Heralding The Era of Curable Therapy for Acute Lymphoblastic Leukemia: Monoclonal Antibodies and Targeted Therapy in Community Oncology

Rare Diseases Symposium
Indianapolis, IN
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Professor of Medicine
August 24, 2024
Mayo Clinic College of Medicine
Mayo Clinic Comprehensive Cancer Center

Scottsdale, Arizona

Rochester, Minnesota

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With thanks to Elias Jabbour, MD, MD Anderson Cancer Center, for use of selected slides.

DISCLOSURES OF COMMERCIAL SUPPORT

Name of Company	Research support	Employee	Consultant	Stockholder	Speaker's Bureau	Scientific Advisory Board	Other
Abbvie	X						
Astellas	X						
Amgen	X						
Actinium	X						
Pluristem	X						
Sanofi	X						
Beigene					X		
Amgen					X		
Biosight							X

Presentation Objectives

- Overview the key advances in the therapy of ALL in adults
- Review studies utilizing immunotherapy upfront for B cell precursor-ALL (BCP-ALL)
- Describe the results of the E1910 clinical trial
- Review the current status of induction therapy for Ph+ ALL including outcomes of recent clinical trials
- Comment on the current role of alloBMT in Ph+ALL

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3 Major Advances Have Improved Outcomes in *BCR::ABL1* negative B Cell Precursor Acute Lymphoblastic Leukemia (BCP-ALL)

- Assessment and Prognostic Significance of Measurable Residual Disease (MRD)
- Development of and Implementation of Immunotherapeutic Approaches to Treatment and Management of BCP-ALL
- Utilization of Pediatric Intensive Chemotherapy Regimens (BFM-based) in Adolescents and Young Adults (AYA)

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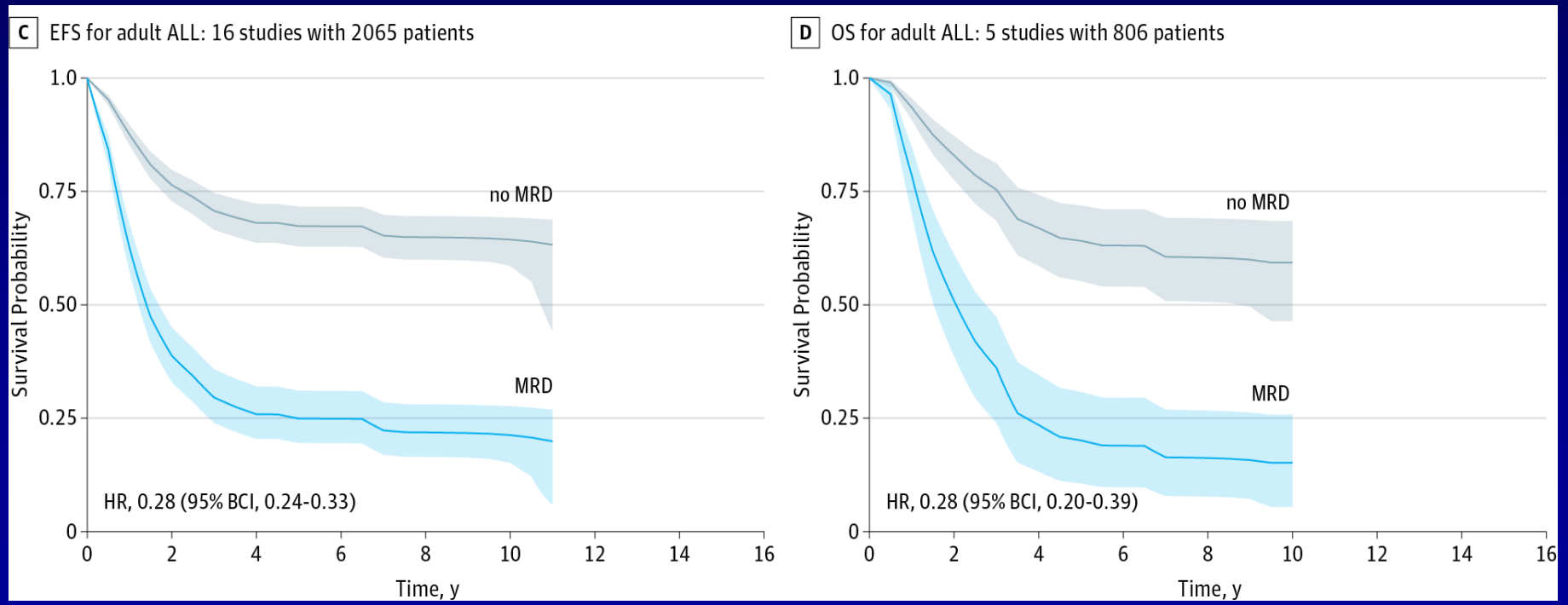
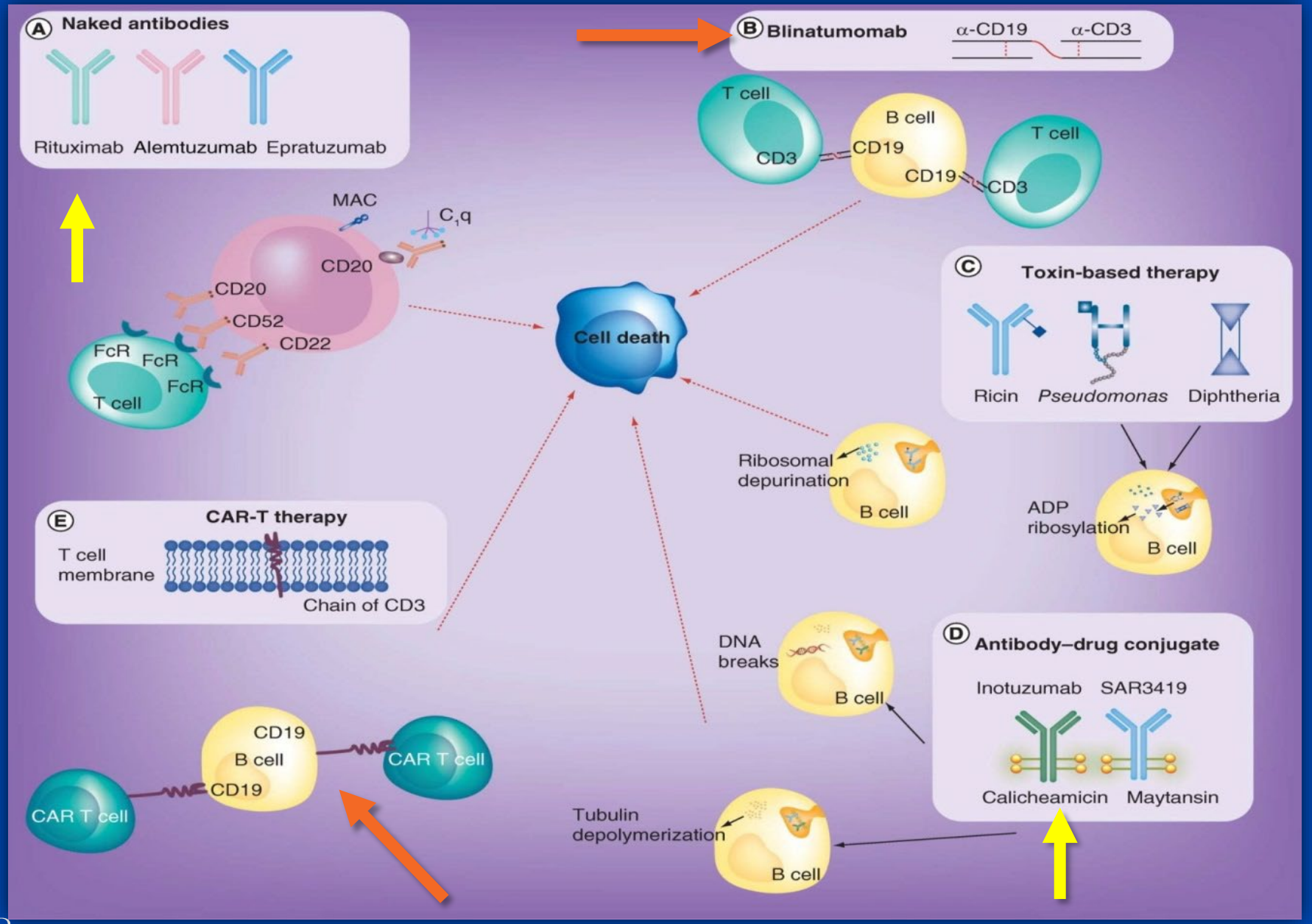
Prognostic Impact of MRD in ALL

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



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



Mechanisms of action of monoclonal antibody conjugates

A. Naked (unconjugated) antibodies

B. Bi-specific T-cell-engager antibody

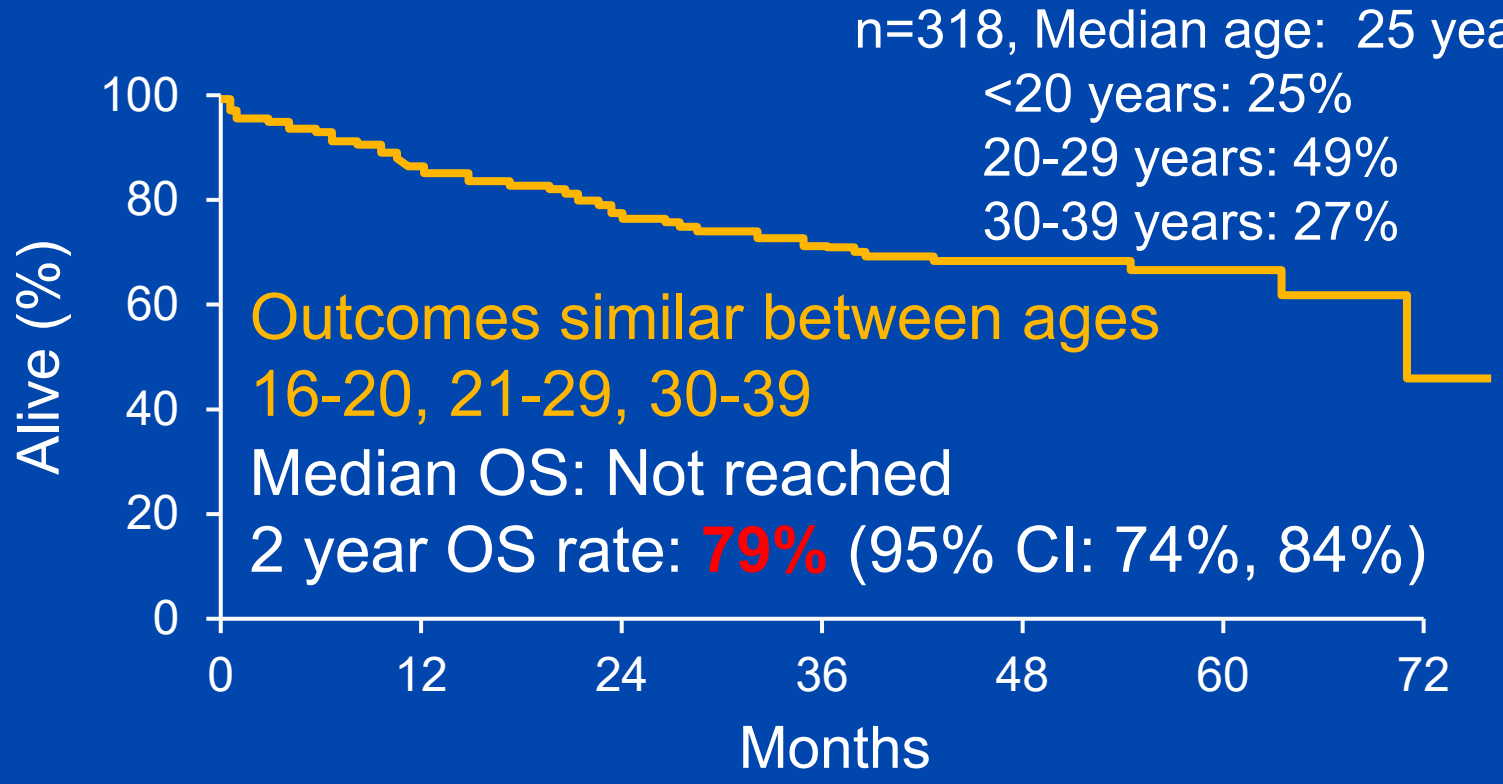
C. Antibodies linked to toxins

D. Antibodies linked to drugs

E. Chimeric antigen receptor T cells

Parikh S, Litzow M. Future Oncology 10:2201, 2014

C10403 - An Intergroup Phase II Trial for AYA With Untreated ALL Using a Pediatric-Intensive Regimen-Overall Survival



BFM-based regimen: **Induction-Consolidation-Interim Maintenance-Delayed Intensification-Maintenance**

Stock, et al. Blood 133(14):1548-59, 2019

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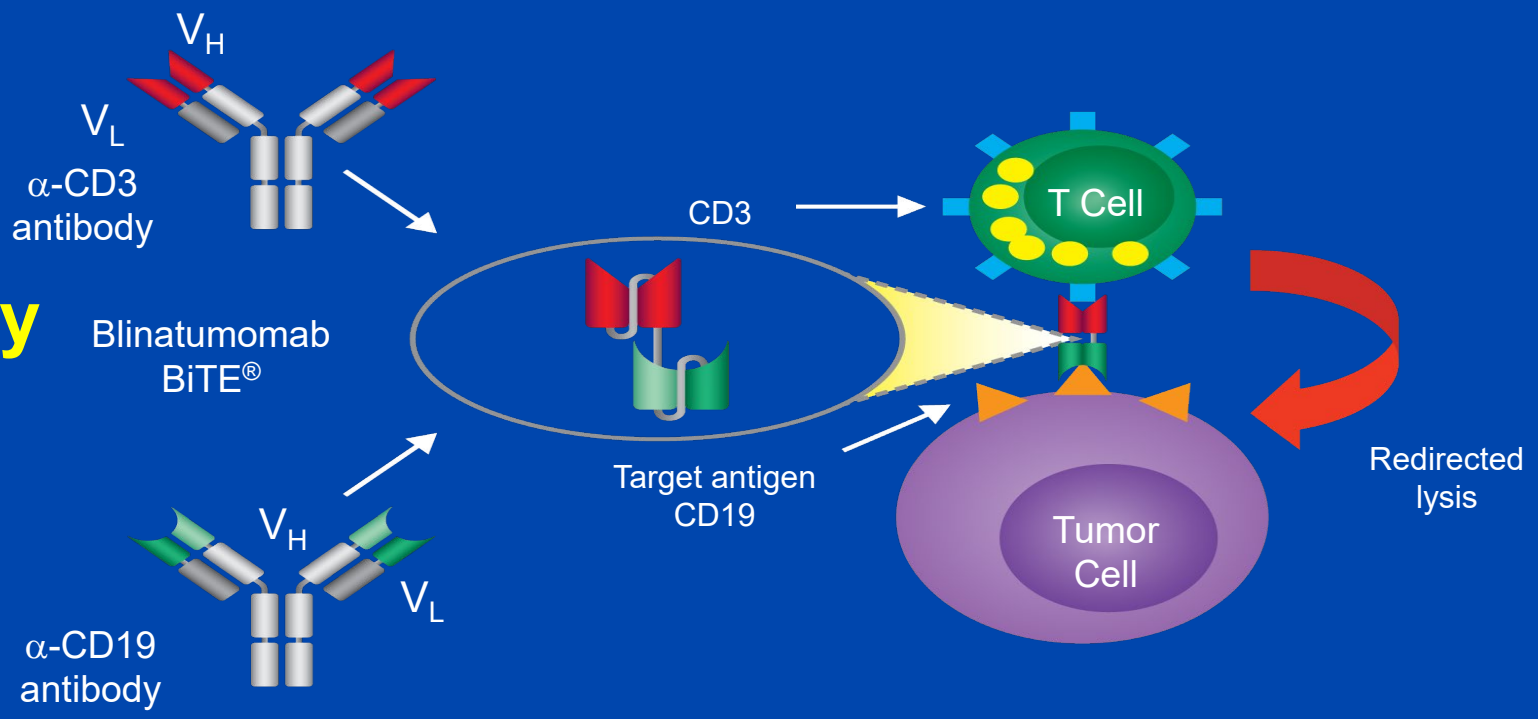
Mode of Action of BiTE® Antibody Blinatumomab

FDA approved for
1. relapsed/refractory B-ALL
2. MRD+ B-ALL in adults and children



Blinatumomab is a bispecific T-cell engager molecule (BiTE®) designed to direct cytotoxic T cells to CD19-expressing cancer cells

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

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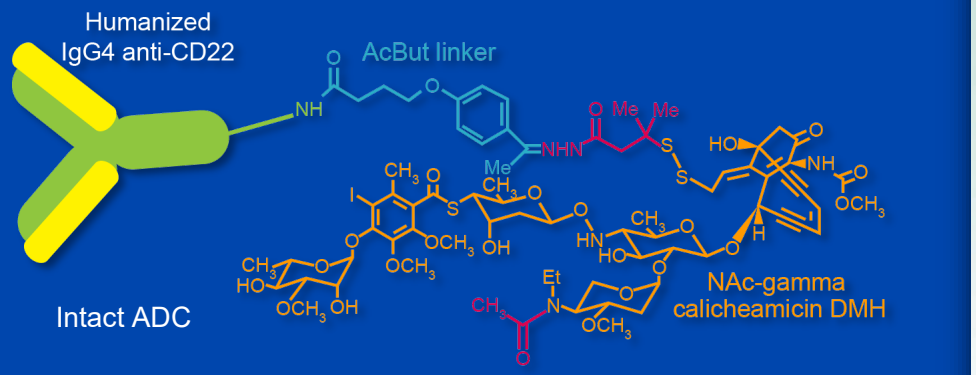
Inotuzumab Ozogamicin (InO)

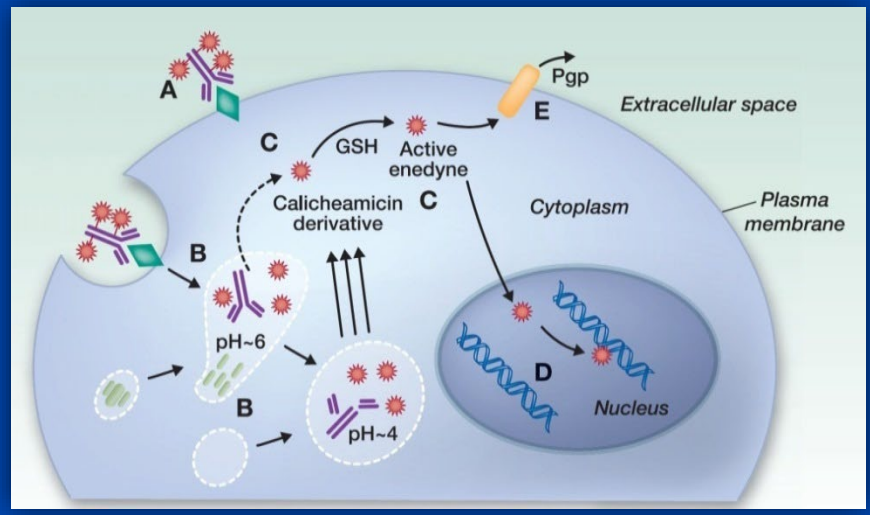
AcBut Linker:
4-(4'-acetylphenoxy) butanoic acid dimethyl hydrazide



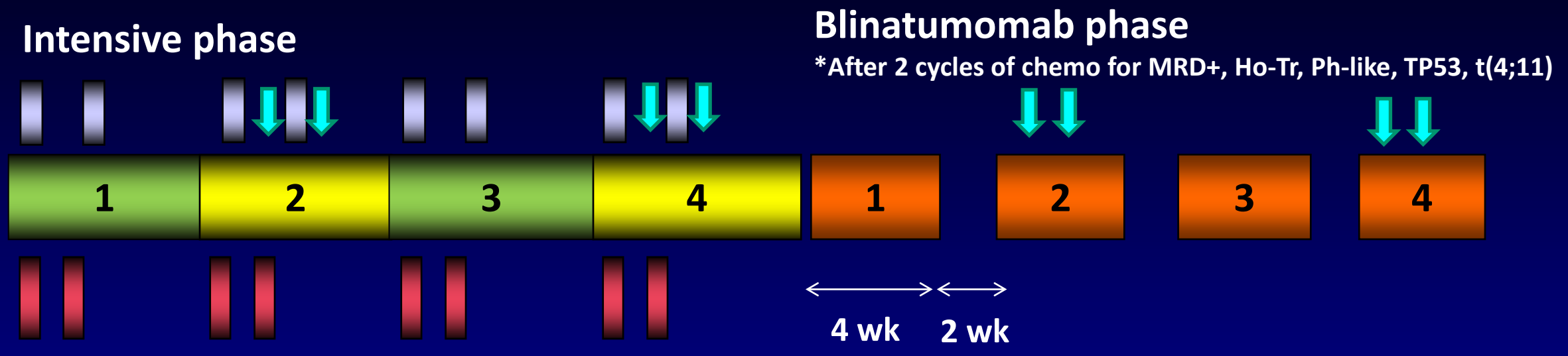
N-Acetyl γ **Calicheamicin**

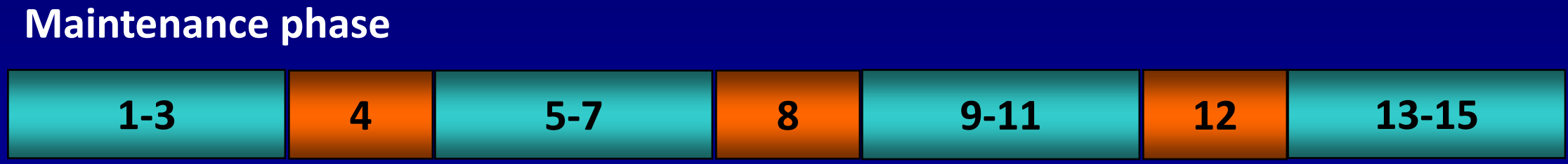
Average loading of calicheamicin derivative on mAb is 5–6 moles of calicheamicin/mole of mAb (range, 3–9) for InO; ~100% of mAbs conjugated

MOA retains activity against tumor cells with slow cycling times



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





Hyper-CVAD

Ofatumumab or rituximab

Blinatumomab

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

IT MTX/Ara-C x 12

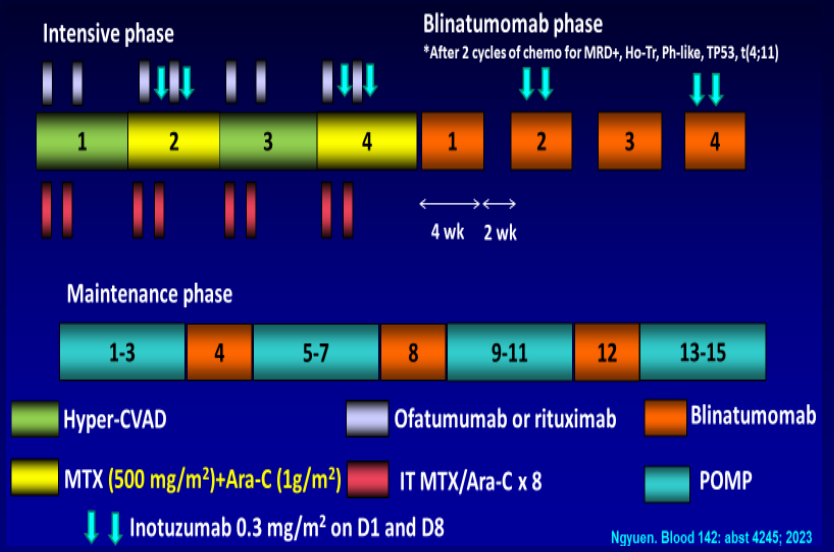
POMP

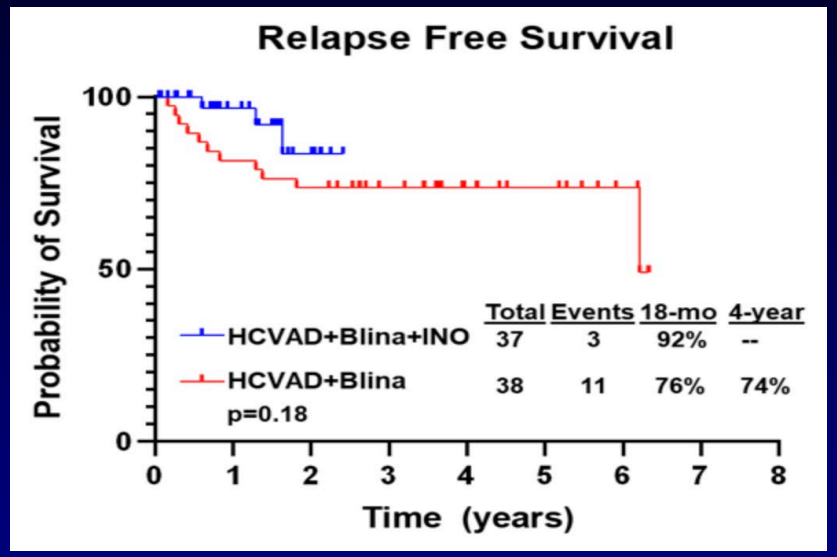
Inotuzumab 0.3 mg/m^2 on D1 and D8

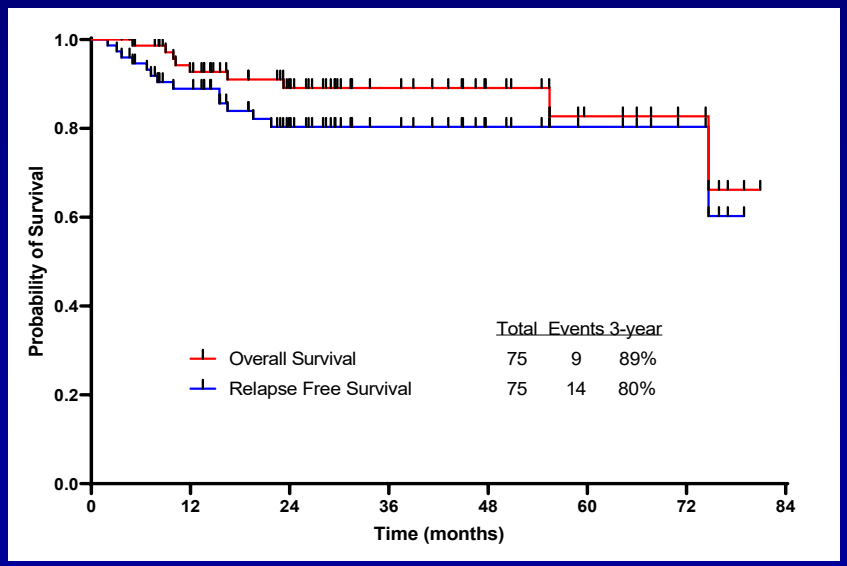
Ngyuen. Blood 142: abst 4245; 2023

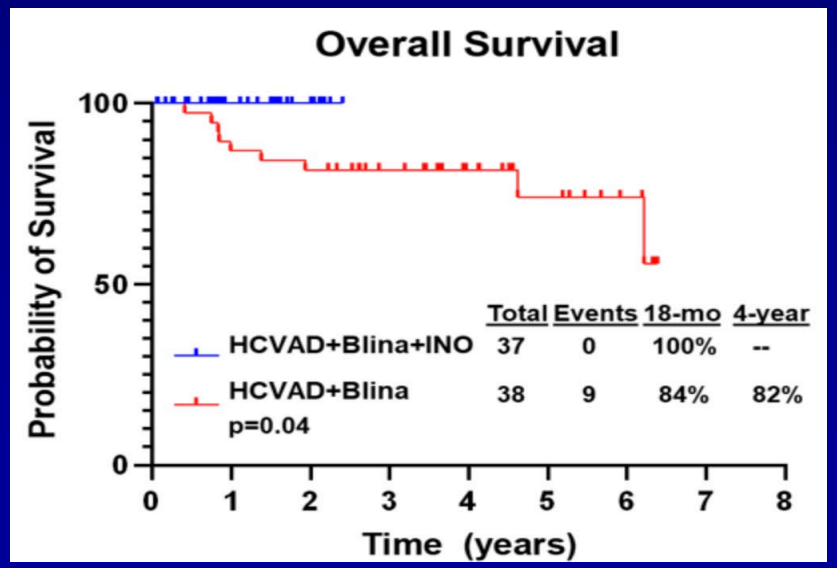
Hyper CVAD-Inotuzumab→Blinatumomab in Newly Dx Adult ALL

- 75 pts; median age 33 yrs (18-59); Median F/U 26 months (1-77)
- CR rate 100%; MRD negative 95% (66% at CR); NGS-MRD negative 73%; 60-day mortality 0%; 24 (32%) allo-SCT;

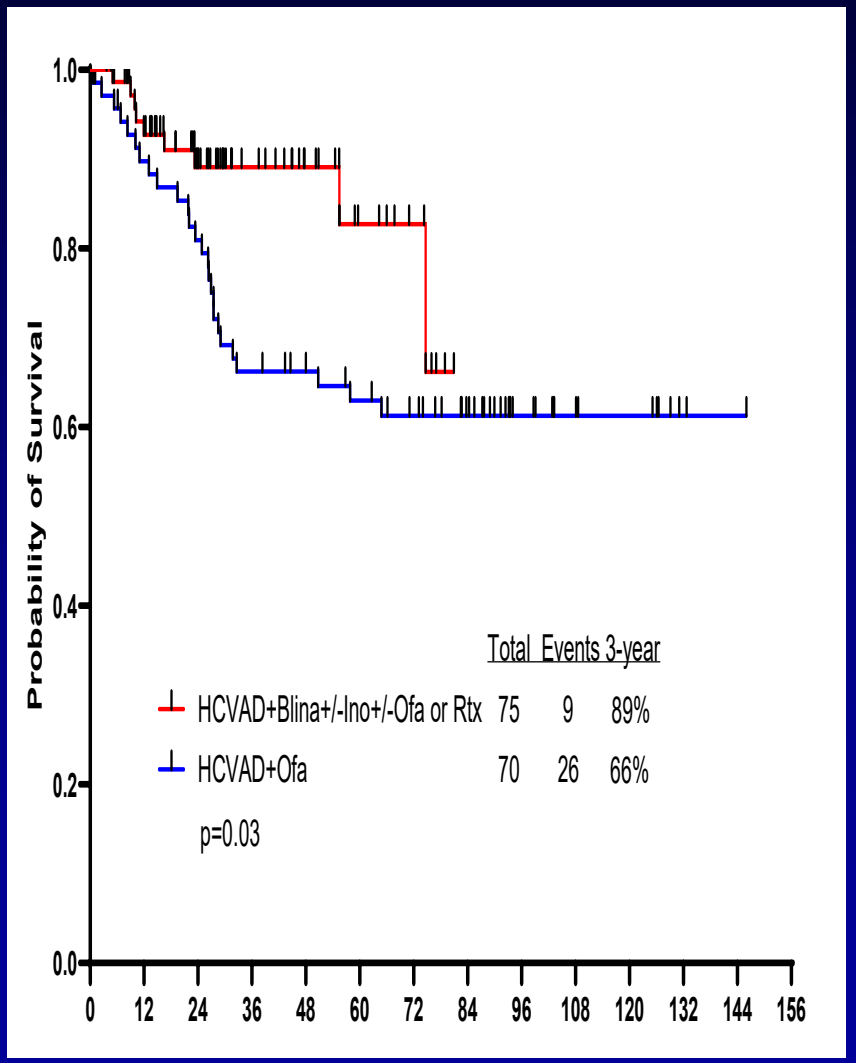








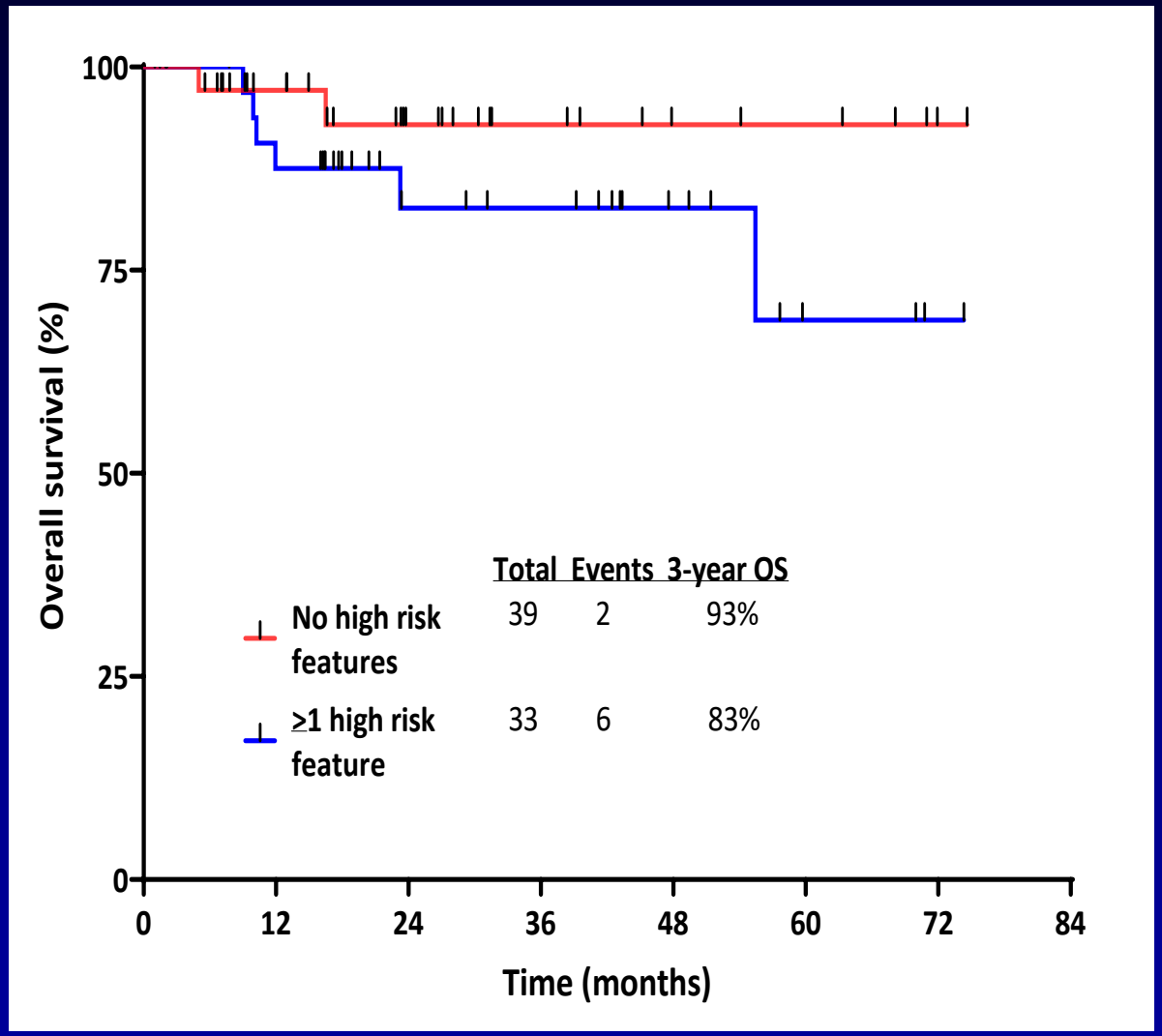
Overall Survival



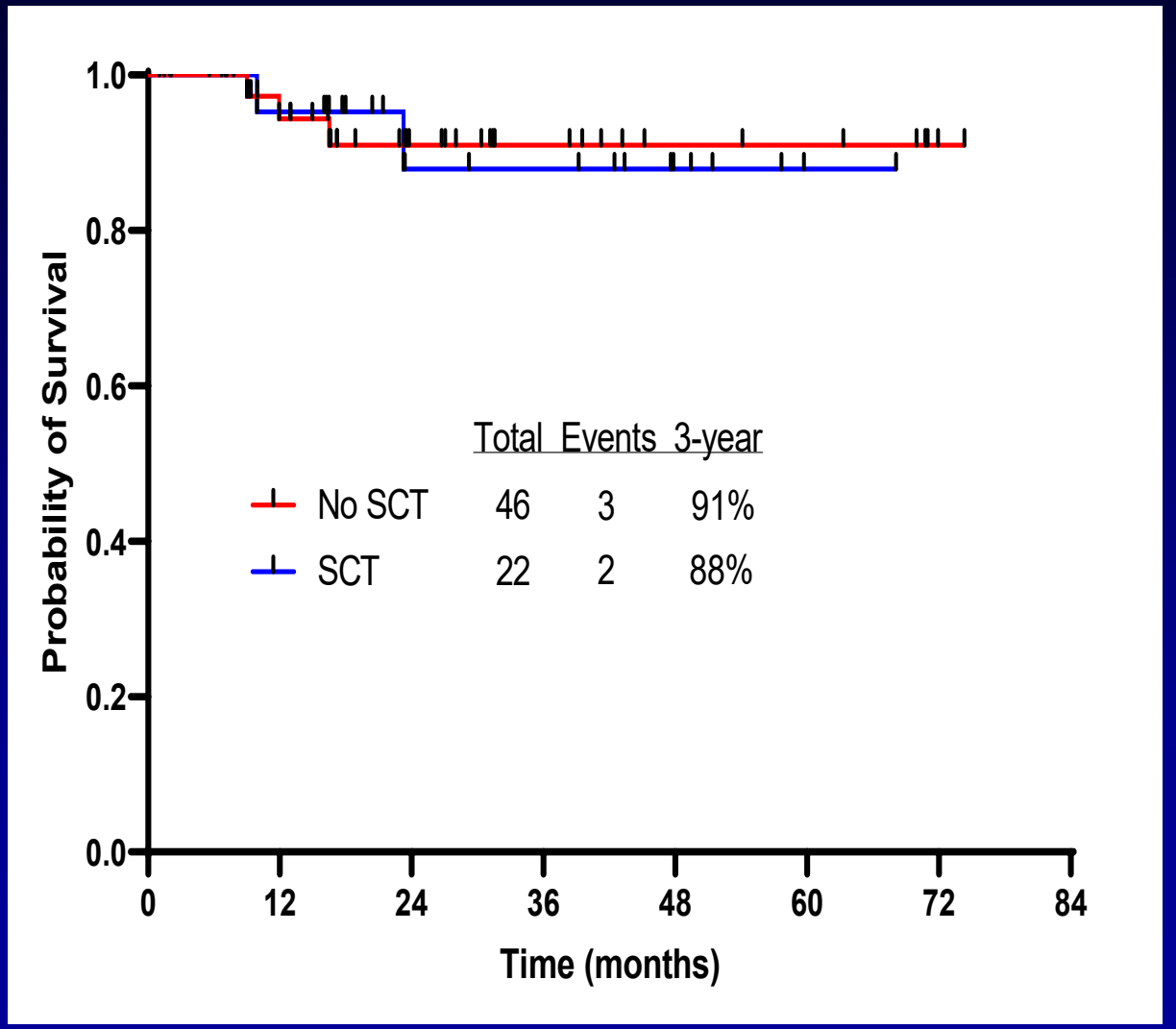
Ngyuen. Blood 142: abst 4245; 2023

Hyper-CVAD + Blinatumomab + Inotuzumab in B-ALL

Outcome by ALL Risk



Outcome by ASCT (5-mo landmark)

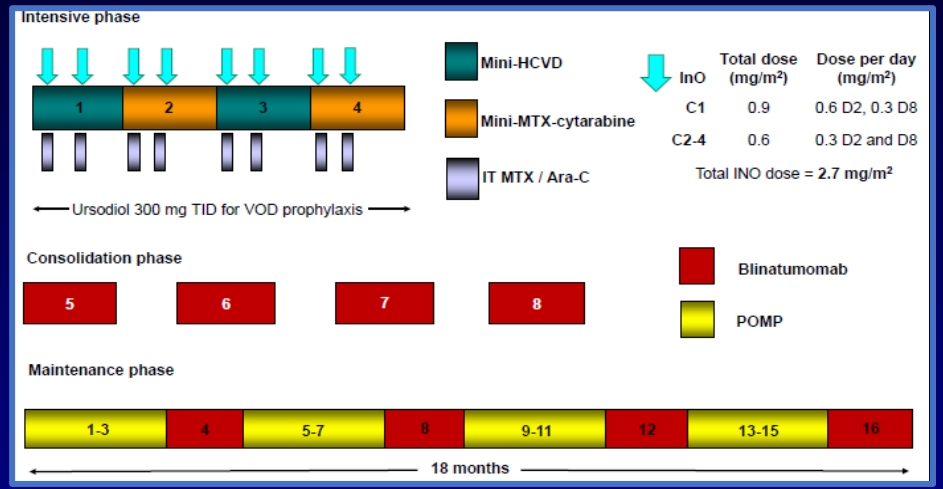


Jabbour. Lancet Haematology 9 : e 878-e885; 2023

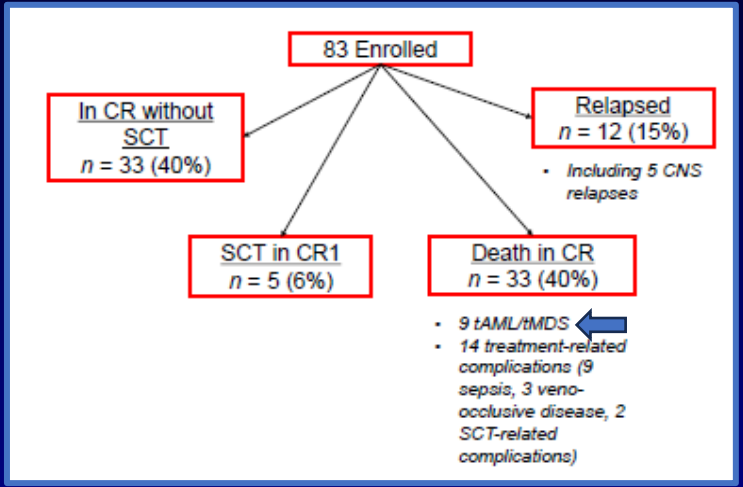
Mini-HCVD + INO ± Blina in Older ALL (N=83)

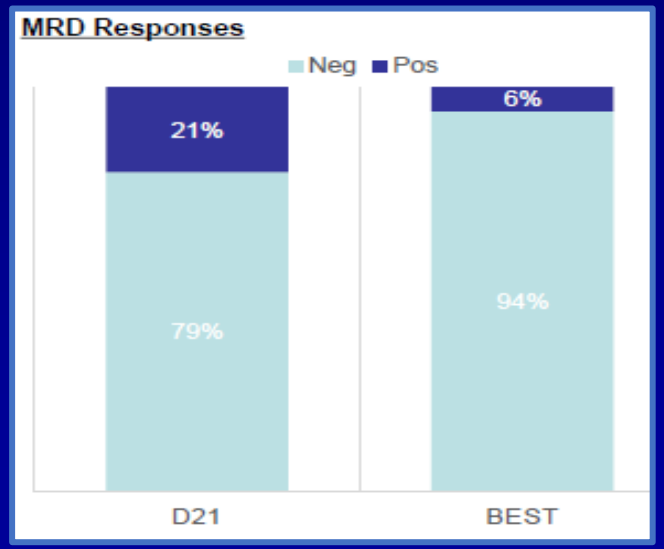
- Median age 68 years (range, 60-87; 34% ≥ 70 years)
- High-risk features: *TP53* 39%; Ph-like 18%; poor cytogenetics 23%
- ORR 99% (CR 90%); MRD negativity 94% (79% at CR)

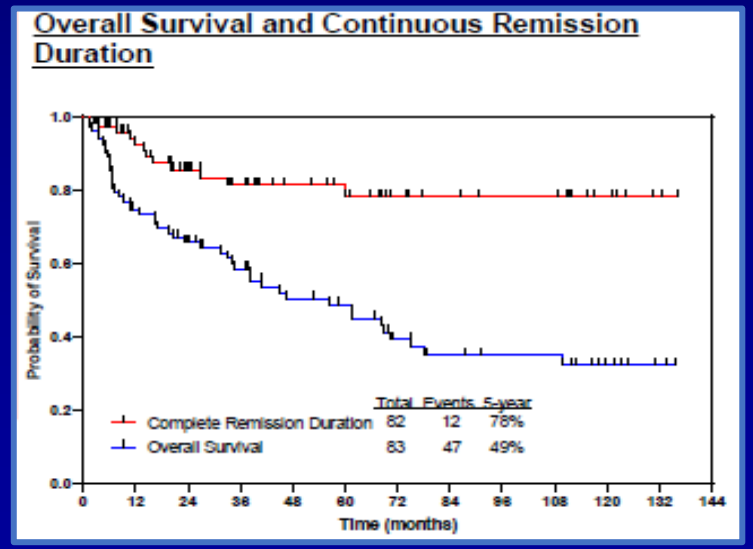
US Intergroup phase 2 trial is randomizing pts to miniHCVD+INO vs dose-adjusted HyperCVAD



Characteristic	Category	N (%) / Median [range]
Age (years)	≥70	68 [60 - 87] 28 (34)
Cytogenetics	Diploid HeH Ho-Tr Tetraploidy Complex t(4;11) Misc IM/ND	27 (33) 5 (6) 12 (14) 3 (4) 3 (4) 1 (1) 16 (19) 16 (19)
CD19 (%)		99.6 [26-100]
CD22 (%)		96.9 [27-100]
CD20	≥20%	46/76 (61)
Ph-like ALL		9/50 (18)
TP53 mutation		25/64 (39)







- **Median F/U 88 months**
- 5/12 pts with relapse (42%) had EMD (1 concurrent BM relapse), all with CNS involvement (5/83; 6%)
- Death due PD/NR: 12/83 (15%); median 23 mos (2-78); median age 64 yrs (60-79)
- Death due to AML/MDS: 9/83 (11%); median 34 mos (7-75); median age 71 yrs (64-87)
- Death in CR: 33/83 (40%); 11/28 (39%) in pts ≥70 yrs
- 14/33 deaths (42%) Rx related (9 sepsis, 3 VOD, 2 ASCT)

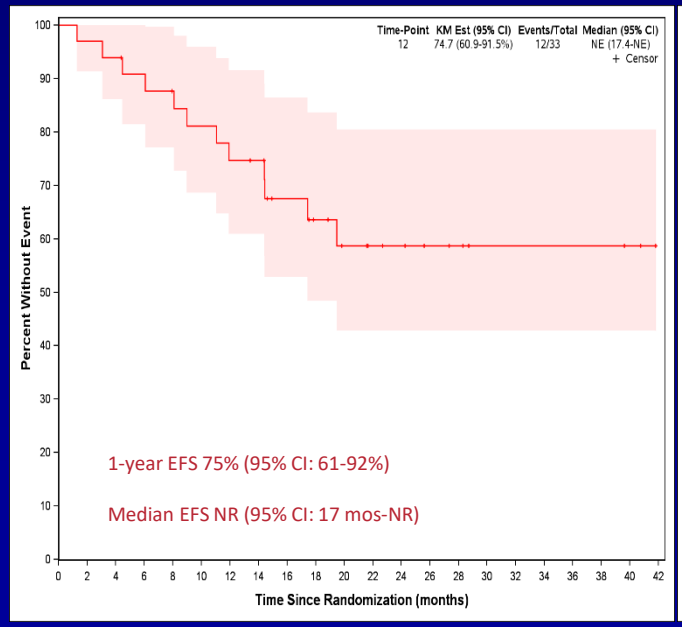
Jen. Blood 142: abst 2878; 2023

Chemo Rx-Free Inotuzumab+Blinatumomab in Pre B-ALL (Alliance A041703)

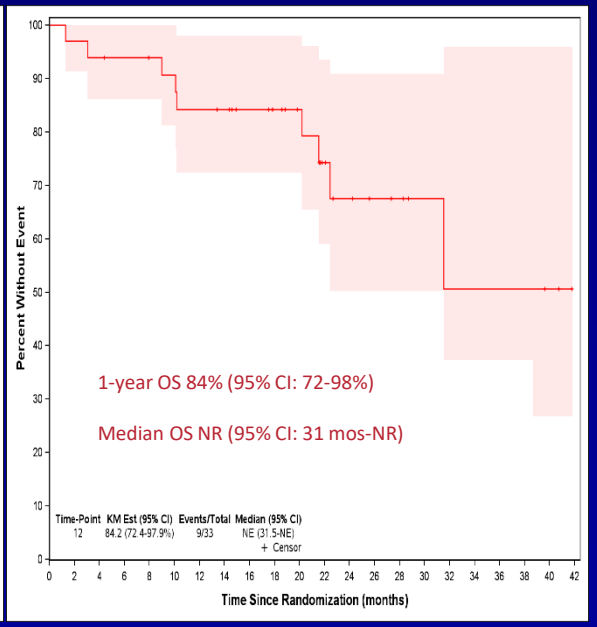
- 33 pts; median age 71 yrs (60-84). Median CD22 92%. F/U 22 months
- Induction: INO 0.8mg/m^2 D1, 0.5mg/m^2 D8 &15 (1.8mg/m^2)
- Maintenance: If CR-CRi INO 0.5mg/m^2 D1,8,15 (1.5mg/m^2) x 2 then BLINAx2
- If no CR-CRi—BLINA 28mcg/Dx21 then x 28 x 3
- IT x 8
- CR 85% post INO x 3; cumulative CR 97%
- 1-yr EFS 75%; 1-yr OS 84%
- 9 relapses; 2 deaths in CR. 9 deaths, 6 post relapse

	Induction with Inotuzumab (IA/B/C)	Consolidation with Blinatumomab
Cumulative CR (CR+CRh+CRi)	28/33 (85 %)	32/33 (97 %)
CR	15/33 (45%)	19/33 (58 %)
CRh	11/33 (33 %)	12/33 (36 %)
CRi	2/33 (6 %)	1/33 (3 %)
Refractory	3/33 (9 %)#	-

EFS

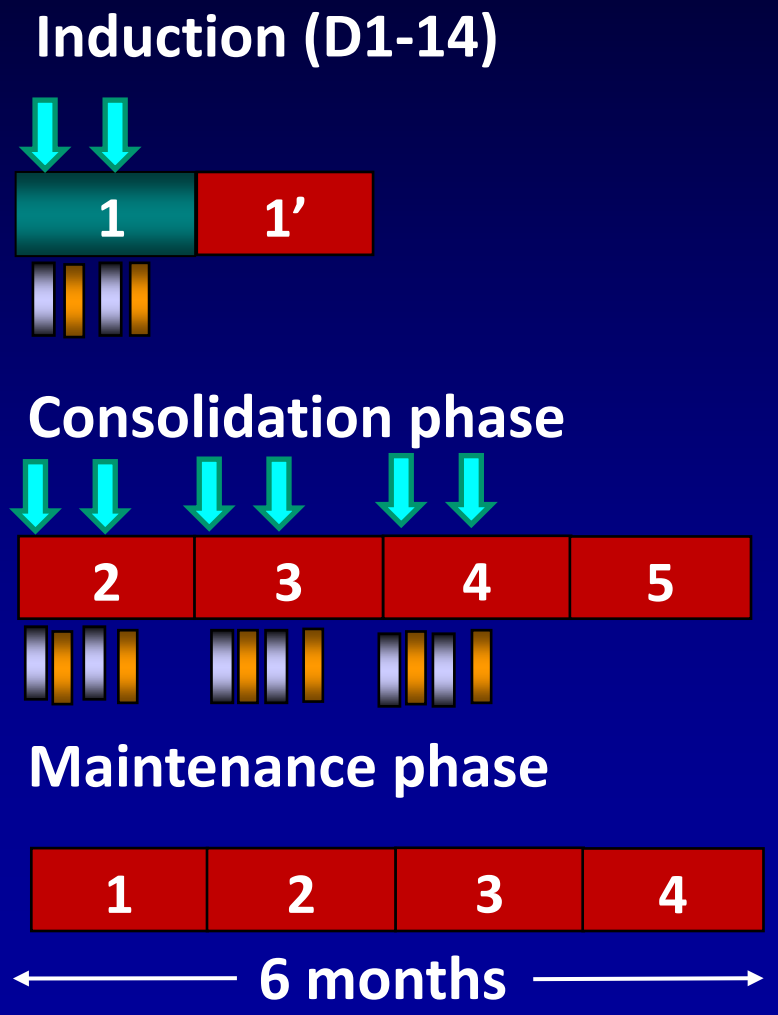


OS



Wieduwilt. HemaSphere 7: abst S117: 2023

INO + Blina in Older ALL. Amended Design (Pts ≥70 years)



Dexa 20 mg D1-4 and VCR 1 mg D4

Blinatumomab

IT MTX, Ara-C

Rituximab if CD20+

1' Blinatumomab for 2 weeks

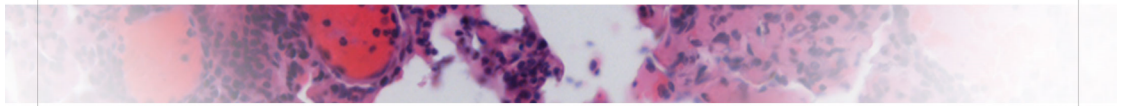
↓ INO*	Total dose (mg/m²)	Dose per day (mg/m²)
C1	0.9	0.6 D1, 0.3 D8
C2-C4	0.6	0.3 D1 and D8

Total INO dose = 2.7 mg/m²

*Ursodiol 300mg tid for VOD prophylaxis

E1910 Study

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



ECOG-ACRIN-E1910 NCTN Clinical Trial: A Phase III Randomized Trial of Blinatumomab for Newly Diagnosed BCR::ABL-negative B lineage Acute Lymphoblastic Leukemia in Adults

Mark R. Litzow, MD **ASH LBA-1, 2022**

Zhuoxin Sun, Elisabeth Paietta, Ryan Mattison, Hillard Lazarus, Jacob Rowe, Daniel Arber, Charles Mullighan, Cheryl Willman, Yanming Zhang, Matthew Wieduwilt, Michaela Liedtke, Julie Bergeron, Keith Pratz, Shira Dinner, Noelle Frey, Steven Gore, Bhavana Bhatnagar, Ehab Atallah, Geoffrey Uy, Deepa Jeyakumar, Tara Lin, Daniel DeAngelo, Richard Stone, Harry Erba, Richard Little, Selina Luger, Martin Tallman

This study was conducted by the ECOG-ACRIN Cancer Research Group (Peter J. O'Dwyer, MD and Mitchell D. Schnall, MD, PhD, Group Co-Chairs) and supported by the National Cancer Institute of the National Institutes of Health under award numbers: U10CA180820, U10CA180794, U10CA180821, U10CA180863, Canadian Cancer Society #704970, U10CA180820, U10CA180888, U10CA180868, UG1CA189856, UG1CA189859, UG1CA232760, UG1CA233180, UG1CA233198, UG1CA233234, UG1CA233253, UG1CA233277, UG1CA233290, UG1CA233320, UG1CA233331, UG1CA233337, and UG1CA233339. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

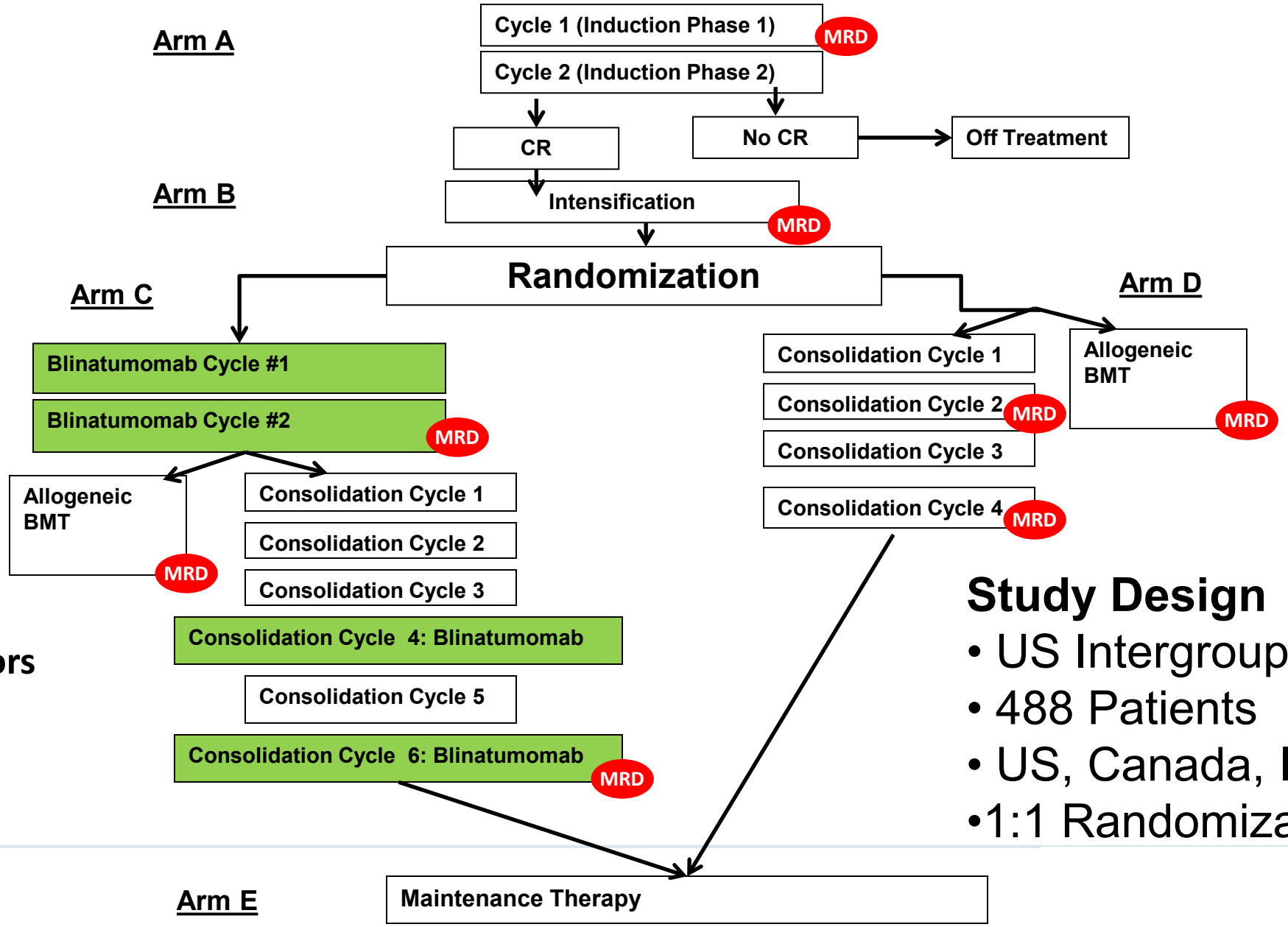
Blinatumomab for MRD-Negative Acute Lymphoblastic Leukemia in Adults

M.R. Litzow, Z. Sun, R.J. Mattison, E.M. Paietta, K.G. Roberts, Y. Zhang, J. Racevskis, H.M. Lazarus, J.M. Rowe, D.A. Arber, M.J. Wieduwilt, M. Liedtke, J. Bergeron, B.L. Wood, Y. Zhao, G. Wu, T.-C. Chang, W. Zhang, K.W. Pratz, S.N. Dinner, N. Frey, S.D. Gore, B. Bhatnagar, E.L. Atallah, G.L. Uy, D. Jeyakumar, T.L. Lin, C.L. Willman, D.J. DeAngelo, S.B. Patel, M.A. Elliott, A.S. Advani, D. Tzachanis, P. Vachhani, R.R. Bhave, E. Sharon, R.F. Little, H.P. Erba, R.M. Stone, S.M. Luger, C.G. Mullighan, and M.S. Tallman

Published July 25, 2024 in NEJM 391(4):320-333, 2024

E1910: Randomized Ph III Adult Frontline ALL

Chemotherapy backbone adapted from prior E2993 trial with changes to make it more pediatric-like



Stratification factors

- Age < or >= 55
- CD20 status
- Rituximab use
- HSCT intent

Study Design

- US Intergroup study
- 488 Patients
- US, Canada, Israel
- 1:1 Randomization

E1910: Objectives and Design

- Primary objective: Compare overall survival (OS) in MRD- patients who received blinatumomab+chemotherapy (CRx) to that of patients who received CRx alone
- Minimum of 190 pts projected to be MRD-, randomized to Step 3
- Accrual goal = 488
- With 190 MRD negative pts, 80% power to detect 45% reduction in hazard rate in the blinatumomab arm relative to the no blinatumomab arm, using one-sided log rank test at the significance level of 0.025 and assuming 2 years of follow-up

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E1910: Methods & Results

- Measurable residual disease (MRD) assessed centrally by standardized 6 color flow cytometry in the E-A Leukemia Translational Research Laboratory by Elisabeth Paietta, PhD with ≥0.01% as the cutoff for positivity
- Patients between the ages of 30 and 70 yrs were eligible
- Age: median 51, range (30, 70), Age range chosen to not compete with Alliance cooperative group AYA trial, A041501
- CR/CRi rate 395/488 (81%); CR 364 (75%), CRi 31 (6%)
- 72% rcvd 72- or 96-hr infusions blina-enhanced feasibility

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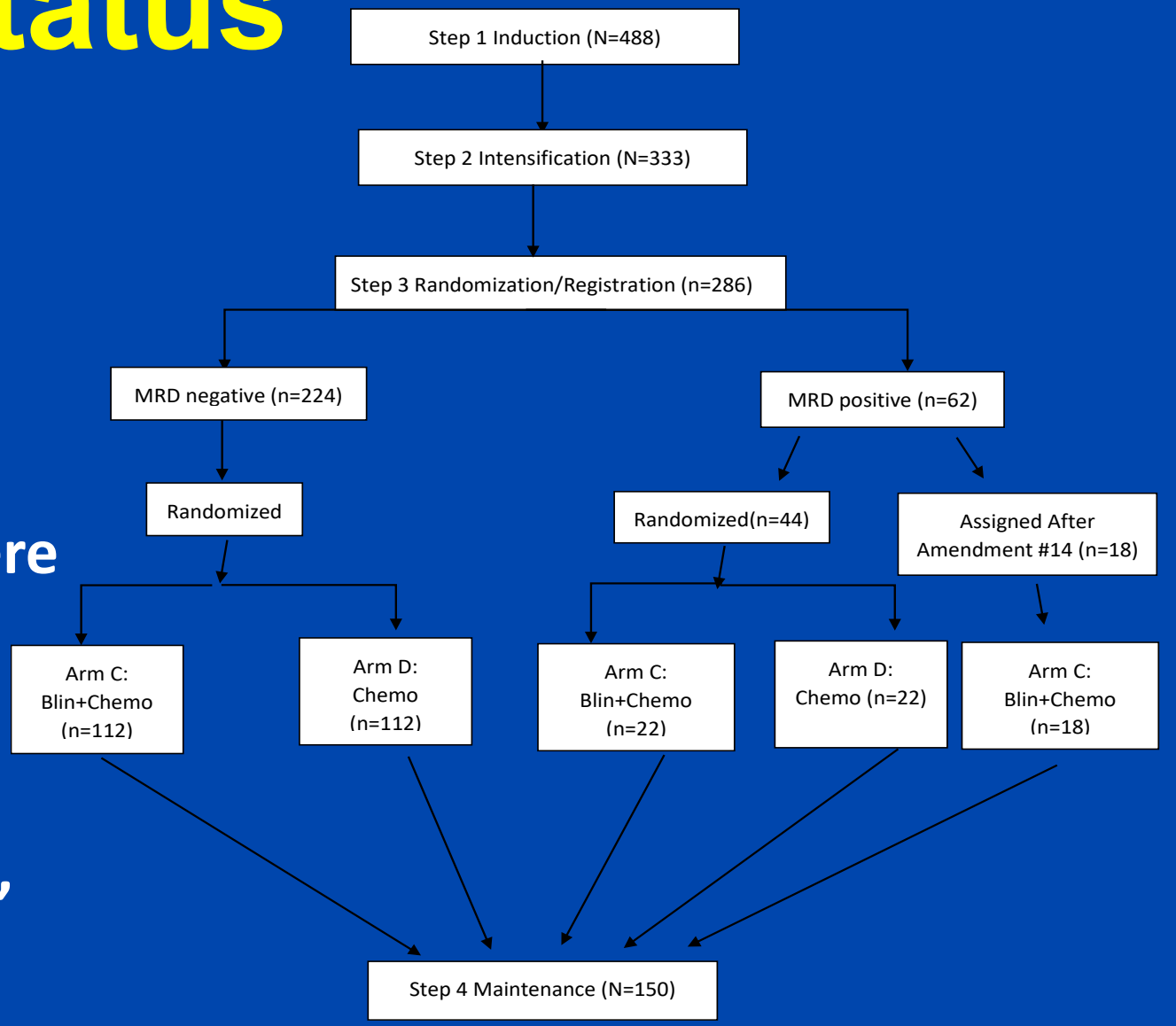
E1910: Patient Status

- Study activated December, 2013, completed accrual 10/15/2019
- 286 patients were randomized/ assigned* to step 3
  - (224 MRD-; 62 MRD+)
- Baseline characteristics examined were well balanced between arms
- Following FDA approval of Blinatumomab for MRD+ disease in 3/18, MRD+ pts no longer randomized, but assigned to Arm C



E1910: Patient Status

- CR/CRi rate as noted 395/488=81%
- Nineteen (4%) patients died of toxicity during induction
  - Causes of death included sepsis, intracranial hemorrhage, pulmonary mucormycosis, hepatic failure, myocardial infarction, stroke and respiratory failure
- Of the 395 patients who achieved remission, 109 did not reach the randomization step
  - Causes of failure to reach randomization included death, recurrent disease, adverse events, or study withdrawal
- 286 patients reached the randomization/assignment at step 3=59%, so so 41% did not.
-

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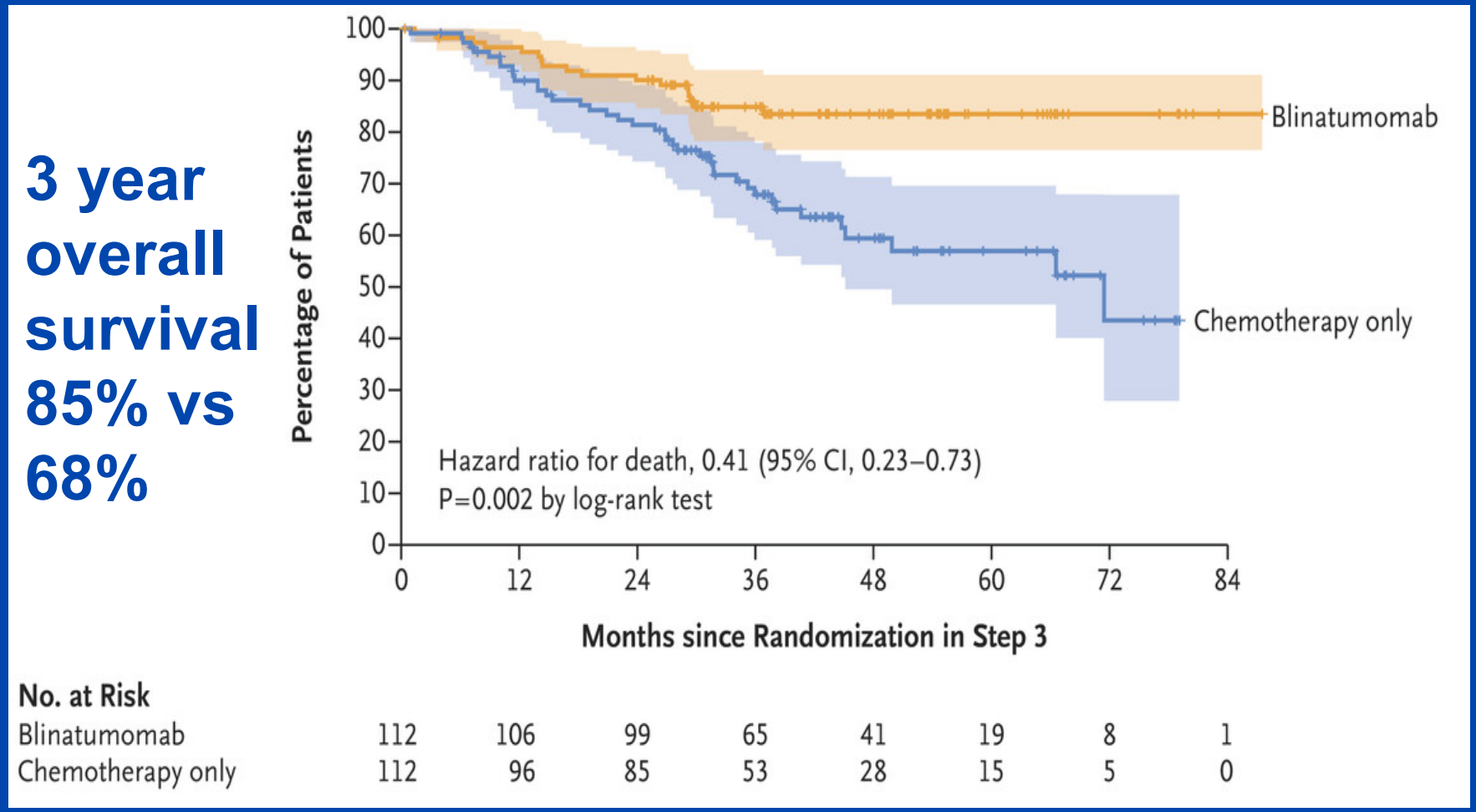
Overall Survival Comparison: MRD negative patients

- Median follow-up at the time of analysis 43 months (3.6 yrs)
- Among the 224 MRD- patients, 22 in each arm underwent on-study allogeneic transplant
- 80% of pts received 2 or more cycles of blinatumomab

3 year overall survival 85% vs 68%



Deaths on Blin+Chemo Arm=17 (2° to ALL=8, NRM=9); Chemo Arm=40 (2° to ALL=31, NRM=7, Unknown=2)

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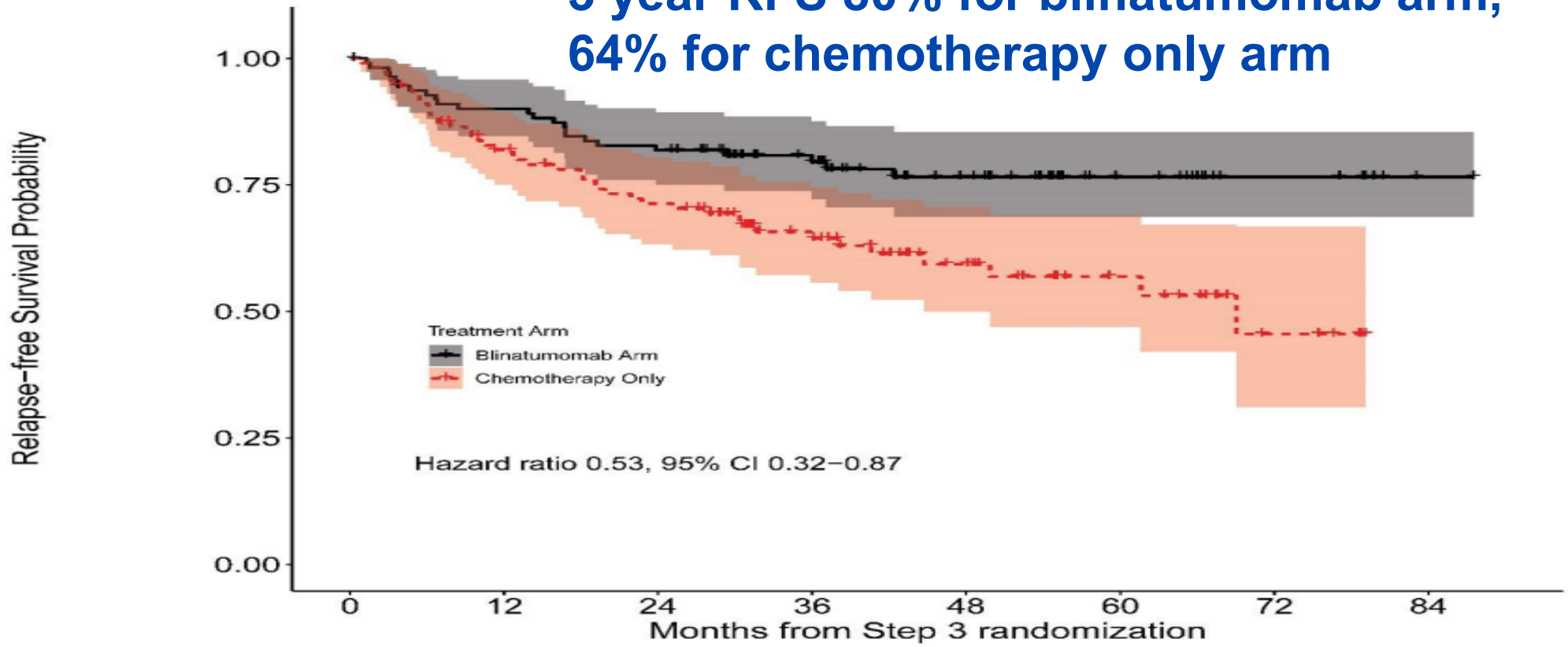
Relapse-Free Survival Comparison: MRD negative patients

Figure S2. Relapse-free survival estimate comparison for the MRD negative patients by treatment arm

3 year RFS 80% for blinatumomab arm, 64% for chemotherapy only arm



Number at risk

Blinatumomab Arm	112	99	90	62	40	19	8	1
Chemotherapy Only	112	87	74	48	28	15	5	0

*The confidence interval widths reported were not adjusted for multiplicity and may not be used in place of hypothesis testing.

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Forest plot of OS Hazard Ratio (Blinatumomab Arm/Chemotherapy Only) Subgroup Analysis

44 pts (22 on each arm) proceeded to an allogeneic transplant on study.
OS with Blinatumomab +chemo after transplant not better than chemo only (median overall survival not reached; Hazard ratio 0.59, 95% CI: 0.17 – 2.09).

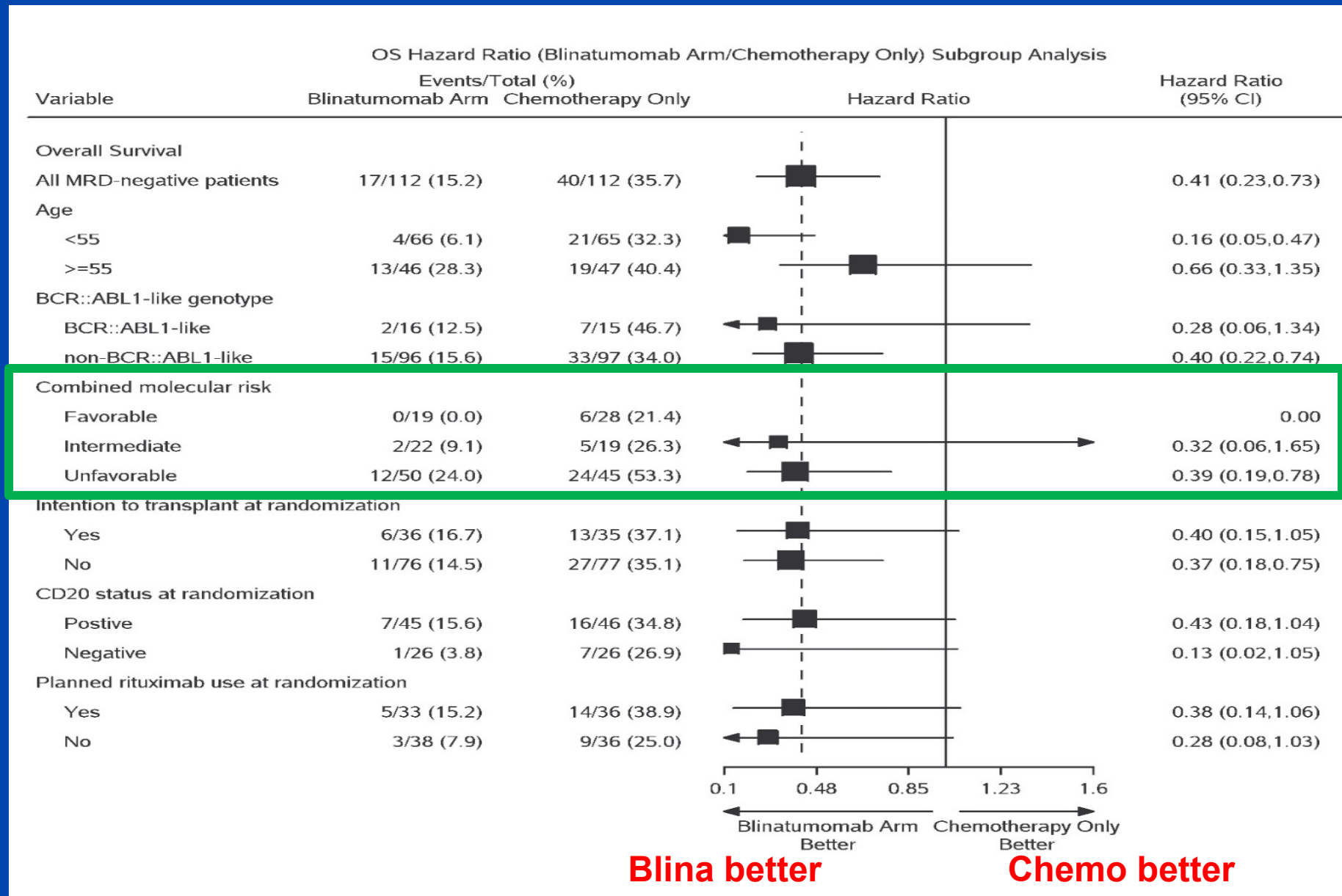
Age

Ph-like

Molecular Risk

Transplant

Rituximab



Blina better

Chemo better

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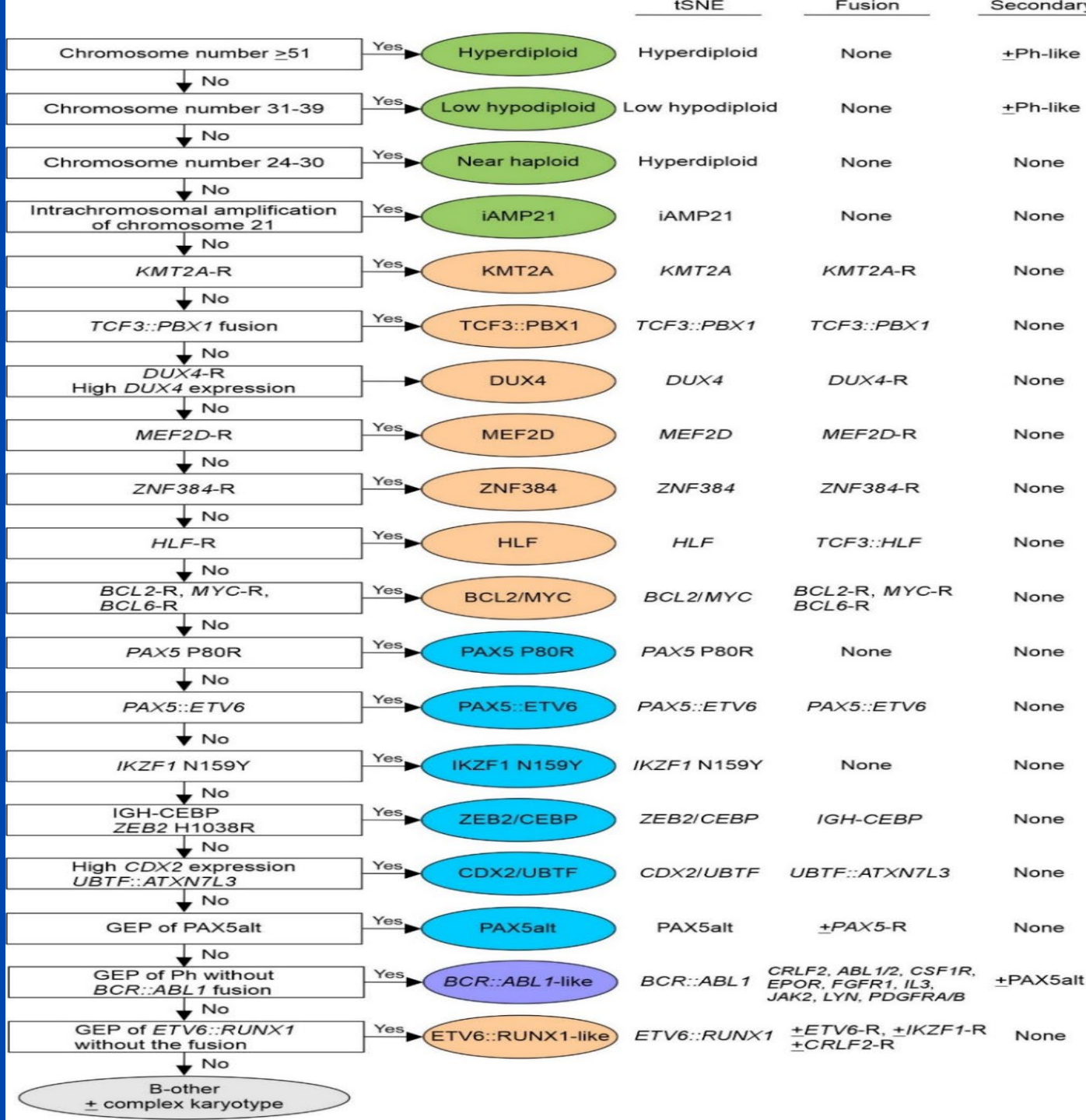
Flow chart for B-ALL subtype classification based on whole transcriptome sequencing or cytogenetics



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Risk assessment based on integrated genetic and genomic analysis*

- **Favorable:** *DUX4*-rearranged (N=17); high-hyperdiploid (N=24); *TCF3::PBX1* (N=13); PAX5 P80R (N=12)
-
- **Intermediate:** PAX5-altered (PAX5alt) (N=34); *PAX5::ETV6* (N=3); *MEF2D*-R (N=8); *ZNF384*-R (N=14)
-
- **Unfavorable:** *KMT2A*-R (N=66); low-hypodiploid/near-haploid (N=90); *BCR::ABL1*-like (N=100); *BCL2/MYC*-R (N=10); *ETV6::RUNX1*-like with *IGH::CRLF2* fusion (N=2); high-hyperdiploid with secondary subgroup *BCR::ABL1*-like, *CRLF2*-R (N=1)
- No outcome risk was assigned to *ZEB2/CEBPE* (N=2) and B-other cases without complex karyotype (N=37)

- Paietta E, et al. Molecular classification improves risk assessment in adult BCR-ABL1-negative B-ALL. Blood 2021;138(11):948-958.

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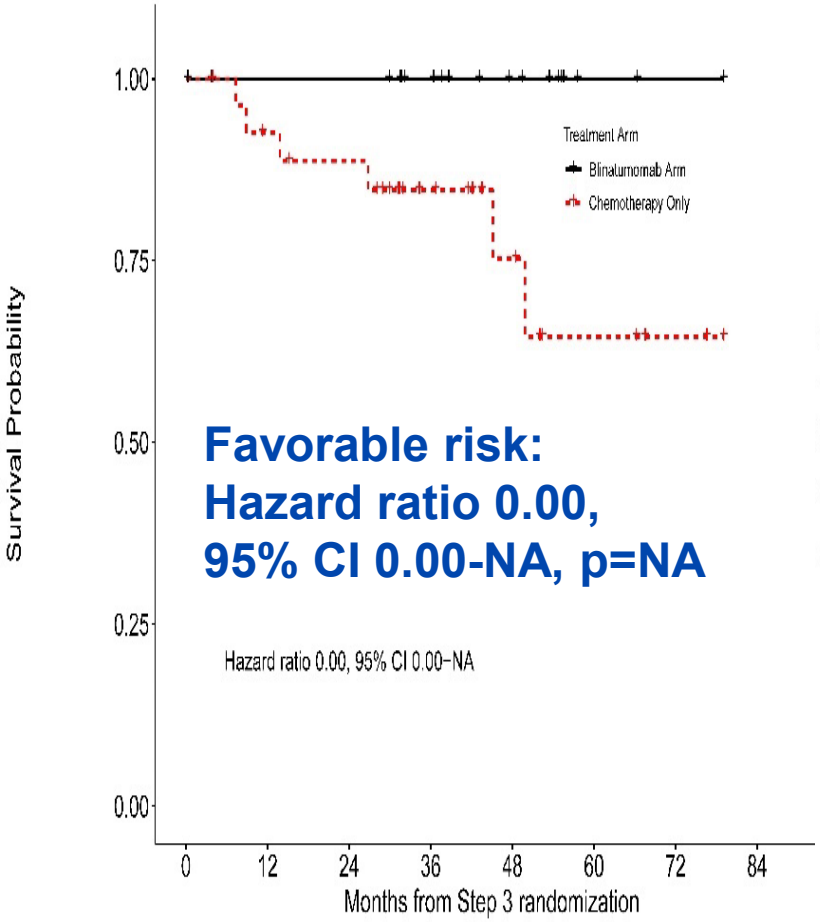
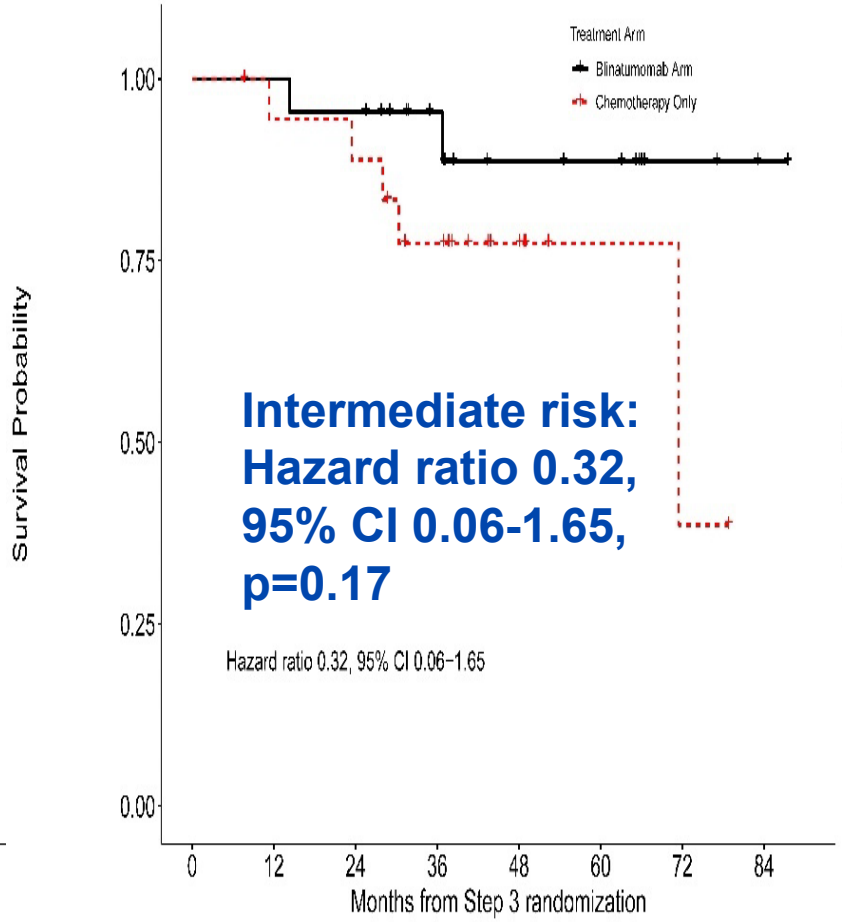
Kaplan-Meier Estimate of Overall Survival for the Patients with Favorable, Intermediate and Unfavorable Combined Molecular Risk by Treatment Arm



Favorable risk:
Hazard ratio 0.00,
95% CI 0.00-NA, p=NA

Number at risk

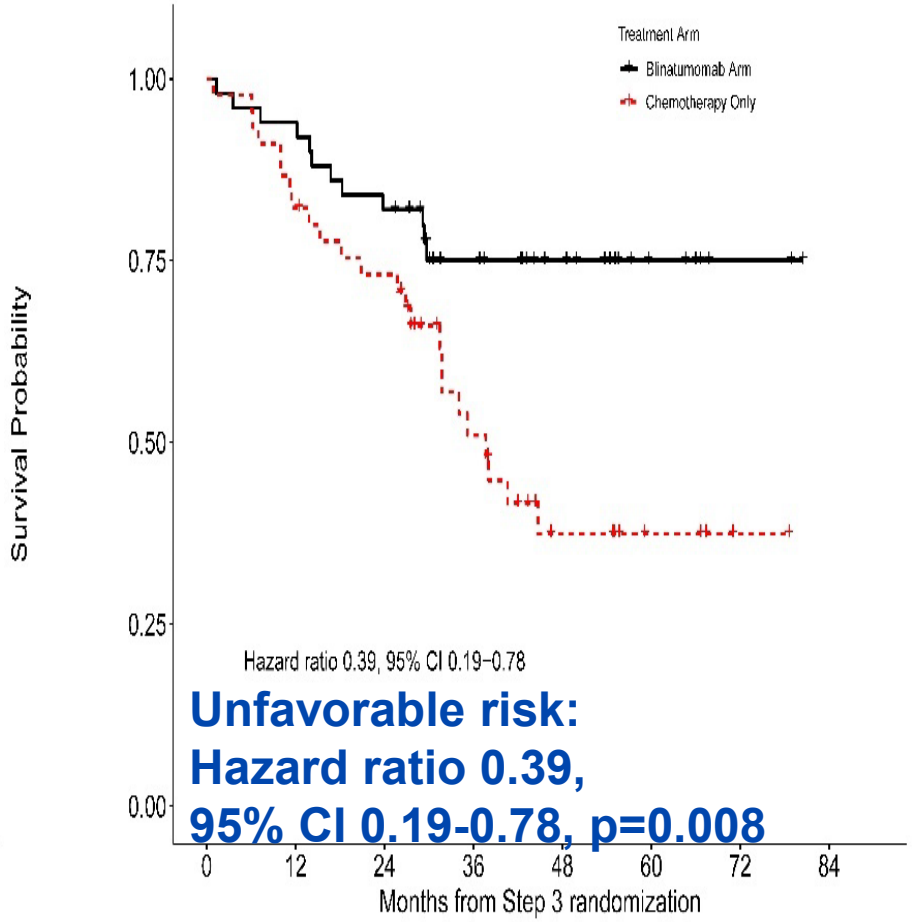
Blinatumomab Arm	19	17	17	13	8	2	1	0
Chemotherapy Only	28	24	22	14	8	4	2	0



Intermediate risk:
Hazard ratio 0.32,
95% CI 0.06-1.65,
p=0.17

Number at risk

Blinatumomab Arm	22	22	21	14	9	8	3	1
Chemotherapy Only	19	17	16	12	6	2	1	0



Unfavorable risk:
Hazard ratio 0.39,
95% CI 0.19-0.78, p=0.008

Number at risk

Blinatumomab Arm	50	47	41	25	17	6	2	0
Chemotherapy Only	45	37	32	17	8	4	1	0

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Black line represents the blinatumomab arm; Red line the chemotherapy only arm

CONCLUSIONS

- In the phase III randomized ECOG-ACRIN & NCTN trial E1910, consolidation with blinatumomab combined with chemotherapy has shown for the first time an overall survival advantage for adult patients with MRD-neg BCR::ABL negative B lineage ALL
- Blinatumomab provided OS benefit to younger and older patients, but to a greater extent for younger patients
- Benefit was also seen for pts with favorable and unfavorable molecular risk
- Patients with undetectable MRD (0%) had improved overall survival with blinatumomab; those with MRD between undetectable (0%) and 0.01% had survival benefit with blinatumomab, but subset numbers were too small to show definitive effect
- These results represent a new standard of care for this group of patients

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Key Takeaways

- Approved for ages 1 month or older
- 3 year OS rates 85% for blinatumomab group; 69% for chemo-only group
- At a median follow-up of 4.5 years, 5 year OS rate 82.4% for blinatumomab; 62.5% for chemo-only

FDA approves blinatumomab as consolidation for CD19-positive Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia

On June 14, 2024, the Food and Drug Administration approved blinatumomab (Blincyto, Amgen Inc.) for adult and pediatric patients one month and older with CD19-positive Philadelphia chromosome-negative B-cell precursor acute lymphoblastic leukemia (Ph-negative BCP ALL) in the consolidation phase of multiphase chemotherapy.

LESSONS LEARNED FROM E1910 AND RECENT TRIALS

- Induction therapy approaches in BCP-ALL include BFM-based regimens and HyperCVAD combined with immunotherapeutic agents
- Blinatumomab can improve outcomes in MRD negative patients and can be combined with chemotherapy, either sequentially after chemotherapy or alternating with chemotherapy; up to 4 cycles can be safely given
- MRD is the most powerful predictor of outcome
- Immunotherapy has great potential to lessen the need for chemotherapy

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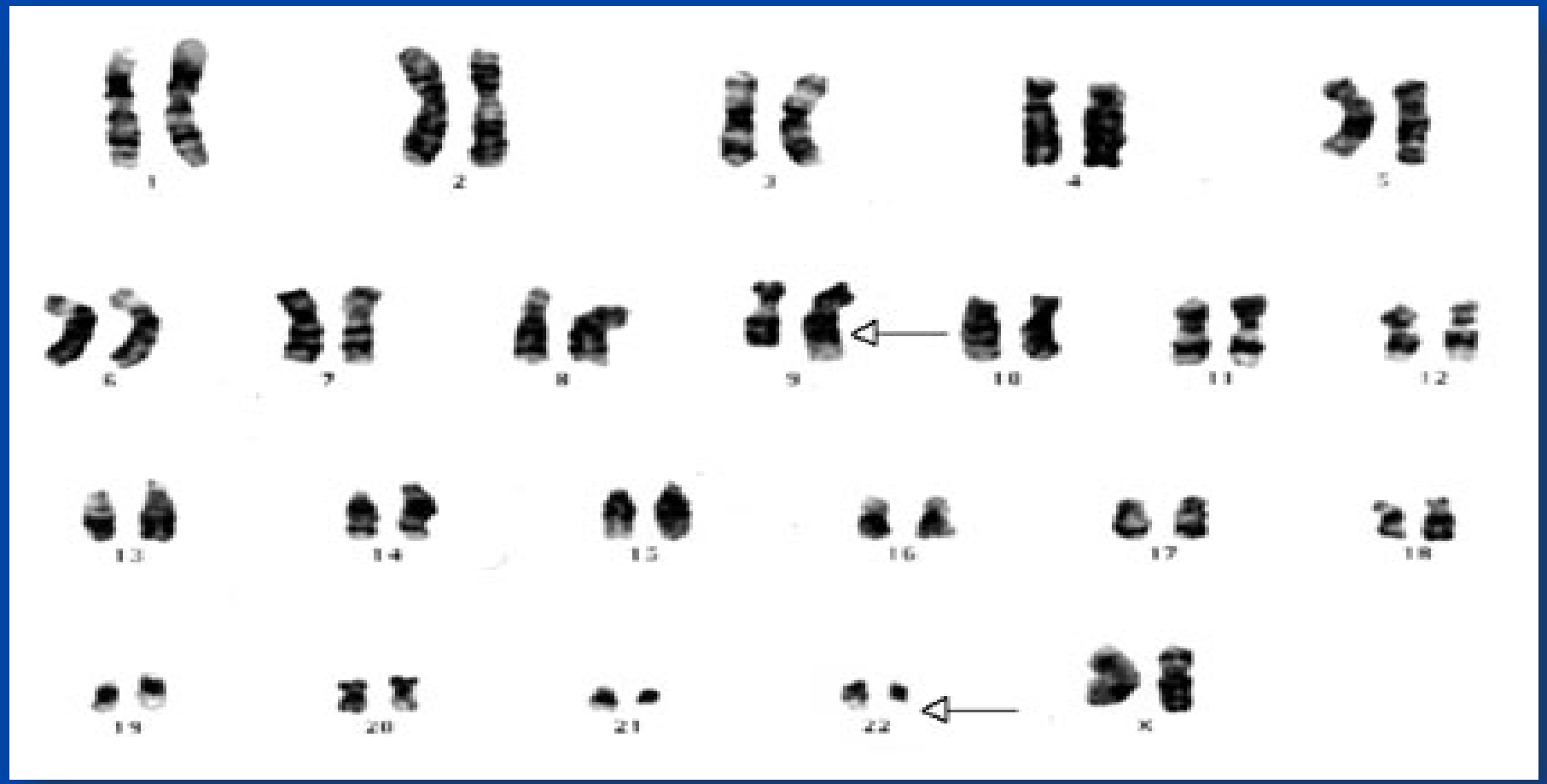
Philadelphia Chromosome

t(9;22)(q34;q11)



MAYO CLINIC

UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia

Blood 123:843-850, 2014.

Adele K. Fielding,[1] Jacob M. Rowe,[2] Georgina Buck,[3] Letizia Foroni,[4] Gareth Gerrard,[4] Mark R. Litzow,[5] Hillard Lazarus,[6] Selina M. Luger,[7] David I. Marks,[8] Andrew K. McMillan,[9] Anthony V. Moorman,[10] Bella Patel,[1] Elisabeth Paietta,[11] Martin S. Tallman,[12] and Anthony H. Goldstone[1]

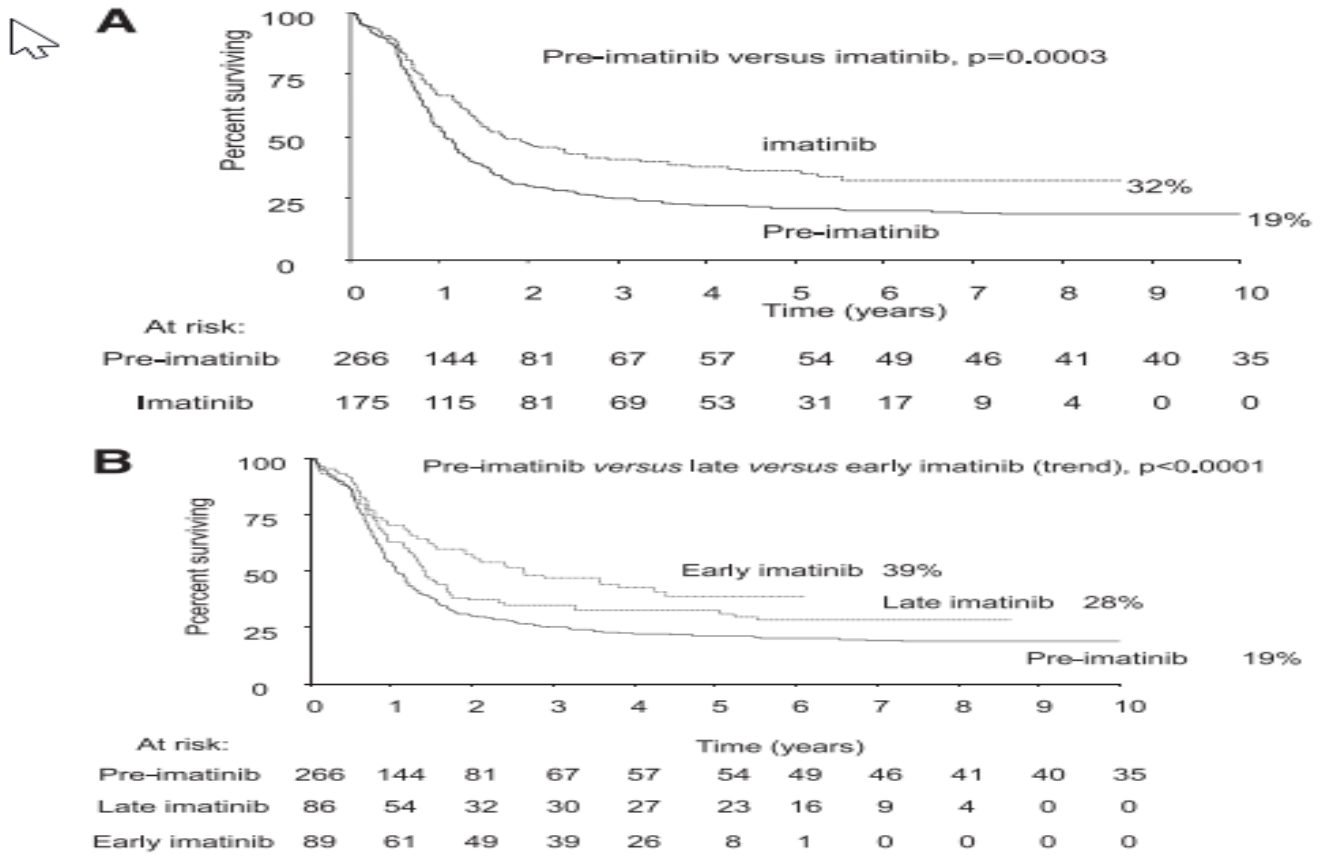


Figure 2. Kaplan Meier plot of 10-year OS of all patients with Ph+ ALL by cohort. (A) Preimatinib vs imatinib. (B) Preimatinib vs late imatinib vs early imatinib.

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US intergroup study of chemotherapy plus dasatinib and allogeneic stem cell transplant in Philadelphia chromosome positive ALL

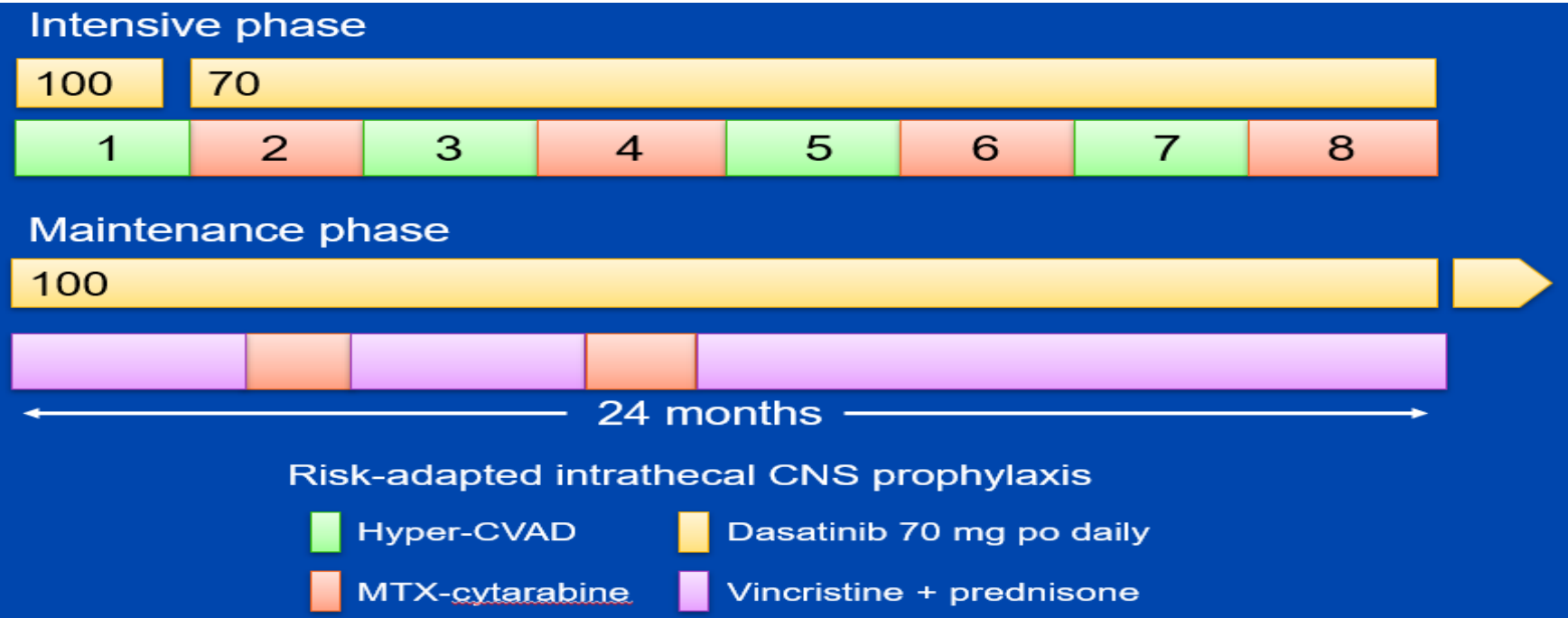
S0805 Phase II trial

Blood Advances 1:250-259, 2016

Farhad Ravandi,[1] Megan Othus,[2] Susan M. O'Brien,[3] Stephen J. Forman,[4] Chul S. Ha,[5] Jeffrey Y. C. Wong,[4] Martin S. Tallman,[6] Elisabeth Paietta,[7,8] Janis Racevskis,[7,8] Geoffrey L. Uy,[9] Mary Horowitz,[10] Naoko Takebe,[11] Richard Little,[11] Uma Borate,[12] Partow Kebriaei,[13] Laura Kingsbury,[2] Hagop M. Kantarjian,[1] Jerald P. Radich,[14] Harry P. Erba,[15] and Frederick R. Appelbaum[16]

[1]Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, TX; [2]SWOG Statistical Center, Seattle, WA; [3]University of California–Irvine, Orange, CA; [4]City of Hope National Medical Center, Duarte, CA; [5]University of Texas Health Science Center, San Antonio, TX; [6]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY; [7]Cancer Center, Montefiore Medical Center, Bronx, NY; [8]Albert Einstein College of Medicine, New York, NY; [9]Division of Oncology, Washington University School of Medicine, St. Louis, MO; [10]Medical College of Wisconsin, Milwaukee, WI; [11]Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, National Institutes of Health, Bethesda, MD; [12]University of Alabama at Birmingham, Birmingham, AL; [13]Department of Stem Cell Transplantation and Cellular Therapy, University of Texas MD Anderson Cancer Center, Houston, TX; [14]Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, WA; [15]University of Alabama at Birmingham (UAB) and UAB Comprehensive Cancer Center, Birmingham, AL; and [16]Fred Hutchinson Cancer Research Center, Seattle, WA

- n=97
- Ages 18-60
- Median age 44
- CR/CRi=88%
- AlloSCT in CR1= patients
- Post-SCT pts received dasatinib for 5 years



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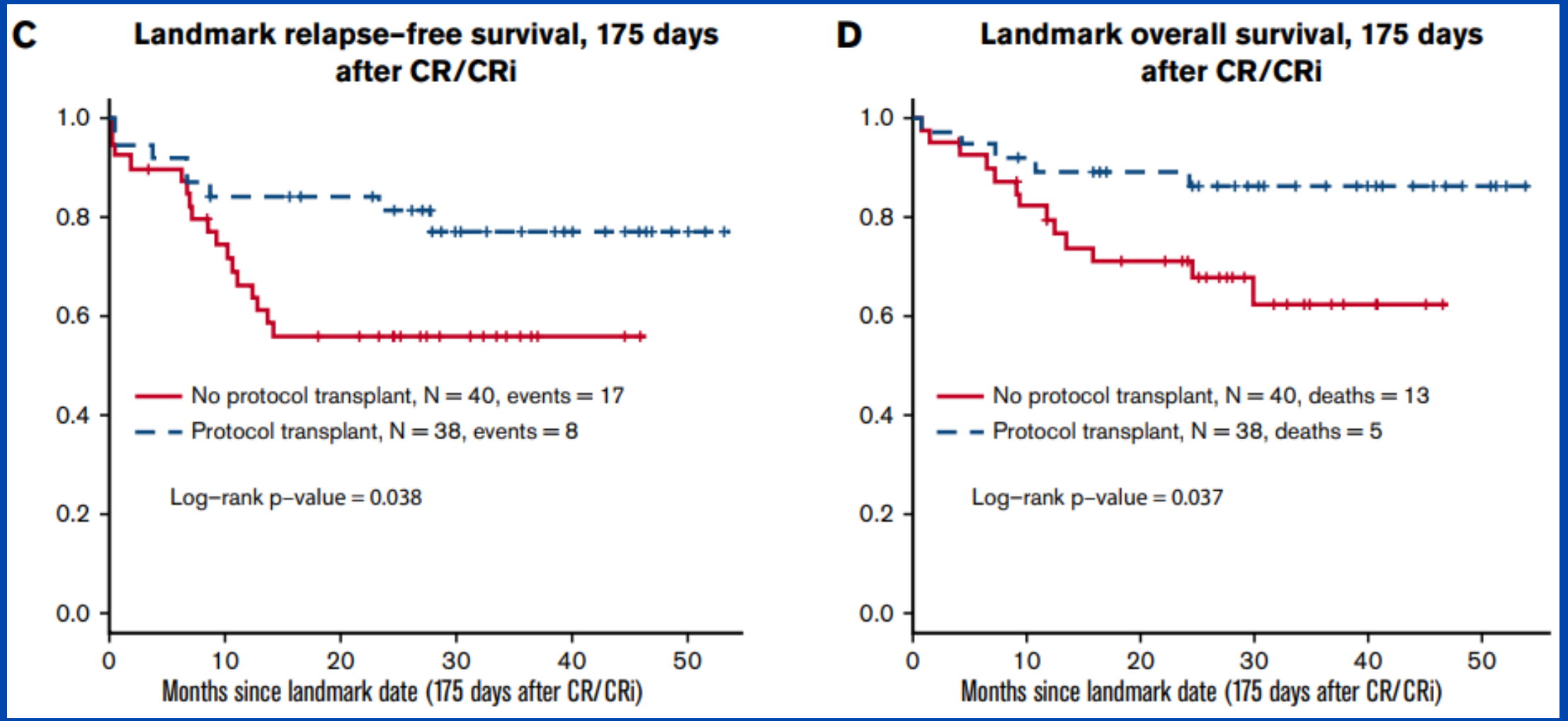
SWOG S0805 - Landmark Analysis; No ASCT vs ASCT



MAYO CLINIC

JAMA | Original Investigation

Ponatinib vs Imatinib in Frontline Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia
A Randomized Clinical Trial

JAMA 331(21):1814-1823, 2024 June 4

Elias Jabbour, MD; Hagop M. Kantarjian, MD; Ibrahim Aldoss, MD; Pau Montesinos, MD, PhD; Jessica T. Leonard, MD; David Gómez-Almaguer, MD; Maria R. Baer, MD; Carlo Gambacorti-Passerini, MD; James McCloskey, MD; Yosuke Minami, MD, PhD; Cristina Papayannidis, MD, PhD; Vanderson Rocha, MD, PhD, MS; Philippe Rousselot, MD, PhD; Pankit Vachhani, MD; Eunice S. Wang, MD; Bingxia Wang, PhD; Meliessa Hennessy, MPH; Alexander Vorog, MD; Niti Patel, PhD; Tammie Yeh, PhD; Jose-Maria Ribera, MD

- PhALLCON (pronounce: falcon) global registrational, phase 3, open-label trial in adults ≥18 years with newly diagnosed Ph+ALL
- From 1/19-5/22 randomized 232 evaluable pts 2:1 at 77 sites to ponatinib 30 mg/d or imatinib 600 mg/d with reduced intensity chemo followed by single agent ponatinib or imatinib after cycle 20. Ponatinib dose reduced to 15 mg/d after obtaining MRD-negative CR
- Primary endpoint for this interim analysis was MRD-negative CR (≤0.01% *BCR-ABL1* [MR4] by RT-PCR) maintained at least 4 wks

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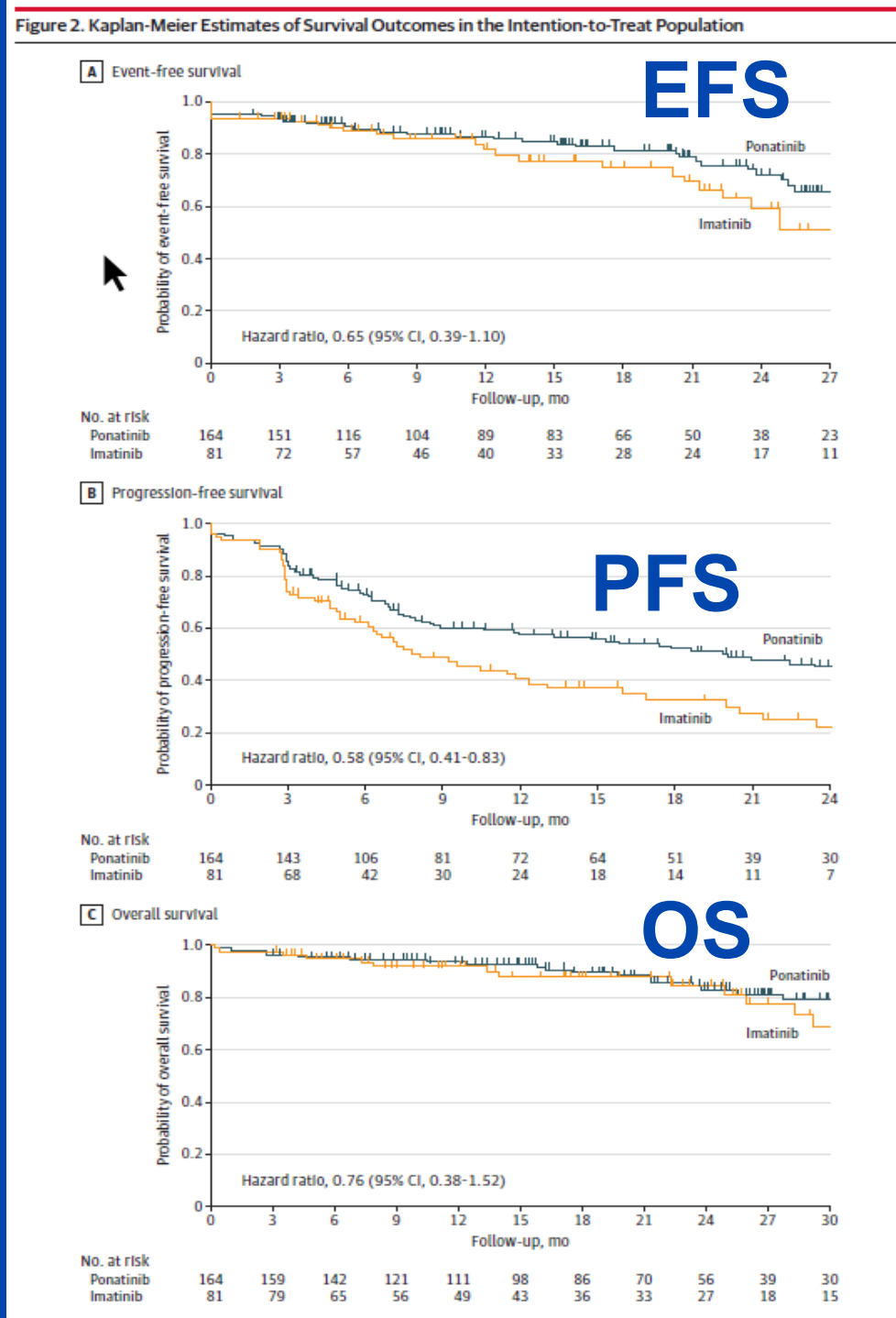
PhALLCON Outcomes

- Median age 54 years
- Ponatinib, n=154, Imatinib n=78
- MRD negative CR (1° endpoint)
  - Ponatinib 34.4%
  - Imatinib 16.7%
  - (HR .18, CI .06-.29, p=0.002)
- Arterial occlusive events infrequent
  - Ponatinib 2.5%
  - Imatinib 1.2%



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FDA grants accelerated approval to ponatinib with chemotherapy for newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia

Accelerated approval allows faster approval of drugs for serious conditions that fill an unmet medical need. Faster approval relies on use of surrogate endpoints (e.g., MRD negative CR).

On March 19, 2024, the Food and Drug Administration granted accelerated approval to ponatinib (Iclusig, Takeda Pharmaceuticals U.S.A., Inc.) with chemotherapy for adult patients with newly diagnosed Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL).

Full prescribing information for Iclusig will be posted here.

Efficacy was evaluated in PhALLCON (NCT03589326), a randomized, active-controlled,

Frontline combination of ponatinib and hyper-CVAD in Philadelphia chromosome-positive acute lymphoblastic leukemia: 80-months follow-up results

AJH 98:493-501, 2023

Hagop Kantarjian[1] | Nicholas J. Short[1] | Nitin Jain[1] | Koji Sasaki[1] | Xuelin Huang[2] | Fadi G. Haddad[1] | Issa Khouri[3] | Courtney D. DiNardo[1] | Naveen Pemmaraju[1] | William Wierda[1] | Guillermo Garcia-Manero[1] | Partow Kebriaei[3] | Rebecca Garris[1] | Sanam Loghavi[4] | Jeffrey Jorgensen[4] | Monica Kwari[1] | Susan O'Brien[5] | Farhad Ravandi[1] | Elias Jabbour[1]

- HyperCVAD+Ponatinib at 45 mg/d for 2 weeks 1st cycle, then 45 mg daily continuously in 1st 37 pts, then 30 mg/d continuously in subsequent 49 pts; then 15 mg/d with achievement of CMR
- Maintenance therapy with ponatinib+VCR/Pred for 2 yrs, then ponatinib daily indefinitely
- 12 intrathecal injections of cytarabine alternating with methotrexate were given as central nervous system prophylaxis
- Median age 46 yrs (range 21-80)
- 68/86 with active disease at enrollment all achieved CR with CMR 86%

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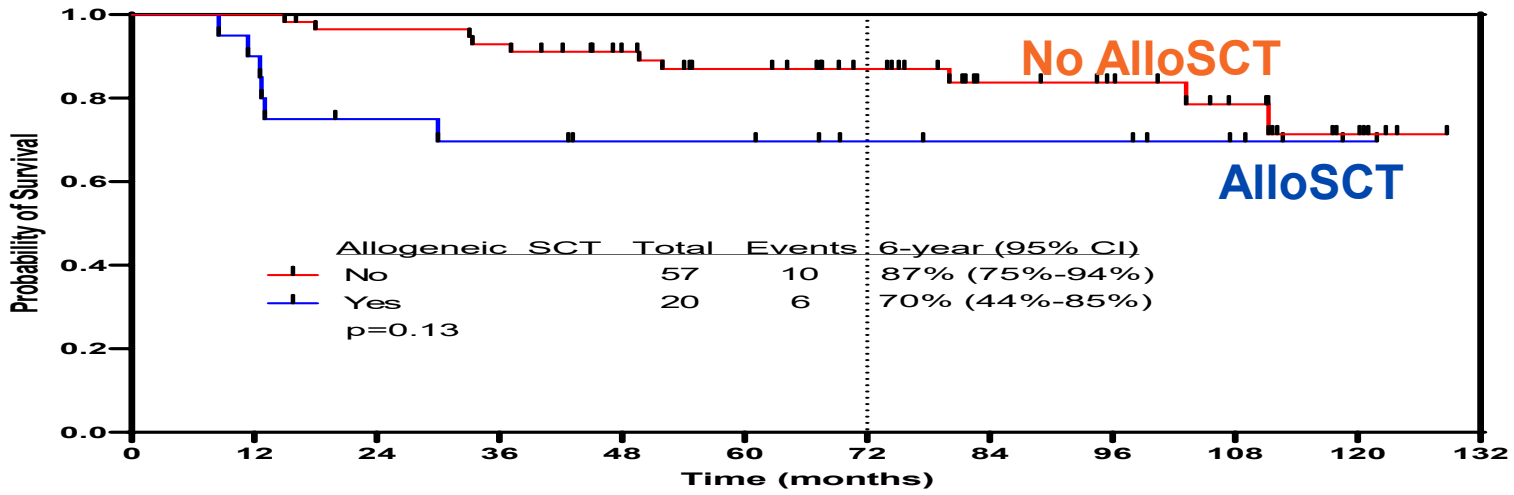
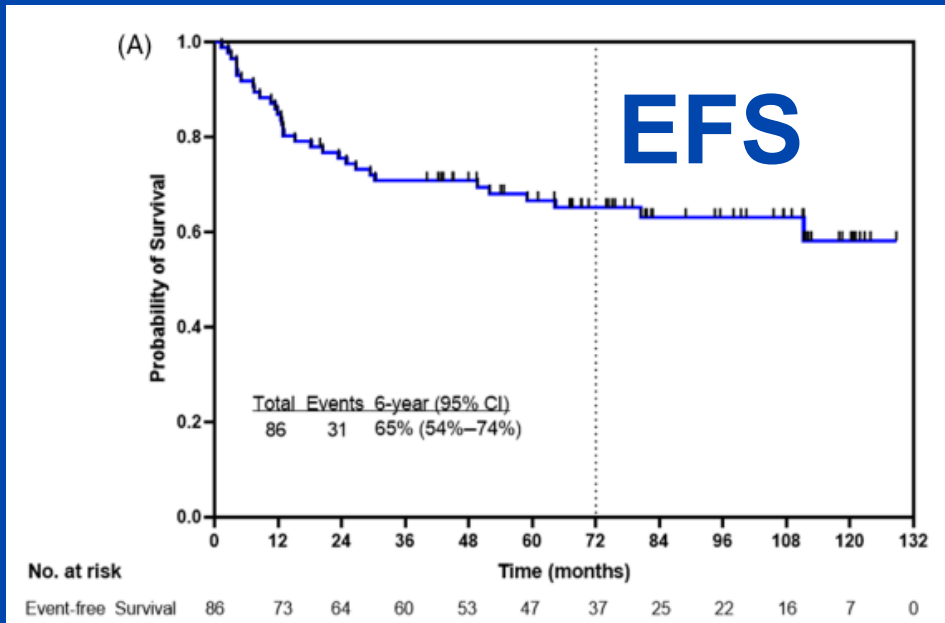
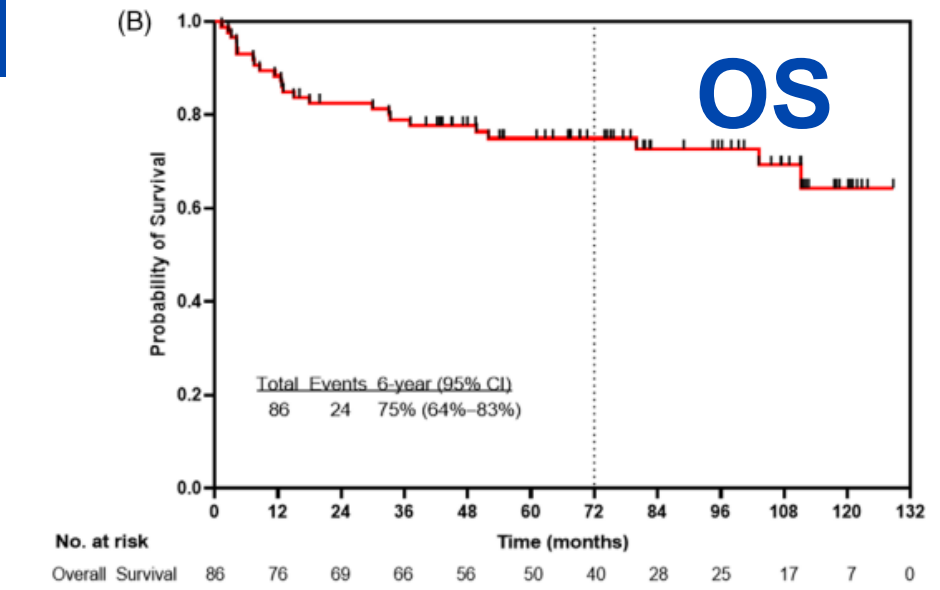
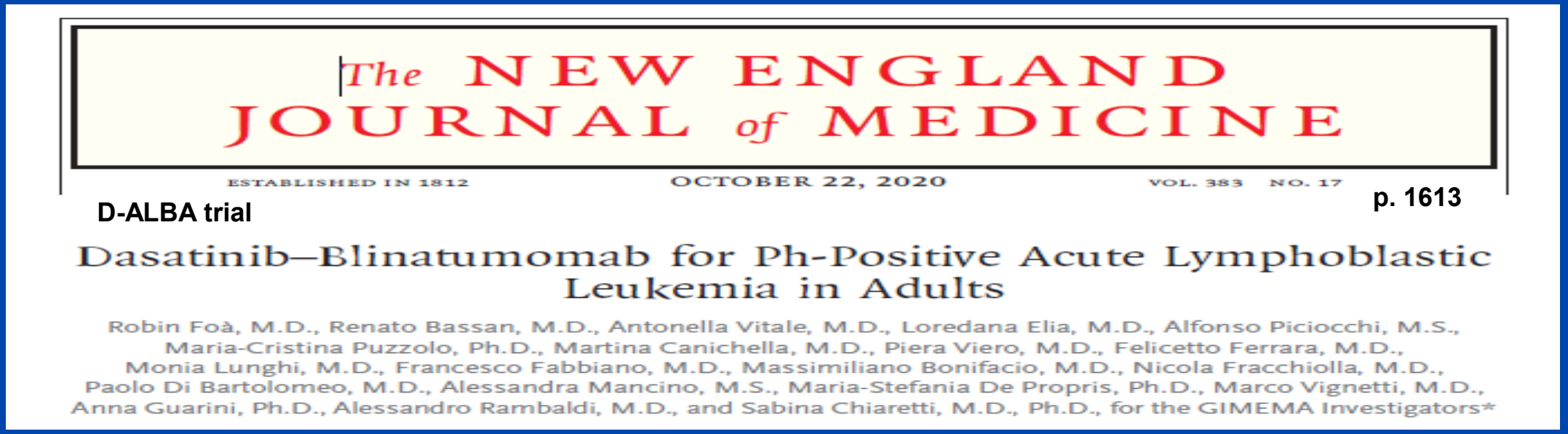
HyperCVAD+Ponatinib

- With median fu 80 mos estimated EFS 65%, OS 75%
- 20 pts went to alloSCT; no outcome for those in CR1
- 2 deaths from MI in 1st 37 pts led to ponatinib dose reductions in subsequent patients









The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 22, 2020 VOL. 383 NO. 17

p. 1613

D-ALBA trial

Dasatinib–Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults

Robin Foà, M.D., Renato Bassan, M.D., Antonella Vitale, M.D., Loredana Elia, M.D., Alfonso Piciocchi, M.S., Maria-Cristina Puzzolo, Ph.D., Martina Canichella, M.D., Piera Viero, M.D., Felicetto Ferrara, M.D., Monia Lunghi, M.D., Francesco Fabbiano, M.D., Massimiliano Bonifacio, M.D., Nicola Fracchiolla, M.D., Paolo Di Bartolomeo, M.D., Alessandra Mancino, M.S., Maria-Stefania De Propris, Ph.D., Marco Vignetti, M.D., Anna Guarini, Ph.D., Alessandro Rambaldi, M.D., and Sabina Chiaretti, M.D., Ph.D., for the GIMEMA Investigators*

- Phase II trial in adults of all ages with newly diagnosed Ph+ ALL
- 63 pts, median age 54 (range 24-82 years)
- 7 days of steroids, then dasatinib 140 mg/d for 85 days (steroids to day +31)
- Then blinatumomab 28 mcg/d for 2-5 cycles
- 61 evaluable; 98% had CR at day+85; 29% molecular response
- After cycle 2 blina, molecular response in 60%
- 24 pts underwent allografting

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Long-Term Results of the Dasatinib-Blinatumomab Protocol for Adult Philadelphia-Positive ALL

JCO 42 (8):881-85, 2024

Robin Foà, MD[1]; Renato Bassan, MD[2]; Loredana Elia, BSc[1]; Alfonso Piciocchi, MS[3]; Stefano Soddu, MS[3]; Monica Messina, PhD[3]; Felicetto Ferrara, MD[4]; Monia Lunghi, MD, PhD[5]; Antonino Mulè, MD[6]; Massimiliano Bonifacio, MD, PhD[7]; Nicola Fracchiolla, MD[8]; Prassede Salutari, MD[9]; Paola Fazi, MD[3]; Anna Guarini, BSc[1]; Alessandro Rambaldi, MD[10]; and Sabina Chiaretti, MD, PhD[1]

- At a median follow-up of 53 months
  - DFS 75.8%
  - EFS 74.6%
  - OS 80.7%
- No events occurred among early molecular responders
- 29 patients (27 with molecular CR) never received chemotherapy/transplant and continued with TKI therapy only
- Allogeneic transplant done in pts with persistent positive MRD with 14% TRM
- 9 relapses and 6 deaths have occurred

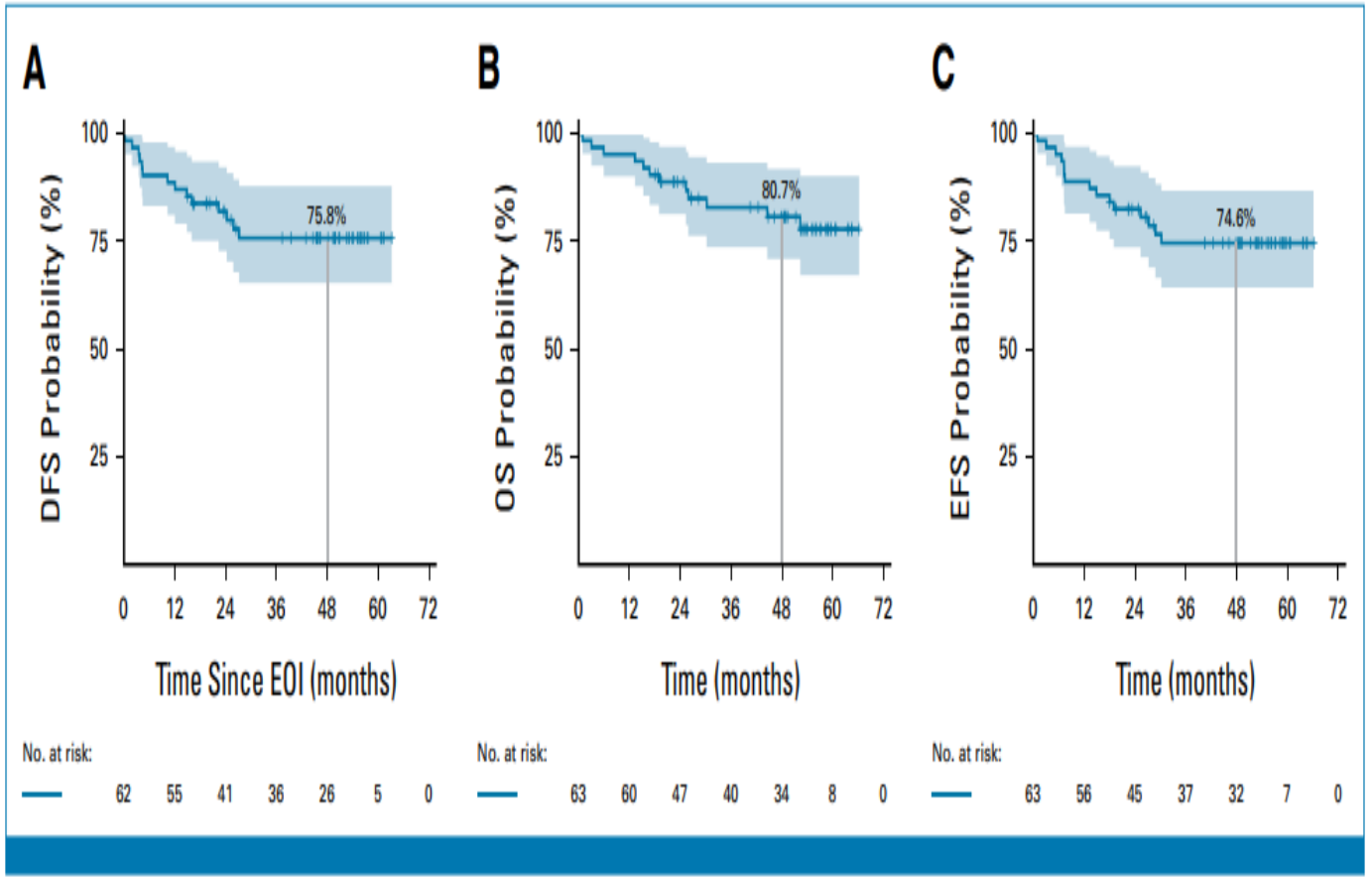

FIG 1. (A) DFS, (B) OS, and (C) EFS calculated from the EOI (d +85) and diagnosis/treatment initiation. The shadings of each curve show the 95% CI at a median follow-up of 53 months. DFS, disease-free survival; EFS, event-free survival; EOI, end of induction; OS, overall survival.

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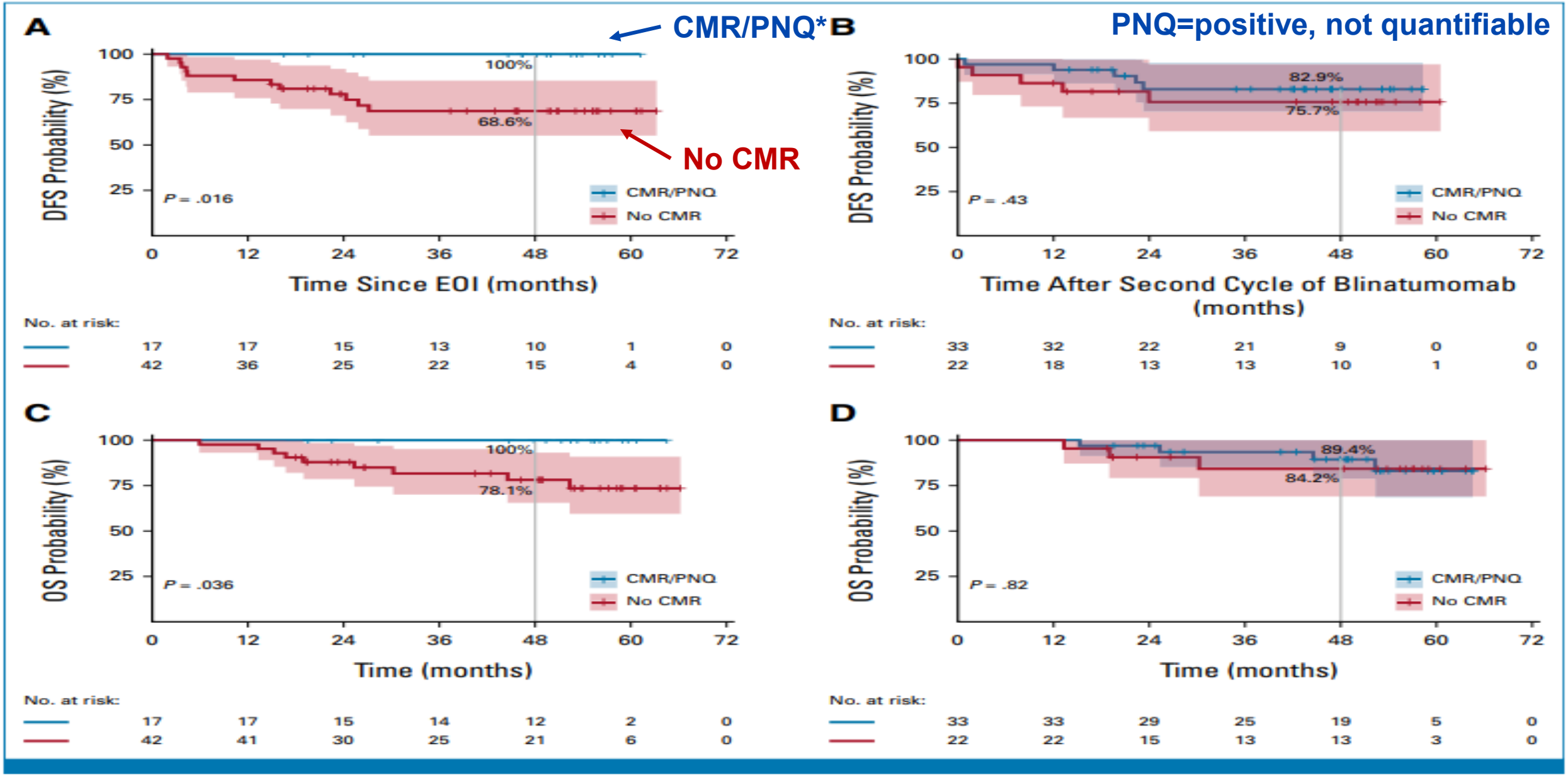
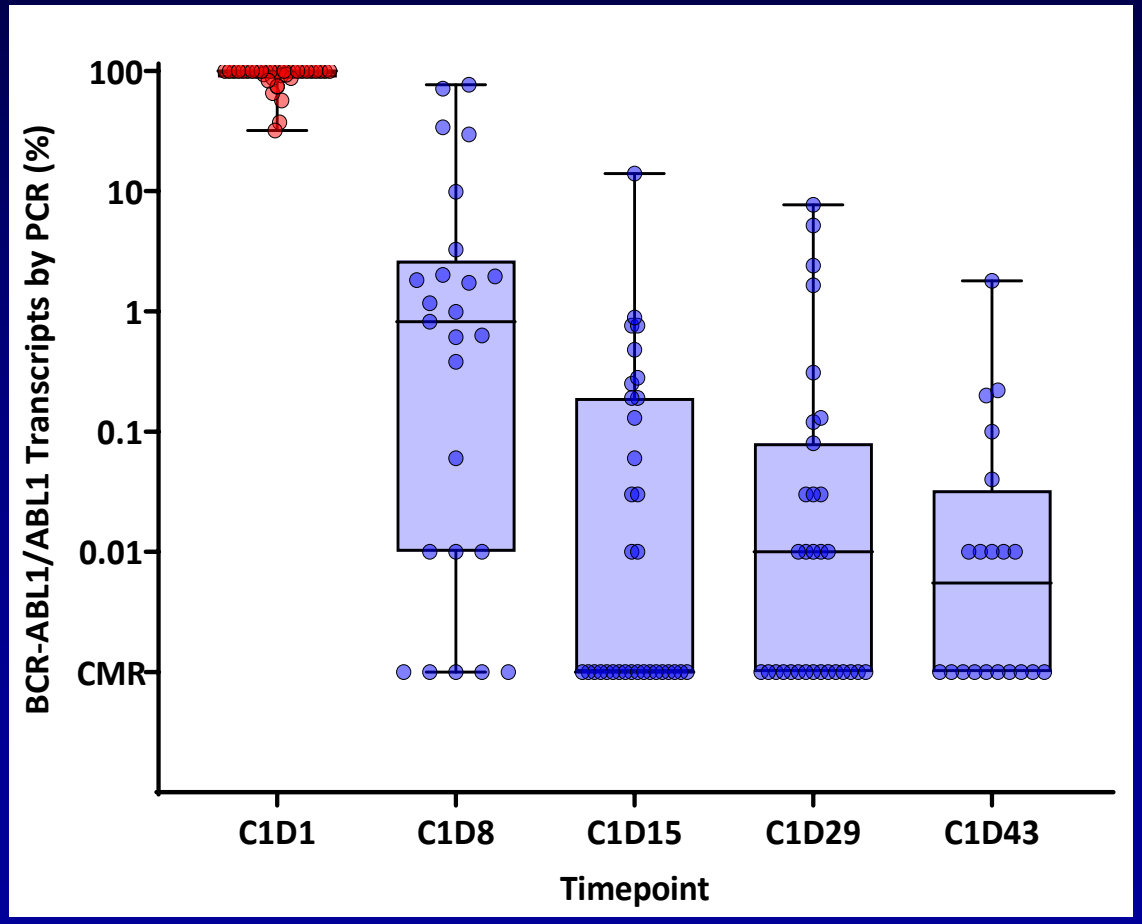
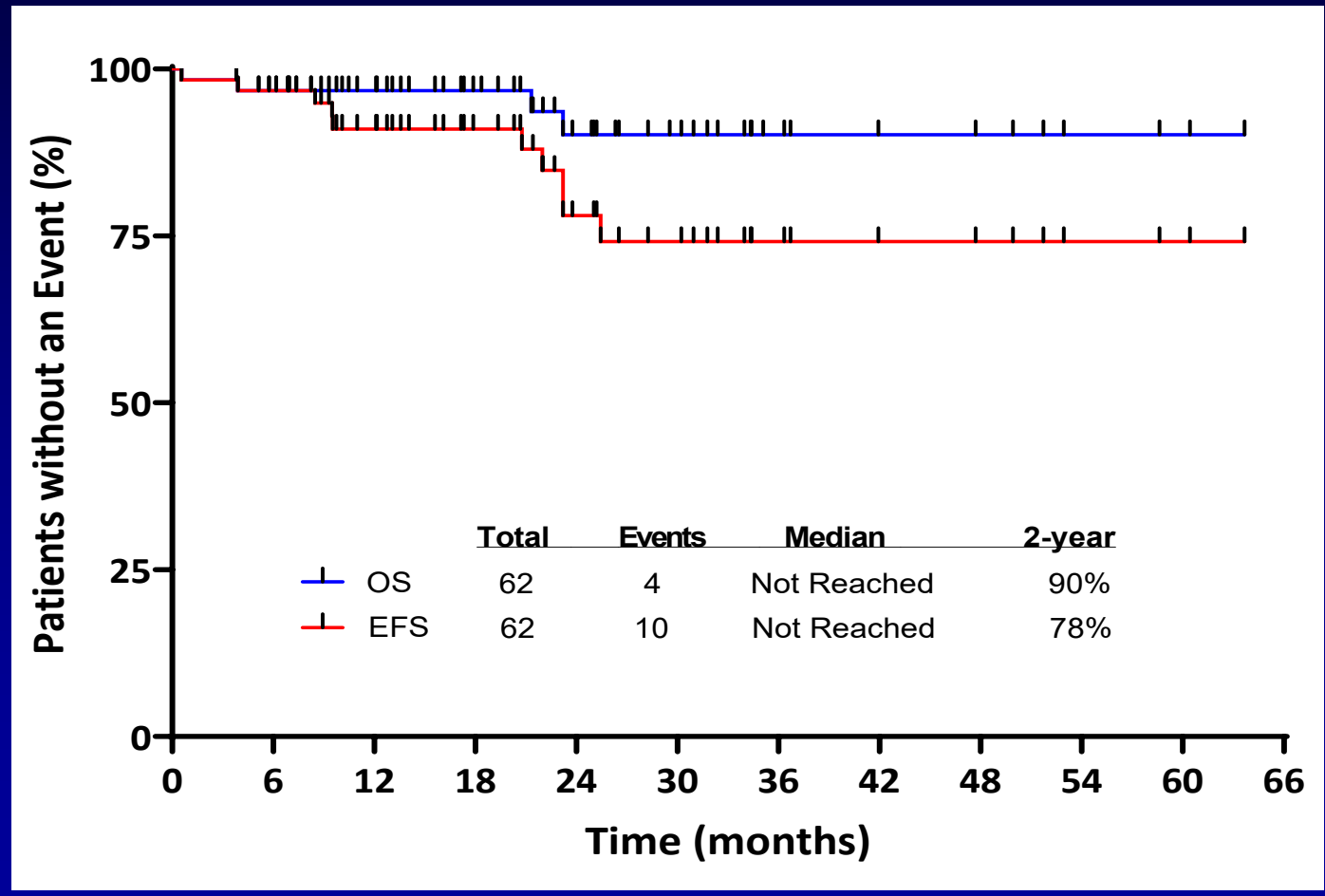


FIG 2. (A and B) DFS and (C and D) OS according to molecular response. DFS was calculated from (A) EOI (d +85) and after the (B) second cycle of blinatumomab (primary end point); OS was calculated from diagnosis/treatment initiation stratifying patients according to molecular response at the (C) EOI (d +85) and (D) after the second cycle of blinatumomab. Blue line: molecular responders; red line: non-molecular responders. The shadings of each curve show the 95% CI. CMR, complete molecular response; DFS, disease-free survival; EOI, end of induction; OS, overall survival; PNQ, positive nonquantifiable.

Ponatinib and Blinatumomab in Newly Dx Ph-Positive ALL

- 62 pts Rx with simultaneous ponatinib 30-15mg/D and blinatumomab x 5 courses. 12-15 ITs
- Only 2 pt had SCT(3%); Median F/U 17 mos.
- CR/CRi 98% (CR 95%); CMR 84% (67% after C1); NGS-MRD negativity 94%
- 2-yr EFS 78%, OS 90%. 7 relapses (all p190): 4 CNS, 1 CRLF2+ (Ph-), 2 systemic. 5/7 WBC>75k





Jabbour. Lancet Haematol. 2023;10(1):e24-e34. . Haddad. Blood 142: abstr 2827;2023

Results of the Simultaneous Combination of Ponatinib and Blinatumomab in Philadelphia Chromosome-Positive ALL

JCO 00:1-6, July 19, 2024

Hagop Kantarjian, MD[1]; Nicholas J. Short, MD[1]; Fadi G. Haddad, MD[1]; Nitin Jain, MD[1]; Xuelin Huang, PhD[2]; Guillermo Montalban-Bravo, MD[1]; Rashmi Kanagal-Shamanna, MD[3]; Tapan M. Kadia, MD[1]; Naval Daver, MD[1]; Kelly Chien, MD[1]; Yesid Alvarado, MD[1]; Guillermo Garcia-Manero, MD[1]; Ghayas C. Issa, MD[1]; Rebecca Garris, MS[1]; Cedric Nasnas, MD[1]; Lewis Nasr, MD[1]; Farhad Ravandi, MD[1]; and Elias Jabbour, MD[1]

- Update on 60 pts with new dx Ph+ ALL
- With median fu of 24 mos
  - CMR by *BCR::ABL1* PCR 83% (67% course 1)
  - MRD by clonoSEQ® 98% (45% course 1)
- Only 2 pts to alloHCT
- 7 pts relapsed (2 systemic, 4 CNS, 1 EM)
- Estimated 3y OS 91%, EFS 77%
- For AE 3 stopped blin, 9 ponatinib (including several with vascular events)

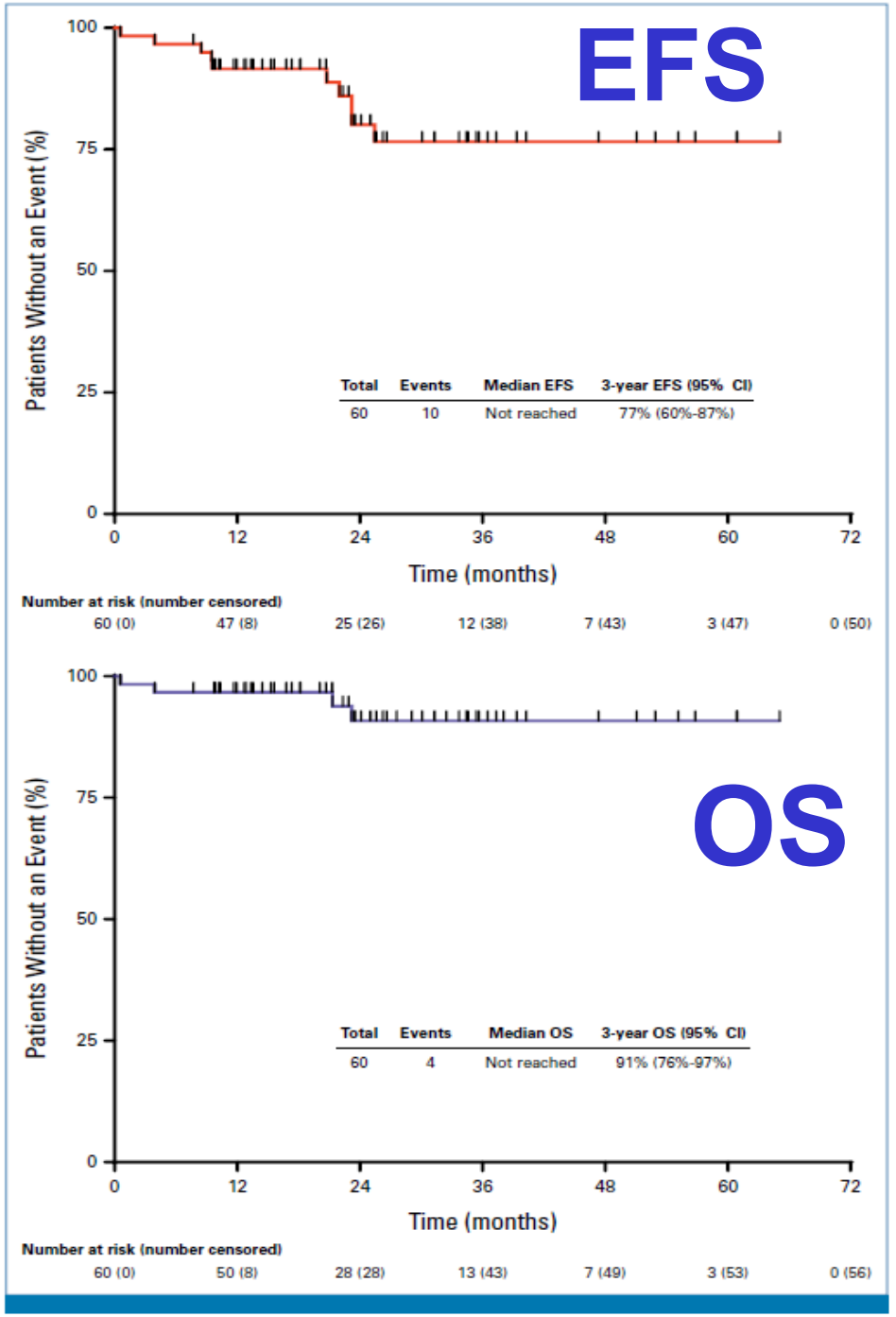
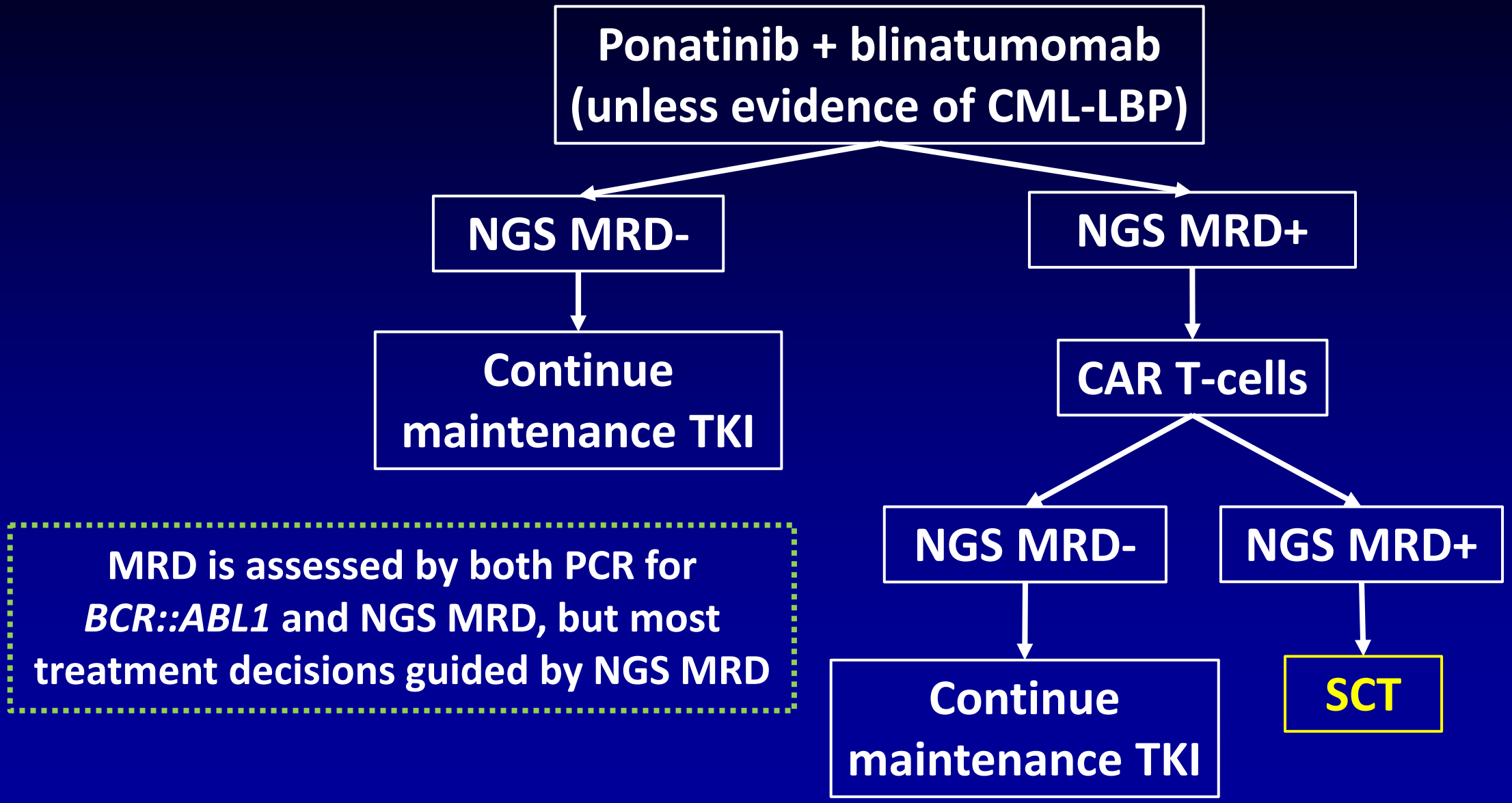
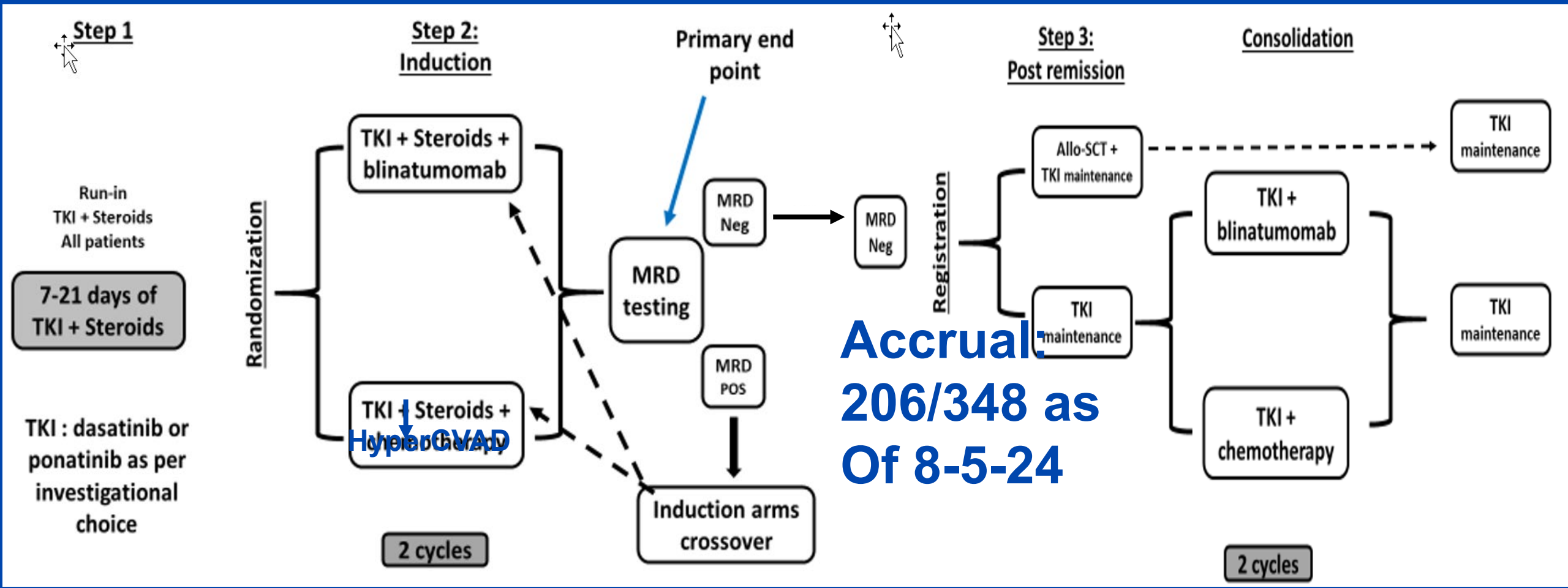


FIG 2. (A) EFS and (B) OS. EFS, event-free survival; OS, overall survival.

Rx Algorithm for Ph+ ALL



US Intergroup Trial: EA9181, A Phase III Randomized Trial of Steroids+TKI Induction with Chemotherapy or Blinatumomab for Newly Diagnosed BCR-ABL-positive ALL in Adults



CLINICAL TRIALS AND OBSERVATIONS

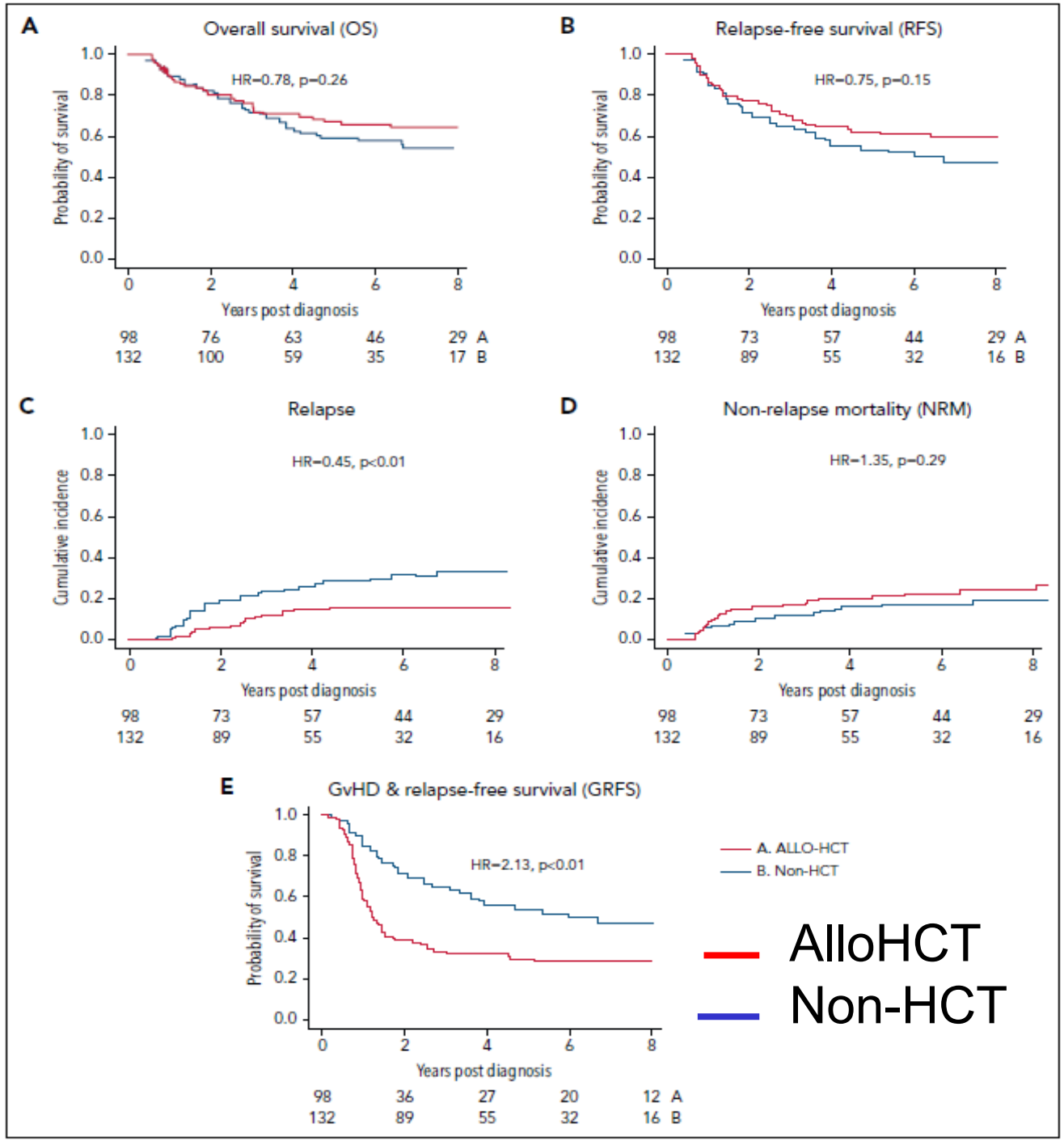
Blood 140:2101, 2022

CME Article

The role of allogeneic transplant for adult Ph+ ALL in CR1 with complete molecular remission: a retrospective analysis

Armin Ghobadi,[1] Michael Slade,[1] Hagop Kantarjian,[2] Julio Alvarenga,[3] Ibrahim Aldoss,[3] Kahee A. Mohammed,[1] Elias Jabbour,[2] Rawan Faramand,[4] Bijal Shah,[4] Frederick Locke,[4] Warren Fingrut,[5] Jae H. Park,[5] Nicholas J. Short,[2] Feng Gao,[1] Geoffrey L. Uy,[1] Peter Westervelt,[1] John F. DiPersio,[1] Richard E. Champlin,[6] Monzr M. Al Malki,[3] Farhad Ravandi,[2,*] and Partow Kebriaei[6,*]

- 230 pts from 5 US centers
- Attained CR w/in 90 days
- Compared +/- alloHCT
- OS HR 1.05 (CI .63-1.73)
- RFS HR .86 (CI .54-1.37)
- Lower relapse with alloHCT
- Higher TRM with alloHCT
- Meta-analysis in Cancer 129: 1523, 2023 confirms same



Diagnosis, prognostic factors, and assessment of ALL in adults: 2024 ELN recommendations from a European expert panel

Blood 143(19):1891-1902, May 9, 2024

Nicola Gökbuget,[1] Nicolas Boissel,[2] Sabina Chiaretti,[3] Hervé Dombret,[4] Michael Doubek,[5] Adele Fielding,[6] Robin Foà,[3] Sebastian Giebel,[7] Dieter Hoelzer,[1] Mathilde Hunault,[8] David I. Marks,[9] Giovanni Martinelli,[10] Oliver Ottmann,[11] Anita Rijneveld,[12] Philippe Rousselot,[13] Josep Ribera,[14] and Renato Bassan[15]

Blood 143(19): 1903-1930, May 9, 2024

Management of ALL in adults: 2024 ELN recommendations from a European expert panel

Nicola Gökbuget,[1] Nicolas Boissel,[2] Sabina Chiaretti,[3] Hervé Dombret,[4] Michael Doubek,[5] Adele Fielding,[6] Robin Foà,[3] Sebastian Giebel,[7] Dieter Hoelzer,[1] Mathilde Hunault,[8] David I. Marks,[9] Giovanni Martinelli,[10] Oliver Ottmann,[11] Anita Rijneveld,[12] Philippe Rousselot,[13] Josep Ribera,[14] and Renato Bassan[15]

CONCLUSIONS

- Induction therapy approaches in BCP-ALL include BFM-based regimens and Hyper-CVAD combined with immunotherapeutic agents
- Blinatumomab can improve outcomes in MRD-negative pts and can be combined with chemotherapy, either sequentially after chemotherapy or alternating with chemotherapy; up to 4 cycles can be safely given
- Induction therapy with a TKI, preferably ponatinib, combine with chemotherapy or blinatumomab provides excellent likelihood of achievement of a CR with CMR in Ph+ ALL
- Patients who achieve CMR within 3 months of diagnosis with Ph+ ALL may not need an alloSCT
- Immunotherapy has great potential to lessen the need for chemotherapy

MAYO CLINIC

Acknowledgments

- ECOG-ACRIN
  - Jacob Rowe
  - Marty Tallman
  - Selina Luger
  - Hillard Lazarus
  - Yishai Ofran
  - Neil Palmisiano
- NCRI
  - Adele Fielding
  - Tony Goldstone
- SWOG
  - Harry Erba
  - Jerry Radich
  - Elias Jabbour
- Alliance
  - Rich Stone
  - Wendy Stock
  - Dan Deangelo
  - Matt Wieduwilt