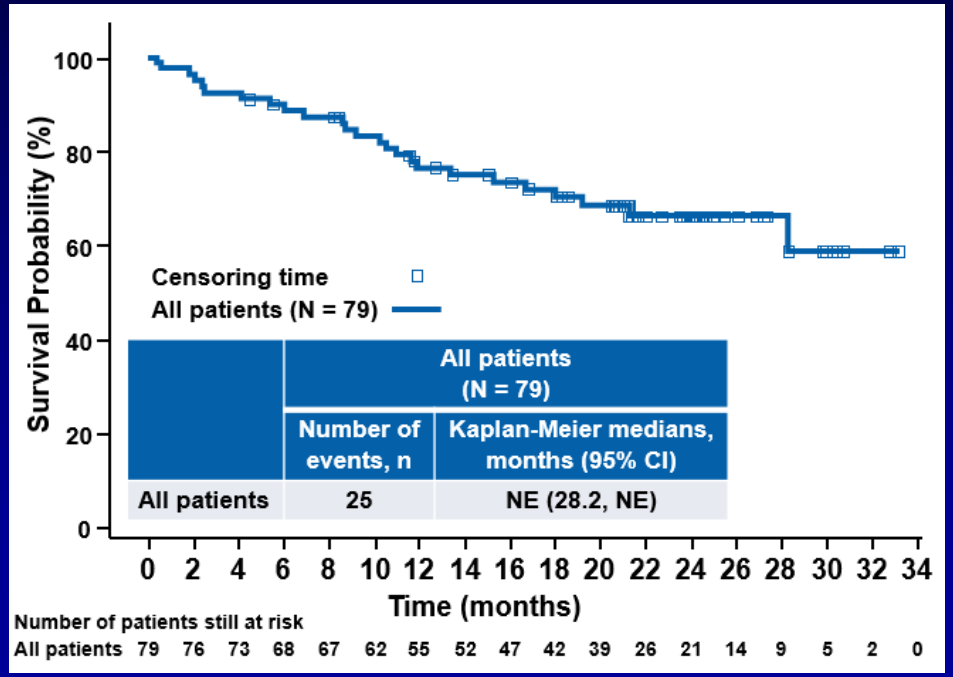


Rafei et al. *Blood*. 2020;134: abstract 1934.

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%

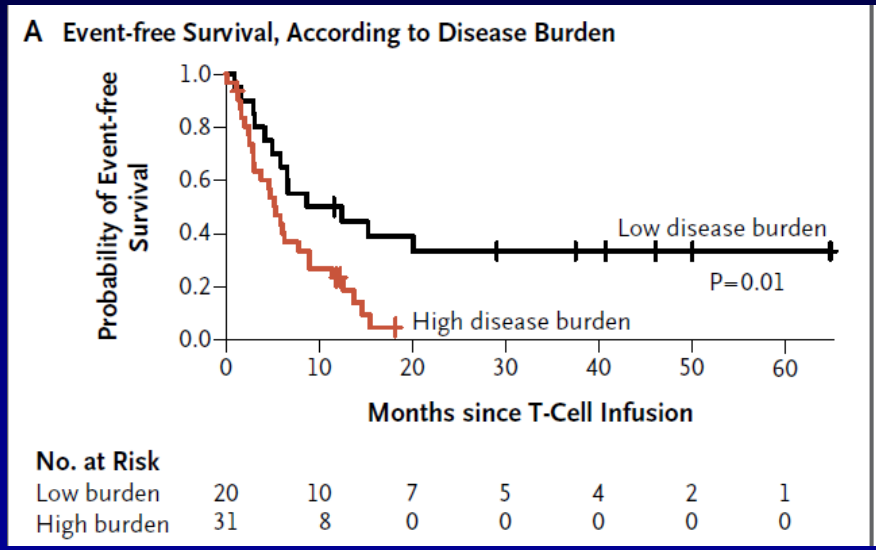


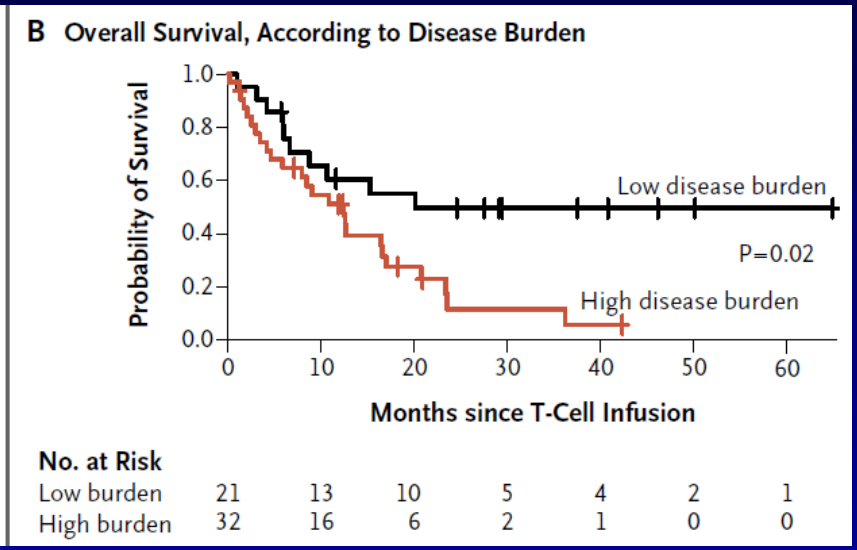


Grupp et al. EHA 2019. Abstract S1618.

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

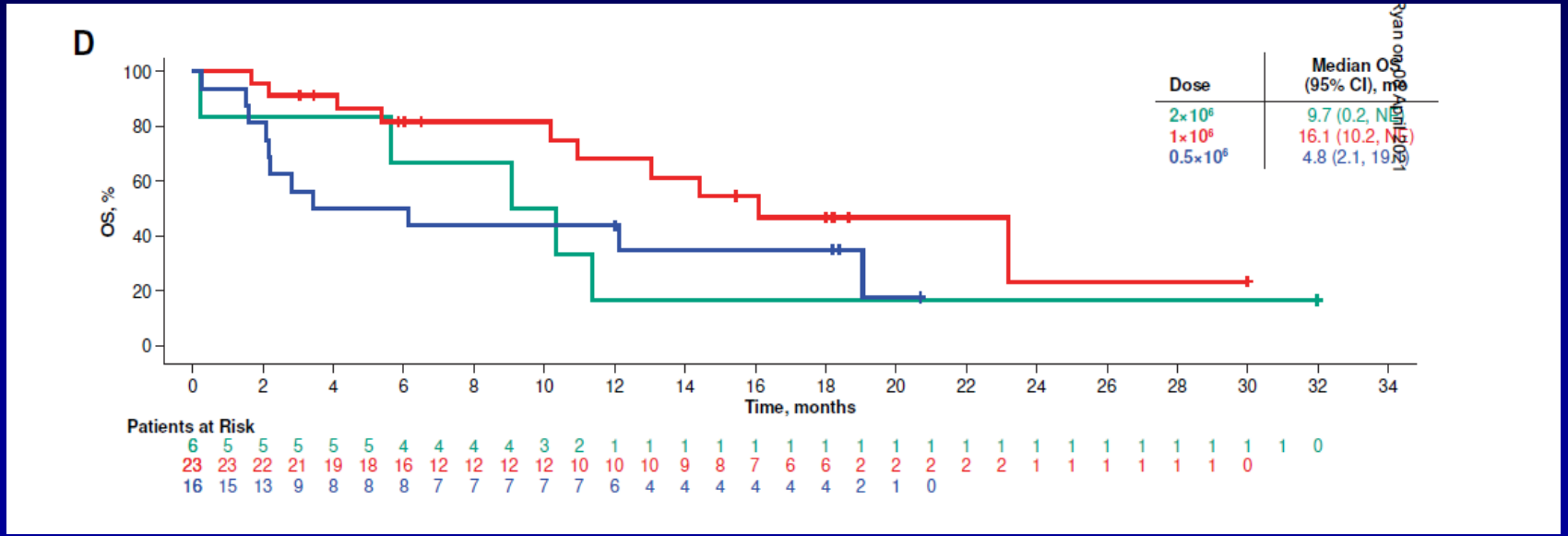
Median OS
Low tumor burden (MRD+): 20.1 mos
High tumor burden: 12.4 mos

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%

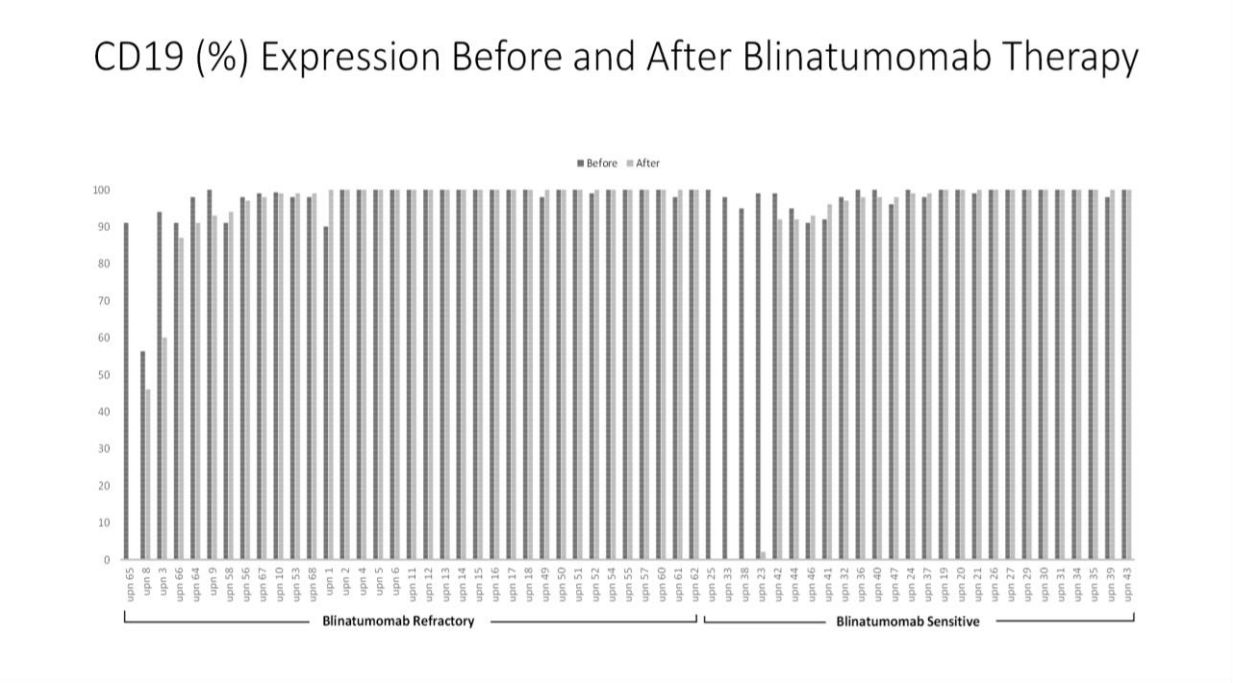


Shah et al. *Blood*. 2021, in press.

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

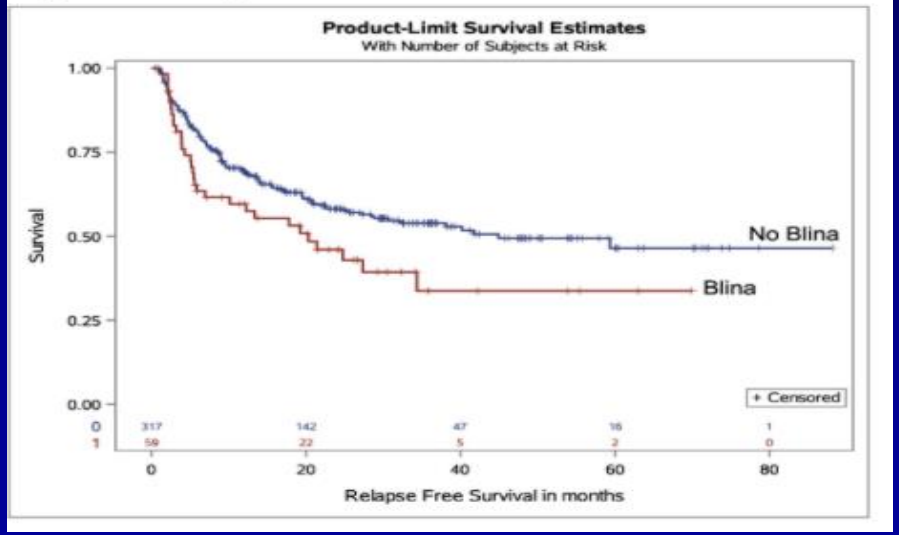
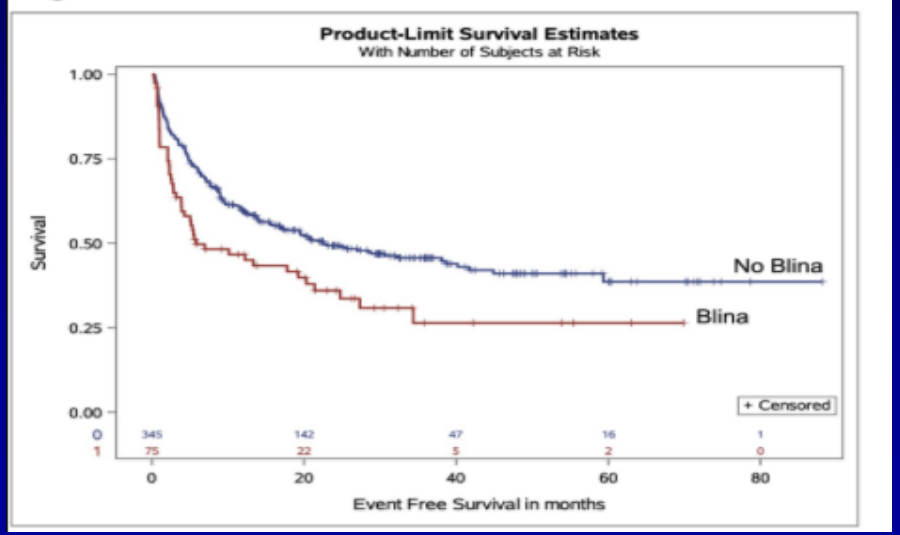


Figure 1B. Event Free Survival



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

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Clinical Hematology Department
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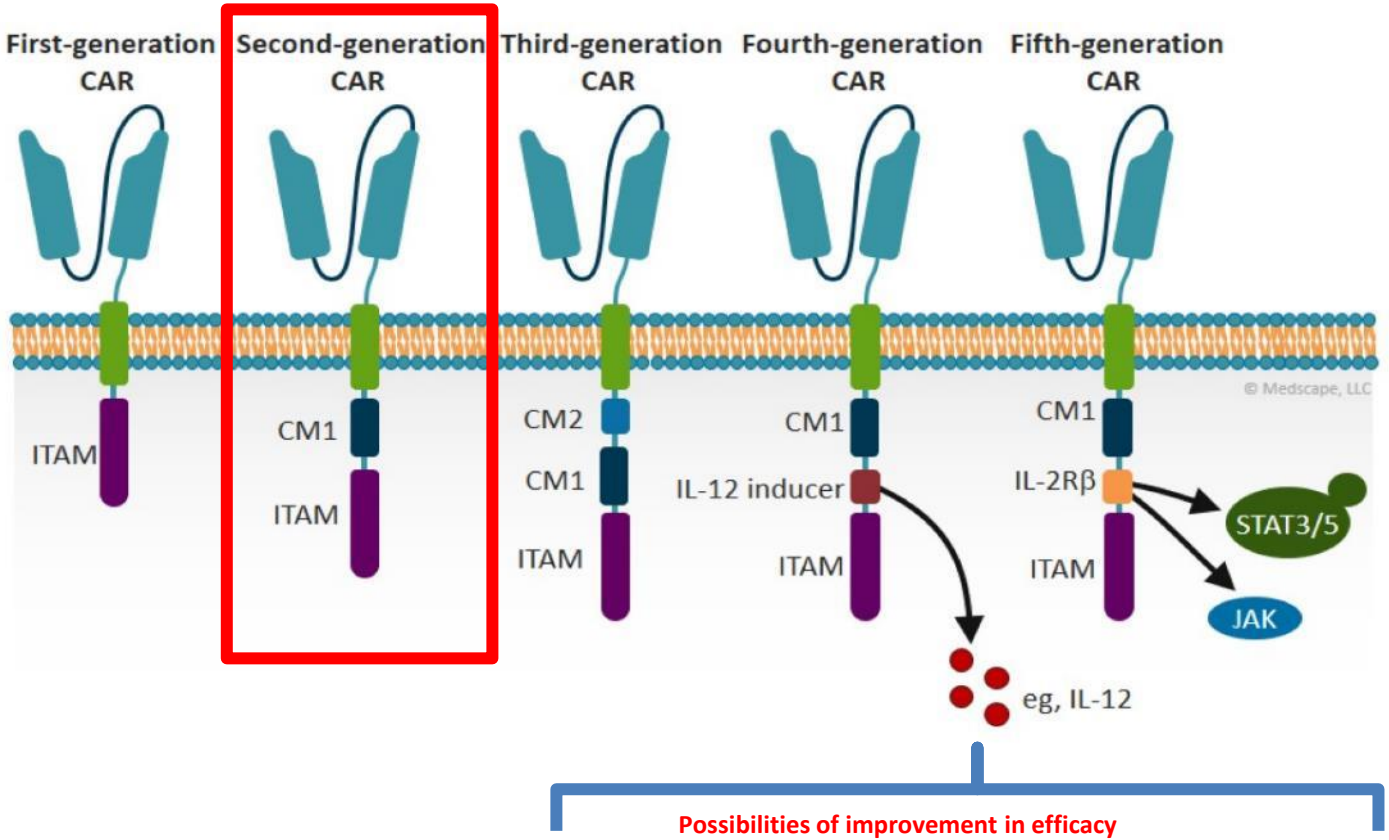
Institut de Recerca contra la Leucemia Josep Carreras
Badalona, Spain

Differences in CAR T-Cell Therapies



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

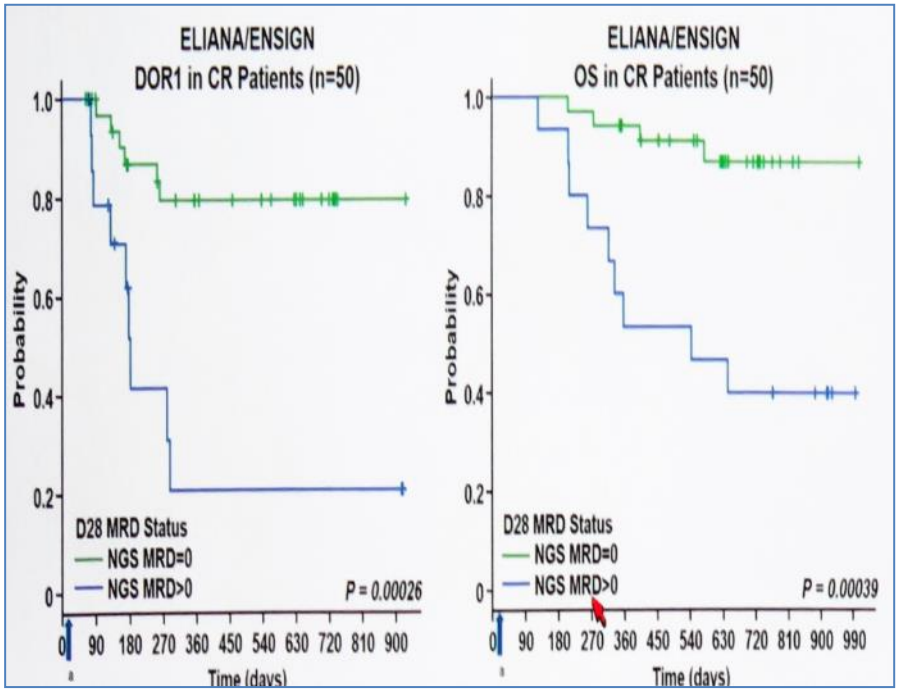
Second-Generation CD19 CAR T in R/R Adult ALL

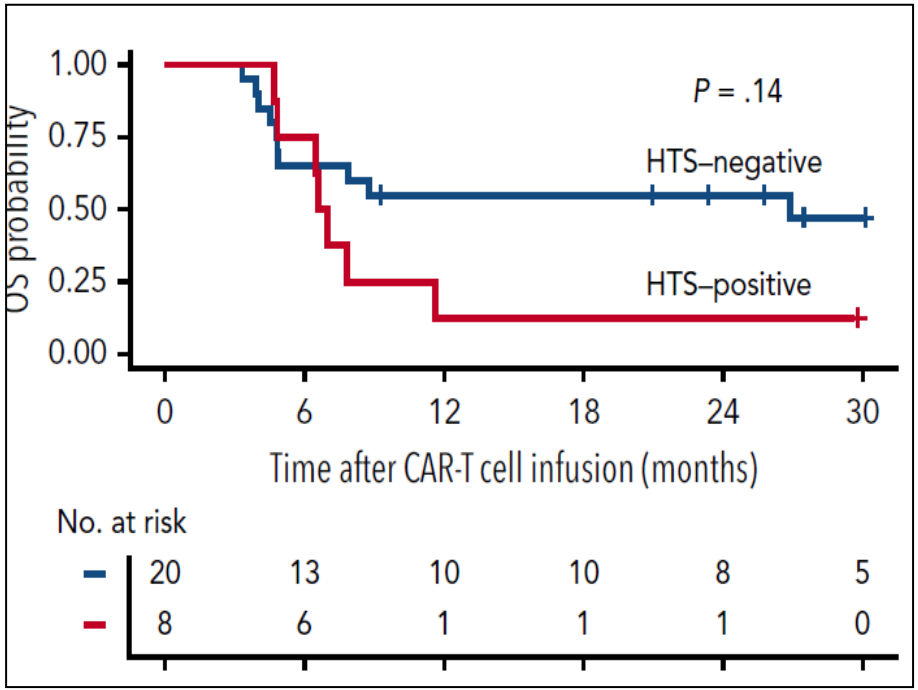
Study	N	Age, Median (range)	CR, %	MRD– in CR, %	Relapse (%)	PFS	OS
UPenn	35	33 (20-70) Single dose, low: 9 Single dose, high: 6 Fractionated dose, high: 20	33 50 90			0% 17% 49% (24 mo)	22% 17% 73% (24 mo)
MSKCC	53	44 (23-74)	83	67	57	Median: 6.1 mo	Median: 12.1 mo
FHCRC	53	39 (20-76)	85	85	49	Median: 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

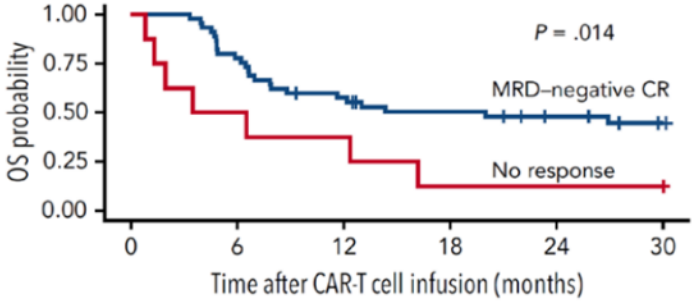
4% (N=2) extramedullary only

32% (N=17) MRD pos

- 3 extramedullary

85% in CR and MRD neg after infusion

Overall survival after infusion



Prognostic factors for EFS

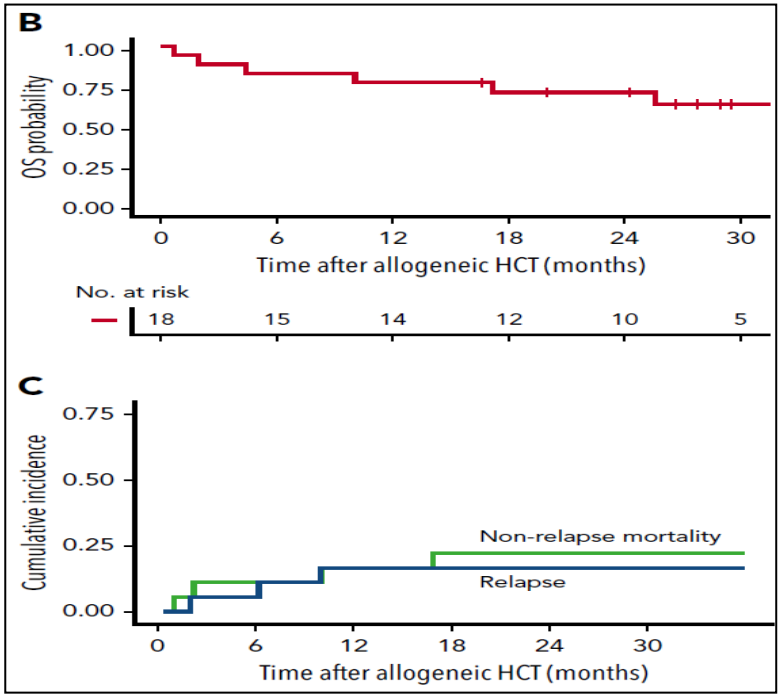
Variable	Multivariable analysis		P
	HR	95% CI	
LDH prelymphodepletion (per 100 U/L increment)	1.39	1.11-1.73	.004
Platelets prelymphodepletion (per 50 000/μL increment)	0.74	0.53-1.03	.069
Fludarabine added to lymphodepletion	0.25	0.15-0.78	.003
HCT after CAR T-cell therapy	0.39	0.13-1.15	.088

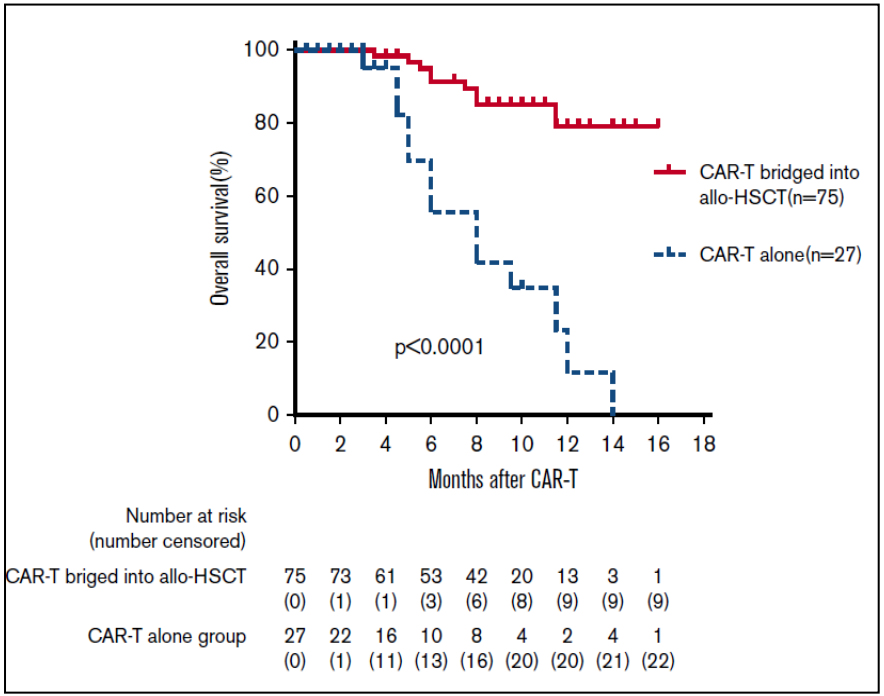
EFS, event-free survival.

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.

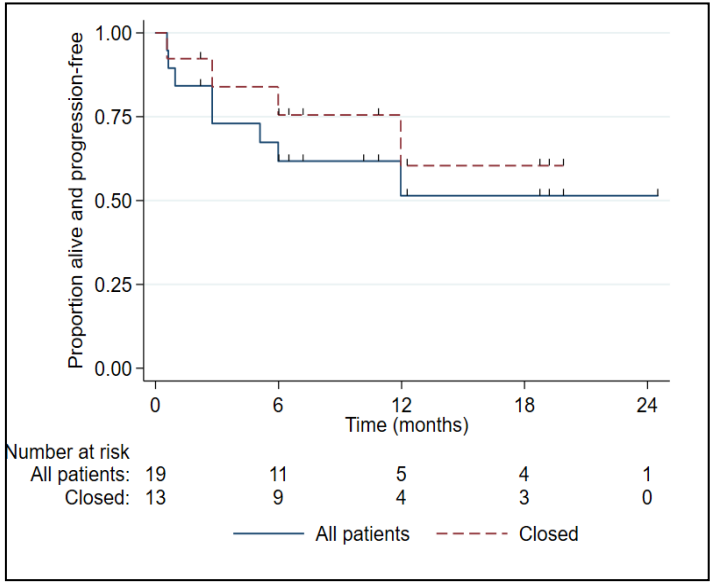
Zhang X, et al. *Blood Adv.* 2020;4:2325-2338.

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%



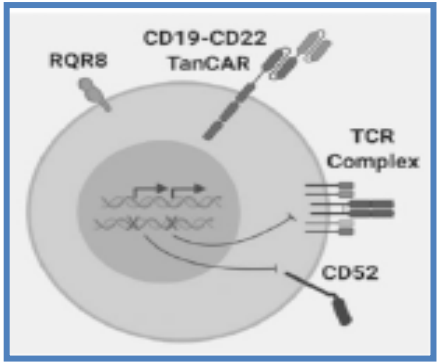
Roddie C, et al. EHA 2020. Abstract S119; SOHO 2020; ASH 2020. Abstract 160.

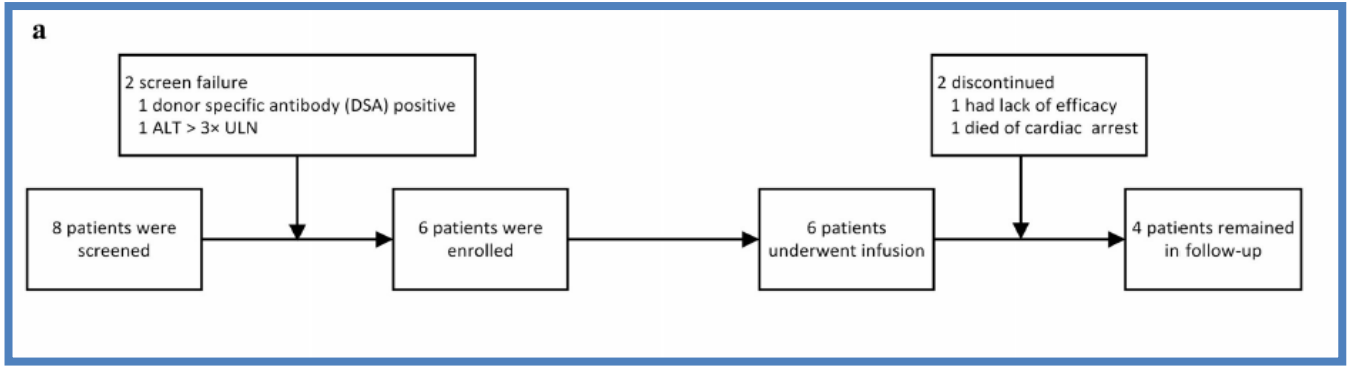
Autologous Dual CAR T 19/22

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)

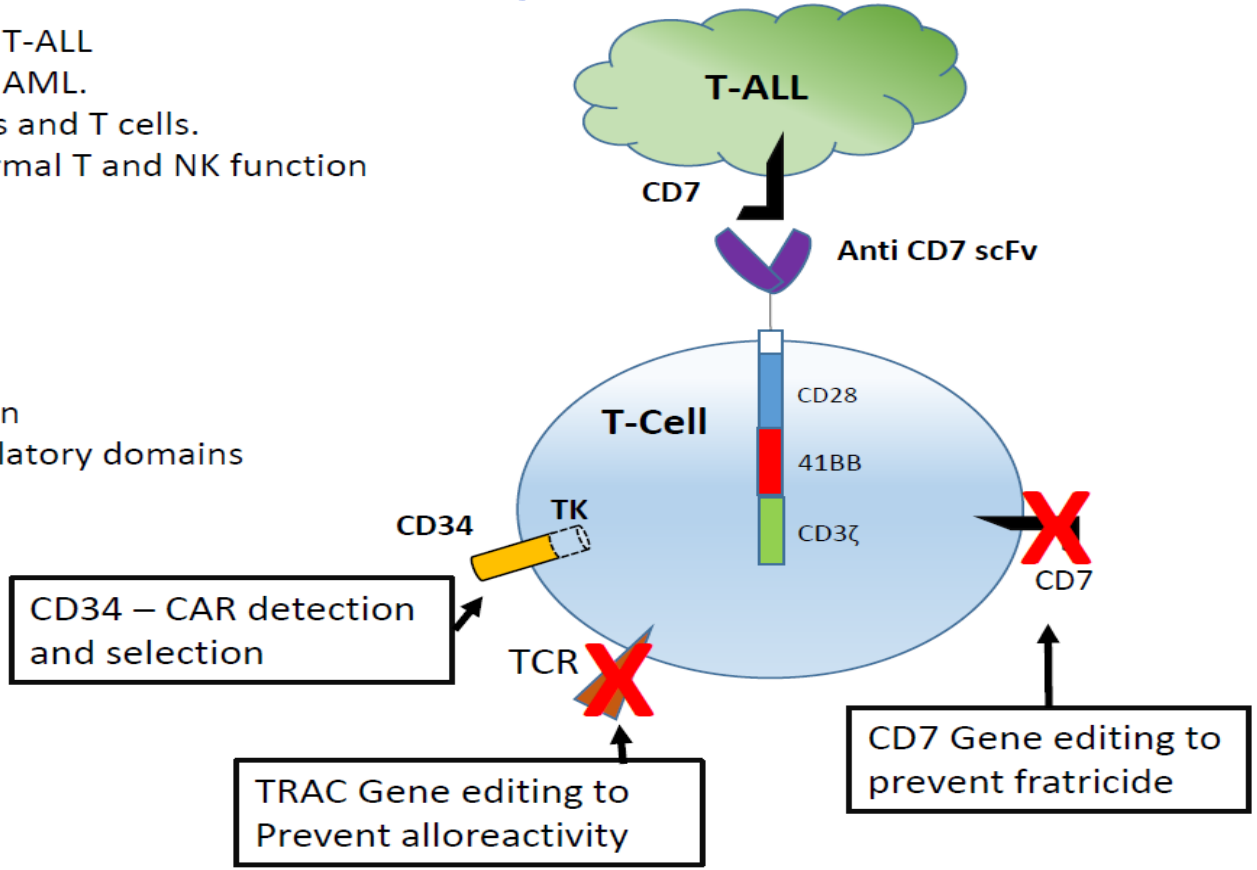
Hu Y. *Clin Cancer Res*. 2021. doi: 10.1158/1078-0432.CCR-20-3863.

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

Leukemia board discussion

Moderator: Elias Jabbour

APTITUDE HEALTH

Global Leukemia Academy

Leukemia board discussion: Cases – important details for consideration throughout LATAM, part 1

María Sara Felice

APTITUDE HEALTH®

Case report: AYA patient with ALL, severe toxicity, and 2 relapses

Maria S. Felice, MD, PhD
Hematology and Oncology Department
Buenos Aires, Argentina

SAHOP
Sociedad Argentina de Hemato-Oncología Pediátrica

Case presentation

- Adolescent boy, 18.9 years old
- When he was 11 years old, he was diagnosed with a common ALL
- G-banding: 47,XY,+5[1],47,XY,+8[1]/46,XY[18]
- RT-PCR: negative for *BCR-ABL1, KMT2A-AF1, ETV6-RUNX1, TCF3-PBX1*
- MLPA: no data available

- PGR (WBC 3,400, 0% blasts)
- MRD day 15: 60% blasts → **HR patient (ALLIC-2009)**
- MRD day 33: 1.5% blasts
- MRD day 78: not evaluable

- **SAE during induction**: osteoarthritis of knee due to *Staphylococcus aureus* and *Enterobacter cloacae*
- **SAE after HR block**: infection due to *Penicillium*
- 2-year treatment completed

MLPA, multiplex ligation-dependent probe amplification.

Outcome

- **First relapse:** hematologic, 34 months from CR1
- Common, 46,XY,-?15,+mar[2]/46,XY[3], RT-PCR: idem. MLPA without *IKZF1* deletion
- Clofarabine + cyclophosphamide + cytarabine (CYCLET) → **CR2**
- MRD TP1, TP2, TP3, and TP4 (previous maintenance): negative

- **Several SAE after CYCLET blocks**: febrile neutropenia, respiratory infection (adenovirus, confirmed by PCR)
- Herpes zoster in thorax
- TC thorax with micronodular and TC paranasal sinus: compromise maxillary sinus
- Sepsis due to *Streptococcus viridans, S. mitis, S. oralis*
- Sepsis due to *Salmonella* no typhi → ICU
- Not MFD and no MUD; 2 years of treatment completed

MLPA, multiplex ligation-dependent probe amplification; CYCLET, clofarabine, cyclophosphamide, cytarabine.

Q

Outcome

- **Second relapse:** hematologic, 25 months from CR2. Same phenotype and genetic-molecular findings

Possible treatment options

a. Palliative care?
b. Third-line chemotherapy?
c. HSCT with no previous chemotherapy?
d. Immunotherapy?
e. Repeat any of the previous schedules of chemotherapy?

Outcome

- **Second relapse:** hematologic, 25 months from CR2
- Chemotherapy third-line (VCR, Peg-Asa, Dexa, and etoposide (oral) **CR3** → IB
- MRD TP1: **0.44%, TP2: 1.4%, TP3: 1.56%**
- **Several SAE during induction:** sepsis, suspected deep fungal infection, neutropenic enteritis

- **Blinatumomab**: 1 cycle (fever and febrile neutropenia) → MRD: **0.005%**
- HSCT with a MUD
- MRD day +30, day +100, day +180, day +270, and day +365: **negative**
- Alive in CR3 and excellent performance status: +92 months from diagnosis

Global Leukemia Academy

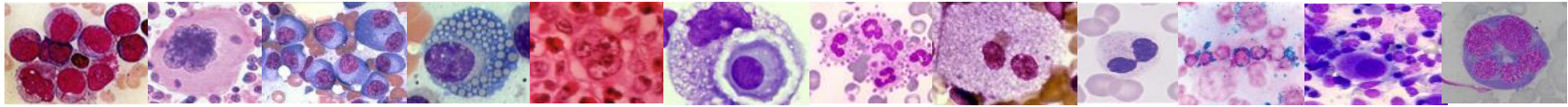
Leukemia board discussion: Regional challenges in times of COVID-19

Roberta Demichelis

APTITUDE HEALTH®

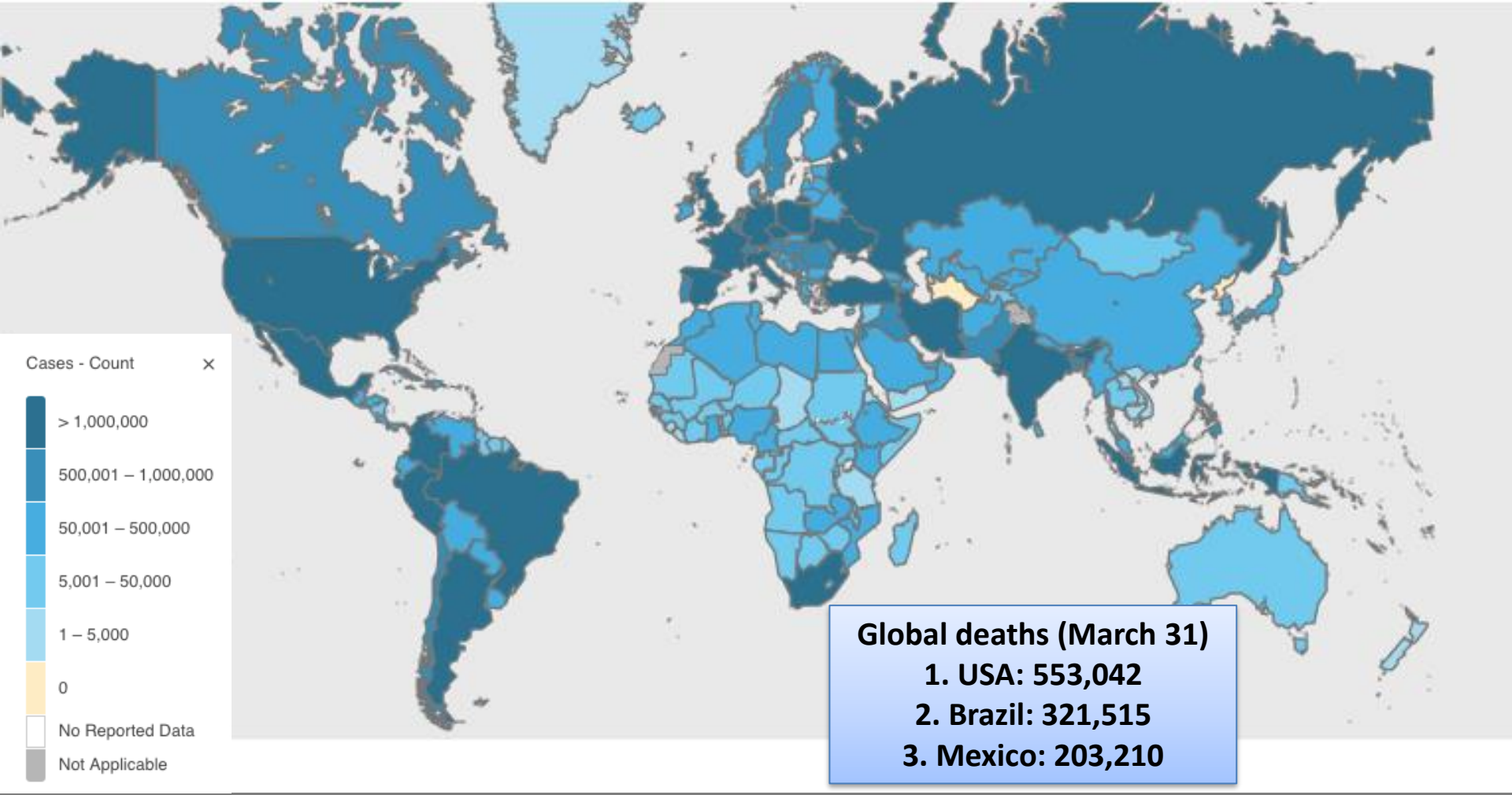
Regional Challenges in Times of COVID-19

Dra Roberta Demichelis
INCMNSZ
Mexico City



DISCLOSURES

- **Advisory/speaker: AbbVie, Amgen, Celgene, Novartis**
- **Research funding: Novartis**



Global deaths (March 31)
1. USA: 553,042
2. Brazil: 321,515
3. Mexico: 203,210

https://covid19.who.int/. https://coronavirus.jhu.edu/map.html

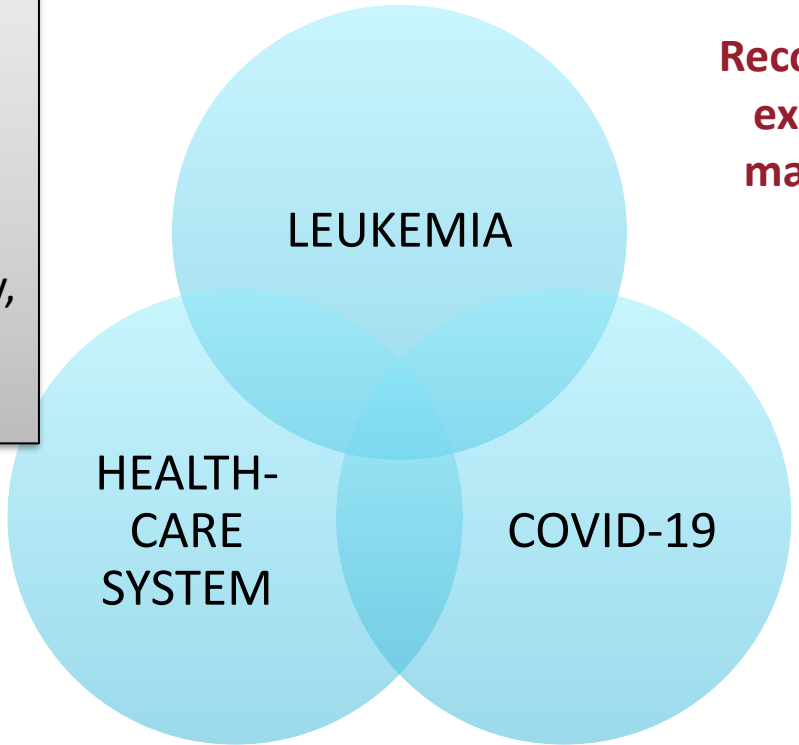
THE PROBLEM

Acute leukemia

- ✓ Can't wait so long without treatment
- ✓ Need to visit the hospital (chemotherapy, transfusions)
- ✓ Use of ER and ICU

Latin America

- **Inequities in healthcare access and disparities**
- **Overwhelmed health systems**



Recommendations by field experts about the ideal management during the pandemic

- ✓ Hematologic malignancies: 3.5× risk of severe COVID-19 disease
- ✓ Acute leukemia: mortality 41% (30%–52%)

Cattaneo, et al. *Cancer.* 2020;126:5069-5076; Vijenthira, et al. *Blood.*2020;136(25):2881-2890.

CASE

59-year-old woman

- **CD20+ B-cell Ph– ALL (Feb 2020)**
- **Complex karyotype**
- **Rituximab + hyperCVAD**
  - **After induction: complete remission, MRD 0.014%**
- **First consolidation, and then . . .**
  - **COVID-19 pandemic**

AGENDA

1. Recommendations about the management of ALL during the COVID-19 pandemic

2. Real-world experience in LATAM

AGENDA

1. **Recommendations about the management of ALL during the COVID-19 pandemic**

2. Real-world experience in LATAM

RECOMMENDATIONS: INDUCTION

General	• Testing for SARS-CoV-2. If positive: delay • Use G-CSF
Ph–	• Patients at high risk for complications of myelosuppression: reduce dauno (50%), pegaspargase (1000 U/m^2)
Ph+	• TKI with steroids is favored over aggressive multiagent chemotherapy (adults) • Children: multidrug induction and TKI

RECOMMENDATIONS: CONSOLIDATION

General	• Home administration of SC cytarabine • If rituximab: consider measuring IgG and replacement • G-CSF
AlloHSCT	• Patients with high-risk ALL: go to alloHSCT (ex. 2nd CR)
If COVID-19	• Wait 14 days before continuing

RECOMMENDATIONS: OTHER

Maintenance	• Some consider 50% dose-reduction of glucocorticoids • Minimize clinic visits, use telemedicine and home blood draws
Relapsed/ Resistant	• Favor inotuzumab or quick transition to outpatient blinatumomab
Vaccines	• May not mount an effective immune response, but it is recommended • Patients with anaphylaxis to PEG-asparaginase: skin testing and if not tolerated, advise against receiving the mRNA vaccines

CASE

59-year-old woman

- CD20+ B-cell Ph– ALL (Feb 2020)
- Complex karyotype
- Rituximab + hyperCVAD
  - After induction: complete remission, MRD 0.014%
- First consolidation, and then . . .
  - COVID-19 pandemic

Hospital converted to a "COVID center"

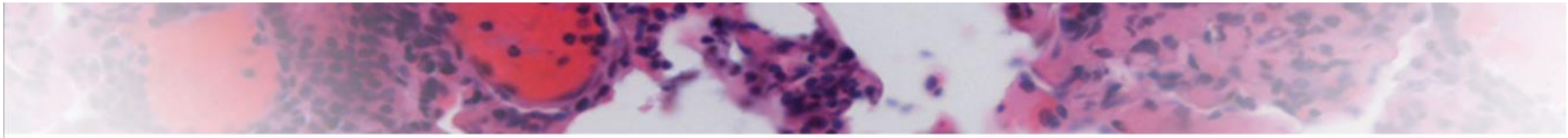
- No possibility of elective hospitalization
- No access to the emergency room for other reasons than COVID-19
- No ICU for patients without COVID-19

AGENDA

1. Recommendations about the management of ALL during the COVID-19 pandemic

2. **Real-world experience in LATAM**

REGIONAL EXPERIENCE



Treating Acute Leukemia during the COVID-19 Pandemic: A Multicenter Latin American Registry

Roberta Demichelis, Martha Alvarado, Jule Vasquez, Nancy Delgado, Cynthia Gómez, Karla Espinosa, Ana Cooke, Andrea Milan, Andrés Gómez-De León, Yu Lee, Daniel Rosales, Alvaro Cabrera, Fabian Amador, Carmina Córdova, Iván
M

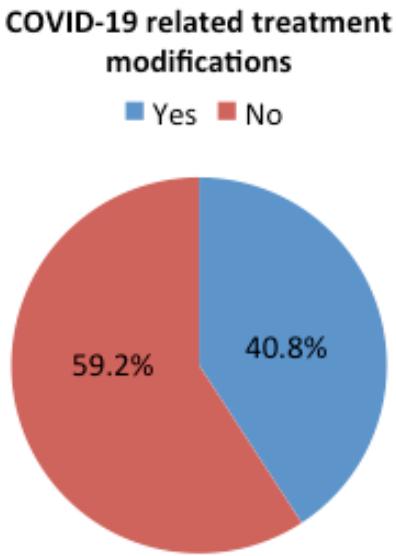
Objective: Describe the modifications in the standard care of patients with acute leukemia as well as their short-term clinical consequences during the COVID-19 pandemic

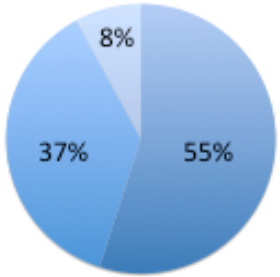
MULTICENTER, PROSPECTIVE COHORT STUDY (N = 635)

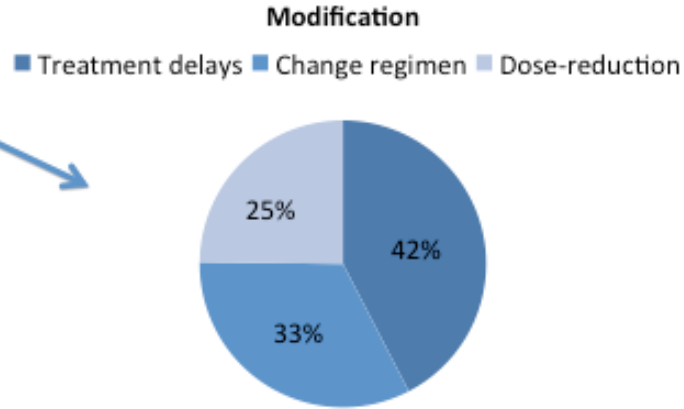
Acute leukemia since first COVID-19 case in the country to July 15
14 centers: Mexico 66.6%, Peru 20%, Guatemala 7.2%, Panama 6.1%

Demography	Age (years), median (range) Sex (female/male)	35 (14–90) 49.6%/50.4%
Diagnosis	ALL (Ph–/Ph+) AML APL	58.1%/7.2% 25.7% 9.0%
Disease status	Newly diagnosed Complete remission Relapsed/refractory	14.5% 68.3% 17.2%
Treatment status	Induction/consolidation Maintenance	59.2% 40.8%

TREATMENT MODIFICATIONS







Induction/consolidation vs maintenance:
45.5% vs 34.0%; *P* = .004

AlloHSCT was planned in 25.2% and postponed in 72.5%

Virtual consultation:
19.7%

COVID-19 INCIDENCE AND RISK FACTORS

COVID-19 incidence: 13.1%

- ✓ **Mild-moderate (54.2%) vs severe-critical (45.8%)**
- ✓ **Mechanical ventilation: 27.7%**

FACTORS	OR (95% CI); *P*
Active leukemia (newly diagnosed or relapsed)	3.46 (2.16-5.5); <.001
High-risk leukemia	1.63 (1.54-4.52); <.001
Treatment in a cancer center where elective hospitalization was possible*	2.17 (1.29-3.67); .004
Virtual appointment	0.46 (0.22-0-94); .037

**91.8% were treated in centers also designated to treat COVID-19 patients and 40.2% in centers where elective hospitalization was suspended due to the conversion of health services in response to the COVID-19 pandemic.*

Treatment modifications were not associated with a reduced risk for developing COVID-19

OUTCOMES OF THE COHORT

- **Acute leukemia and COVID-19 disease**
  - **Mortality rate: 37.7%**
- **Relapse rate: 11.3%**
- **All-cause deaths: 16.7%**
  - **Leukemia-related death (57.7%)**
  - **COVID-19 (29.2%)**
  - **Treatment-related mortality (13.2%)**

Patients who developed COVID-19 had a nonsignificantly higher relapse rate

OR 2.01 (95% CI: 1.00-4.00); P = .057

CONCLUSIONS

1. Treatment modifications in almost 50% (logistics)
2. High incidence of COVID-19 (13.1%) (*consider cutoff July 2020*)
3. High mortality of COVID-19 in patients with acute leukemia (37.7%)
4. Significant benefit of virtual consultation both in terms of risk of developing COVID-19 and mortality
5. The main cause of death was leukemia
6. A longer follow-up of this cohort will allow us to do a survival analysis

CASE: WHAT HAPPENED?

1. We reduced hyperCVAD-cytarabine dose
2. We modified the treatment to be administered in the clinic with daily visits (4-hour methotrexate infusion)
3. Pegfilgrastim
4. After 6 cycles: maintenance
5. We advanced the asparaginase/methotrexate intensifications during maintenance

One episode of febrile neutropenia treated in the clinic/outpatient.
Still in CR; no COVID-19.

FINAL THOUGHTS

- ✓ COVID-19 pandemic has been longer than expected
- ✓ A lot of collateral damage
- ✓ Telemedicine is feasible and useful in some contexts
- ✓ We need to adapt the recommendations with the emerging evidence and to different socioeconomic context and health system characteristics

THANK YOU

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Leukemia board discussion: Cases – important details for consideration throughout LATAM, part 2

Case from Patricia Gonçalves
Presented by Wellington Silva

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PATIENT CASE (1/3)

- 20 years old male patient, diagnosis of B-cell acute lymphoblastic leukemia (ALL) in February 2019
- At diagnosis: CD20 negative, Ph negative, t(12;21) and t(4;11) negative
- Bone marrow aspirate revealed 88% B-cell ALL blasts (CD19++, CD10++, CD34++, CD79++, CD22++, CD58+++, CD8+/++, HLA-DR+++, TDT++, CD13-partial, CD45+)
- He was treated with GMALL protocol, achieving MRD negativity. Central nervous system was disease free (no ALL cells)

PATIENT CASE (2/3)

- During maintenance with GMALL protocol, the patient had ALL relapse
- His health insurance did not allow immunotherapy. He was treated with hyperCVAD protocol for 2 cycles, but was refractory to this salvage strategy
- He was then treated with cyclophosphamide 200 mg/m^2 IV for 5 days, since he had 80,000 leukocytes/circulating blasts (blasts CD10+++, CD19++++, CD34++, CD38+, CD45 negative/CD81+/CD20 negative) in the peripheral blood and intense bone pain
- Central nervous system analysis showed NO involvement, including immunophenotyping negative for ALL. Following the cytoreduction, he was treated with 1 cycle (D1, D8, D15) of inotuzumab ozogamicin (Besponsa®) with great response – bone marrow analysis with flow cytometry showed 0.03% of B-cell blasts

PATIENT CASE (3/3)

- During the treatment with hyperCVAD and inotuzumab, patient related facial paresthesia. Central nervous system analyses with magnetic resonance (MR) and liquor analysis showed NO disease evidence, including immunophenotyping negative for ALL
- After the first cycle of inotuzumab, the patient developed intense headache and neck pain. New liquor analysis and central nervous system MR showed NO disease
- MR of the cervical spine showed a 10-cm compressive mass to epidural space. The biopsy showed extramedullary ALL relapse (CD34+, TDT+, CD10+, Bcl-2+, CD22+, Ki67 60%, CD19 NEGATIVE**, CD20 negative, Bcl-6 negative, CD99 negative, CD30 negative, CD3 negative)
- Now he is in radiotherapy treatment of the mass and receiving a second cycle of inotuzumab. He has a 10/10 HLA-identical sibling for allogenic bone marrow transplant. Patient is waiting for a PET scan to search for other extramedullary sites of relapse

QUESTIONS

- Since the extramedullary ALL mass is CD19 negative and the mass progressed during the hyperCVAD and inotuzumab treatment, what kind of salvage treatment do you suggest?
  - Would you consider the FLAG-IDA protocol, or other salvage chemotherapy-based protocol? Or other immunotherapy?
- Since the patient has an aggressive ALL relapse with great medullary response to inotuzumab, would you consider maintaining inotuzumab protocol associated with radiotherapy, followed by an allogenic bone marrow transplant?
- Do you consider this patient eligible for allogenic bone marrow transplant if he keeps the medullary response despite the extramedullary relapse?

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Leukemia Board Discussion

All faculty

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Session Close

Elias Jabbour

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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

Virtual Breakout: Adult Leukemia Patients (Day 2)

Chair: Elias Jabbour

TIME (UTC-3)	TITLE	SPEAKER
10.00 – 10.15	Session open • Educational ARS questions for the audience	Elias Jabbour
10.15 – 10.35	Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens • Presentation (15 min) • Q&A (5 min)	Elias Jabbour
10.35 – 10.55	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
10.55 – 11.45	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, Andre Schuh, local experts	Roberta Demichelis Wellington Silva
11.45 – 12.00	Break	
12.00 – 12.20	Personalized induction and maintenance approaches for AML • Presentation (15 min) • Q&A (5 min)	Naval Daver
12.20 – 12.40	Optimizing management of relapsed/refractory AML • Presentation (15 min) • Q&A (5 min)	Eunice Wang
12.40 – 13.15	Case-based panel discussion on regional challenges in AML care	Roberta Demichelis Wellington Silva
13.15 – 13.30	Session close • Educational ARS questions for the audience	Elias Jabbour

Virtual Breakout: Pediatric ALL Patients (Day 2)

Chair: Franco Locatelli

TIME (UTC-3)	TITLE	SPEAKER
10.00 – 10.15	Session open • Educational ARS questions for the audience	Franco Locatelli
10.15 – 10.35	First-line treatment of pediatric ALL • Presentation (15 min) • Q&A (5 min)	Lia Gore
10.35 – 10.55	Current treatment options for relapsed ALL in children including HSCT; COVID-19 considerations and vaccinations • Presentation (15 min) • Q&A (5 min)	Franco Locatelli
10.55 – 11.15	Bispecifics for pediatric ALL, focus on frontline therapy • Presentation (15 min) • Q&A (5 min)	Lia Gore
11.15 – 11.45	Case-based panel discussion: Management of long- and short-term toxicities and treatment selection in pediatric patients Panelists: María Sara Felice (ARG), Oscar González Ramella (MEX), Adriana Seber (BRA), Carlos Andres Portilla (COL)	Luisina Peruzzo Jorge Ramirez Melo Gustavo Zamperlini
11.45 – 12.30	Interactive Q&A and session close • Educational ARS questions for the audience	Franco Locatelli

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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!

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SEE YOU TOMORROW!

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