Global Leukemia Academy

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Global Leukemia Academy

Emerging and Practical Concepts and Controversies in Leukemias

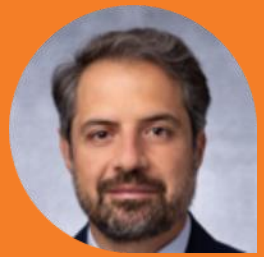
27-28 October 2021

APTITUDE HEALTH

Global Leukemia Academy

Welcome and meeting overview

Elias Jabbour and Franco Locatelli



APTITUDE HEALTH

Global Leukemia Academy

Adult/elderly ALL

Pediatric ALL

AML

CO-CHAIRS

Elias Jabbour, MD
Professor of Medicine
UT MD Anderson Cancer Center, USA

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Professor of Pediatrics
Sapienza, University of Rome and IRCCS Bambino Gesù Children's Hospital, Italy

Naval Daver, MD
Assistant Professor of Medicine
UT MD Anderson Cancer Center, USA

FACULTY

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

Josep-Maria Ribera, MD
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University Hospital Germans
Trias i Pujol, Spain

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Princess Máxima Center for
Pediatric Oncology, University
of Utrecht, The Netherlands

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St. Anna Children's Hospital,
Austria

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Centre for Clinical Haematology at the Queen Elizabeth Hospital, United Kingdom

Nicola Gökbuget, MD
University Hospital Frankfurt,
Germany

Philippe Rousselot, MD, PhD
University of Versailles Saint-
Quentin-en-Yvelines, France

Martin Schrappe, MD, PhD
University Medical Center
Schleswig-Holstein, Germany

Richard Schlenk, MD
University Hospital Heidelberg, Germany

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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
- Explore regional challenges in the treatment of acute leukemias across Europe

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Virtual Plenary Session (Day 1) 16.00 – 20.00 (CET)

Chairs – Elias Jabbour, Franco Locatelli, Naval Daver

Time CET	Title	Speaker/Moderator
16.00 – 16.10	**Welcome and meeting overview**	Elias Jabbour, Franco Locatelli
16.10 – 16.40	**Recent developments in acute leukemias**	Elias Jabbour
16.40 – 17.00	**Review of prognostic value of MRD in acute leukemias**	Josep-Maria Ribera
17.00 – 17.15	**Genetic variants in ALL – Ph+ and Ph-like**	Philippe Rousselot
17.15 – 17.35	**AYA ALL patients – what is the current treatment approach for this diverse patient population?**	Rob Pieters
17.35 – 17.45	**Break**	
17.45 – 18.05	**Bispecifics as post-reinduction therapy improve survival in high-risk first-relapse pediatric and AYA B-ALL**	Patrick Brown
18.05 – 18.25	**Therapeutic approaches in high-risk and older AML patients**	Naval Daver
18.25 – 18.45	**Current and future role of transplantation in acute leukemias**	Charles Craddock
18.45 – 19.15	**Debate on sequencing CD19-targeted approaches** • Monoclonal antibodies and bispecifics first • CAR T first • Discussion and voting	Moderator: Franco Locatelli Elias Jabbour Josep-Maria Ribera All faculty
19.15 – 19.55	**Leukemia board discussion** • Optimal treatment and patient access, regional challenges in Europe • Discussion	Moderator: Elias Jabbour Rob Pieters and Philippe Rousselot All faculty
19.55 – 20.00	**Session close**	Elias Jabbour, Franco Locatelli

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Virtual Breakout – Adult Leukemia Patients (Day 2) 17.00 – 20.00

Chairs – Elias Jabbour, Naval Daver

Time CET	Title	Speaker/Moderator
17.00 – 17.10	**ALL session open**	Elias Jabbour
17.10 – 17.30	**Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens**	Elias Jabbour
17.30 – 17.50	**Current treatment options for relapsed ALL in adult and elderly patients**	Nicola Gökbuget
17.50 – 18.20	**Case-based panel discussion on toxicity management for adult and elderly ALL patients** • Case presentation 1: Fabian Lang • Case presentation 2: Anna Torrent	Moderator: Elias Jabbour *Faculty panel*: E. Jabbour, N. Gökbuget, J.M. Ribera, P. Rousselot
18.20 – 18.30	**Break**	
18.30 – 18.35	**AML session open**	Naval Daver
18.35 – 18.55	**Personalized induction and maintenance approaches for AML**	Richard Schlenk
18.55 – 19.15	**Optimizing management of relapsed/refractory AML**	Charles Craddock
19.15 – 19.45	**Case-based panel discussion or questions to the panel on regional challenges in AML care** • Case presentation 1: Justin Loke • Case presentation 2: Sonia Jaramillo Segura	Moderator: Naval Daver *Faculty panel*: N. Daver, C. Craddock, R. Schlenk
19.45 – 20.00	**Session close**	Elias Jabbour

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Virtual Breakout – Pediatric ALL Patients (Day 2) 17.00 – 19.45

Chair – Franco Locatelli

Time CET	Title	Speaker/Moderator
17.00 – 17.15	**Session open**	Franco Locatelli
17.15 – 17.40	**How to use MRD and genetics for risk stratification and therapy guidance in pediatric ALL**	Rob Pieters
17.40 – 18.05	**First-line treatment of pediatric ALL**	Martin Schrappe
18.05 – 18.30	**Current treatment options for relapsed ALL in children, including HSCT considerations**	Franco Locatelli
18.30 – 18.55	**Bispecific T-cell engagers for pediatric ALL**	Christina Peters
18.55 – 19.25	**Case-based panel discussion on management of long- and short-term toxicities in pediatric ALL patients** • Case presentation 1: Francesca Del Bufalo • Case presentation 2: Natalia Zubarovskaya	Moderator: Franco Locatelli *Faculty panel:* R. Pieters, F. Locatelli, P. Brown, C. Peters, M. Schrappe
19.25 – 19.45	**Final discussion, Q&A, and session close**	Franco Locatelli

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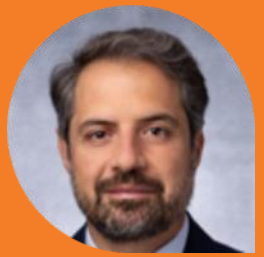
Introduction to the Zoom platform

Elias Jabbour



APTITUDE HEALTH

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Functionality and settings – Q&A

After each presentation, there will be 5 min for Q&A

Questions can be asked live or via the Q&A box

> **Live** – use **“Raise Hand”** function at the bottom of your screen
  – You will be given permission to speak
> **Q&A box** – type your question in the Q&A box

zoom

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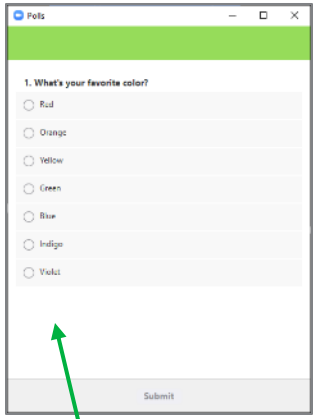
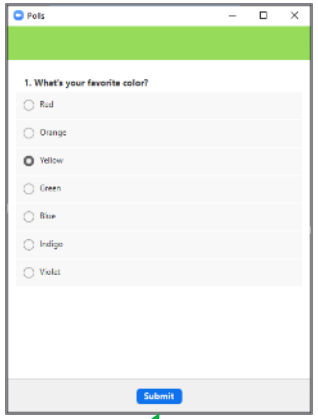
Functionality and settings – polling questions

Desktop View



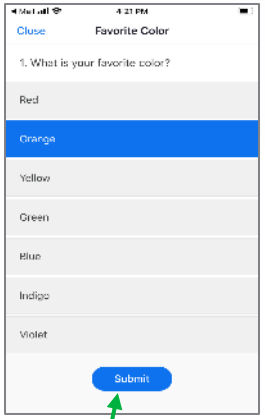
Choose Your Answer
Click on the answer (or answers if multiple choice)



Select Submit
After choosing your answer, select submit to finalize

Mobile View

Choose Your Answer
Click on the answer (or answers if multiple choice)



Select Submit
After choosing your answer, select submit to finalize

zoom

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Question 1

Where are you from?

a) United Kingdom
b) Germany
c) Spain
d) France
e) Italy
f) The Netherlands
g) Poland
h) Russia
i) Other country in Europe
j) Outside Europe

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Question 2

Which patients do you treat?

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

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

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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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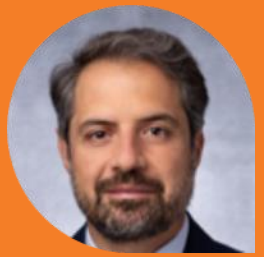
Recent developments in acute leukemias

Elias Jabbour



APTITUDE HEALTH

Recent Developments in Acute Leukemia

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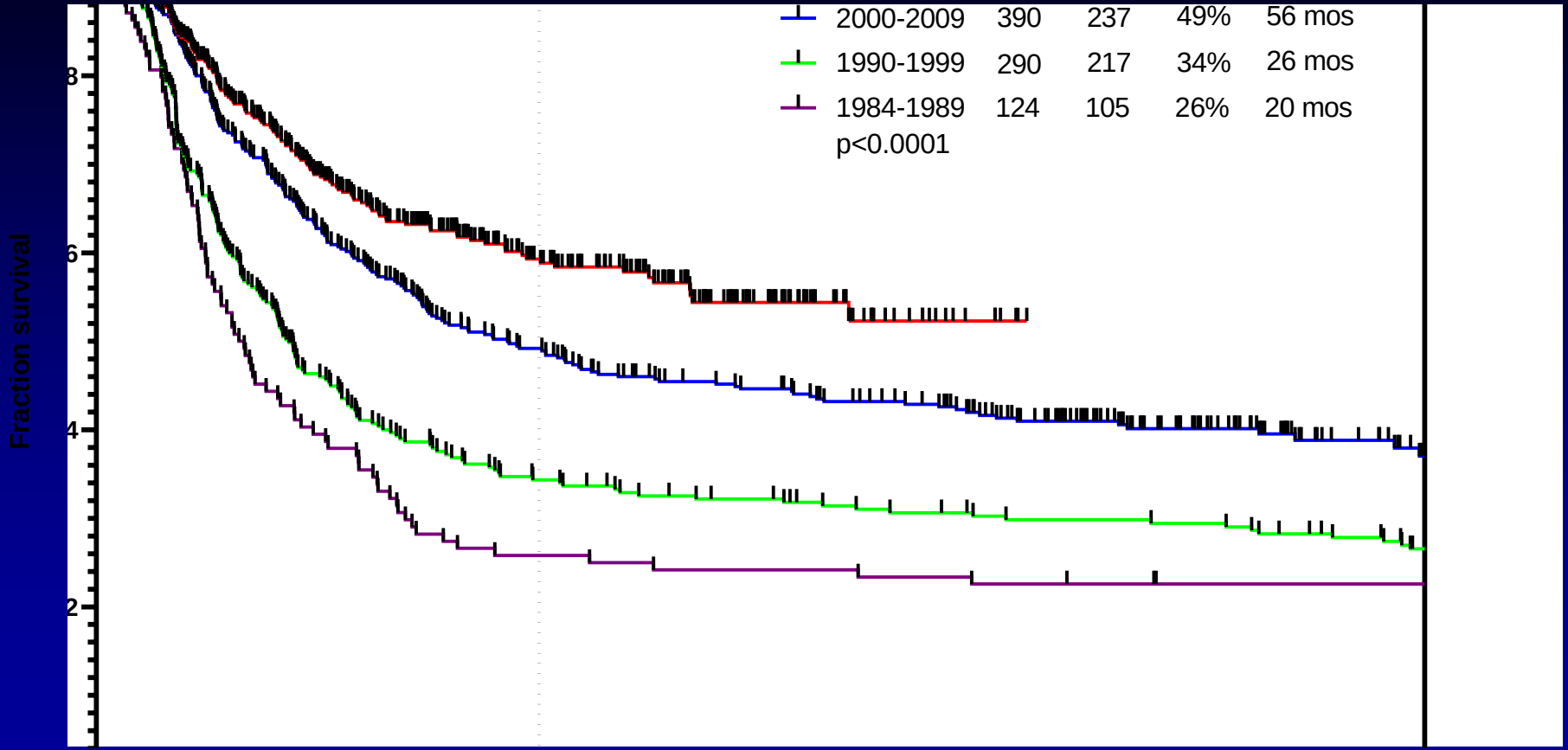
The University of Texas MD Anderson Cancer Center, Houston, TX

GLA, October 2021

Conflict of Interest Disclosure

- Research grants
  - Pfizer, Takeda, Amgen, AbbVie, Novartis
- Consultancy and advisory roles
  - Pfizer, Takeda, Amgen, AbbVie, BMS

ALL: Survival by Decade (MDACC 1985–2020)



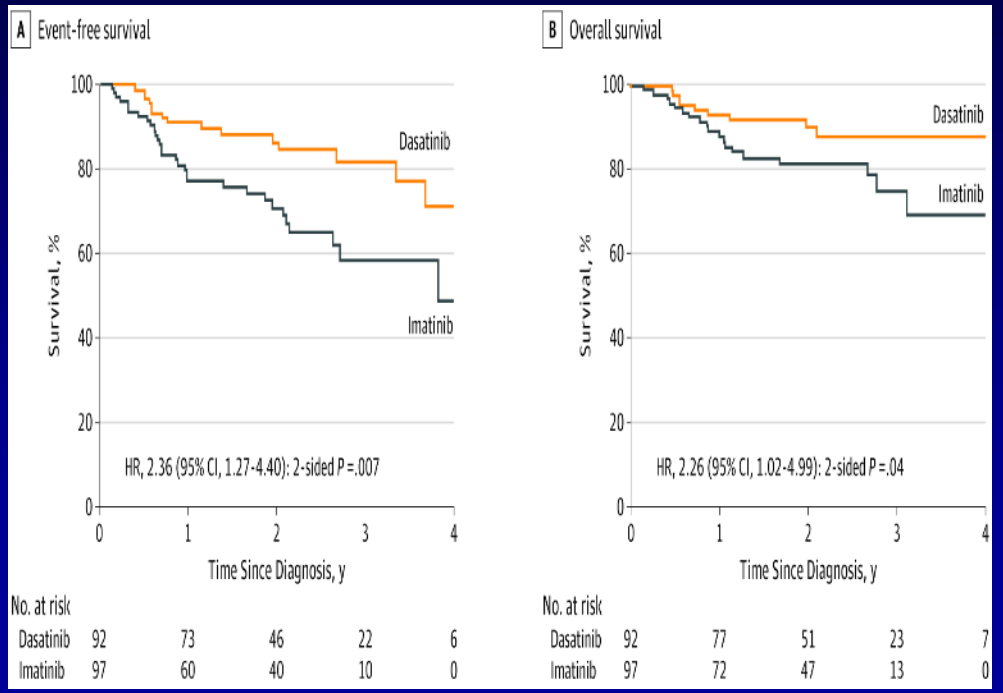
Reasons for Recent Success in Adult ALL

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

Dasatinib vs Imatinib in Pediatric Ph-Positive ALL

- 189 pts randomized Rx + dasatinib (n = 92) or imatinib (n = 97)
- Median F/U 26 mos; Triple IT 19 or 21

% 4-yr	Dasatinib	Imatinib	*P* Value
EFS	71	49	.005
OS	88	69	.04
Relapse	20	34	.01
CNS	2.7	8.4	.06

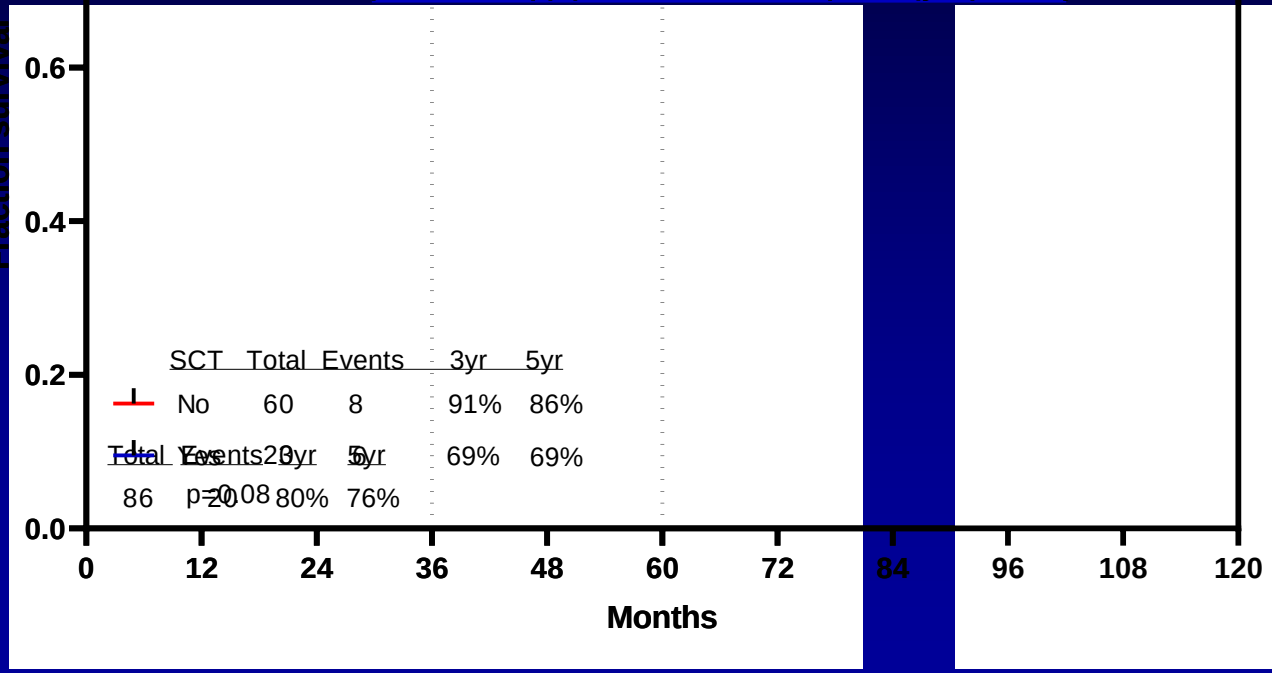


Shen et al. *JAMA Oncol.* 2020;6:358-366.

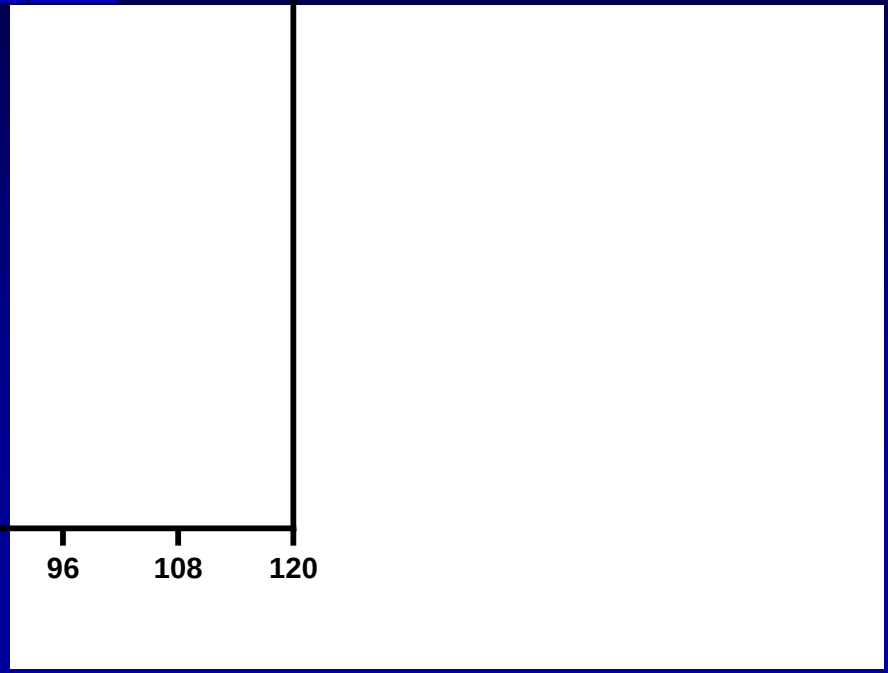
HyperCVAD + Ponatinib in Ph+ ALL

- 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

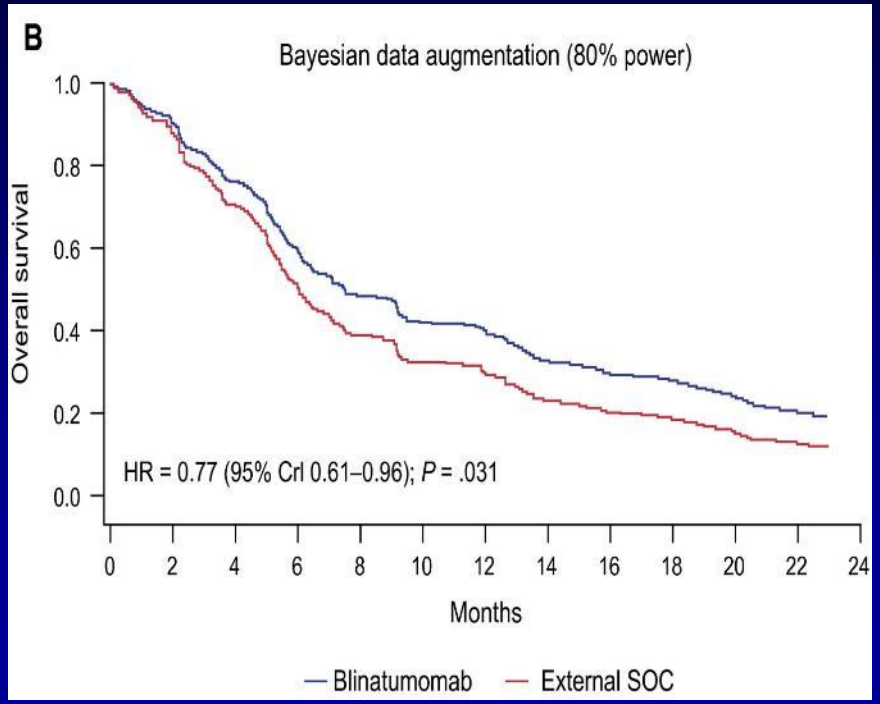


Jabbour E, et al. *Lancet Hematol.* 2018;618:(and update December 2020); Short et al. *Blood.* 2019;134:Abstract 283.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

Blina vs SOC

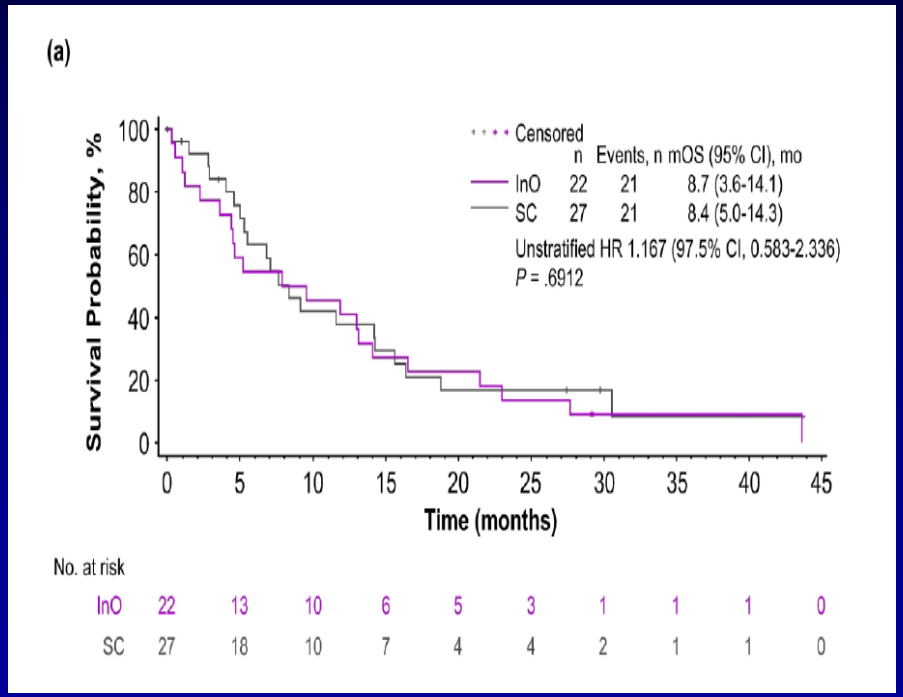
- CR/CRh 36% vs 25%
- 1-yr OS 41% vs 31%



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

Ino vs SOC

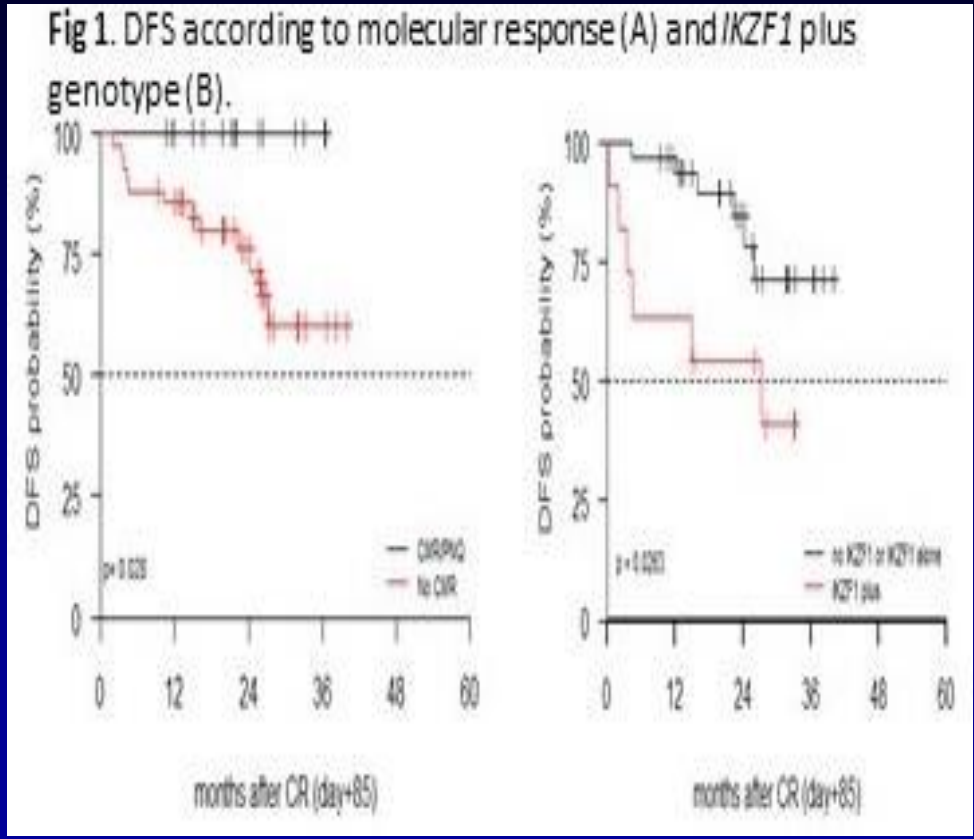
- CR/CRi 73% vs 56%
- 1-yr PFS 20% vs 4.8%



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

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

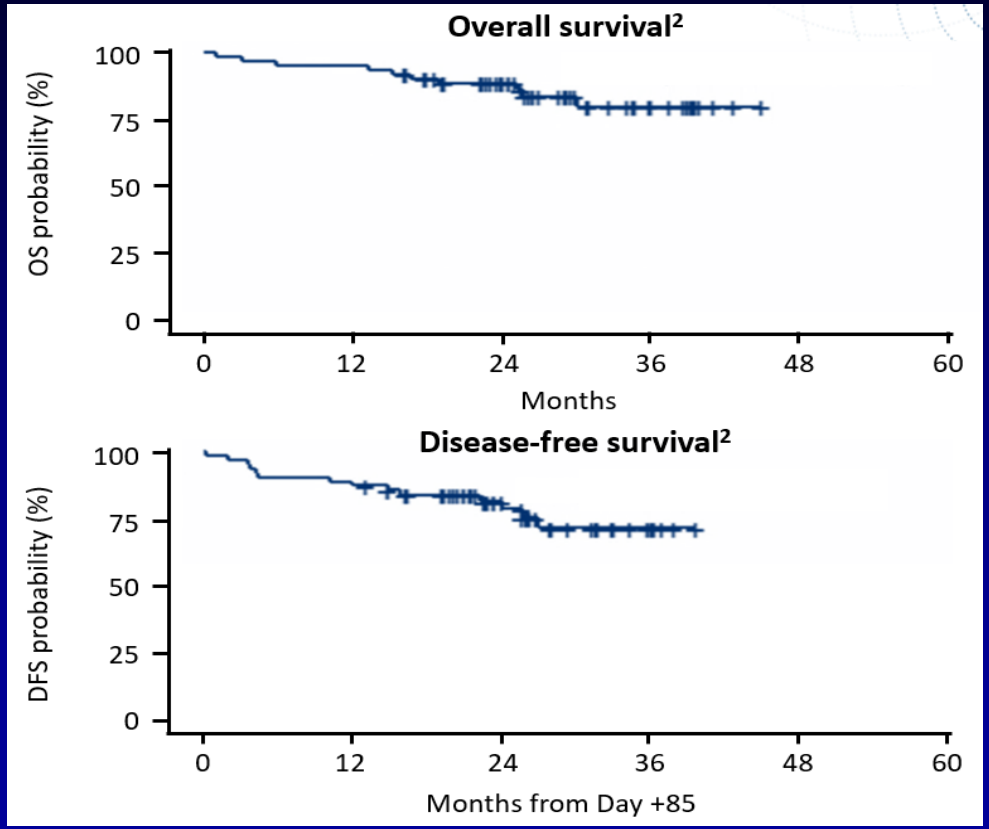
- 64 pts Rx; median age 54 yrs (24-82). Median FU 27 mos
- Molecular response (32/53 = 60%)
  - 22 CMR (41%)
- 29/58 (50%) who started blina has SCT
- 9 relapses: 4 hematologic, 4 CNS, 1 nodal
- 24-mos OS 88%, DFS 80%
- Outcome better if MR: DFS 100% vs 80% (*P* = .028)
- Outcome worse if IKZF1+: 2-yr OS 84% vs 54% (*P* = .026)



Chiaretti. EHA 2021. Abstract S112.

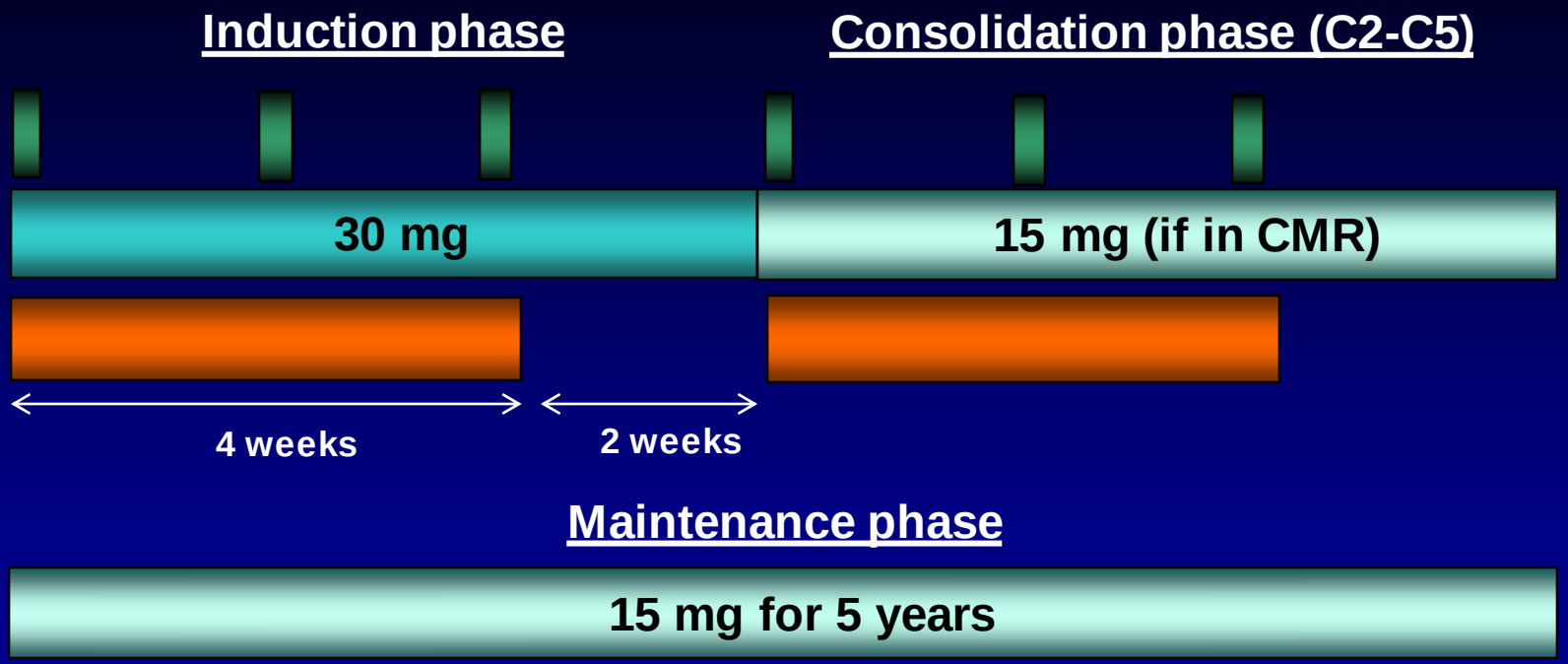
Dasatinib-Blinatumomab in Ph-positive ALL

- 63 pts, median age 54 yrs (24-82). Dasatinib 140 mg/D × 3 mos; add blinatumomab × 2-5
- 53 post dasa-blina × 2-- molecular response 32/53 (60%), 23CMR (42%)
- MRD ↑ in 15— 6 T315I; 9 relapses: 4 hematologic, 4 CNS, 1 nodal
- 3-yr OS 77%; DFS 71%
- 29/58 (50%) allo SCT



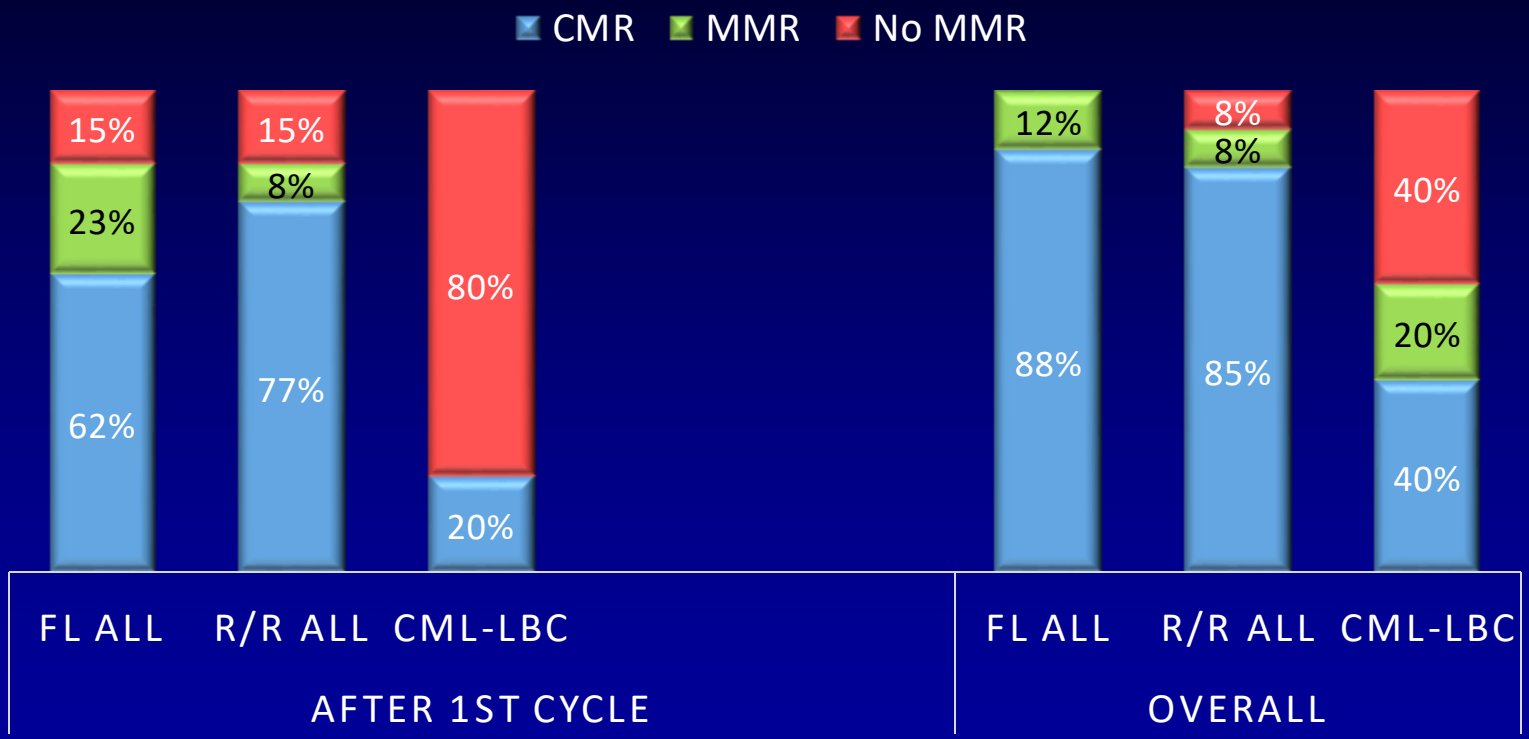
Foa . *N Engl J Med.* 2023;83:1613.

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



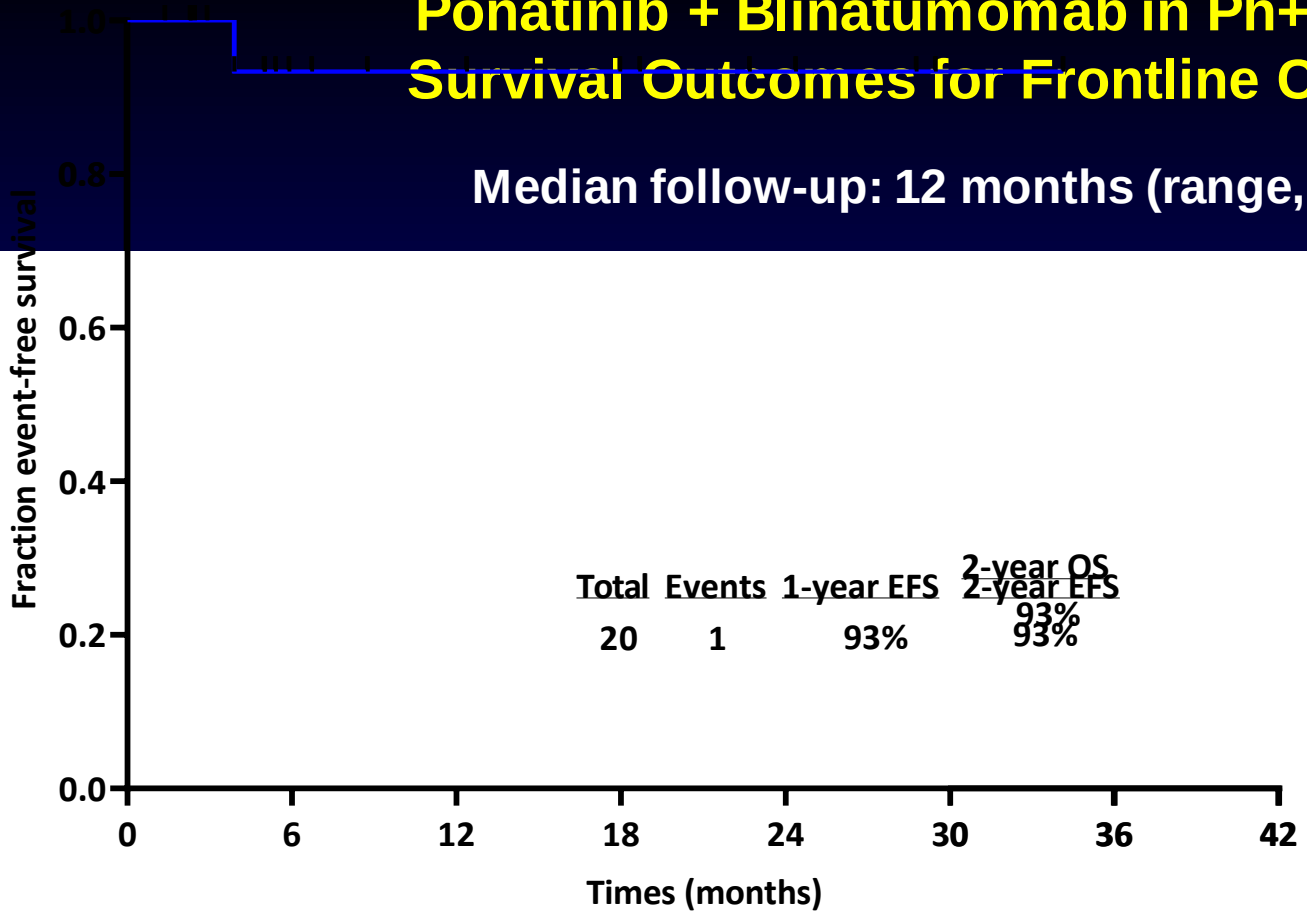
Short NJ, et al. *J Clin Oncol*. 2021;39(suppl 15): abstract 7001.

Ponatinib + Blinatumomab in Ph+ ALL: MRD Response Rates



Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes for Frontline Cohort

Median follow-up: 12 months (range, 1–37)

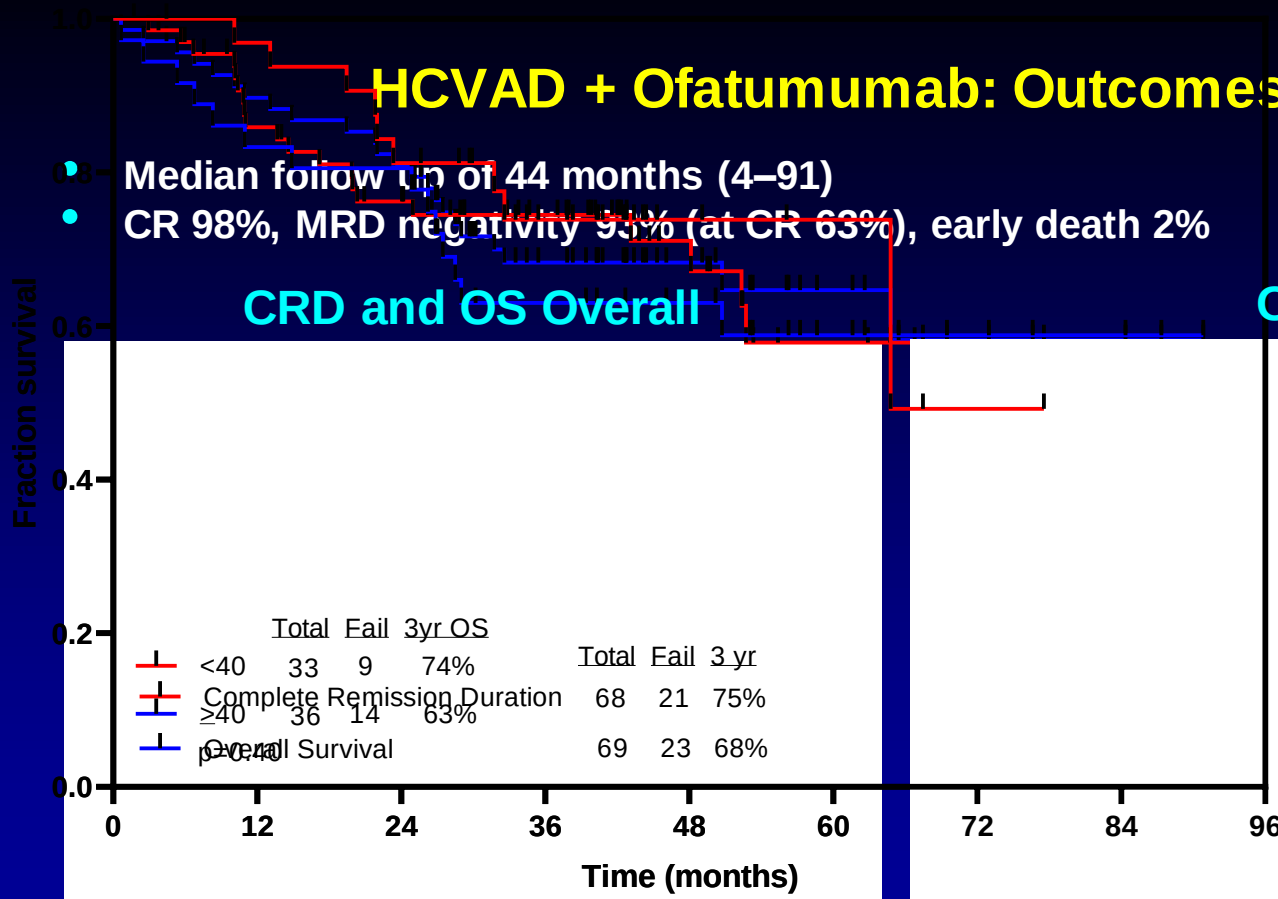


Short NJ, et al. *J Clin Oncol*. 2021;39(suppl 15): abstract 7001.

HCVAD + Ofatumumab: Outcomes (N = 69)

- Median follow up of 44 months (4–91)
- CR 98%, MRD negativity 95% (at CR 63%), early death 2%

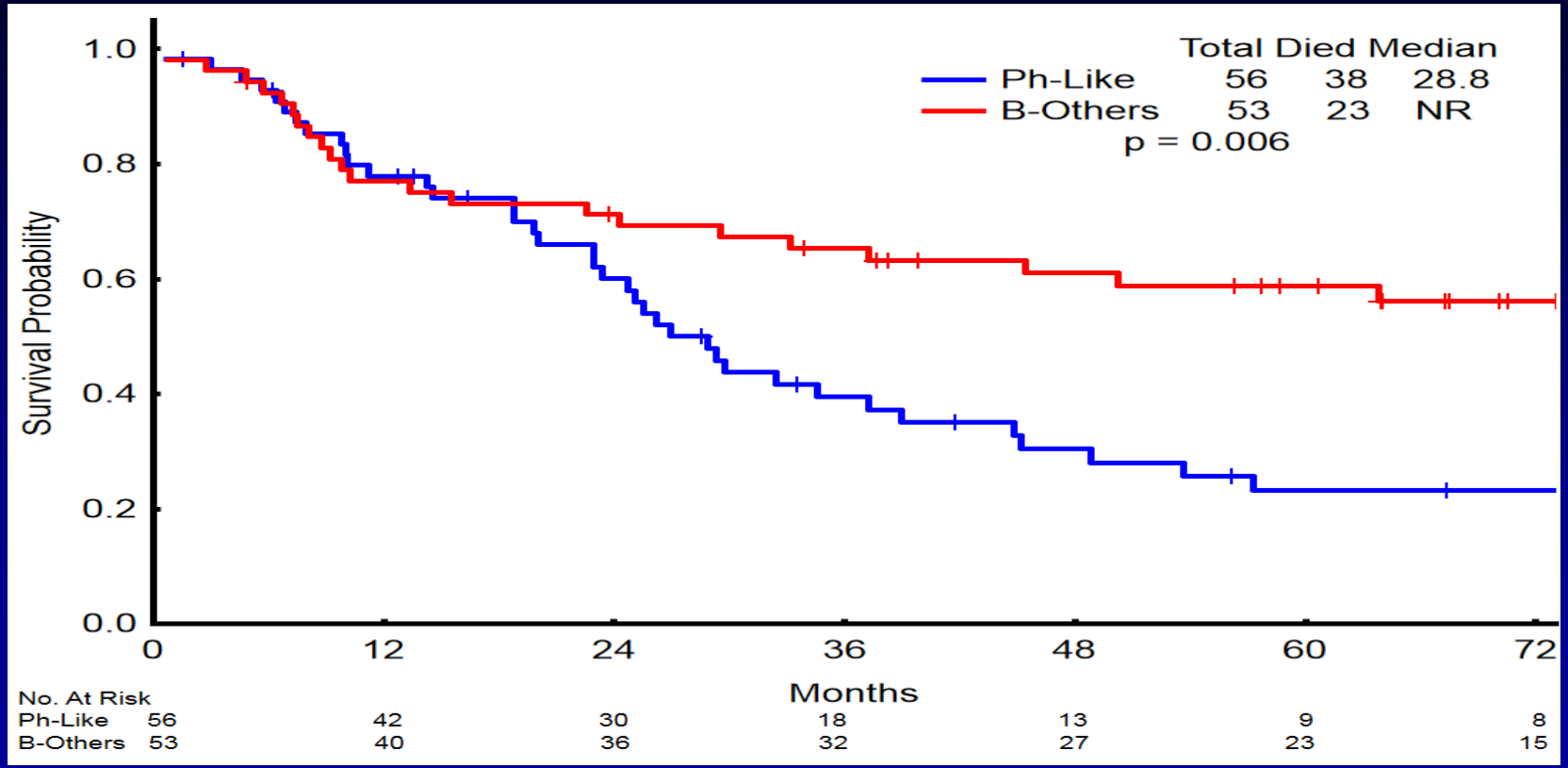
CRD and OS Overall



OS by Age

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

Ph-like ALL – Worse Survival



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

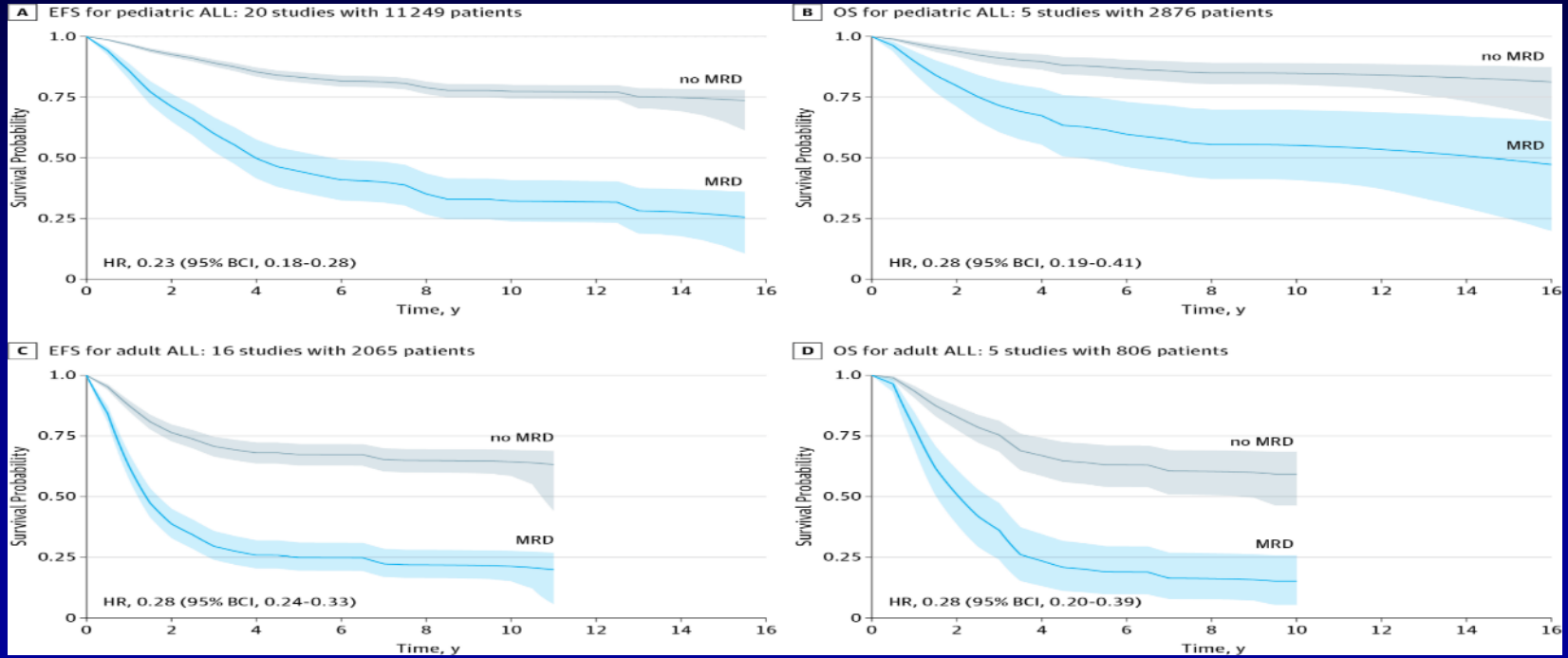
Ph-Like ALL: Higher MRD+ Rate

	B-ALL Categories (N = 155)			
	Ph-like	Ph+	B – other	*P* value
N	56	46	53	
CR/CRp	50 (89)	43 (93)	50 (94)	.57
MRD at CR				
Positive	**23 (70)**	**15 (44)**	**4 (13)**	**<.001**
Negative	10 (30)	19 (56)	27(87)	

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

MRD in ALL

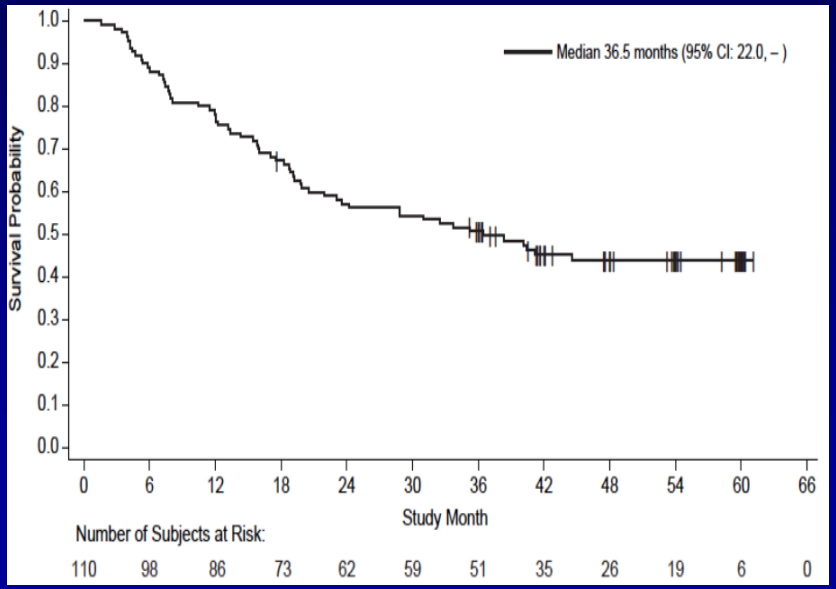
- Meta-analysis of 39 studies (pediatric and adult), including 13,637 patients with all ALL subtypes
- Prognostic impact of MRD clearance consistent across therapies, MRD method, timing, level of cutoff and subtypes

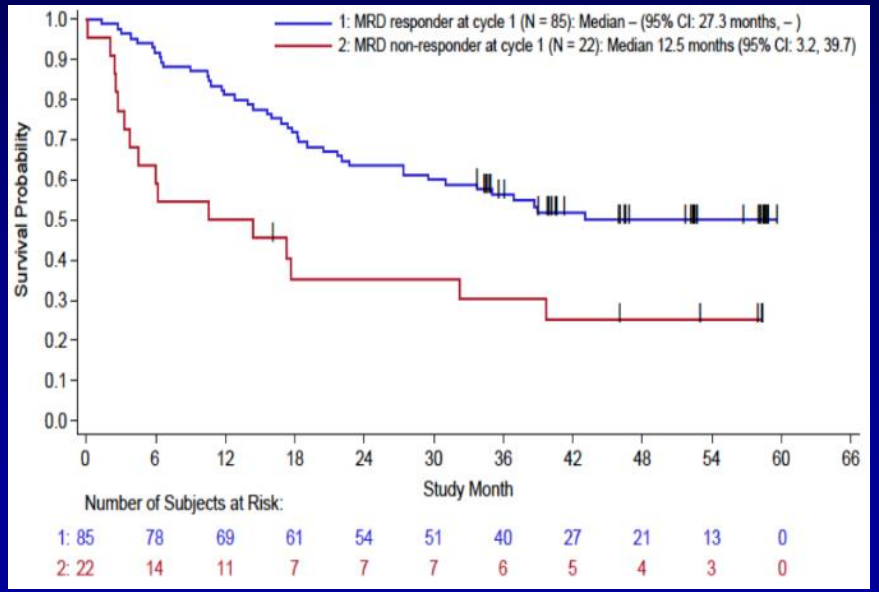


Berry DA, et al. *JAM A Oncol.* 2017;3(7):e170580.

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 F/U 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%)

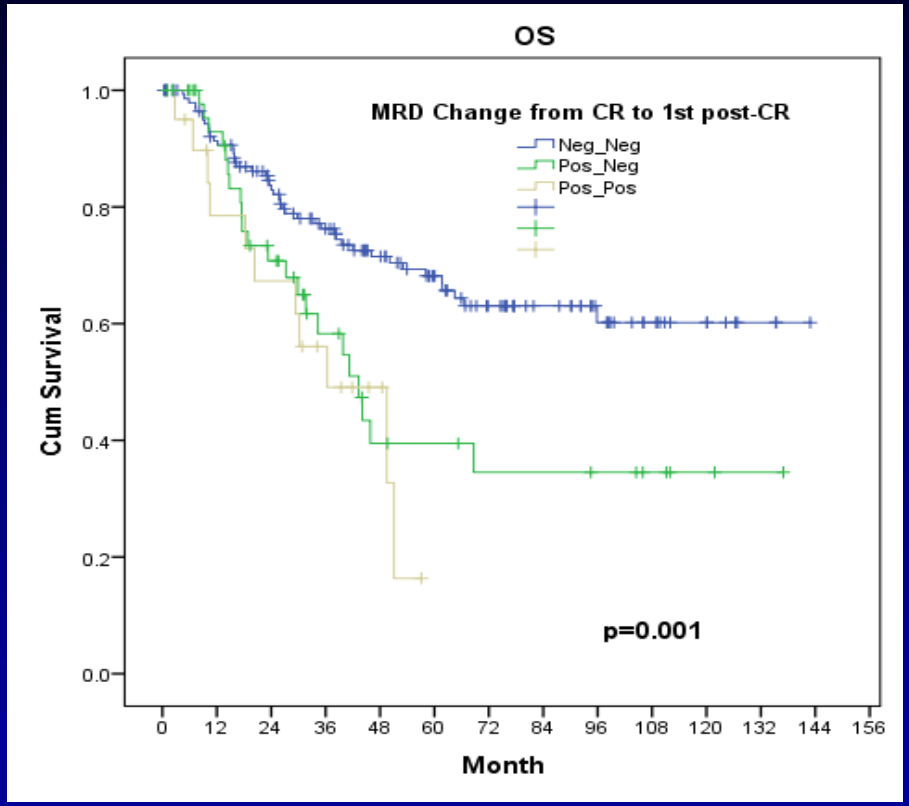




Goekbuget N, et al. *Blood*. 2018;132:abstract 554.

Dynamics of MRD: Outcome

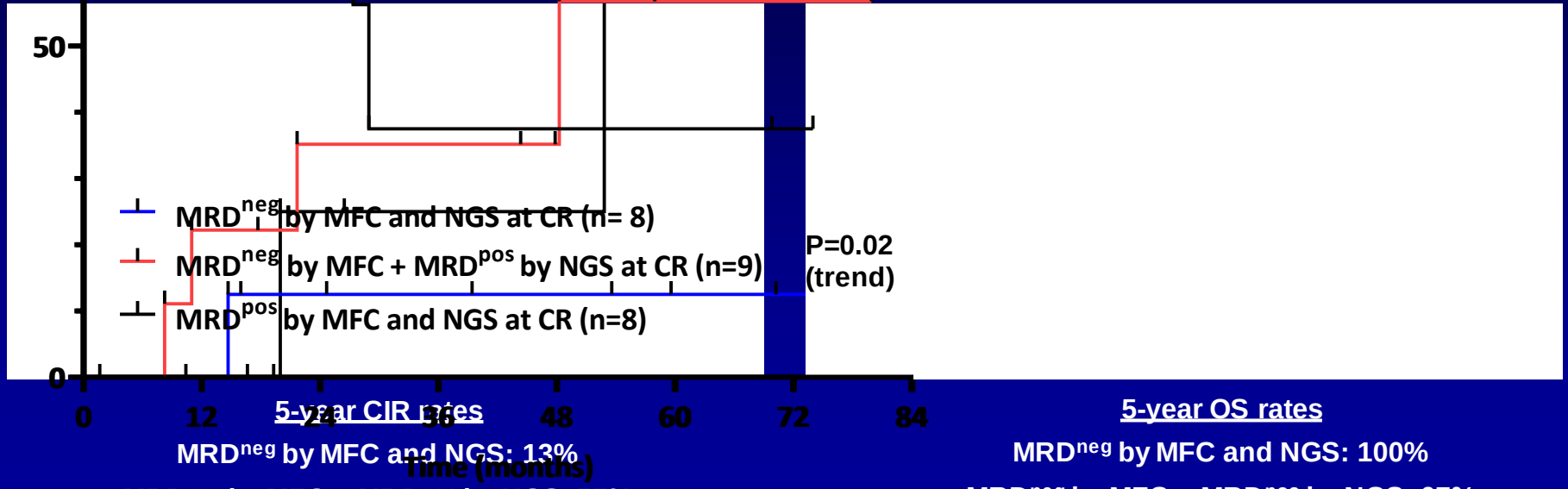
MRD Status		Patients (%) n = 214	5-yr EFS, %	5-yr OS, %
@CR	@ First post-CR			
Negative	**Negative**	**147 (69)**	**56**	**68**
≤0.1%	Negative	14 (7)	31	46
>0.1%	Negative	33 (15)	32	38
Positive	Positive	20 (9)	NA	NA



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

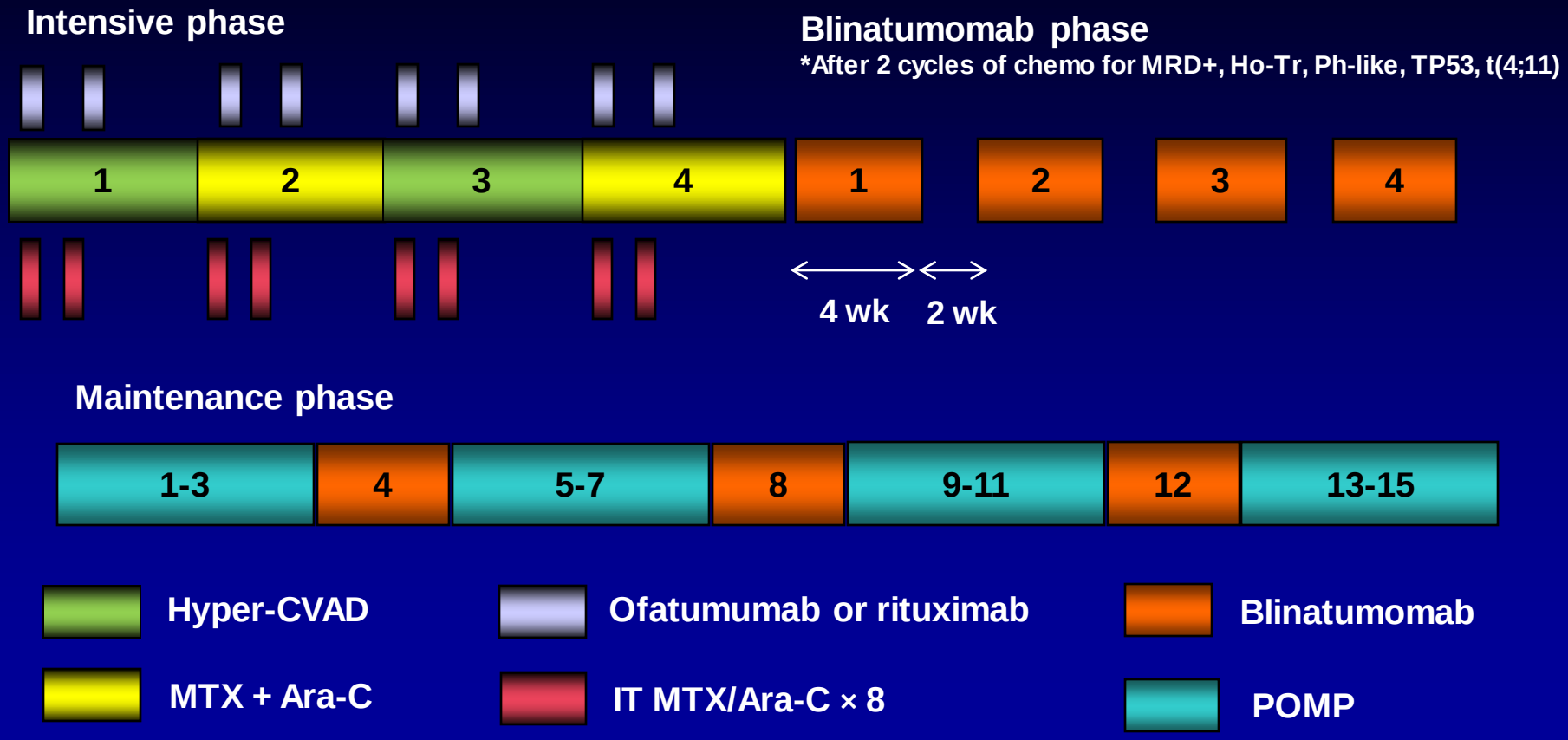
MRD^{neg} by MFC and NGS: 100%

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

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

Short et al. *Blood.* 2020;136:abstract583.

Hyper-CVAD + Blinatumomab in B-ALL: Regimen

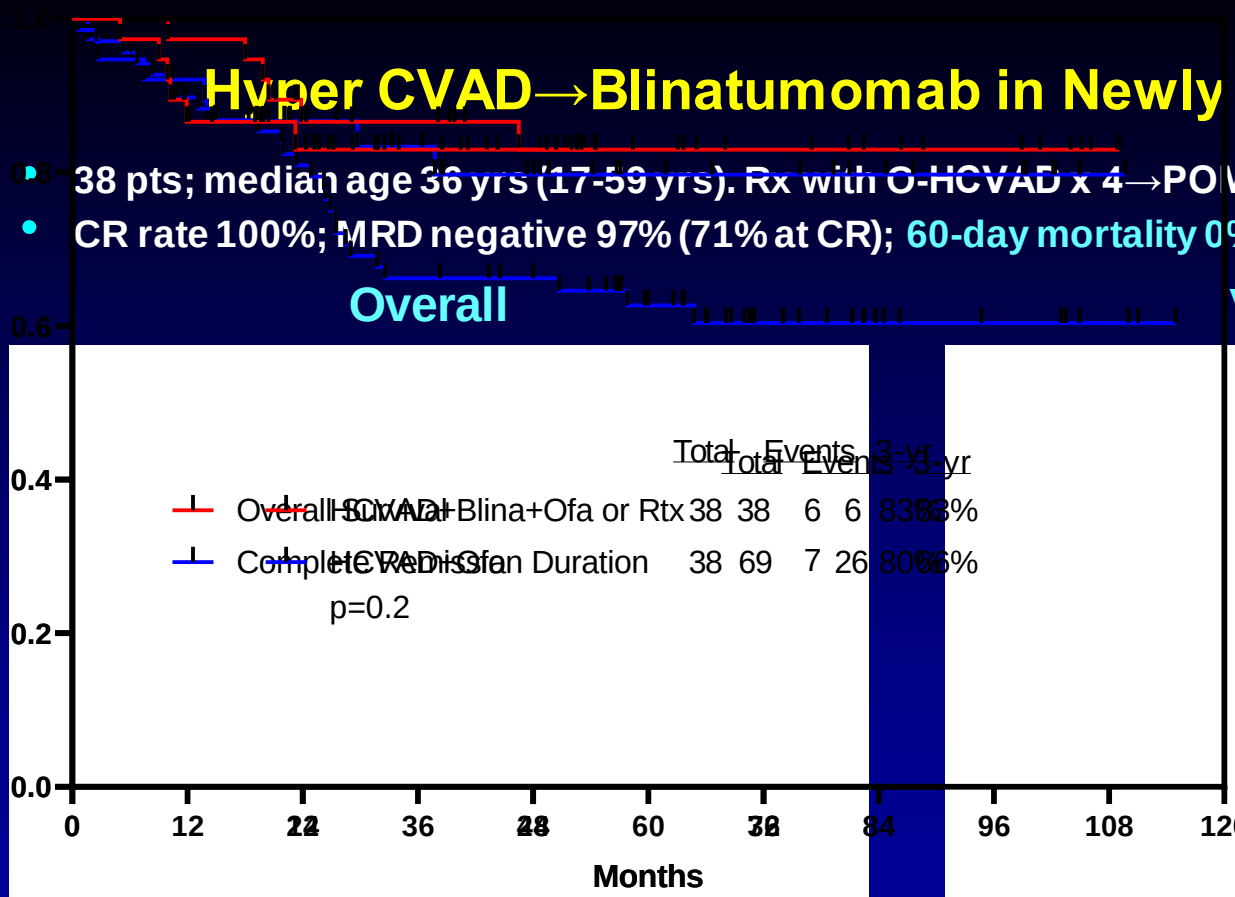


Short et al. *Blood.* 2020;136:abstract 464.

Hyper CVAD→Blinatumomab in Newly Dx Adult ALL

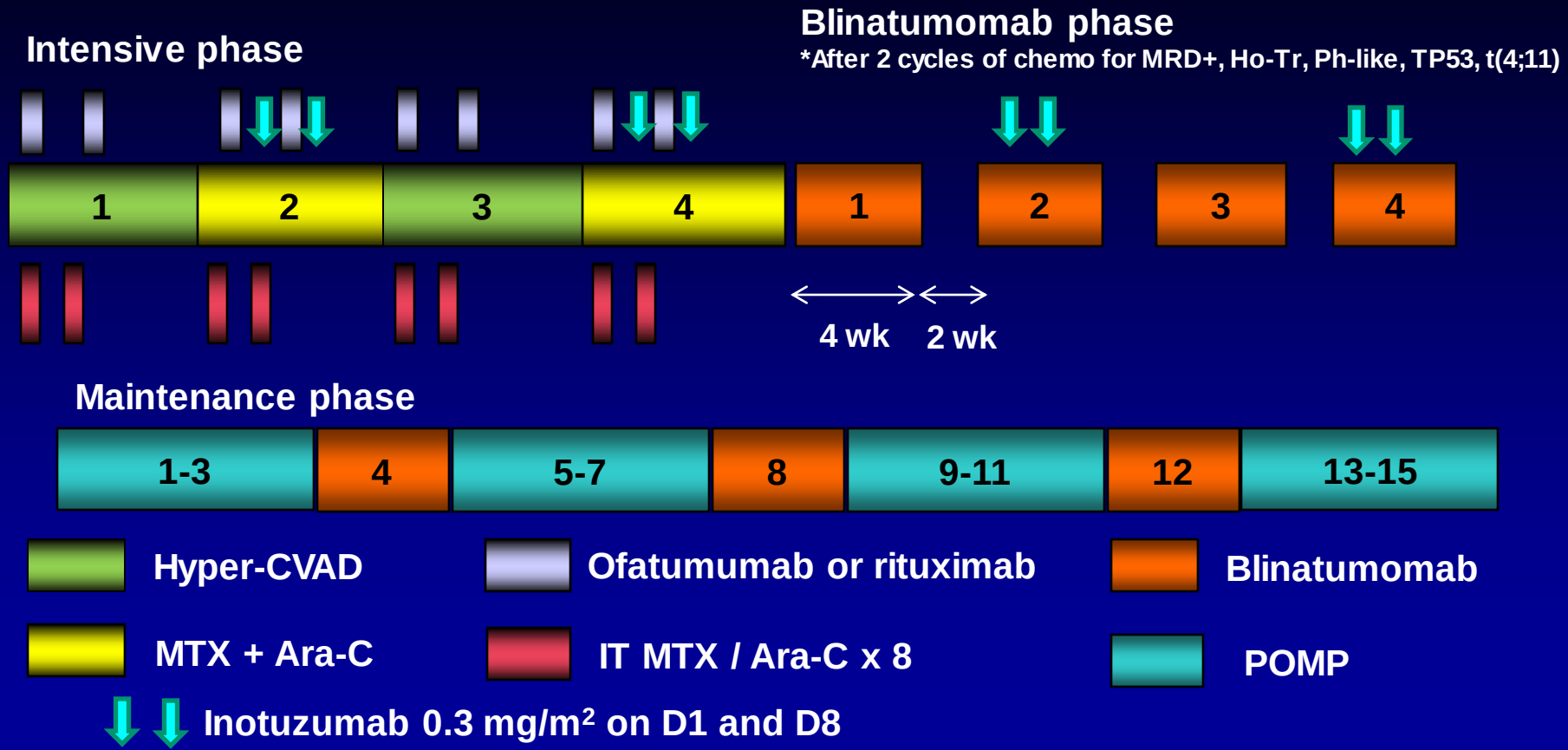
- 38 pts; median age 36 yrs (17-59 yrs). Rx with O-HCVAD x 4→POMP 1 yr with blina Q3 mos
- CR rate 100%; MRD negative 97% (71% at CR); 60-day mortality 0%; 12 (32%) allo-SCT; F/U 24 mos

Overall



Vs Historical

Hyper-CVAD + Blinatumomab in B-ALL: Regimen



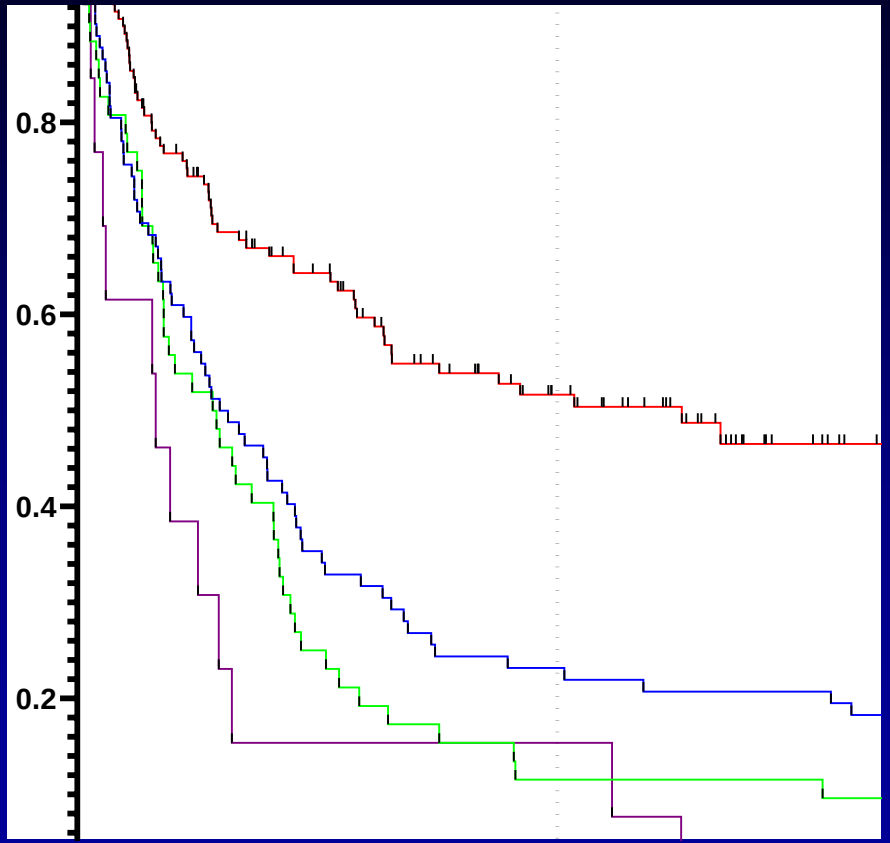
Short et al. *Blood.* 2020;136:abstract 464.

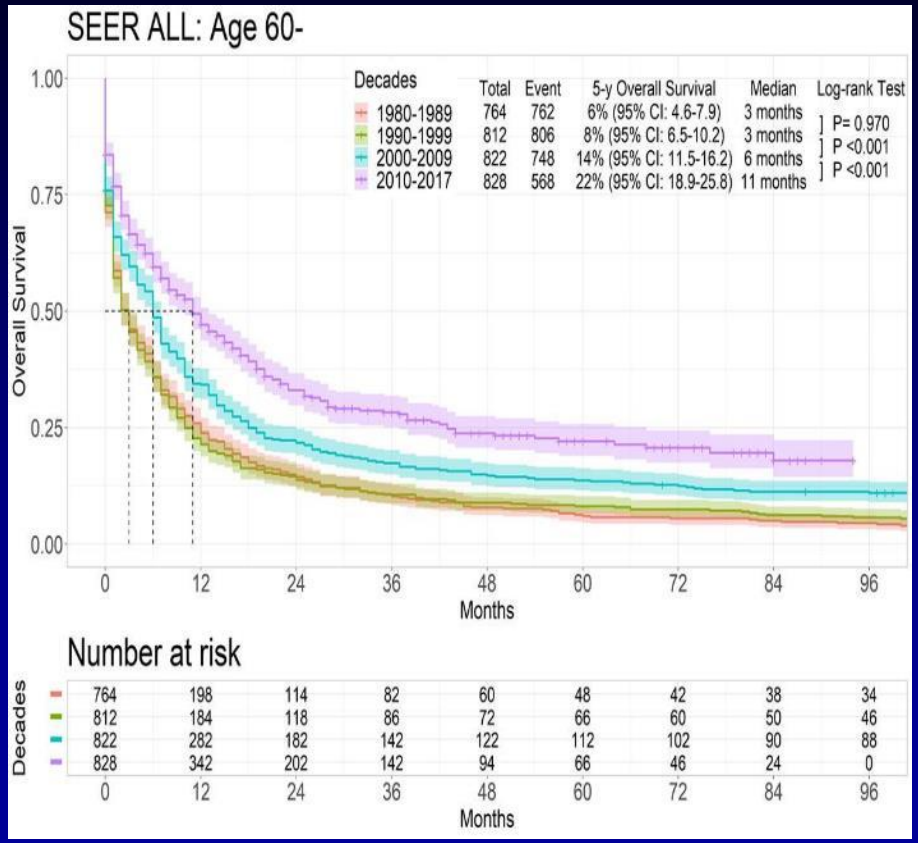
Sequential Chemo Rx and Blinatumomab in Newly Dx ALL

- 149 pts; median age 41 yrs (18–65; 18% >55)
- Chemo Rx GIMEMA LAL1913-blina × 2 post C3 and C6
- CR 90%
- MRD clearance: 73% post early consolidation; 96% post blina × 1. Conversion to MRD-negative post blina 20/23 = 87%
- 12-mos OS 84%, DFS 72%, 12 mos relapse 11%

Bassan et al. EHA 2021. Abstract S114.

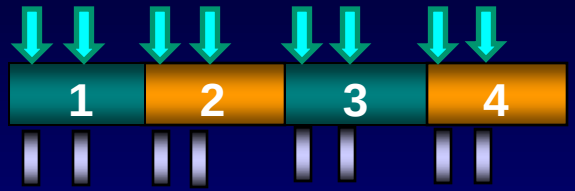
MDACC ALL: Survival by Decades for ≥60 Years





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

Intensive phase



Mini-HCVD

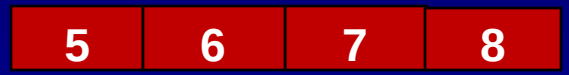
Mini-MTX-cytarabine

IT MTX, Ara-C

Blinatumomab

POMP

Consolidation phase



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

Total INO dose = 2.7 mg/m^2

Maintenance phase

18 months

*Ursodiol 300 mg tid for VOD prophylaxis

Jabbour E, et al. *Cancer*. 2018;124(20):4044-4055; Kantarjian H, et al. *Lancet Oncol*. 2018;19:240.

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

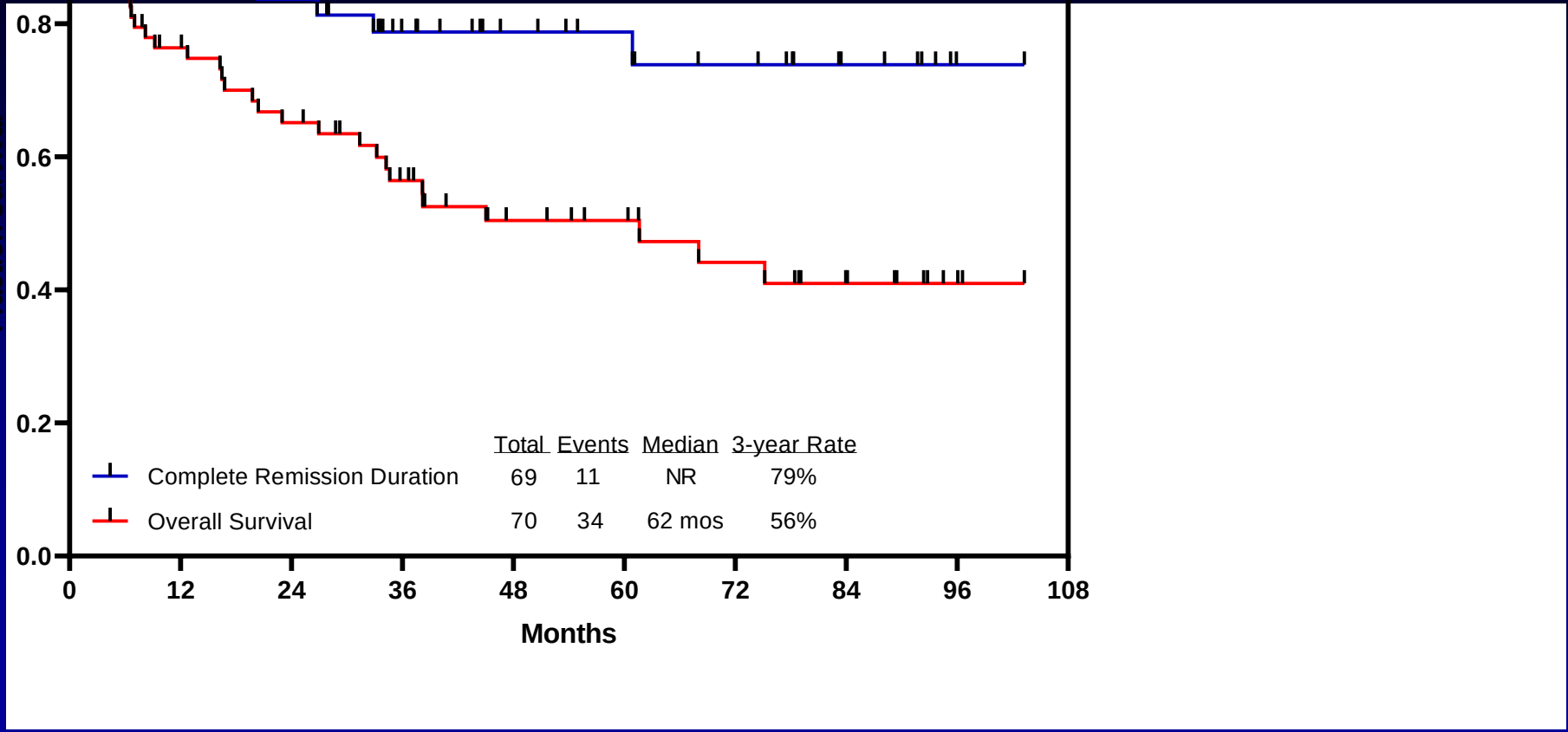
Characteristic	Category	N (%)/Median [range]
Age (years)	**≥70**	**68 [60–81]** **29 (41)**
Performance status	≥2	10 (14)
WBC ($\times 10^9$/L)		3.1 [0.6–111.0]
Karyotype	Diploid HeH **Ho-Tr** **Tetraploidy** **Complex** **t(4;11)** Misc IM/ND	23 (33) 5 (7) **12 (17)** **3 (4)** **3 (4)** **1 (1)** 10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

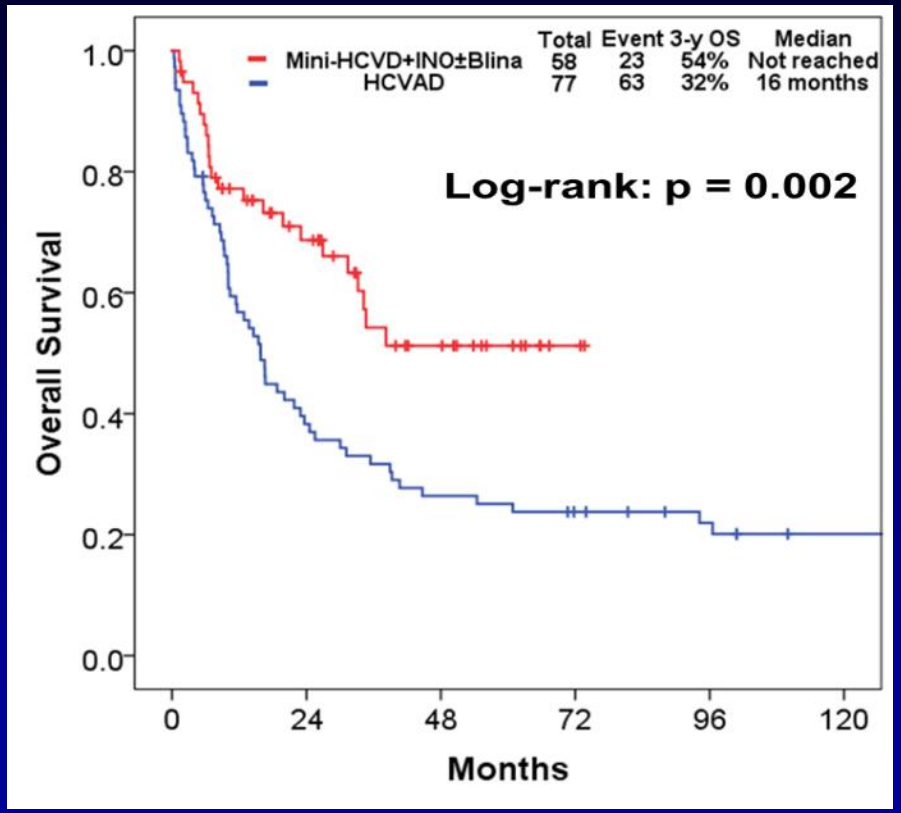
Mini-HCVD + INO ± Blina in Older ALL: CRD and OS (Entire Cohort)



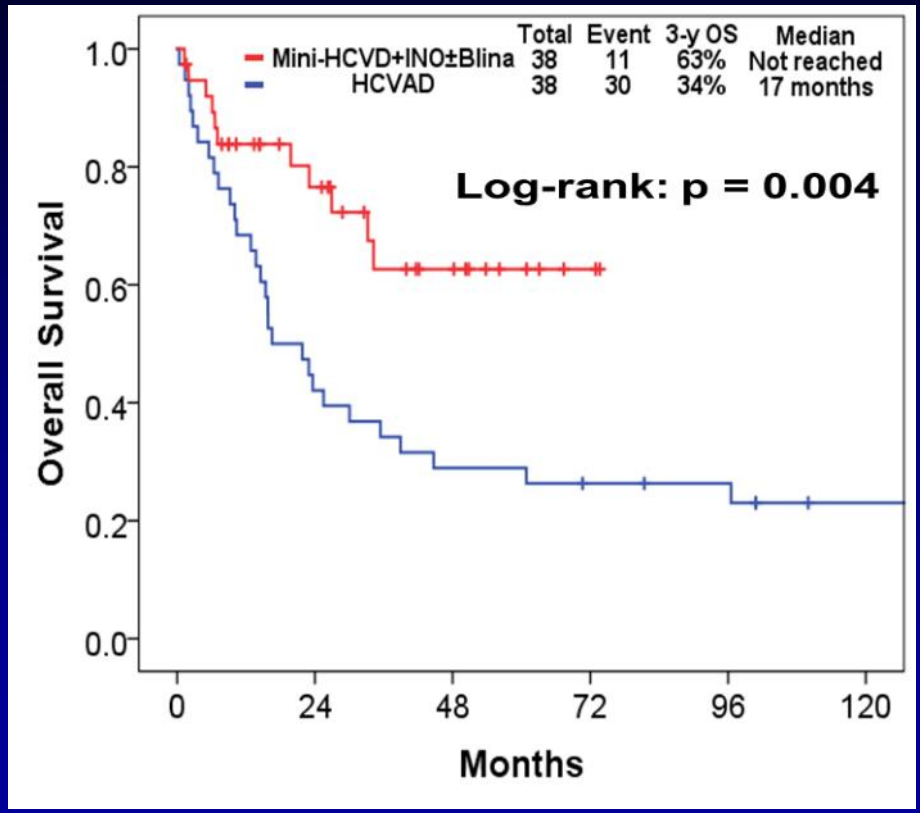
Short et al. *Blood.* 2020;136:abstract 1014.

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

Pre-matched

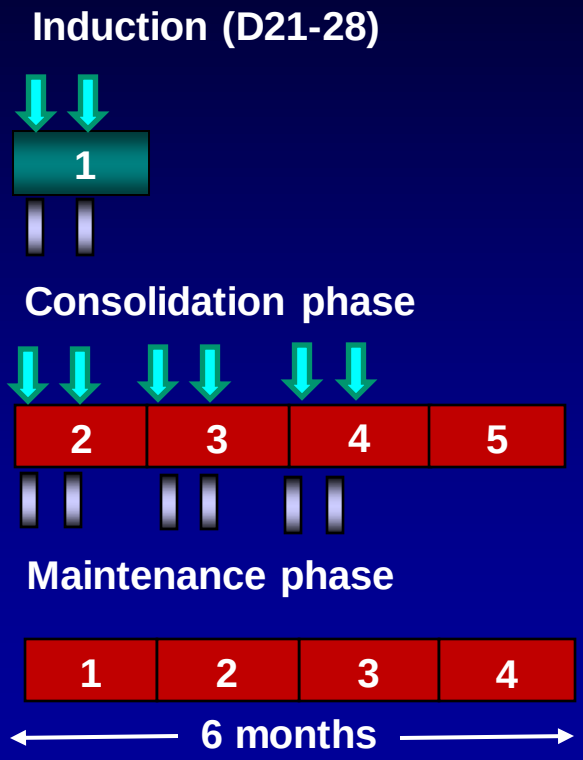


Matched



Sasaki. *Blood.* 2018;132:abstract 34.

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

Inotuzumab Followed by Chemo Rx in ALL 55+ Years

- Course 1 – Ino 0.8 mg/m^2 D1, 0.5 g/m^2 D8 and 15 (1.8 mg/m^2) in Course 1
  - CTX-VCR-steroids pre phase – TIT × 1/course
- Courses 2 and 3 – Ino 0.5 mg/m^2 Days 1, 8, 15 (1.5 mg/m^2)
  - 5 consolidations: 3 MTX/Asp, 2 ID-ara-C→1 reinduction IDA-ara-C-CTX-Dex
  - 6MP-MTX maintenance × 1.5 yr
- 36 Rx, results in 31; Median age 65 years (56–80)
- CR/CRi 31/31 (100%); MRD negative 21/27 (78%)
- 1-yr OS 87%; 1-yr EFS 87%
- No VOD

Stelljes et al. *Blood.* 2020;136:abstract 267.

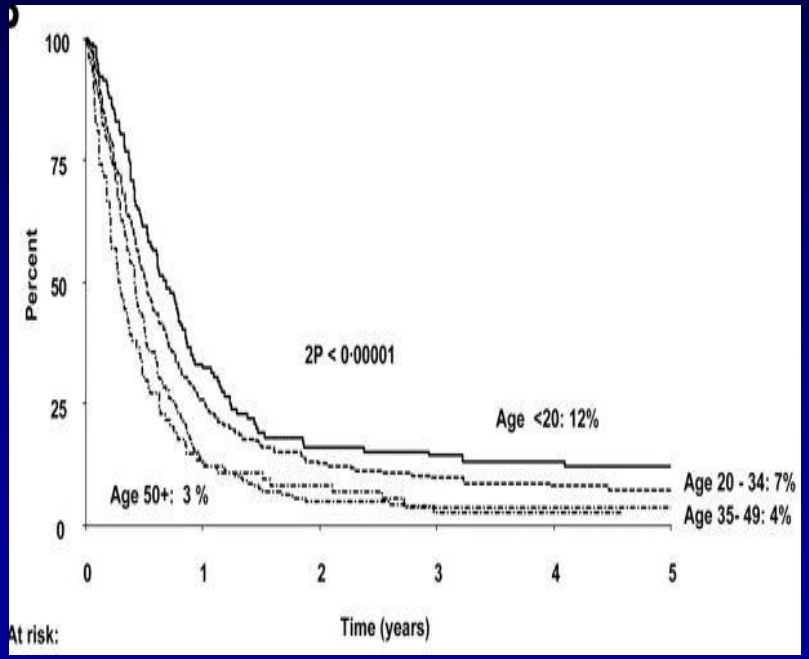
ALL Salvage Standards of Care in 2021

- Refer for investigational therapies – mini-CVD-ino-blina; CAR T
- Ph-positive ALL – TKIs (ponatinib preferred) + chemoRx/blinatumomab
- Pre-B ALL
  - Blinatumomab (FDA approval 12.2014)
  - Inotuzumab (FDA approval 8.2017)
  - CAR Ts (FDA approvals 8.2017 and 10.2021)
- T ALL: nelarabine
- ChemoRx: FLAG IDA, Hyper CVAD, augmented HCVAD, MOAD
- BUT – very promising new therapies with chemoRx + TKIs/BCL2i (venetoclax; navitoclax)/ADCs/BiTES/CAR Ts

ALL – Historical Survival Rates After First Relapse

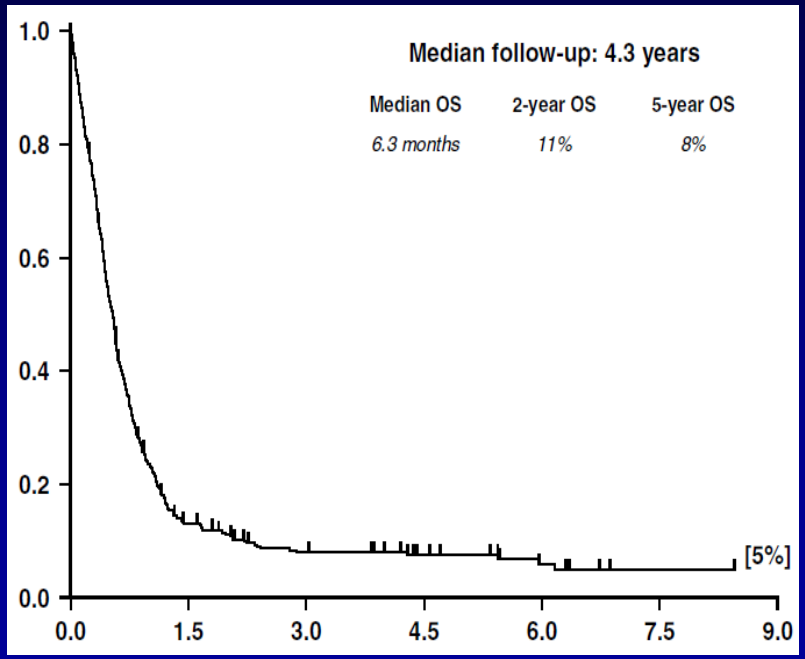
MRC UKALL2/ ECOG2993 Study (n = 609)

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%

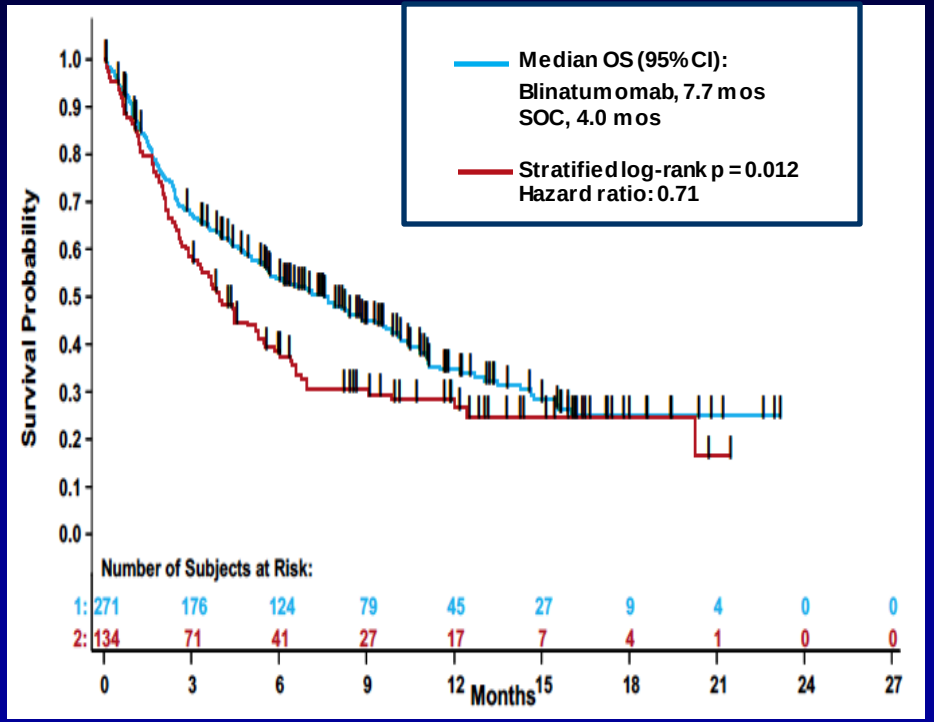


Fielding et al. *Blood*. 2007;109:944-950; Tavernier E, et al. *Leukemia*. 2007;21:1907-1914.

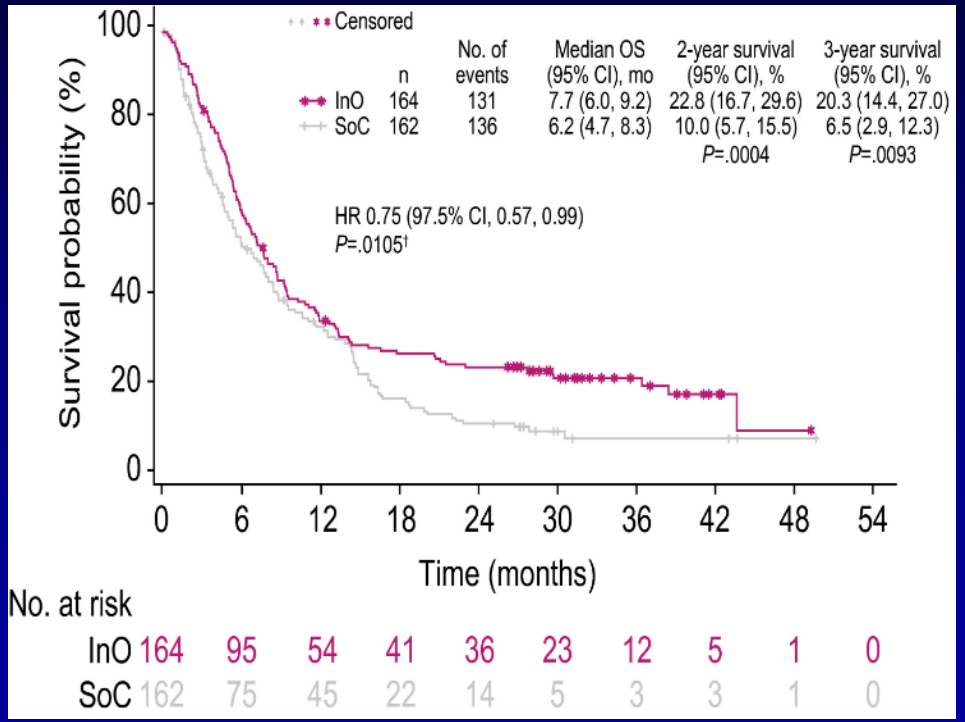
Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

- **Marrow CR**

Blina vs SOC: 44% vs 25%



Ino vs SOC: 74% vs 31%

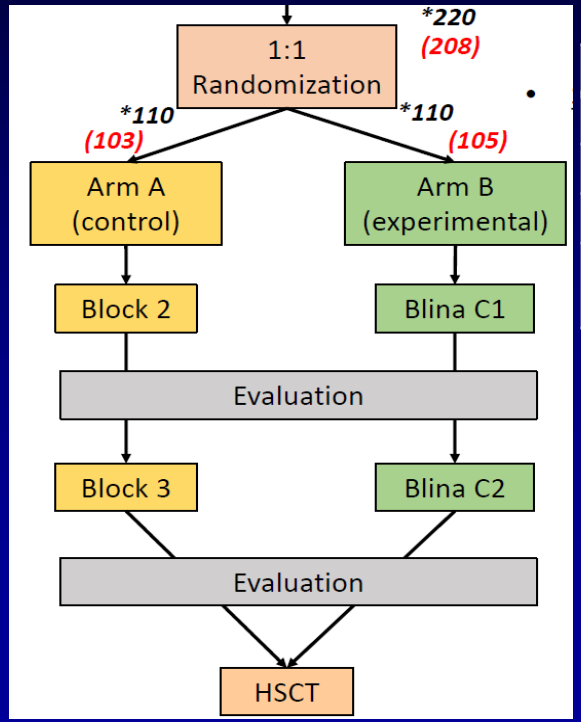


Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

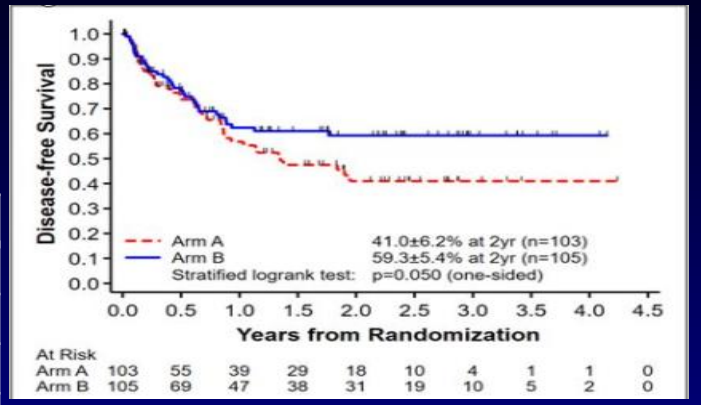
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

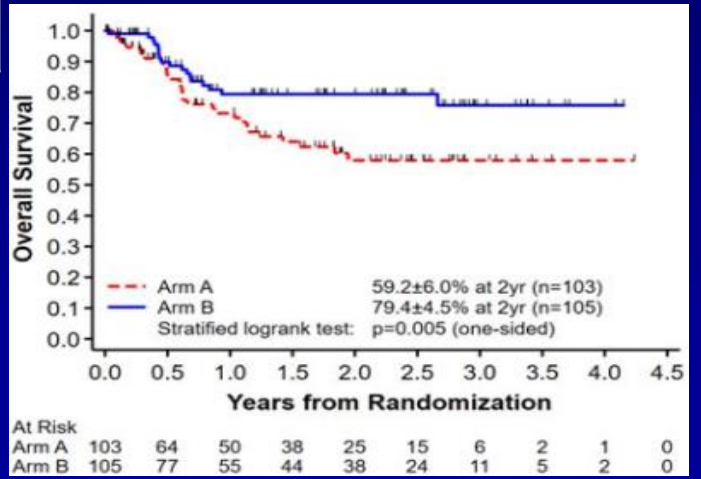
Phase III Study of Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

- 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.

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%)

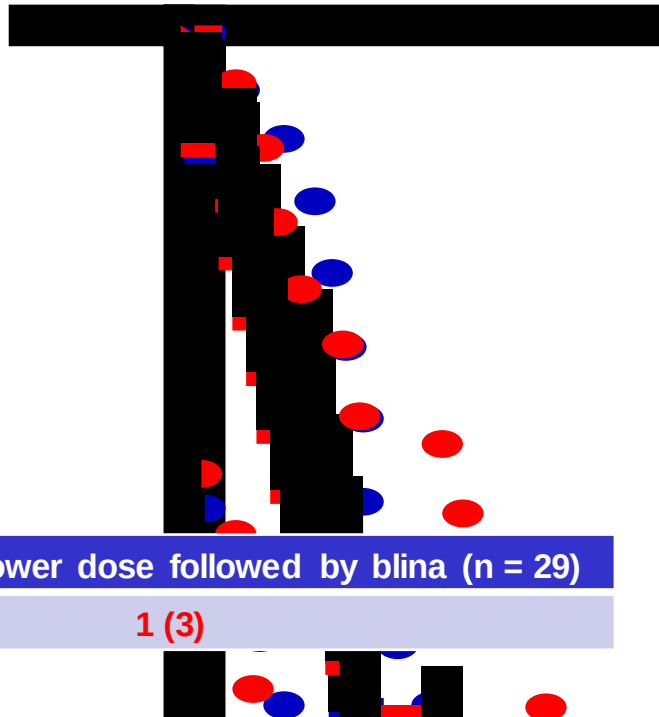
Brivio et al. *Blood*. 2020;136:abstract 164.

Mini-HCVD + INO ± Blina in 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.

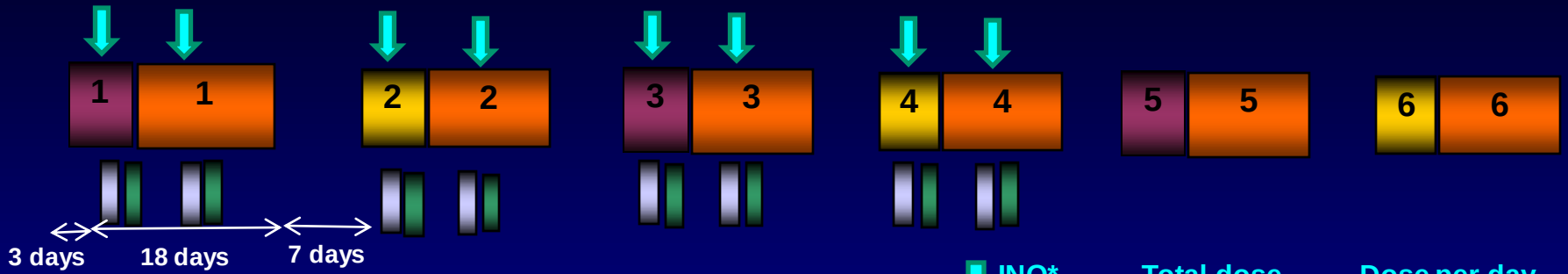


	Single dose (n = 67)	Fractionated lower dose followed by blina (n = 29)
VOD (%)	9 (13)	1 (3)

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

Dose-dense Mini-HCVD + INO ± Blina in ALL: Modified Design

Intensive phase: C1-C6



	INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1		0.9	0.6 D2, 0.3 D8
C2-4		0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300mg tid for VOD prophylaxis

Maintenance phase

Mini-Hyper-CVD

Mini-MTX-Ara-C

Rituximab

IT MTX, Ara-C

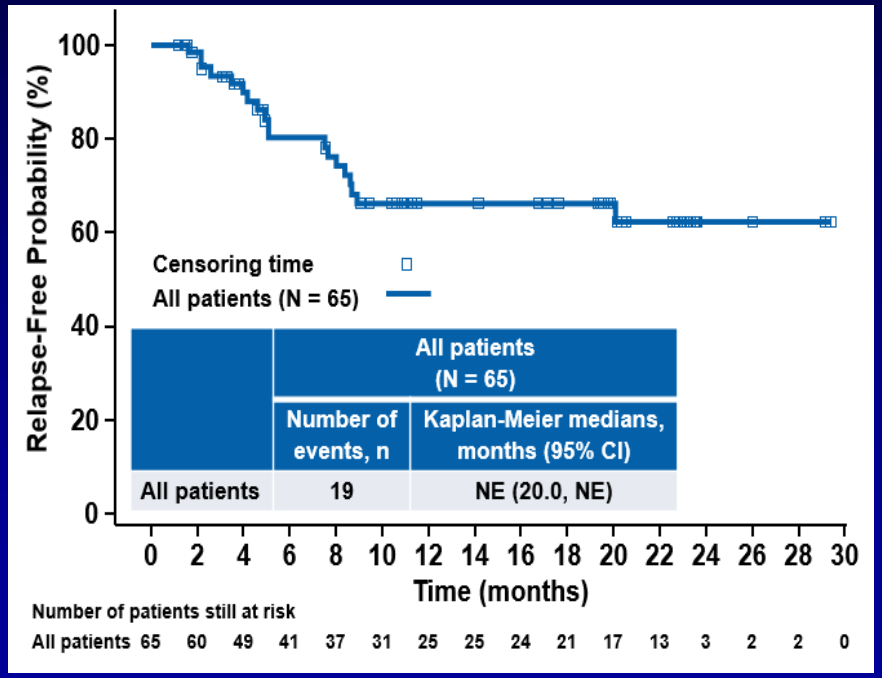
POMP

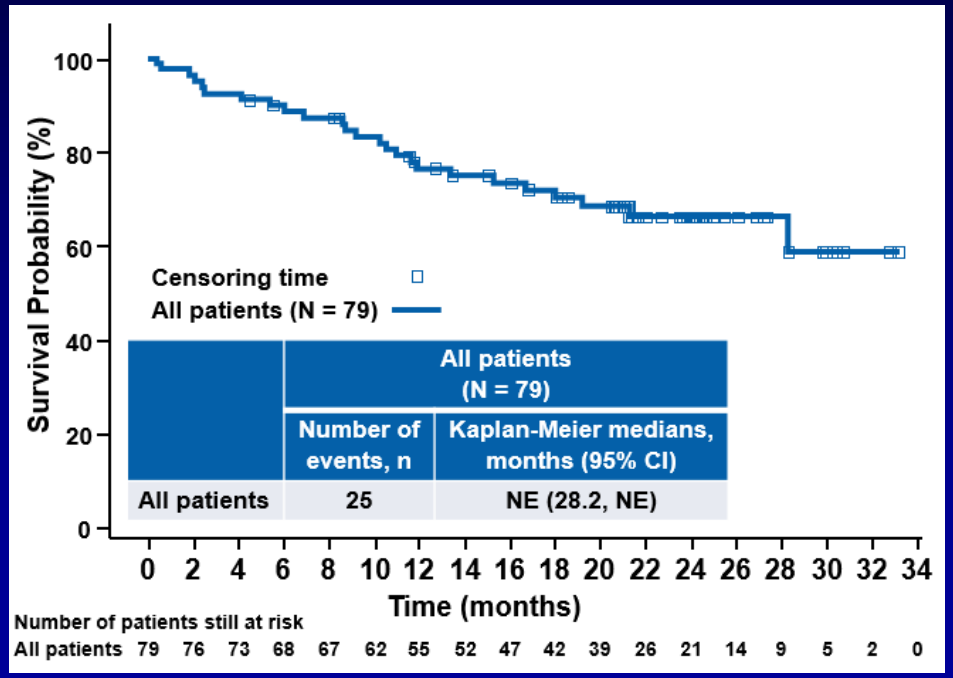
Blinatumomab

VCR/Steroid

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%

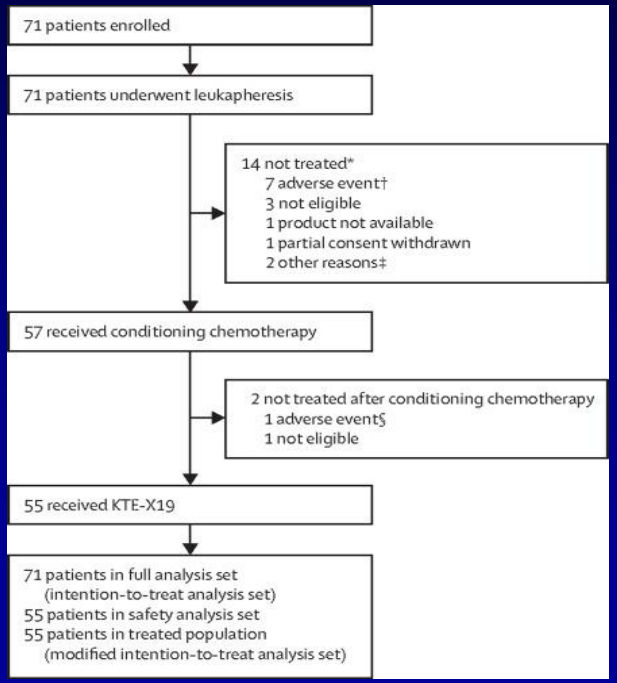


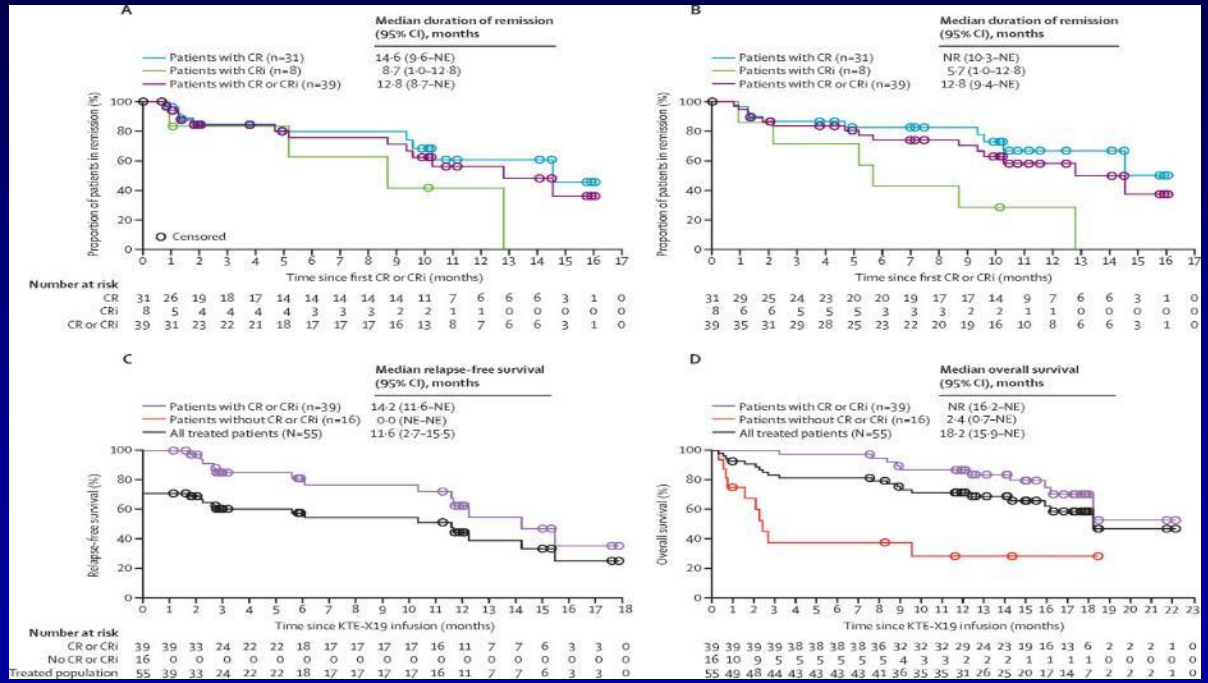


Grupp et al. EHA 2019. Abstract S1618.

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

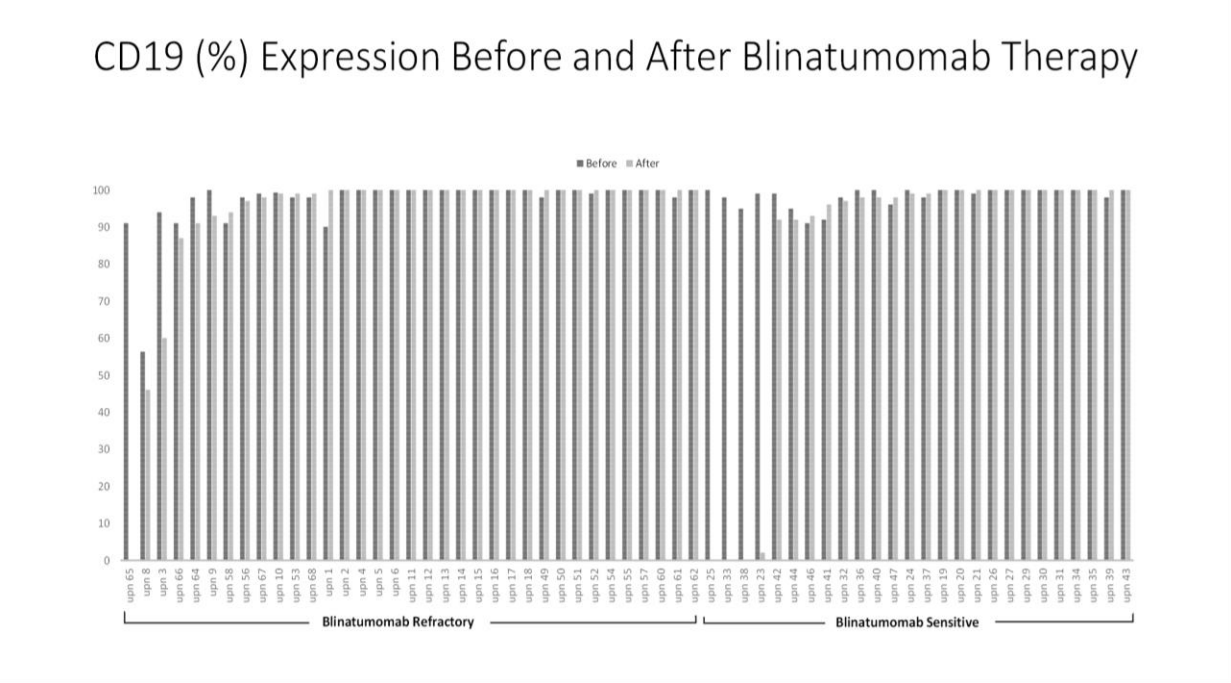
- 71 enrolled, 55 infused; median age 40 yrs (28-52)
- CR/CRi 39/55 (71%, CR 56%); ITT (39/71; 55%---CR 44%); MRD- response 76% (97% among responders); 10 pts (18% Rx ASCT)
- mDOR 12.8 mos; mRFS 11.6 mos; mOS 18.2 mos
- Grade ≥3: CRS 24%; NE 25%





Shah et al. *Lancet*. 2021;S0140-6736.

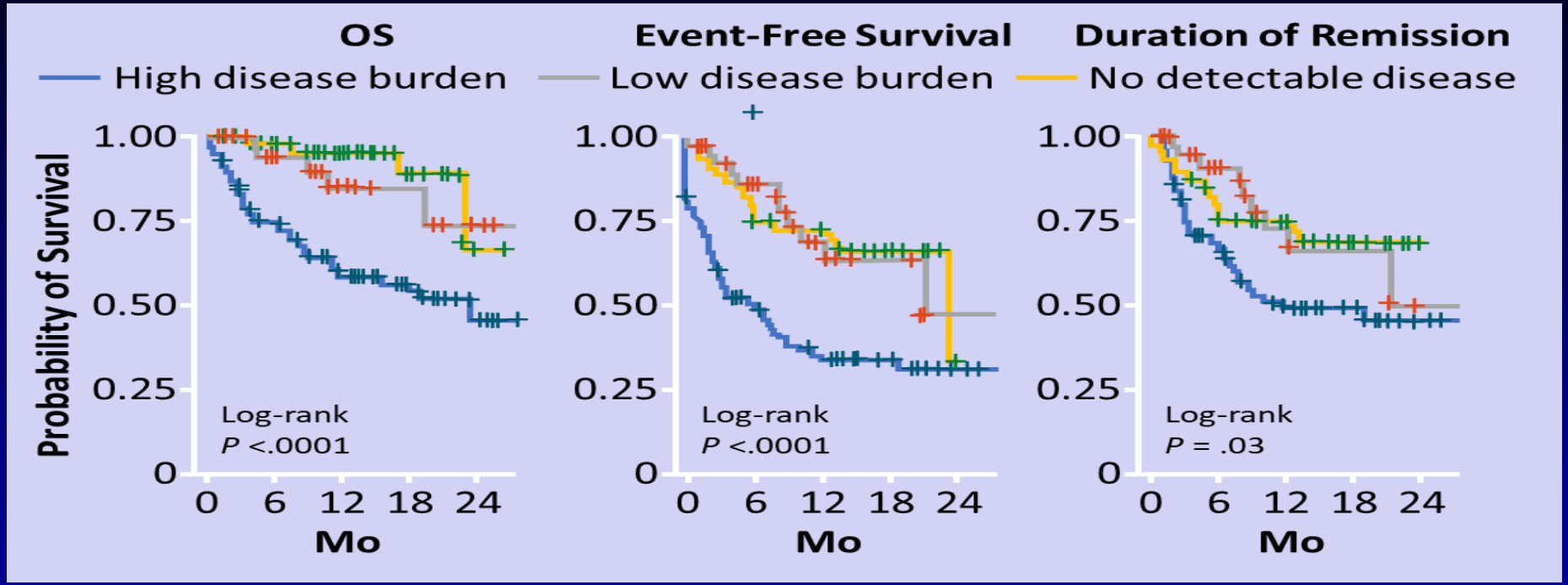
CD19 (%) Expression Before and After Blinatumomab Therapy



- 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.

Real-Word CAR Consortium and Disease Burden



High Burden Disease (n = 94; 47%)

- 1-yr OS 58%
- 1-yr EFS 34%

Low Burden Disease (n = 60; 30%)

- 1-yr OS 85%
- 1-yr EFS 69%

Undetectable Disease (n = 46; 23%)

- 1-yr OS 95%
- 1-yr EFS 72%

Schultz. *Blood.* 2020;136.abstract 468.

CAR T in ALL – The Beginning of a Great Journey

- CART Rx today is what allogeneic SCT was in 1980 – a great beginning
- Improved CAR T designs
- Dual CAR Ts targeting CD19, CD22, CD20
- Allogeneic off-the-shelf CAR Ts
- Smaller repeated allogeneic CAR Ts infusions (fractionated CAR Ts)
- CAR Ts in first CR in MRD to replace allo SCT

ALL Summary

- Significant progress and improved outcomes across all ALL categories: Ph-positive, Burkitt, younger and older pre-B ALL, T-ALL, ALL salvage. Rapidly evolving therapies
- Antibody-based Rxs and CAR Ts both outstanding; not mutually exclusive/competitive (vs); rather complementary (together)
- Future of ALL Rx: 1) less chemotherapy(?) and shorter durations; 2) combinations with ADCs and BiTEs/TriTEs targeting CD19, CD20, CD22; 3) CARTs in sequence in CR1 for MRD and replacing allo SCT
- Importance of MRD testing and changing Rx accordingly

AML in 2021 – The Next Questions

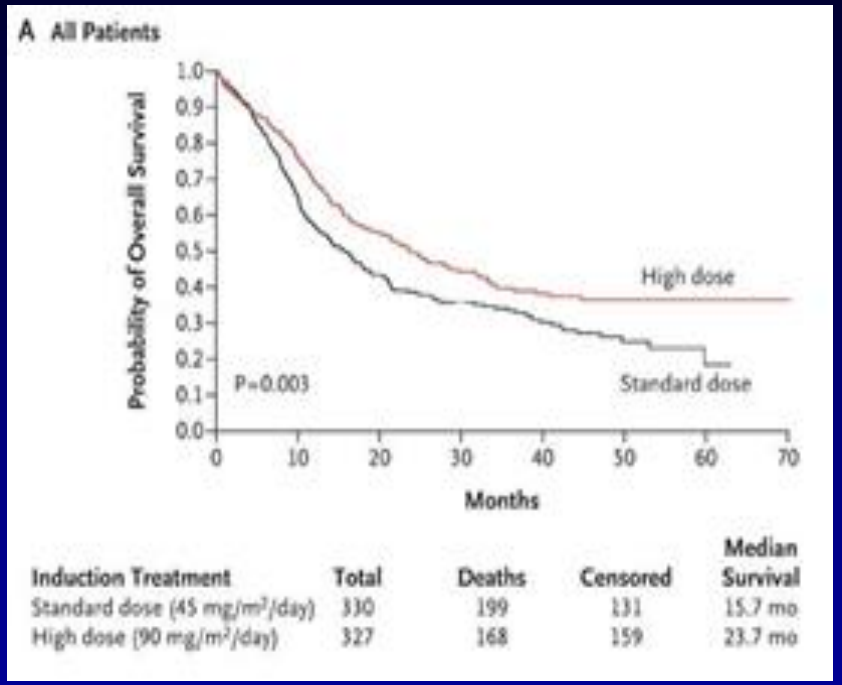
AML in 2017–2020, 10 Agents FDA Approved

- **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

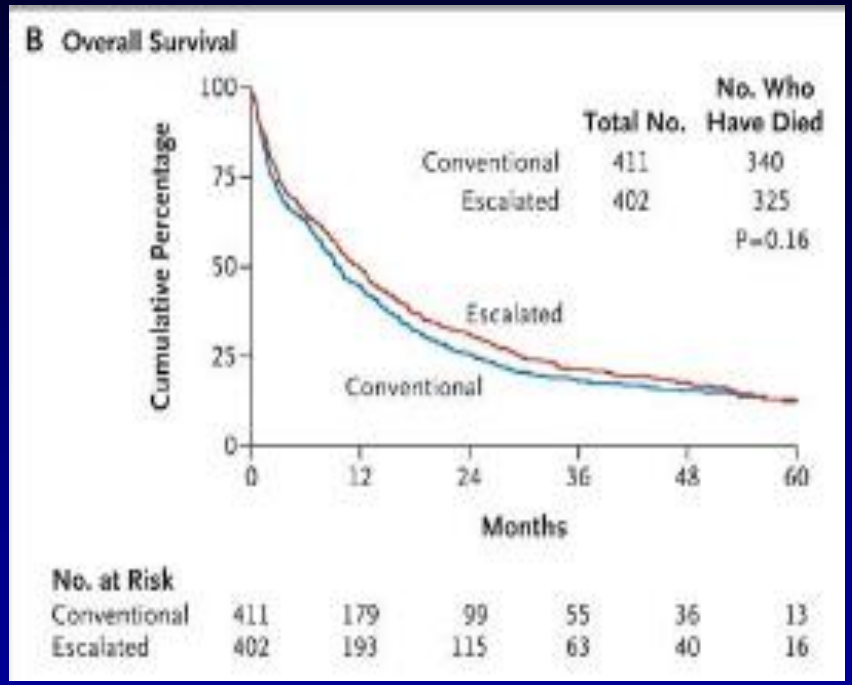
AML in 2021 – Brief Summary

- 3+7 outdated standard of care – Cure in younger AML 30%–40%; in older fit or unfit, cure <10%
- Better intensive + targeted Rxs in younger patients – FLAG-IDA-VEN, CLIA-VEN; also addition of FLT3/IDH inhibitors
- Better lower intensity regimens in older/unfit or even fit patients with proven resistance to intensive chemoRx (complex CG, MECOM, MLL, etc) – Triple nucleosides-VEN/targeted agents
- New Rxs – Venetoclax, FLT3i, IDHi, GO, oral HMAs, menin inhibitors, immuno-Rxs (CLL1 CAR Ts, CD47/SIRP1alpha targeting , NK cells)
- Note – Like with allo SCT, immune-targeting Rx should focus on MRD … Active AML = 1 trillion cells (1 Kg); in CR = 1-20 billion cells (1 g). If we provide >20 billion killer cells (NK) this could eradicate resistant AML

Actual Results of “3+7”



Induction Treatment	Total	Deaths	Censored	Median Survival
Standard dose (45 mg/m²/day)	330	199	131	15.7 mo
High dose (90 mg/m²/day)	327	168	159	23.7 mo



	Total No.	No. Who Have Died
Conventional	411	340
Escalated	402	325

P=0.16

No. at Risk						
Conventional	411	179	99	55	36	13
Escalated	402	193	115	63	40	16

- 5-yr survival 20%–35% in young, 10% in old

Fernandez HF, et al. *N Engl J Med.* 2009;361:1249-1259; Löwenberg B, et al. *N Engl J Med*. 2009;3611235-1248.

FLAG-IDA and CLIA

- Fludarabine 30 mg/m^2/D × 5

  AraC 2 g/m^2/D × 5

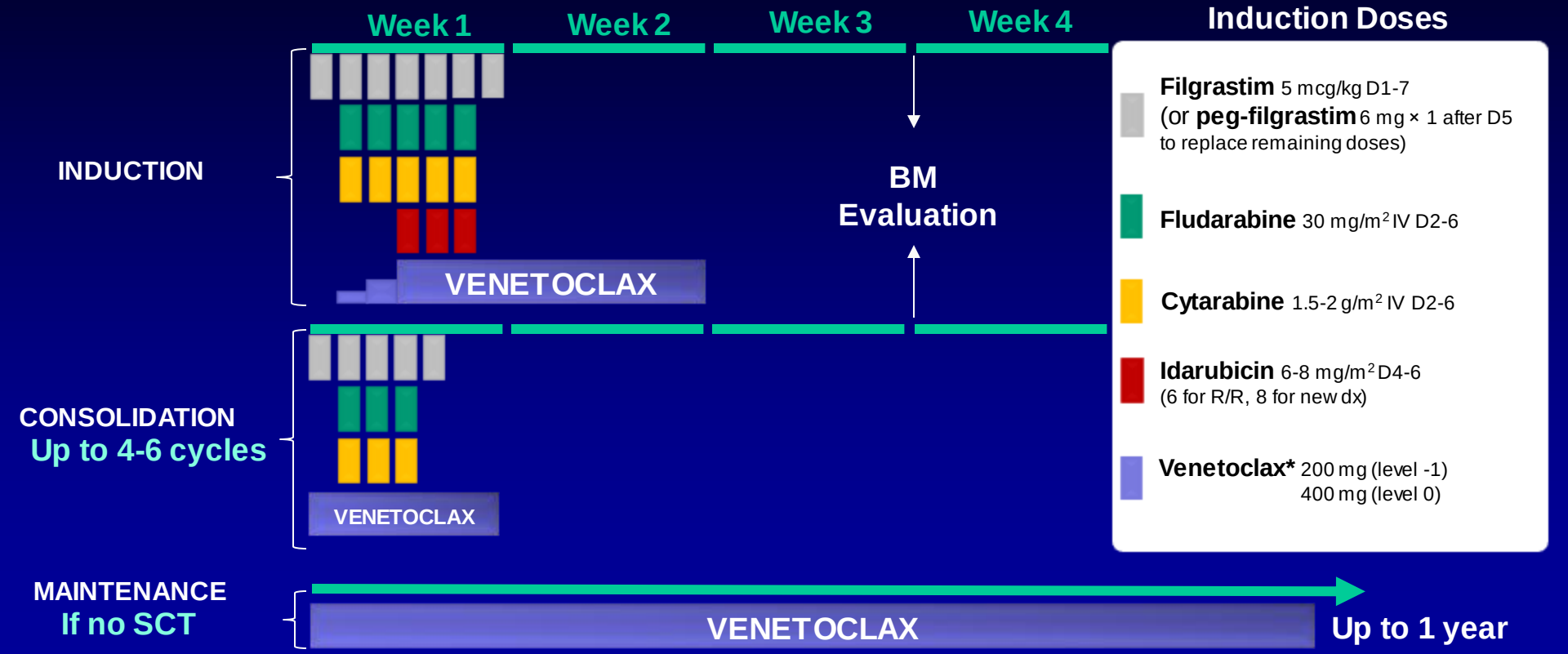
  IDA 8-10 mg/m^2/D × 3

  2 inductions

- FLAG-IDA × 2 → HD Ara C 1.5-3 g/m^2 Q12h D1, 3, 5— × 2
- CLIA – F replaced with CDA 5 mg/m^2 daily × 5 in induction

Burnett. *J Clin Oncol*. 2013;31:3360-3368.

FLAG-IDA-VEN Treatment Plan

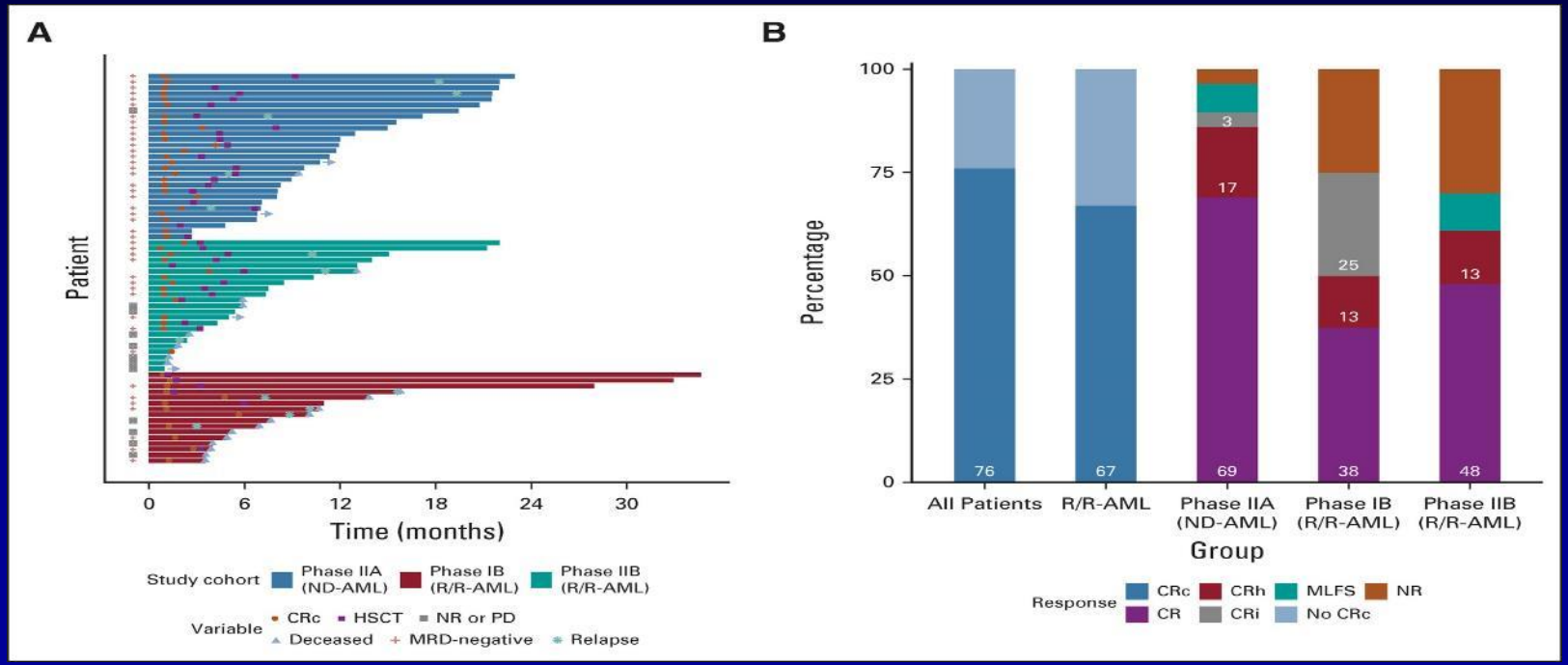


Abou Dalle, et al. *Blood*. 2019;134:abstract 176.

*Concomitant azole permitted with adequate dose reduction.

FLAG-IDA + Venetoclax in AML

- FLAG-IDA + VEN evaluated in R/R AML, then newly Dx AML
- 68 pts Rx: ND AML 29; R/R AML 39

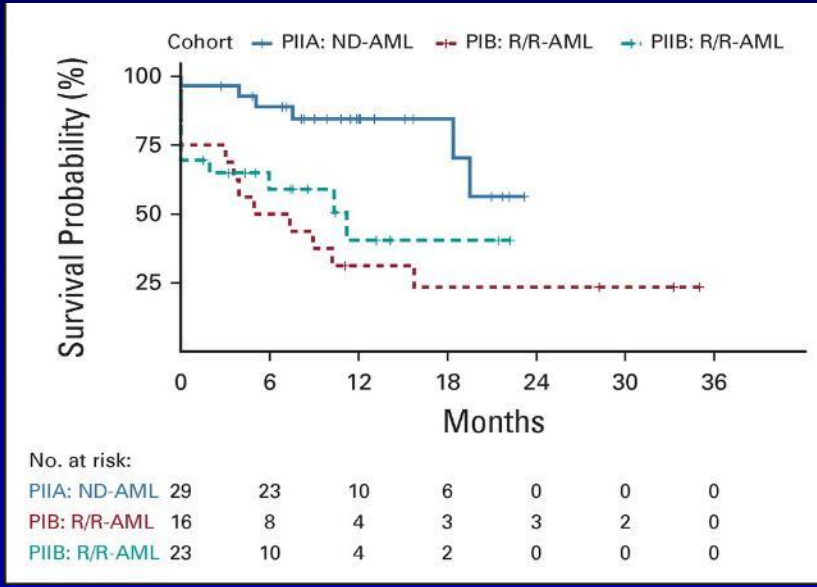


DiNardo CD, et al. *J Clin Oncol*. 2021 May 27. Online ahead of print.

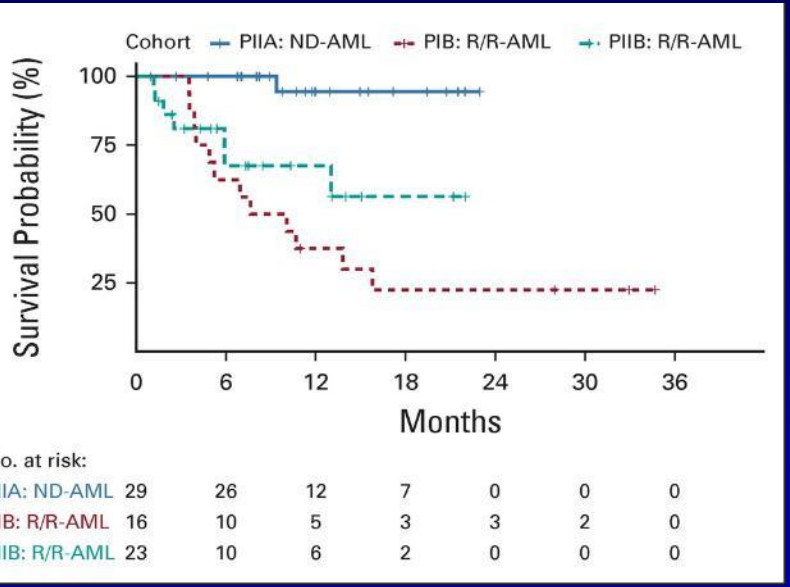
FLAG-IDA + Venetoclax in AML

- FLAG-IDA + VEN evaluated in R/R AML, then newly Dx AML
- 68 pts Rx: ND AML 29; R/R AML 39. Median FU 12 months; ND AML 12-mos OS 94%

EFS



OS



DiNardo CD, et al. *J Clin Oncol*. 2021 May 27. Online ahead of print.

CLIA-Venetoclax: Study Design

Venetoclax Dosing (PO daily on days 2–8 ± 1 day)				
Dose Level	Patients on posaconazole	Patients on strong CYP3A inhibitor	Patients on moderate CYP3A inhibitor	Patients not on CYP3A inhibitor
–1	50 mg	50 mg	100 mg	200 mg
1	70 mg	100 mg	200 mg	400 mg

Induction

Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Cladribine 5 mg/m^2	X	X	X	X	X			
Cytarabine 1500 mg/m^2	X	X	X	X	X			
Idarubicin 10 mg/m^2	X	X	X					
Venetoclax		X	X	X	X	X	X	X

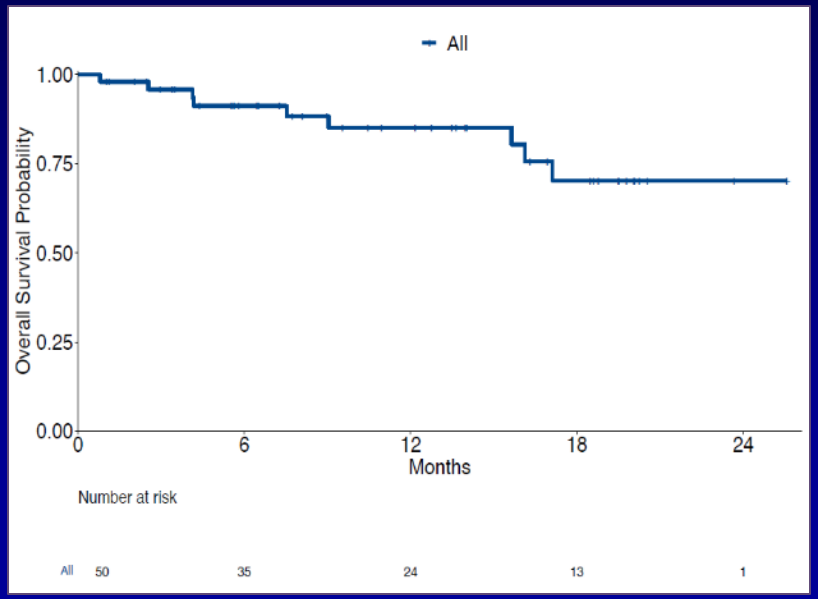
Consolidation

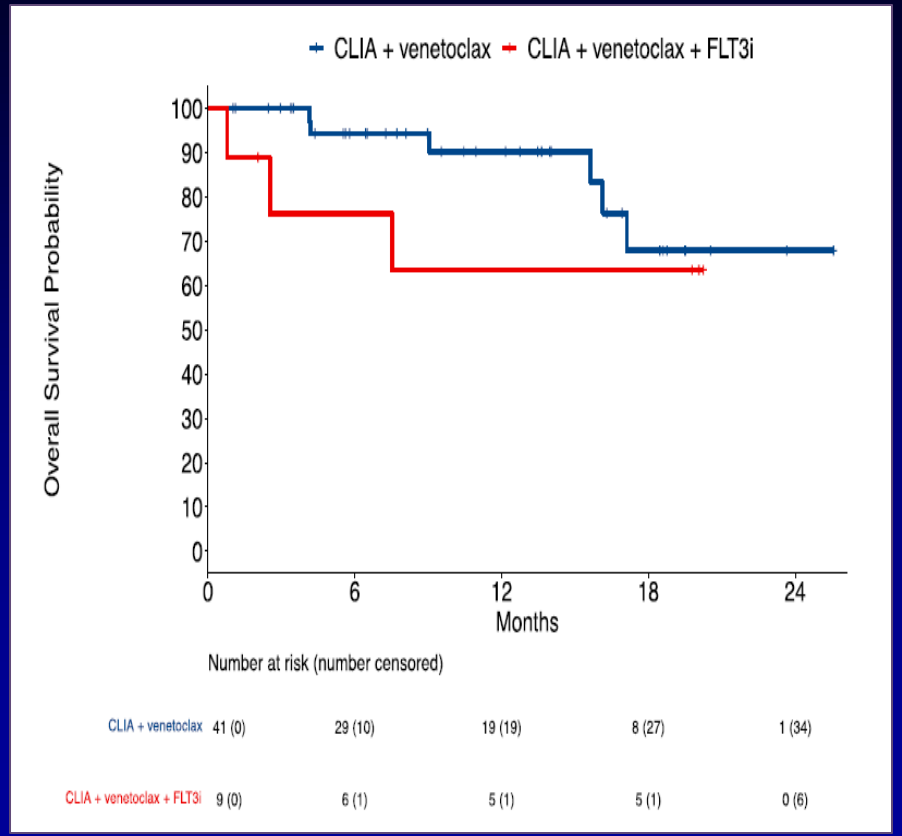
Treatment	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8
Cladribine 5 mg/m^2	X	X	X					
Cytarabine 1000 mg/m^2	X	X	X					
Idarubicin 8 mg/m^2	X	X						
Venetoclax		X	X	X	X	X	X	X

Kadia T, et al. ASCO 2020. Abstract 7539.

CLIA + Venetoclax in Newly Dx AML

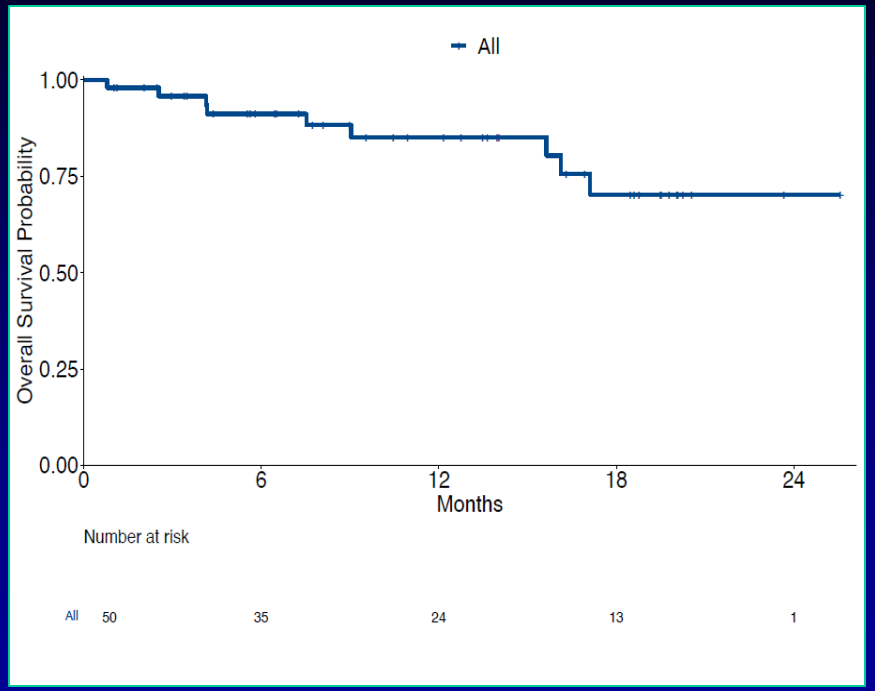
- 31 pts Rx with CLIA-VEN; median age 48 yrs (18–64)
- CR+CRi 28/31 = 90% ; early 4/8-wk mortality 3/3; 12-mo OS 81%

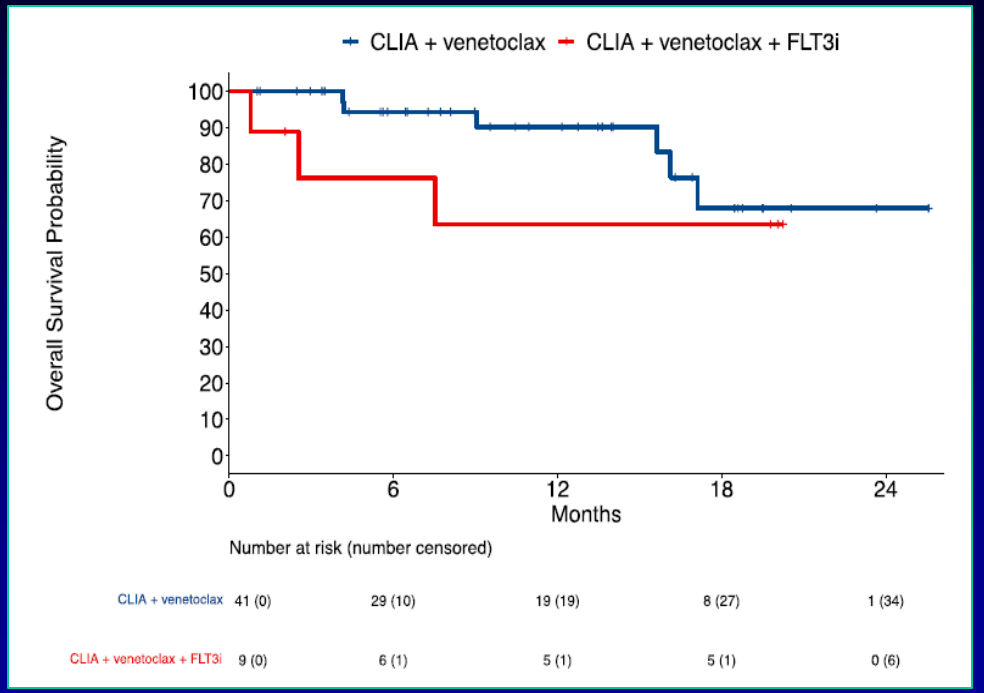




Kadia T, et al. *Lancet Hematol.* 2021;8(8):e552-e561.

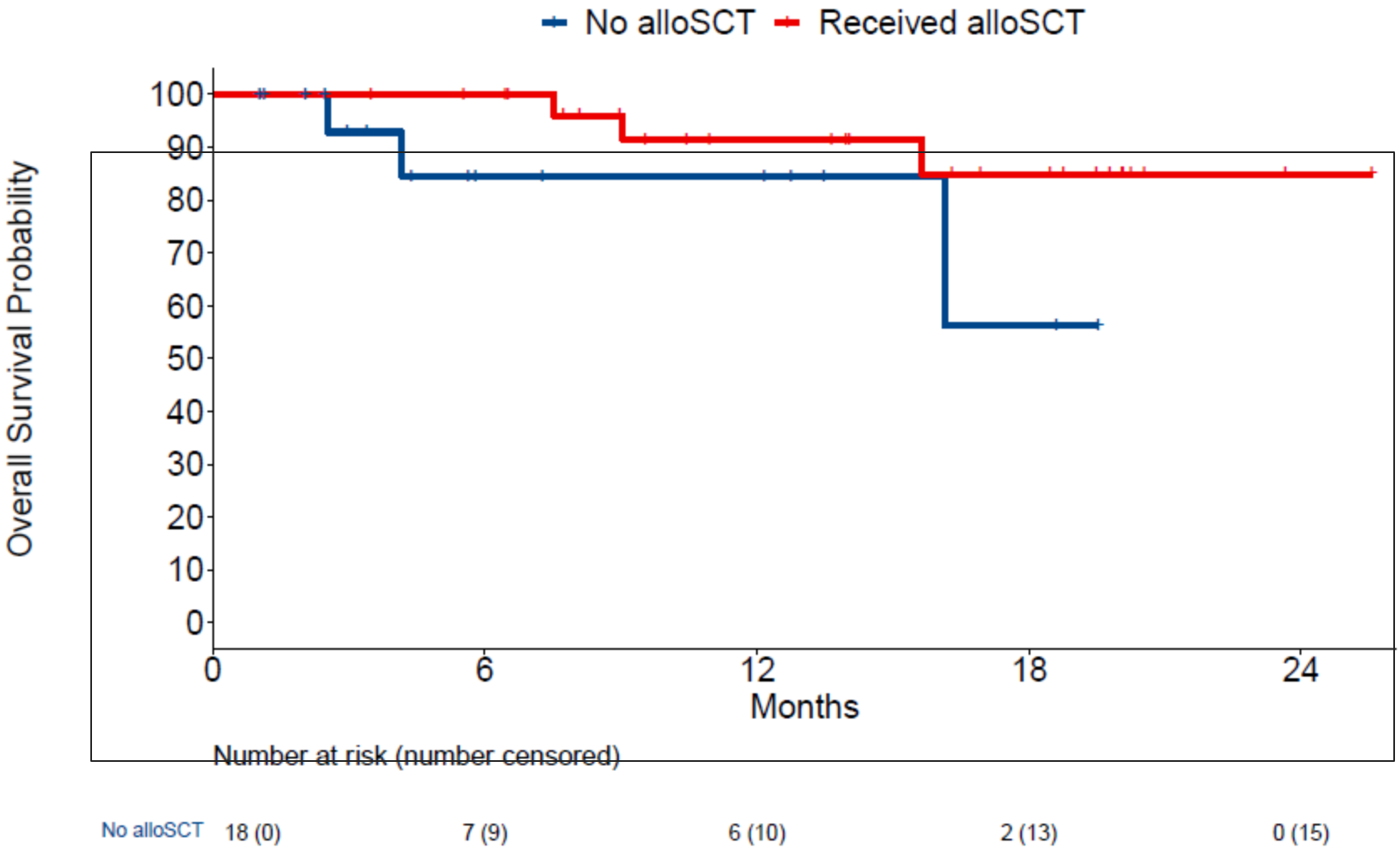
Overall Survival



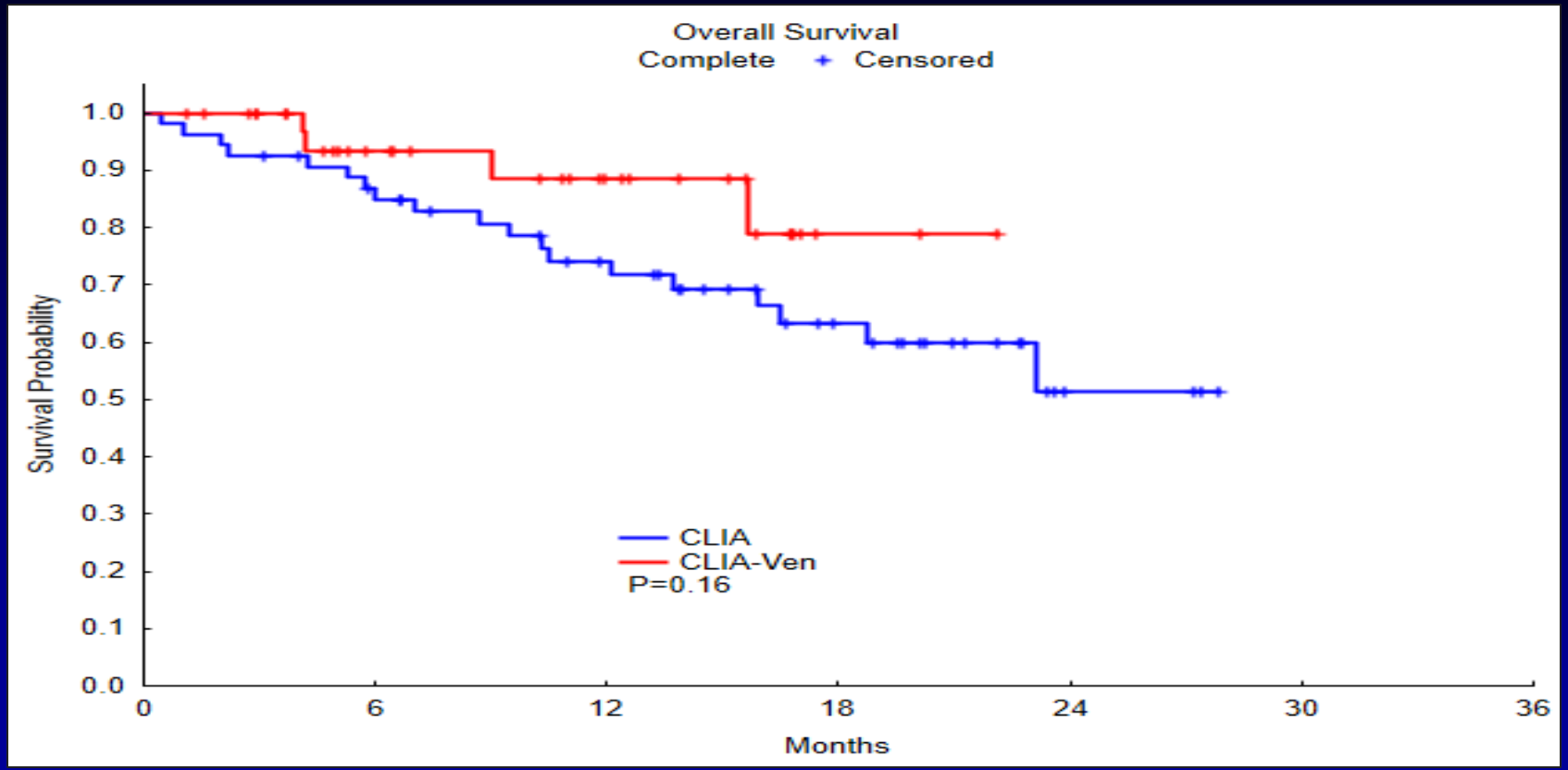


Median follow up of 13+ months

Kadia T, et al. *Lancet Hematol.* 2021;8(8):e552-e561.

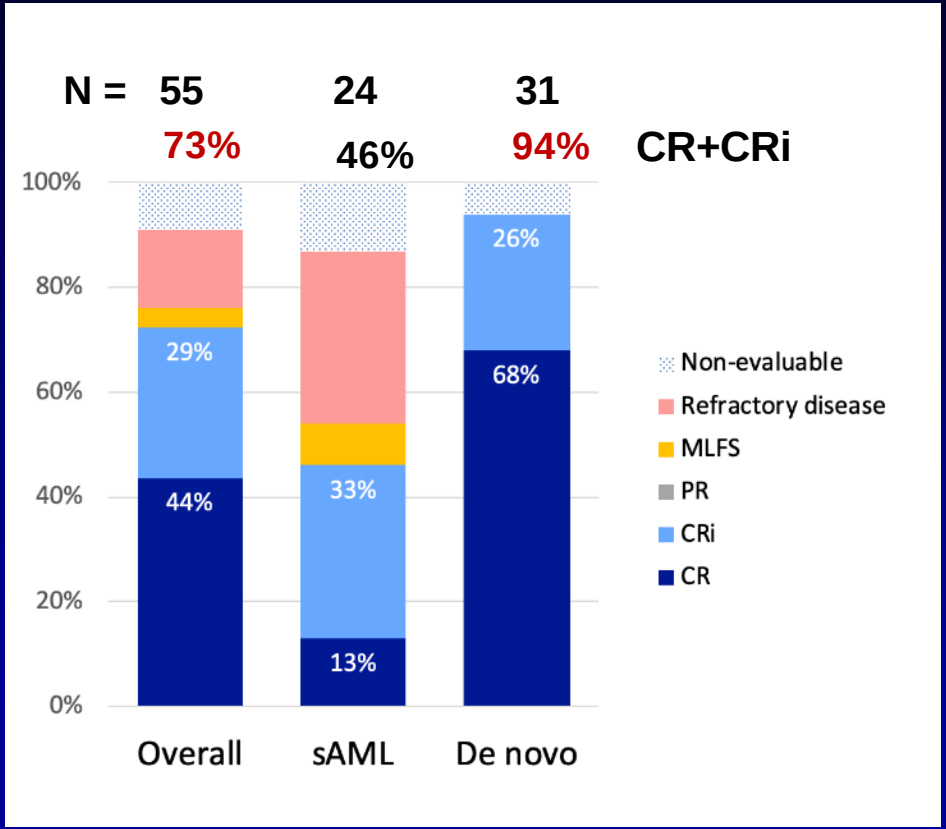

No alloSCT
Received alloSCT
Overall Survival Probability
100
90
80
70
60
50
40
30
20
10
0
0
6
12
18
24
Months
Number at risk (number censored)
No alloSCT
18 (0)
7 (9)
6 (10)
2 (13)
0 (15)

Overall Survival of CLIA-Ven vs CLIA

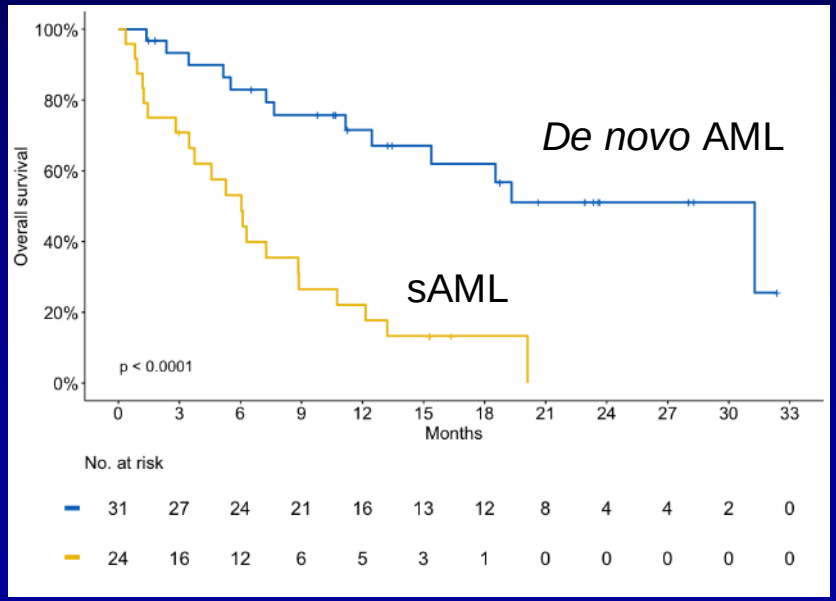


Kadia T, et al. *Lancet Hematol.* 2021;8(8):e552-e561.

2+5 + Venetoclax in Older AML (median age 72 yrs; range 63–82) Frontline Rx



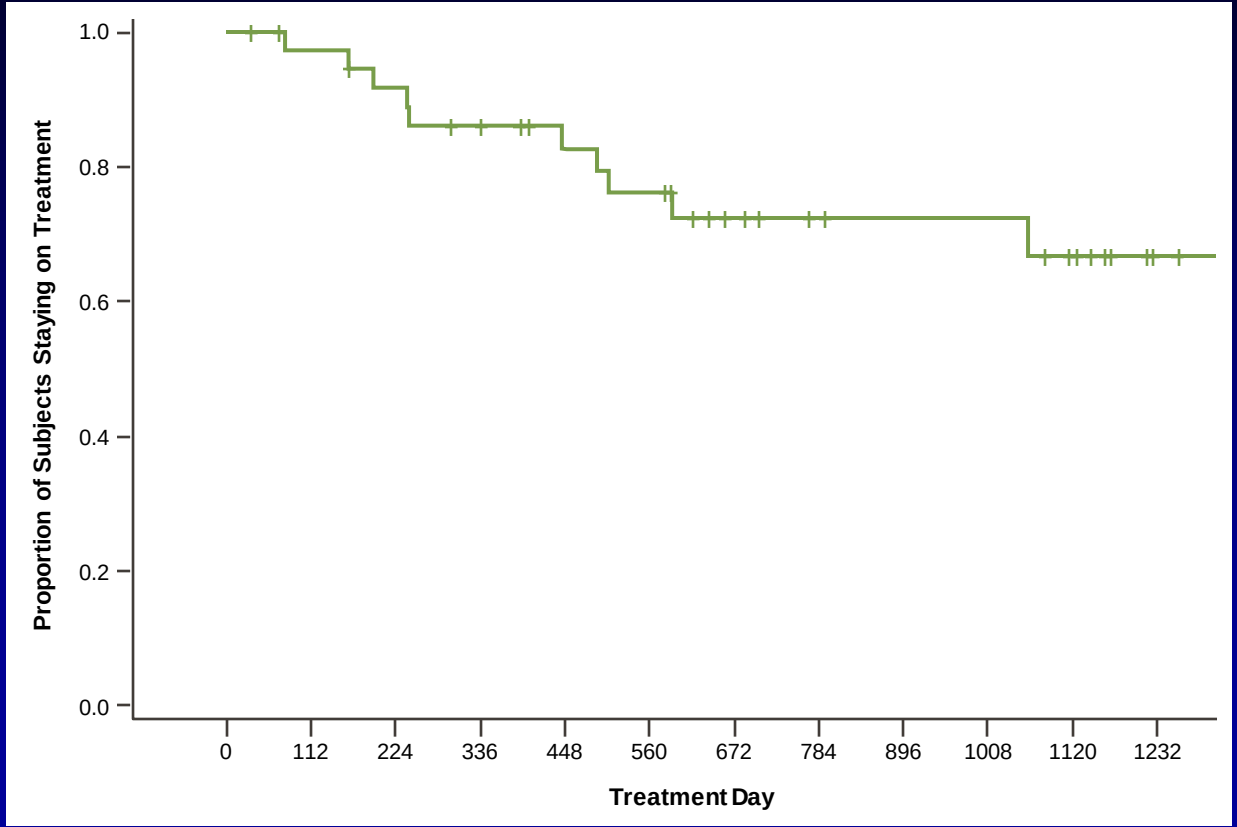
Median follow up: 20.2 months		
	OS at 12m	OS at 18m
Overall	50%	40%
De novo AML	72%	62%
sAML	22%	13%



Chua CC, et al. *J Clin Oncol*. 2020;38(30):3506-3517.

Phase I 3+7 With Gilteritinib in Newly Dx AML

- 79 pts Rx with 3+7 and gilteritinib 120 mg daily × 14; *FLT3*-mut 56%
- Marrow CR 62/76 = 82%; same in FLT3wt
- 4-wk mortality 0%
- Estimated 2-yr survival 70%



Pratz KW, et al. *Blood*. 2020;136: abstract 24.

Older AML. Low Intensity Regimens

	Clo-araC-DAC	CDA-araC-DAC	AZA/DAC+VEN	LD araC + VEN
No Rx	118	118	145	71
% CR	60	58	-	26
% CR + CRi/p	68	68	67	62
Median OS (mos)	11	13.8	17.5 (14.7 in randomized)	11.4
% 2-yr OS	25	28	45	25-30
% 4-wk death	3	1	-	3

Kadia. *Cancer*. 2015;121:2375; Kadia. November 2017. DiNardo. ASH 2017; Wei. ASH 2017. Abstract 890.

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 one of the co-morbidities
    - 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 2:1
N = 433*

Venetoclax + Azacitidine (N = 286)
Venetoclax 400 mg PO, daily, days 1–28 +
Azacitidine 75 mg/m² SC /IV days 1–7

Placebo + Azacitidine (N = 145)
Placebo daily, days 1–28
+ Azacitidine 75 mg/m² SC /IV days 1–7

Endpoints

Primary

- Overall survival

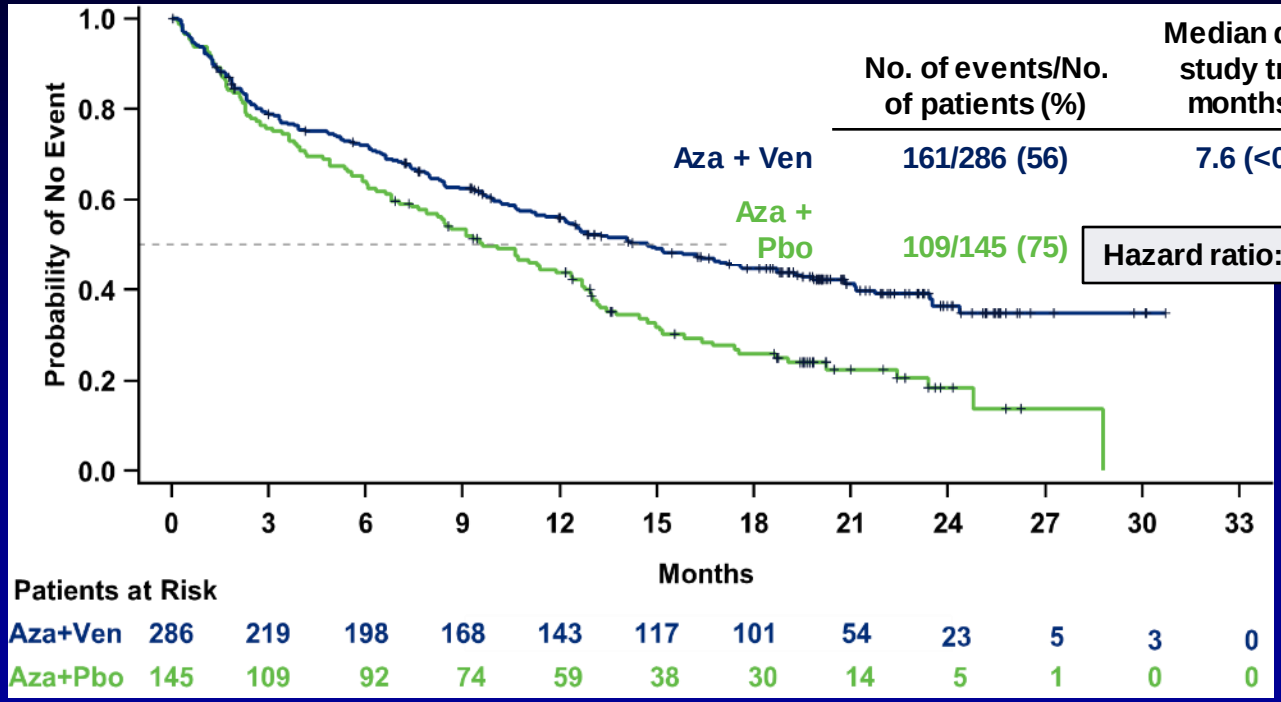
Secondary

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

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

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

AZA +/- VEN in AML – Overall Survival



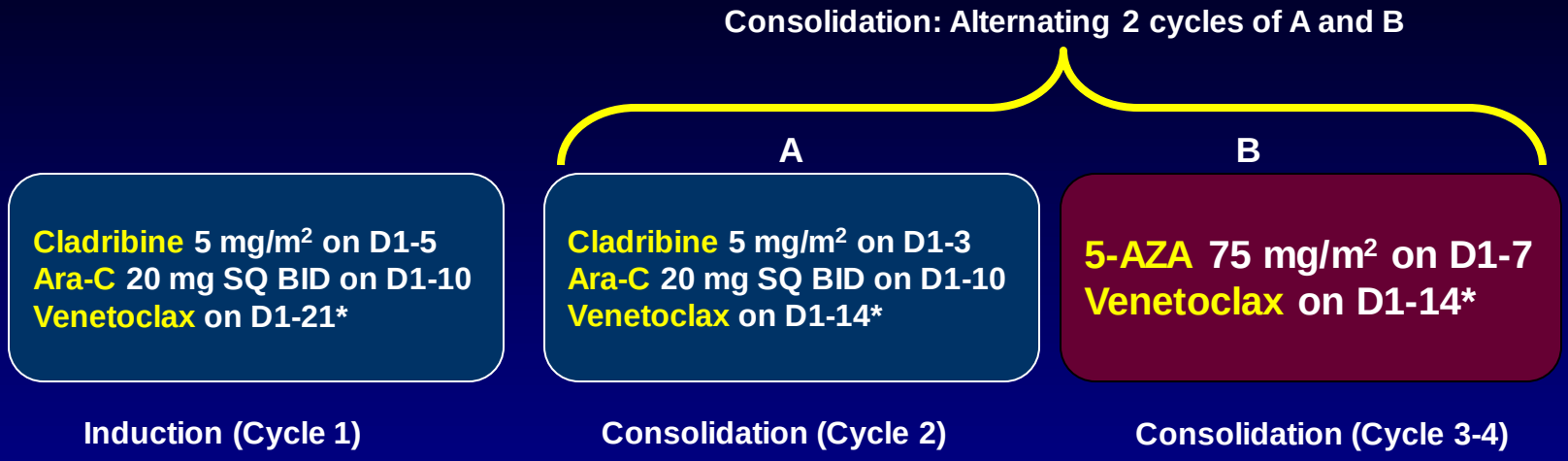
	No. of events/No. of patients (%)	Median duration of study treatment, months (range)	Median overall survival, months (95% CI)
Aza + Ven	161/286 (56)	7.6 (<0.1–30.7)	14.7 (11.9–18.7)
Aza + Pbo	109/145 (75)		

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.

Venetoclax Added to Cladribine/LDAC Alternating With 5-AZA

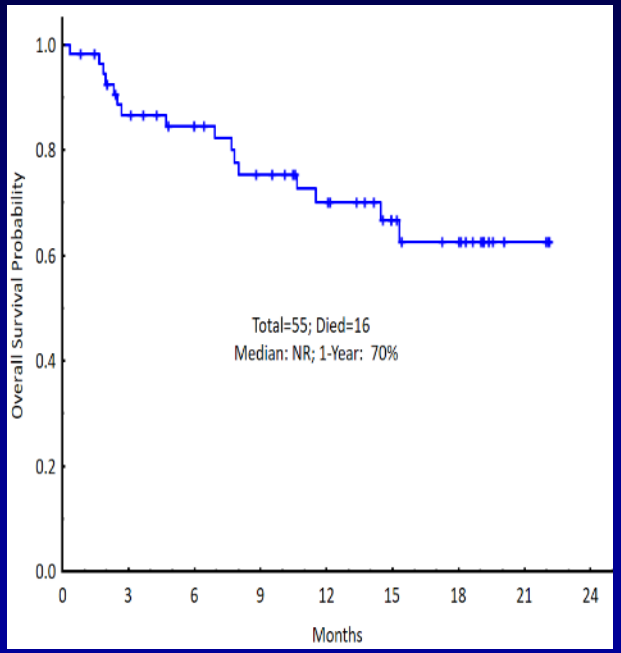


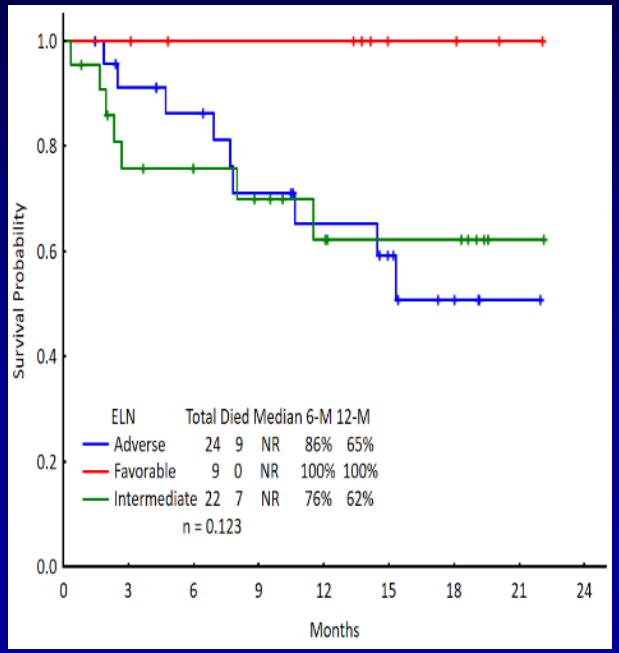
Venetoclax Dosing (PO Daily on Days 1–21)			
Dose Level	**Patients on strong CYP3A inhibitor**	**Patients on moderate CYP3A inhibitor**	**Patients not on CYP3A inhibitor**
-1	50 mg	100 mg	200 mg
1	100 mg	200 mg	400 mg

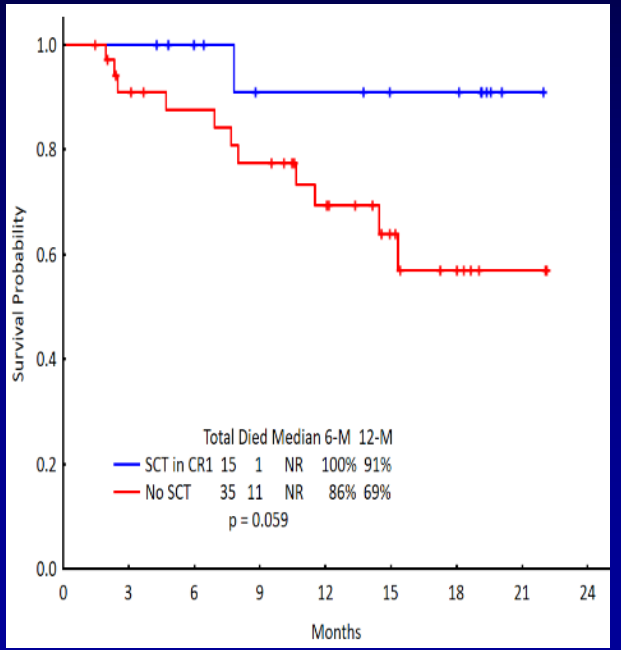
Kadia T, et al. *Blood.* 2020;136: abstract 25.

CDA–LD Ara-C–VEN/AZA-VEN in Older Newly Dx AML

- 55 pts; median age 68 yrs (57–84)
- CR 42/55 = 78%. CR + CRi 50/54 = 93%. MRD negativity 42/50 = 84%
- 4/8-wk mortality 2/4%; 18-mo OS 60%

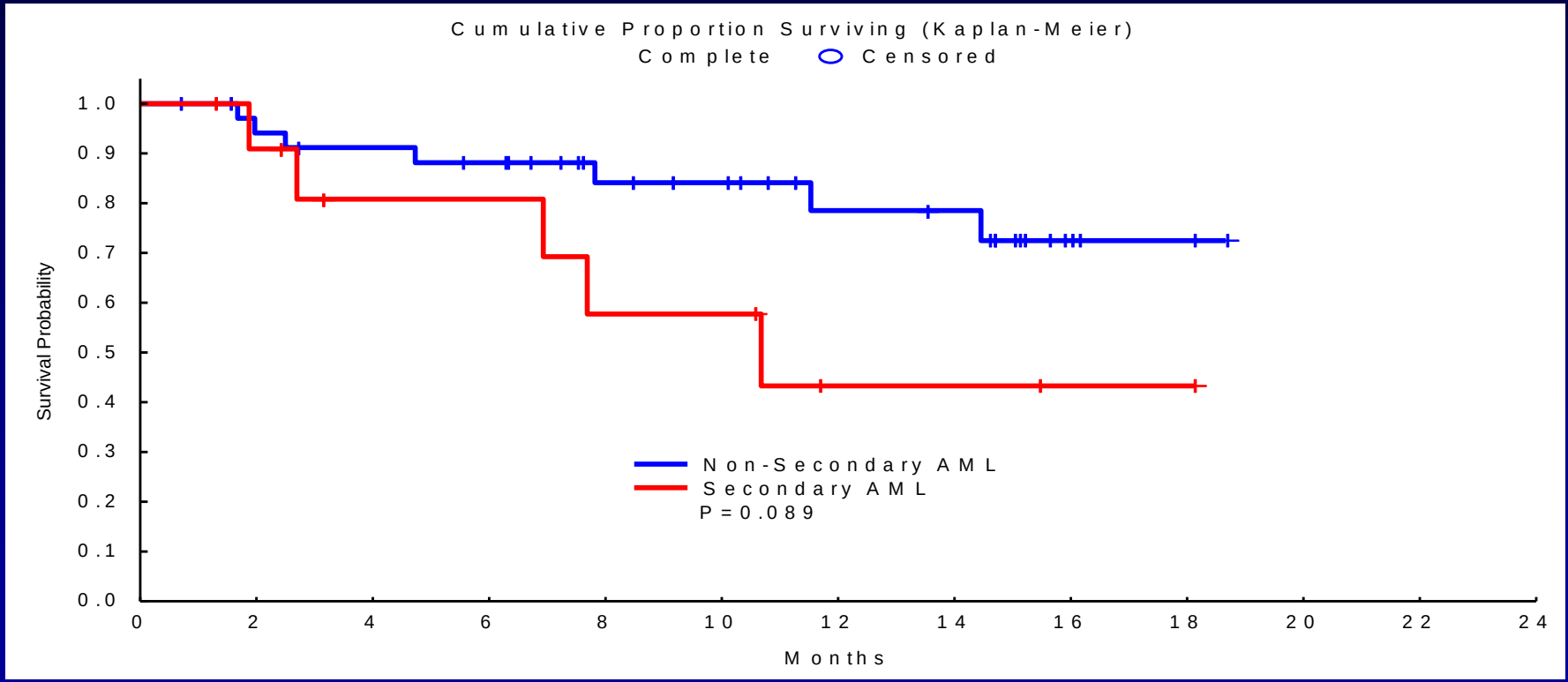




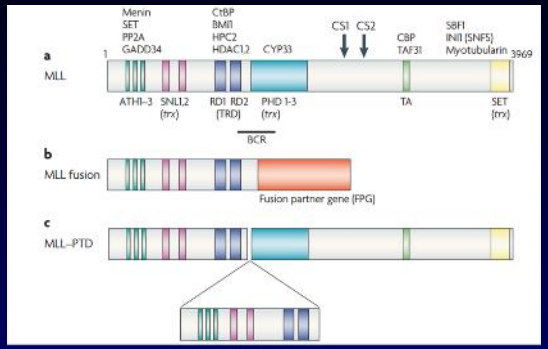


Kadia T, et al. *Blood*. 2020;136: abstract 25.

CDA-araC-VEN/AZA-VEN – Survival

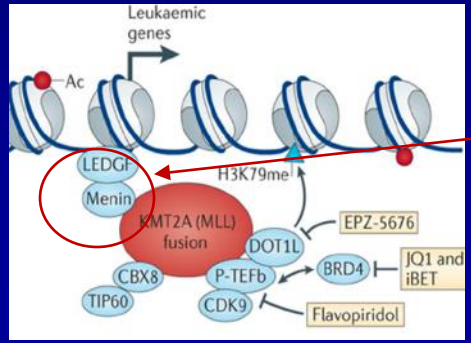


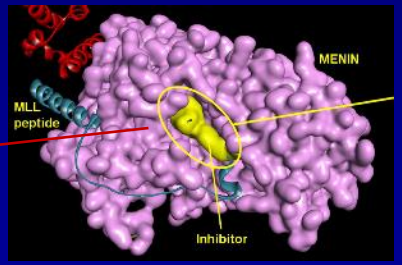
MLLr Leukemias



MLLr is a therapeutic challenge

- Resistance to therapy
- Pediatric and adult leukemia problem
- Unique set of leukemias (ALL, AML, MPAL) (5%–10%)
- Increased understanding of clinical features and biology. No specific Rxs approved





Menin inhibitors target the high affinity binding site of MLL1(aa 9-13) on Menin

SNDX-5613 in R/R AML (mostly MLL)

- 43 pts Rx: 34 AML, 8 ALL, 1MPAL. 26(61%) MLL; 9(21%) NPM1
- SNDX-5613 113-339 mg orally BID
- ORR 15/31 = 48% -- CR/CRh 5,CRi/MLFS 5
- MRD negative 10/15 responders = 67%
- ORR in MLL 13/24 = 54%; ORR NPM1 2/7 (29%)
- Adverse events: QTc prologation 14%

Immune Strategies to Kill AML

- Recruiting CD3 T cell – BiTEs linking to CD3 and targeting CD33/123; CAR Ts with modified CD3 killer cells
- Recruiting macrophages – targeting CD47 on AML (magrolimab. ALX) or SIRP alpha on macrophages (Trillium, CC95251)
- Recruiting NK cells – allo NK-CAR Ts; NK engineered cells/repeated infusions
- Targets other than CD33/123, eg, CLL1

Anti-CLL1 CAR Ts in Children With R/R AML

- Second-generation CLL1 CAR Ts 0.3-1 million/kg single dose post lymphodepletion with Flu-CTX
- 11 children with R/R AML treated
- 9 responses = 82% – 5 CR MRD–, 3 CR MRD+, 1 PR

Zhang. JCO 39 (suppl). May 2021. ASCO 2021

FT 516/FT 516 (NK cells) in R/R AML

- Induced pluripotent stem cells (iPSC) derived NK cells: off the shelf; large volumes 90 million-1.5 billion; repeat infusions (3-6)
- FT538 no need for IL-2 cytokine support
- 12 pts Rx: 5 responses (42%) – 4 CRi, 1 MLFS
- Remission >6 mos in 2

Thank You

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Global Leukemia Academy

Q&A session

APTITUDE HEALTH

Global Leukemia Academy

Review of prognostic value of MRD in acute leukemias

Josep-Maria Ribera

APTITUDE HEALTH

Global Leukemia Academy EU Meeting
October 27–28, 2021

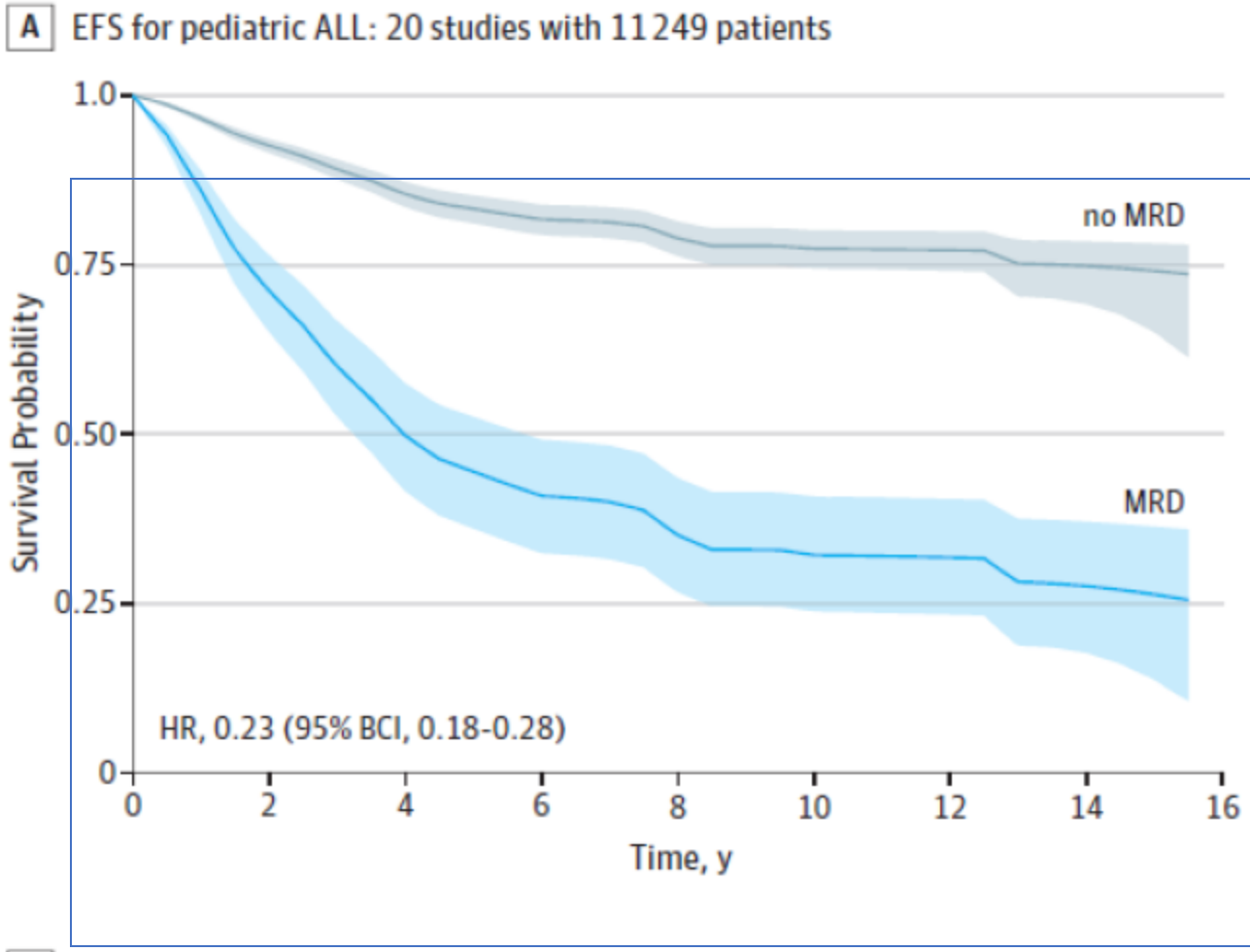
Review of the Prognostic Value of MRD in Acute Leukemias

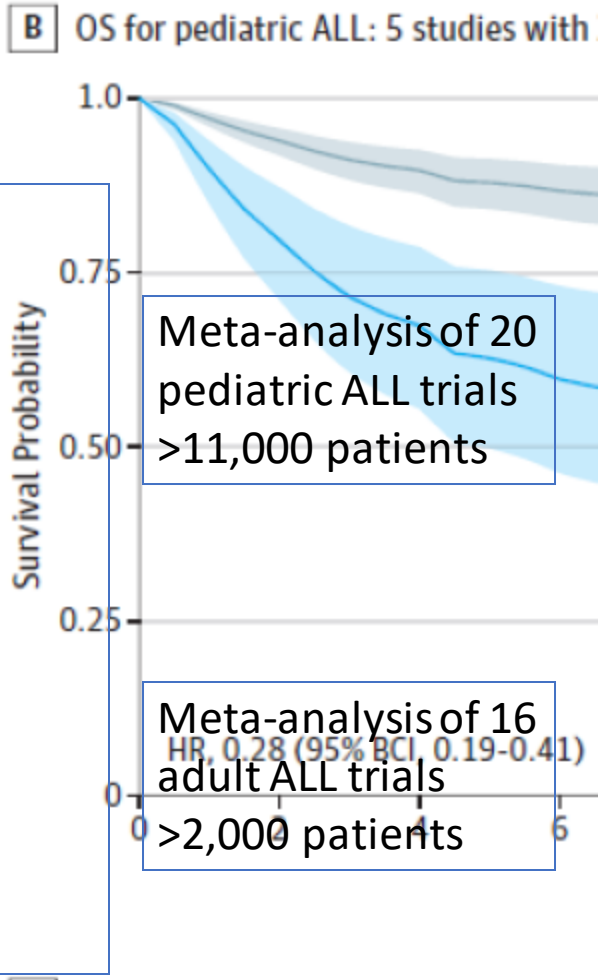
J.M. Ribera
Servicio de Hematologia Clinica
ICO-Hospital Germans Trias i Pujol
Institut de Recerca contra la Leucemia Josep Carreras
Badalona

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





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

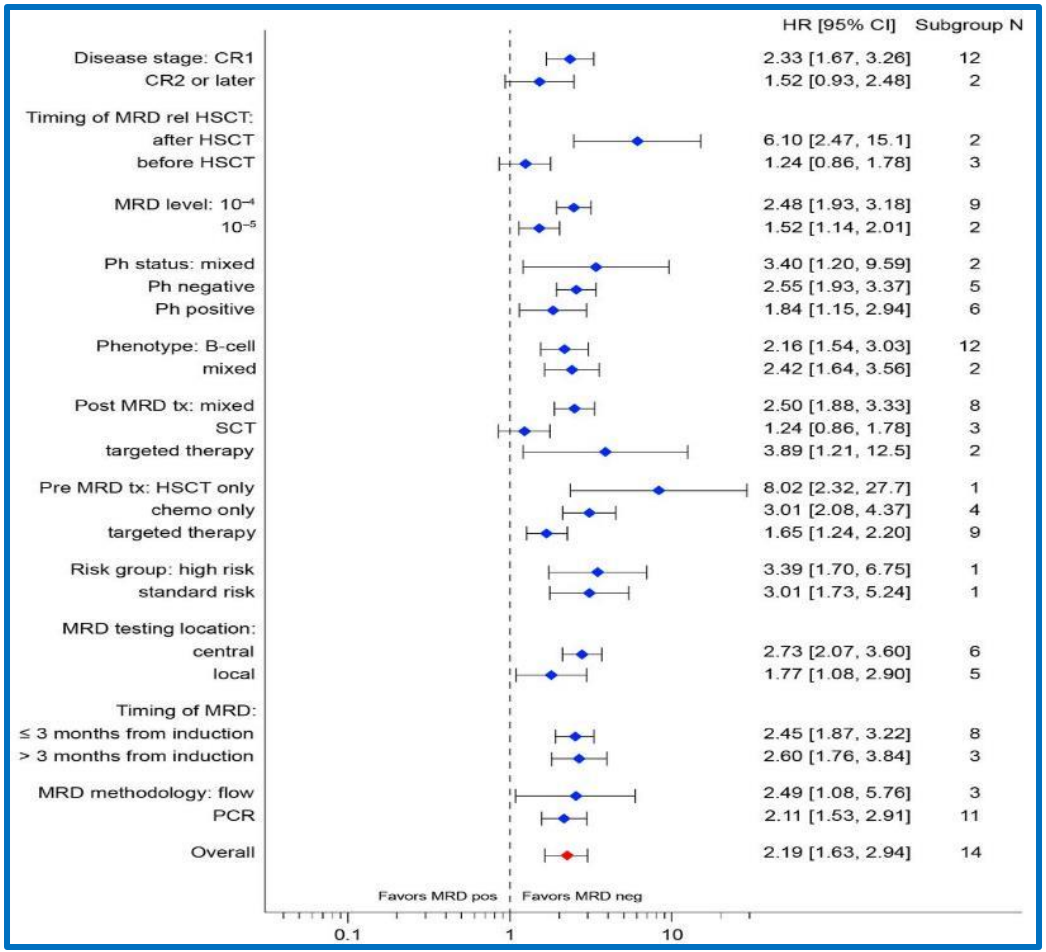
Meta-analysis of 16 adult ALL trials >2,000 patients

C EFS for adult ALL: 16 studies with 2065 patients

D OS for adult ALL: 5 studies with 806

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

Prognostic Value of MRD in All Situations



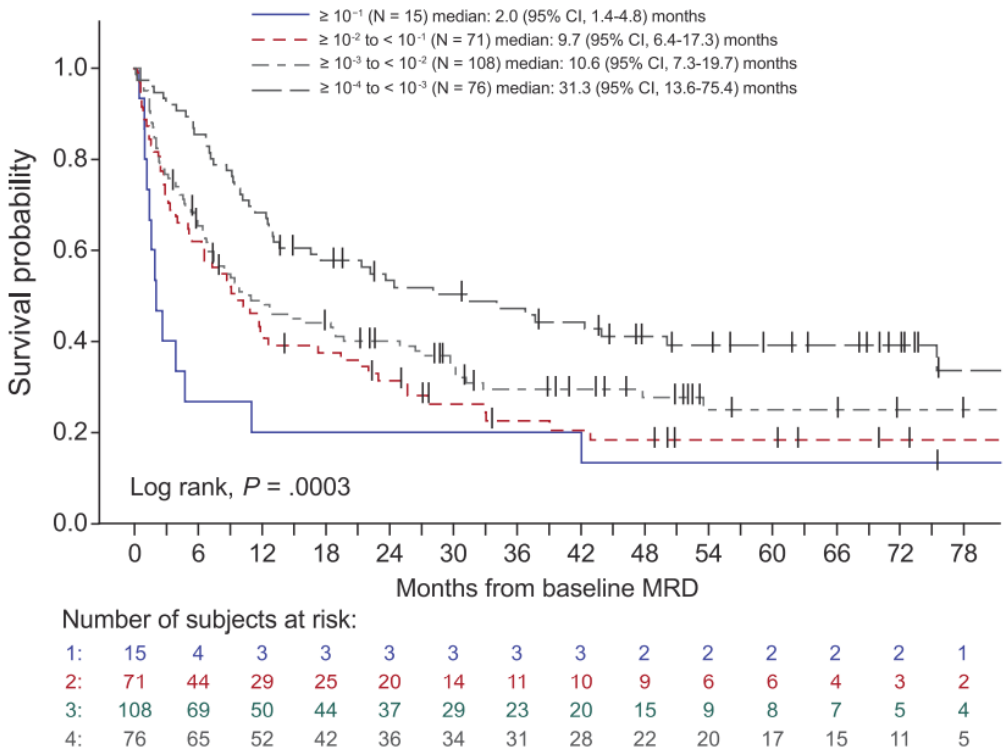
Bassan R, et al. *Haematologica*. 2019;104:2028-2039.

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

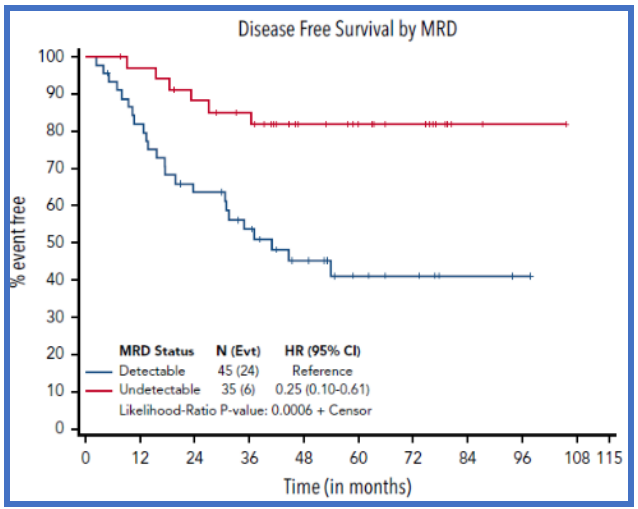
- Median DOR, 18.5 months (95% CI: 11.9, 27.2)
- Median RFS, 12.4 months (95% CI: 10.0, 19.0)
- Median OS, 32.5 months (95% CI: 23.6, 48.0)



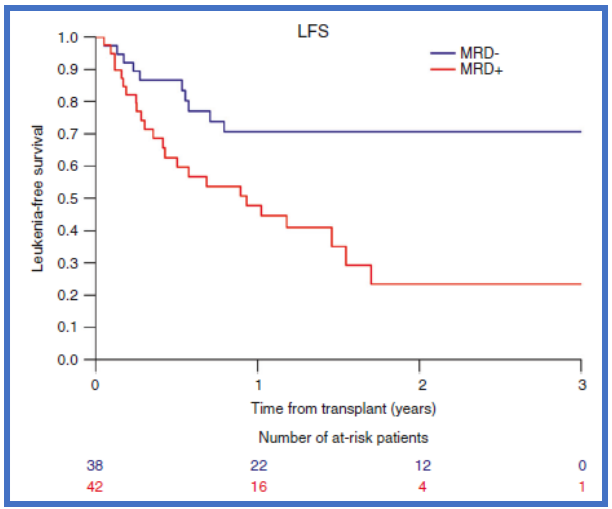
Gökbuget N, et al. *Hematology*. 2019;24:337-348.

Impact of MRD in Some ALL Subtypes

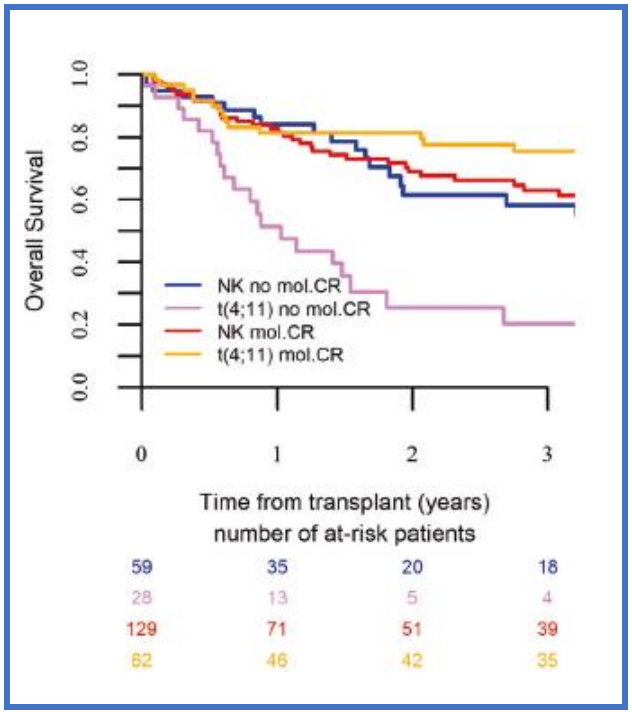
AYA[1]



IKZF1+[2]



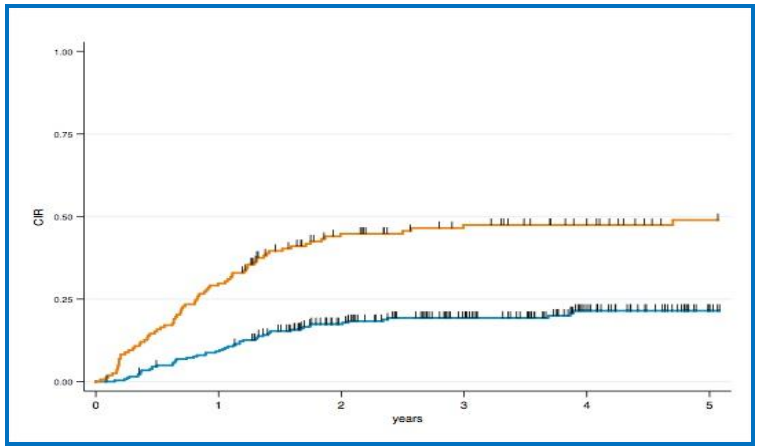
KMT2A+[3]

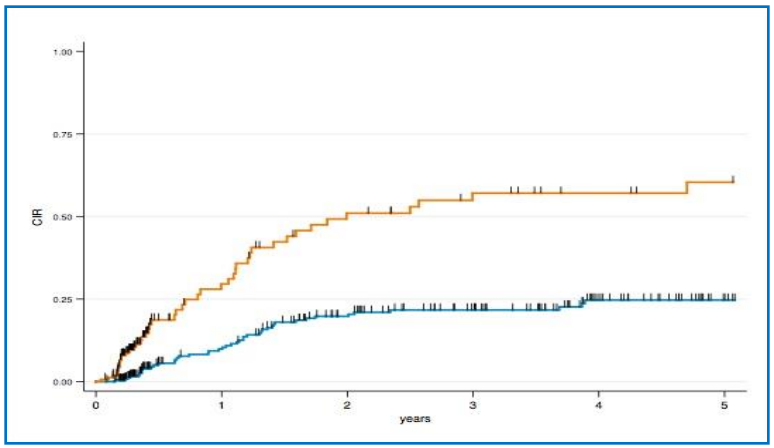


1. Stock W, et al. *Blood.* 2019;133:1548-1559; 2. Giebel S, et al. *Bone Marrow Transplant.* 2020. doi: 10.1038/s41409-020-01139-z; 3. Esteve J, et al. *Leukemia.* 2021. doi: 10.1038/s41375-021-01135-2.

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

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



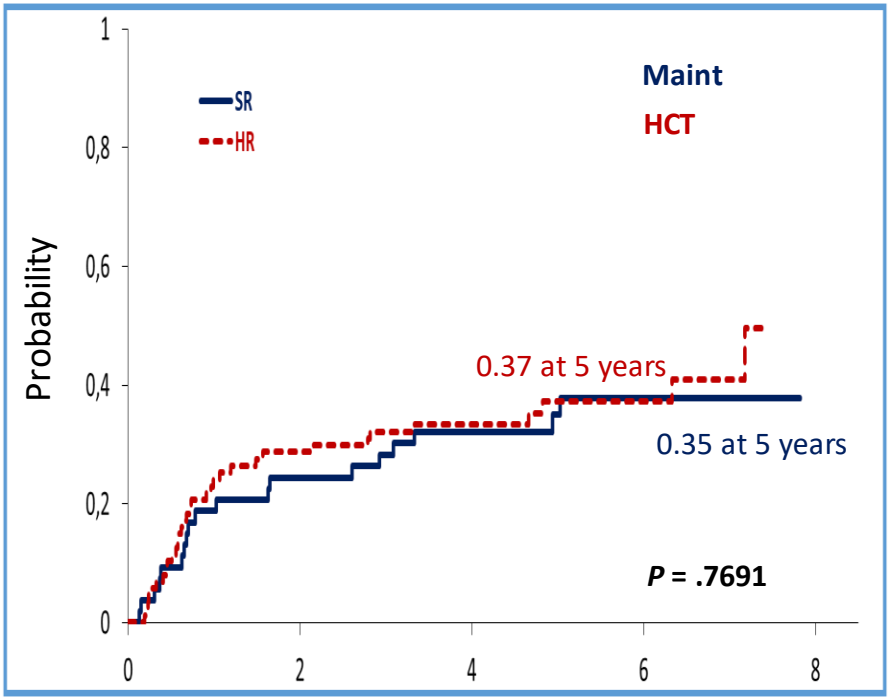


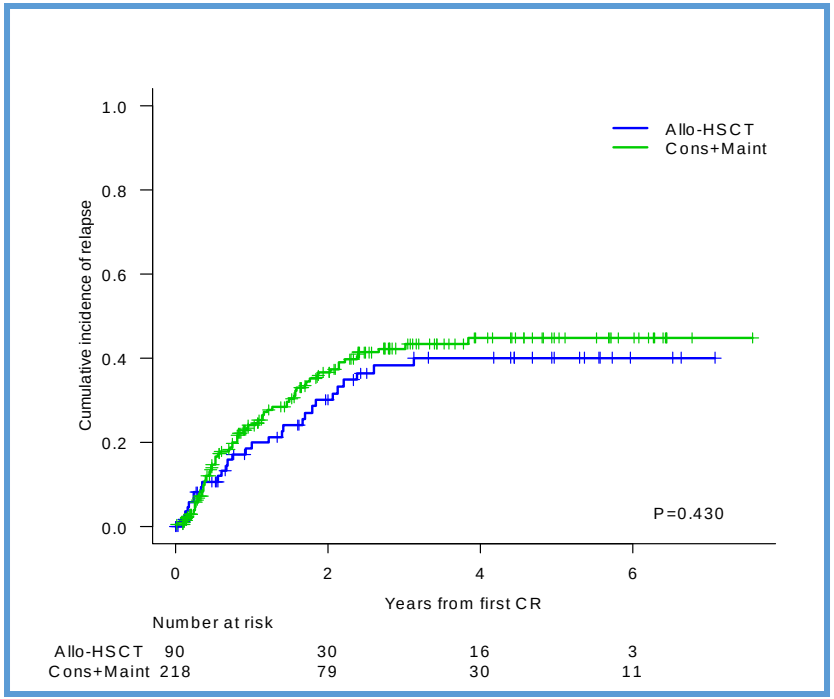
	Without AlloHSCT Censoring	With AlloHSCT Censoring
5-yr CCR in MRD+ pts	51.2%	39.6%
5-yr CIR in MRD– pts	21.2%	24.7%
Harrel's C-index	0.63	0.64

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)

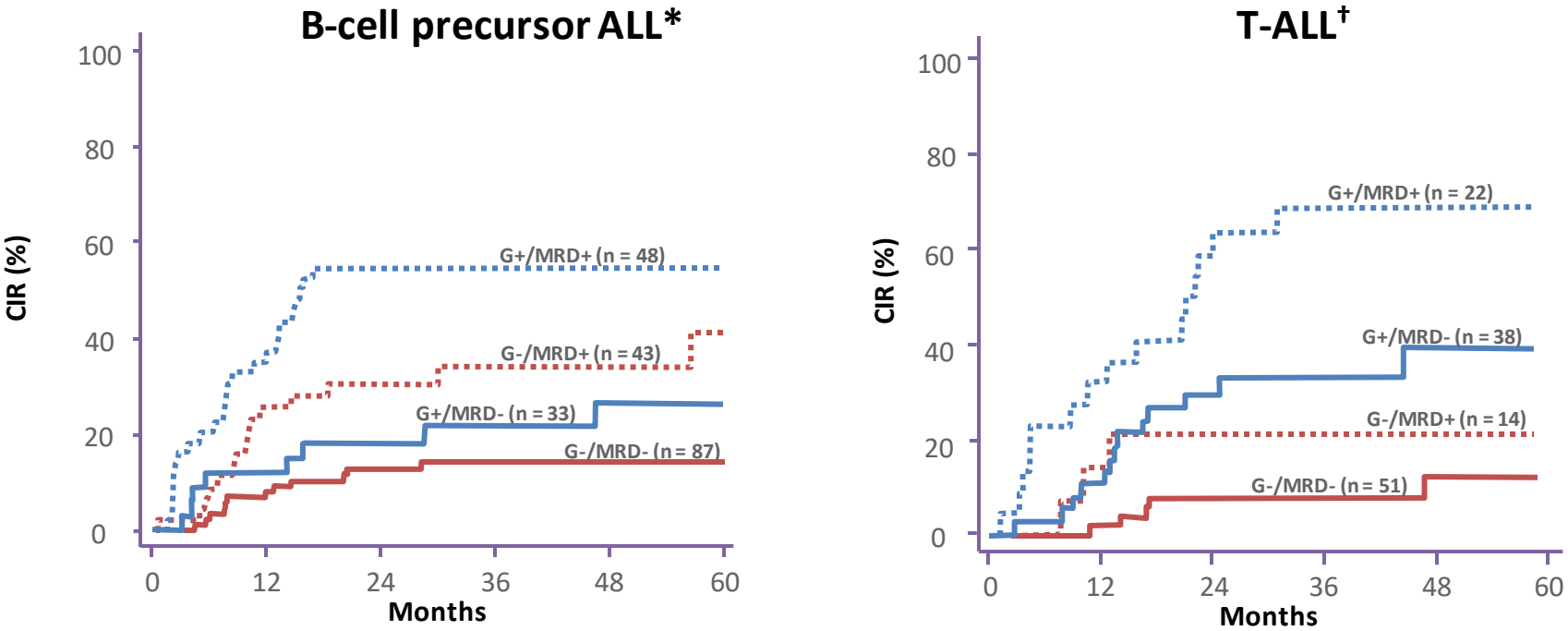




Bassan R, et al. *Blood Cancer J*. 2020;10(11):119.

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

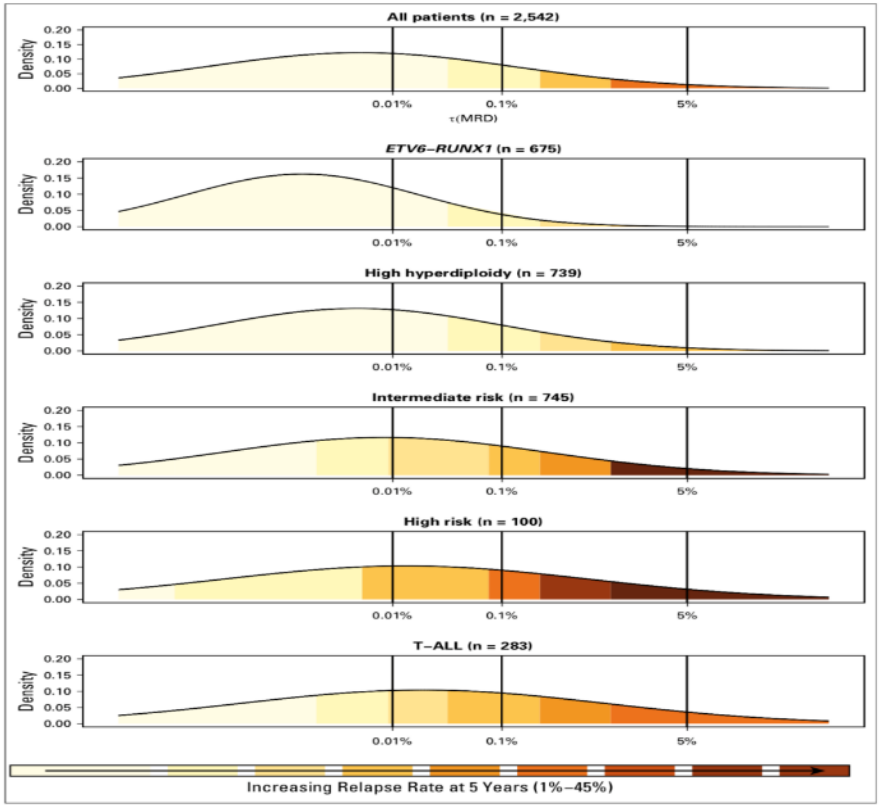
Adapted from Beldjord K, et al. *Blood*. 2014;123:3739-3749.

Value of MRD According to Genetic Subgroups

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

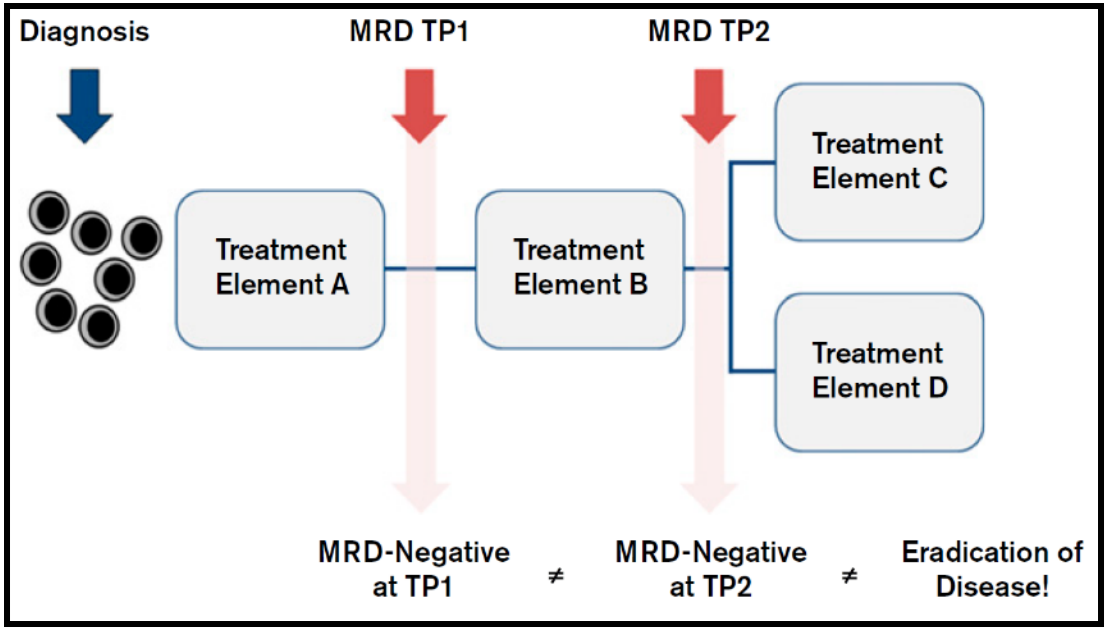
- Pediatric UKALL2003 study
  - –The risk of relapse was proportional to the MRD level within each genetic risk group
  - –However, absolute relapse rate that was associated with a specific MRD value varied significantly by genetic subtype

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

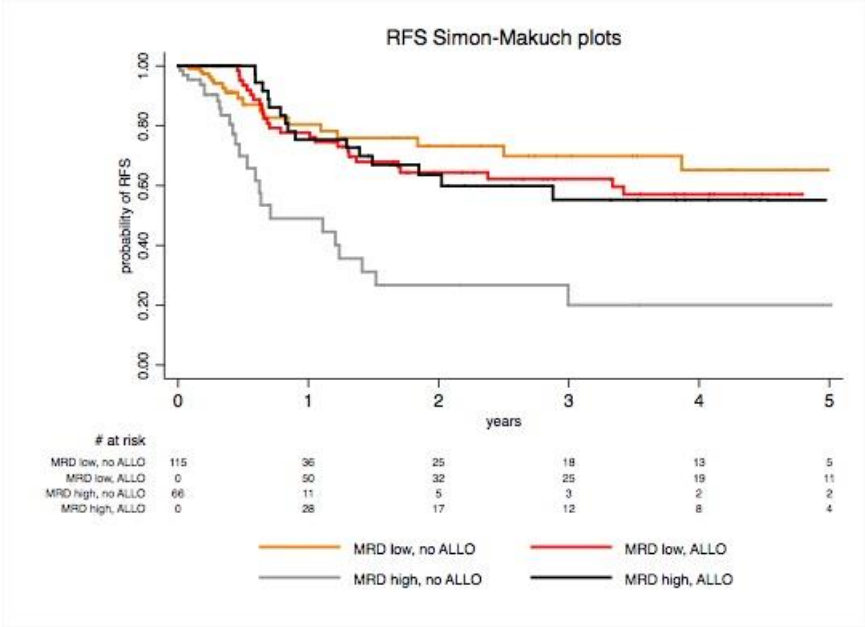
- Blinatumomab
- Inotuzumab ozogamicin
- CAR T cells

3. Targeted therapy

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

Allogeneic HSCT Benefits MRD+ Patients Only

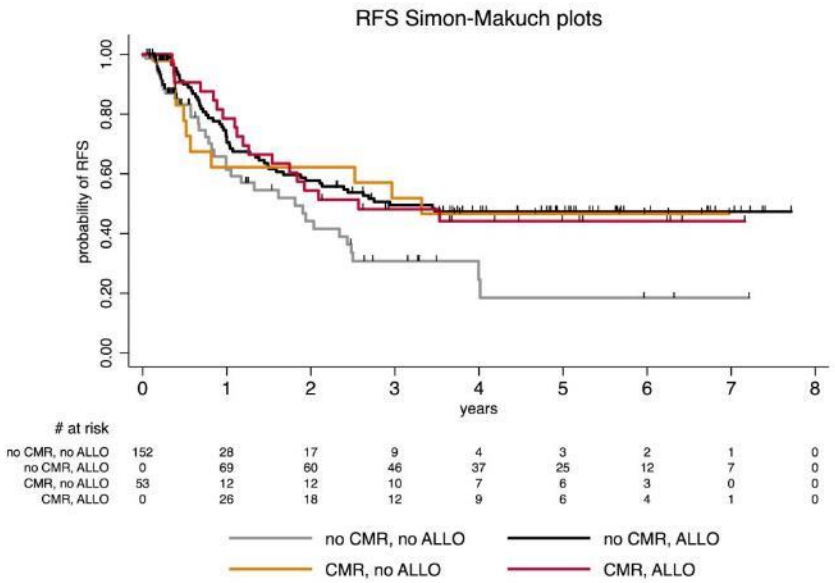
Ph– ALL



Test for interaction, *P* = .001

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

Ph+ ALL



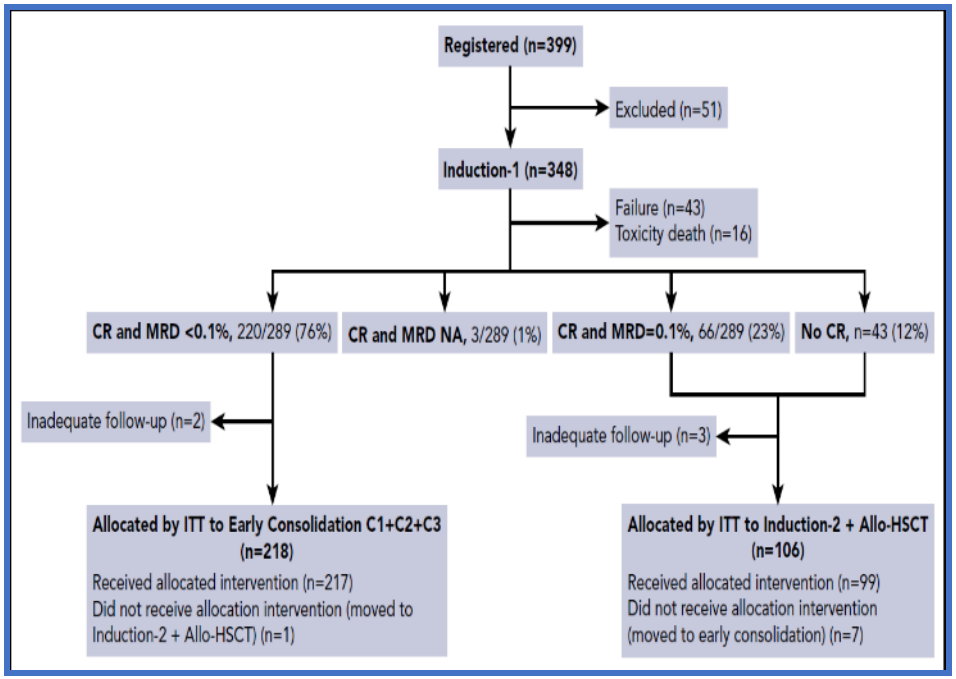
Test for interaction, *P* = .18

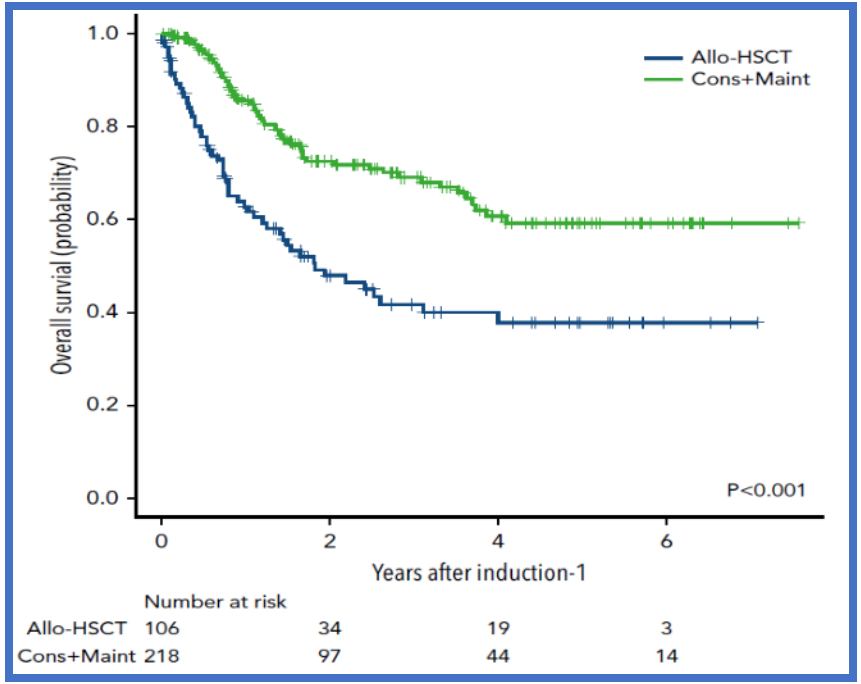
Chalandon Y, et al. *Blood*. 2015;125(24):3711-3719.

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

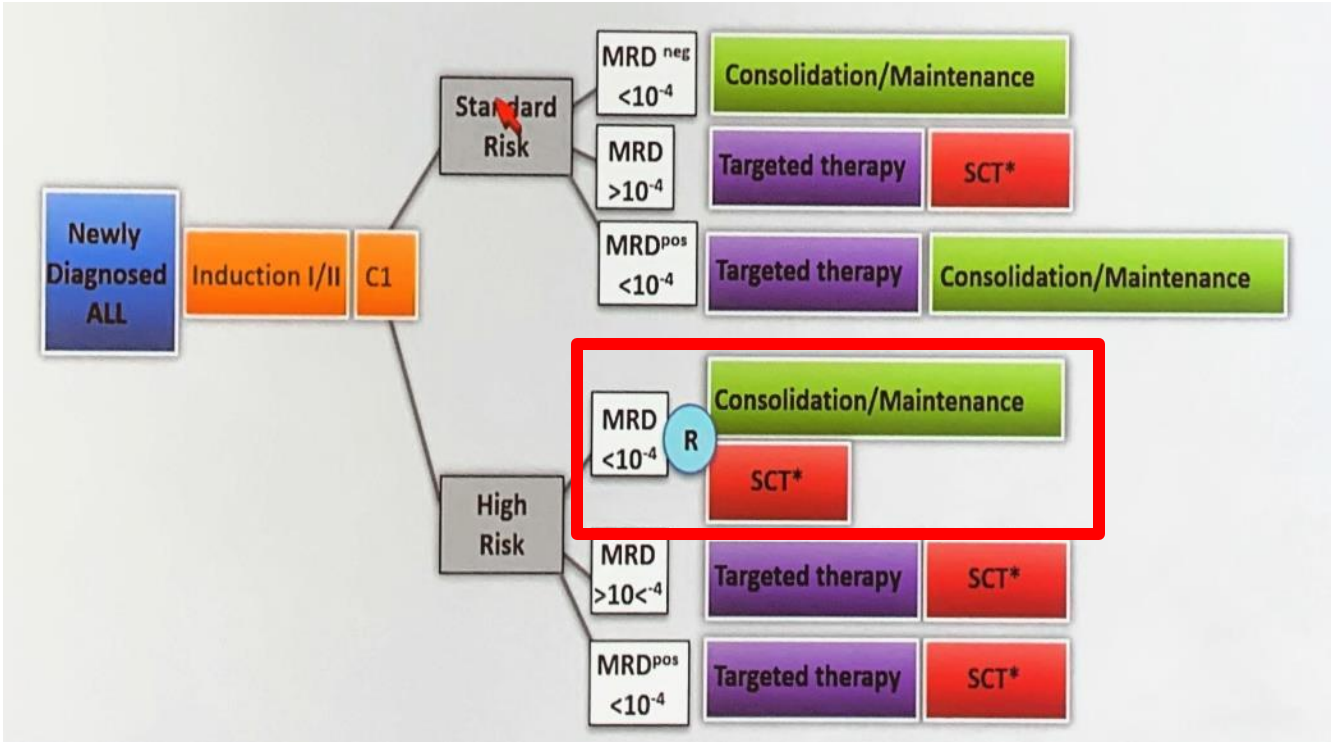
PETHEMA ALL HR11





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

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



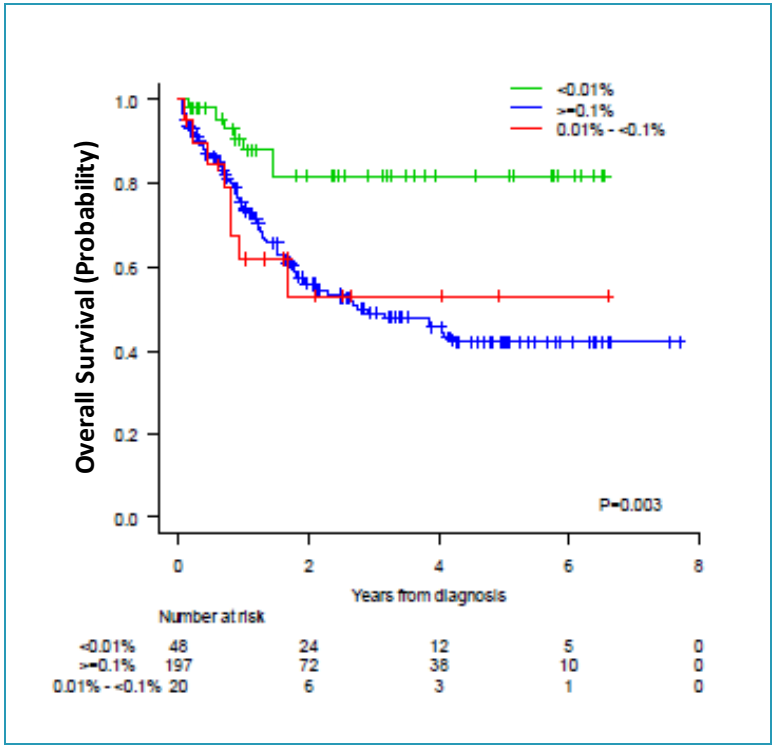
*Dose-reduced conditioning >45 yr.

Courtesy of N. Gokbuget.

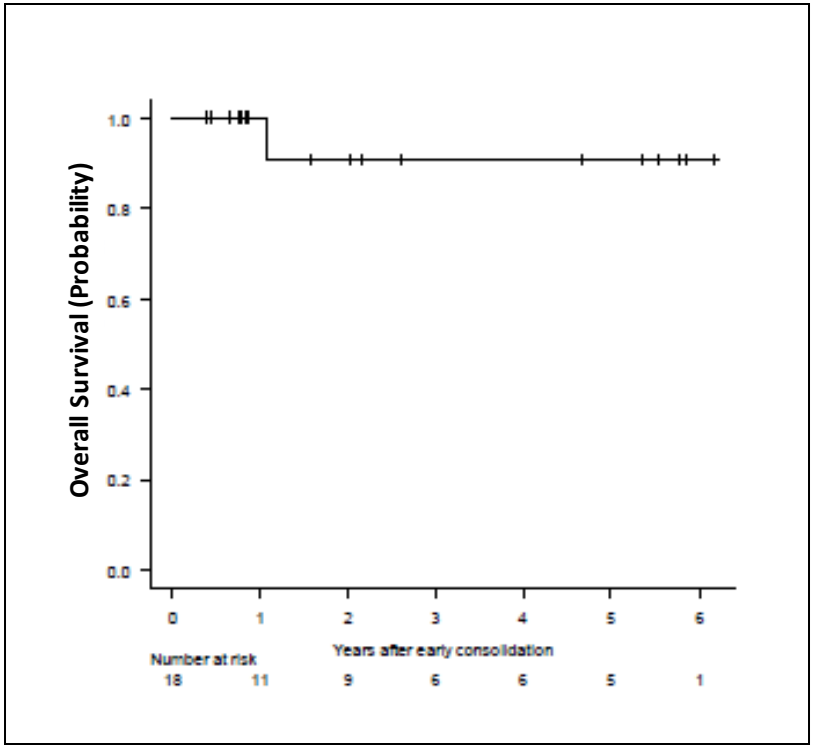
NILG 10/07 Ph- ALL: Clinical Trials.gov NCT-00795756.

Prognostic Importance of Early MRD Response in Ph– ALL

According to post-induction MRD level

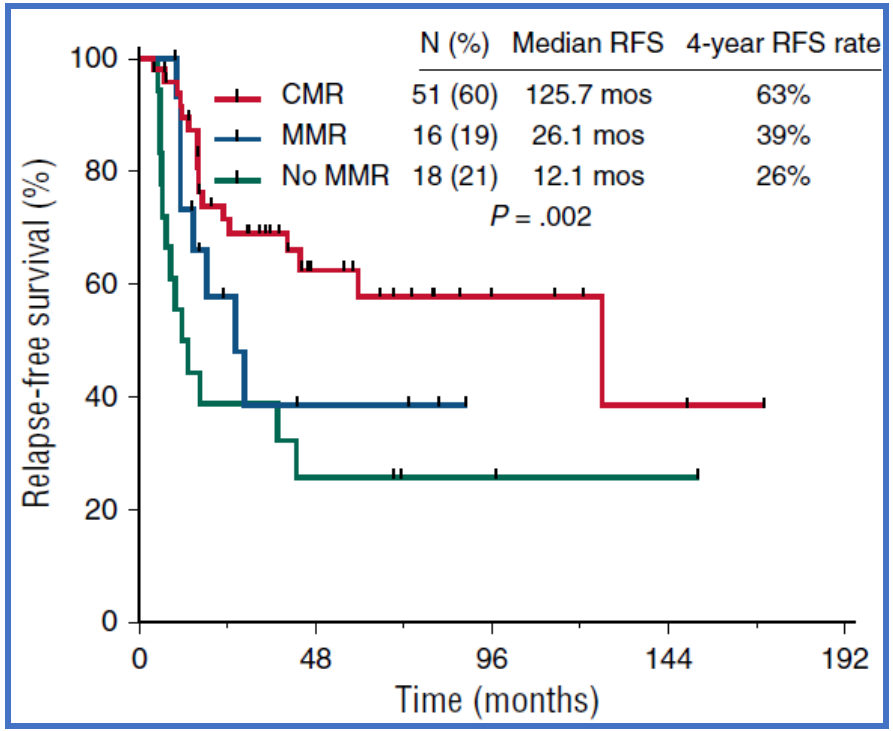


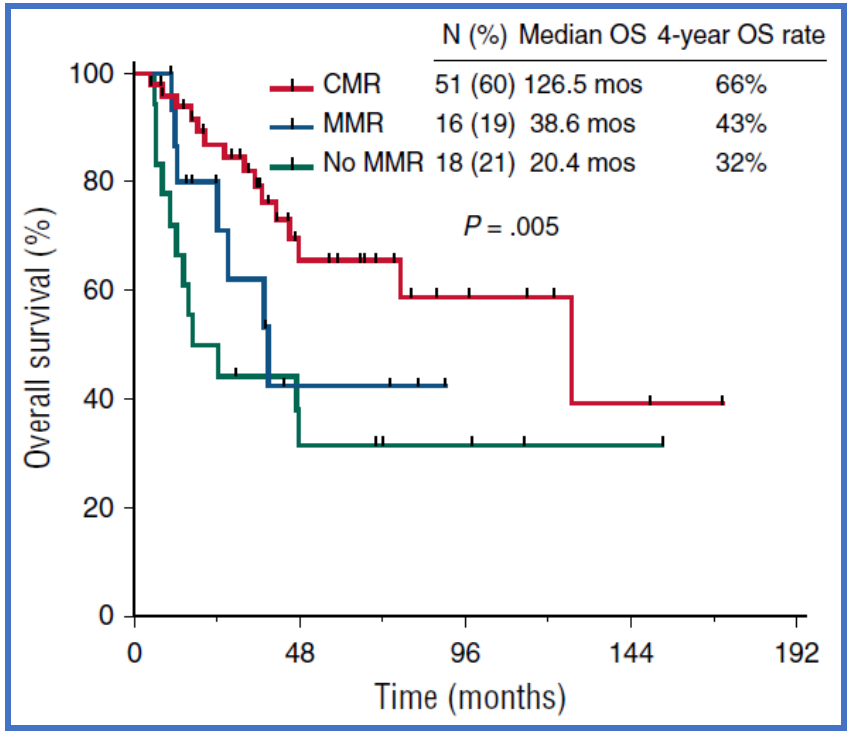
Patients with MRD <0.01% from d14



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

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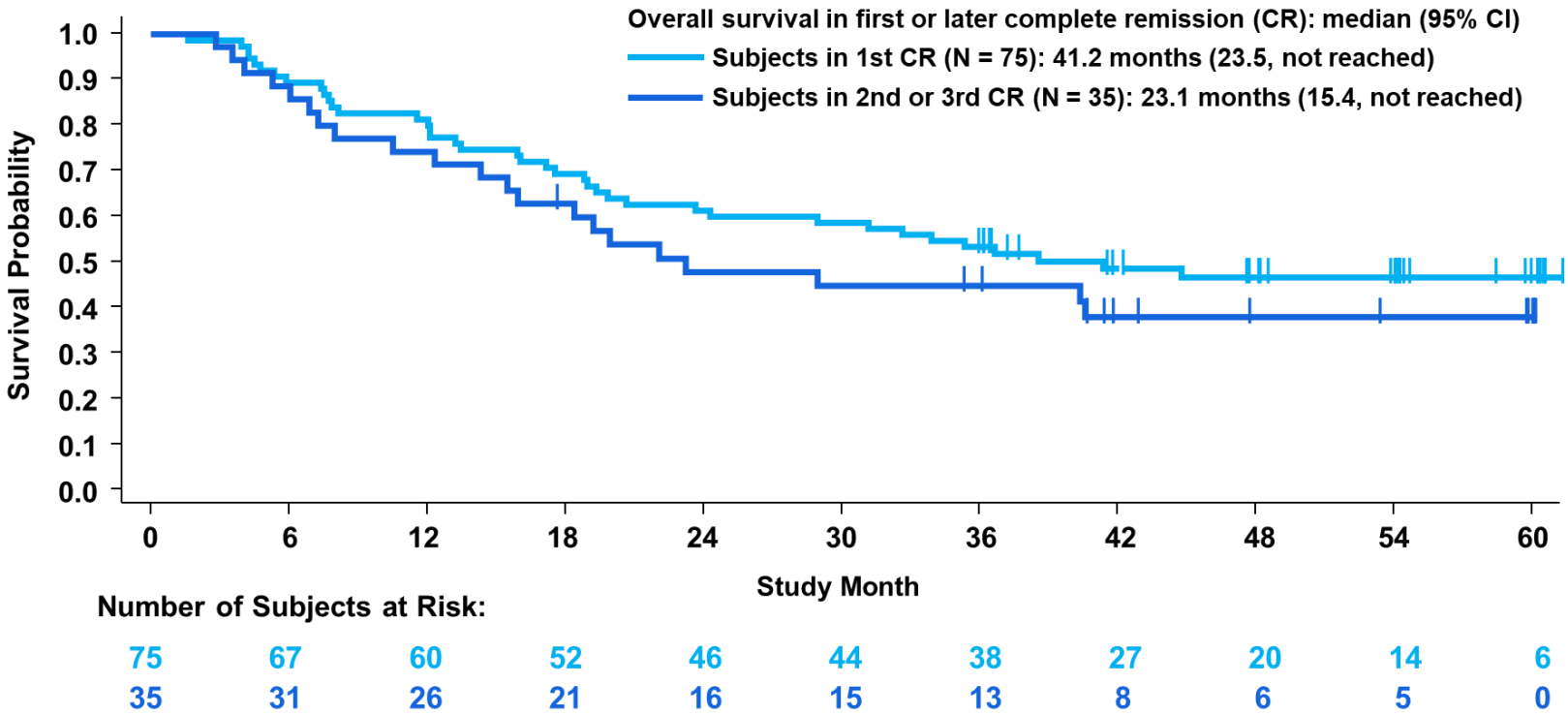
- TKI switch in Ph+ ALL
- Targeted therapy and immunotherapy

Overall Survival
By CR1 or CR2+

BLAST (MT103-203) STUDY

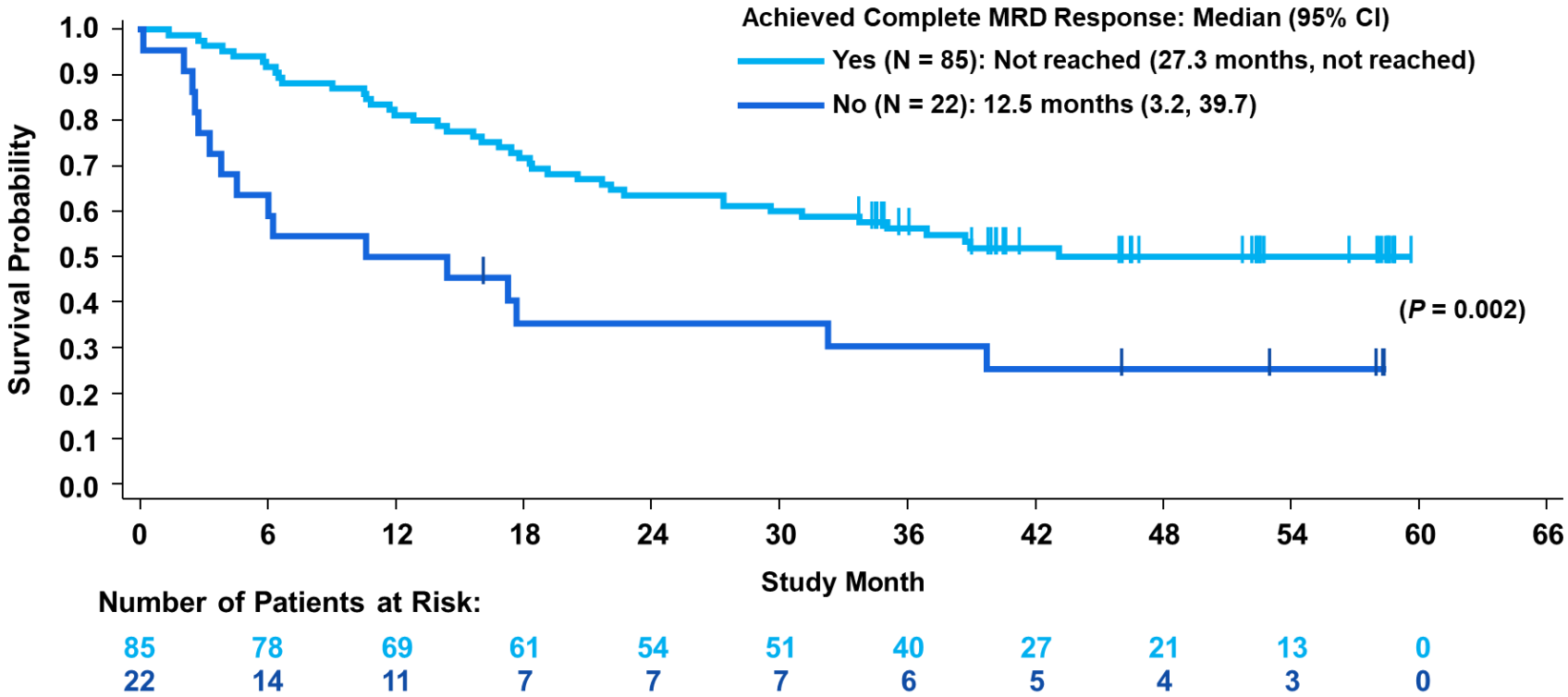


CR1, first complete remission; CR2+, second or later complete remission.

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

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

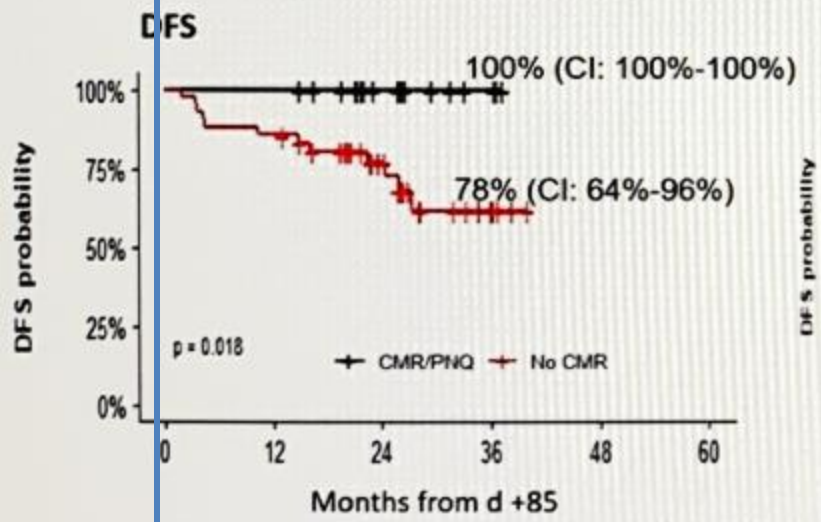
D-ALBA: Molecular Responses

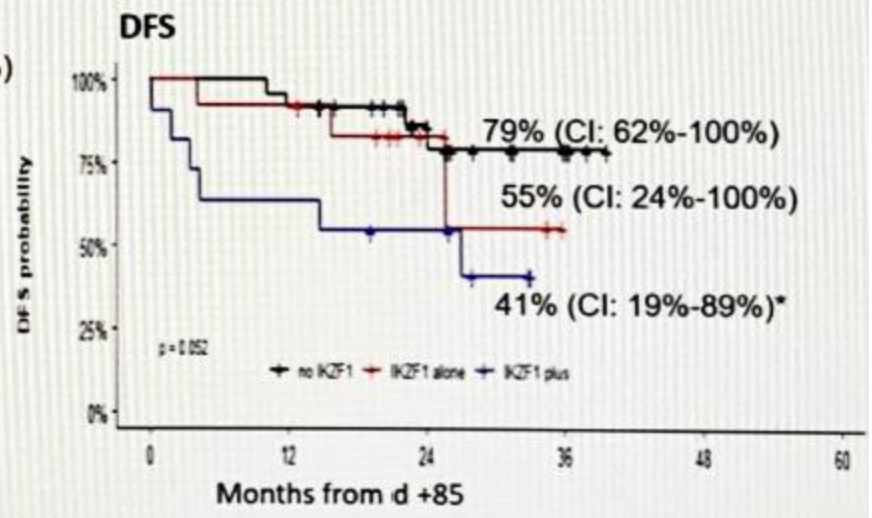
	CMR (%)	PNQ (%)	CMR and PNQ (%)
Day +22	3 (5.2)	7 (12.1)	10 (17.3)
Day +45	9 (15)	8 (13.3)	17 (28.3)
Day +57	11 (20.0)	7 (12.7)	18 (32.7)
Day +85	6 (10.3)	11 (19.0)	17 (29.3)
Post-cycle 1	19 (35.2)	16 (29.6)	35 (64.8)
Post-cycle 2	22 (41.5)	10 (18.9)	32 (60.4)
Post-cycle 3	19 (48.7)	8 (20.5)	21 (69.2)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

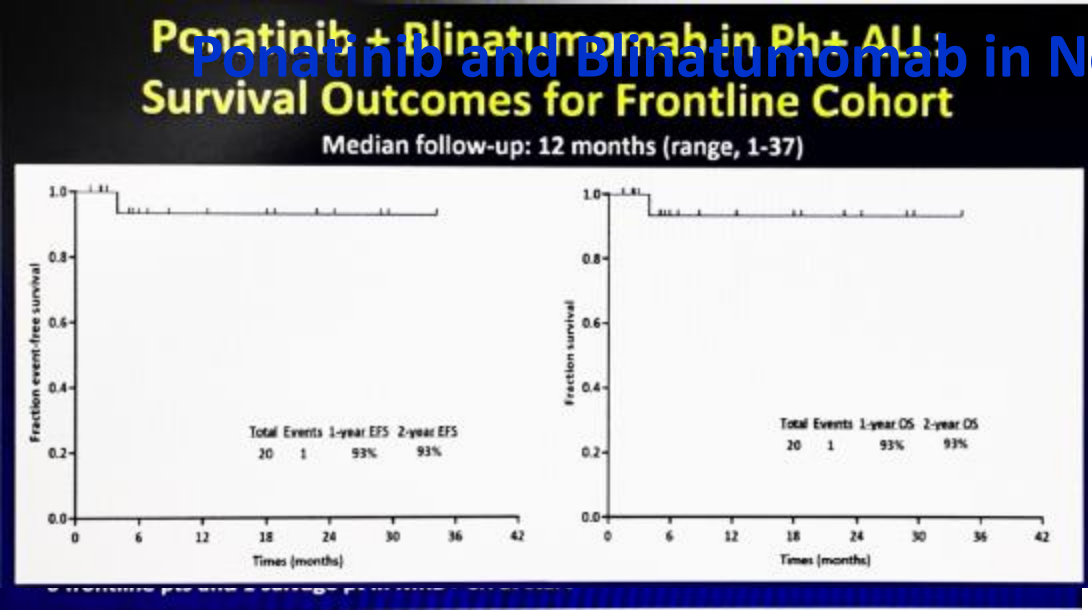
Chiaretti S, et al. *Blood*. 2019;134(suppl 1): abstract 740.

Updated D-ALBA: estimated 36 ms DFS according to molecular responses and CNAs





Ponatinib and Blinatumomab in Newly Diagnosed Ph+ ALL



Short N, et al. EHA 2021. Abstract S113.

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?

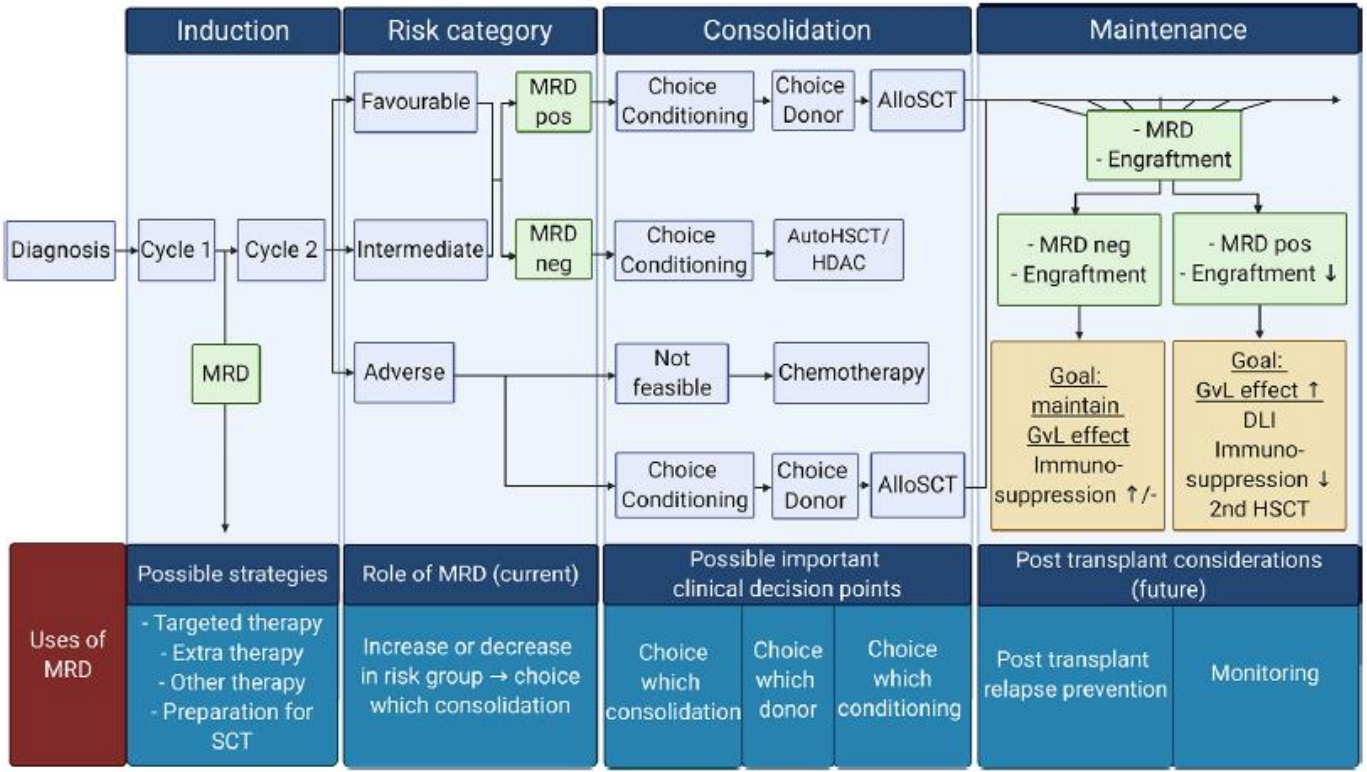
(Potential) Use of MRD in the Clinic

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

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 #2 [repeated question]

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

Q&A session

APTITUDE HEALTH

Global Leukemia Academy

Genetic variants in ALL – Ph+ and Ph-like

Philippe Rousselot

APTITUDE HEALTH

Global Leukemia Academy

Disclosures

- Research grants: Pfizer, Incyte
- Advisory boards: Amgen, Pfizer
- Travel grant: Pfizer

Philadelphia-Positive ALL

- Ph+ ALL are best treated with the combination of chemotherapy and tyrosine kinase inhibitor
- Ph+ ALL develop BCR-ABL TK domain mutations in case of relapse
- Ponatinib is efficient on most TK domain mutations except compound mutations
- Allogenic stem cell transplantation can be avoided in case of a DMR
- Chemo-free regimens are associated with a better OS compared with the combination of chemotherapy and TKI
- Ph-like ALL are of better prognostic as compared with other B-cell ALL

Initial Therapy With TKIs: Similar High CR Rates

Outcomes of newly diagnosed patients with Ph+ ALL: Chemotherapy and a TKI combination

Clinical Trial (year†)	N	Age, median [Range]	Chemotherapy	TKI, mg/day	CR,%
Imatinib					
Yanada (2006)[54]	80	48 [15-63]	JALSG ALL202	IM 600	96
Wassmann (2006)[8]	45	41 [19-63]	GMALL	IM 400	96
Fielding (2014)[9]	175	42 [16-64]	UKALLXII/ECOG2993	IM 400 - 600	92
Chalandon (2015)[12]	135	49 [18-59]	Low int. induction	IM 800	98
	133	45 [21-59]	High int. induction	IM 800	91
Bassan (2010)[55]	59	45 [20-66]	NILG	IM 600	92
Daver (2015)[10]	54	51 [17-84]	HyperCVAD	IM 400 - 800	93
De Labarthe (2007)[56]	45	45 [16-59]	GRAAPH 2003	IM 600 - 800	96
Lim (2015)[11]	87	41 [16-71]	Multiagent Chemo	IM 600	94
Nilotinib					
Kim (2015)[22]	90	47 [17-71]	Multiagent Chemo	NIL 800	90
Dasatinib					
Foa (2011)[29]	53	54 [24-76]	Prednisone	DAS 100-140	93
Ravandi (2015)[57]	72	55 [21-80]	HyperCVAD	DAS 100	96
Ravandi (2015)[58]	94	44 [20-60]	HyperCVAD	DAS 70-100	88
Ponatinib					
Jabbour (2015)[34,35]	64	48 [21-80]	HyperCVAD	PON 30-45	100

Imatinib: 94% CR

Nilotinib: 91% CR

Dasatinib: 92% CR

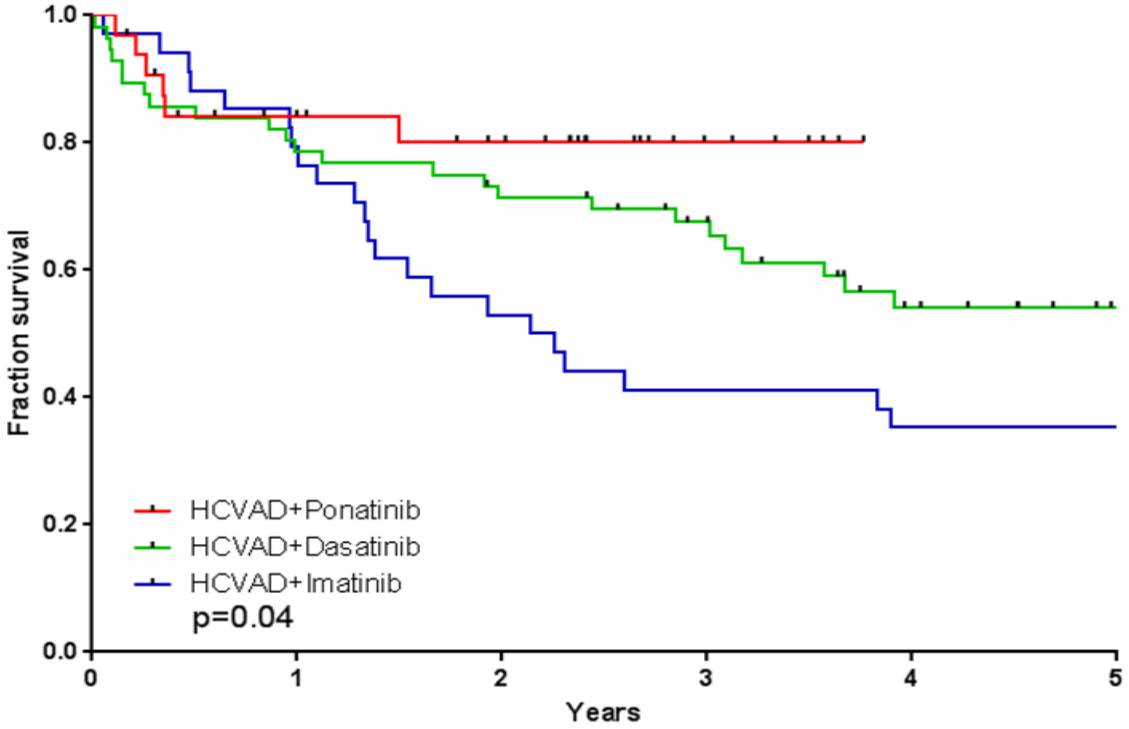
Ponatinib: 100% CR

Courtesy of M Yilmaz.

Ph+ ALL, Philadelphia chromosome positive acute lymphoblastic leukemia; TKI, tyrosine kinase inhibitor; N, number of patients; m,

Yilmaz M, et al. *Clin Adv Hematol Oncol*. 2018;16(3):216-223.

Relapse-free Survival and OS Summary From MDACC: HCVAD + TKIs



Courtesy of E Jabbour.

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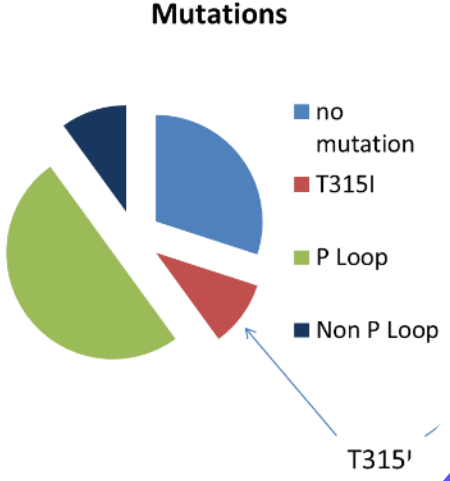
Best TKI for BCR-ABL tk Domain Mutations

Mutations analysis in relapse

AFR07 : IMATINIB



EWALL-PH-01 : DASATINIB

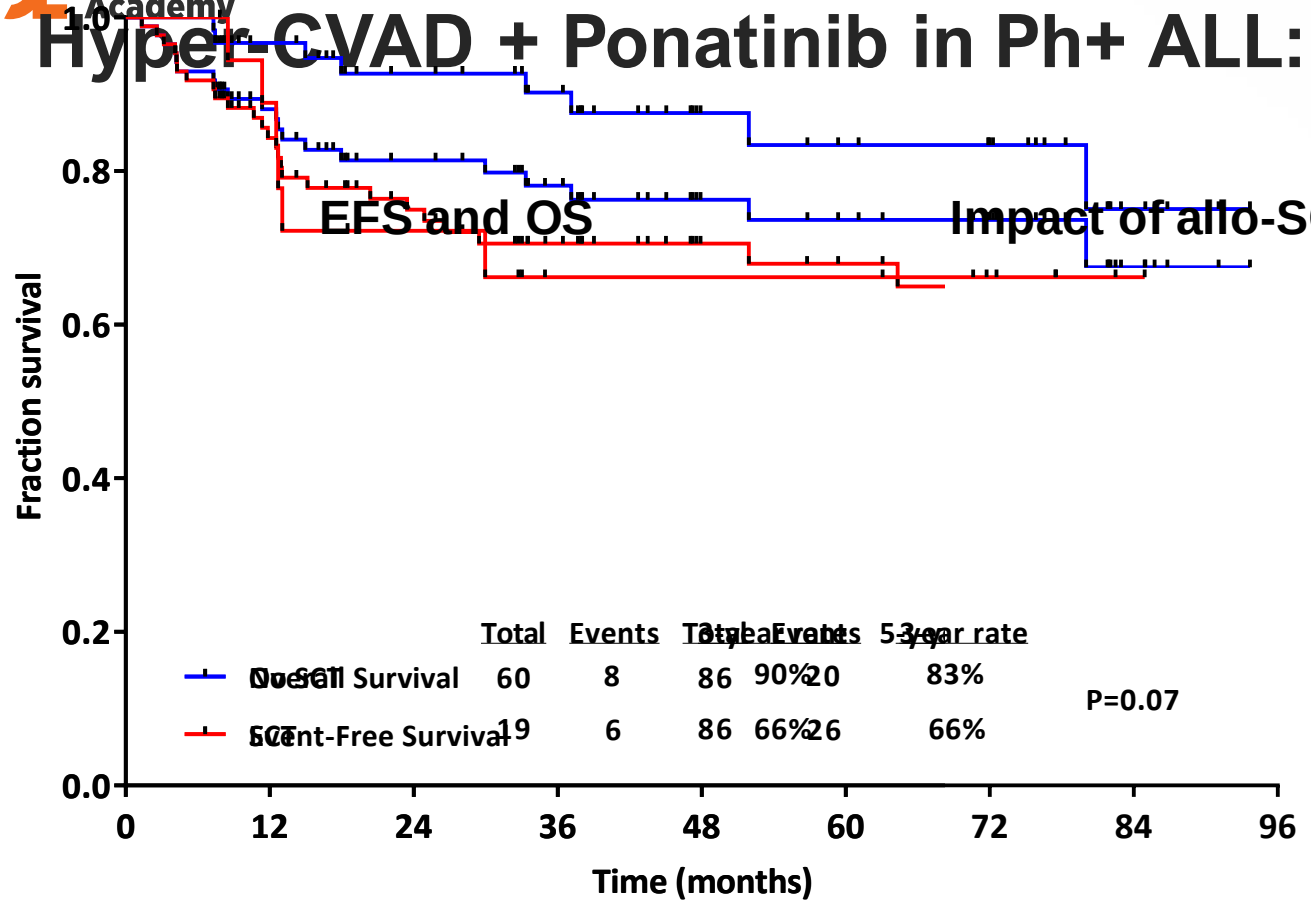
GRAAPH 2014: NILOTINIB

Rousselot P, et al. *Bloo*

Hyper-CVAD + Ponatinib in Ph+ ALL: Outcome

EFS and OS

Impact of allo-SCT: 6-month landmark



Short NJ, et al. *Blood*. 2019;134:abstract 283.

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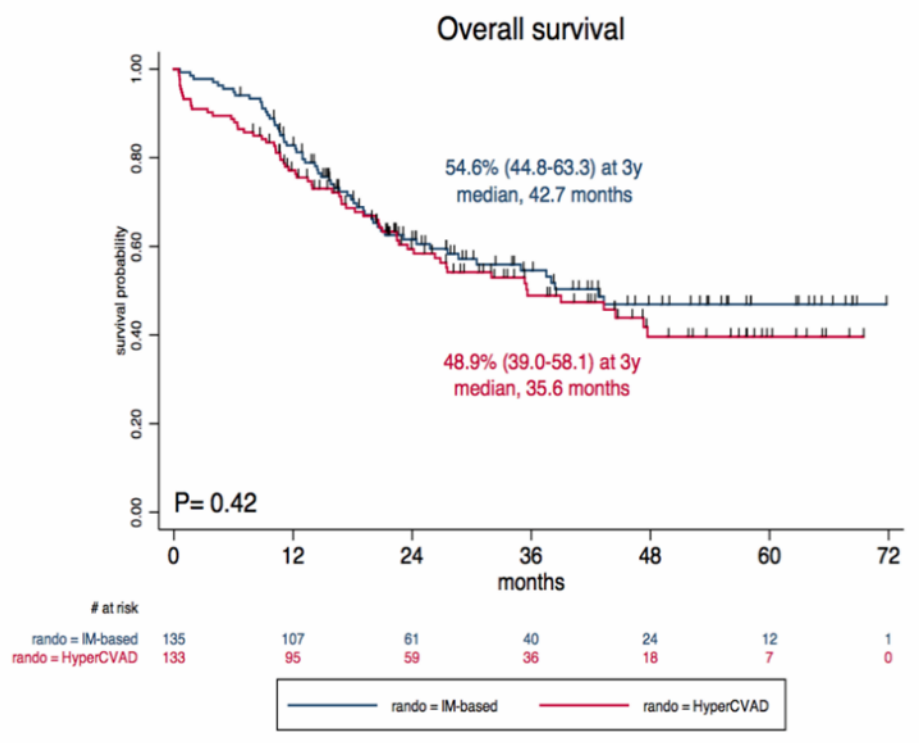
Two Ongoing Randomized Trials

- PONATINIB 3001 (Takeda)
  - EudraCT: 2018-000397-30
  - Imatinib 600 mg vs ponatinib 30 mg
  - Ph+ ALL 18y and older
  - Primary endpoint: molecular response (end of induction)

- EWALL-PH-03 (Cardiff University)
  - EudraCT : 2018-0003350-25
  - Imatinib 600 mg vs ponatinib 30 mg
  - Ph+ ALL 55y and older
  - Primary endpoint: molecular response (during consolidation)

High-Intensity vs Low-Intensity Chemotherapy for Induction – GRAAPH 2005



	IM-based (n= 135)	IM-HyperCVAD (n=133)	p	Total (n=268)
CR	**133 (98.5%)**	**121 (91.7%)**	**0.006**	**254 (94.8%)**
Courses to CR				
one	132 (97.8%)	118 (88.7%)	0.003	250 (93.2%)
two	1 (0.7%)	3 (2.2%)	-	4 (1.5%)
Resistance after 2 cycles	1 (0.7%)	3 (2.2%)	0.35	3 (1%)
D60 mortality	**1 (0.7%)**	**9 (6.7%)**	**0.01**	**10 (3.7%)**

Chalandon Y, et al. *Blood.* 2015;125:3711.

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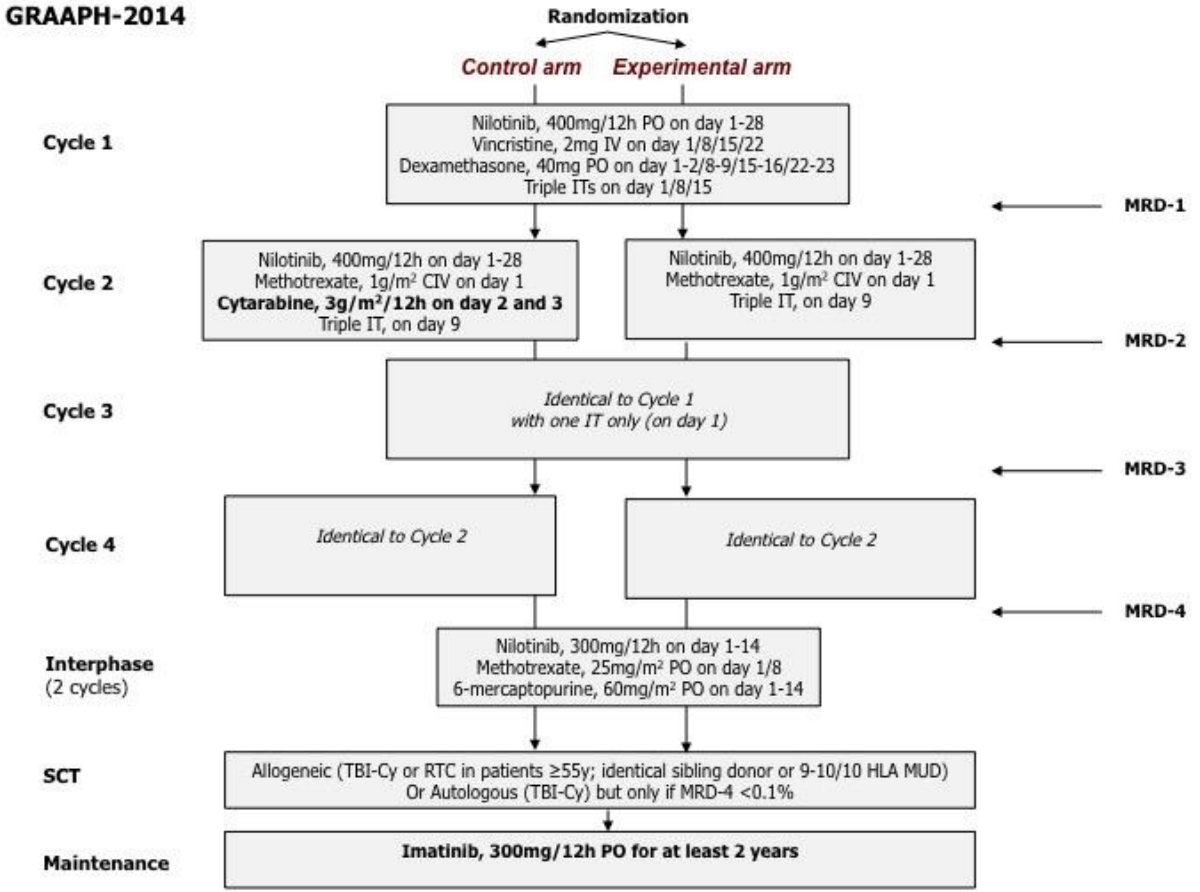
GRAAPH 2014

Ph+ ALL frontline 18–60 yrs



Interim analysis
Aim
80%: BCR-ABL1 <0.1%

Final analysis
BCR-ABL1 <0.1%
Equivalent

GRAALL

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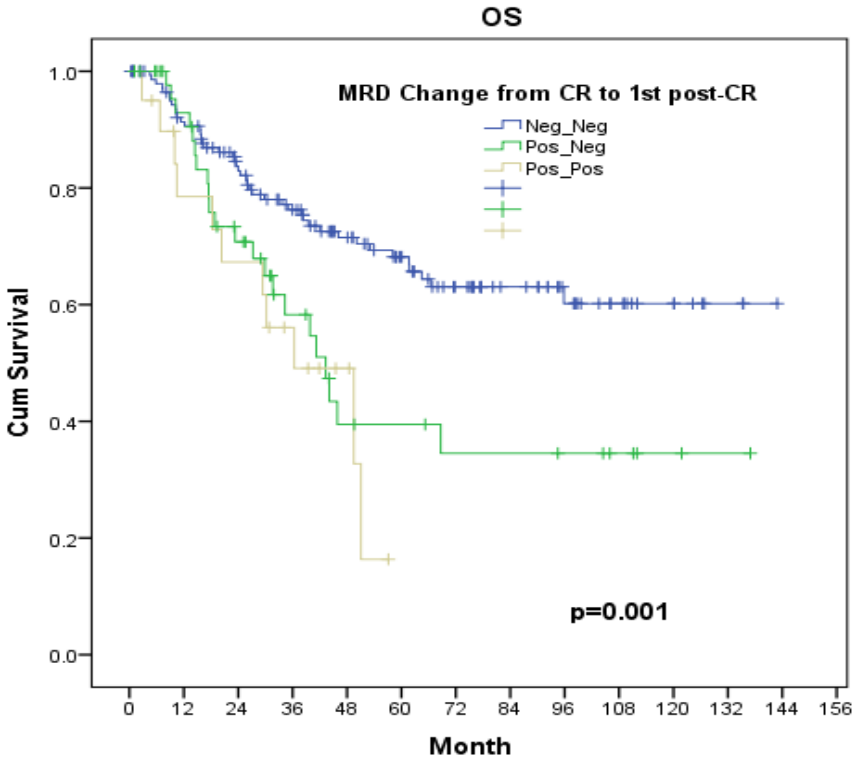
GRAAPH 2014
Final Analysis of the 156 Randomized Patients

ASH 2021

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 M, et al. *Blood.* 2019;134:abstract 1297.

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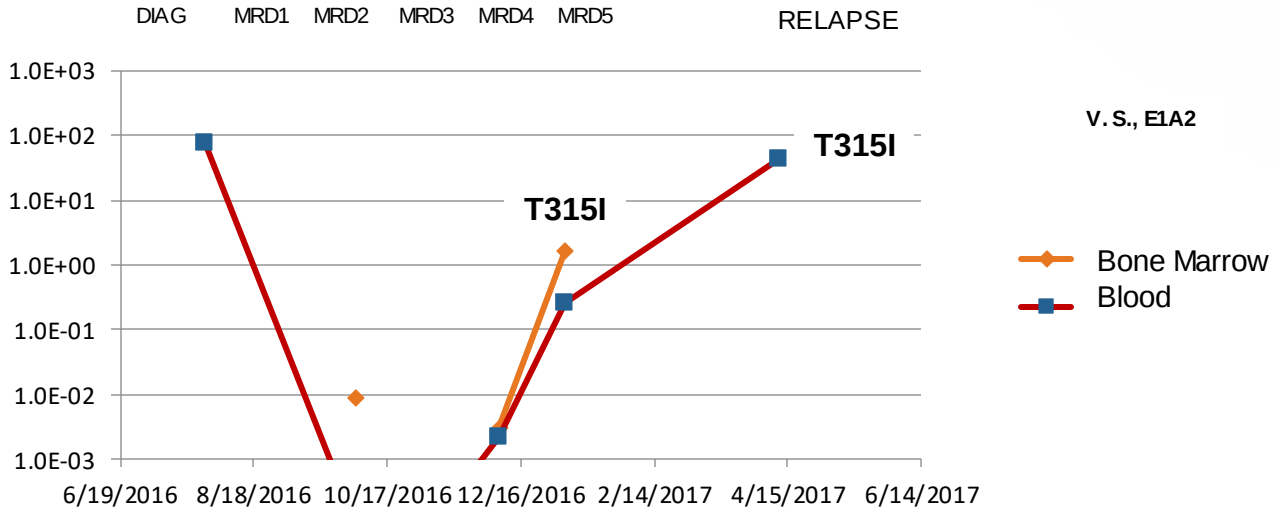
GRAAPH 2014 004-1016-V-S (nilotinib)



- T315I 25% at MRD5
- Relapse 3 months later with T315I at 100%
- No mutation detected at diagnosis

Courtesy of JM Cayuela.

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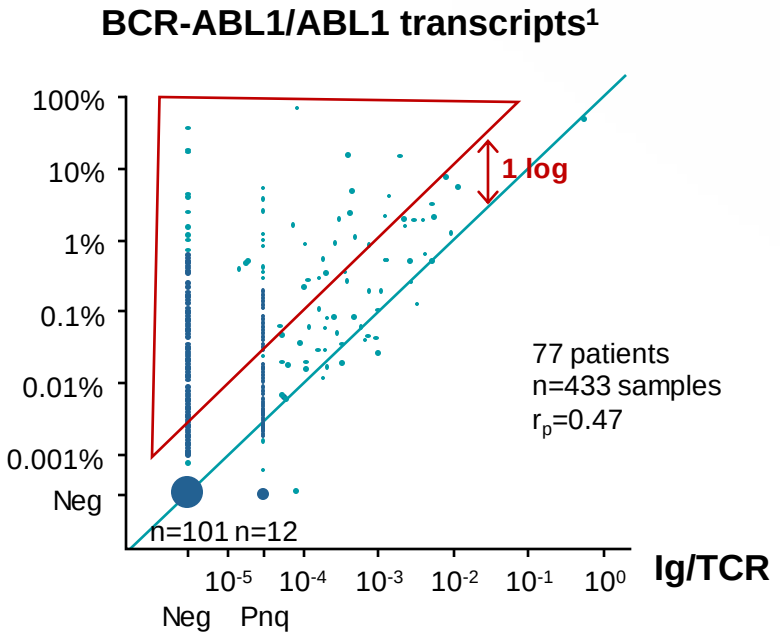
MRD: BCR-ABL vs IgH/TCR

47% of patients show persistence of BCR-ABL1 along with Ig/TCR decrease (disassociated kinetics)[1]

- Suggests the existence of BCR-ABL1 clonal hematopoiesis in a subtype of adult Ph+ ALL
- This resembles a “CML-like” entity, as previously described,[2,3] in a fraction of patients with Ph+ ALL



Ig/TCR, immunoglobulin/T-cell receptor; neg, negative; pnq, positive not quantifiable; r_p, Pearson linear.

1. Clappier E, et al. EHA 2018. Abstract S1568; 2. Hovorkova L, et al. *Blood*. 2017;129:2771-2781;
3. Nagel I, et al. *Lymphoid Neoplasia*. 2007;130:2027-2031.

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Prospective Analysis of the GRAAPH 2014 MRD

> Next ASH 2021!

Two Evolving Strategies to Treat Ph+ ALL

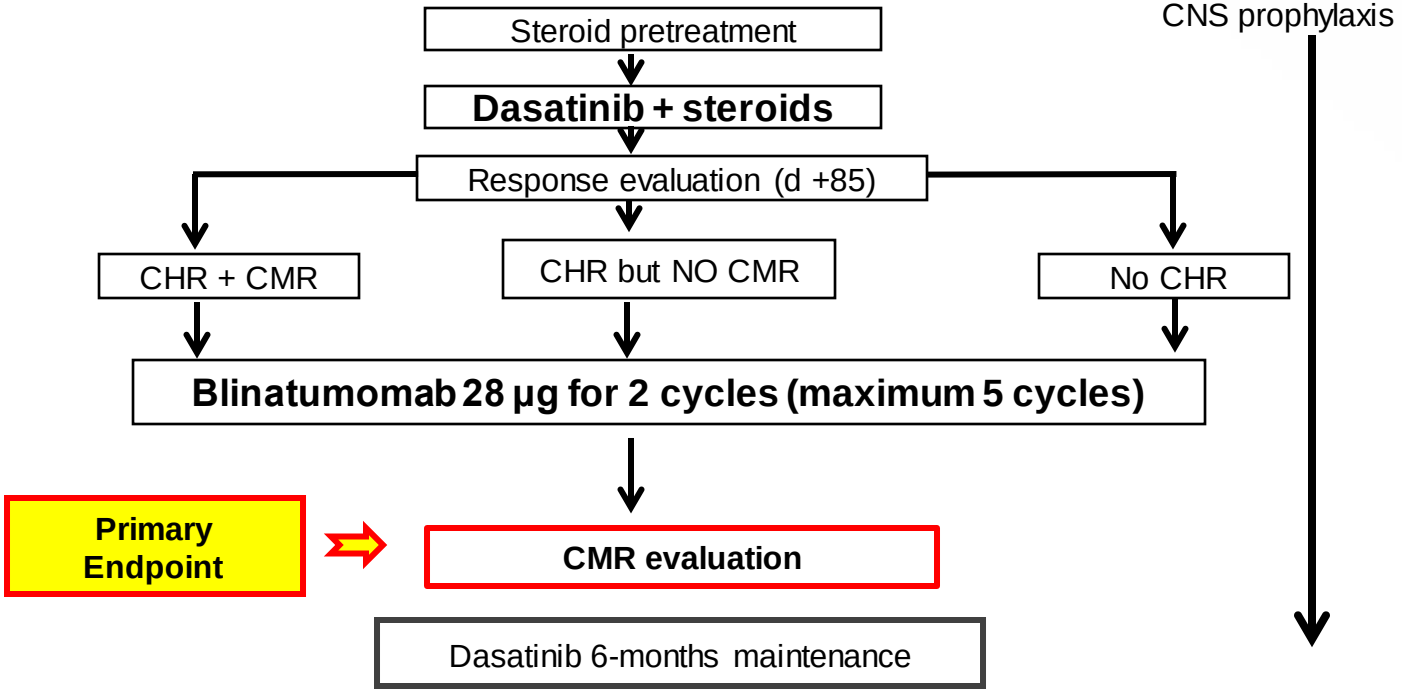
Parameter	Hyper-CVAD + ponatinib	TKIs with reduced chemo
% CR	90–100	90–100
% CMR	80	60
Allo-SCT required	Only if no CMR	In all
% 3-yr survival/DFS	80	80

A third strategy: Chemo free?

Jabbour E, et al. *Lancet Oncol.* 2015;16:1547; Chiaretti S, et al. *Blood.* 2015;126:abstract 81.

Dasatinib + Blinatumomab for First-line Treatment of Ph+ ALL: Preliminary Results of the GIMEMA LAL2116 D-ALBA trial

D-ALBA: treatment scheme



Courtesy of Sabina Chiaretti

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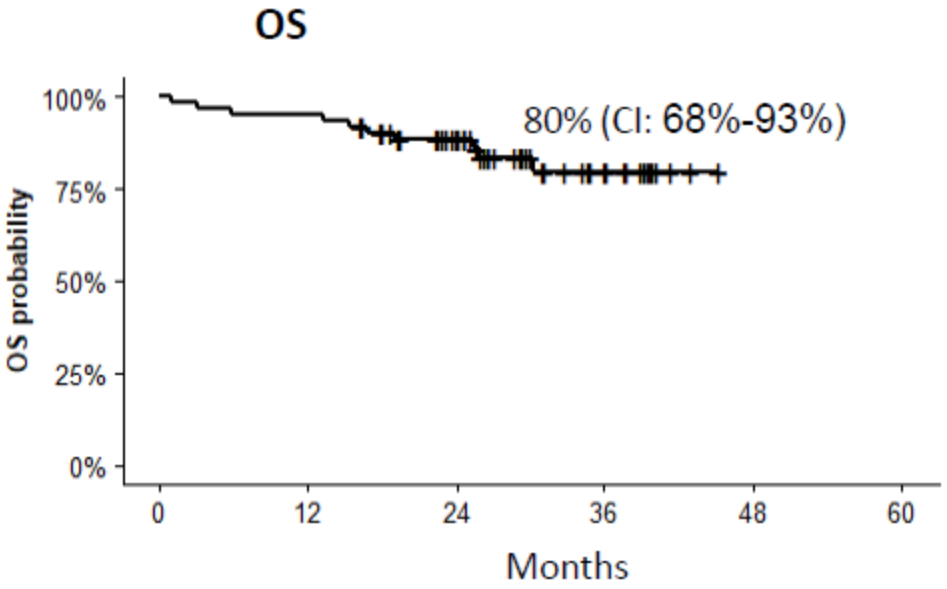
Dasatinib-Blinatumomab in Ph+ ALL

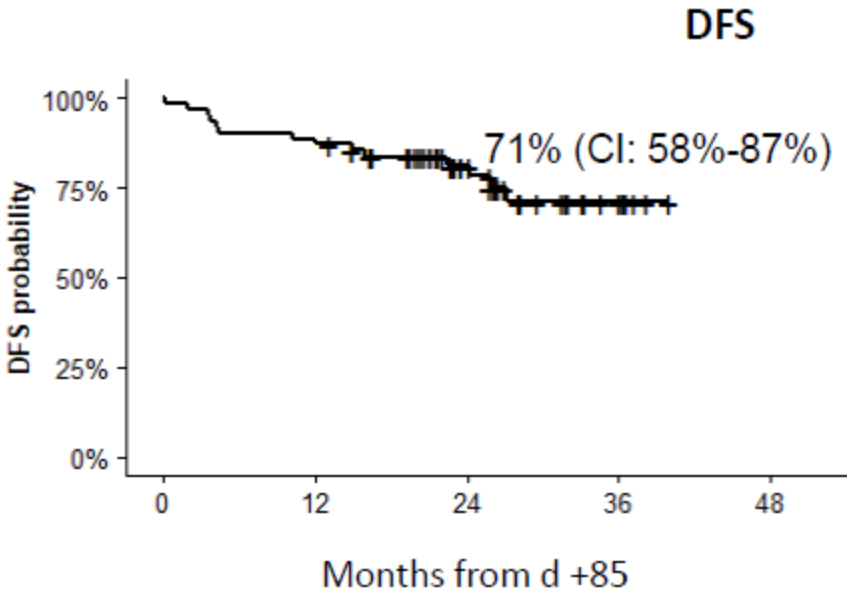
- 63 pts, median age 54 yr (24–82)
- CR: 98%

Table 2. Molecular Responses during Induction Therapy, at the End of Induction Therapy (Day 85), and after Each Blinatumomab Cycle.

Assessment	No Molecular Response	Complete Molecular Response	Positive Nonquantifiable Response	Overall Molecular Response
	number of patients/total number (percent)			
Induction period				
Day 22	48/58 (83)	3/58 (5)	7/58 (12)	10/58 (17)
Day 45	43/60 (72)	9/60 (15)	8/60 (13)	17/60 (28)
Day 57	38/56 (68)	11/56 (20)	7/56 (12)	18/56 (32)
Day 85	42/59 (71)	6/59 (10)	11/59 (19)	17/59 (29)
Blinatumomab cycle				
After cycle 1	20/55 (36)	19/55 (35)	16/55 (29)	35/55 (64)
After cycle 2	22/55 (40)	23/55 (42)	10/55 (18)	33/55 (60)
After cycle 3	12/40 (30)	20/40 (50)	8/40 (20)	28/40 (70)
After cycle 4	7/36 (19)	17/36 (47)	12/36 (33)	29/36 (81)
After cycle 5	8/29 (28)	16/29 (55)	5/29 (17)	21/29 (72)

Updated D-ALBA: estimated 36 ms OS and DFS





Median follow-up: 28.81 ms (0.9-45.16)

Foa R, et al. *N Engl J Med.* 2020;383:1613-1623; Chiaretti S, et al. EHA 2021.

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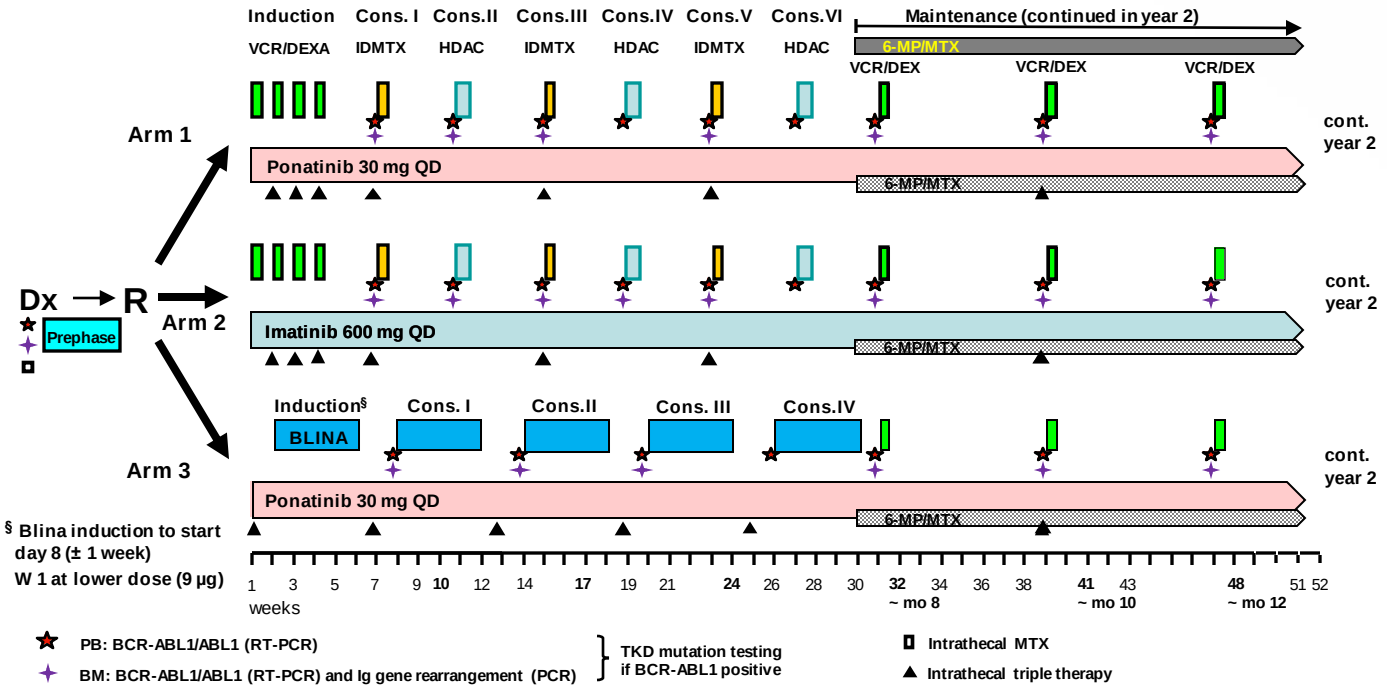
EWALL PH03: Study Design

Patients aged 55 yrs or older (ongoing, 7 patients included)



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BCR-ABL+-like ALL

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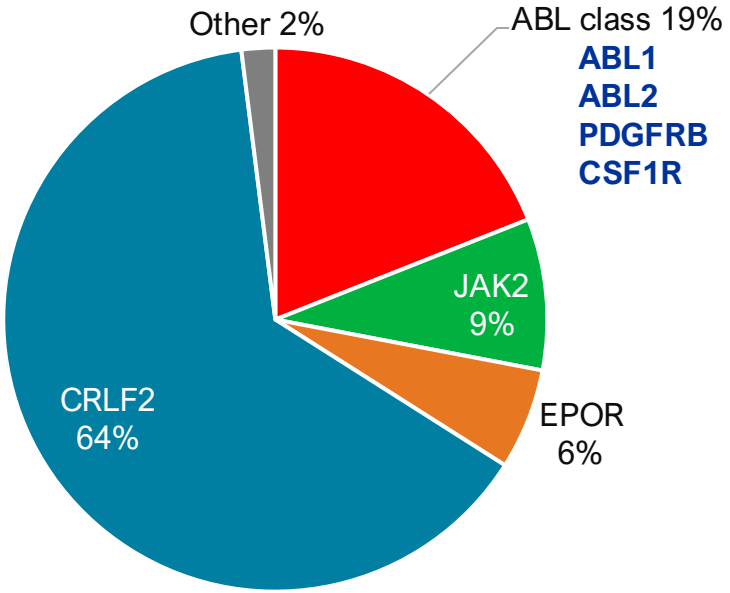
Ph-like BCP-ALL

Relative frequency of Ph-like ALL alterations in children, adolescents, and adults



Summary data from 5 recent clinical studies (n = 2506 cases) depict the most common ABL class and CRLF2/JAK pathway-associated translocations occurring in children and adults with Ph-like ALL.

Adapted from Harvey RC, Tasian SK. *Blood Adv.* 2020.
Hunger SP, Mullighan CG. *Blood.* 2015;125(26):3977-3987; Harvey RC, Tasian SK. *Blood Adv.* 2020;4(1):218-228.

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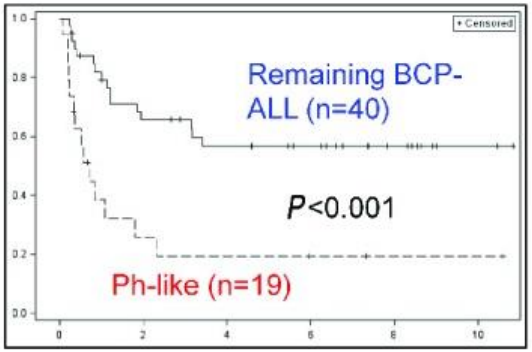
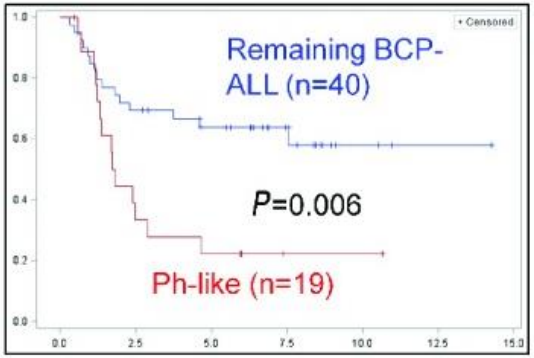
Ph-like ALL Outcome in Adults

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

DFS

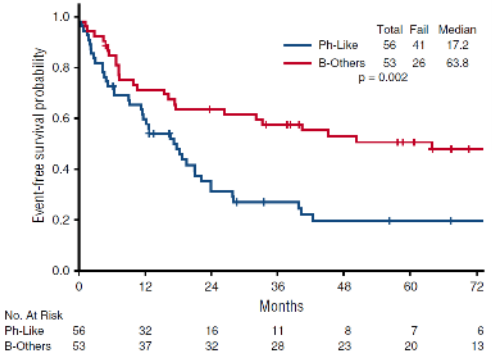


OS

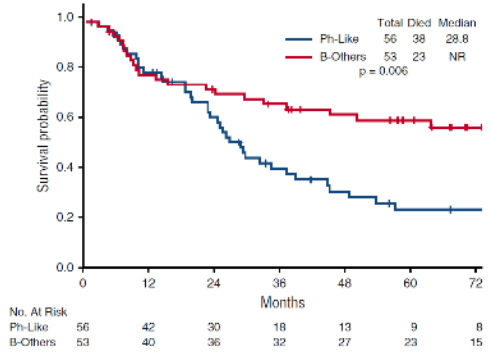


MDACC: HyperCVAD/A-BFM[2]

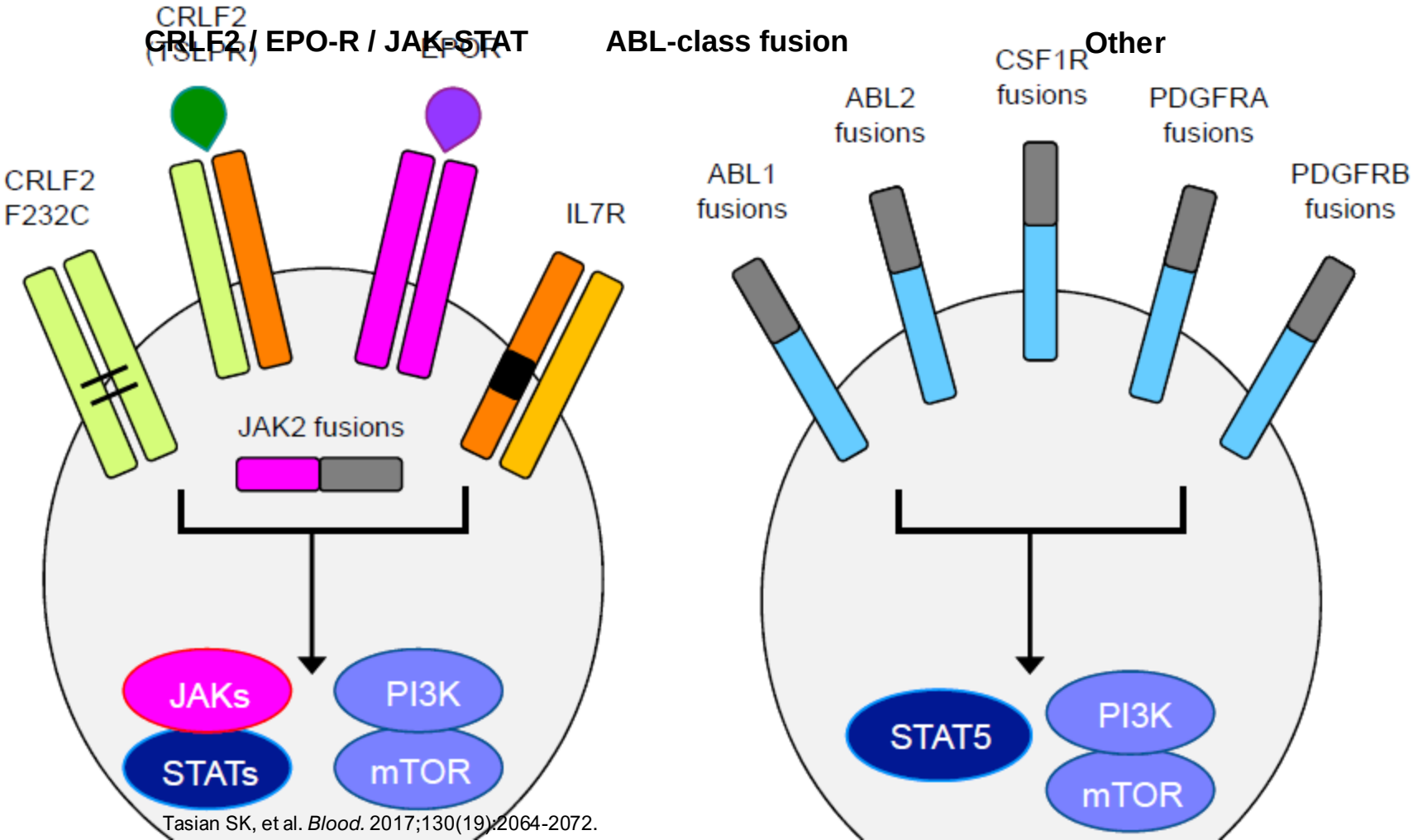
EFS



OS



1. Herold T, et al. *Haematologica*. 2017;102:130-138; 2. Jain N, et al. *Blood*. 2017;129:572-581.



Tasian SK, et al. *Blood.* 2017;130(19):2064-2072.

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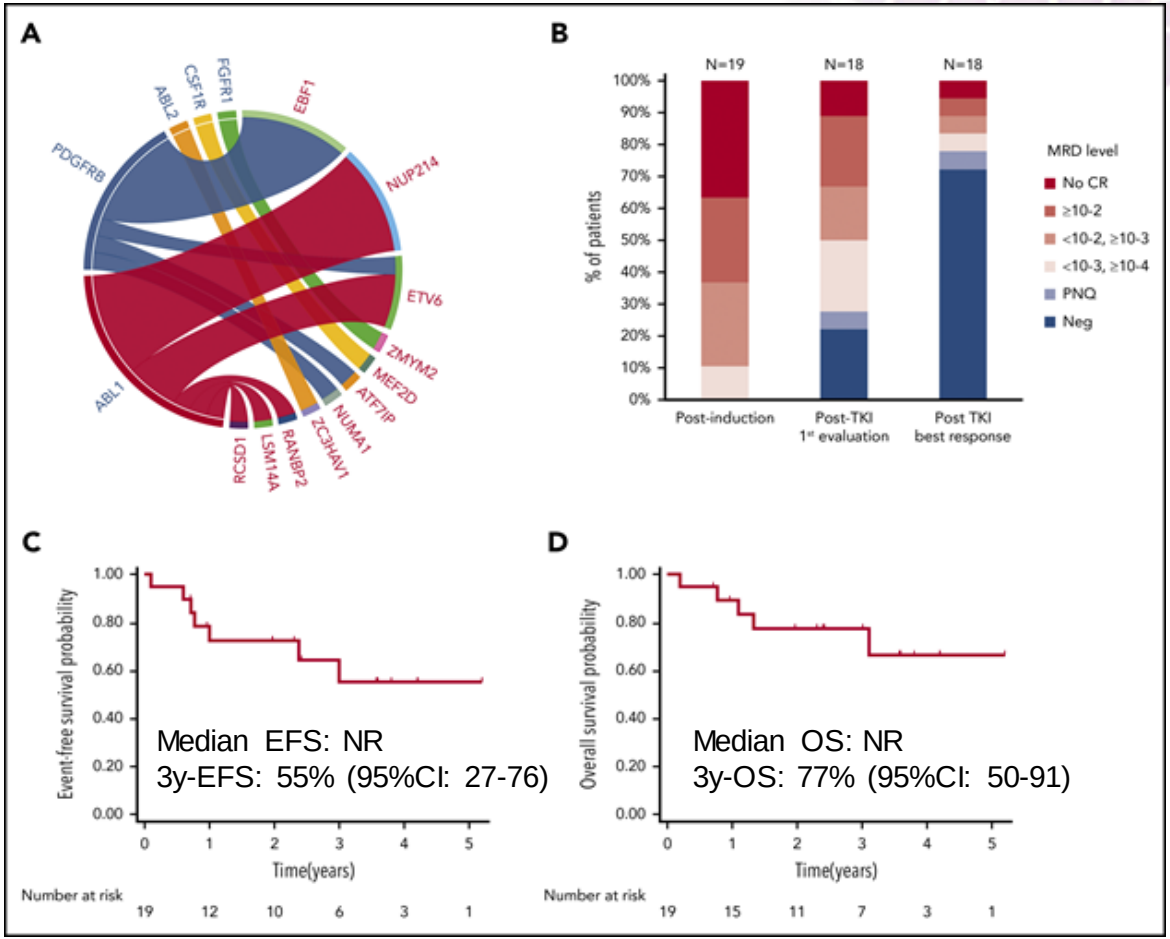
Ph-like ALL With Targetable ABL-family Gene

French TKI experience



Tanasi I, et al. *Blood.* 2019;134(16):1351-1355.

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Conclusions

- Induction therapy: low-intensity chemotherapy + TKI
- Best TKI: no direct comparison, ponatinib 45 mg if possible
- Consolidation therapy: conventional chemotherapy + TKI
- Allogeneic HSCT: still recommended, may be avoided in MRD-neg patients
- Autologous HSCT: not recommended
- MRD: evaluated by BCR-ABL1 quantification, discrepancies with IgH/TCR (CML-like Ph+ ALL)
- Maintenance: indefinitely outside allo-HSCT
- Relapse: no efficient therapy, mutation driven, ponatinib + blina may be the best option
- CAR T-cell positioning: unknown
- Chemo-free regimens: the future but CNS prophylaxis mandatory for BCR-ABL–like
  - Not so few patients
  - Personalized therapy?

Philadelphia-positive ALL

- Ph+ ALL are best treated with the combination of chemotherapy and tyrosine kinase inhibitor
- Ph+ ALL develop BCR-ABL TK domain mutations in case of relapse
- Ponatinib is efficient on most TK domain mutations except compound mutations
- Allogenic stem cell transplantation can be avoided in case of a DMR
- Chemo-free regimens are associated with a better OS as compared to the combination of chemotherapy and TKI
- Ph like ALL are of better prognostic as compared to other B-cell ALL

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  - E Clappier
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ELN European LeukemiaNet

GRAALL LALA GOELAMS SAKK

UVSQ université PARIS-SACLAY UFR Simone Veil - Santé CAMPUS DE SAINT-QUENTIN-EN-YVELINES

CHV

Global Leukemia Academy

Q&A session

APTITUDE HEALTH

Global Leukemia Academy

AYA ALL patients – what is the current treatment approach for this diverse patient population?

Rob Pieters

APTITUDE HEALTH

Adolescents/young adults (AYA) with ALL

Rob Pieters
Chief Medical Officer

Question 1: Which assertion is NOT correct for adolescent and young adult ALL patients?

a) Pediatric-inspired protocols lead to a better outcome than adult-inspired protocols

b) Osteonecrosis and anaphylactic reactions to asparaginase are more often seen in adults than in children and teenagers

c) AYA patients experience more liver toxicity and thrombosis than children <10 years old

d) *BCR-ABL1*–like ALL is more frequent in AYA ALL than in children <10 years old with ALL

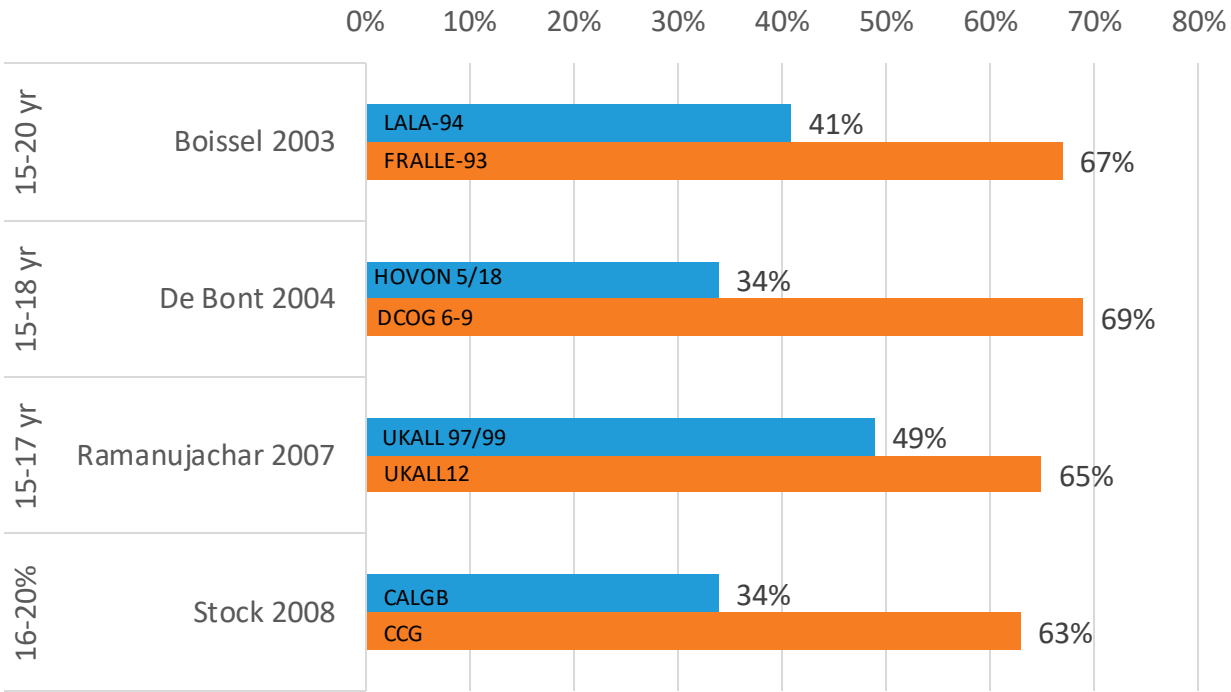
Inferior outcome for AYA patients: Why?

- Role of “pediatric-“ vs “adult-inspired” treatment protocols
- Site of treatment
- Trial enrollment
- Toxicity profile
- Biology/genetics of the leukemia
- Adherence

Pediatric vs adult treatment protocols

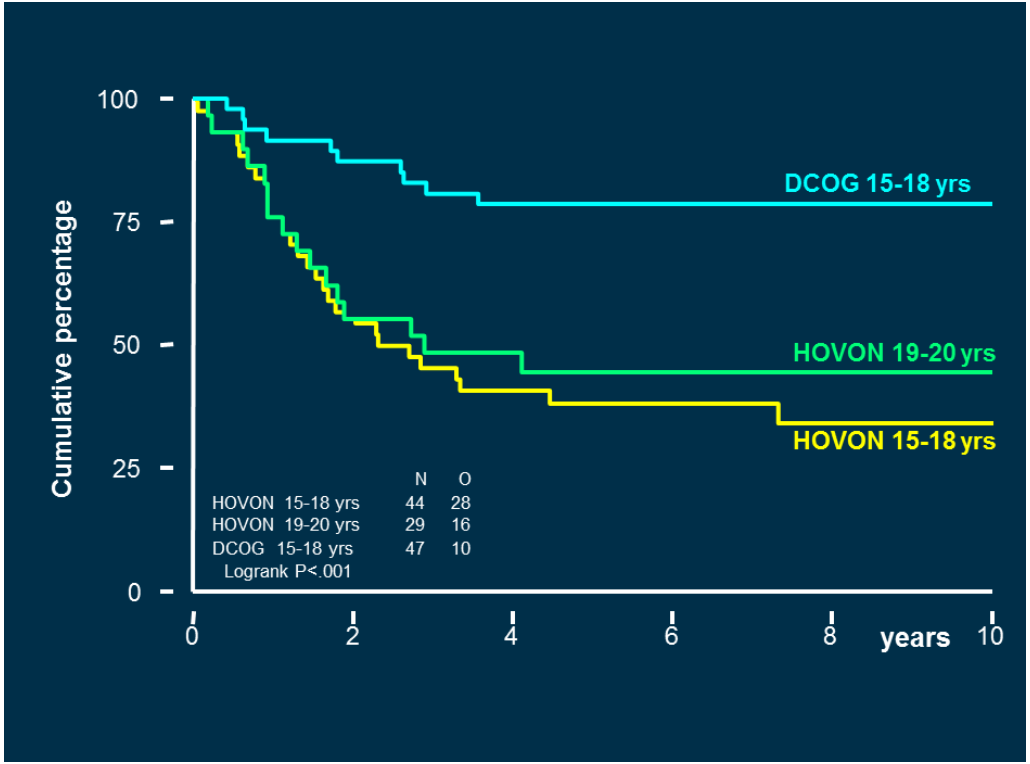
- More intensive use of
  - Glucocorticoids
  - Vincristine
  - Asparaginase
  - Methotrexate
  - 6-mercaptopurine
- Less intensive use of
  - Anthracyclines
  - Cyclophosphamide
- Less frequent use of alloSCT
- Prolonged maintenance, delayed intensification, CNS-directed therapy

Comparison of 5-year EFS in adolescent and young adult (AYA) patients treated on pediatric and adult protocols



Boissel N, et al. *J Clin Oncol*. 2003;21(5):774-780; De Bont JM, et al. *Leukemia*. 2004;18(12):2032-2035; Ramanujachar R, et al. *Pediatr Blood Cancer*. 2007;48(3):254-261; Stock W, et al. *Blood*. 2008;112(5):1646-1654.

Adolescent ALL on pediatric DCOG vs adult HOVON protocol in the Netherlands



De Bont, Leukemia 2004

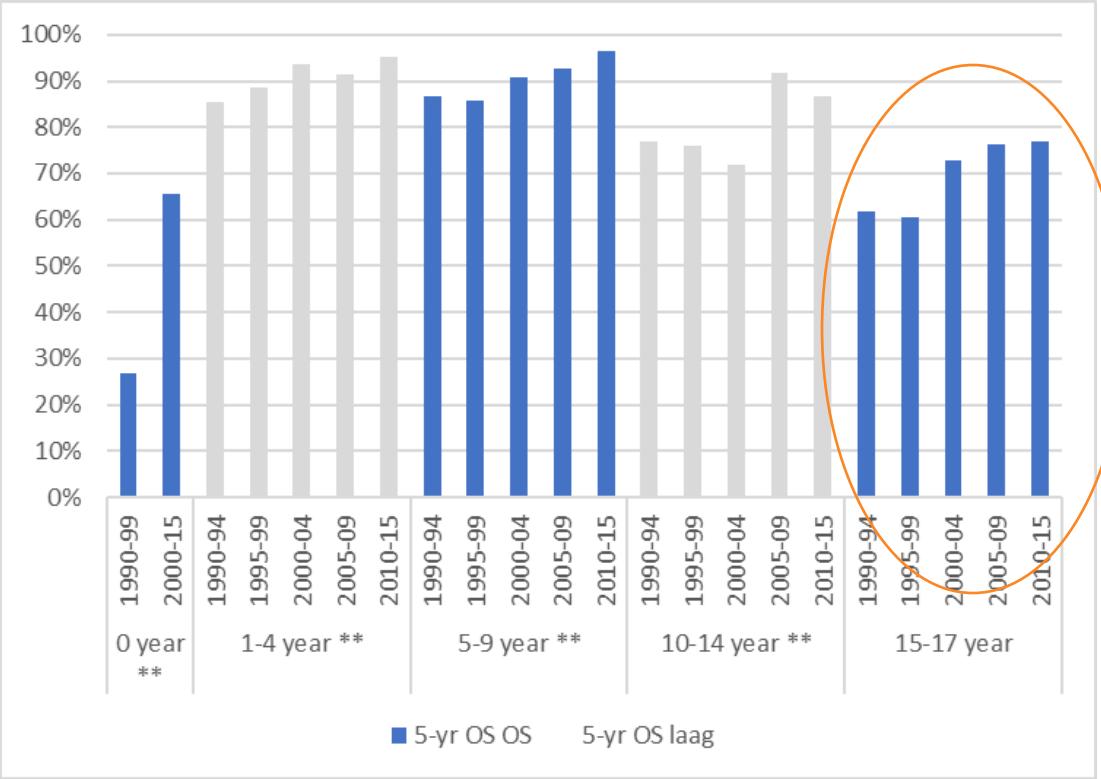
Adolescent ALL on pediatric DCOG vs adult HOVON protocol in the Netherlands

5 yrs actuarial probabilities

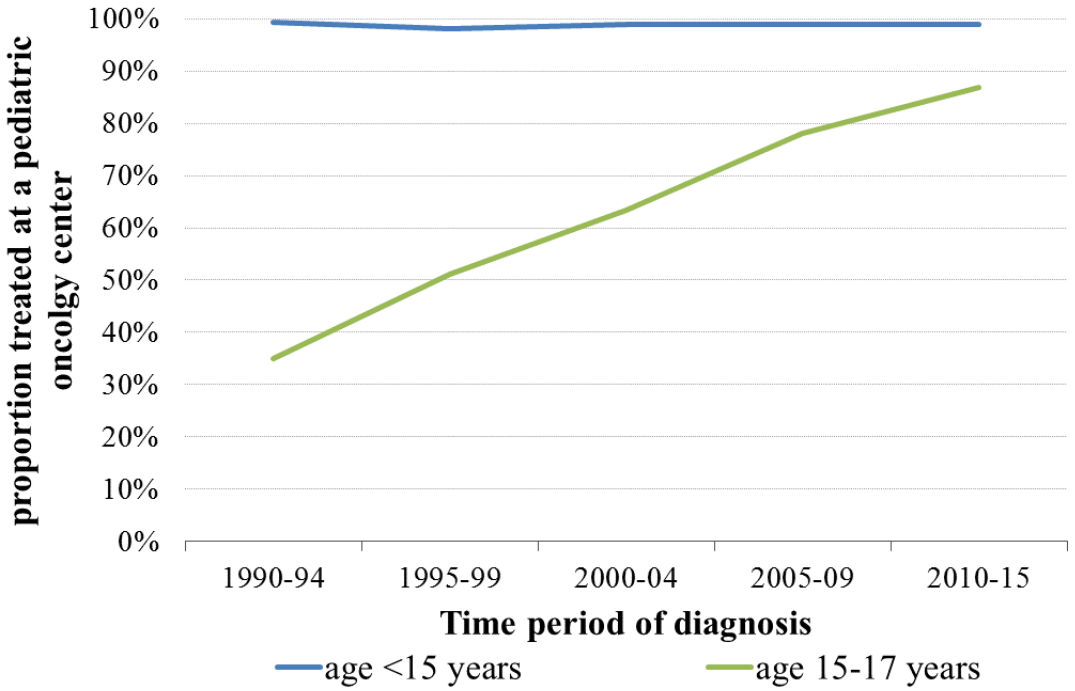
	CR	*OS (sd)*	*EFS (sd)*	*DFS (sd)*	*pREL (sd)*	*TRM (sd)*
DCOG 15-18 yrs (n=47)	**98%**	**79%** (±6)	**69%** (±7)	**71%** (±7)	**27%** (±7)	**4%** (±3)
HOVON 15-18 yrs (n=44)	**91%**	**38%** (±7)	**34%** (±7)	**37%** (±8)	**55%** (±8)	**25%** (±7)
HOVON 19-20 yrs (n=29)	**90%**	**44%** (±9)	**34%** (±9)	**38%** (±10)	**50%** (±10)	**21%** (±8)
p-value	***0.24***	***0.0001***	***<0.0001***	***0.0002***		

De Bont, Leukemia 2004

5-year overall survival by age group over time in the Netherlands



Proportion of patients with ALL treated at a pediatric oncology center in the Netherlands



Reedijk, Leukemia 2020

Multivariate analysis of risk of death: Patients 15–17 years old with ALL in the Netherlands between 1990 and 2015

		Hazard risk	95% CI	95% CI	*P* value
Period	1990-94	Reference			
	1995-99	0.97	0.50	1.91	.94
	2000-04	0.67	0.32	1.42	.30
	2005-09	0.64	0.30	1.37	.25
	2010-15	0.80	0.38	1.68	.56
Sex	Male	Reference			
	Female	1.45	0.89	2.37	.14
Immunophenotype	Precursor B cell	Reference			
	Precursor T cell	1.59	0.97	2.62	.07
Site of treatment	Outside pediatric oncology center	Reference			
	Pediatric oncology center	0.32	0.20	0.53	<.01

Reedijk, Leukemia 2020

Outcomes of older adolescents treated on recent pediatric trials

Trial	No. of patients	Age range, yr	Early death, %	Death in CR, %	HSCT, %	EFS		OS	
						Y	%	Y	%
CCG 1961	262	16-21	2	3	4	5	72	5	78
DFCI 9101/9501	51	15-18	4	2	NR	5	78	5	81
Total Therapy XV	45	15-18	0	7	11	5	86	5	88
UKALL 2003	229	16-24	NR	6	6.1	5	72	5	76
FRALLE 2000	186	15-19	2	2	12	5	74	5	80
DCOG ALL-10	57	15-18	3.5	3.5	12	5	79	5	82

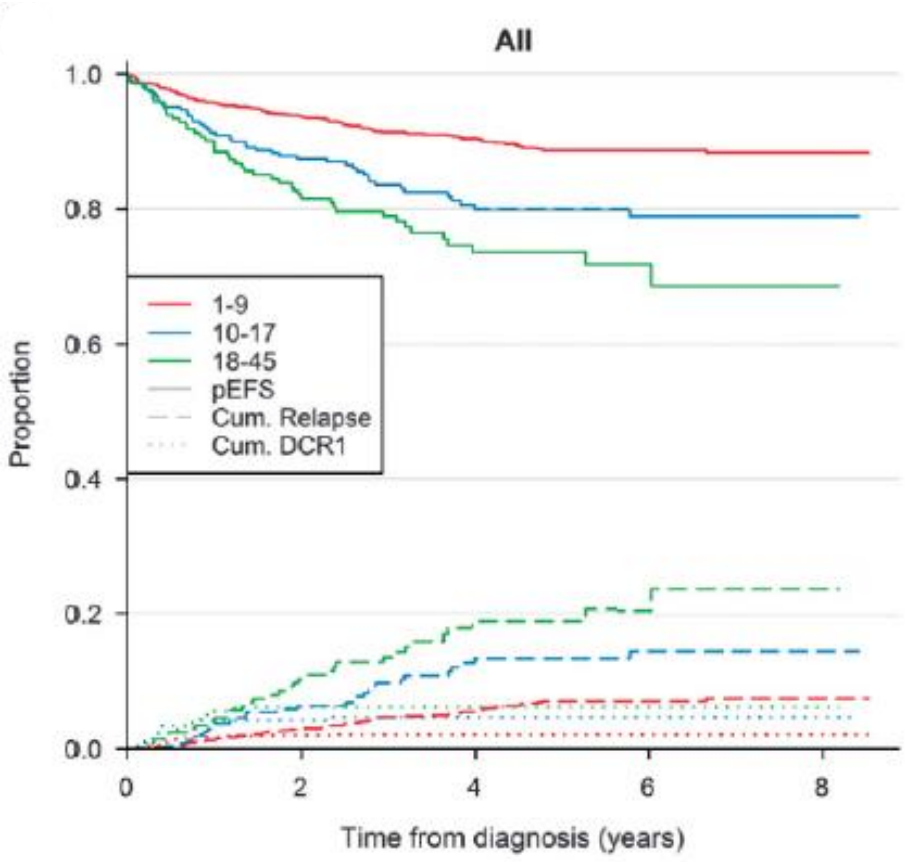
Adapted from Boissel, 2018 and Pieters, 2016

Outcomes of young adults on recent pediatric-inspired protocol (HOVON)

Trial	No. of pts	Age range, yr	Early death, %	Death in CR, %	HSCT, %	EFS		OS	
						Y	%	Y	%
CCG 1961	262	16-21	2	3	4	5	72	5	78
DFCI 9101/9501	51	15-18	4	2	NR	5	78	5	81
Total Therapy XV	45	15-18	0	7	11	5	86	5	88
UKALL 2003	229	16-24	NR	6	6.1	5	72	5	76
FRALLE 2000	186	15-19	2	2	12	5	74	5	80
DCOG ALL-10	57	15-18	2.5	2.5	12	5	79	5	82
HOVON 100	***77***	***18-25***			***44%***	***5***	***59***	***5***	***77***
HOVON 100	***82***	***26-40***			***41%***	***5***	***61***	***5***	***72***

Courtesy of Anita Rijneveld and Lotte van der Wagen (HOVON study group)

EFS, relapse, and death in first remission by age



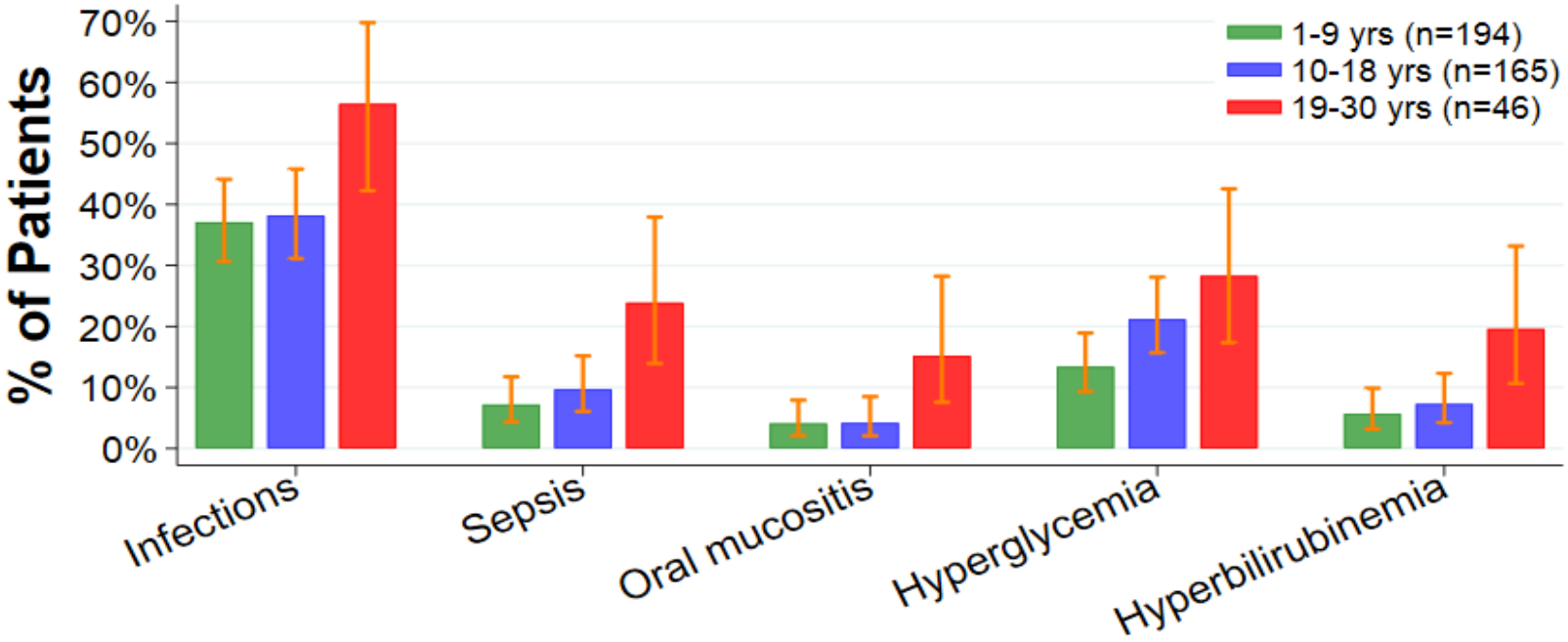
Toft N, 2018

Toxicity by age

	Y/N (%)	OR (95% CI)	P
Intensive care w/wo assisted ventilation			
1-9	145 / 864 (14.4%)	1.0 (1.0- 1.0)	
10-17	54 / 208 (20.6%)	1.3 (0.9- 1.9)	0.14
18-45	40 / 172 (18.9%)	1.1 (0.7- 1.6)	0.68
Anaphylatic reaction to asparaginase			
1-9	146 / 863 (14.5%)	1.0 (1.0- 1.0)	
10-17	25 / 237 (9.5%)	0.6 (0.4- 0.9)	0.016
18-45	11 / 201 (5.2%)	0.3 (0.1- 0.5)	<0.001
Invasive Fungal infection			
1-9	98 / 911 (9.7%)	1.0 (1.0- 1.0)	
10-17	32 / 230 (12.2%)	0.9 (0.6- 1.4)	0.68
18-45	28 / 184 (13.2%)	0.9 (0.5- 1.4)	0.54
Peripheral paralysis			
1-9	100 / 909 (9.9%)	1.0 (1.0- 1.0)	
10-17	30 / 232 (11.5%)	1.3 (0.8- 2.1)	0.21
18-45	20 / 192 (9.4%)	1.1 (0.7- 1.9)	0.61
Pancreatitis			
1-9	60 / 949 (5.9%)	1.0 (1.0- 1.0)	
10-17	29 / 233 (11.1%)	2.2 (1.3- 3.5)	0.001
18-45	24 / 188 (11.3%)	2.4 (1.4- 4.0)	0.001
Hyperlipidemia			
1-9	72 / 937 (7.1%)	1.0 (1.0- 1.0)	
10-17	26 / 236 (9.9%)	1.7 (1.0- 2.8)	0.027
18-45	15 / 197 (7.1%)	1.3 (0.7- 2.3)	0.37
Thrombosis			
1-9	36 / 973 (3.6%)	1.0 (1.0- 1.0)	
10-17	40 / 222 (15.3%)	5.0 (3.1- 8.2)	<0.001
18-45	37 / 175 (17.5%)	6.0 (3.6-10.1)	<0.001
Osteonecrosis			
1-9	23 / 986 (2.3%)	1.0 (1.0- 1.0)	
10-17	35 / 227 (13.4%)	8.0 (4.6-14.1)	<0.001
18-45	18 / 194 (8.5%)	5.3 (2.7-10.3)	<0.001
Seizures			
1-9	38 / 971 (3.8%)	1.0 (1.0- 1.0)	
10-17	16 / 246 (6.1%)	1.7 (0.9- 3.1)	0.086
18-45	5 / 207 (2.4%)	0.7 (0.2- 1.6)	0.39
PCP			
1-9	29 / 980 (2.9%)	1.0 (1.0- 1.0)	
10-17	11 / 251 (4.2%)	1.3 (0.6- 2.6)	0.48
18-45	13 / 199 (6.1%)	1.8 (0.9- 3.7)	0.089
PRES			
1-9	37 / 972 (3.7%)	1.0 (1.0- 1.0)	
10-17	9 / 253 (3.4%)	0.8 (0.4- 1.7)	0.60
18-45	5 / 207 (2.4%)	0.5 (0.2- 1.3)	0.18

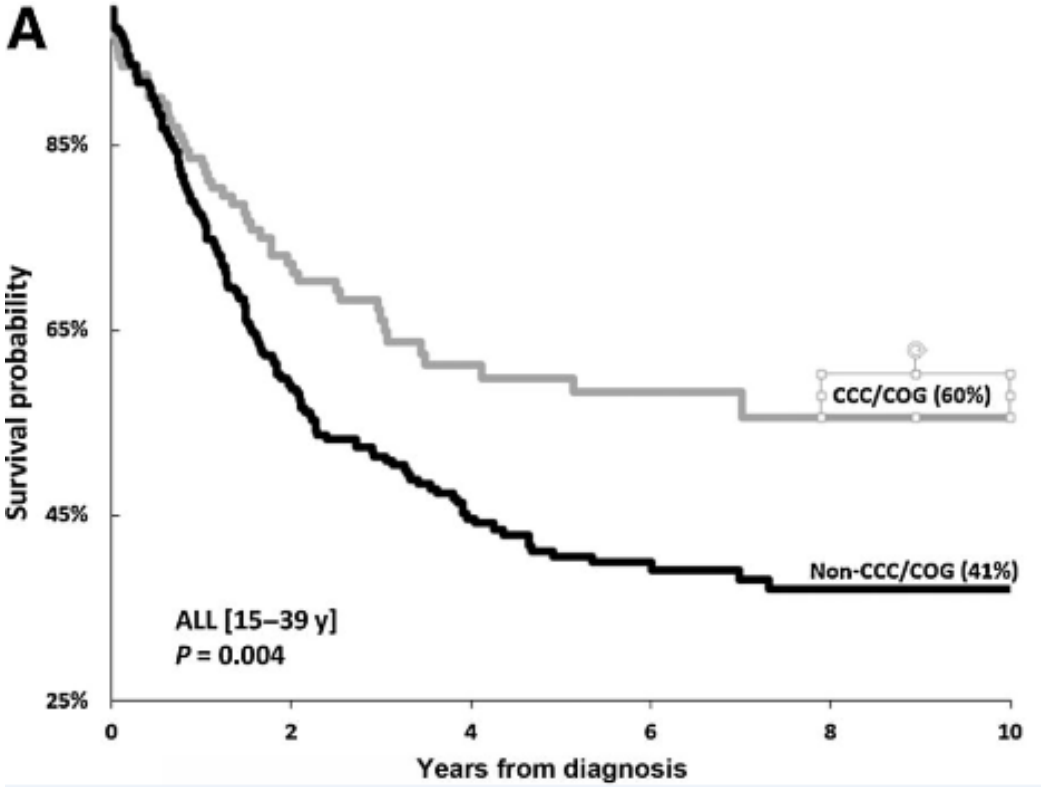
Toft N, 2018

Induction toxicities by age (COG first-relapse B-ALL clinical trial AALL1331)



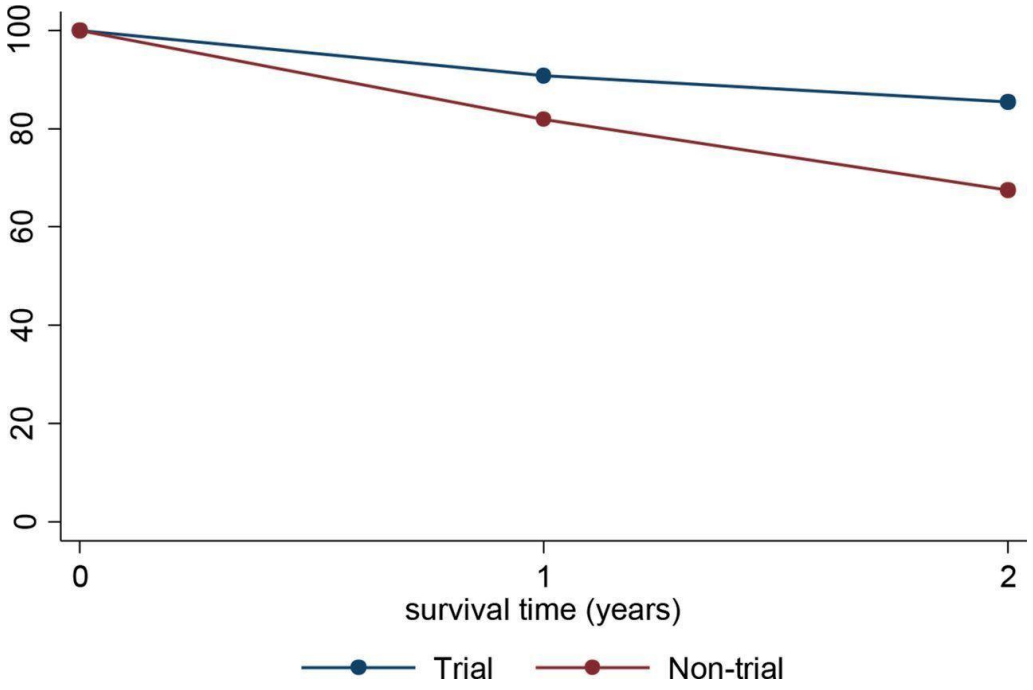
Hogan et al. Blood 2018; 132:1382 (courtesy of Mignon Loh)

Survival in AYA with ALL by treatment site in North America



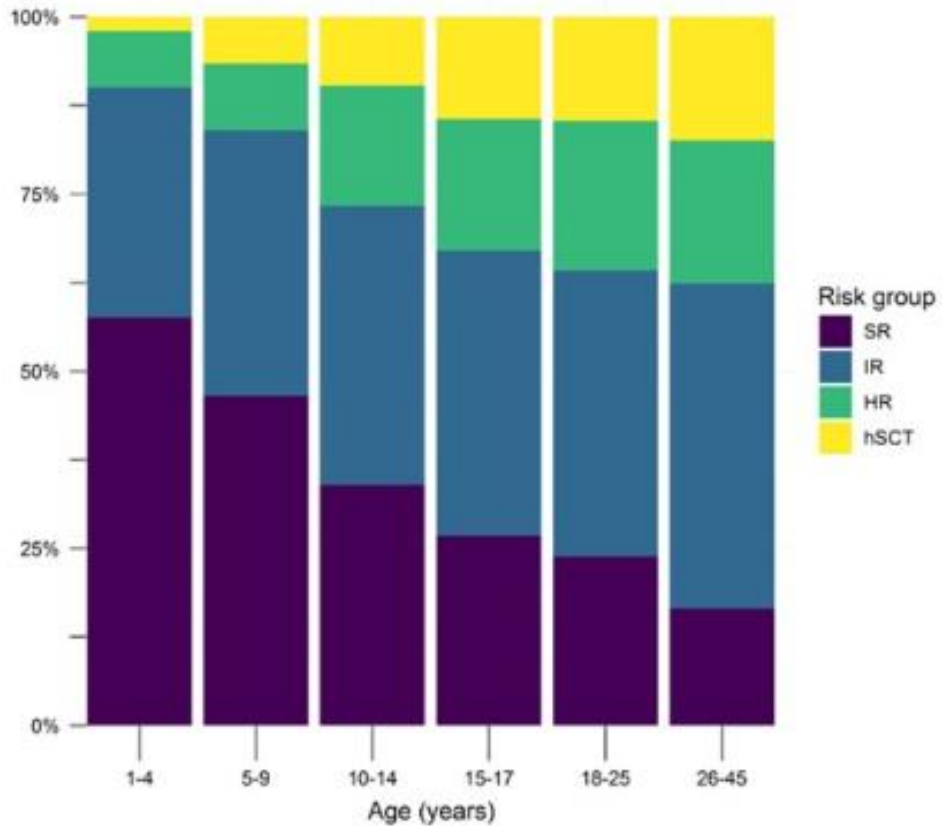
Wolfson J, 2017

Survival in 15- to 24-year-old ALL patients (n = 503) by trial status



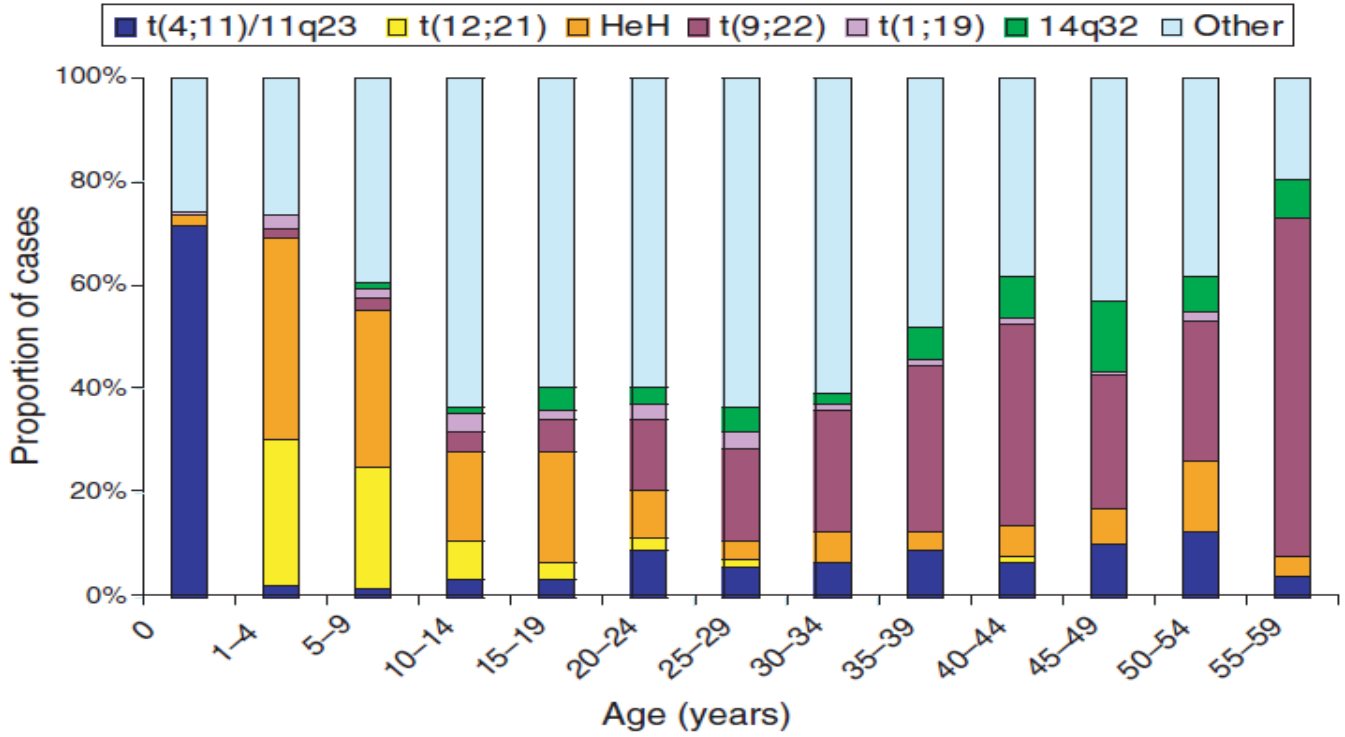
Hough R, 2017

Risk group distribution (MRD based) by age



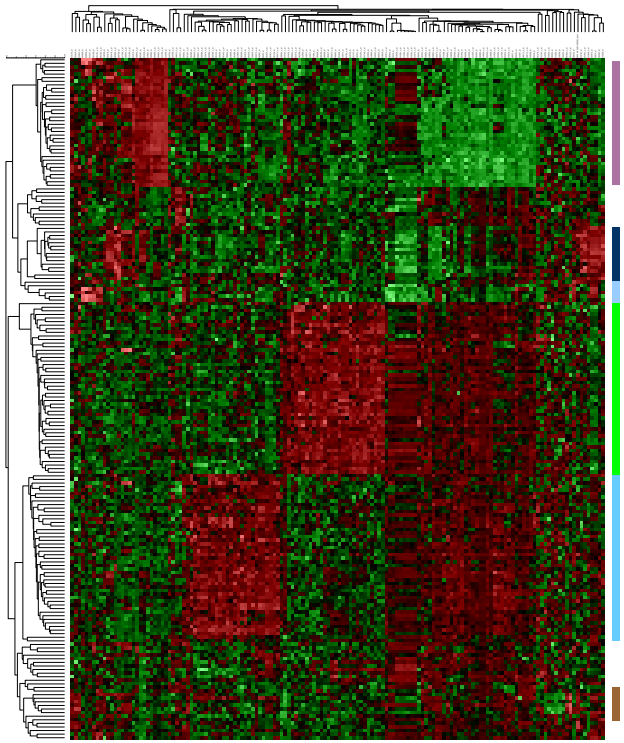
Toft N, 2018

Distribution of cytogenetic subtypes of ALL by age



Harrison, 2008

Discovery of *BCR-ABL1*–like ALL in 2009



T-ALL

***E2A*-rearranged**

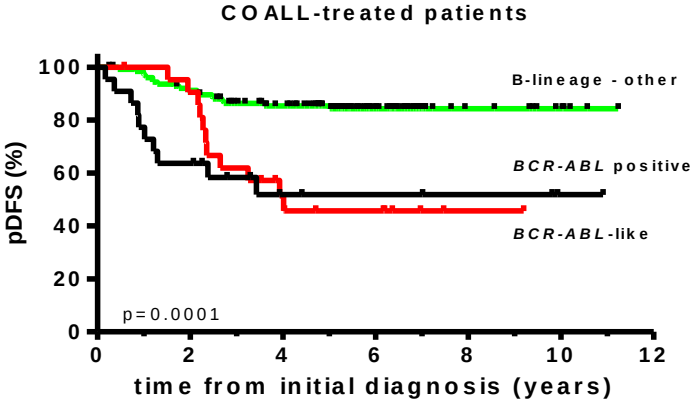
***MLL*-rearranged**

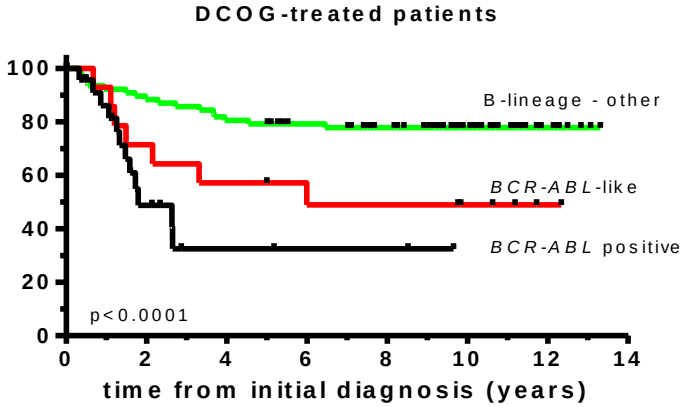
TEL-AML1

Hyperdiploid

BCR-ABL1

5 real *BCR-ABL1*
30 *BCR-ABL1*–like





Den Boer et al. Lancet Oncol. 2009

Frequency of identified tyrosine kinase fusion genes in *BCR-ABL1*–like ALL and remaining B-other ALL

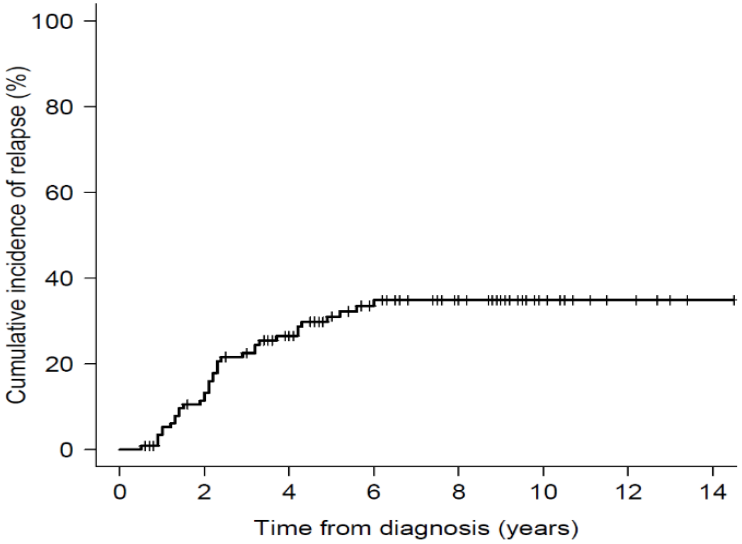
Marker	*BCR-ABL1*-like (n=77)	Remaining B-other (n=76)
***ABL1/ABL2* fusion**	**3.9%**	0%
ZMIZ1-ABL1	1	
FOXP1-ABL1	1	
RCSD1-ABL2	1	
***PDGFRB* fusion**	**5.2%**	0%
EBF1-PDGFRB	4	
***CSF1R* fusion**	**2.6%**	0%
SSBP2-CSF1R	2	
***JAK2* fusion**	**6.5%**	0%
PAX5-JAK2	3	
BCR-JAK2	1	
TERF2-JAK2	1	
CRLF2* high expression	15.6%	15.8%
PAR1 deletion**	10.5%	10.7%

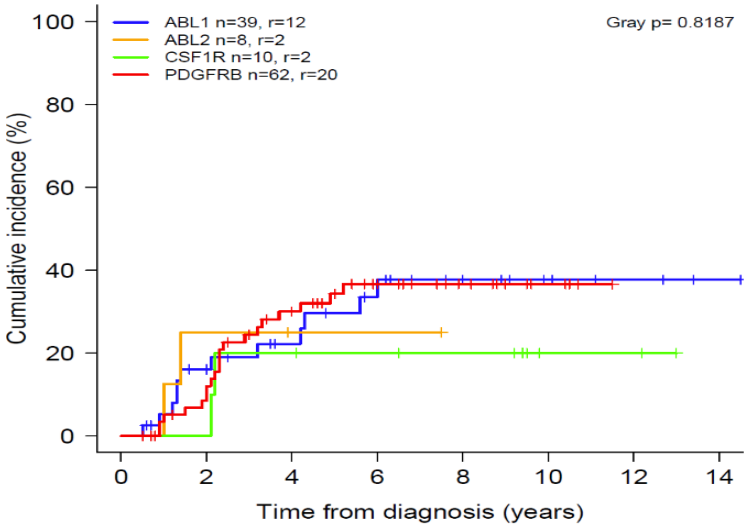
12% with **ABL-class** fusions
Targetable with TKI, eg, imatinib/dasatinib

6% with *JAK2* fusions
Targetable with ruxolitinib????

Boer, Oncotarget 2016

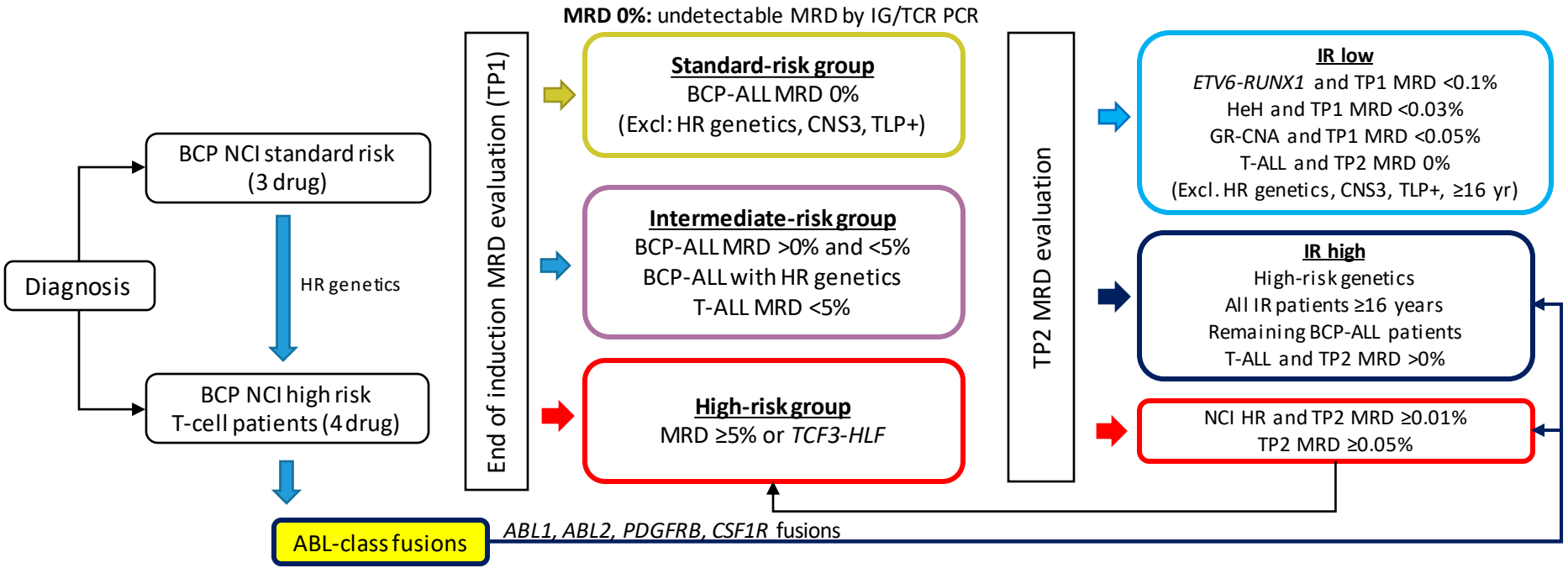
Cumulative incidence of relapse in ABL-class patients





Den Boer ML, Lancet Haematol 2020

Risk-stratification algorithm



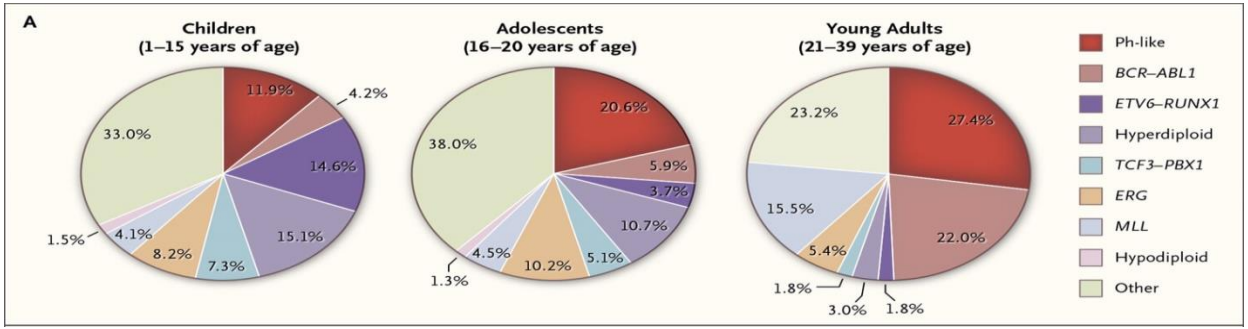
High-risk genetics: *KMT2A/MLL* fusions, near haploidy, low hypodiploidy, iAMP21

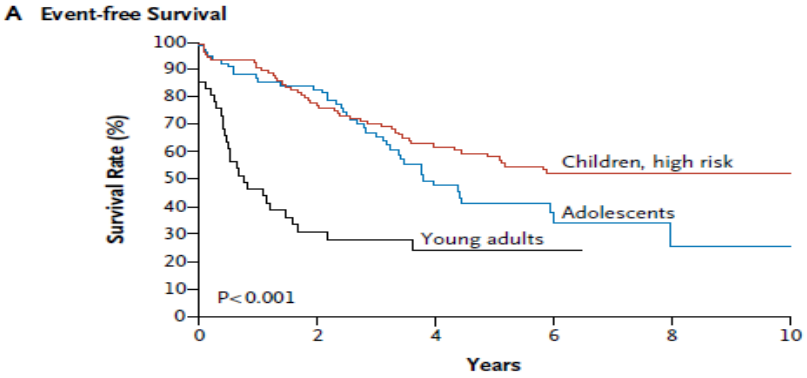
GR-CNA profile

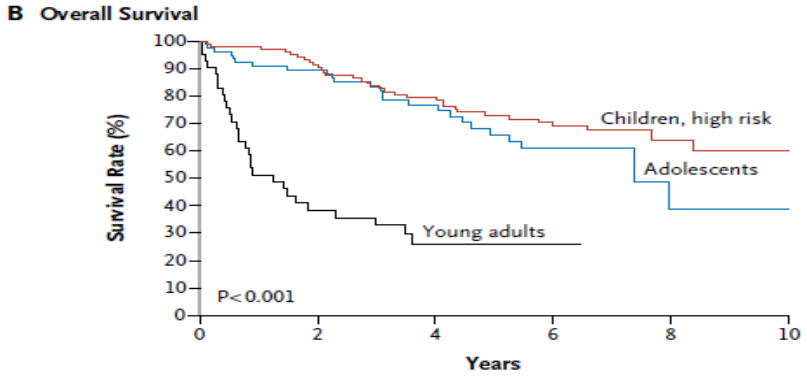
- No deletion of *IKZF1, CDKN2A/B, PAR1, BTG1, EBF1, PAX5, ETV6, RB1*
- Isolated deletions of *ETV6, PAX5, BTG1*
- *ETV6* deletions with a single additional deletion of *BTG1, PAX5, CDKN2A/B*

Ph-like ALL: Prevalence and outcomes

- 154 cases Ph-like ALL analyzed by NGS
- Kinase activating alterations in 91%
- Prevalence increased with age
- Inferior outcomes among all age groups

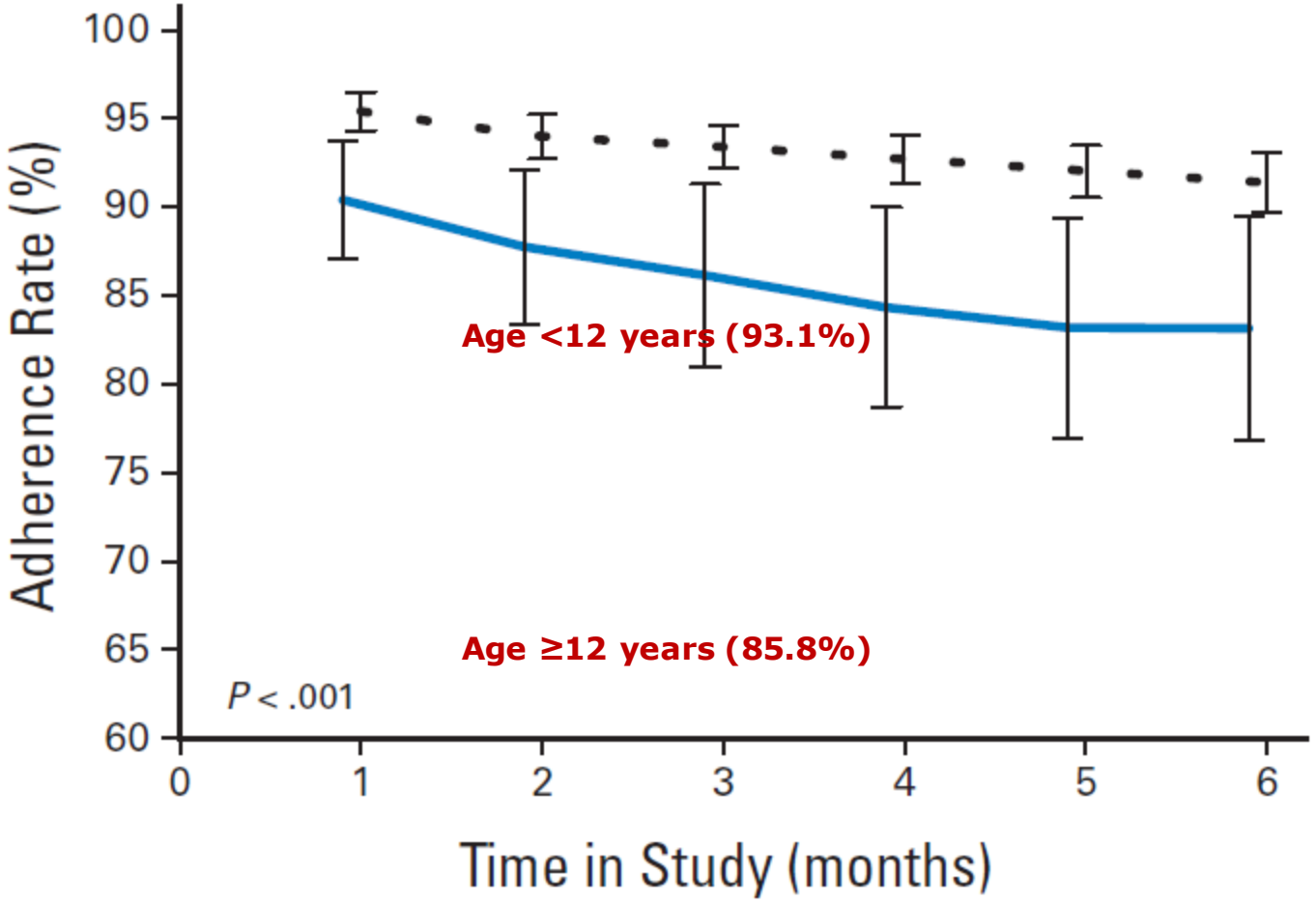






Roberts KG et al. *N Engl J Med* 2014;371:1005-1015; Graubert TA. *N Engl J Med* 2014;371:1064-1066 (courtesy of Mignon Loh)

depends



13.9% (2.6%)

4.7% (1.3%)

Bhatia et al. *J Clin Oncol* 2012; 30:2094-2102 and *JAMA Oncol*. 2015; 3:287–295 (courtesy of Mignon Loh)

AYA conclusions

- Outcomes improved but still inferior to those in younger children
- Pediatric-inspired protocols better than adult-inspired protocols
- Treatment within trials – better outcomes
- Higher toxicity in AYA than in younger children, but manageable
- Higher incidence of unfavorable biology/genetics
- Lower adherence to medication

[repeated question] Question 1: Which assertion is NOT correct for adolescent and young adult ALL patients?

a) Pediatric-inspired protocols lead to a better outcome than adult-inspired protocols

b) Osteonecrosis and anaphylactic reactions to asparaginase are more often seen in adults than in children and teenagers

c) AYA patients experience more liver toxicity and thrombosis than children <10 years old

d) *BCR-ABL1*–like ALL is more frequent in AYA ALL than in children <10 years old with ALL

Thank you

Global Leukemia Academy

Q&A session

APTITUDE HEALTH

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Break

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

Patrick Brown

APTITUDE HEALTH

Bispecific T-Cell Engagers as Post-reinduction Therapy Improves Survival in Pediatric and AYA B-ALL

Patrick Brown, MD

Professor of Oncology, Johns Hopkins University

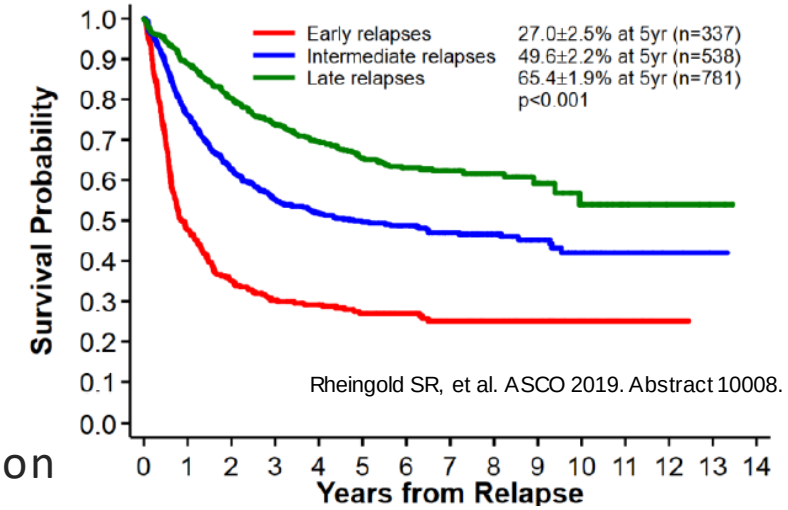
Director, Pediatric Leukemia Program, Sidney Kimmel Comprehensive Cancer Center

Vice Chair for Relapse, COG ALL Committee

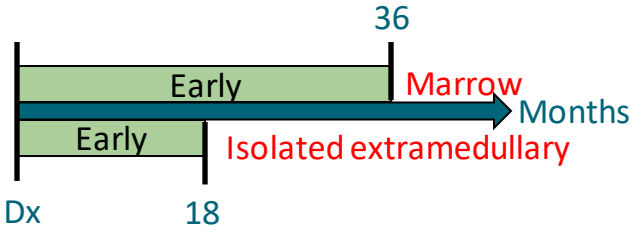
Chair, NCCN ALL Guidelines Panel

Relapsed Pediatric/AYA ALL

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



- Standard treatment approach
  - Reinduction chemotherapy → second remission
  - Consolidation
    - Early relapse: intensive chemo → HSCT
      - Goal: MRD negativity prior to HSCT
    - Late relapse
      - "MRD high": same as early
      - "MRD low": intensive chemo → maintenance therapy



How can we improve on this "standard"?

CHILDREN'S ONCOLOGY GROUP

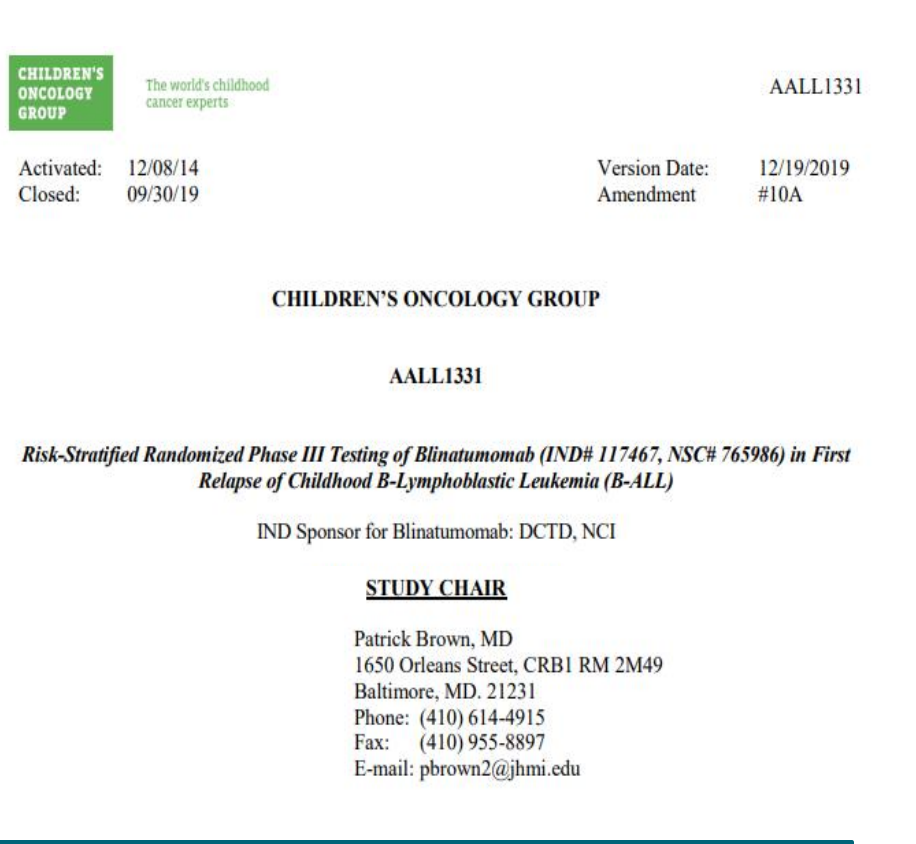
Blinatumomab (CD19 BiTE)

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

von Stackelberg A, et al. J Clin Oncol. 2016;34:4381-4389.

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

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



CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

AALL1331

Activated: 12/08/14
Closed: 09/30/19

Version Date: 12/19/2019
Amendment #10A

CHILDREN'S ONCOLOGY GROUP

AALL1331

Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC# 765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL)

IND Sponsor for Blinatumomab: DCTD, NCI

STUDY CHAIR

Patrick Brown, MD
1650 Orleans Street, CRB1 RM 2M49
Baltimore, MD. 21231
Phone: (410) 614-4915
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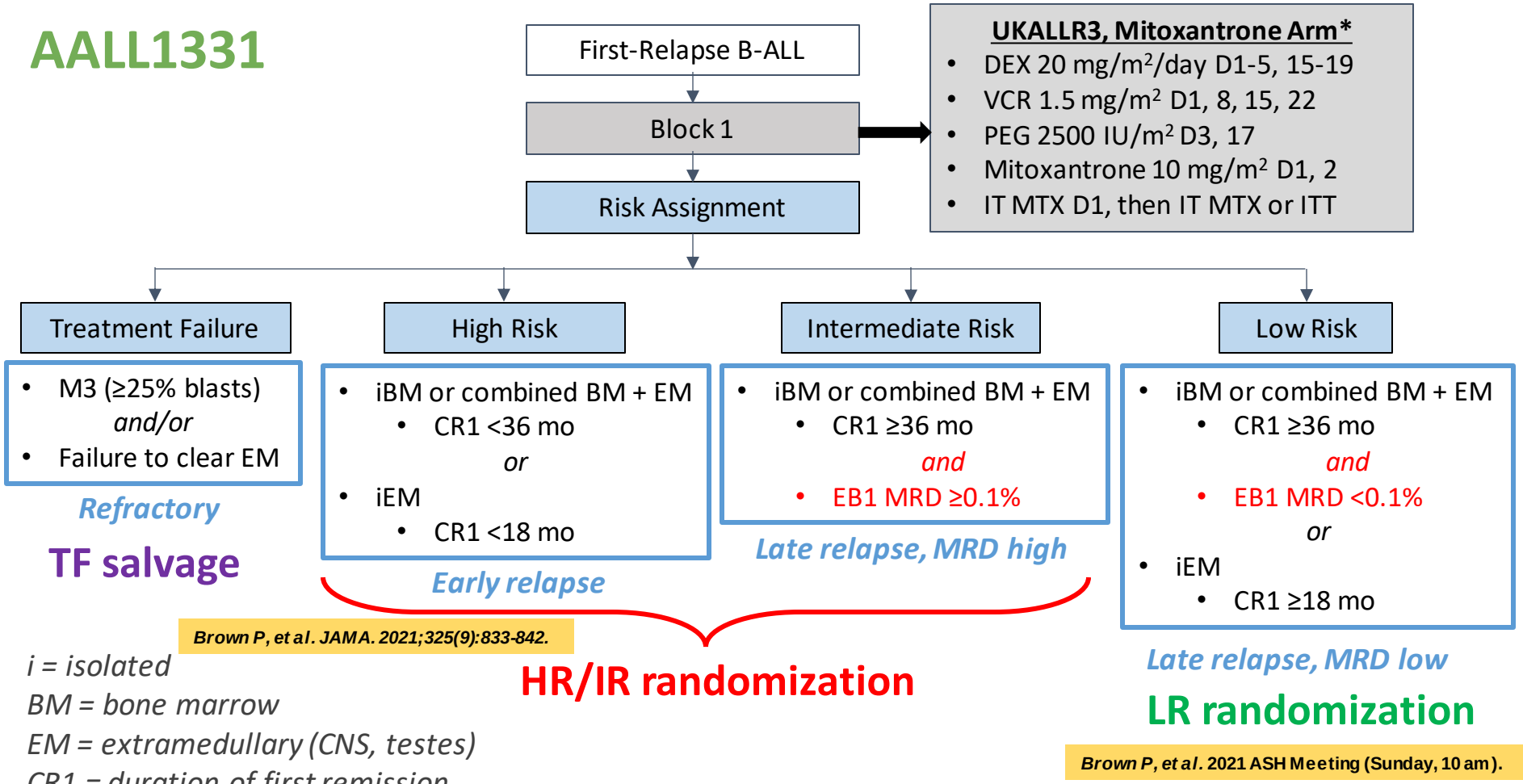
E-mail: pbrown2@jhmi.edu

CHILDREN'S ONCOLOGY GROUP

Overall objective of COG AALL1331:
To determine if substituting blinatumomab for intensive consolidation chemotherapy improves survival in first relapse of childhood/AYA B-ALL

AALL1331



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

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

Stratifications

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

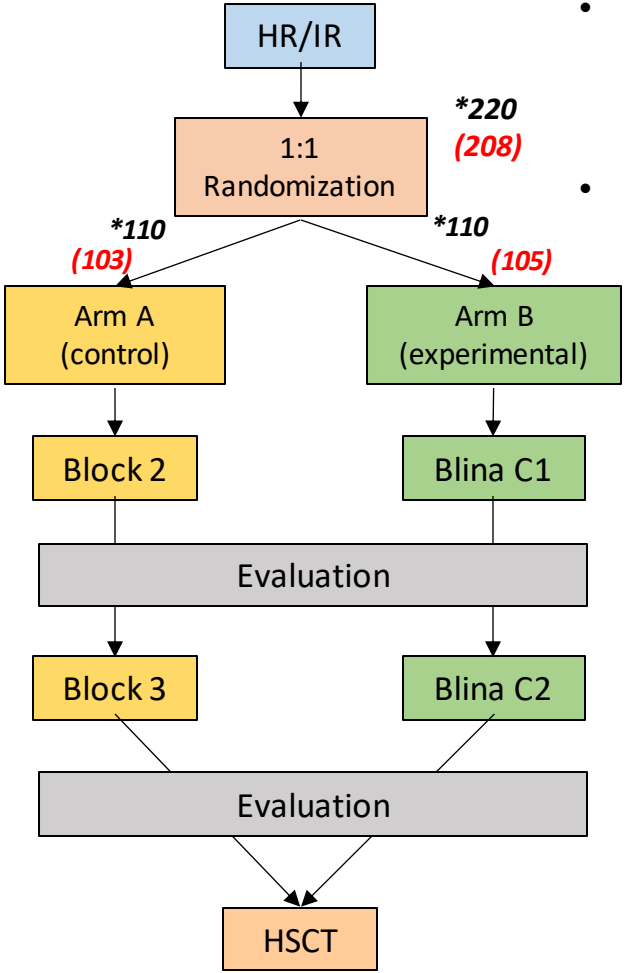
UKALLR3, Block 2*

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

UKALLR3, Block 3*

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

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



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

Blina C1 and Blina C2

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

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

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

Early Closure Recommended by DSMC

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

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

Baseline Characteristics

16% AYA

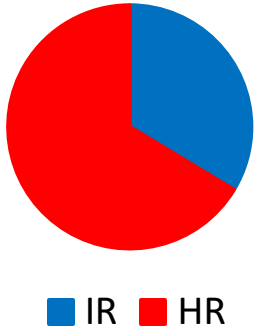
	Arm A (n = 103)	Arm B (n = 105)
Age at enrollment (years)		
Median (range)	*9 (1-27)*	*9 (1-25)*
1-9	55 (53%)	55 (52%)
10-17	30 (29%)	35 (33%)
18-30	18 (18%)	15 (14%)
Sex		
Female	49 (48%)	48 (46%)
Male	54 (52%)	57 (54%)
NCI risk group at diagnosis		
High risk	60 (58%)	59 (56%)
Standard risk	43 (42%)	46 (44%)
Cytogenetic groups at diagnosis		
Favorable (Tri 4/10, *ETV6-RUNX1*)	16 (18%)	21 (23%)
KMT2A-rearranged	9 (10%)	7 (8%)
Hypodiploidy	1 (1%)	0
Other	65 (71%)	63 (69%)
None	12	14

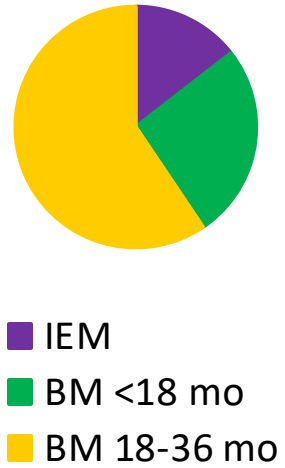
CHILDREN'S ONCOLOGY GROUP

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

Randomization Stratification Factors

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

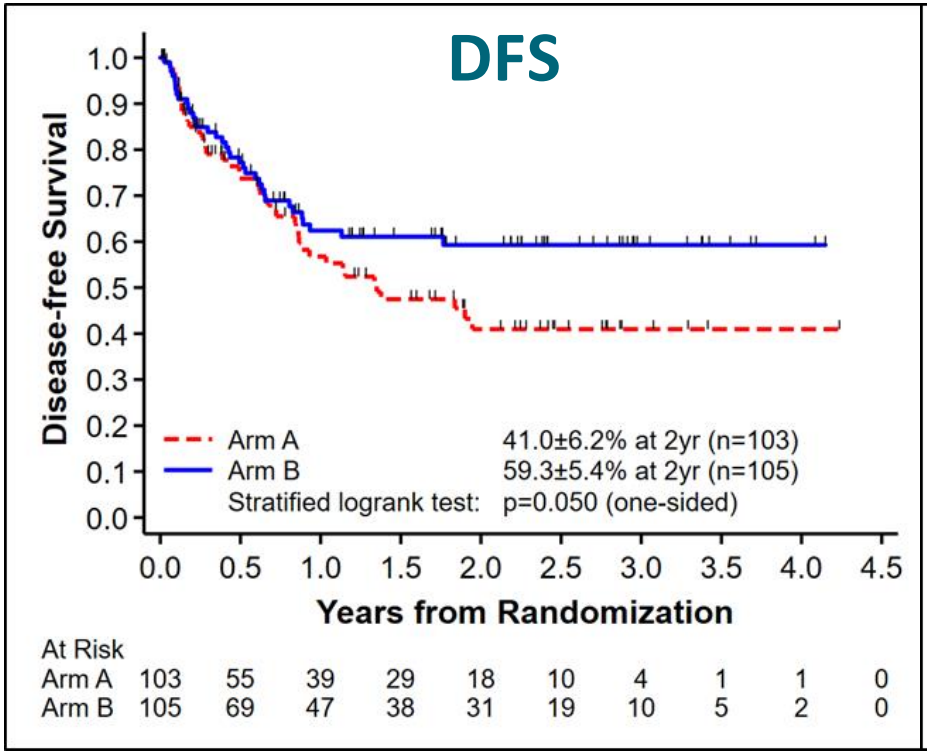


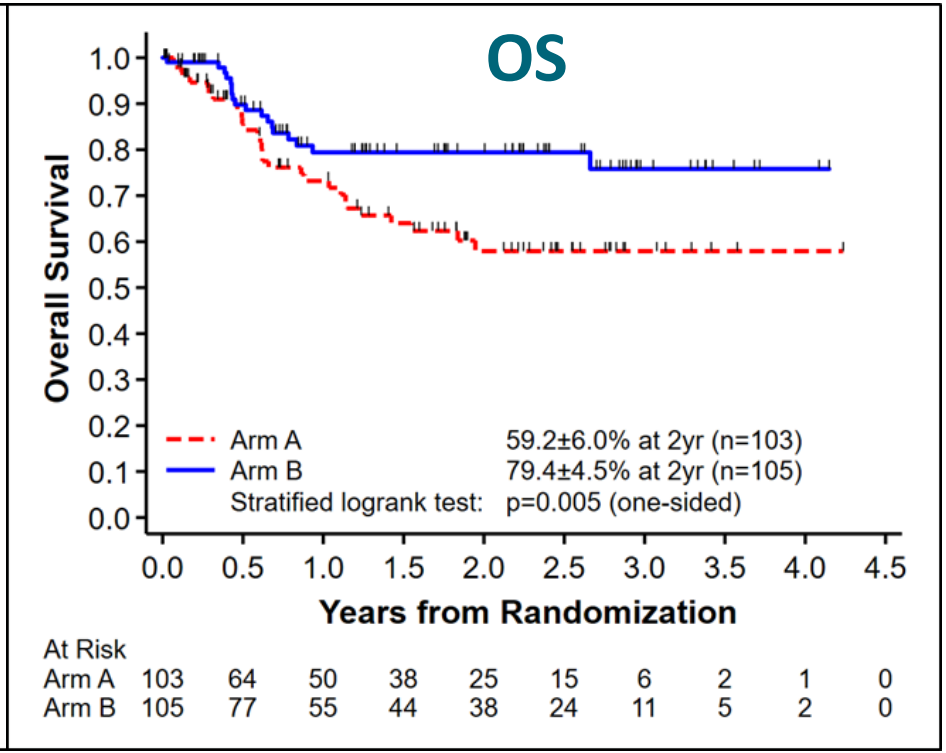


CHILDREN'S ONCOLOGY GROUP

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

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



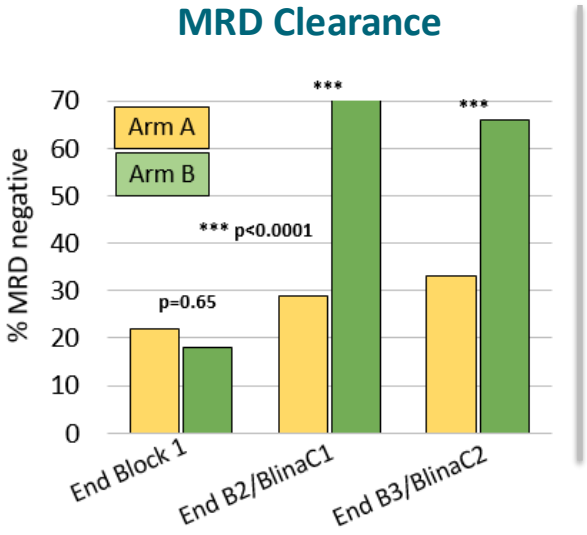


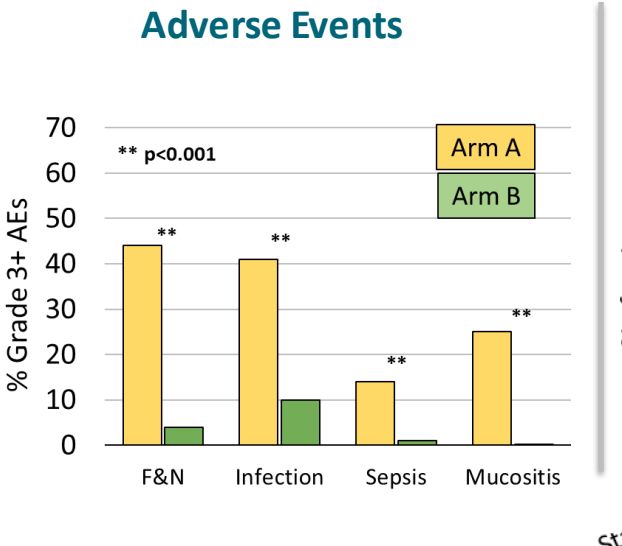
CHILDREN'S ONCOLOGY GROUP

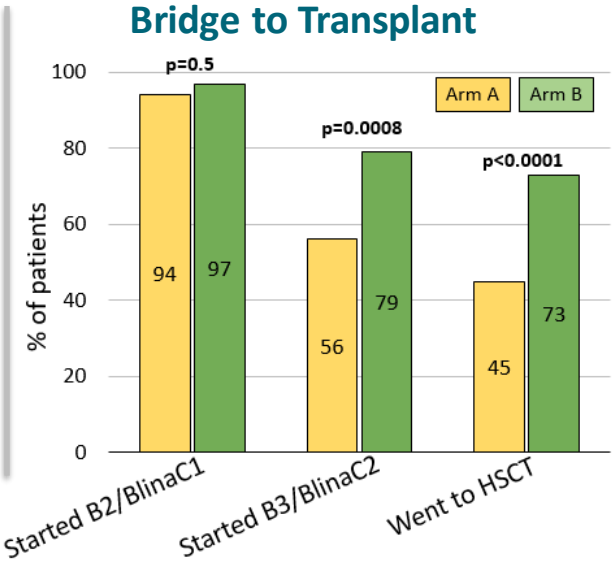
Median follow up 2.9 years

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

Other Endpoints: MRD, AEs, HSCT Bridging







Significant contributors to the improved outcomes for Arm B (blina) vs Arm A (chemo) in HR/IR relapses may include better **MRD clearance, less toxicity, and greater ability to successfully bridge to HSCT**

CHILDREN'S ONCOLOGY GROUP

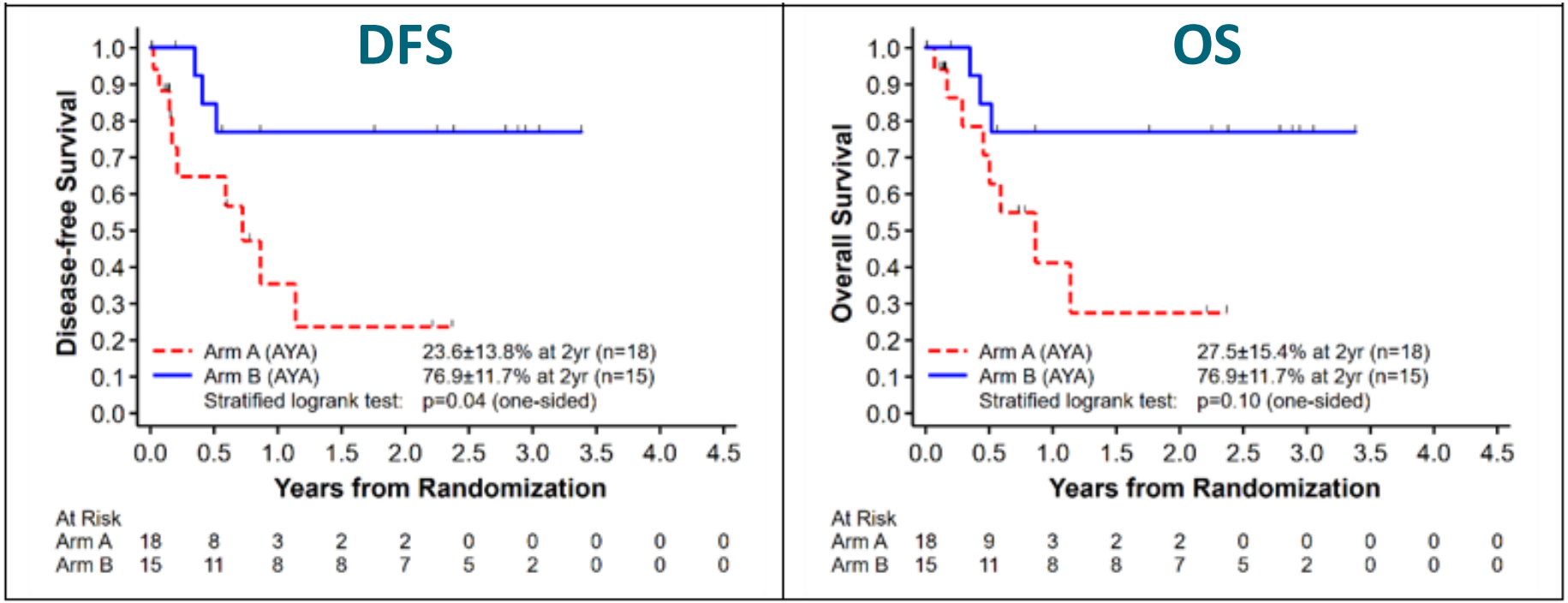
Brown P, et al. *JAMA*. 2021;325(9):833-842.

Blinatumomab-Related AEs on Arm B

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

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

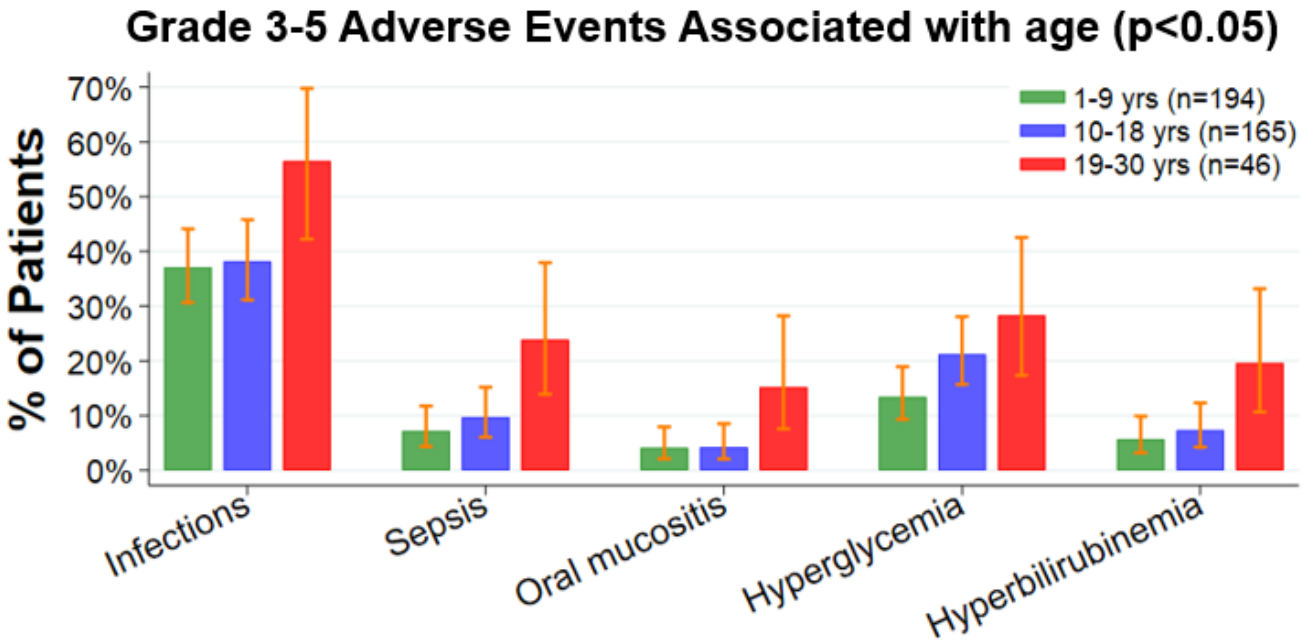
Results AYA Patients (ages 18–30 at relapse; N = 33/16%)



CHILDREN'S ONCOLOGY GROUP

Median follow-up 2.9 years

Results AYA Patients (ages 18–30 at relapse)



CHILDREN'S ONCOLOGY GROUP

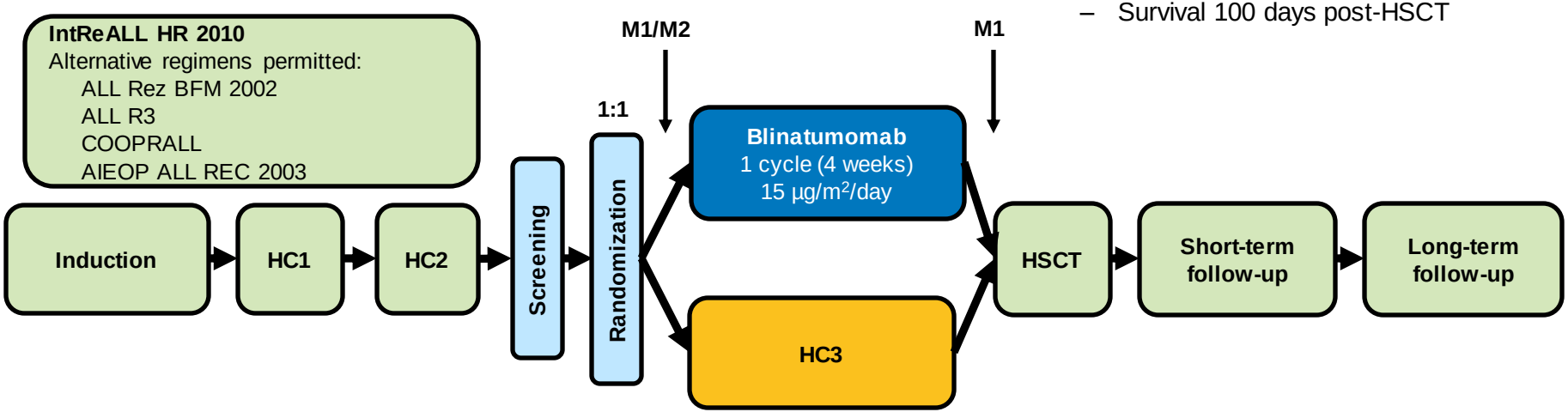
Hogan LB, et al. *Blood.* 2018;132(suppl 1): abstract 1382.

Amgen 20120215: Open-Label, Randomized, Phase III Trial: 47 Centers, 13 Countries

Key eligibility criteria
- Age >28 days <18 years
- HR first relapse Ph– BCP-ALL
- M1 or M2 marrow at randomization
- No CNS disease, unless treated before enrollment
- No clinically relevant CNS pathology

Stratification
- Age: <1 year, 1 to 9 years, >9 years
- BM status at end of HC2
  - M1 with MRD >10^{-3}
  - M1 with MRD <10^{-3}
  - M2

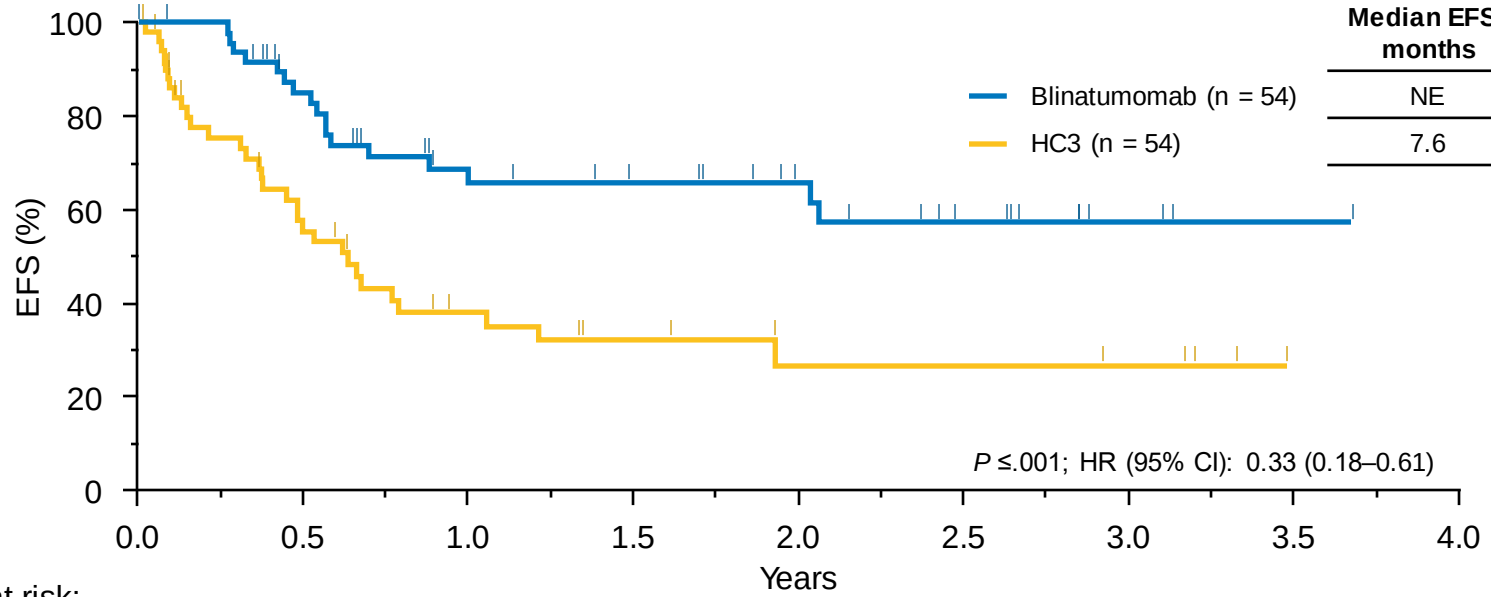
Endpoints
- Primary: EFS
- Secondary
  - OS
  - MRD response (end of blinatumomab or HC3)
  - Cumulative incidence of relapse
  - Incidence of AEs
  - Survival 100 days post-HSCT



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

BCP, B-cell precursor; EFS, event-free survival; HC, high-risk consolidation.

Superior EFS in the Blinatumomab Arm



	Median EFS, months	95% CI
Blinatumomab (n = 54)	NE	24.4–NE
HC3 (n = 54)	7.6	4.5–12.7

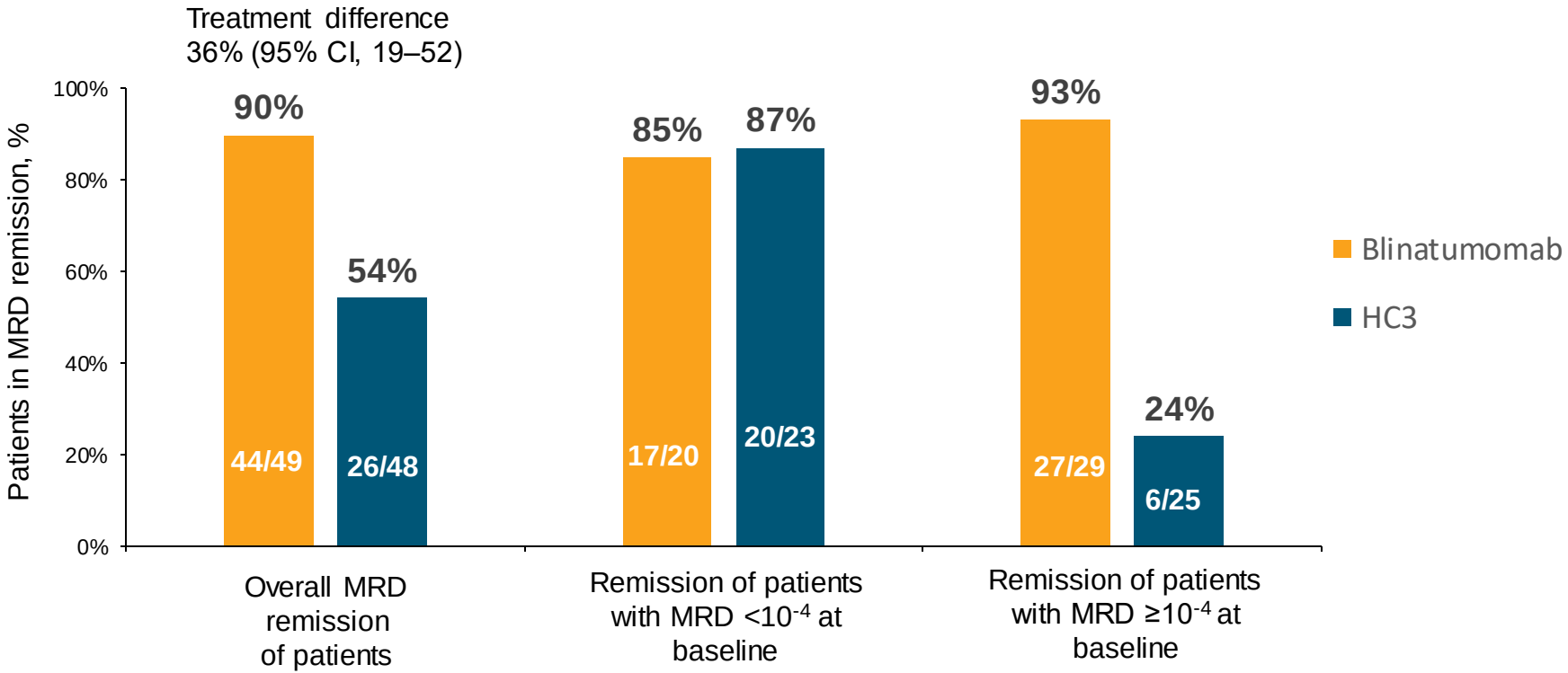
Patients at risk:

Blinatumomab	54	50	38	29	24	23	21	19	16	13	10	7	4	1	1	0
HC3	54	35	25	17	13	11	9	8	5	5	5	5	4	2	0	

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

P, stratified log rank *P* value; HR, hazard ratio from stratified Cox regression.

Superior MRD Remission by PCR in the Blinatumomab Arm (overall and by baseline* MRD status)



*Baseline: end of HC2 (screening sample before enrollment).
PCR, polymerase chain reaction.

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

Stratifications

- Site (BM vs iEM)
- End-Block 1 MRD (<0.01% vs 0.01%-0.099%)

UKALLR3, Block 2*

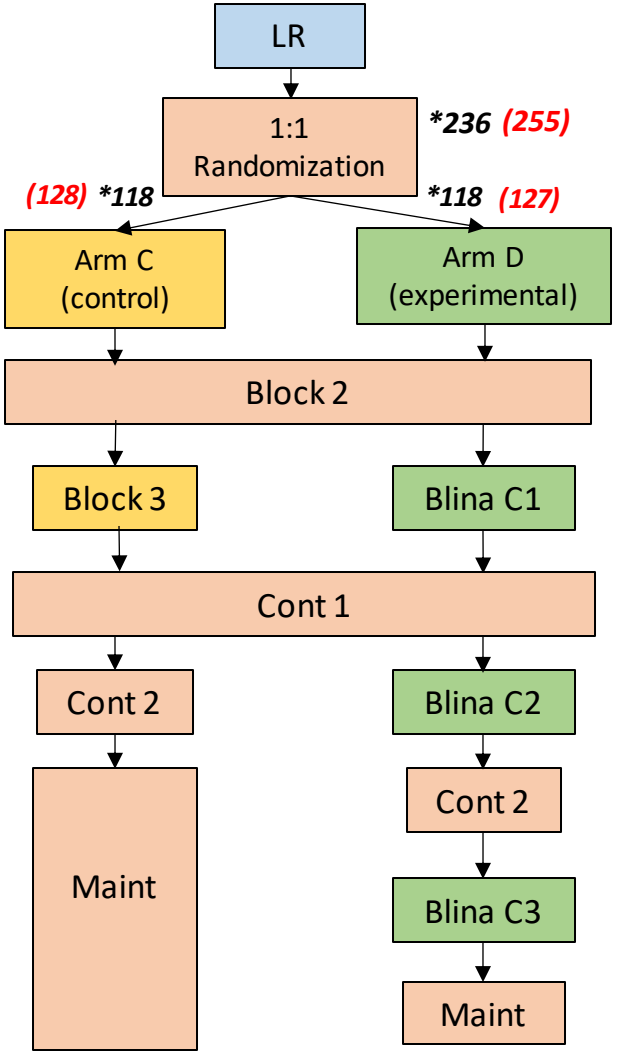
- VCR, DEX week 1
- ID MTX, PEG week 2
- CPM/ETOP week 3
- IT MTX or ITT

UKALLR3, Block 3*

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

UKALLR3, Continuation 1/2*

- VCR, DEX week 1
- 6MP week 1-6
- PO MTX week 2, 3, 5, 6
- ddMTX (CNS1/2) or ID MTX (CNS3) week 4
- CPM/ETOP/TG/ARAC week 7, 8
- IT MTX or ITT

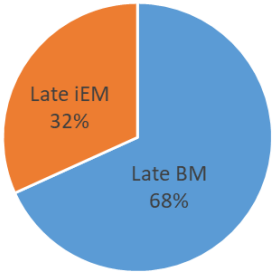


- Endpoints
  - Primary: DFS
  - Secondary: OS
- Sample size n = 236 (118 per arm)
  - Power 83% to detect HR 0.55 with 1-sided $\alpha = 0.05$
  - Increase 3-yr DFS from 73% to 84%

Blina C1, C2, C3

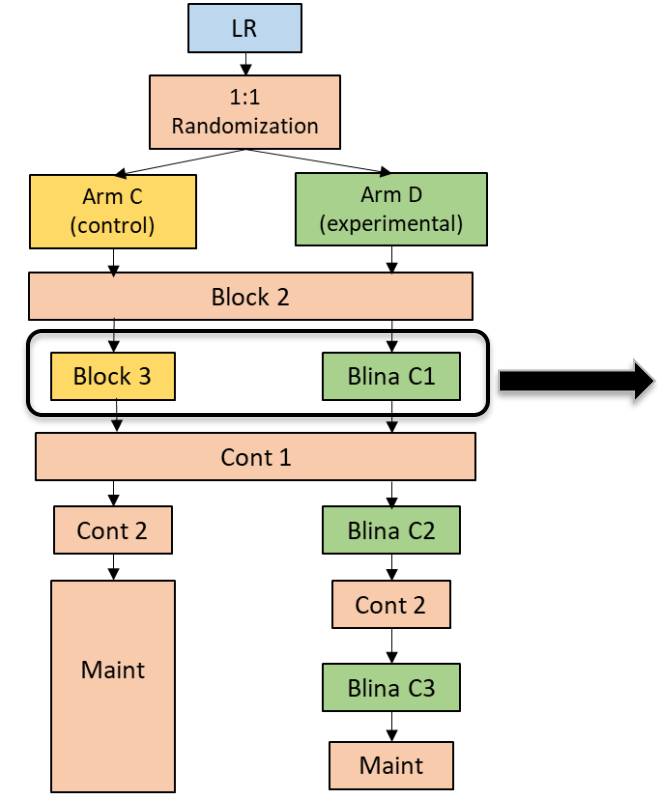
- Blinatumomab 15 $\mu g/m^2$/day × 28 days, then 7 days off
- Dex 5 mg/m^2/dose × 1 premed (C1 only)

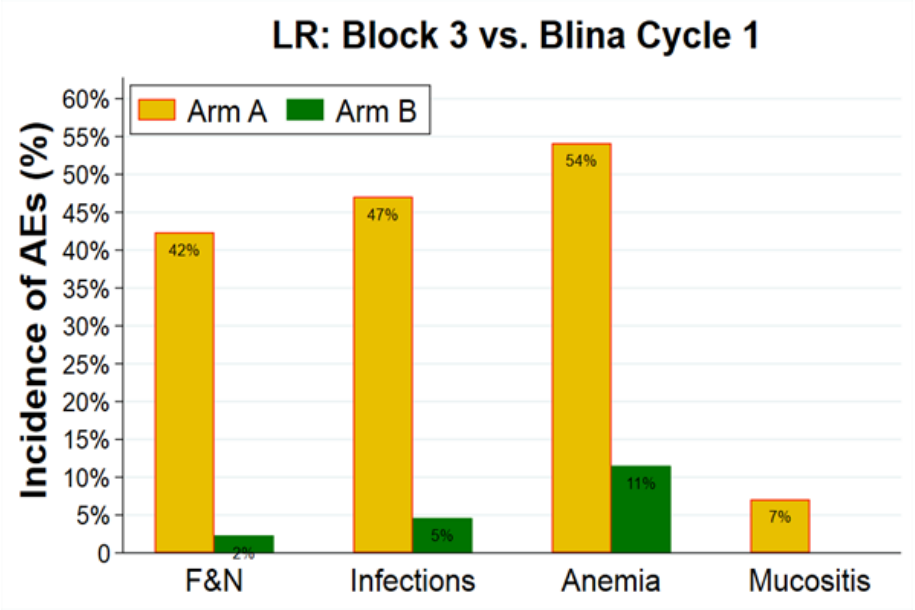
- ***First patient randomized Jan 2015***
- ***Last patient randomized Sep 2019***



ASH 2021 -> Sunday, 10am

Adverse Events





There was a striking difference in the toxicity profile (grade 3+ AEs) between the arms, with blina cycle 1 far less toxic than Block 3.

Unpublished data.

Conclusions for AALL1331 (so far . . .)

- For children and AYA patients with HR/IR first relapse of B-ALL, blinatumomab is superior to standard chemotherapy as post-reinduction consolidation prior to HSCT, resulting in
  - Fewer and less-severe toxicities (especially AYA)
  - Higher rates of MRD response
  - Greater likelihood of proceeding to HSCT
  - Improved disease-free and overall survival
- Blinatumomab constitutes a new standard of care in this setting
- Future
  - Finalize/publish results of LR randomization
  - Overcoming early failures associated with reinduction chemotherapy
  - Enhancing the efficacy of immunotherapy

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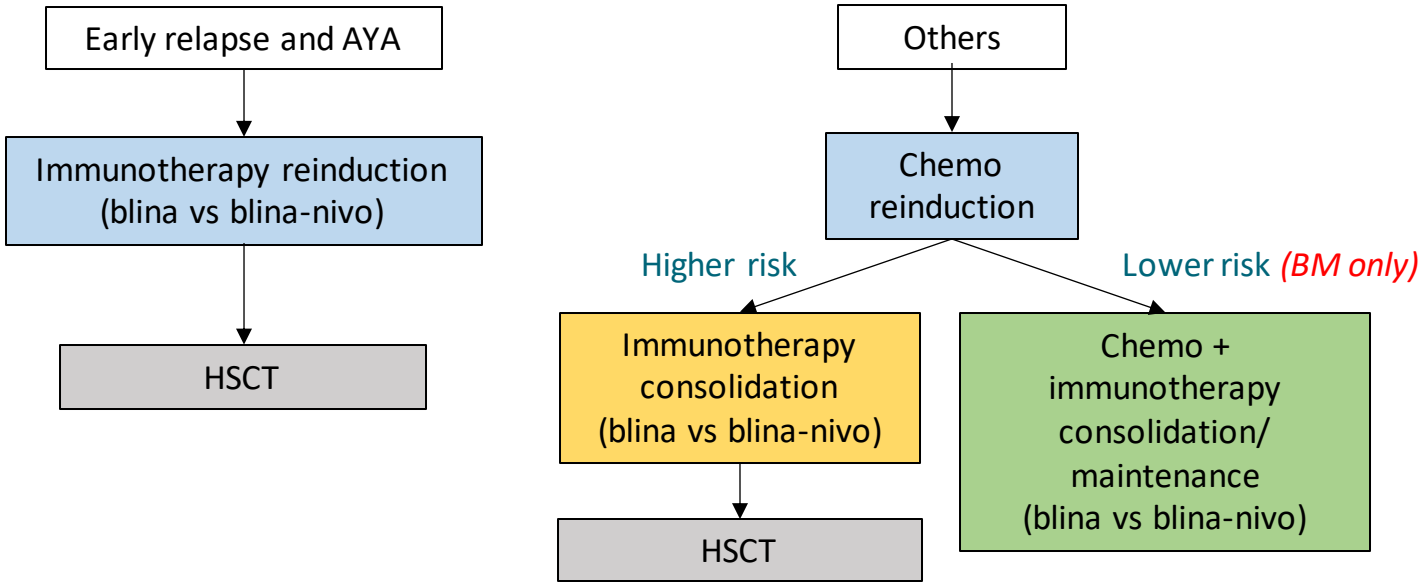
AALL1821: Blinatumomab + Nivolumab



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

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

AALL1331 Study Committee

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

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Brown PA, et al. *Blood.* 2019;134(suppl_2):LBA-1.

Funding

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

THANK YOU: Patients, families, caregivers, and collaborators!

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Questions?

Global Leukemia Academy

Q&A session

APTITUDE HEALTH

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

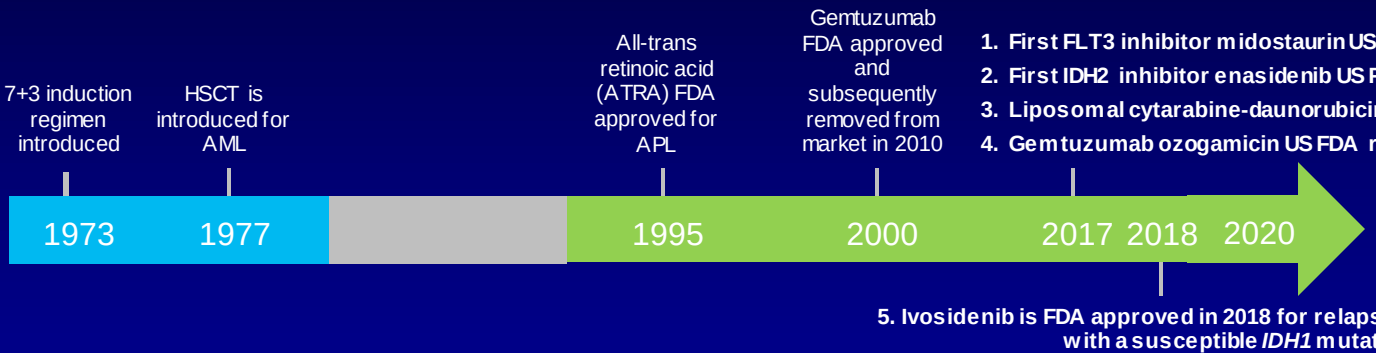
Global Leukemia Academy

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

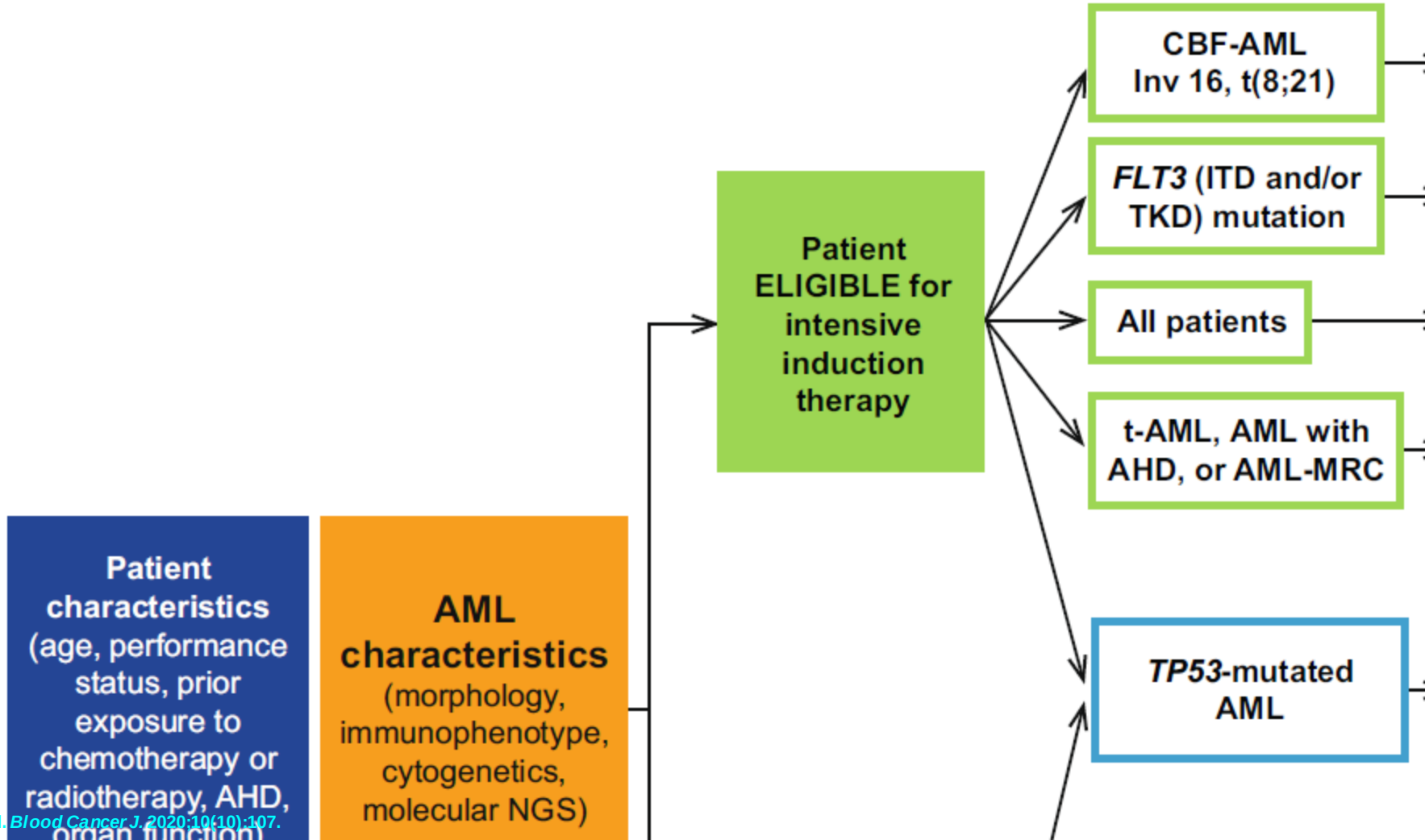
Treatment of AML (accelerated progress 2017–2020): History

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

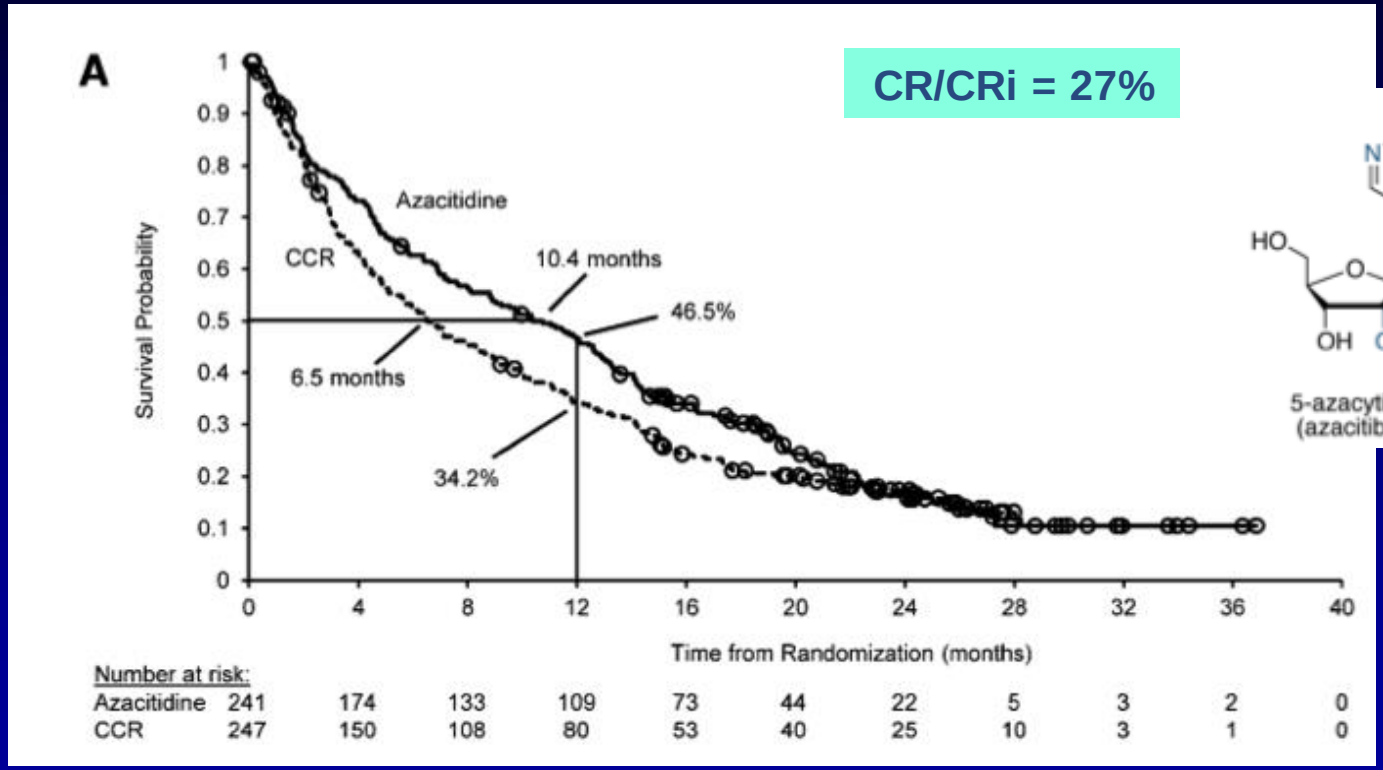


Year	1975	1980	1990	1995	2000	2005	2009	2013	2022
5-year survival	6.3%	6.8%	11.4%	17.3%	16.8%	25.7%	28.1%	27%	??

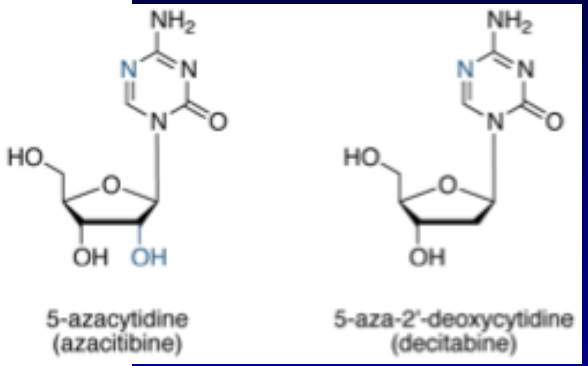


Daver N, et al. *Blood Cancer J.* 2020;10(10):107.

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

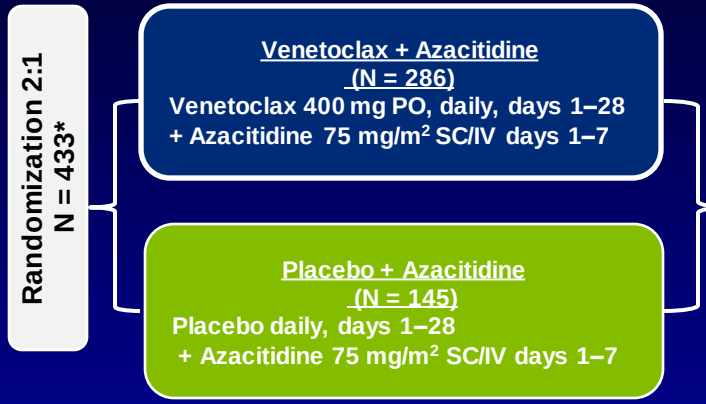
Inclusion

- 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

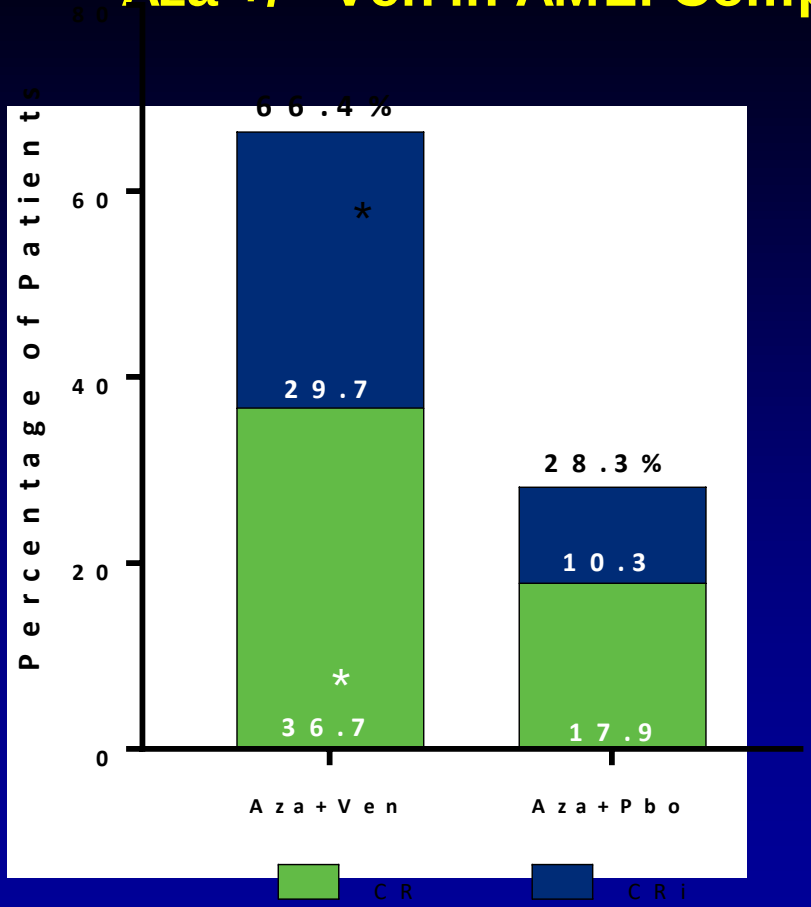
Characteristics	Ven + Aza (n = 286)	Pbo + Aza (n = 145)
Age		
Median (range) years	76 (49–91)	76 (60–90)
≥75 years, n (%)	174 (61)	87 (60)
Male, n (%)	172 (60)	87 (60)
AML type, n (%)		
De novo	214 (75)	110 (76)
Secondary	72 (25)	35 (24)
Secondary AML		
Post-MDS, CMML*	46 (64)	26 (74)
Therapy-related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

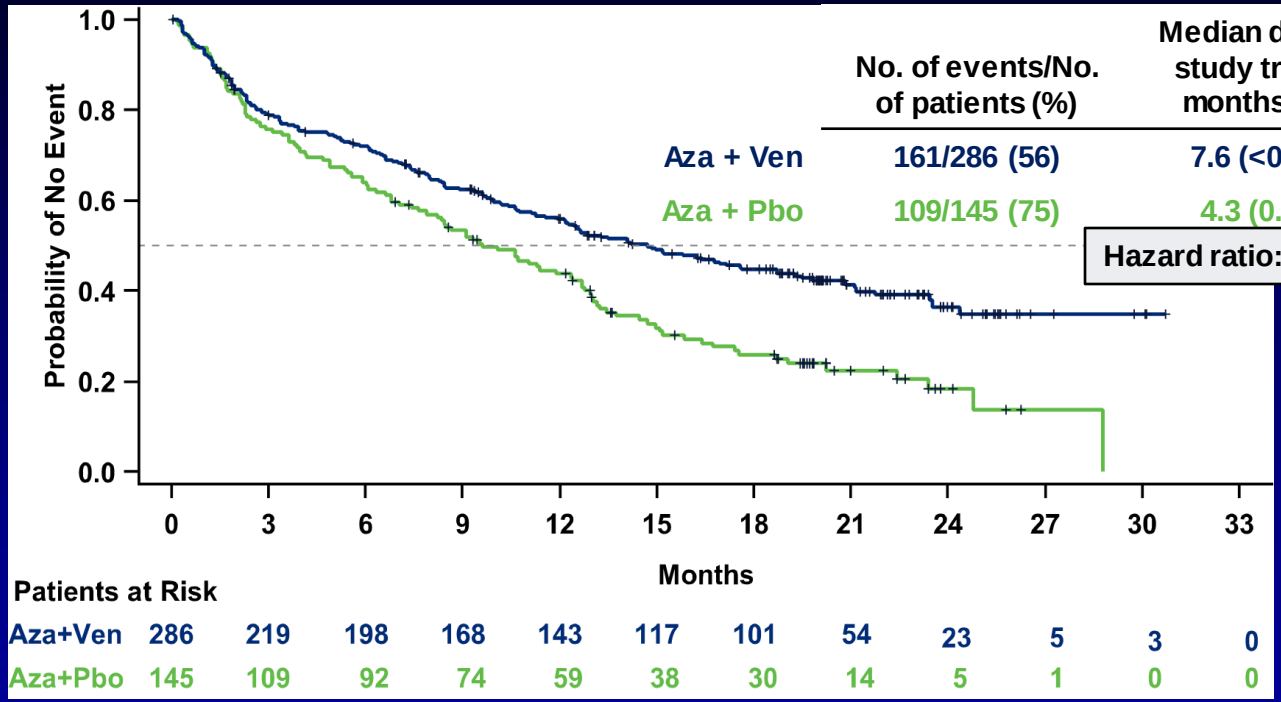


	No. of treatment cycles, median (range)	Median time to CR/CRi, Months (range)	*CR + CRi by initiation of Cycle 2, n (%)
Aza + Ven (n = 286)	7.0 (1.0–30.0)	1.3 (0.6–9.9)	124 (43.4)
Aza + Pbo (n = 145)	4.5 (1.0–26.0)	2.8 (0.8–13.2)	11 (7.6)

*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

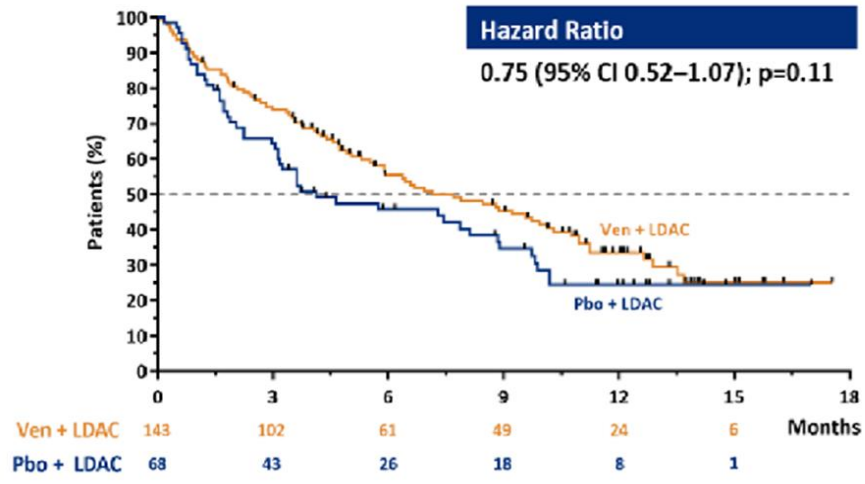
Median follow-up time: 20.5 months (range: <0.1 – 30.7)

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

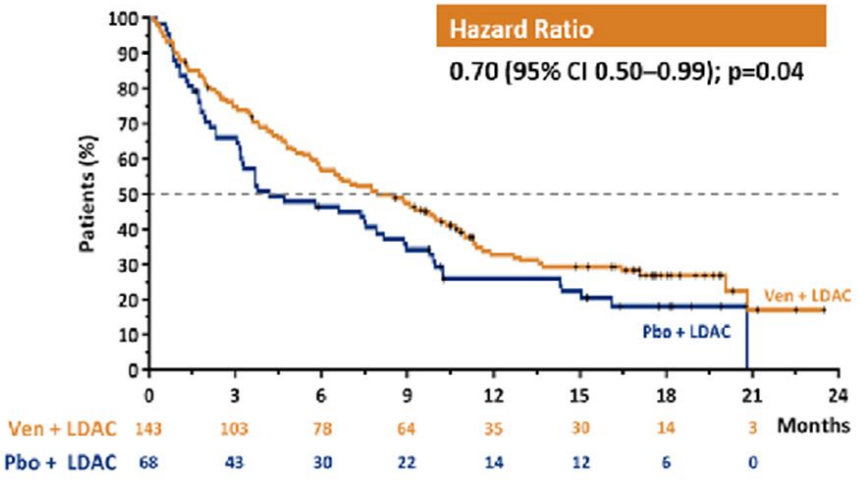
Low-Dose Cytarabine ± Venetoclax in AML: Results

	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.

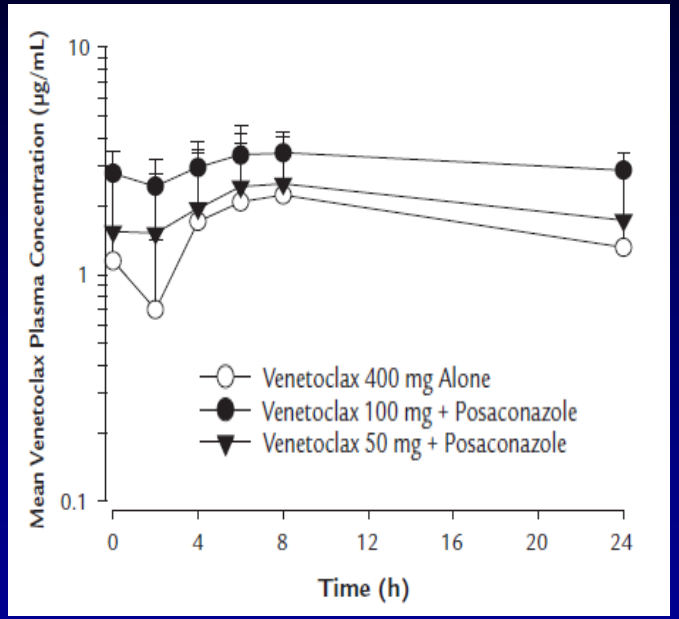
MDACC-Recommended Dosing Schema

- 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)

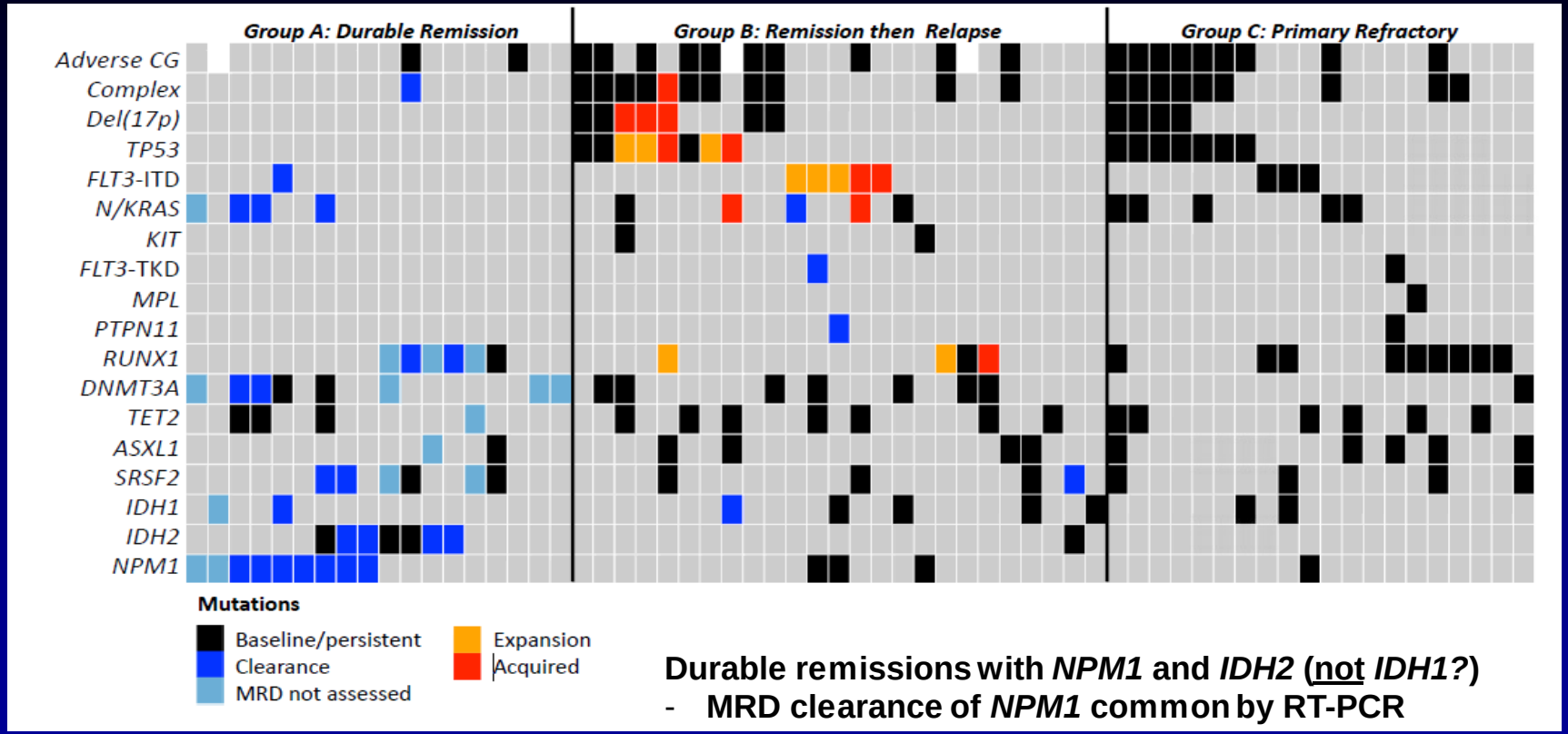


Agarwal SK, et al. *Clin Ther.* 2017;39:359-367.

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**

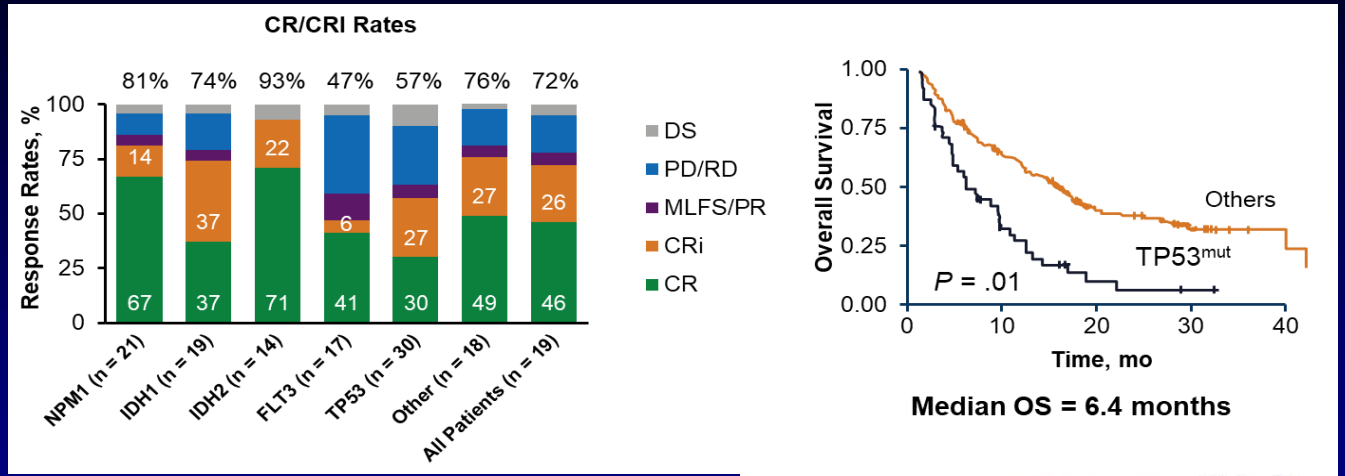
Patients treated at MDACC and The Alfred (n = 81)

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.

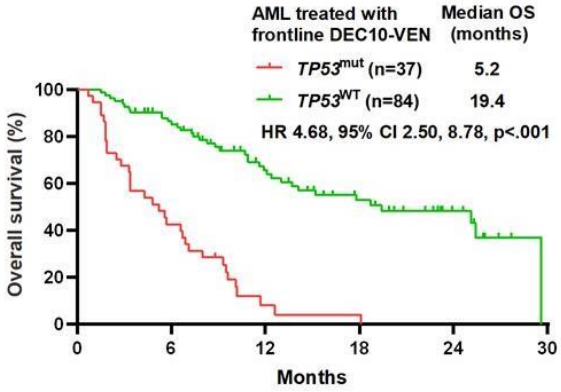
1. Poor Outcomes in *TP53*-Mutant AML, Even With Venetoclax-Based Treatment

Venetoclax + LDAC or HMA[1]



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

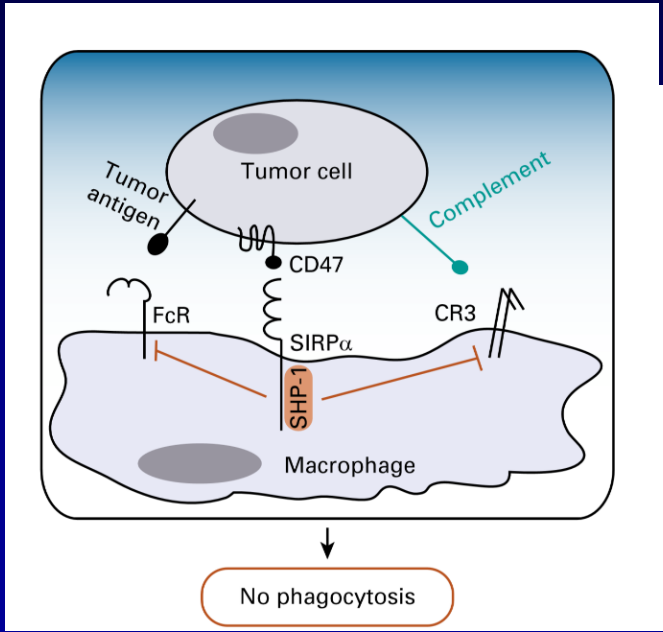
- **Those with *TP53*^{mut} had a lower rate of CR at 35% vs 57% in pts with *TP53*^{WT} (*P* = .026)**
- Lower rate of CR/CRi (54% vs 76%; *P* .015)



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

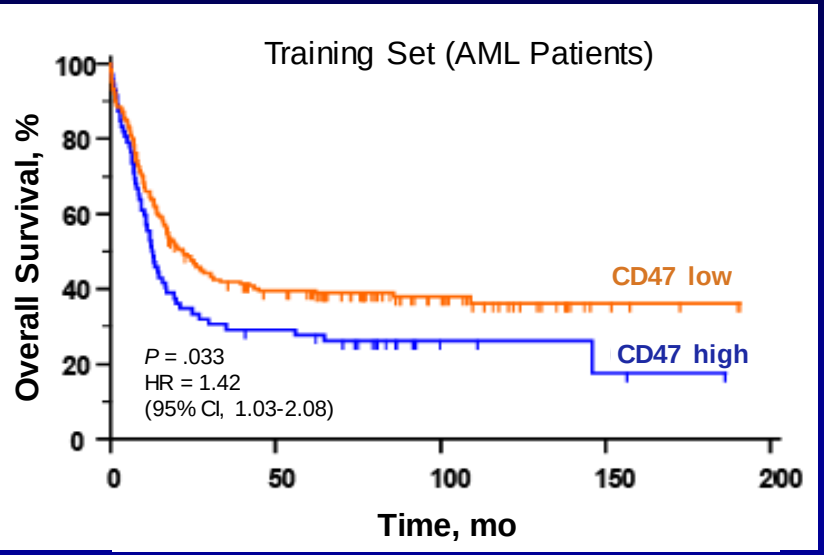


Figure at left adapted from Veillette A, Tang Z. *J Clin Oncol*. 2019;37:1012-1014 and Chao MP, et al. *Curr Opin Immunol*. 2012;24:225-232.
Figure at right adapted from Majeti R, et al. *Cell*. 2009;138:286-299.

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%)

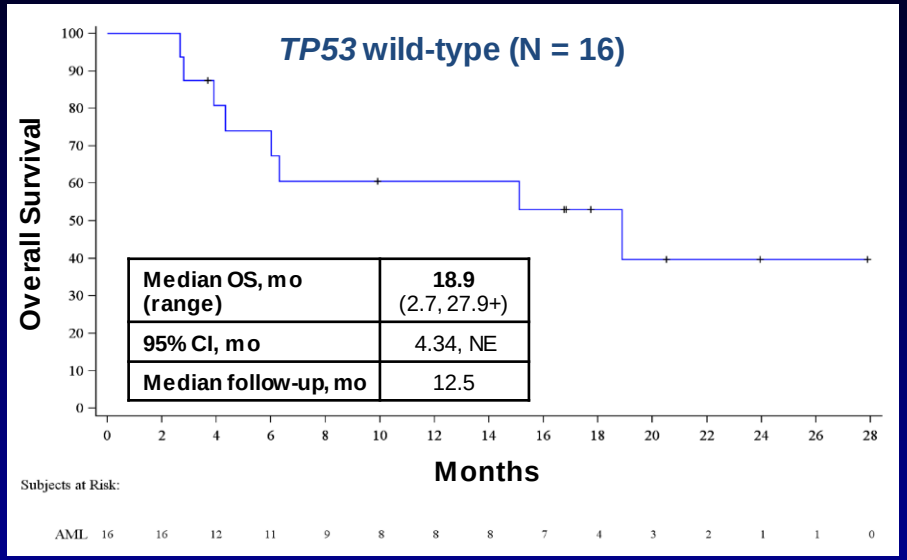
- **Magrolimab + Aza induces a 63% ORR and 42% CR rate in AML, including similar responses in *TP53*-mutant patients**
- Median time to response is **1.95 months** (range 0.95 to 5.6 mo), more rapid than Aza monotherapy
- 9.6% of patients proceeded to bone marrow stem cell transplantation
- Magrolimab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

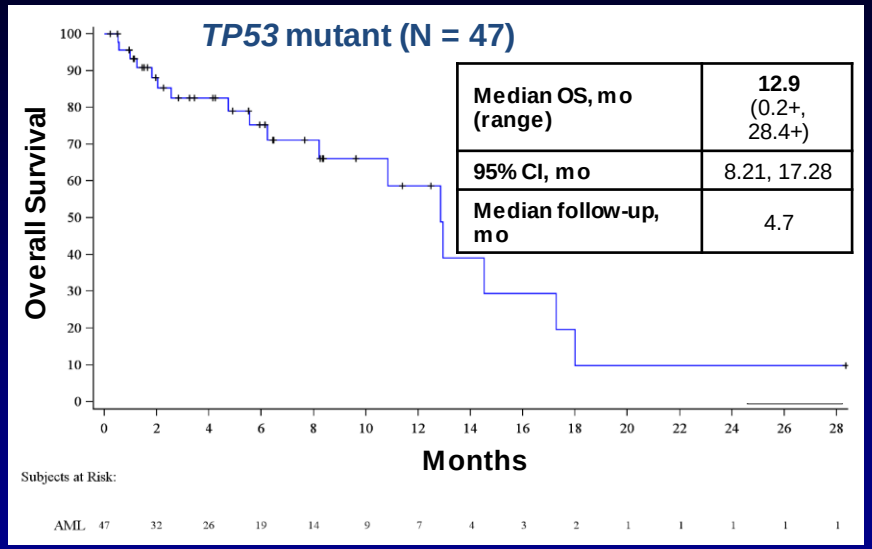
Response assessments per 2017 AML ELN criteria. Patients with at least 1 post-treatment response assessment are shown. *Three patients not shown due to missing values; <5% blasts imputed as 2.5%.

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

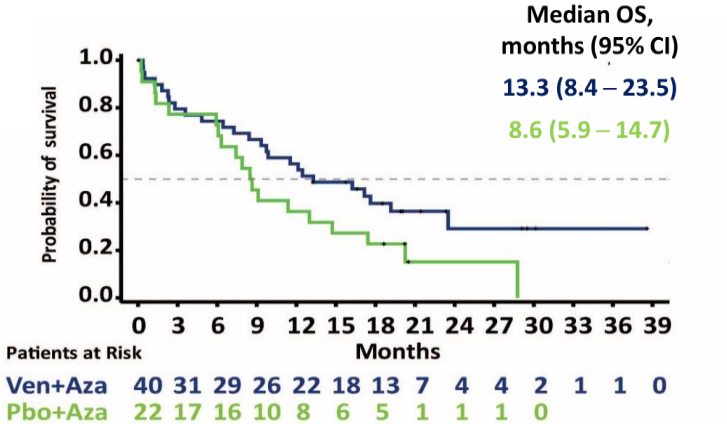
Frontline Therapy	N	Age, median	CRc (or CR/CRi)	OS, median	Ref.
Midostaurin + Aza	16	74 [59-85]	31%	8.7 mo	Gallogly, ASH 2017
Sorafenib + Aza	27	74 [61-86]	70%*	8.3 mo	Ohanian, Am J Hem 2018
Gilteritinib + Aza	15	75 [65-86]	67%	n/a	Esteve, ASH 2018
Quizartinib + Aza/LDAC	16	74 [62-83]	83%*	17.0 mo	Swaminathan,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

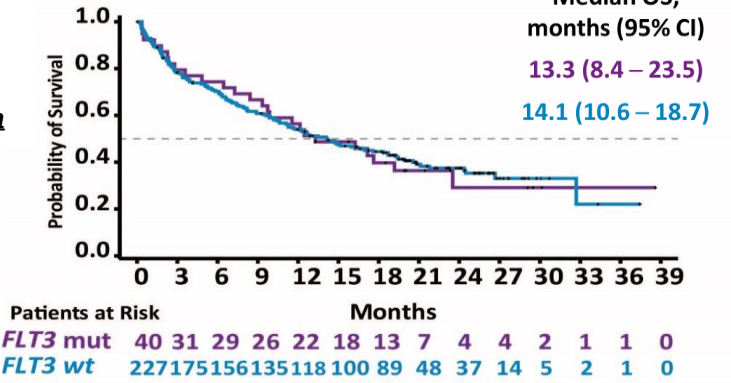
Yilmaz M, et al. ASH 2020. Abstract 26.

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

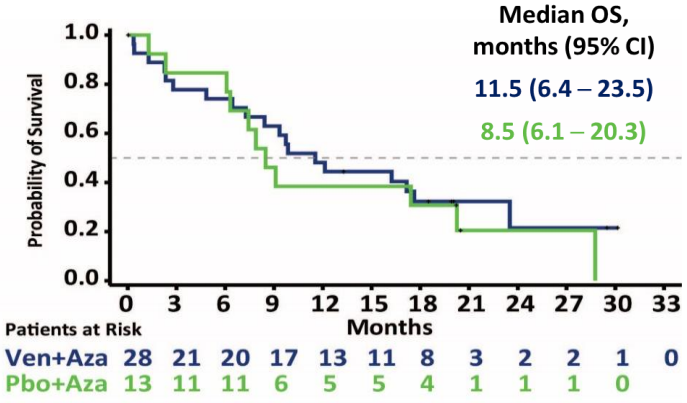
A. FLT3mut



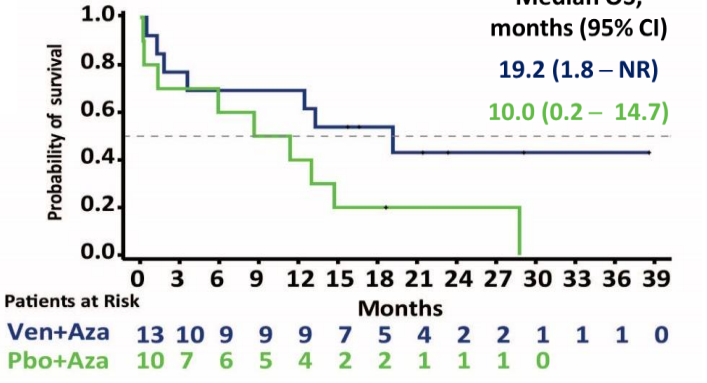
B. FLT3mut vs wt in Ven + Aza



C. FLT3-ITD



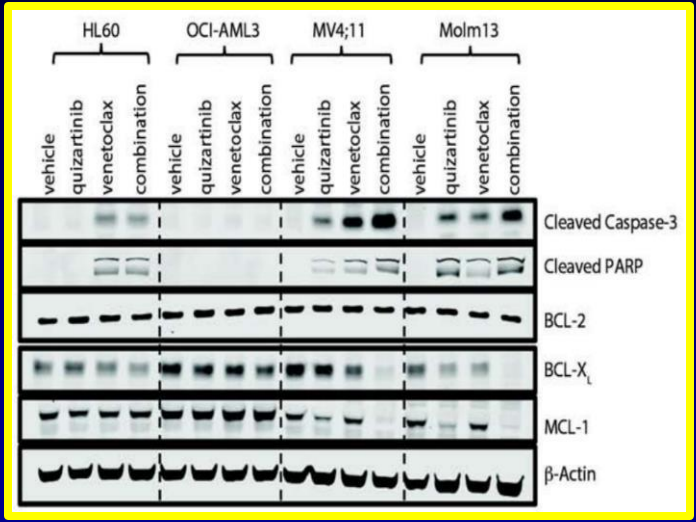
D. FLT3-TKD

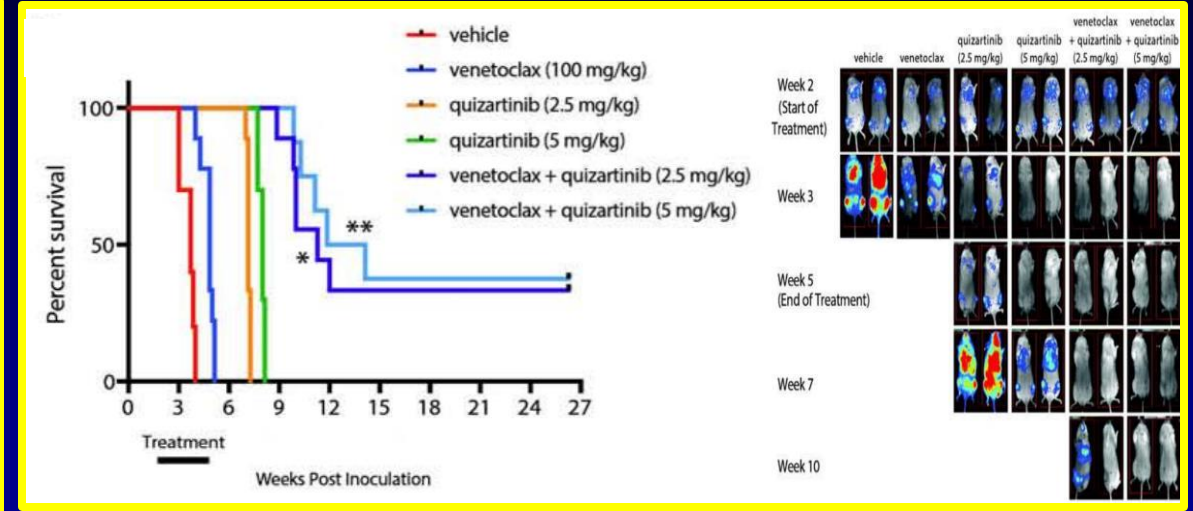


Konopleva M, et al. *Blood*. 2020;136:abstract 1904.

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

Venetoclax Combines Synergistically With Quizartinib



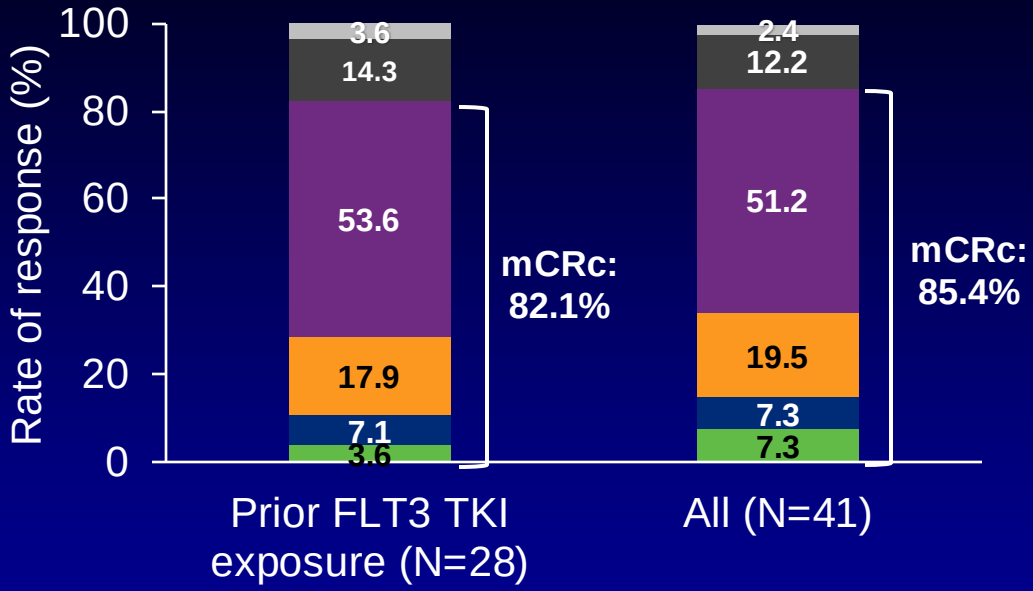


Cell lines were treated with combination – ↓ MCL-1, ↓ BCL-X$_L$

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.

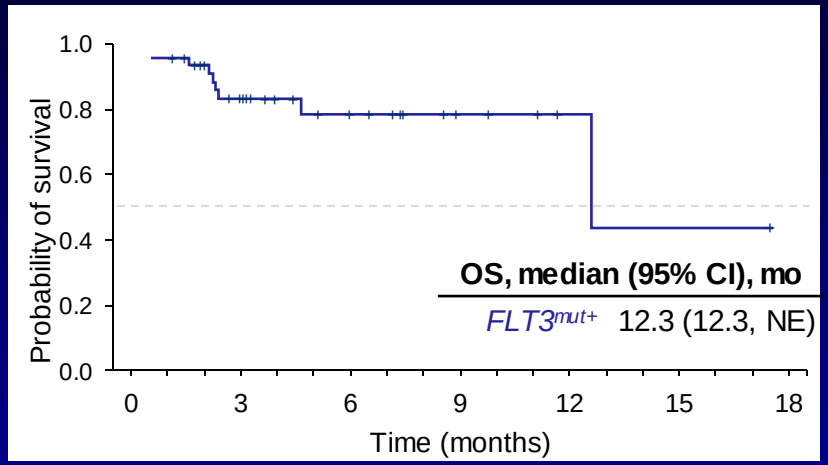
AML, acute myeloid leukemia; CI, confidence interval; CR, complete remission; CRi, CR with incomplete blood count recovery; CRp, CR with incomplete platelet recovery; FLT3, FMS-like tyrosine kinase 3; Gilt, gilteritinib; ITD, internal tandem duplications; ITT, intention to treat; mCRc, modified composite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

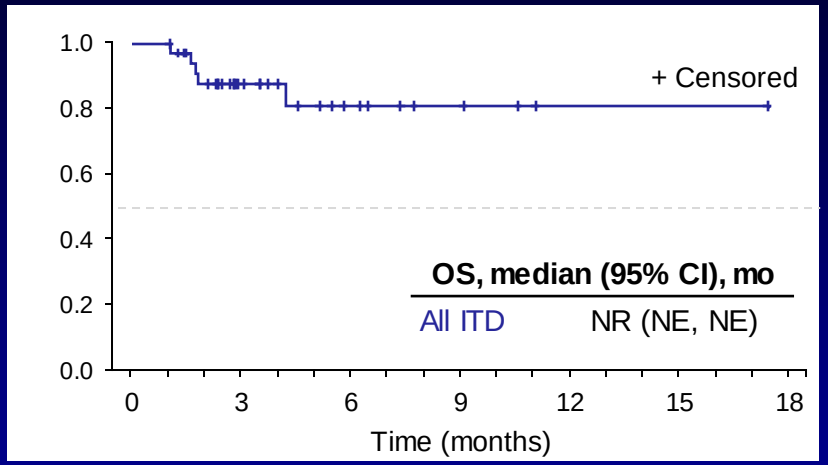
OS in all *FLT3*$^{mut+}$ patients (N = 41)



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

Q&A session

APTITUDE HEALTH

Global Leukemia Academy

Current and future role of transplantation in acute leukemias

Charles Craddock

APTITUDE HEALTH

Current and future role of transplantation in acute leukemias

Charlie Craddock FRCP, FRCPath, FMedSCI

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

Disclosures: Professor Charles Craddock

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

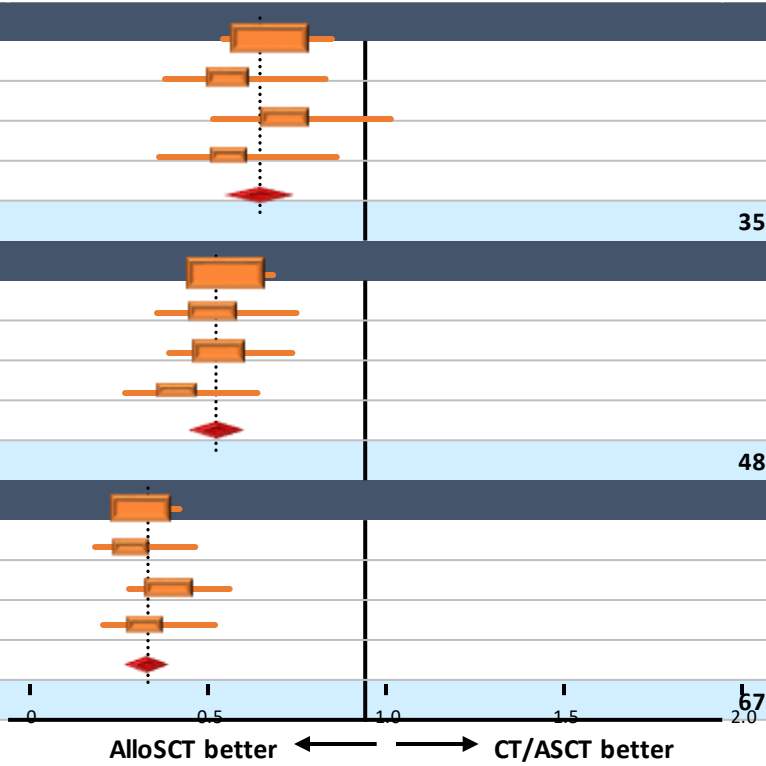
Central role of allografting in the management of high-risk AML

- Allografting delivers maximal anti-leukaemic activity in AML – a potent and manipulable anti-tumour effect across all cytogenetic groups
- The toxicity of allogeneic stem cell transplantation (allo-SCT) has steadily declined - estimated 15%-20% 1 year TRM in fit adults with a well matched donor
- Increased donor availability and decreased transplant toxicity have resulted in allo-SCT becoming a centrally important treatment modality in most fit adults with AML in CR1
- Allografting exerts a potent and broadly equivalent anti-tumour effect across all cytogenetic groups.

Loke et al, Br J Haematol. 2020

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

Cytogenic group	Events/patients CT/ASCT	Events/patients AlloSCT	HR and 95% CI (CT/ASCT : alloSCT)	Reduction SD	P value
OVERALL SURVIVAL					
CN	389/688	129/306			
CA	111/168	34/87			
CA unfav	84/115	63/117			
CA MK	58/62	36/45			
Total	**642/1033** (62%)	**262/555** (47%)		**35%** (5%) **reduction**	**2P<0.001**
RELAPSE-FREE SURVIVAL					
CN	448/688	136/306			
CA	119/168	38/87			
CA unfav	99/115	68/117			
CA MK	59/62	36/45			
Total	**725/1033** (70%)	**278/555** (50%)		**48%** (4%) **reduction**	**2P<0.001**
RELAPSE					
CN	412/688	73/306			
CA	115/168	21/87			
CA unfav	95/115	49/117			
CA MK	57/62	28/45			
Total	**679/1033** (66%)	**117/555** (31%)		**67%** (3%) **reduction**	**2P<0.001**



Cornelissen JJ, et al. *J Clin Oncol* 2012; 30:2140–2146.

The identification of patients with AML CR1 who will benefit from allo-SCT is based on a dynamic risk assessment

- All decisions concerning allo-SCT are patient specific, and survival benefit is dependent on the reduction in relapse risk outweighing TRM
- Relapse risk can be predicted by:

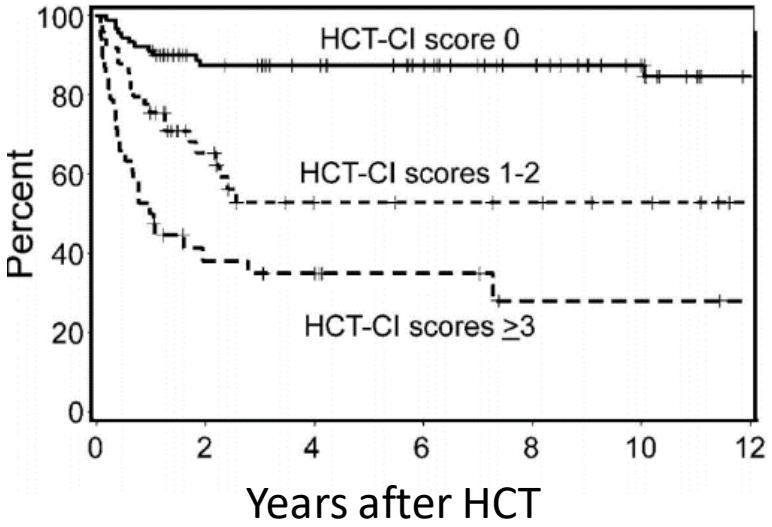
  Molecular stratification

  MRD status after IC
- TRM is determined by:

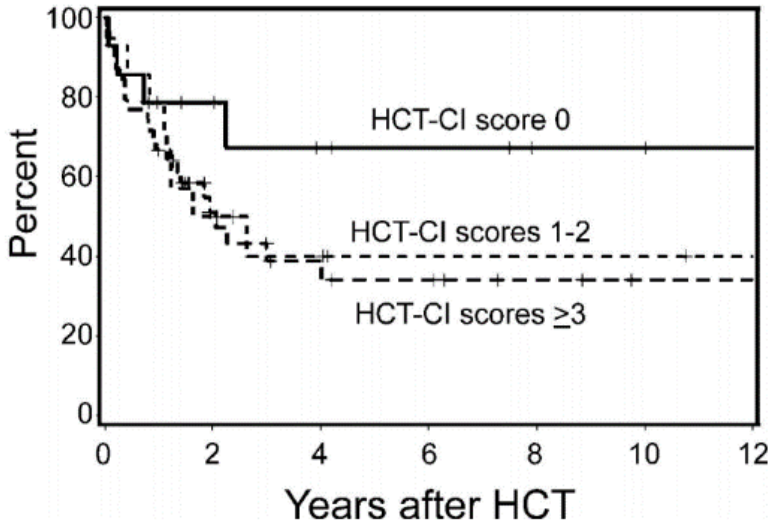
  Age and co-morbidity

Impact of HCT-CI on overall survival

Patients in First CR with Comorbidity Data Available, Who Underwent Transplantation at FHCRC between 1990 and 2004 (N=177)



Patients in First CR with Comorbidity Data Available, Who Underwent Transplantation at MDACC between 1990 and 2001 (N=67)

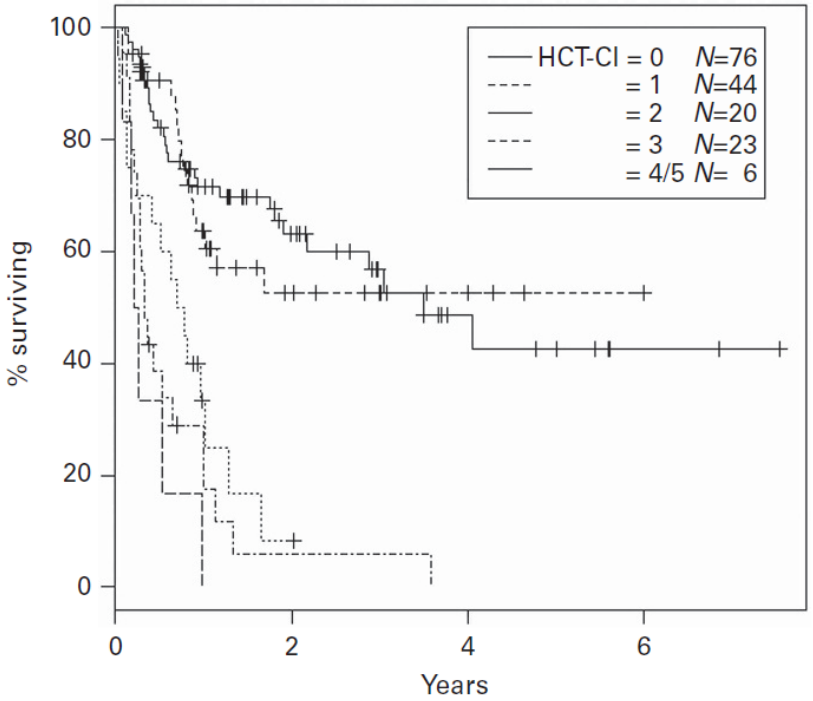


HCT-CI: hematopoietic cell transplant comorbidity index; CR: complete response; FHCRC, Fred Hutchinson Cancer Research Center; MDACC, M. D. Anderson Cancer Center.

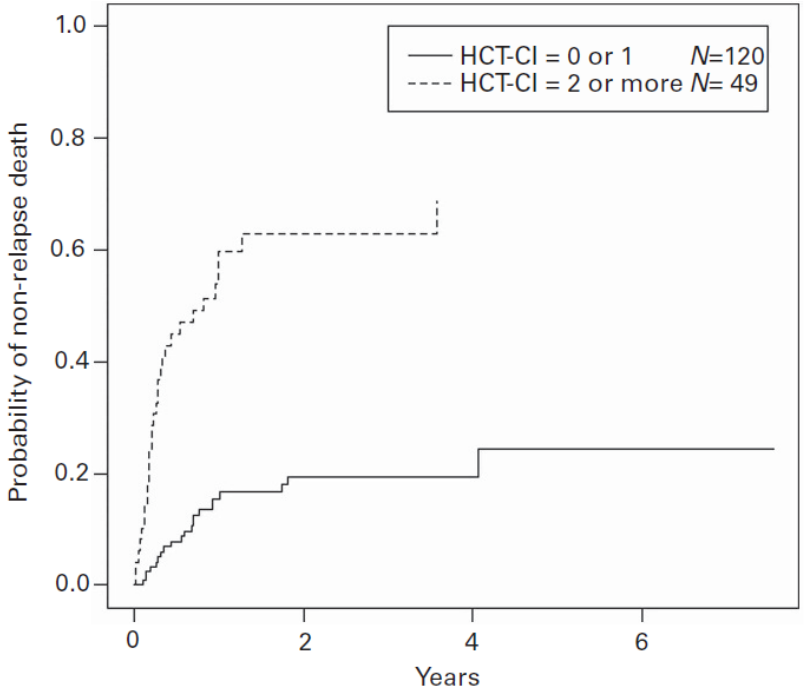
Sorror ML, *et al. J Clin Oncol* 2007.

Outcome in patients ≥ 60 years-old transplanted using an alemtuzumab-based RIC regimen

Overall Survival by Pre-transplant HCT-CI



Non-relapse Mortality by Pre-transplant HCT-CI



RIC: reduced-intensity conditioning; HCT-CI: hematopoietic cell transplant comorbidity index

Nikolousis E, *et al. Bone Marrow Transplant* 2015.

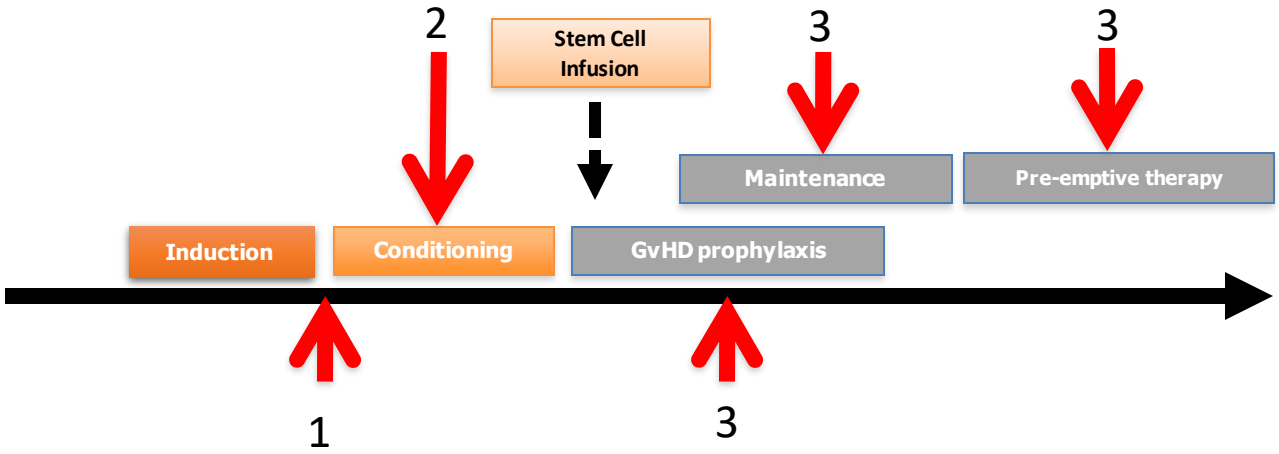
Transplant indications in 2021

2017 ELN Risk stratification by genetics	MRD after cycle 2 chemotherapy	Estimated risk of relapse based on consolidation with:		Maximal tolerated NRM prognostic scores for allo-SCT to be beneficial	
		Chemotherapy alone (%)	Allo-SCT (%)	HCT-CI score	NRM risk (%)
Favourable	Negative	25-35	15-20	N/A (<1)	5
	Positive	70-80	30-40	≤3-4	<30
Intermediate	Negative	50-60	25-30	≤2	<20
	Positive	70-80	30-40	≤3-4	<30
Adverse	N/A	>90	45-55	<5	<35

Loke et al 2021

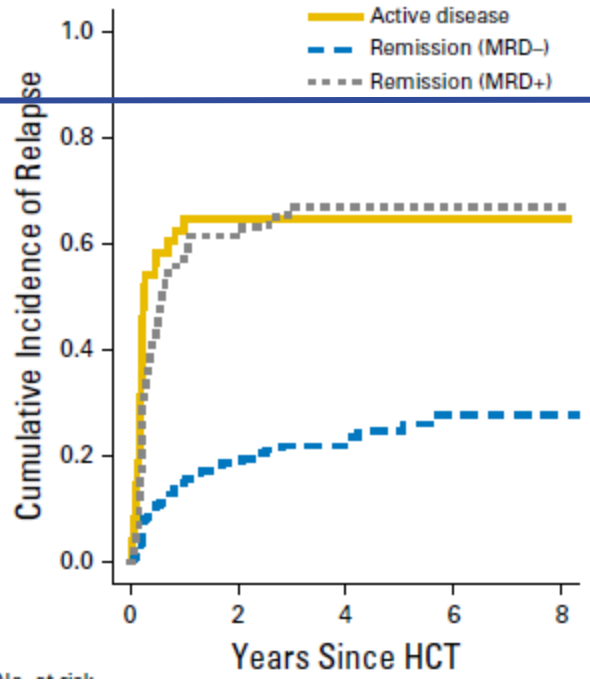
Strategies to reduce relapse risk in patients allografted for AML- the impact of conditioning regimen intensity

1) Minimise pre-transplant disease burden
2) Optimise cytotoxic properties of the conditioning regimen
3) Maintenance drug or cellular therapies which:
   - Target residual leukaemic stem/progenitors
   - Optimise a GvL effect



Craddock, et al. Bone Marrow Transplant. 2019

splant MRD on Transplant Outcome in AML



splant

Summary of Published Data with MRD testing across genetic subtypes

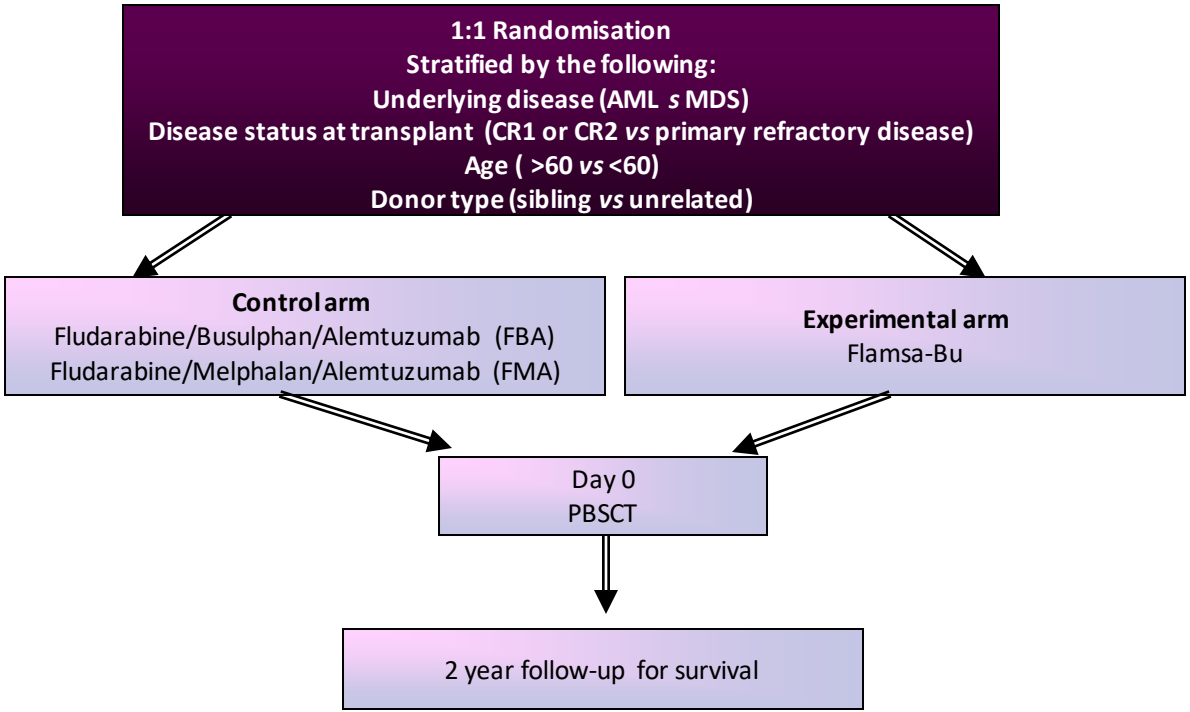
Relapse Incidences for transplant cohorts

- Large EBMT study/CTN 0901 Retrospective Randomised (NGS MRD)
  - 2 yr CIR ~ 25% MRD negative vs ~40% MRD+
- Other Retrospective studies by Flow or NGS
  - 2 yr CIR ~30% to 60%

Seattle (Flow)> Heuser (NGS) > MD Andersen (Flow)

Araki, et al. J Clin Oncol. 2015

Pre-transplant and post-transplant flow MRD prospectively evaluated in all FIGARO patients

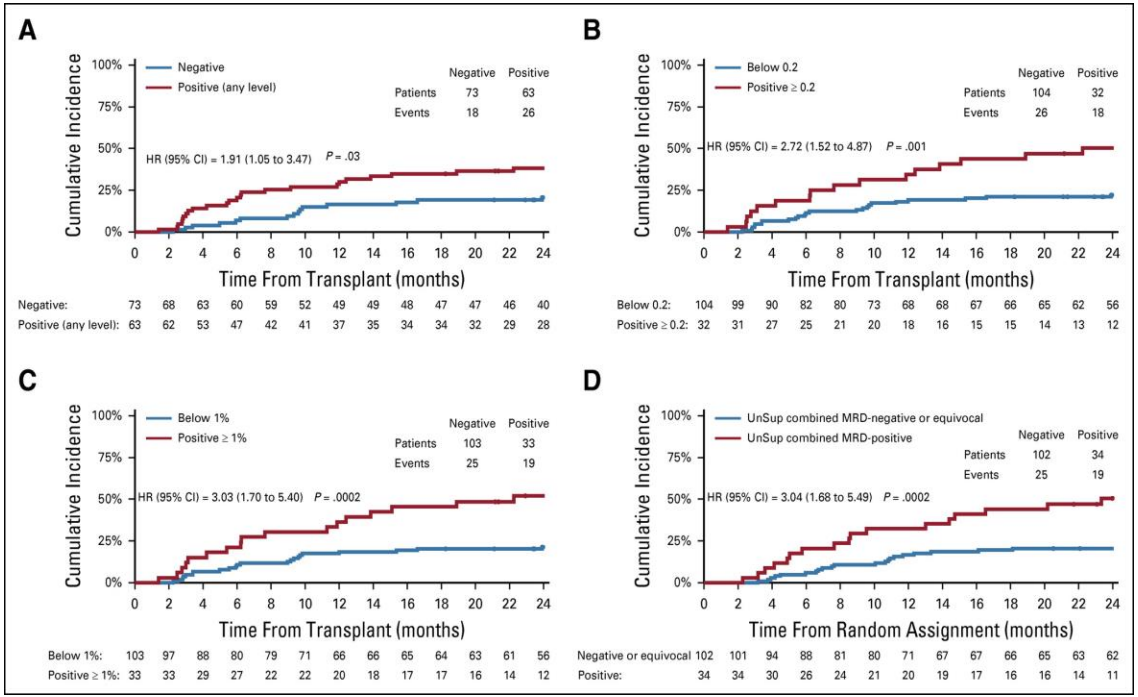


Impact of pre-transplant MRD Measured by Unsupervised Methodology on Cumulative Incidence of Relapse in patients allografted on FIGARO trial

- No interaction observed between MRD status and conditioning regimen
- CIR MRD –ve 20%
  MRD +ve 41%
- 2 yr MRD –ve 70%
  OS MRD +ve 51%

p= 0.01

p= 0.05



Craddock, et al. J Clin Oncol 2020

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

272 patients with AML and MDS (<5% blasts pre-transplant)

Age 18-65

MAC- Bu/Cy or Cy/TBI

RIC- Flu/Bu_2 or Flu/Mel

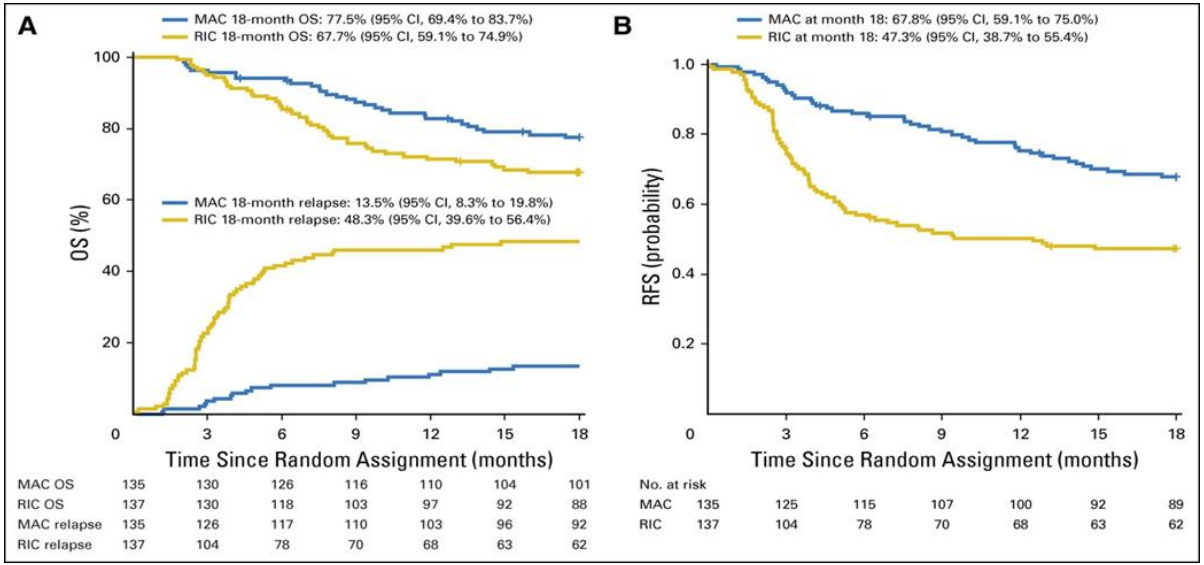
GVHD prophylaxis CsA/MTX. CsA levels and taper not specified

Reduced risk NRM (4% v 16% p=0.002) of Grade 2-4 acute GVHD in RIC arm (31% v 44% p=0.02) and chronic GVHD (47% v 64% p=0.19)

Increased relapse in patients with AML but not MDS

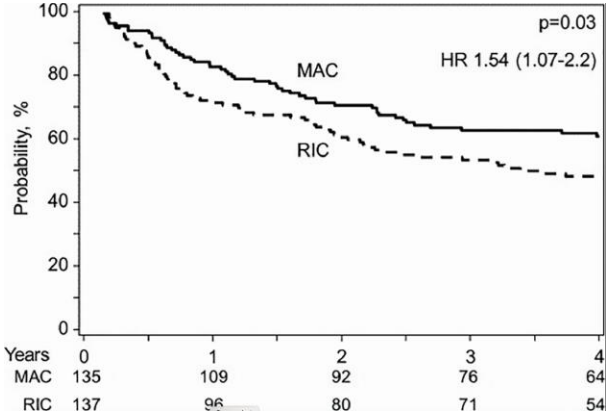
Equivalent OS

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

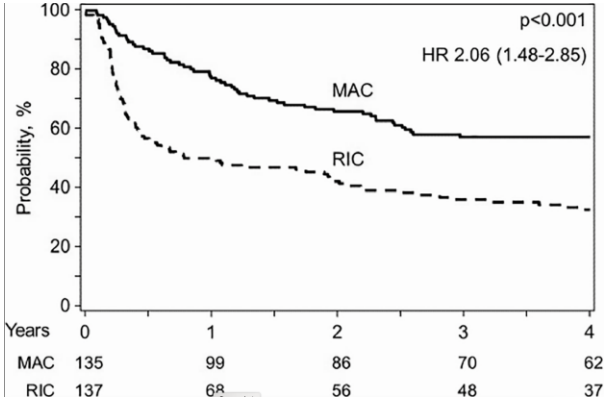


Scott et al, J Clin Oncol. 2017

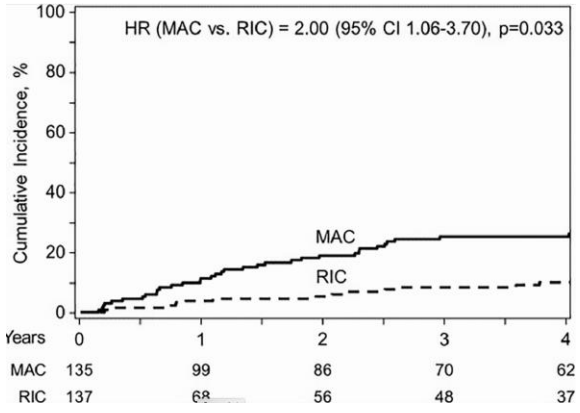
Long term follow up of BMT CTN 0901 Trial



OS



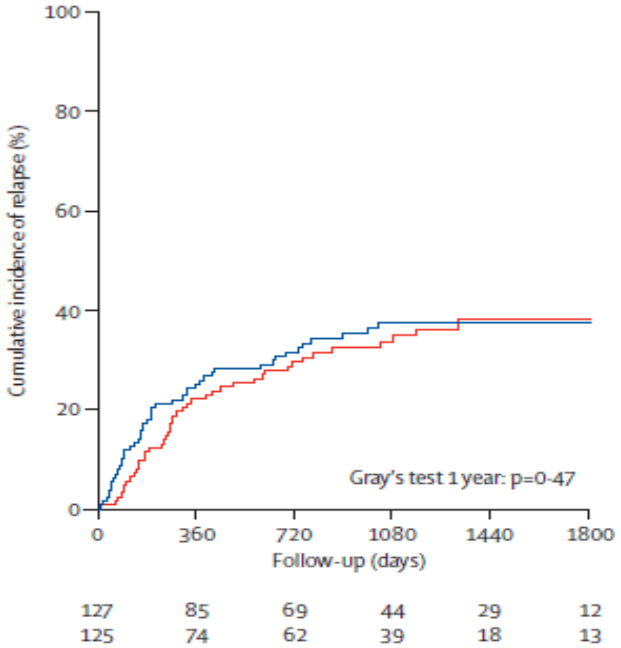
RFS



TRM

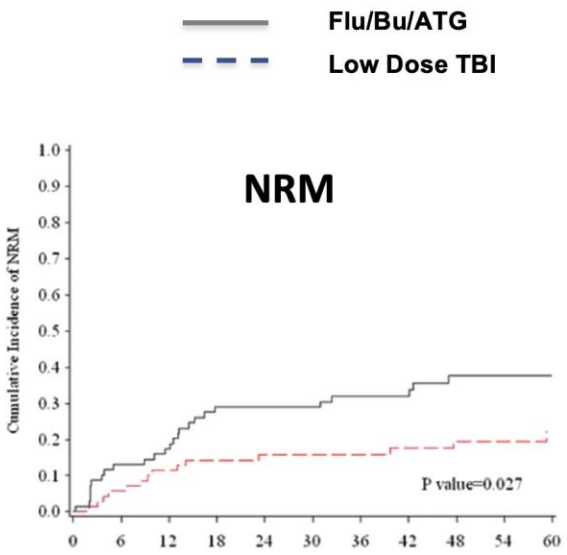
Scott et al, Transplantation and Cellular Therapy. 2021

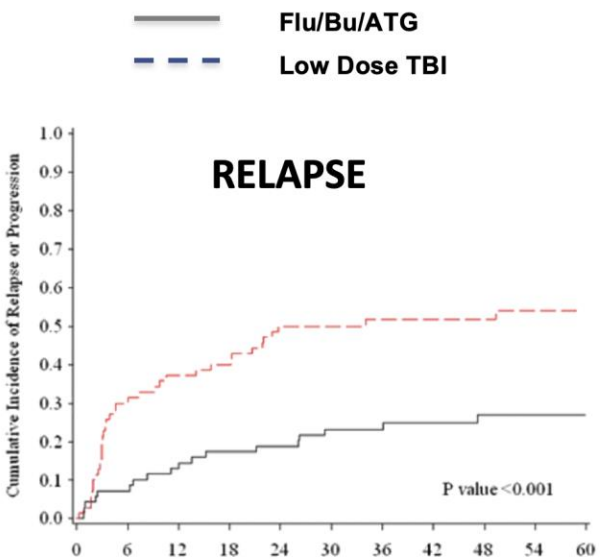
Cumulative incidence of relapse in patients with AML or randomised to receive Bu/Cy FLU/Bu_4



Rambaldi, et al. Lancet Oncology. 2015

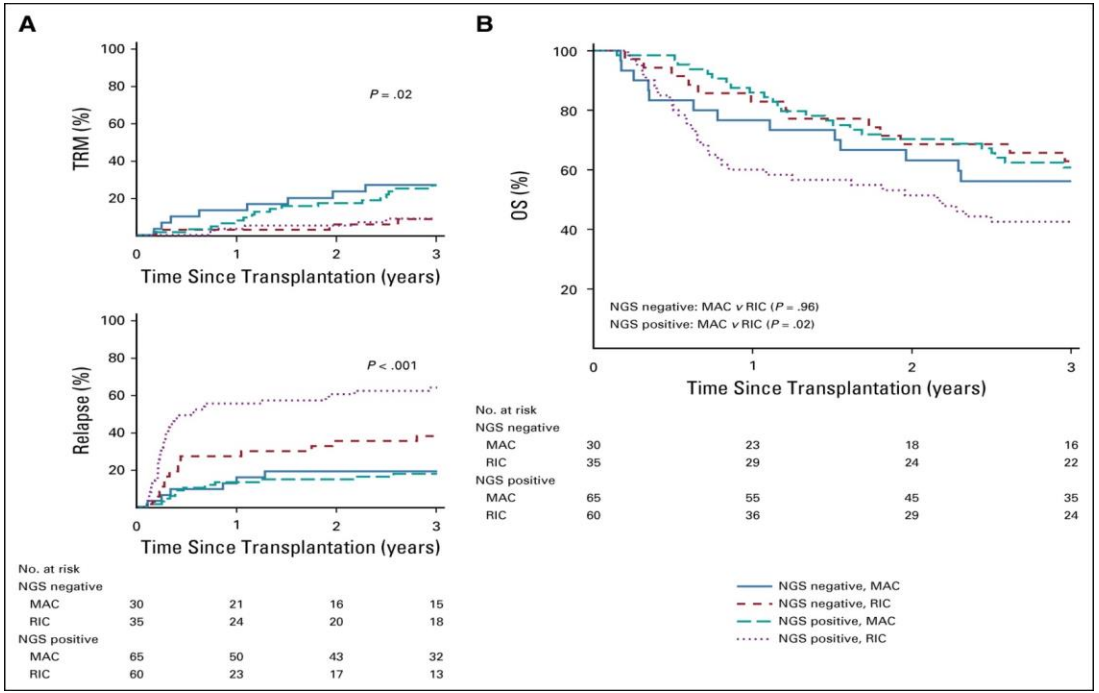
Relapse Rates Previously Reported with Flu/Bu_2 Regimen





Blaise, et al. Cancer. 2013

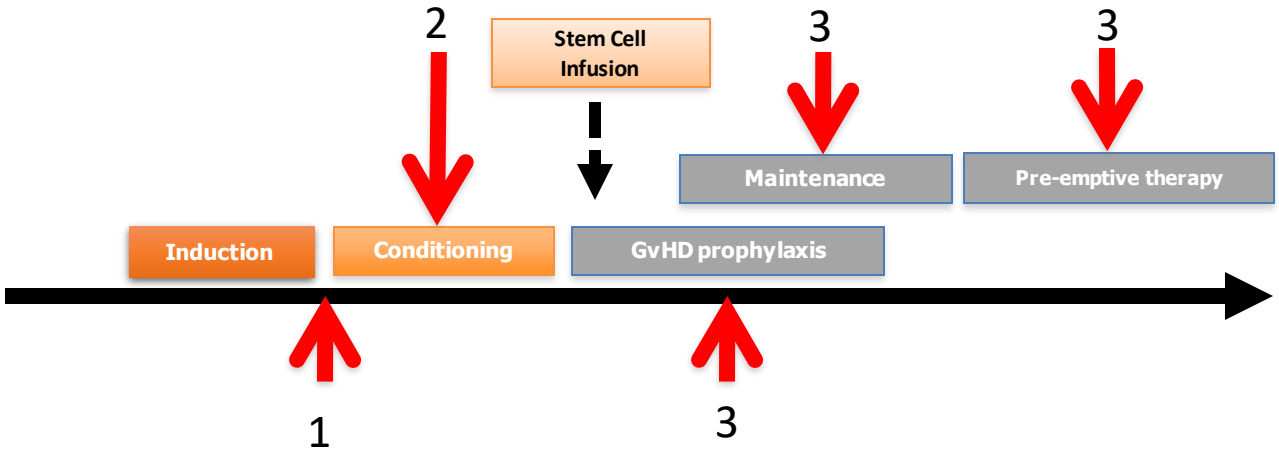
Outcome according to Conditioning Regimen Intensity and Pre-Transplant NGS MRD status



Hourigan, et al. J Clin Oncol. 2019

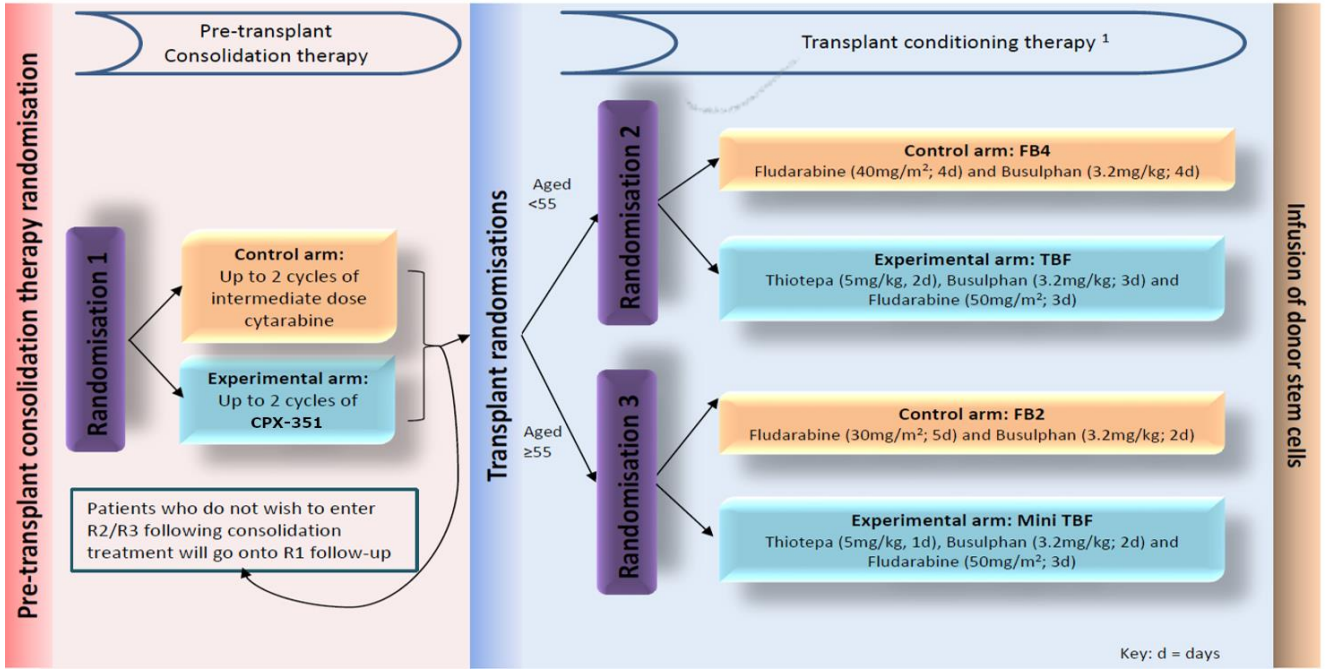
Strategies to reduce relapse risk in patients allografted for AML- the impact of conditioning regimen intensity

1) Minimise pre-transplant disease burden
2) Optimise cytotoxic properties of the conditioning regimen
3) Maintenance drug or cellular therapies which:
   - Target residual leukaemic stem/progenitors
   - Optimise a GvL effect

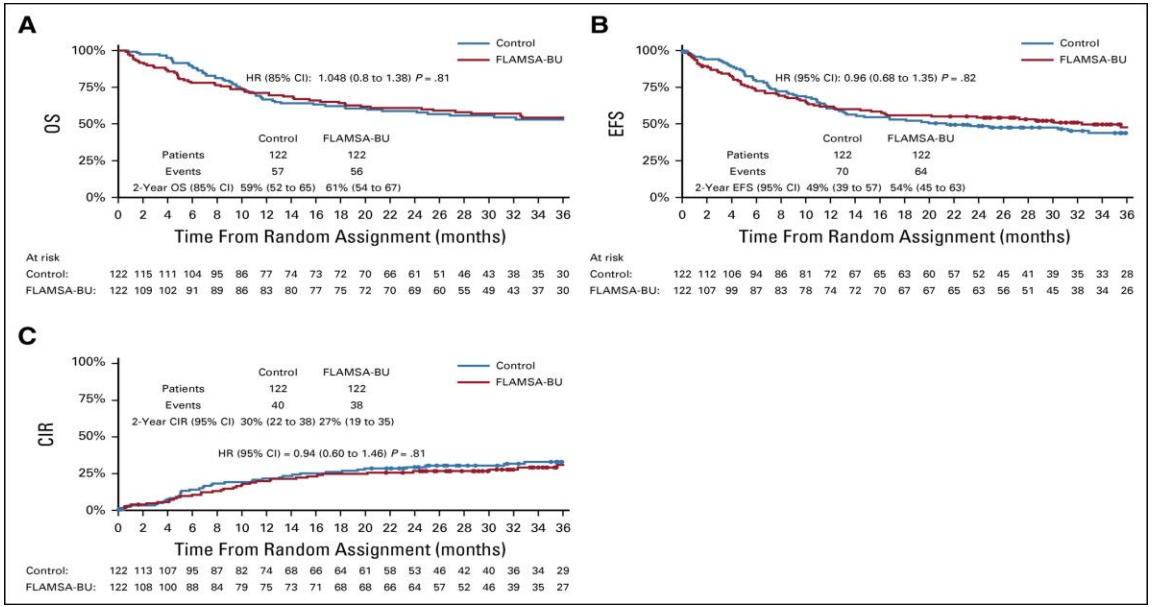


Craddock, et al. Bone Marrow Transplant. 2019

COSI trial schema-randomisation 1

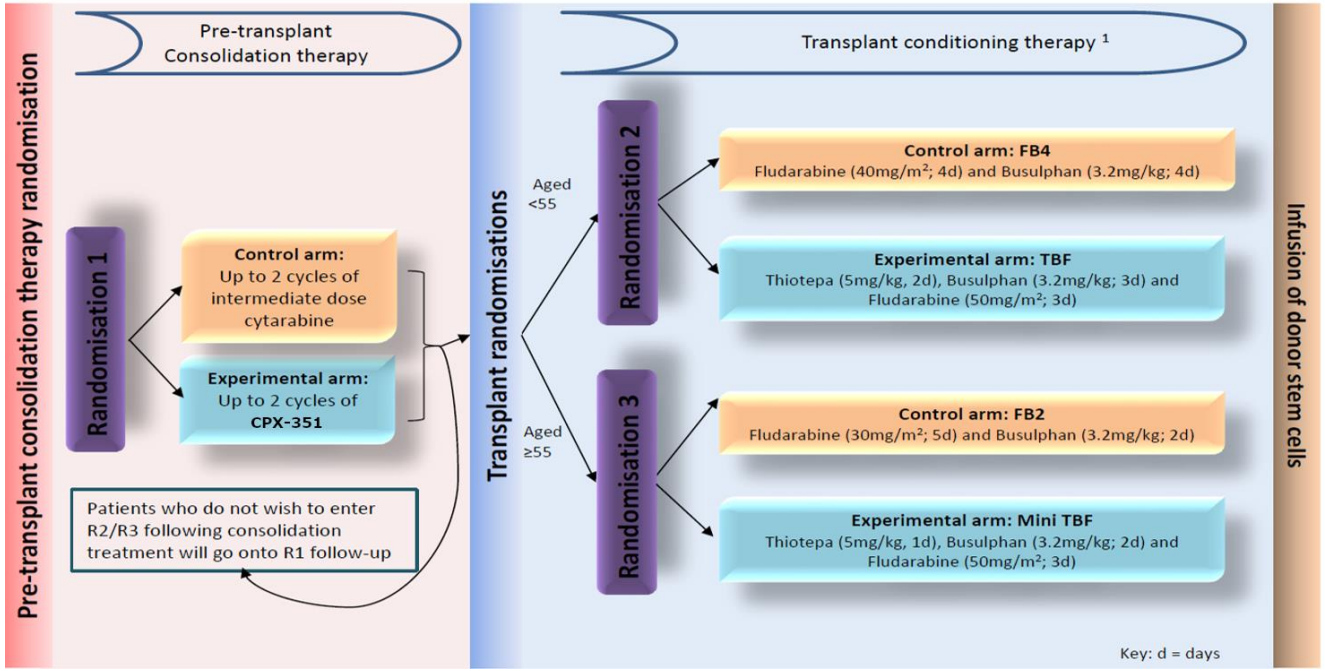


Impact of FLAMSA-Bu Regimen on Transplant Outcome in High Risk AML: FIGARO

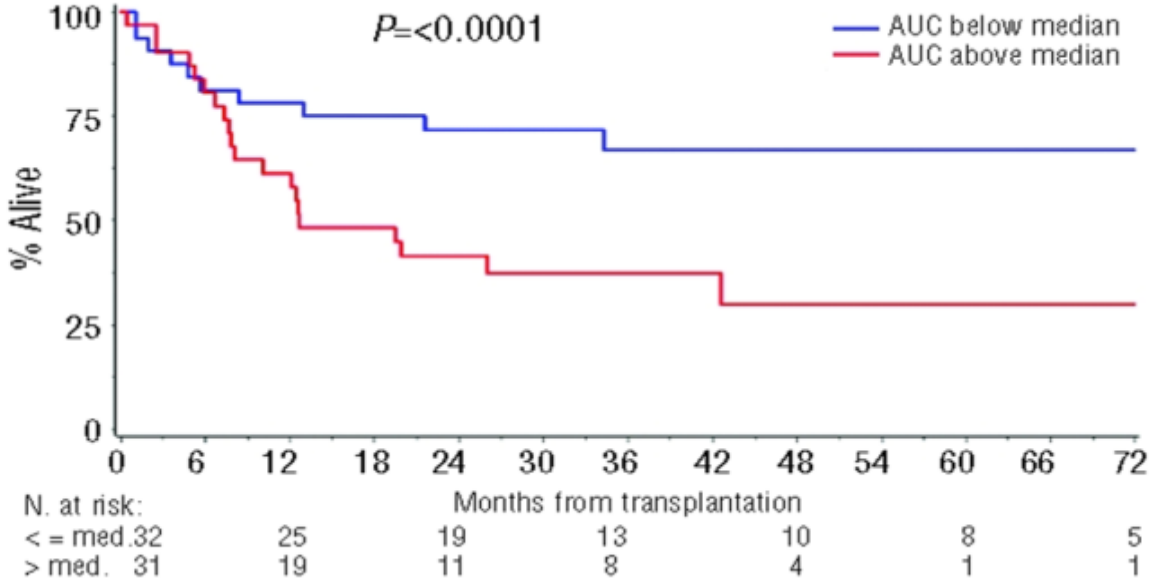


Craddock, et al. J Clin Oncol. 2020

COSI trial schema-randomisation 2 and 3

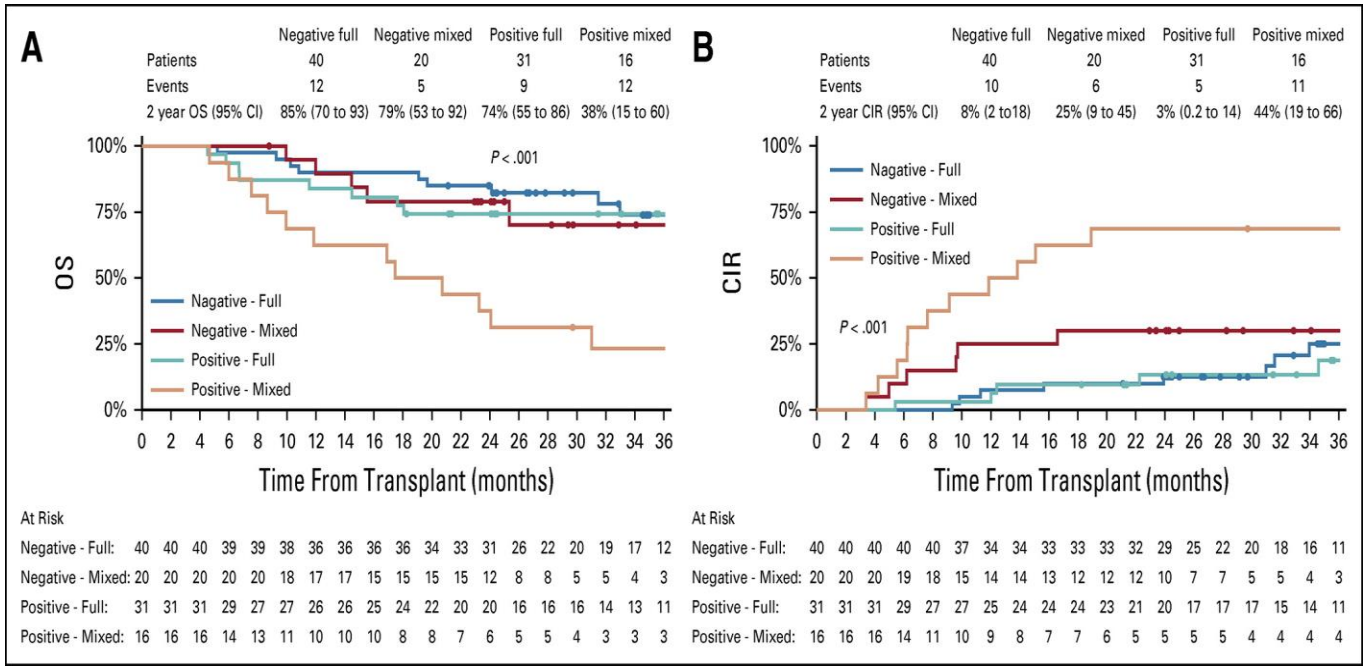


A potent and manipulable GVL effect is exerted after a RIC allograft for AML



Craddock C, et al. Haematologica. 2010

FIGARO: Acquisition of full donor T-cell chimerism overcomes the adverse impact of pre-transplant MRD

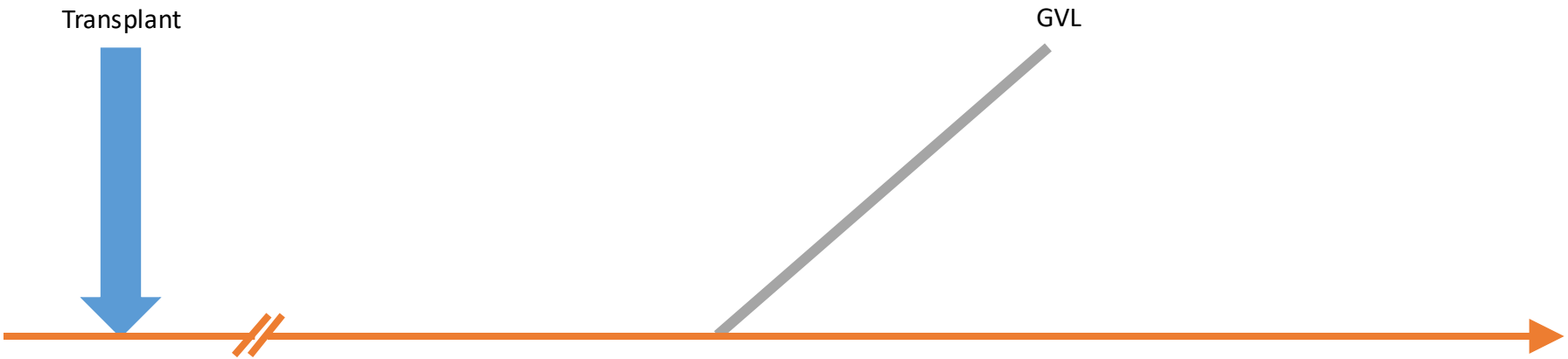


Craddock C et al J Clin Oncol 2020

Agents under investigation in post-transplant maintenance

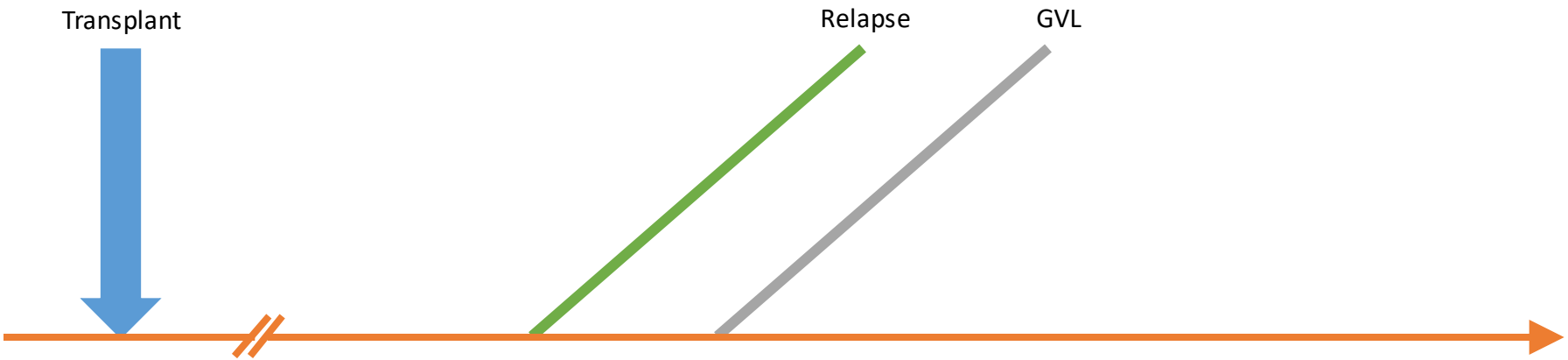
Agent	Study	Population	Reference
Sorafenib	Randomised Prospective Phase II Trials	FLT3-ITD AML who received HCT in first CR	Burchert A, et al. J Clin Oncol 2020: 38:2993-3002
Gilteritinib	Phase 3, multicentre, randomised	FLT3-ITD AML who received HCT in first CR	Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT02997202 (accessed Sep 2020)
CC486	AMADEUS, Phase 3, randomised	Patients with AML or MDS post allograft	Clinicaltrials.gov. Available at: https://clinicaltrials.gov/ct2/show/NCT04173533 (accessed Sep 2020)

Buying time for the GvL effect



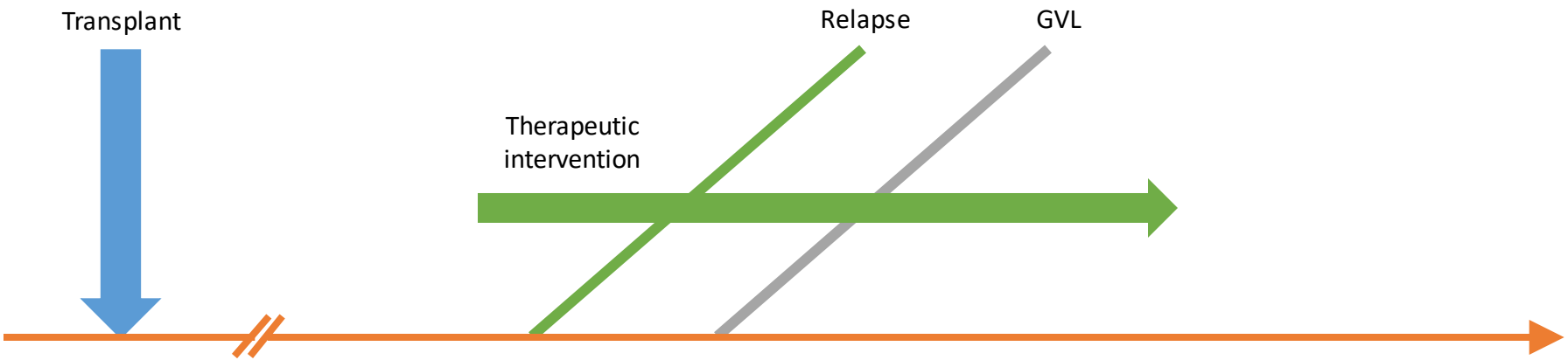
GvL: graft versus leukaemia

Buying time for the GvL effect



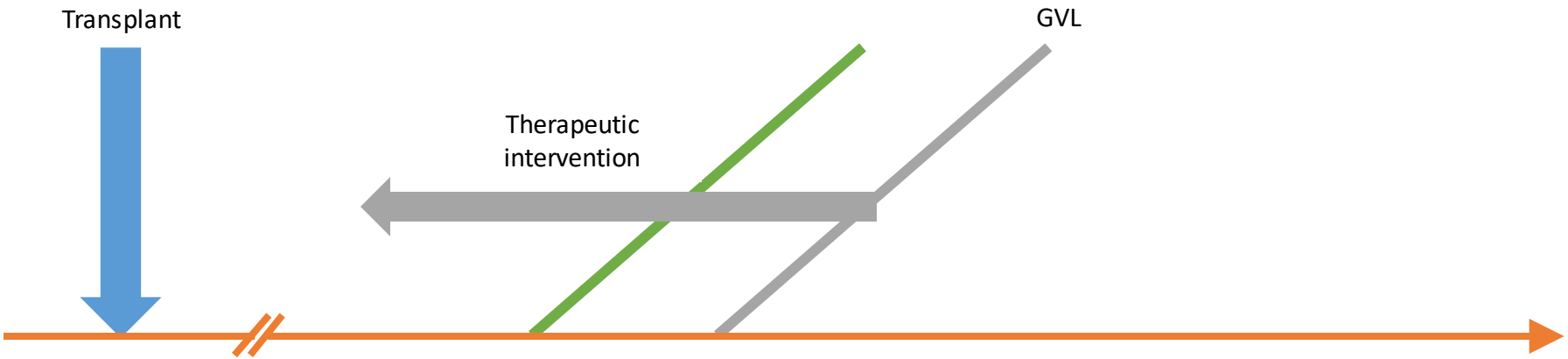
GvL: graft versus leukaemia

Buying time for the GvL effect



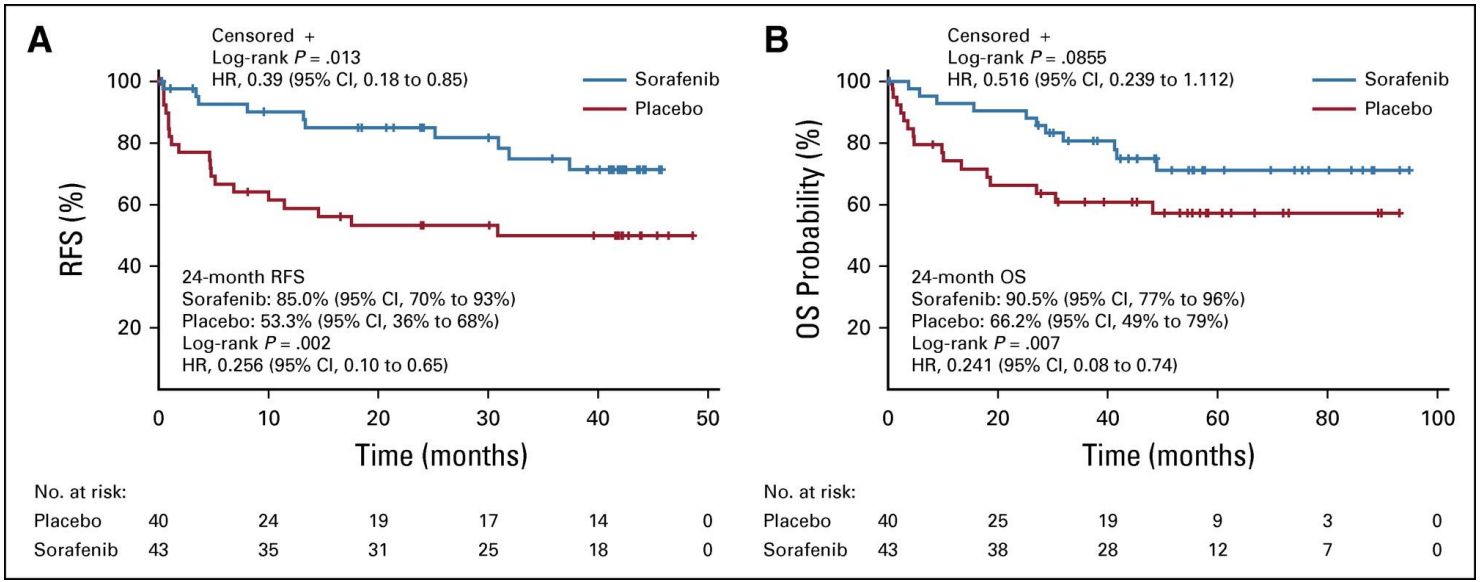
GvL: graft versus leukaemia
Speaker opinion

Buying time for the GvL effect



GvL: graft versus leukaemia
Speaker opinion

Post-transplant Sorafenib Maintenance Improves Outcome After Allo-SCT in Patients Allografted for Flt3 ITD+ AML



Burchert, et al. J Clin Oncol. 2020

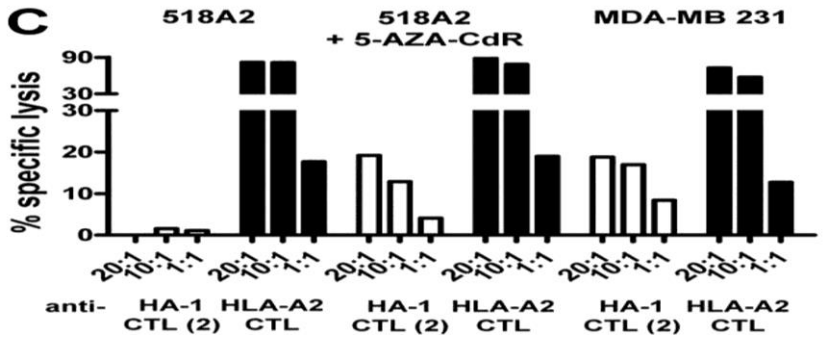
BMT CTN 1506

A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III trial of the FLT3 Inhibitor Gilteritinib Administered as Maintenance Therapy Following Allogeneic Transplant for Patients with FLT3-ITD AML

Study Chairs: Yi-Bin Chen, MD, Mark Levis, MD, PhD

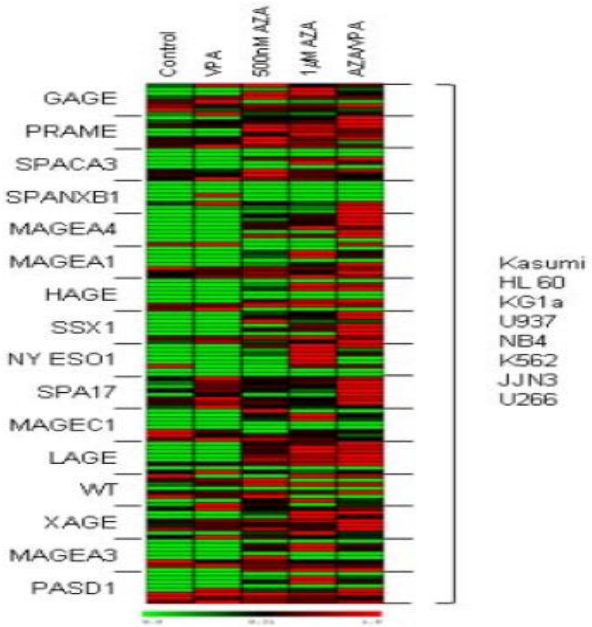
AZA up-regulates the expression of epigenetically silenced putative GVL targets

AZA up-regulates mHAg expression on AML blasts



Hambeach, et al. Blood 2009

AZA up-regulates MAGE-A1 expression on AML blasts



Goodyear, et al. Blood. 2010

AMADEUS: Randomized Trial CC486 Maintenance in Patients Allografted for AML

Between 42 and 84 days post allo-SCT patients randomised

Control Arm
Placebo

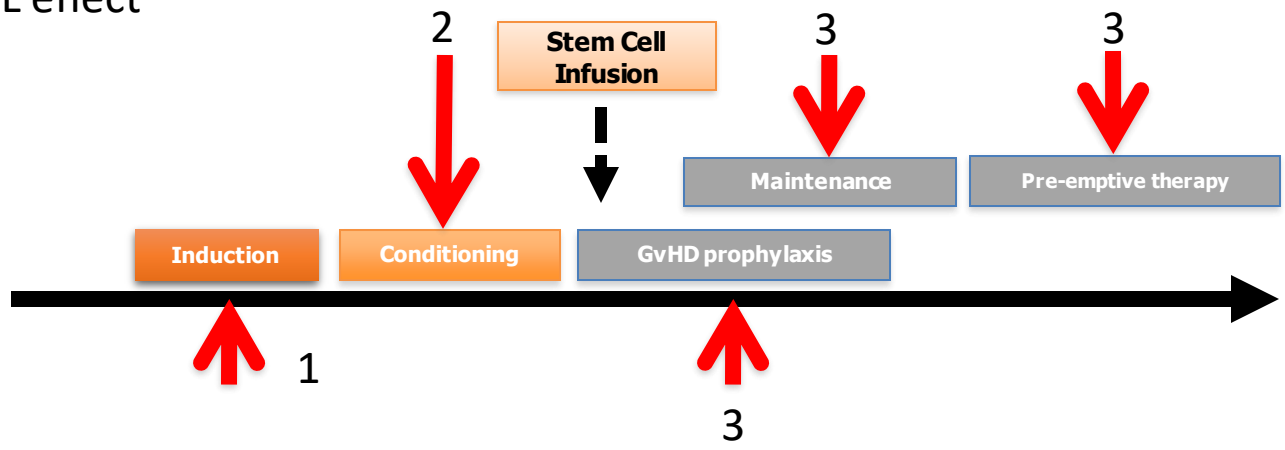
Experimental arm
Oral azacitidine 200 m
od daily days 1-14

Patients will receive 14 days of either placebo or oral AZA (CC-486) at the beginning of a 28 day cycle.

24 months
Relapse Free Survival

Strategies to reduce relapse risk in patients allografted for AML

1) Minimize pre-transplant disease burden
2) Optimize cytotoxic properties of the conditioning regimen
3) Maintenance drug or cellular therapies which:
   - Target residual leukemic stem/progenitors
   - Optimize a GVL effect



AML: acute myeloid leukemia; GvL: graft versus leukaemia; GvHD: graft versus host disease

What is the optimal strategy to allografts adults with allomandatory AML in CR1?

- In fit adults under 55 a MAC regimen is to be preferred- especially in patients who are MRD+
- Older adults (55-75) can safely proceed to allograft if they are fit with a low HCT-Ci status
- Older adults who are MRD+ can still achieve good post-transplant outcomes with RIC regimen but novel conditioning/post-transplant strategies are required
- There is no evidence that transplant should be deferred in patients who are in morphological CR but have detectable flow based MRD
- Prospective examination of novel strategies with the potential to improve transplant outcome is required- embedded MRD and genomic studies are key

Global Leukemia Academy

Q&A session

APTITUDE HEALTH

Global Leukemia Academy

Debate on sequencing CD19-targeted approaches

Moderator: Franco Locatelli

APTITUDE HEALTH

Global Leukemia Academy

Question

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

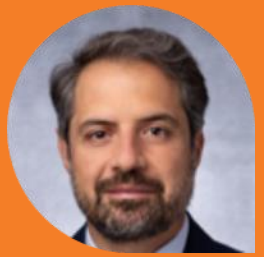
a) CAR T therapies

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

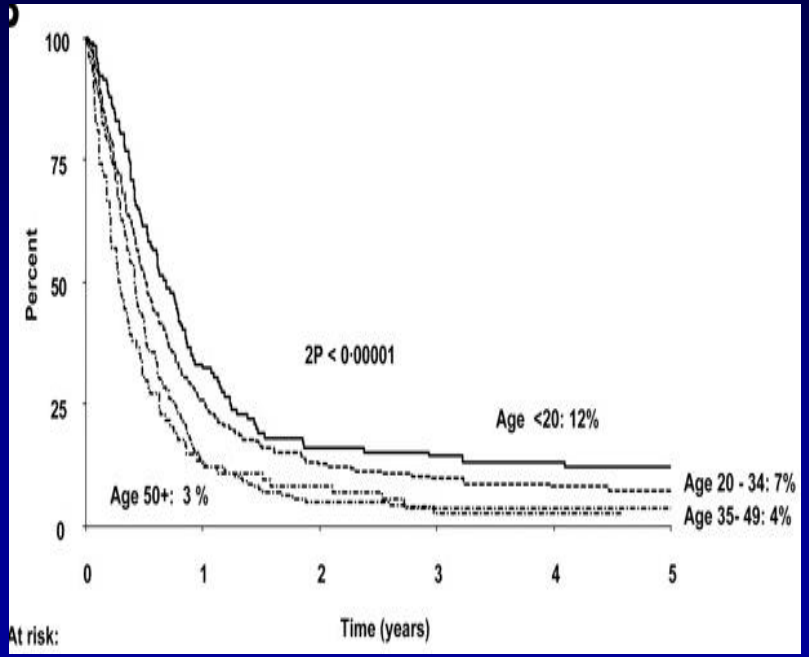
Rate (95% CI)	No prior salvage (S1)	One prior salvage (S2)	≥2 prior salvages (S3)
Rate of CR, %	40	21	11
Median OS, months	5.8	3.4	2.9

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

ALL – Historical Survival Rates After First Relapse

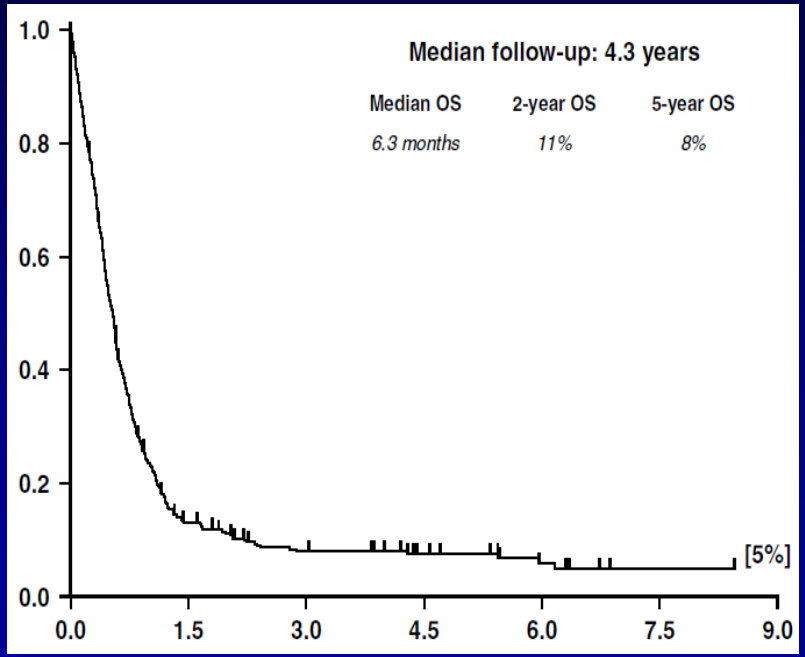
MRC UKALL2/ ECOG2993 Study (n = 609)

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%

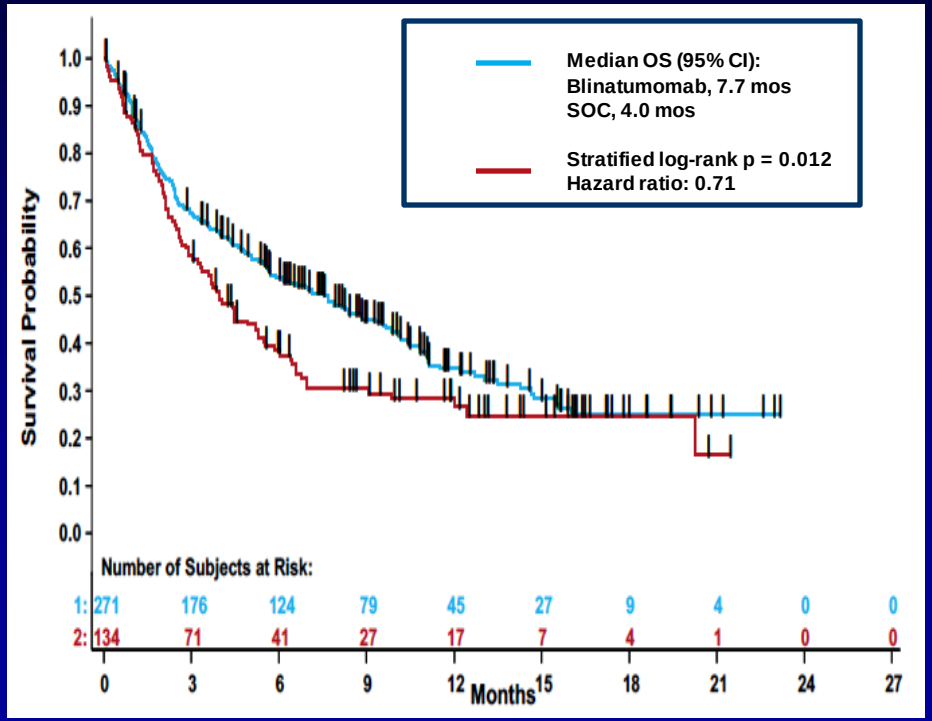


Fielding et al. *Blood*. 2007;109:944-950; Tavernier E, et al. *Leukemia*. 2007;21:1907-1914.

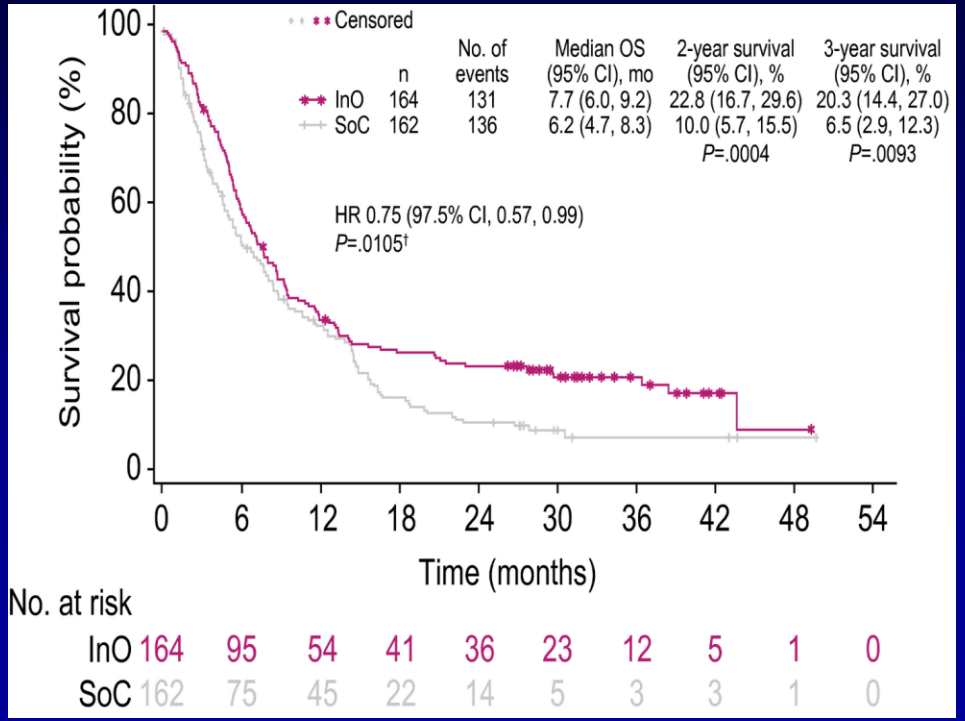
Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

- **Marrow CR**

Blina vs SOC: 44% vs 25%



Ino vs SOC: 74% vs 31%

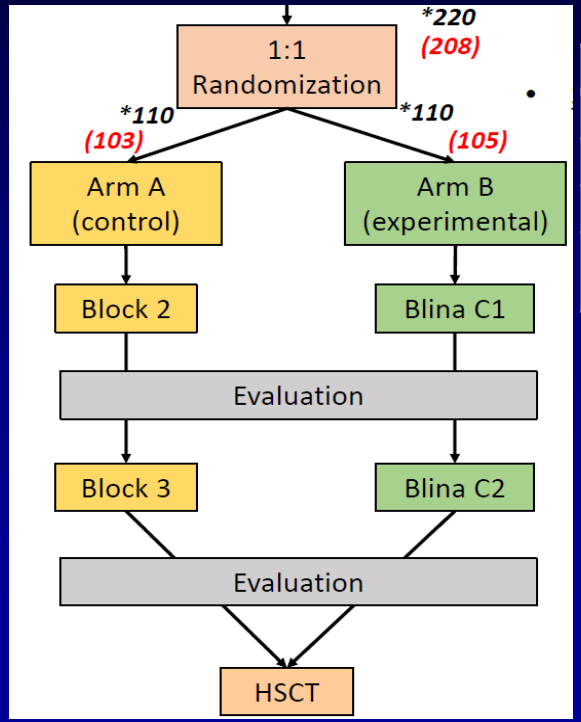


Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

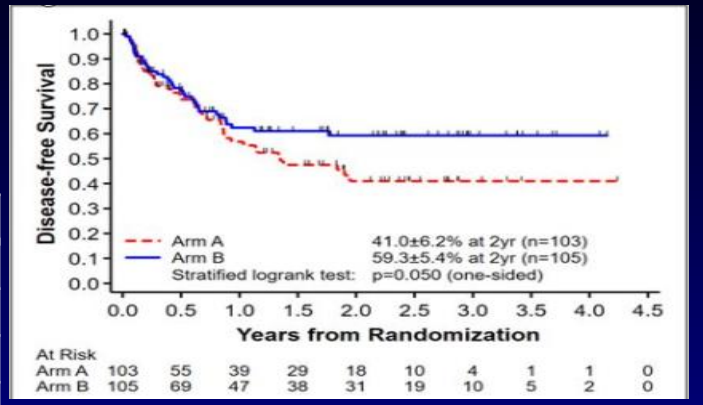
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

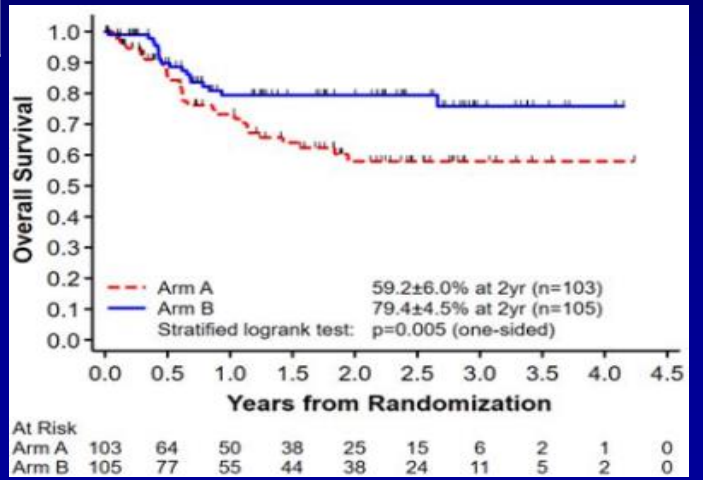
Phase III Study of Blinatumomab vs ChemoRx in Children-AYA in Salvage 1

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

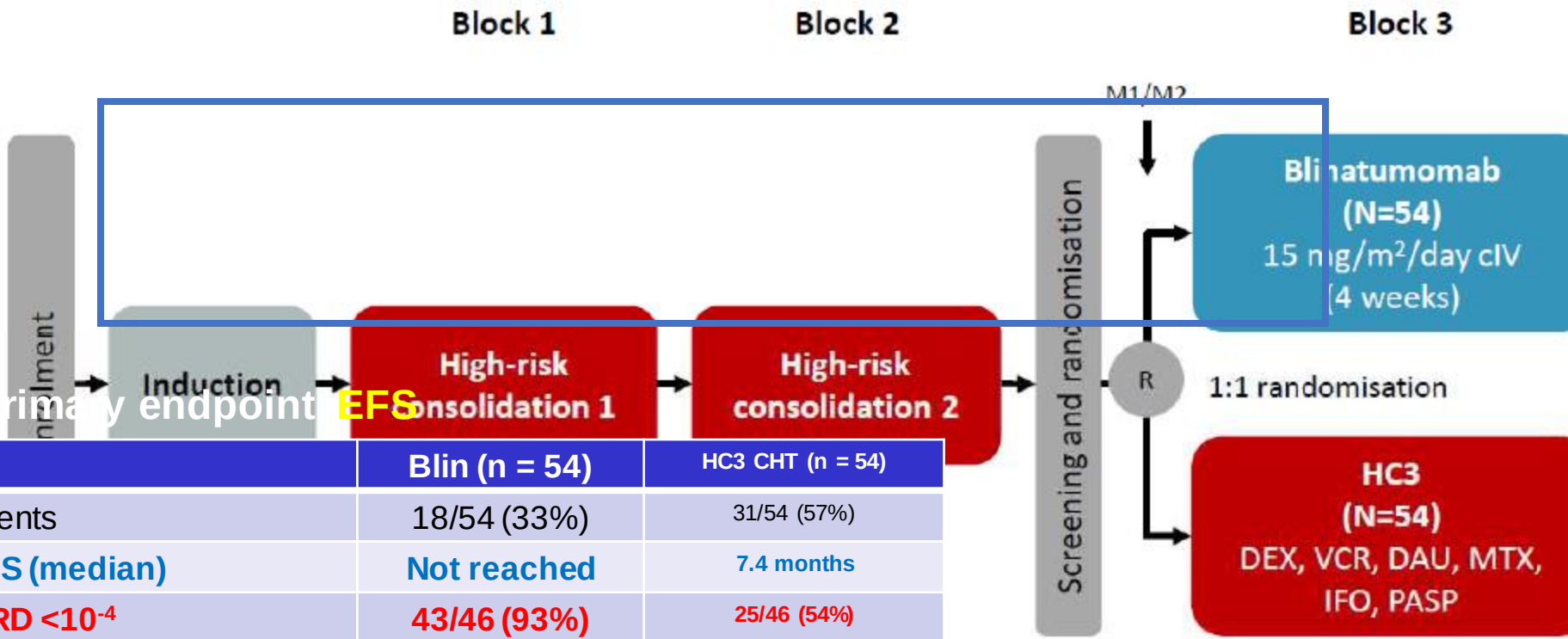


Parameter	Blina	Chemo	*P*
% 2-yr DFS	59	41	.05
% 2-yr OS	79	59	.005
% SCT	73	49	<.001
% MRD clearance	79	21	<.001



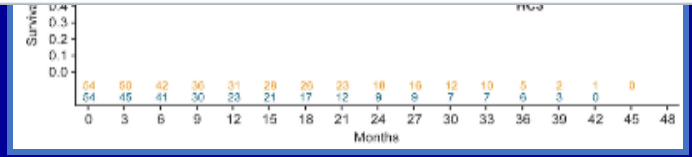


Brown et al. *JAMA*. 2021:325(9):833-842.



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.

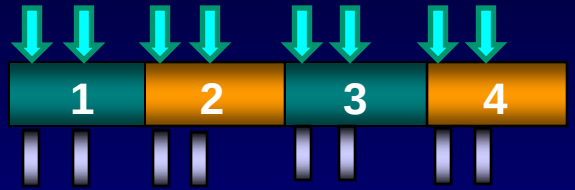
Mini-HCVD + INO + Blina in ALL: Design

- 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

Intensive phase



Mini-HCVD

Mini-MTX-cytarabine
IT MTX, Ara-C

Blinatumomab

POMP

Consolidation phase

INO	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2-4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m²

Maintenance phase

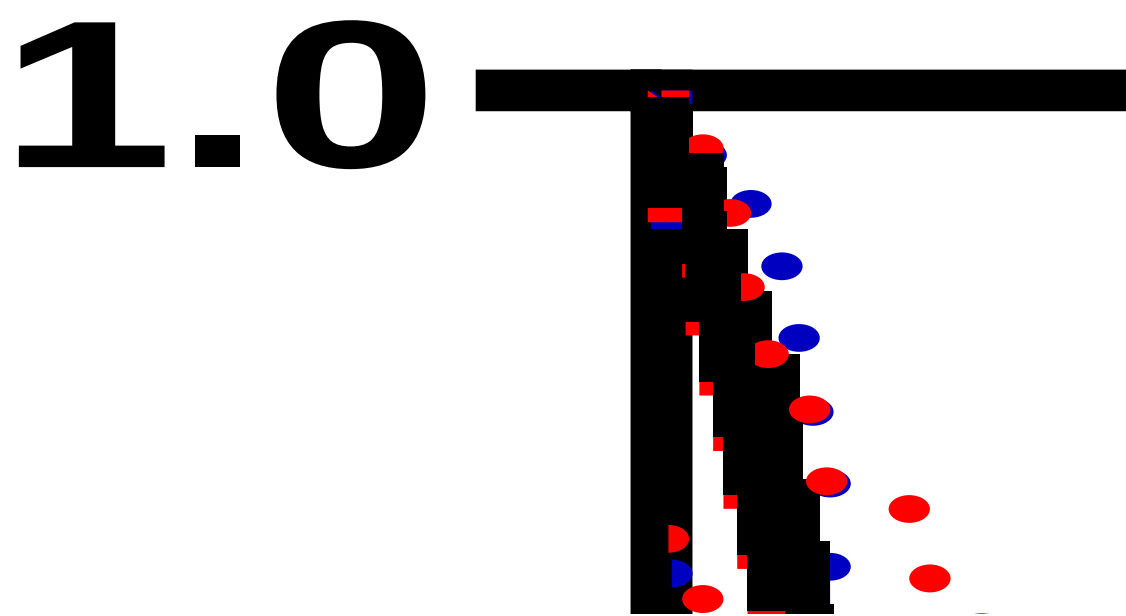
Sasaki et al. *Blood*. 2020;136: abstract 1895.

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)

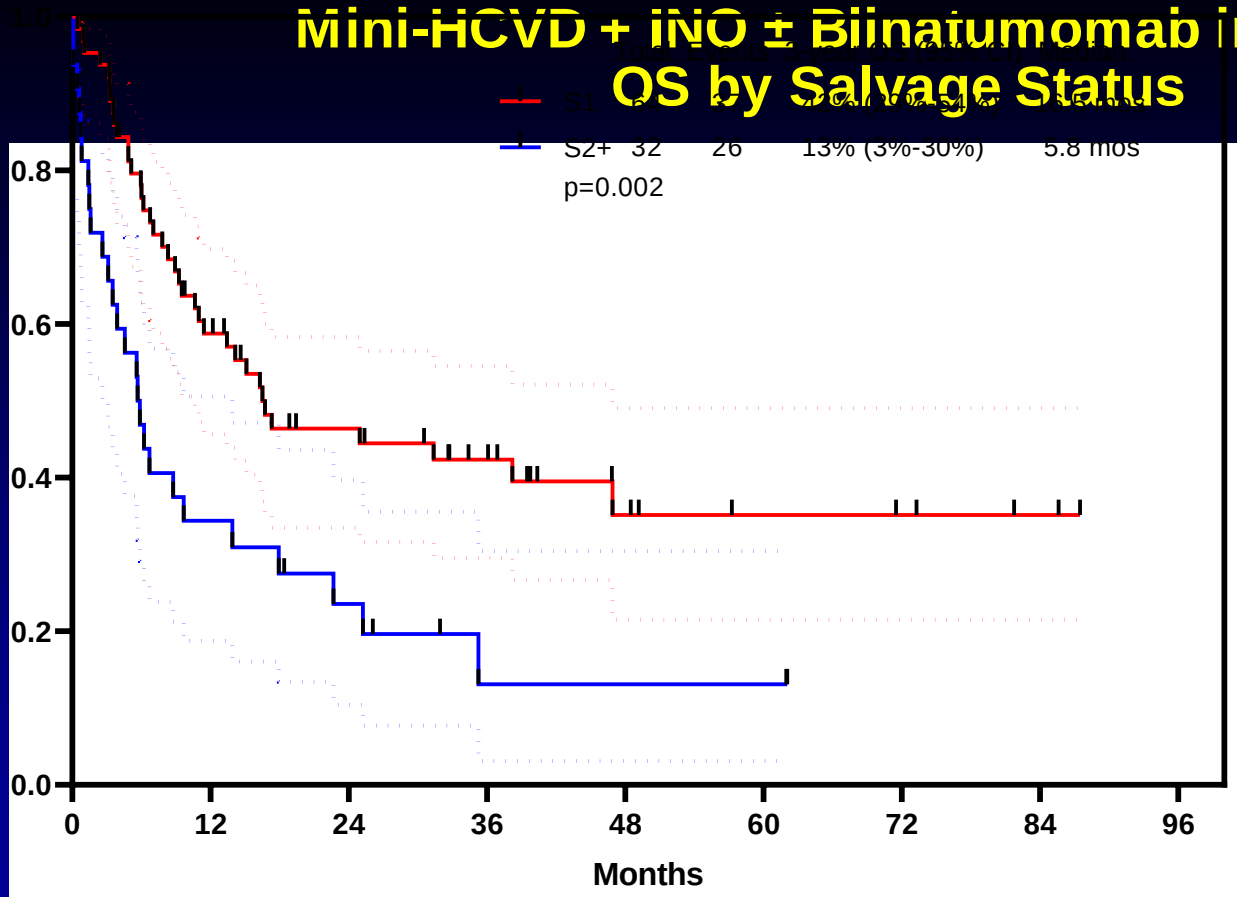
Sasaki et al. *Blood*. 2020;136: abstract 1895.



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

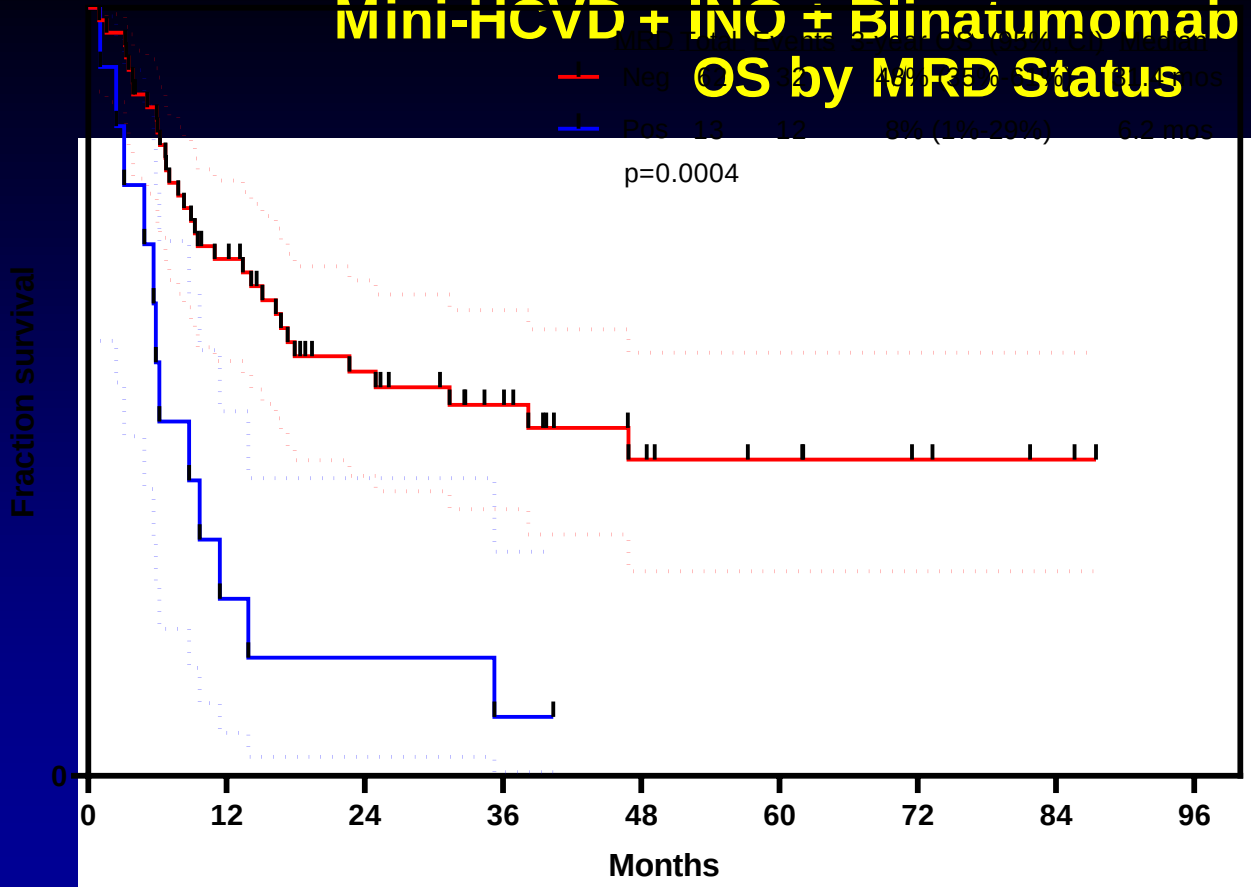
Sasaki et al. *Blood*. 2020;136: abstract 1895.

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



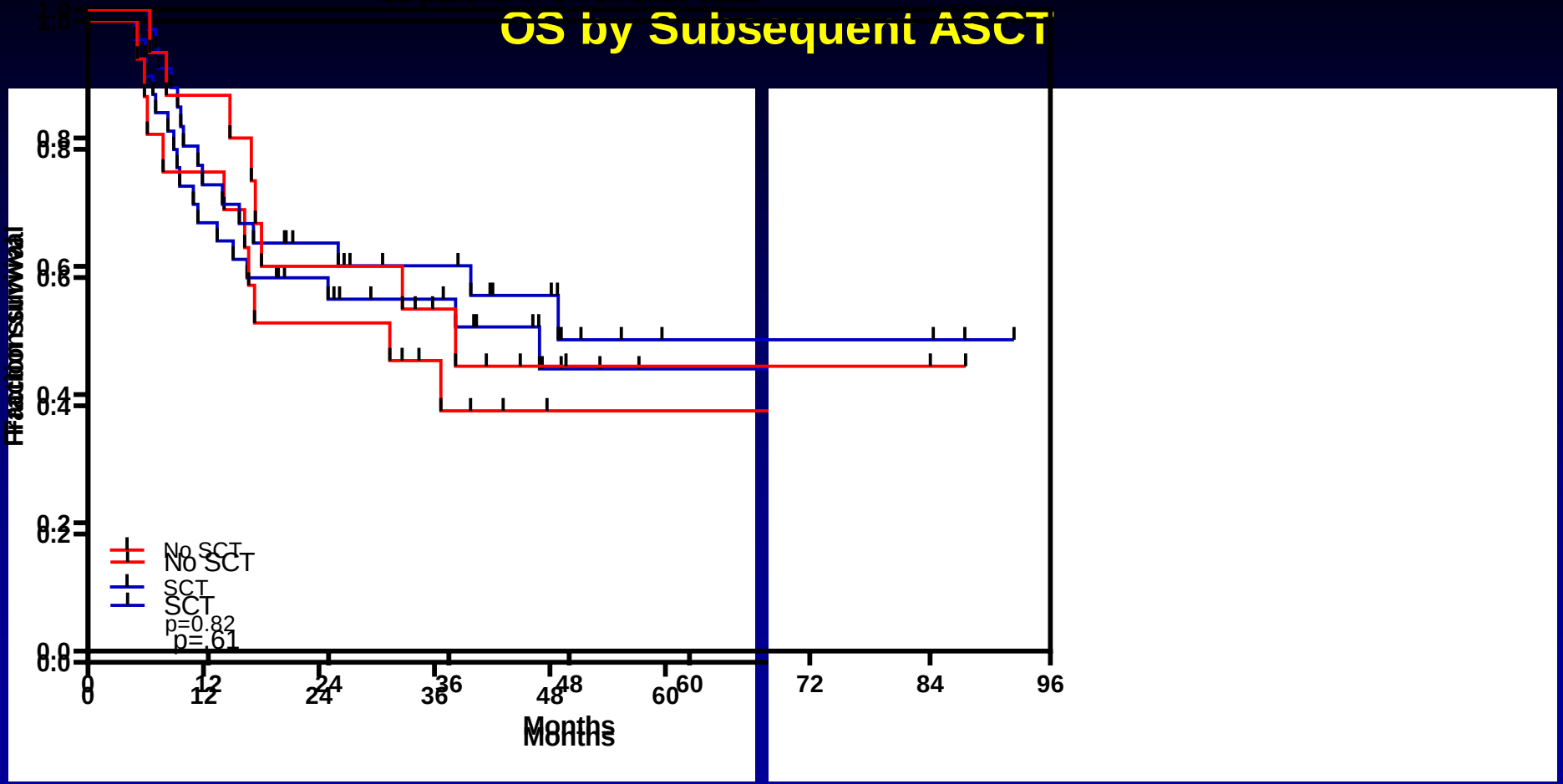
Rafei et al. *Blood.* 2020;134: abstract 1932.

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



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

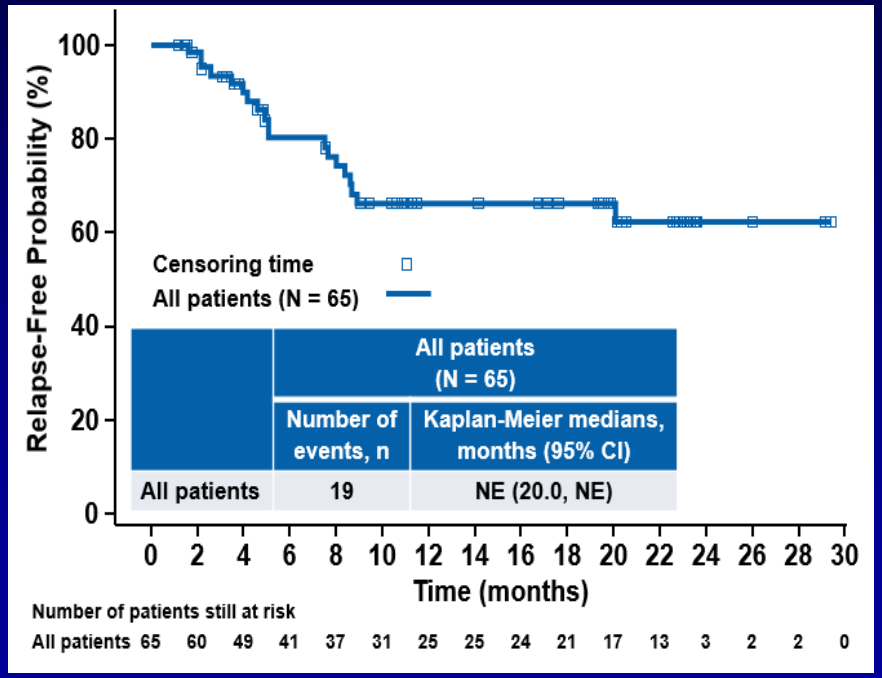
Mini-HCVD + INO ± Blinatumomab in S1 ALL
OS by Subsequent ASCT

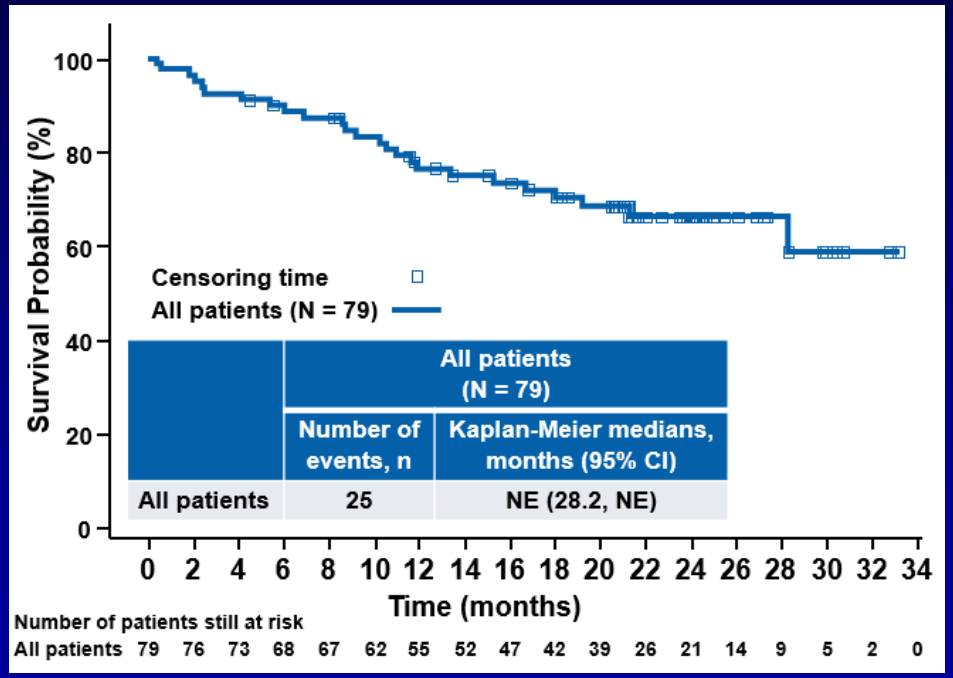


Rafei et al. *Blood.* 2020;134: abstract 1934.

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%

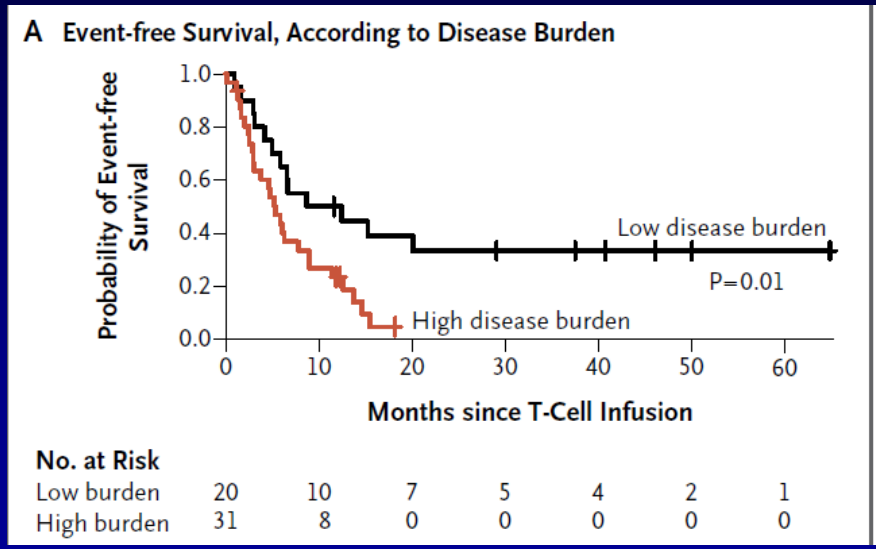


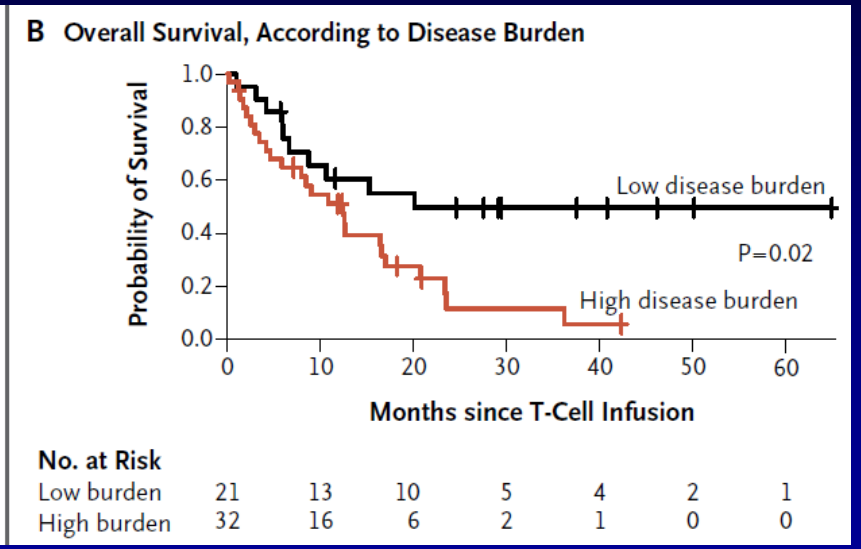


Grupp et al. EHA 2019. Abstract S1618.

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)



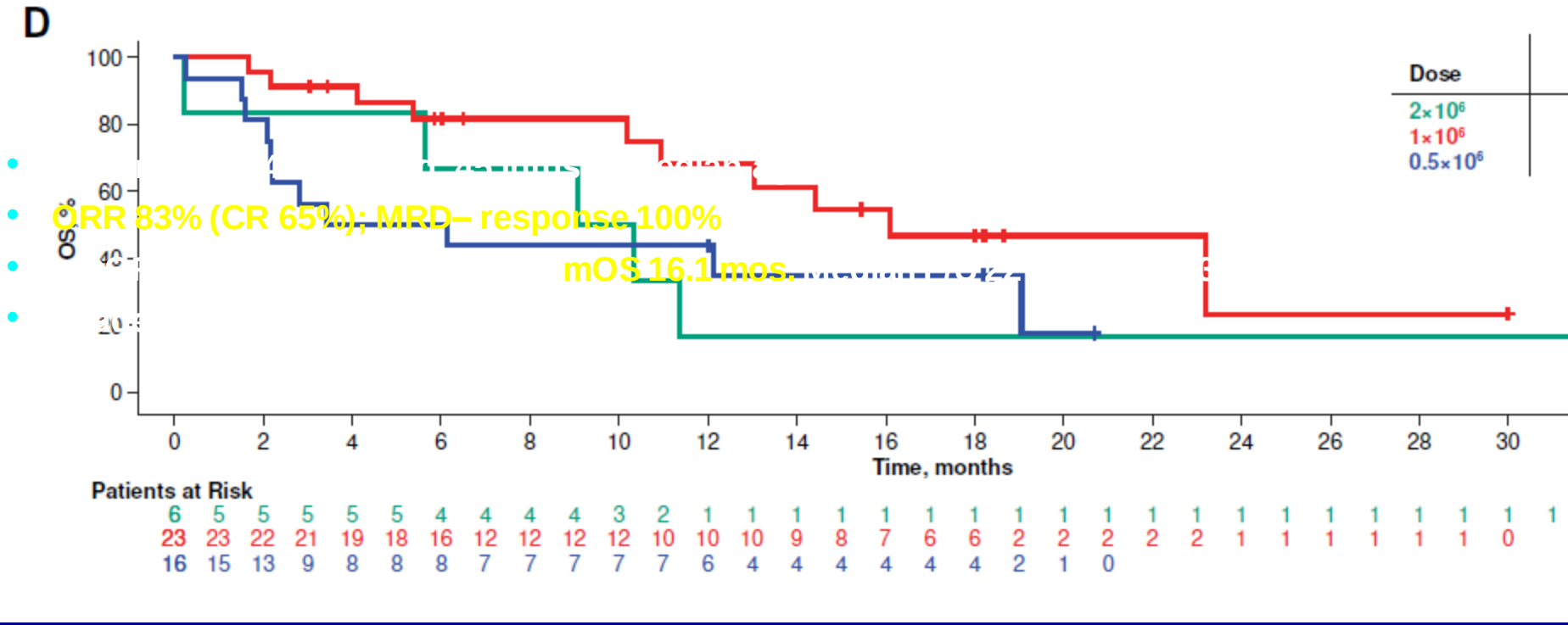


Median EFS
Low tumor burden (MRD+): 10.6 mos
High tumor burden: 5.3 mos

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



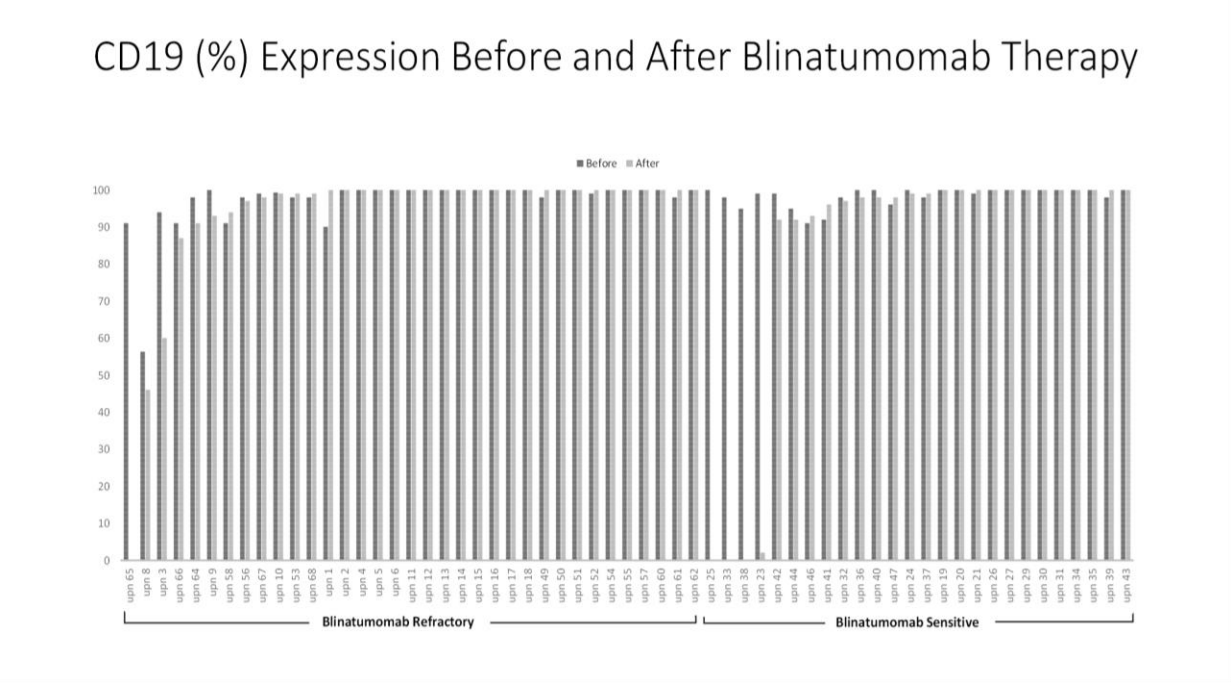
- ORR 83% (CR 65%); MRD– response 100%
- mOS 16.1 mos.

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

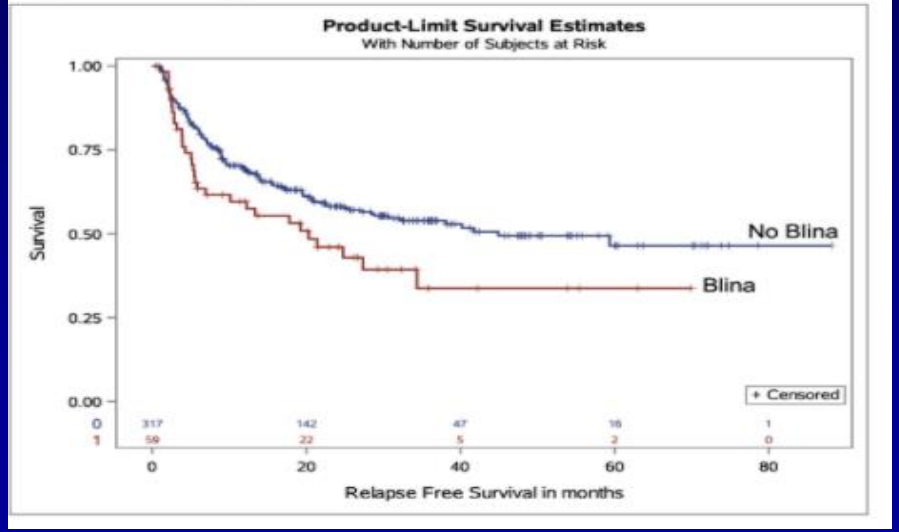
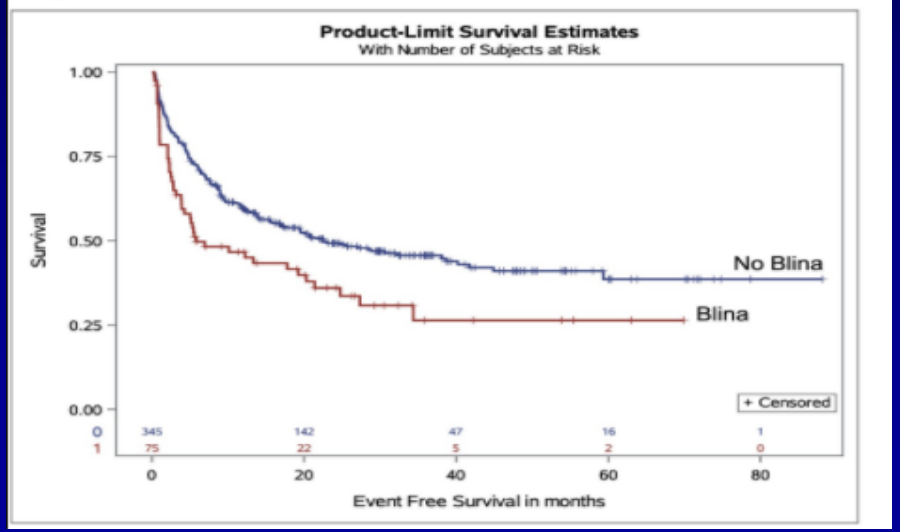


Figure 1B. Event Free Survival



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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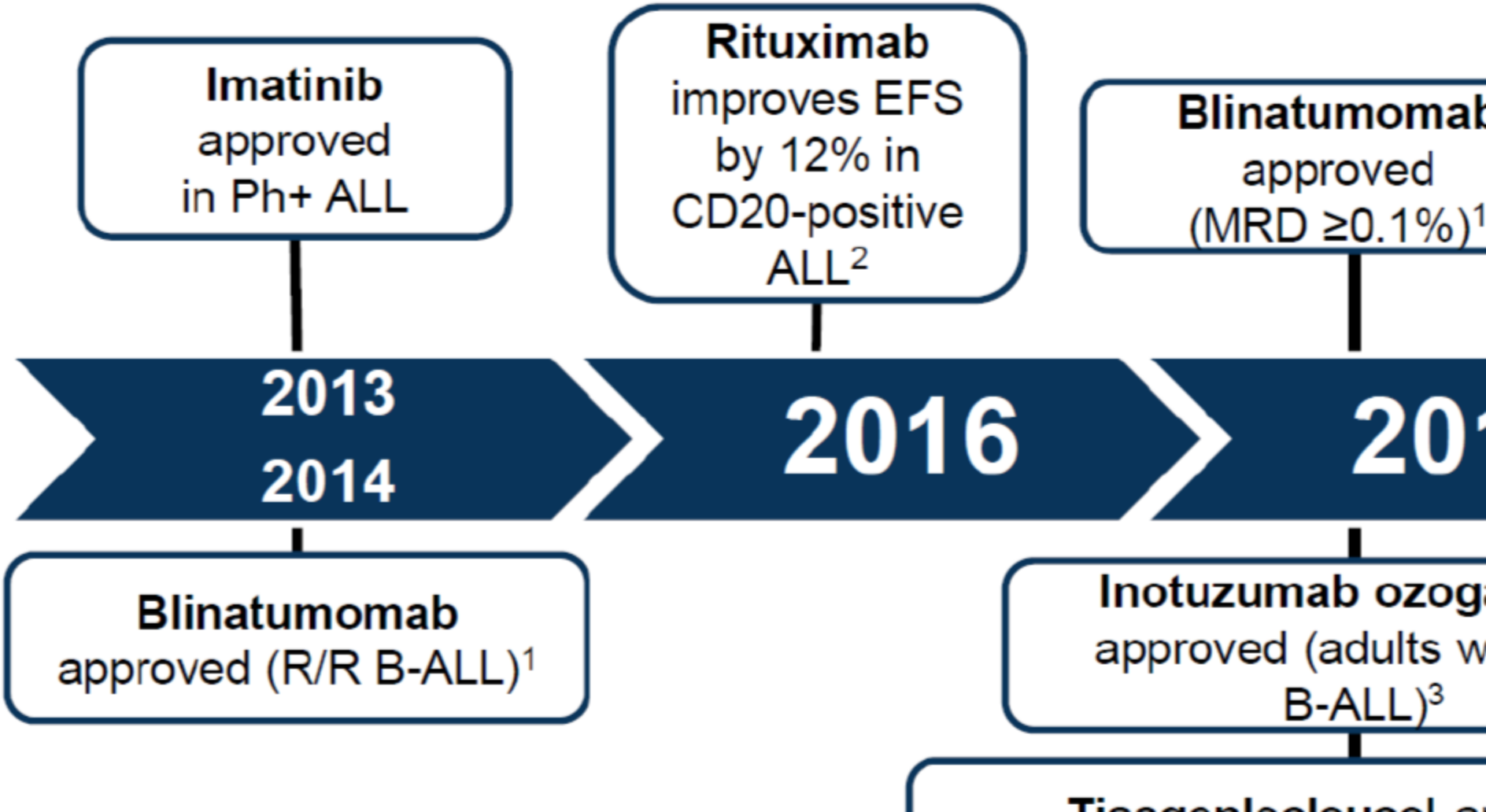
Global Leukemia Academy

Debate on sequencing CD19-targeted approaches: CAR T first

Josep-Maria Ribera

APTITUDE HEALTH


Imatinib
approved
in Ph+ ALL
Rituximab
improves EFS
by 12% in
CD20-positive
ALL[2]
Blinatumomab
approved
(MRD ≥0.1%)[1]
2013
2014
2016
20
Blinatumomab
approved (R/R B-ALL)[1]
Inotuzumab ozoga
approved (adults w
B-ALL)[3]

Immunological Therapies for B-cell Precursor ALL

	Blinatumomab		Inotuzumab	Bretxucabtagene autoleucel		Tisa-cel
FDA approval	2014		2017	October 2021		2017
Approved indication	CD19+ BCP R/R adults & children MRD+ BCP CD19+ ALL		R/R CD22+ ALL in adults	Adults R/R BCP ALL (review) BCP children & AYA (≤21 yr)(devel)		BCP children & AYA (≤25 yr)
Clinical trial	BLAST	TOWER	INO-VATE	ZUMA-3	ZUMA-4	ELIANA
N Pts (ITT)	118	405	326	71	31	97
N (evaluable)	113/110	376	326 (OS/PFS) 218 (CR)	55	24	79
CR/CRi (%)	-	43.9 vs. 24.6 (ITT)	80.7 vs. 29.4 (evaluable)	71 (evaluable)	67 (evaluable)	82.3 (evaluable)
RFS/PFS/EFS	mRFS 18.9 m (evaluable)	6m EFS: 31% vs. 12% (ITT)	mPFS: 5.0 vs 1.8 m (ITT)	mRFS 11.6 m (evaluable)	mRFS NR (evaluable)	18m RFS: 66% (evaluable)
OS	mOS 36.5 (evaluable)	mOS 7.7 vs 4.0 (ITT)	mOS 7.7 vs 6.7 (ITT)	mOS 18.2 m (evaluable)	2yr OS 87.5% (evaluable)	18m OS: 70% (evaluable)
G ≥3 AE (%)	60	86.5 vs 91.7	46 vs 43	95	100	-
G ≥3 CRS (%)	1.7	4.9 vs 0.0	-	24	22	48
G ≥3 neurol ev.	13	9.4 vs 8.3	-	25	11	13

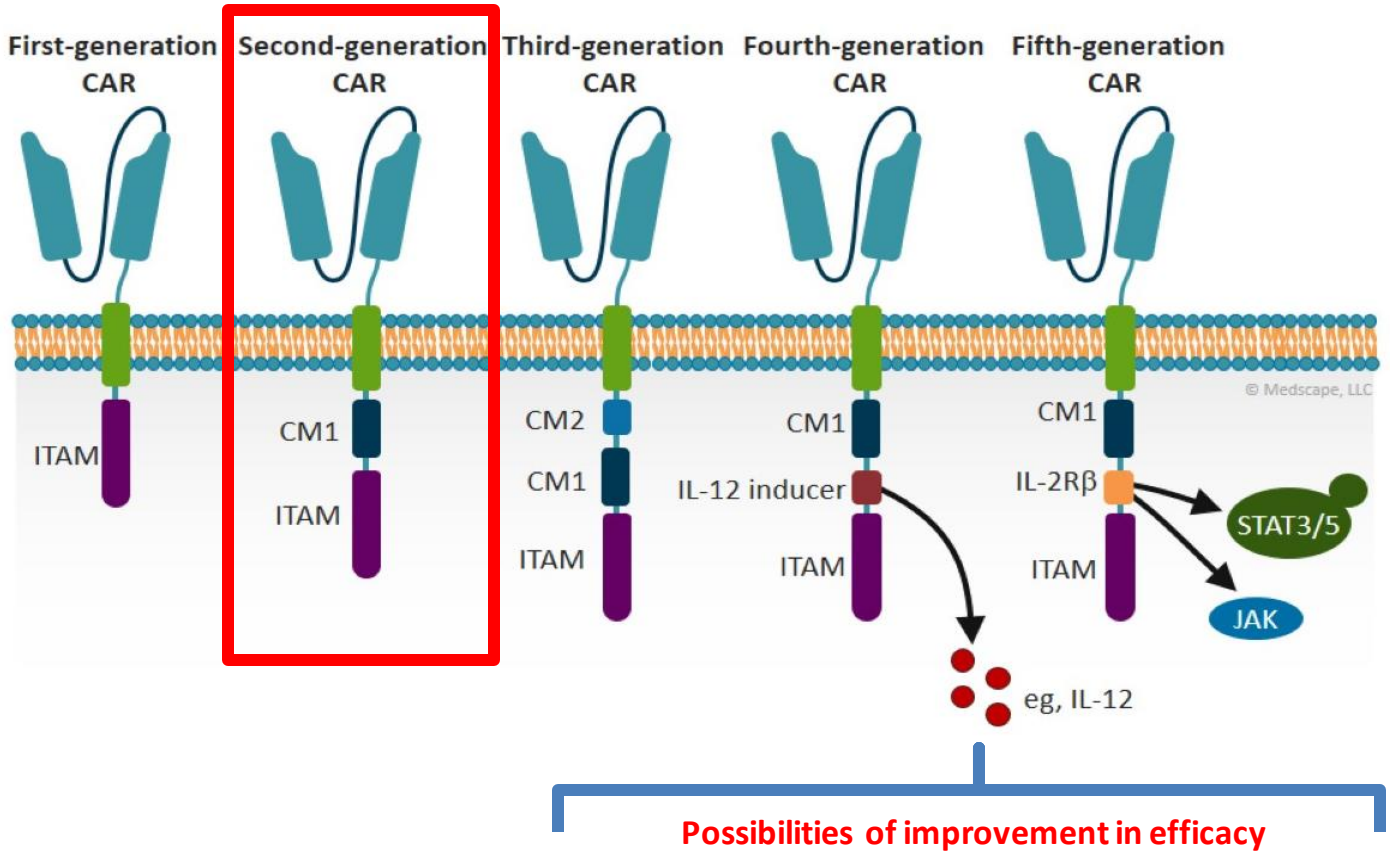
Debate on CD19-Targeted Approaches

- **There is no debate!**
- Immunotherapeutic strategies are not mutually exclusive and can (should?) be used sequentially
- Quick improvement in the results of immunotherapy in ALL
- Immunoconjugates and bispecific MoAb were developed before CAR T and more mature results are available
- Face-to-face comparison MoAb vs CAR T not available to date
- **Main objective**: timely use of the most adequate strategy to maximize the efficacy with minimal toxicity

¿Why Are All CAR T Not Equal?

- Construct: antigen, co-stimulatory molecule
- Specificity: single antigen, dual, triple
- Origin of T cells: autologous, allogeneic (off the shelf)
- Production: commercial, academic
- Dose: single, fractioned

Differences in CAR T-cell Therapies



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

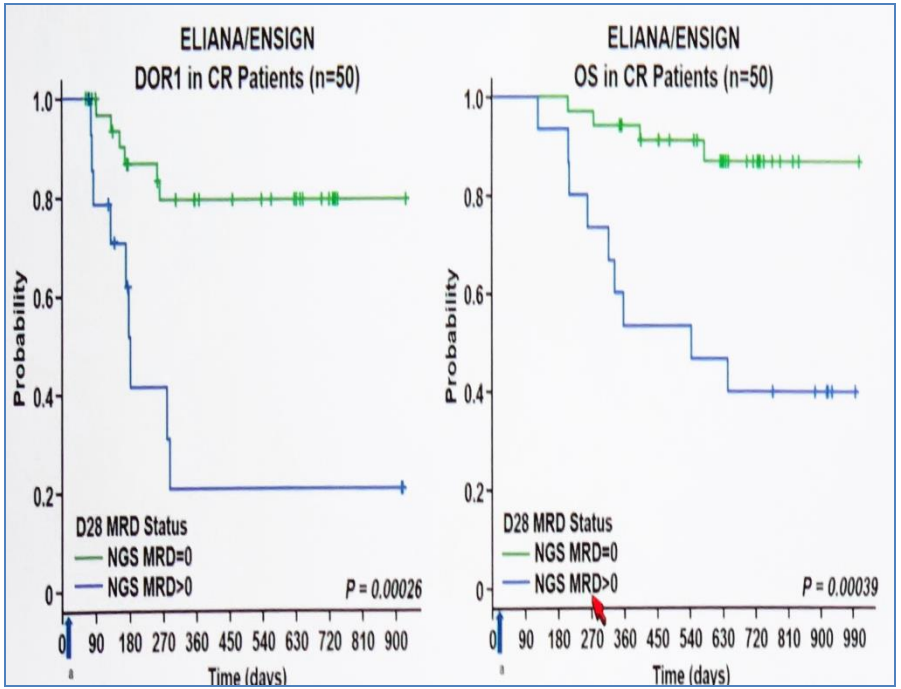
Second-Generation CD19 CAR T in R/R Adult ALL: Facts

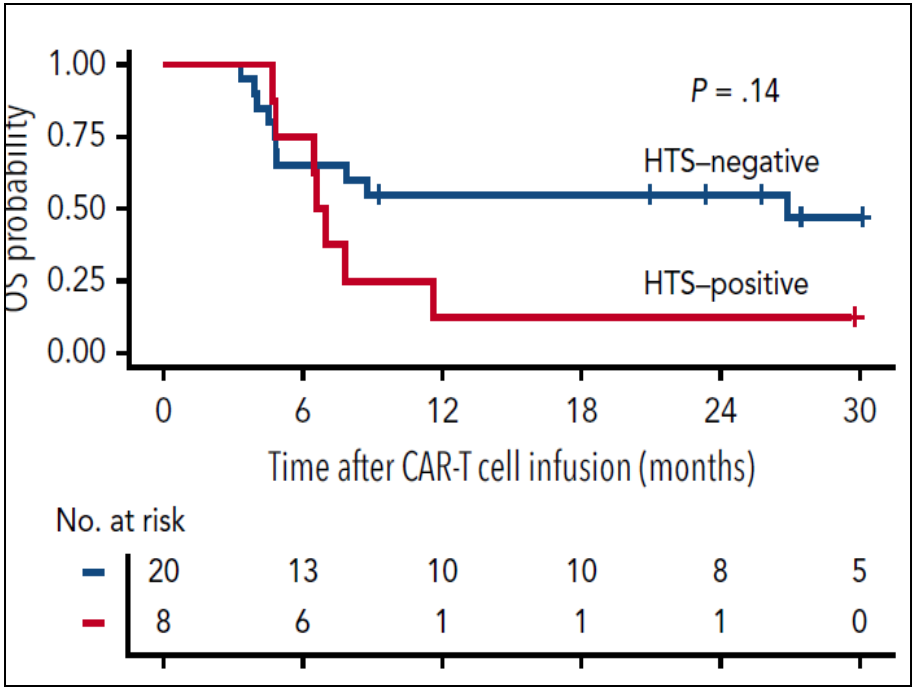
- Limited experience, short-term results
- High CR rate (80%–90%), MRD–neg in 60%–80%
- Short duration of response (median 8–18 months)
- Better results in patients with low tumor mass, promising in MRD+ patients
- Need for subsequent alloHSCT unclear, with good results in some series
- Early MRD assessment by high-throughput sequencing predicts outcome
- Prognostic factors in MRD–neg CR patients identified
- Major concerns: durability, CD19–neg relapses
- **First CAR T for adult ALL (brexucabtagene autoleucel) approved for adults with R/R ALL on October 1, 2021**

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 phase I	45	46 (18–77)	83	100		Median: 17.6 mo	Median: 16.1 mo
KTE-X19 phase II *Infused	55	40 (19–84)	71	97		Median 11.6 mo	Median 18.2 mo

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





Median OS 26.9 vs 6.8 months

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

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

CD19 CAR T Cells in Relapsed/Refractory Adult ALL

CAR: CD19 4-1BB

59 pts apheresis

53 infused

Patient characteristics

Median age: 39 (20–76) years

21% Ph+

43% prior SCT

26% bridging

Disease at lymphodepletion:

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

- 13 extramedullary

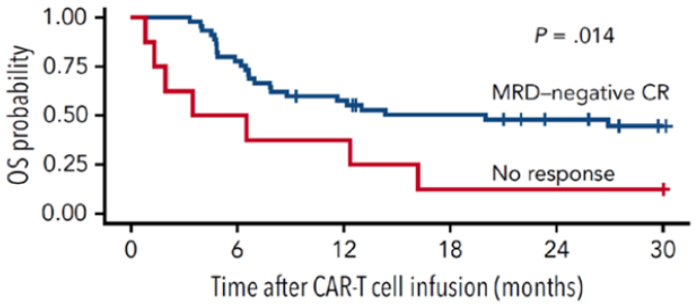
4% (N=2) extramedullary only

32% (N=17) MRD pos

- 3 extramedullary

85% in CR and MRD neg after infusion

Overall survival after infusion



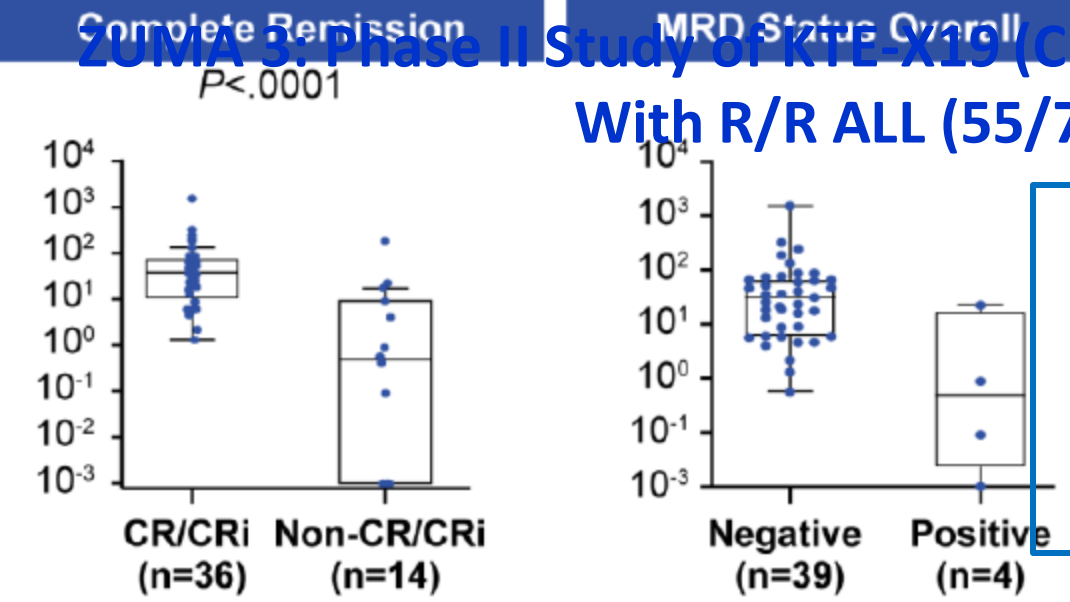
Prognostic factors for EFS

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

EFS, event-free survival.

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

ZUMA 3: Phase II Study of KTE-X19 (CD19. 28z) CAR T Cell in Adults With R/R ALL (55/71 Infused)



	All (N=71)
	49 (69)
	13 (24)
	46 (94)
	33 (67)
	5
	7.5
Neurologic Events	
Any grade neurologic event, n (%)[b]	33 (60)
Grade ≥3	14 (25)
Most common any grade symptoms, n (%)	
Tremor	15 (27)
Confusional state	14 (25)

Median f-u: 16.4 m

Shah BD, et al. *Lancet*. 2021;398:491-502.

Improvements in CAR T

- Humanized CAR T (Myers RM. *J Clin Oncol.* 2021;39:3044-3055)
- Fast-off rate, low-affinity CAR T 19 (Roddie C. *J Clin Oncol*. 2021)
- CAR T 22
- Dual CAR T (Spiegel JY. *Nat Med*. 2021;27:1419-1431)
- Off-the-shelf CAR T
- CAR T combined with checkpoint inhibitors
- CAR T for T-ALL
- NK CAR

icity: Fast Off-rate

Maximum grade CRS (ASTCT criteria)	
CRS (any)	11 of 20 (55)
Grade 2	8 of 20 (40)
≥ Grade 3	0 of 20 (0)
Maximum grade neurotoxicity (ICANS)	
ICANS (any)	4 of 20 (20)
Grade 2	1 of 20 (5)
Grade 3	3 of 20 (15)
Cytopenias at day 28[a]	
≥ Grade 3 neutropenia	9 of 18 (50)
≥ Grade 3 thrombocytopenia	10 of 18 (56)

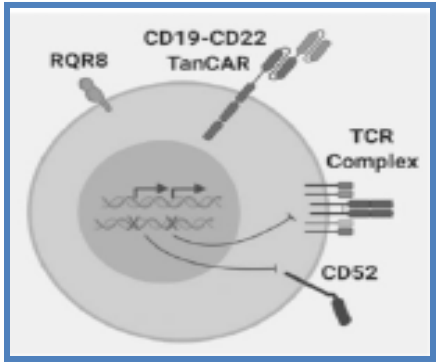
Roddie C, et al. *J Clin Oncol*. 2021 doi: 10.1200/JCO.21.00917.

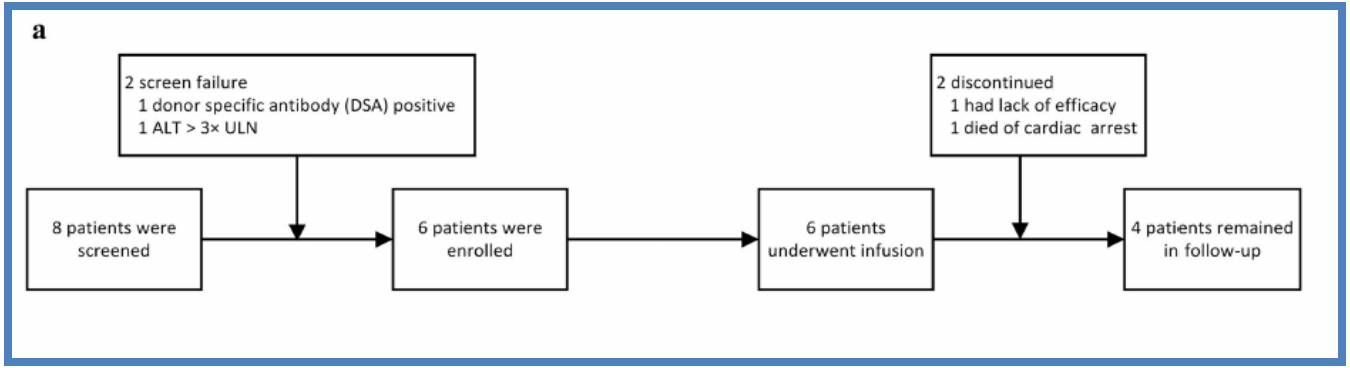
Autologous Dual CAR T 19/22

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
Spiegel JY	I	17 (26–68 yr)	14/17 (88%)	14/14 (100%)	Median 11.8 mo	2	2
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)

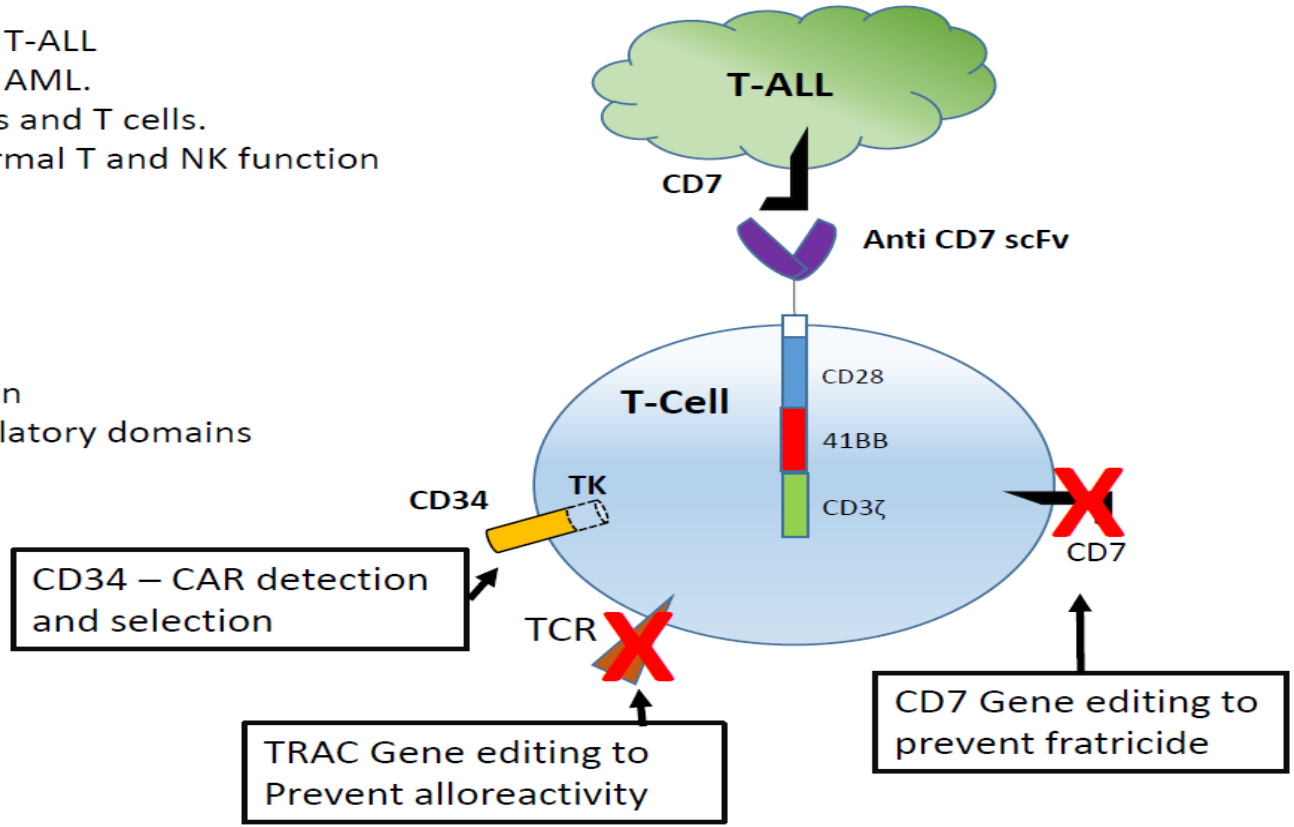
Hu Y. *Clin Cancer Res*. 2021. doi: 10.1158/1078-0432.CCR-20-3863.

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.

Integrative Debate on CD19-Targeted Approaches: Conclusions

- Immunotherapy with MoAb should be first used in patients with R/R ALL as well in first-line therapy (elderly, MRD+)
- MoAb can be used as bridging therapy to HSCT and CAR T
- CAR T only recently approved for R/R adult ALL
- **The main current role for CAR T are relapses after HSCT**
- CAR T as consolidation therapy evaluated in very high-risk ALL (clinical trials in children)
- CAR T are quickly improved (availability, lower toxicity, improved efficacy, use in R/R BCP and T ALL) and could replace HSCT for most patients in the near future

Global Leukemia Academy

Debate on sequencing CD19-targeted approaches – discussion and voting

Moderator: Franco Locatelli

APTITUDE HEALTH

Global Leukemia Academy

Repeated 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 – discussion

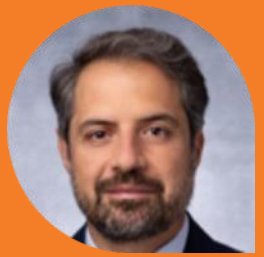
All faculty

APTITUDE HEALTH

Global Leukemia Academy

Leukemia board discussion

Moderator: Elias Jabbour



APTITUDE HEALTH

Global Leukemia Academy

Leukemia board discussion – optimal treatment and patient access, regional challenges in Europe – part 1

Rob Pieters

APTITUDE HEALTH

Global Leukemia Academy

Regional Challenges in Europe

- Financial challenges
  - Costs for travel and lodging for patients and parents
  - Trial costs are covered, but who covers the costs of standard care around the trial? Insurance companies often do not want to guarantee this
- Geographic challenges
  - Return to home country when therapy is not successful
  - Translation costs, communication and cultural differences: child and parents may feel displaced in other countries in stressful situations despite good care
  - Difficulties in obtaining detailed information of a patient from abroad (eg, surgical reports, genetic diagnostics, radiation fields)
- European centers have insufficient resources to run phase I–II programs
- EMA approval: large differences in HTA approvals per country (reimbursement/insurance) resulting in unequal access

Global Leukemia Academy

Leukemia board discussion – optimal treatment and patient access, regional challenges in Europe – part 2

Philippe Rousselot

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Optimal Treatment and Patient Access

France

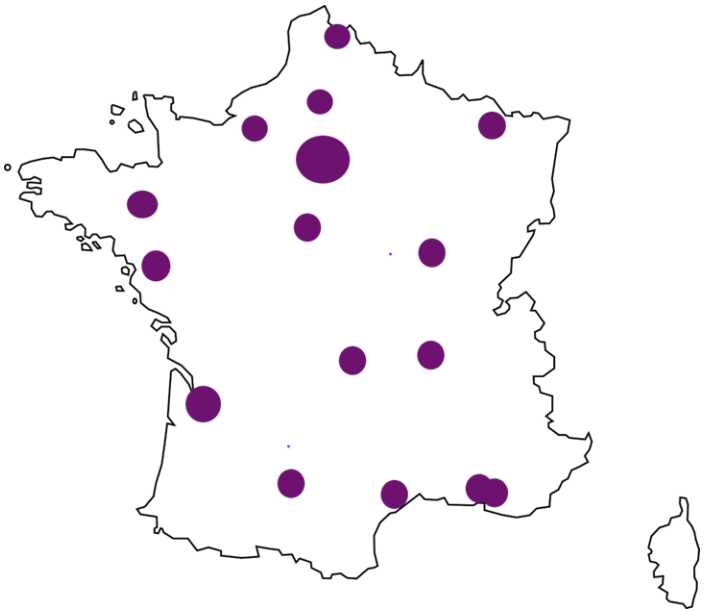
Autorisation Temporaire d'Utilisation (ATU) Program in France

- Two new mechanisms: Early access authorization (EAA) and Compassionate use (CU)
- Patients can be treated with medications before their marketing authorization
- The program was amended in July 2021
  - EAA: access to innovative therapies with an ongoing labelling process
    - Named authorization: the labelling process is planned
    - Cohort authorization: just before the labelling
  - CU: access to innovative therapies without a labelling process

Medications With Ongoing ATU in Hematology

- Idecabtagene vicleucel (CAR T): since May 2021
  - Multiple myeloma in fourth line
- Atgam (antilymphocyte globulin): since May 2018
  - Aplastic anemia
- Zanubrutinib (BTK inhibitor): since July 2021
  - Waldenstrom macroglobulinemia after ibrutinib or intolerant
- Inolimomab (IL2R antibody): since Dec 2019
  - GvHD
- Vyxeos (DNR AraC): since Aug 2020
  - AML in relapse in pediatric and young adults
- Crizotinib (ALK inhibitor): since Dec 2020
  - T lymphoma ALK+ in second line

CAR T Availability in France



22 centers authorized for "Axi-Cel" and "Tisa-Cel"

1. APHP Créteil Henri Mondor
2. APHP Saint Louis
3. APHP Pitié Salpêtrière
4. APHP Saint-Antoine
5. APHP Necker
6. APHP Robert Debré
7. CHU d'Amiens
8. CHU Bordeaux
9. CHU Clermont Ferrand
10. CHU Dijon
11. CHU Lille
12. CHU Lyon-Sud
13. CHU Nancy
14. CHU Nantes
15. CHU Montpellier
16. CHU Reims
17. CHU Rennes
18. CHU Strasbourg
19. CHU La Timone
20. Institut Paoli-Calmettes
21. Oncopole de Toulouse
22. Institut Gustave Roussy à Villejuif

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Leukemia board discussion

All faculty

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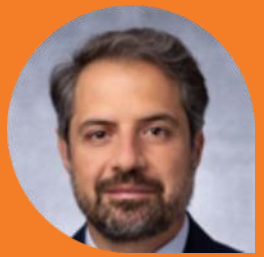
Session close

Elias Jabbour



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Repeated 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– ALL
d) CAR T approaches are not active beyond 2L in Ph– ALL

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Virtual Breakout – Adult Leukemia Patients (Day 2) 17.00 – 20.00

Chairs – Elias Jabbour, Naval Daver

Time CET	Title	Speaker/Moderator
17.00 – 17.10	**ALL session open**	Elias Jabbour
17.10 – 17.30	**Optimizing first-line therapy in adult and older ALL – integration of immunotherapy into frontline regimens**	Elias Jabbour
17.30 – 17.50	**Current treatment options for relapsed ALL in adult and elderly patients**	Nicola Gökbuget
17.50 – 18.20	**Case-based panel discussion on toxicity management for adult and elderly ALL patients** • Case presentation 1: Fabian Lang • Case presentation 2: Anna Torrent	Moderator: Elias Jabbour *Faculty panel*: E. Jabbour, N. Gökbuget, J.M. Ribera, P. Rousselot
18.20 – 18.30	**Break**	
18.30 – 18.35	**AML session open**	Naval Daver
18.35 – 18.55	**Personalized induction and maintenance approaches for AML**	Richard Schlenk
18.55 – 19.15	**Optimizing management of relapsed/refractory AML**	Charles Craddock
19.15 – 19.45	**Case-based panel discussion or questions to the panel on regional challenges in AML care** • Case presentation 1: Justin Loke • Case presentation 2: Sonia Jaramillo Segura	Moderator: Naval Daver *Faculty panel*: N. Daver, C. Craddock, R. Schlenk
19.45 – 20.00	**Session close**	Elias Jabbour

Global Leukemia Academy

Virtual Breakout – Pediatric ALL Patients (Day 2) 17.00 – 19.45

Chair – Franco Locatelli

Time CET	Title	Speaker/Moderator
17.00 – 17.15	**Session open**	Franco Locatelli
17.15 – 17.40	**How to use MRD and genetics for risk stratification and therapy guidance in pediatric ALL**	Rob Pieters
17.40 – 18.05	**First-line treatment of pediatric ALL**	Martin Schrappe
18.05 – 18.30	**Current treatment options for relapsed ALL in children, including HSCT considerations**	Franco Locatelli
18.30 – 18.55	**Bispecific T-cell engagers for pediatric ALL**	Christina Peters
18.55 – 19.25	**Case-based panel discussion on management of long- and short-term toxicities in pediatric ALL patients** • Case presentation 1: Francesca Del Bufalo • Case presentation 2: Natalia Zubarovskaya	Moderator: Franco Locatelli *Faculty panel:* R. Pieters, F. Locatelli, P. Brown, C. Peters, M. Schrappe
19.25 – 19.45	**Final discussion, Q&A, and session close**	Franco Locatelli

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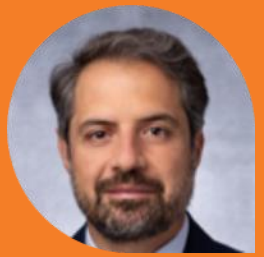
Closing remarks

Elias Jabbour



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- Please complete the **evaluation survey** 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
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SEE YOU TOMORROW!

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