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A Worldwide Collaboration to Define and Refine the Most Effective Treatments in Leukemias

6 December 2022

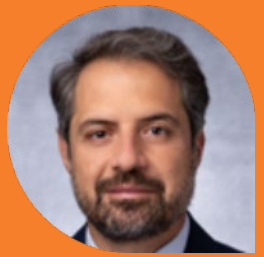
Virtual Breakout: Adult Leukemia Patients

APTITUDE HEALTH

Global Leukemia Academy

ALL Session Open

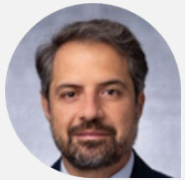
Elias Jabbour



APTITUDE HEALTH

Meet the Faculty

CHAIR



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

FACULTY

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Michael Osborn, MBBS, FRACP, FRCPA
SA Pathology, Adelaide, SA, Australia

Jae Park, MD
Memorial Sloan Kettering Cancer Center, New York, NY, USA

Co-chair (Pediatric Session)
Elizabeth Raetz, MD
NYU Grossman School of Medicine, New York, NY, USA

Objectives of the Program

- Examine current treatment patterns and technological developments in ALL
- Learn how MRD is being used in ALL management and monitoring
- Discuss the latest developments in bispecific antibodies used for ALL
- Understand how stem cell transplantation is being utilized as a consolidation choice in first remission
- Learn current genomic testing practices and how these results inform treatment choices
- Learn how current antibody-drug conjugate treatments are being used in ALL
- Gain insights into promising novel and emerging therapies in ALL
- Learn about the regional challenges and differences in ALL treatment patterns in the Asia Pacific region

Virtual Breakout – Adult ALL Sessions (Day 2)

Tuesday, December 6 | 9.00 AM – 11.45 AM (GMT+8) Shanghai

ARS voting system will be used throughout the meeting

Time	Title	Speaker
9.00 – 9.10	**Session Open** • ARS questions	Elias Jabbour
9.10 – 9.35	**Optimizing First-Line Therapy in Adult and Older ALL: Integration of Immunotherapy Into Frontline Regimens** • Optimal use of treatment choices in frontline ALL	Elias Jabbour
9.35 – 10.00	**Current Treatment Options for Relapsed ALL in Adult and Elderly Patients** • Optimal use of treatment choices in relapsed/refractory ALL	Jae Park
10.00 – 10.40	**ALL Case-Based Panel Discussion** • Local case 1: Frontline setting (10 min) • Local case 2: Relapsed/refractory setting (10 min) • Discussion and Q&A (20 min)	Moderators: Shaun Fleming and Elias Jabbour Huai-Hsuan Huang Michael Ashby All faculty
10.40 – 10.50	***Break***	
10.50 – 11.10	**Beyond the Horizon: New and Future Treatment Approaches for Adult and Older ALL** • Future perspectives and emerging therapies	Jae Park
11.10 – 11.35	**Interactive Discussion: Treatment Landscape Evolution** • Interactive discussion and Q&A (2–3 questions to trigger discussion; no presentation slides)	Moderator: Elias Jabbour All faculty
11.35 – 11.45	**Session Close** • ARS questions	Elias Jabbour

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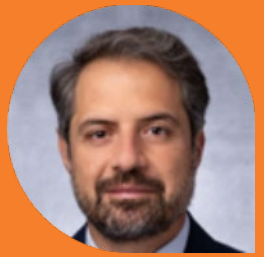
Introduction to the Voting System

Elias Jabbour



APTITUDE HEALTH

Question 1

In which country do you currently practice?

A. Australia
B. China
C. Hong Kong
D. Japan
E. Malaysia
F. Singapore
G. South Korea
H. Taiwan
I. Other country in Asia Pacific
J. Other country outside Asia Pacific

Question 2

What age group is considered elderly ALL patients?

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

Question 3

At what time points is MRD quantification prognostic for survival?

A. End of induction (at CR)
B. After consolidation
C. Prior to allogeneic hematopoietic cell transplant
D. After transplant
E. All of the above

Question 4

Which of the following is NOT true for treating ALL?

A. There are more Ph+ and Ph-like adult ALL patients compared with pediatric ALL

B. *ETV6-RUNX1* fusion (t12;21) is a common genetic subtype in pediatric ALL

C. Hyperdiploid phenotype is more prevalent in adult ALL compared with pediatric ALL

D. Patients with *ETV6-RUNX1* fusion (t12;21) have favorable prognosis

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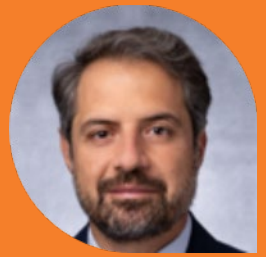
Optimizing First-line Therapy in Adult and Older ALL – Integration of Immunotherapy Into Frontline Regimens

Elias Jabbour



APTITUDE HEALTH

Incorporation of Antibodies Into the Management of Frontline ALL

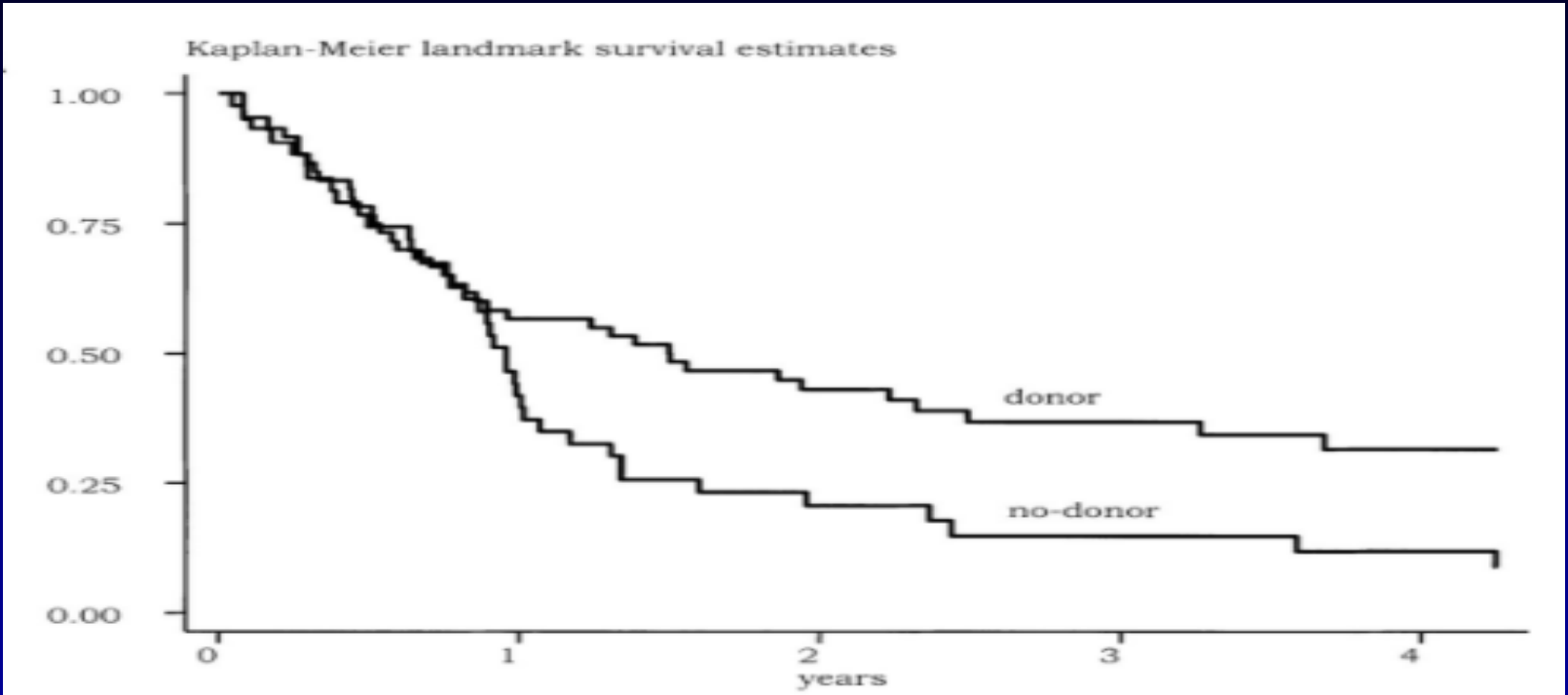
Elias Jabbour, MD
Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, TX

2022

Conflict of Interest Disclosure

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

SCT for Ph+ ALL: Pre-TKI

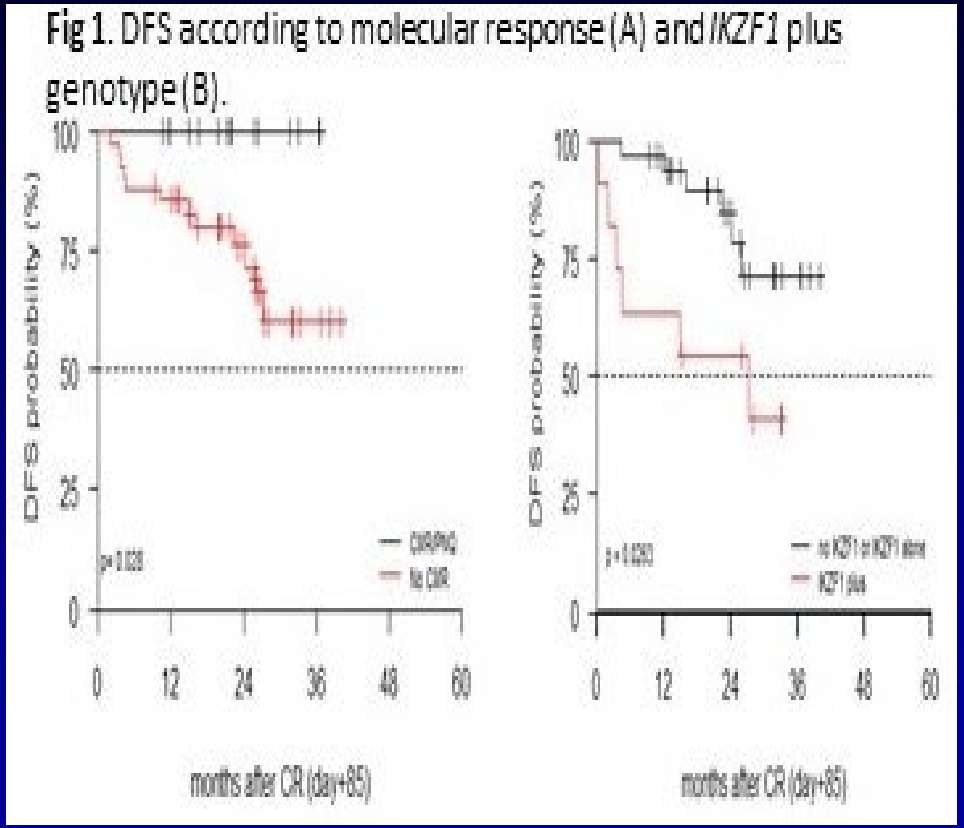


- Donor (n = 60) – 3-year OS: 37%
- No donor (n = 43) – 3-year OS: 12%

Dombret H, et al. *Blood.* 2002.

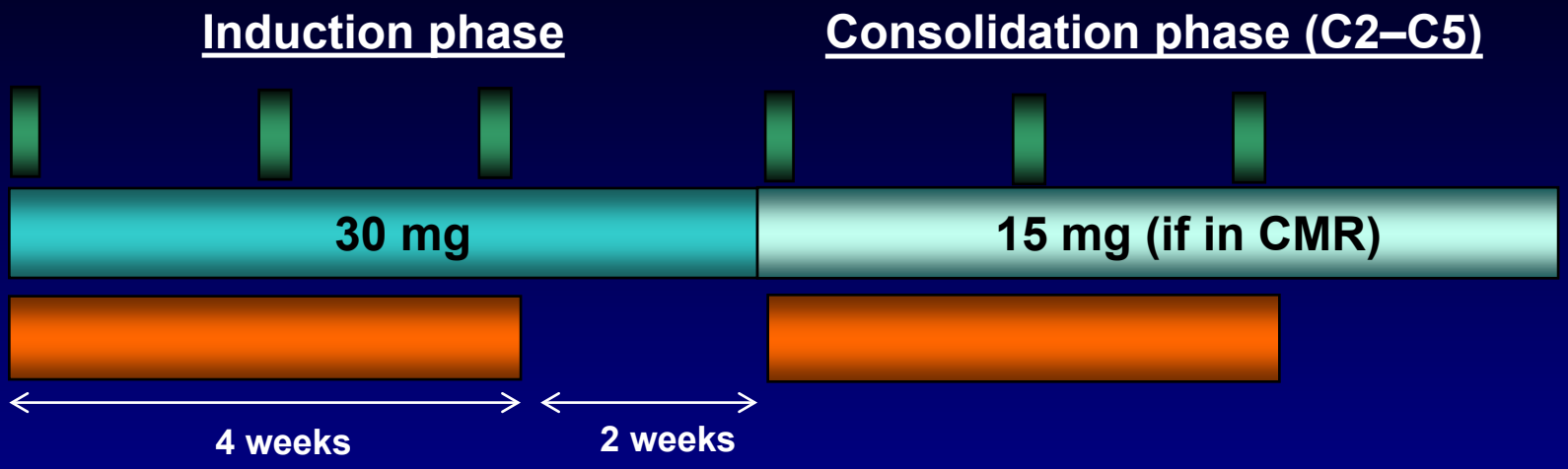
Dasatinib + Blinatumomab (D-ALBA) in Newly Dx Ph+ ALL – Update

- 63 pts Rx; median age 54 yrs (24–82). Median FU 40 mos
- Molecular response (32/53 = 60%)
  - 22 CMR (41%)
- 29/58 (50%) who started blina have SCT – 6 in CR2
- SCT did not impact OS or DFS, but SCT "enriched" by 23 pts who did not have molecular response
- 9 relapses: 4 hematologic, 4 CNS, 1 nodal
- 48-mos OS 78%, DFS 75%



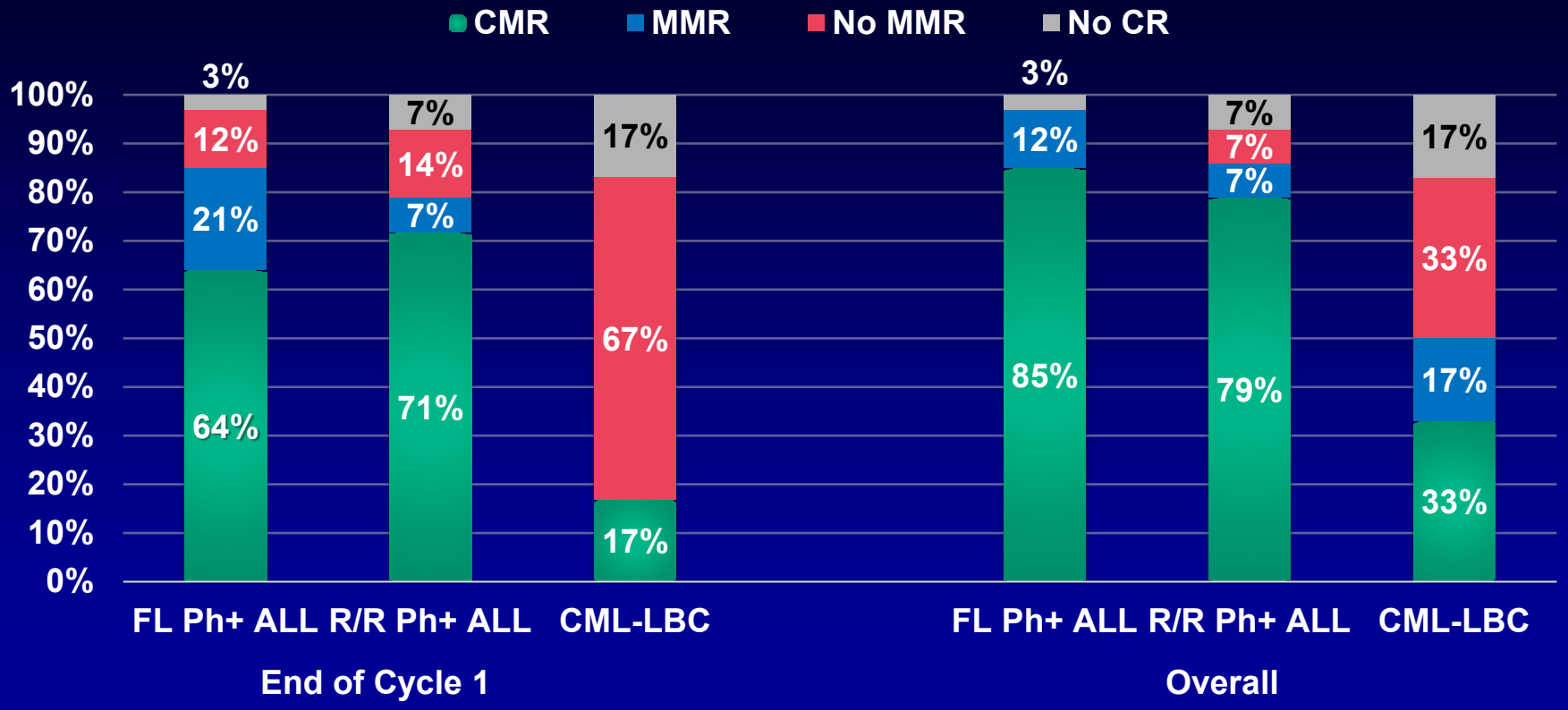
Chiaretti et al. EHA 2022. Abstract P353.

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Short NJ, et al. EHA 2022. Abstract S114.

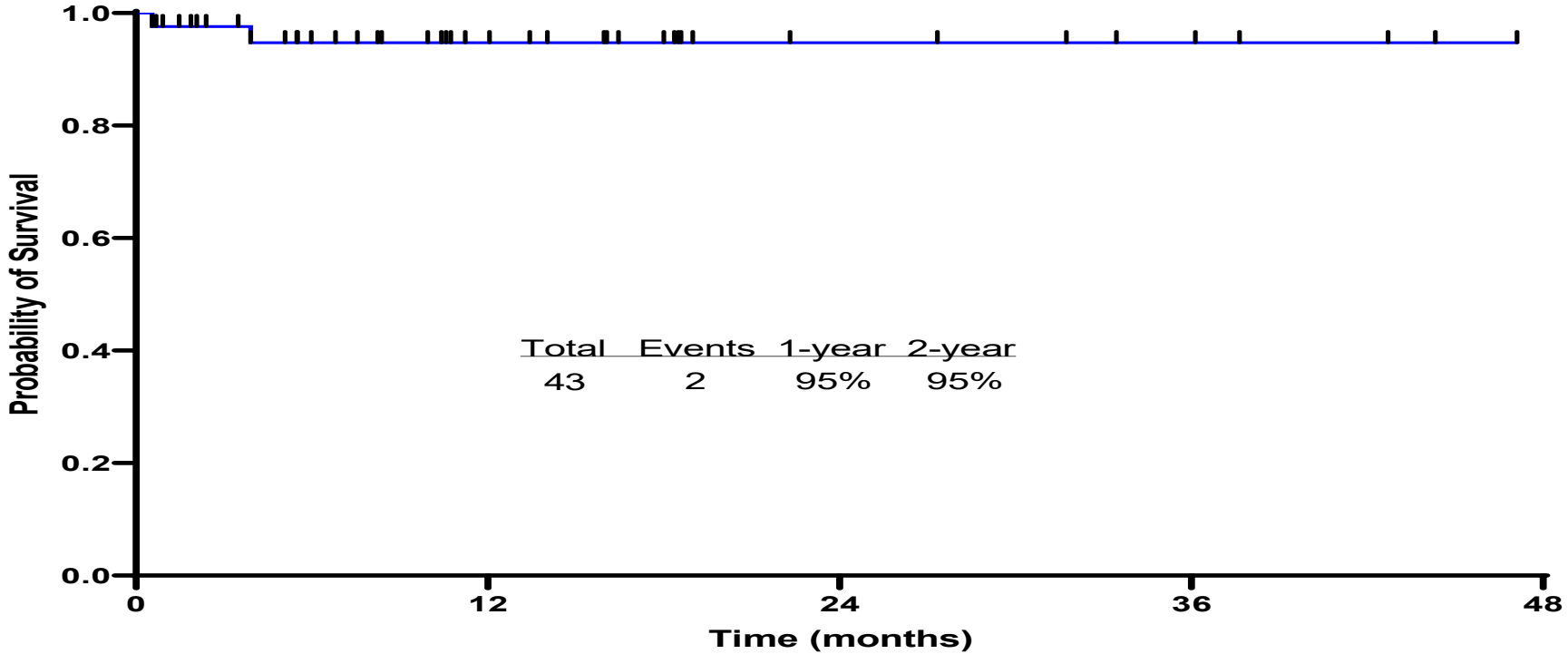
Ponatinib + Blinatumomab in Ph+ ALL: MRD Response Rates



Short NJ, et al. EHA 2022. Abstract S114.

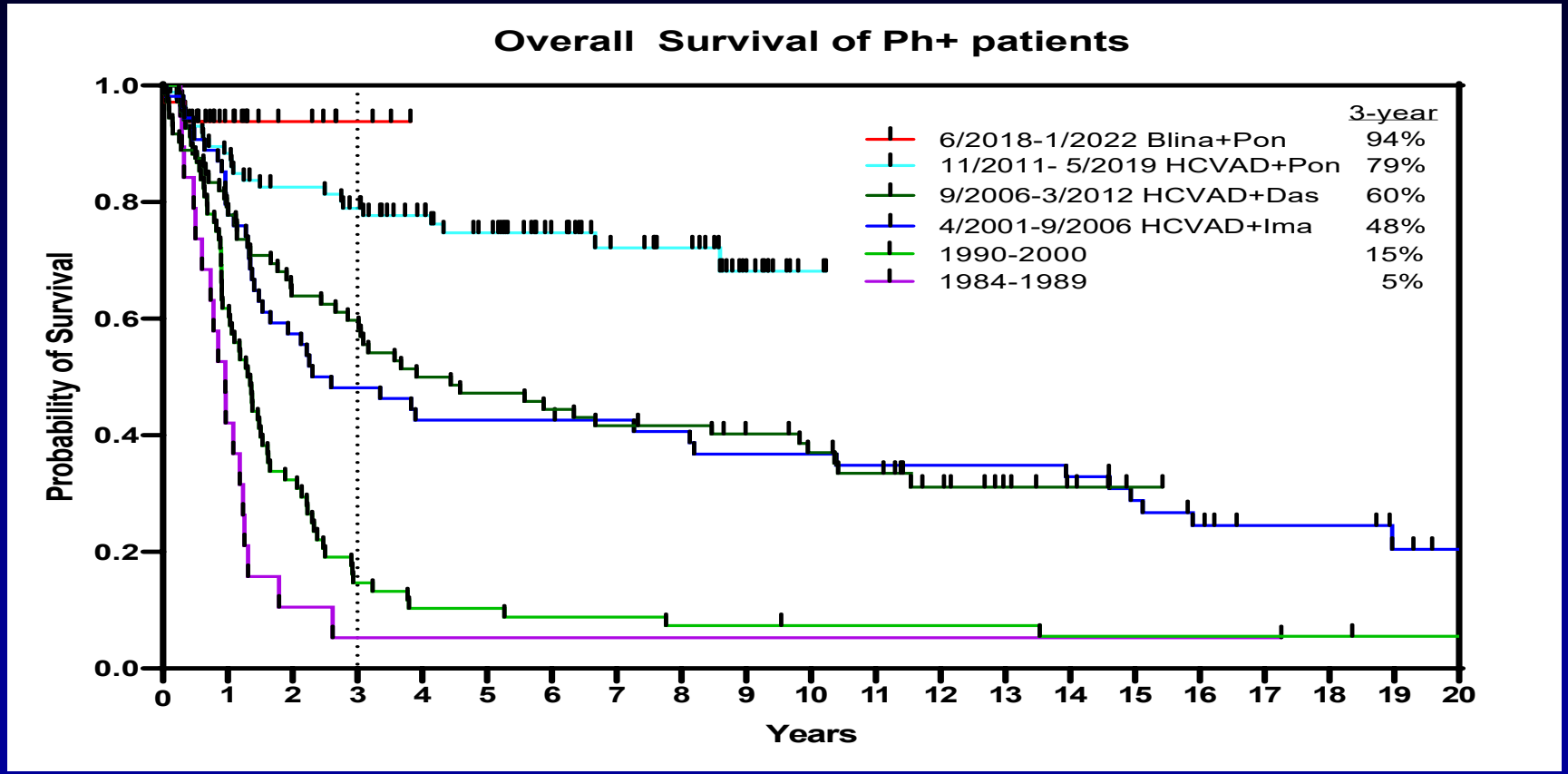
Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes for Frontline Cohort

Median follow-up: 14 months (range, <1–51)

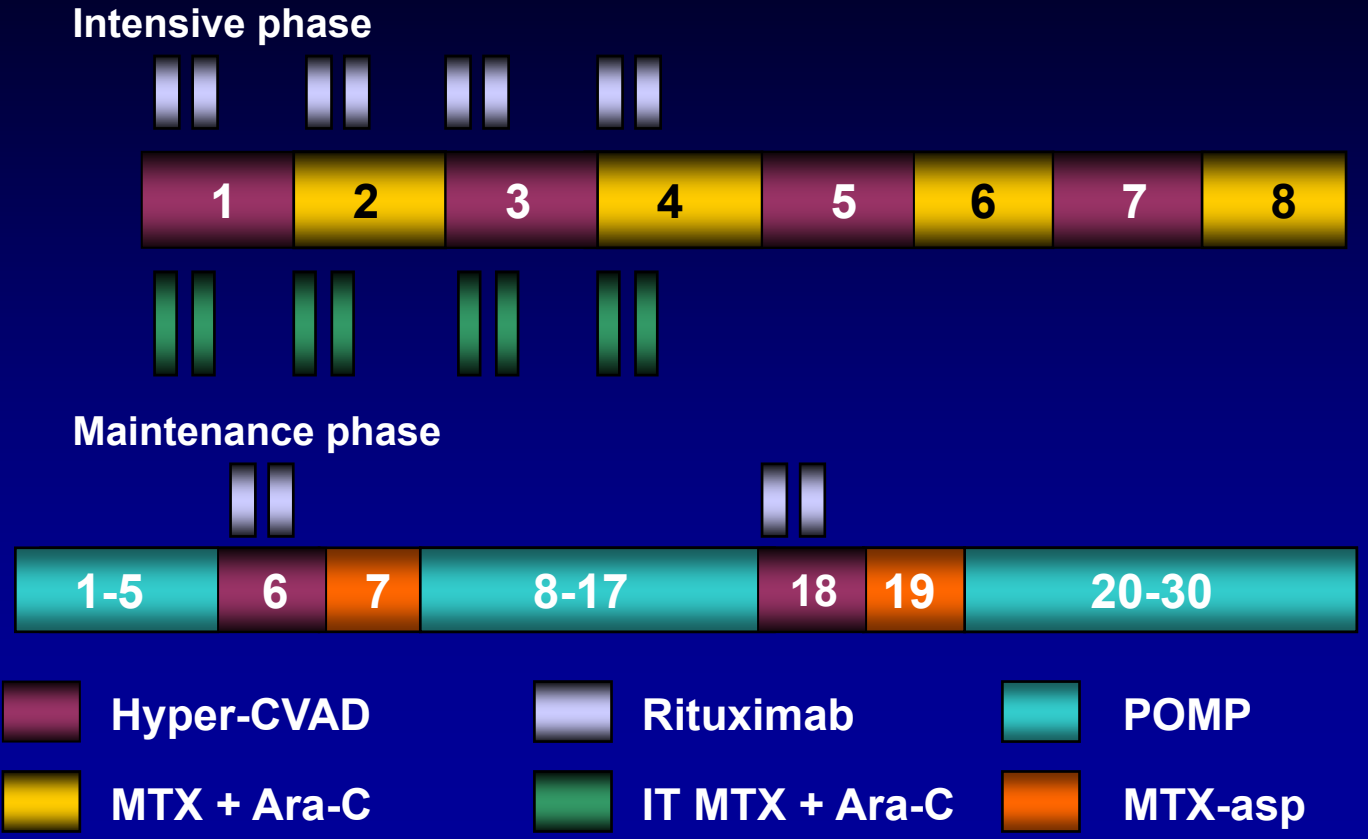


Jabbour E, et al. *Lancet Haematol.* 2022 Nov 16;S2352-3026(22)00319-2.

ALL: Survival by Decade (MDACC 1985–2022)



Hyper-CVAD + Rituximab in Precursor B-ALL

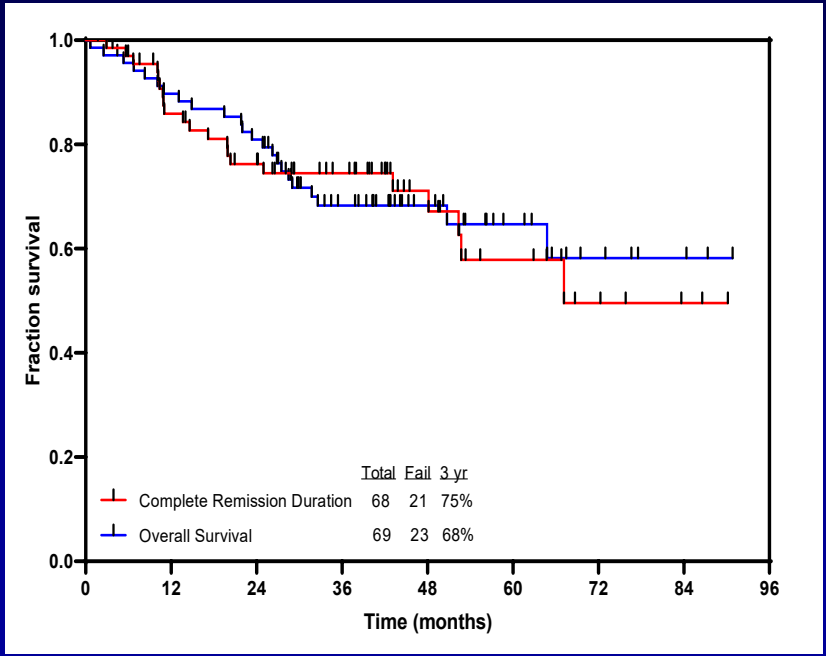


Thomas. *J Clin Oncol.* 2010;28:3880-3889.

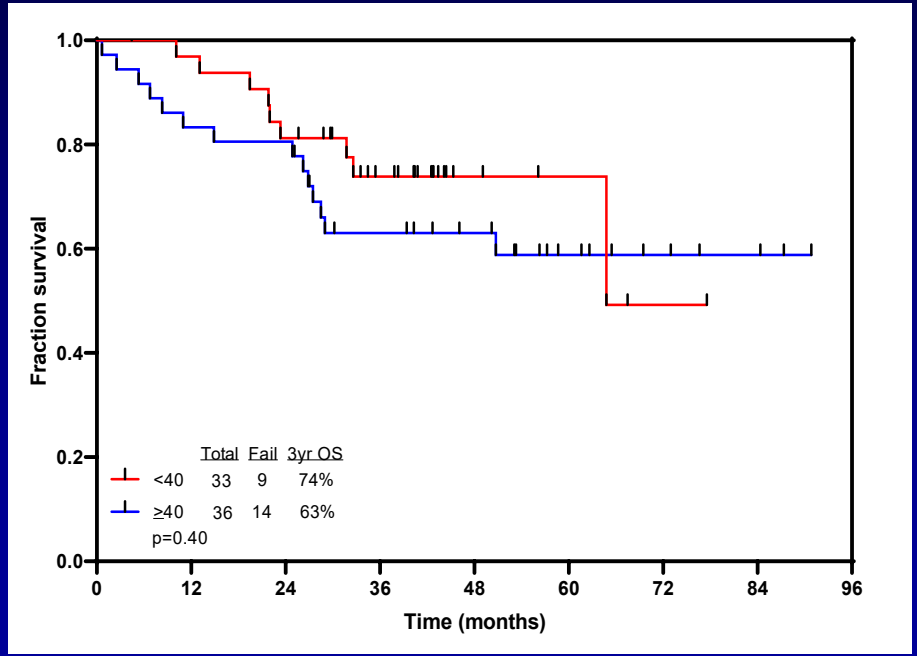
HCVAD + Ofatumumab: Outcomes (N = 69)

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

CRD and OS Overall

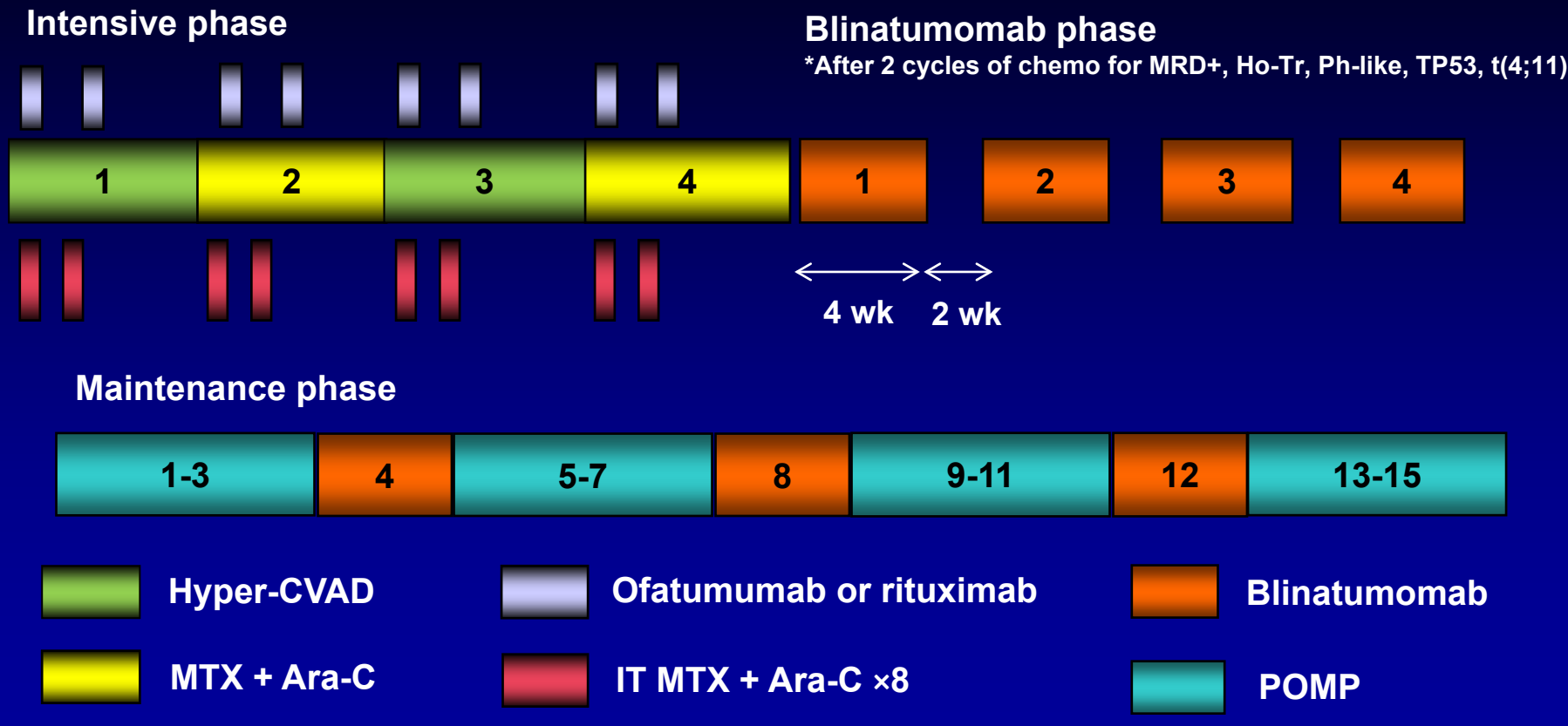


OS by Age



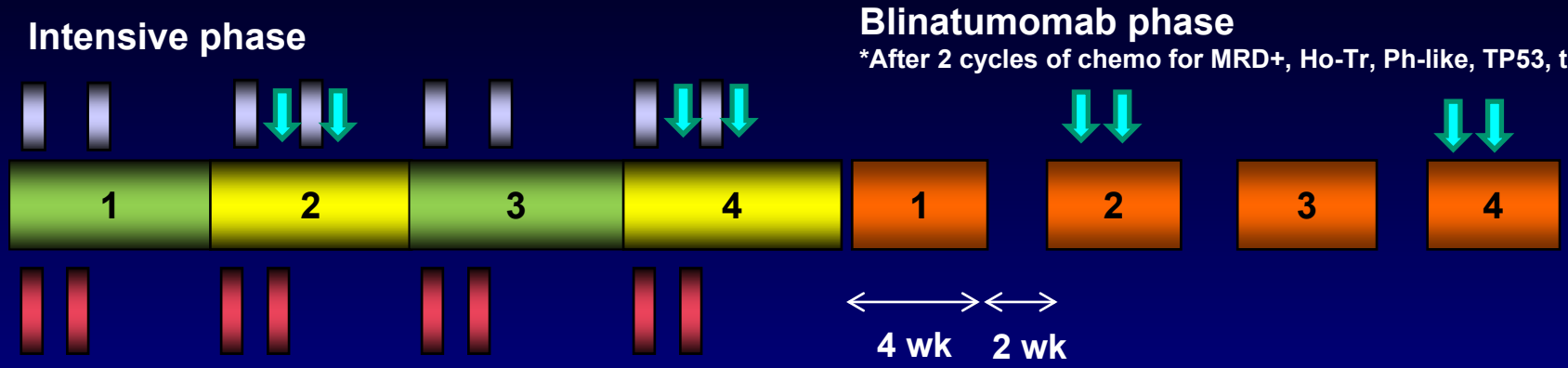
Jabbour E, et al. *Lancet Haematol.* 2020;7:e523-e533.

Hyper-CVAD + Blinatumomab in B-ALL: Regimen (1st cohort; N = 38)



Short NJ, et al. EHA 2022. Abstract P371.

Hyper-CVAD + Blina + InO in B-ALL: Regimen



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

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

IT MTX + Ara-C ×8

POMP

Inotuzumab 0.3 mg/m^2 on D1 and D8

Short NJ, et al. EHA 2022. Abstract P371.

Hyper-CVAD + Blina + InO in B-ALL: Patient Characteristics (N = 63)

Characteristic (N = 63)		Overall (n = 63)	Cohort 1 (n = 38)	Cohort 2 (n = 25)
Age, years [range]		33 [18–59]	37 [18–59]	24 [18–54]
Sex	Male	44 (70)	26 (68)	18 (72)
PS (ECOG)	0–1	52 (83)	30 (79)	22 (88)
WBC (× 10^9/L) [range]		4.3 [0.5–553]	3.12 [0.5–360.9]	8.6 [1.2–553]
CNS disease		6 (10)	4 (11)	2 (8)
CD19 ≥50 %		52/53 (98)	31/32 (97)	21/21 (100)
CD20 ≥20 %		28/54 (52)	17/33 (52)	11/21 (52)
TP53 mutation		14/58 (24)	10/37 (27)	4/21 (19)
CRLF2+		9/53 (17)	6/33 (18)	3/20 (15)
JAK2+		4/58 (7)	2/37 (5)	2/21 (10)
Cytogenetics	Diploid	21 (33)	11 (29)	10 (40)
	Low hypodiploidy/near triploidy	8 (13)	6 (16)	2 (8)
	Complex (≥5 anomalies)	4 (6)	3 (8)	1 (4)
	High hyperdiploidy	5 (8)	3 (8)	2 (8)
	KMT2A rearrangement	5 (8)	3 (8)	2 (8)
	Other	20 (32)	12 (32)	8 (32)

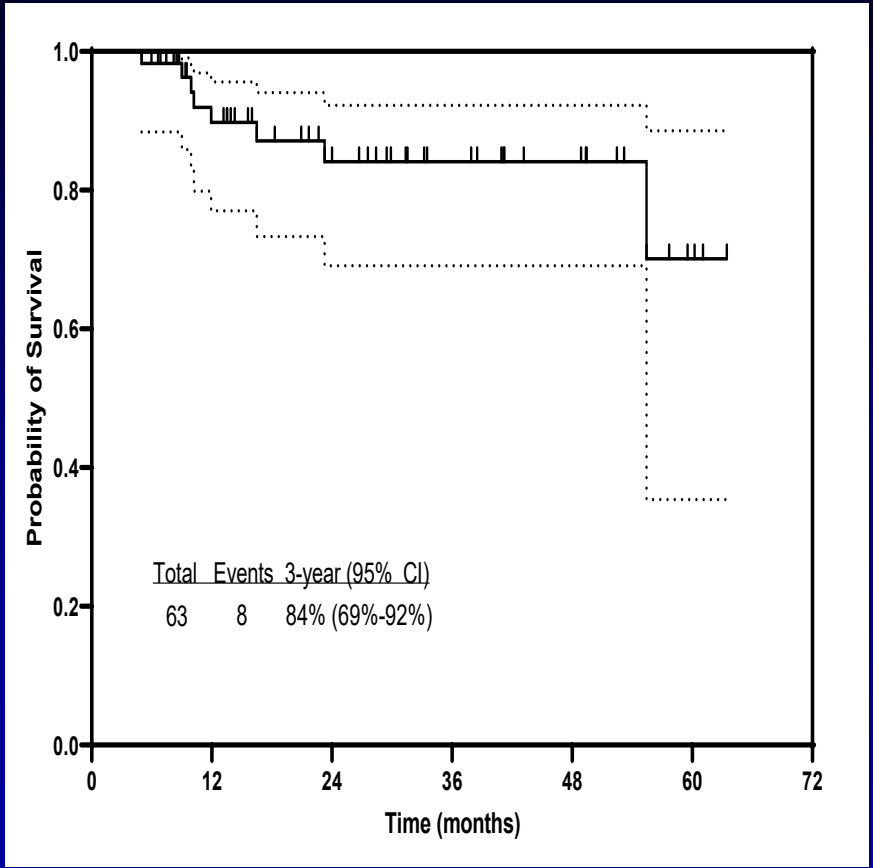
Hyper-CVAD + Blina + InO in B-ALL: Response Rates

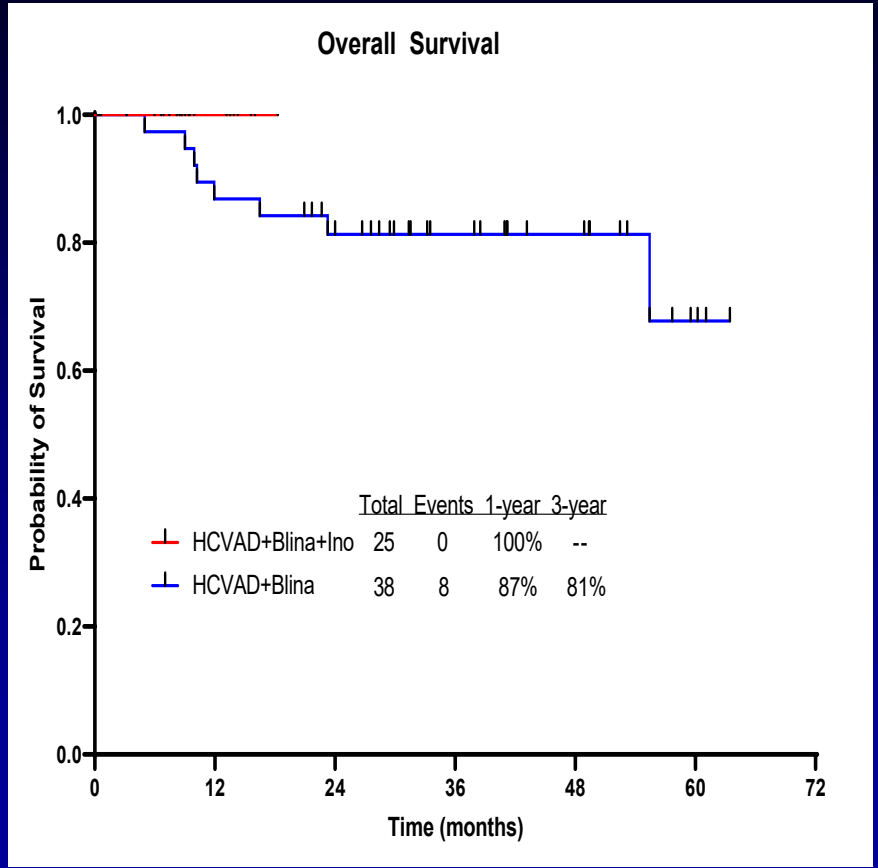
Response assessment	Overall N (%) (N = 63)	Cohort 1 (n = 38)	Cohort 2 (n = 25)
CR after induction	38/47 (81)	26/32 (81)	12/15 (80)
CR at any time	47/47 (100)	32/32 (100)	15/15 (100)
MRD negativity after induction	33/44 (75)	22/26 (85)	11/18 (61)
MRD negativity at any time	58/61 (95)	37/38 (97)	21/23 (91)
NGS MRD negativity at any time	12/20 (60)	1/2 (50)	11/18 (61)
Early death (30-day)	0	0	0

- Six are CR at start (Cohort 1); 8 are CR at start (Cohort 2); 2 are too early
- Median time to MRD negativity: 20 days

Short NJ, et al. EHA 2022. Abstract P371.

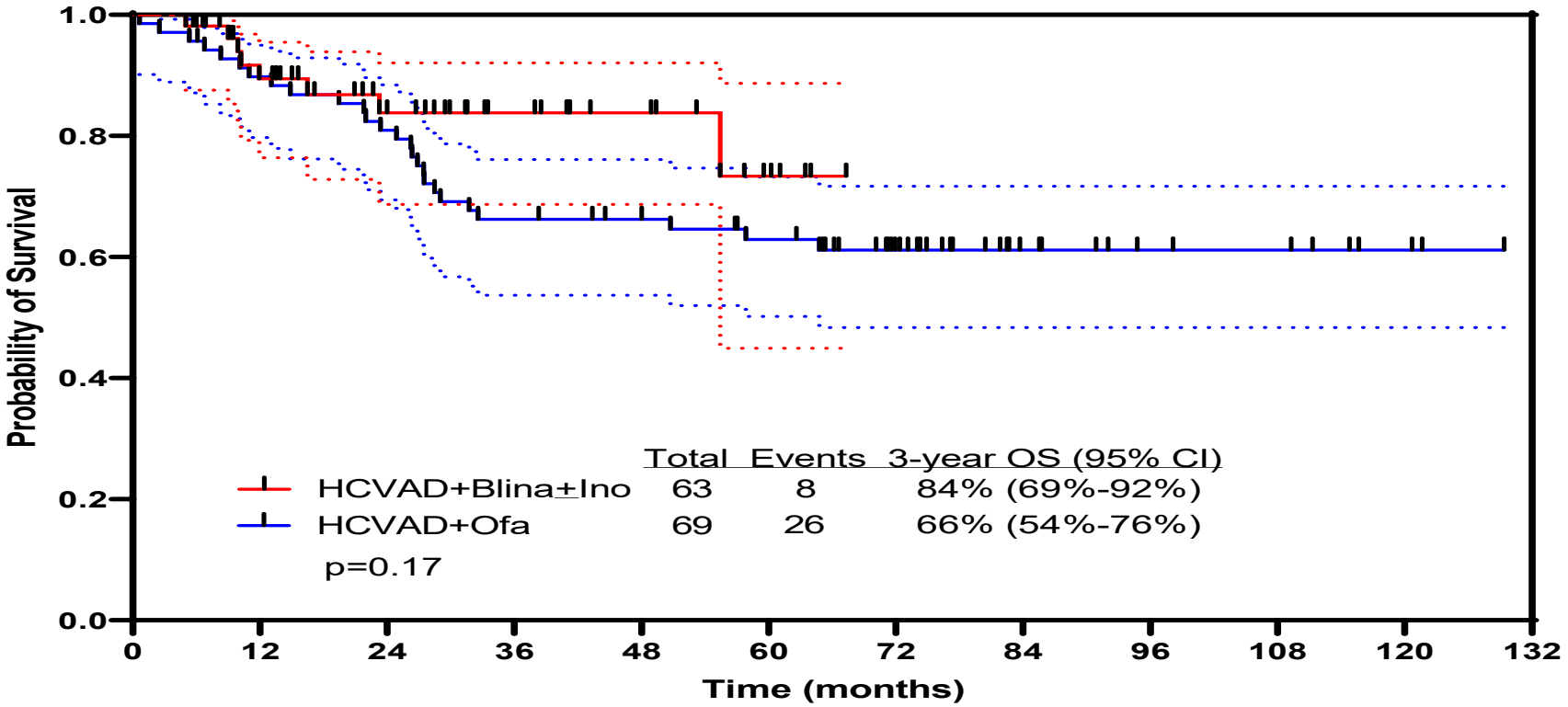
Hyper-CVAD + Blina + InO in B-ALL: Outcomes





Short NJ, et al. EHA 2022. Abstract P371.

Hyper-CVAD + Blina + InO in B-ALL: Outcome vs Historical Control



Short NJ, et al. EHA 2022. Abstract P371.

Single-Cycle Blinatumomab Followed by HD Rx in Ph– ALL: Blina-Cell Trial

- 29 pts; median age 41 yrs (19–65)
- Rx: Run-in phase: Dex-VCR-CTX-Dauno followed by induction 1 blina D12–40 followed by consolidation (GMALL 07/2003)
- 25/27 (93%) CR. No early death; CMR 13/25 (52%) at D40
- Primary endpoint – CMR at week 11: 20/80 (80%)
- 16% received allo-SCT
- F/U 18 months; median OS 18.2 mos and EFS 15.9 mos

Salek et al. *Blood*. 2022;141:abstract1413.

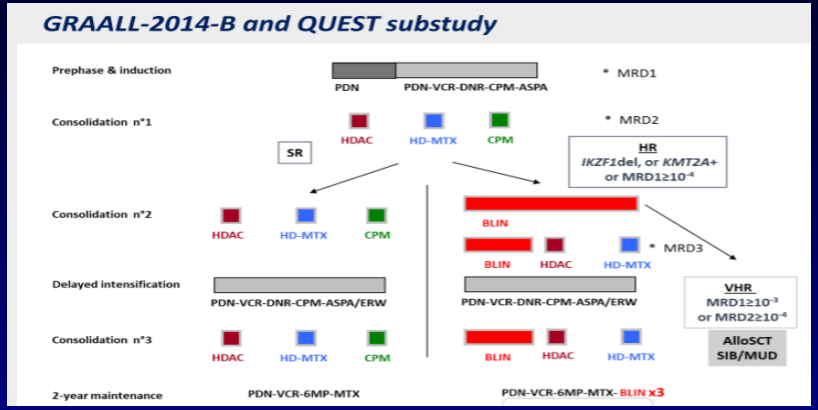
Blinatumomab in Combination With Intensive Pediatric Protocol: Preliminary Results of the ALLG ALL09 "Sublime" Study

- 55 pts; median age 25 yrs (16–39); CNS disease (5.5%)
- Replacement of CTX-Ara-C-6MP with blina in protocol I and II phase 2 vs ALL06
- CR 68% D15, 95% D33, and 100% D79
- MRD negativity 16/47 (34%) D33 and 34/48 (71%) D79
- D79 MRD negativity 71% vs 60% (ALL06; *P* = .037)
- 2 relapses; 6 allo
- 1 CRS; 1 seizure

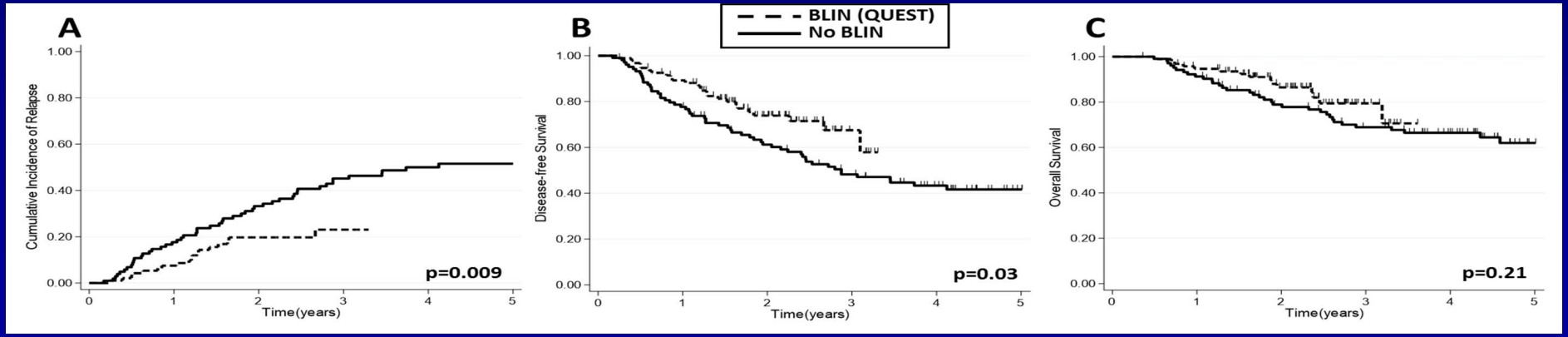
Greenwood et al. *Blood*. 2022;141:abstract 4045.

Blinatumomab Consolidation for HR Frontline Adult B-ALL: GRAALL-2014-QUEST Phase II Study

- 94/266 pts HR Ph– B-ALL Rx blinatumomab at week 12 vs 104 control

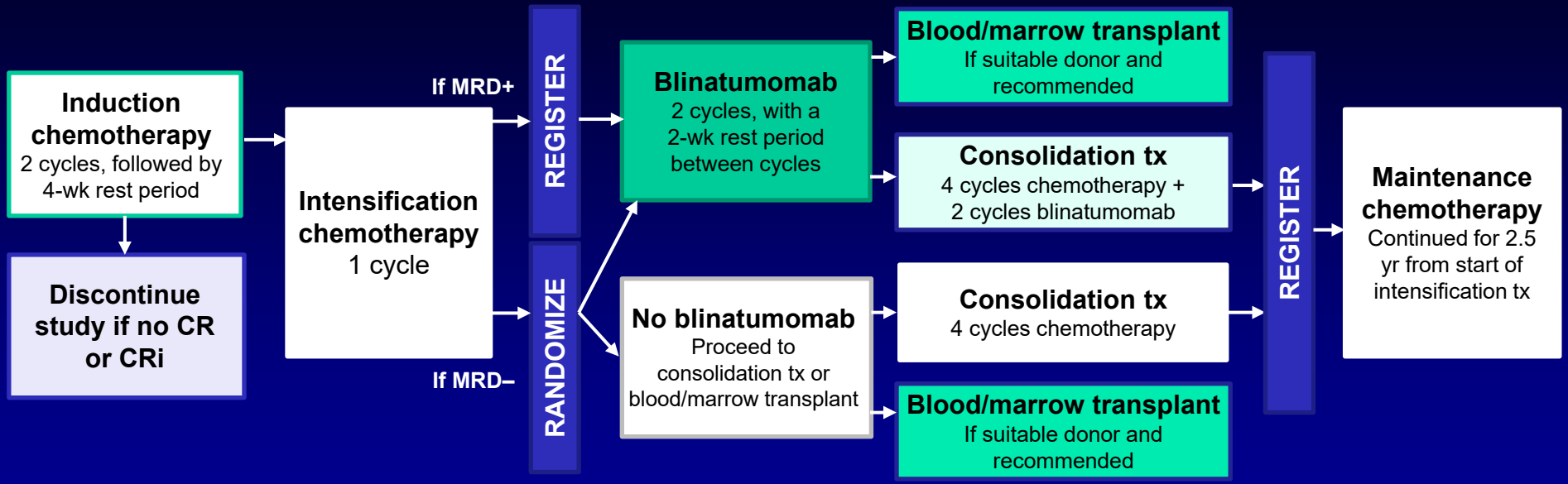


	BLIN (QUEST) n=94	No BLIN N=104	p
Median age (y)	34 (18-59)	36 (18-59)	0.78
Male/Female	51/43	46/58	0.20
Median WBC (G/L)	11.5 [1-449]	7.5 [0-712]	0.27
CNS	0	0	0.99
Genetics			
KMT2A-r	16/94 (17)	23/104 (22)	0.38
*IKZF1*del	37/93 (40)	32/102 (31)	0.23
Early outcome (before conso 2)			
CR	94 (100)	104 (100)	0.99
CR after salvage	5 (5)	10 (10)	0.29
MRD1 ≥ 10^{-4}	66/92 (72)	76/96 (79)	0.31
MRD2 ≥ 10^{-4}	43/89 (48)	38/95 (40)	0.30
Late outcome (after conso2)			
$MRD3_{neg}$	62/86 (72)	42/79 (53)	0.02
$MRD3_{neg}$ if MRD2 ≥ 10^{-4}	23/41 (56)	4/29 (14)	<0.001
Allo-HSCT rate	44 (47%)	38 (37%)	0.15
Median follow-up	2.3	4.3	<0.001
2.5y-CIR (95%CI)	20% (13-30)	41% (32-51)	0.009
2.5y-DFS (95%CI)	72% (60-80)	54% (43-63)	0.03
2.5y-OS (95%CI)	79% (67-88)	76% (66-83)	0.21



Boissel et al. *Blood.* 2022;141:abstract 211.

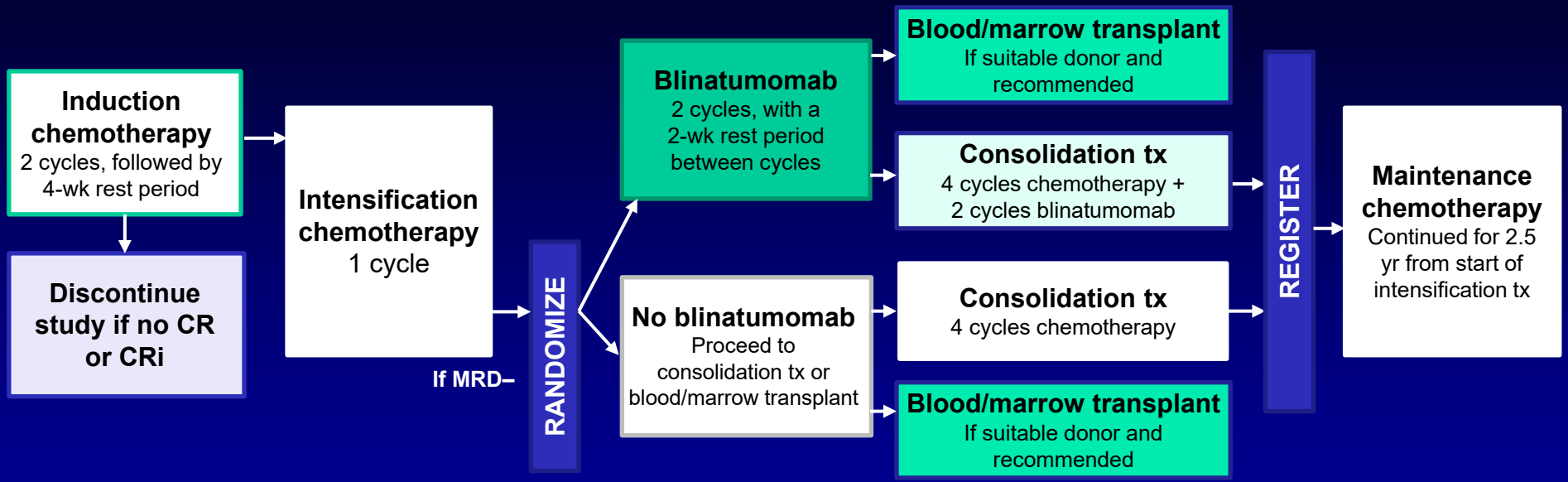
E1910 Randomized Phase III Trial: Blina vs SOC as Consolidation in MRD– CR



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

https://clinicaltrials.gov/ct2/show/NCT02003222

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



- Accrual = 488
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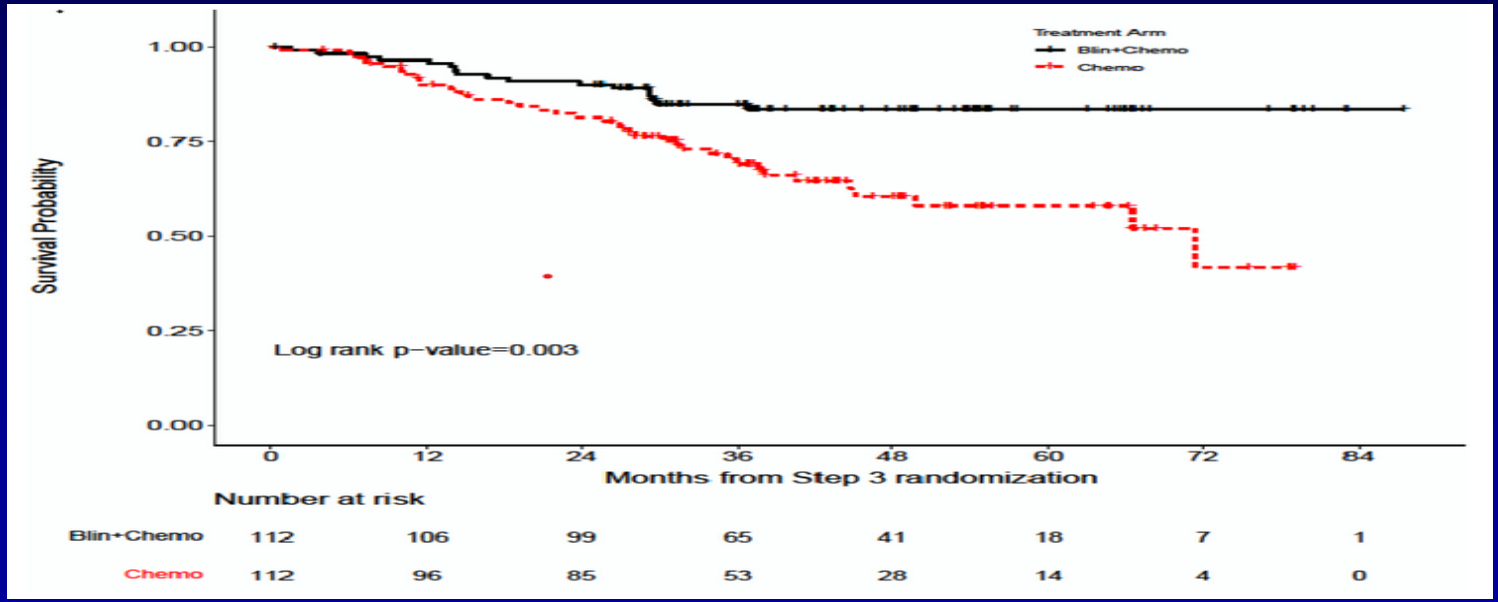
- USA, Canada, Israel
- 1:1 randomization

Litzow et al. *Blood.* 2022;141:abstract LBA-1.

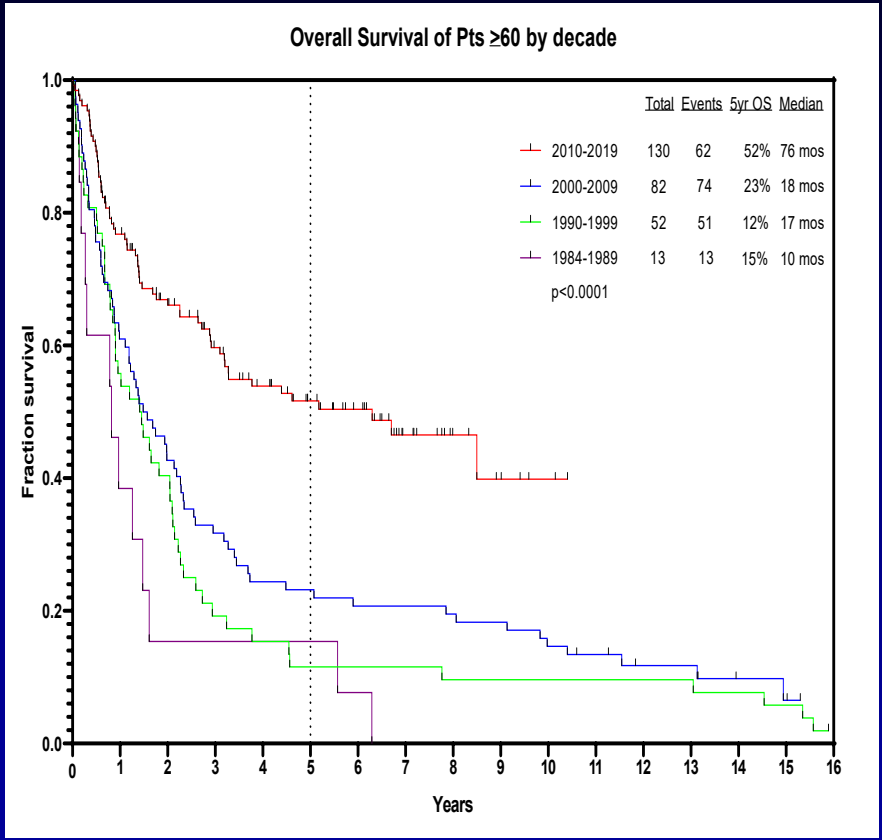
E1910 Randomized Phase III Trial: Blina vs SOC as Consolidation in MRD– CR

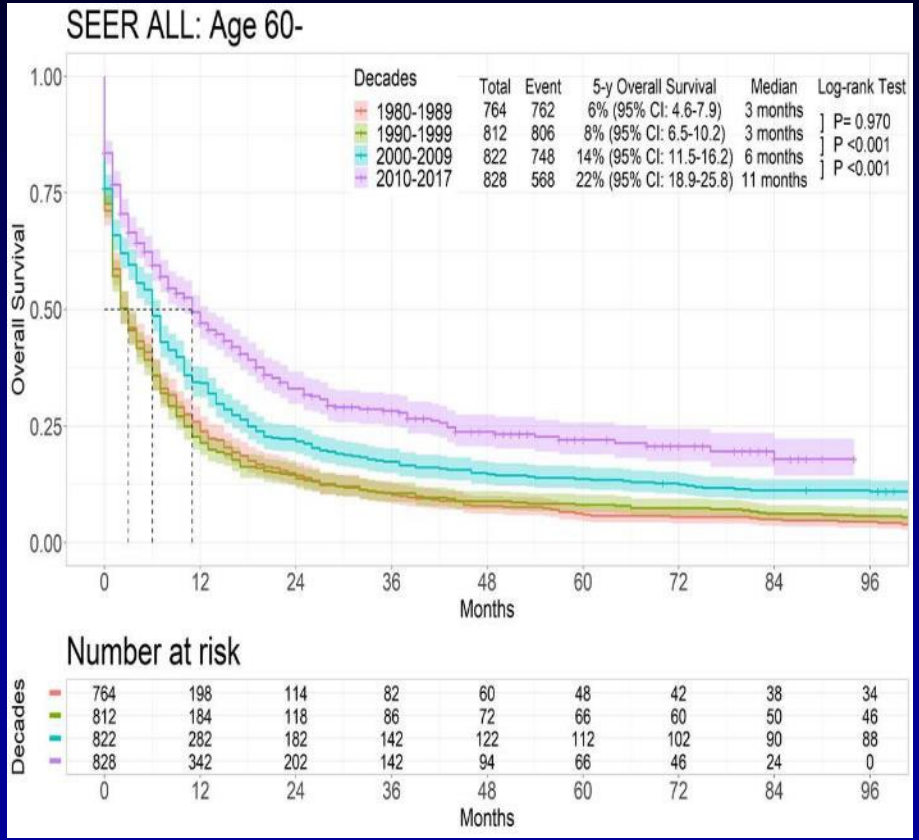
- 488 pts; median age 51 yrs (30–70)
- 224 MRD– CR randomized 1:1
- 22 pts (20%) Rx ASCT in each arm
- Median F/U 43 months; median OS NR vs 71.4 mos (HR = 0.42; *P* = .003)



Litzow et al. *Blood.* 2022;141:abstract LBA-1.

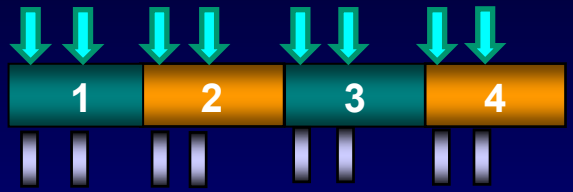
MDACC ALL: Survival by Decades for ≥60 Years



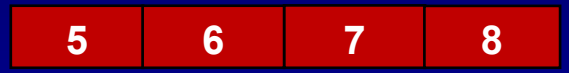


Mini-HCVD + INO ± Blina in Older ALL: Modified Design

Intensive phase



Consolidation phase



Maintenance phase

Mini-HCVD

Mini-MTX + Ara-C

IT MTX + Ara-C

Blinatumomab

POMP

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

Total INO dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis

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

Mini-HCVD + INO ± Blina in Older ALL (N = 80)

Characteristic	Category	N (%) / median [range]
Age (years)	≥70	68 [60–87] 30 (38)
Performance status	≥2	10 (13)
WBC ($\times 10^9$/L)		3.1 [0.3–111.0]
Karyotype	Diploid HeH Ho-Tr Tetraploidy Complex t(4;11) Misc IM/ND	26 (33) 5 (6) 12 (15) 3 (4) 3 (4) 1 (1) 15 (19) 15 (19)
CNS disease at diagnosis		4 (5)
CD19 expression (%)		99.5 [26–100]
CD22 expression (%)		96.9 [27–100]
CD20 expression	≥20%	44/73 (60)
Ph-like ALL		9/47 (19)
TP53 mutation		24/61 (39)

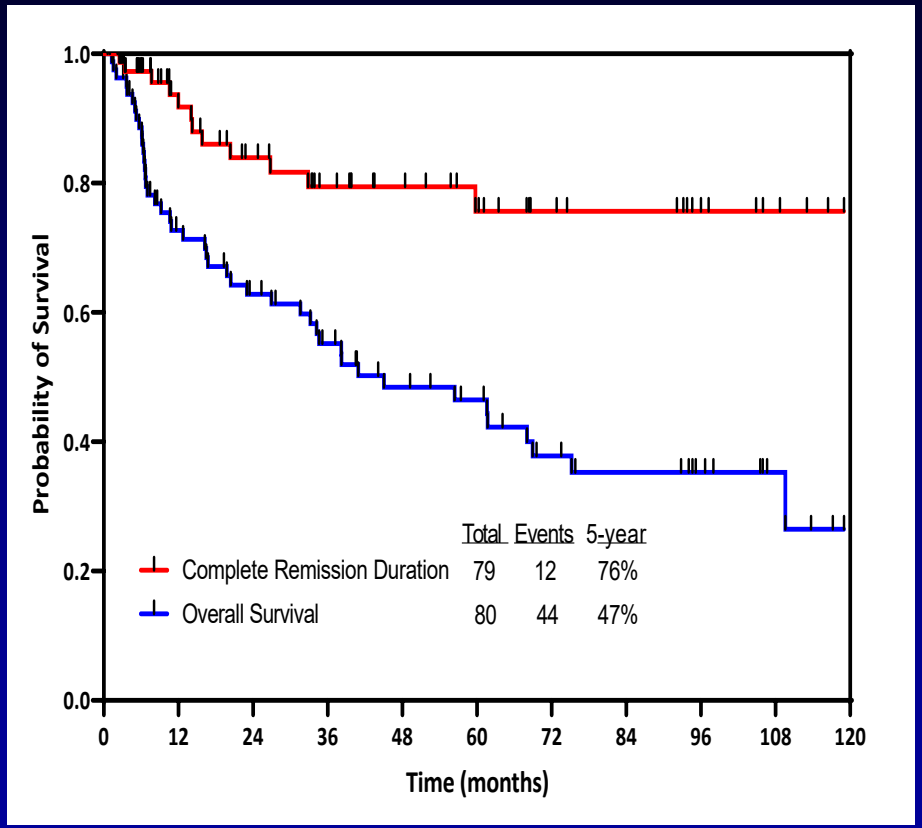
Response (N = 74*)	N (%)
ORR	73 (99)
CR	66 (89)
CRp	6 (8)
CRi	1 (1)
No response	1 (1)
Early death	0

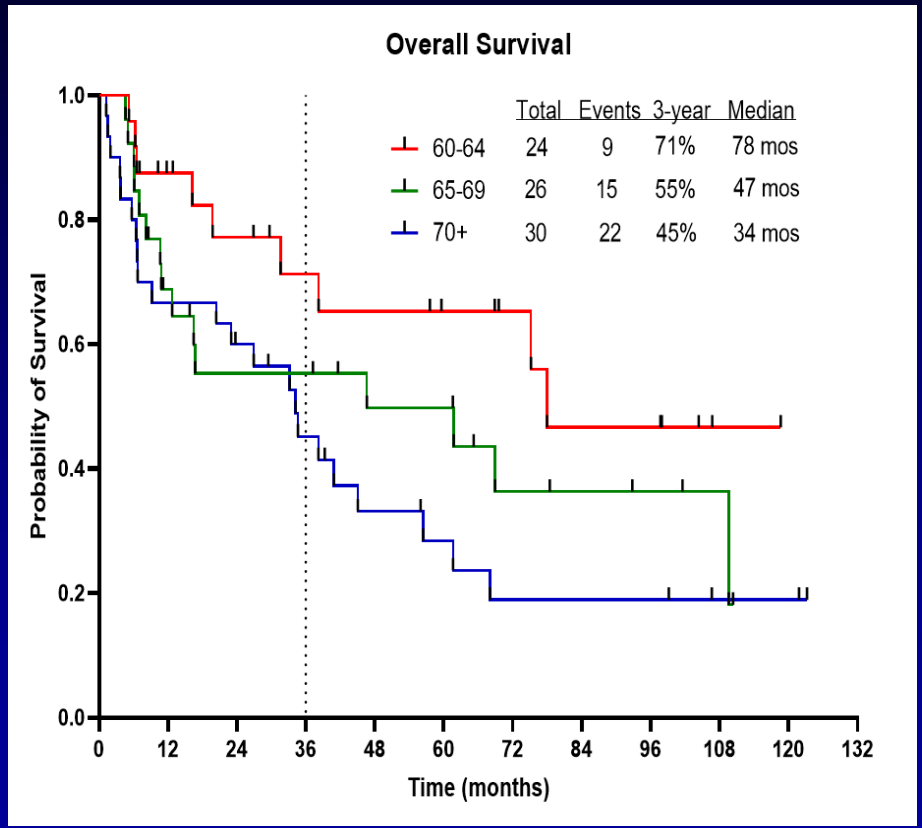
Flow MRD response	N (%)
Cycle 1, Day 21	61/76 (80)
Overall	74/79 (94)

*Six pts were enrolled in CR

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

Mini-HCVD + INO ± Blina in Older ALL: Outcomes

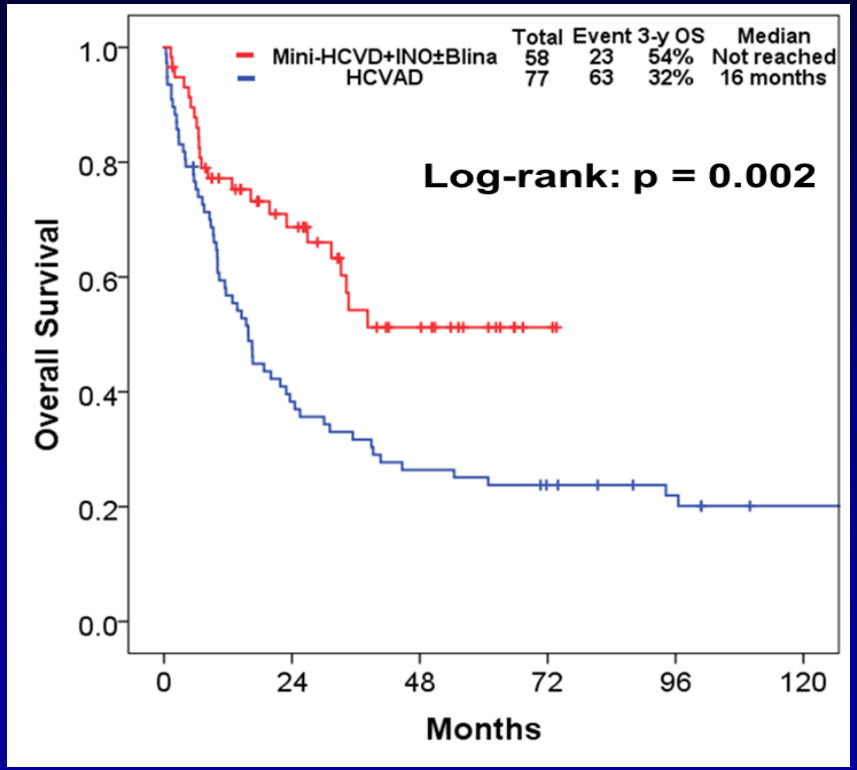




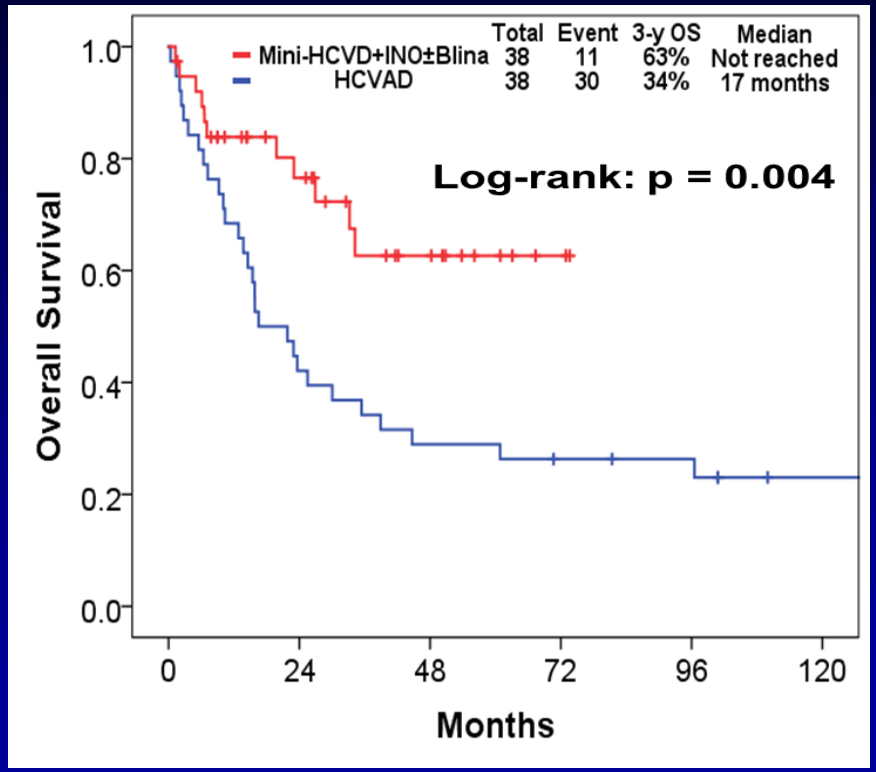
Haddad F, et al. EHA 2022. Abstract P355.

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

Pre-matched

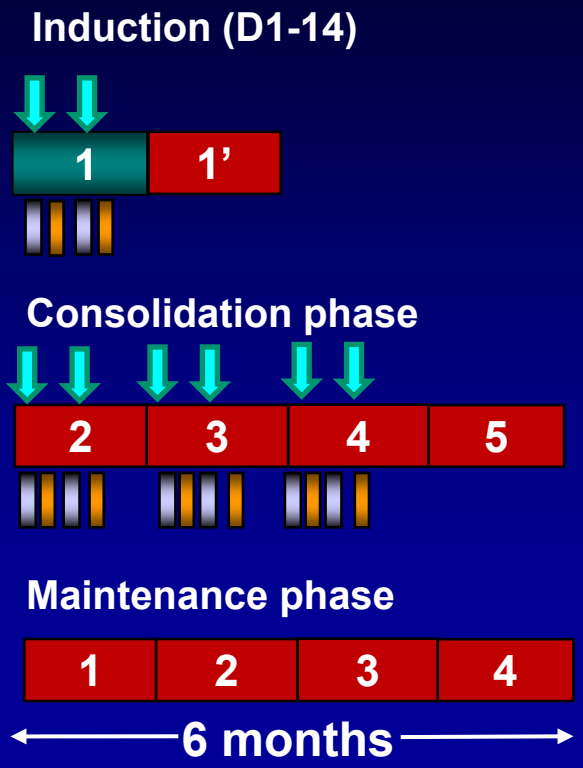


Matched



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

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



Dexa 20 mg D1–4 and VCR 1 mg D4

Blinatumomab

IT MTX + Ara-C

Rituximab if CD20+

1' Blinatumomab for 2 weeks

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

Total INO dose = 2.7 mg/m^2

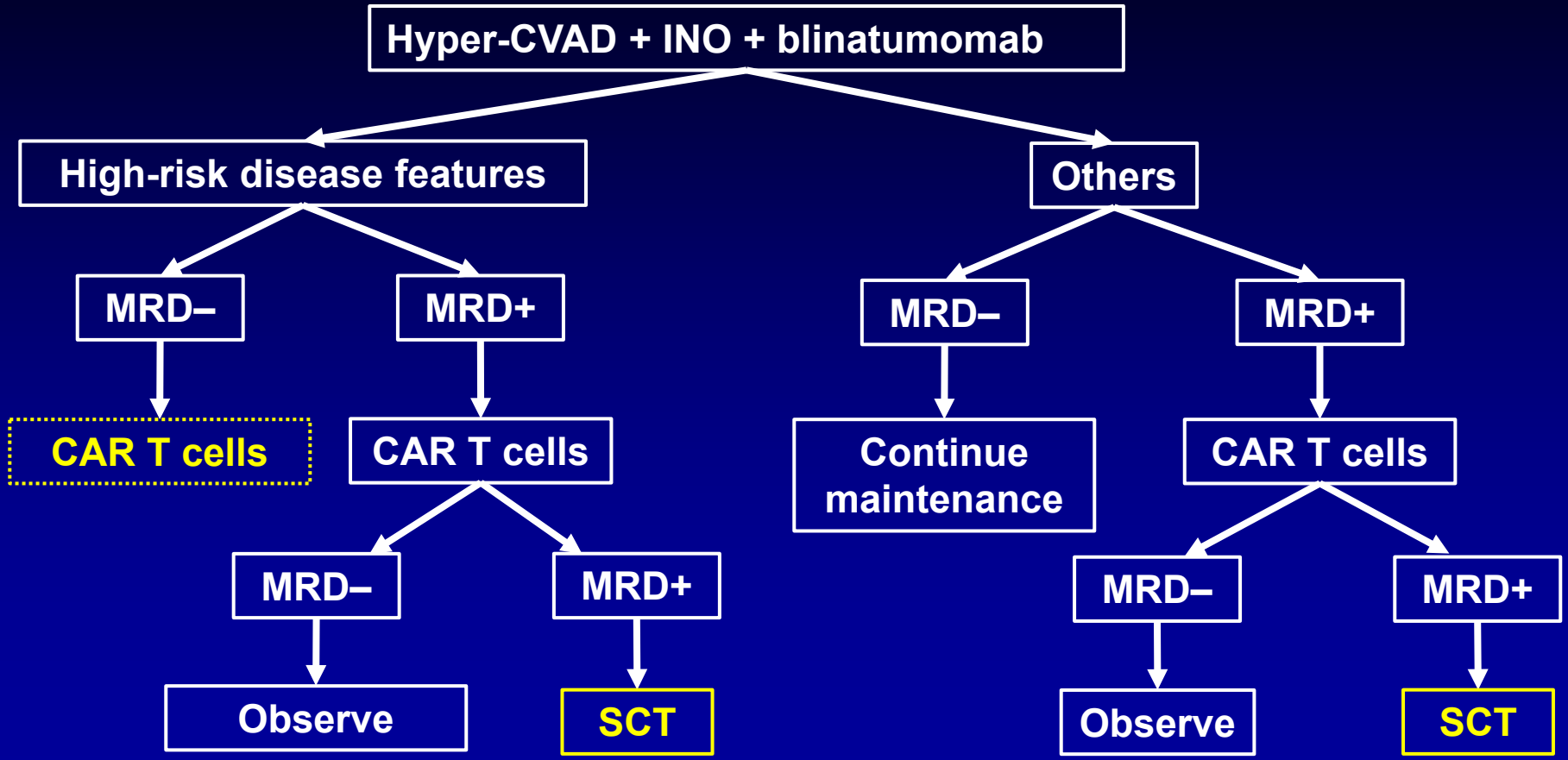
*Ursodiol 300 mg tid for VOD prophylaxis

Frontline Blina and Inotuzumab Combinations in Newly Dx Older ALL

	Agent	N	Median Age (yrs, range)	% CR	% MRD negativity	% OS (x-yr)
Mini-HCVD-INO-blina	Blinatumomab and inotuzumab	80	68 (60–87)	89	47	55 (8-yr)
SWOG-1318	Blinatumomab	31	73 (66–86)	66	92	37 (3-yr)
EWALL-INO	Inotuzumab	115	69 (55–84)	88	73	78 (1-yr)
GMALL Bold	Blinatumomab	34	65 (56–76)	76	69	89 (1-yr)
INITIAL-1	Inotuzumab	45	65 (56–80)	100	74	77 (2-yr)

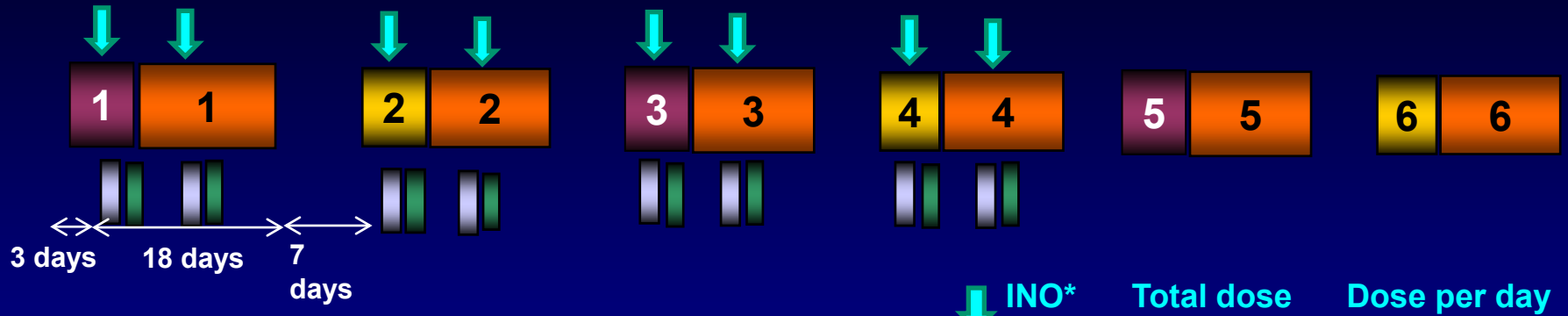
Short. *Blood.* 2021;138:3400; Advani. *J Clin Oncol.* 2022 Feb 14; Chevallier. *Blood.* 2021;140:abstract 511; Goekbuget. *Blood.* 2021;140:abstract 3399; Stelljes. *Blood.* 2021;140:abstract 2300.

Algorithm for Ph-Negative B-ALL in 2022+



Dose-Dense Mini-HCVD + INO + Blina + CAR T Cells in ALL: The CURE

Induction phase: C1–C6



Consolidation phase

CAR T Consolidation

↓ INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2–C4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis

Mini-Hyper-CVD

Rituximab

Mini-MTX + Ara-C

IT MTX + Ara-C

Blinatumomab

ALL Summary

- Significant progress and improved outcomes across all ALL categories: Ph+, 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) CAR Ts in sequence in CR1 for MRD and replacing allo-SCT
- Importance of MRD testing and changing Rx accordingly

Thank You

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Global Leukemia Academy

Current Treatment Options for Relapsed ALL in Adult and Elderly Patients

Jae Park

APTITUDE HEALTH

Current Treatment Options for Relapsed ALL in Adults and Elderly Patients

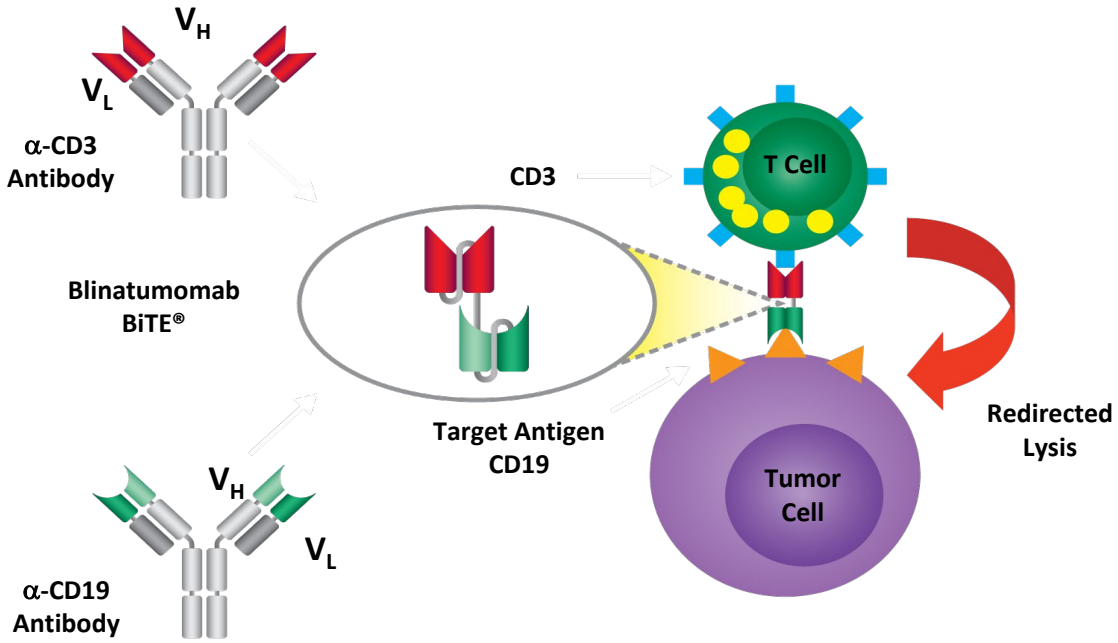
Jae H. Park, MD
Associate Attending Physician
Director, Adult ALL Clinical Program
Acting Chief, Cellular Therapeutics Service
Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

Adult ALL: Key Breakthroughs

- Novel effective immunotherapies
  - Technologies to engage tumor antigen and activate endogenous T cells → blinatumomab (CD19-CD3 bispecific T-cell engager)
  - Tumor antigen-specific antibody conjugated to chemotherapy → inotuzumab ozogamicin (CD22 mAb-calicheamicin)
  - Technologies to modify autologous T cells ex vivo to target ALL cells → CAR T cells
- Well-established prognostic role of **MRD** ***and*** actionable
- Targeted agents: BCL antagonists (eg, venetoclax, navitoclax)

Blinatumomab: T-Cell–Engaging BiTE Antibody



- Blinatumomab is a **bispecific T-cell engager antibody** designed to direct cytotoxic T cells to CD19-expressing cancer cells

Bargou R, et al. *Science.* 2008;321:974-977.

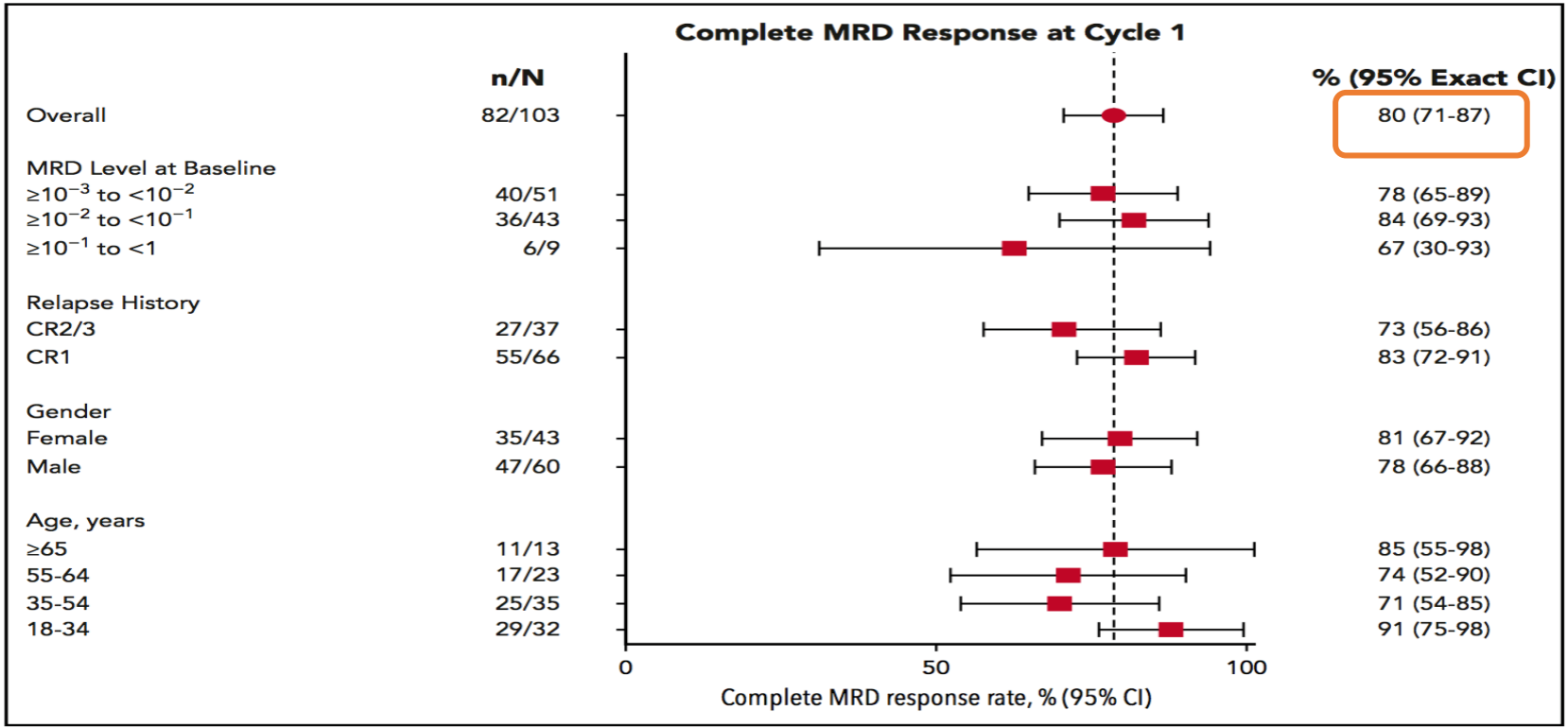
Blinatumomab in MRD+ B-ALL

- **Eligibility criteria**
  - *First or later* CR *AND*
  - Persistent or recurrent **MRD ≥10^{-3}** after minimum 3 blocks of intense chemo
- **Primary endpoint**
  - MRD CR after 1 cycle
- **Secondary endpoint**
  - RFS at 18 months

Characteristic	Patients (n = 116)
Relapse history, n (%)	
In first CR	75 (65)
In second CR	39 (34)
In third CR	2 (2)
Baseline MRD levels	
≥10^{-1} to <1	9 (8)
≥10^{-2} to <10^{-1}	45 (39)
≥10^{-3} to <10^{-2}	52 (45)
<10^{-3}	3 (3)

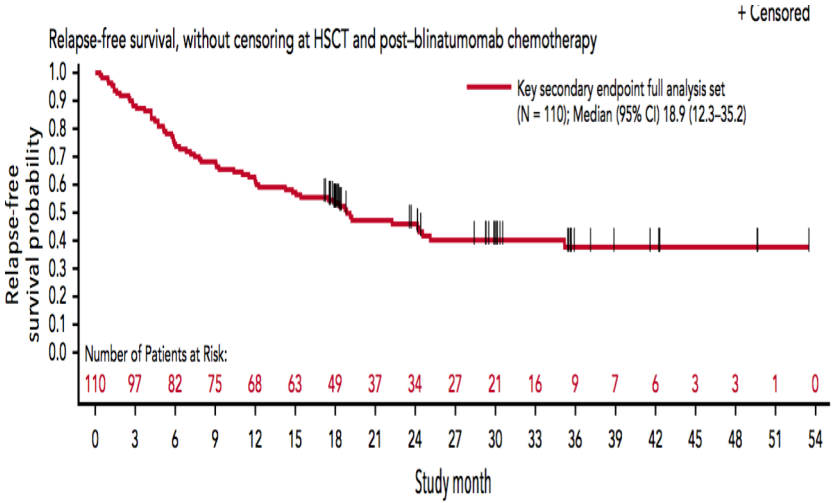
Gökbuget N, et al. *Blood.* 2018;131(14):1522-1531.

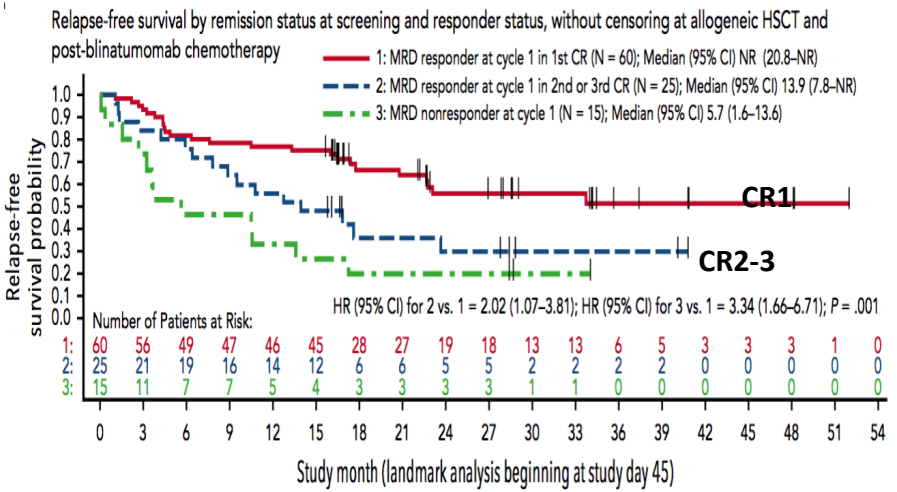
CR Rates by Subgroups in MRD+ B-ALL



Gökbuget N, et al. *Blood.* 2018;131(14):1522-1531.

RFS of MRD+ ALL Patients After Blinatumomab





70% of pts proceed to alloHSCT

Gökbuget N, et al. *Blood.* 2018;131(14):1522-1531.

Phase II Study of Blinatumomab in R/R Ph+ B-ALL (ALCANTARA)

Characteristic	Patients (N = 45) No.	%
Sex		
Male	24	53
Female	21	47
Median age, years (range)	55 (23-78)	
Age group, years		
18 to < 55	22	49
≥ 55	23	51
Cytogenetics and molecular analyses*		
Philadelphia chromosome and other cytogenetic abnormalities	22/38	58
ABL1 kinase domain mutations	17/37	46
T315I mutation	10/37	27
No. of prior TKI treatments†		
1	7	16
2	21	47
3	13	29
4	4	9
Prior TKI‡	45	100
Imatinib	25	56
Dasatinib	39	87
Nilotinib	16	36
Ponatinib	23	51
Prior alloHSCT		
Yes	20	44
No	25	56
Bone marrow blasts (central review)		
< 10%	2	4
10% to < 50%	9	20
50% to < 75%	6	13
≥ 75%	28	62

Eligibility Criteria

- Relapsed after or refractory to at least one 2nd/3rd-gen TKI
- Intolerant or refractory to imatinib
- >5% BM blasts

Exclusion Criteria

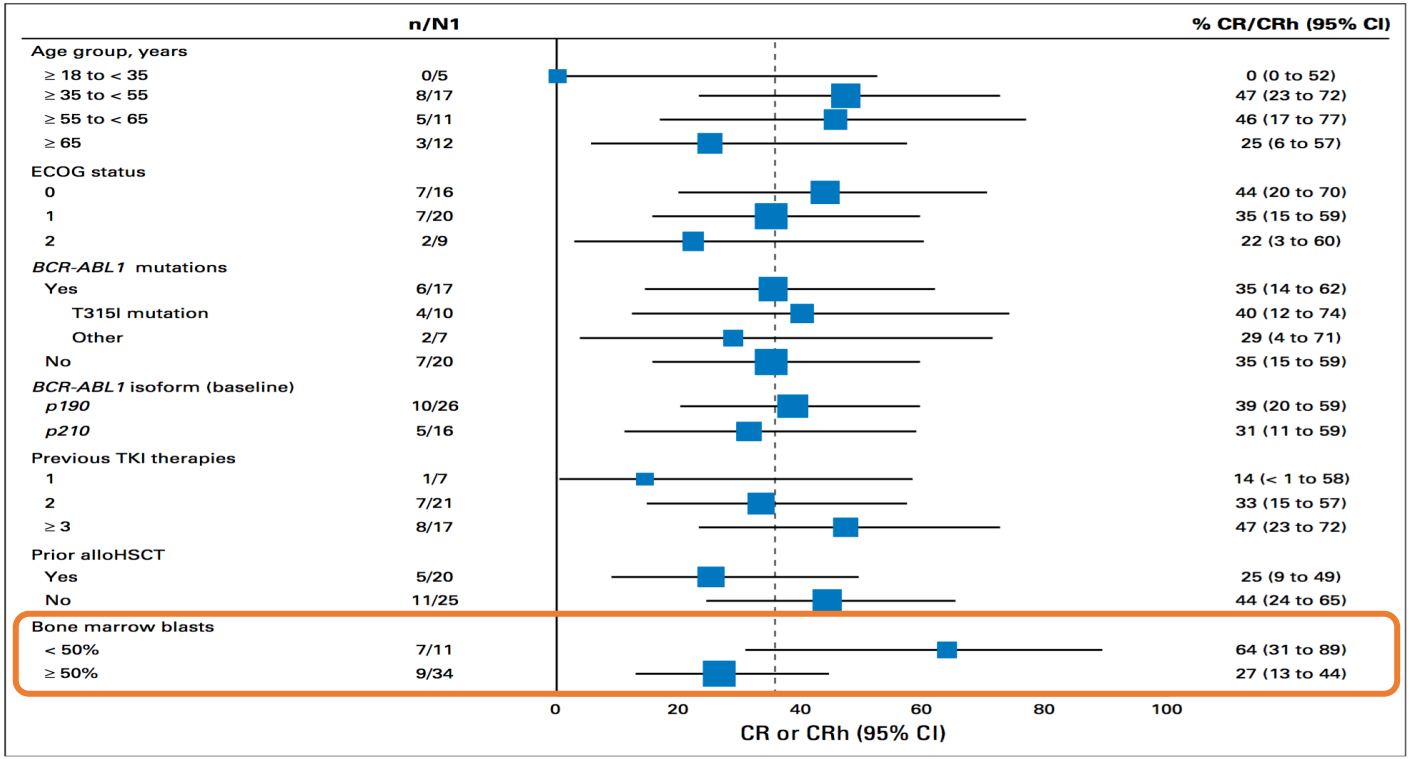
- AlloHSCT within 12 weeks; active GvHD
- Active CNS disease, isolated EM disease

Treatment Scheme

- 9 µg/d in week 1 → 28 µg/d week 2-4 at 4-weeks-on/2-weeks-off schedule
- Pts with >50% BM blasts or ≥15K PB blasts → *prephase tx with Dex 10 mg/m²/d* for up to 5 days
- If CR/CRh, receive up to 3 additional cycles (ie, total cycles = 5)

Martinelli G, et al. *J Clin Oncol.* 2017;35(16):1795-1802.

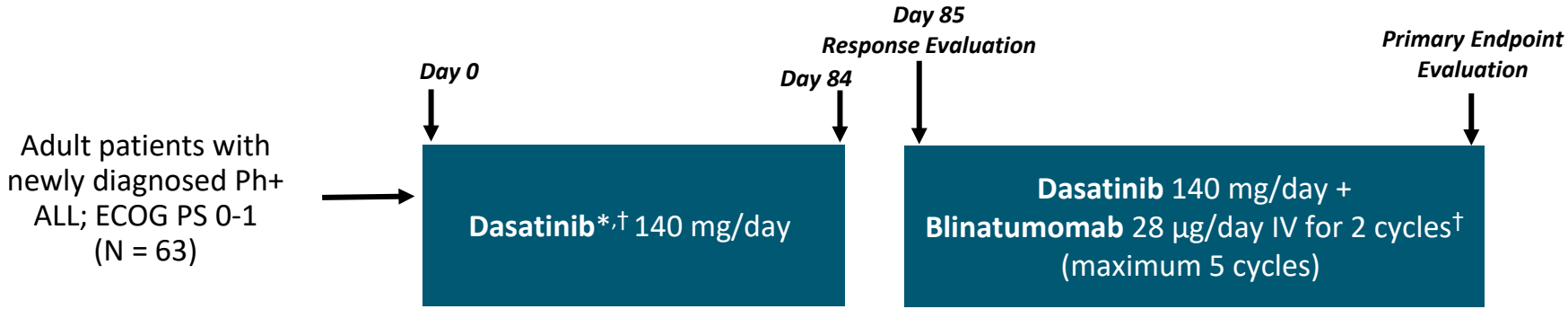
CR/CRh by Subgroups (ALCANTARA)



Martinelli G, et al. *J Clin Oncol.* 2017;35(16):1795-1802.

Blinatumomab + Dasatinib for Frontline Ph+ ALL

- Multicenter, phase II study

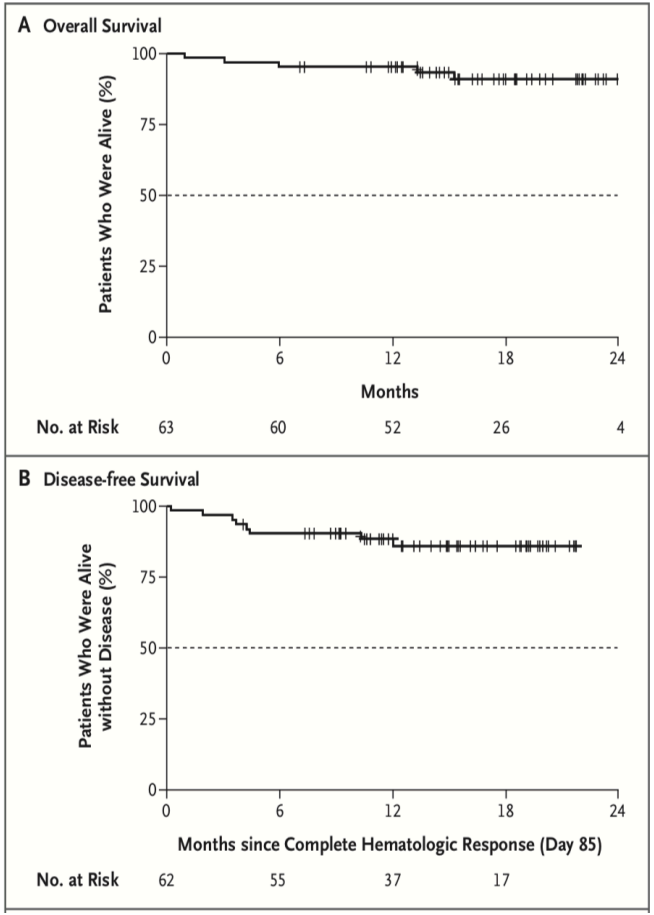


*Prednisone administered from day -6 to day 0 at escalating doses up to 60 mg/m^2; continued up to day 24 and tapered to day 31.
†CNS prophylaxis throughout treatment.

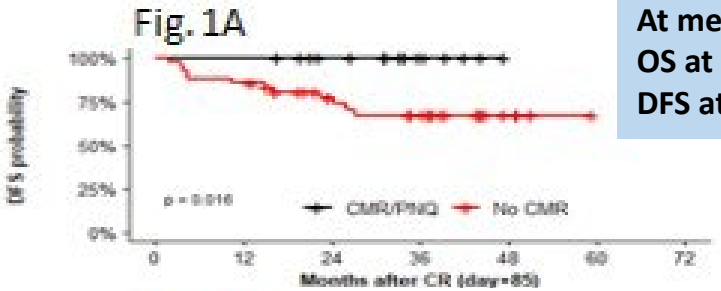
- Primary endpoint: CMR and MRD negativity after 2 cycles
- Secondary endpoints: CMR after dasatinib induction, CMR duration, OS, DFS, CIR, safety, MRD change after blinatumomab

Chiaretti S, et al. ASH 2019. Abstract 740.

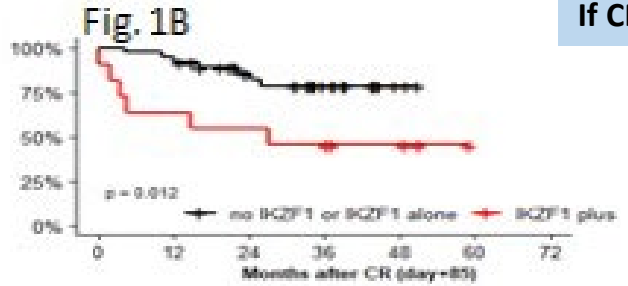
Blinatumomab + Dasatinib for Frontline Ph+ ALL



Updated Results



At median follow-up of 40 mo
OS at 4 years: 78%
DFS at 4 years: 75%



If CMR after induction, DFS 100%

Allogeneic HSCT in 24 pts (38%)

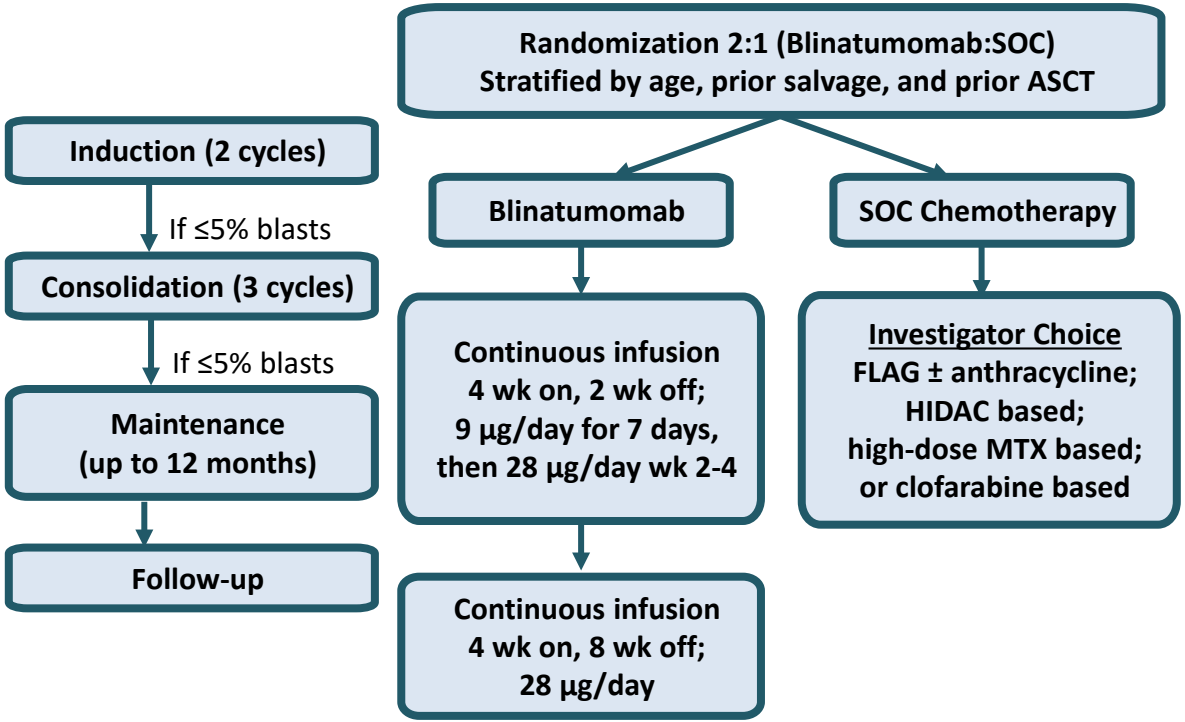
Foa R, et al. *N Engl J Med.* 2020;383:1613-1623; EHA 2022. Abstract P353.

Blinatumomab vs SOC (TOWER) in R/R B-ALL

Eligible Patients

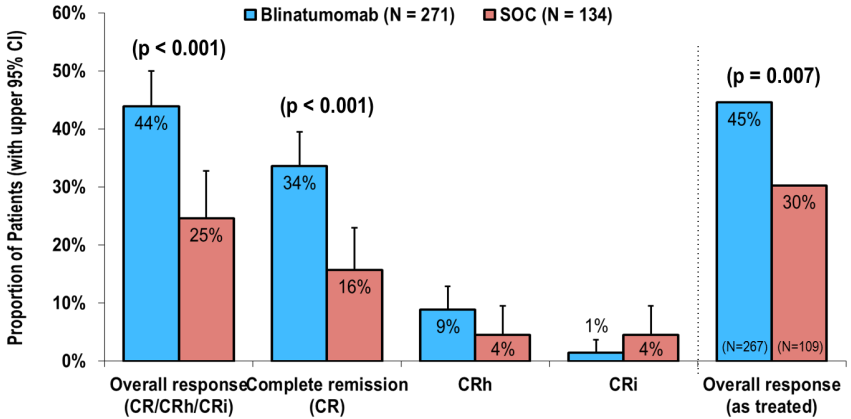
- Primary refractory or refractory to salvage, or
- 1st relapse, <12 mo, or
- ≥2nd relapse, or
- Relapse after alloHSCT

- >5% BM blasts

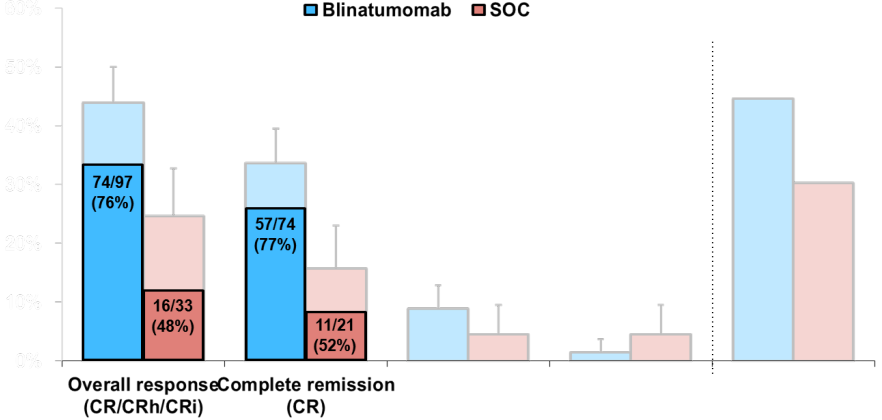


Topp MS, et al. EHA 2016. Abstract S149.

TOWER Results: Response in Induction



Hazard ratio for EFS 0.55 (0.43, 0.71); p < 0.001

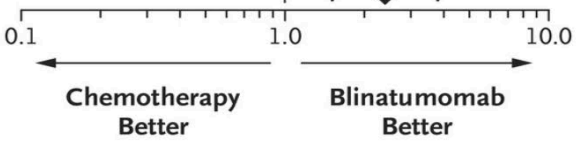


Molecular remission was defined as $<10^{-4}$ blasts in the first 12 weeks

Topp MS, et al. EHA 2016. Abstract S149; Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

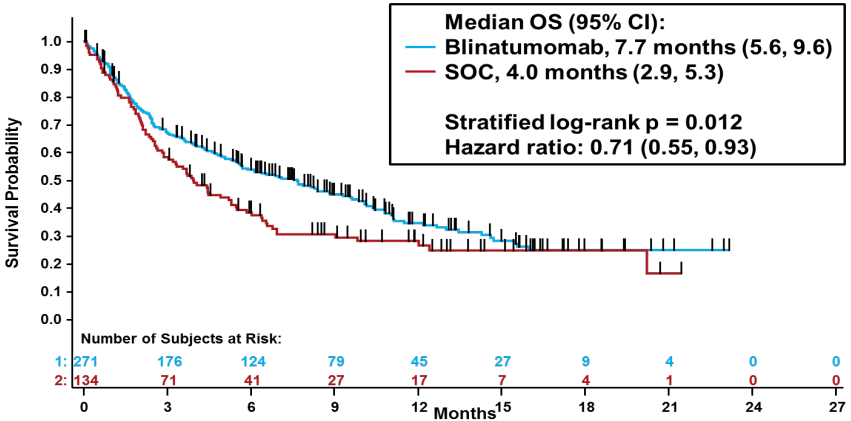
TOWER Results: CR Rates by Prespecified Subgroups

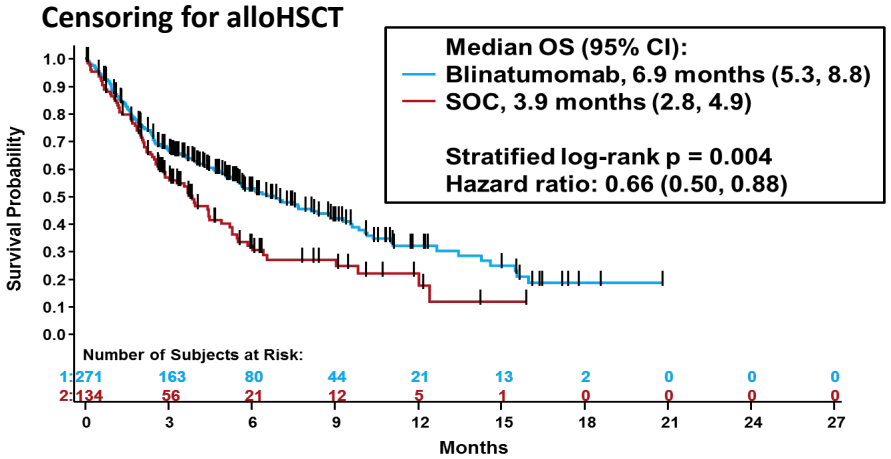
Subgroup	Blinatumomab	Chemotherapy	Odds Ratio (95% CI)
	no. of events/no. of patients (%)		
Age			
<35 yr	53/123 (43.1)	15/60 (25.0)	2.27 (1.15–4.50)
≥35 yr	66/148 (44.6)	18/74 (24.3)	2.50 (1.34–4.66)
Salvage-treatment phase			
First	60/114 (52.6)	23/65 (35.4)	2.03 (1.08–3.80)
Second	36/91 (39.6)	7/43 (16.3)	3.37 (1.35–8.38)
Third or later	23/66 (34.8)	3/26 (11.5)	4.10 (1.11–15.12)
Previous allogeneic stem-cell transplantation			
Yes	38/94 (40.4)	5/46 (10.9)	5.56 (2.02–15.36)
No	81/177 (45.8)	28/88 (31.8)	1.81 (1.06–3.09)
Bone marrow blasts			
<50%	55/84 (65.5)	13/38 (34.2)	3.65 (1.63–8.17)
≥50%	64/186 (34.4)	20/96 (20.8)	1.99 (1.12–3.55)
Overall	119/271 (43.9)	33/134 (24.6)	2.40 (1.51–3.80)



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

TOWER Results: Overall Survival (ITT)



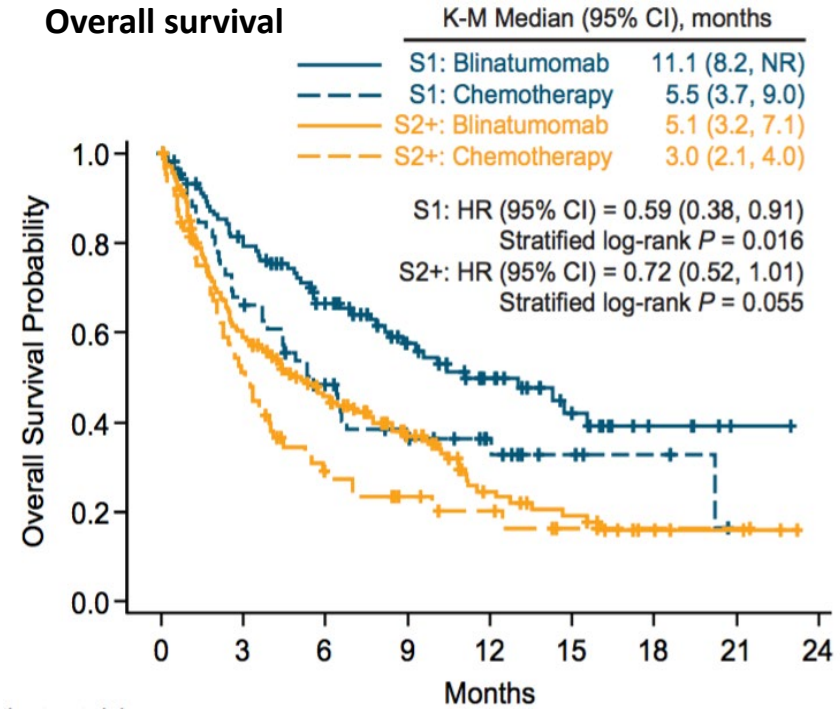


	Blinatumomab (N = 271)	SOC (N = 134)
AlloHSCT post-baseline – n (%); [95% CI]	65 (24%); [19%, 30%]	32 (24%); [17%, 32%]

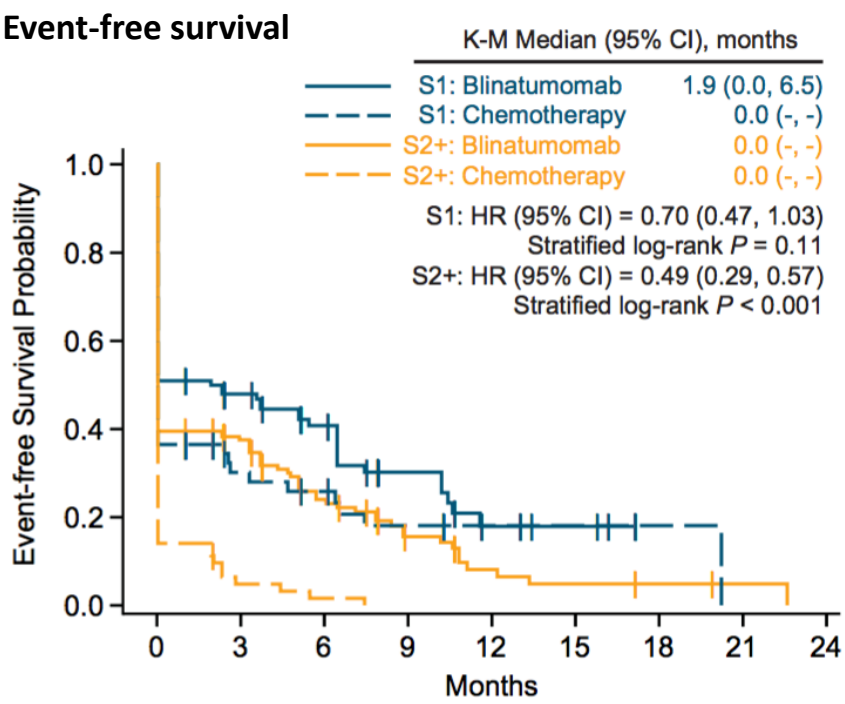
Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Blinatumomab Shows Its Best Outcomes if Delivered in Earlier Stages of Disease

Overall survival



Event-free survival



Dombret H, et al. *Leuk Lymphoma.* 2019;60:2214-2222.

Blinatumomab Adverse Events (TOWER)

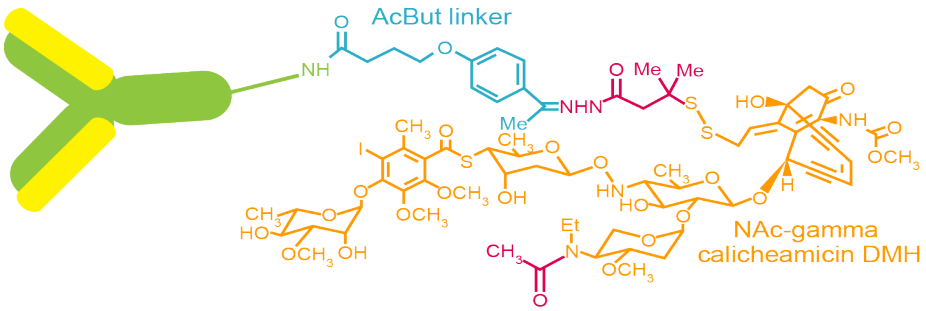
	Blinatumomab Treated (N = 267)	SOC Treated (N = 109)
Any AE, n (%)	263 (99)	108 (99)
Any grade 3 AE	98 (37)	33 (30)
Any grade 4 AE	82 (31)	48 (44)
Any grade 5/fatal AE	51 (19)	19 (17)
Grade 5 infection	30 (11)	13 (12)
Grade ≥3 AE of interest, n (%)		
Neutropenia	101 (38)	63 (58)
Infection	91 (34)	57 (52)
Neurologic event	25 (9)	9 (8)
Cytokine release syndrome	13 (5)	0 (0)

CRS and NTX are reversible and can be managed with either dose interruptions or corticosteroids.

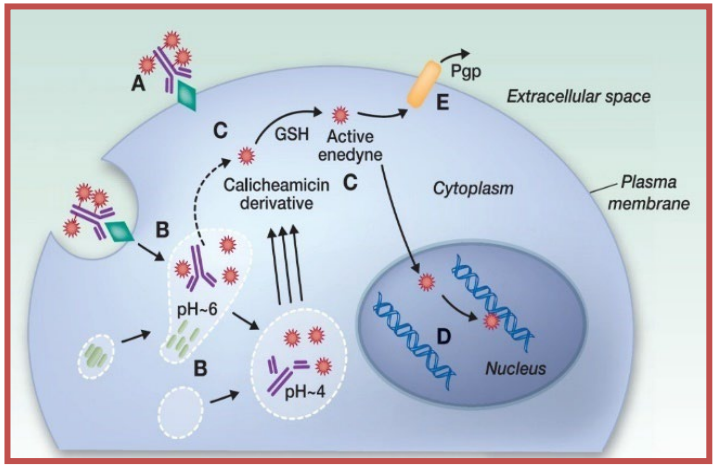
Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Inotuzumab Ozogamicin (InO) Targeting CD22

AcBut linker:
4-(4’-acetylphenoxy) butanoic acid dimethyl hydrazide



MOA retains activity against tumor cells with slow cycling times



N-acetyl γ calicheamicin

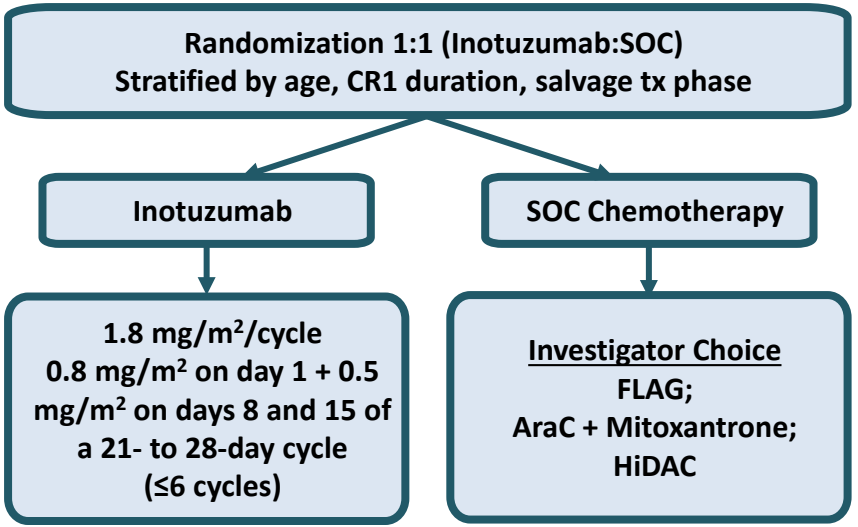
Average loading of calicheamicin derivative on mAb is
5–6 moles of calicheamicin/mole of mAb (range, 3–9) for InO

Inotuzumab vs SOC in R/R B-ALL (INO-VATE)

Eligible Patients

- Relapsed or refractory Ph– or Ph+ B-ALL due to receive salvage 1 or 2 therapy
- Relapse after alloHSCT
- ≥5% BM blasts

Patients with ≥10K/µL PB blasts were excluded (hydroxyurea and/or steroids/vincristine within 2 weeks of randomization allowed to reduce blasts)



Primary Endpoints: CR and Overall survival

Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753.

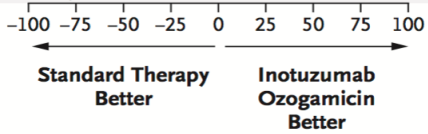
InO vs SOC Chemo (INO-VATE) in R/R B-ALL

	InO N = 109	SOC N = 109	2-Sided *P* Value
CR/CRi, %	80.8	29.4	<.001
CR, %	35.8	19.8	.002
MRD negative (responders), %	78.4	28.1	<.001
Proceed to transplant	41%	11%	.03
VOD, N (%)	13%*	<1%	
In patients w/ HSCT after InO	22%†	3%	
In patients w/o HSCT after InO	3%	0%	
In patients w/ HSCT before trial	45%		

*Thirteen percent all grades (82% were grade ≥3).
†Includes 6% fatal cases.
Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753; Kantarjian HM, et al. *Lancet Haematol.* 2017;4:e387-e398.

CR Rates per Patient Characteristic

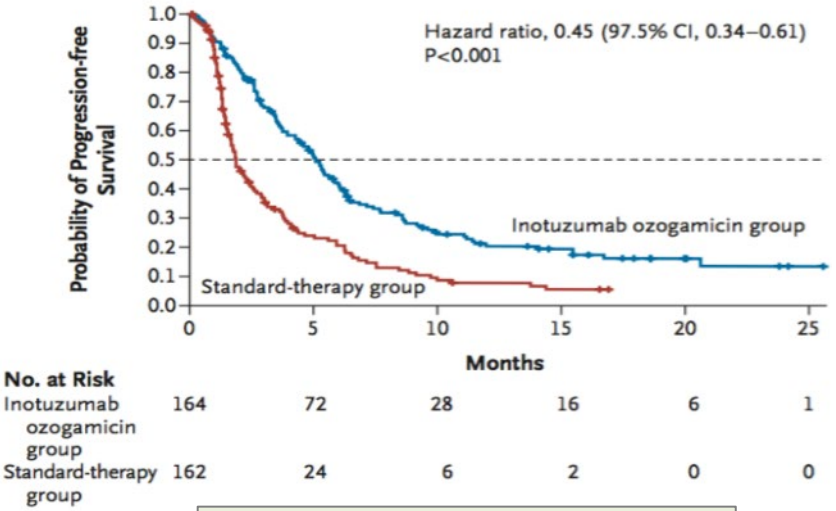
Subgroup	No. of Patients		Complete Remission		Between-Group Difference (97.5% CI)	P Value
	Inotuzumab Ozogamicin Group	Standard-Therapy Group	Inotuzumab Ozogamicin Group	Standard-Therapy Group		
			% (95% CI)		percentage points	
All patients	109	109	80.7 (72.1 to 87.7)	29.4 (21.0 to 38.8)	51.4 (38.4 to 64.3)	<0.001
Peripheral blasts						
0	42	48	90.5 (77.4 to 97.3)	41.7 (27.6 to 56.8)	48.8 (29.9 to 67.7)	<0.001
>0 to 1000	32	35	71.9 (53.3 to 86.3)	20.0 (8.4 to 36.9)	51.9 (28.5 to 75.3)	<0.001
>1000	34	25	76.5 (58.8 to 89.3)	20.0 (6.8 to 40.7)	56.5 (32.2 to 80.7)	<0.001
Bone marrow blasts						
<50%	30	29	86.7 (69.3 to 96.2)	41.4 (23.5 to 61.1)	45.3 (20.5 to 70.1)	<0.001
≥50%	77	78	77.9 (67.0 to 86.6)	24.4 (15.3 to 35.4)	53.6 (38.4 to 68.8)	<0.001
CD22 expression						
<90%	24	24	79.2 (57.8 to 92.9)	25.0 (9.8 to 46.7)	54.2 (27.0 to 81.3)	<0.001
≥90%	74	63	82.4 (71.8 to 90.3)	36.5 (24.7 to 49.6)	45.9 (29.1 to 62.8)	<0.001
Karyotype						
Normal	20	20	95.0 (75.1 to 99.9)	30.0 (11.9 to 54.3)	65.0 (39.6 to 90.4)	<0.001
Ph-positive	14	18	78.6 (49.2 to 95.3)	44.4 (21.5 to 69.2)	34.1 (−1.8 to 70.1)	0.08
t(4;11)-positive	3	6	33.3 (0.8 to 90.6)	33.3 (4.3 to 77.7)	0.0 (−74.7 to 74.7)	1.00
Other abnormalities	49	46	85.7 (72.8 to 94.1)	26.1 (14.3 to 41.1)	59.6 (41.3 to 78.0)	<0.001
Previous stem-cell transplantation						
Yes	17	22	76.5 (50.1 to 93.2)	27.3 (10.7 to 50.2)	49.2 (17.8 to 80.6)	0.004
No	92	87	81.5 (72.1 to 88.9)	29.9 (20.5 to 40.6)	51.6 (37.4 to 65.9)	<0.001



Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753.

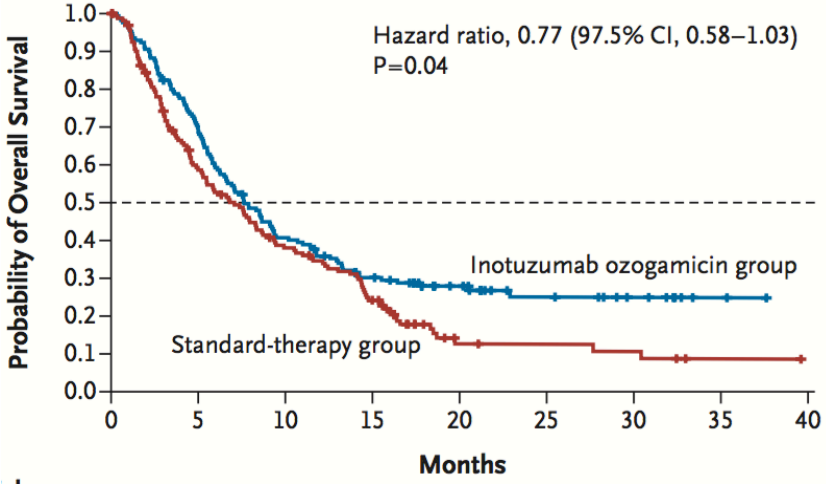
InO vs SOC Chemo (INO-VATE) in R/R B-ALL

Progression-Free Survival



Median PFS: 5 mo (95% CI, 3.7-5.6)

Overall Survival



Median OS: 7.7 mo (95% CI, 6.0-9.2)

41% of patients proceeded to alloHSCT after InO vs 11% in SOC arm

Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753.

Inotuzumab-Associated Toxicity (INO-VATE)

	InO N = 109	SOC N = 109	2-Sided *P* Value
CR/CRi, %	80.8	29.4	<.001
CR, %	35.8	19.8	.002
MRD negative (responders), %	78.4	28.1	<.001
Proceed to transplant	41%	11%	.03
VOD, N (%)	13%*	<1%	
In patients w/ HSCT after InO	22%†	3%	
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Kantarjian H, et al. *N Engl J Med.* 2016;375:740-753; Kantarjian HM, et al. *Lancet Haematol.* 2017;4:e387-e398.

Clinical Factors a/w VOD After InO

	Number of patients in each subset	Odds ratio (95% CI)	p value
Univariate analysis (n=77)			
Duration† (continuous)	75	1·006 (0·989–1·023)	0·48
Conditioning regimen with two alkylating agents (two *vs* one)	11 *vs* 52	6·600 (1·618–26·917)	0·009
Busulfan-containing regimen (yes *vs* no)	13 *vs* 64	4·130 (1·161–14·693)	0·029
Type of HSCT (myeloablative *vs* non-myeloablative)	51 *vs* 26	0·662 (0·218–2·006)	0·47
Donor for HSCT (alternate donor *vs* matched related)	56 *vs* 21	2·000 (0·511–7·821)	0·32
Previous HSCT (yes *vs* no)	11 *vs* 66	3·749 (0·980–14·341)	0·054
Number of treatment cycles received (continuous)	77	1·483 (0·950–2·316)	0·083
Salvage treatment phase (≥2 *vs* 1)	20 *vs* 56	2·477 (0·788–7·787)	0·12
Pre-HSCT bilirubin concentration (≥ULN *vs* <ULN)	12 *vs* 65	7·699 (2·035–29·133)	0·003
Pre-HSCT AST or ALT concentration (>1·5 × ULN *vs* ≤1·5 × ULN)	14 *vs* 63	0·955 (0·234–3·903)	0·95
Pre-HSCT platelet count (<100 × 10^9 per L *vs* ≥100 × 10^9 per uL)	42 *vs* 35	2·400 (0·753–7·652)	0·14
Age (≥55 years *vs* <55 years)	17 *vs* 60	3·500 (1·075–11·398)	0·038
History of liver disease or hepatitis (yes *vs* no)	20 *vs* 57	2·531 (0·806–7·950)	0·11
Baseline ECOG performance status (2 *vs* 0–1)	9 *vs* 68	1·010 (0·190–5·378)	0·99

	Number of patients in each subset	Odds ratio (95% CI)	p value
Multivariate analysis (n=62)‡			
Conditioning regimen with two alkylating agents (two *vs* one)	11 *vs* 51	8·606 (1·516–48·861)	0·015
Pre-HSCT bilirubin concentration (≥ULN *vs* <ULN)	11 *vs* 51	15·308 (1·950–120·206)	0·009
Pre-HSCT AST or ALT concentration (>1·5 × ULN *vs* ≤1·5 × ULN)	11 *vs* 51	0·027 (<0·001–0·833)	0·039
History of liver disease or hepatitis (yes *vs* no)	15 *vs* 47	5·133 (0·907–29·060)	0·064

Median time from last dose of InO to HSCT with VOD vs no VOD

- 37 days (IQR 29–58) vs 35.5 days (24–51)

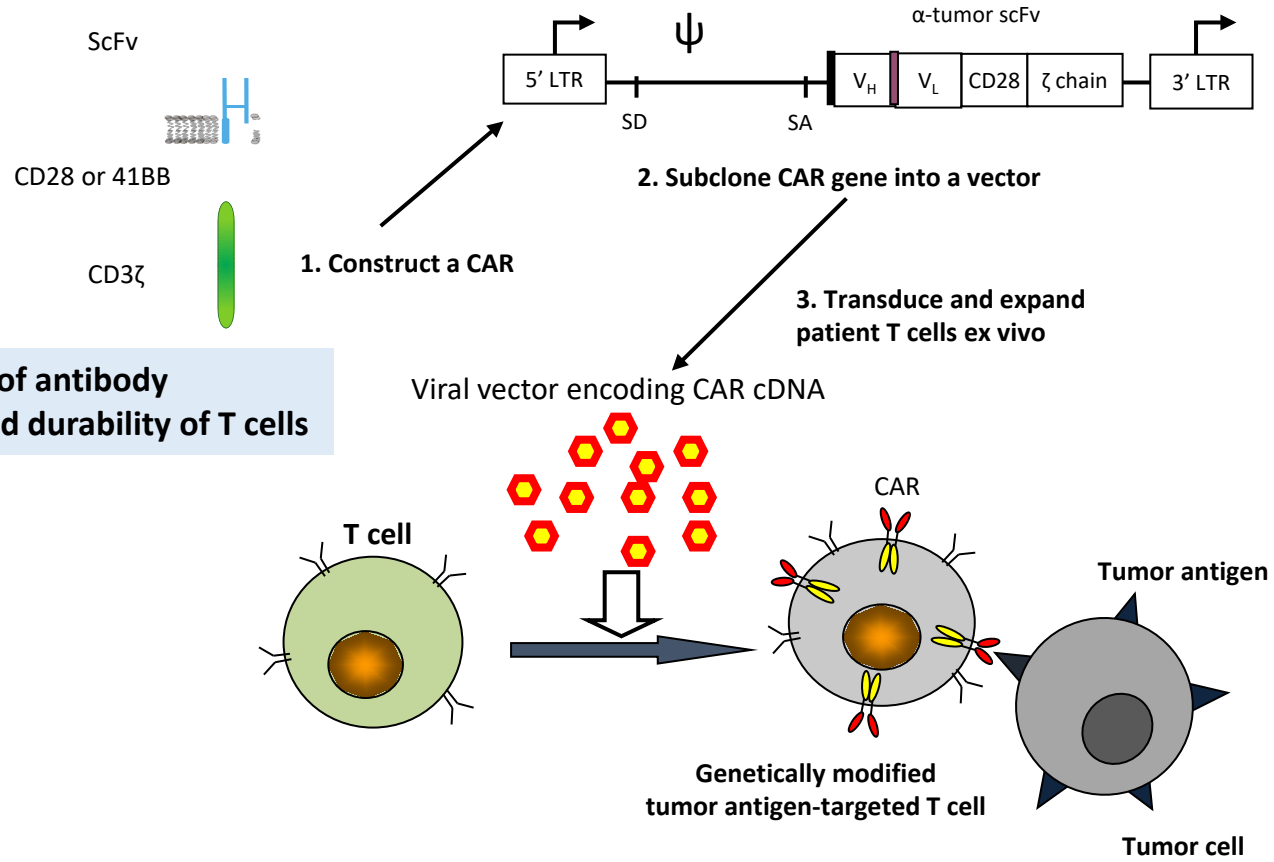
Kantarjian HM, et al. *Lancet Haematol.* 2017;4:e387-e398.

Expert Panel Recommendation for VOD

- In patients for whom HSCT is considered, the number of InO cycles should be limited to 2, if feasible
- Conditioning regimens with dual alkylating agents (eg, thiotepa and melphalan) should be avoided
- Ursodiol to be given to all patients exposed to InO
- Bilirubin, LFTs, and weight should be measured before each dose of InO for careful monitoring of VOD

Kebriael P, et al. *Bone Marrow Transplant.* 2018;53:449-456.

Generation of CAR T Cells

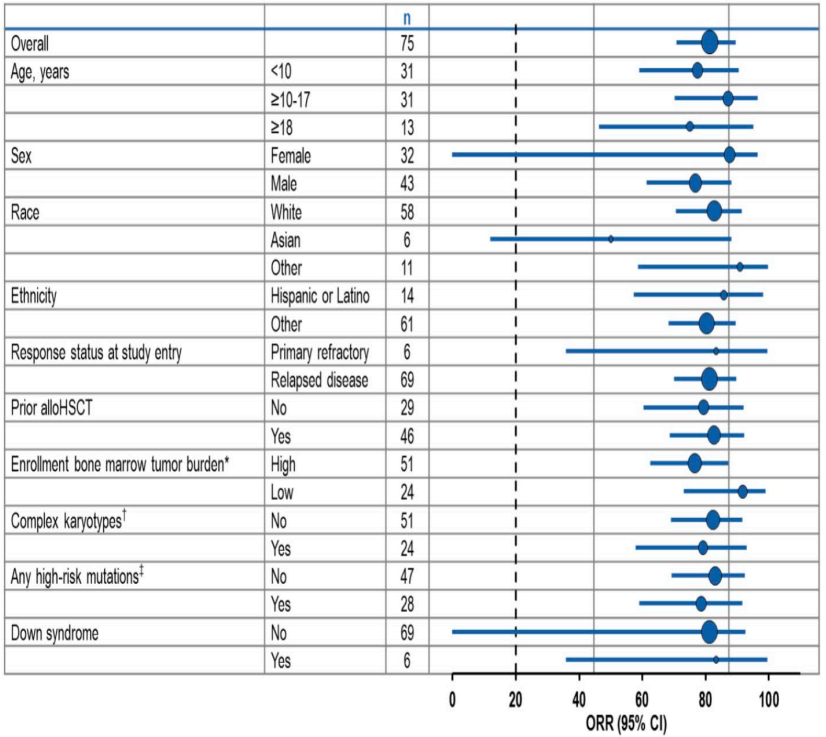


Specificity of antibody
Potency and durability of T cells

Tisagenlecleucel in Children and Young Adults With R/R B-ALL (ELIANA)

	Patients (N = 75)
Age, median (range), years	11 (3-23)
Prior HSCT, n (%)	46 (61)
Prior lines of Tx, median (range), n	3 (1-8)
Morphologic BM blasts, median (range), %	74 (5-99)
High-risk genomic lesions, n (%)*	28 (37)
Down syndrome, n (%)	6 (8)
Time from enrollment to infusion, median, (range), days	45 (30-105)
CAR T-cell dose, median (range) Total CAR T-cell dose infused (10^8 cells) Weight-adjusted CAR T-cell dose (10^6/kg)	 1.1 (0.60) 2.9 (1.2)

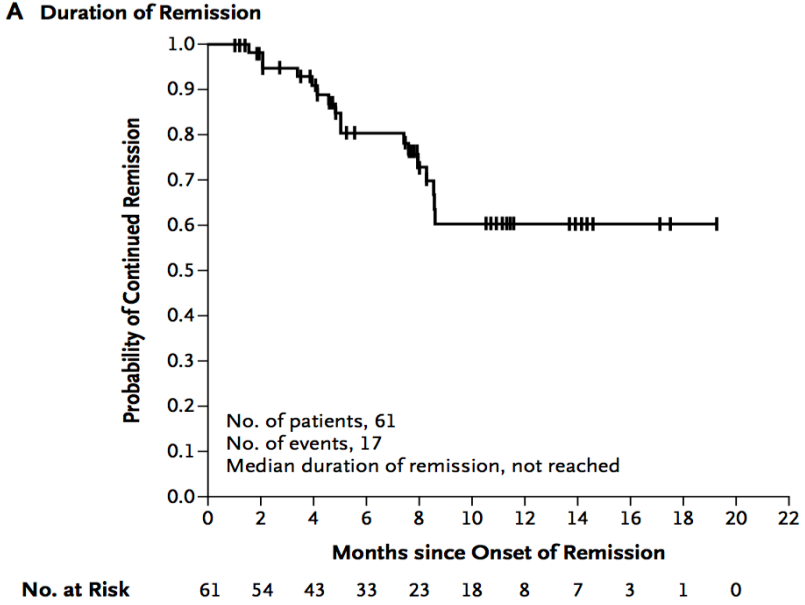
Overall Response Rate: 81%
- **60% CR + 21% CRi**



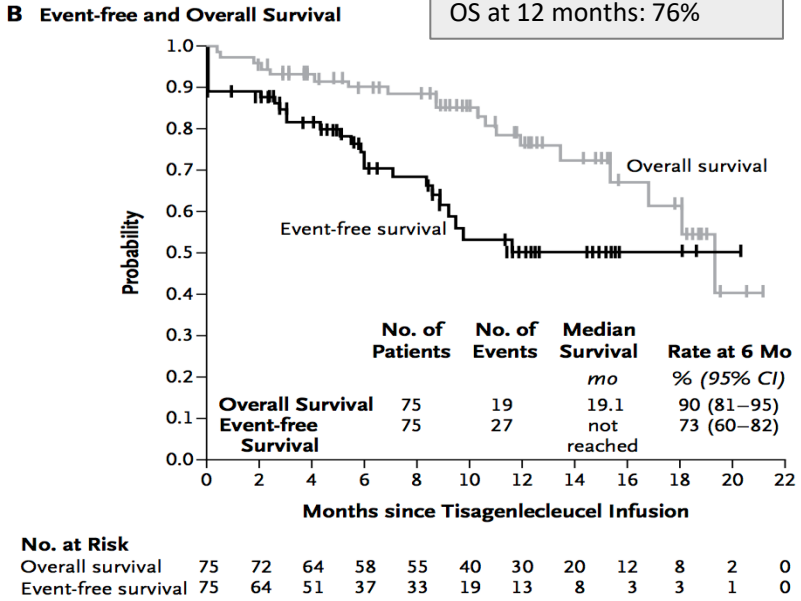
*BCR-ABL1, MLL rearrangement, hypodiploidy, Ph-like gene signature, or complex karyotype.

Maude S, et al. *N Engl J Med.* 2018;378:439-448.

Tisagenlecleucel: Duration of Remission and Survival



EFS at 12 months: 50%
OS at 12 months: 76%



8 patients (11%) proceeded to post-CAR alloHSCT

Maude S, et al. *N Engl J Med.* 2018;378:439-448.

Approved CAR Therapy in B-Cell ALL in the US

- **FDA approved tisagenlecleucel (Kymriah) August 2017** for treatment of patients **up to age 25** years with B-cell precursor ALL that is refractory or in second or later relapse
  - First chimeric antigen receptor T-cell immunotherapy approved by FDA
- **No CAR T cells approved for adults older than 25 with ALL**

Brexucabtagene in Adults With R/R B-ALL (ZUMA-3)

Characteristic	Treated Patients (N = 55)
Median age, yr (range)	40 (19–84)
Male, n (%)	33 (60)
ECOG PS 1, n (%)	39 (71)
Ph+, n (%)	15 (27)
CNS-1 disease at BL, n (%)	55 (100)
Median no. of prior therapies, n (range) • **≥3 prior lines of therapy, n (%)**	2 (1–8) 26 (47)
Prior blinatumomab, n (%)	25 (45)
Prior inotuzumab ozogamicin, n (%)	12 (22)
Prior alloSCT, n (%)	23 (42)

Characteristic	Treated Patients (N = 55)
R/R subgroup, n (%) • Primary refractory • R/R to ≥2 prior systemic therapy lines • First relapse with remission ≤12 mo • R/R post-SCT	 18 (22) 43 (78) 16 (29) 24 (44)
Median BM blasts at screening, % (range)	65.0 (5–100)
Median BM blasts at preconditioning after bridging CT, % (range)	59.0 (0–98)

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

Brexucabtagene in Adults With R/R B-ALL (ZUMA-3)

Response, n (%)	Treated Patients (N = 55)
CR/CRi • CR • CRi	39 (70.9) 31 (56.4) 8 (14.5)
BFBM*	4 (7.3)
No response	9 (16.4)
Unknown/NE	3 (5.5)

*≤5% blasts by morphology in BM and any ANC or platelet count that does not meet criteria for CR, CRi, or CR with partial hematologic recovery.

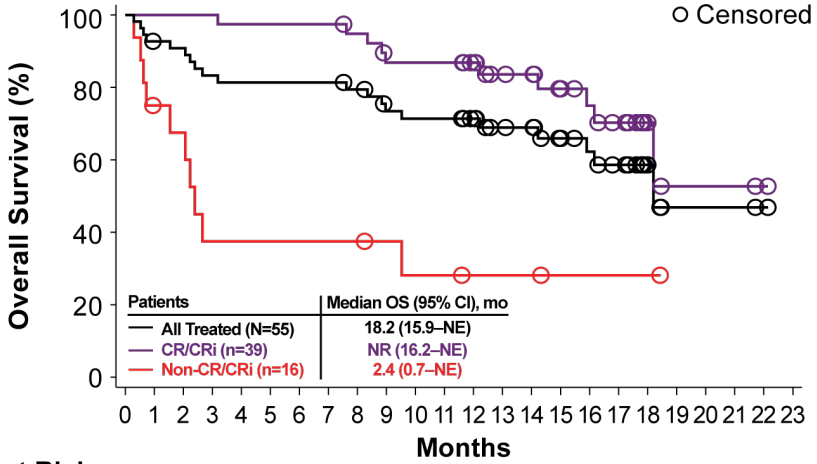
Outcome, mo (95% CI)	Treated Patients (N = 55)	Patients With CR/CRi (n = 39)	Patients Without CR/CRi (n = 16)
Median OS	18.2 (15.9-NE)	NR (16.2-NE)	2.4 (0.7-NE)
Median RFS	11.6 (2.7-15.5)	14.2 (11.6-NE)	0 (NE-NE)

- **CRS: all grade, 89%; grade ≥3, 24%; ICANS: all grade, 60%; grade ≥3, 25%**

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

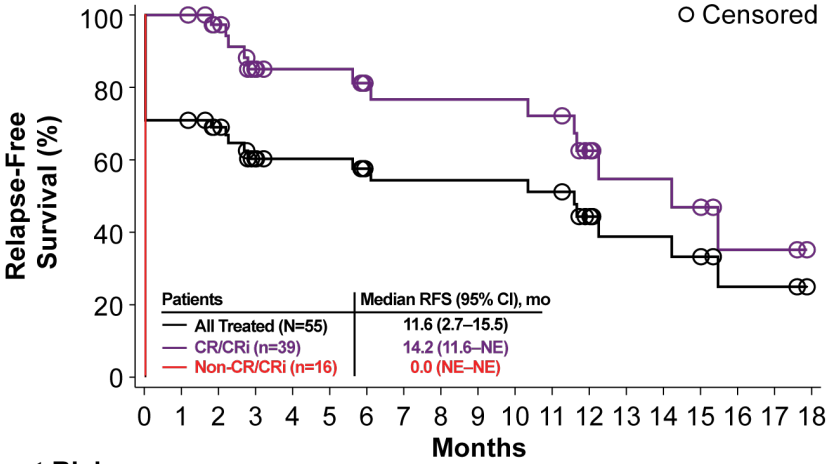
Brexucabtagene in Adults With R/R B-ALL (ZUMA-3): Survival

Overall survival



No. at Risk																							
CR/CRi	39	39	39	39	38	38	38	38	36	32	32	32	29	24	23	19	16	13	6	2	2	2	1	0
Non-CR/CRi	16	10	9	5	5	5	5	5	5	4	3	3	2	2	2	1	1	1	1	0	0	0	0	0
All Treated	55	49	48	44	43	43	43	43	41	36	35	35	31	26	25	20	17	14	7	2	2	2	1	0

Relapse-free survival

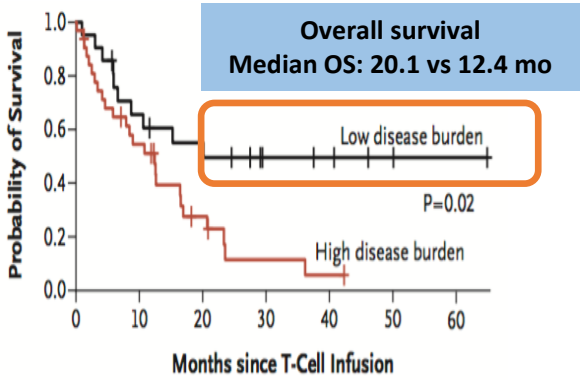


No. at Risk																			
CR/CRi	39	39	33	24	22	22	18	17	17	17	17	16	11	7	7	6	3	3	0
Non-CR/CRi	16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
All Treated	55	39	33	24	22	22	18	17	17	17	17	16	11	7	7	6	3	3	0

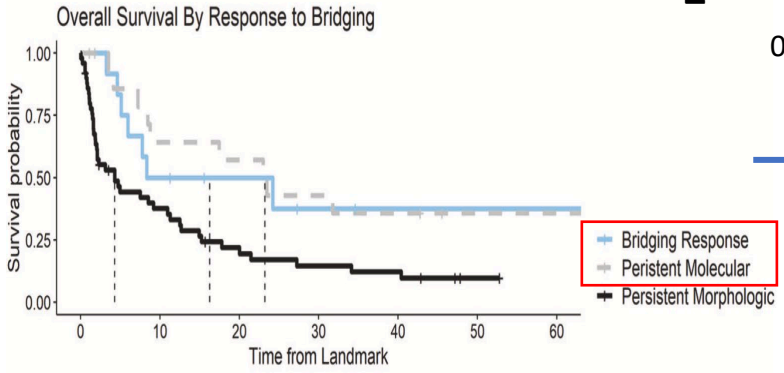
18% of the patients received alloSCT at a median 98 days (range, 60–207) post–KTE-X19 infusion

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

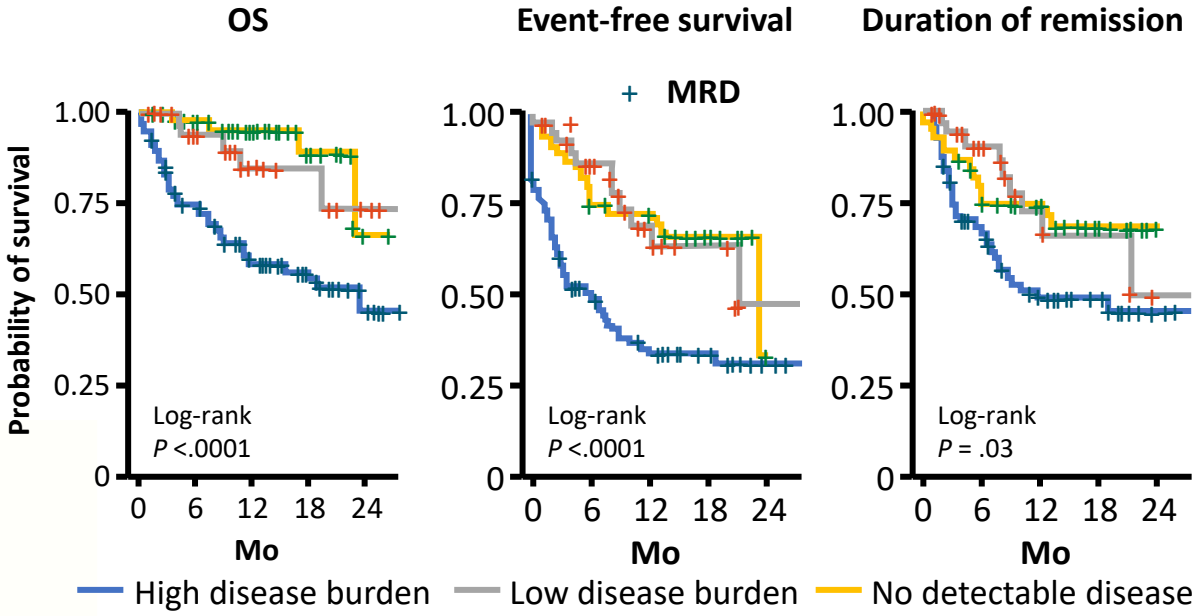
Low Disease Burden Associated With Improved Remission Duration and Long-term Survival



Park J, et al. *N Engl J Med.* 2018;378(5):449-459.



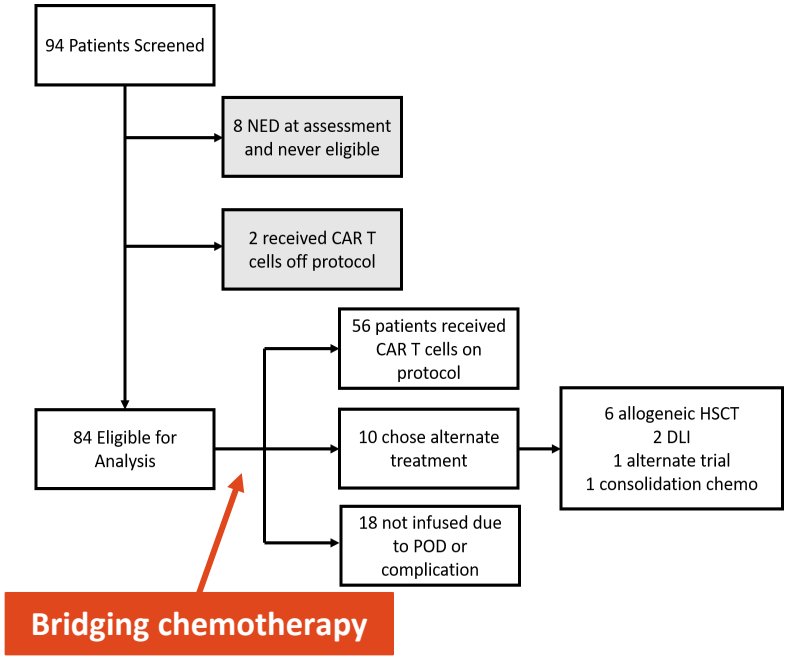
Perica K, Park JH, et al. *Leukemia.* 2021;35(11):3268-3271.



Schultz LM, et al. ASH 2020. Abstract 468.

Use of Bridging Chemotherapy in Adult ALL CAR T-Cell Therapy Trial

- Retrospective review of bridging therapy strategies in adult patients with R/R ALL who received 19-28z CAR T-cell therapy at MSKCC (N = 84)



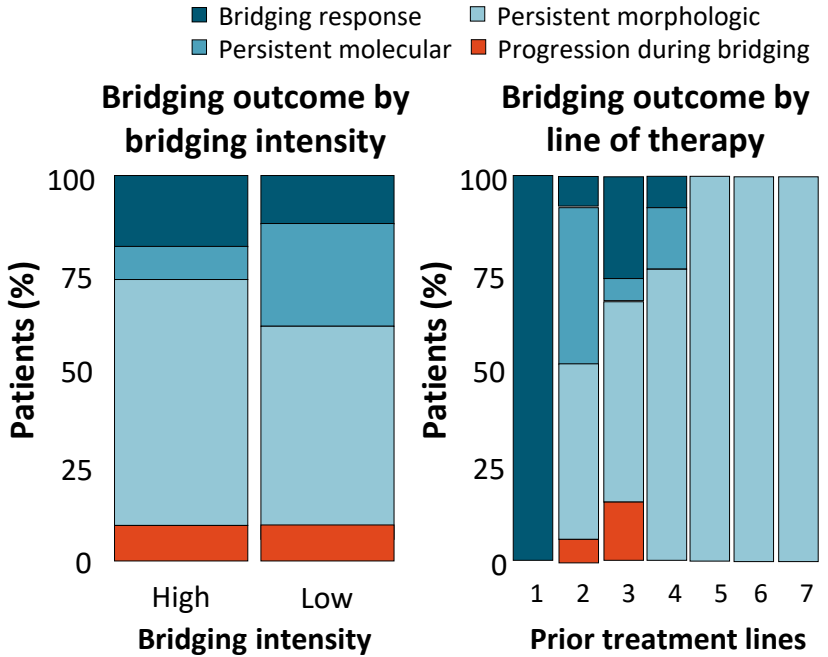
Baseline Characteristic	Bridging Therapy Intensity		*P*
	High	Low or None	
Patients, n (%)	33 (41)	48 (59)	
Age, yr	46 (22-73)	42 (22-74)	.5
Ph+ disease, n (%)	6 (18)	14 (29)	.3
Median no. prior tx lines	3 (1-7)	3 (2-7)	.2
Prior blinatumomab, n (%)	9 (28)	14 (29)	>.9
Prior HSCT, n (%)	12 (36)	17 (35)	>.9
MRD+ disease, n (%)	5 (15)	13 (27)	.2
Median BM blasts	52 (0-99)	35 (0-95)	.2
EMD, n (%)	6 (18)	4 (8.3)	.3

Perica K, Park JH, et al. *Leukemia.* 2021;35(11):3268-3271.

Use of Bridging Chemotherapy in Adult ALL CAR T-Cell Therapy Trial

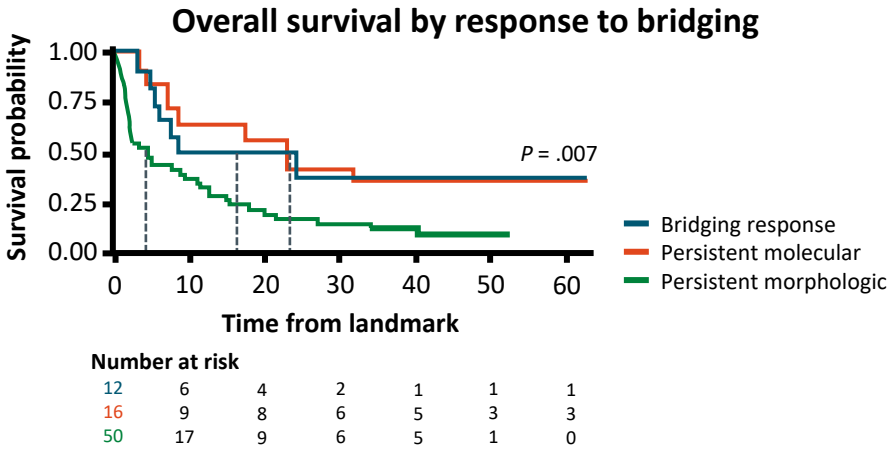
- Retrospective review of bridging therapy strategies in adult patients with R/R ALL who received 19-28z CAR T-cell therapy at MSKCC (N = 84)

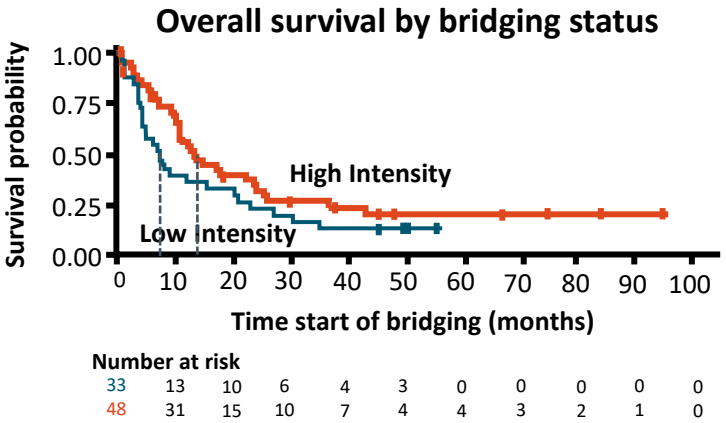
Bridging Therapy Regimens	
Low Intensity	**High Intensity**
POMP maintenance regimen	HyperCVAD
Liposomal vincristine ± steroids	High-dose cytarabine (eg, HiDAC, MEC)
Mini-CVD	FLAG/FLAG-IDA
Blinatumomab or inotuzumab	Cyclophosphamide/etoposide
3-drug pediatric type induction (vincristine-steroids-asparaginase)	4-drug pediatric type induction (vincristine-steroids-asparaginase-anthracycline)
Hydroxyurea or steroids	

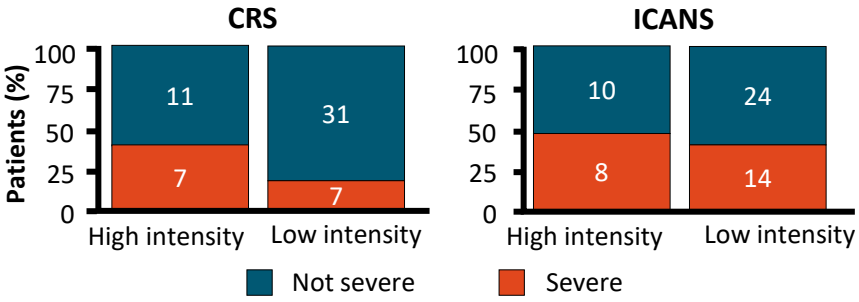


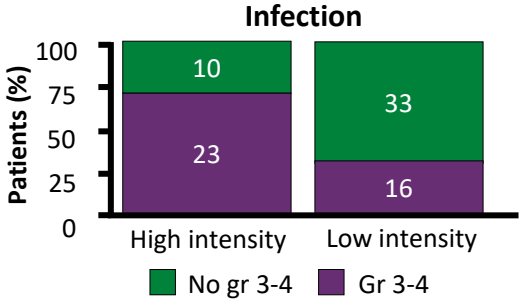
Perica K, Park JH, et al. *Leukemia.* 2021;35(11):3268-3271.

Impact of Bridging Chemotherapy on Clinical Outcome After CD19 CAR Therapy in Adult ALL



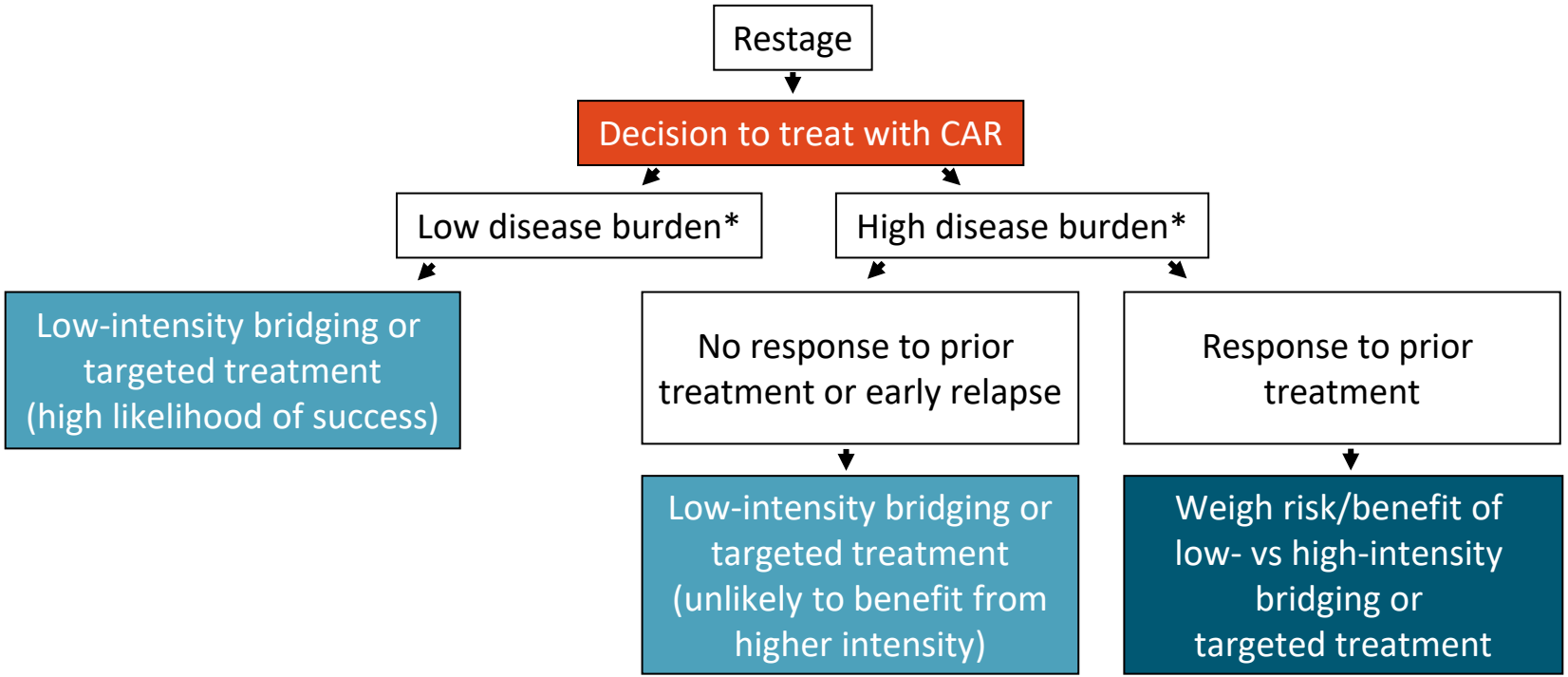






Perica K, Park JH, et al. *Leukemia.* 2021;35(11):3268-3271.

Proposed Schema for Patient-Specific Selection of Bridging Therapy

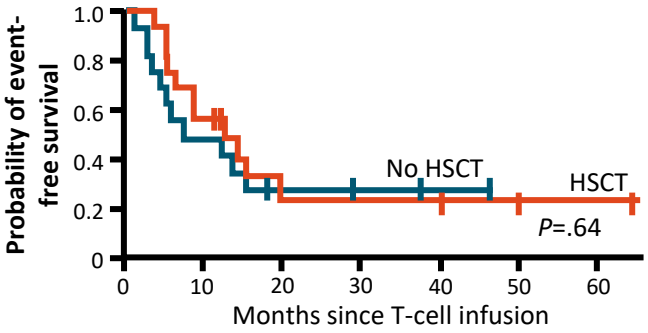


*Low (eg), BM blasts <5%, no EMD; high (eg), BM blasts ≥5%, no EMD.

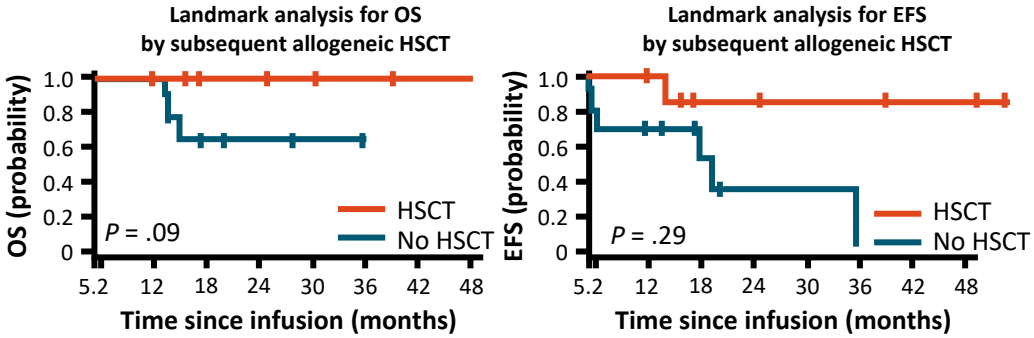
Perica K, Park JH, et al. *Leukemia.* 2021;35(11):3268-3271.

Post-CAR HSCT in Adult ALL

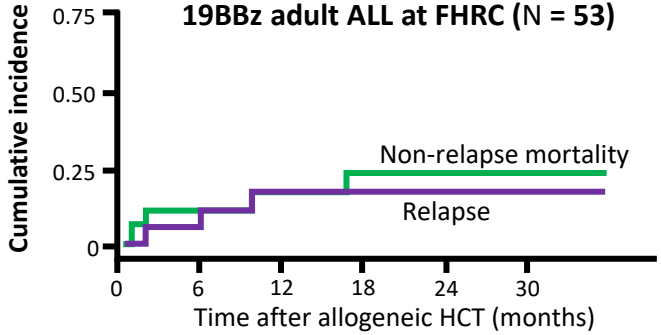
1928z adult ALL at MSK (N = 53)



CTL019 in adult ALL at UPenn (N = 35)



19BBz adult ALL at FHRC (N = 53)



~40% of responding pts proceeded to alloHSCT

38% of responding pts proceeded to alloHSCT

Variable	Multivariable Analysis		
	HR	95% CI	*P*
LDH pre-lymphodepletion (per 100 U/L increment)	1.39	1.11-1.73	.004
Platelets pre-lymphodepletion (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

Park J, et al. *N Engl J Med*. 2018;378(5):449.-459; Hay KA, et al. *Blood*. 2019;133:1652-1663; Frey NV, et al. *J Clin Oncol*. 2019;38:415-422.

Take-Home Points

	Pros	Cons
Blinatumomab	Manageable and reversible AE profiles CR rates of 40%–50% Highly effective in **MRD+ setting** (CR 80%) **Chemotherapy free**	Less effective in high BM blasts Continuous infusion/pump
Inotuzumab	Well tolerated CR/CRi 80% **Easy administration**	VOD (increased risk in prior HSCT and liver disease) Most data in S1/2 setting only Prolonged cytopenia in some cases
CD19 CAR	CR rates 80% Equally **effective in multiple prior tx** **Single infusion** can generate a long-term remission	Bridging time during cell manufacturing CRS and NTX

- Choosing among these agents requires a careful evaluation of previous treatments including HSCT, goal of therapy, patient comorbidities, disease kinetics, and side effect profiles of each agent
- Consult with or refer to large ALL-focused centers for clinical trials, esp for initial therapy, and additional diagnostics (Ph-like signature, mutation profiles, MRD evaluation), and side effect management recs

Summary

- Blinatumomab and inotuzumab have replaced salvage chemotherapy for adults with R/R ALL on the basis of the randomized clinical trial data
  - It is best utilized in early lines of therapy to successfully bridge patients to allogeneic HSCT
  - Both have unique but manageable AE profiles
  - Blinatumomab can be safely combined with TKI
- CD19 CAR T-cell therapy approved for AYA and older adults with R/R B-ALL
  - A subset of patients can achieve durable remissions and long-term survival *without* subsequent alloHSCT
  - Lower disease burden is associated with higher EFS/OS and low toxicity
  - CAR in earlier lines of setting or after more effective bridging/cytoreduction may further improve outcome
  - Toxicity profiles of new products and management strategies are improving

Global Leukemia Academy

Case 1: Adult ALL

Huai-Hsuan Huang

APTITUDE HEALTH

Case Sharing
– Frontline Treatment

Huai-Hsuan Huang, MD

Division of Hematology, Department of Internal Medicine,
National Taiwan University Hospital, Taipei, Taiwan

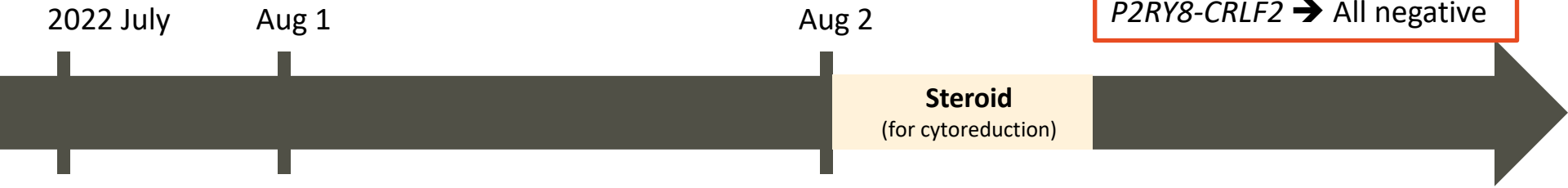
52-year-old woman

- Past history
  - Acute pyelonephritis, with abscess formation in March 2021
  - Uterine myoma and adenomyosis s/p hysterectomy in 2014
  - Thyroid nodules, follow-up for 10 years

- She presented with dizziness and dyspnea

52-year-old woman

KMT2A-AFF1
BCR-ABL1(p190)
BCR-ABL1(p210)
ETV6-RUNX1
TCF3-PBX1
P2RY8-CRLF2 ➔ All negative



Dyspnea
Dizziness

Other local hospital:
Hb: 6 g/dL
WBC: 22.73K/μL, blast: 49.0%
elevated LDH (494)
→ Refer to our hospital
Hb: 6 g/dL, PLT 109K/μL
WBC: 25.02K/μL, blast: 67.0%

Our hospital:
BM smear and flow report
early pre–B-ALL, CD20+

Dim CD45, CD34+, **CD19+, CD10+, CD20+** (~90% of blasts), CD38+, CD66c+, CD58+, surface light chain-, **CyIgMu-**, SmIgM/CD117-, CD33-, **CD22+** (~93% blasts), **nuTdT+**, CD24+, sub CD9+, CD13-, NG2-, CD15/CD65-, CD21-, CD81+, CD123-

Available treatments for frontline non-Ph B-ALL in Taiwan

- Chemotherapies
- Targeted therapies
  - Rituximab (self-paid)
  - Blinatumomab (self-paid . . . but too expensive)
  - Inotuzumab ozogamicin (self-paid . . . also very expensive)

Which treatment will you suggest for her?

A. Steroid only
B. Low-dose chemotherapy
C. Pediatric-inspired regimens for adult ALL patients, such as GRAALL
D. Pediatric-inspired regimens combined with rituximab

Which treatment will you suggest for her?

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B. Low-dose chemotherapy
C. Pediatric-inspired regimens for adult ALL patients, such as GRAALL
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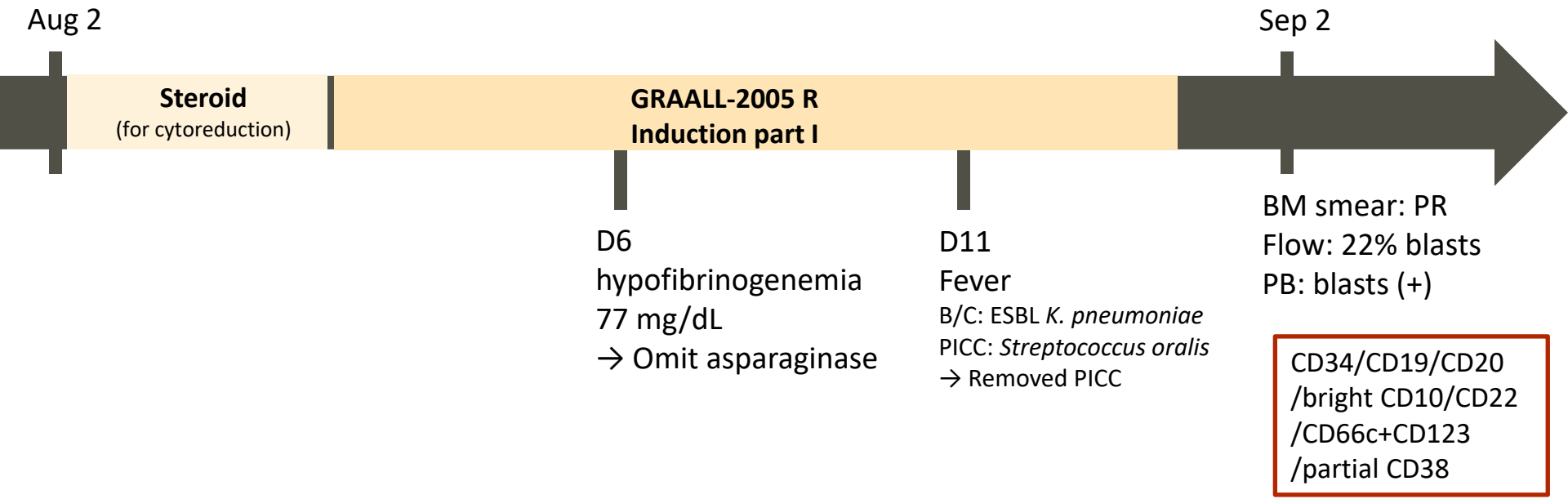
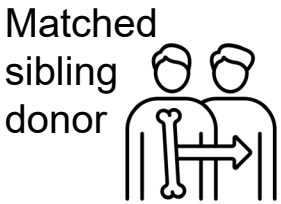
52-year-old woman



52-year-old woman



Sep 2

Sep 6

GRAALL-2005 R
Induction part II

BM smear: PR
Flow: 22% blasts
PB: blasts (+)

EBF1 heterozygous deletion
IKZF1 exon 2–7 heterozygous deletion
PAX5 exon 2–10 heterozygous deletion
BTG1 exon 2 homozygous deletion
RB1 exon 19–26 heterozygous deletion

Which is the treatment plan for her?

A. Keep on GRAALL 2005 consolidation with rituximab
B. Keep on consolidation therapy before allo-HSCT
C. Give blinatumomab only
D. Give blinatumomab and followed by allo-HSCT

Which is the treatment plan for her?

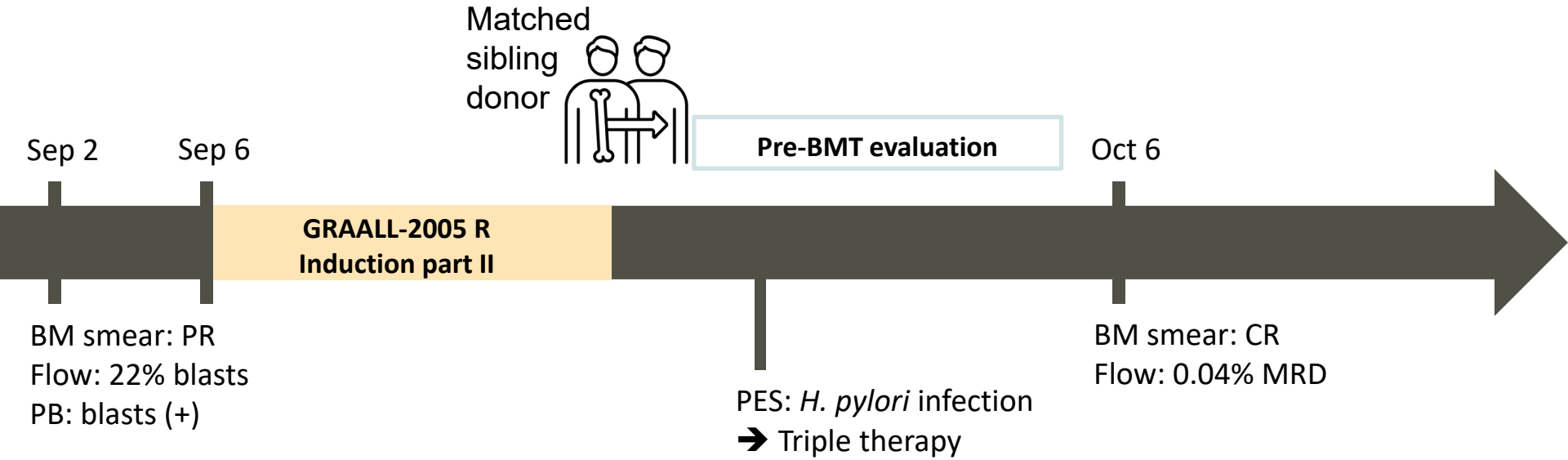
A. Keep on GRAALL 2005 consolidation with rituximab

B. Keep on consolidation therapy before allo-HSCT

C. Give blinatumomab only

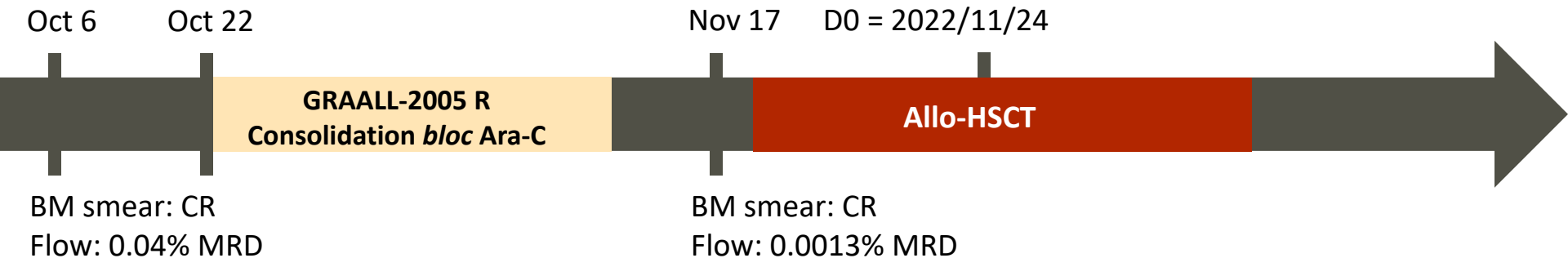
D. Give blinatumomab and followed by allo-HSCT (if money is not a problem . . .)

52-year-old woman



EBF1 heterozygous deletion
IKZF1 exon 2–7 heterozygous deletion
PAX5 exon 2–10 heterozygous deletion
BTG1 exon 2 homozygous deletion
RB1 exon 19–26 heterozygous deletion

52-year-old woman



Summary

- 52-year-old woman
  - Diagnosis: early pre-B ALL, Ph(–), CD20+
    - *EBF1* heterozygous deletion, *IKZF1* exon 2–7 heterozygous deletion, *PAX5* exon 2–10 heterozygous deletion, *BTG1* exon 2 homozygous deletion, *RB1* exon 19–26 heterozygous deletion
  - Induction: GRAALL-2005-R (rituximab for CD20+)
  - Response: CR with MRD by flow cytometry
  - Current status
    - She is hospitalized at BMT unit for allo-HSCT

Conclusion

- Pediatric-inspired regimen is still effective and tolerable for adult ALL patients
- Additional targeted therapies improve the treatment response
- Risk-stratification, including genetic abnormalities and the detection of minimal residual disease, is important for treatment planning in adult ALL patients

Thank you

Global Leukemia Academy

Case 2: Adult ALL

Michael Ashby

APTITUDE HEALTH

Case Summary: Relapsed/Refractory Adult ALL

Dr Michael Ashby

Melbourne, Australia

Clinical information

- 48-year-old male
- Newly diagnosed Ph-negative precursor B-ALL
- Presented with B symptoms and circulating blasts
- Referred from external hospital for evaluation

Past medical history

- Ex-smoker, 20 pack-year history
- Anxiety
- Married with 2 children

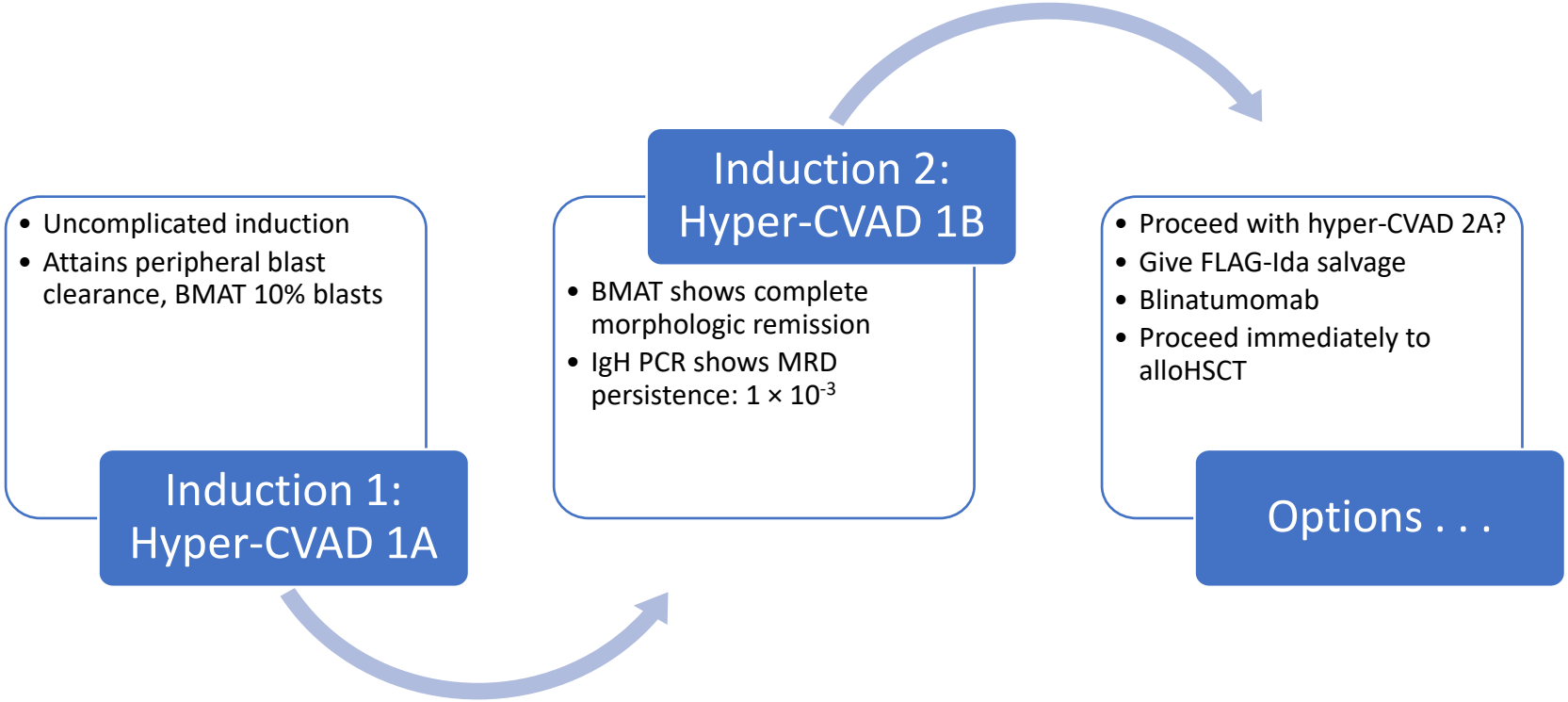
Risk stratification

- High white cell count at diagnosis: 50 × 10^9/L
  High LDH: 500
  No CNS involvement
- Complex cytogenetics
  Genomic sequencing not undertaken
- CD20 negative

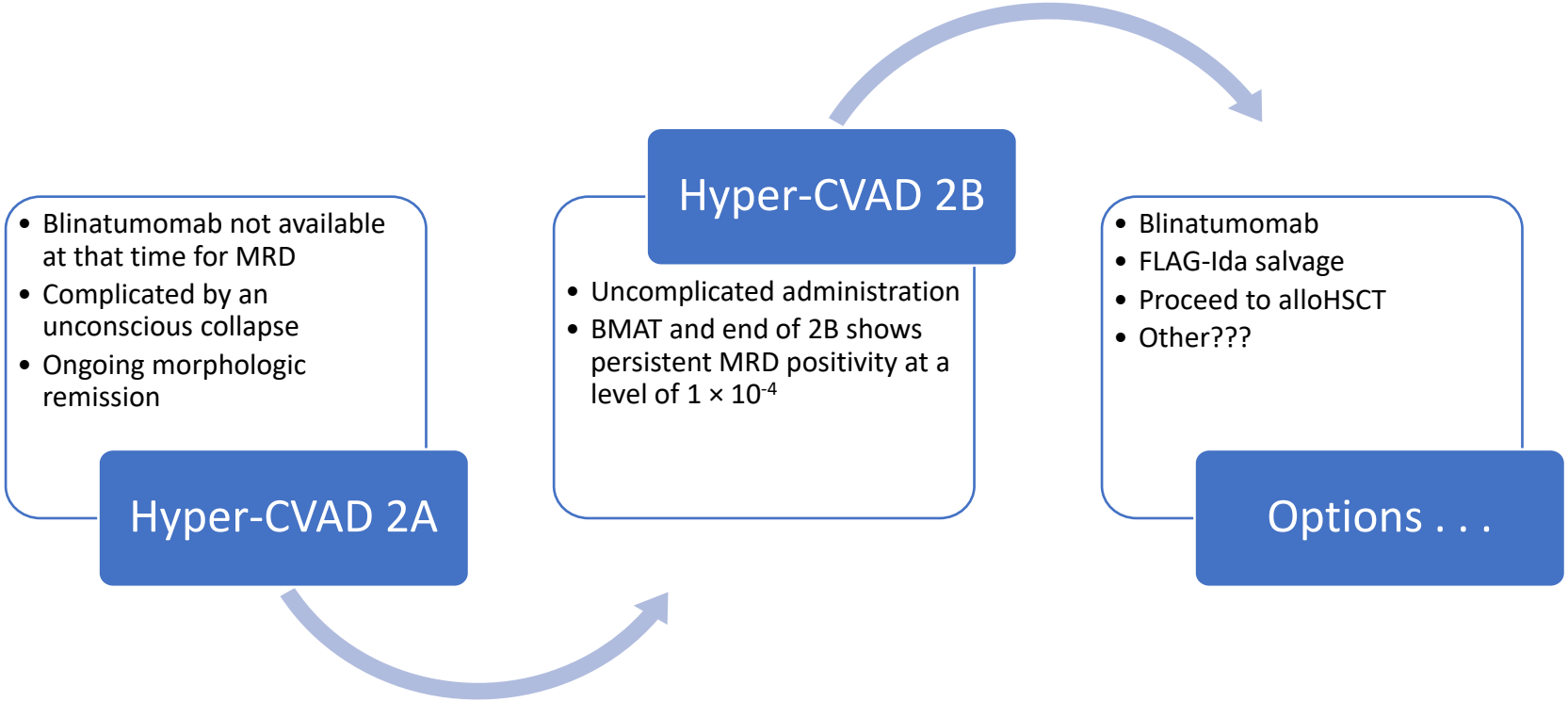
Treatment options

- Hyper-CVAD
- Modified BFM induction (pediatric-inspired regimen)
- LALA-94 (adult regimen)
- Immediate allogeneic stem cell transplant

Clinical progress



Progress continues . . .



Proceeded to alloHSCT

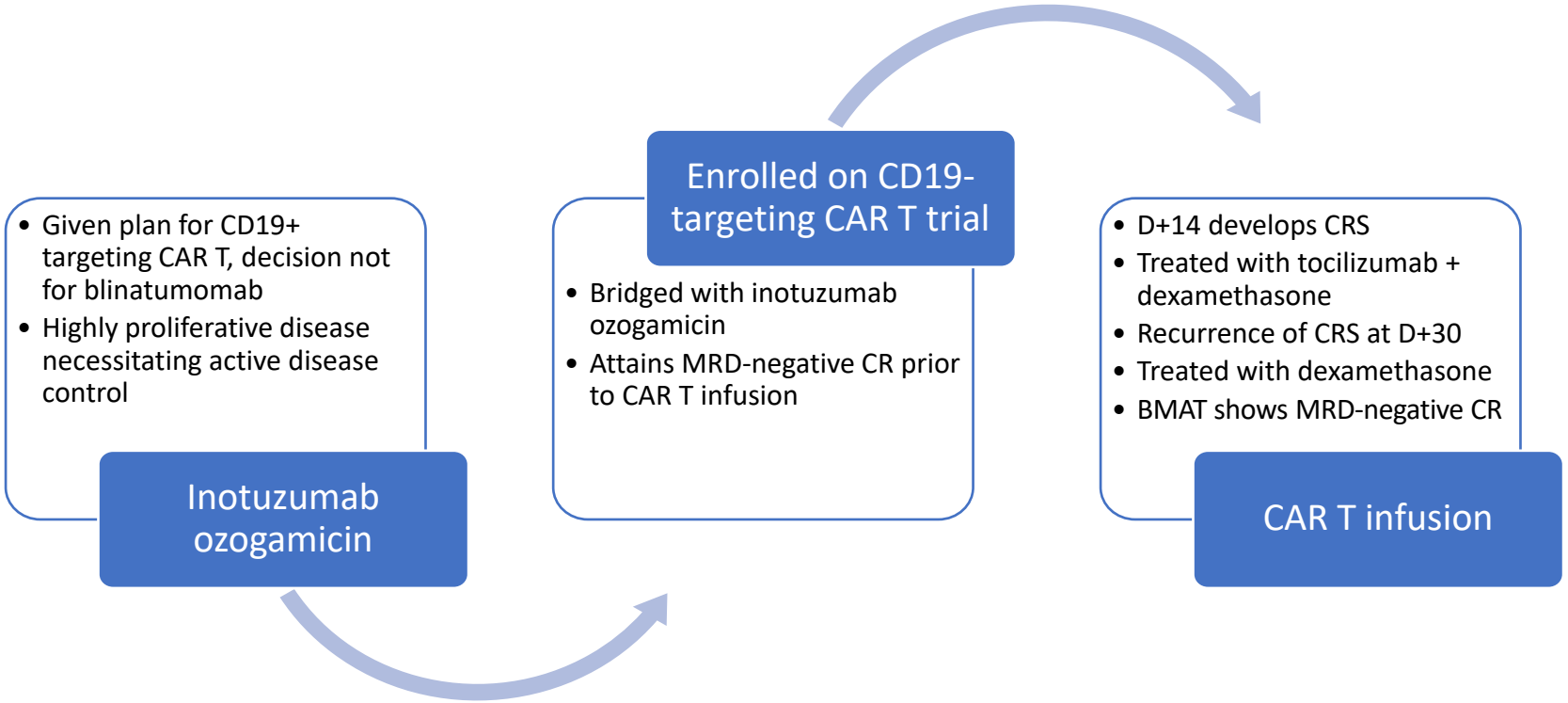
- Received a myeloablative (Cy/TBI) conditioned alloHSCT from sibling donor
- D+30 BMAT: MRD-negative remission
- D+90 BMAT: ongoing MRD-negative remission

- **So a happy ending, right?**

All good things must come to an end

Admitted 12 months post-transplant	Initial therapy	Therapeutic options
• High white cell count • Recurrence of B symptoms • Bone marrow aspirate confirms relapsed B-ALL	• Admitted to hospital • Received dexamethasone and vincristine to control peripheral blasts	• Blinatumomab • Inotuzumab ozogamicin • FLAG-Ida • Venetoclax + navitoclax • CAR T?

Therapy continues . . .



6 months post-CAR T . . .

Presents for routine follow-up	Frank discussions with patient	Options
• Blasts in peripheral blood • Bone marrow biopsy confirms relapsed B-ALL • Flow shows persistent CD19+ expression	• Outcome likely to be poor • Any therapy at this stage is almost certainly palliative • He is keen to have whatever therapy he can	• Second allograft • Blinatumomab • Inotuzumab ozogamicin • FLAG-Ida salvage • Venetoclax/navitoclax • Others???

Commenced on blinatumomab + DLI

- Commences first cycle of blinatumomab
  - Attains a morphologic complete remission
  - MRD positive 1×10^{-4}
- Given first cycle of sequential DLI – no GVHD
- Second cycle of blinatumomab
  - MRD negative
- Given second cycle of sequential DLI – develops cutaneous GVHD
- Completes 5 cycles of blinatumomab

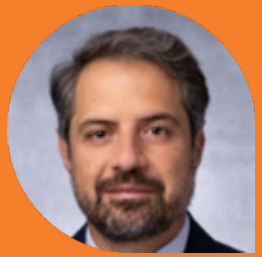
Outcome . . . so far

- Now 3 years post-completion of blinatumomab DLI
  - Monitoring for 2 years with 3 monthly bone marrow biopsies + MRD testing → remained MRD negative throughout
  - Last review 3 weeks ago
    - Well
    - Back at work
    - Normal blood counts
    - No cGVHD

Global Leukemia Academy

ALL Case-Based Panel Discussion

Moderators: Elias Jabbour and Shaun Fleming



APTITUDE HEALTH

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BREAK

APTITUDE HEALTH

Global Leukemia Academy

Beyond the Horizon: New and Future Treatment Approaches for Adult and Older ALL

Jae Park

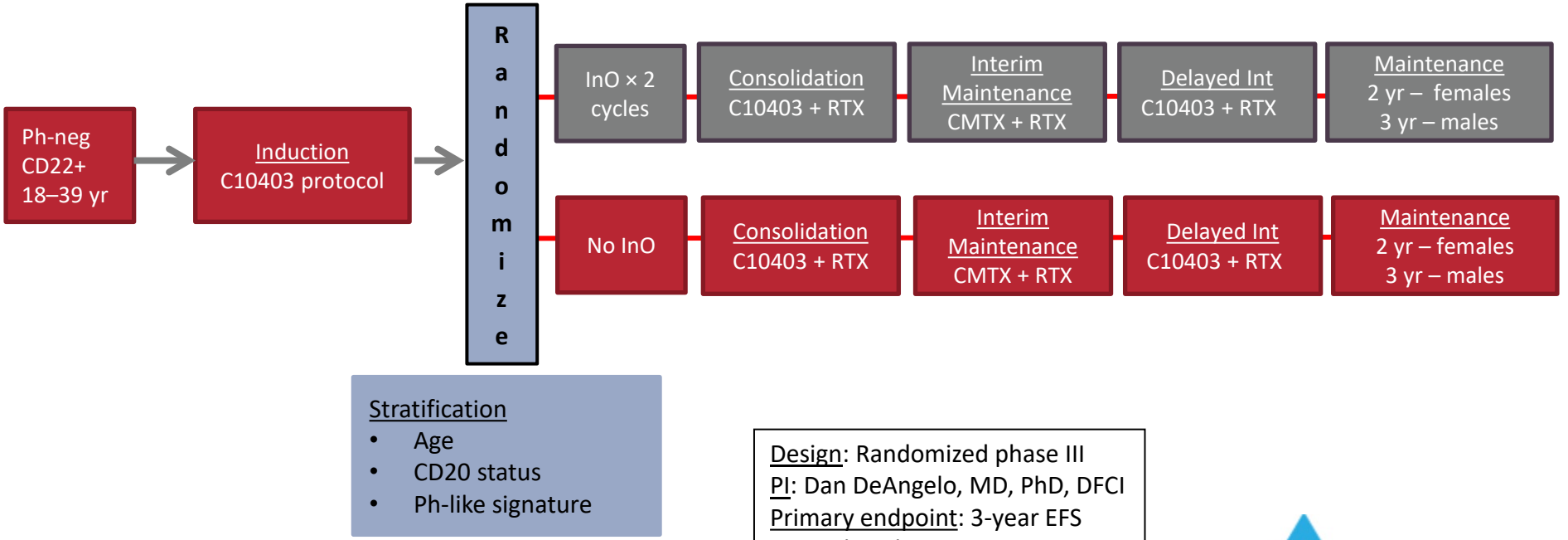
APTITUDE HEALTH

Beyond the Horizon: New and Future Treatment Approaches for Adult and Older ALL

Jae H. Park, MD
Associate Attending Physician
Director, Adult ALL Clinical Program
Acting Chief, Cellular Therapeutics Service
Memorial Sloan Kettering Cancer Center

Memorial Sloan Kettering Cancer Center

A041501: Frontline Chemo ± InO for AYA Patients



Design: Randomized phase III
PI: Dan DeAngelo, MD, PhD, DFCI
Primary endpoint: 3-year EFS
Accrual goal: 341
Accrual to date: 243

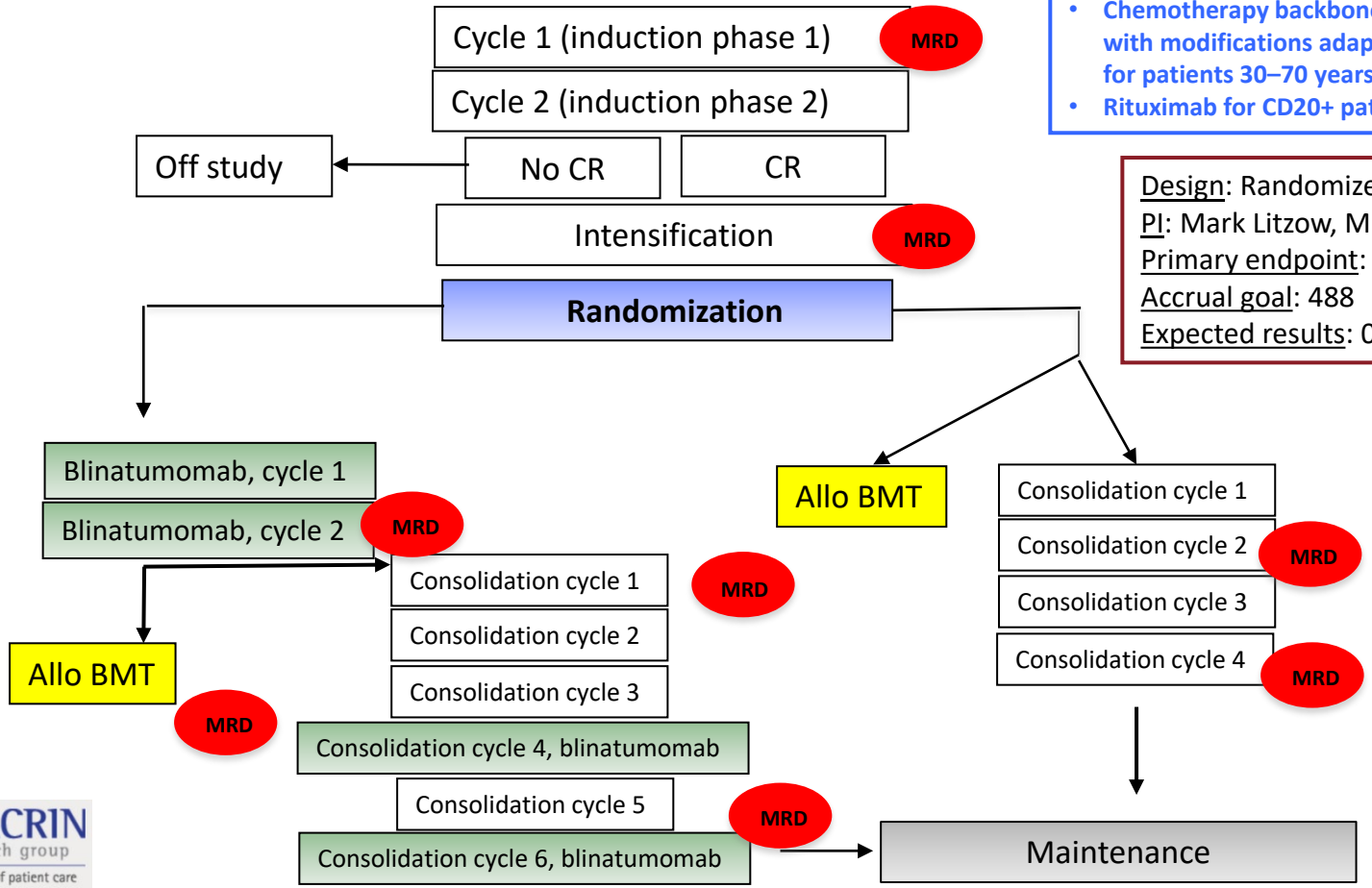
Alliance for Clinical Trials in Oncology

Clinical Trials Identifier NCT03150693.

E1910: Frontline Chemo ± Blinatumomab in Ph-Neg B-ALL

- Chemotherapy backbone hybrid of E2993 with modifications adapted from C10403 for patients 30–70 years
- Rituximab for CD20+ patients

Design: Randomized phase III
PI: Mark Litzow, MD, Mayo
Primary endpoint: 3-year OS
Accrual goal: 488
Expected results: 09/2025



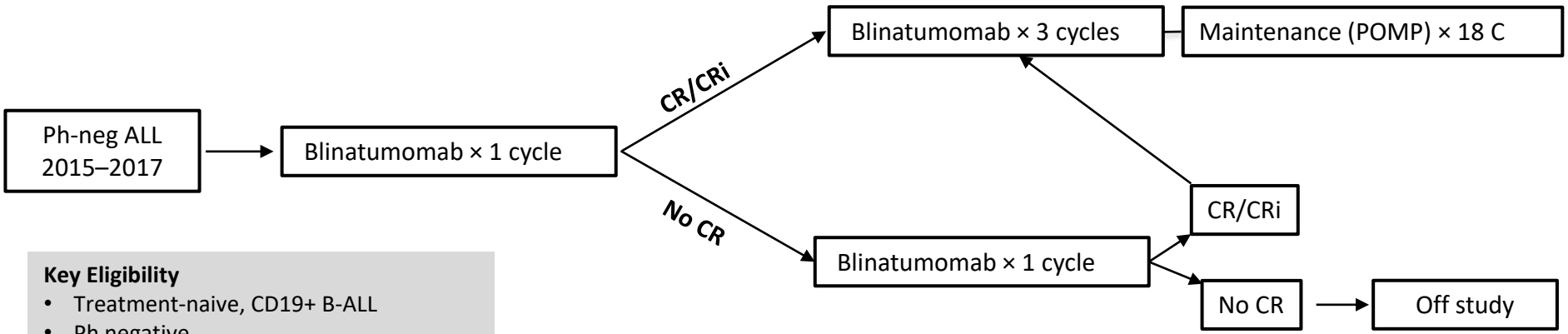
ECOG-ACRIN cancer research group
Reshaping the future of patient care

Older Adults With B-ALL

- Approximately 25% of new cases of B-ALL are diagnosed in adults >55 years
  - 4/5 deaths occur in adult patients
- Trials of intensive chemotherapy among older adults associated with
  - Low CR rates (~50-75%)
  - High rates of early mortality (~20%)
  - Poor long-term survival (~20%)
- No standard-of-care chemotherapy for older patients
- Novel agents incorporated as a “substitution strategy” and to reduce and/or eliminate cytotoxic chemotherapy and the associated toxicity
  - Antibody-based therapy
  - Small-molecule targeted therapy (BCL-2)

Sive JI, et al. *Br J Haematol.* 2012;157:463-471; Larson RA, et al. *Blood.* 1998;92:1556-1564; O’Brien S, et al. *Cancer.* 2008;113:2097-2101; Kantarjian H, et al. *Lancet Haematol.* 2018;19:240-248; Cancer Facts and Figures 2022. Atlanta, GA: American Cancer Society; 2022.

SWOG 1318: Blinatumomab + POMP Maintenance



Key Eligibility

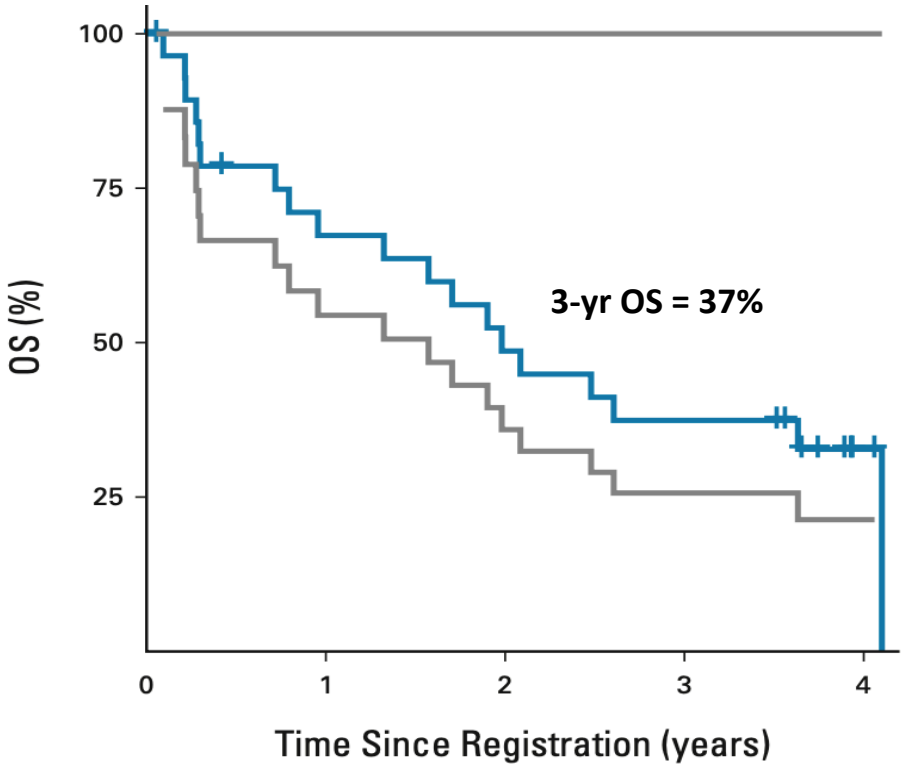
- Treatment-naive, CD19+ B-ALL
- Ph negative
- Age ≥65 years
- ECOG ≤2, ECOG 3 if due to disease
- Adequate organ function
- No uncontrolled infection, cardiac disease, CNS disease, other cancer

Design: Single-arm phase II
PI: Anjali Advani, MD, Cleveland Clinic
Primary endpoint: 3-year OS (goal >10%)
Accrual goal: 26

SWOG CANCER RESEARCH NETWORK

Advani AS, et al. *J Clin Oncol.* 2022;40:1574-1582.

SWOG 1318: Blinatumomab + POMP Maintenance

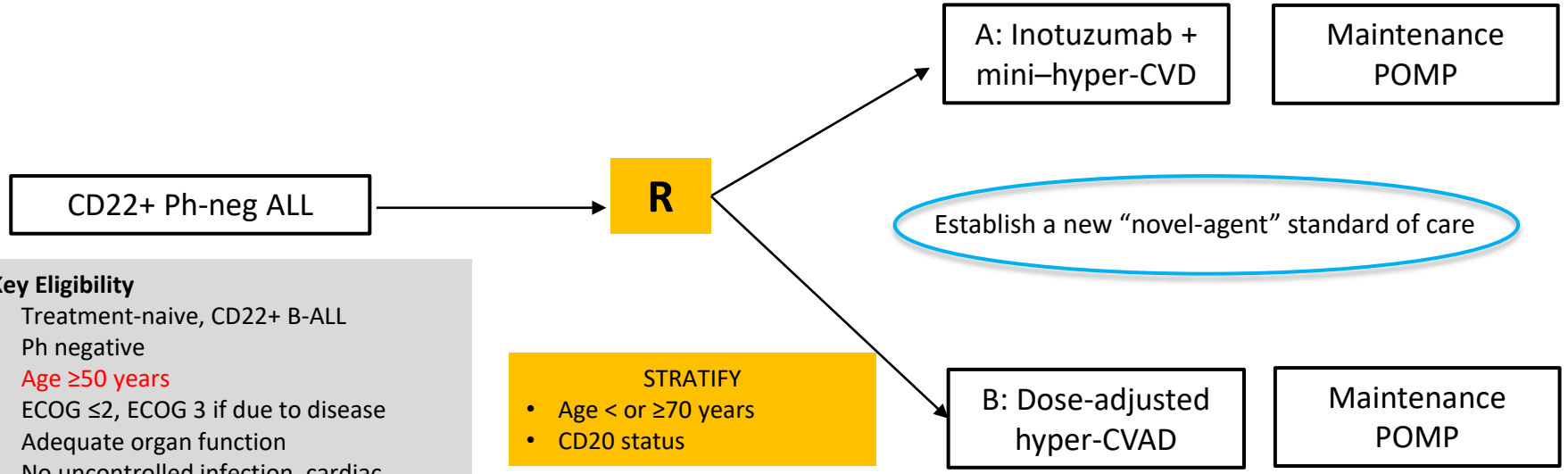


Median age: 75 years	
Median marrow blast count: 87%	
CR/CRi:	66%
MRD^{neg}	92%
Early death rate:	0%
CD19 relapse:	7/13

Advani AS, et al. *J Clin Oncol.* 2022;40:1574-1582.

SWOG CANCER RESEARCH NETWORK

A042001: InO + Mini–Hyper-CVD vs Age-Adjusted Hyper-CVAD

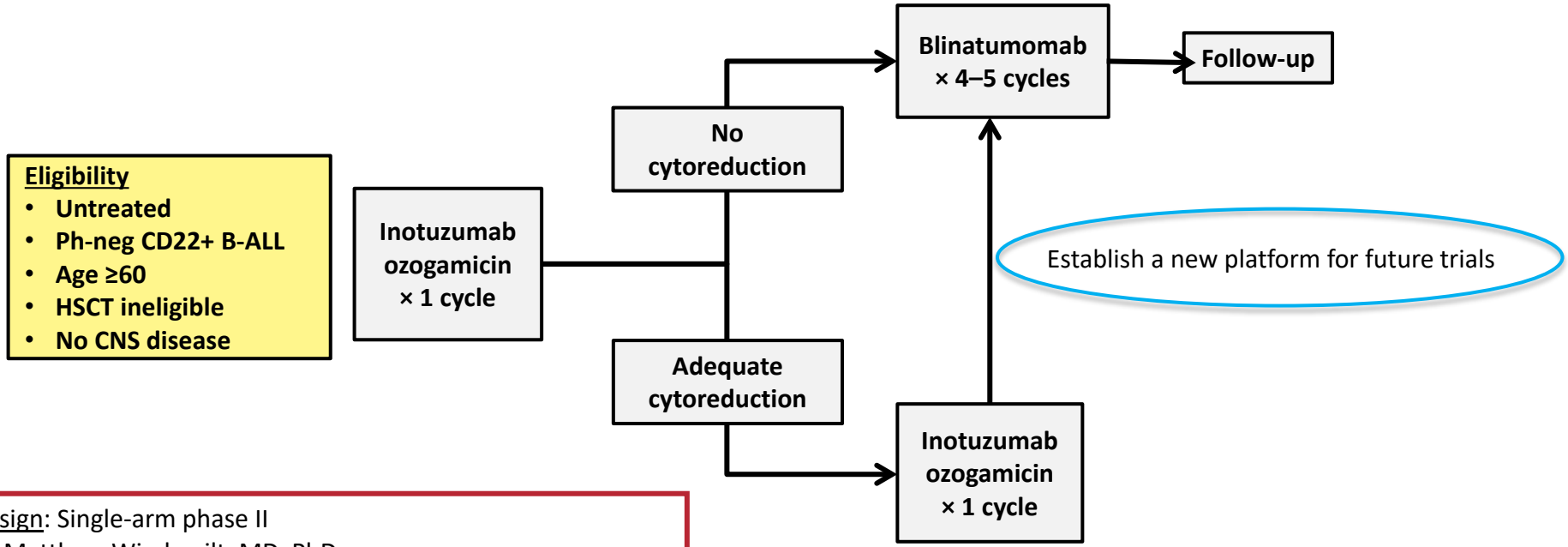


Design: Randomized phase II
PI: Marlise Luskin, MD, DFCI, and Elias Jabbour, MD, MDACC
Primary endpoint: EFS following cycle 2
Accrual goal: 80

Alliance for Clinical Trials in Oncology

Clinical Trials identifier: NCT05303792.

A041703 (Cohort 1): InO + Blinatumomab

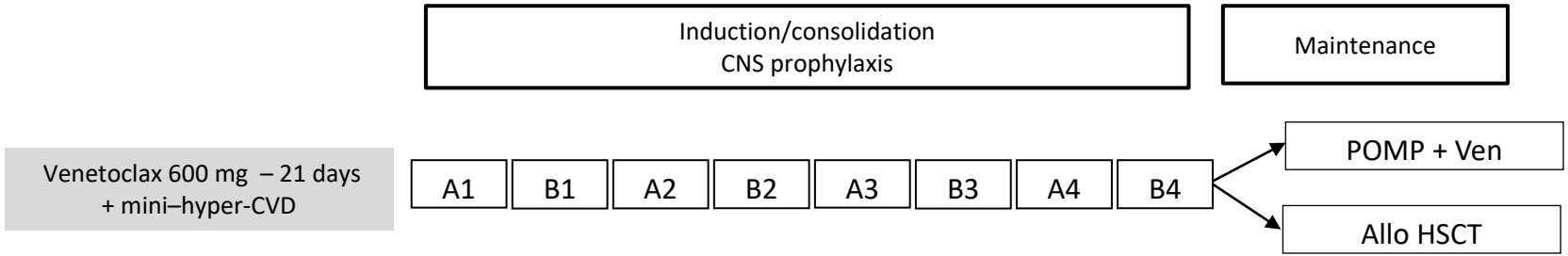


Design: Single-arm phase II
PI: Matthew Wieduwilt, MD, PhD
Primary endpoint: 1-year EFS (goal >30%)
Accrual goal: 29
Accrual complete: June 2021, primary analysis expected 06/22

Alliance for Clinical Trials in Oncology

Clinical Trials Identifier NCT03739814.

MDACC/DFCI: Phase Ib Trial of Venetoclax + Mini–Hyper-CVD



Key Eligibility

- B- and T-lineage ALL
- Age ≥60 years for new diagnosis
- Age ≥18 years with R/R ALL
- ECOG ≤2, ECOG 3 if due to disease
- Adequate organ function
- No uncontrolled infection, cardiac disease, CNS disease, other cancer

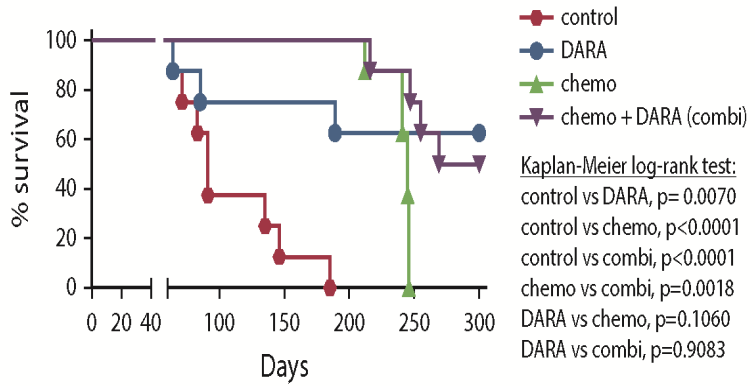
	Patients, n	Response, n (%)	MRD negative, n (%)
De novo ALL	10 pts	9 CR/CRi (90%) 1 PR (10%)	9 (90%)
R/R ALL	8 pts	1 CR and 2 CRp (37.5%)	2 (25%)

Jain N, et al. ASH 2019. Abstract 3867. Clinical Trials Identifier NCT03319901.

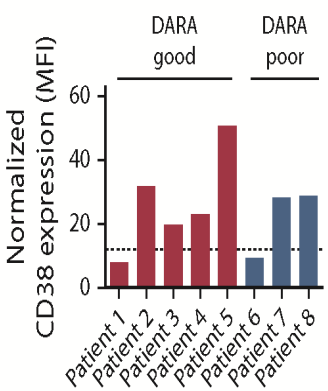
Trial, Phase II	Chemoimmunotherapy	N	Age	Outcome
MDACC *NCT01371630*	**Induction/consolidation: Mini-CVD, INO ± blinatumomab** Maintenance: POMP CNS prophylaxis: MTX and Ara-C	70	≥60	50%, 4-yr OS
SWOG 1318 *NCT02143414*	**Induction: blinatumomab** **Consolidation: blinatumomab** Maintenance: POMP CNS prophylaxis: MTX	29	≥65	37%, 3-yr OS
GMALL-INITIAL1 *NCT03460522*	**Induction: INO + DEX** Consolidation: ID-MTX + PEG + ID + Ara-C, IDA + Ara-C + CYC + DEX + RTX Maintenance: 6MP + MTX CNS prophylaxis: MTX + DEX + Ara-C	45	≥55	91%, 1-yr OS
EWALL-INO *NCT03249870*	Prephase: DEX 10 mg **Induction1: INO + VCR + DEX** **Induction2: INO + DEX + CY** Consolidation: Ara-C + DEX, MTX + VCR + 6-MP, CY + VP16 + MTX Maintenance: POMP CNS prophylaxis: MTX + DEX + Ara-C	115	≥55	78.5%, 1-yr OS
Alliance 041703 *NCT03739814*	Induction: **inotuzumab** Consolidation: **blinatumomab** CNS prophylaxis: MTX	29	≥60	Expected in 2022
HOVON 146-ALL *NCT03541083*	**Pre-phase: PRED/blinatumomab** Induction: VCR + DNR + PRED Consolidation: 6TG + VP16 + Ara-C, 6TG + VCR + PRED + ITD-MTX, blinatumomab Intensification I: DEX + VBL + DOX + PEG Interphase: PRED + VCR + RTX + 6TG + HD-MTX Intensification II: PRED + VCR + RTX + DNR + PEG + Blin Maintenance: POMP + RTX CNS prophylaxis: MTX + DEX	71	18–70	Expected in 2022

Daratumumab Efficacy for T-Lineage ALL

A



C



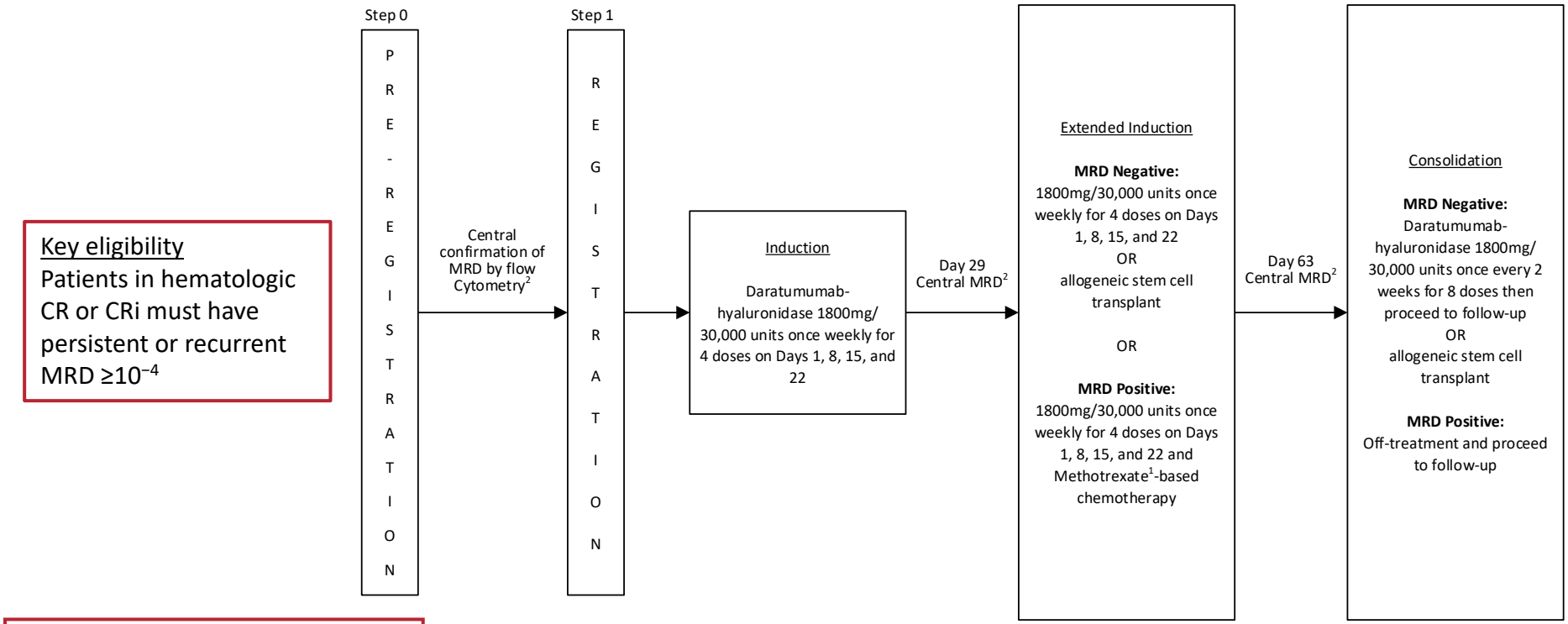
B

	DARA			chemo + DARA		
	Marker 1	Marker 2	Marker 3	Marker 1	Marker 2	Marker 3
Patient 1	10^{-6*}	negative	negative	positive	positive	positive
Patient 2	negative	negative		negative	negative	
Patient 3	negative	negative		negative	negative	
Patient 4	n. d.	n. d.	n. d.	n. d.	n. d.	n. d.
Patient 5	negative	negative		negative	negative	

- CD38 expression is maintained on T-ALL cells after chemo exposure
- Both dara and dara + chemo improved OS and cleared MRD, no significant difference
- CD38 expression did not correlate with response
- Case reports of clinical efficacy

Bride K, et al. *Blood.* 2018;131:995-999; Vogiatzi F, et al. *Blood.* 2019;134:713-716; Ofran Y, et al. *Leukemia.* 2020;34:293-295.

EA9213: Daratumumab for MRD in T-ALL

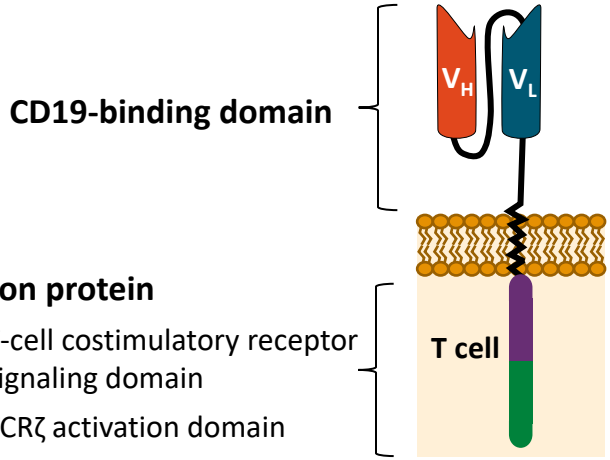


Key eligibility
Patients in hematologic CR or CRi must have persistent or recurrent MRD $\geq 10^{-4}$

Design: Single-arm phase I/II
PI: Shira Dinner, MD, Northwestern
Primary endpoint: MRD^{neg} rate
Accrual goal: 20

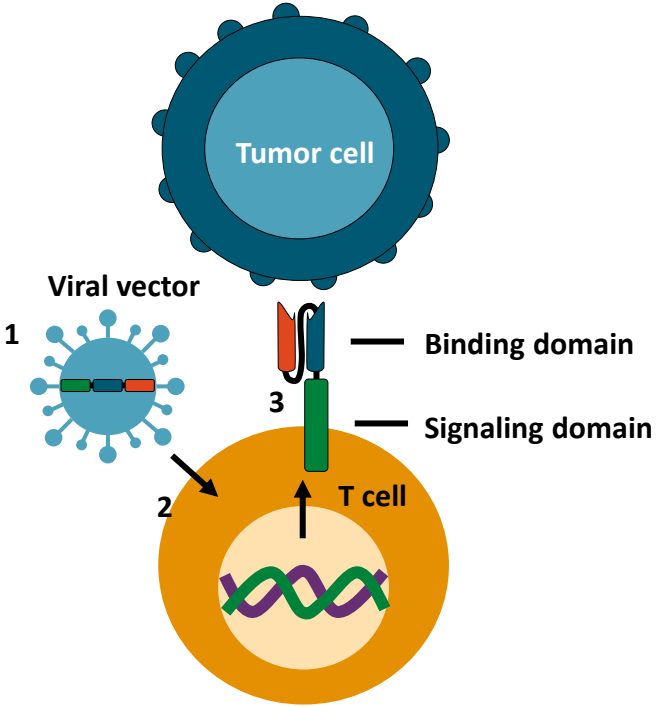
ECOG-ACRIN cancer research group
Reshaping the future of patient care

CD19-Directed CAR T Cell



Fusion protein

- T-cell costimulatory receptor signaling domain
- TCRζ activation domain



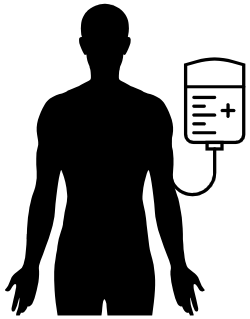
CD19-directed CAR T cell

- Comprising a CD19 antigen-binding domain, a costimulatory domain (generally CD28 or 4-1BB), and CD3-ζ signaling domain

Autologous CAR T-Cell Therapy: Underlying Principles

Leukapheresis

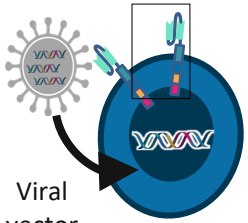
Collect patient's white blood cells

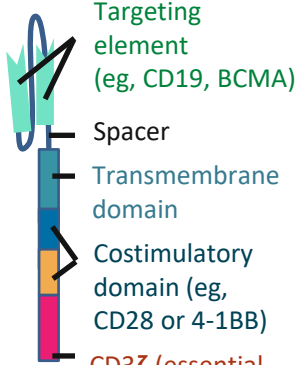


Manufacturing

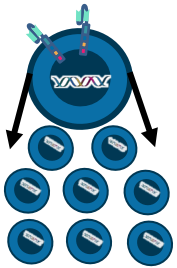
Isolate and activate T cells

Engineer T cells with CAR gene





Expand CAR T cells

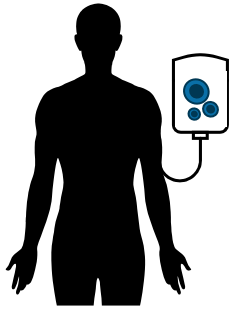


Median manufacturing time: 17–28 days

Patients undergo lymphodepleting (and possibly salvage/bridging) therapy

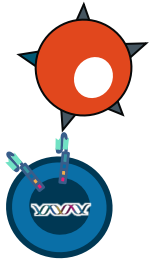
Infusion

Infuse same patient with CAR T cells



Activity

eg, CD19, BCMA



Majors B, et al. EHA 2018. Abstract PS1156; Lim WA, June CH. *Cell*. 2017;168:724-740; Sadelain M, et al. *Nat Rev Cancer*. 2003;3:35-45; Brentjens RJ, et al. *Nat Med*. 2003;9:279-286; Park J, et al. ASH 2015. Abstract 682. Axicabtagene ciloleucel PI. Tisagenlecleucel PI.

FDA-Approved CAR T-Cell Therapies in ALL

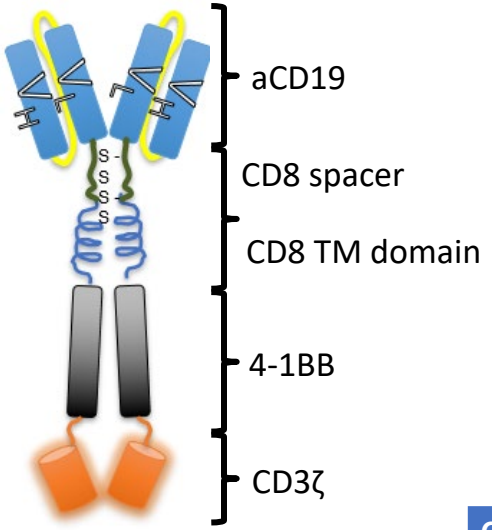
Therapy	Target	Approval Date	Indications
Tisagenlecleucel	CD19	August 30, 2017	**Patients aged up to 25 yr with B-cell precursor ALL that is refractory or in second/later relapse**
Brexucabtagene autoleucel	CD19	October 1, 2021	**Adults with relapsed or refractory B-cell ALL**

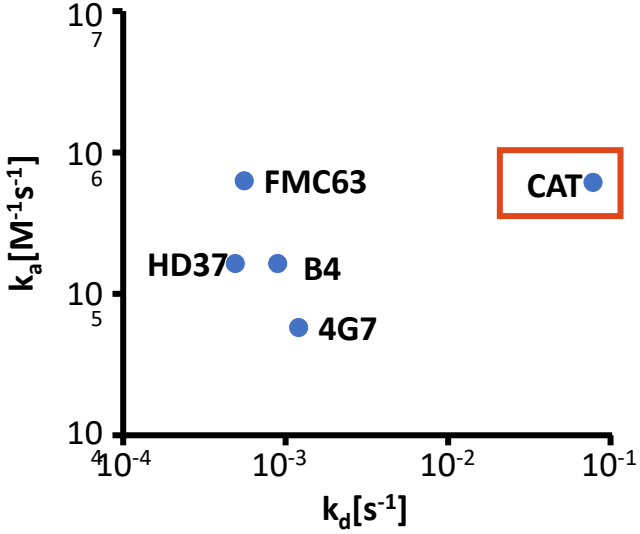
Remaining Questions for CAR in ALL

- Reduce toxicity
- Increase duration of remission
- Increase accessibility (patients not receiving cells due to rapid POD)
- T-ALL

ALLCAR19: Low-Affinity CD19 CAR T-Cell Therapy AUTO1

- Hypothesis: lowering CAR affinity may be advantageous to CAR T-cell effector function
- ALLCAR19: phase I/II study of second-generation AUTO1 for R/R B-ALL (N = 13)
  - AUTO1: CD19 CAR T-cell therapy with a faster “off rate” but similar “on rate” vs earlier generation CARs
  - AUTO1 binder has a 40× lower affinity for CD19

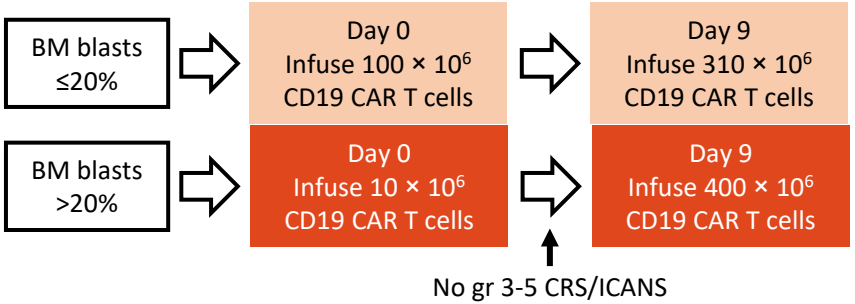




Clone	*ka* (1/Ms)	*kd* (1/s)	KD (M)
CAT	2.153E+5	0.003096	1.438E-8
FMC63	2.076E+5	6.810E-5	3.280E-10

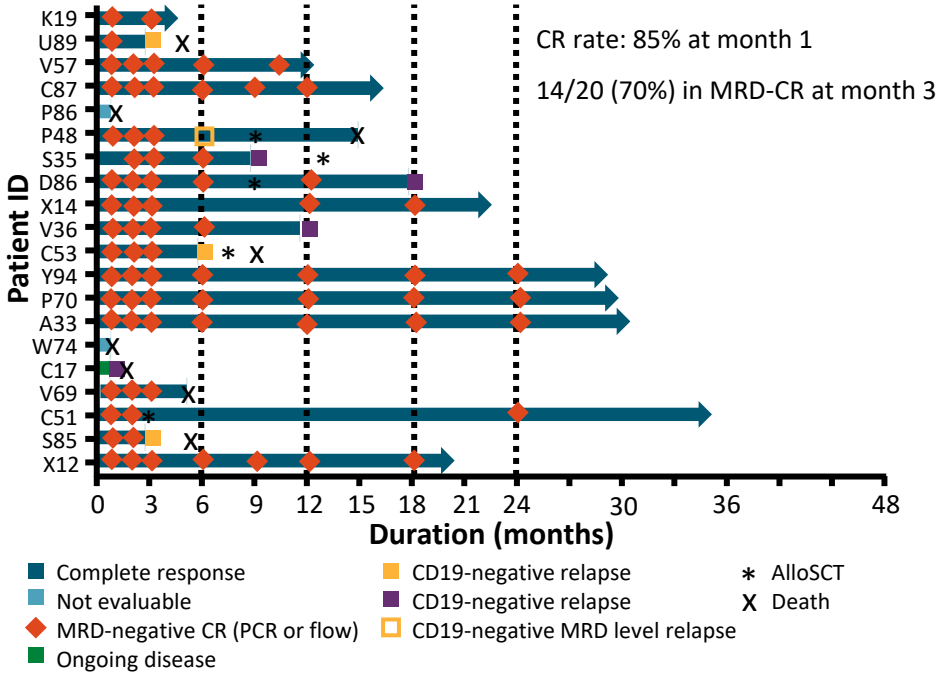
Roddie C, et al. ASH 2019. Abstract 226.

ALLCAR19: CD19-Targeted CAR (AUTO1) for R/R Adult B-ALL



75% >20% blasts received 410 × 10^6 cells; 25% received 10 × 10^6 cells due to ongoing grade 1 CRS at D10.

Parameter, %	Patients (N = 20)
Prior blinatumomab	25
Prior inotuzumab	50
Prior HSCT	65
BM blasts before LD chemo	
<5% blasts	35
5-49% blasts	20
≥50% at T-cell infusion	45



- 13% of responders proceeded to alloHSCT
- EFS at 6 and 12 mo: 68% and 48%
- CRS: 55% (all grade 1-2)
- ICANS: 20% (any grade); 15% grade 3

Roddie C, et al. *J Clin Oncol*. 2021;39:3352-3363.

CD19-Negative Disease and Relapse Following CD19 CAR T-Cell Therapy for B-ALL

Trial	Phase	Population	CD19 CAR Construct	Relapse Rate, % (n/N)	CD19-Negative Relapse Rate, % (n/N)
Children's Hospital of Philadelphia	I	Pediatric	FMC63-4-1BB-ζ	36 (20/55)	24 (13/55)
ELIANA	II	Pediatric	FMC63-4-1BB-ζ	33 (20/61)	25 (15/61)
Seattle Children's	I	Pediatric	FMC63-CD28-ζ	45 (18/40)	18 (7/40)
NCI	I	Pediatric	FMC63-4-1BB-ζ	29 (8/28)	18 (5/28)
MSKCC	I	Adult	SJ25C1-CD28-ζ	57 (25/44)	9 (4/44)
FHCRC	I	Adult	FMC63-4-1BB-ζ	31 (9/29)	7 (2/29)

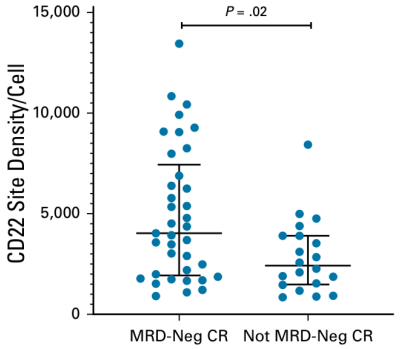
Treatment failure after CAR T-cell therapy

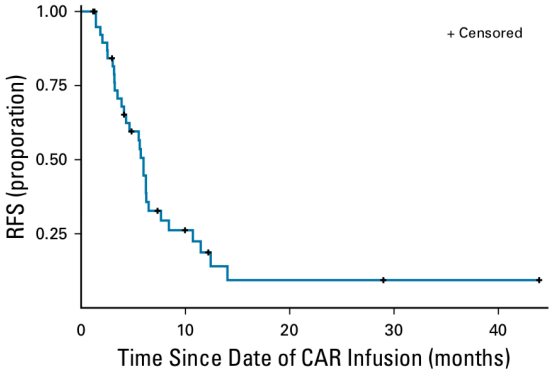
- Long-term outcomes confounded across trials by differing HCT use and other unique practices following CAR T-cell therapy
- True incidence of CD19+ and CD19- relapse unknown

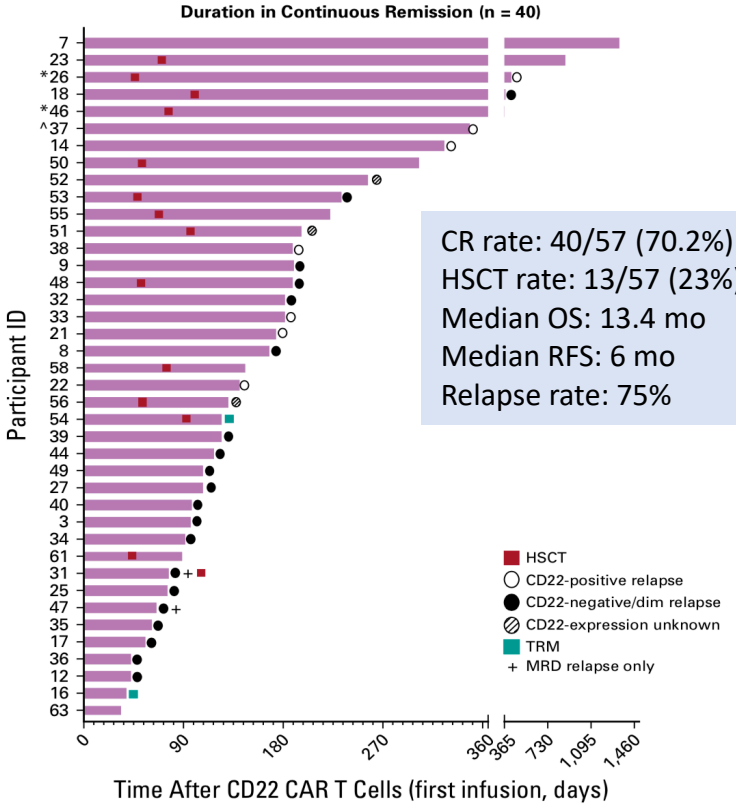
Schultz LM, et al. ASH 2019. Abstract 744.

CD22 CAR in Children and AYA With R/R B-ALL

Demographic	All Participants (treated)	DL1 (3×10^5/kg)	DL2[a] (1×10^6/kg)	DL3 (3×10^6/kg)	DL2-TCS (1×10^6/kg)	DL1-TCS[b] (3×10^5/kg)
No. of participants	58	6 (10.3)	18 (31.0)	2 (3.4)	7 (12.1)	25 (43.1)
Median age, years (range)	17.5 (4.4-30.6)	21.3 (7.3-22.7)	16.7 (8.0-30.6)	17.1 (7.9-26.4)	12.8 (4.4-28.9)	15.8 (4.7-30.4)
Prior HSCT	39 (67.2)	6 (100)	13 (72.2)	2 (100)	6 (85.7)	12 (48)
Prior CD19-targeted therapy	51 (87.9)	6 (100)	13 (72)	2 (100)	7 (100)	23 (92)
Prior CD19 CAR	36 (62.0)	6 (100)	11 (61.1)	1 (50)	5 (71.4)	13 (52)
Prior blinatumomab	23 (39.7)	1 (16.7)	4 (22.2)	2 (100)	2 (28.6)	14 (56)
Prior inotuzumab	14 (24.1)	1 (16.7)	4 (22.2)	1 (50)	3 (42.9)	5 (20)
Prior CD22 CAR exposure[c]	5 (8.6)	0	0	0	2 (28.6)	3 (12)
Any CD19-negative population[d]	33 (56.9)	4 (66.7)	9 (50)	0	5 (71.4)	15 (60)
≥ M2 marrow	44 (75.9)	4 (66.7)	11 (61.1)	2 (100)	6 (85.7)	21 (84)
Isolated CNS disease[e]	1 (1.7)	0	1 (5.6)	0	0	0





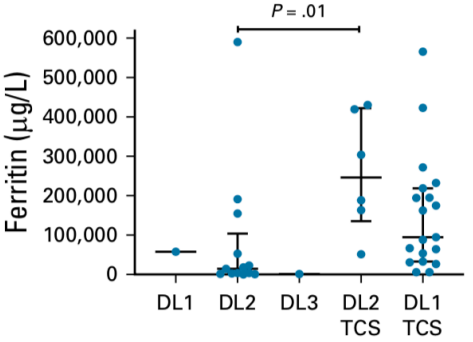


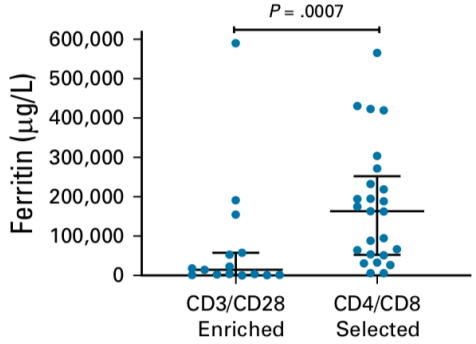
CR rate: 40/57 (70.2%)
HSCT rate: 13/57 (23%)
Median OS: 13.4 mo
Median RFS: 6 mo
Relapse rate: 75%

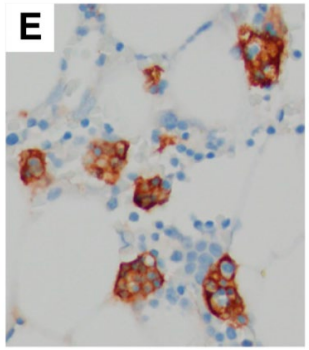
Shah N, et al. *J Clin Oncol.* 2020;38:1938-1950.

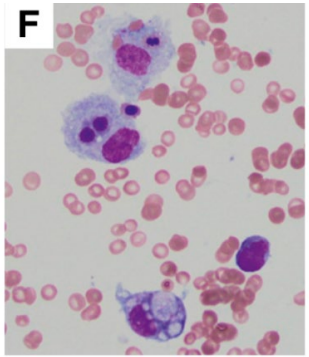
CD22 CAR in Children and AYA With R/R B-ALL: Toxicity

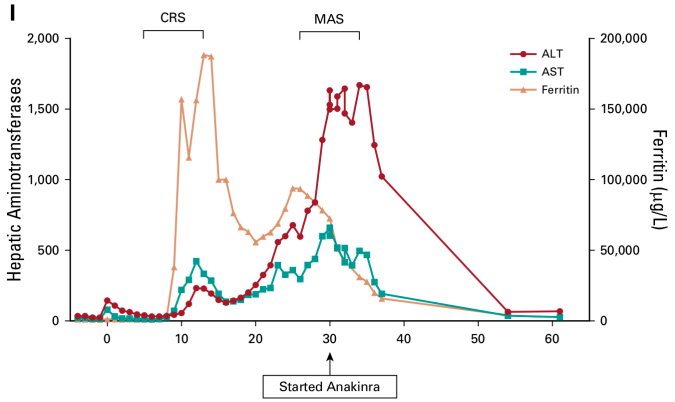
Variable	All Participants	DL1 (3×10^5/kg)	DL2 (1×10^6/kg)	DL3 (3×10^6/kg)	DL2-TCS (1×10^6/kg)	DL1-TCS[a] (3×10^5/kg)
Total No. of participants	58	6	18	2	7[b]	25
Participants with CRS	50 (86.2)	3 (50)	16 (88.9)	2 (100)	6 (85.7)	23 (92)
CRS grades 1-2	45 (90)	3 (100)	15 (93.8)	2 (100)	6 (100)	19 (82.6)
CRS grades ≥ 3	5 (10)	0	1 (6.3)	0	0	4 (17.4)
CRS grades ≥ 3 ASTCT CRS scale	12 (24)	1 (33.3)	3 (18.8)	0	1 (16.7)	7 (30.4)
Any neurotoxicity	19 (32.8)	2 (33.3)	4 (22.2)	1 (50)	3 (42.9)	9 (36)
Severe neurotoxicity	1 (1.7)	0	0	0	0	1 (4)
Received tocilizumab	23 (39.7)	0	3 (16.7)	0	4 (57.1)	16 (64)
Received corticosteroids	18 (31.0)	0	2 (11.1)	1 (50)	4 (57.1)	13 (52)
Developed DIC	14 (24.1)	0	6 (33.3)	0	4 (57.1)	4 (16)
Developed symptomatic coagulopathy	9 (15.5)	0	3 (16.7)	0	4 (57.1)	2 (8)
Developed HLH	19 (32.7)	0	3 (16.7)	0	5 (71.4)	11 (44)
Developed CLS	3 (5.2)	0	1 (5.6)[c]	0	0	2 (8)
Developed aHUS	3 (5.2)	0	0	0	1 (14.3)	2 (8)
Grade 5 events	2 (3.4)	0	2 (11.1)	0	0	0





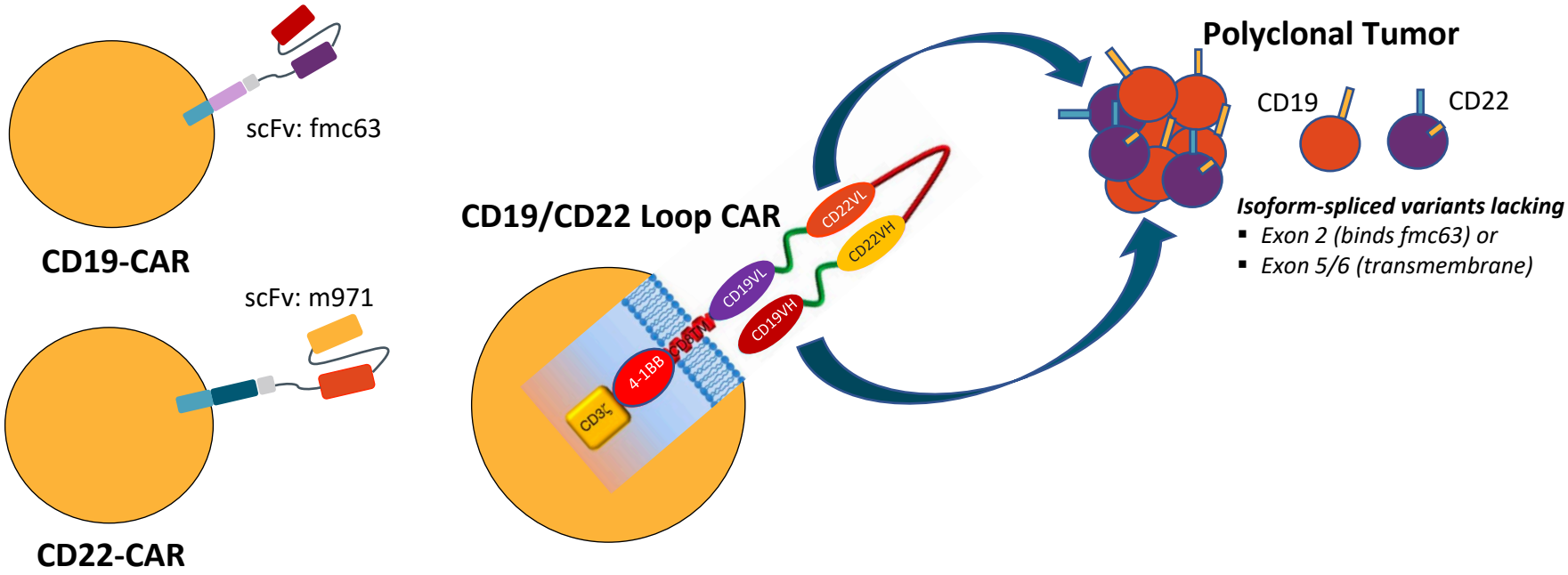






Shah N, et al. *J Clin Oncol.* 2020;38:1938-1950.

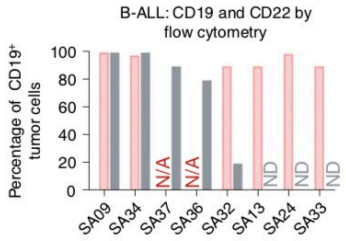
Development of Bispecific CAR-Targeting CD19/CD22

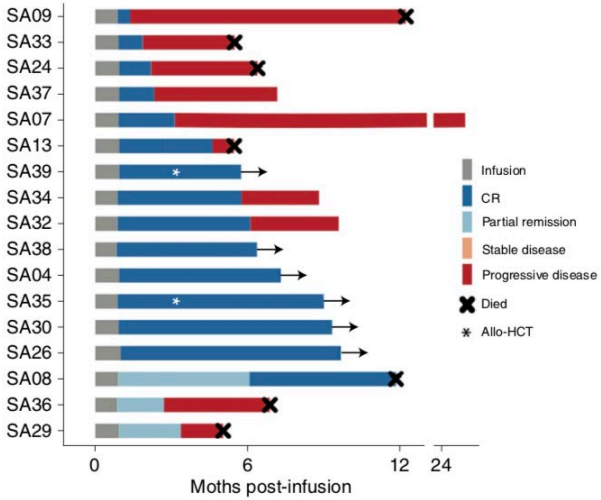


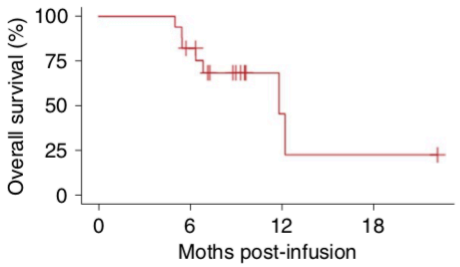
Fry TJ, et al. *Nat Med.* 2018;24:20-28.

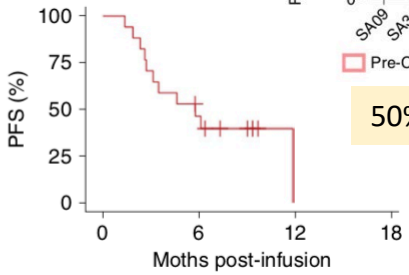
Phase I Trial Using CD19/CD22 Bispecific CAR T Cells in Adult ALL

Parameter	N = 17
Prior HSCT	12 (71%)
Prior blinatumomab	10 (59%)
Prior inotuzumab	6 (35%)
Prior CD19 CAR	1 (6%)
BM blasts >5%	7 (41%)
CR rate as best response	15 (88%)









50% relapse with CD19-

CD19-22 CAR exert less immune pressure to CD22+ leukemic cells vs CD19

Spiegel J, et al. *Nat Med.* 2021;27:1419-1431.

Bispecific CARs in ALL: ASH 2021 Updates

Abstract 469: CART22-65s co-administered with huCART19 in adult patients with R/R ALL [Frey N, et al]

Co-infusion of 2 CAR products
(humanized CD19 and CD22 CAR)

- Fractionated adoptive dosing
- Target dose: 2×10^6 CART22 and 2×10^6 CART19

13 adult patients treated

- 2 deaths w/in 30d due to grade 4 ICANS and sepsis
- 100% CR in 11 evaluable patients
  - 1 molecular relapse at 9 months
  - 10 pts in continued remission w/o HSCT
- CD19 CAR expand first then CD22 CAR
  - Median time to peak: 9 vs 16d
  - At 6 mo, 7/8 CD19 CAR persisted vs 4/8 CD22 CAR

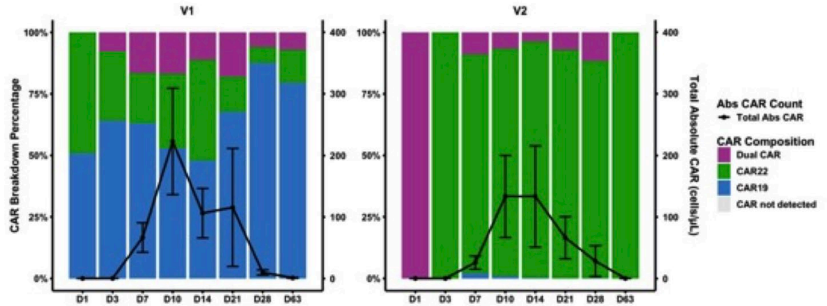
Abstract 470: SCRI-CAR19 × 22v2 T-cell product demonstrates bispecific activity in B-ALL [Annesley C, et al]

Infusion of double transduced CD19 or CD22 CAR

- Phase I dose-escalation study
- 3 dose levels: 0.5×10^6, 1×10^6, and 3×10^6 CAR T cells/kg

12 pediatric patients treated

- Skewing toward CD22 CAR transduction
  - 42% CD22 only, 33% CD19 + CD22, 3.2% CD19 only
- No DLT: no sCRS and 1 grade 3 ICANS
- 91% CR
- Peak CAR expansion b/w D7 and D14



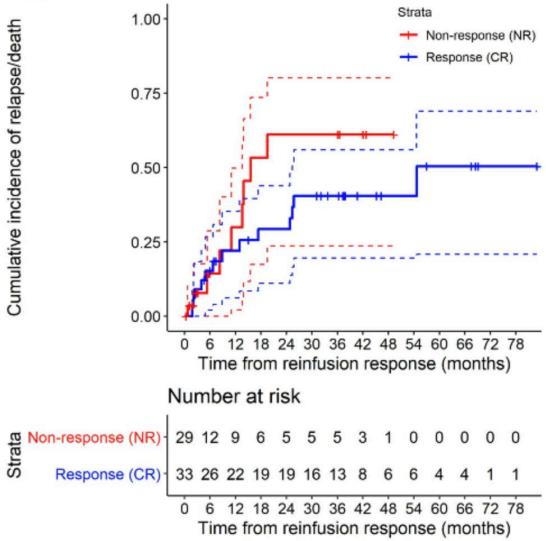
Reinfusion of CD19 CAR: ASH 2021 Updates

Abstract 474: Outcomes after reinfusion of CD19 CAR T cells in children and young adults with R/R B-ALL [Myers R, et al]

Single-center clinical experience of 81 patients

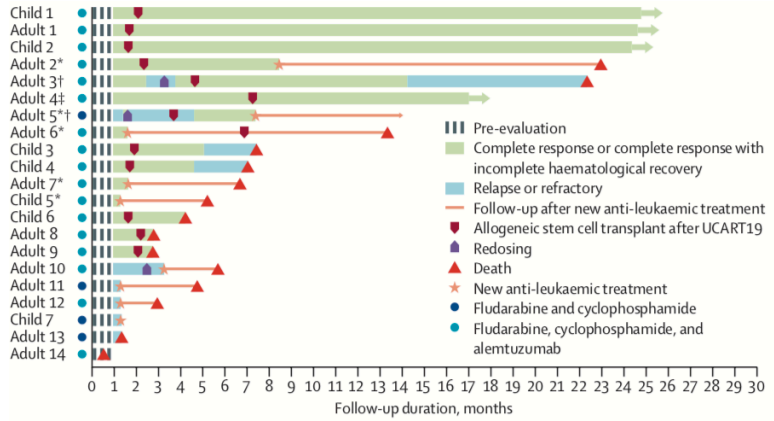
- Reinfusion criteria
  - PB B-cell or BM CD19+ hematogone recovery w/in 6 months (n = 53, 65%)
  - New CD19+ MRD or morphologic relapse (n = 10, 12%)
  - Nonresponse to initial infusion (n = 5, 6%)
- Products: CTL019 (n = 44), commercial tisagen (n = 11), huCART19 (n = 26)
- Primary outcome: CR with establishment or maintenance of BCA at D28

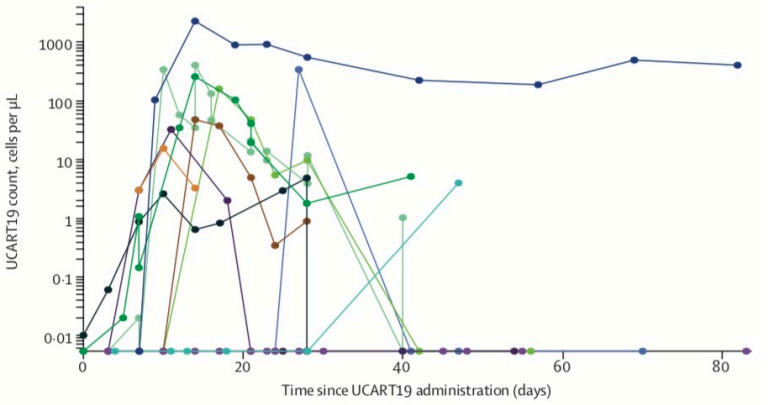
- Among 63 pts reinfused for relapse prevention
  - 52% CR at D28 → 39% relapse (~50% CD19-) + 60% in continuous remission (majority w/o HSCT)
- Among 10 pts reinfused for refractory disease
  - 50% CR → 50% relapse



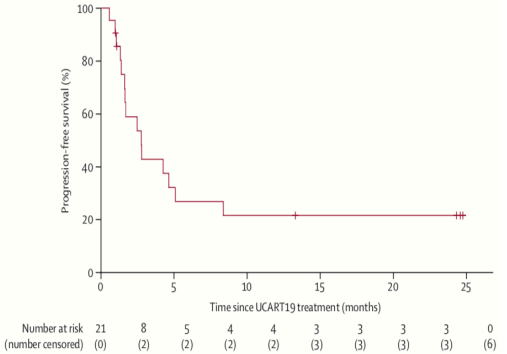
UCART19 (“off-the-shelf”) in Pediatric and Adults With R/R B-ALL

	CALM (n=14)	PALL (n=7)	Pooled (n=21)
Age, years			
Median (IQR)	29·5 (22·0–45·0)	2·7 (2·2–14·0)	22·0 (14·0–39·0)
Range	18·0–62·0	0·8–16·4	0·8–62·0
Number of previous lines of therapy			
1–3	4 (29%)	3 (43%)	7 (33%)
≥4	10 (71%)	4 (57%)	14 (67%)
Median (IQR)	4 (3–4)	4 (3–6)	4 (3–5)
Range	1–5	2–6	1–6
High cytogenetic risk*	6 (43%)	3 (43%)	9 (43%)
Previous treatments			
Inotuzumab ozogamicin	6 (43%)	2 (29%)	8 (38%)
Blinatumomab	4 (29%)	1 (14%)	5 (24%)
Allogeneic stem cell transplant	10 (71%)	3 (43%)	13 (62%)
Time to relapse following previous allogeneic stem cell transplant			
<6 months	4 (29%)	1 (14%)	5 (38%)
≥6 months	6 (43%)	2 (29%)	8 (62%)
Cytoreduction before lymphodepletion†	7 (50%)	5 (71%)	12 (57%)
Bone marrow tumour burden before lymphodepletion			
<5% of blasts	3 (21%)	3 (43%)	6 (29%)
5–25% of blasts	4 (29%)	2 (29%)	6 (29%)
>25% of blasts	7 (50%)	2 (29%)	9 (43%)
Bone marrow tumour burden, median percentage of blasts (range)	27·5% (0·0–96·0)	6·0% (0·0–80·0)	8·0% (0·0–96·0)





67% CR/CRi
Median DOR: 4.1 mo
PFS at 6 months: 27%



Benjamin R, et al. *Lancet.* 2020;396:1885-1894.

“Off-the-Shelf” Allogeneic CAR in ALL: PBCAR0191

Abstract 650: Preliminary safety and efficacy of PBCAR0191, an allogeneic off-the-shelf CD19 CAR T for patients with R/R B-ALL [Jain N, et al]

Lymphodepletion

Standard (Flu 30 mg/m^2/d × 3d + Cy 500 mg/m^2/d × 3d)
Enhanced (Flu 30 mg/m^2/d × 4d + Cy 1000 mg/m^2/d × 3d

Median time from screening to infusion: 7d

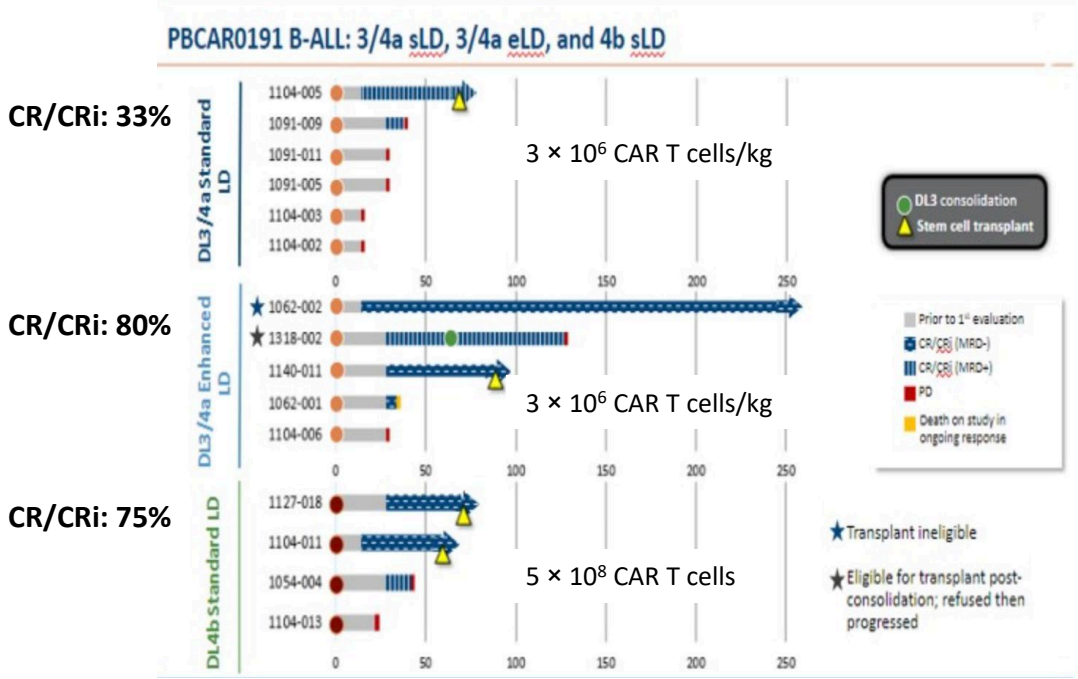
15 patients treated

- 4/15 (27%) responding pts → HSCT

Toxicity

- No GvHD
- Grade 3 CRS (6%); Gr 3 ICANS (20%)

DL3/4a: 3 × 10^6 CAR T cells/kg
DL4b: 5 × 10^8 CAR T cells



CD7 CAR for T-ALL/LBL

Abstract 473: High effectiveness and safety of anti-CD7 CAR T cell therapy in treating R/R T-ALL [Yang J, et al]

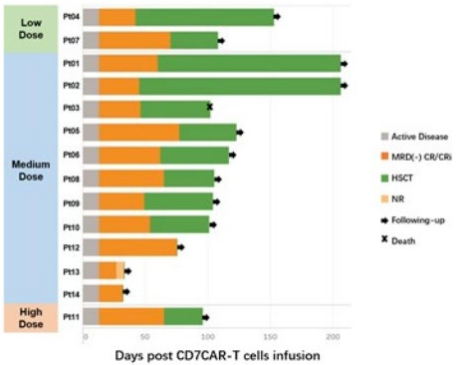
Lentiviral transduced, CD7 w/41BB co-stim
- Doses: 0.5 × 10^5 → 1–1.5 × 10^6 → 2 × 10^6 CAR T cells/kg

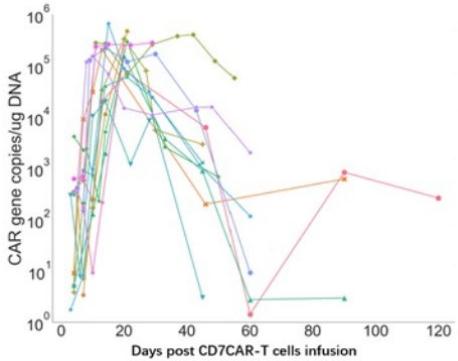
17 patients enrolled and 14 treated
- 3 pts not treated due to rapid POD
- Median age, 17 (range 3–42)
- ORR 93%: CR 29%, CRi 64% (4/5 EM achieved CR)
- 11/14 pts proceeded to consolidative allo HSCT
- CRS 93% (Gr 3 in 1 pt) and ICANS Gr 1 only

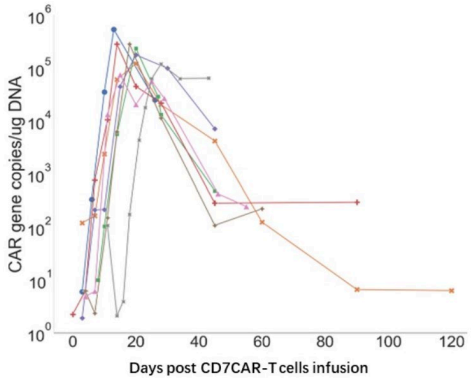
Abstract 652: A novel and successful patient or donor-derived CD7 CAR for R/R T-LBL [Yang J, et al]

Lentiviral transduced, CD7 w/41BB co-stim
- Patient derived (n = 7) or donor derived (n = 1)
- Doses: 0.5 × 10^5 → 1 × 10^6 → 2 × 10^6 CAR T cells/kg

8 patients treated; 7 with EMD
- Median age, 37 (range 14–47)
- Of 7 pts with EMD: CR 71% (5/7)
- 6/8 pts proceeded to consolidative allo HSCT
- CRS 100% (Gr 3 in 1 pt) and ICANS Gr 1 only







Summary

- Immunotherapy agents (blinatumomab, inotuzumab, daratumumab) and targeted agents (venetoclax) are being incorporated into frontline therapy
  - Younger adults: added to the multiagent chemotherapy backbone
  - Older adults: reduce chemotherapy (lower toxicity) and test chemo-free regimen
  - MRD eradication is a key endpoint, and incorporation of these agents is more likely to achieve higher rates of MRD negativity
- CD19 CAR T-cell therapy is the most potent single-agent therapy in ALL
  - Currently approved in relapsed or refractory setting
  - Investigated in the frontline setting in children
  - Newer CARs are being investigated to achieve lower toxicity, target alternate antigen (CD22, CD7), increase access (off-the-shelf), and enhance duration of remission

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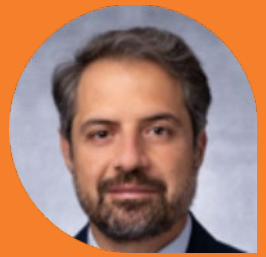
Interactive Discussion: Treatment Landscape Evolution

Moderator: Elias Jabbour



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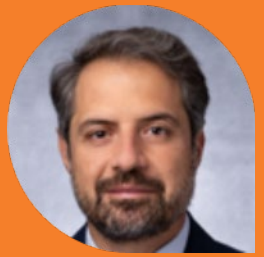
Session Close

Elias Jabbour



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Repeat Question 2

What age group is considered elderly ALL patients?

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

Repeat Question 3

At what time points is MRD quantification prognostic for survival?

A. End of induction (at CR)
B. After consolidation
C. Prior to allogeneic hematopoietic cell transplant
D. After transplant
E. All of the above

Repeat Question 4

Which of the following is NOT true for treating ALL?

A. There are more Ph+ and Ph-like adult ALL patients compared with pediatric ALL

B. *ETV6-RUNX1* fusion (t12;21) is a common genetic subtype in pediatric ALL

C. Hyperdiploid phenotype is more prevalent in adult ALL compared with pediatric ALL

D. Patients with *ETV6-RUNX1* fusion (t12;21) have favorable prognosis

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