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Global Leukemia Academy

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

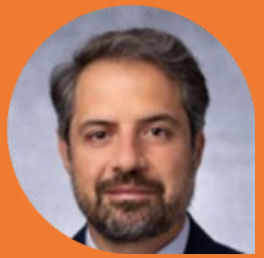
5 December 2022

APTITUDE HEALTH

Global Leukemia Academy

Welcome and Meeting Overview

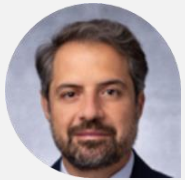
Elias Jabbour



APTITUDE HEALTH

Meet the Faculty

CHAIR



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

FACULTY

Marcos de Lima, MD
Ohio State University, Columbus, OH, USA

Stephanie Dixon, MD, MPH
St. Jude Children's Research Hospital, Memphis, TN, USA

Shaun Fleming, MBBS(Hons), FRACP, FRCPA
Alfred Hospital, Melbourne, VIC, Australia

Stephen P. Hunger, MD
Children's Hospital of Philadelphia, PA, USA

Hagop Kantarjian, MD
MD Anderson Cancer Center, Houston, TX, USA

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 Plenary Sessions (Day 1)

Monday, December 5 | 9.00 AM – 12.30 PM (GMT+8) Shanghai

ARS voting system will be used throughout the meeting

Time	Title	Speaker
9.00 – 9.10	**Welcome and Meeting Overview** • Introduction to audience response system (ARS)	Elias Jabbour
9.10 – 9.30	**What's New in ALL? Recent Developments in Research and Management** • Overview of recent data in ALL	Hagop Kantarjian
9.30 – 9.50	**The Clinical Value of MRD in ALL: How MRD Can Guide the Use of Targeted Agents or Immunotherapy** • Prognostic value, clinical relevance, and MRD-guided treatment strategies	Jae Park
9.50 – 10.10	**Recent Insights in Genetic Variants in ALL: Ph+ and Ph-Like**	Elias Jabbour
10.10 – 10.30	**Current and Future Role of Transplantation in ALL**	Marcos de Lima
10.30 – 11.00	**Debate: How to Optimally Sequence CD19-Targeted Approaches in ALL** • Monoclonal antibodies and bispecifics first (10 min) • CAR T first (10 min) • Discussion and voting (10 min)	Moderator: Elias Jabbour Shaun Fleming Jae Park All faculty
11.00 – 11.10	***Break***	
11.10 – 11.30	**Changing Landscape of Treatment Options in Pediatric and AYA ALL** • Definition, and evolving insights into the treatment of this diverse patient population	Stephen P. Hunger
11.30 – 11.55	**AYA Patient Case Discussion and Debate: The Evolving Concept of Transplantation in AYA**	Michael Osborn and Marcos de Lima
11.55 – 12.20	**Interactive Discussion: Regional Challenges of ALL Management** • Interactive discussion and Q&A (with questions to trigger discussion)	Moderators: Shaun Fleming and Michael Osborn All faculty
12.20 – 12.30	**Session Close** • ARS questions	Elias Jabbour

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

Virtual Breakout – Pediatric 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	Elizabeth Raetz
9.10 – 9.40	**Optimizing First-Line Therapy in Pediatric ALL: How to Balance Cure and Long-term Risks?** • Optimal use of treatment choices in frontline pediatric ALL, including HSCT	Michael Osborn
9.40 – 10.00	**Optimal Management and Treatment Coordination of Long-term Toxicities in Pediatric ALL** • Long-term follow-up care for pediatric ALL survivors	Stephanie Dixon
10.00 – 10.40	**ALL Case-Based Panel Discussion** • Local case 1: Frontline setting (10 min) • Local case 2: Management of long-term toxicities (10 min) • Discussion and Q&A (20 min)	Moderators: Michael Osborn and Elizabeth Raetz Savenaca Seduadua Claudia Toro All faculty
10.40 – 10.50	***Break***	
10.50 – 11.15	**Current Treatment Options for Relapsed ALL in Children** • Optimal use of treatment choices in relapsed/refractory ALL, including HSCT	Elizabeth Raetz
11.15 – 11.35	**ALL Case-Based Panel Discussion** • Local case 3: Relapsed/refractory setting (10 min) • Discussion and Q&A (10 min)	Moderators: Michael Osborn and Elizabeth Raetz Miri Tukana All faculty
11.35 – 11.45	**Session Close** • ARS questions	Elizabeth Raetz

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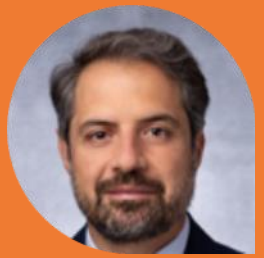
Introduction to the Voting System

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

Which patients do you treat?

A. Adults only

B. Children only

C. Adults and children

Question 3

Which of the following is NOT true?

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

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

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

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

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What's New in ALL? Recent Developments in Research and Management

Hagop Kantarjian

APTITUDE HEALTH

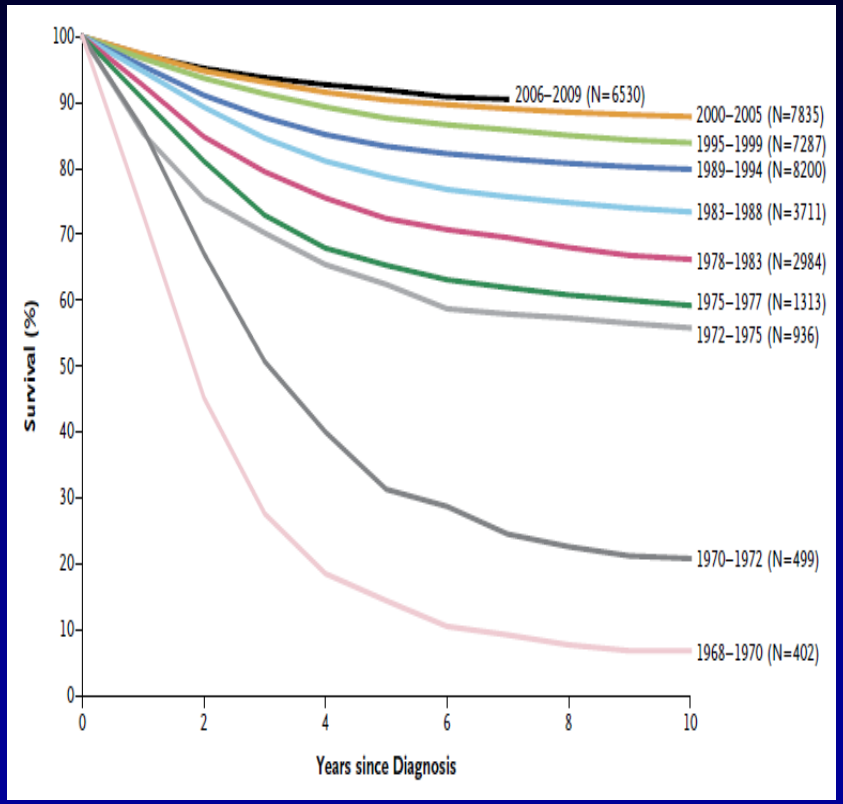
ALL – Progress in Research and Therapy in 2022

Hagop Kantarjian, MD

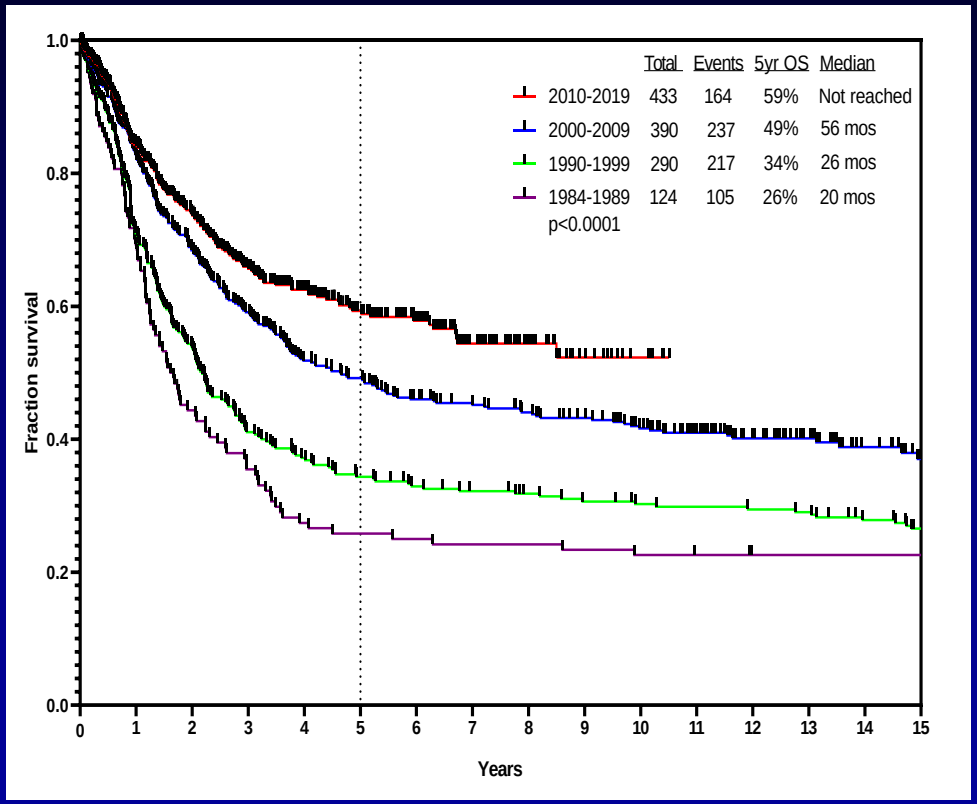
MD Anderson Cancer Center, Houston

December 2022

Survival in Pediatric and Adult ALL With Classical Intensive ChemoRx Regimens



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



Kantarjian. *Cancer.* 2022;128:240-259.

Adult ALL – the Cost of Traditional Intensive Chemotherapy

- 15 chemoRx agents used in intensive induction, consolidation, intensification, maintenance courses over 3 years
- Manageable in leukemia research “ivory towers”
- High dropout rates in practice/emerging nations, poorer and disadvantaged populations, due to socioeconomic and infrastructure/support hurdles
- Cost about $0.5–1 million for frontline cure, $2+ million if failure
- Long-term multiple organ problems, health care, psychological and social problems among cured patients

ALL Outcomes in Practice

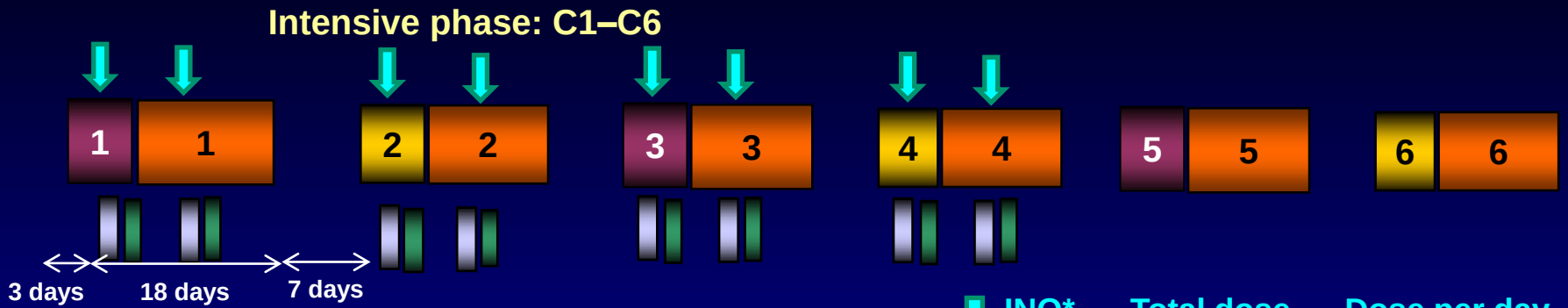
Age	3-yr OS, % (Peru, n = 378)	4-yr EFS, % (India, n = 273)
0–10	70	57
10–20	37	35–44
46–65	12	20–27

Espinoza-Morales. *J Clin Oncol*. 2022;40(suppl 16): abstract 7012; Vaid. *HemaSphere*. 2022;6: abstract P375.

Adult ALL Therapy – the Solution

- Shorter dose-dense curative regimens that combine traditional less intensive chemoRxs with the novel targeted and immune therapies: new BCR::ABL1 TKIs; antibodies targeting CD19 (blinatumomab), CD22 (inotuzumab), and CD20 antibodies (rituximab, CD20 BiTEs); CAR T consolidation instead of alloSCT
- Measure residual disease by next-generation sequencing (NGS-MRD for IgHV; analyzes >1 million cells) to decide on changes in, and duration of, therapy
- Dose-dense mini-CVD–inotuzumab–blinatumomab ± CAR T regimen: 7 months of Rx

Blinatumomab-Rituximab-Inotuzumab-Condensed With KemoRx (BRICK Regimen)



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

Total INO dose = 2.7 mg/m²

*Ursodiol 300 mg tid for VOD prophylaxis.

Mini-hyperCVD

Mini-MTX + Ara-C

Rituximab

IT MTX + Ara-C

POMP

Blinatumomab

VCR/Steroid

Adult ALL – Time to Break With a Half-Century of Traditions

- **Ph+ ALL: Ponatinib-blinatumomab**
- **Pre-B ALL: 1) Less chemoRx and shorter durations; 2) Addition of CD19/20/22 antibodies to chemoRx; 3) ? CAR Ts in MRD/CR instead of SCT; 4) NGS-MRD to monitor response and decide on change of Rx**
- **T-ALL: Not sure yet; asparaginase-nelarabine; role of decitabine/HMAs, venetoclax**

TO TREAT OR NOT TO TREAT?

"And there is a price to that orthodox position. It's true that the life expectancy of patients with AGL who

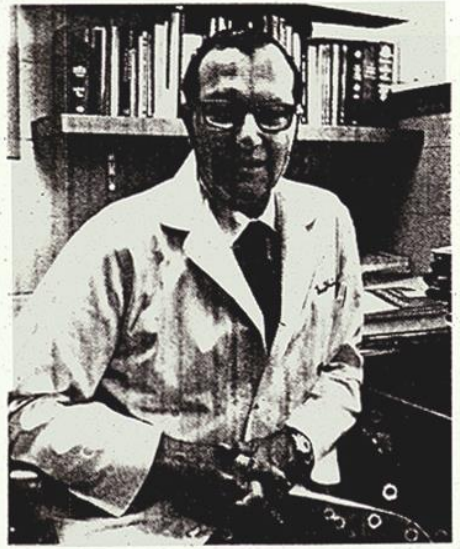
out, "ten of 43 patients with the blast crisis form have had complete or partial remissions. And I now have a pa-

Now if you use that reasoning, the answer will always be the same—chemotherapy doesn't work."

out, the most important diagnostic factor for patients with AGL was the white count at the time of diagnosis

'Chemotherapy should be used only sparingly in selected cases [of leukemia] since the treatment may be killing more patients than proponents of aggressive therapy realize.'

DR. CROSBY



'There are patients living today who without treatment would be dead. And without chemotherapy the per cent of patients surviving at six months is almost zero.'

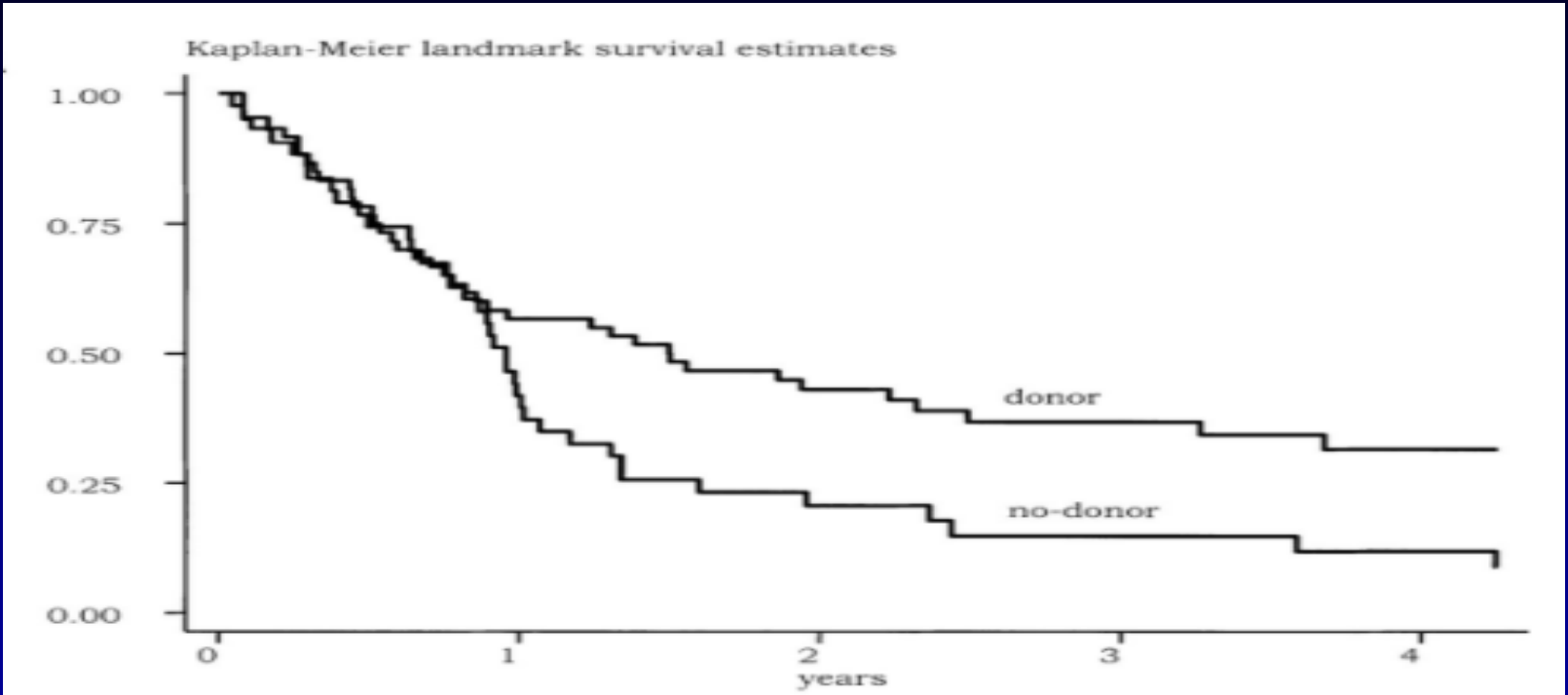
DR. FREIREICH

Hyper-CVAD in ALL – Pearls and Vignettes to Optimize Rx

- Even courses: MTX 750 mg/m^2; ara-C 2 g/m^2. Dose-adjust for older age
- Check Cr after MTX; if increase (>1.4), hold ara-C (avoid renal failure and cerebellar toxicity)
- VCR 2-mg flat dose (not 2 mg/m^2). If constipation or neuropathy, omit VCR
- Prophylaxis: levofloxacin or cefpodoxime; posaconazole or voriconazole; valaciclovir
- Hold azoles day –1, 0, +1 of VCR (avoid excess neurotoxicity)
- Switch IT day 2 from MTX to ara-C in even courses (neurotoxicity with IT MTX and HD systemic MTX)

Rausch. *Cancer.* 2020;126:1152-1160.

SCT for Ph+ ALL: Pre-TKI



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

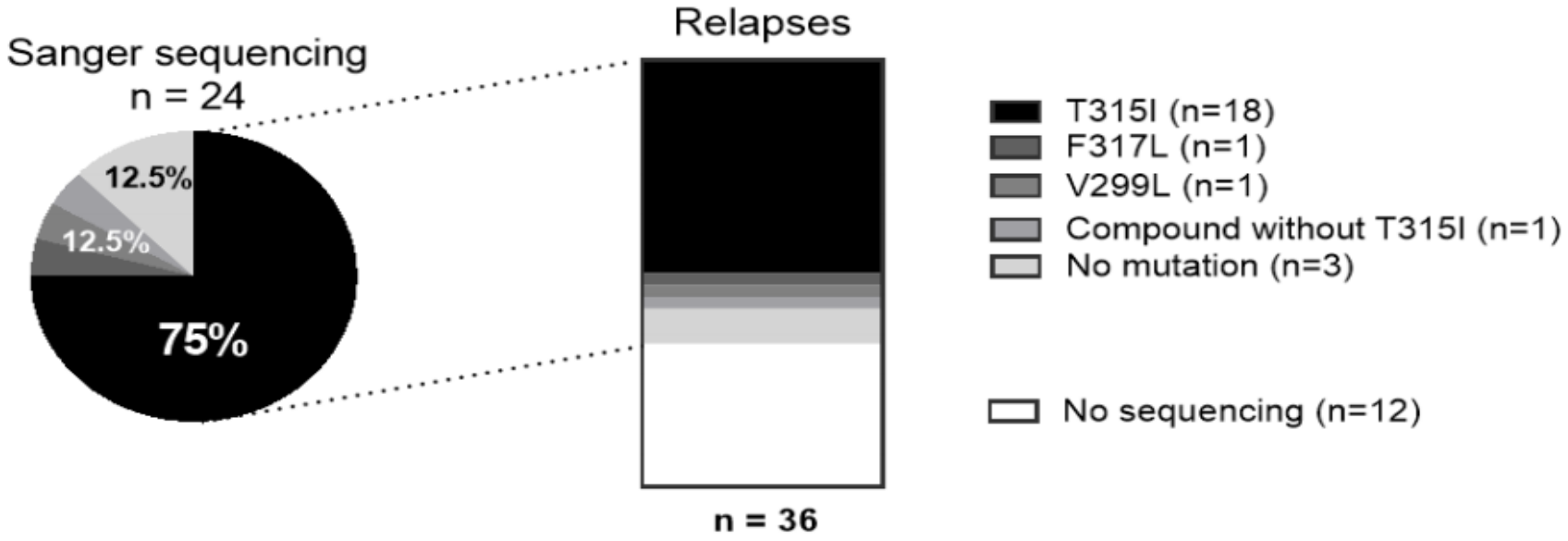
Dombret H, et al. *Blood.* 2002.

Evolution of Ph+ ALL Research and Rx at MDACC (1992–2022)

- 1992: HyperCVAD; 8 IT; alloSCT when possible
- 2000: HyperCVAD + imatinib; 8 IT; alloSCT in CR
- 2006: HyperCVAD + dasatinib; 8 IT; alloSCT in CR if no CMR by 3+ mo
- 2010: HyperCVAD + ponatinib; 12 IT; alloSCT less and only if no MMR by 3+ mo
- 2017: Ponatinib dose-response adjusted + blinatumomab; 12 IT; alloSCT rare

T315I Mutations at Diagnosis and Relapse in Ph+ ALL

- ***T315I*** **kinase domain mutation present in 18/24 patients (75%) at time of relapse**

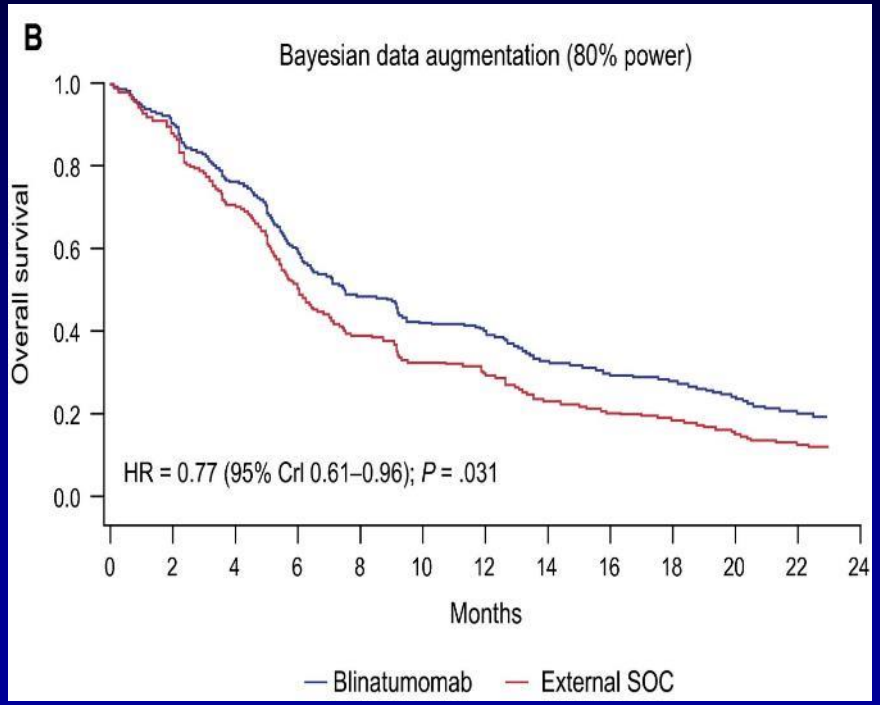


Rousselot. *Blood*. 2016;128:774-782.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

Blina vs SOC

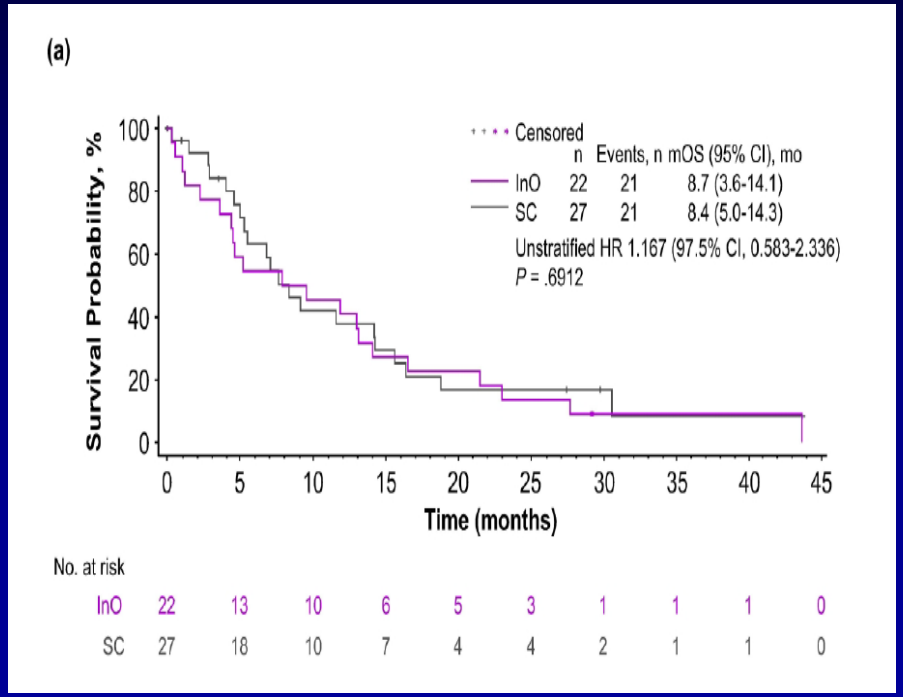
- **CR/CRh 36% vs 25%**
- **1-yr OS 41% vs 31%**



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

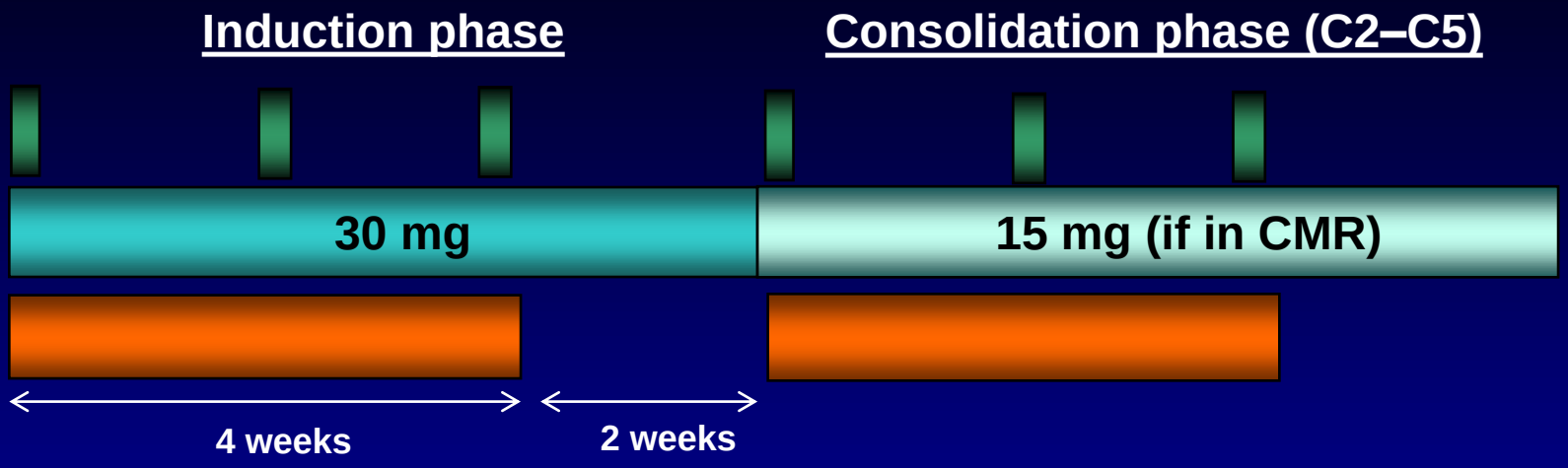
Ino vs SOC

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



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

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Ponatinib 30 mg

Ponatinib 15 mg

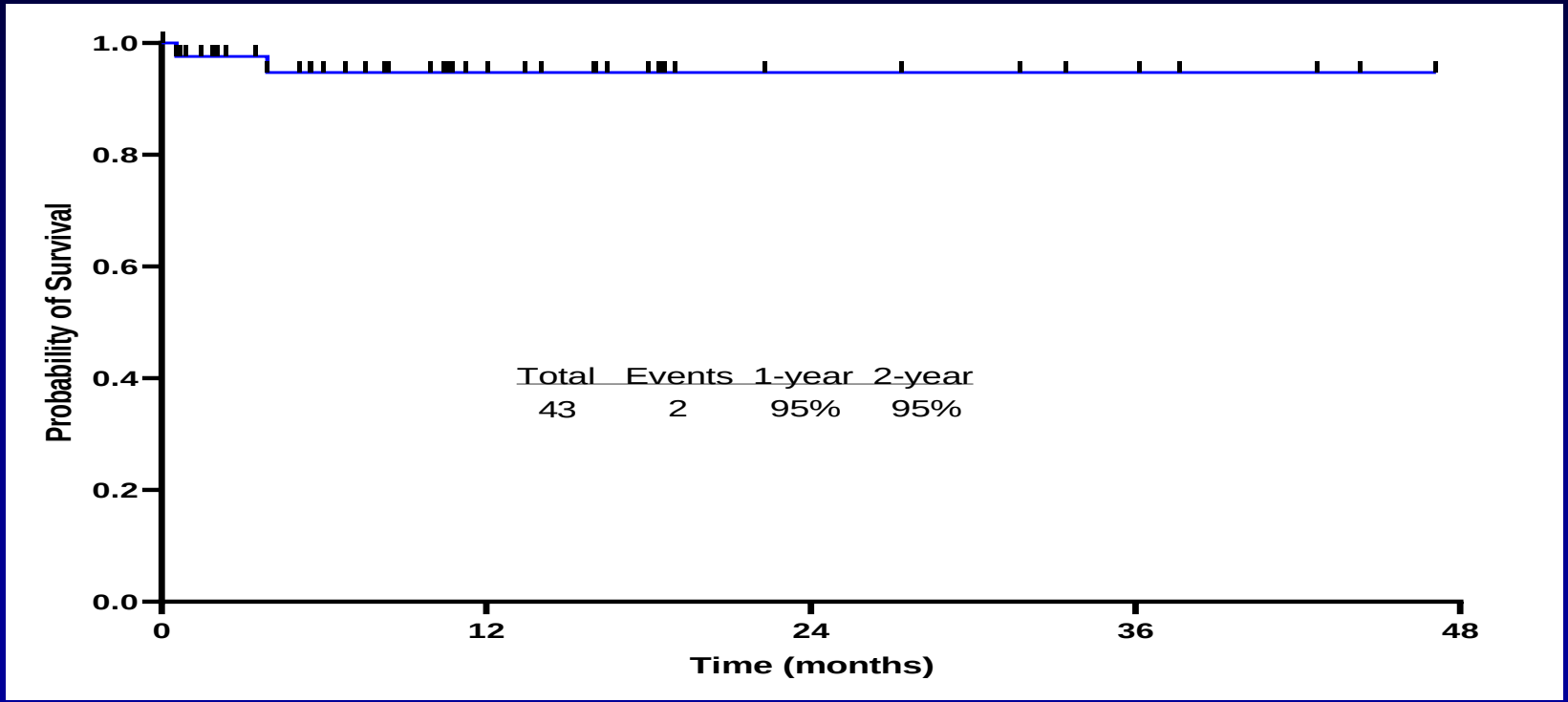
Blinatumomab

IT MTX, Ara-C × 12

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

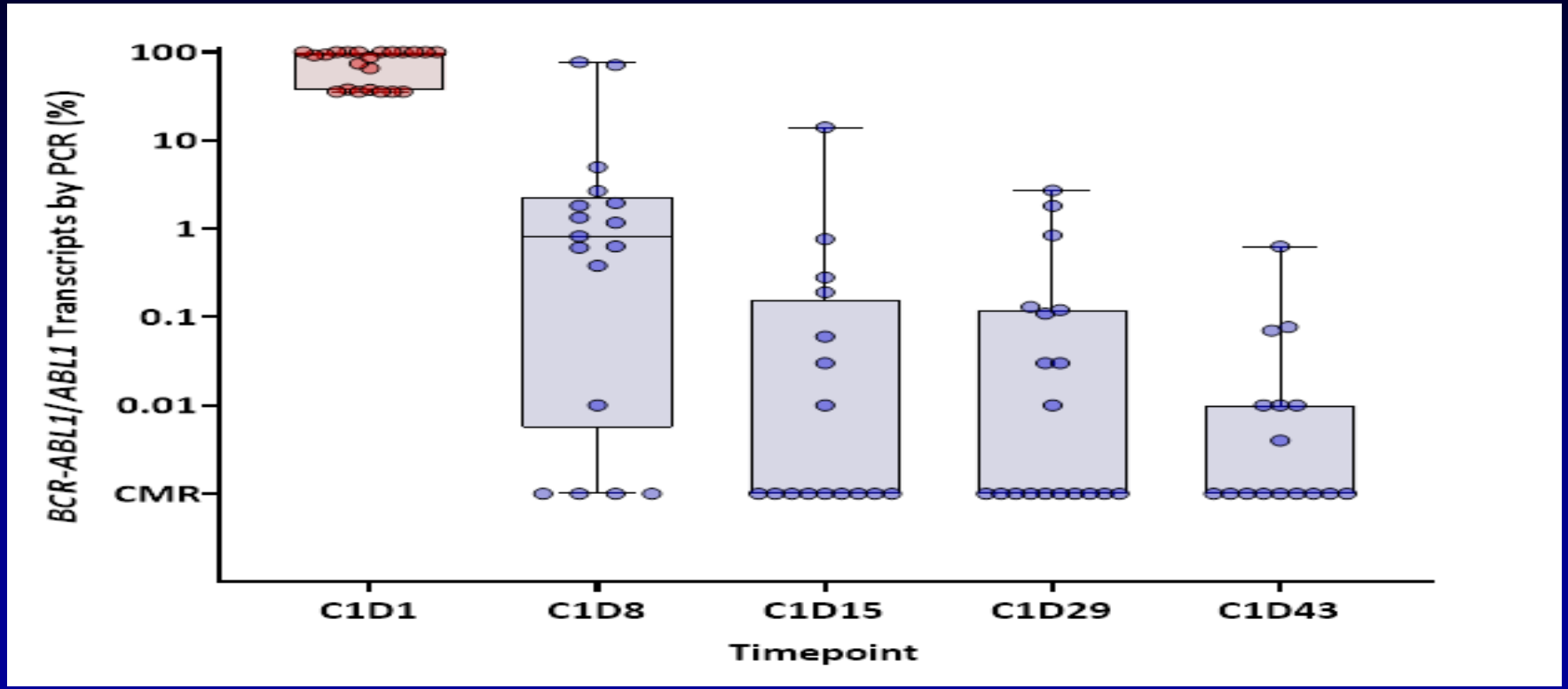
Ponatinib + Blinatumomab in Newly Dx Ph+ ALL – Update

- 43 pts Rx with ponatinib-blinatumomab; median FU 14 mo – CR 42/43 = 97%. CMR 79%. 3-yr OS 95%. Only 1/43 patients (2%) underwent allo-SCT in CR1



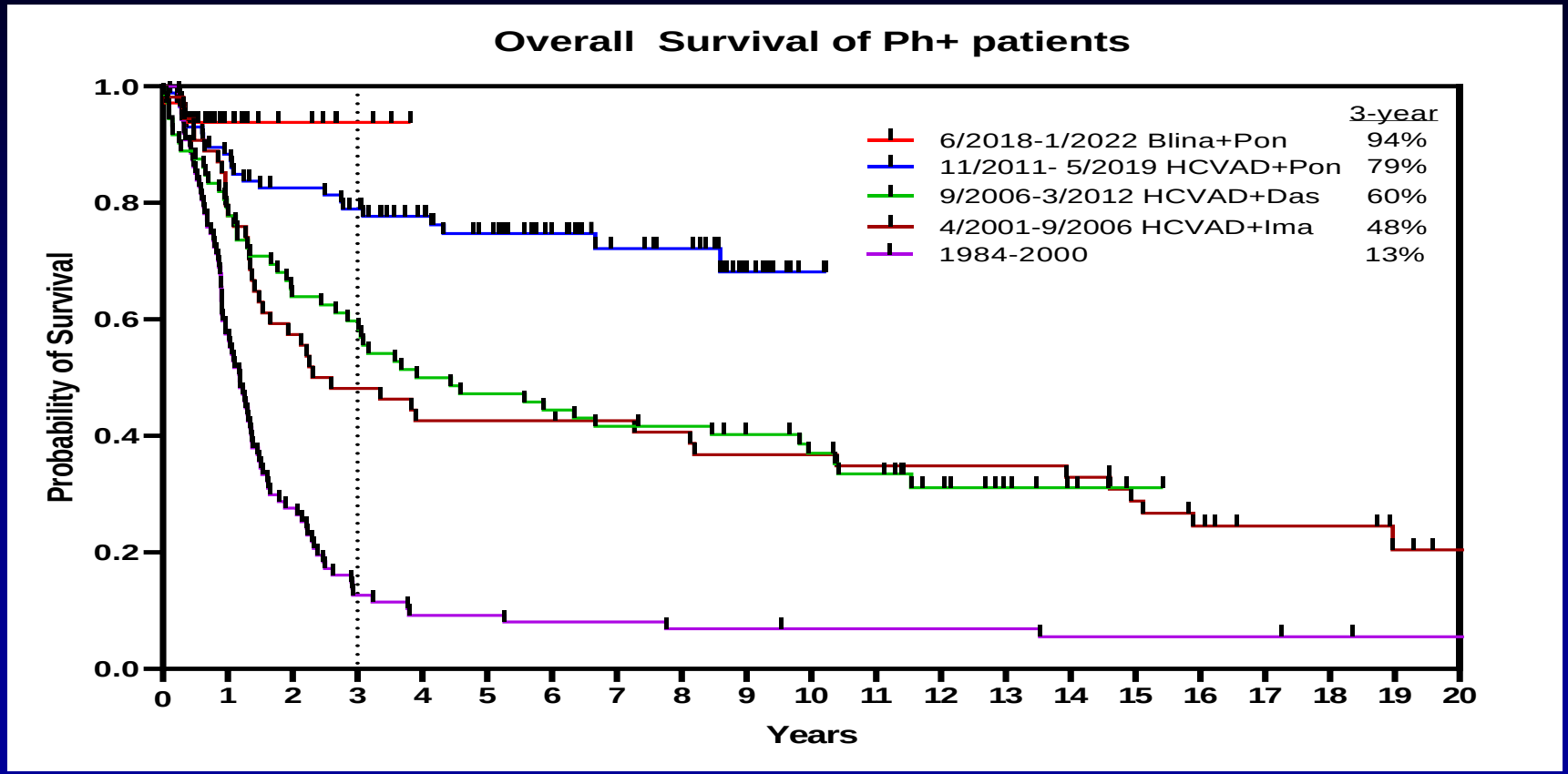
Jabbour E, et al. *Lancet Haematol.* 2022 Nov 16;S2352-3026(22)00319-2.

Ponatinib + Blinatumomab in Ph+ ALL: Early MRD Responses in Frontline Cohort



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

Ph+ ALL: Survival by Decade (MDACC 1985–2022)

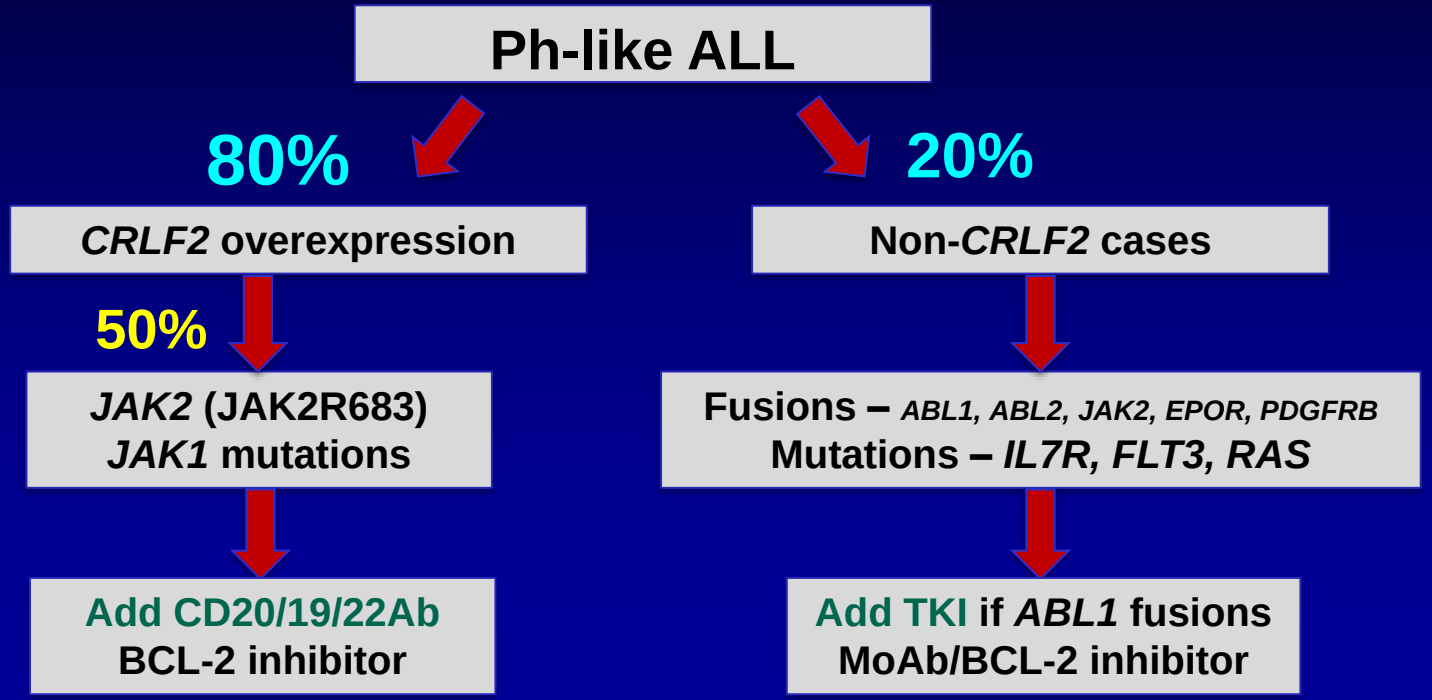


Ph+ ALL – Who Still Needs Intensive ChemoRx and AlloSCT?

- Ph+ ALL with FISH+ for Ph on mature granulocytes at Dx (can be P210 de novo CML-lymphoid BP, or rarely p190 Ph+ ALL)
- Ph+ ALL and *CRLF2*+ (rare)
- CML with evolution to CML-lymphoid BP
- Refractory-relapsed Ph+ ALL

Ph-Like ALL Molecular Lesions

- Ph-like 25%–30% of ALL; poor prognosis
- Ph-like ALL misleading. Better: *CRLF2+* ALL; true Ph ALL with *ABL1/PDGFR* translocations



Ph-like ALL – BCR::ABL1 TKIs Responsive Translocations

Alterations activating cytokine receptor and tyrosine signaling

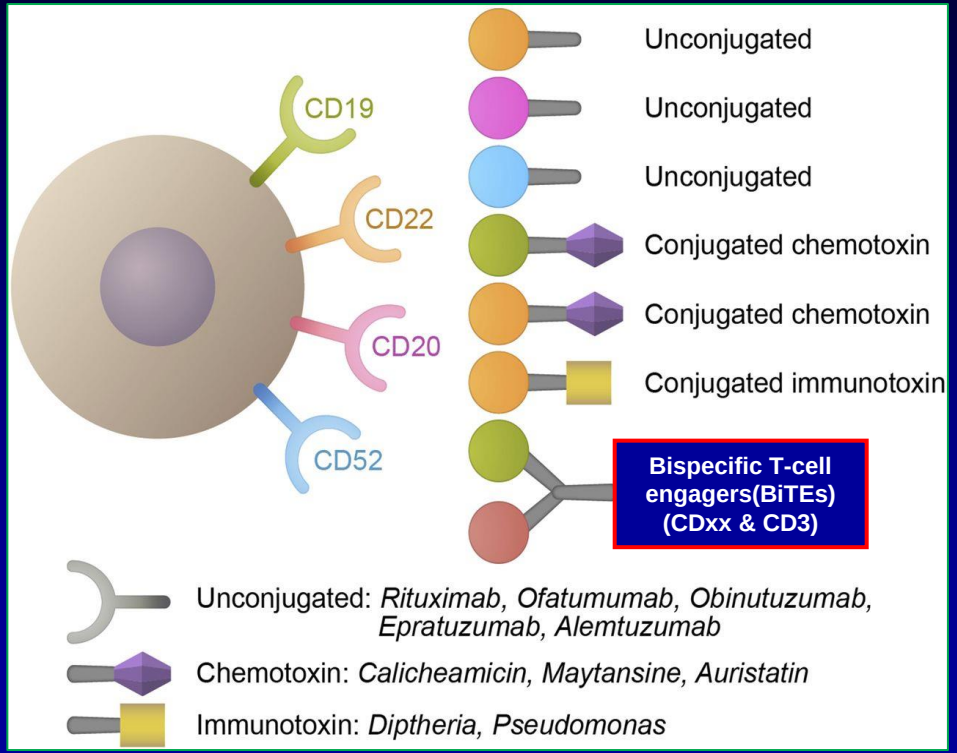
- Genes deregulating tyrosine kinases/receptors
  - *NUP214-ABL1, ETV6-ABL1, RANBP2-ABL1, RCSD1-ABL1*
  - *BCR-JAK2, PAX5-JAK2, STRN3-JAK2*
  - *EBF1-PDGFRB*
  - *IGH-EPOR*
- Activate signaling pathways
  - *ABL1, PDGFRB* fusions: BCR-ABL1 TKIs–based Rxs
  - *JAK2* fusions: Ruxolitinib??

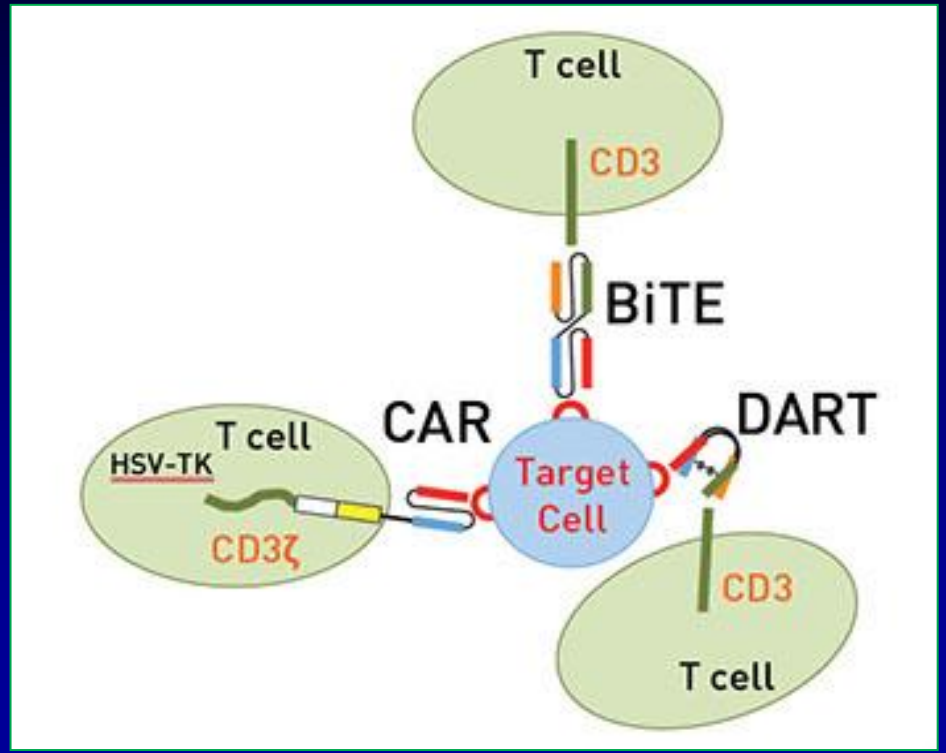
Ph-Like ALL – Summary

- Genomic profile similar to Ph+ ALL
- 25% of adult ALL; poor prognosis historically (not anymore with regimens incorporating BCR::ABL1 TKIs and CD19/22 antibodies)
- More common among Hispanics (50%??)
- High incidence of MRD positivity in CR
- 2 distinct entities: 1) *CRLF2* overexpression ± *JAK* mutations (80%); 2) *ABL*-translocations (true Ph-like; 20%)
- Standard of care still alloSCT in CR1
- Newer approaches: Chemo combos with blinatumomab and inotuzumab; TKIs-based regimens in *ABL*-translocated ALL

Immuno-oncology in ALL

- **Antibodies, ADCs, immunotoxins, BiTEs, CAR T cells**



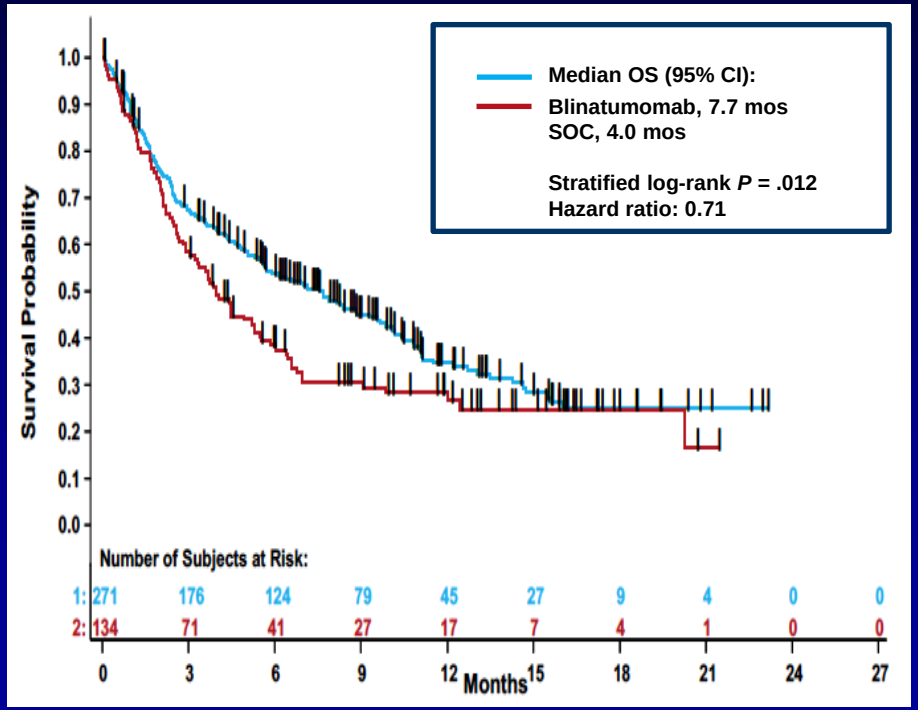


Jabbour E, et al. *Blood*. 2015;125:4010-4016.

Blinatumomab/Inotuzumab vs ChemoRx in R/R ALL

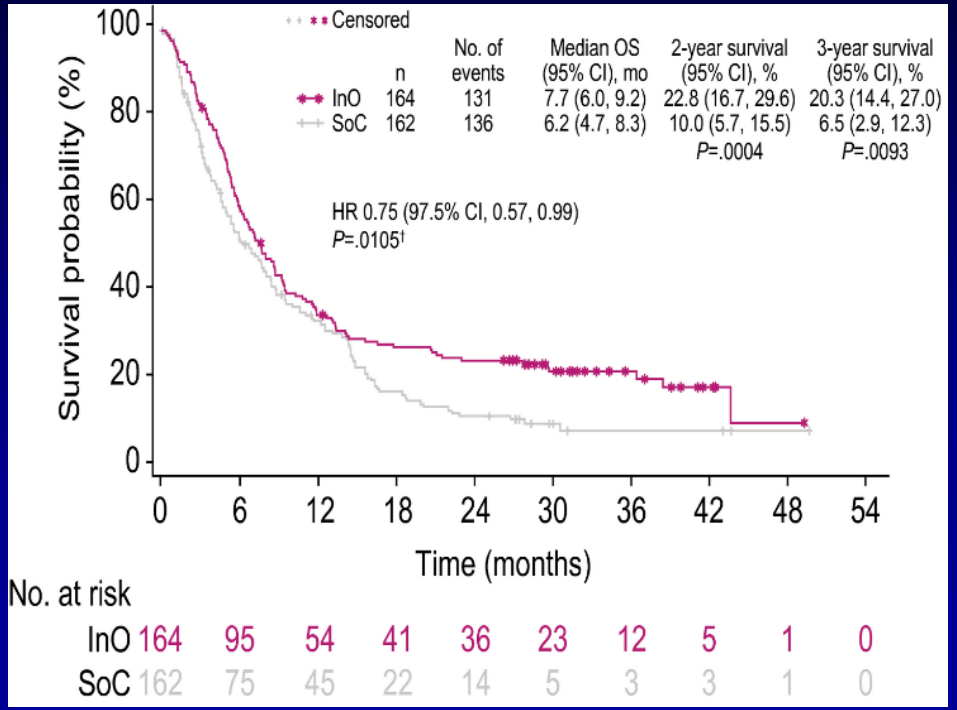
- **Marrow CR**

Blina vs SOC: 44% vs 25%



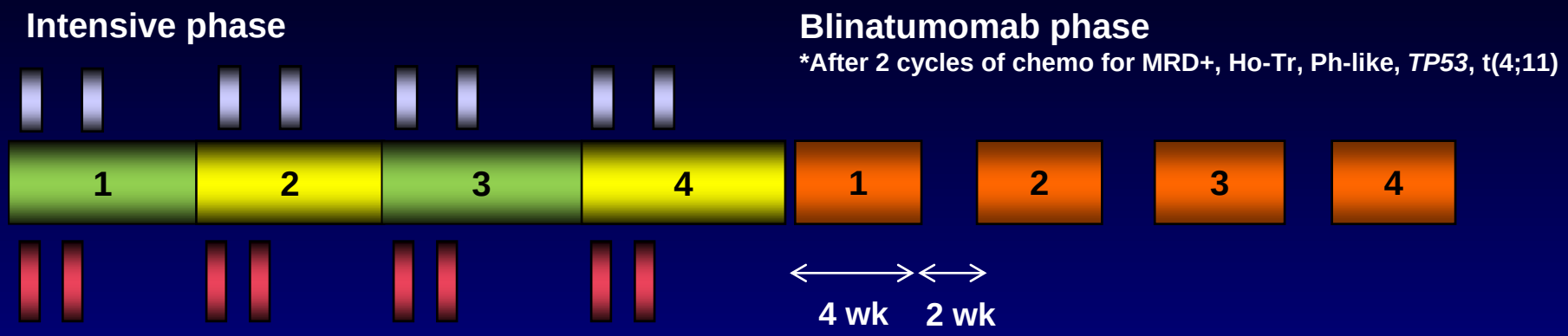
Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847.

Ino vs SOC: 74% vs 31%



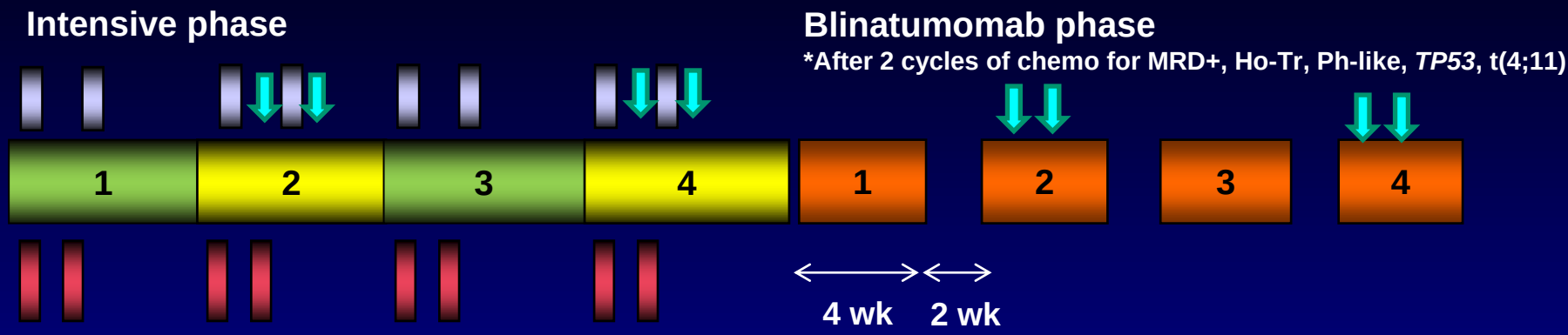
Kantarjian H, et al. *N Engl J Med.* 2016;375:740; Kantarjian H, et al. *Cancer.* 2019;125(14):2474-2487.

Hyper-CVAD + Blinatumomab in B-ALL: Regimen



Jabbour E, et al. *Lancet Haematol.* 2022 Oct 21;S2352-3026(22)00285-X.

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



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

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

IT MTX + Ara-C × 8

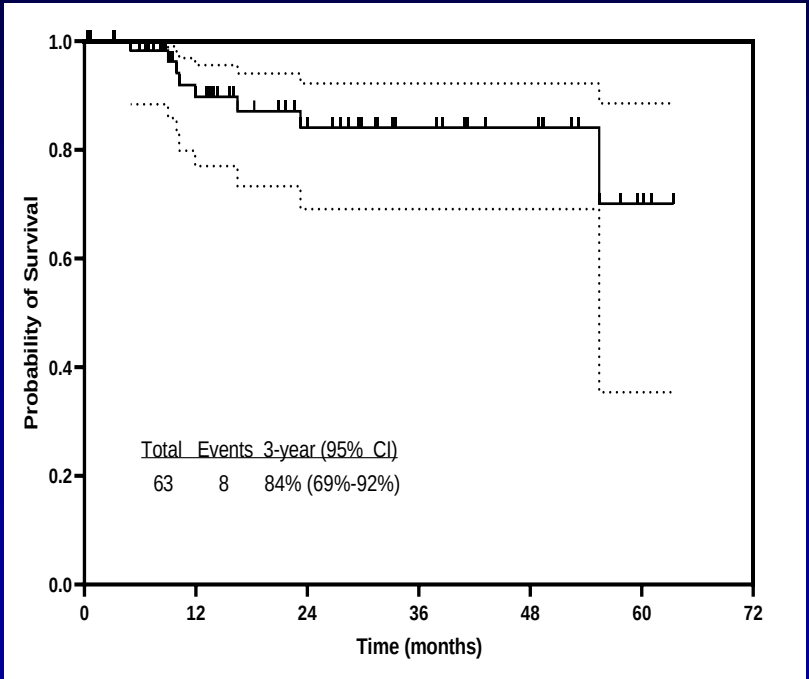
POMP

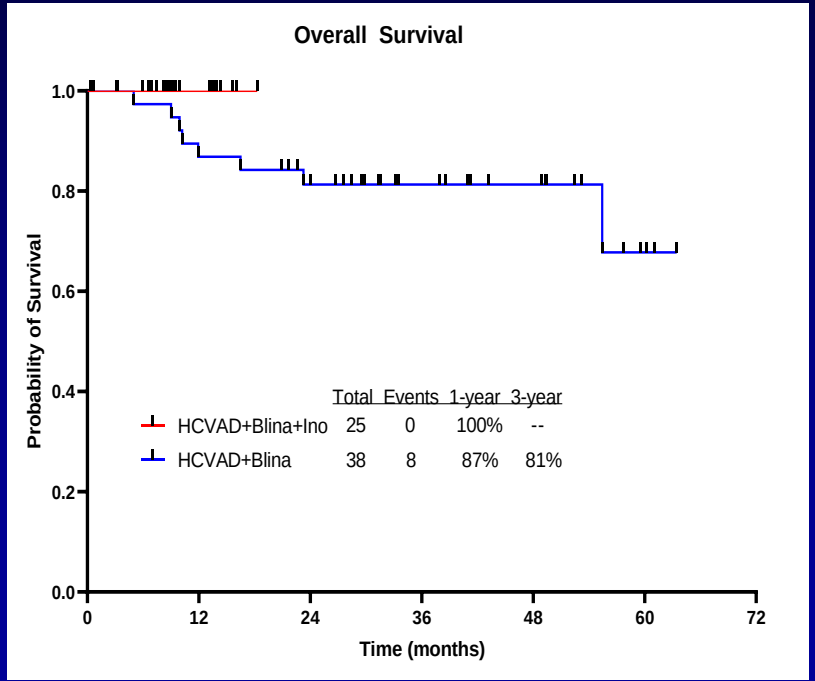
Inotuzumab 0.3 mg/m^2 on D1 and D8

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

Hyper-CVAD → Blinatumomab in Newly Dx Adult ALL

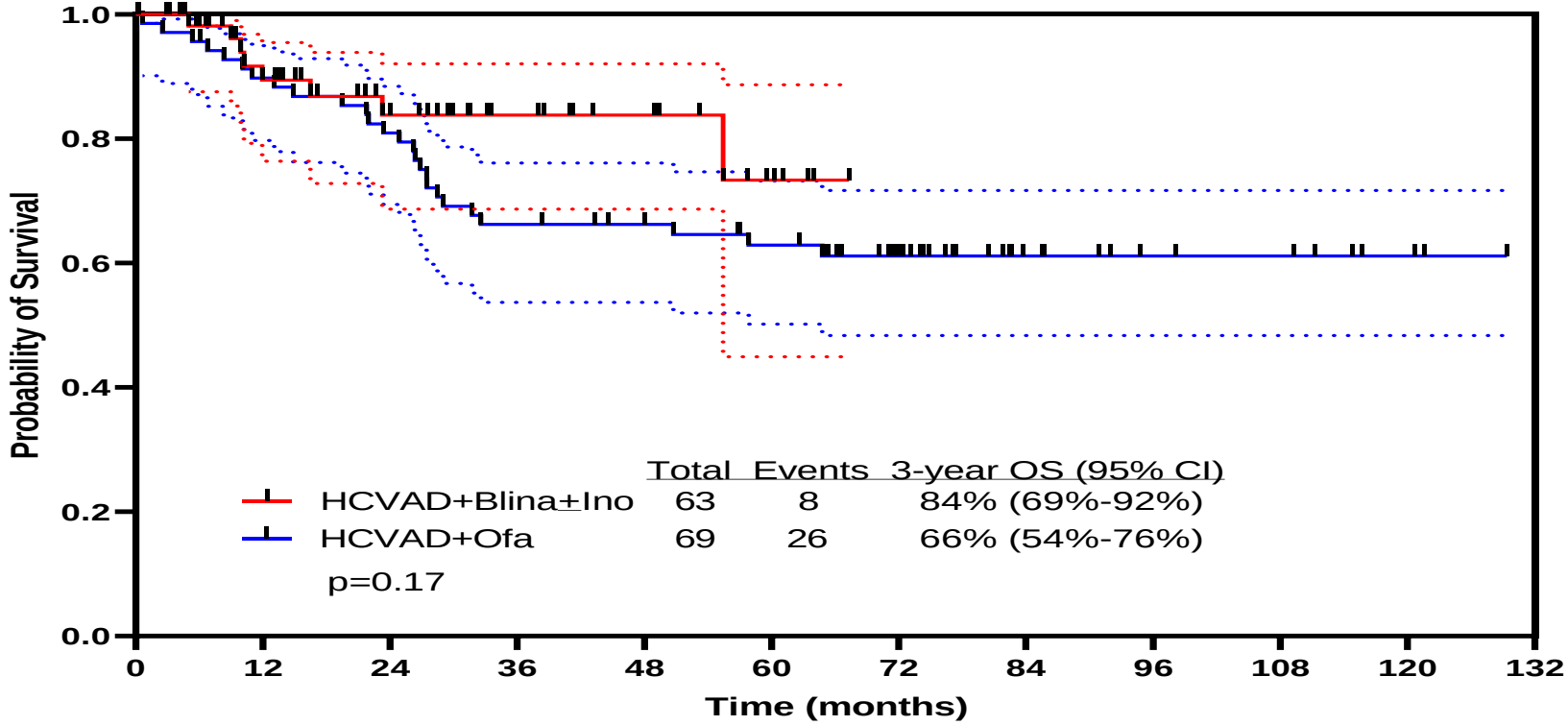
- 63 pts; median age 33 yr (18–59). Rx with O-HCVAD × 4; Blina × 4 → POMP 1 yr with blina Q3 mo
- CR rate 100%; MRD negative 95% (75% at CR); 60-day mortality 0%; 12 (32%) allo-SCT; F/U 24 mo





Jabbour E, et al. *Lancet Haematol.* 2022 Oct 21;S2352-3026(22)00285-X.

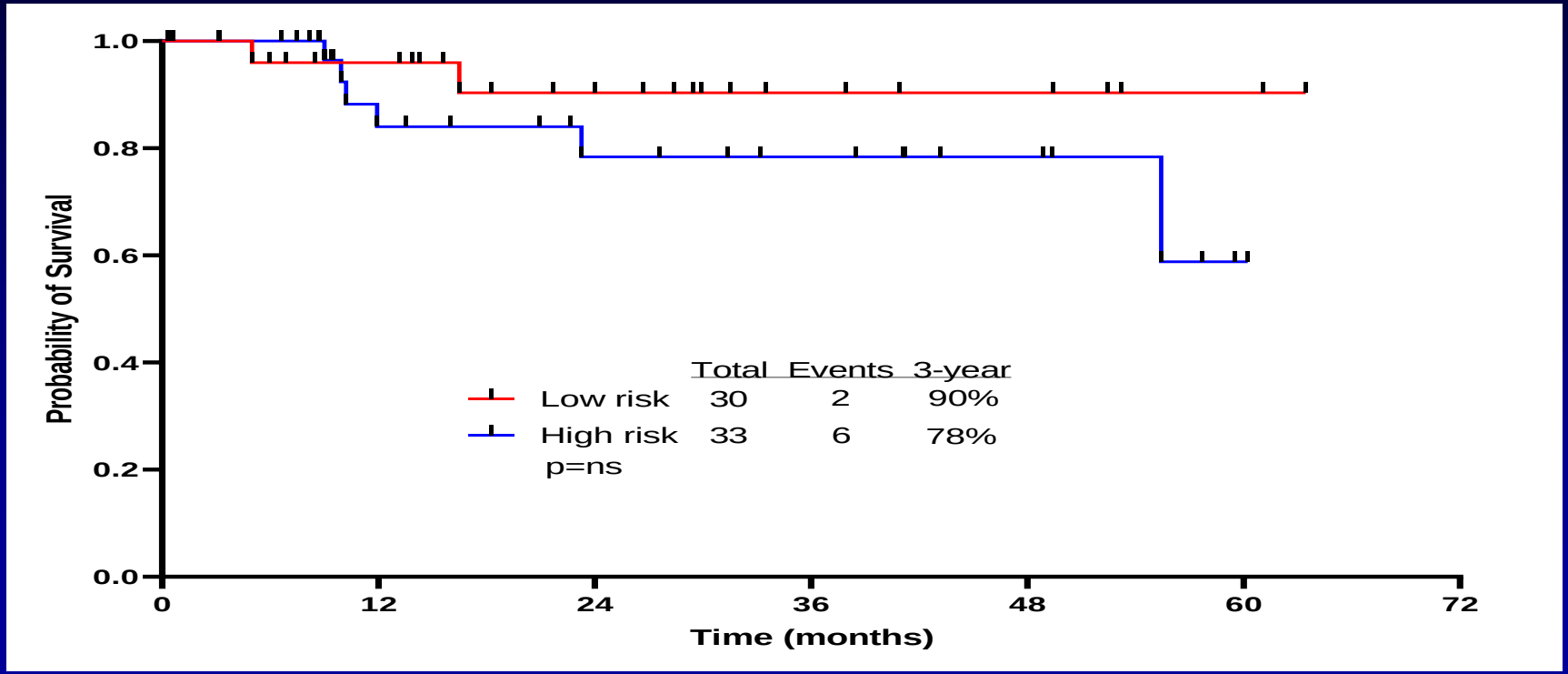
Hyper-CVAD + Blina + InO in B-ALL: Outcome vs Historical Control



Jabbour E, et al. *Lancet Haematol.* 2022 Oct 21;S2352-3026(22)00285-X (and update).

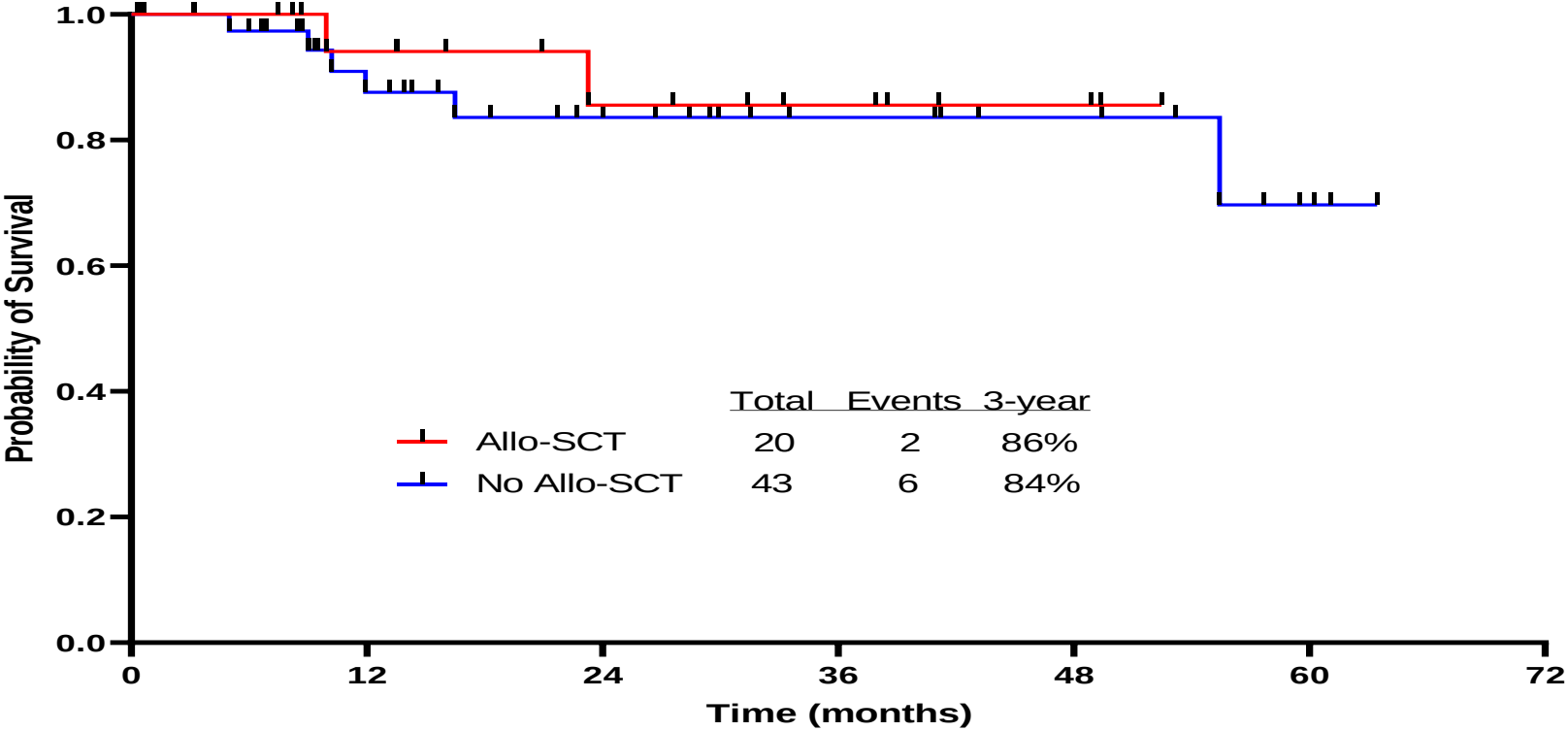
Hyper-CVAD + Blina + InO in B-ALL: Outcome by Risk

- High-risk defined *CRLF2+/JAK2+/TP53*-mutated and poor-risk cytogenetics



Jabbour E, et al. *Lancet Haematol.* 2022 Oct 21;S2352-3026(22)00285-X (and update).

Hyper-CVAD + Blina + InO in B-ALL: Outcome by Allo-SCT



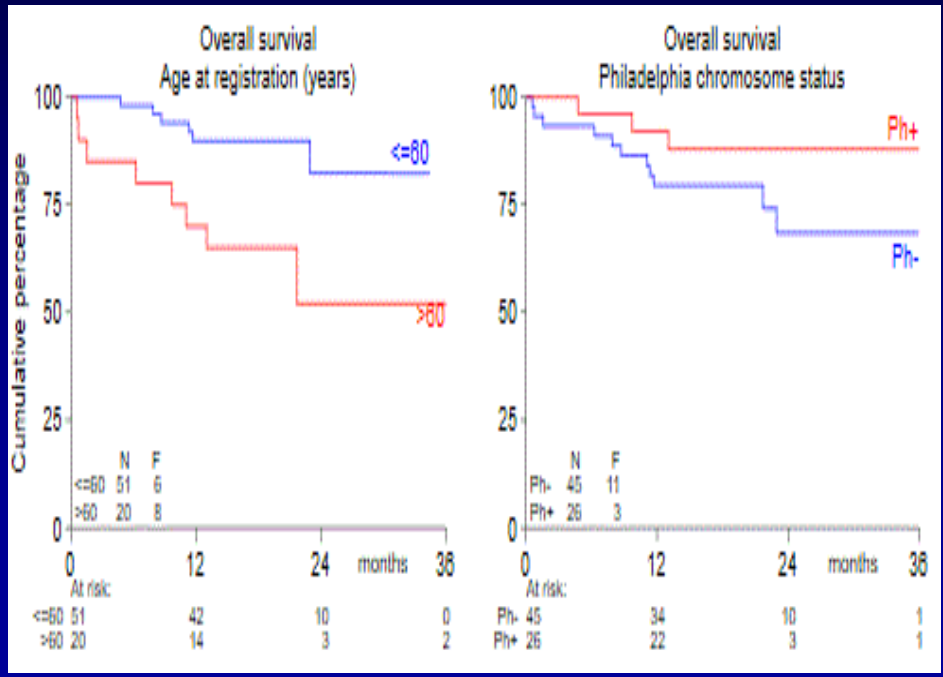
Jabbour E, et al. *Lancet Haematol.* 2022 Oct 21;S2352-3026(22)00285-X (and update).

How to Reduce Inotuzumab-Associated VOD

- Fractionated inotuzumab: C1, 0.6 mg/m^2 D2 and 0.3 mg/m^2 D8; C2–4, 0.3 mg/m^2 days 2 and 8. Cap total dose at 2.7 mg/m^2 (4 courses); 5.6 mg/m^2 = increased VOD
- Ursodiol 300 mg TID
- Do not use concomitant hepatotoxic drugs (particularly asparaginase; be careful with azoles)
- Monitor LFT; if bili >1.5, hold inotuzumab and give methylprednisolone 50 mg BID × 3–5 days
- Distance last inotuzumab from alloSCT by at least 2–3 months; insert blinatumomab 2 courses in between. Or do CAR T instead of SCT

Blinatumomab Pre-Phase Then 2 Consolidations in ALL (HOVON)

- 71 pts, age 18–70 yr Rx
- Pre-phase 10 days steroids + blina × 14d. ChemoRx HOVON 70 (amended 2× to ↓ PEG-ASP and reduce Int 1). Consolidation-intensification. Blina × 2 (4-wk courses). Ph+ ALL – add imatinib
- After pre-phase CR 63%
- 60/71 achieved CR = 85%
- CR 55/56 = 98%; MRD negativity 50/55 = 91%
- 9 pts DC blina due to toxicity!!
- Ph+ ALL: 2-yr OS 88%
- 22 pts had allo SCT
- 5 relapses (8%), 6 deaths (10%)



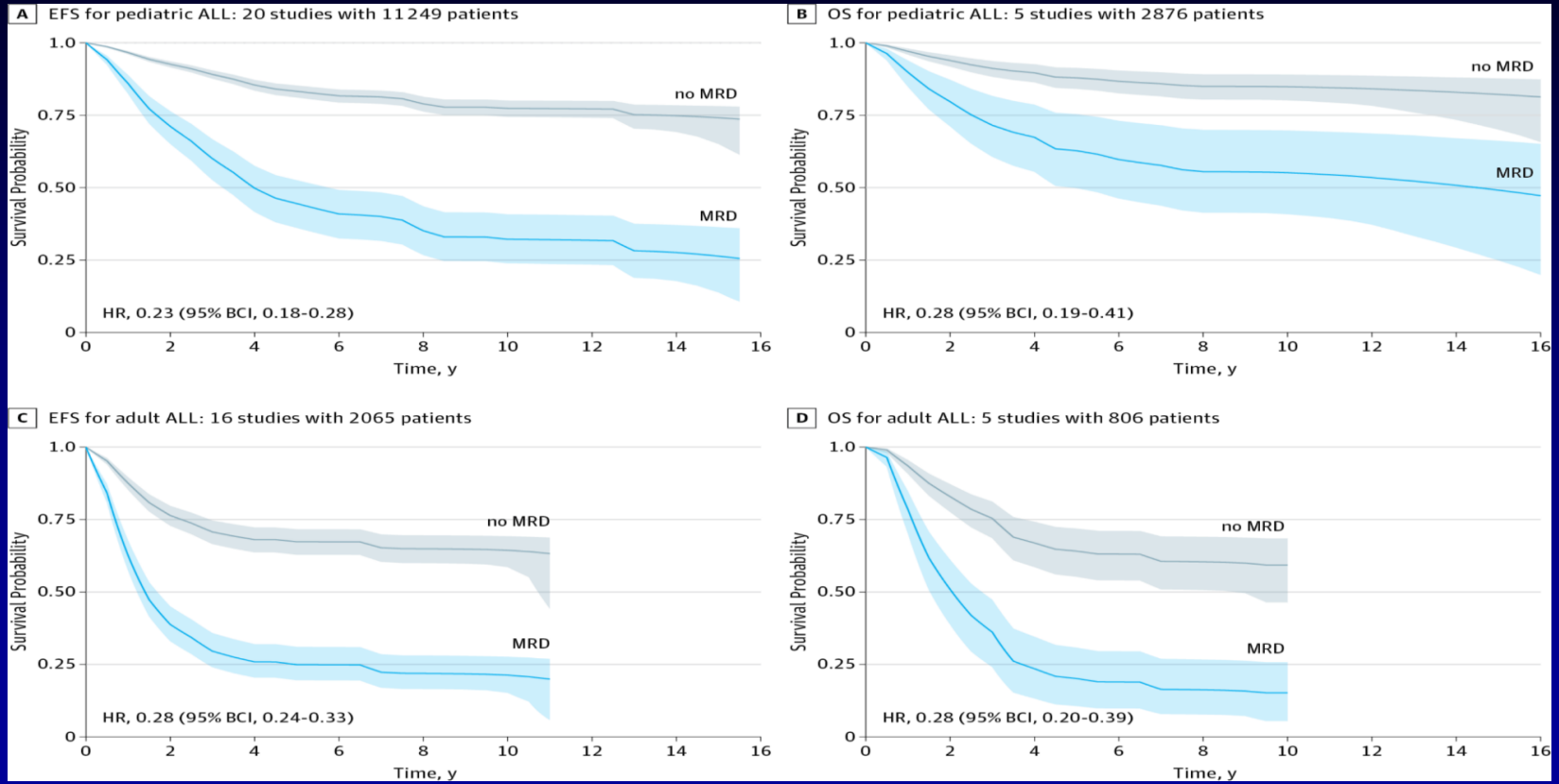
Parameter	Overall	Age <60	Age 60+
% 2-yr EFS	64	71	47
% 2-yr OS	73	82	52

Rijneveld A, et al. *HemaSphere.* 2022;6:266-267.

How to Manage Blinatumomab Toxicities

- Relevant toxicities: handwriting worse, tremors, neurologic (stupor, mental changes), CRS (fever, low bp), seizures (1–2%; Down). All more frequent in older pts/less neuronal reserve
- Hold blina; dexamethasone 8 mg Q8 hr × 3–6
- Restart blina same dose. Or dose reductions to 15, 9, even 5 µg/D
- IT chemoRx with Ara-C or MTX kills CD3 cells causing CNS irritability
- Levetiracetam 500–1000 mg BID: May help not only for seizures, but to prevent CNS toxicities

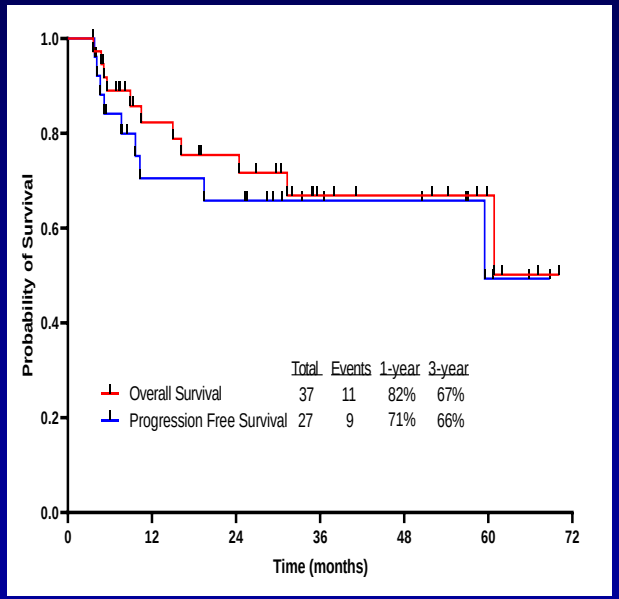
MRD in ALL

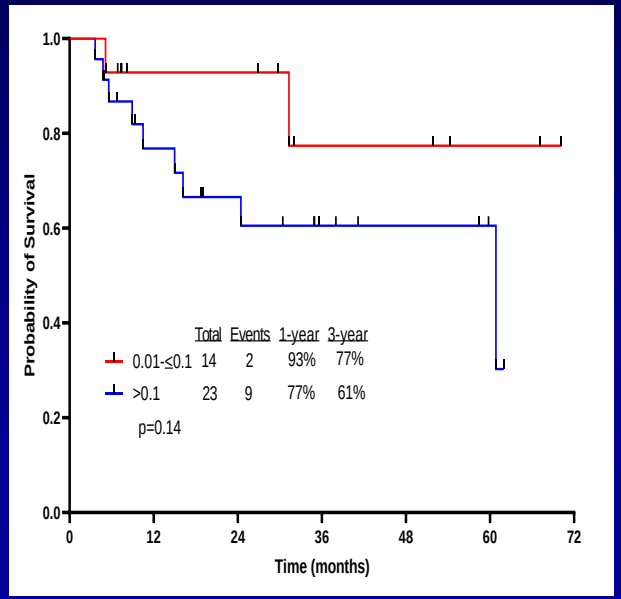


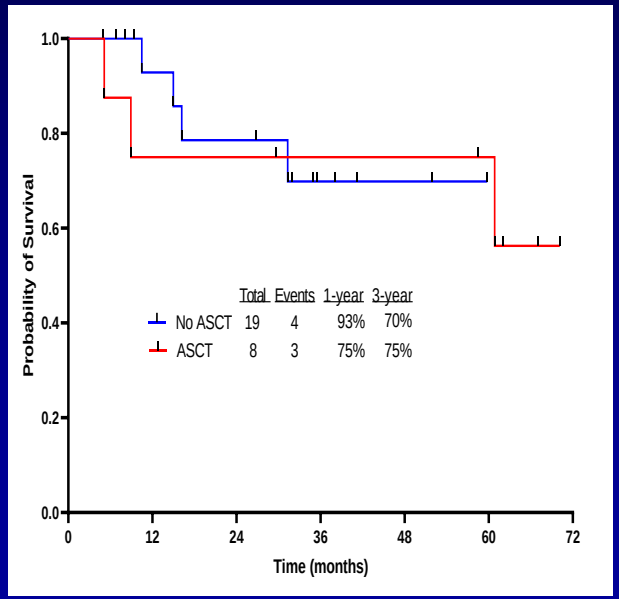
Berry DA. *JAMA Oncol.* 2017;3(7):e170580.

Blinatumomab for MRD+ ALL in CR1/CR2+

- 37 pts Rx. Post-blina MRD– 27/37 = 73%; 83% in Ph– ALL
  - 70% after C1
- Median number of cycles 3 (1–9); Median F/U = 31 mos (5–70+)
- 14 pts 0.01 to <0.1%: 3-yr OS 77%; 23 pts ≥0.1%: 3-yr OS 61%
- 3-yr OS 67%; 3-yr OS if MRD– 72%



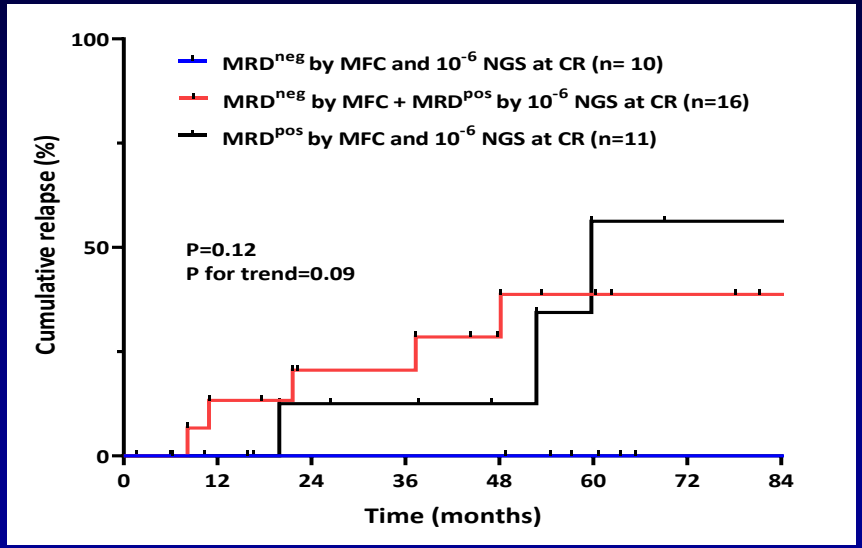


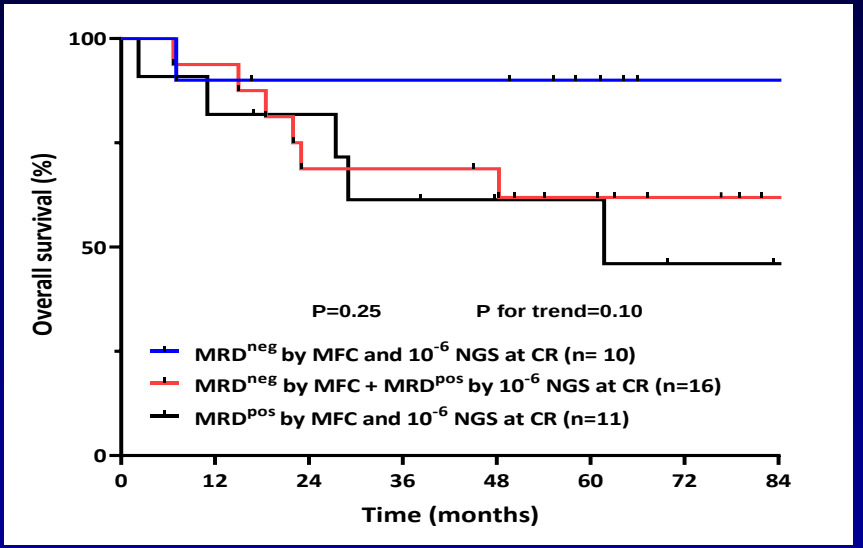


Jabbour E, et al. *Am J Hematol.* 2022;97(9):1135-1141.

MRD in ALL – NGS vs FCM

- 74 pts Rx (66% HCVAD; 34% mini-HCVD)
- 32/84 (38%) discordant (ie, MRD– by MFC but MRD+ by NGS)
- MRD– by NGS highly predictive at CR



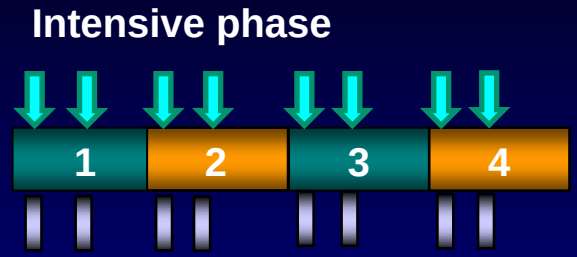


5-year CIR rates
MRD– by MFC and NGS: 0%
MRD– by MFC + MRD+ by NGS: 39%
MRD+ by MFC and NGS: 56%

5-year OS rates
MRD– by MFC and NGS: 90%
MRD– by MFC + MRD+ by NGS: 62%
MRD+ by MFC and NGS: 61%

Short N, et al. *Blood Adv*. 2022;6:4006-4014.

Mini-HCVD + INO ± Blina in Older ALL: Modified Design (pts 50+)



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

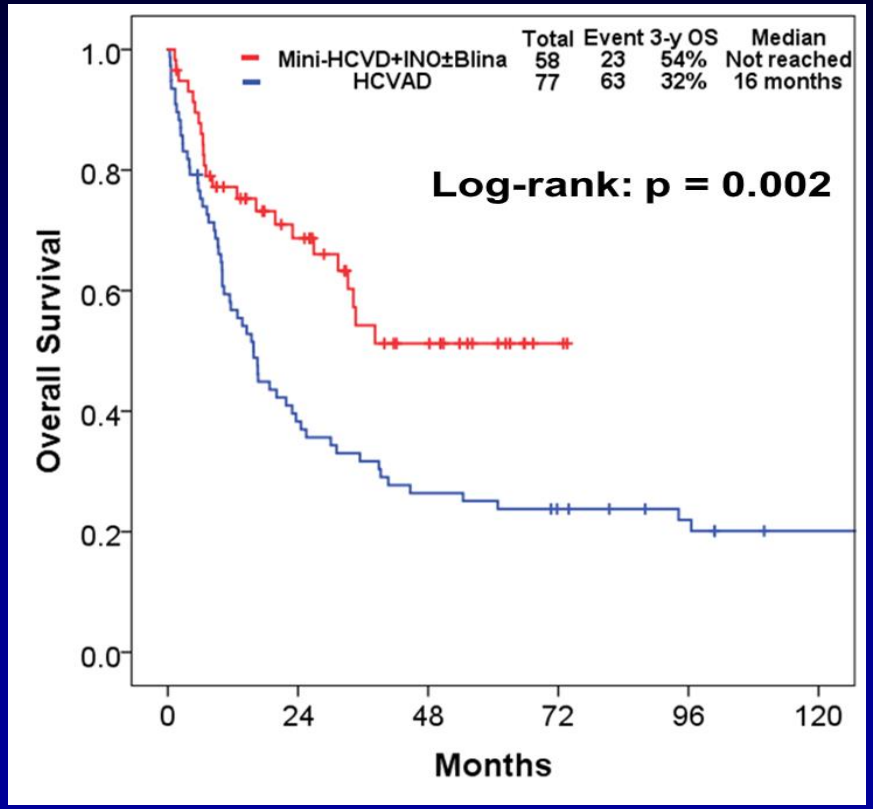
Total INO dose = 2.7 mg/m^2

*Ursodiol 300 mg tid for VOD prophylaxis.

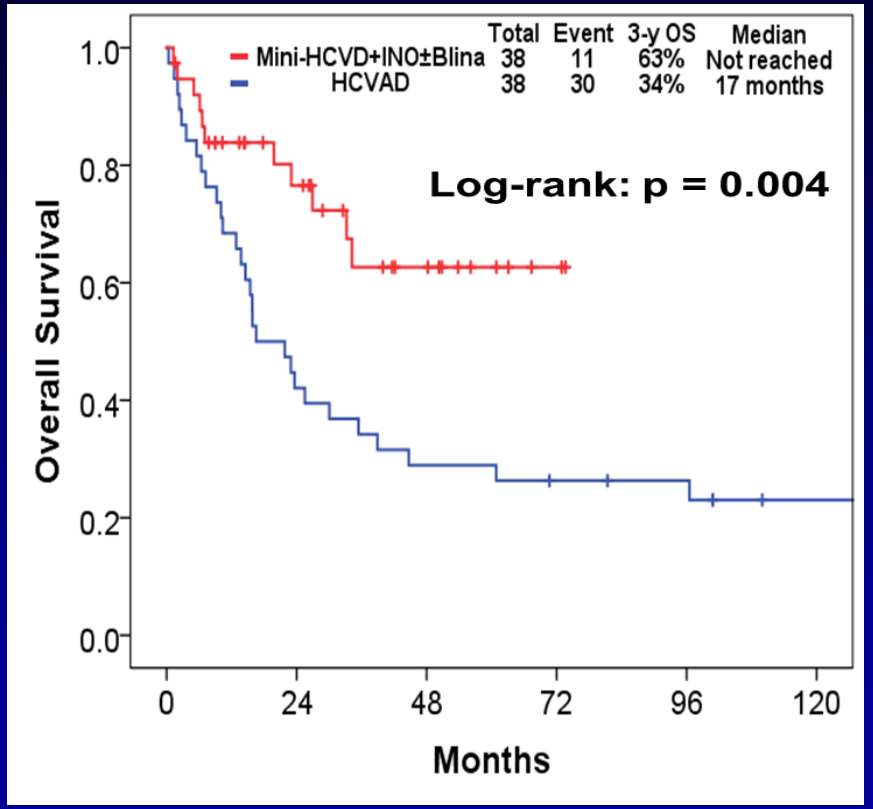
Jabbour E, et al. *Cancer.* 2018;124(20):4044-4055.

Mini-HCVD + INO ± Blina vs HCVAD in Elderly ALL – Survival

Pre-matched



Matched



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

T-ALL – A Separate Disease and Dilemma

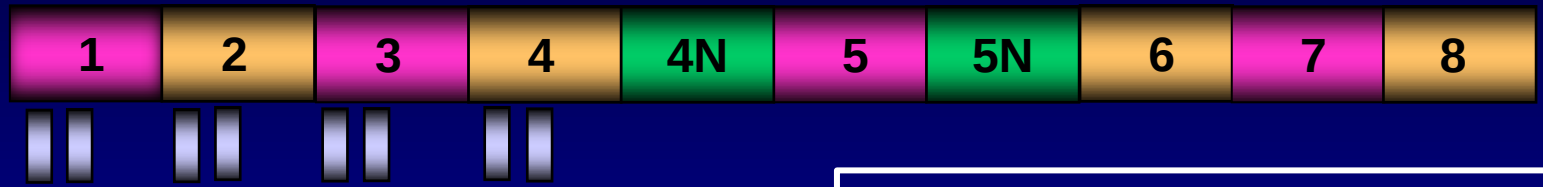
- What works: ALL chemoRx + lots of MTX, HD ara-C, asparaginase
- No active Abs yet (like in pre–B-ALL)
- New effective Rxs: venetoclax, decitabine, novel CAR Ts
- Precursor T-ALL: adverse; genomic-epigenetic more like AML; AML regimens work: FAI, DAC10-ven, GO

Hyper-CVAD + Nel in T-ALL/T-LL – Design

Regimen 4 (N = 15)

Venetoclax: initially 2 weeks per cycle, then 1 week per subsequent cycles

Induction-Consolidation

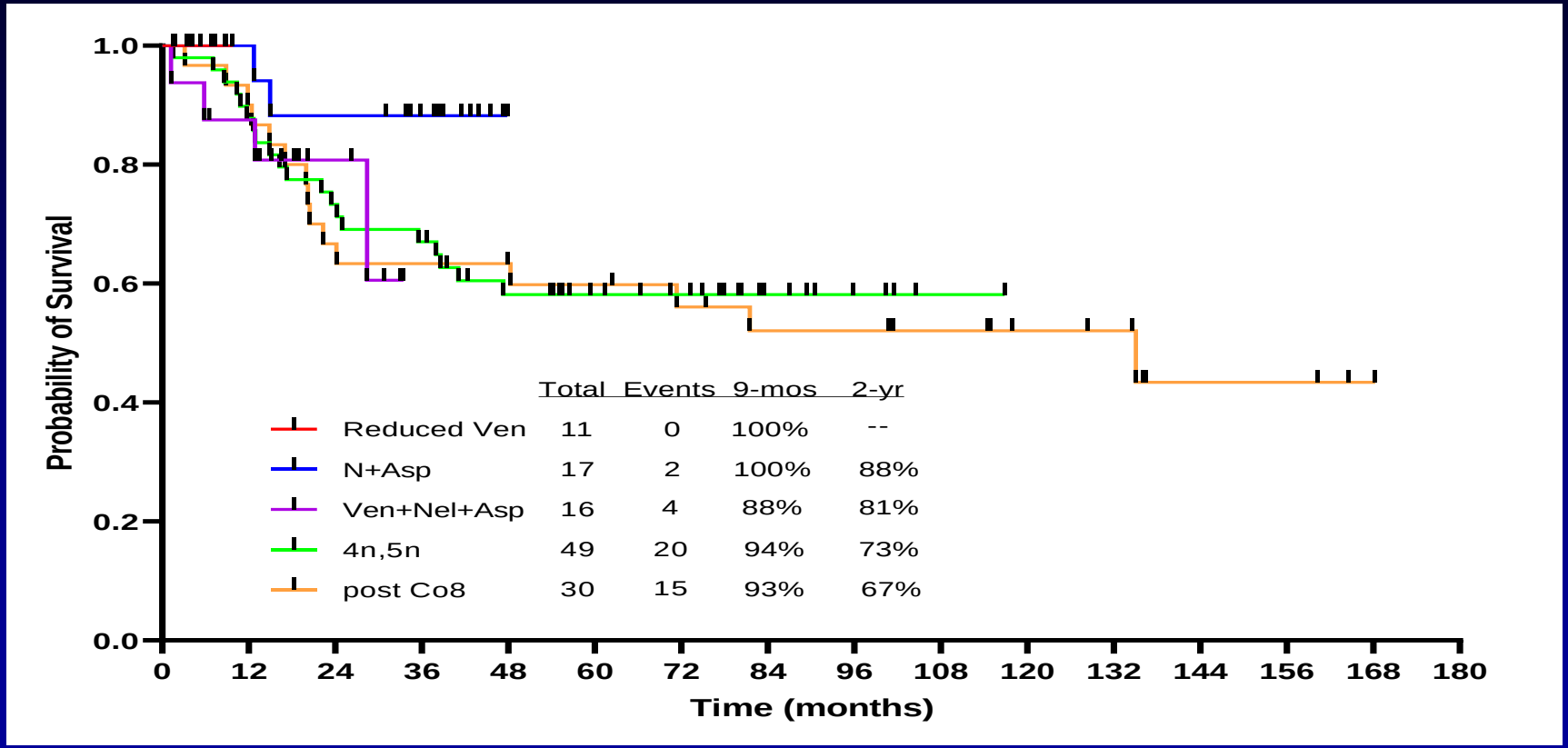


Nelarabine: 650 mg/m^2 IV daily for 5 days
PEG asparaginase: 1500 IU/m^2; capped

Maintenance

Hyper-CVAD
MTX + Ara-C
Nelarabine/PEG asparaginase
IT MTX + Ara-C
POMP
Mediastinal XRT
MTX + PEG asparaginase

T-ALL – Overall Survival With Modified H-CVAD Regimens



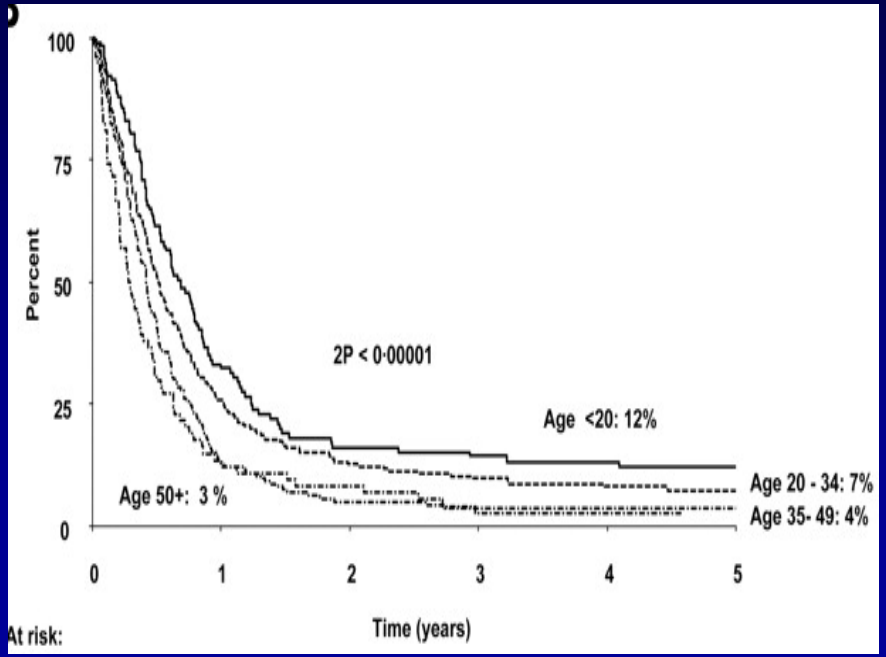
ALL – Role of Allogeneic SCT

- ALL-MLL; t(11q23; ---)
- Precursor T ALL
- Complex CG ≥5 abn; near hypoploid + p53
- Ph-like if *CRLF2* + *JAK2* mutation
- Others: Ph+ ALL PCR+ in CR3 mos; other Ph-like ALL; ALL CR1 MRD+ – may be managed with blina-ino

ALL – Historical Survival Rates After First Relapse

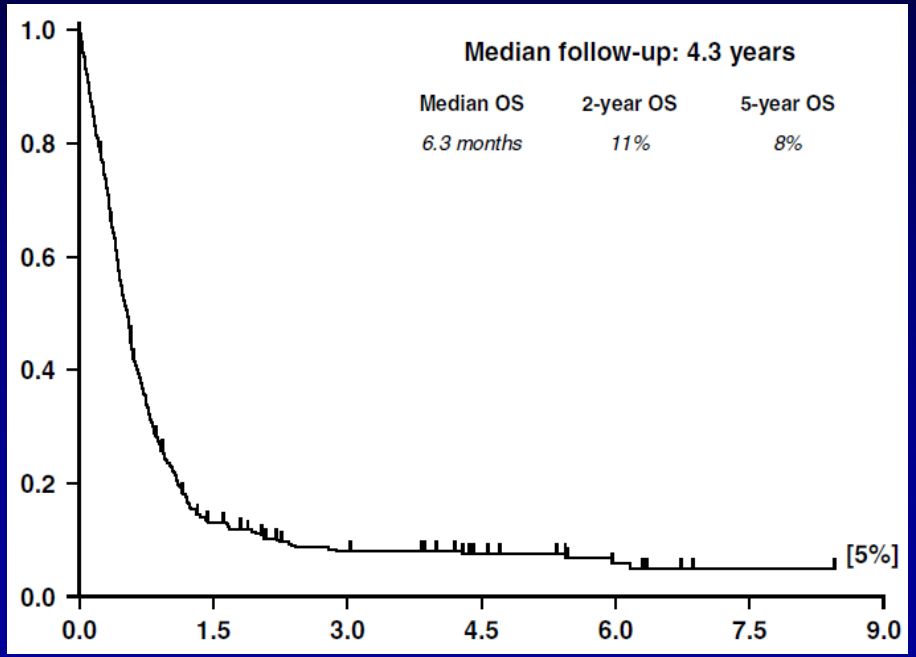
MRC UKALL2/ECOG2993 Study (n = 609)

Outcome of patients after <u>first relapse</u>
5-yr OS: 7%



LALA-94 Study (n = 421)

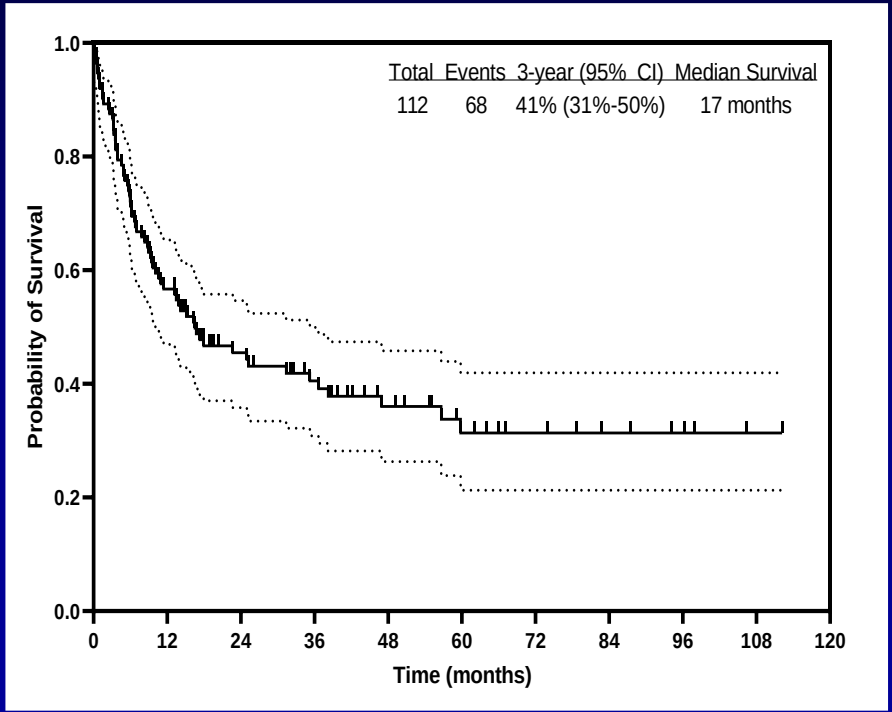
Outcome of patients after <u>first relapse</u>
2-yr OS: 11% and 5-yr OS: 8%

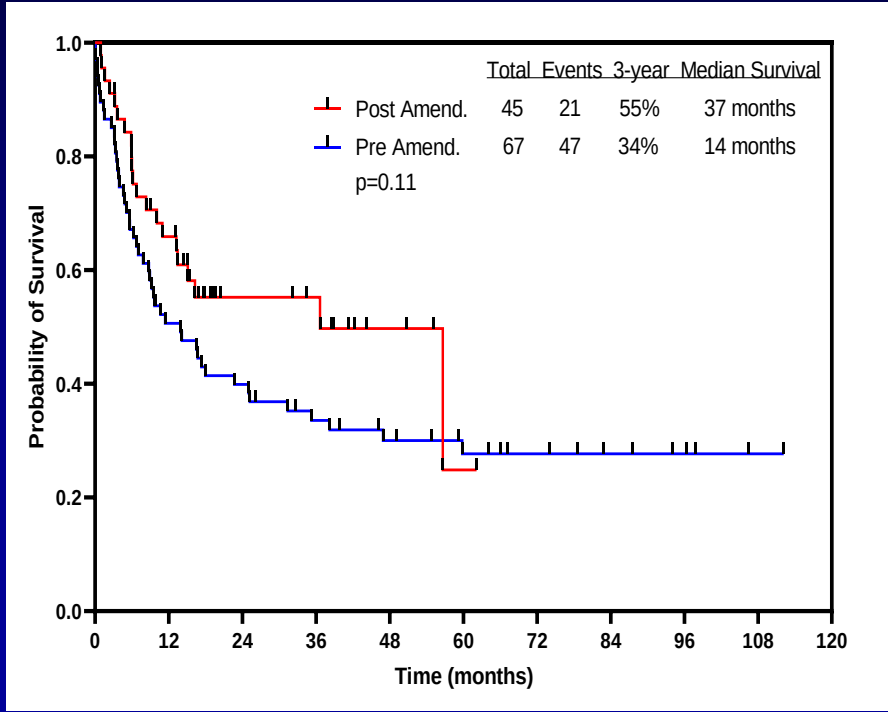


Fielding. *Blood*. 2007;109:944-950; Tavernier. *Leukemia*. 2007;21:1907-1914.

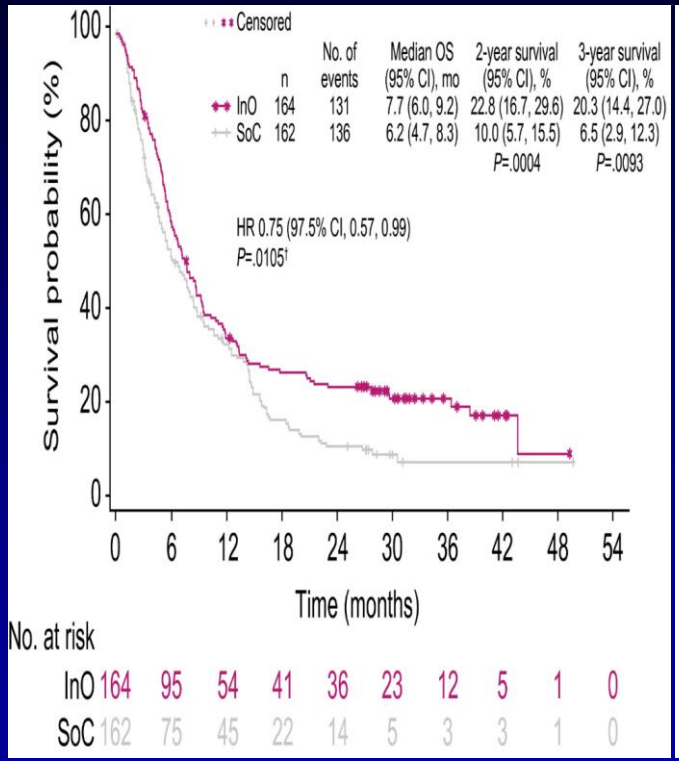
ALL Salvage – Mini-CVD–Inotuzumab ± Blinatumomab

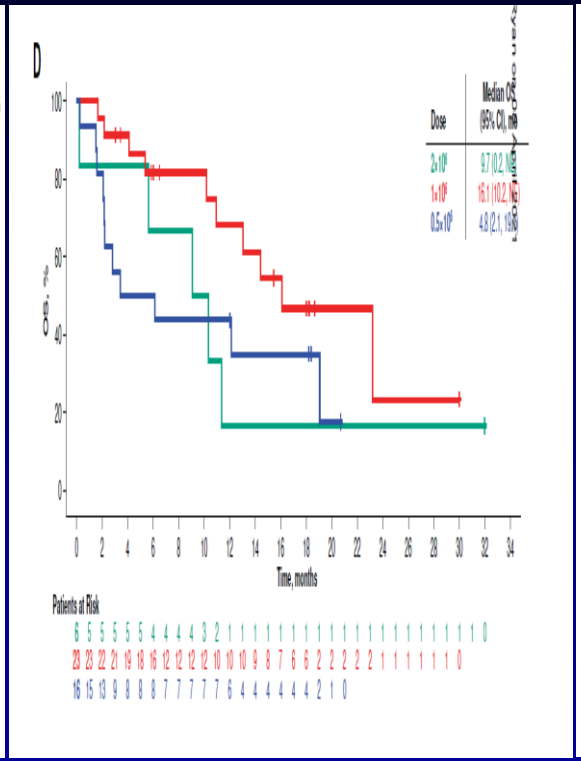
- 112 pts Rx for R/R ALL: 80 in S1; 32 in S2+
- CR 70/112 = 62%; ORR 93/112 = 83%. MRD-negative 76/91 = 83%. VOD 10/112 = 9%; 1% post-amendment

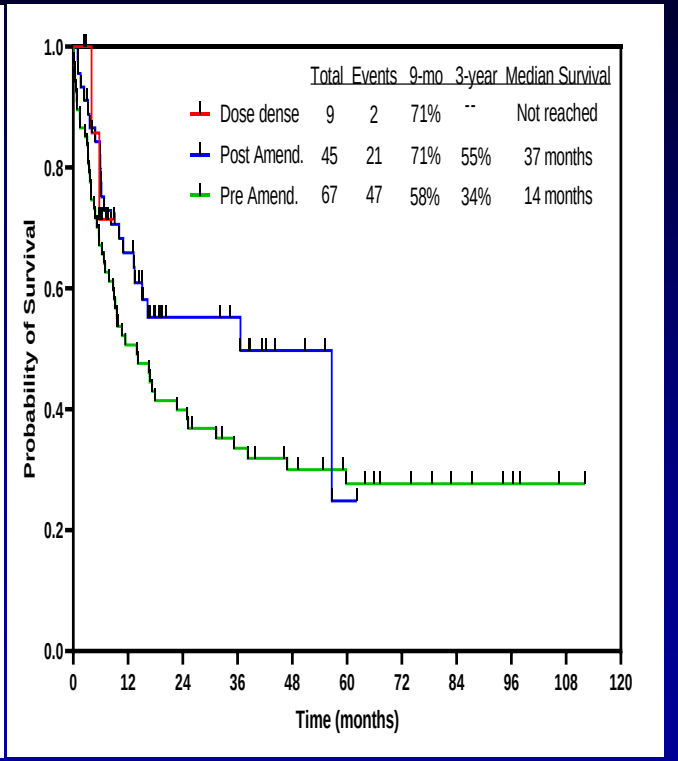




ALL Salvage – SOCs vs Newer Approaches





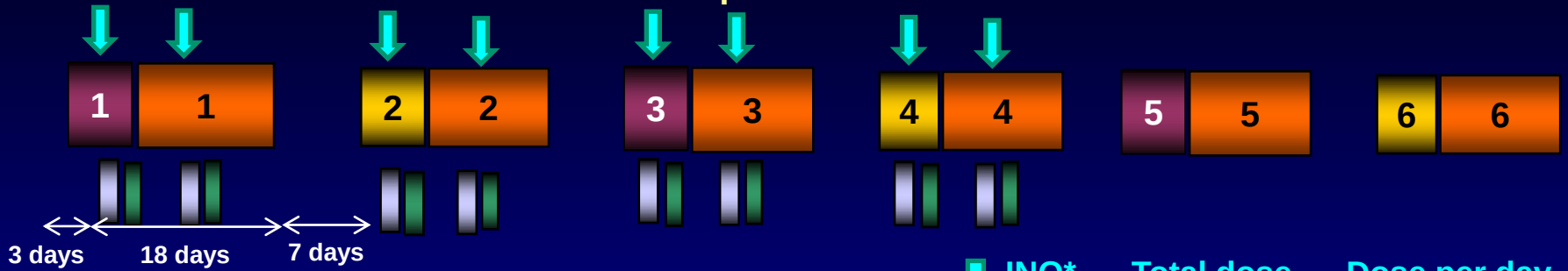


ALL – Summary

- Ph+ ALL: Ponatinib (dasatinib)-blinatumomab
- Antibody-based Rxs and CAR Ts both outstanding. But uses different from FDA approvals
- Future of pre-B 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 alloSCT; 4) Monitor MRD by NGS (MRD in 1 million cells) to decide on Rx changes and Rx duration
- SQ easily deliverable BiTEs; CD20 BiTEs

BRICK Regimen – Dose-Dense Mini-HCVD + Inotuzumab + Blinatumomab (± CAR T) in ALL

Induction phase: C1–C6



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

Total INO dose = 2.7 mg/m²

Monitor MRD by NGS and decide

CAR T Consolidation

*Ursodiol 300 mg tid for VOD prophylaxis.

Mini-HyperCVD

Mini-MTX + Ara-C

Rituximab

IT MTX + Ara-C

Blinatumomab

Can We Do Even Better? Yes, We Can!

- Mild chemoRx (vcr-steroids) induction
- Induction-consolidation with TriTEs/TetraTEs—trispecific/tetraspecific T-cell engagers that target CD19/20/22 and engage CD3 T cells—1–3 months
- Evaluate NGS-MRD
- Dual CD19/22-targeting CAR T consolidation in CR1 (regardless of NGS-MRD status)
- Total Rx duration 3–4 months

Leukemia Questions?

- Email: hkantarjian@mdanderson.org
- Cell: 281-705-7207
- Office: 713-792-7026

Global Leukemia Academy

The Clinical Value of MRD in ALL: How MRD Can Guide the Use of Targeted Agents or Immunotherapy

Jae Park

APTITUDE HEALTH

The Clinical Value of MRD in ALL: How MRD Can Guide the Use of Targeted Agents or Immunotherapy

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

Measurable/Minimal Residual Disease in ALL

- The single most predictive marker for outcome in childhood ALL
  - Identifies patients who will have an unfavorable outcome
  - Identifies patients who may benefit from more-intensive/alternative therapies

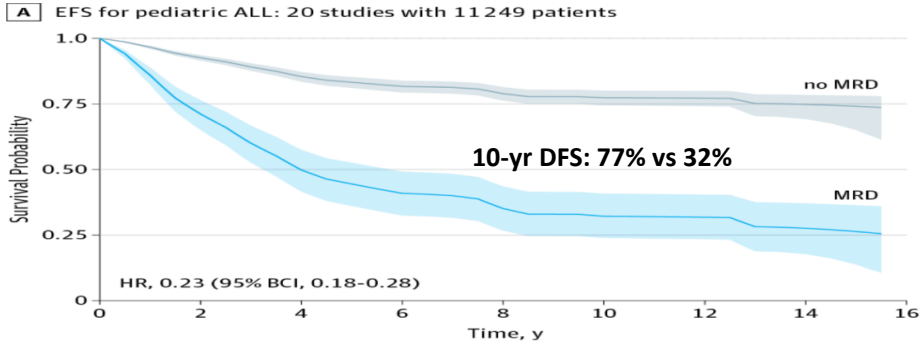
- Defined as the detection of at least 1 leukemia cell in 10,000 normal cells
  - 0.01% (10^{-4})
  - Used to evaluate post-induction therapeutic response

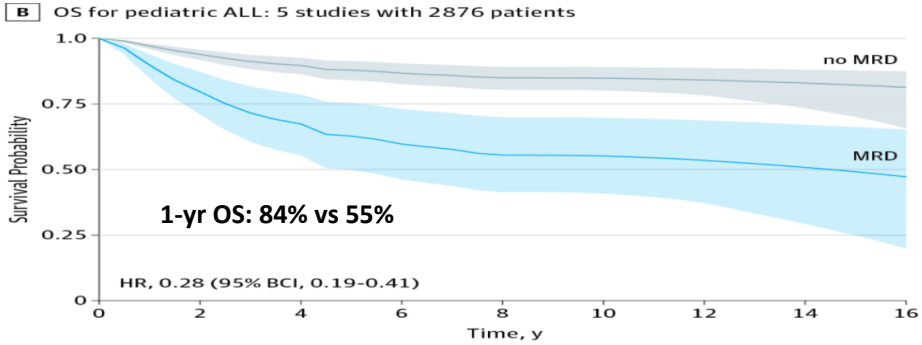
- Pediatric groups for ALL have used MRD for risk stratification and therapeutic decision-making for years
  - MRD assessments are incorporated into treatment algorithms

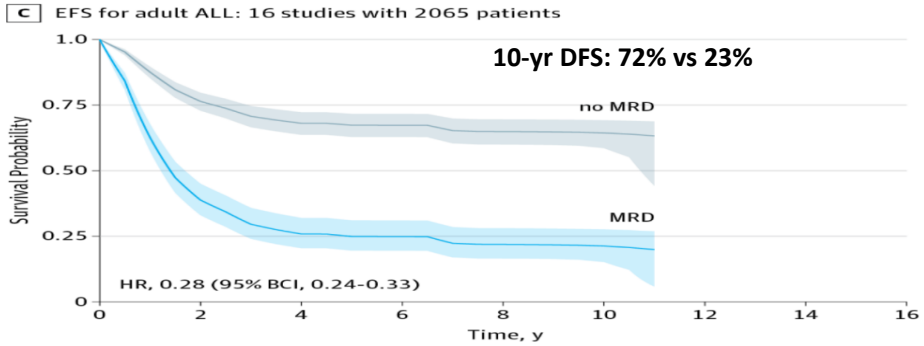
Van Dongen JJ, et al. *Lancet*. 1998;352(9142):1731-1738; Borowitz MJ, et al. *Blood*. 2008;111(12):5477-5485.

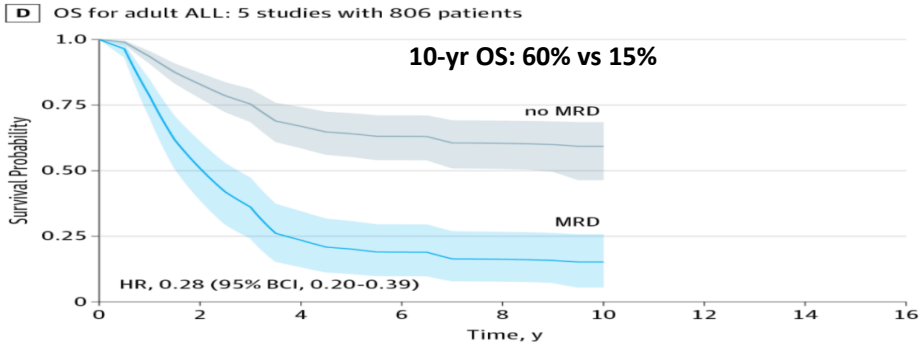
Meta-analysis Evaluating MRD in ALL

- Meta-analysis of 39 studies (pediatric and adult); 13,637 patients with ALL
- Prognostic significance of MRD clearance was demonstrated for all therapies, MRD method (PCR vs flow), timing, and MRD cut points



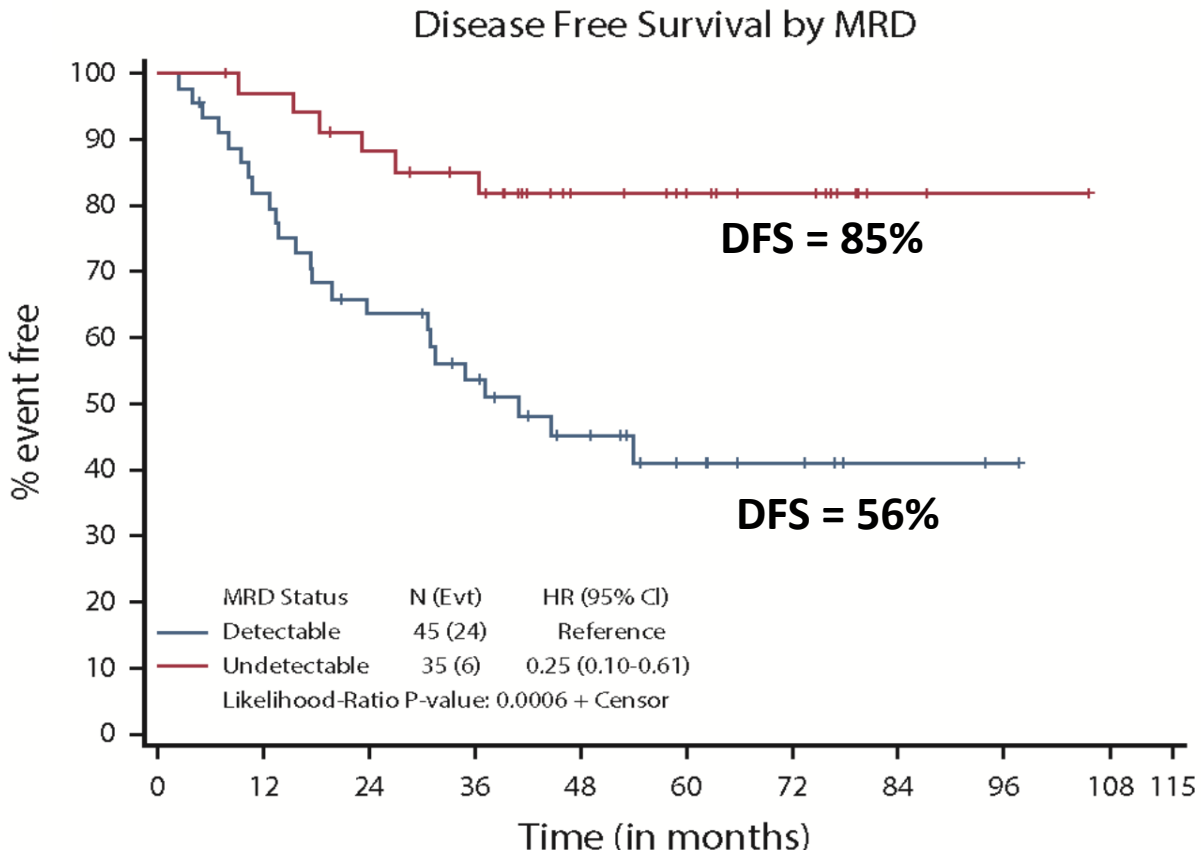






Berry DA, et al. *JAMA Oncol*. 2017;3(7):e170580.

CALGB 10403 (AYA): Outcome by MRD Status



Of patients in CR1 at EOI, only 43% had undetectable MRD

Stock W, et al. *Blood.* 2019;133(14):1548-1599.

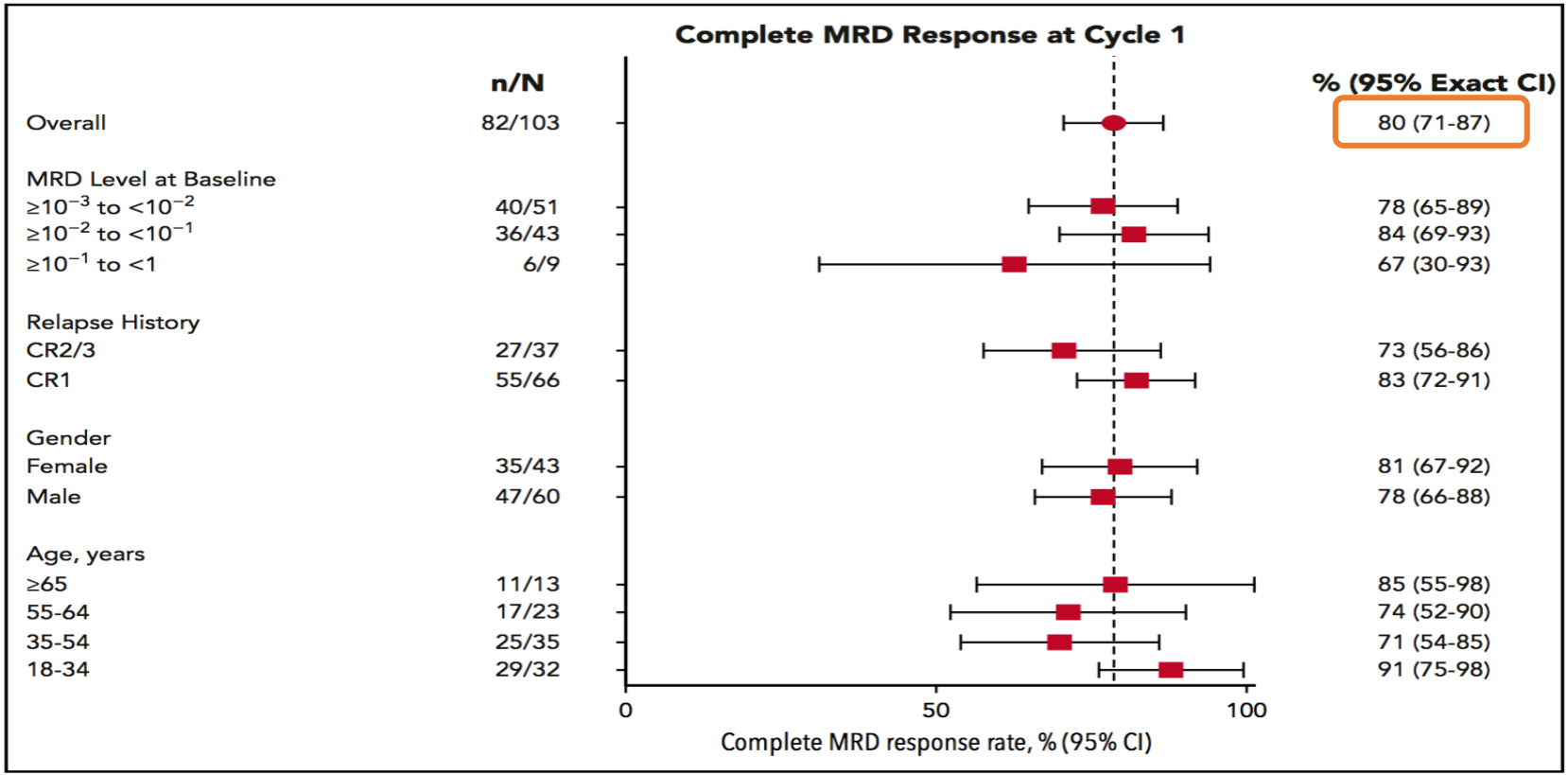
Blinatumomab in MRD+ B-ALL

- **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)

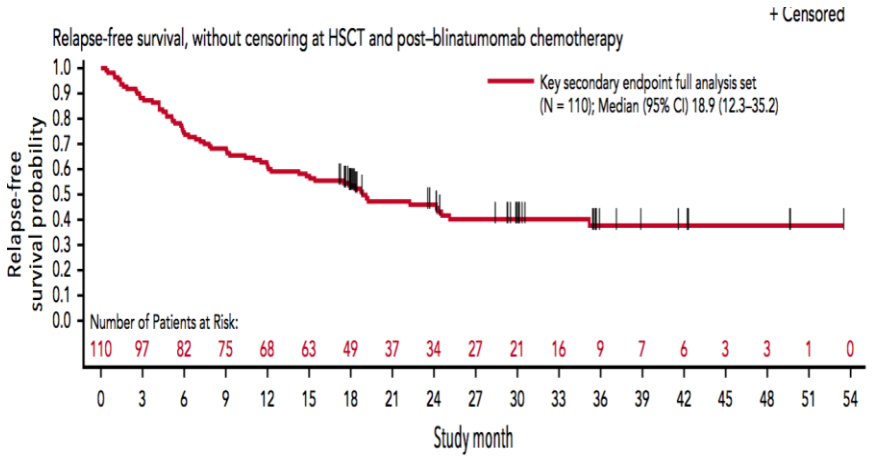
Gökbuget N, et al. *Blood.* 2018;131(14):1522-1531.

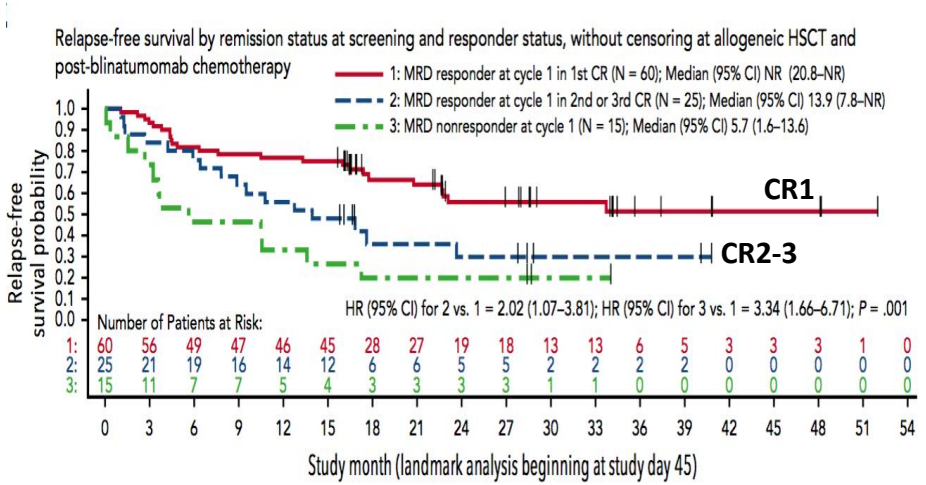
CR Rates by Subgroups in MRD+ B-ALL



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

RFS of MRD+ ALL Patients After Blinatumomab





70% of pts proceed to alloHSCT

Response	First CR (N = 60)	Second CR (N = 26)
cMRDa	85.2%	72%
hRFSb	35.2 months	12.3 months

[a]Complete MRD response is defined as the absence of detectable MRD confirmed in an assay with minimum sensitivity of 0.01%.

[b]Time from start of blinatumomab to hematologic or extramedullary relapse, secondary leukemia, or death due to any cause; includes time after transplantation; Kaplan-Meier estimate.

Gökbuget N, et al. *Blood.* 2018;131(14):1522-1531; Jen EY, et al. *Clin Cancer Res.* 2019;25(2):473-477.

FDA Approval of Blinatumomab for MRD+ B-ALL in US

- Blinatumomab approved for the treatment of B-ALL in first or second complete remission with MRD ≥0.1%
- Prior to the approval, MRD results did not change patient management
- With the approval, the incorporation of MRD as standard of care for all subtypes of ALL
- In January 2020, the FDA released guidance for industry on the use of MRD in the development of investigational agents for hematologic malignancies
  - FDA accepts MRD levels of <0.01% as evidence of efficacy
  - ALL is the only disease in which MRD has been used as a surrogate endpoint supporting drug approval

https://www.fda.gov/drugs/resources-you-drugs; US Department of Health and Human Services. Food and Drug Administration. Hematologic malignancies: Regulatory considerations for use of minimal residual disease in development of drug and biological products for treatment. Guidance for industry. 2020. www.fda.gov/media/134605/download. Accessed December 1, 2022.

Inotuzumab Ozogamicin in Adults With MRD+ B-Cell Precursor ALL: Study Design and Patient Characteristics

Adults with B-cell precursor ALL in MRD+[a] CR (N = 16)

- **CR1 (n = 11)**
  - Did not achieve MRD negativity or experienced MRD recurrence after ≥3 mo from start of frontline therapy
- **CR2+ (n = 5)**
  - Experienced MRD relapse after 1 month from start of salvage therapy

Inotuzumab ozogamicin

- 0.6 mg/m^2 D1 and 0.3 mg/m^2 D8 in cycle 1
- 0.3 mg/m^2 on D1 and D8 in subsequent cycles up to 6[b]

Endpoints

- MRD negativity
- OS
- RFS

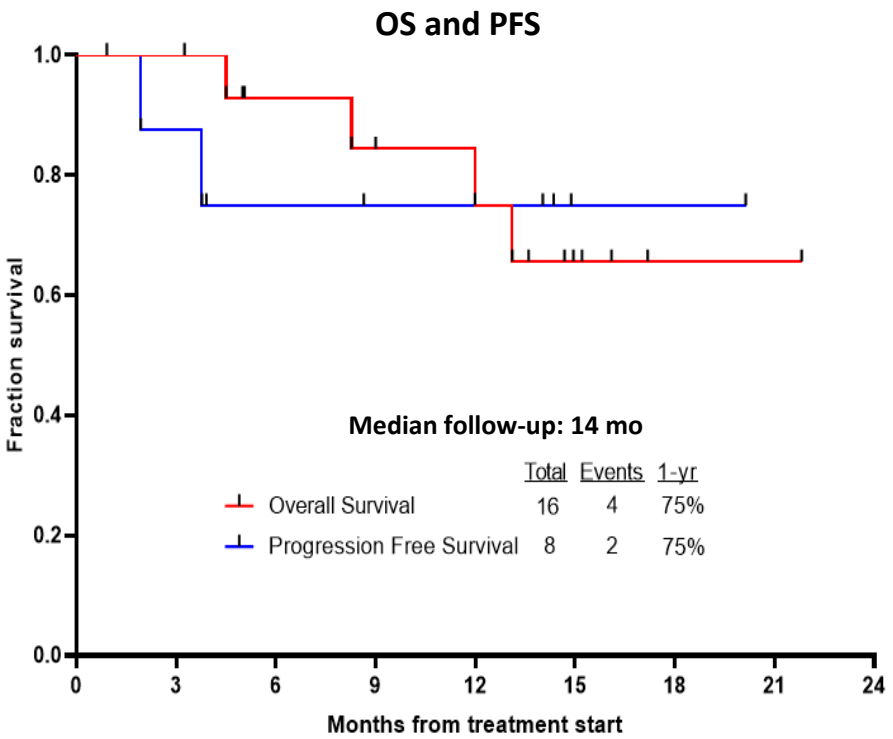
Patient Characteristics, n (%)	Inotuzumab Ozogamicin N = 16
Ph+ ALL	10 (63)
Received concomitant TKI	
Ponatinib	9
Dasatinib	1
Persistent MRD	10 (62.5)
MRD recurrence	6 (37.5)
Prior therapy	
Blinatumomab	9 (56)
AlloHSCT	3 (19)
CAR T-cell therapy	1 (6)

[a]Defined as ≥0.01% by multiparameter flow cytometry in patients with Ph– ALL and a BCR-ABL1 to ABL1 transcript ratio by PCR of ≥0.01% for patients with Ph+ ALL. [b]Patients received a median of 3 cycles.

Short NJ, et al. ASH 2021. Abstract 2299.

Inotuzumab Ozogamicin in Adults With MRD+ B-Cell Precursor ALL: Efficacy

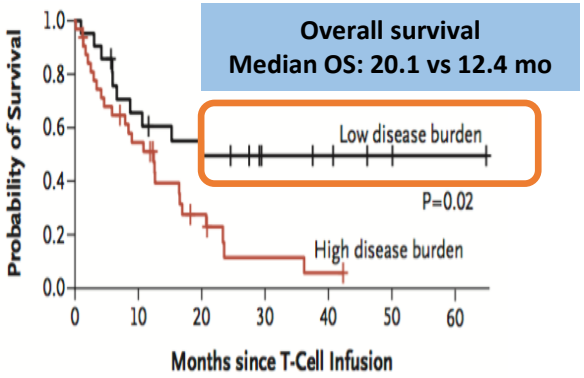
	Inotuzumab Ozogamicin (N = 16)
MRD– at any time, n (%) Ph– ALL (n = 6) Ph+ ALL (n = 10)	8 (50) 4 (67) 4 (40)
MMR as best response	4[a]
Response by prior therapy Prior blinatumomab (n = 9) No prior blinatumomab (n = 7)	 3 (33) 5 (71)
Received alloHSCT	5 (31)[b]



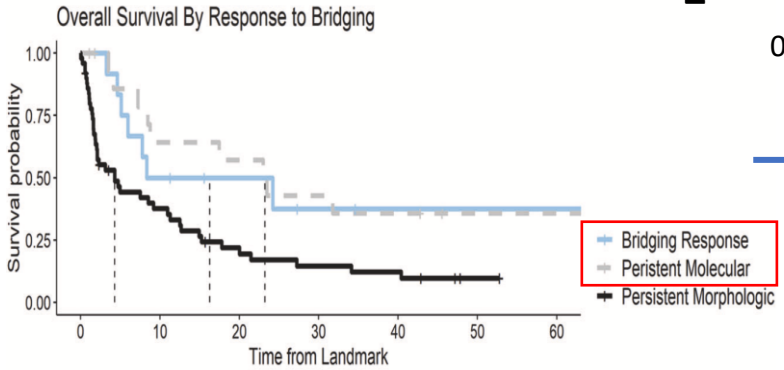
[a]Major molecular response achieved by patients with Ph+ ALL. [b]63% of MRD responders.

Short NJ, et al. ASH 2021. Abstract 2299.

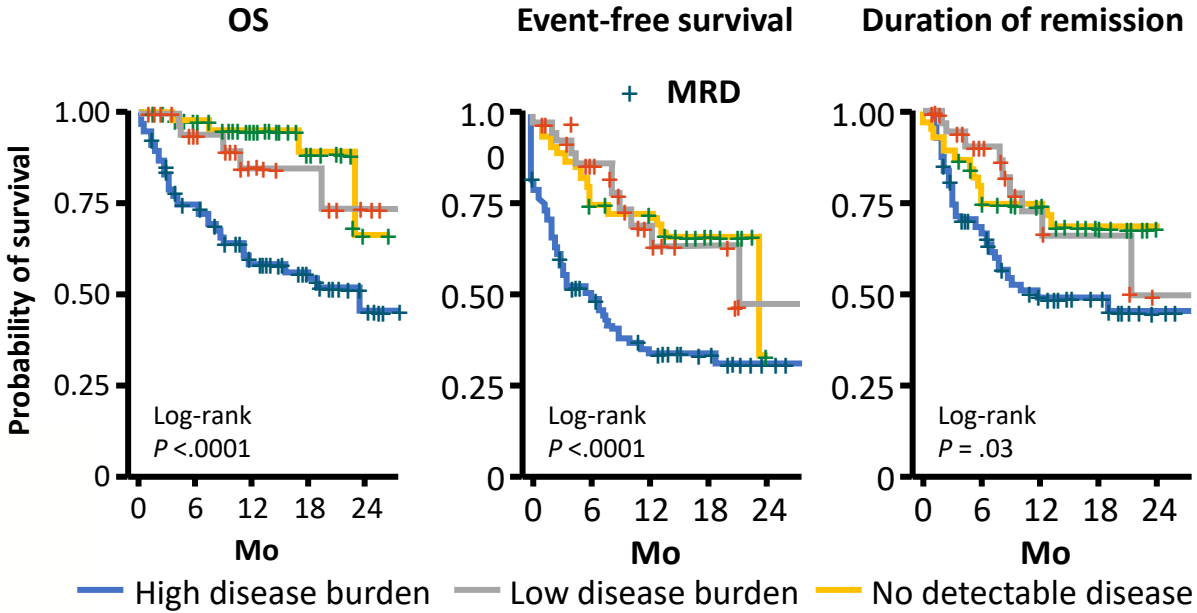
Low Disease Burden Associated With Improved Remission Duration and Long-term Survival With CD19 CAR



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.

Current Challenges With MRD

- When to measure?
  - Currently, MRD is focused (generally) on a single time point – EOI
  - ALL therapy extends well beyond a day 29 endpoint
  - Very few data on serial monitoring

- MRD assays differ
  - Multiparameter flow (MFC)
  - Next-generation sequencing (NGS)
  - Quantitative PCR (qPCR)

- Limited data on concordance of the different assays and risk-stratification

Comparison of MRD Assays

MRD Method	Sensitivity	Advantages	Disadvantages
Multiparameter flow cytometry (FCM)	10^{-4} (0.01%)	• Fast • Cost-effective • Widely available platform • Clinically proven platform	• Subjective interpretation • Immunophenotype may change during treatment • Inadequate standardization • Immunotherapy treatment can complicate interpretation
RQ-PCR for IgH/TCR gene rearrangements	10^{-4} to 10^{-5} (0.01%-0.001%)	• Well standardized • More sensitive than FCM	• Technically labor-intensive • Requires technical expertise • Expensive
RQ-PCR for gene fusions	10^{-4} to 10^{-5} (0.01%-0.001%)	• More sensitive than FCM • Technically simpler	• Need for baseline specimen • Limited standardization • Not all ALL cases have a gene rearrangement – immature T-ALL
Next-generation sequencing	10^{-6} (0.0001%)	• Very sensitive • Relatively fast	• Not standardized yet • Requires bioinformatics • Limited clinical validation • Expensive

Chen X, Wood BL. *Blood Rev*. 2017;31(1):63-76; Short NJ, Jabbour E. *Curr Oncol Rep*. 2017;19(1):6.

Children's Oncology Group Comparison of MRD by FCM and NGS

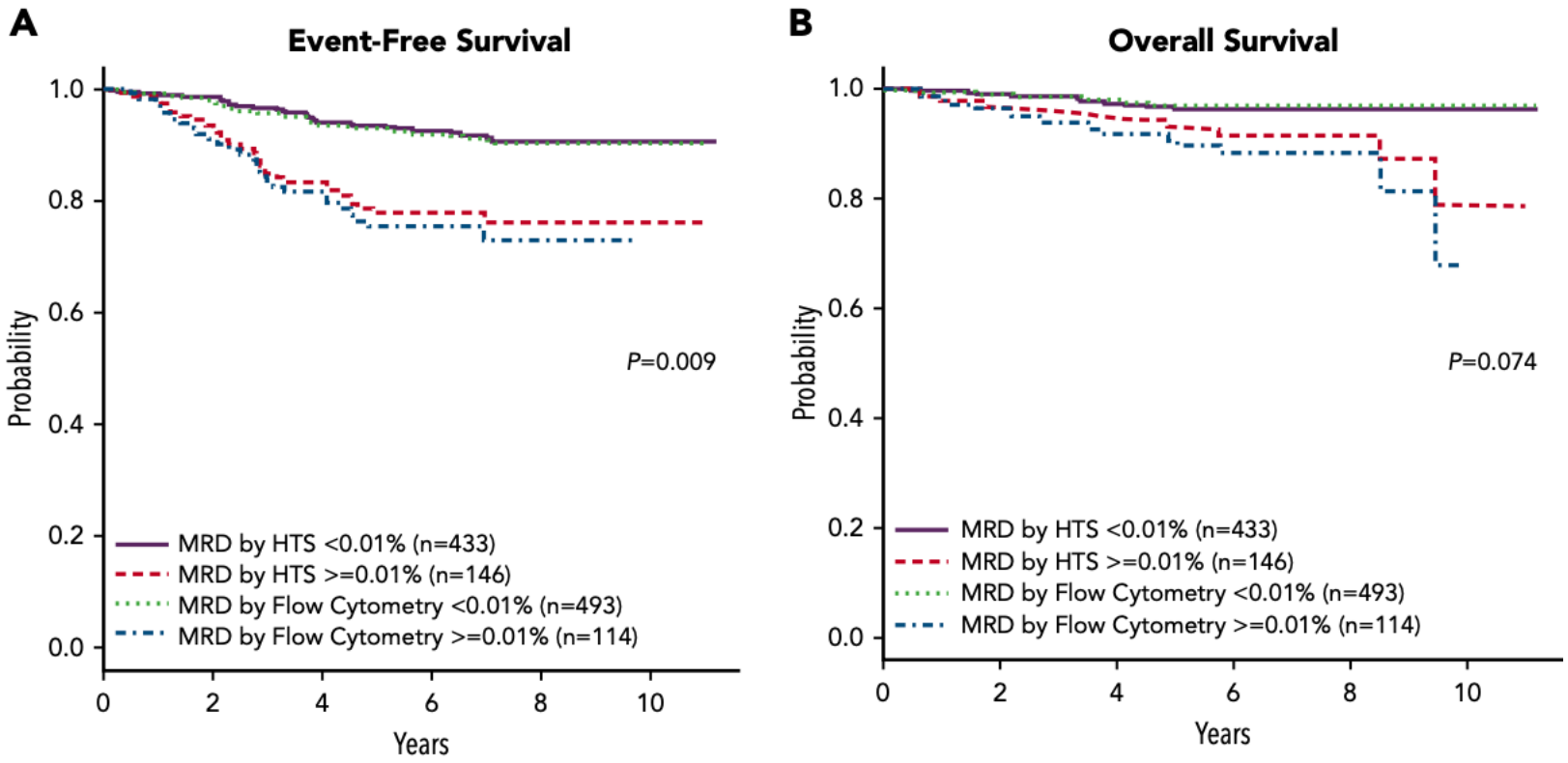
- Paired pretreatment and EOI (day 29) samples from 619 patients enrolled on AALL0331 (standard-risk protocol) and AALL0232 (high-risk protocol) were used for the analysis
  - 315 samples were high risk
  - 304 samples were standard risk

- FCM MRD done at University of Washington or Johns Hopkins
- Tissue-banked specimens were sent to Adaptive Biotechnologies for DNA extraction and immunosequencing
  - IGH and TRC CDR3 regions were amplified and sequenced
  - immunoSEQ platform was used

- EFS and OS were evaluated and compared with MRD assays

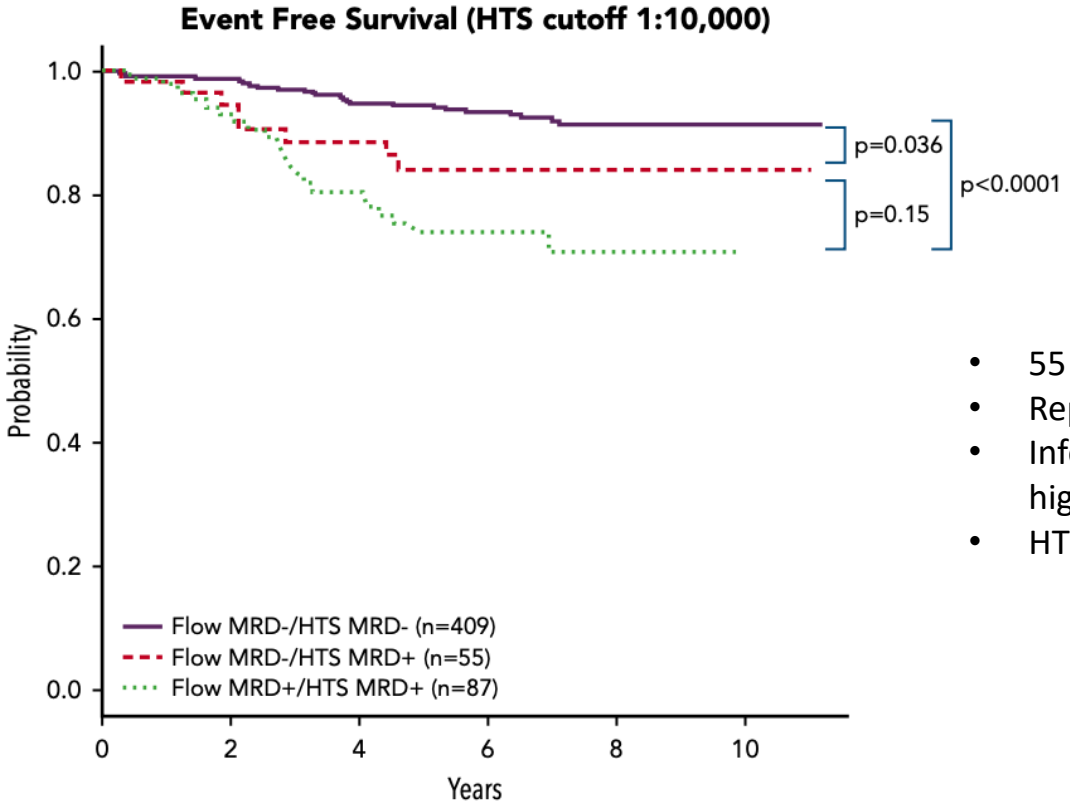
Wood B, et al. *Blood*. 2018;131(12):1350-1359.

Strong Correlation Between MRD by HTS or FCM (0.01%)



Wood B, et al. *Blood*. 2018;131(12):1350-1359.

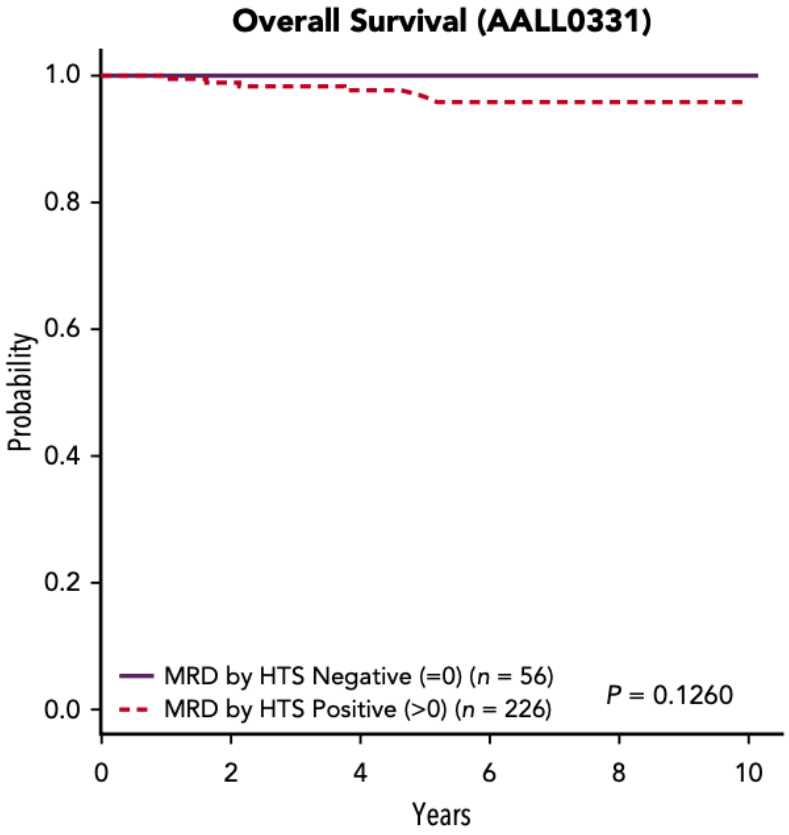
Discordant MRD by HTS or FCM Has Intermediate Prognosis



- 55 patients with **FCM MRD–/HTS MRD+**
- Represented ~**38% of patients in SR group**
- Inferior 5-year EFS, so may be considered as higher-risk and ? intensification of therapy
- HTS in this study can identify higher-risk patients

Wood B, et al. *Blood*. 2018;131(12):1350-1359.

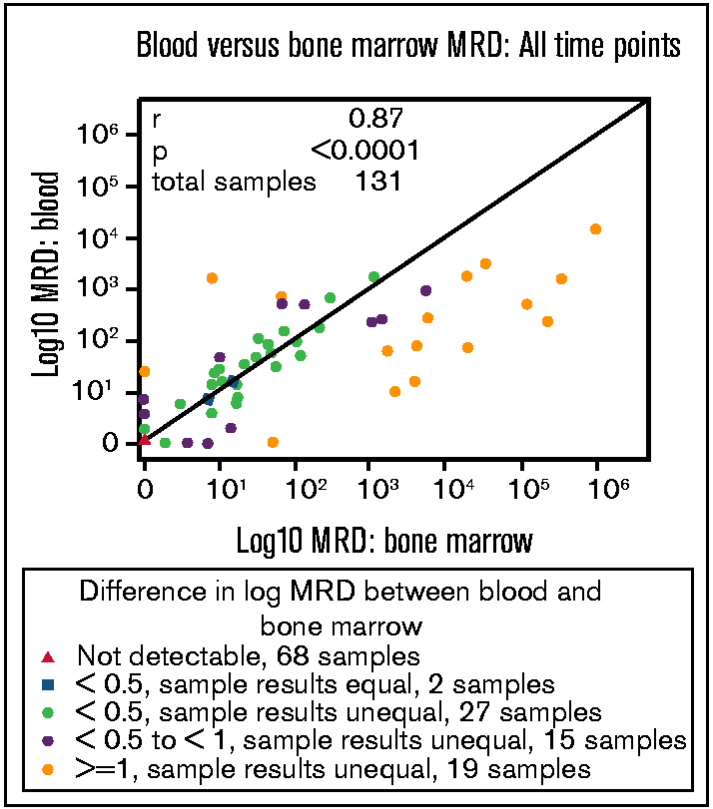
HTS Can Identify Patients With Excellent Outcomes



- 56 patients **HTS MRD– at EOI** down to a cutoff of 0.0001%
- Represented ~20% of patients in SR group
- 8-year OS of 100%
- These patients require no further therapy intensification or novel therapy to attain cure
- Will not contribute to further randomized questions
- May be candidates for treatment reductions instead
- Importantly, the HTS MRD– patients in the HR population did NOT show the uniformly 100% OS

Wood B, et al. *Blood*. 2018;131(12):1350-1359.

Concordance of BM and PB MRD Assessment



Prospective observational study evaluating MRD in patients receiving HSCT or CAR T-cell therapy (n = 69)

- Strong correlation between PB and BM MRD: sensitivity 87% and specificity 90% in PB vs BM
- Median time from MRD to clinical relapse
  - Post-HSCT: 90 days
  - Post-CAR: 60 days
- PB MRD NGS monitoring appears to be adequate alternative to BM

Muffly L, et al. *Blood Adv.* 2021;5(16):3147-3151.

Conclusions

- MRD monitoring throughout therapy is needed *and* critical to guide prognosis and risk-directed treatments

- MRD monitoring should include early assessment of response to therapy (EOI) and post-treatment monitoring for early relapse detection and to guide therapeutic intervention prior to overt relapse, ie, continued assessment vs one-time

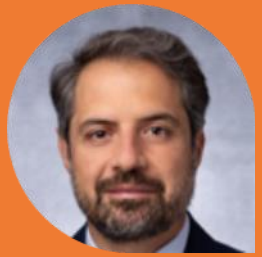
- NGS/HTS is a robust clinical platform for MRD determination

- Possible strategy for monitoring may include different MRD platforms at different time points during therapy in ALL
  - PB MRD monitoring by NGS may substitute for post-treatment monitoring (more suitable for later time points at present)

Global Leukemia Academy

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

Elias Jabbour



APTITUDE HEALTH

Philadelphia-Positive and Ph-Like ALL: How to Treat?

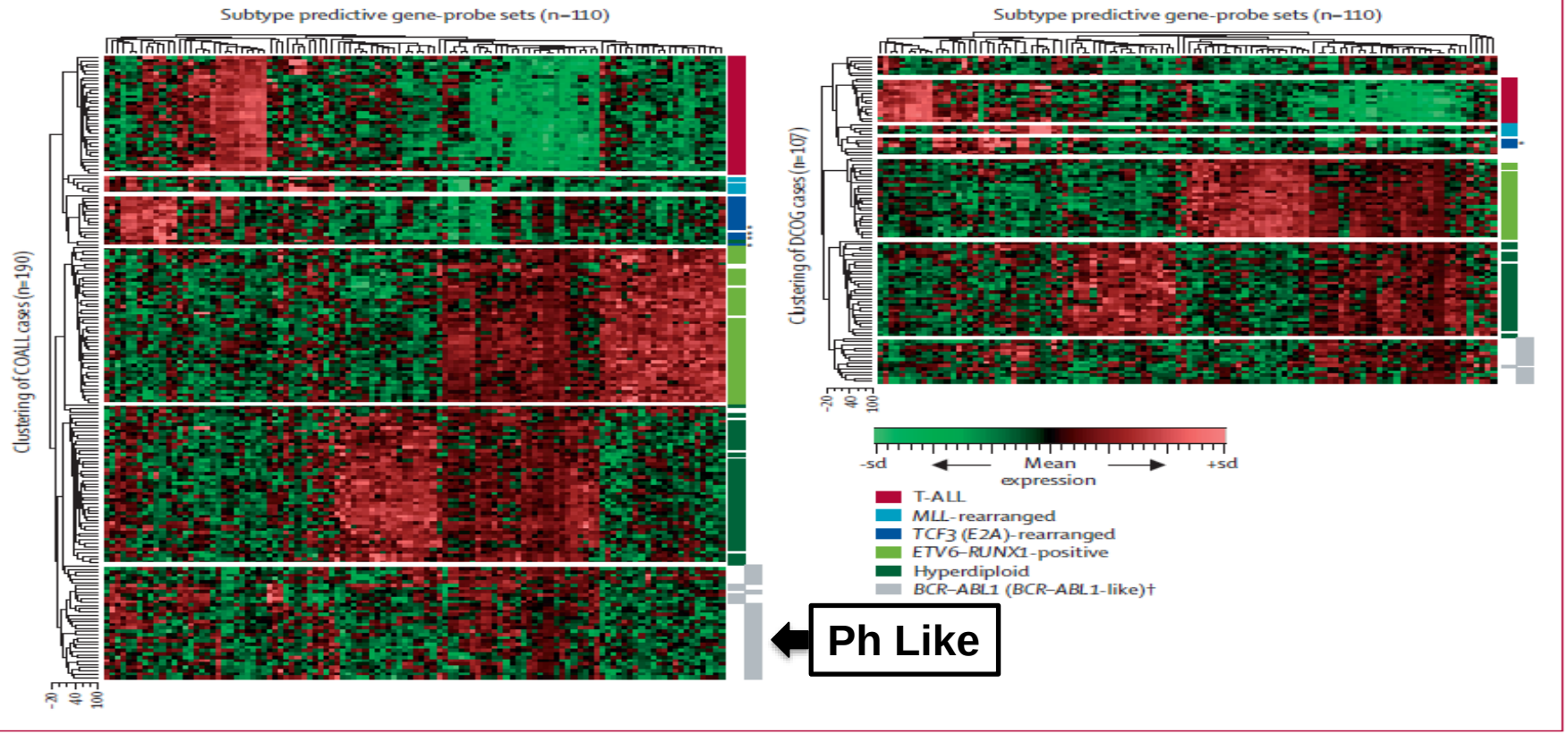
Elias Jabbour, MD
Professor of Medicine
Department of Leukemia
The University of Texas MD Anderson Cancer Center, Houston, TX

Conflict of Interest Disclosure

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

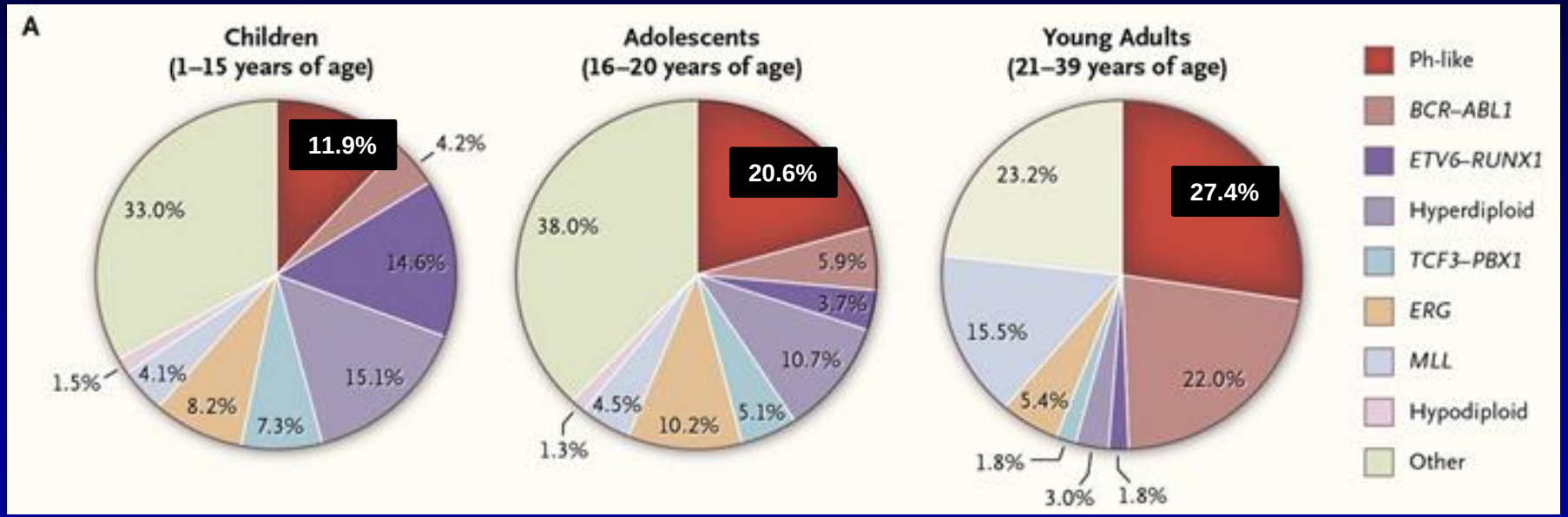
- **Consultancy and advisory roles**
  - **Pfizer, Takeda, Amgen, AbbVie, BMS**

Ph-Like ALL



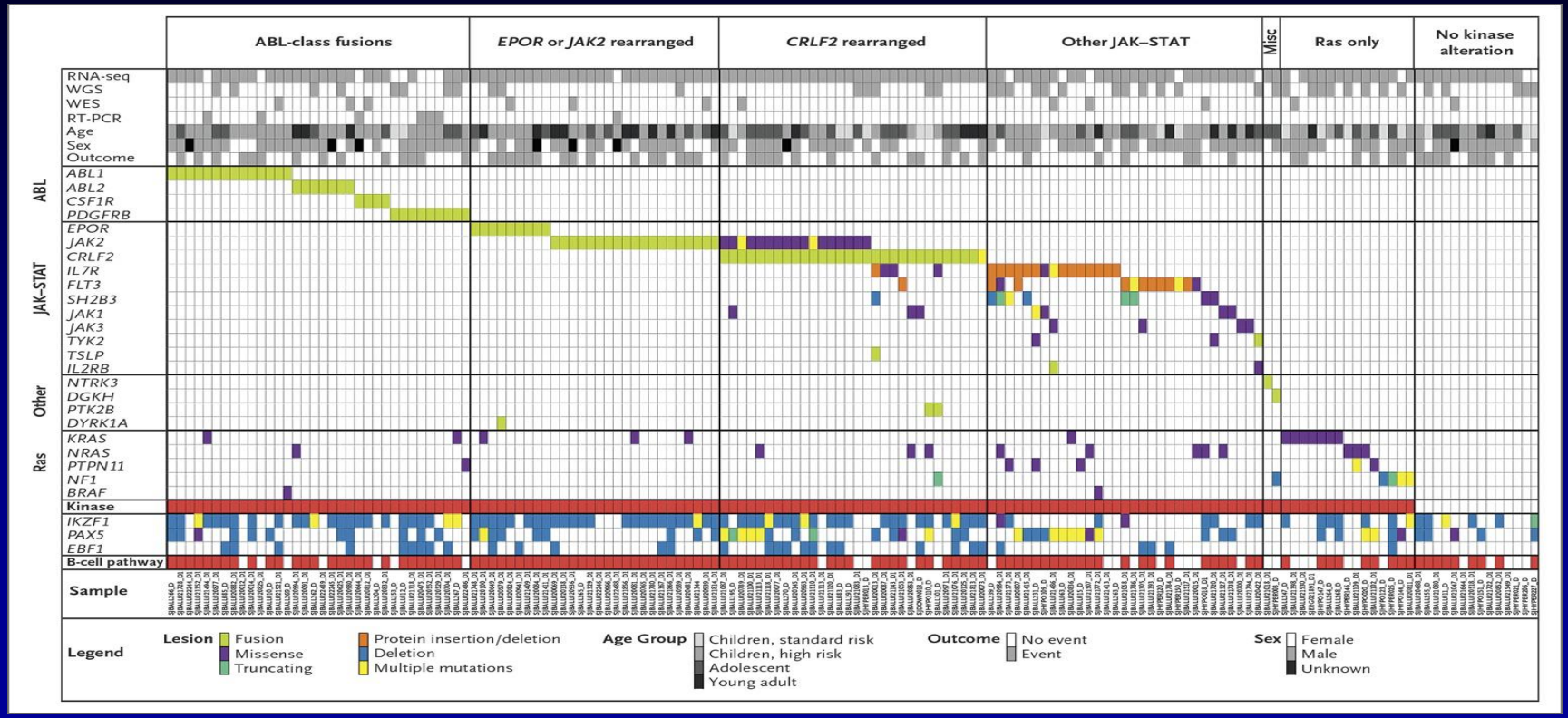
Den Boer et al. *Lancet Oncol*. 2009.

Ph-Like ALL Occurs in 25%–30% of Young Adults With B-Cell ALL



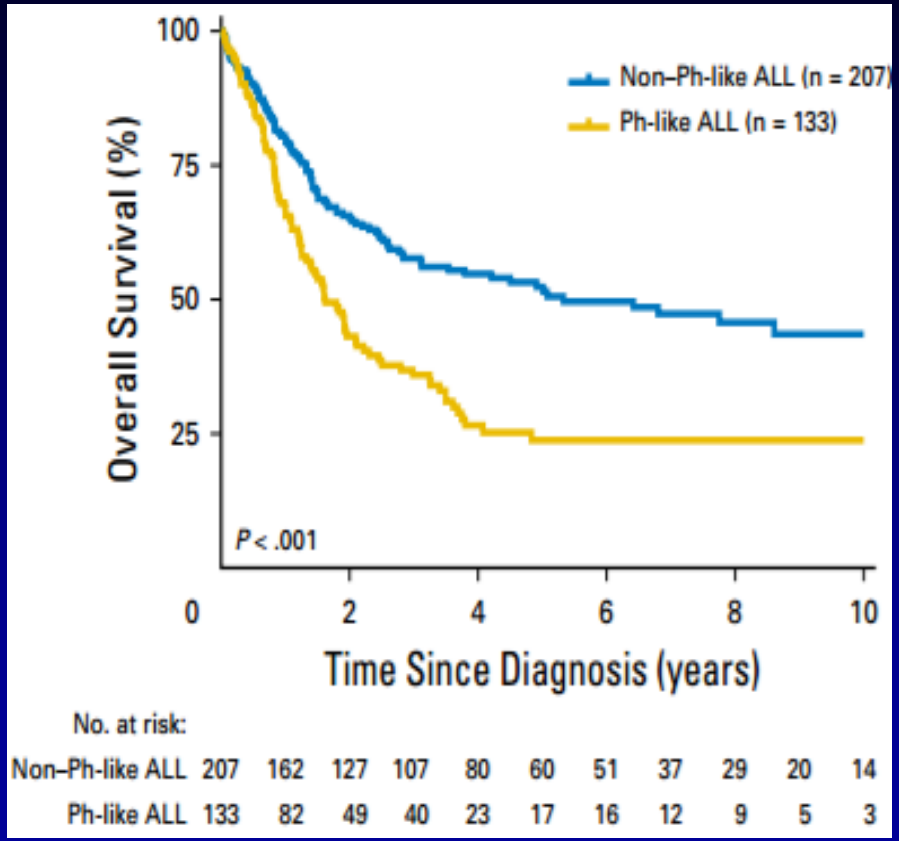
Roberts et al. *N Engl J Med*. 2014;371:1005-1015.

Recurring Kinase Alterations in Ph-Like ALL

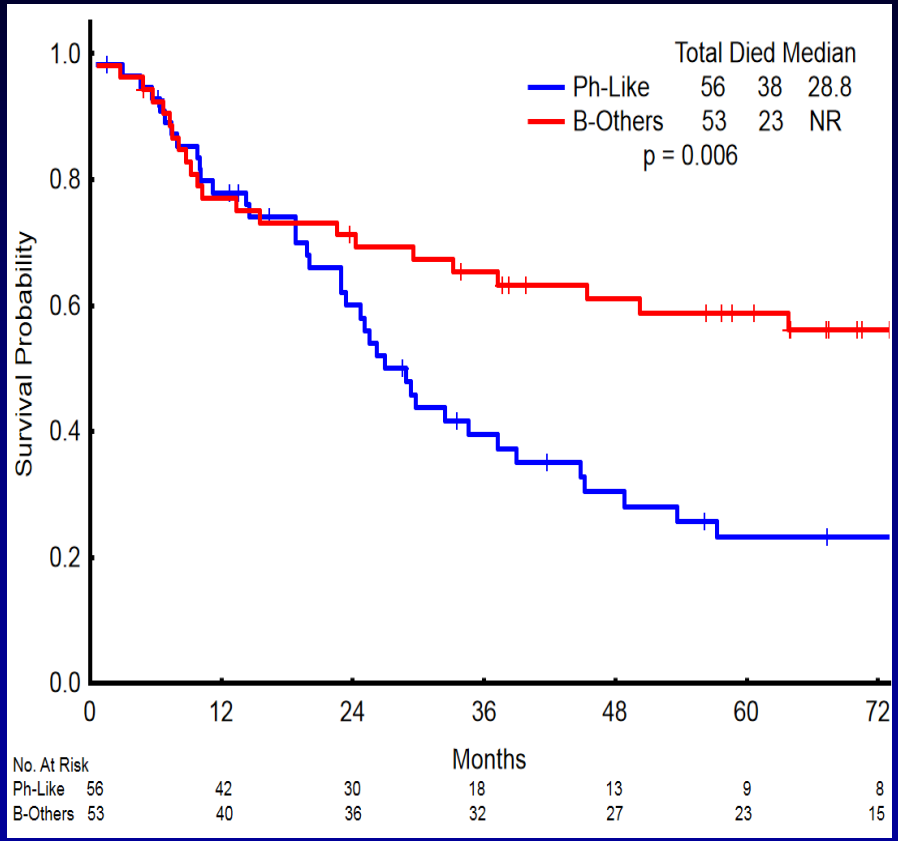


Roberts et al. *N Engl J Med*. 2014;371:1005-1015.

Ph-Like ALL – Survival and EFS

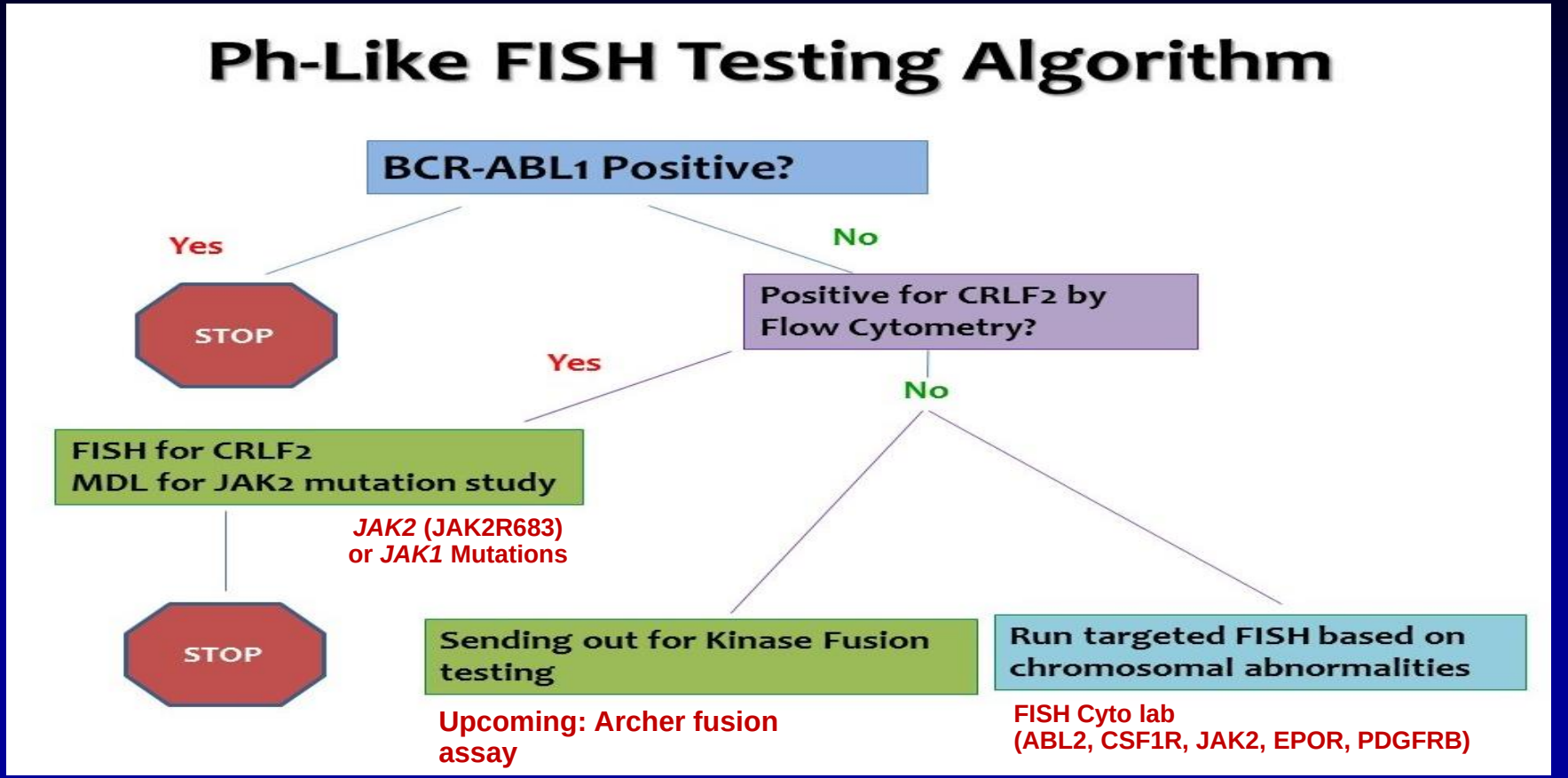


Roberts et al. *J Clin Oncol.* 2017;35:394.



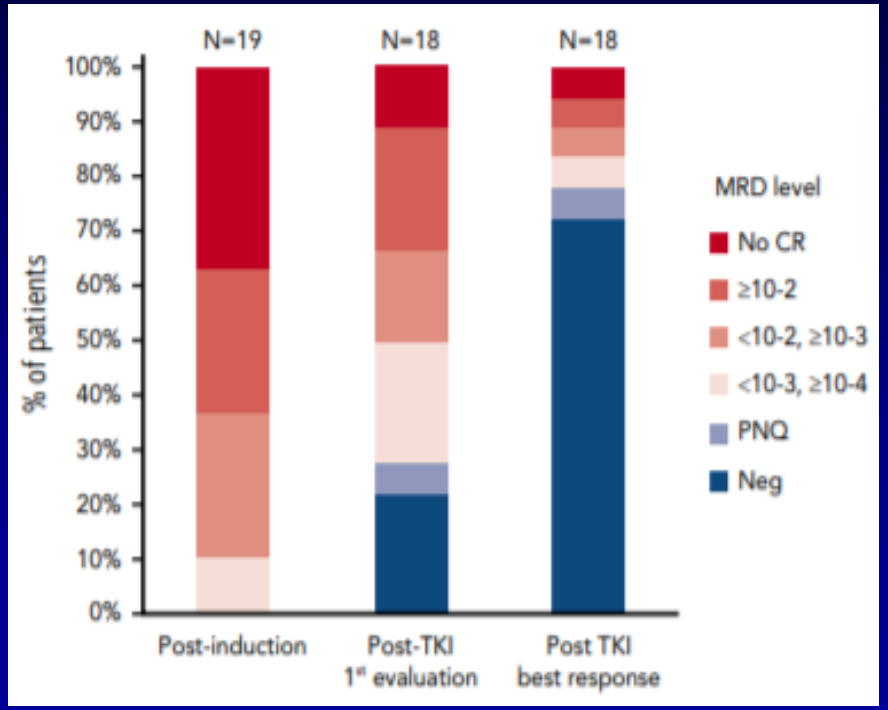
Jain N, et al. *Blood.* 2017;129:572-581.

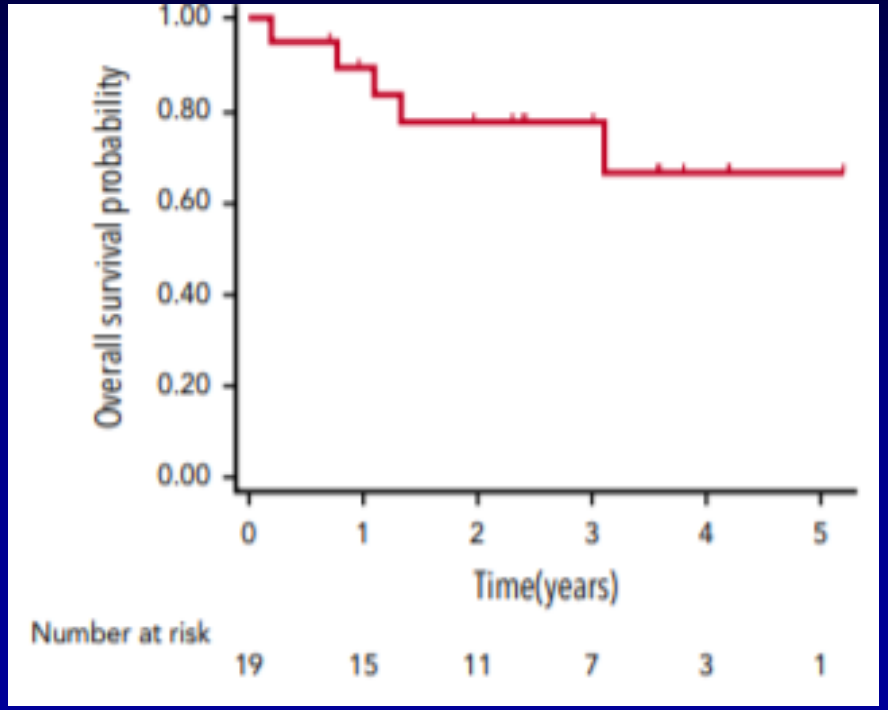
Ph-Like ALL Testing Algorithm MDACC



BCR-ABL TKIs + Chemo Rx in Ph-Like ALL

- 24 pts with Ph-like ALL: NUP214-ABL1-- 6, ETV6-ABL1-- 3, others -- 9. 19 frontline; 5 relapsed. All Rx with chemo Rx + TKI





Tanasi et al. *Blood.* 2019;134:1351.

Ph-Like ALL – Higher MRD + Rate

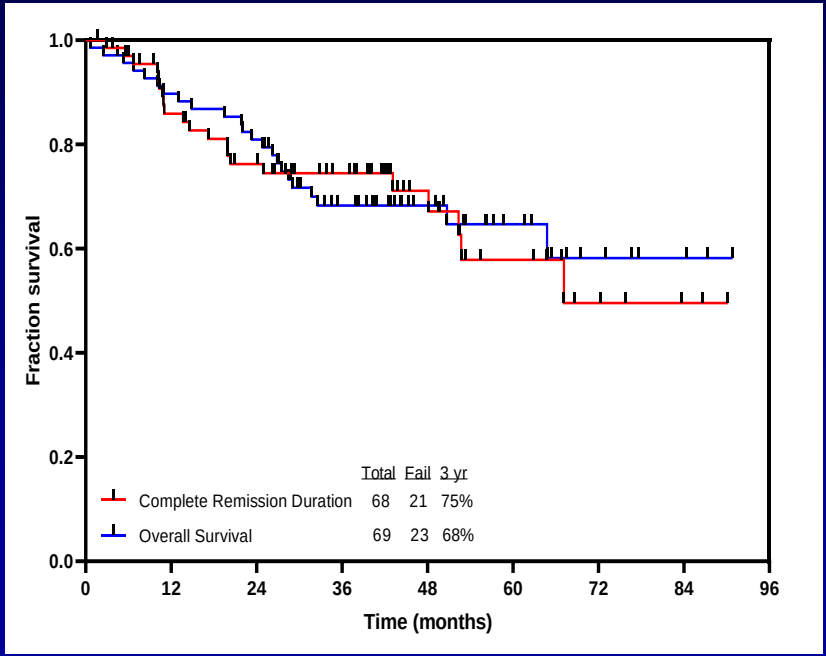
	B-ALL Categories (N = 155)			*P* Value
	Ph-Like	Ph+	B-other	
N	56	46	53	
CR/CRp	50 (89)	43 (93)	50 (94)	.57
MRD at CR				
Positive	23 (70)	15 (44)	4 (13)	<.001
Negative	10 (30)	19 (56)	27(87)	

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

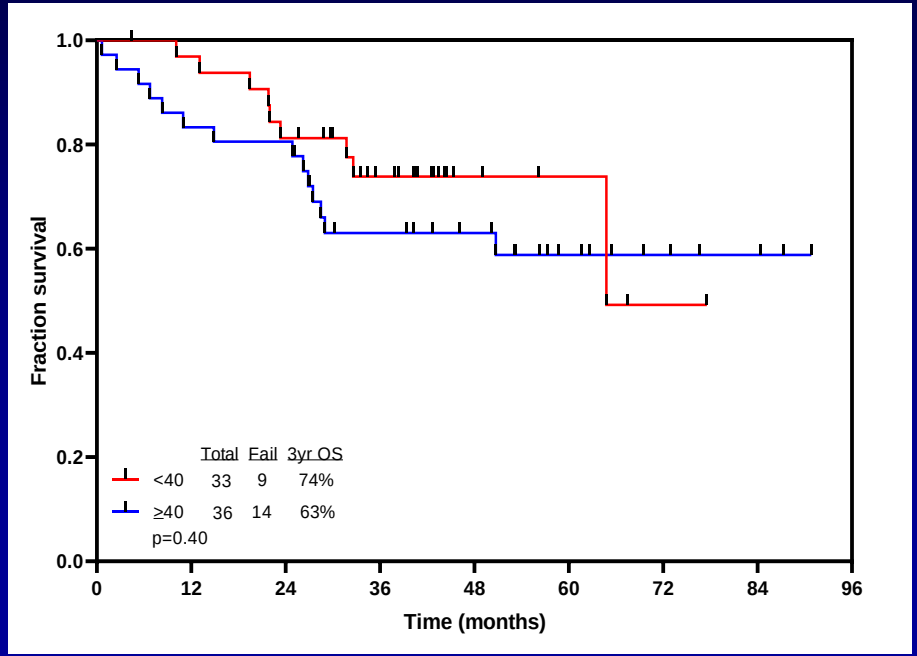
HCVAD + Ofatumumab: Outcomes (N = 69)

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

CRD and OS Overall

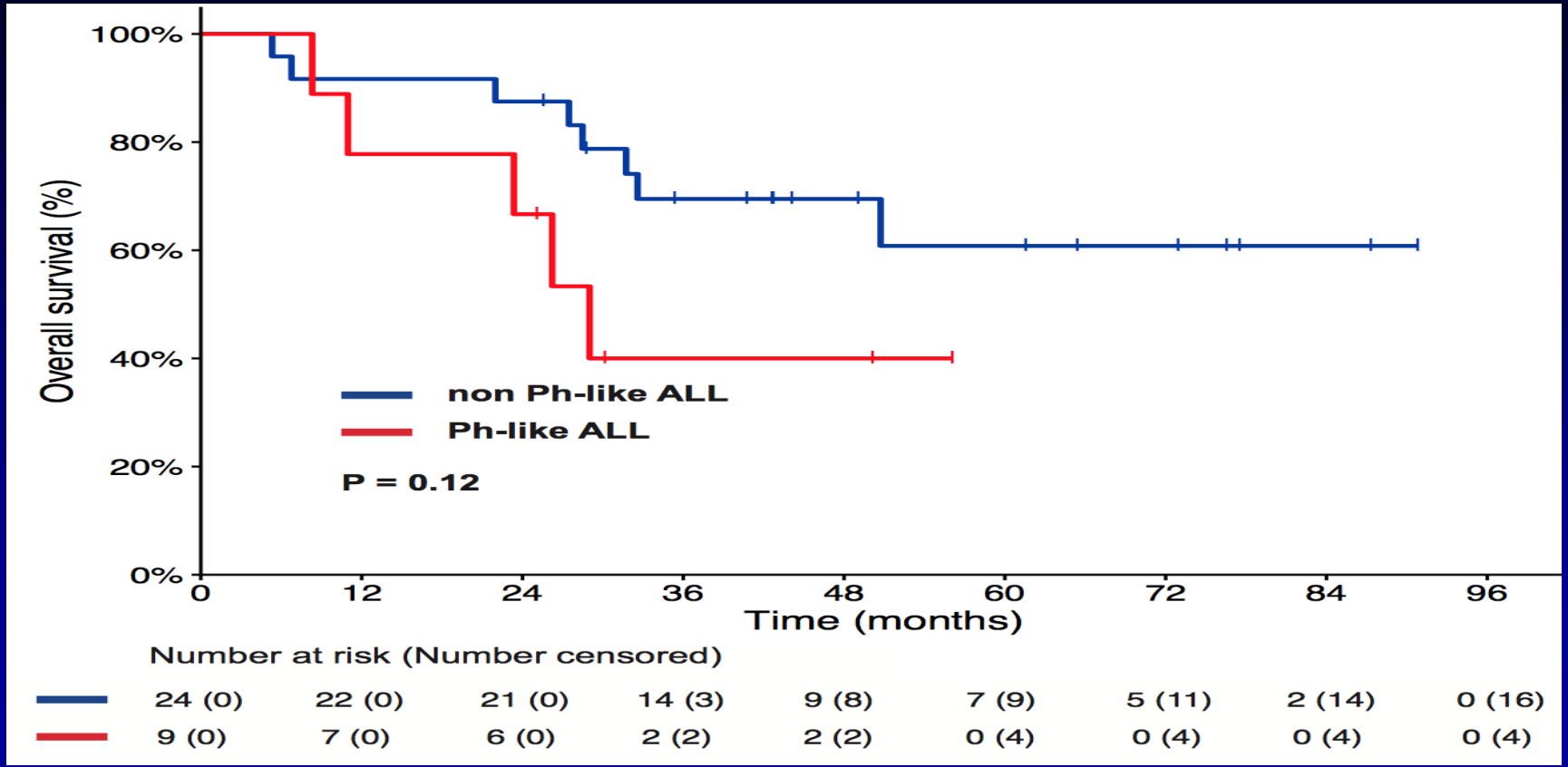


OS by Age



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

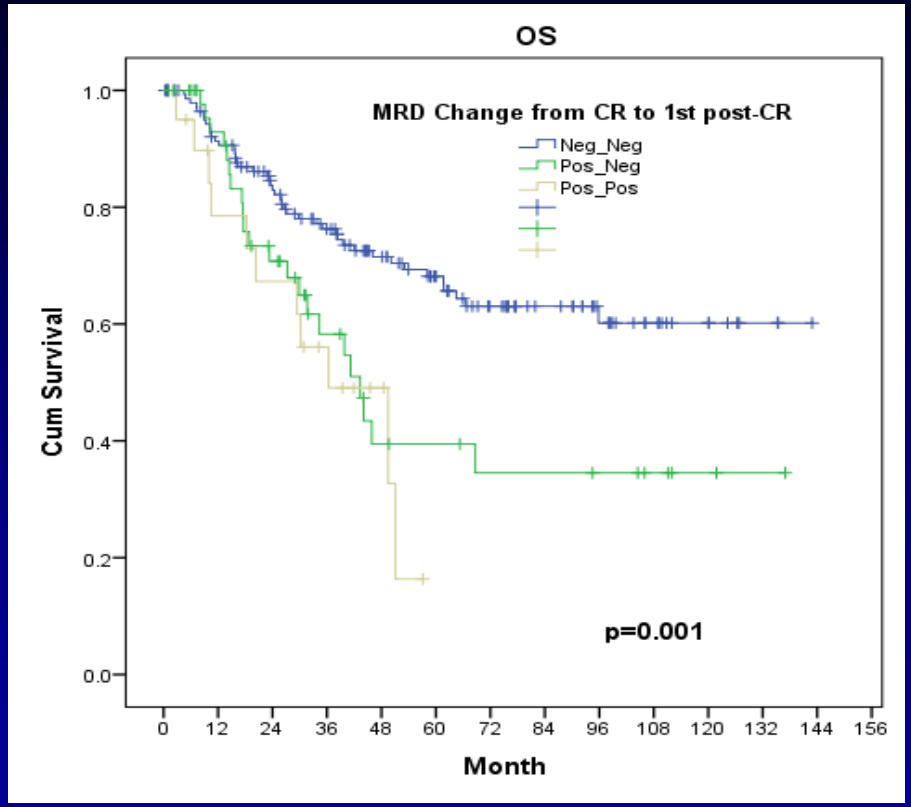
HCVAD + Ofatumumab – Outcome by Ph-Like (RNA-seq)



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

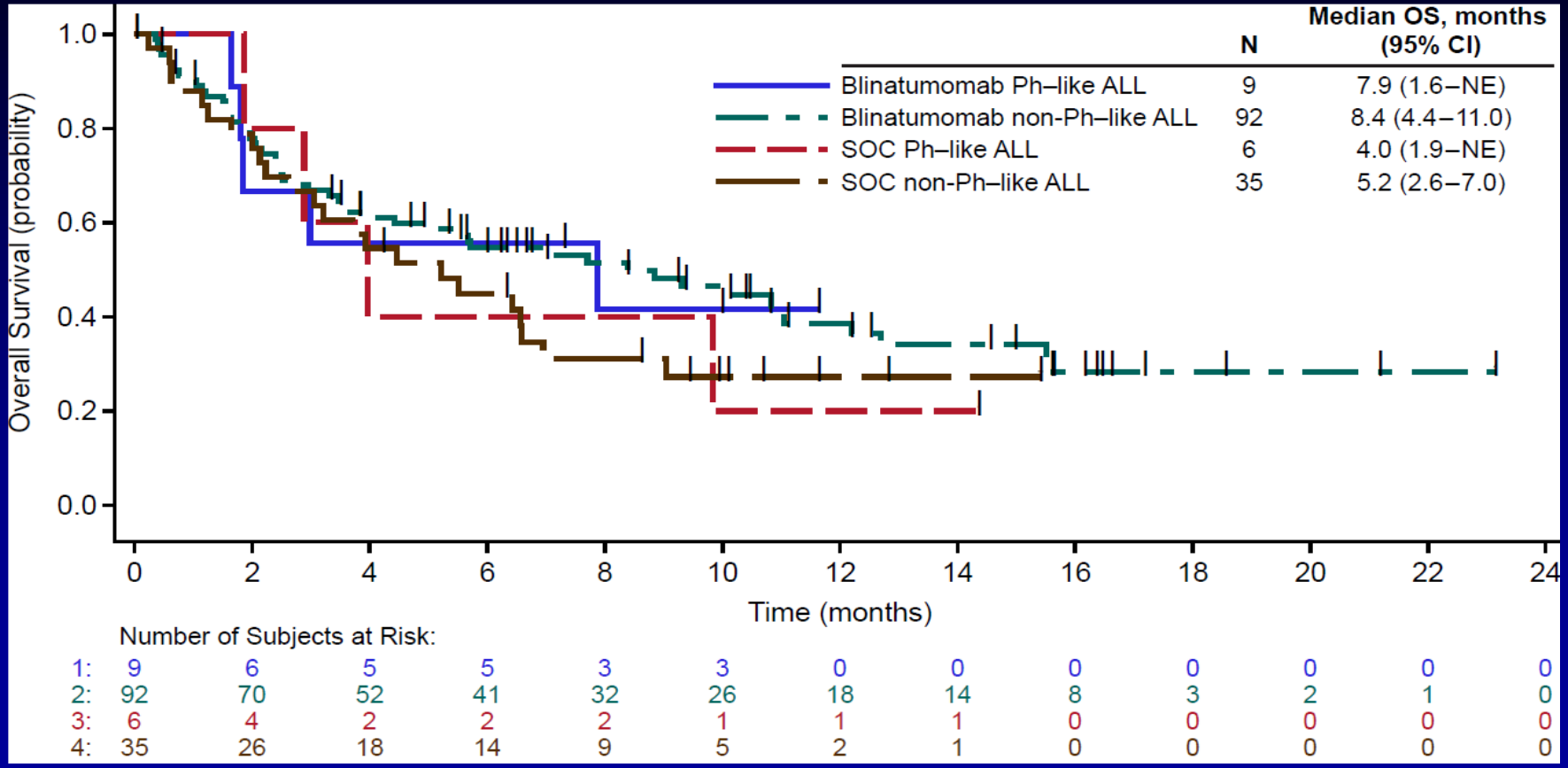
Dynamics of MRD: Outcomes

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



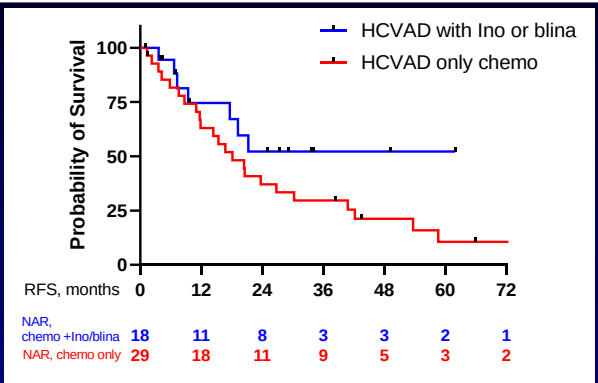
Yilmaz et al. *Am J Hematol.* 2020;95(2):144-150.

Impact of Ph-Like on Blinatumomab RX in R/R ALL

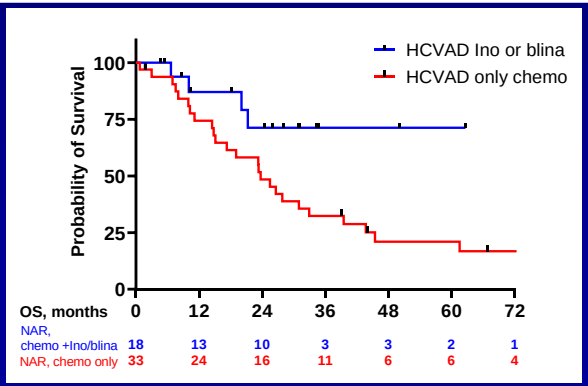


✓ Use of targeted therapy improves outcomes in *CRLF2*-rearranged patients (**N = 51; HCVAD treated patients**)

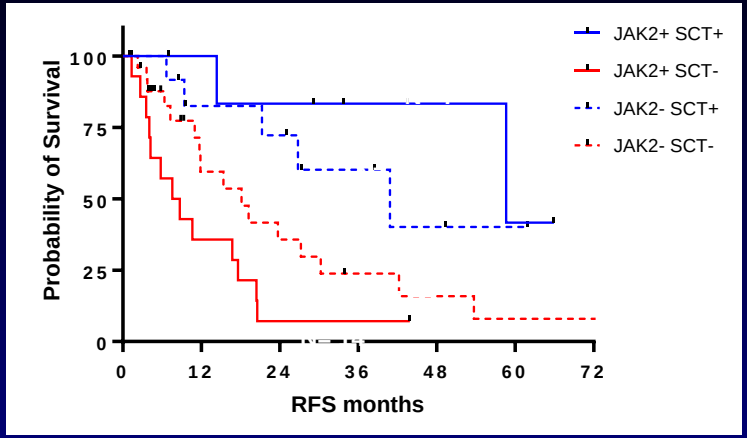
mRFS (not censored for SCT) = NR vs 18.1 mos
(HR = 0.5, 95% CI = 0.25–1.1, ***P* = .2**)



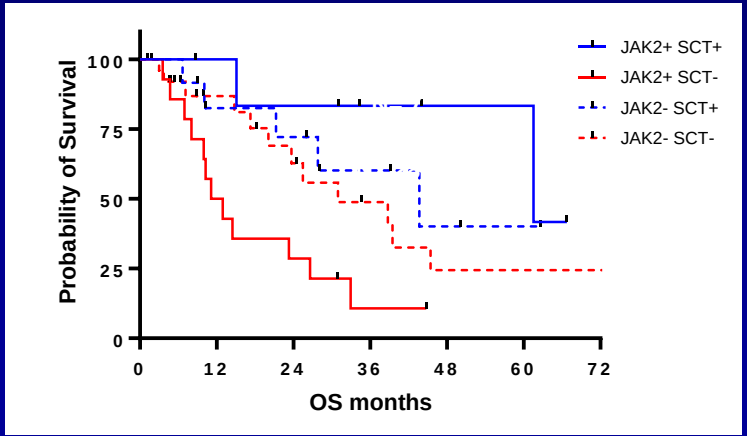
mOS = NR vs 23.7 mos
(HR = 0.3. 95% CI = 0.15–0.7, ***P* = 0.03**)



✓ Allo-SCT preferentially benefits patients with *JAK2*-mutated *CRLF2*-rearranged B-ALL **(N = 61; HCVAD/mCVD patients in CR/CRp)**



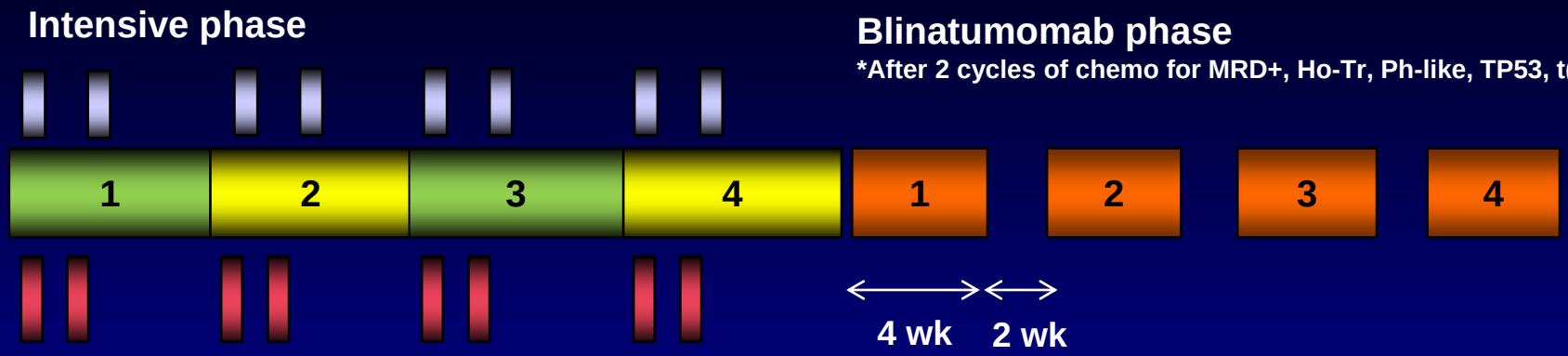
Median RFS:
58.6 vs
40.8 vs
18.1 vs
8.1 months

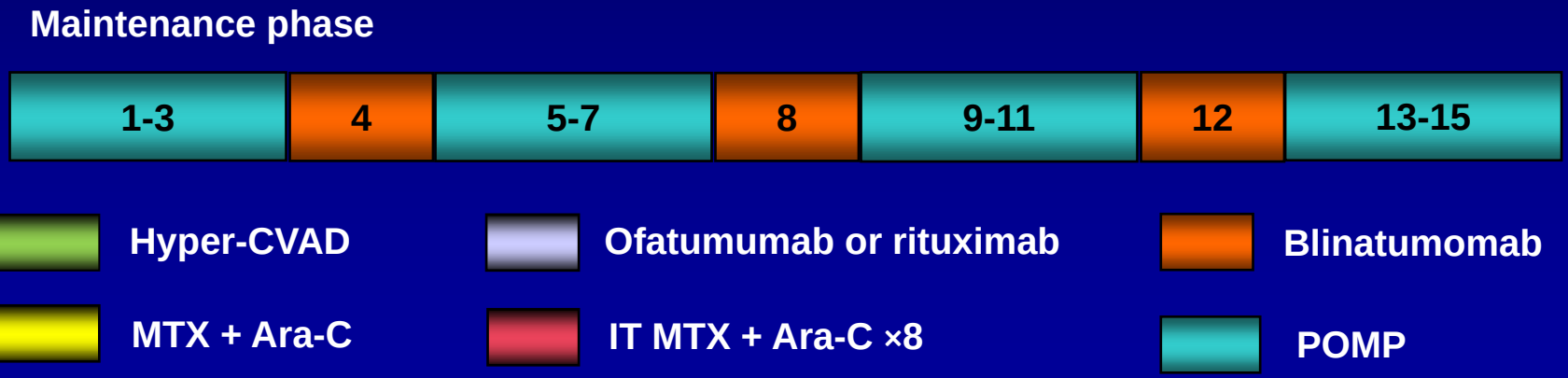


Median OS:
61.5 vs
43.7 vs
30.9 vs
12 months

Senapati J, et al. EHA 2022. Abstract P367.

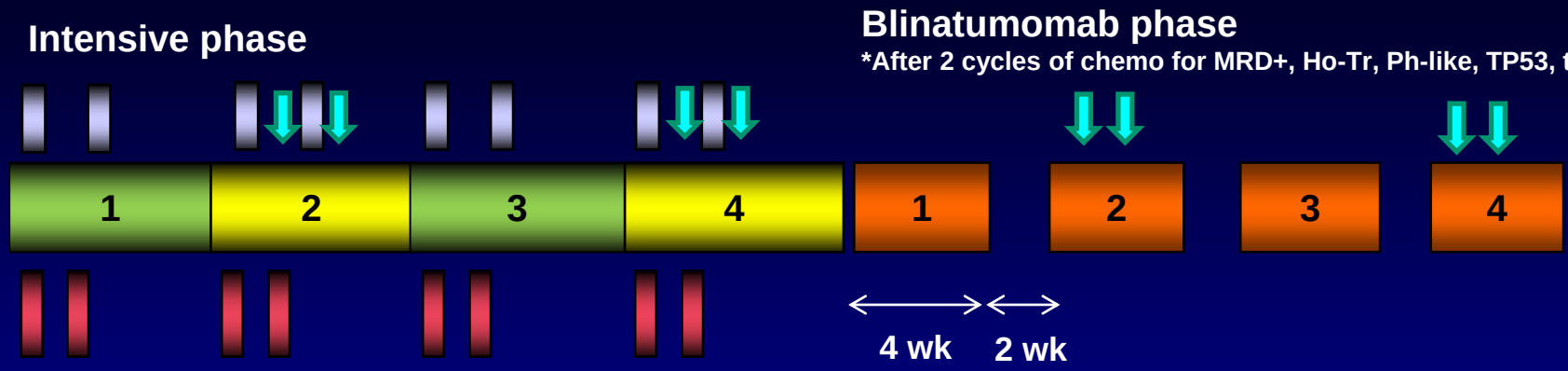
Hyper-CVAD + Blinatumomab in B-ALL: Regimen (1st cohort; N = 38)





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

Hyper-CVAD + Blina + InO in B-ALL: Regimen (2nd cohort)



Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

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

IT MTX + Ara-C ×8

POMP

Inotuzumab 0.3 mg/m^2 on D1 and D8

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

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

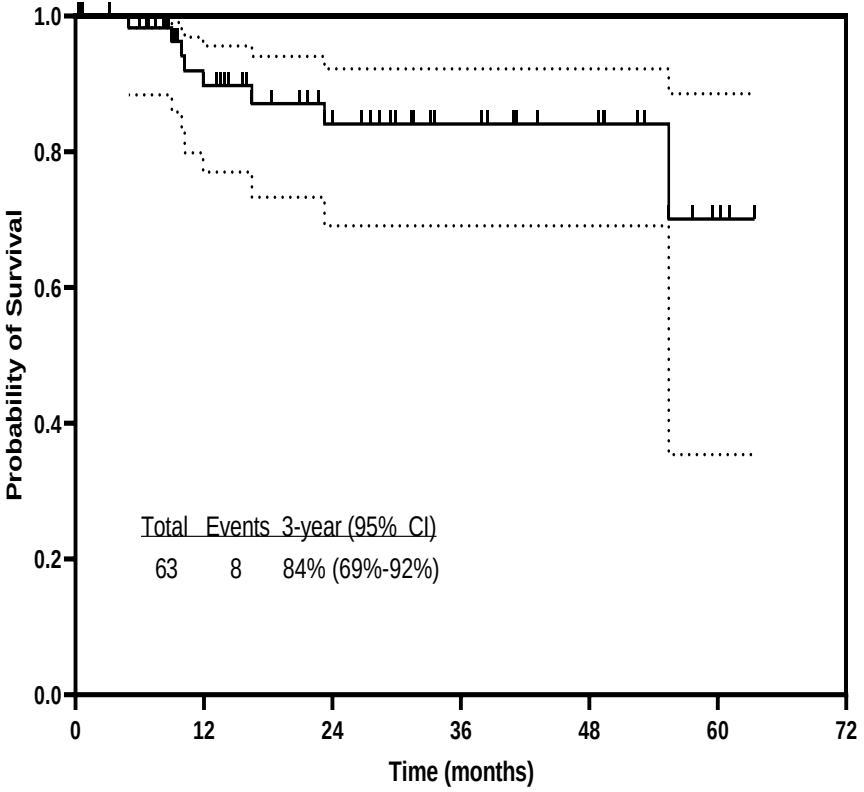
Characteristic (N = 58)		Overall (n = 63)	Cohort 1 (n = 38)	Cohort 2 (n = 25)
Age, years [range]		33 [18–59]	37 [18–59]	24 [18–54]
Sex	Male	44 (70)	26 (68)	18 (72)
PS (ECOG)	0–1	52 (83)	30 (79)	22 (88)
WBC (× 10^9/L) [range]		4.3 [0.5–553]	3.12 [0.5–360.9]	8.6 [1.2–553]
CNS disease		6 (10)	4 (11)	2 (8)
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)	6/32 (19)	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)

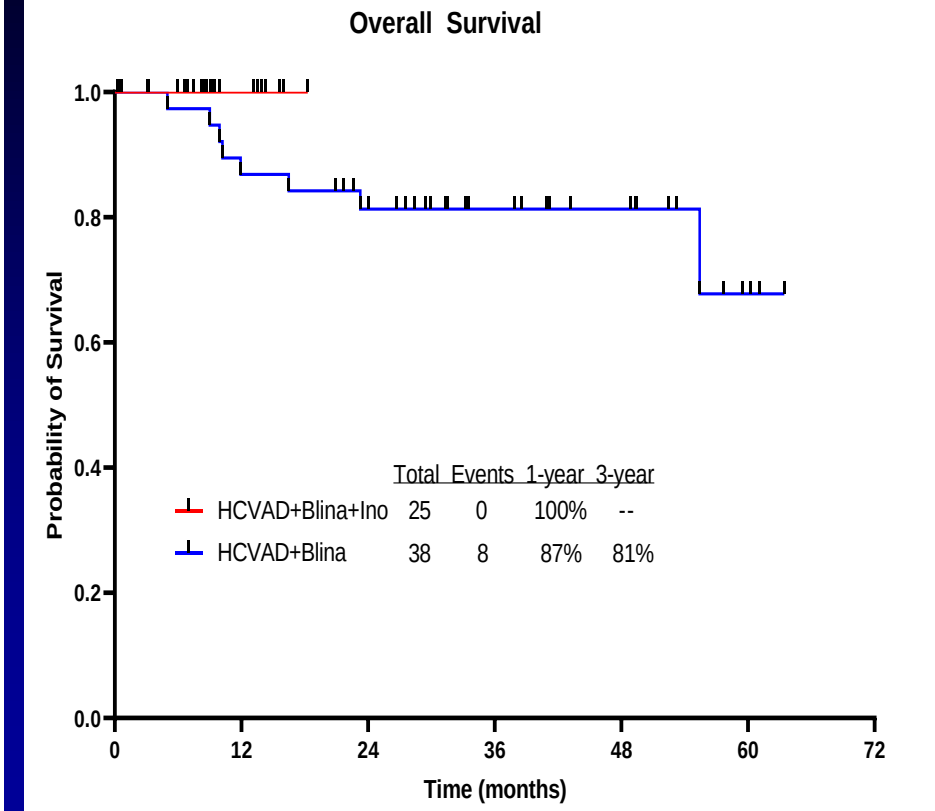
Hyper-CVAD + Blina + InO in B-ALL: Response Rates

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

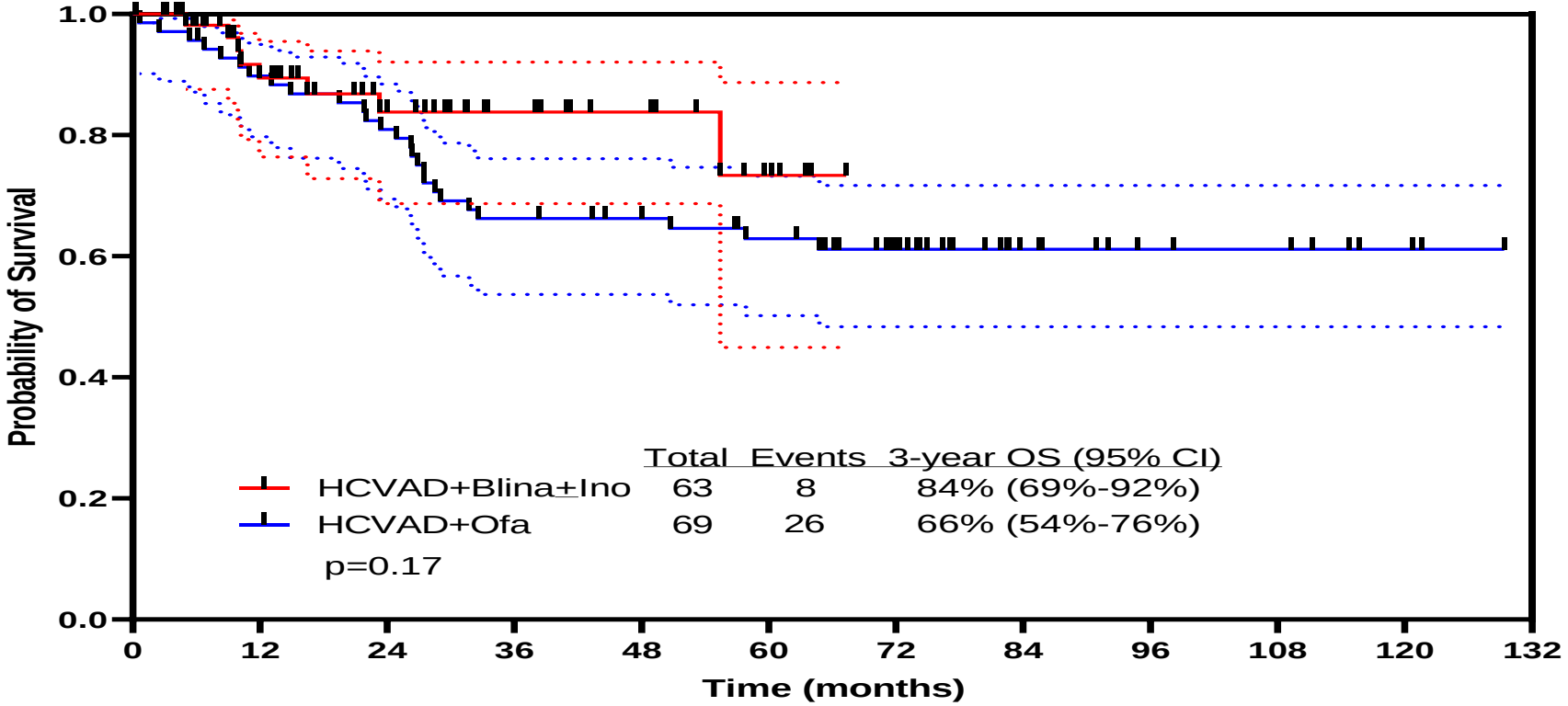
Hyper-CVAD + Blinatumomab + InO in B-ALL – Outcome





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

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

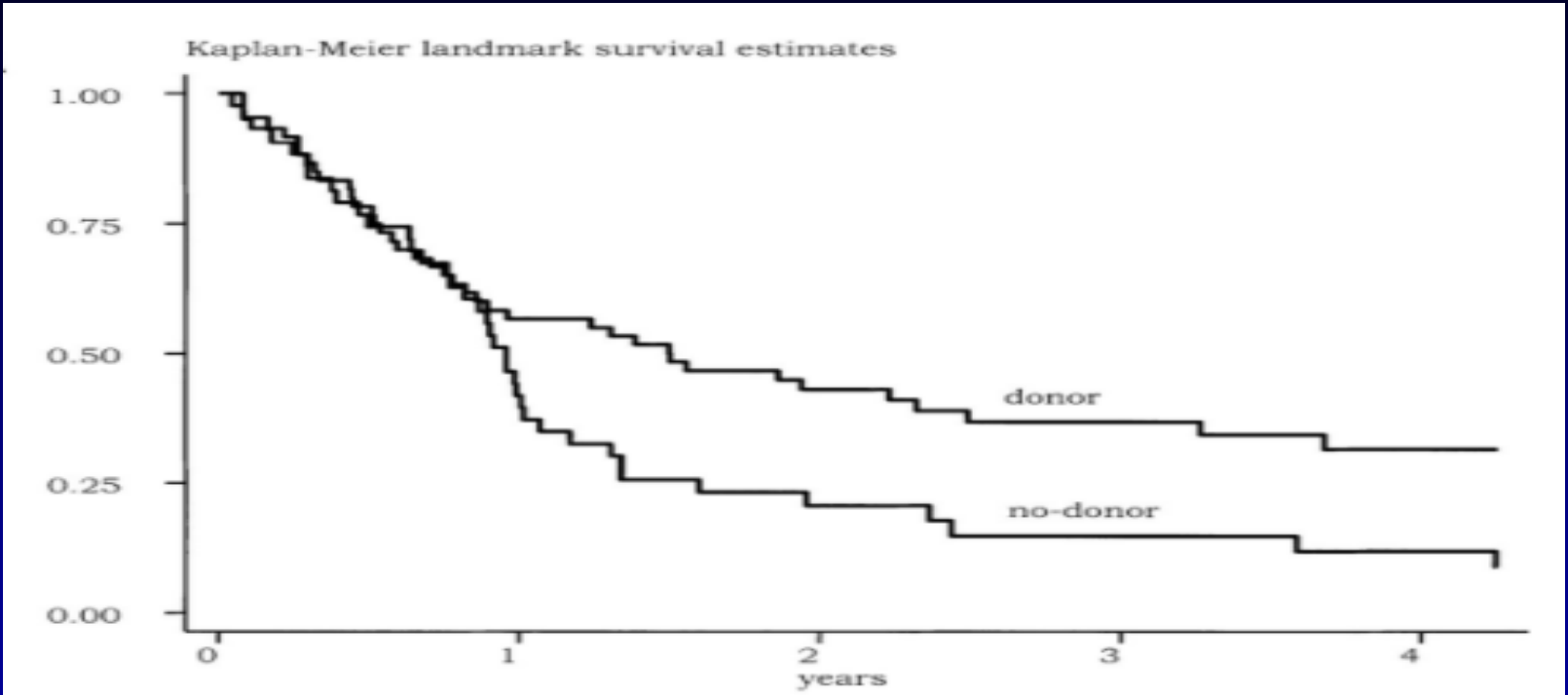


Short NJ, et al. EHA 2022. Abstract P371.

Ph-Like ALL – Summary

- Genomic profile similar to Ph+ ALL
- 25% of adult ALL; poor prognosis historically (not anymore with regimens incorporating BCR::ABL1 TKIs and CD19/22 antibodies)
- More common among Hispanics (50%??)
- High incidence of MRD-positivity in CR
- Two distinct entities: 1) *CRLF2* overexpression ± JAK mutations (80%); 2) *ABL* translocations (true Ph-like; 20%)
- Standard of care still allo SCT in CR1
- Newer approaches: Chemo combos with blinatumomab and inotuzumab; TKI-based regimens in *ABL*-translocated ALL

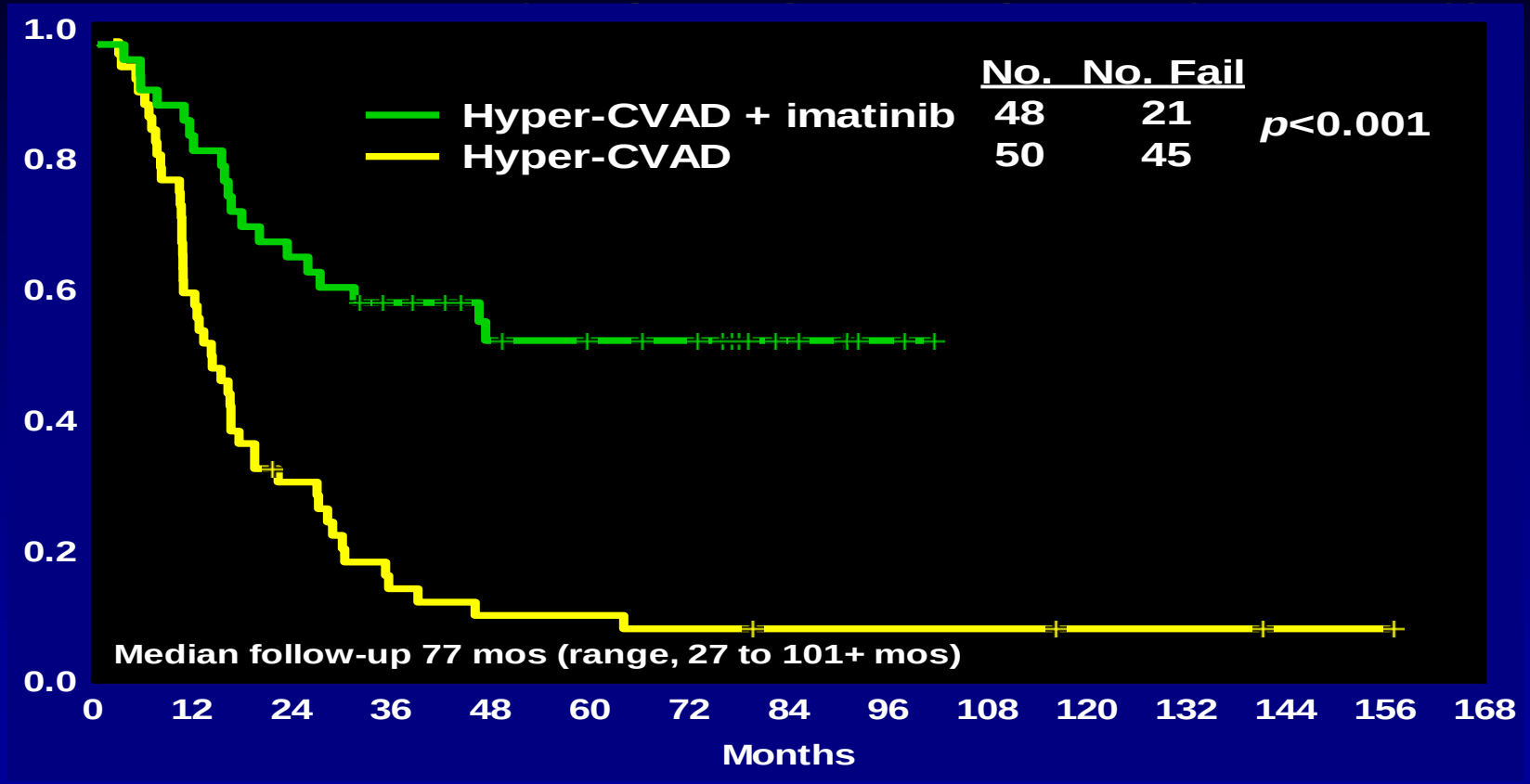
SCT for Ph+ ALL: Pre-TKI



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

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

Survival in Ph+ ALL by Regimen (excluding primary refractory)

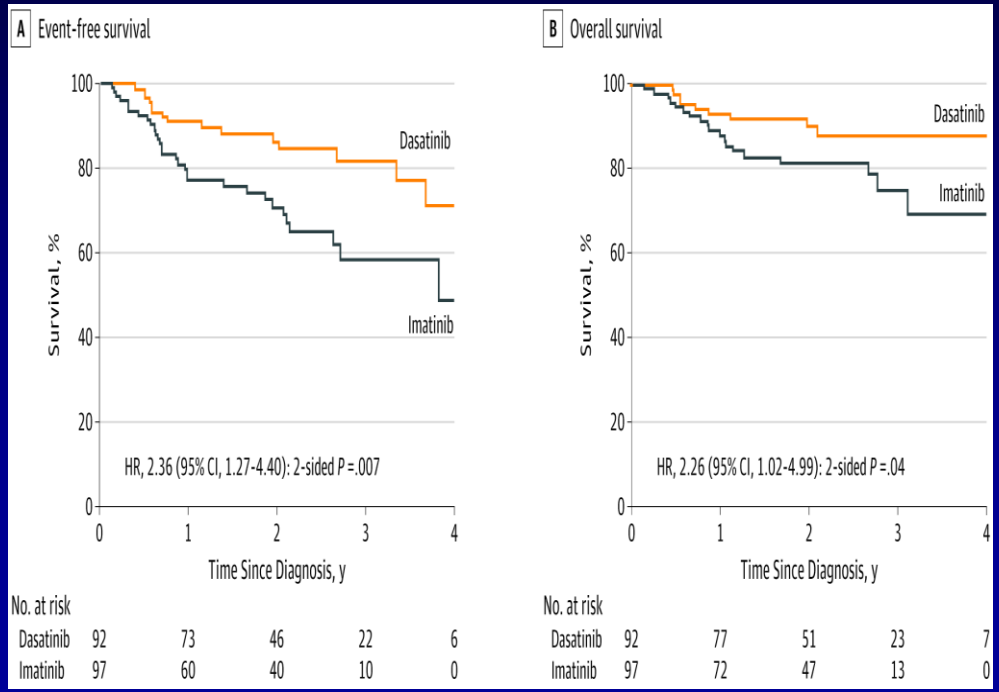


Thomas DA, et al. ASCO 2010. Abstract 6506.

Dasatinib vs Imatinib in Pediatric Ph+ ALL

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

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



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

Low-Intensity Chemo Rx + Dasatinib in Ph+ ALL ≥55 yrs

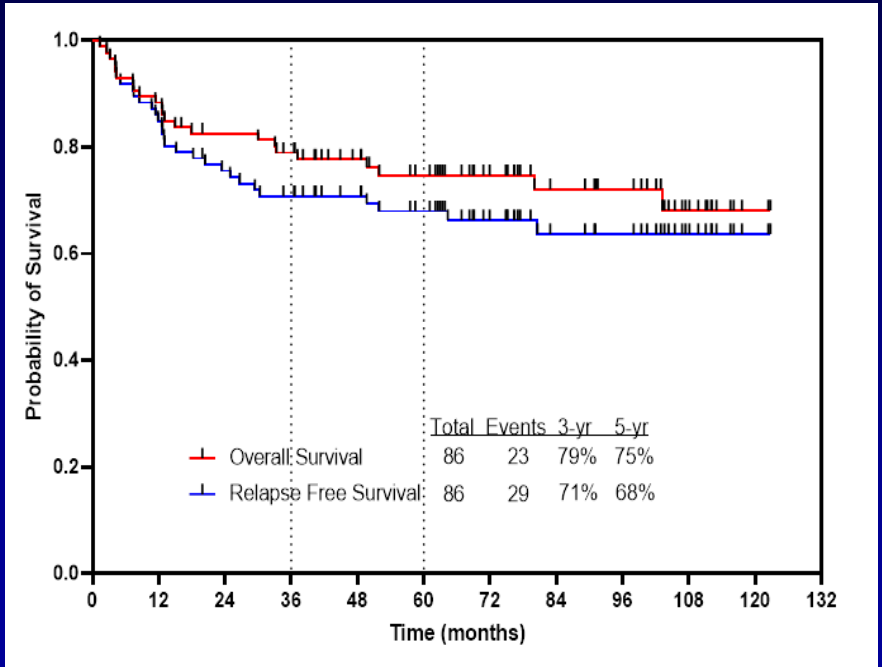
- 71 pts (2007–2010); median age 69 yrs (58–83)
- Dasatinib 100–140 mg/D, VCR 1 mg Q wk, Dex 20–40 mg/D × 2, Qwk
- Consolidations: dasatinib 100 mg/D; MTX-Asp C1, 3, 5; ara-C C2, 4, 6. Maintenance: dasatinib + POMP
- CR 96%; MMR 65%; CMR 24%
- 5-yr survival 36%; EFS 25%
- T315I at Dx 23% by NGS
- 36 relapses; T315I in 75%

Rousselot et al. *Blood*. 2016;128(6):774-782.

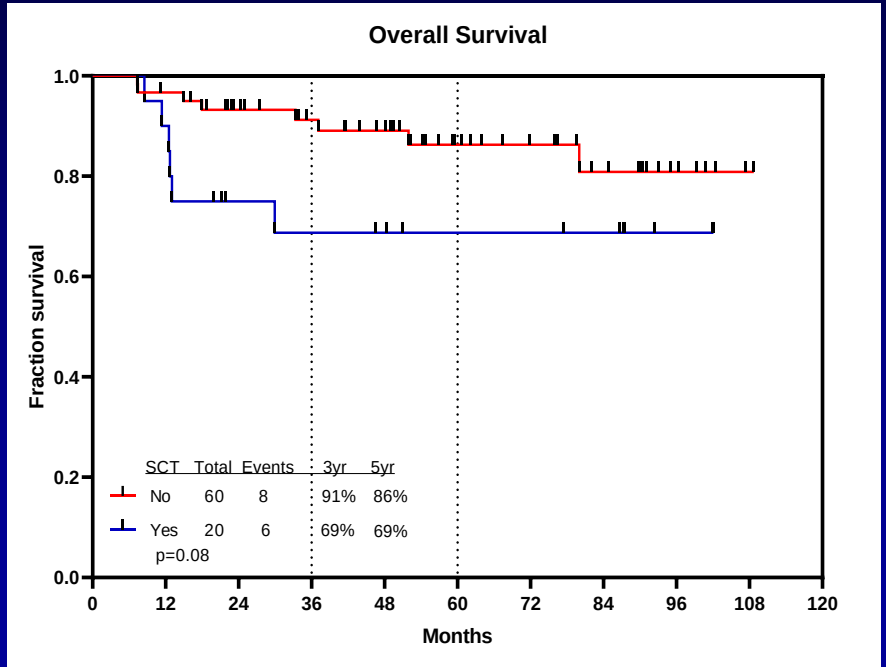
HyperCVAD + Ponatinib in Ph+ ALL

- 86 pts Rx; median age 47 yrs (39–61); median FU 75 mos (16–123)
- CR 68/68 (100%); FCM-MRD negative 85/86 (99%); CMR 84%; 3/5-yr OS 79/75%, EFS 71/68%

Relapse-Free and Overall Survival



6-Month Landmark

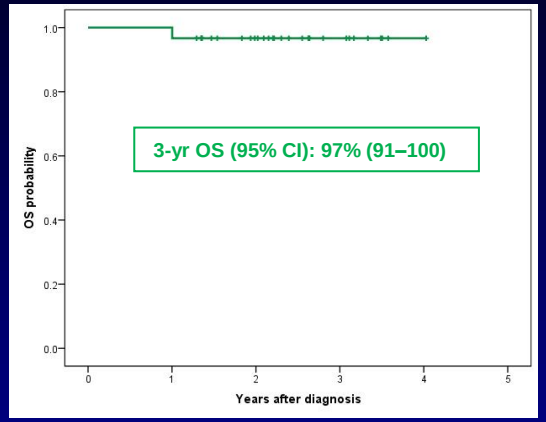


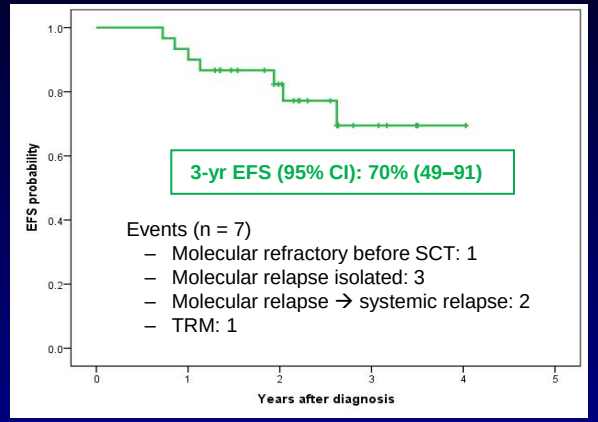
Jabbour E, et al. *Lancet Hematol.* 2018;618:(and update April 2022).

Ponatinib + Chemo Rx in Ph+ ALL (PONALFIL)

- 30 pts, median age 49 yrs (19–59)
- Ponatinib + VCR-DNR-pred → HD MTX/araC-6MP-VP16 → allo SCT
- CR 30/30 (100%), CMR 14/30 (47%)
- Allo SCT 26/30
- 3-yr OS 97%; EFS 70%

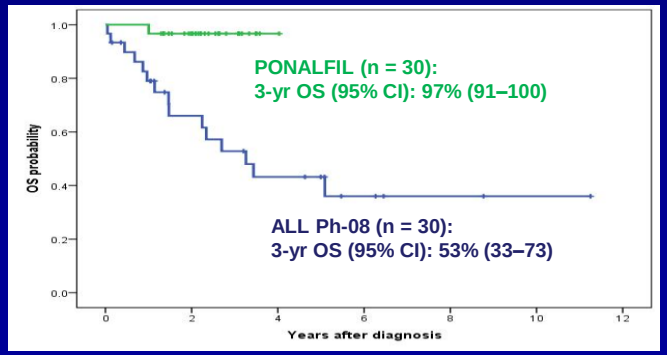
OS and EFS (median f/u: 2.5 yr)





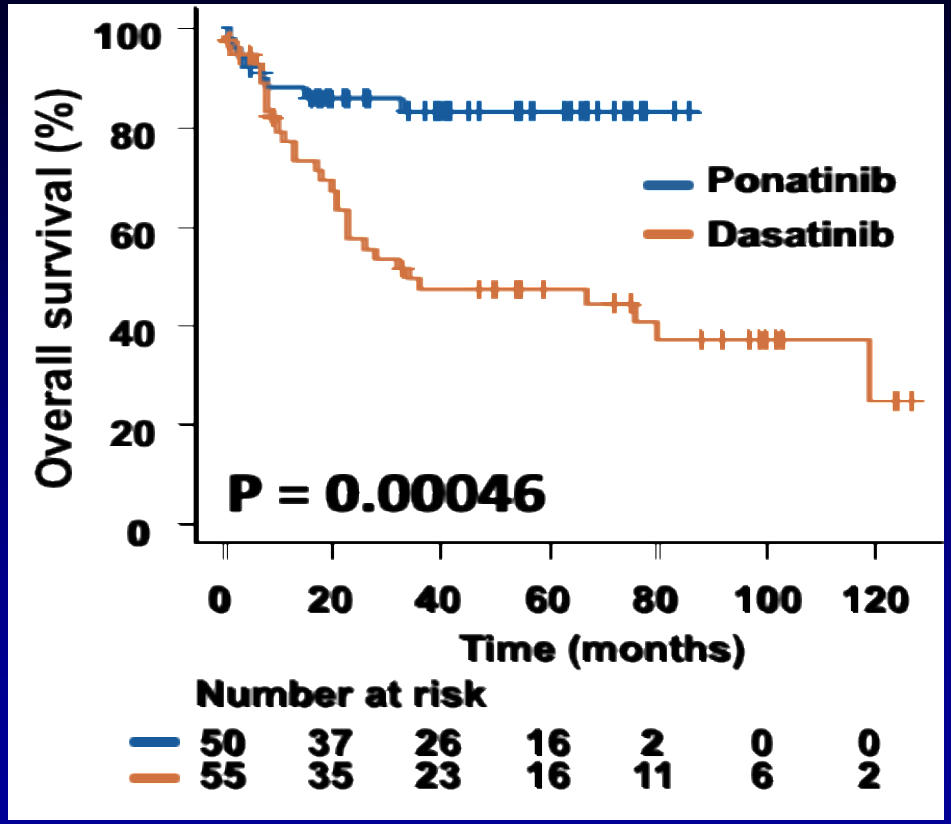
	Post-induction (n = 30)	Post-consol/ Pre-HSCT (n = 28)	Post-HSCT (n = 26)
CMR (<0.01%)	14/30 (47%)	20/28 (71%)	26/26 (100%)
MMR (<0.1%)	5/30 (17%)	7/28 (25%)	-
No response (>0.1%)	11/30 (36%)	1/28 (4%)	-

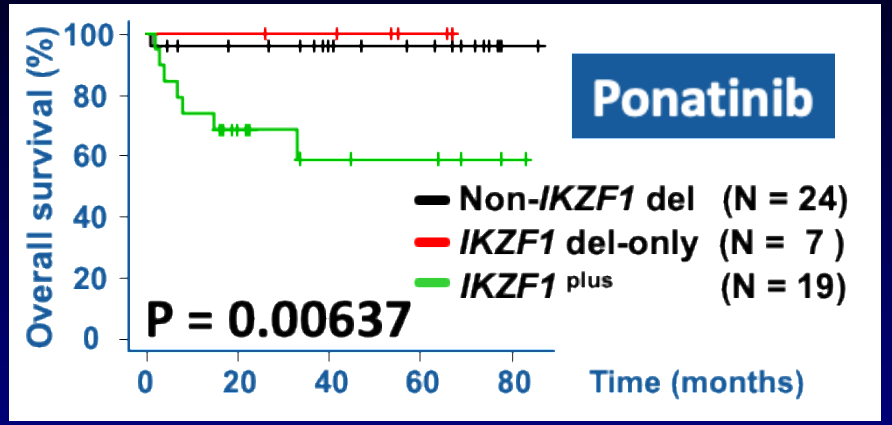
Propensity score: PONALFIL vs ALL Ph-08 (imatinib)

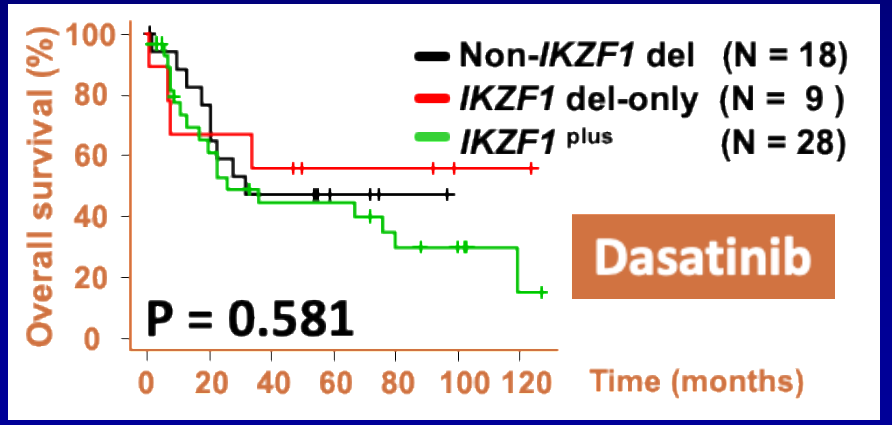


Ribera et al. *Blood.* 2021;140:abstract 1230.

Impact of *IKZF1* plus on OS According to TKI Type

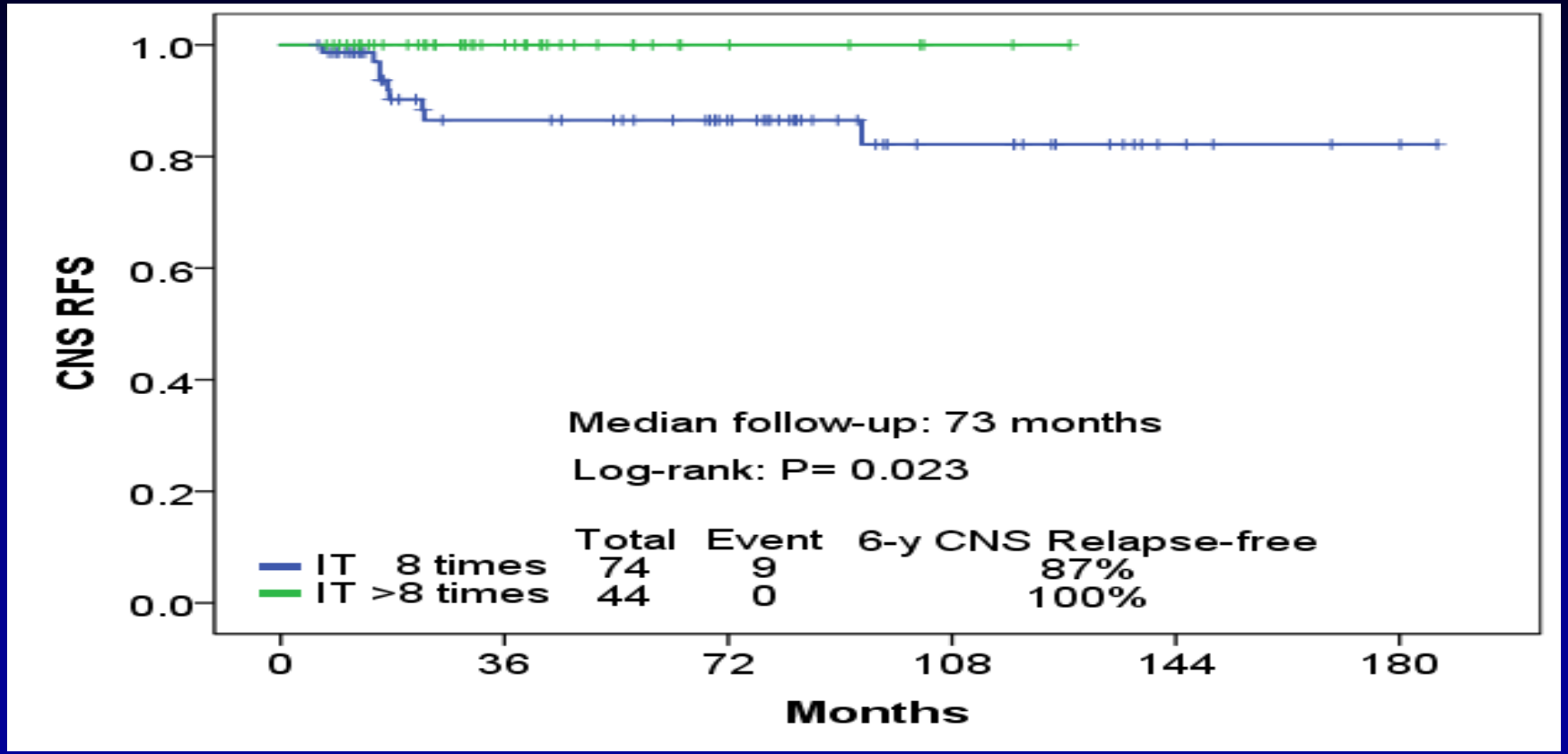






Sasaki et al. *Leukemia*. 2022;36(5):1253-1260.

IT×8 vs IT×12 in Ph+ ALL: 6-Month Landmark – CNS Relapse-Free Survival

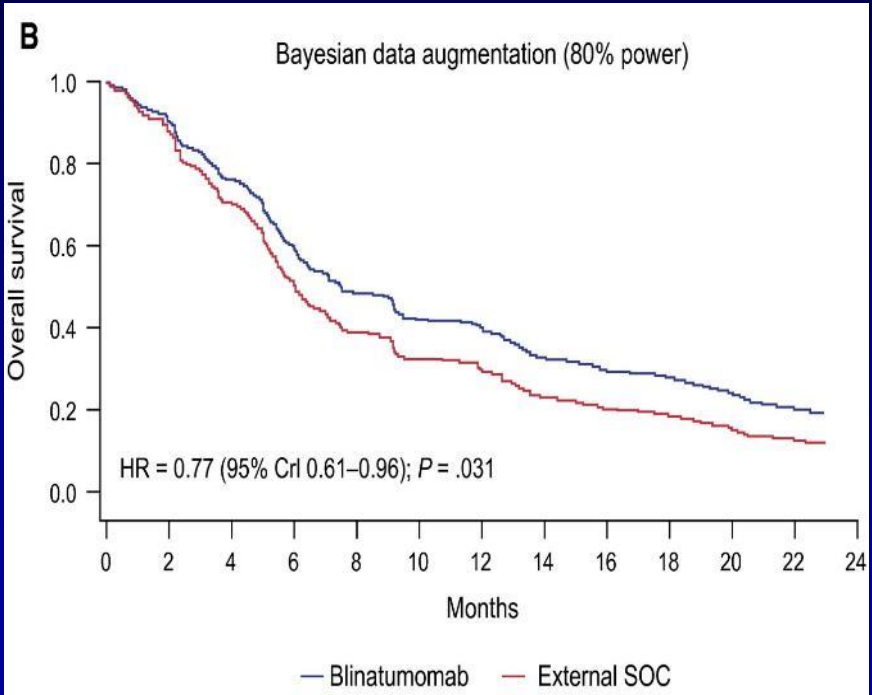


Paul et al. *Am J Hematol.* 2022 May 28.

Blinatumomab and Inotuzumab in R/R Ph+ ALL

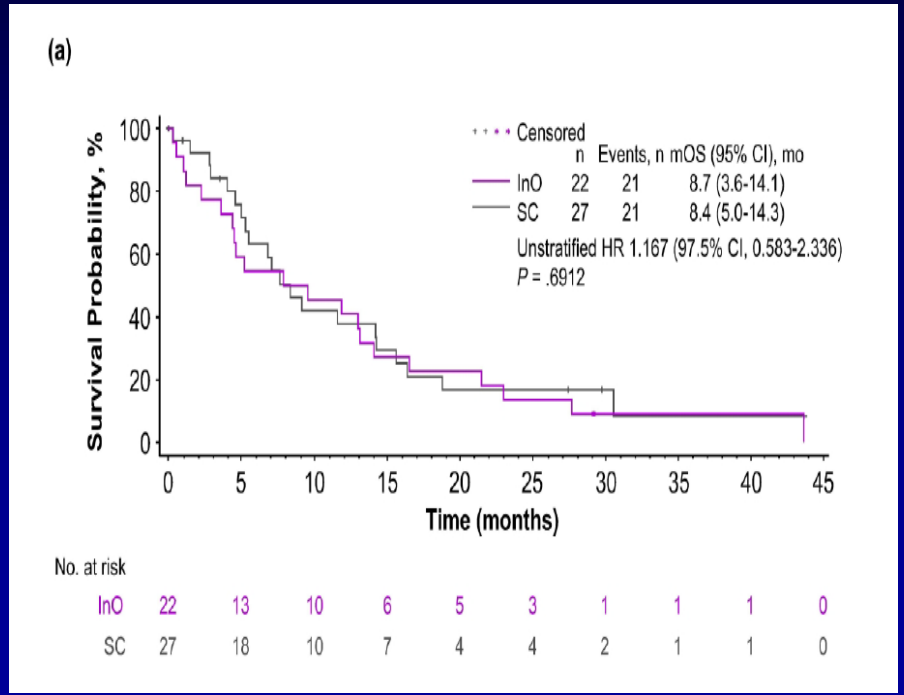
Blina vs SOC

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



Ino vs SOC

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

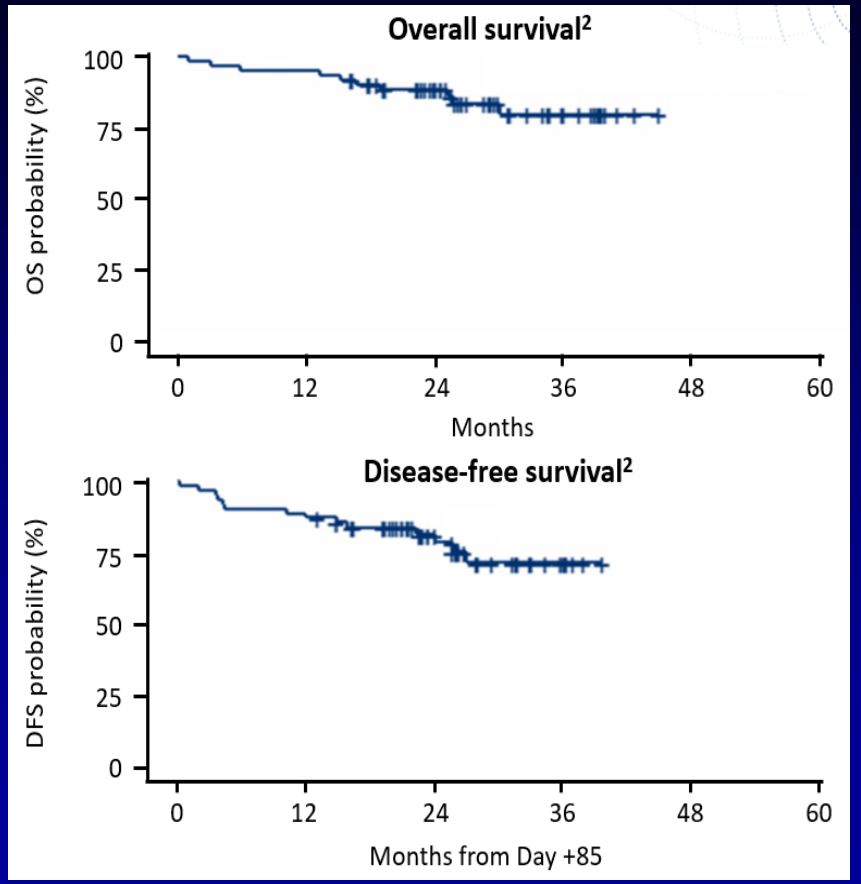


Rambaldi et al. *Cancer.* 2019;126:304-310.

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

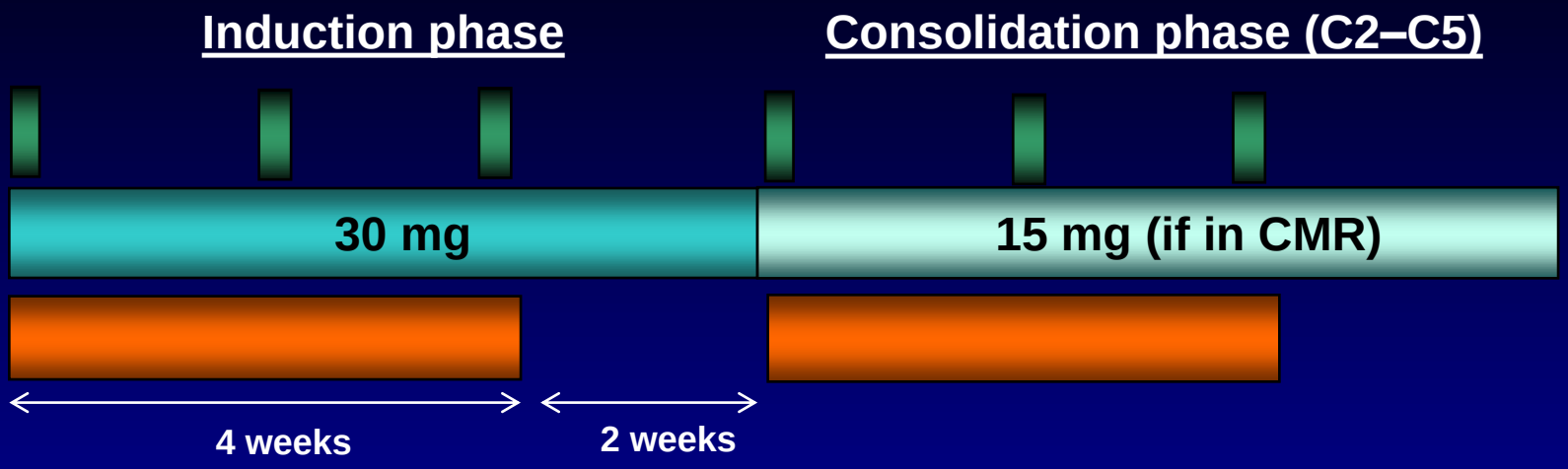
Dasatinib + Blinatumomab (D-ALBA) in Newly Dx Ph+ ALL – Update

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



Chiaretti et al. EHA 2022. Abstract P353.

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



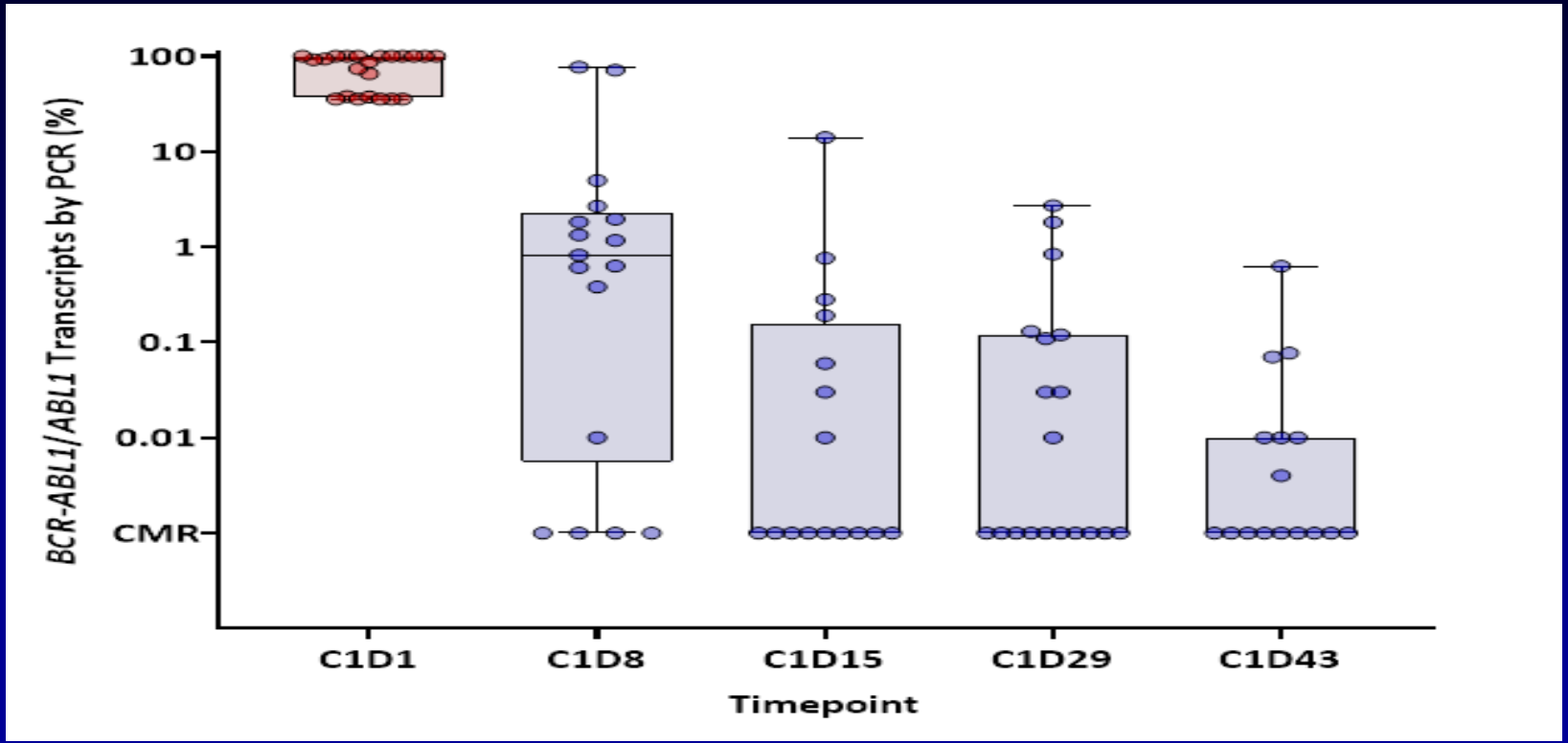
Short NJ, et al. EHA 2022. Abstract S114.

Ponatinib + Blinatumomab in Ph+ ALL – Response Rates

Response, n/N (%)	All N = 63	Frontline Ph+ ALL n = 43	R/R Ph+ ALL n = 14	CML-LBC n = 6
CR/CRp/CRi*	45/48 (94)	28/29 (97)	12/13 (92)	5/6 (83)
CR	42 (88)	27 (93)	11 (85)	4 (67)
CRp/CRi	3 (6)	1 (3)	1 (8)	1 (17)
PR	1 (2)	0	0	1 (17)
MMR	52/59 (88)	37/39 (95)	12/14 (86)	3/6 (50)
CMR	46/59 (78)	33/39 (85)	11/14 (79)	2/6 (33)
NGS	25/29 (86)	22/25 (88)	2/3 (67)	1/1 (100)
Early death	1 (2)	1 (3)	0	0

*13 frontline pts and 1 salvage pt in MRD+ CR at start; 1 pt too early but BCR/ABL, pb is neg

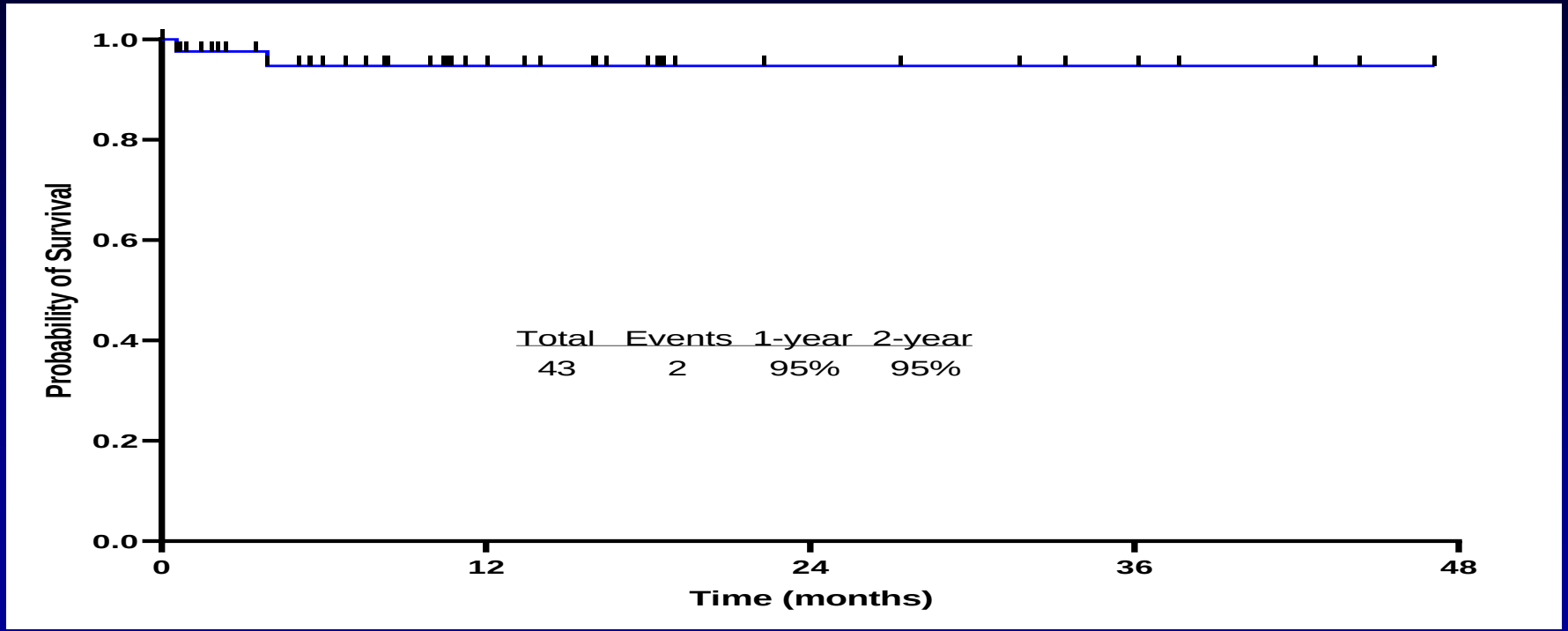
Ponatinib + Blinatumomab in Ph+ ALL: Early MRD Responses in Frontline Cohort



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

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

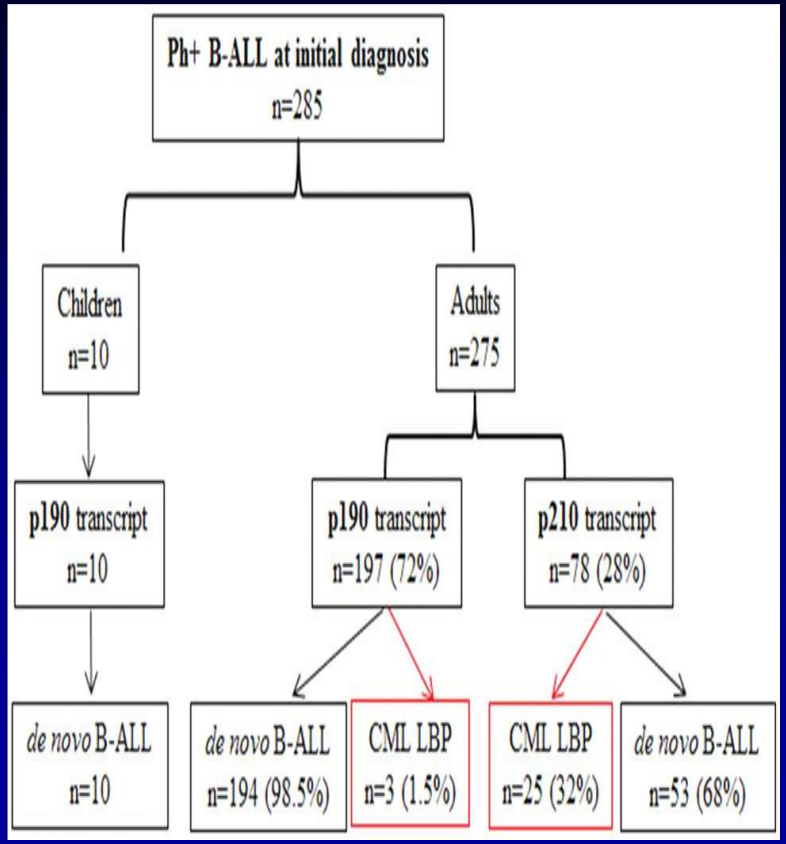
Median follow-up: 14 months (range, <1–51)



Only 1 patient received subsequent allo-SCT

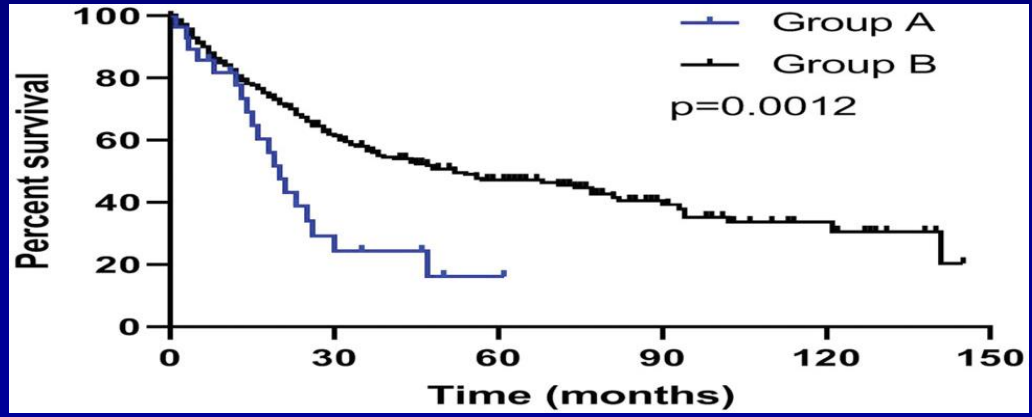
Jabbour E, et al. *Lancet Haematol.* 2022 Nov 16;S2352-3026(22)00319-2.

CML-LBC vs Ph+ ALL – Differences and Outcome



CML-LBP if any of the following:

1) **A large discrepancy (≥50%) between the blast count and the size of Ph+ clone at initial diagnosis**
2) **A large Ph+ clone (≥50%) paired with minimal residual lymphoblasts (<5%), or a negative MRD by flow cytometry paired with ≥10% Ph+ clone after chemotherapy**
3) **BCR/ABL1 fusion signal(s) detected in segmented nuclei (neutrophils) by interphase FISH**

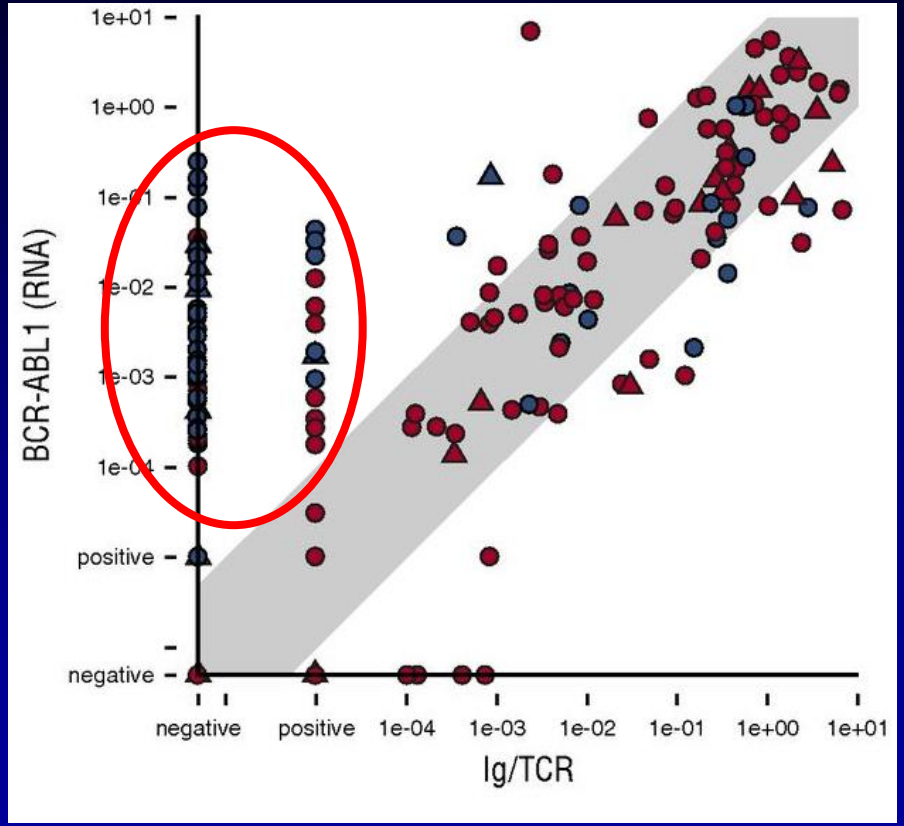


Chen Z et al. *Leukemia Lymphoma.* 2020;61:2831-2838.

MRD Quantification in Ph+ ALL: *BCR::ABL1* Q-PCR vs Ig/TCR (EuroMRD)

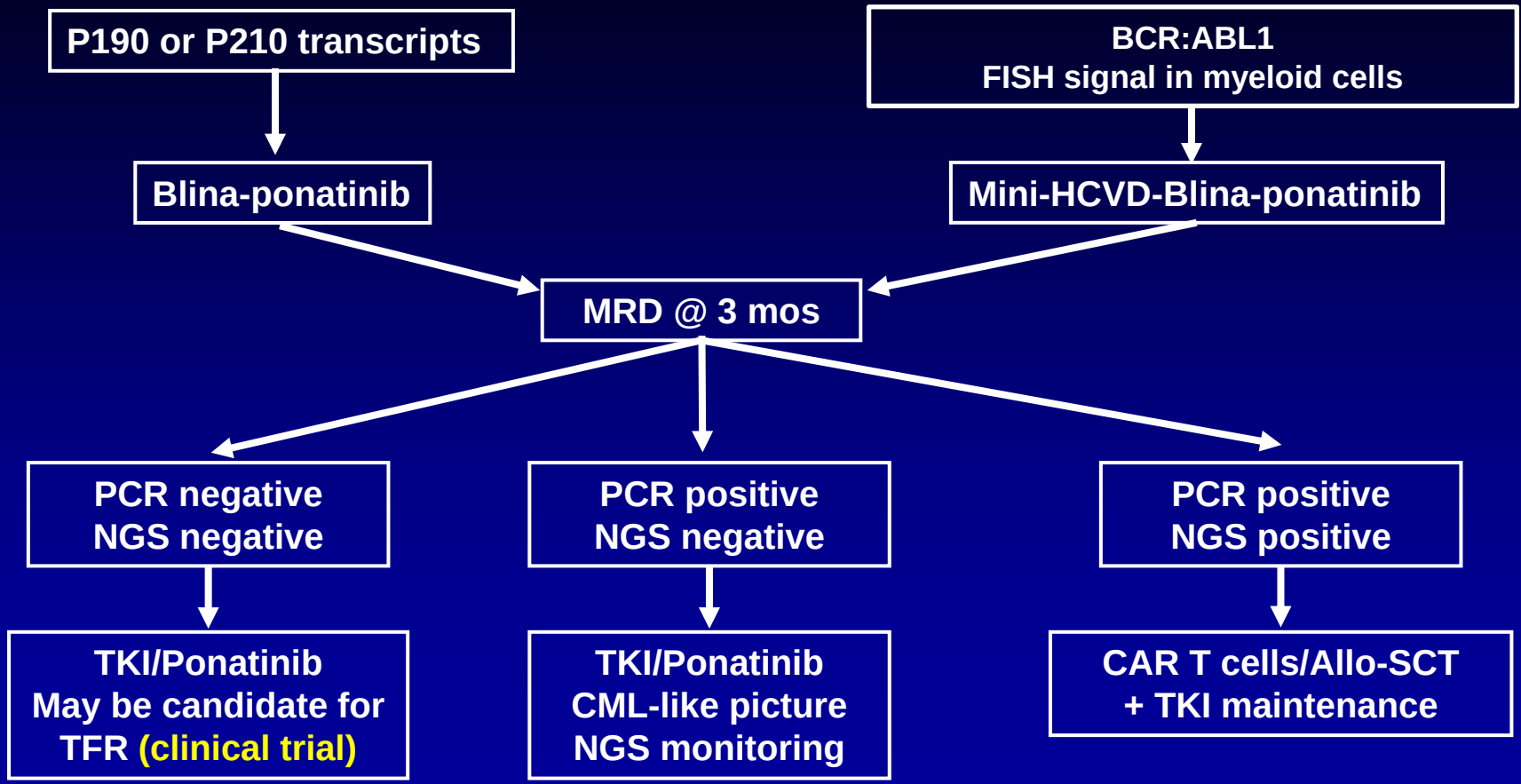
N = 48 children with B-ALL

- Discordant results 22.5%
- Multipotent progenitors carrying BCR::ABL1 translocation can lead to discrepancy results
- If concordant = no allo-SCT
- If BCR::ABL1 PCR positive and NGS MRD negative?
  - TKI maintenance vs allo-SCT

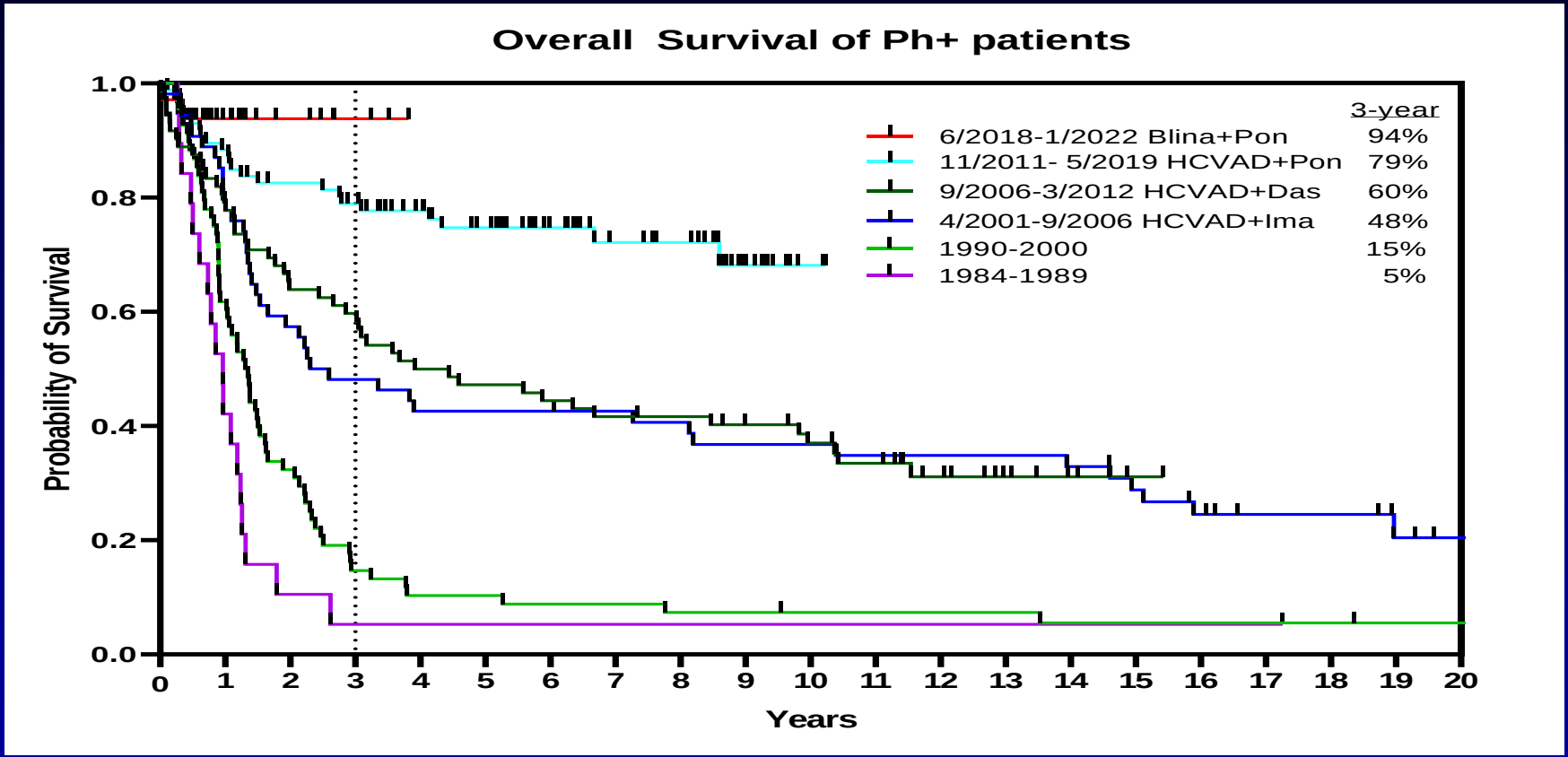


Hovorkova et al. *Blood*. 2017;129(20):2771-2781.

MDACC Proposed Management of Ph+ ALL in 2022+



ALL – Survival by Decade (MDACC 1985–2022)



Jabbour E, et al. *JAMA Oncol.* 2022;8(9):1340-1348.

Thank You

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Global Leukemia Academy

Current and Future Role of Transplantation in ALL

Marcos de Lima

APTITUDE HEALTH

Current and Future Role of Transplantation in Acute Lymphocytic Leukemia

Marcos de Lima, MD

Disclosures

- Scientific advisory board, research support: Celgene
- Scientific advisory board: Pfizer, BMS, Pharmacyclics
- Research support: Lentigen/Miltenyi Biotec

ARS Question

Autologous transplant should be considered vs allogeneic transplant in ALL.

A. True

B. False

ARS Question

Is there an age limit for myeloablative conditioning with 12-Gy total-body irradiation (TBI) in allogeneic transplantation for ALL?

A. There is no age limit
B. 70 years old
C. 40–50 years old
D. TBI is not indicated in ALL

Outline

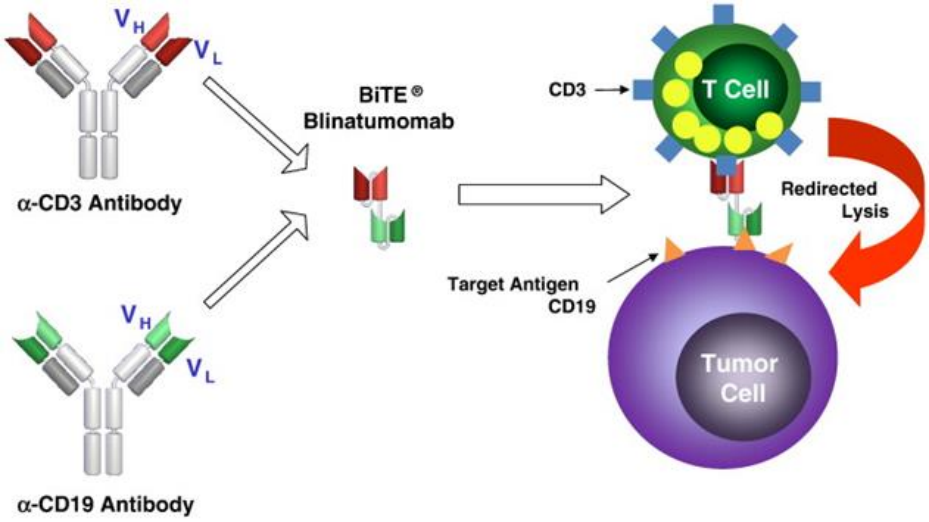
- Targeted cellular therapy and monoclonal antibodies are changing the treatment landscape in B-ALL
  - High rates of deep remissions c/w historical cytotoxic chemotherapy combinations
  - Unique toxicities

- Where do cellular (novel) immunotherapies fit in the treatment landscape of ALL?

  Is HCT still needed for curative intent?

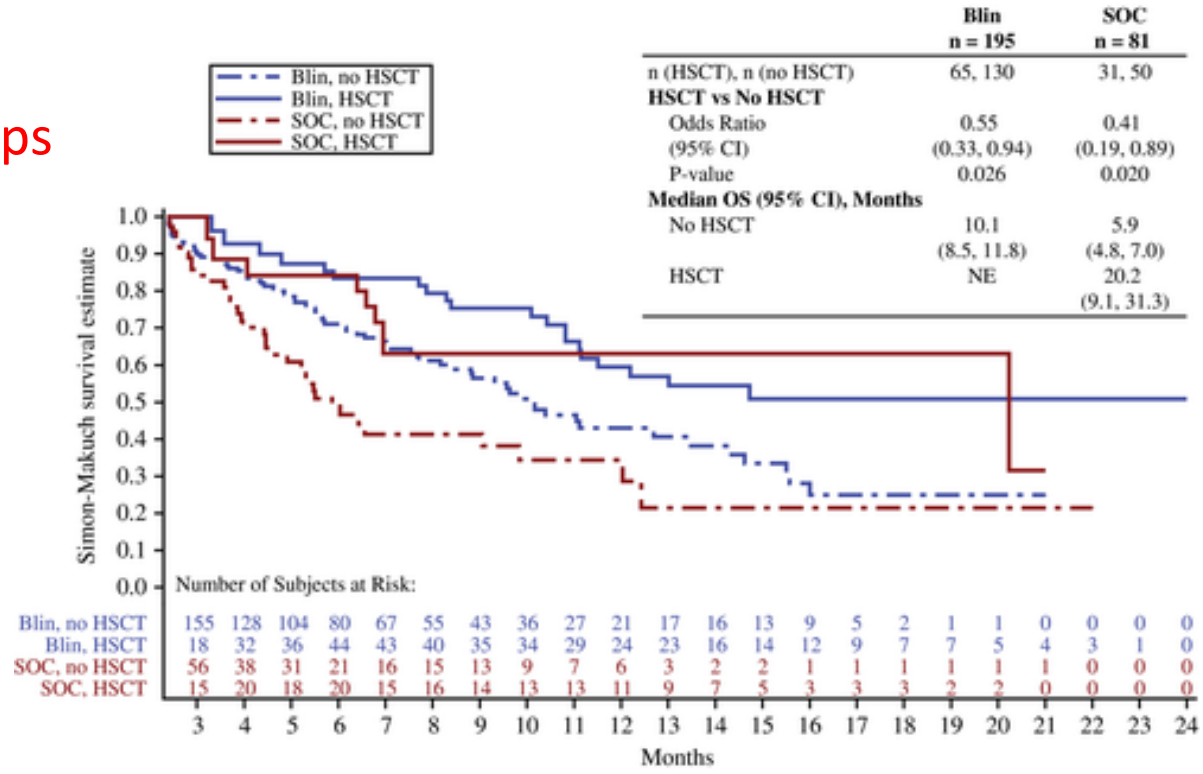
Blinatumomab in ALL

- Blinatumomab is a bispecific, single-chain antibody construct that recruits and activates T cells through CD3 of the T-cell receptor complex for redirected lysis of CD19-expressing cells
- High levels of CD19 on B-ALL blast surface
- FDA approval 12.2014 for relapse, MRD; kids, adults



TOWER: Impact of HCT in Blin and SOC Groups

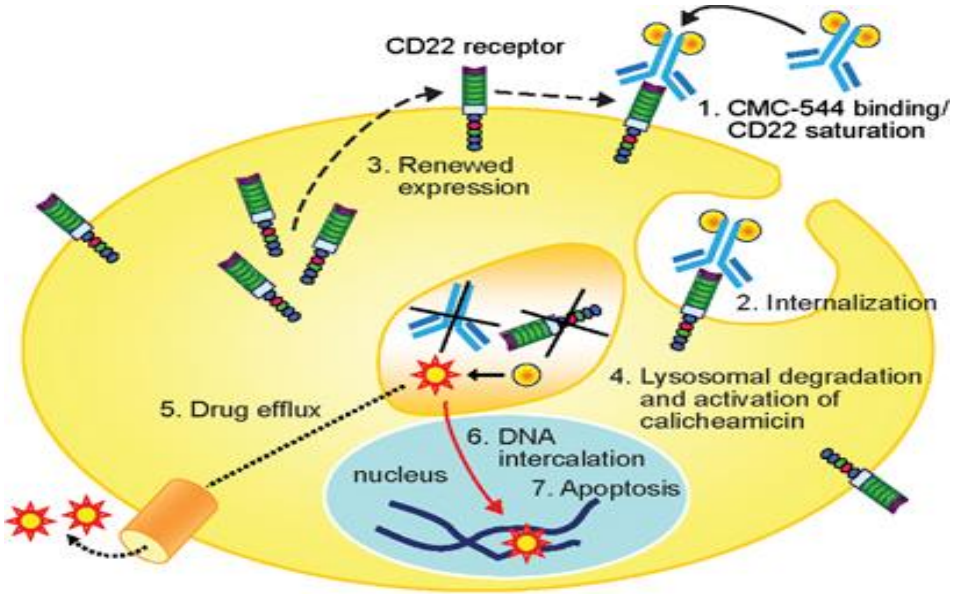
- HCT significantly improved survival in both Blin and SOC groups
- No difference in HCT benefit by treatment group



	Blin n = 195	SOC n = 81
n (HSCT), n (no HSCT)	65, 130	31, 50
HSCT vs No HSCT		
Odds Ratio	0.55	0.41
(95% CI)	(0.33, 0.94)	(0.19, 0.89)
P-value	0.026	0.020
Median OS (95% CI), Months		
No HSCT	10.1 (8.5, 11.8)	5.9 (4.8, 7.0)
HSCT	NE	20.2 (9.1, 31.3)

Jabbour EJ, et al. *Cancer*. 2019;125:4181-4192.

Inotuzumab



- The antibody-antigen complex is rapidly internalized upon binding to CD22
- Calicheamicin is released inside the tumor cell, binds to DNA, inducing double-stranded DNA breaks, followed by apoptosis of the tumor cell
- Approved in US August 2017

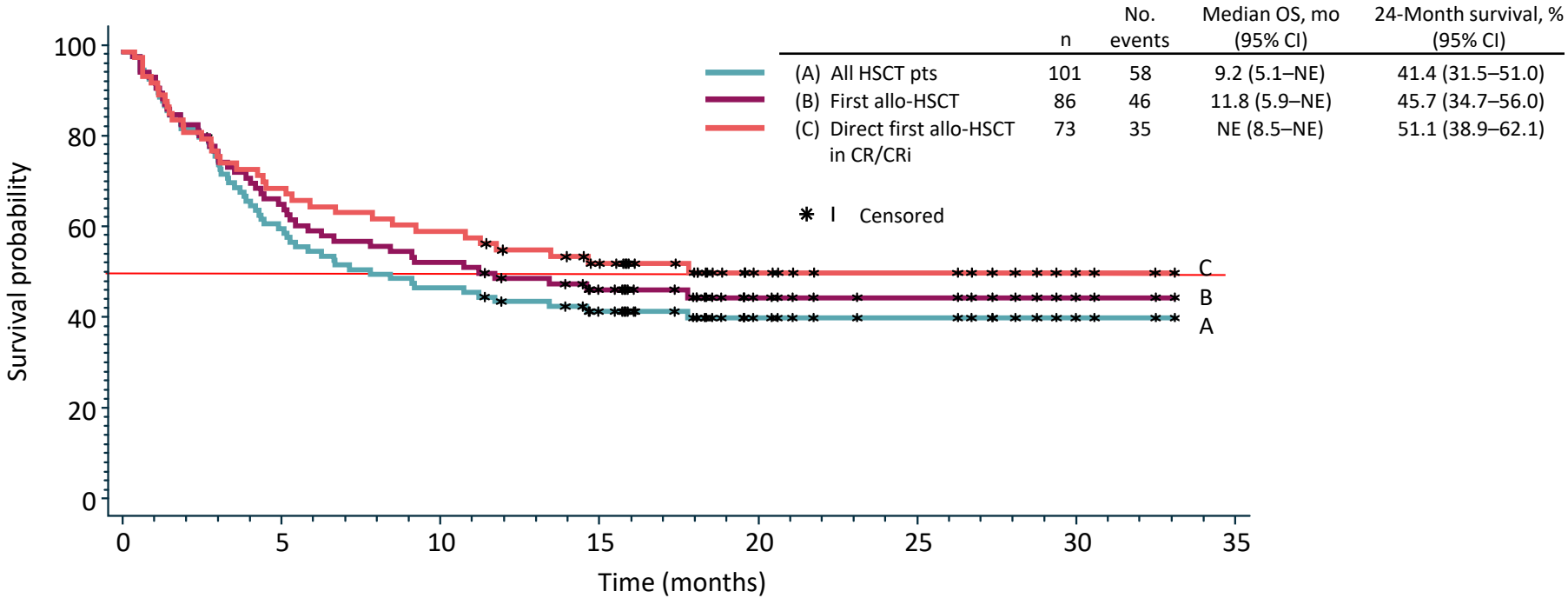
Ricart AD. *Clin Cancer Res*. 2011;17:6417-6427.

Post-inotuzumab Transplants

- Analyzed R/R ALL pts who were treated with IO and went to HCT as part of 2 clinical trials: NCT01363297, phase I/II trial, and NCT01564784, phase III trial
- N = 236 patients Rx on 2 studies; 101 went to HCT
- Median age 37 yr, 62% received IO as first salvage, and 85% had no prior SCT
- 70% matched grafts; 60% MAC regimens
- MVA
  - Factors predicting better survival: MRD^{neg} during IO, no prior HCT associated with lower risk of mortality post-HCT
  - Factors predicting worse OS: older age, higher baseline LDH, higher bili prior to HCT, thiotepa/dual alkylator

Marks DI, et al. *Biol Blood Marrow Transplant*. 2019;25:1720-1729.

Survival for Patients Who Received Inotuzumab and Proceeded to HCT



	n	No. events	Median OS, mo (95% CI)	24-Month survival, % (95% CI)
(A) All HSCT pts	101	58	9.2 (5.1–NE)	41.4 (31.5–51.0)
(B) First allo-HSCT	86	46	11.8 (5.9–NE)	45.7 (34.7–56.0)
(C) Direct first allo-HSCT in CR/CRi	73	35	NE (8.5–NE)	51.1 (38.9–62.1)

Intent-to-treat population.

Marks DI, et al. *Biol Blood Marrow Transplant*. 2019;25:1720-1729.

INO-VATE: Post-HCT VOD

- Median days to VOD after HCT: 15.0 (range, 3–57) days
  - 5 VOD events fatal (days from post-HCT VOD to death: D 6, 27, 31, 34, 57)
- No difference in median days to HCT from last dose in patients w/ vs w/o VOD
  - 37 (range, 17–135) vs 35 (9–167) days, respectively
- UVA: age ≥55 yr, busulfan-containing regimens were associated with VOD

	Primary analysis[1]		Long-term follow-up[2]	
	InO	SC	InO	SC
Patients proceeding to HSCT, n	48	20	**79**	**36**
Post-HSCT VOD/SOS, n (%)	10/48 (21)	1/20 (5)	18/79 (**23**)	3/35 (**9**)

Multivariate analysis (n = 62)	Odds ratio (95% CI)[3]	*P* value
Dual alkylator conditioning (dual vs single)	**8.606 (1.516–48.861)**	**.015**
Pre-HSCT bilirubin level (≥ULN vs <ULN)	**15.308 (1.950–120.206)**	**.009**
Pre-HSCT AST or ALT level (>1.5 × ULN vs ≤1.5 × ULN)	0.027 (<0.001–0.833)	.039
Prior history of liver disease (yes vs no)	5.133 (0.907–29.060)	.064

1. Kantarjian HM, et al. *N Engl J Med*. 2016;375:740-753; 2. de Lima M, et al. ASH 2021; 3. Kantarjian HM, et al. *Lancet Haematol.* 2017;4:e387-e398.

Where do novel therapies fit in the treatment landscape of ALL?

ROLE OF TRANSPLANT

Better Transplants . . .

- Tools for refined risk-stratification in CR1
  - Molecular subtypes
  - MRD
- Greater numbers of patients eligible for HCT in CR2
  - Highly effective salvage therapies
- Greater donor availability
  - Post-transplant Cy (US) – ATG-based regimens (China)
- Decrease rate of relapse post-HCT
  - Is there a role for maintenance therapy?

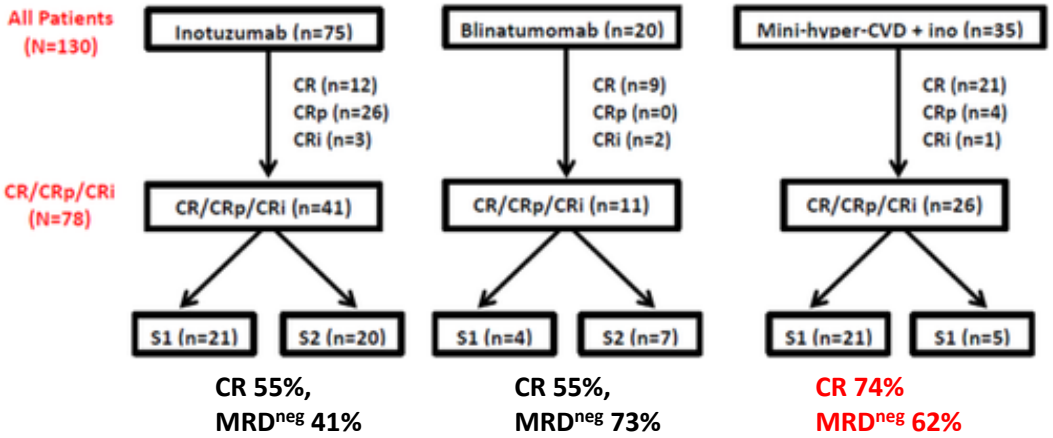
Indications for Transplant

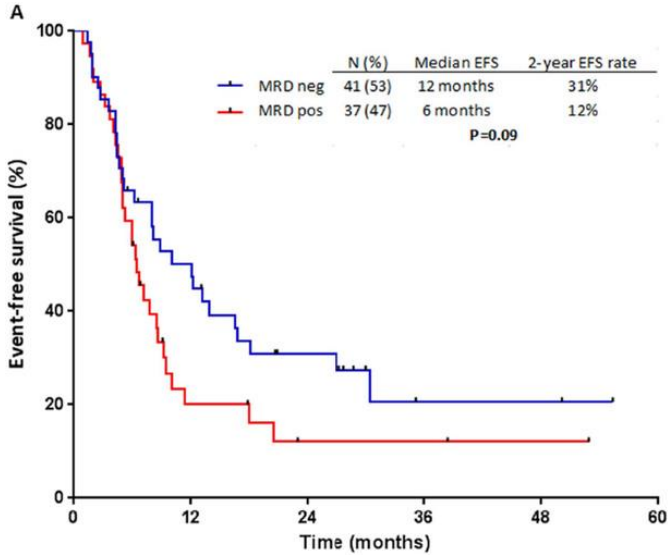
- CR1
  - High-risk karyotype: complex, hypodiploid, 11q23, iAMP21 (pedi)
  - High-risk immune phenotype: ETP, Ph-like
  - Poor Rx response: MRD
  - Ph-like ALL
  - Ph?
    - HCT if persistent MRD after 3 months therapy
- CR2 and greater remission
  - All patients

<u>Disease status remains a powerful prognosticator</u>

Higher Probability of Survival From Relapse

- 130 adults with ALL received therapy in salvage 1 (S1) or S2 at MDACC between 2010–2015
- ORR 60%, MRD^{neg} 32% by MFC; best response in chemo-immunotherapy group
- Med 27 mo FU, stratified by MRD and salvage
  - 2-yr EFS and OS rates were 31% vs 12%, *P* = .09, and 40% vs 26%, *P* = .18, respectively
  - MRD significantly impacts EFS in S1 only

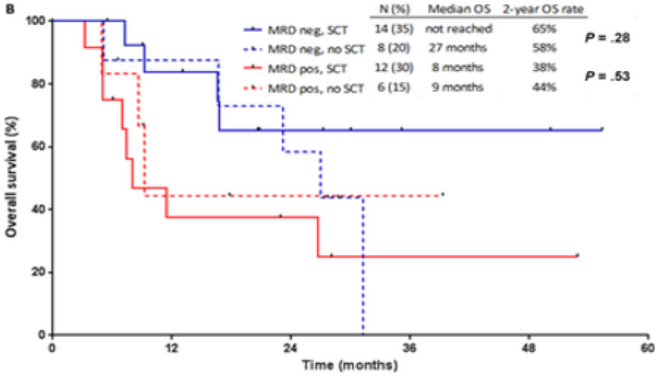




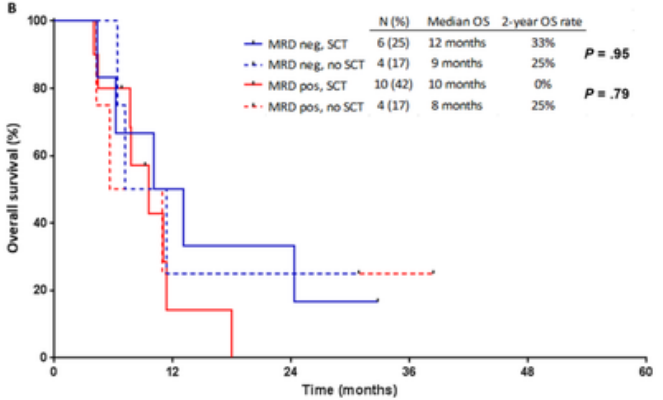
Jabbour E, et al. *Cancer*. 2017;23:294-302.

Transplant After Salvage

- 66% of patients underwent HCT
- 48% MRD^{neg} at time of HCT
- Landmark analysis showed trend for improved outcomes with HCT; small numbers likely precluded statistical significance
- Among HCT patients, those who were MRD^{neg} at HCT had longer EFS (*P* =.006) and OS (*P* = .02) c/w MRD^{pos}
- Best outcomes for HCT in MRD^{neg} after S1



OS on the basis of MRD and HCT in salvage 1



OS on the basis of MRD and HCT in salvage 2

Jabbour E, et al. *Cancer*. 2017;23:294-302.

Blinatumomab Maintenance Post-HCT: Trial at MDACC

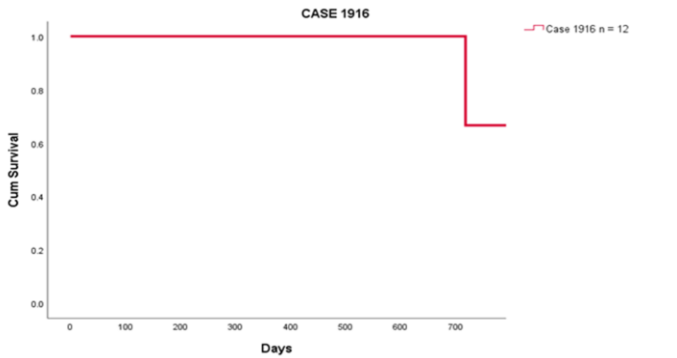
- Study group: ALL with MRD^{pos}, and/or beyond CR1
- Treatment plan: 4 cycles of blinatumomab as a 4-week continuous infusion at 28 µg/m^2/24 hours at 2–3, 6, 9, and 12 months following HCT
- Median age 30 years (range, 21–65); cumulative 26 cycles Blin administered
  - Toxicity: seven grade 3 or 4 AEs reported (leukopenia n = 4, transaminitis n = 2, rash n = 1). No CRS. One grade 2 neurotoxicity
  - Patients with more effector T cells were more likely to maintain remission
  - Survival and PFS were not better than historical controls, however

Kebriaei P, et al. *Biol Blood Marrow Transplant*. 2020;26:S102-S103.

Multicenter Study of Low-Dose Inotuzumab Maintenance Post-transplant

- Study group: ALL with MRD^{pos}, and/or beyond CR1, recipients of RIC
- Treatment plan: 4–12 cycles of inotuzumab single dose monthly starting at 40–100 days post-transplant
- N = 22 patients, med age 48 years (range, 17–67)

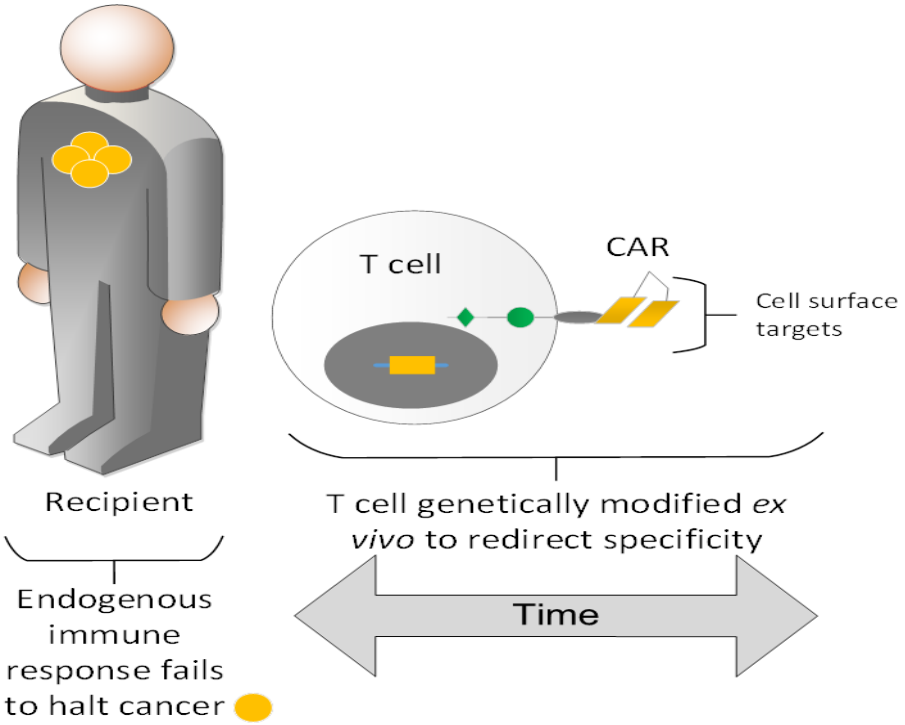
- Doses administered: 0.3, 0.4, 0.5, 0.6 mg/m^2
  - Toxicity: mostly thrombocytopenia; no VOD
  - Day-100 and 1-year non-relapse mortality is 0
  - Median follow-up of 16 months post-HCT (range, 4–50); 20/22 patients are alive in CR



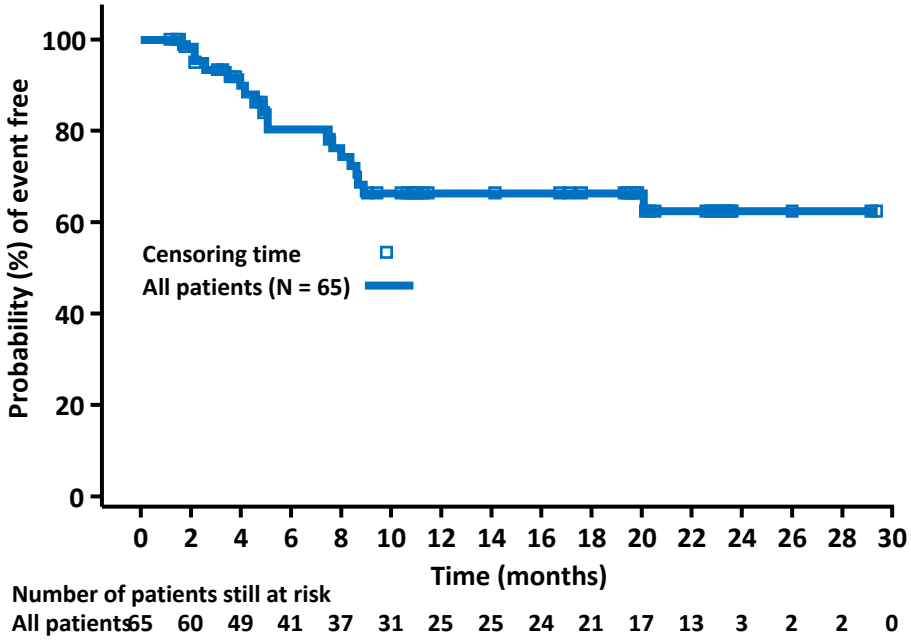
Metheny L III, et al. ASH 2021. Abstract 2899.

CAR T Cells

- Uses a genetically engineered chimeric antigen receptor (CAR) that is
  - Transduced into T cells using viral or non-viral vectors and
  - Expressed in T cells that are expanded ex vivo and then administered to patients to target tumor cells in the body
- The introduced CAR redirects T-cell specificity to target cancer cells



CAR T in Pediatrics: ELIANA Study Update



- Median age = 11 yr
- 12- and 18-month relapse-free survival rate among responders was 66% (95% CI, 52–77)
- Overall remission rate (CR + CRi) within 3 months was 82% (95% CI, 72–90)
  - Among patients with CR/CRi within 3 months, 98% (64/65) achieved MRD^{neg} bone marrow

Grupp SA, et al. ASH 2018. Abstract 895.

MSKCC: Long-term Follow-up of CAR T in Adults With R/R ALL

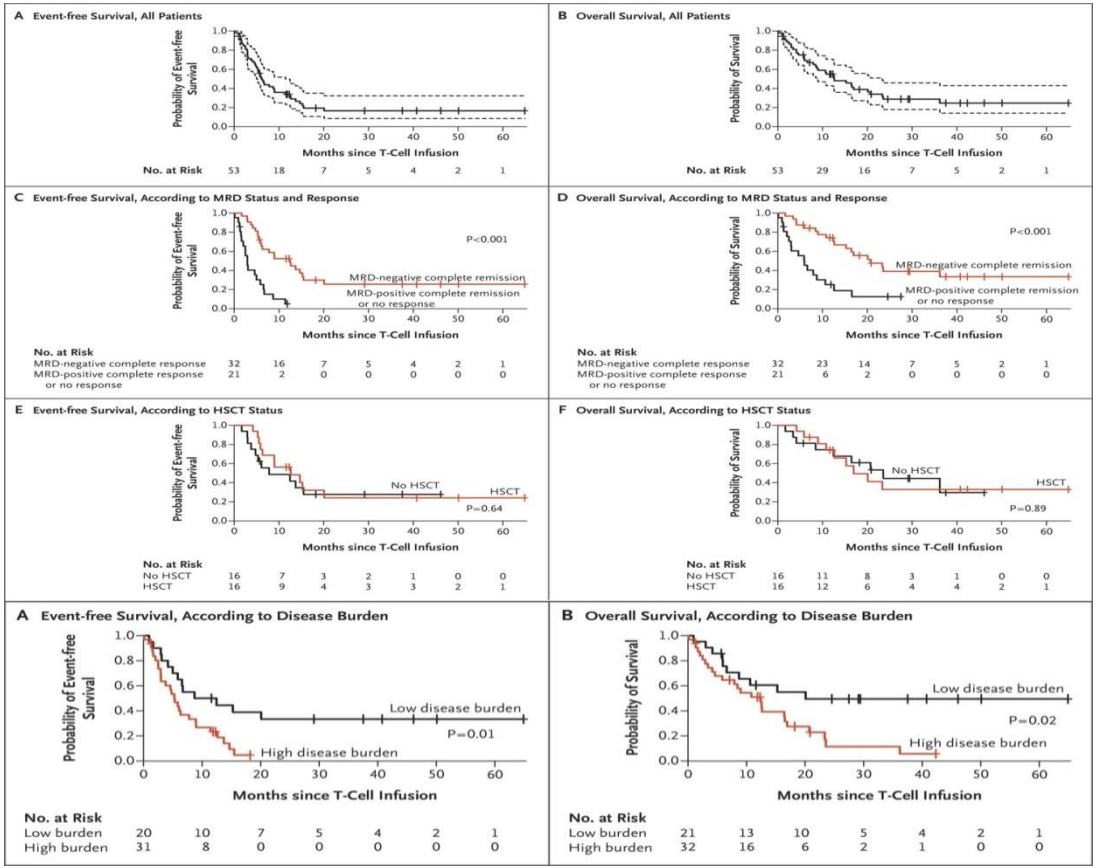
- Single-center, phase II trial CD19, 2010–2016
- CD19 CAR with CD28 costim; retrovirus transduction
- Cy or FluCy, followed by 1 × 106 or 3 × 106 CD19 CAR T cell/kg
- 87 patients screened, 83 enrolled, 53 infused
- Manufacture failure 3%

Table 1. Characteristics of the 53 Patients at Baseline.*

Characteristic	Value
Age	
Median (range) — yr	44 (23–74)
Distribution — no. (%)	
18–30 yr	14 (26)
31–60 yr	31 (58)
>60 yr	8 (15)
No. of previous therapies — no. (%)	
2	21 (40)
3	13 (25)
≥4	19 (36)
Primary refractory disease — no. (%)	
Yes	12 (23)
No	41 (77)
Previous allogeneic HSCT — no. (%)	
Yes	19 (36)
No	34 (64)
Previous treatment with blinatumomab — no. (%)	
Yes	13 (25)
No	40 (75)
Pretreatment disease burden†	
Median bone marrow blasts (range) — %	63 (5–97)
Bone marrow blasts — no. (%)	
≥5%	27 (51)
<5% with extramedullary disease	5 (9)
≥0.01% and <5%	15 (28)
<0.01%	6 (11)
Philadelphia chromosome–positive — no. (%)	
Yes	16 (30)
No	37 (70)

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

MSKCC Long-term Follow-up: Patient Outcomes, n = 53

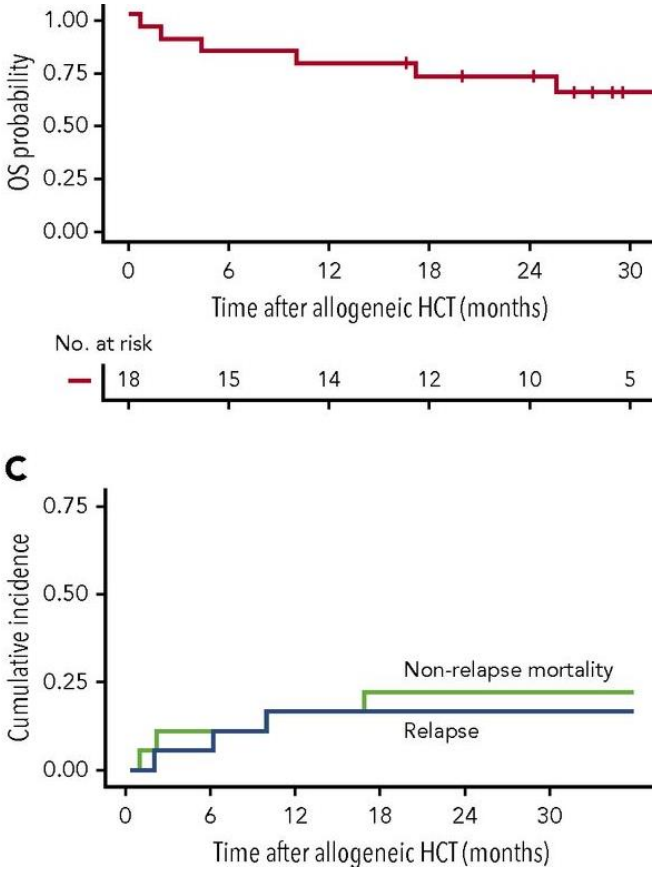


- CR 83%, intent to treat 53%, MRD^{neg} 67%
- Median follow-up 29 mo (range, 1–65)
  - 66% of pts relapsed or died from toxicity
  - Med EFS 6.1 mo, OS 20.1 mo
- 39% underwent HCT – no benefit
- Patients with low disease burden at time of CAR infusion had less toxicity, longer survival

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

FHCRC: HCT Post-CAR Improves EFS

- 18/45 patients received HCT consolidation at median 70 days post-CAR
- Median 28 mo post-HCT, 2-yr EFS 61%, OS 72%, CIR 17% (all CD19+), NRM 23%
- 17% grade 3–4 aGVHD; 44% cGVHD
  - No correlation b/w CRS and GVHD
- HCT independent predictor of better EF on MVA, HR 0.39, *P* = .088



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

Brexucabtagene Autoleucel Efficacy

Median age = 40 years

	Treated patients (n=55)
Overall complete remission or complete remission with incomplete haematological recovery	39 (71%)*
Complete remission	31 (56%)
Complete remission with incomplete haematological recovery	8 (15%)
Blast-free hypoplastic or aplastic bone marrow	4 (7%)
No response	9 (16%)
Unknown or not evaluable†	3 (5%)

Data are n (%). *95% CI 57–82, p<0·0001. †The three patients who were unknown or not evaluable died (at days 8, 15, and 18) before the first disease assessment.

Table 2: **Rate of overall complete remission or complete remission with incomplete haematological recovery based on central assessment**

Updated follow-up

No response: 14/55

Out of 39 responders (CR/CRi) in treated phase II patients (median follow-up 27 months)

–

6 were in ongoing remission without receiving subsequent stem cell transplant or anticancer therapy

–

6 received subsequent anticancer therapy; 4 remained in remission, 2 died

–

10 received subsequent allo-SCT; 6 remained in remission, 3 died, 1 relapsed

Shah B, et al. *Lancet.* 2021;398:491-502; Shah BD, et al. ASCO 2022. Abstract 7010.

CAR T for Adults With ALL

- CAR T-cell studies in aggregate demonstrate
  - Feasibility to manufacture in 80%–90% of patients – but delays are problematic (local manufacture [?]; off-the-shelf products)
  - High and deep initial response rates but 40%–60% relapse rate by 1 year
  - Current constructs associated with serious toxicity
- Algorithms needed to determine CAR sequence in therapy
- Future CARs to address toxicity, antigen-negative relapse

Vercellino L, et al. *Blood Adv*. 2020;4:5607-5615; Turtle CJ, et al. *J Clin Invest.* 2016; 126:2123-2138.

Antigen Escape Is Prevented With Trispecific CAR T

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

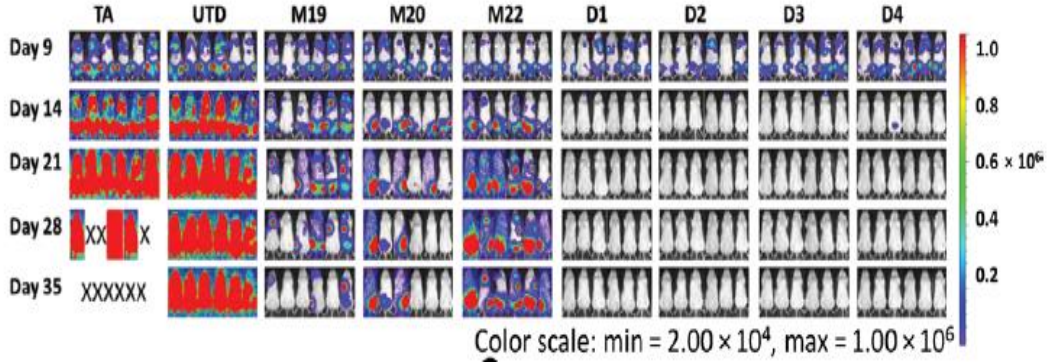
CANCER

Trispecific CD19-CD20-CD22–targeting duoCAR-T cells eliminate antigen-heterogeneous B cell tumors in preclinical models

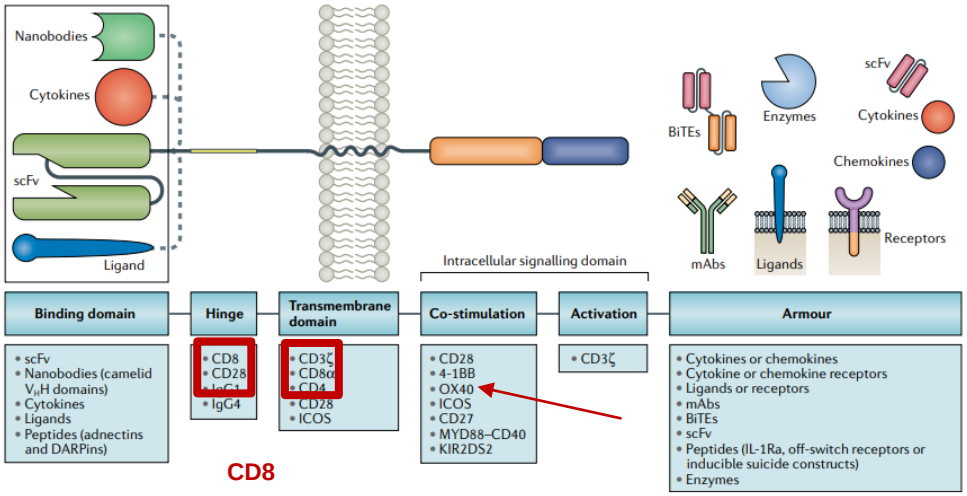
Dina Schneider*†, Ying Xiong*, Darong Wu, Peirong Hu, Leah Alabanza, Brittany Steimle, Hasan Mahmud, Kim Anthony-Gonda, Winfried Krueger, Zhongyu Zhu, Dimiter S. Dimitrov‡, Rimas J. Orentas§, Boro Dropulić†||

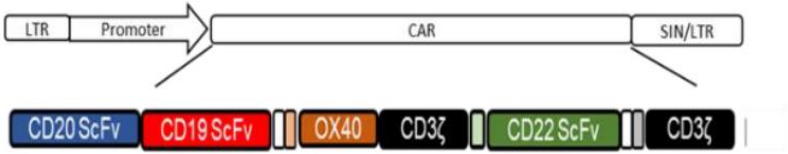
A substantial number of patients with leukemia and lymphoma treated with anti-CD19 or anti-CD22 monoCAR-T cell therapy relapse because of antigen loss or down-regulation. We hypothesized that B cell tumor antigen escape may be overcome by a chimeric antigen receptor (CAR) design that simultaneously targets three B cell leukemia antigens. We engineered trispecific duoCAR-T cells with lentiviral vectors encoding two CAR open reading frames that target CD19, CD20, and CD22. The duoCARs were composed of a CAR with a tandem CD19- and CD20-targeting binder, linked by the P2A self-cleaving peptide to a second CAR targeting CD22. Multiple combinations of intracellular T cell signaling motifs were evaluated. The most potent duoCAR architectures included those with ICOS, OX40, or CD27 signaling domains rather than those from CD28 or 4-1BB. We identified four optimal binder and signaling combinations that potently rejected xenografted leukemia and lymphoma tumors in vivo. Moreover, in mice bearing a mixture of B cell lymphoma lines composed of parental triple-p CD20-negative, and CD22-negative variants, only the trispecific duoCAR-T cells ra the tumors. Each of the monoCAR-T cells failed to prevent tumor progression. Anal profiles demonstrates that the distinct signaling of the intracellular domains used m ential effects. Multispecific duoCAR-T cells are a promising strategy to prevent antig the down-regulation of target antigen in patients with B cell malignancies.

Dina Schneider, PhD
Lentigen/Miltenyi



CAR Construct of Trispecific CD19, CD20, and CD22





- 6-day, local manufacturing
- First in human using OX40 co-stimulation
- 40% of cell dose infused on day 0, 60% on day 7

Conclusions

- Currently consider all cellular therapy as a bridge to transplant
- Decision to transplant in CR1 risk-stratified
- Transplant most effective when patients MRD^{neg} at HCT, but MRD^{pos} patients still benefit, especially with myeloablative transplants
- Maintenance other than TKI investigational

Conclusions

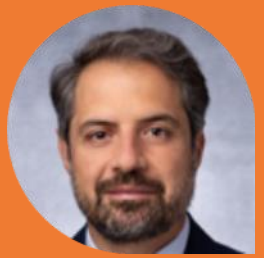
- The ideal sequence of current available salvage options is unknown
- Treatment with anti-CD19 CAR T cells likely needs to be consolidated with allogeneic transplant in adults – but this is controversial
- Donor availability is almost universal now

Marcos.delima@osumc.edu

Global Leukemia Academy

Debate: How to Optimally Sequence CD19-Targeted Approaches in ALL

Elias Jabbour



APTITUDE HEALTH

Please vote

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

A. CAR T therapies

B. Monoclonal antibodies or bispecifics

Global Leukemia Academy

Monoclonal Antibodies and Bispecifics First

Shaun Fleming

APTITUDE HEALTH

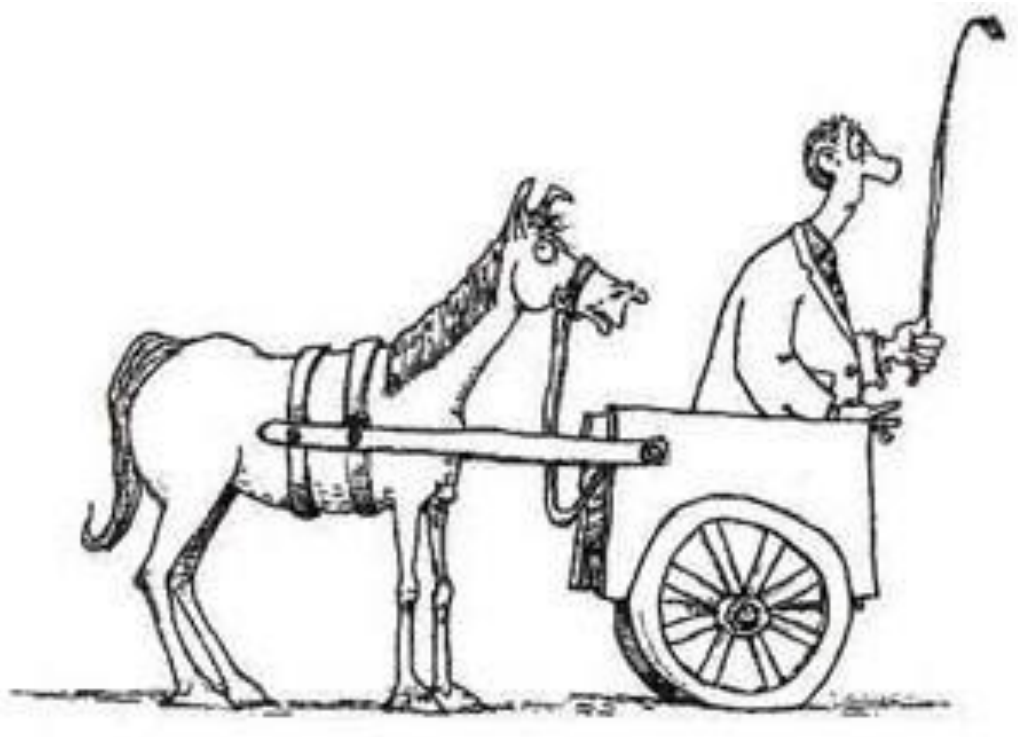
How to Optimally Sequence CD19-Targeted Approaches in ALL – Antibodies and Bispecifics First

Shaun Fleming, MBBS(Hons), FRACP, FRCPA

Clinical and Laboratory Haematologist

Alfred Hospital, Melbourne, Australia

So, to summarize before I begin . . .



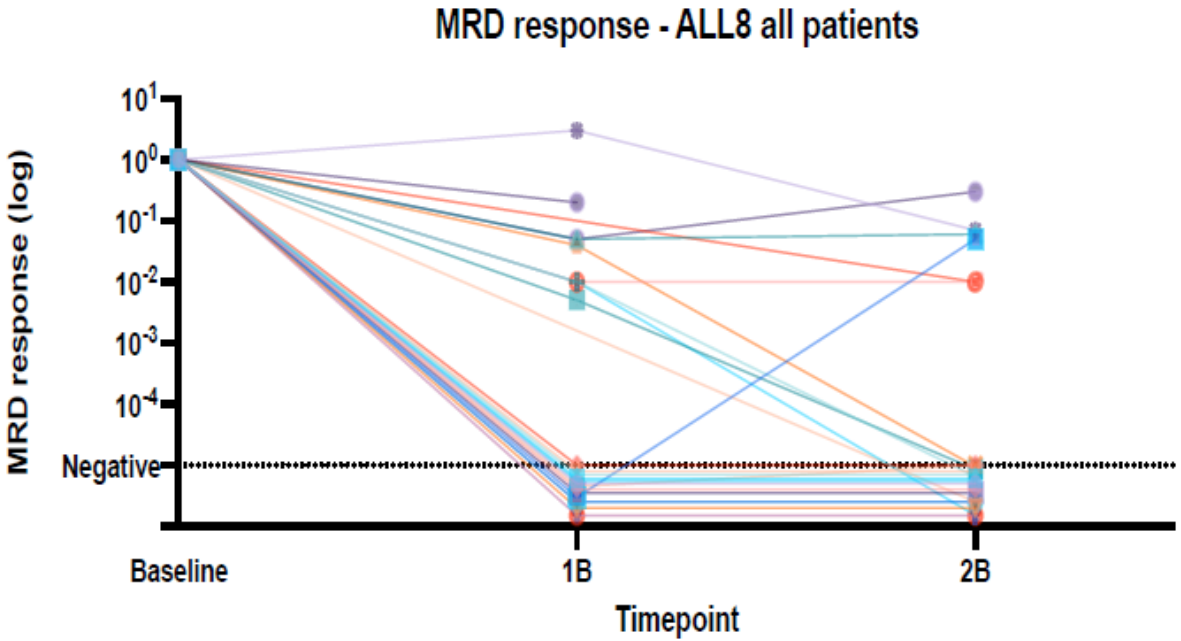
Why Bispecifics and Monoclonals Should Come Before CAR T

- Application into frontline disease
- Treatment of measurable residual disease
- Real-world effectiveness of CAR T
- Allograft maintains a role in treatment of ALL
- CAR T remains an option after failure of bispecifics

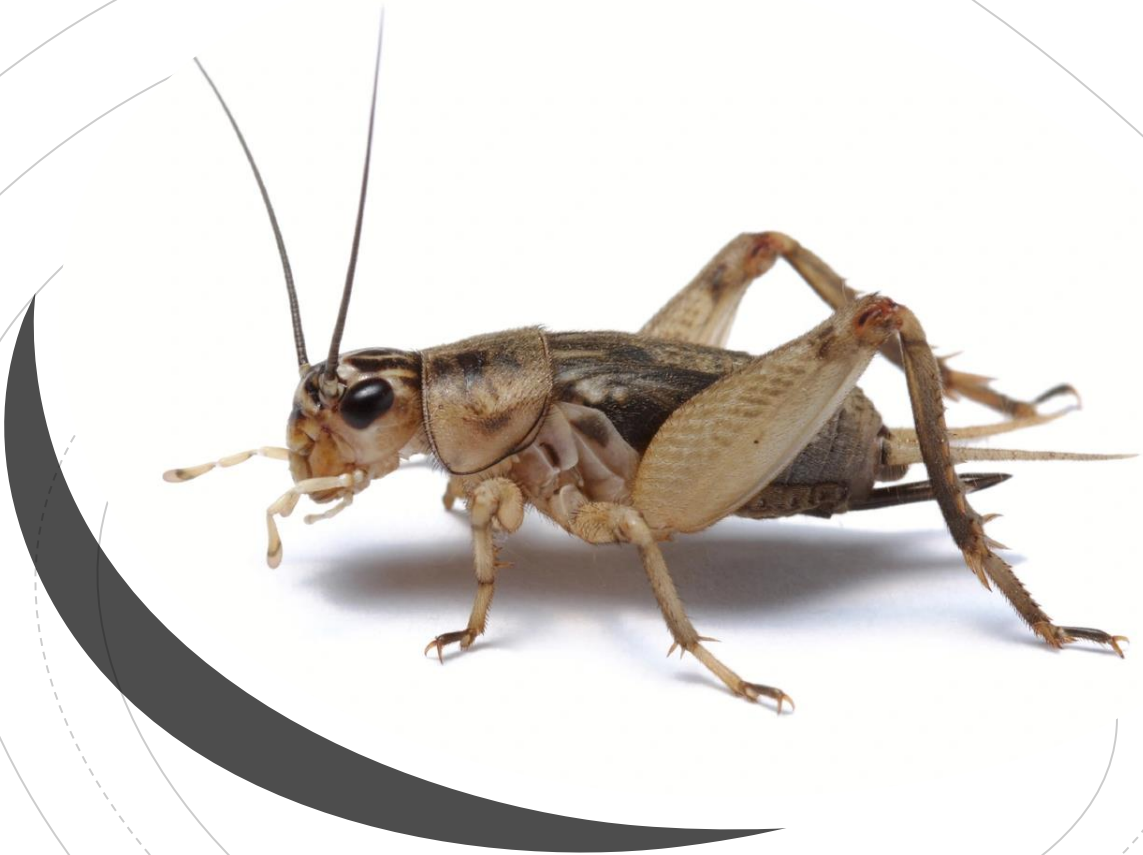
Frontline Therapy With Blinatumomab

- Ph+ disease
  - D-ALBA (GIMEMA)
  - Blina plus Ponatinib (MD Anderson)
- Ph– disease
  - ALL08 (Australia)
  - ALL09 (Australia)
  - Hyper-CVAD plus Blinatumomab (MD Anderson)
  - Mini–hyper-CVD plus Ino plus Blin (MD Anderson)
  - EWALL-BOLD (EWALL)
  - Blinatumomab plus POMP (SWOG)
  - . . .

Lower-Intensity Chemotherapy With Blinatumomab Preserves MRD Responses With Reduced Treatment-Related Mortality

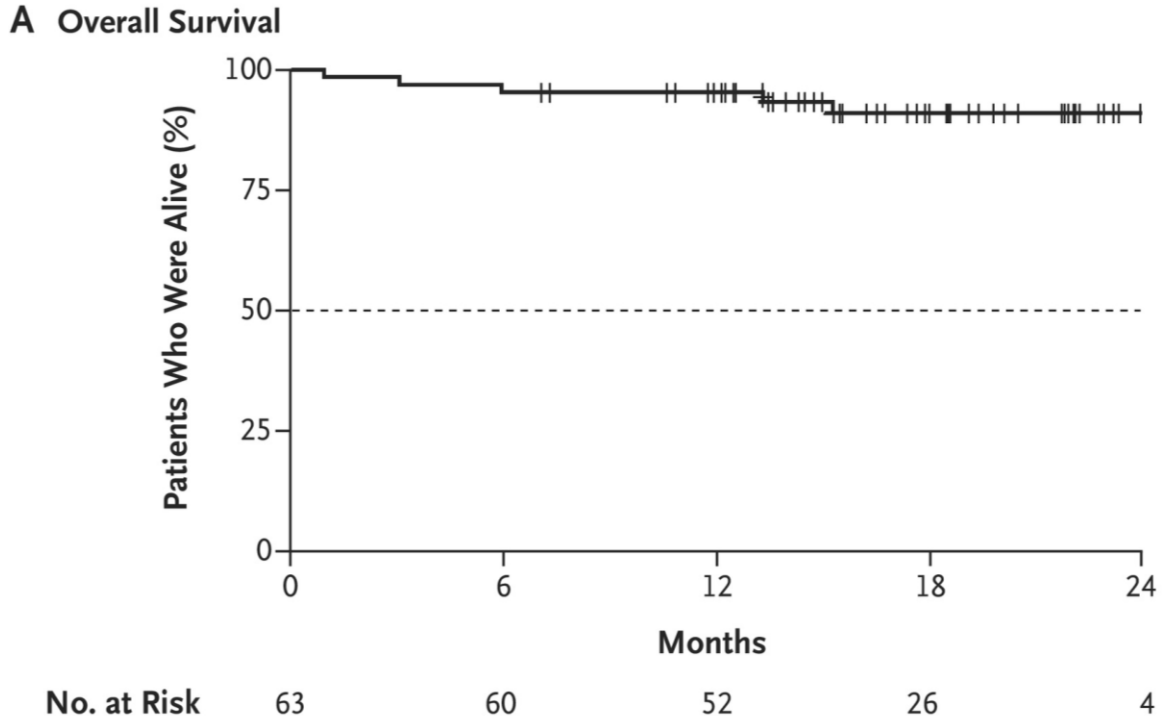


Fleming S, et al. *Blood.* 2021;138(suppl 1):1234.



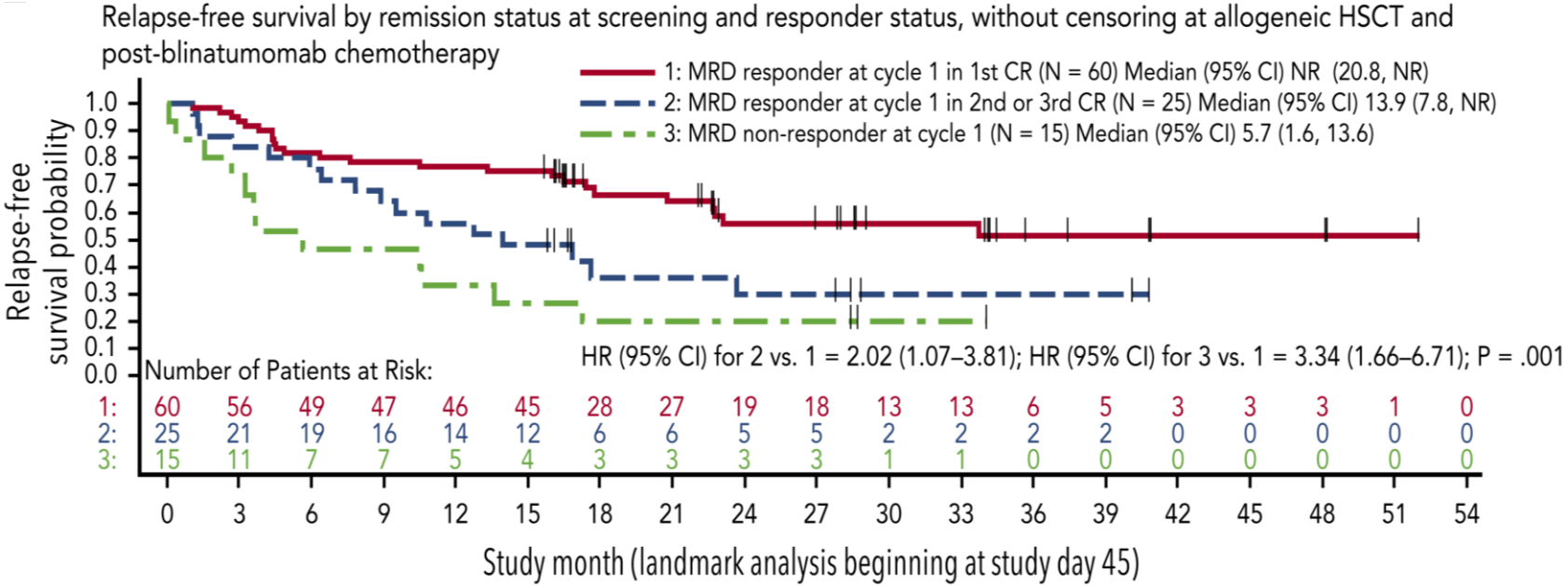
On the Flip Side . . . Frontline Studies of CAR T in ALL

D-ALBA – If We Can Get Frontline Right . . . Where Do We Need CAR T?



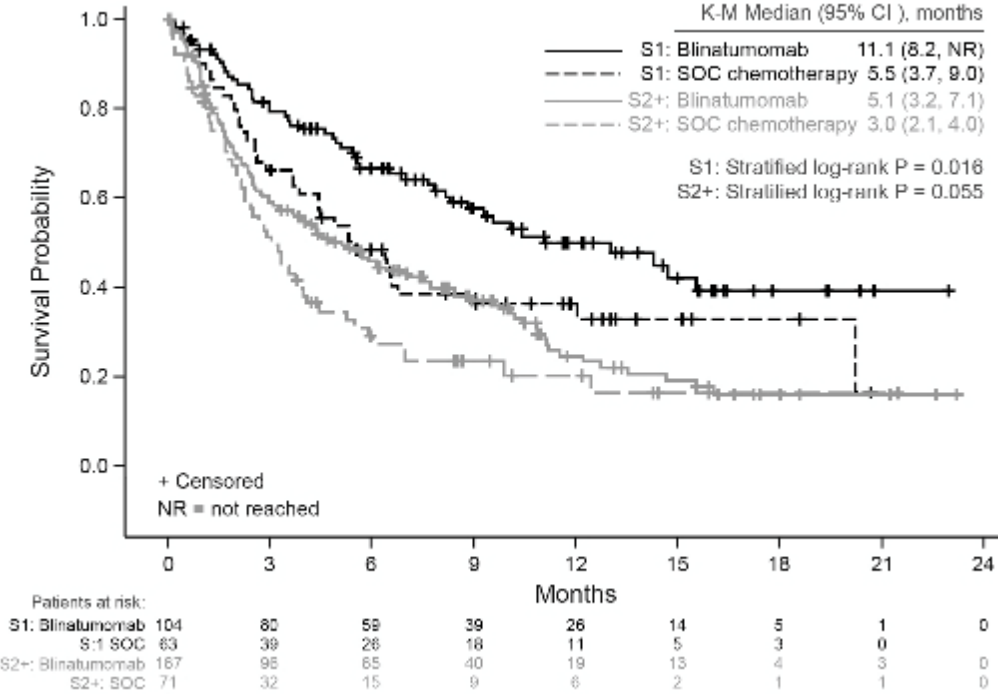
Foa R, et al. *N Engl J Med*. 2020;383:1613-1623.

Blinatumomab When Used in MRD+ ALL Can Salvage to Deliver Patients to Allo-HSCT



When Should Novel Therapies Be Applied at Relapse? Early

Figure. Overall survival among patients with no (S1) or prior (S2+) salvage treatment

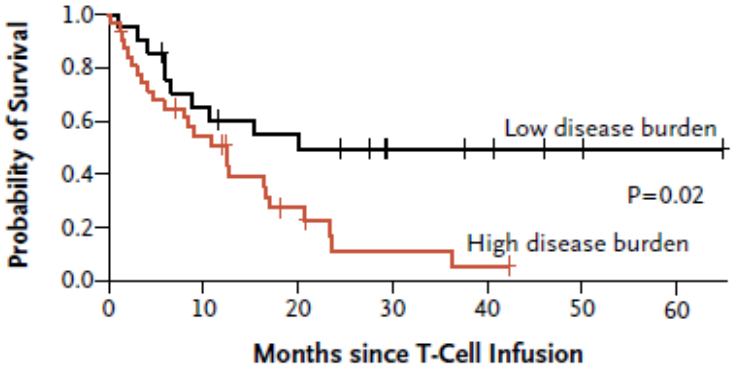


Dombret H, et al. EHA 2017. Abstract S478.

The Evidence for CAR T for MRD+ ALL Is Inferred Rather Than Directly Demonstrated . . .

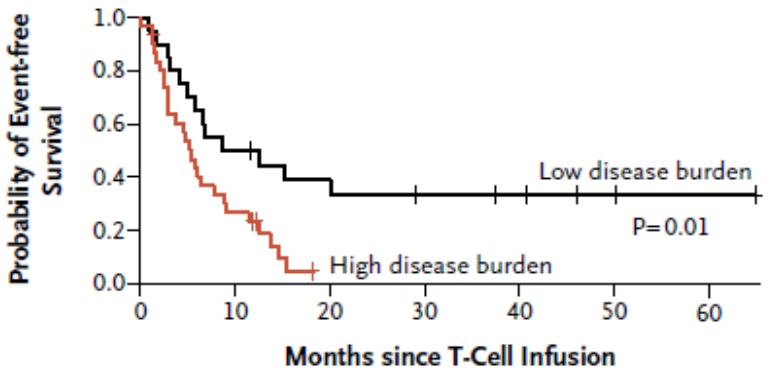
- Median EFS 6.1 months
- Median OS 12.9 months
- Longer EFS and OS in patients in MRD– remission
  - EFS of 12.5 vs 3.1 months (*P* <.001)
  - OS of 20.7 vs 6.6 months (*P* <.001)

B **Overall Survival, According to Disease Burden**



No. at Risk							
Low burden	21	13	10	5	4	2	1
High burden	32	16	6	2	1	0	0

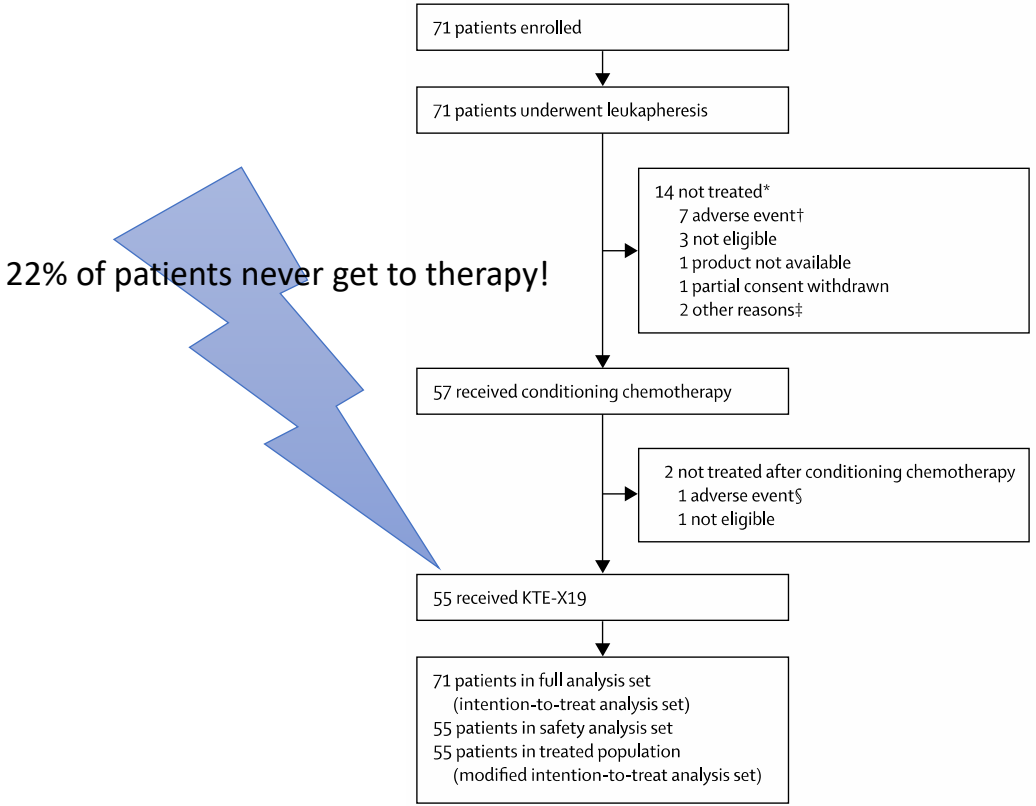
A **Event-free Survival, According to Disease Burden**

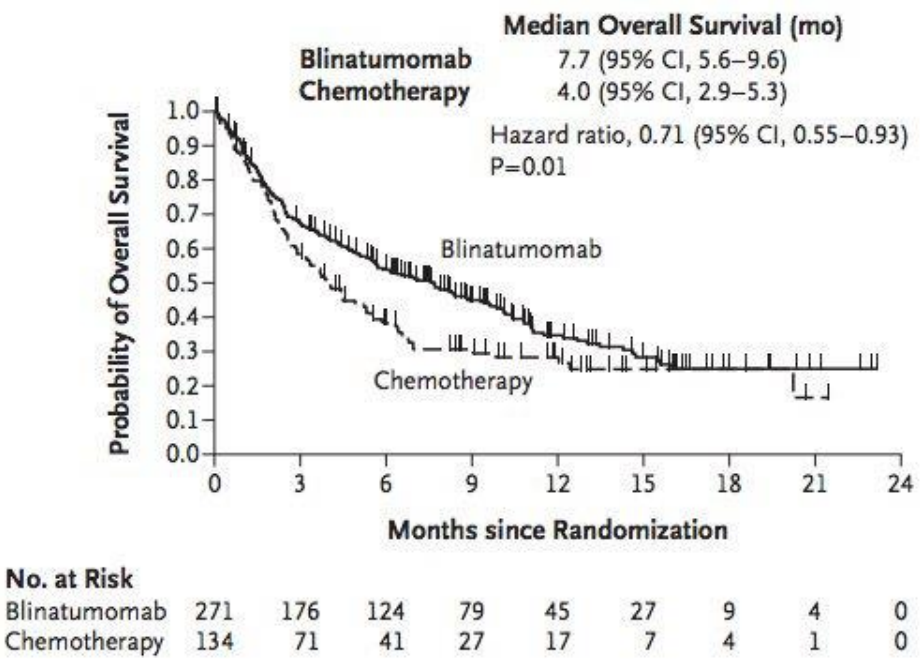


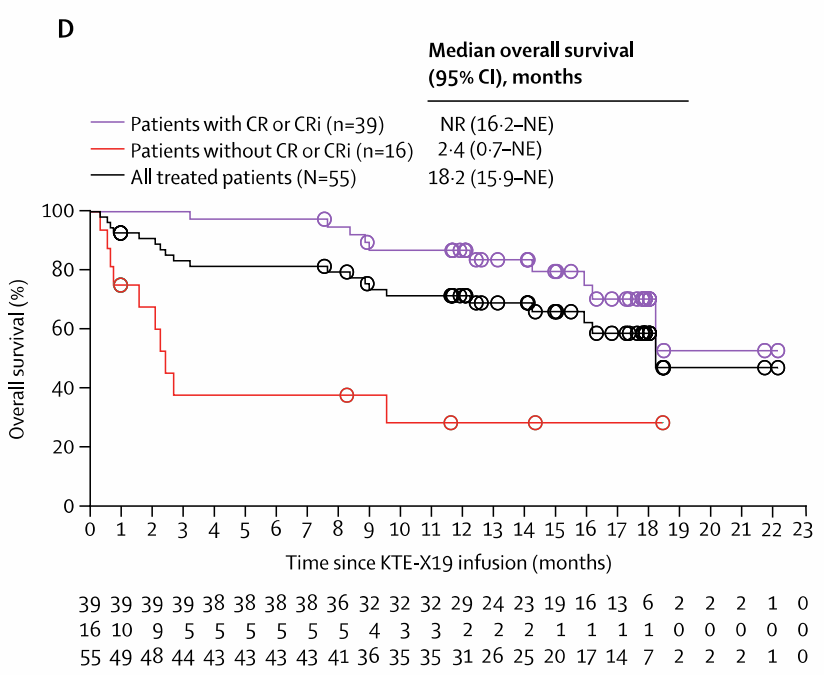
No. at Risk							
Low burden	20	10	7	5	4	2	1
High burden	31	8	0	0	0	0	0

ZUMA-3 Study – Brexucabtagene

- 71 patients enrolled
  - Aged 18 years or older
  - Relapsed/refractory B-ALL
    - 1’ refractory disease
    - Relapse within 12 months
    - Relapse after 2 lines of therapy
    - Relapsed/refractory after allo-HSCT
- Infusion following standard lymphodepletion




Median Overall Survival (mo)
Blinatumomab 7.7 (95% CI, 5.6–9.6)
Chemotherapy 4.0 (95% CI, 2.9–5.3)
Hazard ratio, 0.71 (95% CI, 0.55–0.93)
P=0.01
Probability of Overall Survival
Blinatumomab
Chemotherapy
Months since Randomization
No. at Risk
Blinatumomab 271 176 124 79 45 27 9 4 0
Chemotherapy 134 71 41 27 17 7 4 1 0


D
Median overall survival (95% CI), months
Patients with CR or CRi (n=39) NR (16·2–NE)
Patients without CR or CRi (n=16) 2·4 (0·7–NE)
All treated patients (N=55) 18·2 (15·9–NE)
Overall survival (%)
Time since KTE-X19 infusion (months)
39 39 39 39 38 38 38 38 36 32 32 32 29 24 23 19 16 13 6 2 2 2 1 0
16 10 9 5 5 5 5 5 5 4 3 3 2 2 2 1 1 1 1 0 0 0 0 0
55 49 48 44 43 43 43 43 41 36 35 35 31 26 25 20 17 14 7 2 2 2 1 0

Patient Demographics

	Treated patients (n=55)	Enrolled patients (n=71)
Age, years	40 (28–52)	44 (30–59)
≥65 years	8 (15%)	11 (15%)
Sex		
Female	22 (40%)	30 (42%)
Male	33 (60%)	41 (58%)
Race		
White	37 (67%)	51 (72%)
Asian	3 (5%)	4 (6%)
Black or African American	1 (2%)	2 (3%)
American Indian or Alaska Native	1 (2%)	1 (1%)
Other	9 (16%)	9 (13%)
Missing	4 (7%)	4 (6%)
ECOG performance status of 1*	39 (71%)	53 (75%)
Philadelphia chromosome positive	15 (27%)	19 (27%)
Extramedullary disease at screening	6 (11%)	8 (11%)
CNS-1 disease at baseline†‡	55 (100%)	69 (97%)
Number of previous therapies§	2 (2–3)	2 (2–3)
Three or more	26 (47%)	35 (49%)
Previous blinatumomab	25 (45%)	33 (46%)
Previous inotuzumab ozogamicin	12 (22%)	16 (23%)
Previous allogeneic SCT	23 (42%)	28 (39%)
Relapsed or refractory subgroup		
Primary refractory	18 (33%)	21 (30%)
Relapsed or refractory to two or more previous systemic therapy lines	43 (78%)	54 (76%)
First relapse with remission ≤12 months	16 (29%)	20 (28%)
Relapsed or refractory post allogeneic SCT¶	24 (44%)	29 (41%)

(Table 1 continues in next colum)

	Treated patients (n=55)	Enrolled patients (n=71)
(Continued from previous column)		
Bone marrow blasts at screening		
n	55	70
Median (IQR)	65% (24–87)	70% (25–89)
≤5%‖	0	1 (1%)
>5% to 25%‖	16 (29%)	17 (24%)
M3 bone marrow involvement (>25% blasts)‖	39 (71%)	52 (73%)
Bone marrow blasts at baseline‡		
n	55	70
Median (IQR)	60% (17–90)	67% (34–90)
≤5%‖	5 (9%)	6 (8%)
>5% to 25%‖	10 (18%)	10 (14%)
M3 bone marrow involvement (>25% blasts)‖	40 (73%)	54 (76%)
Bone marrow blasts at preconditioning after bridging chemotherapy		
n	46	48
Median (IQR)	59% (25–87)	63% (27–89)
≤5%‖	5 (9%)	5 (7%)
>5% to 25%‖	7 (13%)	7 (10%)
M3 bone marrow involvement (>25% blasts)‖	34 (62%)	36 (51%)

Data are median (IQR) or n (%), unless otherwise indicated. ECOG=Eastern Cooperative Oncology Group. SCT=stem-cell transplant. *All other patients had ECOG performance status of 0. †Among treated patients, five had CNS-2 disease at screening and data were missing for three patients; per protocol, sites could administer intrathecal chemotherapy between screening and baseline, which could have resulted in a change of CNS status. ‡Baseline refers to the last value taken before conditioning chemotherapy. §Among treated patients, six had previous blinatumomab and previous inotuzumab ozogamicin, 11 patients had previous blinatumomab and previous SCT, five patients had previous inotuzumab ozogamicin and previous SCT, and two patients had previous blinatumomab, previous inotuzumab ozogamicin, and previous SCT. ¶Includes one patient who received autologous SCT. ‖The denominator for percentages is 55 for treated patients and 71 for enrolled patients.

Table 1: **Baseline characteristics**

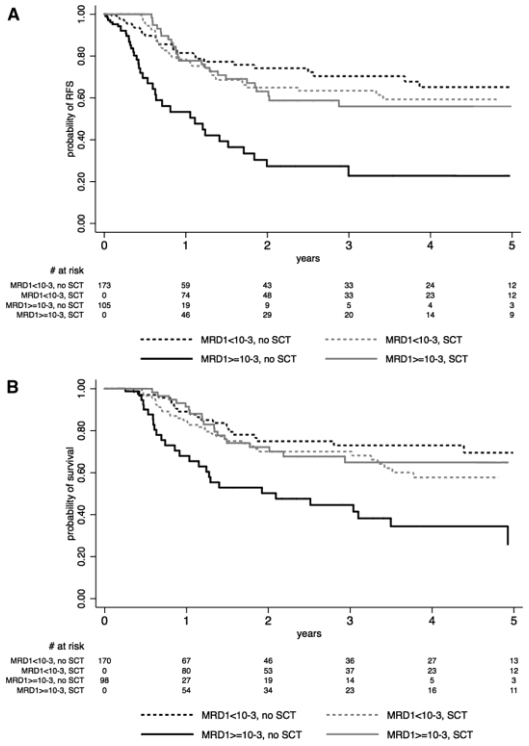
- Relatively young cohort of adult ALL
  - Only 15% over 65 years
- All CNS disease negative at time of treatment
- Almost half had prior blinatumomab exposure
- Almost half had a prior allo-HSCT
- Most were refractory to 2 or more lines of therapy

CD19– Relapse With T-Cell–Directed Therapies

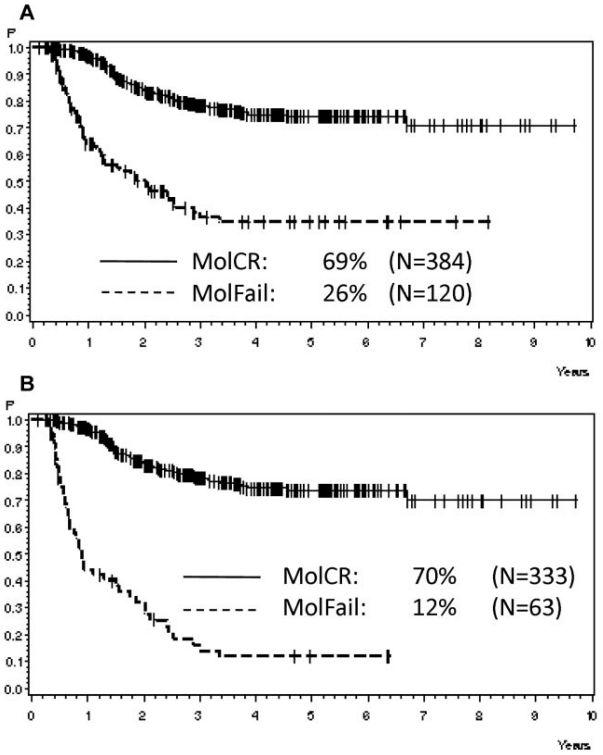
- **CD19– relapses occur in 10%–20% of post-blinatumomab relapses[1]**
  - Other factors such a T-cell exhaustion with increased expression of PD-1, CD69, and CD25 in incubation of T cells with B-ALL blasts and blinatumomab[2]
  - Response rates of 36% were seen with blinatumomab retreatment in patients, with a response duration of at least 3 months[3]
- **Loss of CD19 is more common in relapses post–CD19-directed CAR T therapy (30%–50% of relapses)[4]**
  - CD22-directed CAR T may provide a mechanism to overcome this

1. Braig F, et al. *Blood.* 2016;129(1):100-104; 2. Benjamin JE, et al. *Ther Adv Hematol.* 2016;7(3)142-156; 3. Topp MS, et al. EHA 2015. Abstract P165;
4. Ruella M, et al. *J Immunother Cancer.* 2015;3(2):O5.

MRD+ Patients Can Be Salvaged by an Allograft . . .



- Minimal residual disease is the strongest predictor of outcome in Ph– ALL
- Conventional risk factors lose prognostic significance when MRD is taken into account
  - MLL translocations may retain significance
- Definitions of molecular failure (for FRALLE-93–treated patients)
  - ≥10^{-2} at d35
  - >10^{-4} (MRD negativity) at d90

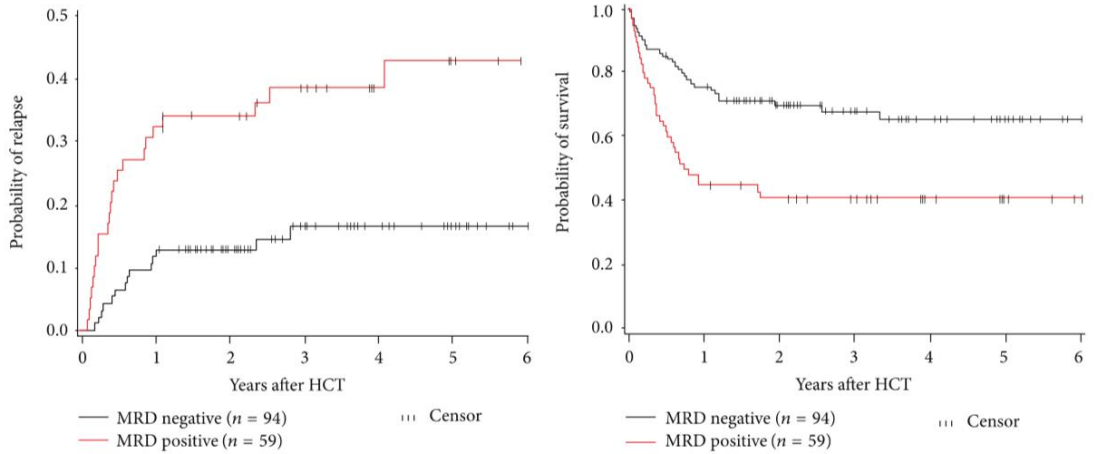


Dhedin N, et al. *Blood.* 2015;125(16):2486-2496.

Gokbuget N, et al. *Blood.* 2013;122(21):839-839.

Ideally, Post-MRD Eradication With Immunotherapies

Prognostic value of MRD: at transplant
(Fred Hutchinson CRC, Seattle)



CR1, first complete remission; CR2, second complete remission.
Bar M, et al. Leuk Res Treatment 2014;2014:421723.

CR1 = 90, CR2 = 58, >CR2 = 12
MRD status not influenced by adjusting for CR status (P=0.70)

Finally . . .

Late Breaking ASH 2022

- ECOG-ACRIN E1910 study
  - Randomized phase III study of blinatumomab consolidation vs SOC for Ph– ALL
  - Included patients up to 70 years of age
- 112 patients per arm
  - Randomized at time of MRD negativity
  - Improved OS – median NR vs 71.4 months
- **Blinatumomab is the new SOC in frontline Ph– B-ALL → irrespective of favorable MRD response!**

Figure 1. Schema

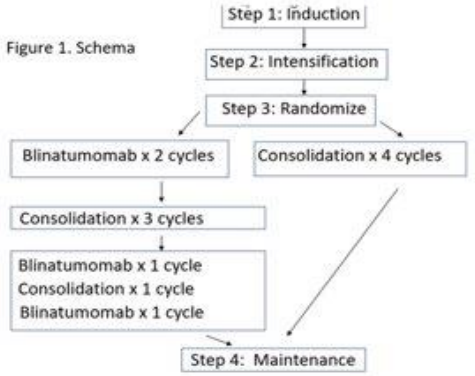
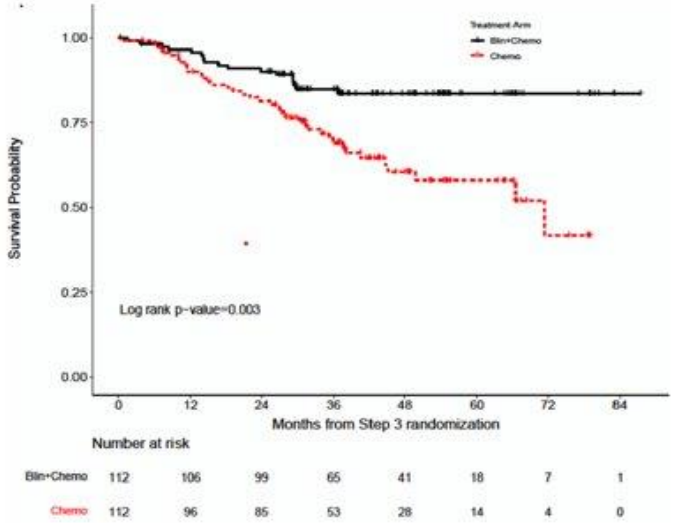


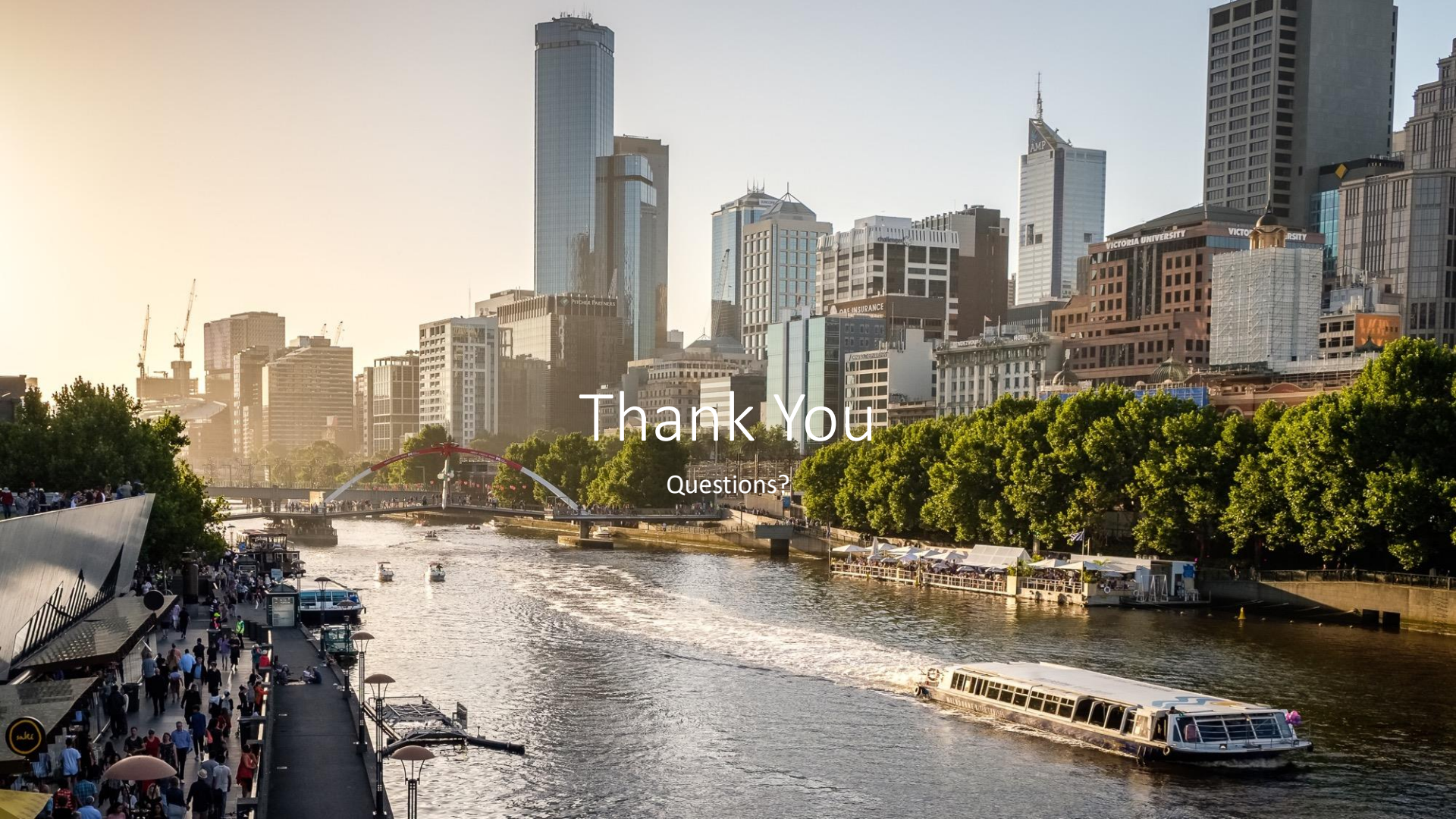
Figure 2: Overall Survival



Litzow et al. ASH 2022.

Why Bispecifics and Monoclonals Should Come Before CAR T

- Bispecifics have demonstrated a role in frontline ALL; CAR T has not
- CAR T does not have direct evidence as MRD; bispecifics do
- Even on well-designed clinical trials a proportion of patients never get to CAR T
- Allograft following bispecifics remains the treatment of choice in MRD+ ALL
- Use of bispecifics does not prevent later CAR T salvage if required



Thank You

Questions?

Global Leukemia Academy

CAR T First

Jae Park

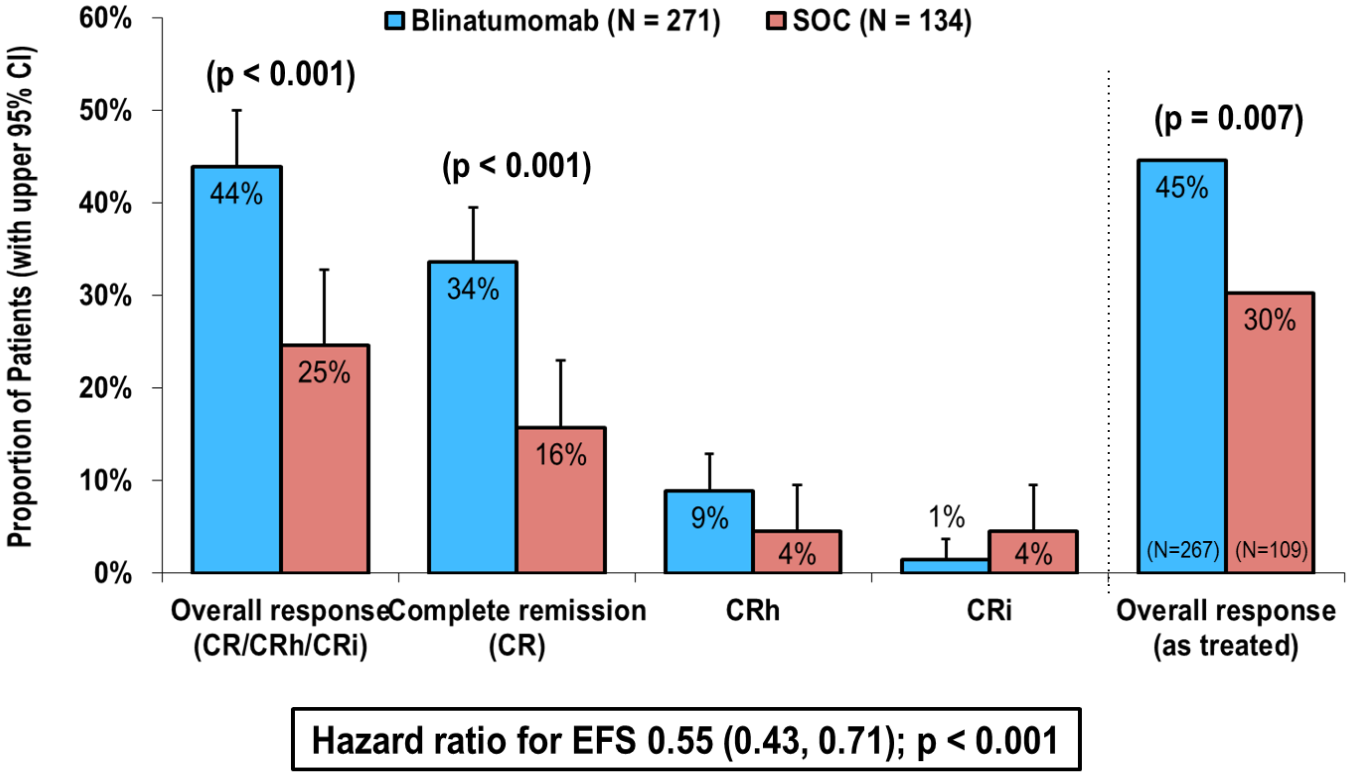
APTITUDE HEALTH

Debate: How to Optimally Sequence CD19-Targeted Approaches in ALL: CAR T First

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

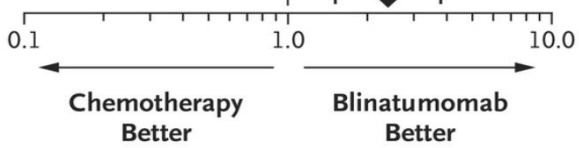
Response Rates With Blinatumomab in R/R ALL



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

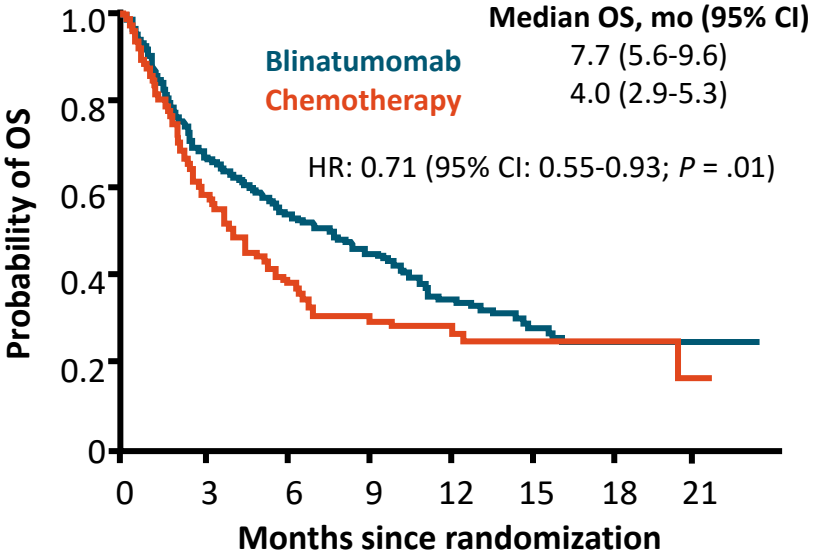
Response Rates With Blinatumomab in R/R ALL

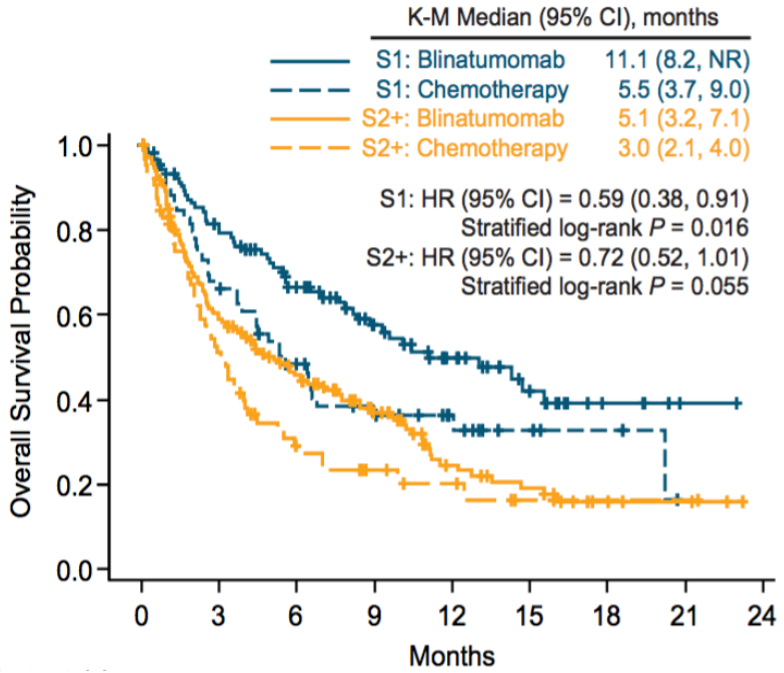
Subgroup	Blinatumomab	Chemotherapy	Odds Ratio (95% CI)
	no. of events/no. of patients (%)		
Age			
<35 yr	53/123 (43.1)	15/60 (25.0)	2.27 (1.15–4.50)
≥35 yr	66/148 (44.6)	18/74 (24.3)	2.50 (1.34–4.66)
Salvage-treatment phase			
First	60/114 (52.6)	23/65 (35.4)	2.03 (1.08–3.80)
Second	36/91 (39.6)	7/43 (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)



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

Overall Survival With Blinatumomab in R/R Adult ALL

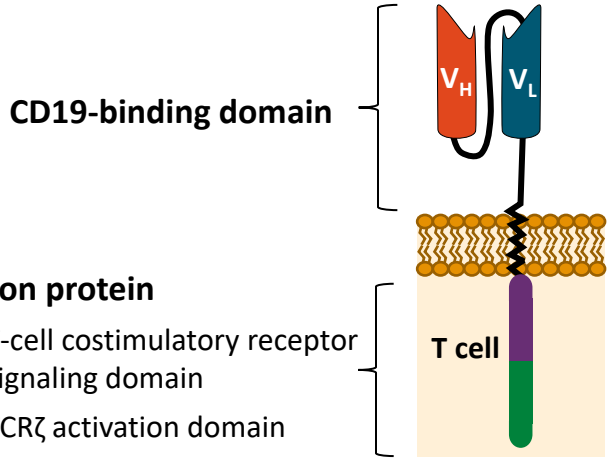




24% of overall patients proceeded to alloHSCT;
26% in blinatumomab arm died post-alloHSCT during follow-up

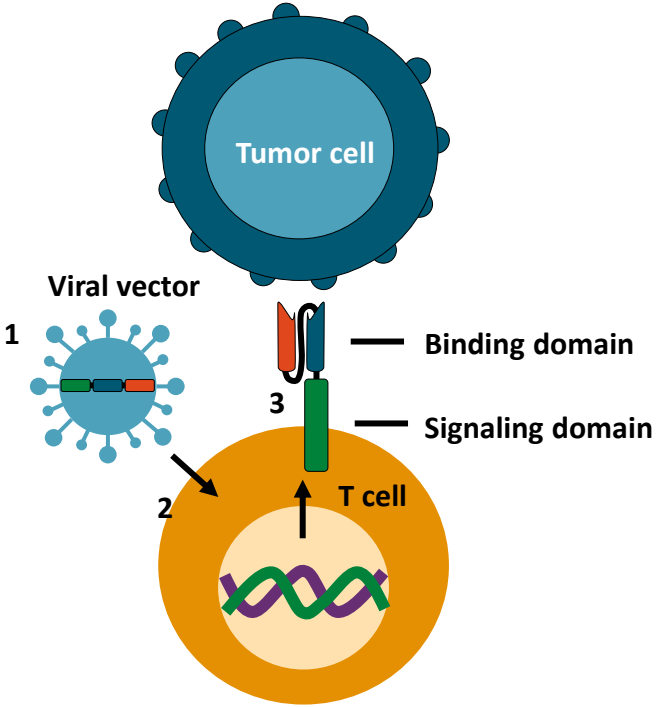
Kantarjian H, et al. *N Engl J Med.* 2017;376:836-847; Kantarjian HM, et al. *N Engl J Med.* 2016;375:740-753; Kantarjian HM, et al. ASH 2017. Abstract 574.

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

Rationale for Clinical Development of CAR T-Cell Therapy in ALL

- Despite blinatumomab and inotuzumab, median OS for R/R B-ALL remains low at 7-8 months
- Blinatumomab and inotuzumab have less curative potential as monotherapy in R/R ALL
  - <50% of the responding patients proceed to alloHSCT
  - Blinatumomab is administered as continuous infusions over 4 wk
  - Inotuzumab is associated with VOD/SOS
- CD19 CAR T cells can induce high CR rates even in patients with blinatumomab/inotuzumab failure
- A subset of patients achieve durable remissions after a single infusion of CAR T cells, some without subsequent alloHSCT, although the role of subsequent alloHSCT remains unclear
  - Significantly improved remission duration and survival in patients with lower disease burden
  - May generate better long-term survival and higher potential as a definitive therapy in earlier lines of tx
  - CARs allow additional genetic modifications

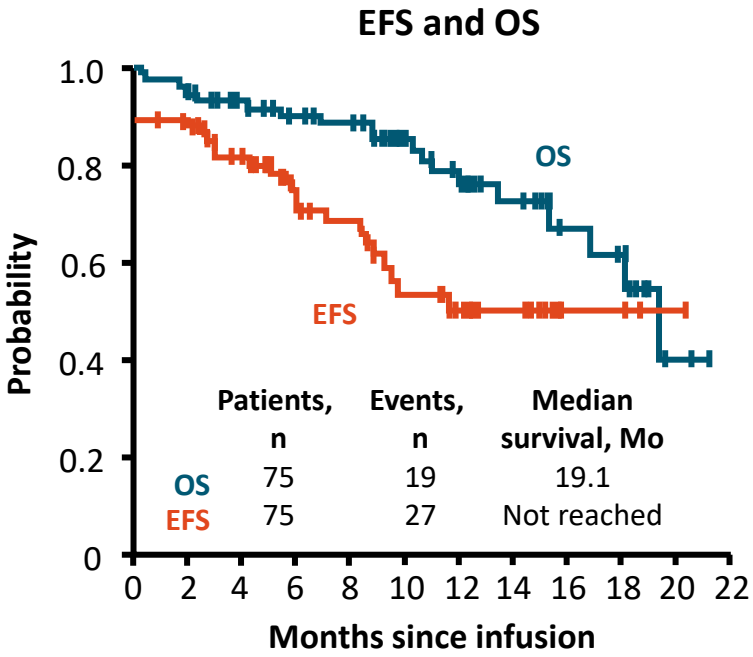
FDA-Approved CAR T-Cell Therapies in ALL in US

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**

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

- International, open-label, single-arm phase II study (N = 92)
  - Patients aged 3-21 yr with relapsed or refractory B-cell ALL
  - Patients underwent lymphodepletion with fludarabine + cyclophosphamide followed by single-dose tisagenlecleucel
  - At baseline: median number of prior therapies, 3; prior allogeneic SCT, 46%; median BM blast count at time of treatment, 74%
- **ORR at 3 mo: 81%**

Outcome, %	Mo 6	Mo 12
OS	90	76
Event-free survival	73	50



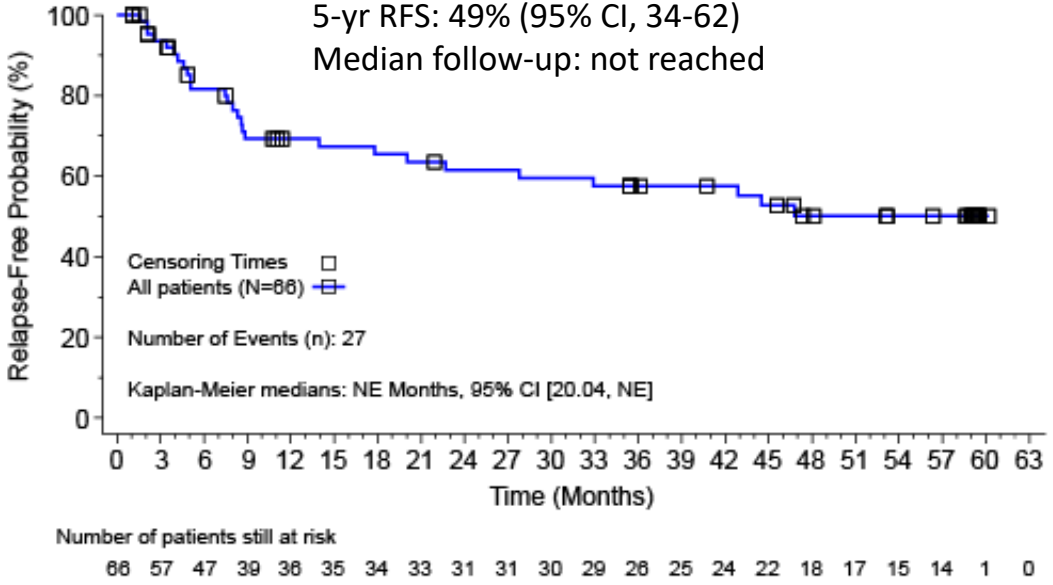
11% proceeded to HSCT

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

Final Data Analysis and Updated Results From ELIANA

Relapse-free survival

5-yr RFS: 49% (95% CI, 34-62)
Median follow-up: not reached



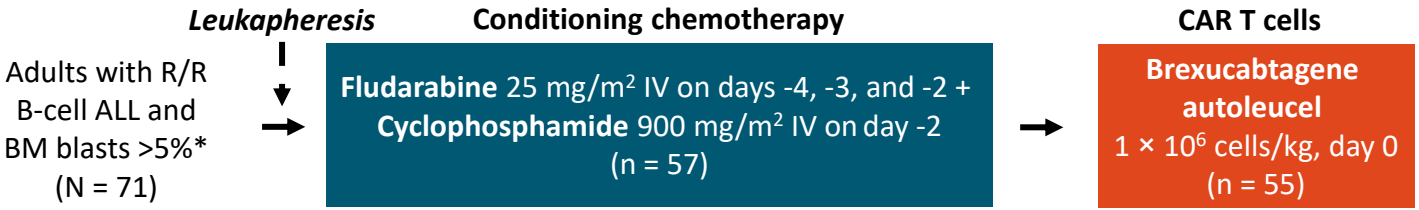
64 patients with >5 years of follow-up
- 5-yr EFS: 42% (95% CI, 29-54)
- 5-yr OS: 55% (95% CI, 43-66)

No difference in efficacy endpoint between pediatric (<18) vs AYA (≥18)

Rives S, et al. EHA 2022. Abstract S112.

ZUMA-3 (phase II): Brexucabtagene Autoleucel (KTE-X19) for Adults With Relapsed/Refractory ALL

- Multicenter, open-label phase I/II trial



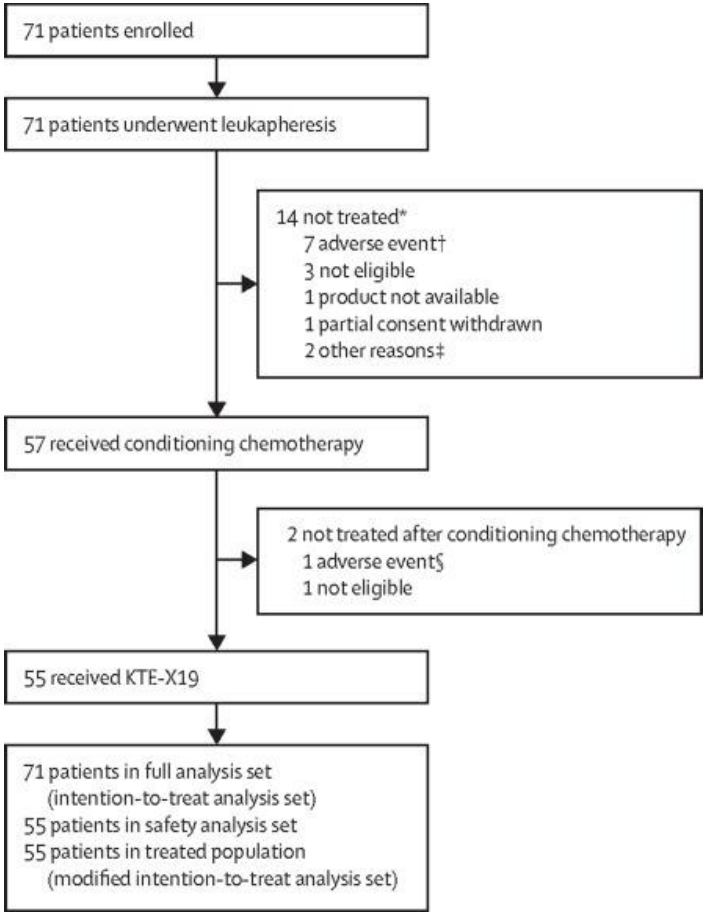
*Prior blinatumomab permitted.

- Primary endpoint: CR/CRi by central assessment
- Secondary endpoints: MRD negativity, DOR, RFS, OS, safety, CAR T-cell levels in blood, and cytokines in serum
- Median follow-up: 16.4 mo (range: 10.3–22.1)

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

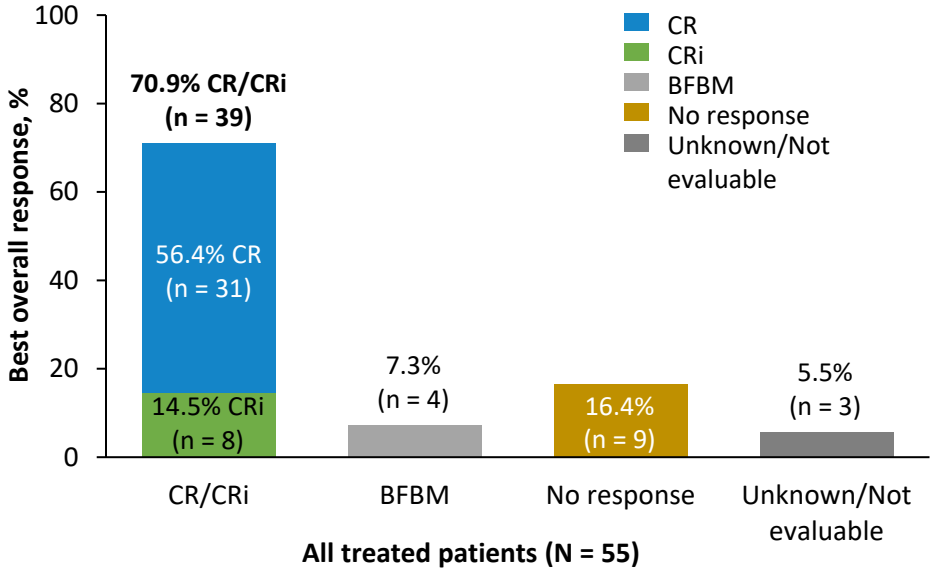
ZUMA-3 (phase II): Patients

- Brexucabtagene autoleucel successfully manufactured in 65 of 71 (92%) of patients; median time from leukapheresis to CAR T-cell delivery was 13 days in US and 14.5 days in Europe
- 55 of 71 patients (77.5%) received the infusion



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

ZUMA-3: Clinical Outcome



Covariates		Responding Patients/ Evaluable Patients	Percent of Patients With Response (95% CI)
Overall		39/55	71 (57–82)
Sex	Male	25/33	76 (58–89)
	Female	14/22	64 (41–83)
Age (years)	18-39	16/26	62 (41–80)
	40-64	15/21	71 (48–89)
	≥65	8/8	100 (63–100)
Baseline extramedullary disease	Yes	3/6	50 (12–88)
	No	36/49	73 (59–85)
CNS status at screening	CNS-1	34/47	72 (57–84)
	CNS-2	4/5	80 (28–99)
CD19 % lymphoblast baseline category based on central lab	≥95	29/41	71 (54–84)
	<95	9/12	75 (43–95)
% blasts in bone marrow at baseline	0–5	4/5	80 (28–99)
	>5–25	9/10	90 (55–100)
	>25–50	10/11	91 (59–100)
	>50–75	8/10	80 (44–97)
	>75–100	8/19	42 (20–67)
Philadelphia chromosome	Yes	12/15	80 (52–96)
	No	27/40	68 (51–81)

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

Two grade 5 events (neurotoxicity, sepsis): 3.6% TRM

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

Subgroup Analysis of Brexucabtagene Autoleucel by Prior Therapy

Table. Efficacy Results in Pooled Analysis of Phase 1 and 2 (N=78) by Independent Review

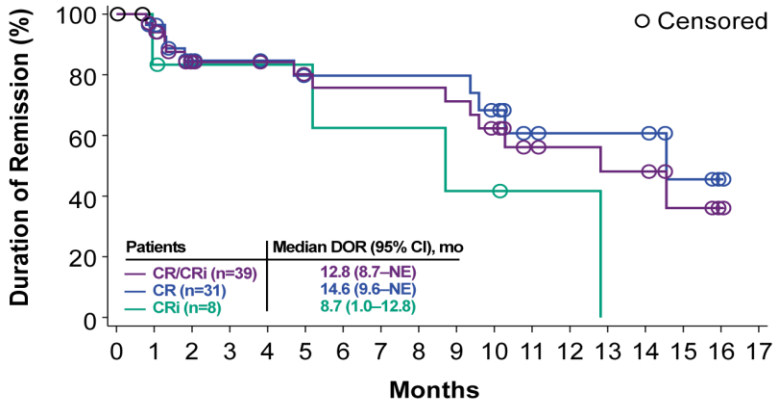
Subgroup	N	CR/CRi Rate (95% CI)	Median DOR (95% CI)	Median OS (95% CI)
Lines of prior therapy				
1	15	87% (60-98)	4.9 months (1.8-NE)	NR (7.6-NE)
≥2	63	70% (57-81)	20.0 months (10.3-NE)	25.4 months (15.9-NE)
Prior blinatumomab				
Yes	38	63% (46-78)	14.6 months (9.6-NE)	15.9 months (8.3-25.4)
No	40	83% (67-93)	18.6 months (5.2-NE)	47.0 months (18.6-NE)
Prior SCT				
Yes	29	76% (56-90)	14.6 months (8.7-23.6)	25.4 months (14.2-NE)
No	49	71% (57-83)	NR (5.2-NE)	47.0 months (10.9-NE)

CR, complete remission; CRi, complete remission with incomplete hematologic recovery; DOR, duration of remission; OS, overall survival; NE, not estimable; NR, not reached; SCT, stem cell transplant.

Shah B, et al. EHA 2022. Abstract P356.

ZUMA-3: Duration of Remission

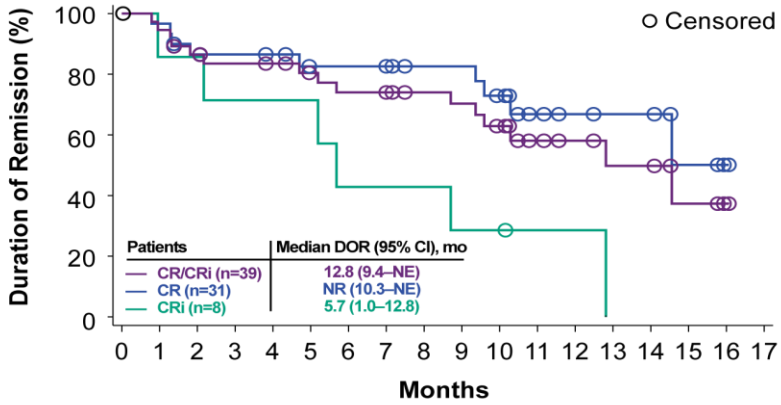
DOR with censoring at subsequent alloSCT



No. at Risk

CR	31	26	19	18	17	14	14	14	14	14	11	7	6	6	6	3	1	0
CRi	8	5	4	4	4	4	3	3	3	2	2	1	1	0	0	0	0	0
CR/CRi	39	31	23	22	21	18	17	17	17	16	13	8	7	6	6	3	1	0

DOR without censoring at subsequent alloSCT



No. at Risk

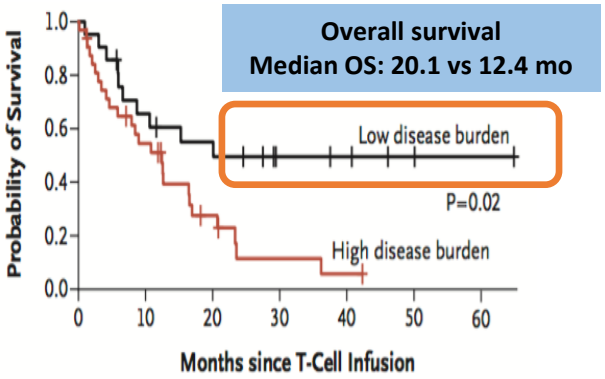
CR	31	29	25	24	23	20	20	19	17	17	14	9	7	6	6	3	1	0
CRi	8	6	6	5	5	5	3	3	3	2	2	1	1	0	0	0	0	0
CR/CRi	39	35	31	29	28	25	23	22	20	19	16	10	8	6	6	3	1	0

- Ten patients (18%), including 9 with CR/CRi and 1 with BFBM, received alloSCT at a median 98 days (range, 60–207) post–KTE-X19 infusion
- As of the data cutoff, 12 of 39 patients who achieved CR/CRi (31%) were in ongoing remission without alloSCT

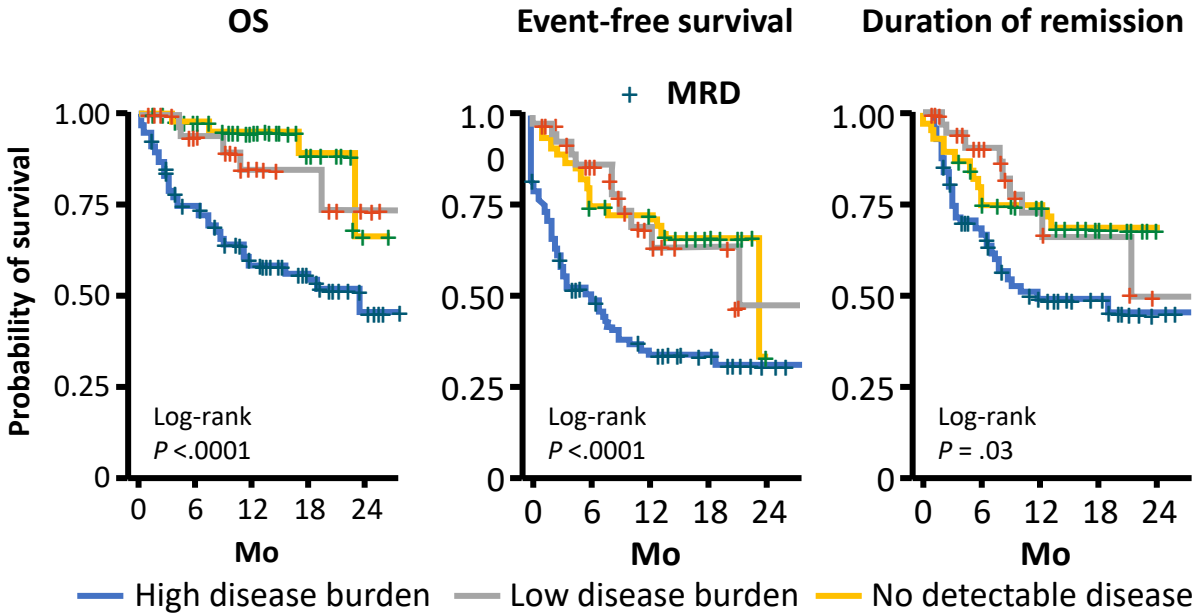
Shah B, et al. *Lancet*. 2021;398:491-502.

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

1928z CAR in adult ALL



Tisagenlecleucel in children and AYA R/R ALL

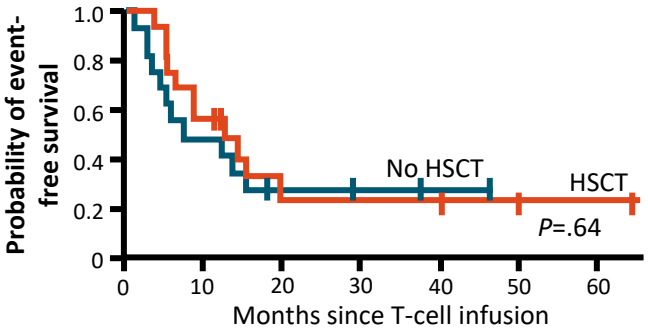


Park J, et al. *N Engl J Med.* 2018;378(5):449-459.

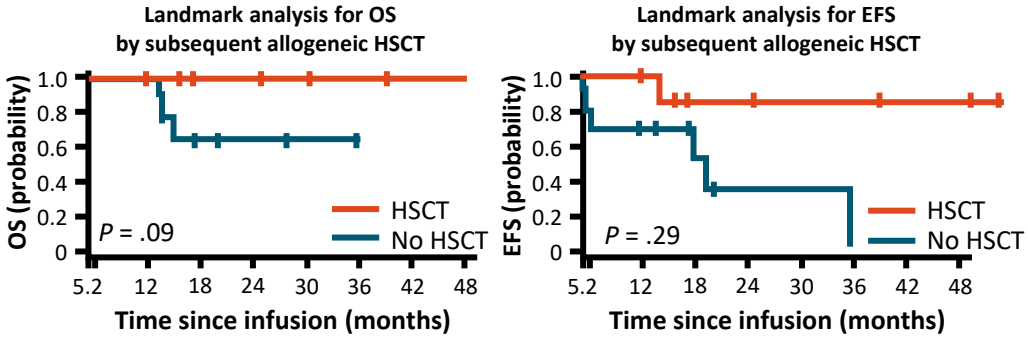
Schultz LM, et al. ASH 2020. Abstract 468.

Post-CAR HSCT in Adult ALL

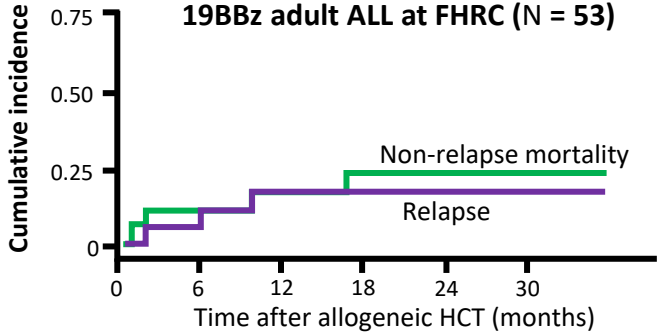
1928z adult ALL at MSK (N = 53)



CTL019 in adult ALL at UPenn (N = 35)



19BBz adult ALL at FHRC (N = 53)



~40% of responding pts proceeded to alloHSCT

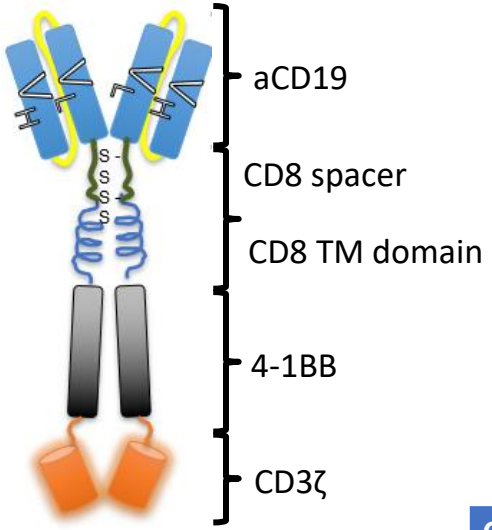
38% of responding pts proceeded to alloHSCT

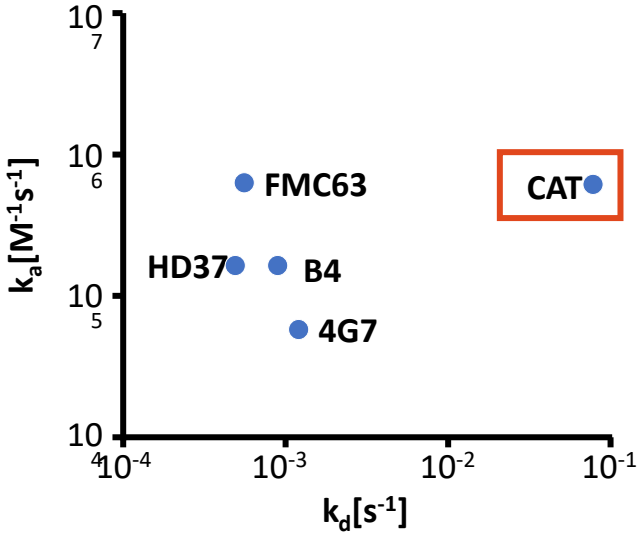
Variable	Multivariable Analysis		
	HR	95% CI	*P*
LDH pre-lymphodepletion (per 100 U/L increment)	1.39	1.11-1.73	.004
Platelets pre-lymphodepletion (per 50,000/µL increment)	0.74	0.53-1.03	.069
Fludarabine added to lymphodepletion	0.25	0.15-0.78	.003
HCT after CAR T-cell therapy	0.39	0.13-1.15	.088

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.

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

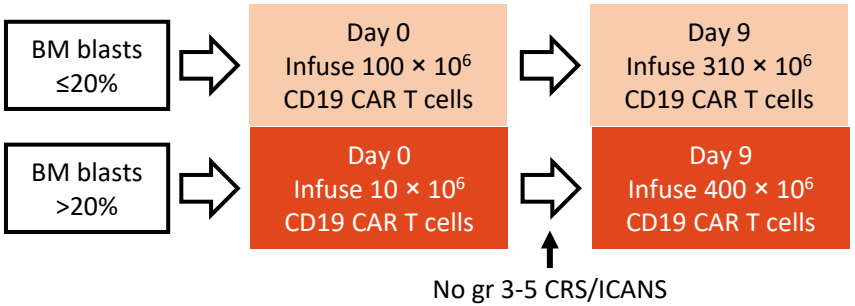




Clone	*ka* (1/Ms)	*kd* (1/s)	KD (M)
CAT	2.153E+5	0.003096	1.438E-8
FMC63	2.076E+5	6.810E-5	3.280E-10

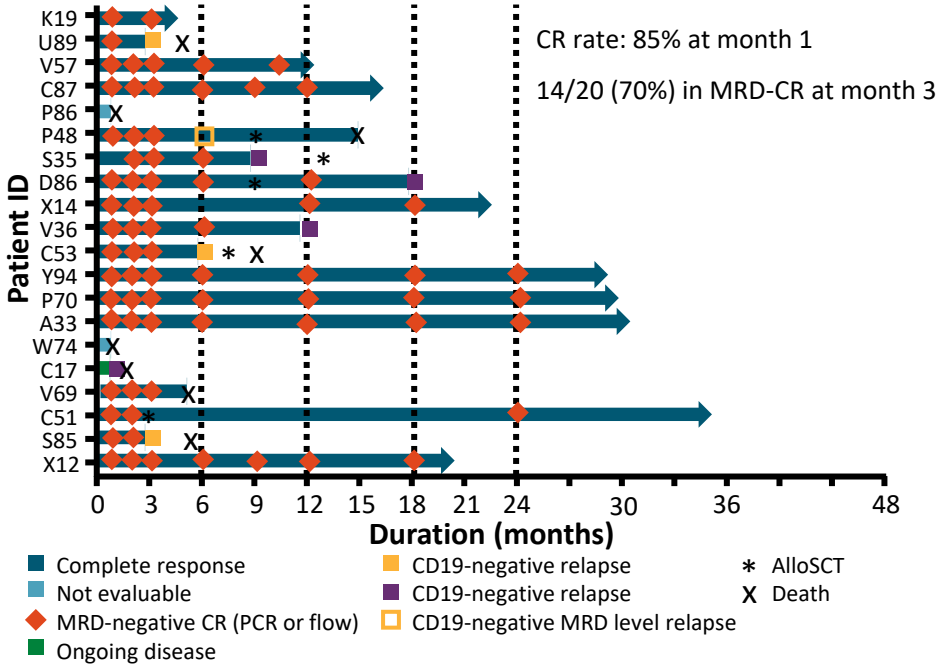
Roddie C, et al. ASH 2019. Abstract 226.

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.

Summary

- CD19 CAR T-cell therapy is the most potent single-agent therapy in ALL
  - 80% CR/CRi in R/R B-ALL regardless of BM blasts and prior therapy including EMD vs blinatumomab with lower overall CR rates and less efficacy in EMD
  - One-time treatment, a single infusion of cells
  - A subset of patients can achieve durable remissions w/o HSCT
- Lower-disease-burden patients appear to gain the most clinical benefit, with long-term remission and lowest toxicity
  - More opportunity to modify the disease to achieve low burden in earlier lines of tx when disease is most chemo-sensitive
- Toxicity profiles of CAR and management strategies are improving
- Further genetic modifications to enhance efficacy and safety of CARs to make it more definitive therapy. It's just a beginning!

Why should we save the best therapy for the last?

Please vote

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

A. CAR T therapies

B. Monoclonal antibodies or bispecifics

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Global Leukemia Academy

Changing Landscape of Treatment Options in Pediatric and AYA ALL

Stephen Hunger

APTITUDE HEALTH

Changing Landscape of Treatment Options in Pediatric and AYA Acute Lymphoblastic Leukemia

Global Leukemia Academy

December 5, 2022

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Disclosures

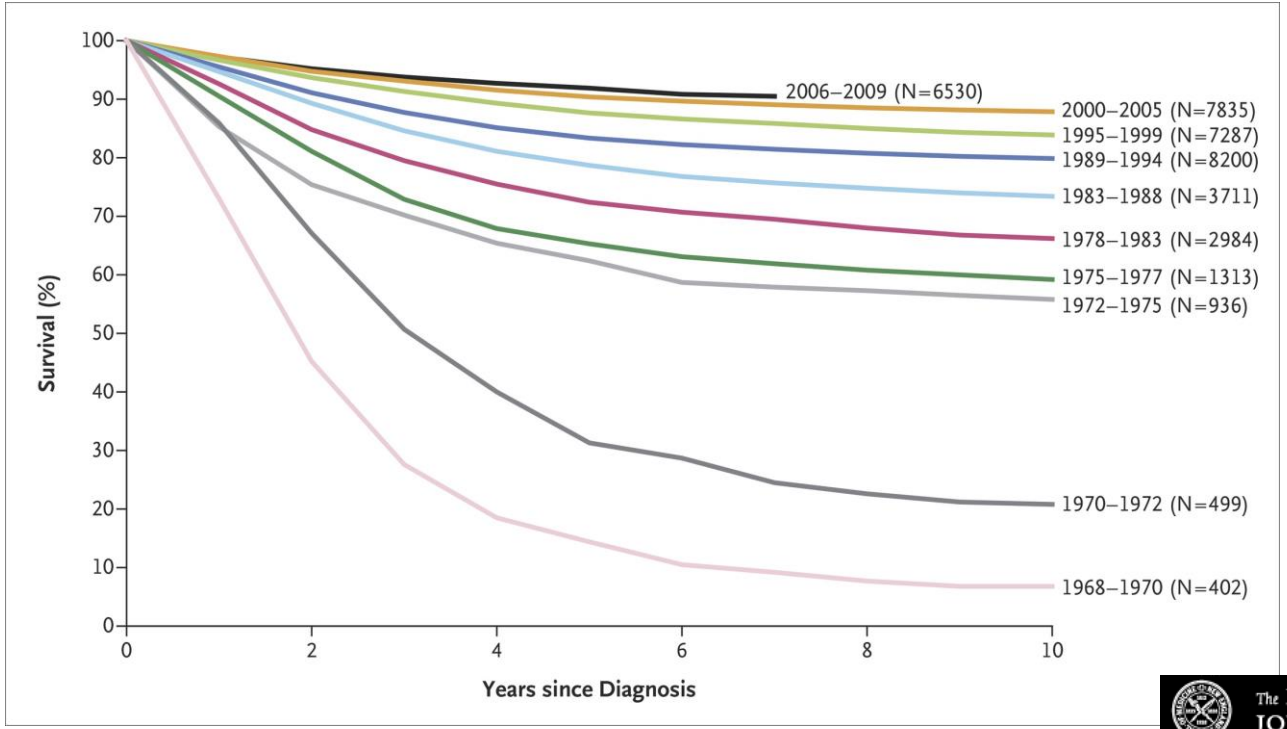
- Stock ownership
  - Amgen
- Honoraria/consulting fees
  - Amgen, Jazz Pharmaceuticals, Novartis, Servier
  - Dr Hunger will receive an honorarium for this presentation

Children's Oncology Group ALL Trials

- Only National Cancer Institute (NCI)-sponsored pediatric cooperative group
- ~220 member institutions in the US, CA, AUS, and NZ
  - 90%–95% of enrolled patients reside in the US
- About 2000 newly diagnosed ALL patients enroll in COG ALL trials each year
- About two-thirds of US ALL cases among those 0–19.99 years old enroll in a COG ALL trial
  - ~70% of those 0–14.99 years old
  - ~50% of those 15–19.99 years old

Hunger SP, et al. *J Clin Oncol.* 2012;10;30(14):1663-1669.

Improved Survival in Childhood ALL
CCG/COG Trials 1968–2009 (n = 39,697)



The NEW ENGLAND JOURNAL of MEDICINE

Hunger SP, et al. *N Engl J Med*. 2015;373:1541-1552.

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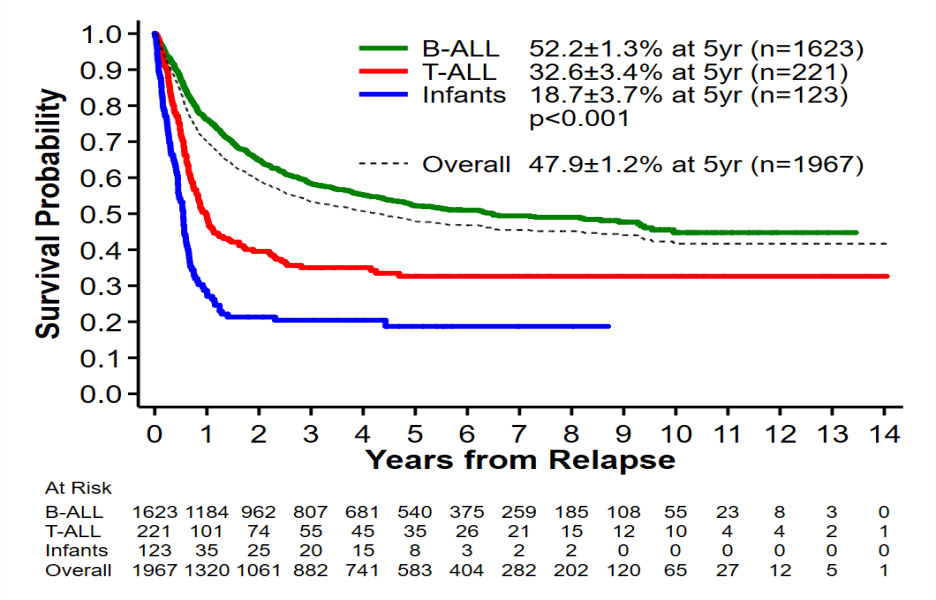
Chemotherapy Agents Used in Childhood ALL: Year of FDA Approval

Agent	Year Approved by FDA
6-Mercaptopurine	1953
Methotrexate	1953
Prednisone	1955
Dexamethasone	1958
Cyclophosphamide	1959
Vincristine	1964
Cytarabine	1969
L-asparaginase	1978
Daunorubicin	1979

ALL: Survival Following Relapse Remains Poor



- 15,874 pts enrolled in 10 COG trials between 1996–2004
- 1967 (12%) of these pts relapsed
- Graph shows survival post-relapse

Limited improvement over time with chemotherapy intensification and HSCT

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

Major Questions in Pediatric ALL

- How do we increase cure rates?
  - Decrease relapse rates and treatment-related mortality in newly diagnosed ALL
  - Improve cure rates for relapsed ALL
- How do we optimize therapy for patients highly likely to be cured to minimize short- and long-term adverse effects?
- How do we operationalize delivery of curative therapies worldwide?
  - Different strategies likely needed for middle- and upper–middle-income countries and resource-limited low-income countries

ALL: Risk Factors and Treatment Stratification

- Clinical
  - Age, initial white blood cell count (WBC), central nervous system (CNS) status
- Immunophenotype (85% B-ALL and 15% T-ALL in children and AYA)
  - Historically, T-ALL outcomes inferior in pediatrics
- Treatment response
  - Assessed by minimal residual disease (MRD) levels at end induction (EOI) and end of consolidation (EOC)
- Sentinel genetic lesions
  - Ploidy (chromosome number)
  - Structural rearrangements, particularly chromosome translocations
  - Point mutations
- COG risk-stratification systems use a combination of clinical features, immunophenotype, MRD, and sentinel genetic lesions to classify patients into different risk groups (others use similar systems)
  - Different treatment backbones for different groups
  - Different randomized questions in different groups
  - Identify small high-risk patient subsets to test precision medicine therapies

ARTICLE

ACUTE LYMPHOBLASTIC LEUKEMIA

Outcomes in adolescent and young adult patients (16 to 30 years) compared to younger patients treated for high-risk B-lymphoblastic leukemia: report from Children's Oncology Group Study AALL0232

Michael J. Burke[1✉], Meenakshi Devidas[2], Zhiguo Chen[3], Wanda L. Salzer[4], Elizabeth A. Raetz[5], Karen R. Rabin[6], Nyla A. Heerema[7], Andrew J. Carroll[8], Julie M. Gastier-Foster[6], Michael J. Borowitz[9], Brent L. Wood[10], Naomi J. Winick[11], William L. Carroll[5], Stephen P. Hunger[12], Mignon L. Loh[13] and Eric C. Larsen[14]

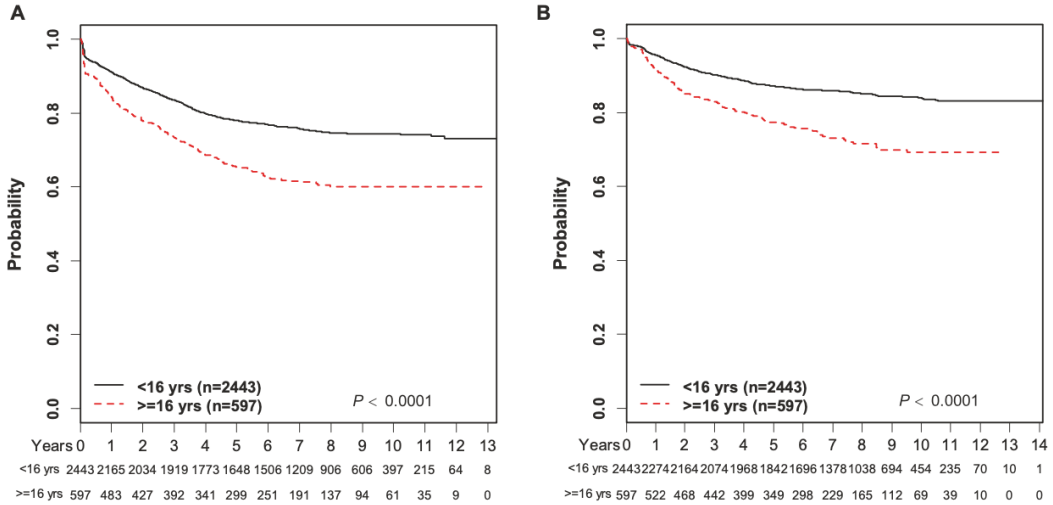
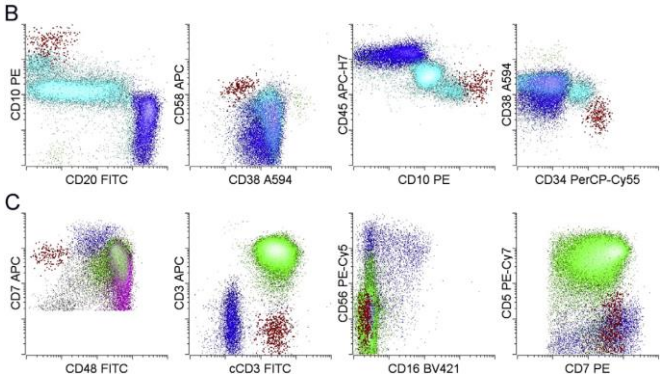
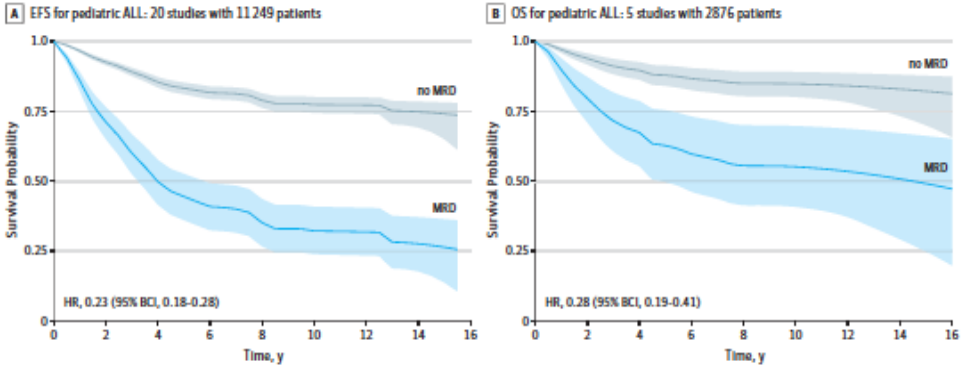


Fig. 2 5-year Event-Free Survival and Overall Survival rates for AYA and younger patients with High-Risk BALL treated on COG AALL0232. **A** EFS for <16 vs. ≥16 years old; 5-year EFS: 78.1 ± 0.9% vs. 65.4 ± 2.2%; **B** OS for <16 vs. ≥16 years old; 5-year OS: 87.3 ± 0.7% vs. 77.4 ± 2.0%.

Minimal Residual Disease (MRD) in ALL



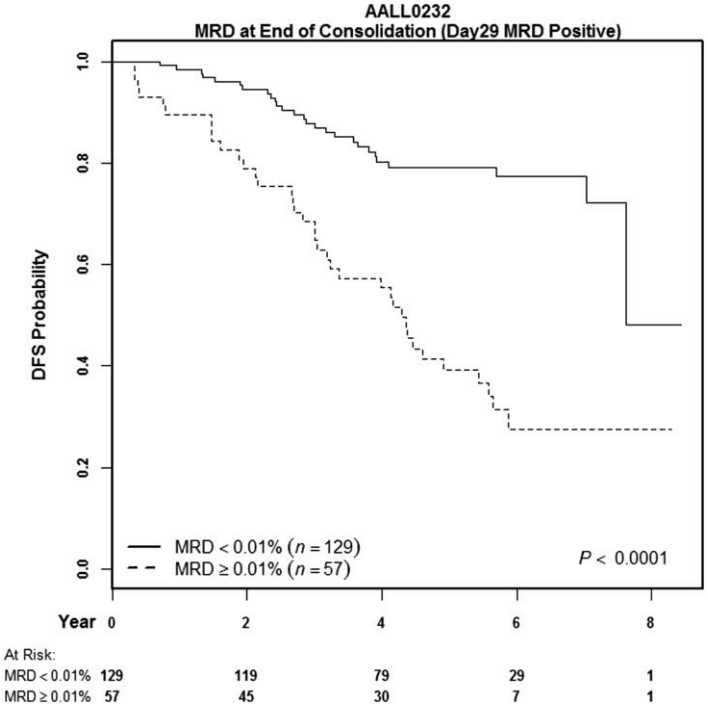
Measurement of MRD via flow cytometry in B-ALL (B) and T-ALL (C)[1]



Hazard ratio of 0.23 (EFS) and 0.28 (OS) for MRD-negative vs -positive patients means that MRD-positive patients have ~4-fold higher risk of relapse or death than MRD-negative patients[2]

1. Chen X, Wood B. *Blood Rev.* 2017;31(2):63-75;
2. Berry DA, et al. *JAMA Oncol.* 2017;3(7):e170580.

End-of-Consolidation MRD Predicts Outcome in High-Risk B-ALL: COG AALL0232



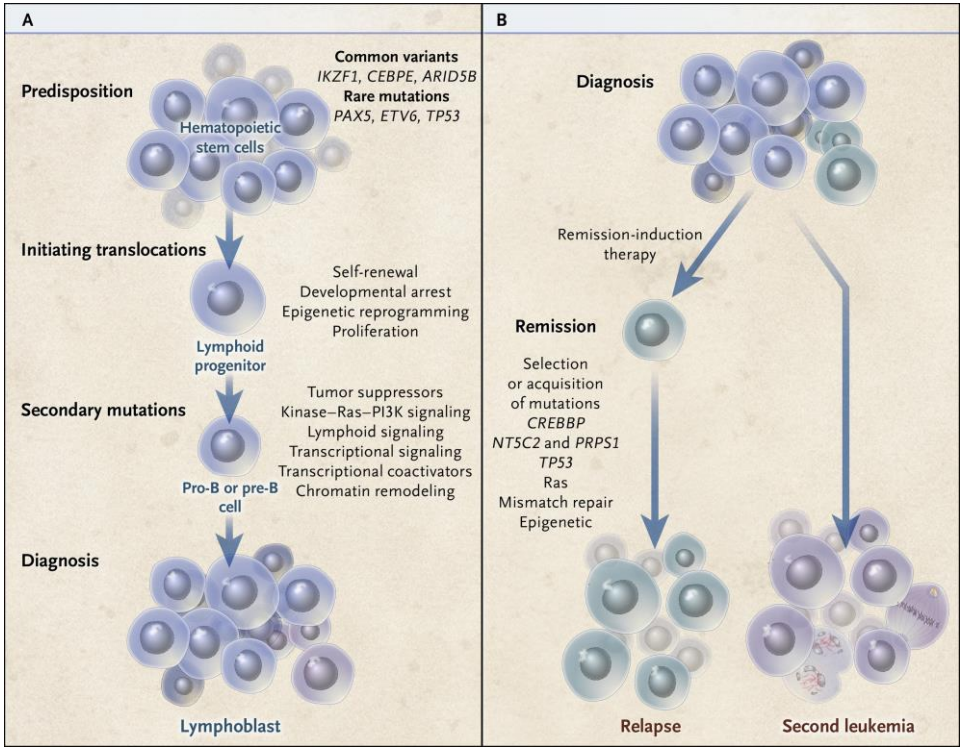
Day 29 MRD ≥0.1%

5-year DFS by EOC MRD
MRD <0.01%: 79% ± 5%
MRD ≥0.01%: 39% ± 7%

Most EOI MRD+ patients become MRD– at EOC. Those with EOI MRD ≥1% have about a 50% chance of being MRD+ at EOC

Borowitz MJ, et al. *Blood.* 2015;126(8):964-971.

Sequential Acquisition of Genetic Alterations Contributes to ALL Pathogenesis and Relapse



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Sentinel Genomic Alterations in ALL: The Classics

ALL Subtype	Details	Category	Frequency (peds)	Prognostic Import
Hyperdiploid	N >50–53 and/or favorable trisomies	Aneuploidy	20%–25% Decreases with age	Excellent
Hypodiploid	N <40–43	Aneuploidy	1.5% Increases with age	Poor
t(9;22)(q34;q11.2)/Ph^{+}	*BCR-ABL1*	Kinase driven	3%–5% Increases with age	Poor pre-TKI
t(1;19)(q23;p13.3)	*TCF3* (*E2A*)-*PBX1*	TF rearrangement	Increased in Blacks	Neutral
t(11q23;V)	*KMT2A* (*MLL*)-R	TF rearrangement	70% infants 2%–5% children	Poor
t(17;19)(q23;p13.3)	*TCF3* (*E2A*)-*HLF*	TF rearrangement	<1%	Very poor
t(12;21)(p13;q22)	*ETV6-RUNX1* (*TEL-AML1*)	TF rearrangement	20%–25% Decreases with age	Excellent
Intrachromosomal amplification of chromosome 21 (iAMP21)	≥4 copies *RUNX1* on abnml chr 21	Copy number gain	2%–3%	Poor/Neutral

Genotype Predicts Outcome of B-ALL With Current Therapy

Outcomes based on NCI risk group and leukemia cytogenetics

Table 1. Genotypic features of 8,133 children enrolled on AALL03B1 (5-year EFS and OS in %)

NCI RG	TT		*ETV6/RUNX1*		*E2A/PBX1*		*MLLr*		iAMP21		*BCR/ABL1*		Hypodiploidy	
	%N	EFS OS	%N	EFS OS	%N	EFS OS	%N	EFS OS	%N	EFS OS	%N	EFS OS	%N	EFS OS
SR	24.7	95.7 99.0	30.6	93.7 98.2	4.0	83.7 89.7	1.1	80.6 87.2	1.4	67.0 88.3	1.2	85.4 95.0	0.9	59.1 66.5
HR	12.2	88.7 94.2	14.0	86.6 95.3	7.2	82.5 88.7	3.9	69.3 80.1	2.9	74.6 88.7	5.0	51.7 66.2	2.9	46.8 53.4
Total	20.5	94.3 98.0	25.1	92.8 97.7	5.1	83.1 89.2	2.0	73.2 82.5	1.9	71.0 88.5	2.6	62.2 75.2	1.6	51.3 58.2

t(17;19) and *TCF-HLF* also associated with dismal outcome but too rare to be formally included in most risk-stratification schemas

Loh ML, et al. ASH 2016. Abstract 451.

How Do We Increase Cure Rates?

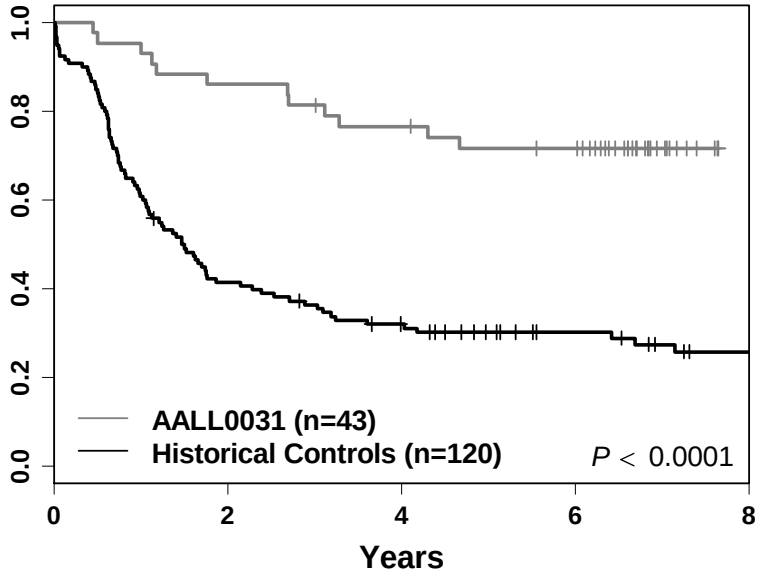
- Optimize risk-stratification to identify high-risk patients
- Test new treatment regimens
  - Cytotoxic chemotherapy: marginal benefits
  - Apply precision medicine (“targeted”) therapies
  - New immunotherapies

Improved Early Event-Free Survival With Imatinib in Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia: A Children's Oncology Group Study

Kirk R. Schultz, W. Paul Bowman, Alexander Aledo, William B. Slayton, Harland Sather, Meenakshi Devidas, Chenguang Wang, Stella M. Davies, Paul S. Gaynon, Michael Trigg, Robert Rutledge, Laura Burden, Dean Jorstad, Andrew Carroll, Nyla A. Heerema, Naomi Winick, Michael J. Borowitz, Stephen P. Hunger, William L. Carroll, and Bruce Camitta

VOLUME 27 · NUMBER 31 · NOVEMBER 1 2009

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT



7-yr EFS

AALL0031c5: **72%**

POG ALinc 14–16: **27%**

CHILDREN'S ONCOLOGY GROUP

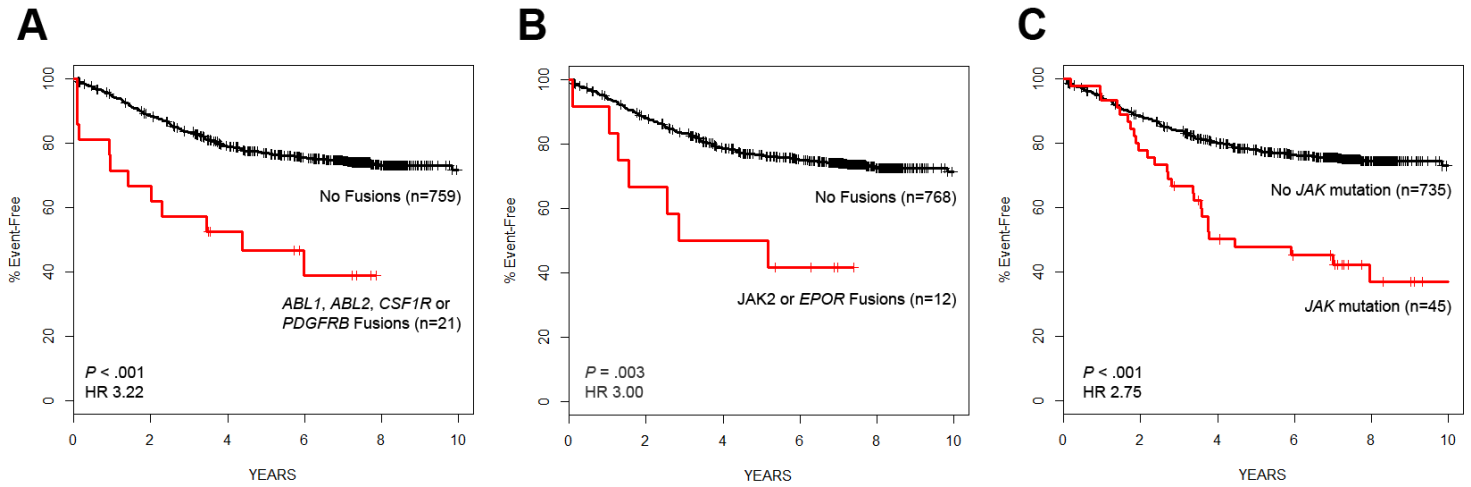
The world's childhood cancer experts

Schultz KR, et al. *J Clin Oncol.* 2009;27(31):5175-5181;
Schultz KR, et al. *Leukemia.* 2014;28(7):1467-1471.

Philadelphia Chromosome-Like B-ALL
Ph-like or BCR-ABL1–like

- Described independently by 2 groups
  - COG/St. Jude: Mullighan CG, et al. *N Engl J Med.* 2009;360:470-480 and Harvey RC, et al. *Blood.* 2010;116(23):4874-4884
  - DCOG: Den Boer M, et al. *Lancet Oncol.* 2009;10(2):125-134
- Defined by a gene expression profile similar to that of Ph+ ALL (without *BCR-ABL1* fusion) and showing activated kinase signaling
  - Gene expression profile of Ph-like ALL clusters with Ph+ ALL and is also identified by unsupervised clustering in cohorts lacking Ph+ cases
- Ph-like ALL is a heterogeneous leukemia subtype with a diverse variety of driver mutations
  - *The underlying mutations, not the gene expression profile, are the critical entities for diagnosis, prognosis, and precision medicine therapies*

Ph-Like ALL: Genomic Features and Outcome in HR B-ALL



- HR B-ALL with targetable ABL-class fusions (*ABL1*, *ABL2*, *CSF1R,* and *PDGFRB*) have extremely poor outcomes
  - ABL class fusions phenocopy BCR-ABL in vitro
- Other potentially targetable fusions (*JAK2* and *EPOR*) have similarly poor outcomes
- HR B-ALL with *JAK* point mutations have similarly dismal responses

Data from COG AALL0232.

Activated: 07/28/17 Version Date: 07/15/2021
Closed: Amendment 4

CHILDREN'S ONCOLOGY GROUP

AALL1631

International Phase 3 trial in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) testing imatinib in combination with two different cytotoxic chemotherapy backbones.

An EsPhALL Intergroup Phase 3 Study with COG Participation
Coordinating Center: EsPhALL, University of Milano-Bicocca

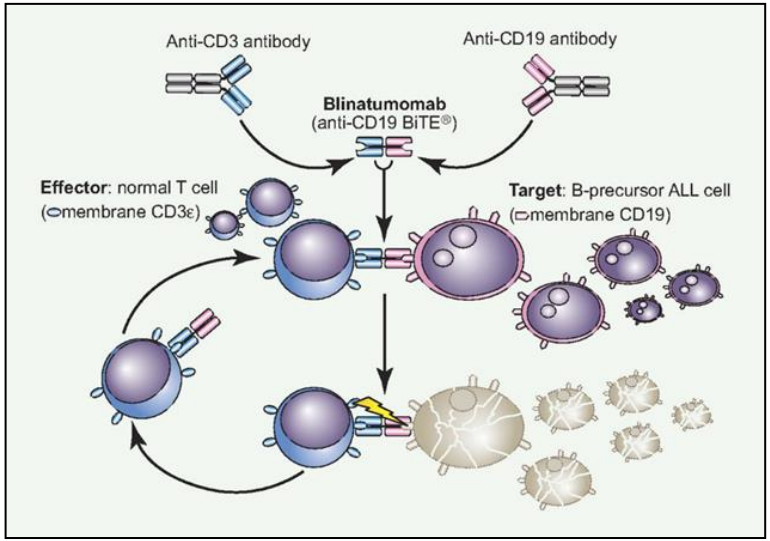
1.2 Secondary Aims

1.2.1 To compare DFS of SR pediatric Ph+ and ABL-class fusion positive ALL patients treated with continuous imatinib combined with either a high-risk COG-ALL chemotherapy backbone or the more intensive EsPhALL chemotherapy backbone.

New Immunotherapies

- Three immunotherapies are highly active in relapsed and refractory (R/R) ALL. What is their role in newly diagnosed ALL?
  - Blinatumomab
  - Inotuzumab
  - Chimeric antigen receptor (CAR) T cells
- Each is very expensive. If effective, how will they be affordable worldwide?

Blinatumomab

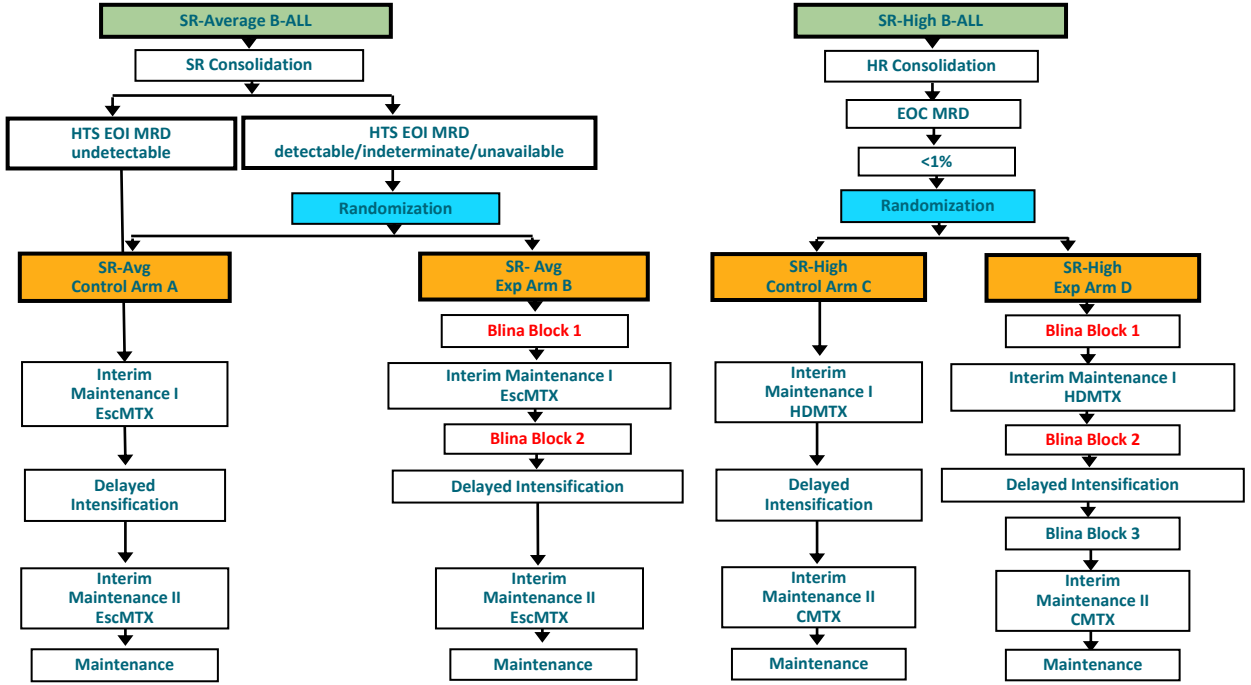


Adapted from Brown P. *Blood.* 2018;131:1497–1498.

- Bispecific T-cell engager (BiTE) antibody that links CD3+ T cells to CD19+ cells, enabling killing of the CD19+ cells by the patient's own cytotoxic T cells
- Given by continuous 28-day infusion
- Side effect profile very different from cytotoxic chemotherapy
  - Causes lymphopenia but little anemia, thrombocytopenia, or neutropenia
  - Very low incidence of serious infections
  - Unique CNS toxicities including hallucinations and seizures

COG AALL1731: SR B-ALL Trial

Opened to Accrual June 2019



Backbone therapy

- 1 DI and 2 IM phases
- Maint length same for boys and girls
- Every-12-week pulses

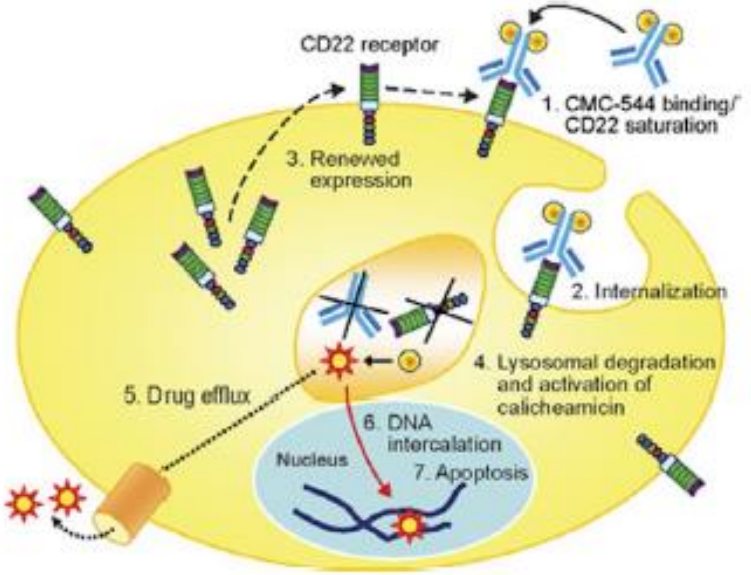
Randomized question

- ±2 courses blina
- SR backbone for SR-Avg
- HR backbone for SR-high (D29 MRD >0.01% or adverse genetics)

SR-low

- Standardized less-intensive therapy

Inotuzumab Ozogamicin (InO)

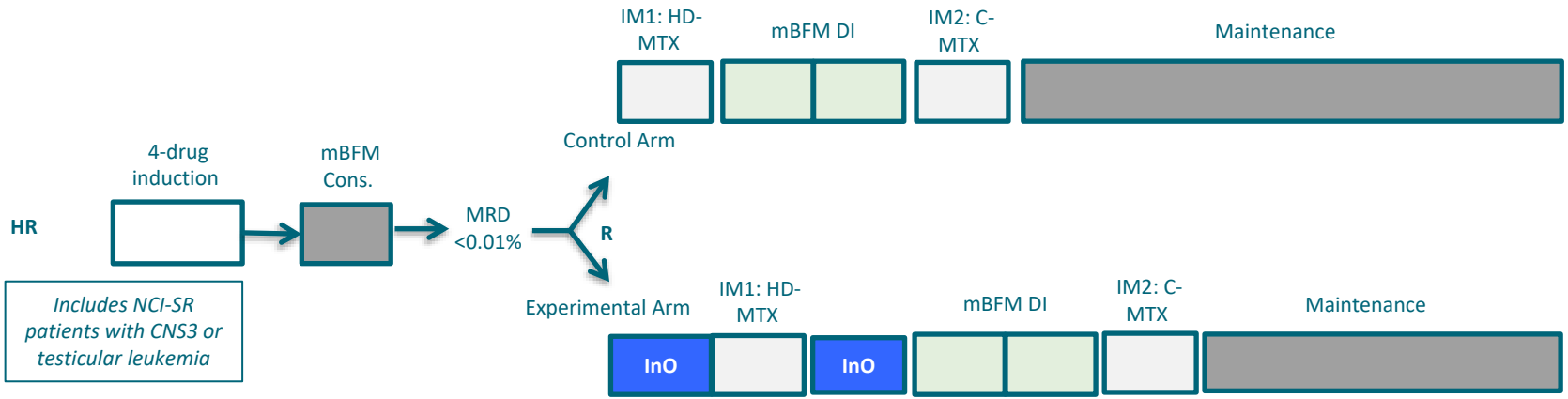


- CD22 expressed universally on B-ALL
- InO is a humanized IgG4 anti-CD22 antibody conjugated to calicheamicin
- Binds to CD22, internalized, and calicheamicin is released
- Given via IV infusion over 1 hour on day 1, 8, and 15 of a 4-week cycle

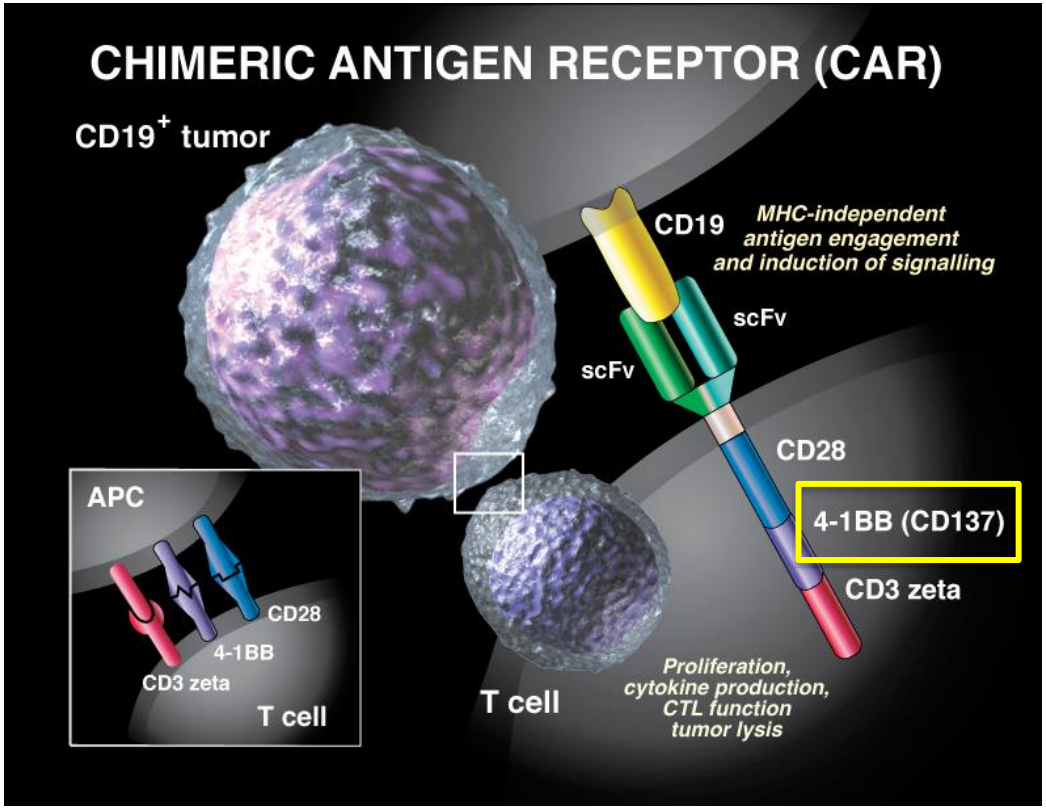
Thota S, Advani A. *Eur J Haematol.* 2017;98(5):425-434.

COG AALL1732 HR B-ALL Trial: Design

Testing InO in Newly Diagnosed ALL



CART19: Chimeric Antigen Receptor T Cells Targeting CD19



COG AALL1721/CTL019G2201J (CASSIOPEIA): Tisagenlecleucel in Very-High-Risk B-ALL

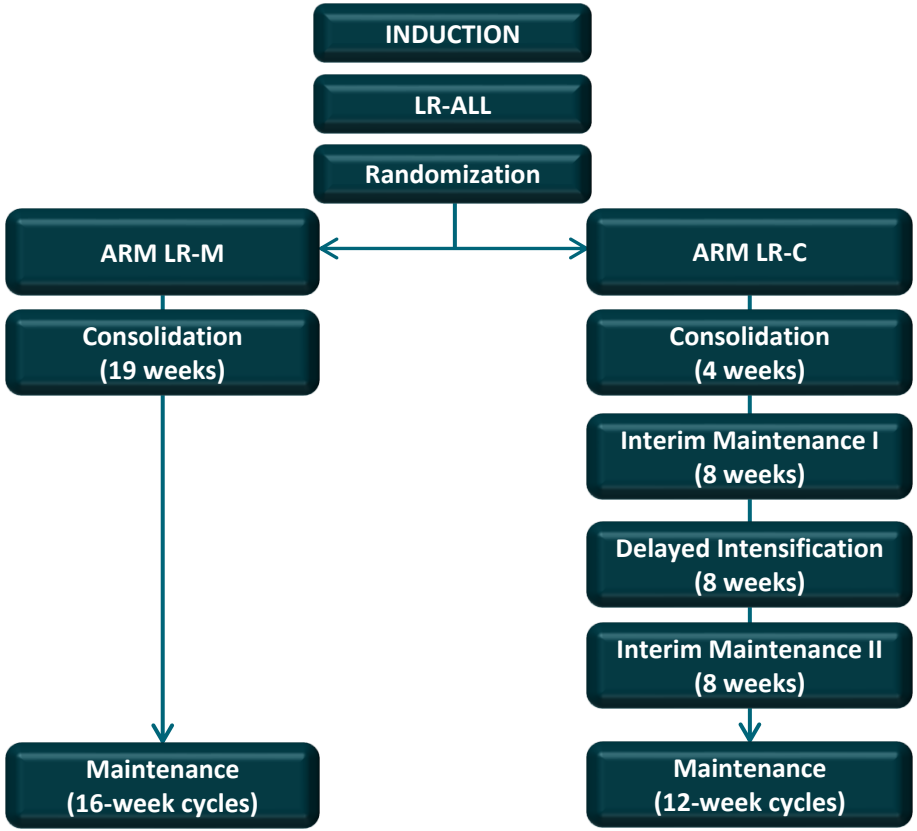
- Eligibility
  - NCI HR ALL with MRD >0.01% at end of consolidation therapy
    - 2%–3% of B-ALL patients
- Primary endpoint
  - 5-yr DFS >55% (compared with 39% for EOC MRD+ historical control)
- Key secondary endpoints
  - OS
  - Quality of life
  - MRD conversion rate
  - Rate of BMT

How Do We Optimize Therapy for Curable Patients?

- Using clinical features, tumor genetics, and MRD we can identify patient subsets almost certain to be cured
  - These children account for 25%–50% of those with pediatric ALL
  - Many, perhaps most, could be cured with less therapy
  - These children may have 70–80 years of future life
- How do we optimize identification of low-risk ALL patients and maintain outstanding cure rates, while decreasing short- and long-term adverse effects of therapy?

AALL0932: Low-Risk (LR) Randomization

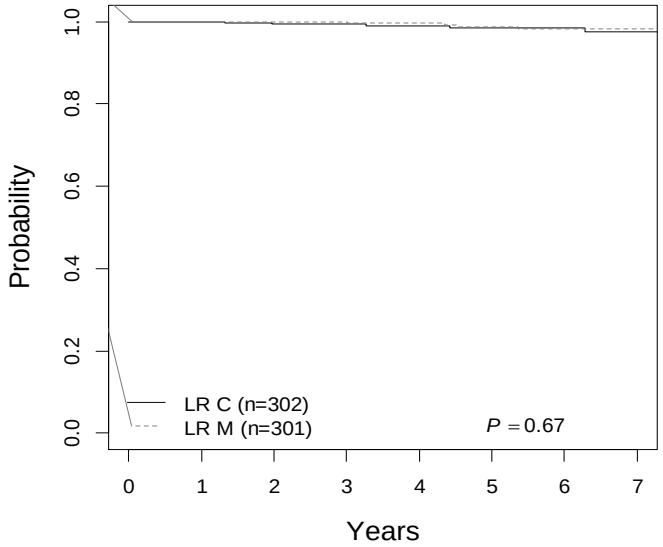
- Low risk is ~15%–20% of SR B-ALL
- CNS1 (no CNS leukemia)
- No steroid pretreatment
- *ETV6/RUNX1* or double trisomies of chromosomes 4 and 10
- Day 8 peripheral blood and day 29 bone marrow MRD both <0.01%
- Following induction randomized to
  - POG intermediate-dose MTX-based regimen (LR-M)
  - COG BFM-based regimen (LR-C)



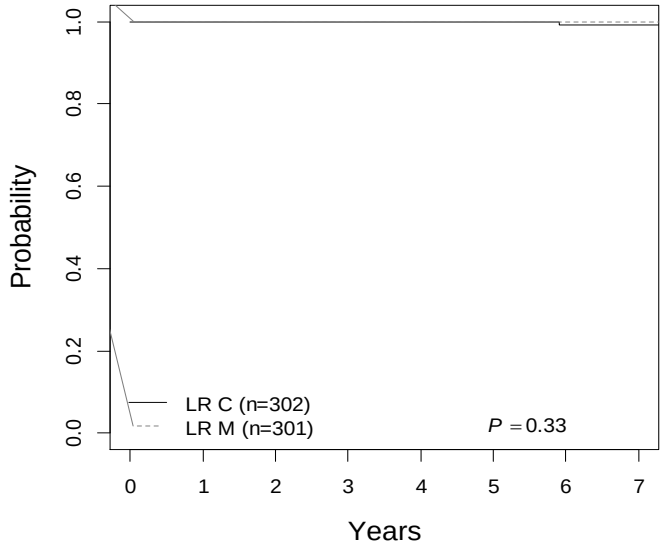
Schore, Submitted.

AALL0932 Low-Risk Randomization Results

5-yr disease free survival [DFS] (±SE): LR-M 98.8% (±0.8%); LR-C 98.5% (±0.9%)



5-yr overall survival (OS): 100% for both arms



Schore, Submitted.

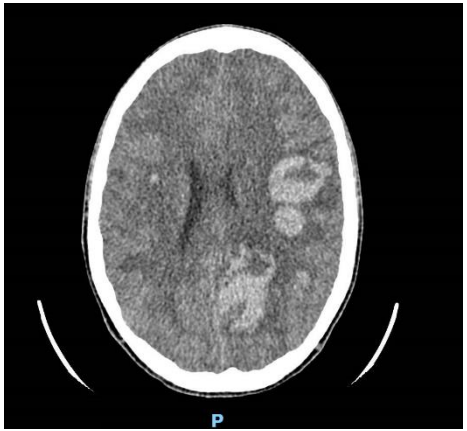
Global Leukemia Academy

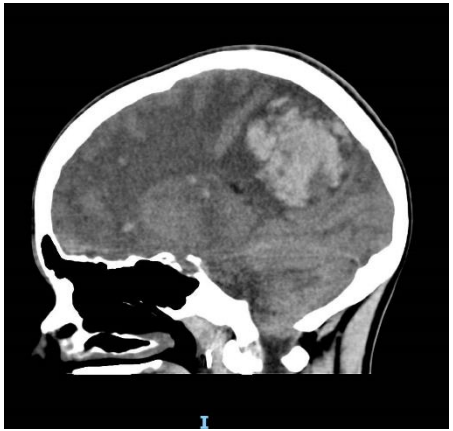
AYA Patient Case Discussion and Debate: The Evolving Concept of Transplantation in AYA

Michael Osborn and Marcos de Lima

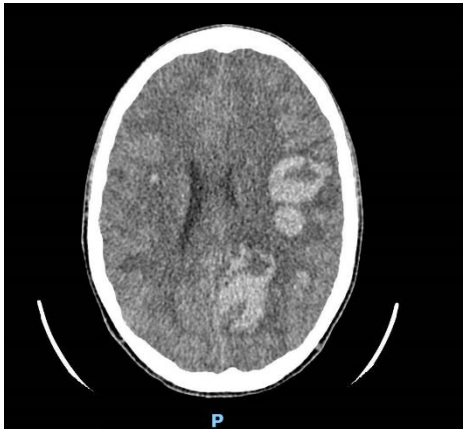
APTITUDE HEALTH

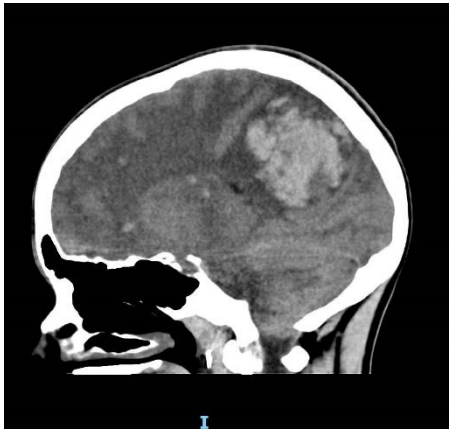
16-Year-Old Male With Intracranial Hemorrhage

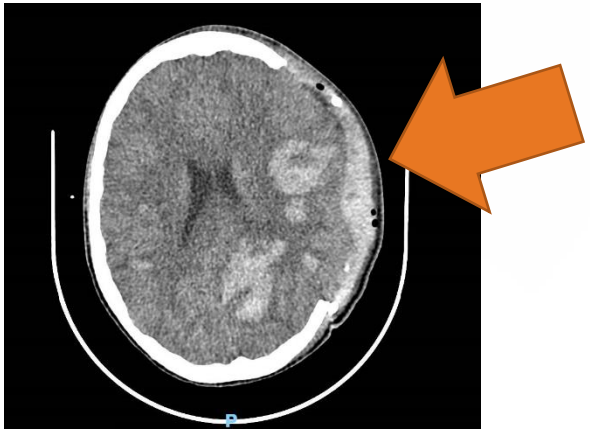




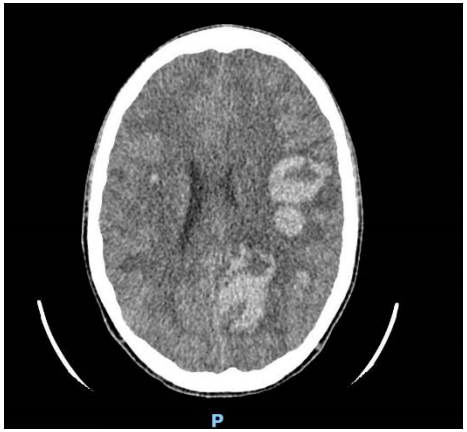
16-Year-Old Male With Intracranial Hemorrhage

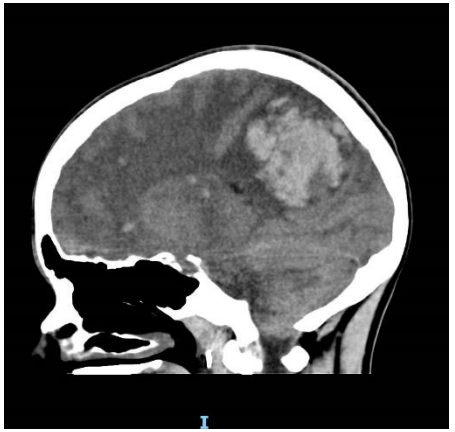


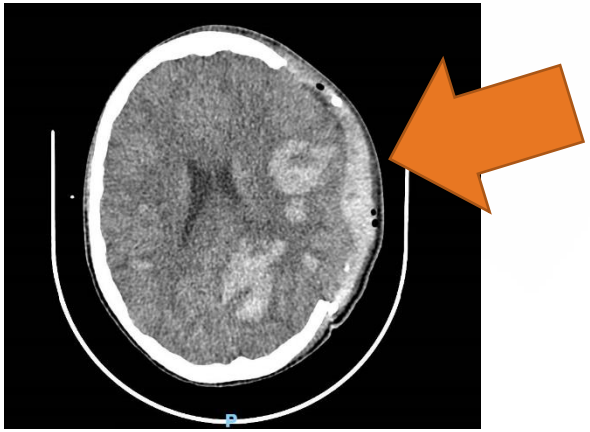


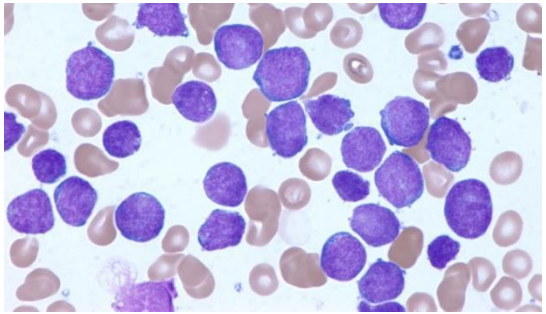


16-Year-Old Male With Intracranial Hemorrhage



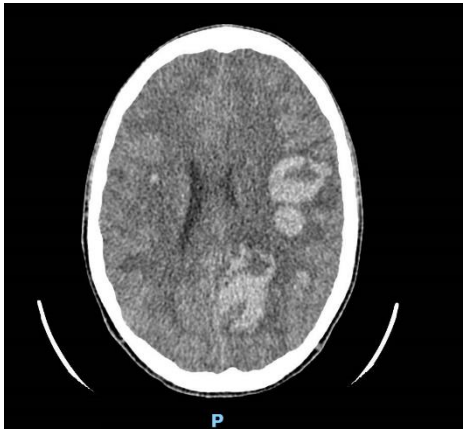


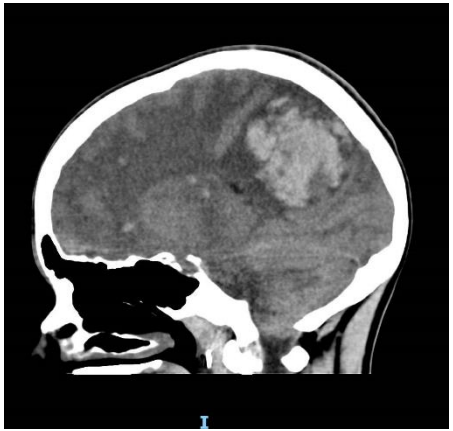


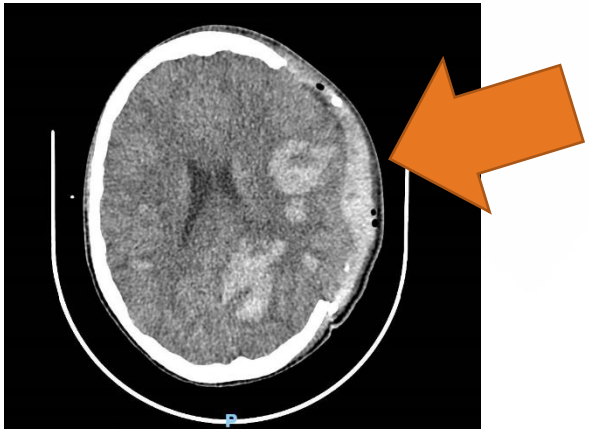


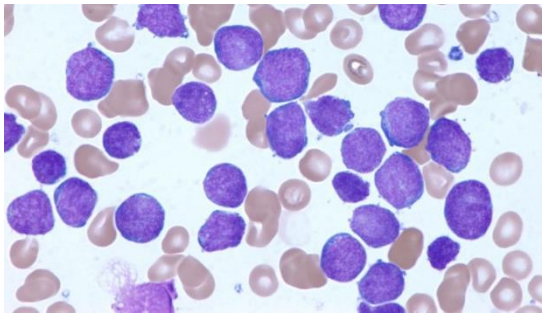
> Hb 39, Plts 21, WCC 462, 97% blasts

16-Year-Old Male With Intracranial Hemorrhage









- Hb 39, Plts 21, WCC 462, 97% blasts
- Immunophenotype
  - CD19+ CD10– CD20– CD22+(dim) CD34+ CD38+ CD81+(dim) CD123+(dim) CD45+ sIg– TdT+ cCD79a+ cCD3– MPO–
- Cytogenetics
  - t(4;11) and isochromosome 7q and 12p

Indications for HSCT in ALL

TABLE 2 | Current indications for hematopoietic stem cell transplant (HSCT) by the cooperative study group.

B-ALL Newly Diagnosed	**COG**	**BFM-AIEOP**	**ALLTogether1**
Hypodiploid ALL	Positive EOC-MRD	Positive EOC-MRD	As below, according to MRD
Induction Failure	Positive EOC-MRD	Positive EOC-MRD	
Positive MRD	NCI HR: EOC MRD any value NCI SR: EOC MRD ≥1%	All PCR-MRD ≥5×10^{-4} at EOC	*All patients ≤ 18 years of age:* MRD ≥0.05% at EOC (TP2) or MRD ≥5% at EOI (TP1) and ≥0.5% mid-consolidation day 50 (TP1.5) unless targeting for CASSIOPEIA MRD re-appearance (early B-cell recovery following CAR T cell (re-)infusion in CASSIOPEIA *Additionally, in patients ≥16 years at diagnosis:* MRD at TP1 ≥5% regardless of subsequent MRD levels or NCI high-risk disease at diagnosis and MRD at TP2 ≥0.01% or Extramedullary disease not in CR1 at TP2
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IKZF1^{plus}		*IKZF1*^{plus} and FCM MRD d15 ≥10% and PCR-MRD EOI pos, EOC pos <5×10^{-4} *IKZF1*^{plus} and FCM MRD d15 <10% and EOC ≥5×10^{-4}	As above, according to MRD
T-ALL Newly Diagnosed	**COG**	**BFM- AIEOP**	**ALLTogether1**
	Positive EOC MRD ≥0.1% T-ALL with PIF	T-ALL: PPR and/or FCM-MRD d15 ≥10% with either: PCR-MRD positive at EOI, or EOC MRD ≥5×10^{-4}	MRD ≥5% at TP1 and MRD ≥0.5% at TP1.5 or MRD ≥5% at TP1, MRD <0.5% at TP1.5, but detectable at TP2 or MRD <5% at TP1, but MRD ≥0.05% at TP2 or Extramedullary disease, who are not in CR1 at TP2
ALL Relapse	**COG**	**IntReALL**	
	Marrow relapse: early or late with MRD >0.1% IEM relapse: early or late relapse with MRD >0.1% T-cell ALL: any relapse	All HR relapse (see IntReALL risk groups in **Table 1**) SR relapse with positive MRD EOI, or early isolated EM relapse if MD available	
Special Groups			
Infant ALL	**COG**	**Interfant group**	
	KMT2A-AFF1 rearrangement and positive EOC-MRD	*Interfant-06 criteria: KMT2A*-rearranged and age <6 months at diagnosis with either WBC ≥ 300,000/µl or PPR	
Ph+ ALL	**COG**	**EsPhALL**	
	Positive EOC-MRD	*Current EsPhALL criteria:* EOC MRD ≥5×10^{-4} (high positive) or <5×10^{-4} (low positive) at EOC and still positive at any level at end of HR block 3	
MPAL	**COG**	**BFM- AIEOP**	**I-BFM AMBI 2018**
	Positive EOC-MRD	Positive EOC-MRD	No CR at defined time points during ALL or AML therapy

Truong TH, et al. *Front Pediatr.* 2021;9:782785.

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ASTCT™ American Society for Transplantation and Cellular Therapy

Guideline

Hematopoietic Cell Transplantation in the Treatment of Adult Acute Lymphoblastic Leukemia: Updated 2019 Evidence-Based Review from the American Society for Transplantation and Cellular Therapy

Zachariah DeFilipp[1,*], Anjali S. Advani[2], Veronika Bachanova[3], Ryan D. Cassaday[4], Daniel J. Deangelo[5], Partow Kebriaei[6], Jacob M. Rowe[7], Matthew D. Seftel[8], Wendy Stock[9], Martin S. Tallman[10], Suzanne Fanning[11], Yoshihiro Inamoto[12], Ankit Kansagra[13], Laura Johnston[14], Arnon Nagler[15], Craig S. Sauter[16], Bipin N. Savani[17], Miguel-Angel Perales[16], Paul A. Carpenter[18], Richard A. Larson[9], Daniel Weisdorf[3]

Table 1
Transplantation Indications

Indication	Recommendation	Grade of Recommendation	Highest Level of Evidence
Ph-negative disease			
Should allo-HCT be offered for adults with standard-risk ALL in CR1?	Unclear	A	1++
Should allo-HCT be offered for adults with high-risk ALL in CR1?	Yes	A	1++
Should allo-HCT be offered for adults with ALL in ≥CR2?	Yes	D	2+
Should allo-HCT be considered for refractory ALL?	Unclear	D	2+
Ph+ disease			
Should allo-HCT be offered for patients with Ph+ ALL in CR1 who receive TKIs?	Yes	B	1+
Should allo-HCT be offered for patients with Ph+ ALL in CR1 who receive TKIs who achieve complete molecular remission?	Unclear	B	2++
AYA with Ph-negative disease			
Should allo-HCT be considered for AYA with otherwise standard- isk, MRD-negative ALL in CR1 if treated with pediatric-inspired regimens?	No	A	1++
Should allo-HCT be considered for AYA in CR1 with high-risk features or persistent MRD after induction?	Yes	A	1++
Auto-HCT			
Should auto-HCT be offered for Ph-negative ALL in CR1?	No	A	1++
Should auto-HCT be offered for Ph+ ALL in CR1?	Unclear	C	2+

Truong TH, et al. *Front Pediatr.* 2021;9:782785.

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Truong TH, et al. *Front Pediatr.* 2021;9:782785.

Initial Treatment

Date	Treatment	Response
Jan 7, 2021	Dexamethasone	
Jan 15, 2021		
Feb 16, 2021		

Initial Treatment

Date	Treatment	Response
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Initial Treatment

Date	Treatment	Response
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Jan 15, 2021	4-drug induction (as per AALL1732) Pred + Vinc + Daun + PEG-Asp	
Feb 16, 2021		

Initial Treatment

Date	Treatment	Response
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Jan 15, 2021	4-drug induction (as per AALL1732) Pred + Vinc + Daun + PEG-Asp	Not in remission on day 29 7%–16% blasts PCR MRD MLL-AFF1 3×10^{-1}; IGH-VH6 6×10^{-1}; TCR D4 4×10^{-1}
Feb 16, 2021		

Initial Treatment

Date	Treatment	Response
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“Treatment Failure” in ALL

blood Special Report

Remission, treatment failure, and relapse in pediatric ALL: an international consensus of the Ponte-di-Legno Consortium

Swantje Buchmann,[1,*] Martin Schrappe,[1,*] Andre Baruchel,[2,3] Andrea Biondi,[4] Michael Borowitz,[5,6] Myriam Campbell,[6] Gunnar Cario,[1] Giovanni Cazzaniga,[4] Gabriele Escherich,[7] Christine J. Harrison,[8] Mats Heyman,[9] Stephen P. Hunger,[10] Csongor Kiss,[11] Hsi-Che Liu,[12] Franco Locatelli,[13] Mignon L. Loh,[14,15] Atsushi Manabe,[16] Georg Mann,[17] Rob Pieters,[18] Ching-Hon Pui,[19] Susana Rives,[20] Kjeld Schmiegelow,[21] Lewis B. Silverman,[22] Jan Stary,[23] Ajay Vora,[24] and Patrick Brown,[25] on behalf of the Ponte-di-Legno Consortium

Table 2. Definitions of treatment failure events in current treatment protocols

Event	Methods	Study group
Induction failure (EOI) ≥5% blasts in BM	Cytomorphology and/or FCM-/PCR-MRD or genetics	JCCG, SEHOP-PETHEMA, SFCE, SJCRH, TPOG
Induction failure (EOI) ≥25% blasts in BM	See above	DFCI, UKALL
No induction failure events; treatment failure is an event if CR has not been achieved at later timepoints	Different combinations of methods	AIEOP-BFM, ALLTogether, ALL-IC-BFM, CoALL, COG, DCOG, EsPhALL-COG, NOPHO

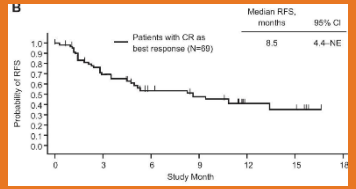
- Treatment failure
  - Failure to achieve CR at a clearly predefined timepoint (EOI, EOC, or other timepoints during intensification)
  - This timepoint should be specified at the onset of the clinical trial
  - Progress toward consensus that TF is defined no earlier than the EOC

Buchmann S, et al. *Blood*. 2022;139(12):1785-1793.

Treatment Options in Refractory ALL?

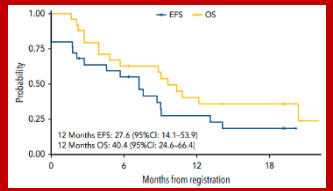
Blinatumomab

RIALTO study
- CR 63%
- Median OS 13.1 mo



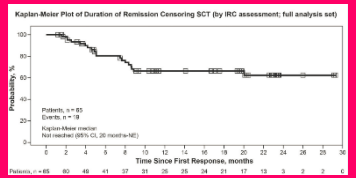
Inotuzumab ozogamicin

ITCC-059
- CR 80%
- 12-mo EFS 28%, OS 40%



Tisagenlecleucel

ELIANA study
- 82% CR/CRi
- 18-mo RFS 66%, OS 80%



Clinical trials of targeted or experimental therapies

TKI (Ph-like), menin inhibitors, CDK4/6 inhibitors, BCL2 inhibitors, proteasome inhibitors, mTOR

Global Leukemia Academy

Regulatory approval for these agents varies between countries.

Locatelli F, et al. *Blood Cancer J*. 2020;10(7):77; Brivio E, et al. *Blood*. 2021;137(12):1582-1590; Grupp SA, et al. *Blood*. 2018;132(suppl 1): abstract 895.

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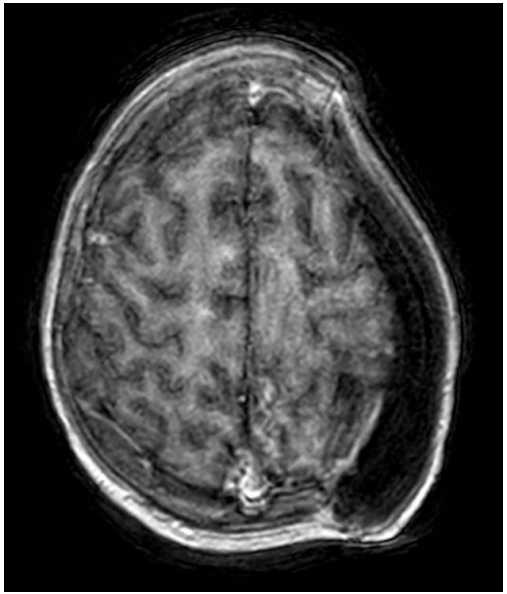
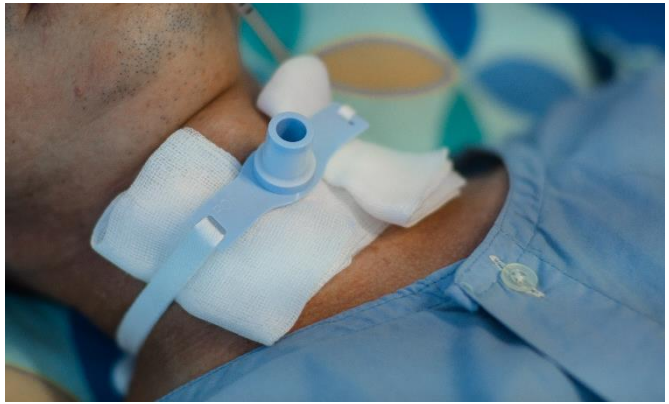
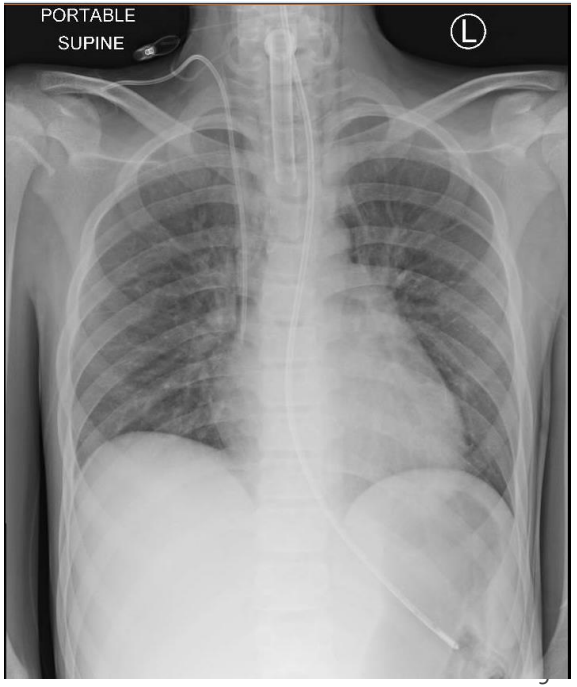
Flow cytometry: 34% of blasts were **CD19 negative**

- Also present on day 29 BMB in retrospect
- Immunophenotype was CD22 negative

Complications







Venetoclax and Navitoclax in Combination With Chemotherapy in Patients With Relapsed or Refractory ALL and Lymphoblastic Lymphoma

Pullarkat VA, et al. *Cancer Discovery* 2021

- Phase I dose-escalation study (AbbVie M16-106)
- N = 47
  - Median age 29 years (range: 6–72); 12 to <18 years old
  - 53.2% B-ALL, 40.4% T-ALL, 6.4% B-LL or T-LL
  - Heavily pretreated: median 4 lines (range: 1–10)

Venetoclax and navitoclax are not currently approved for ALL or lymphoblastic lymphoma.
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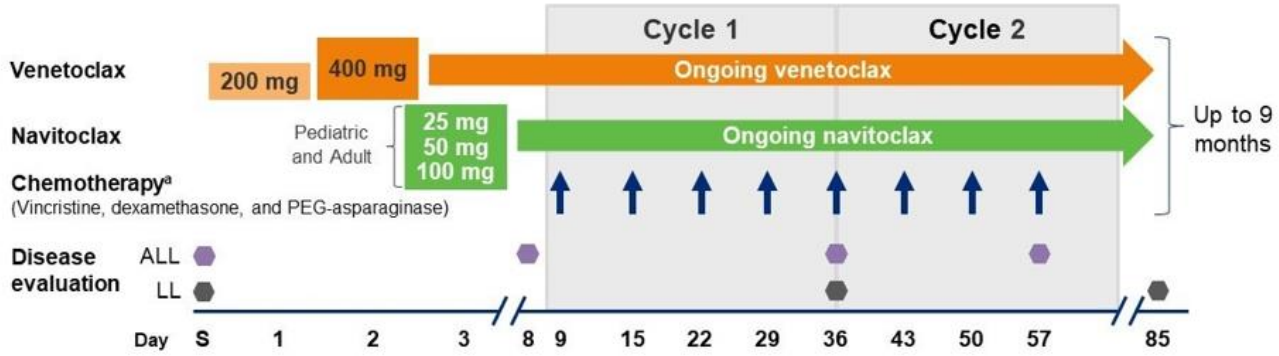

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> Delayed hematopoietic recovery is main dose-limiting complication

> Efficacy
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  - Outcomes similar in posthoc analysis of age, immunophenotype, no. of prior Rxs, and prior Rx
  - **Median duration of response 4.2 mo** (2.3–11.5 mo)
  - **Median duration of survival 7.8 mo** (4–12 mo)
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  - Compares favorably to blina, ino, and nelarabine
  - 27% had HSCT or CAR T cells
  - **11/13 who had HSCT/CAR T cells were alive at end of follow-up**

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Salvage Therapy

	Timepoint	FISH for MLL	PCR MRD		
			MLL-AFF1	IGH VH6	TCR D4
Feb 11, 2021	End of induction	Positive (1/29)	3×10^{-1}	6×10^{-1}	4×10^{-1}
Mar 17, 2021	Midway through consolidation	Positive (1/28)	5×10^{-1}	7×10^{-1}	4×10^{-1}

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May 13, 2021	**Post-course 1 ven-nav**	**Negative**	**3×10^{-4}**	**5×10^{-4}**	

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May 13, 2021	Post-course 1 ven-nav	Negative	3×10^{-4}	5×10^{-4}	
July 20, 2021	**Post-course 2 ven-nav**	**Negative**	**Negative**	**Negative**	**Negative**
Aug 3, 2021		Negative	Negative	Negative	Negative

Salvage Therapy

	Timepoint	FISH for MLL	PCR MRD		
			MLL-AFF1	IGH VH6	TCR D4
Feb 11, 2021	End of induction	Positive (1/29)	3×10^{-1}	6×10^{-1}	4×10^{-1}
Mar 17, 2021	Midway through consolidation	Positive (1/28)	5×10^{-1}	7×10^{-1}	4×10^{-1}
May 13, 2021	Post-course 1 ven-nav	Negative	3×10^{-4}	5×10^{-4}	
July 20, 2021	**Post-course 2 ven-nav**	**Negative**	**Negative**	**Negative**	**Negative**
Aug 3, 2021		Negative	Negative	Negative	Negative

Referred for HSCT

Assessing Fitness for HSCT Is Difficult in Young People

> HCT Comorbidity Index[1]
  - Children were included in original validation cohort, but <10%
  - Unclear whether HCT-CI predicts OS or NRM in children[2-4]
    - Different reference ranges, difficulty performing spirometry, comorbidities may relate to the (nonmalignant) indication (eg, hemoglobinopathies), children tolerate transplant better
  - Does not measure “frailty”

Comorbidity	HCT-CI weighted scores
Arrhythmia	1
Cardiac	1
Inflammatory bowel disease	1
Diabetes	1
Cerebrovascular disease	1
Psychiatric disturbance	1
Hepatic, mild	1
Obesity	1
Infection	1
Rheumatologic	2
Peptic ulcer	2
Moderate/severe renal	2
Moderate pulmonary	2
Prior solid tumor	3
Heart valve disease	3
Severe pulmonary	3
Moderate/severe hepatic	3

1. Sorror ML, et al. *Biol Blood Marrow Transplant.* 2015;21(8):1479-1487; 2. Broglie L, et al. *Transplant Cell Ther.* 2021;27(1):74.e1-74.e9 (no); 3. Smith AR, et al. *Blood.* 2011;117(9):2728-2734 (yes); 4. Figueroa Turienzo CM, et al. *Arch Argent Pediatric.* 2016;114(4):337-342 (yes).

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  - 6MWT (pretransplant) was an independent predictor of survival on univariate but not multivariate analysis (including Karnofsky, age, LVEF)[8]
- Validated "pediatric disease risk index" for ALL and AML does not include HCT-CI or performance score[9]

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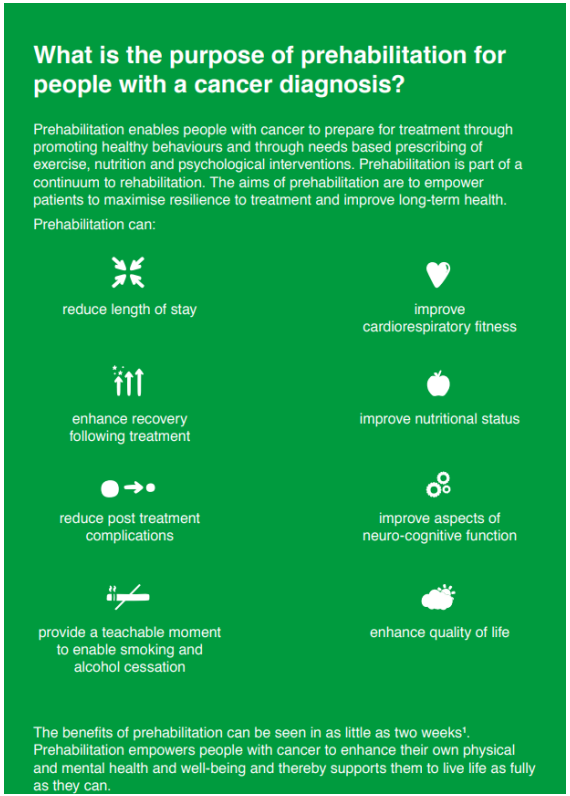
“Prehabilitation” Before HSCT



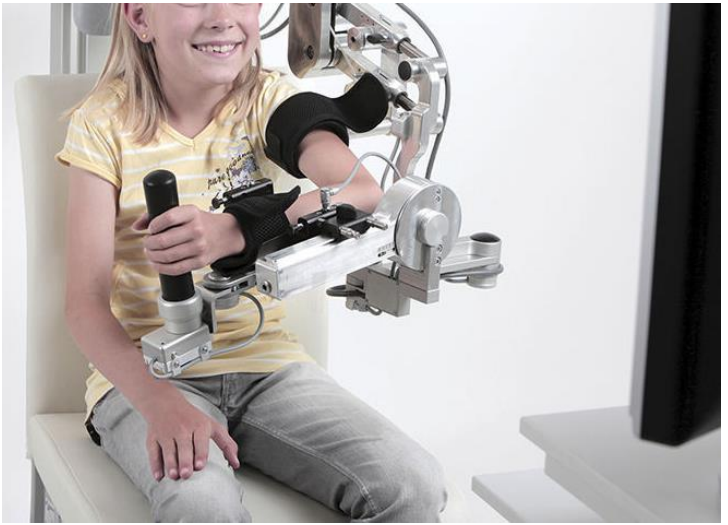
- Meta-analysis[1]
  - Physical activity is safe, feasible, and efficacious to prevent decline in QOL and improve physical capacity in children and adolescents undergoing HSCT
- Randomized controlled trial[2]
  - A supervised exercise program during pediatric HSCT has positive effects on endurance, functional mobility, and muscle strength
  - High frequency, low intensity

Macmillan Cancer Support. Prehabilitation for people with cancer. https://www.macmillan.org.uk/healthcare-professionals/news-and-resources/guides/principles-and-guidance-for-prehabilitation. Accessed December 2, 2022.
1. Dias do Lago, AL, et al. *Hematol Transfus Cell Ther*. 2021(3):313-323; Smith C, et al. *Pediatr Blood Cancer*. 2022;69(5):e29618.

Rehabilitation Robotics in Children and AYA With Cancer:

Safe and Feasible With Preliminary Evidence of Efficacy (but expensive)

Lokomat®



Armeo®

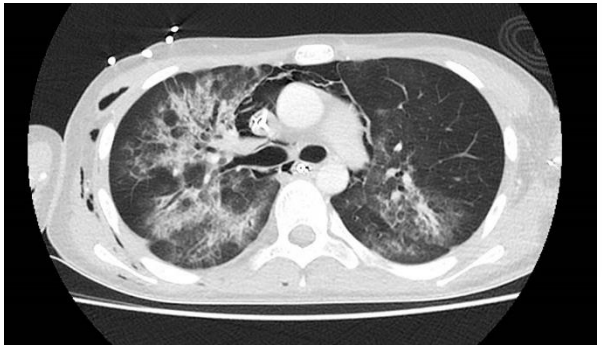
Matched Sibling Donor HSCT

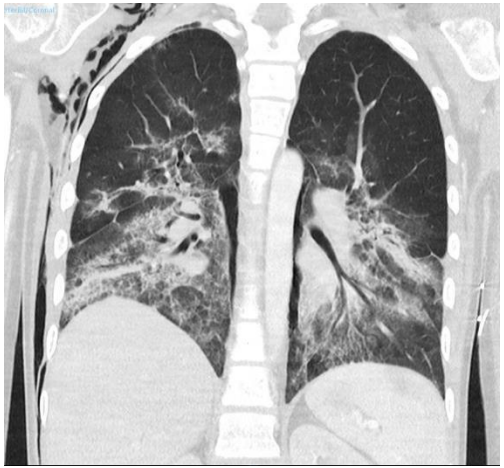
	Age: 15y	DOB 30/11/2006		MRN	11492161	Wt (kg)	44.2	Ht (cm)	175.5	BSA (m^2)	1.468
Diagnosis & stage		ALL CR1		Donor:	Matched sibling				HPC source:	Marrow	
Patient:	O Pos	Male			CMV Neg		HSV IgG Neg				
Donor:	O Pos	Male			CMV Neg		Not tested		MRN: 11519772		
Patient HLA	A 01:01	B 52:01, 57:01		C 06:02, 12:02		DRB1 01:01, 15:02			DQ 05:01, 06:01		Match
Donor HLA	A 01:01	B 52:01, 57:01		C 06:02, 12:02		DRB1 01:01, 15:02			DQ 05:01, 06:01		10/10
Conditioning		TBI		200 cGy/fraction			x 6 fractions		days -10, -9, -8		
		Thiotepa		5 mg/kg/dose		IV	x 2 doses		day -6, -5		
		Cyclophosphamide		60 mg/kg/dose		IV	x 2 doses		days -3, -2		

- 4.6 × 10^8/kg TNC (4.1 × 10^6/kg CD34+ cells) plasma-reduced bone marrow
- Neutrophil engraftment day +27
- Platelet engraftment day +36
- Post-transplant complications
  - Mucositis – nutritional support with TPN
  - Febrile neutropenia – *Acinetobacter ursingii*
  - *C. difficile* diarrhea
  - No graft-vs-host disease
- Discharged day +32

Idiopathic Pneumonia Syndrome

- Day +42: readmitted with fever and vomiting
  - Cefepime escalated to meropenem-vancomycin
- Day +46: ARDS (aspiration?) – ICU admission
  - Dyspnea, hypoxia, and difficulty with sputum
  - Tracheostomy changed from size 6 uncuffed fenestrated to size 7 cuffed unfenestrated
  - Dexamethasone (day +47)
  - Etanercept* (day +49) – continued twice weekly
  - Initial improvement
- Day +56: severe respiratory deterioration
  - Hypoxia, temperature >40˚C, ↑ inflammatory markers
  - Required maximal ventilatory support, FiO_2 70%–100%
    - Several peri-respiratory arrests precipitated by coughing and loss of recruitment
    - ECMO considered
  - High-dose pulse steroids and nursed prone
  - Meropenem, vancomycin, sulfamethoxazole-trimethoprim, posaconazole, etanercept
  - Tocilizumab*
    - Gradually wean off ventilatory support





*Off-label use.

Idiopathic Pneumonia Syndrome

- Widespread alveolar injury in the absence of LRTI, cardiac or renal dysfunction, or iatrogenic fluid overload
- Presentation
  - Fever, nonproductive cough, dyspnea, tachypnea, hypoxemia, rales, and multilobar, diffuse alveolar, or interstitial infiltrates on CT
  - Usually within first 120 days, typically day +18 to +21; “late onset” is less common
- Pathogenesis
  - Immune-mediated lung injury via T-cell axis and inflammatory cytokine axis
- Risk factors
  - Older age/poor performance score; MAC or TBI ≥12 Gy; HLA disparity; GvHD prophylaxis with MTX; acute GvHD; previous viruses
- Treatment
  - Supportive care: supplemental O_2; mechanical ventilation (high flow, CPAP); empiric antimicrobials; strict fluid balance
  - Methylprednisolone; etanercept* (anti-TNFα; CR 71%, 63% 1-year survival); tocilizumab* (anti-IL6)
- Mortality 59%–80% at 2 weeks of evolution (95% if mechanical ventilation required)

*Off-label use.

Carreras E, Cooke KR. Noninfectious pulmonary complications. In: Carreras E, Dufour C, Mohty M, Kröger N, eds. *The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies.* 7th ed. Cham, Switzerland: Springer; 2019:393-401; Yanik GA, et al. *Biol Blood Marrow Transplant*. 2015;21(1):67-73; Varelias A, et al. *Blood*. 2015; 125(15):2435-2444; Thompson J, et al. *Biol Blood Marrow Transplant*. 2017;23(11):1955-1960.

Current Status

- **Remains in CR 11 months after HSCT**
- Tracheostomy remains in situ
  - Attempted tracheal dilatation failed
- Several respiratory tract infections managed as an outpatient over winter
- Avascular necrosis of both knees and hips
  - Stabilized with conservative management
- Have not yet had a discussion about fertility
- **Attending school, helps on the family farm, about to get his driver's license**

Global Leukemia Academy

Interactive Discussion: Regional Challenges of ALL Management

Shaun Fleming and Michael Osborn

APTITUDE HEALTH

Interactive Discussion: Regional Challenges of ALL Management (1/2)

- What regional **barriers** exist when it comes to **diagnostic testing** (eg, identification of Ph+ and Ph-like patients) and MRD assessment? Are they the same for pediatric/AYA vs adult patients? **Are there ways to overcome these?**
- How do you approach diagnostic and treatment barriers for patients with limited insurance?
- What steps have you taken to optimize multidisciplinary care coordination in your centers for pediatric/AYA patients? And for adult patients? **Is multidisciplinary care a challenge in some areas, and how do you manage this?**
- What strategies have you used to optimize management of patients in **remote areas**?
- Do you see the use of **telemedicine** as a solution for some of the problems mentioned above? Other solutions and approaches?

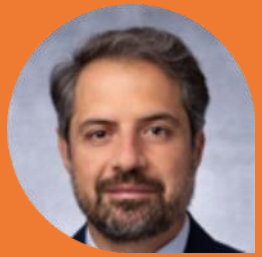
Interactive Discussion: Regional Challenges of ALL Management (2/2)

- What have been your strategies to accelerate access to diagnostic testing/MRD assessment and access to novel drugs?
- Do you perform MRD, and by which test?
- Have you been able to integrate immunotherapy as a consolidation therapy in the frontline setting?
- What is the accessibility to and the role of transplant in your region?
- How do you keep up-to-date? Congresses? Which congresses? Literature, local guidelines?

Global Leukemia Academy

Session Close

Elias Jabbour



APTITUDE HEALTH

Repeat Question 3

Which of the following is NOT true?

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

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

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

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

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

Virtual Breakout – Pediatric 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	Elizabeth Raetz
9.10 – 9.40	**Optimizing First-Line Therapy in Pediatric ALL: How to Balance Cure and Long-term Risks?** • Optimal use of treatment choices in frontline pediatric ALL, including HSCT	Michael Osborn
9.40 – 10.00	**Optimal Management and Treatment Coordination of Long-term Toxicities in Pediatric ALL** • Long-term follow-up care for pediatric ALL survivors	Stephanie Dixon
10.00 – 10.40	**ALL Case-Based Panel Discussion** • Local case 1: Frontline setting (10 min) • Local case 2: Management of long-term toxicities (10 min) • Discussion and Q&A (20 min)	Moderators: Michael Osborn and Elizabeth Raetz Savenaca Seduadua Claudia Toro All faculty
10.40 – 10.50	***Break***	
10.50 – 11.15	**Current Treatment Options for Relapsed ALL in Children** • Optimal use of treatment choices in relapsed/refractory ALL, including HSCT	Elizabeth Raetz
11.15 – 11.35	**ALL Case-Based Panel Discussion** • Local case 3: Relapsed/refractory setting (10 min) • Discussion and Q&A (10 min)	Moderators: Michael Osborn and Elizabeth Raetz Miri Tukana All faculty
11.35 – 11.45	**Session Close** • ARS questions	Elizabeth Raetz

Thank You!

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

THANK YOU!

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

SEE YOU TOMORROW!

APTITUDE HEALTH