2024 American Society of Hematology (ASH) Blinatumomab Post-Congress Deck

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Blinatumomab Poster Presentations

Amgen Sponsored Studies

Single-Agent Subcutaneous Blinatumomab for Advanced B-Cell Acute Lymphoblastic Leukemia: Long-Term Follow-Up from a Phase 1b Dose Expansion Cohort– Elias Jabbour
Poster ID: Poster 1440

Poster

ASH 2024

Blinatumomab Oral Presentations

Non-Amgen Sponsored Studies

Blinatumomab added to chemotherapy improves disease-free survival in newly diagnosed NCI standard risk pediatric B-acute lymphoblastic leukemia: Results from the randomized Children's Oncology Group Study AALL1731 - Rachel E. Rau
Oral Presentation ID: Plenary-Oral 1

Blinatumomab and Ponatinib for Adults with Newly Diagnosed Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Updated Results and Predictors of Relapse – Nicholas J. Short
Oral Presentation ID: 837

Assessment of Outcomes of Allogeneic Stem Cell Transplantation By Treatment Arm in Newly Diagnosed Measurable Residual Disease Negative Patients with B-Lineage Acute Lymphoblastic Leukemia Randomized to Conventional Chemotherapy +/- Blinatumomab in the ECOG-ACRIN E1910 Phase III National Clinical Trials Network Trial – Michaela Liedtke
Oral Presentation ID: 779

Oral

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Blinatumomab Poster Presentations

Non-Amgen Sponsored Studies

Safety and Feasibility of Blinatumomab as Frontline Therapy for Pediatric Patients with B-Acute Lymphoblastic Leukemia and Lymphoma: St. Jude Total Therapy Study XVII – Caitlyn Duffy
Poster ID: Poster 4208

Updated Results of the Combination of Mini-Hyper-CVD with Inotuzumab Ozogamicin and Blinatumomab in Patients with Relapsed/Refractory B-Cell ALL – Fadi G. Haddad
Poster ID: Poster 2811

Updated Results from a Phase 2 Study Hyper-CVAD, with or without Inotuzumab Ozogamicin, and Sequential Blinatumomab in Patients with Newly Diagnosed B-ALL– Daniel Nguyen
Poster ID: Poster 1439

Clearance of Very Low Levels of Measurable Residual Disease with Blinatumomab Significantly Improves Outcomes in B-cell ALL–Daniel Nguyen
Poster ID: Poster 1465

Poster

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Blinatumomab Poster Presentations

Non-Amgen Sponsored Studies

Addition of Blinatumomab to Consolidation Therapy Among Older Newly Diagnosed Patients (pts) with BCR::ABL1 Negative B-Lineage Acute Lymphoblastic Leukemia (ALL) in the ECOG-ACRIN E1910 Randomized Phase III Trial – Nikolai A. Podoltsev
Poster ID: Poster 4211

Chemotherapy Free Regimen of Inotuzumab Ozogamicin and Blinatumomab in Frontline Therapy of Older Patients with Philadelphia Negative B-Cell Acute Lymphoblastic Leukemia – Jayastu Senapati
Poster ID: Poster 1442

Low Intensity Mini-HyperCVD (mHCVD), Inotuzumab Ozogamicin (Ino) with/without Blinatumomab (Blina) in Older Patients with Newly Diagnosed Philadelphia Negative B-Cell Acute Lymphoblastic Leukemia (B-ALL): 10 Years Update – Jayastu Senapati Poster ID: Poster 1441

Outcomes of Adult Patients with Philadelphia Negative B-Cell Acute Lymphoblastic Leukemia (B-ALL) Having Myeloid Type Mutations Treated with Inotuzumab/Blinatumomab Containing Frontline Regimens – Jayastu Senapati
Poster ID: Poster 1461

Poster

AMGEN

Single-Agent Subcutaneous Blinatumomab for Advanced B-Cell Acute Lymphoblastic Leukemia: Long-Term Follow-Up From a Phase 1b Dose Expansion Cohort

Elias Jabbour[1], Gerhard Zugmaier[2], Pilar Martínez-Sánchez[3], José J. Rifón[4], Vaibhav Agrawal[5], Ryan D. Cassaday[6,7], Thomas Cluzeau[8], Françoise Huguet[9], Vladan Vucinic[10], Boris Böll[11], Anita W. Rijneveld[12], Mar Tormo[13], Maher Abdul-Hay[14], Paul R. Gordon[15], Alessandro Rambaldi[16], Hagop M. Kantarjian[1]

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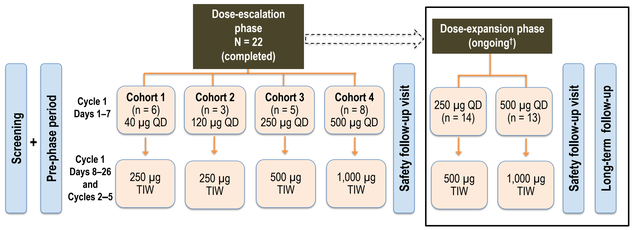
BACKGROUND

- Blinatumomab, a BiTE® (bispecific T-cell engager) molecule that redirects CD3+ T cells to engage and lyse CD19+ target cells, has demonstrated efficacy for patients with B-ALL when administered as a 28-day continuous intravenous infusion (cIV).[1]
- Subcutaneous (SC) administration of blinatumomab monotherapy can:
  - Simplify administration and improve convenience.
  - Eliminate the need for a device (pump) for infusion, thus abrogating the risk of device-related complications such as incorrect pump settings, dose interruptions from intravenous line occlusion, and line infections.
  - Deliver earlier target dose and overall higher dose of blinatumomab to patients.
  - Improve patients' overall health-related quality of life.
- We previously reported from the dose expansion of this phase 1b trial (NCT04521231) that SC blinatumomab monotherapy can provide high efficacy with an acceptable safety profile and is well tolerated in adults with advanced R/R B-ALL.[2] Here, we provide follow-up data.

B-ALL, B-cell acute lymphoblastic leukemia; BiTE®, bispecific T-cell engager; cIV, continuous intravenous infusion; R/R, relapsed/refractory; SC, subcutaneous.

STUDY OVERVIEW

Figure 1. Study Design



- Adult patients with R/R B-ALL* could receive 1–5 cycles of SC blinatumomab as monotherapy. Transplantation any time after the end of the first cycle was permitted. Each cycle included a 26-day treatment period and an 8-day treatment-free interval.
- Blinatumomab monotherapy was given in one of two dosing regimens:
  1. 250 µg once-daily (QD) for Week 1 and 500 µg three times weekly (TIW) thereafter (250 µg QD→500 µg TIW) OR
  2. 500 µg QD for Week 1 and 1000 µg TIW thereafter (500 µg QD→1000 µg TIW)

Study design described in Jabbour et al. *Am J Hematol*. 2024: 99(4):586-595. Data are as of September 13, 2024. *Patients had ≥5% blasts in the BM and were either: 1) Refractory to primary induction therapy or salvage therapy OR 2) Had relapsed disease including untreated relapse (any stage), refractory relapse, or relapse after any salvage therapy or allogeneic HSCT. †Two additional cohorts are being enrolled to generate additional data. BM evaluation was performed on Day 27 of each cycle and additionally on Day 12 of Cycle 1. Adverse events were graded per CTCAE version 5.0. B-ALL, B-cell acute lymphoblastic leukemia; BM, bone marrow; HSCT, hematopoietic stem cell transplant; QD, once daily; R/R, relapsed/refractory; SC, subcutaneous; TIW, three times weekly.

Efficacy Assessments

The primary efficacy endpoint was complete remission with full hematologic recovery (CR) or complete remission with only partial hematologic recovery (CRh) within two cycles.

- Patients with incomplete hematologic recovery (CRi) and bone marrow response (BMR) were included in the analysis.
- Duration of CR/CRh/CRi/BMR was defined from initial remission until relapse or latest disease assessment.

Table 1. Efficacy Measures

Response	Definition
CR	<5% blasts in the BM, no evidence of disease, and full recovery of peripheral blood counts (platelet count >100,000/µL, ANC >1,000/µL)
CRh	<5% blasts in the BM, no evidence of disease, and partial recovery of peripheral blood counts (platelet count >50,000/µL, ANC >500/µL)
CRi	<5% blasts in the BM, no evidence of disease, and incomplete recovery of peripheral blood counts (platelet count >100,000/µL OR ANC >1000/µL)
BMR	<5% blasts in the BM not meeting CR, CRh, or CRi criteria
MRD-negative	$<10^{-4}$ leukemic blasts detectable by flow cytometry or polymerase chain reaction

ANC, absolute neutrophil count; BM, bone marrow; BMR, bone marrow response; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; MRD, measurable residual disease.

Key Takeaways

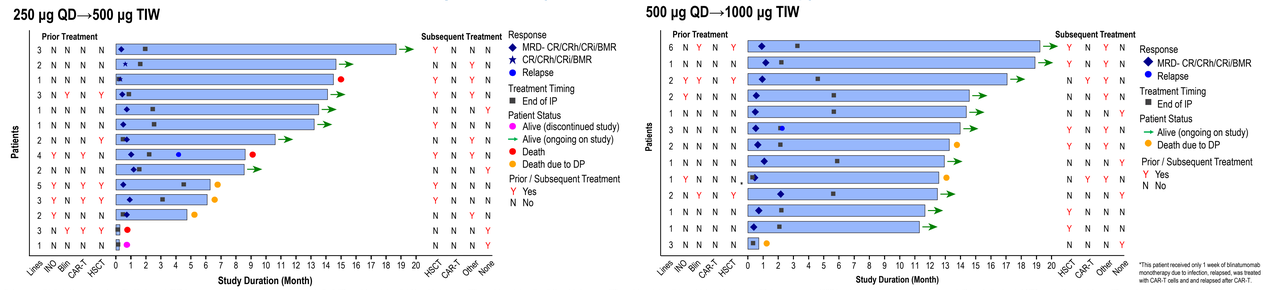
- **Compared with continuous intravenous infusion, subcutaneous (SC) blinatumomab monotherapy is more convenient, providing high efficacy as measured by CR/CRh and acceptable safety.**
- **This phase 1b follow-up of two dosing regimens of SC blinatumomab monotherapy in adults with advanced R/R B-ALL demonstrated the following:**
  - **24/27 patients (89%) achieved a complete remission within 2 cycles, with deep and durable remissions and survival. Of these, 22/24 (92%) were negative for MRD ($<10^{-4}$).**
  - **Median (range) duration of response was 5.8 (3.8–7.4+)* months for the 250 µg QD→500 µg TIW cohort and 12.6 (1.8–13.9+)* months for 500 µg QD→1000 µg TIW cohort.**
  - **The safety profile was manageable.**

Data are n (%)	250 µg QD→500 µg TIW n = 14	500 µg QD→1000 µg TIW n = 13
Grade ≥3 cytokine release syndrome	3 (21.4)	4 (30.8)
Grade ≥3 blinatumomab-associated neurotoxicity	6 (42.9)	3 (23.1)
Grade ≥3 infections	2 (14.3)	2 (15.4)
Deaths in remission	1 (7.1)	0 (0.0)

Complete remission included CR, CRh, CRi, and BMR. *+ indicates a patient is still in follow up. B-ALL, B-cell acute lymphoblastic leukemia; BMR, bone marrow response; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; MRD, measurable residual disease; QD, once daily; SC, subcutaneous; R/R, relapsed/refractory; TIW, three times weekly.

RESULTS

Figure 2. Efficacy with SC Blinatumomab Monotherapy



First response within the first two cycles is shown. Blin, blinatumomab; BMR, bone marrow response; CAR-T, chimeric antigen receptor T cell; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DP, disease progression; HSCT, hematopoietic stem cell transplant; INO, inotuzumab; IP, investigational product; MRD, measurable residual disease; QD, once daily; SC, subcutaneous; TIW, three times weekly.

Table 2. Demographics of Patients with R/R B-ALL Treated with SC Blinatumomab Monotherapy

	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)	Total (n = 27)
Age in years, median (range)	46 (19–78)	56 (25–74)	52 (19–78)
Age group, years, n (%)			
18–54	9 (64.3)	6 (46.2)	15 (55.6)
55–64	3 (21.4)	4 (30.8)	7 (25.9)
≥65	2 (14.3)	3 (23.1)	5 (18.5)
Sex, n (%)			
Male	8 (57.1)	8 (61.5)	16 (59.3)
Race, n (%)			
White	12 (85.7)	7 (53.8)	19 (70.4)
Asian	0 (0.0)	1 (7.7)	1 (3.7)
Other*	2 (14.3)	5 (38.5)	7 (25.9)
Ethnicity, n (%)			
Hispanic/Latino	8 (57.1)	5 (38.5)	13 (48.1)
Not Hispanic/Latino	6 (42.9)	7 (53.8)	13 (48.1)
Data not available	0 (0.0)	1 (7.7)	1 (3.7)

*Other implies races other than White, American Indian or Alaska Native, Asian, Black or African American, or Native Hawaiian or Other Pacific Islander. B-ALL, B-cell acute lymphoblastic leukemia; QD, once daily; R/R, relapsed/refractory; SC, subcutaneous; TIW, three times weekly.

Table 3. Baseline Disease Characteristics

	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)	Total (n = 27)
Bone marrow blasts, %, median (range)	70 (15–95)	80 (5–98)	74 (5–98)
Prior treatment lines, median (range)	2 (1–5)	2 (1–6)	2 (1–6)
Prior inotuzumab ozogamicin	4 (28.6)	3 (23.1)	7 (25.9)
Previously received cIV blinatumomab	2 (14.3)	3 (23.1)	5 (18.5)
Primary refractory	7 (50.0)	2 (15.4)	9 (33.3)
Relapsed after prior HSCT	5 (35.7)	3 (23.1)	8 (29.6)
Relapsed after prior CD19 CAR T–cell therapy	4 (28.6)	0 (0.0)	4 (14.8)
Extramedullary disease	1 (7.1)	0 (0.0)	1 (3.7)
Central nervous system	0 (0.0)	0 (0.0)	0 (0.0)
Testis	0 (0.0)	0 (0.0)	0 (0.0)
Other sites	1 (7.1)	0 (0.0)	1 (3.7)

Data are n (%) unless otherwise indicated. CAR, chimeric antigen receptor; cIV, continuous intravenous infusion; HSCT, hematopoietic stem cell transplant; QD, once daily; TIW, three times weekly.

Table 4. Exposure

	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)	Total (n = 27)
# cycles received, median (range)	1 (0–4)	2 (0–5)	2 (0–5)
Ended during Cycle 1	3 (21.4)	2 (15.4)	5 (18.5)
1 cycle	5 (35.7)	0 (0.0)	5 (18.5)
2 cycles	4 (28.6)	5 (38.5)	9 (33.3)
3 cycles	1 (7.1)	1 (7.7)	2 (7.4)
4 cycles	1 (7.1)	1 (7.7)	2 (7.4)
5 cycles	0 (0.0)	4 (30.8)	4 (14.8)

Data are n (%) unless indicated otherwise.

SAFETY

Table 5. Summary of Treatment-emergent Adverse Events

	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)
Treatment-emergent adverse events (TEAEs), any grade	14 (100.0)	13 (100.0)
Grade ≥ 3 TEAEs	14 (100.0)	11 (84.6)
Serious TEAEs	11 (78.6)	12 (92.3)
Serious TEAEs leading to D/C of SC blinatumomab monotherapy (excluding DP)	3 (21.4)	2 (15.4)
Fatal adverse events*	1 (7.1)	1 (7.7)
Grade ≥ 3 TEAEs of interest		
Cytokine release syndrome	3 (21.4)†	4 (30.8)
Blinatumomab-associated neurotoxicity‡	6 (42.9)§	3 (23.1)
Infections	2 (14.3)	2 (15.4)
Alanine aminotransferase increased	2 (14.3)	3 (23.1)
Aspartate aminotransferase increased	2 (14.3)	1 (7.7)

Data are n (%). *One patient in the blinatumomab monotherapy 250→500 µg QD cohort developed cerebral edema and one patient in the blinatumomab monotherapy 500→1,000 µg QD cohort developed DP with hepatic failure, both considered unrelated to SC blinatumomab. †One grade 3 CRS event at 250→500 µg occurred on Day 7, 1 day after restarting SC blinatumomab monotherapy following 5 days of interruption due to a grade 1 CRS. ‡Two grade 3 neurologic events occurred in Cycle 2, one at 250→500 µg (Cycle 2 Day 8) and one at 500→1,000 µg (Cycle 2 Day 3). §Includes one grade 3 headache associated with lumbar puncture. CRS, cytokine release syndrome; D/C, discontinuation; DP, disease progression; QD, once daily; SC, subcutaneous; TEAE, treatment-emergent adverse event; TIW, three times weekly.

EFFICACY

Table 6. Efficacy with SC Blinatumomab Monotherapy

	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)	All (n = 27)
Achieved CR/CRh/CRi/BMR within 2 cycles*	12/14 (85.7%)	12/13 (92.3%)	24/27 (88.9%)
Relapsed	1/12 (8.3%)	1/12 (8.3%)	2/24 (8.3%)
Death due to disease progression	3/12 (25%)	2/12 (16.7%)	5/24 (20.8%)
Duration of response (DOR), Kaplan-Meier, months, median (range)†	5.8 (3.8–7.4+)†	12.6 (1.8–13.9+)†	12.2 (1.8–13.9+)†
Follow-up for DOR, Kaplan-Meier, months, median (range)	5.9 (0.7–7.4)	6.3 (0.5–13.9)	5.9 (0.5–13.9)
Negative for MRD ($<10^{-4}$) within 2 cycles	10/12 (83.3%)	12/12 (100%)	22/24 (91.7%)
Received HSCT	7/12 (58.3%)	6/12 (50%)	13/24 (54.2%)
Alive in relapse	0	1	1
Alive in remission	3	4	7
Died in relapse or due to disease progression	3	1	4
Died in remission	1‡	0	1‡
Deaths	6/14 (42.9%)	3/13 (23.1%)	9/27 (33.3%)
Time to death, Kaplan-Meier, months, median (range)†	14.5 (0.3–18.7+)†	NE (0.7–19.3+)†	NE (0.3–19.3+)†
Follow-up for survival, Kaplan-Meier, months, median (range)	13.5 (0.2–18.7)	14.4 (11.3–19.3)	14.1 (0.2–19.3)

Data are n (%) unless indicated otherwise.*Three patients did not have response evaluation - two due to fatal adverse events, unrelated to SC blinatumomab monotherapy, and one patient requested to discontinue treatment. †+ indicates a patient is still in follow up. ‡Cause of death is unknown for this patient (best response CR). BMR, bone marrow response; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; HSCT, hematopoietic stem cell transplant; MRD, measurable residual disease; NE, not estimable; QD, once daily; SC, subcutaneous; TIW, three times weekly.

- Of the 27 patients, 24 (89%)* achieved a remission (CR/CRh/CRi/BMR) within 2 cycles.
- Of the 24 patients in remission, two relapsed and five died of disease progression. Of the two patients who relapsed:
  - One patient in the 250→500 µg cohort with 4 prior lines, including inotuzumab and CAR-T treatment, with MRD-negative CR and HSCT on study, relapsed after early discontinuation, with a DOR of 3.5 months.
  - One patient in the 500→1000 µg cohort with 3 prior lines, with MRD-negative CR and HSCT on study, had a CD19-negative relapse after Cycle 2 with a DOR of 1.8 months.
- At data cut off, 18 patients were alive and nine patients dead.
- Five of 12 responders treated with 250→500 µg received SC blinatumomab monotherapy without proceeding to HSCT.
  - Prior treatments included one with prior inotuzumab and one with prior HSCT.
  - Median (range) survival of 10.6 (4.7–14.7) months with four alive (none relapsed) and one dead due to disease progression (best response of BMR).
- Six of 12 responders treated with 500→1000 µg received SC blinatumomab monotherapy without proceeding to HSCT, five completed ≥4 cycles of SC blinatumomab monotherapy.
  - Prior treatments included three with prior inotuzumab, two with prior blinatumomab, and two with prior HSCT.
  - Median (range) survival of 13.7 (12.5–17.1) months with five alive (none relapsed) and one dead due to disease progression.

*Three patients did not have response evaluation – two due to fatal adverse events, unrelated to SC blinatumomab monotherapy, and one patient requested to discontinue treatment. BMR, bone marrow response; CAR-T, chimeric antigen receptor T cell; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DOR, duration of response; HSCT, hematopoietic stem cell transplant; MRD, measurable residual disease; SC, subcutaneous.

SUMMARY

- Results from this phase 1b dose-expansion study showed that treatment with SC blinatumomab monotherapy in heavily pretreated patients with R/R B-ALL resulted in:
  - High response rates.
  - Deep and durable remissions and survival.
  - A manageable safety profile.
- The trial continues to accrue.
- These results support further evaluation of SC blinatumomab monotherapy as a treatment option for patients with R/R B-ALL.

REFERENCES

1. Blinatumomab [Blincyto®] US prescribing information, 2024.
2. Jabbour et al. *Am J Hematol*. 2024: 99(4):586-595.

ACKNOWLEDGMENTS

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Single-Agent Subcutaneous Blinatumomab for Advanced B-Cell Acute Lymphoblastic Leukemia: Long-Term Follow-Up from a Phase 1b Dose Expansion Cohort

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[1] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA. [2] Amgen Research (Munich) GmbH, Munich, Germany. [3] Hematology Department, Hospital Universitario 12 de Octubre, Madrid, Spain. [4] Hematology and Hemotherapy Department, Clínica Universidad de Navarra, Pamplona, Spain. [5] Department of Hematology and Hematopoietic Cell Transplantation, Gehr Family Center for Leukemia Research, City of Hope National Medical Center, Duarte, CA, USA. [6] Division of Hematology and Oncology, Department of Medicine, University of Washington School of Medicine, Seattle, WA, USA. [7] Clinical Research Division, Fred Hutchinson Cancer Center, Seattle, WA, USA. [8] Université Côte d'Azur, CHU de Nice, Nice, France. [9] Department of Hematology, Institut Universitaire du Cancer-Oncopole CHU de Toulouse, Toulouse, France. [10] Department of Hematology, Cellular Therapy, Hemostaseology and Infectious Diseases, Universitätsklinikum Leipzig, Leipzig, Germany. [11] Department of Internal Medicine I, University Hospital of Cologne, Cologne, Germany. [12] Department of Hematology, Erasmus University Medical Center Cancer Institute, Rotterdam, The Netherlands. [13] Hematology Department, Hospital Clínico Universitario de Valencia, Instituto de Investigación Sanitaria INCLIVA, Valencia, Spain. [14] Laura and Isaac Perlmutter Cancer Center at New York University Langone Health, New York, NY, USA. [15] Amgen Inc., Thousand Oaks, CA, USA. [16] Department of Oncology-Hematology, University of Milan, Milan and Azienda Socio Sanitaria Territoriale Papa Giovanni XXIII, Bergamo, Italy.

Key Takeaways

- Compared with continuous intravenous infusion, subcutaneous (SC) blinatumomab monotherapy is more convenient, providing high efficacy as measured by CR/CRh and acceptable safety.
- This phase 1b follow-up of two dosing regimens of SC blinatumomab monotherapy in adults with advanced R/R B-ALL demonstrated the following:
  - 24/27 patients (89%) achieved a complete remission within 2 cycles, with deep and durable remissions and survival. Of these, 22/24 (92%) were negative for MRD ($<10^{-4}$).
  - Median (range) duration of response was 5.8 (3.8–7.4+)* months for the 250 µg QD→500 µg TIW cohort and 12.6 (1.8–13.9+)* months for 500 µg QD→1000 µg TIW cohort.
  - The safety profile was manageable.

Data are n (%)	250 µg QD→500 µg TIW n = 14	500 µg QD→1000 µg TIW n = 13
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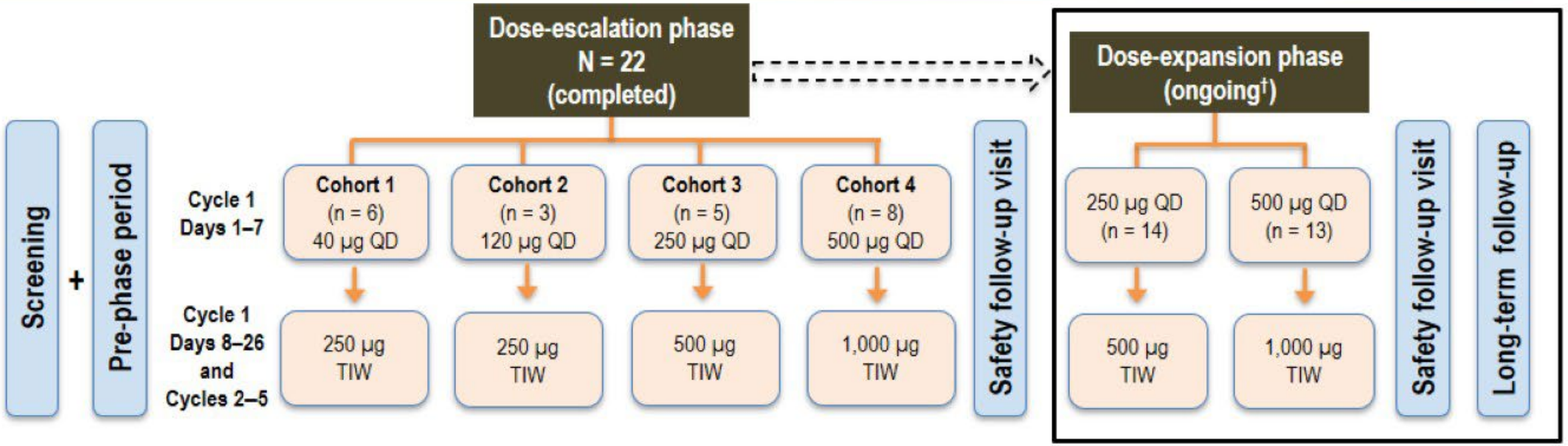
1 Blinatumomab [Blincyto®] US prescribing information, 2024. 2 Jabbour et al. *Am J Hematol*. 2024: 99(4):586-595. B-ALL, B-cell acute lymphoblastic leukemia; BiTE®, bispecific T-cell engager; cIV, continuous intravenous infusion; R/R, relapsed/refractory; SC, subcutaneous.

STUDY OVERVIEW

Figure 1. Study Design



- Adult patients with R/R B-ALL* could receive 1–5 cycles of SC blinatumomab as monotherapy. Transplantation any time after the end of the first cycle was permitted. Each cycle included a 26-day treatment period and an 8-day treatment-free interval.
- Blinatumomab monotherapy was given in one of two dosing regimens:
  1) 250 µg once-daily (QD) for Week 1 and 500 µg three times weekly (TIW) thereafter (250 µg QD→500 µg TIW) OR
  2) 500 µg QD for Week 1 and 1000 µg TIW thereafter (500 µg QD→1000 µg TIW)

Study design described in Jabbour et al. *Am J Hematol*. 2024: 99(4):586-595. *Patients had ≥5% blasts in the BM and were either: 1) Refractory to primary induction therapy or salvage therapy OR 2) Had relapsed disease including untreated relapse (any stage), refractory relapse, or relapse after any salvage therapy or allogeneic HSCT. †Two additional cohorts are being enrolled to generate additional data. BM evaluation was performed on Day 27 of each cycle and additionally on Day 12 of Cycle 1. Adverse events were graded per CTCAE version 5.0. B-ALL, B-cell acute lymphoblastic leukemia; BM, bone marrow; HSCT, hematopoietic stem cell transplant; QD, once daily; R/R, relapsed/refractory; SC, subcutaneous; TIW, three times weekly.

STUDY OVERVIEW

Efficacy Assessments

The primary efficacy endpoint was complete remission with full hematologic recovery (CR) or complete remission with only partial hematologic recovery (CRh) within two cycles.

- Patients with incomplete hematologic recovery (CRi) and bone marrow response (BMR) were included in the analysis.
- Duration of CR/CRh/CRi/BMR was defined from initial remission until relapse or latest disease assessment.

BMR, bone marrow response; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery.

RESULTS

Table 1. Demographics of Patients with R/R B-ALL Treated with SC Blinatumomab Monotherapy

	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)	Total (n = 27)
Age in years, median (range)	46 (19–78)	56 (25–74)	52 (19–78)
Age group, years, n (%)			
18–54	9 (64.3)	6 (46.2)	15 (55.6)
55–64	3 (21.4)	4 (30.8)	7 (25.9)
≥65	2 (14.3)	3 (23.1)	5 (18.5)
Sex, n (%)			
Male	8 (57.1)	8 (61.5)	16 (59.3)
Race, n (%)			
White	12 (85.7)	7 (53.8)	19 (70.4)
Asian	0 (0.0)	1 (7.7)	1 (3.7)
Other*	2 (14.3)	5 (38.5)	7 (25.9)
Ethnicity, n (%)			
Hispanic/Latino	8 (57.1)	5 (38.5)	13 (48.1)
Not Hispanic/Latino	6 (42.9)	7 (53.8)	13 (48.1)
Data not available	0 (0.0)	1 (7.7)	1 (3.7)

Data as of September 13, 2024. *Other implies races other than White, American Indian or Alaska Native, Asian, Black or African American, or Native Hawaiian or Other Pacific Islander.
B-ALL, B-cell acute lymphoblastic leukemia; QD, once daily; R/R, relapsed/refractory; SC, subcutaneous; TIW, three times weekly.

RESULTS

Table 2. Baseline Disease Characteristics

	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)	Total (n = 27)
Bone marrow blasts, %, median (range)	70 (15–95)	80 (5–98)	74 (5–98)
Prior treatment lines, median (range)	2 (1–5)	2 (1–6)	2 (1–6)
Prior inotuzumab ozogamicin	4 (28.6)	3 (23.1)	7 (25.9)
Previously received cIV blinatumomab	2 (14.3)	3 (23.1)	5 (18.5)
Primary refractory	7 (50.0)	2 (15.4)	9 (33.3)
Relapsed after prior HSCT	5 (35.7)	3 (23.1)	8 (29.6)
Relapsed after prior CD19 CAR T–cell therapy	4 (28.6)	0 (0.0)	4 (14.8)
Extramedullary disease	1 (7.1)	0 (0.0)	1 (3.7)
Central nervous system	0 (0.0)	0 (0.0)	0 (0.0)
Testis	0 (0.0)	0 (0.0)	0 (0.0)
Other sites	1 (7.1)	0 (0.0)	1 (3.7)

Data are n (%) unless otherwise indicated. Data as of September 13, 2024. CAR, chimeric antigen receptor; cIV, continuous intravenous infusion; HSCT, hematopoietic stem cell transplant; QD, once daily; TIW, three times weekly.

RESULTS

Table 3. Exposure

	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)	Total (n = 27)
# cycles received, median (range)	1 (0–4)	2 (0–5)	2 (0–5)
Ended during Cycle 1	3 (21.4)	2 (15.4)	5 (18.5)
1 cycle	5 (35.7)	0 (0.0)	5 (18.5)
2 cycles	4 (28.6)	5 (38.5)	9 (33.3)
3 cycles	1 (7.1)	1 (7.7)	2 (7.4)
4 cycles	1 (7.1)	1 (7.7)	2 (7.4)
5 cycles	0 (0.0)	4 (30.8)	4 (14.8)

Data are n (%) unless indicated otherwise. Data as of September 13, 2024.

RESULTS: SAFETY

Table 4. Summary of Treatment-emergent Adverse Events

	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)
Treatment-emergent adverse events (TEAEs), any grade	14 (100.0)	13 (100.0)
Grade ≥ 3 TEAEs	14 (100.0)	11 (84.6)
Serious TEAEs	11 (78.6)	12 (92.3)
Serious TEAEs leading to D/C of SC blinatumomab monotherapy (excluding DP)	3 (21.4)	2 (15.4)
Fatal adverse events*	1 (7.1)	1 (7.7)
Grade ≥ 3 TEAEs of interest		
Cytokine release syndrome	3 (21.4)†	4 (30.8)
Blinatumomab-associated neurotoxicity‡	6 (42.9)§	3 (23.1)
Infections	2 (14.3)	2 (15.4)
Alanine aminotransferase increased	2 (14.3)	3 (23.1)
Aspartate aminotransferase increased	2 (14.3)	1 (7.7)

Data are n (%) and as of September 13, 2024. *One patient in the blinatumomab monotherapy 250→500 µg cohort developed cerebral edema and one patient in the blinatumomab monotherapy 500→1,000 µg cohort developed DP with hepatic failure, both considered unrelated to SC blinatumomab monotherapy. †One grade 3 CRS event at 250→500 µg occurred on Day 7, 1 day after restarting SC blinatumomab monotherapy following 5 days of interruption due to a grade 1 CRS. ‡Two grade 3 neurologic events occurred in Cycle 2, one at 250→500 µg (Cycle 2 Day 8) and one at 500→1,000 µg (Cycle 2 Day 3). §Includes one grade 3 headache associated with lumbar puncture. CRS, cytokine release syndrome; D/C, discontinuation; DP, disease progression; QD, once daily; SC, subcutaneous; TEAE, treatment-emergent adverse event; TIW, three times weekly.

RESULTS: EFFICACY

Table 5. Efficacy with SC Blinatumomab Monotherapy

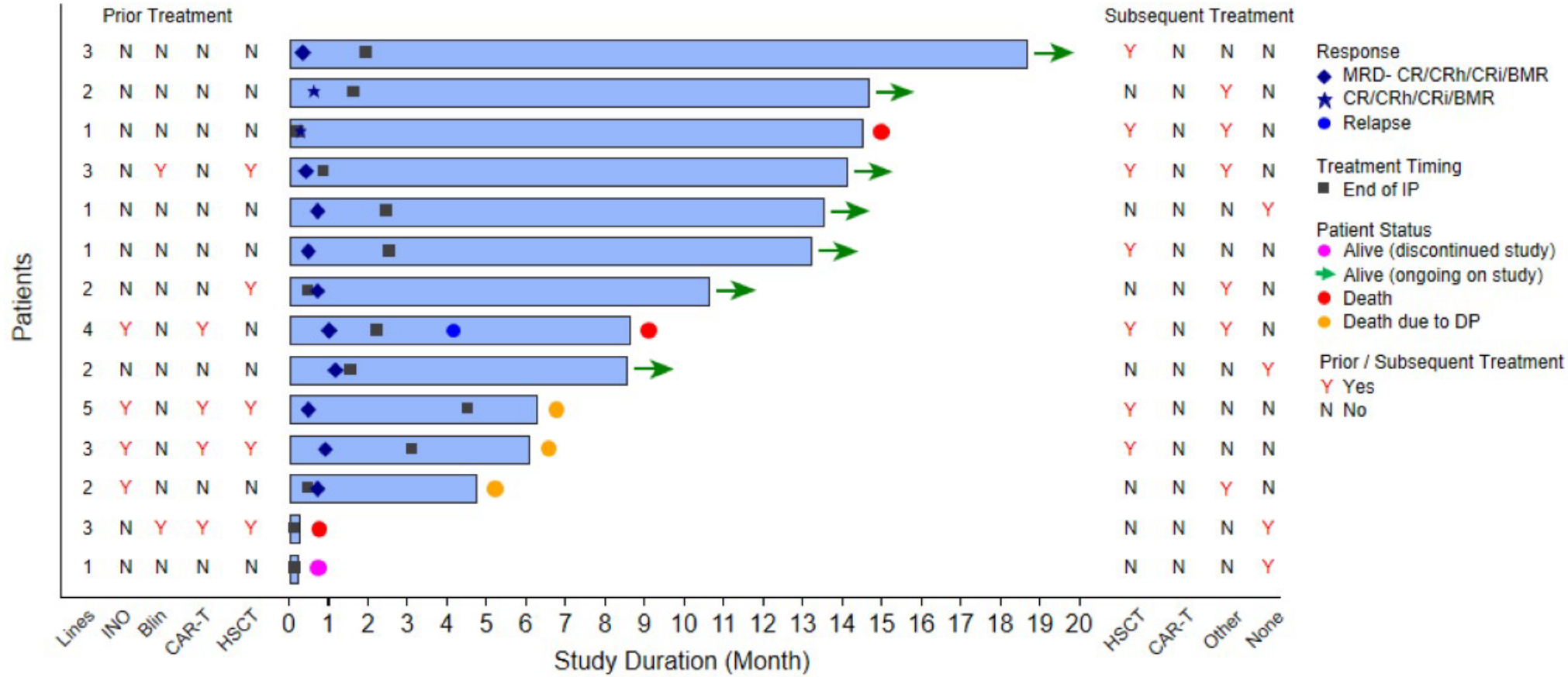
	250 µg QD→500 µg TIW (n = 14)	500 µg QD→1000 µg TIW (n = 13)	All (n = 27)
Achieved CR/CRh/CRi/BMR within 2 cycles*	12/14 (85.7%)	12/13 (92.3%)	24/27 (88.9%)
Relapsed	1/12 (8.3%)	1/12 (8.3%)	2/24 (8.3%)
Death due to disease progression	3/12 (25%)	2/12 (16.7%)	5/24 (20.8%)
Duration of response (DOR), Kaplan-Meier, months, median (range)†	5.8 (3.8–7.4+)†	12.6 (1.8–13.9+)†	12.2 (1.8–13.9+)†
Follow-up for DOR, Kaplan-Meier, months, median (range)	5.9 (0.7–7.4)	6.3 (0.5–13.9)	5.9 (0.5–13.9)
Negative for MRD ($<10^{-4}$) within 2 cycles	10/12 (83.3%)	12/12 (100%)	22/24 (91.7%)
Received HSCT	7/12 (58.3%)	6/12 (50%)	13/24 (54.2%)
Alive in relapse	0	1	1
Alive in remission	3	4	7
Died in relapse or due to disease progression	3	1	4
Died in remission	1‡	0	1‡
Deaths	6/14 (42.9%)	3/13 (23.1%)	9/27 (33.3%)
Time to death, Kaplan-Meier, months, median (range)†	14.5 (0.3–18.7+)†	NE (0.7–19.3+)†	NE (0.3–19.3+)†
Follow-up for survival, Kaplan-Meier, months, median (range)	13.5 (0.2–18.7)	14.4 (11.3–19.3)	14.1 (0.2–19.3)

Data are n (%) unless indicated otherwise. Data as of September 13, 2024. *Three patients did not have response evaluation - two due to fatal adverse events, unrelated to SC blinatumomab monotherapy, and one patient requested to discontinue treatment. †+ indicates a patient is still in follow up. ‡Cause of death is unknown for this patient (best response CR). BMR, bone marrow response; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; HSCT, hematopoietic stem cell transplant; MRD, measurable residual disease; NE, not estimable; QD, once daily; SC, subcutaneous; TIW, three times weekly.

RESULTS: EFFICACY

Figure 2. Efficacy with SC Blinatumomab Monotherapy

250 µg QD→500 µg TIW

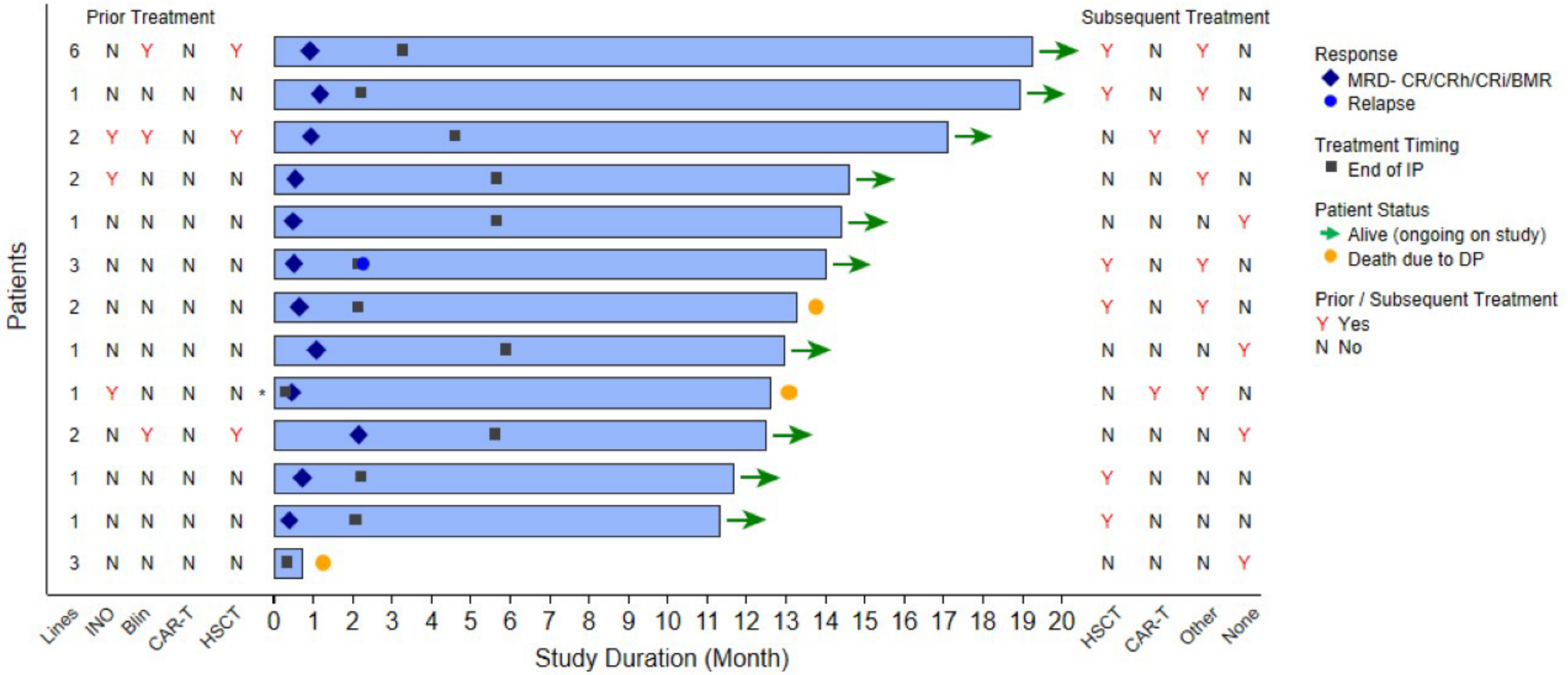


Data as of September 13, 2024. First response within the first two cycles is plotted. Blin, blinatumomab; BMR, bone marrow response; CAR-T, chimeric antigen receptor T cell; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DP, disease progression; HSCT, hematopoietic stem cell transplant; INO, inotuzumab; IP, investigational product; MRD, measurable residual disease; QD, once daily; SC, subcutaneous; TIW, three times weekly.

RESULTS: EFFICACY

Figure 2. Efficacy with SC Blinatumomab Monotherapy

500 µg QD→1000 µg TIW



Data as of September 13, 2024. First response within the first two cycles is plotted. *This patient received only 1 week of blinatumomab monotherapy due to infection, relapsed, was treated with CAR-T cells and and relapsed after CAR-T. Blin, blinatumomab; BMR, bone marrow response; CAR-T, chimeric antigen receptor T cell; CR, complete remission with full hematologic recovery; CRh, complete remission with partial hematologic recovery; CRi, complete remission with incomplete hematologic recovery; DP, disease progression; HSCT, hematopoietic stem cell transplant; INO, inotuzumab; IP, investigational product; MRD, measurable residual disease; QD, once daily; SC, subcutaneous; TIW, three times weekly.

SUMMARY

- Results from this phase 1b dose-expansion study showed that treatment with SC blinatumomab monotherapy in heavily pretreated patients with R/R B-ALL resulted in:
  - High response rates.
  - Deep and durable remissions and survival.
  - A manageable safety profile.
- The trial continues to accrue.
- These results support further evaluation of SC blinatumomab monotherapy as a treatment option for patients with R/R B-ALL.

B-ALL, B-cell acute lymphoblastic leukemia; R/R, relapsed/refractory; SC, subcutaneous.

REFERENCES

1. Blinatumomab [Blincyto®] US prescribing information, 2024.
2. Jabbour et al. *Am J Hematol*. 2024;99:586–595.

ACKNOWLEDGMENTS

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Blinatumomab added to chemotherapy improves disease-free survival in newly diagnosed NCI standard risk pediatric B-acute lymphoblastic leukemia: Results from Children's Oncology Group Study AALL1731

Study Chairs:
Rachel Rau
Sumit Gupta

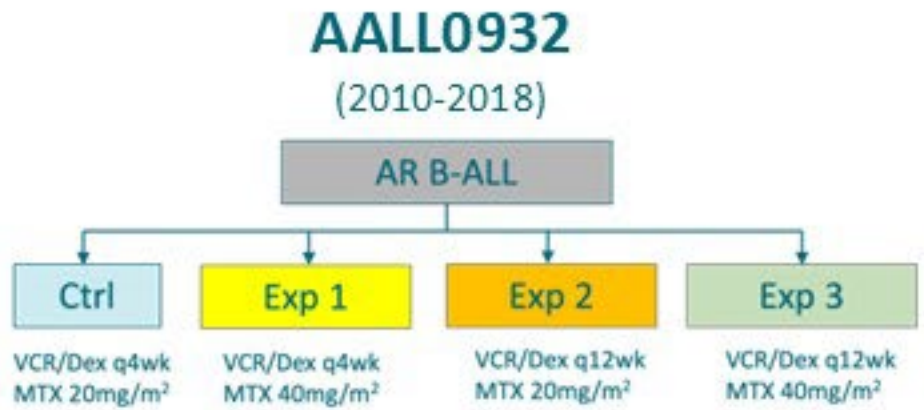
Sr. Statistician:
John Kairalla

Vice Chair:
Karen Rabin

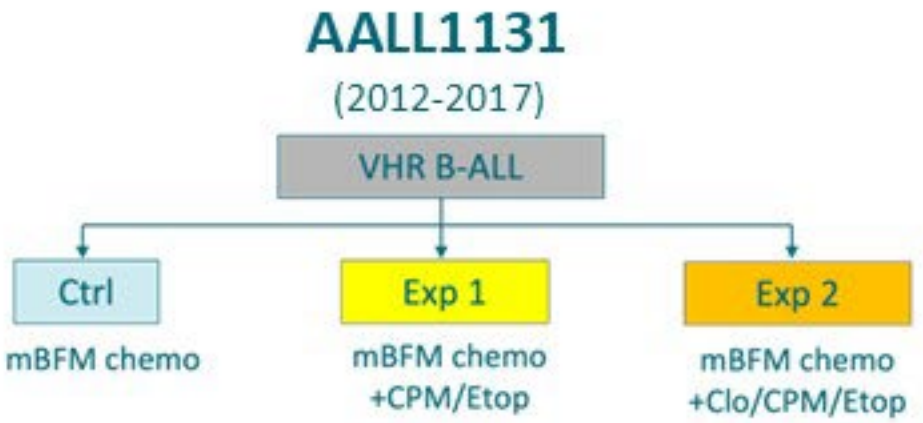
COG ALL Leads:
Mignon Loh
Elizabeth Raetz

CHILDREN'S ONCOLOGY GROUP

Further intensification of chemotherapy will not improve outcomes



Ø Improved outcomes



Ø Improved outcomes

↑↑ Infectious toxicity

Agent with distinct mechanism of action and toxicity profile

CHILDREN'S ONCOLOGY GROUP

Angiolillo, et al, *Blood*. 2017

Salzer and Burke, et al, *Cancer*. 2018

Agent with distinct mechanism of action and toxicity profile

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Targeted Therapy With the T-Cell–Engaging Antibody Blinatumomab of Chemotherapy-Refractory Minimal Residual Disease in B-Lineage Acute Lymphoblastic Leukemia Patients Results in High Response Rate and Prolonged Leukemia-Free Survival

Topp, et al. *JCO*. 2011

JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

Phase I/Phase II Study of Blinatumomab in Pediatric Patients With Relapsed/Refractory Acute Lymphoblastic Leukemia

von Stackleberg, et al. *JCO*. 2016

Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study

Topp, et al. *Lancet Oncol*. 2015

THE NEW ENGLAND JOURNAL of MEDICINE

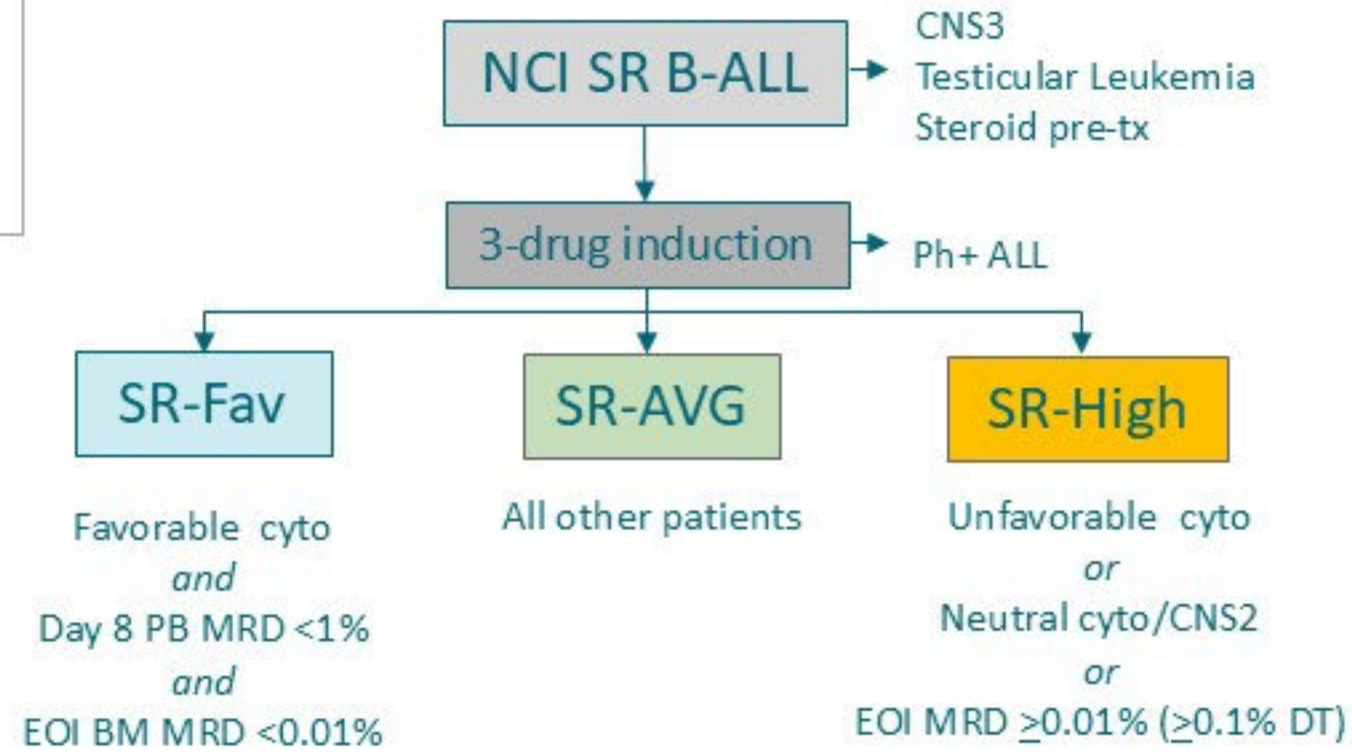
Blinatumomab versus Chemotherapy for Advanced Acute Lymphoblastic Leukemia

Kantarjian, et al. *NEJM*. 2017

Blinatumomab selected as investigational agent for AALL1731

AALL1731 risk stratification

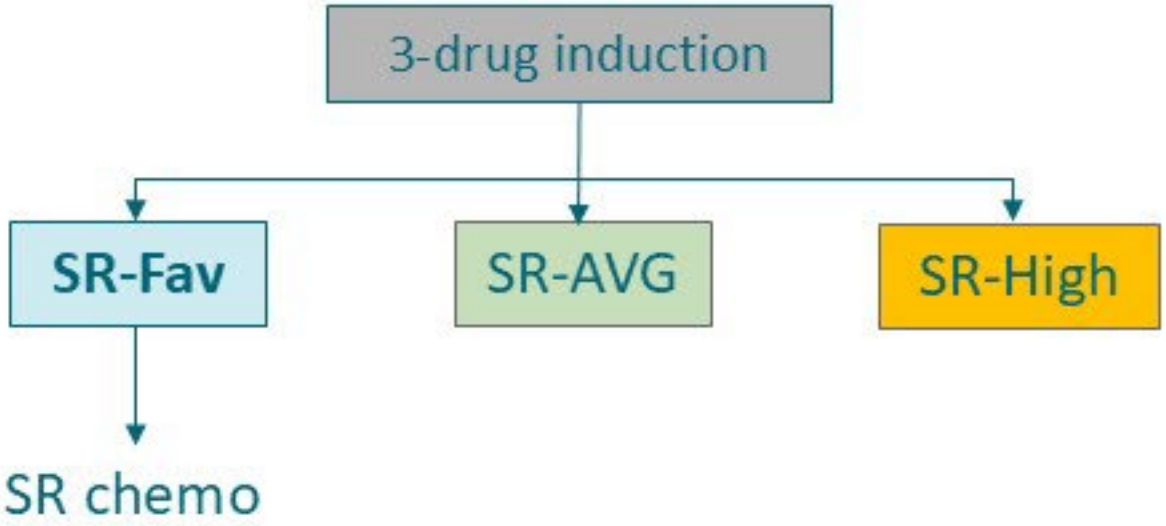
NCI SR B-ALL
At diagnosis:
Age 1-<10yrs
WBC <50,000/µL



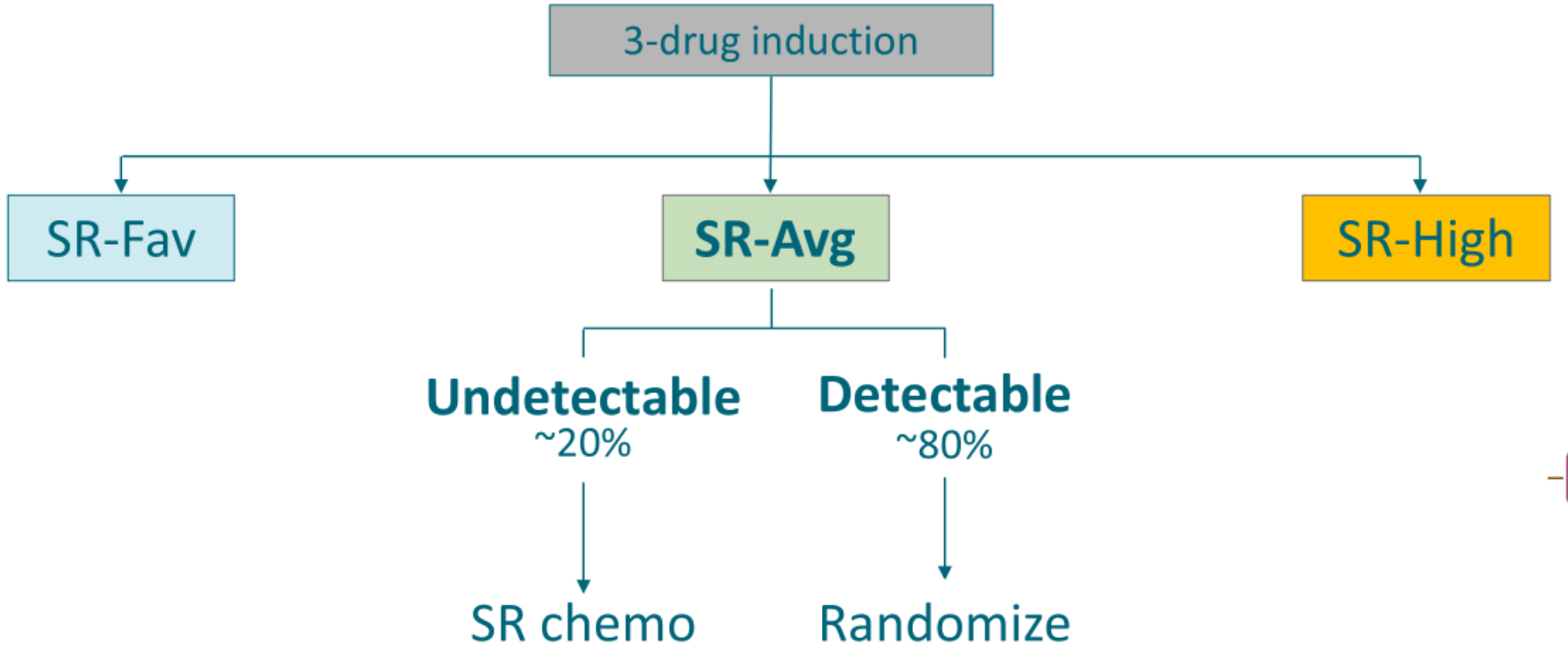
CHILDREN'S ONCOLOGY GROUP

Favorable cyto = ETV6::RUNX1 or double trisomies chr 4 and 10 (DT)
Unfavorable cyto = iAMP21, KMT2Ar, hypodiploidy (<44chr), t(17;19)
Neutral cyto = no favorable or unfavorable lesions present

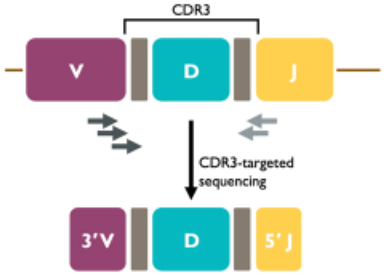
AALL1731 randomized study design



AALL1731 randomized study design



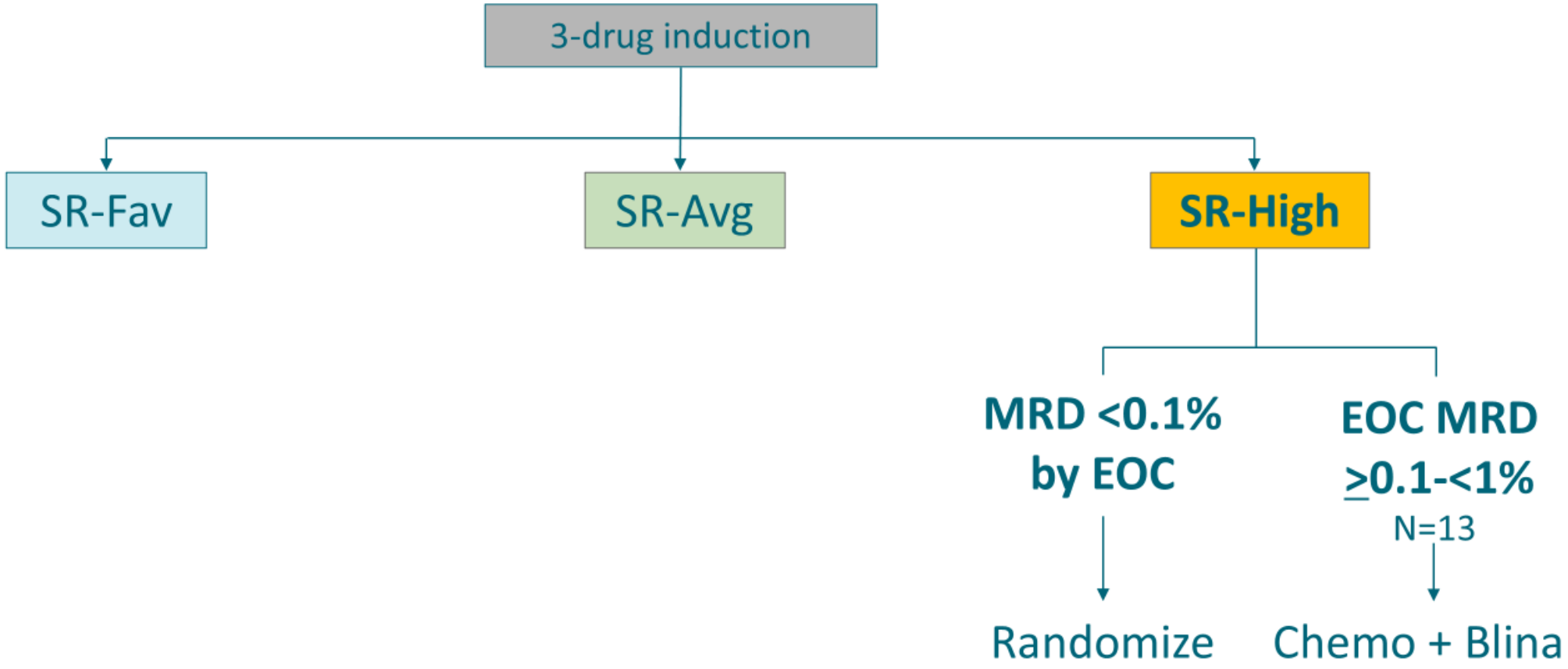
HTS MRD



Sensitivity ~10^{-6}

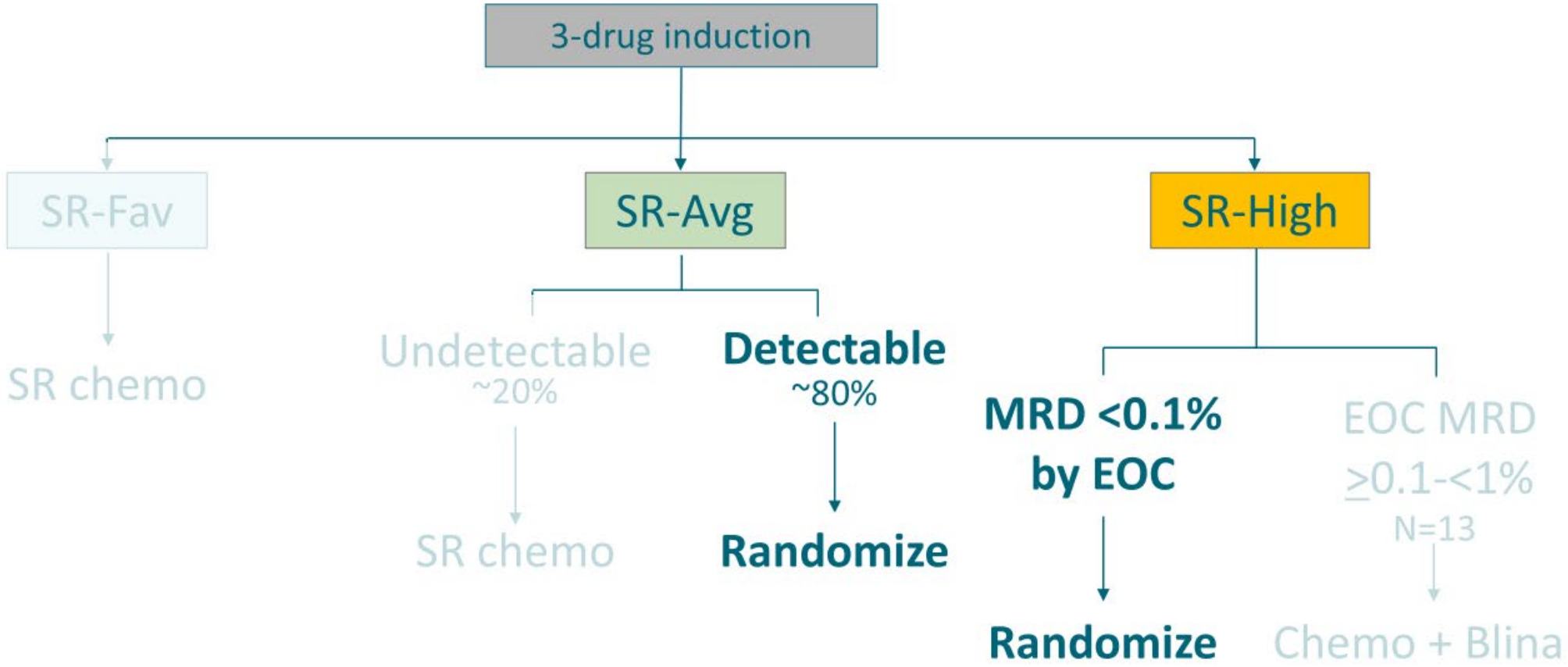
HTS = high throughput sequencing

AALL1731 randomized study design

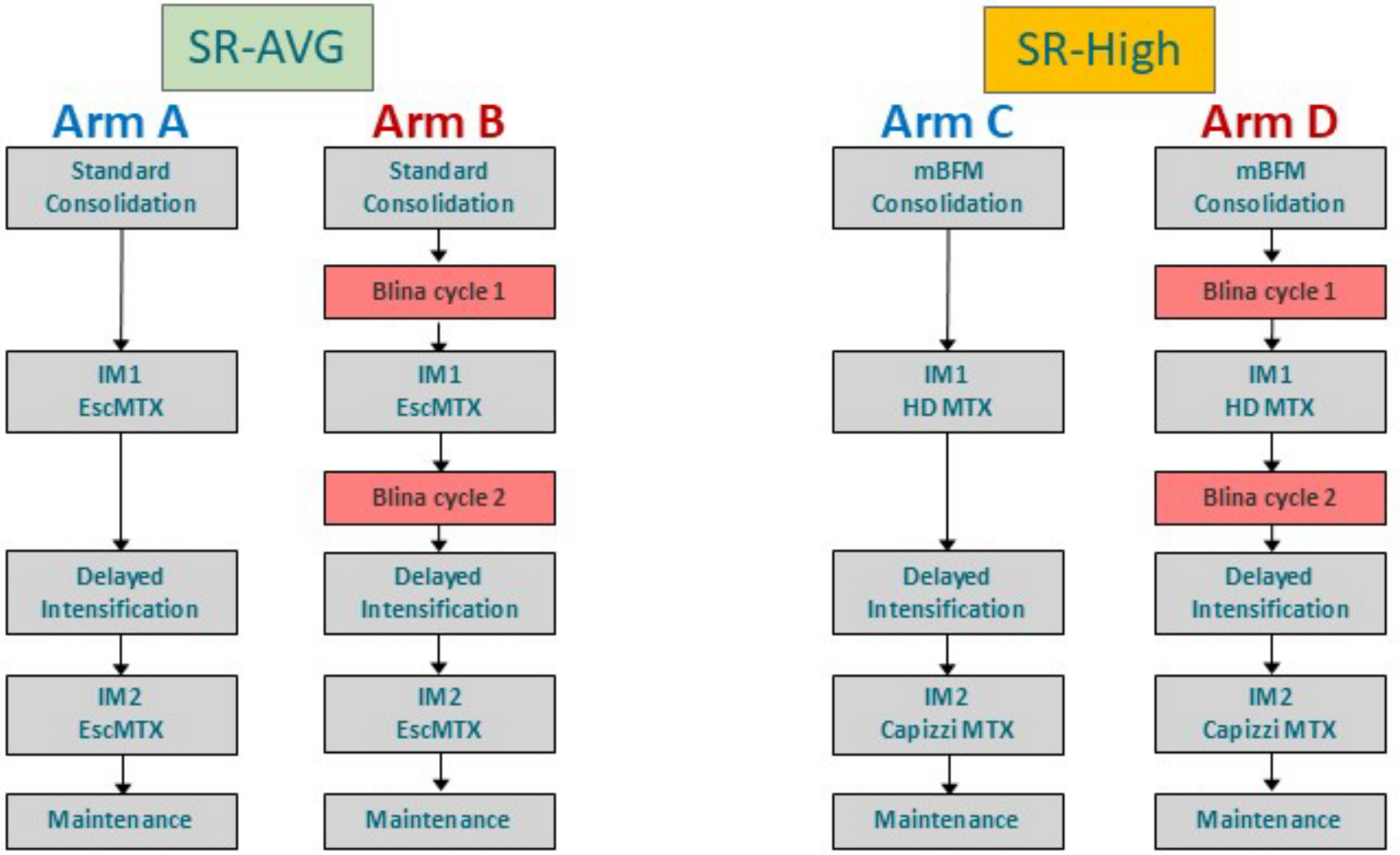


EOC = end of consolidation

AALL1731 randomized study design



Randomization



CHILDREN'S ONCOLOGY GROUP

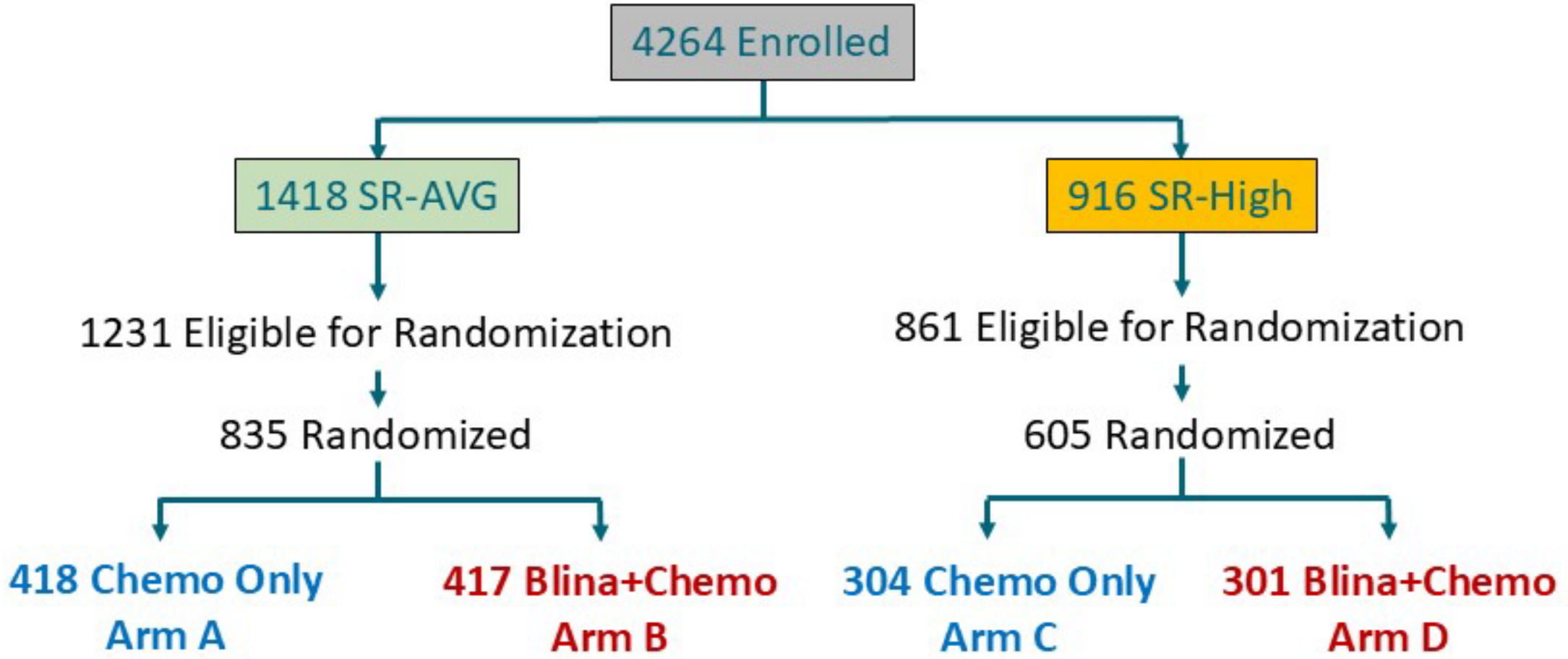
Blinatumomab cycle

15mcg/m^2/day x 28 days via continuous IV infusion

Study design: Primary aim

- Primary endpoint: Improved disease-free survival (DFS) due to addition of 2 cycles of blinatumomab
  - 1:1 randomization stratified by risk group and Down syndrome
- June 30, 2024 - reached first interim efficacy monitoring point (40% of expected events)
  - 1,440 patients randomized (64% of planned)
- **Based on these interim data, DSMC recommended early termination of randomization**

AALL1731 NCI SR B-ALL Patients

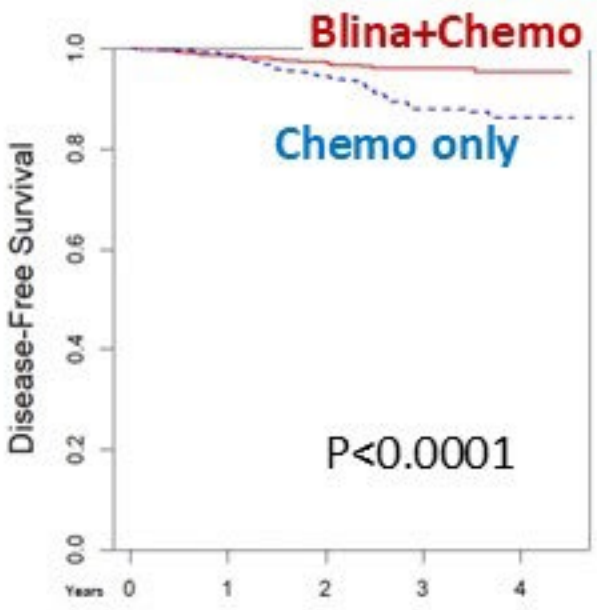


Demographic features of randomized patients

Characteristic	SR-AVG		SR-High	
	Chemo Only (N=418)	Blina + Chemo (N=417)	Chemo Only (N=304)	Blina + Chemo (N=301)
Median age (range) - yr	4.3 (1.0-10.0)	4.0 (1.0-9.9)	4.2 (1.1-9.9)	4.6 (1.0-10.0)
Sex – N (%)				
Female	195 (46.7%)	207 (49.6%)	137 (45.1%)	143 (47.5%)
Male	223 (53.3%)	210 (50.4%)	167 (54.9%)	158 (52.5%)
Race/ethnicity – N (%)				
Hispanic	104 (24.9%)	100 (24.0%)	84 (27.6%)	84 (27.9%)
Non-Hispanic Asian	19 (4.5%)	20 (4.8%)	10 (3.3%)	13 (4.3%)
Non-Hispanic Black	20 (4.8%)	26 (6.2%)	18 (5.9%)	16 (5.3%)
Non-Hispanic White	213 (51.0%)	217 (52.0%)	140 (46.1%)	156 (51.8%)
Other/Unknown	62 (14.8%)	54 (12.9%)	52 (17.1%)	32 (10.6%)

Blinatumomab significantly improves DFS

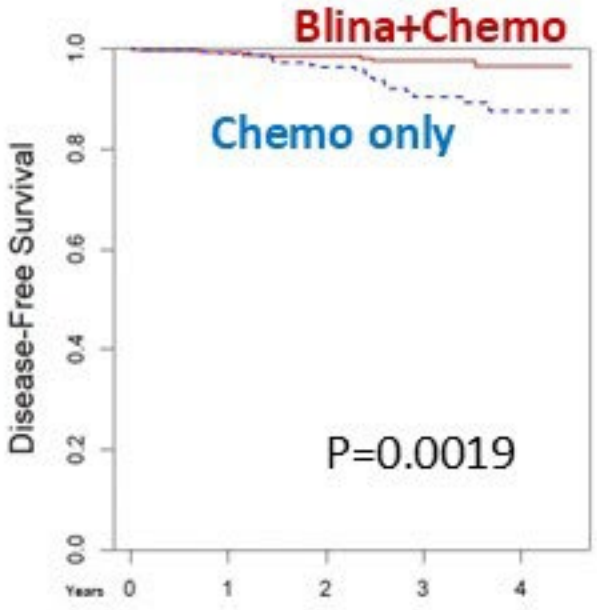
Overall cohort



3-yr DFS 87.9 vs 96%

HR 0.39

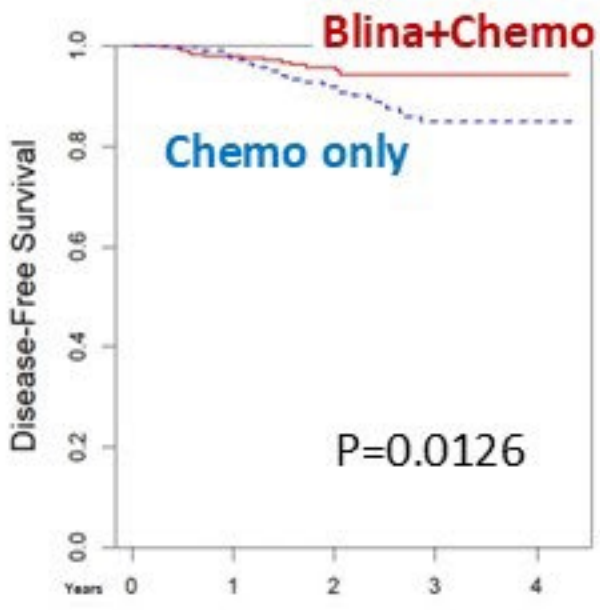
SR-AVG



3-yr DFS 90.2 vs 97.5%

HR 0.33

SR-High

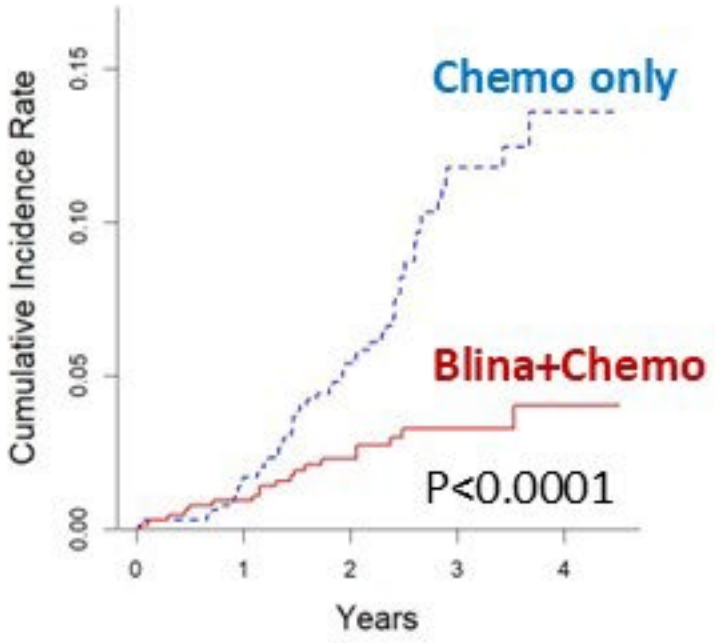


3-yr DFS 84.8 vs 94.1%

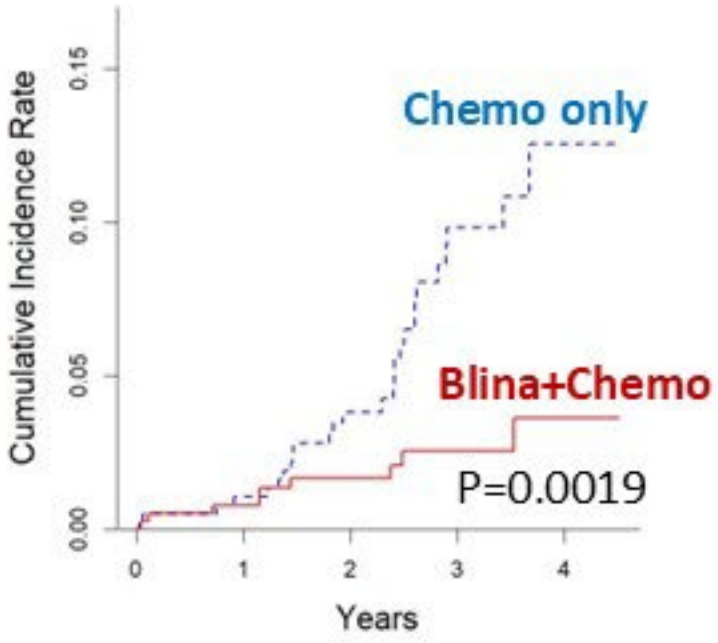
HR 0.45

Blinatumomab reduces relapses

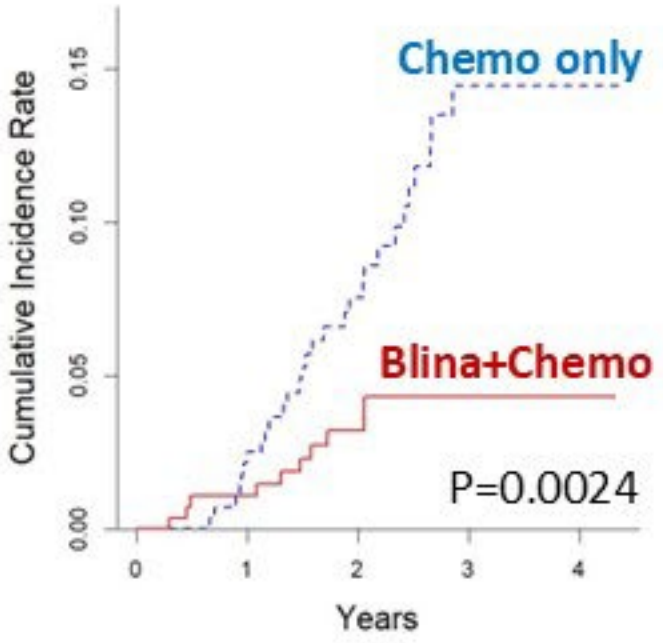
Overall cohort



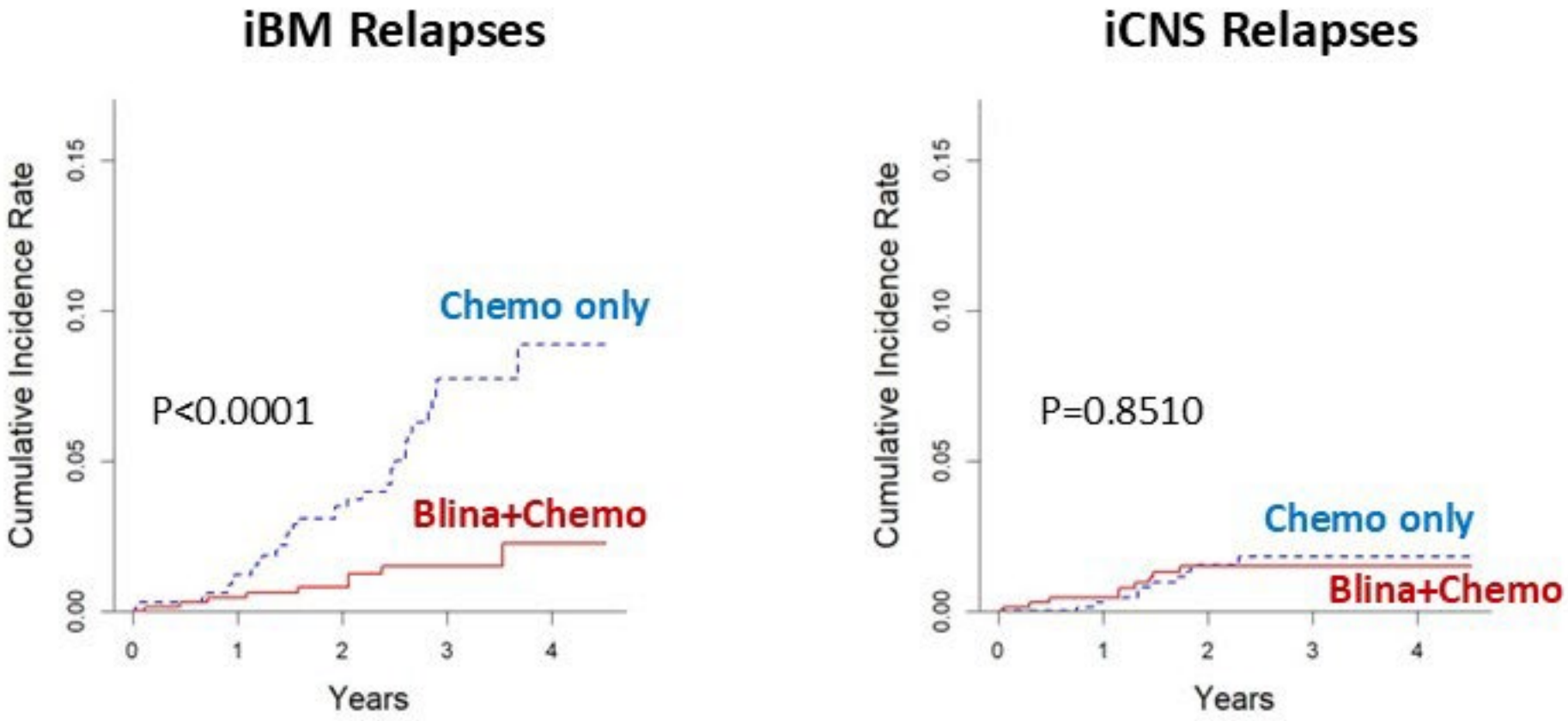
SR-AVG



SR-High

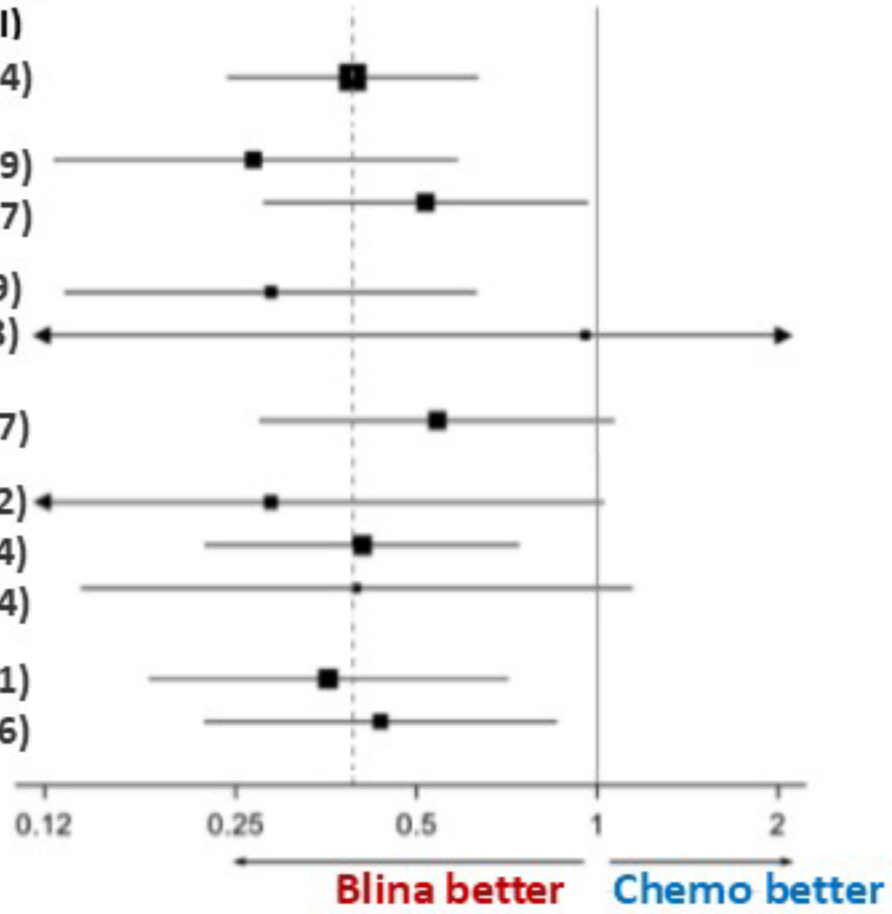


Blinatumomab reduces BM but not CNS relapses



Blinatumomab benefits across subgroups

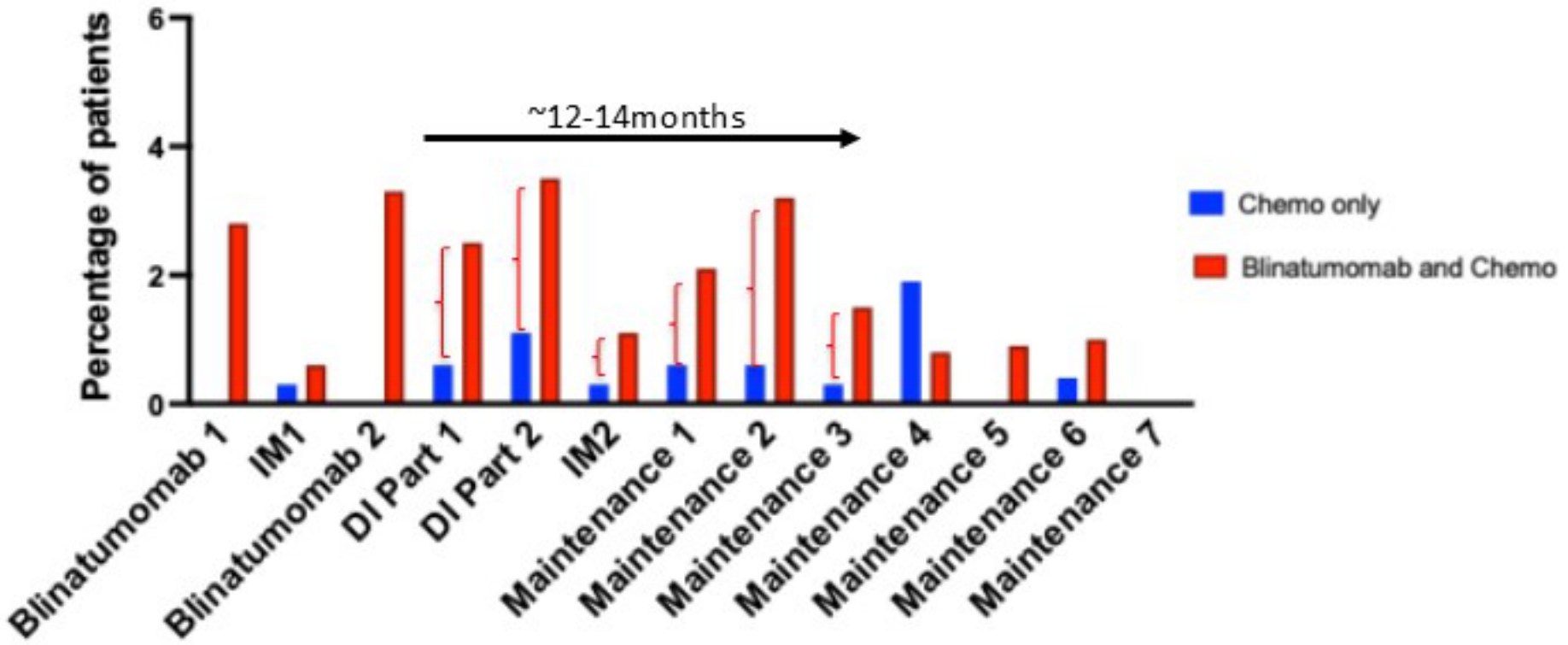
Subgroup	Blina+Chemo Event %	Chemo Only Event %	Hazard Ratio for DFS (95% CI)
All Patients	3.2%	8%	**0.39 (0.24-0.64)**
Female	2.3%	8.7%	**0.27 (0.12-0.59)**
Male	4.1%	7.4%	**0.52 (0.28-0.97)**
Hispanic	4.3%	14.4%	**0.29 (0.13-0.69)**
Non-Hisp. Asian	3.0%	3.4%	**0.96 (0.06-15.3)**
Non-Hisp Black	**0.0%**	**5.3%**	
Non-Hisp. White	4.1%	7.4%	**0.52 (0.28-0.97)**
Favorable cyto	1.5%	5.2%	**0.29 (0.08-1.02)**
Neutral cyto	3.3%	8.0%	**0.41 (0.22-0.74)**
Unfavorable cyto	7.8%	18.3%	**0.40 (0.14-1.14)**
EOI MRD<0.01%	2.4%	6.6%	**0.36 (0.18-0.71)**
EOI MRD≥0.01%	4.5%	10.4%	**0.44 (0.22-0.86)**



Blinatumomab specific toxicities

	Blina Cycle 1 (N=624)		Blina Cycle 2 (N=552)	
	Grade 2+	**Grade 3+**	Grade 2+	**Grade 3+**
Cytokine release syndrome	18 (2.9%)	**2 (0.3%)**	9 (1.6%)	**0 (0.0%)**
Seizure	9 (1.4%)	**5 (0.8%)**	5 (0.9%)	**4 (0.7%)**
Encephalopathy	1 (0.2%)	**1 (0.2%)**	0 (0.0%)	**0 (0.0%)**

Grade 3+ sepsis/catheter related infections SR-AVG



Sepsis Grading

Grade 3: "Blood culture positive with signs or symptoms; treatment indicated"

Grade 4: "Life-threatening consequences; urgent intervention indicated"

CHILDREN'S ONCOLOGY GROUP

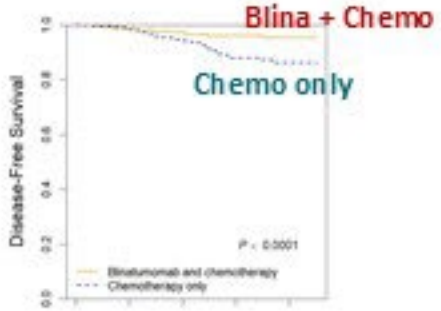
*No difference in rates of Grade 4 or 5 infectious toxicity

Conclusions

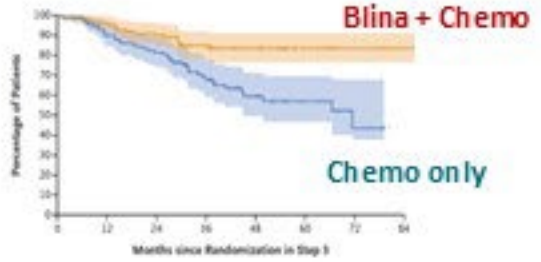
- Blinatumomab added to chemotherapy significantly improves DFS in NCI SR B-ALL of average and higher relapse risk
- Blinatumomab reduces marrow relapses, not CNS involving relapses
- While overall well tolerated, blinatumomab was associated with higher rates of subsequent sepsis and catheter related infections
- **Blinatumomab added to chemo represents a new treatment standard**

Blinatumomab benefits across age and risk groups

van der Sluis et al. *NEJM* 2023



AALL1731 data



Litzow et al. *NEJM* 2024

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Blinatumomab in Standard-Risk B-Cell Acute Lymphoblastic Leukemia in Children

Sumit Gupta, Ph.D., Rachel E. Rau, M.D., John A. Kairalla, Ph.D., Karen R. Rabin, Ph.D., Cindy Wang, M.Sc., Anne L. Angiolillo, M.D., Sarah Alexander, M.D., Andrew J. Carroll, Ph.D., Susan Conway, B.A., Lia Gore, M.D., Ilan Kirsch, M.D., Holly R. Kubaney, M.S.N., Amanda M. Li, M.D., Jennifer L. McNeer, M.D., Olga Militano, Pharm.D., Tamara P. Miller, M.D., Yvonne Moyer, M.B.A., Maureen M. O'Brien, M.D., Maki Okada, M.S., Shalini C. Reshmi, Ph.D., Mary Shago, Ph.D., Elizabeth Wagner, M.S., Naomi Winick, M.D., Brent L. Wood, Ph.D., Tara Haworth-Wright, Pharm.D., Faraz Zaman, M.D., Gerhard Zugmaier, Ph.D., Sue Zupanec, M.N., Meenakshi Devidas, Ph.D., Stephen P. Hunger, M.D., David T. Teachey, M.D., Elizabeth A. Raetz, M.D., and Mignon L. Loh, M.D.

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- Jen McNeer, Maureen O'Brien
- Dave Teachey
- Steve Hunger
- Naomi Winick
- Lia Gore
- Peter Adamson
- Doug Hawkins

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Every site that opened AALL1731

Every patient/family who considered AALL1731

CHILDREN'S ONCOLOGY GROUP

Blinatumomab and Ponatinib for Adults with Newly Diagnosed Ph+ ALL: Updated Results and Predictors of Relapse

NJ Short, H Kantarjian, N Jain, K Takahashi, K Furudate, J Senapati, FG Haddad, O Karrar, TM Kadia, K Chien, K Sasaki, E Kugler, R Garris, F Ravandi, E Jabbour

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Ponatinib + Blinatumomab in Ph+ ALL: Background

- Historical standard of care in newly diagnosed Ph+ ALL: chemotherapy + TKI followed by allogeneic HSCT
  - 5-year OS with 1st or 2nd generation TKIs: 35-50%[1-3]
  - T315I mutations are dominant mechanism of relapse (up to 75% at relapse)[3]
- Ponatinib: pan-BCR-ABL TKI with activity in T315I mutations
  - Combination of hyper-CVAD + ponatinib: higher rates of complete molecular response (CMR) and 6-year OS of 75%, without need for HSCT in most pts[4]
- Blinatumomab + TKI in newly diagnosed Ph+ ALL → high rates of CMR
  - Dasatinib + blinatumomab: 38% transplanted in CR1, 4-year OS of 81%[5]
    - Worse DFS with lack of early CMR and/or IKZF1^{plus} genotype
  - Predictors of outcomes with ponatinib + blinatumomab not well-established

[1]Daver N et al. *Haematologica* 2015;100(5):563-61
[2]Ravandi F et al. *Cancer* 2015;121(23):4158-64
[3]Rousselot P et al. *Blood* 2016;128(6):774-82
[4]Kantarjian H et al. *Am J Hematol* 2023;98(3):493-501
[5]Foa R et al. *N Engl J Med* 2020;383(17):1613-23

Ponatinib + Blinatumomab in Ph+ ALL: Endpoints

- Primary endpoint
  - CMR rate
- Secondary endpoints
  - Event-free survival
  - Overall survival
  - Safety
- Exploratory endpoint
  - Clinical and molecular predictors of relapse

Ponatinib + Blinatumomab in Ph+ ALL: Eligibility

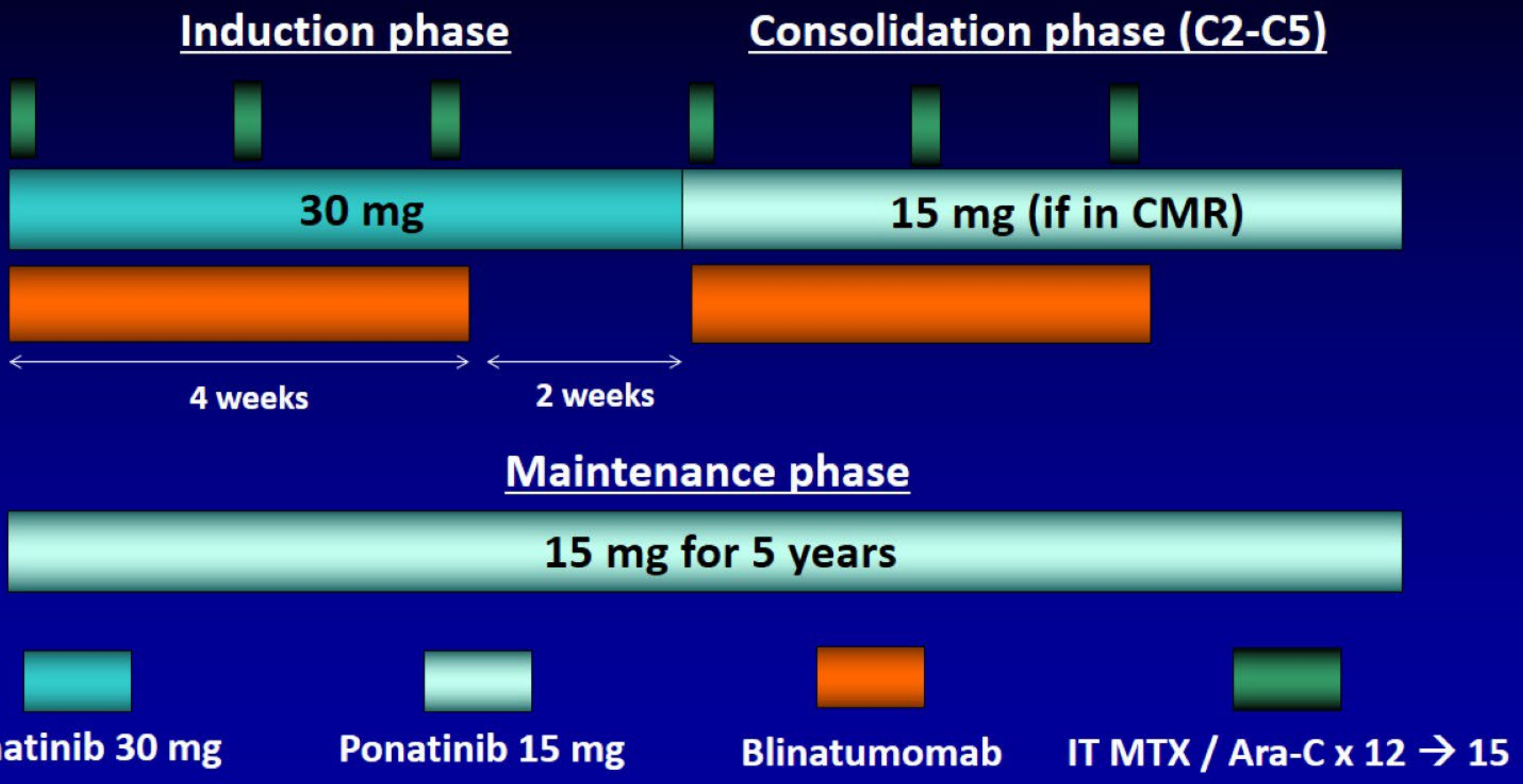
Inclusion criteria

- **Newly diagnosed Ph+ ALL**, relapsed/refractory Ph+ ALL, or lymphoid accelerated or blast phase CML
  - Previous therapy with 1-2 courses of chemotherapy ± TKI was allowed in newly diagnosed cohort
- Age ≥ 18 years
- ECOG performance status ≤ 2
- Adequate hepatic function
  - Bilirubin ≤ 2 mg/dL
  - AST and ALT ≤ 3 x ULN

Exclusion criteria

- Uncontrolled, active CV disease
  - History of MI, CVA, or revascularization within 3 months
  - Congestive heart failure with reduced LVEF
  - Atrial of ventricular arrhythmia
  - History of arterial or venous thromboembolism
  - Uncontrolled hypertension (>140/90)
- Significant CNS pathology (excluding CNS leukemia)

Ponatinib + Blinatumomab in Ph+ ALL: Regimen



Ponatinib + Blinatumomab in Ph+ ALL: Patients (N=76)

Characteristic	Category	N (%) / median [range]
Age (years)		50 [18-83]
	≥ 60	28 (37)
Performance status	0-1	66 (87)
	2	10 (13)
CV risk factors	Hypertension	32 (42)
	Hyperlipidemia	23 (30)
	Diabetes	14 (18)
	Coronary artery disease	1 (1)
≥1 CV risk factor		40 (53)
WBC ($x10^9$/L) at diagnosis		15.4 [0.6-322.1]
CNS involvement		3 (4)
CD19 expression		99.8 [74.9-100]
BCR::ABL1 transcript	p190	60/75 (80)
	p210	15/75 (20)

Ponatinib + Blinatumomab in Ph+ ALL: Response Rates

Response, n/N (%)	N = 76
CR/CRi*	52/53 (98)
CR	51/53 (96)
CRi	1/53 (2)
Early death	1/53 (2)
MMR**	64/66 (97)
CMR**	57/69 (83)
After 1 cycle	41/69 (59)
NGS MRD negative	55/57 (96)
After 1 cycle	17/36 (47)

* 23 pts in CR at start

** 10 pts were in MMR, 7 were in CMR, and 2 were NGS MRD negative at start

8/8 of tested pts not achieving CMR were NGS MRD negative

Ponatinib + Blinatumomab in Ph+ ALL: Disposition

N=76 pts

Death in CR, n=3

- Post-procedural bleeding and hypovolemic shock
- Cerebral aneurysm
- Respiratory failure

Relapse, n=10

Died, n=3

- Also with *IGH::CRLF2*, extramedullary-only Ph-negative relapse (MYC rearranged) (n=1)
- CNS-only relapse (n=5)
  - After median 21 months (range, 9-23)
- BM-only relapse (n=4)
  - After median 14 months (range, 8-24)

Ongoing response without HSCT, n=58

- INO for MRD+, n=1
- CAR T-cells for MRD+, n=2

Early Death, n=1

Due to intracranial hemorrhage from prior chemotherapy

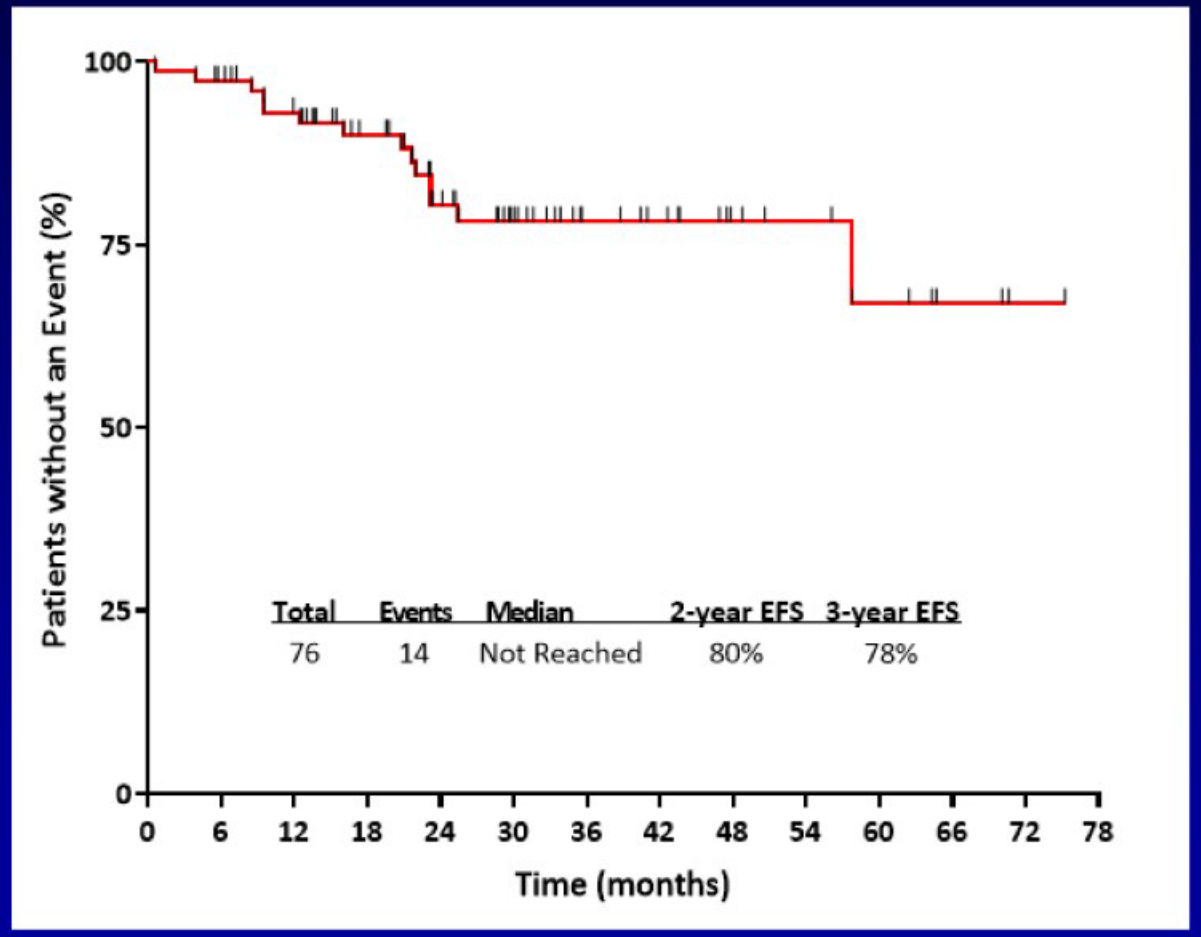
HSCT in CR1, n=2

Transplanted due to persistent *BCR::ABL1* transcripts

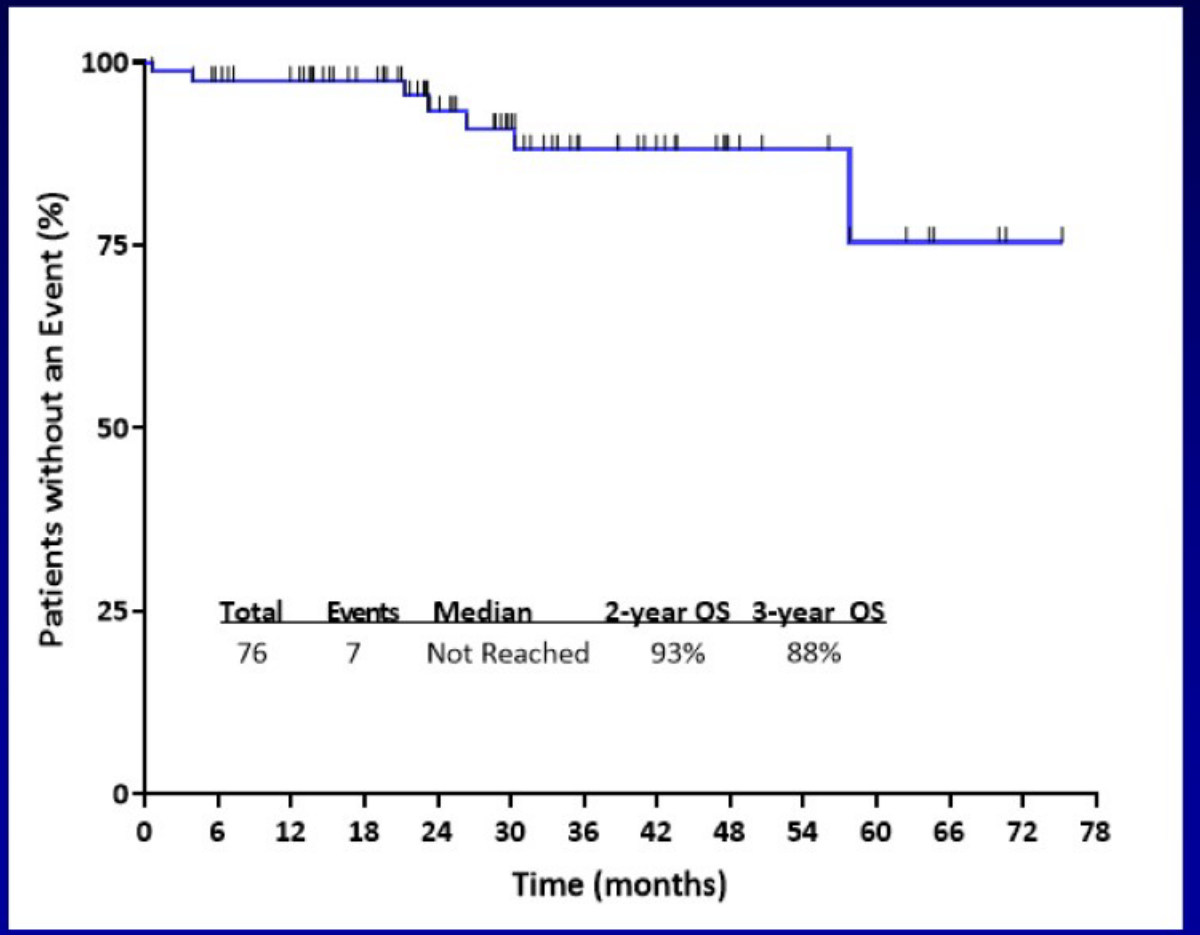
Ponatinib + Blinatumomab in Ph+ ALL: Survival Outcomes

Median follow-up: 29 months (range, 5-75 months)

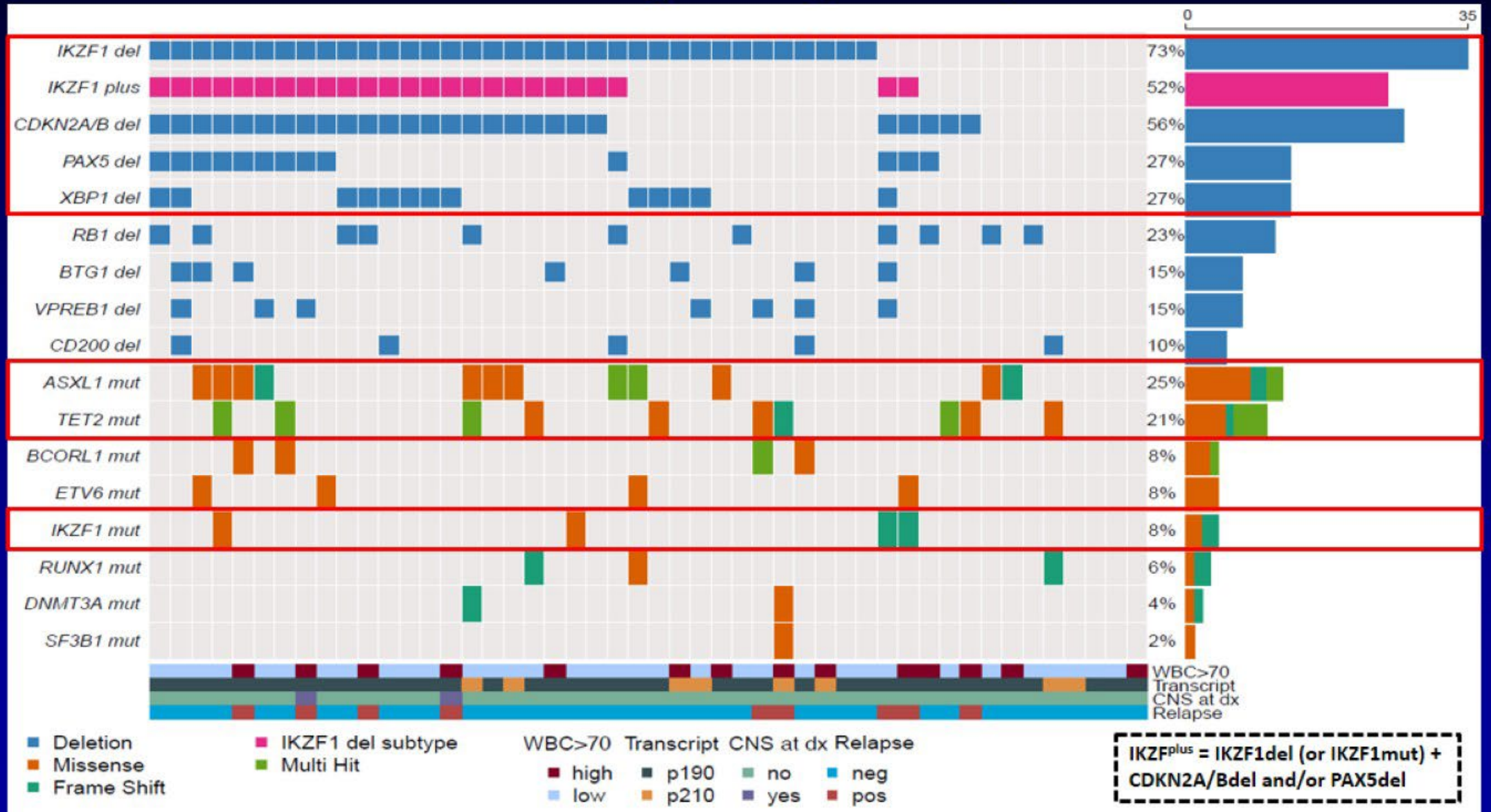
Event-Free Survival



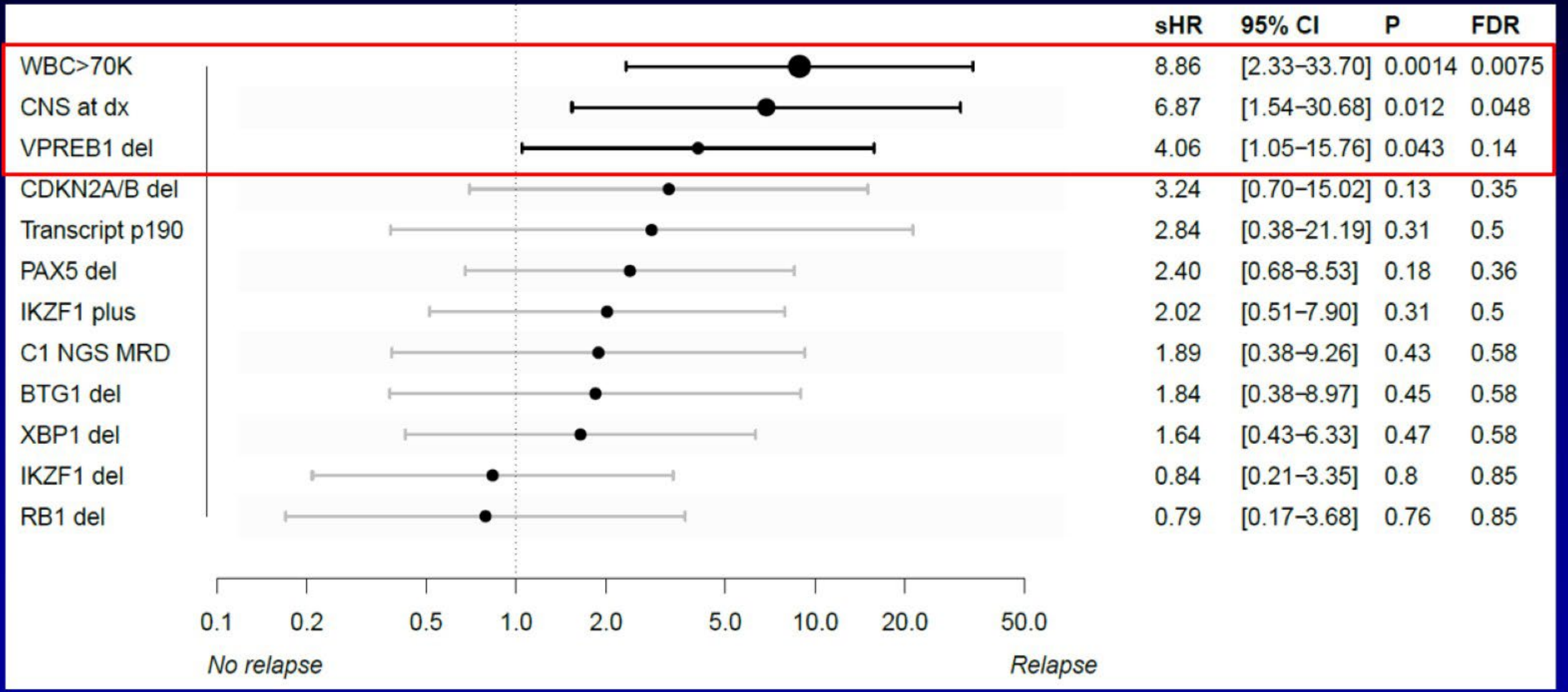
Overall Survival



Ponatinib + Blinatumomab in Ph+ ALL: Oncoplot (N=48)

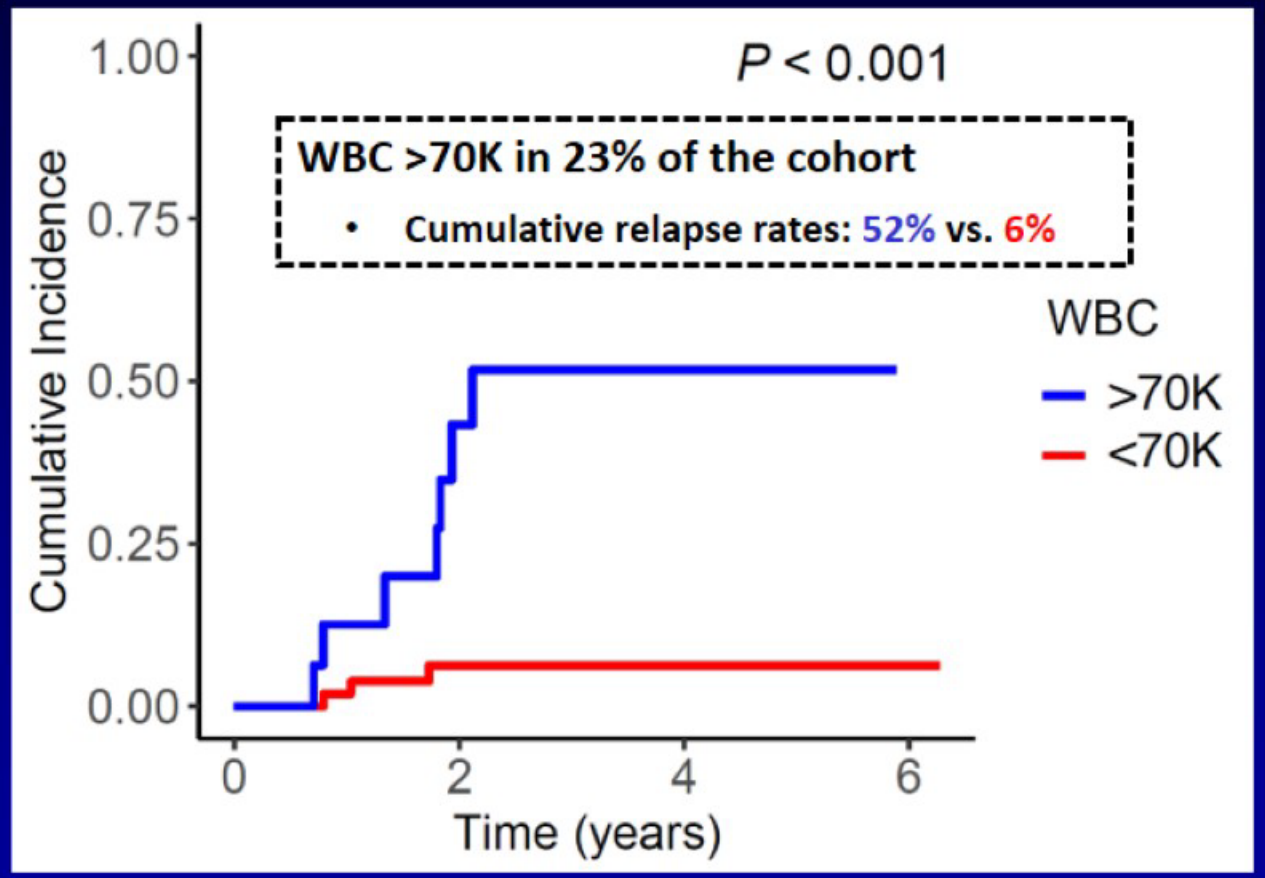


Ponatinib + Blinatumomab in Ph+ ALL: UVA for Relapse Risk

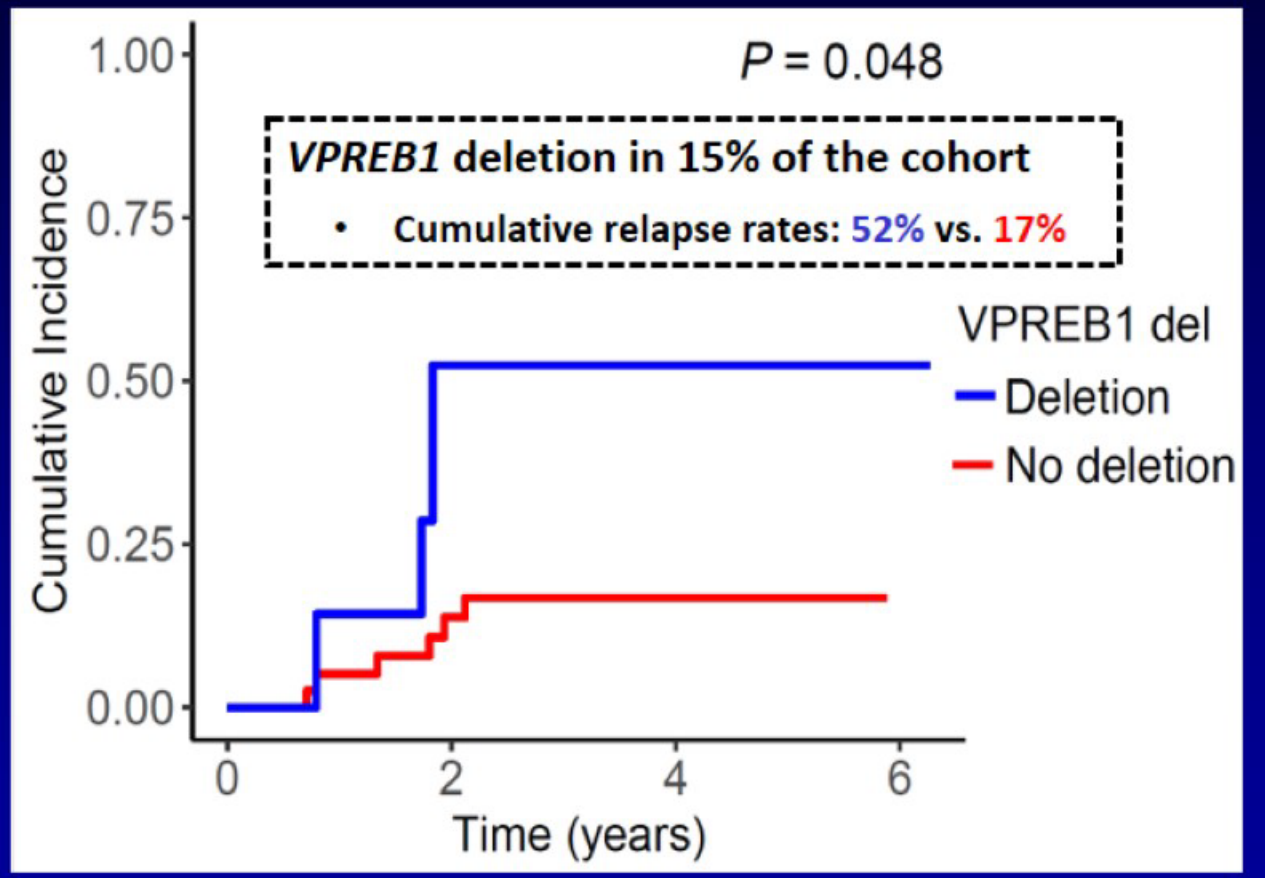


Ponatinib + Blinatumomab in Ph+ ALL: Relapse Risk by WBC and *VPREB1* deletion

WBC at diagnosis



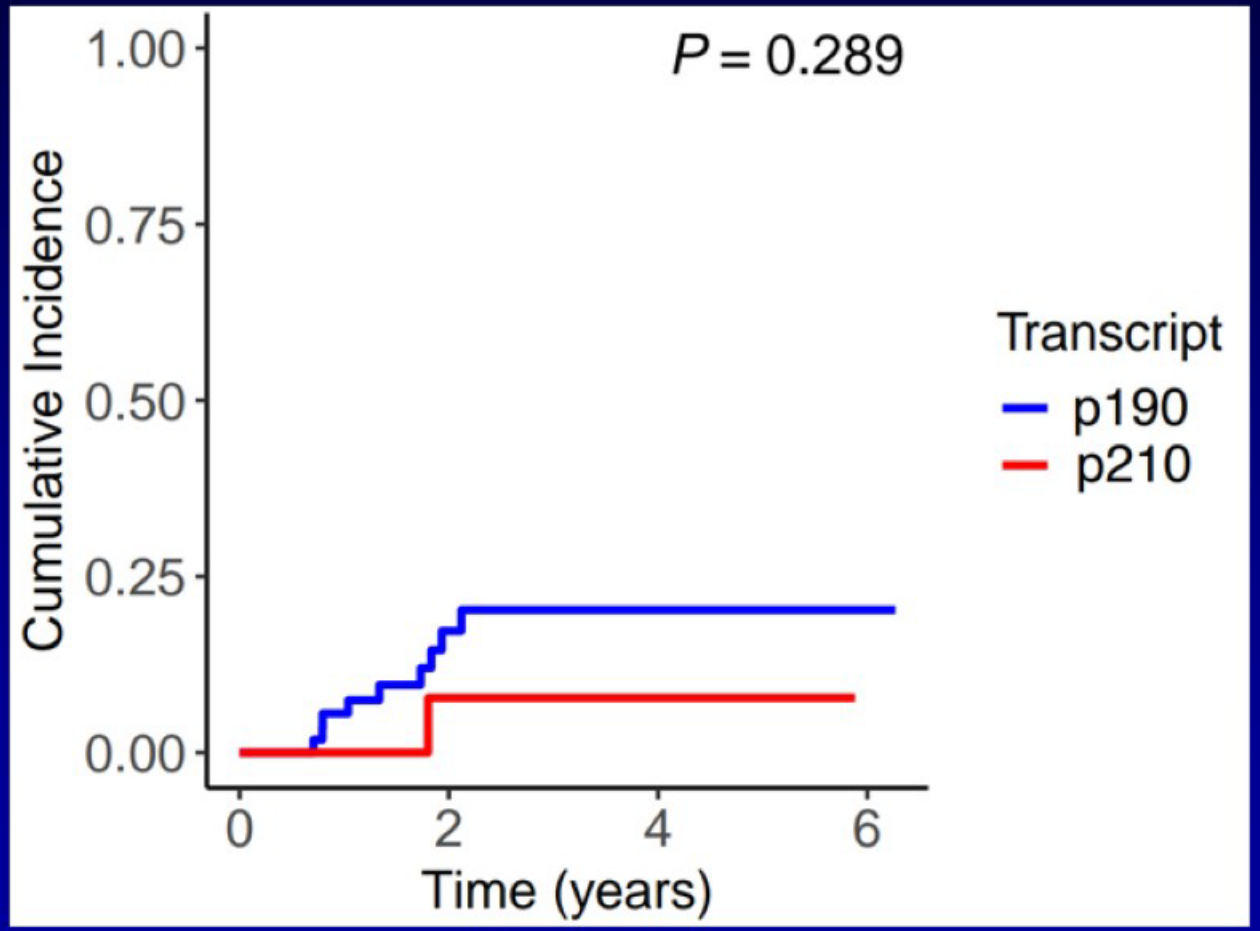
VPREB1 deletion



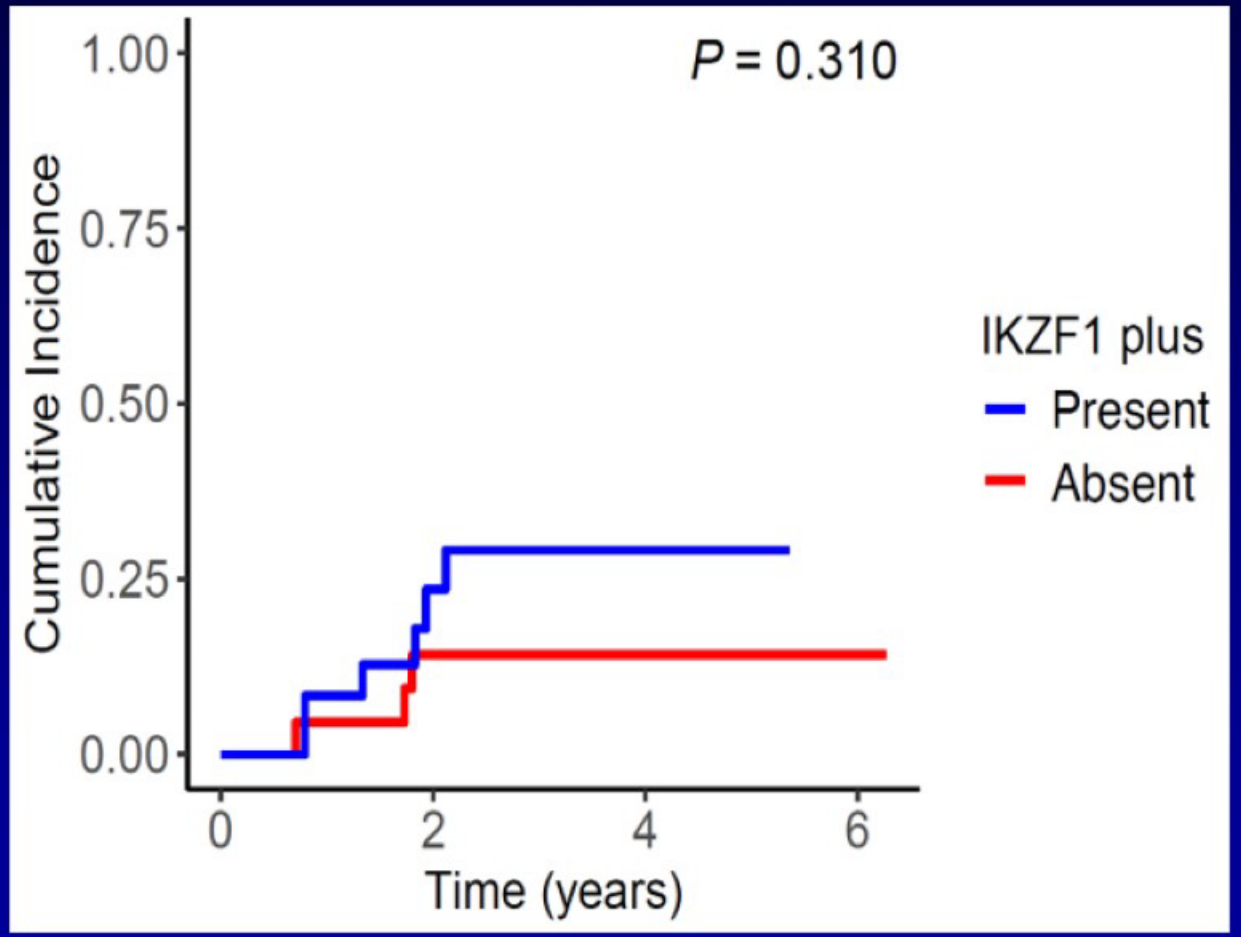
Among 3 pts with WBC <70K who relapsed: 2 had *VPREB1* del and 1 was not tested

Ponatinib + Blinatumomab in Ph+ ALL: Relapse Risk by Transcript Type and *IKZF1*^{plus}

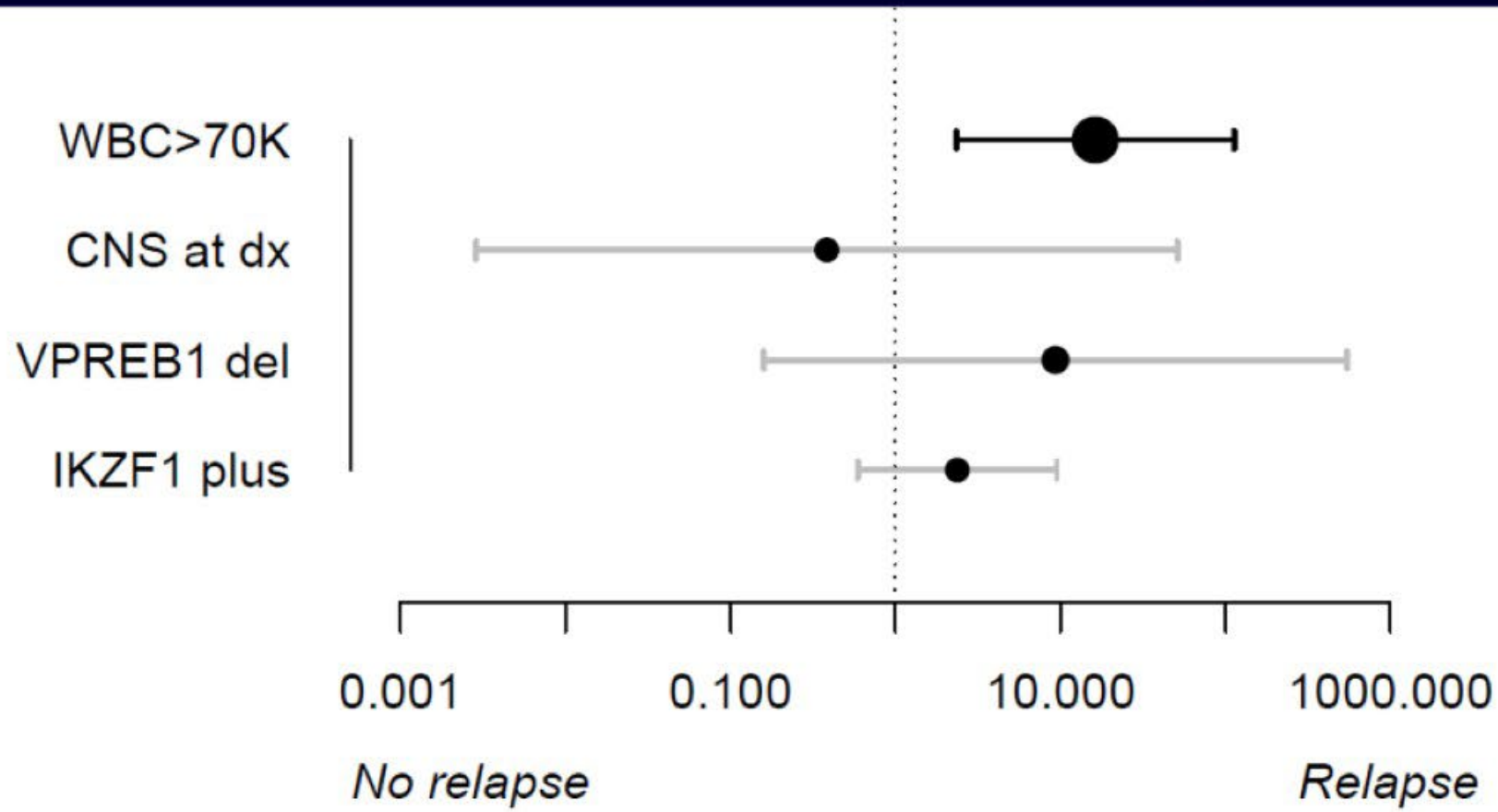
Transcript type



IKZF1^{plus}



Ponatinib + Blinatumomab in Ph+ ALL: MVA for Relapse Risk



	sHR	95% CI	P
WBC>70K	16.29	[2.35–113.00]	0.0047
CNS at dx	0.38	[0.00–51.50]	0.7
VPREB1 del	9.34	[0.16–546.30]	0.28
IKZF1 plus	2.37	[0.59–9.53]	0.22

WBC >70K at diagnosis was only factor independently predictive of relapse risk on MVA

Ponatinib + Blinatumomab in Ph+ ALL: Conclusions

- Chemotherapy-free combination of ponatinib + blinatumomab achieves deep responses in pts with newly diagnosed Ph+ ALL
  - CR/CRi 98%, CMR 83%, NGS MRD negativity 96%
- Durable remissions without HSCT in first remission
  - Estimated 3-year RFS 78%; 3-year OS 88%
  - Only 2 pts (3%) underwent HSCT in first remission
  - 10 relapses to date (13% relapse rate; half in CNS)
- WBC >70K only factor predictive for relapse; ? role of *VPREB1* deletion
  - Very high-risk feature → CIR rate ~50%
- Novel strategies needed for pts with high-risk Ph+ ALL

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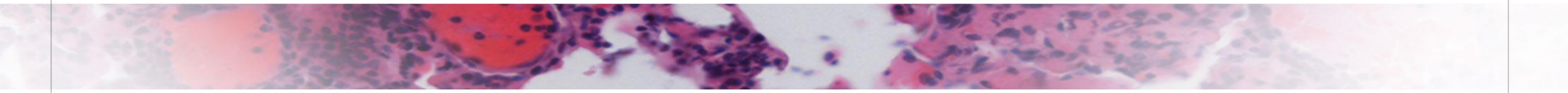

Assessment of Outcomes of Allogeneic Stem Cell Transplantation by Treatment Arm in Newly Diagnosed Measurable Residual Disease Negative Patients with B-Lineage Acute Lymphoblastic Leukemia Randomized to Conventional Chemotherapy +/- Blinatumomab in the ECOG-ACRIN-E1910 Phase III NCTN Trial

Michaela Liedtke, MD

Zhuoxin Sun, Mark Litzow, Ryan Mattison, Elisabeth Paietta, Kathryn Roberts, Yanming Zhang, Janice Racevskis, Hillard Lazarus, Jacob Rowe, Daniel Arber, Julie Bergeron, Brent Wood, Yaqi Zhao, Gang Wu, Ti-Cheng Chang, Wenchao Zhang, Keith Pratz, Shira Dinner, Noelle Frey, Steven Gore, Bhavana Bhatnagar, Ehab Atallah, Geoffrey Uy, Deepa Jeyakumar, Tara Lin, Cheryl Willman, Daniel DeAngelo, Shejal Patel, Michelle Elliott, Anjali Advani, Dimitrios Tzachanis, Pankit Vachhani, Rupali Bhave, Elad Sharon, Richard Little, Harry Erba, Richard Stone, Selina Luger, Charles Mullighan, Martin Tallman, Matthew Wieduwilt

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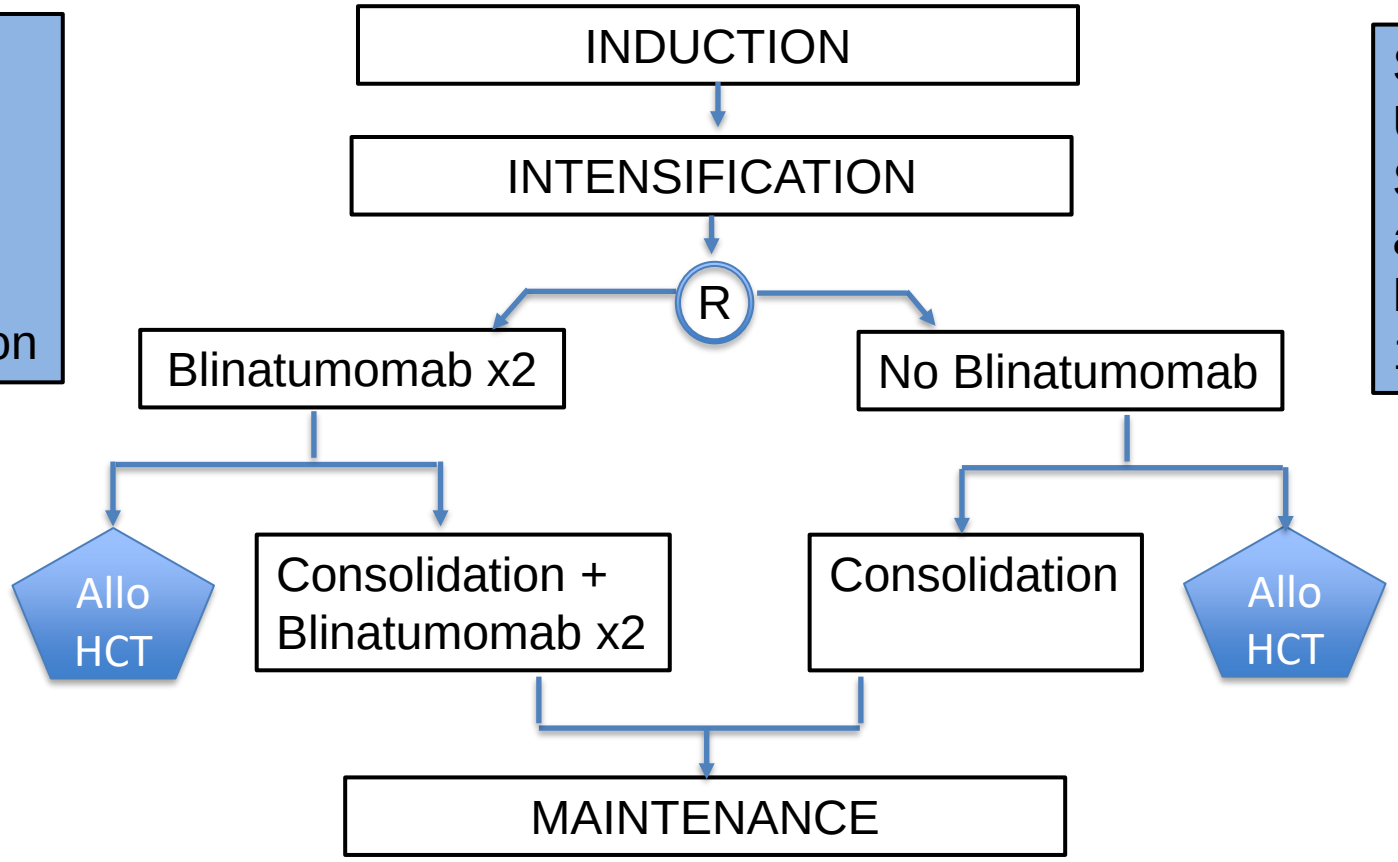
Introduction

- **UKALLXII/E2993 showed a survival benefit for adults with ALL who underwent allogeneic hematopoietic stem cell transplant in first CR based on a donor versus no-donor analysis.**
- **E1910 randomized pts with newly diagnosed BCR::ABL1-negative B-lineage ALL in measurable residual disease (MRD)-negative CR after intensification to receive 4 cycles of consolidation chemotherapy +/- 4 cycles of blinatumomab.**
- **A significant improvement in overall survival was observed with blinatumomab:**
  - **Overall survival at 3 years 85% (Blin+Chemo) vs 68% (Chemo)**
- **Pts were allowed to receive alloHCT after at least two cycles of blinatumomab in the blinatumomab group or any time after intensification chemotherapy in the chemotherapy-only group**

E1910: Randomized Phase 3 Adult Frontline ALL

Stratification:
Age <55 y
CD20 status
Rituximab use
Intent to transplant
MRD at randomization



Study Design:
US Intergroup study
Sites in US, Canada and Israel
N=488
1:1 randomization

Objectives/Methods

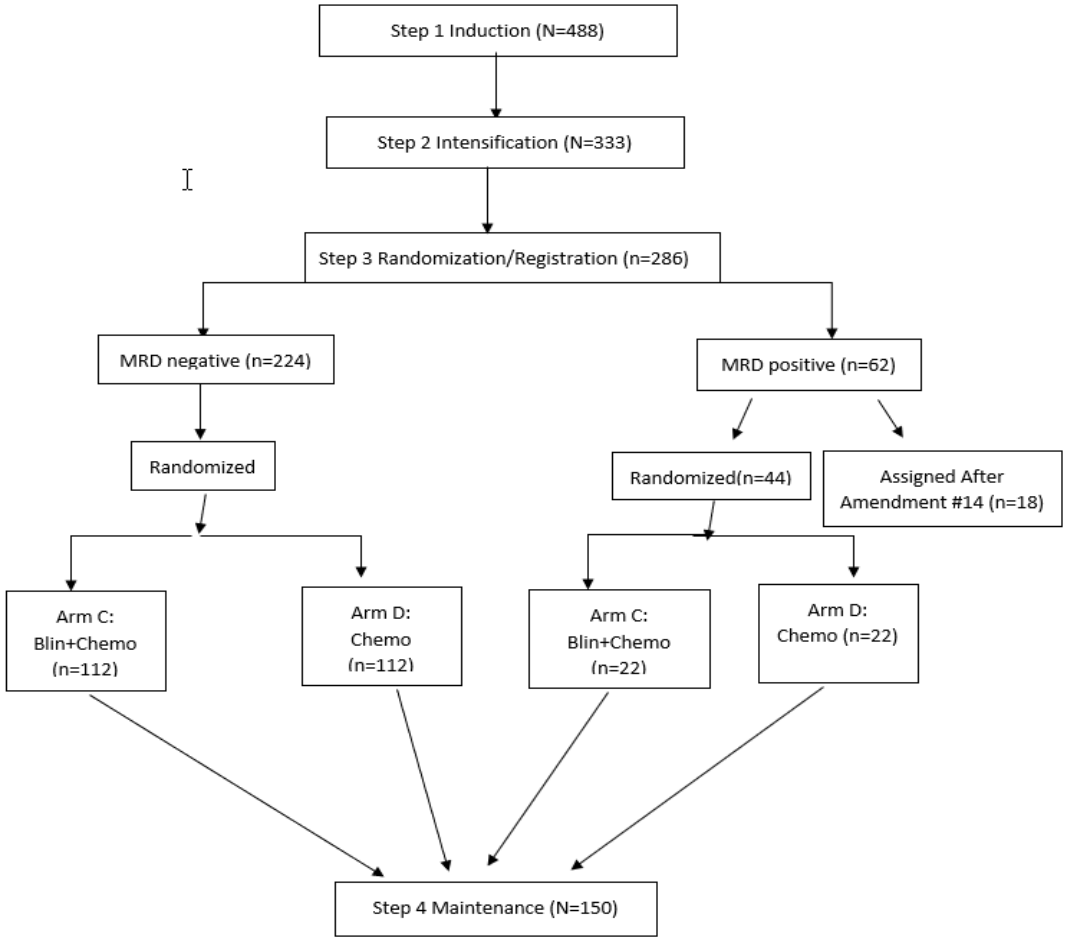
- **Objective: Assess effect of alloHCT on outcomes of MRD-negative patients randomized on E1910**
  - **Compare relapse-free and overall survival of alloHCT patients randomized to chemotherapy alone versus chemotherapy + blinatumomab**
  - **Multivariable analysis in all MRD-negative patients with allo-HCT as a time-dependent variable**
  - **Landmark analysis of MRD-negative patients with unfavorable risk ALL randomized to chemo + blinatumomab who underwent alloHCT versus patients who did not undergo alloHCT**

Definitions

- Measurable residual disease (MRD) was 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
- Unfavorable risk was defined as low-hypodiploid or near-haploid, *BCR::ABL1*-like, rearrangement involving *KMT2A*, *BCL-2*, *MYC*, *CRLF2*, *ETV6::RUNX1*-like with *IGH::CRLF2* fusion, complex karyotype; *TCF3:HLF*, *CDX2/UBTF*

Patient Status

- 488 pts enrolled 2013-2019
- CR/CRi rate 395/488 (81%)
- 224 MRD- pts randomized
- 44 pts underwent alloHCT on trial
  - 22 pts each in chemo and chemo+blin arm
  - Median time from randomization to alloHCT was 3.2 months
  - Median follow up from registration ~5 years



Baseline Demographics

	Chemo + Blin n=22 (%)	Chemo N=22 (%)
Age <55	50	50
Female/Male	41/59	55/45
Performance Status		
0-1 vs =/>2	91/9	96/4
Race		
Black	9	4.5
White	86	91
Not reported or unknown	5	4.5
Ethnicity		
Hispanic/Latino	9	4.5
Non-Hispanic/Latino	82	94.5
Not reported or unknown	9	0

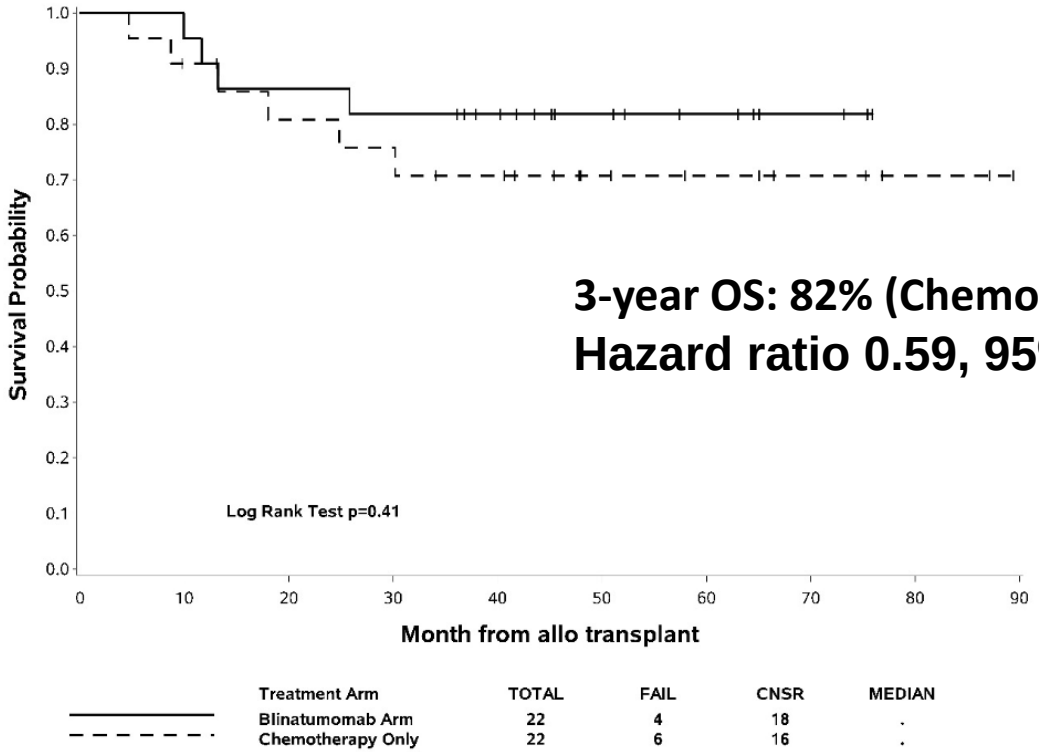
	Chemo + Blin n=22 (%)	Chemo n=22 (%)
Combined risk		
Favorable	13.6	22.7
Intermediate	9.1	9.1
Unfavorable	63.6	54.5
No risk assigned	13.6	13.6
MRD post induction		
MRD negative	63.6	77.3
MRD positive	31.8	22.7
Missing	4.5	0

Allogeneic stem cell transplantation

- Myeloablative conditioning was given to the majority of pts (68% CC arm and 73% CC+blin arm) and the most common graft versus host disease prophylaxis was tacrolimus-based on both arms.

	Chemo + Blin n=22 (%)	Chemo N=22 (%)
Regimen		
Myeloablative	73	68
Reduced intensity	18	23
Nob-myeloablative	9	9
GvHD Prophylaxis		
Tacrolimus	36.5	41
Sirolimus	4.5	0
ATG	4.5	13.5
MTX	9	23
Mycophenolate	4.5	4.5
Other	41	18

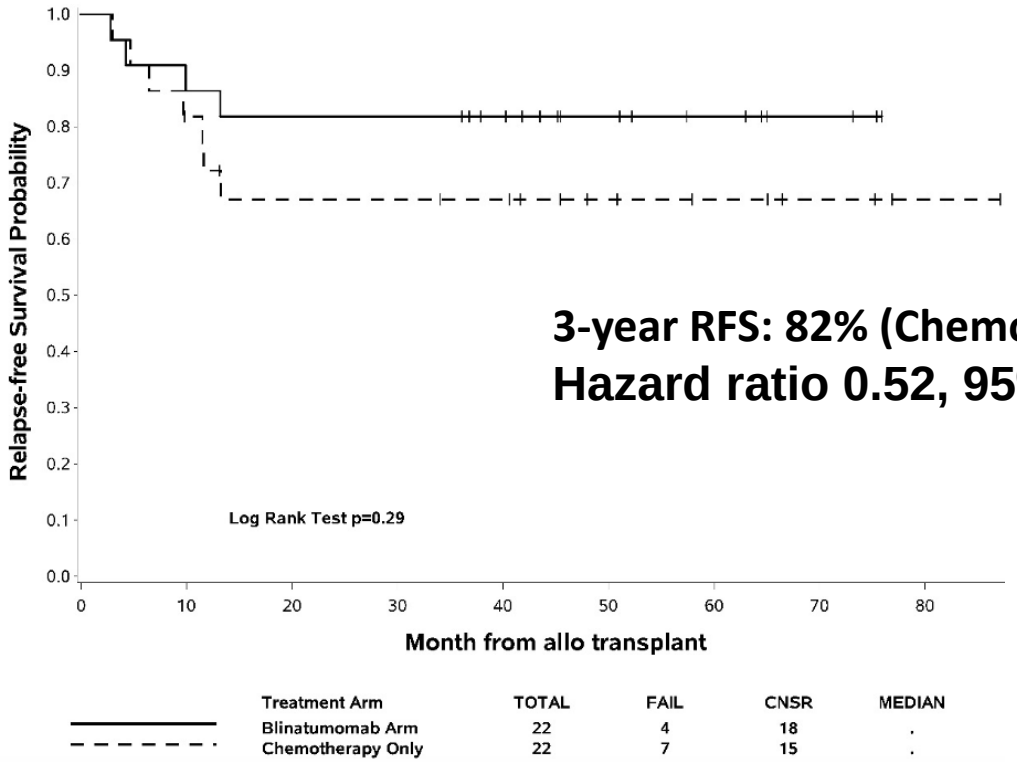
Overall Survival Comparison: MRD negative patients who underwent alloHCT



3-year OS: 82% (Chemo+ Blin) vs 71% (Chemo);
Hazard ratio 0.59, 95% CI: 0.12-2.11

In patients with unfavorable risk disease 3-year OS in each treatment arm was 71% versus 65%.

Relapse Free Survival Comparison: MRD negative patients who underwent alloHCT



3-year RFS: 82% (Chemo+ Blin) vs 67% (Chemo);
Hazard ratio 0.52, 95% CI: 0.15-1.79

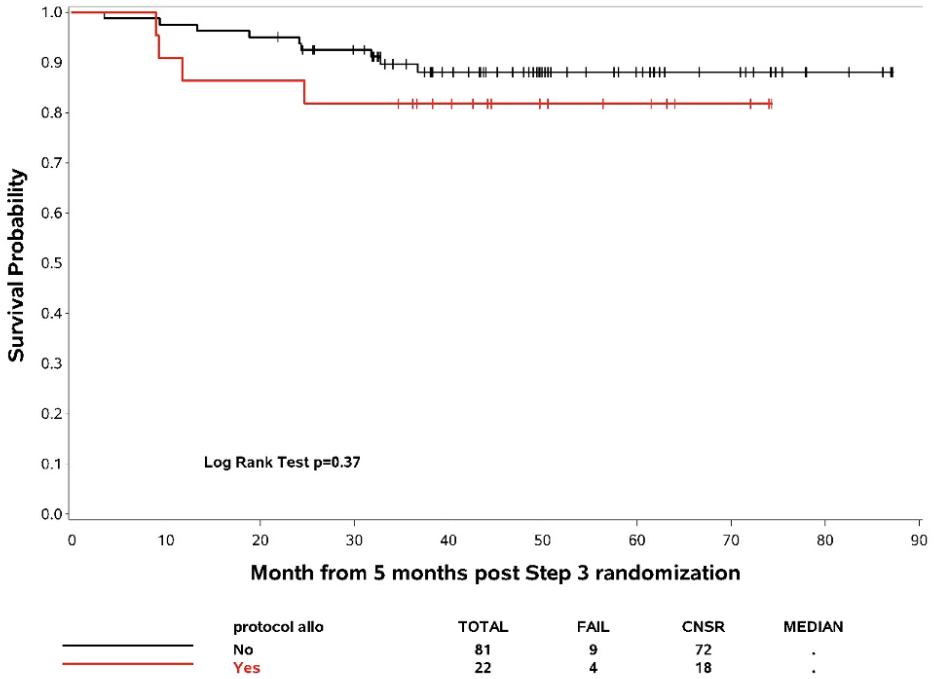
In patients with unfavorable risk disease 3-year RFS in each treatment arm was 71% versus 65%.

Multivariable Analysis:
All MRD-negative patients who were randomized on study

Variable		Hazard Ratio	Confidence Interval		P-value
Treatment	Blina vs chemo	0.462	0.257	0.829	**0.0096**
WBC		1.000	1.000	1.000	0.4003
Hb		1.062	0.895	1.261	0.4896
Peripheral blood blasts		1.005	0.993	1.018	0.3832
Platelets		1.000	1.000	1.000	0.6539
Bone marrow blasts		1.001	0.987	1.014	0.9388
Gender	Female vs Male	0.808	0.434	1.505	0.5016
Performance Status	0-1 vs, =/>2	0.303	0.122	0.753	**0.0101**
Combined Risk	Favorable vs unfavorable	0.215	0.071	0.651	**0.0065**
Combined Risk	Intermed. vs unfavorable	0.401	0.163	0.987	0.0469
Combined Risk	Missing vs unfavorable	0.673	0.281	1.614	0.3753
AlloHCT	AlloHCT vs no alloHCT	0.996	0.493	2.010	0.9908

Significant association between longer OS and receipt of blinatumomab, better PS and favorable risk.
The receipt of alloHCT had no effect on overall survival.

Overall survival of MRD-negative patients randomized to chemotherapy + blinatumomab: alloHCT vs no alloHCT



no alloHCT
alloHCT

Five-month landmark analysis shows no benefit to alloHCT.

Outcomes of MRD-negative patients with unfavorable risk randomized to chemotherapy + blinatumomab

- 50 pts with unfavorable risk in MRD-negative CR after intensification were randomized to chemotherapy + blinatumomab
- 14 pts underwent alloHCT compared to 36 pts who received chemo+blin alone
- A landmark analysis performed at 5 mos post randomization showed 3-year OS rates of 71% versus 90% between the 14 pts who underwent alloHCT and those who did not.
- The corresponding 3-year RFS rates were 71% versus 86% between the 14 pts who underwent alloHCT and those who did not.

CONCLUSIONS

- **Within the constraints of a small sample size, our exploratory analysis shows that in pts with newly diagnosed BCR::ABL-negative B-ALL who are MRD-negative after intensification, alloHCT outcomes are similar with and without blinatumomab in consolidation:** 3-year OS: 82% (Chemo+ Blin) vs 71% (Chemo); Hazard ratio 0.59
- **In a multivariate analysis of all MRD-negative pts receipt of blinatumomab but not alloHCT is associated with improved overall survival**
- **Further investigation is warranted to assess the benefit of blinatumomab in pts receiving alloHCT in frontline consolidation**

ACKNOWLEDGMENTS

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- Patients and Families

SAFETY AND FEASIBILITY OF BLINATUMOMAB AS FRONTLINE THERAPY FOR PEDIATRIC PATIENTS WITH B-ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOMA: ST. JUDE TOTAL THERAPY STUDY XVII

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INTRODUCTION

- St. Jude Total Therapy Studies XV and XVI demonstrated that, for children with acute lymphoblastic leukemia (ALL), minimal residual disease (MRD) ≥ 0.01% at the end of induction (EOI) and/or high-risk (HR) genetic subtypes were associated with poorer survival.
- TOTXVII aimed to improve cure and quality of life by employing precision medicine guided by flow cytometry-based MRD detection and next-generation sequencing-based genetic characterization in children with ALL and lymphoblastic lymphoma (LLy).
- Blinatumomab, a bispecific T-cell engager, is approved for adult and pediatric patients with B-ALL. Like other immunotherapies, blinatumomab is associated with an increased risk of cytokine release syndrome (CRS) and neurotoxicity and is complex to administer due to continuous 28-day infusion.
- Further work is needed to optimize patient selection and characterize how practical challenges impact patient subgroups.

AIM

- This study evaluated the safety and feasibility of blinatumomab during treatment in pediatric patients with B-ALL or B-LLy with high-risk features and those who were intolerant of conventional chemotherapy.
- ClinicalTrials.gov ID NCT03117751

RESULTS

- 621 patients (612 B-ALL, 9 B-Lly) were enrolled in TOTXVII, 147 received blinatumomab (116 Protocol defined; 31 Interim Therapy)
- 279 cycles were observed, 57 interruptions occurred in 46 cycles (16.5% cycles affected)
  - 68.4% (n=39) of interruptions ≥4 hours requiring readmission
  - Interruptions attributed to AEs (n=25, 43.9%), equipment issue (n=21, 36.8%), physician or family preference (n=11, 19.3%)
  - 33.3% (n=19) of interruptions resulted in permanent discontinuation (neurotoxicity responsible for 31.6%, n=6)

Table 1. TOTXVII blinatumomab patient demographics

Characteristic	Protocol Defined, n=116 (%)	Interim Therapy, n=31 (%)
Age at diagnosis, years		
1-10	67 (57.8)	19 (61.3)
>10	49 (42.2)	12 (38.7)
Sex		
Male	65 (56.0)	18 (58.1)
Female	51 (44.0)	13 (41.9)
Race		
White	73 (62.9)	25 (80.1)
Black	12 (10.3)	1 (3.2)
Others	31 (26.7)	5 (16.1)
Diagnosis		
ALL	113 (97.4)	31 (100.0)
LLy	3 (2.6)	0 (0)
Leukocyte count, cells/μL		
<10,000	53 (45.7)	10 (32.3)
10,000 to <50,000	29 (25.0)	10 (32.3)
50,000 to <100,000	16 (13.8)	6 (19.4)
≥ 100,000	14 (12.1)	5 (16.1)
Unknown	4 (3.4)	0 (0)
CNS Status		
CNS1	80 (69.0)	21 (67.7)
CNS2	18 (15.5)	6 (19.4)
CNS3	8 (6.9)	1 (3.2)
Traumatic with blasts	7 (6.0)	3 (9.7)
Unknown	3 (2.6)	0 (0)
Down Syndrome		
Present	7 (6.0)	3 (9.7)
Absent	109 (94.0)	28 (90.3)
MRD at end of induction, % (ALL only)		
<0.01	79 (68.1)	28 (90.3)
0.01-0.99	33 (28.4)	1 (3.2)
1-4.99	0 (0)	1 (3.2)
≥ 5	0 (0)	1 (3.2)
Unknown	1 (0.9)	0 (0)

Figure 1. TOTXVII Blinatumomab Indications

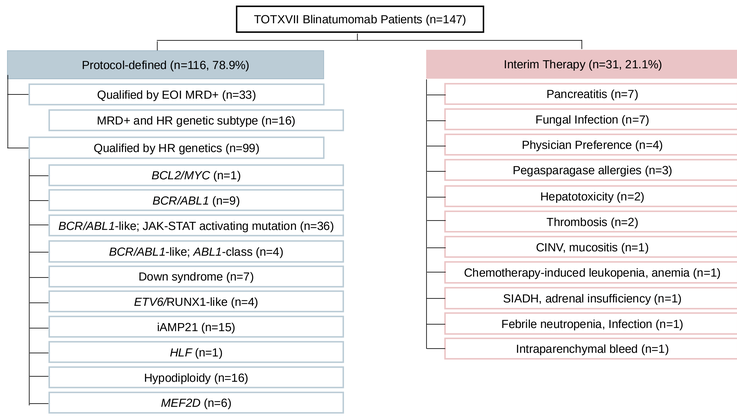

Table 2. Feasibility: Blinatumomab infusion interruptions and discontinuations

	Protocol Defined, n=116		Interim Therapy, n=31	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2
Total interruptions	**23**	**20**	**7**	**7**
Patients with interruptions	14	20	7	5
Discontinuations	4	9	2	4
Interruption duration				
<4 hours	11	5	1	1
AEs	Seizure (1)	CRS (1)	Fungal Infection (1)	Neurotoxicity (1)
Other	Equipment (9) Physician preference (1)	Equipment (4)	-	-
≥4 hours (interruption only)	8	6	4	3
AEs	CRS (2), Neurotoxicity (1), Seizure (1), ALT elevation (1)	CRS (1)	CRS (1), Seizure (1), Other (1)	Neurotoxicity (2), CRS (1)
Other	Equipment (2) Family preference (1)	Equipment (4) Family preference (1)	Physician Preference (1)	
Prolonged interruptions resulting in discontinuation	4	9	2	4
AEs	Seizure (2), Neurotoxicity (1), Allergic reaction (1)	Neurotoxicity (2), Other (1), ALT elevation (1)	Cardiac Event (1)	Pancreatitis (1), Cardiac event (1), Neutropenia (1) Neurotoxicity (1),
Other	-	Physician preference (2), Family Preference (1), Equipment (1) Disease progression (1)	Family preference (1)	-

3 patients with interruptions during cycle 1 and cycle 2, counted in both categories. Other = decompensation NOS (n=1), possible infection (n=1), rash (n=1)

Table 3. Safety: Adverse events during blinatumomab infusion

	Protocol Defined (n=116)		Interim Therapy (n=31)	
	Cycle 1	Cycle 2	Cycle 1	Cycle 2
Cytokine Release Syndrome (CRS):				
Median day of onset	2	1.5	N/A	2
Any grade	8	2	0	1
≥3 grade	2	1	0	0
Neurotoxicity (including seizure)				
Median day of onset	2.5	N/A	8	7.5
Any grade	4	0	1	2
≥3 grade	1	0	0	2
Seizure				
Median day of onset	2	N/A	8	N/A
Any grade	3	0	1	0
≥3 grade	0	0	0	0
Infection				
Any grade	14	17	1	2
≥3 grade	7	7	1	2
Upper Respiratory Infection	10	11	0	1
COVID-19	4	2	0	0
Rhinovirus A	2	3	0	0
Respiratory Syncytial Virus	2	1	0	0
Metapneumovirus	1	0	0	1
Influenza A	0	1	0	0
Influenza B	0	1	0	0
Parainfluenza Virus	0	2	0	0
Unknown	1	1	0	0
Bacteremia (*S. epidermidis*)	1	0	0	0
Enterocolitis	1	1	0	0
Ear Infection	0	1	0	1
Skin Infection/Paronychia	1	4	0	0
Viral Exanthem	1	0	0	0
Catheter Related Infection	0	0	1	0
Fever				
Any grade	19	11	1	1
≥3 grade	19	10	1	1
Febrile Neutropenia				
Any grade	6	1	0	0
≥3 grade	6	1	0	0
Increased Alanine Aminotransferase				
Any grade	6	3	0	0
≥3 grade	6	3	0	0
Hyperglycemia				
Any grade	5	1	0	0
≥3 grade	5	1	0	0
Hypokalemia				
Any grade	3	2	0	0
≥3 grade	3	2	0	0
Pancreatitis				
Any grade	0	0	0	1
≥3 grade	0	0	0	1
Acute Kidney Injury				
Any grade	0	1	0	0
≥3 grade	0	0	0	0
Thrombus				
Any grade	1	0	0	0
≥3 grade	1	0	0	0

METHODS

- Between 2017-2023, children aged 1–18 years at diagnosis received up to 2 consecutive cycles of blinatumomab in TOTXVII.
- **Indications**
  1. Protocol-defined patients with HR features:
     - EOI MRD of 0.01%–1.00%
       and/or
     - HR genetic subtypes (*BCR::ABL1*, *BCR::ABL*-like [with JAK–STAT activating mutations or *ABL1*-class fusions], iAMP21, hypodiploidy, *MEF2D* fusions, *ETV6::RUNX1*-like, *TCF3::HLF*, *BCL2*/*MYC*) or Down syndrome (DS)
  2. Interim therapy: patients intolerant of conventional chemotherapy
- **Feasibility** assessed by evaluation of cycle interruptions and discontinuations during blinatumomab treatment
  - Interruptions classified by frequency, indication, and duration (<4 hours or ≥4 hours), and if they resulted in permanent discontinuation
  - Interruptions lasting ≥4 hours required readmission for reinitiation
  - Patients who received 1 cycle of blinatumomab but did not receive a second due to toxicity or other unanticipated reason were considered discontinued.
- **Safety** assessed by evaluating AE frequency and severity based on CTCAE version 4.0.

CONCLUSIONS

- Blinatumomab is feasible and well-tolerated as part of frontline therapy for pediatric patients with B-ALL/LLy and high-risk features (EOI MRD 0.01%-<1.00% and/or genetic subtype) or are intolerant of conventional therapy with expected AE profiles. Most AEs observed in protocol-defined patients.
- Tolerability may be improved with efforts to prevent short and long-term interruptions, especially due to non-clinical causes such as equipment issues.
- Further analysis will (1) compare AEs in TOTXVII patients receiving blinatumomab to those in TOTXVI who received conventional chemotherapy and (2) evaluate survival outcomes associated with blinatumomab in this patient population.

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Updated Results of the Combination of Mini-Hyper-CVD with Inotuzumab Ozogamicin and Blinatumomab in Patients with Relapsed/Refractory B-Cell Acute Lymphoblastic Leukemia

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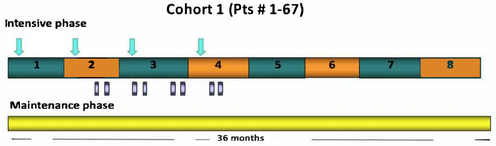
Background

- The combination of low-intensity mini-Hyper-CVD and inotuzumab (INO) with or without blinatumomab (blina) was safe and had promising activity in patients with relapsed-refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL).
- An early and concomitant administration of blina in a dose-dense fashion was deemed safe and effective in R/R B-ALL in a retrospective analysis.
- Compared to the sequential addition of blina, results from the dose-dense cohort showed improved outcomes with high rates of measurable residual disease (MRD) negativity.
- Here, we report updated results of this Phase II trial, including all three cohorts.

Methods

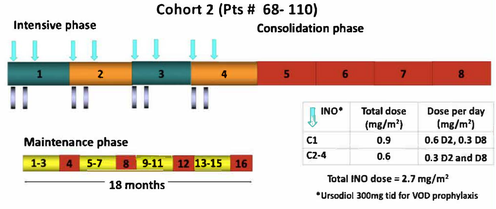
Study Design

Original study design
Cohort 1 (Pts # 1-67)



INO	Total dose (mg/m²) Pts 1 - 6	Total dose (mg/m²) Pts 7 - 34	Total dose (mg/m²) Pts 35 - 67
C1	1.3	1.8	1.3
C2-4	0.8	1.3	1.0

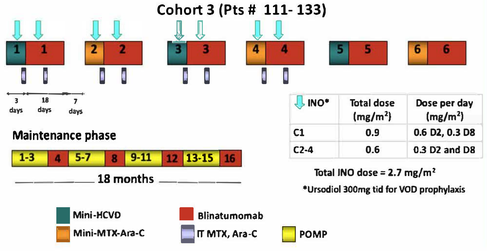
Modified study design
Cohort 2 (Pts # 68- 110)



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

Total INO dose = 2.7 mg/m²
*Ursodiol 300mg tid for VOD prophylaxis

Dose-Dense study design
Cohort 3 (Pts # 111- 133)



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

Total INO dose = 2.7 mg/m²
*Ursodiol 300mg tid for VOD prophylaxis

Inclusion Criteria

- R/R B-ALL
- ≥ 18 years old
- Performance status 0-3
- Adequate organ function
  - Bilirubin ≤ 2 mg/dL
  - AST & ALT ≤ 3x ULN
  - Creatinine clearance ≥50 mL/hr
  - Left ventricular ejection fraction ≥ 40%.
- Consolidation with allogeneic stem cell transplantation (ASCT) or chimeric antigen receptor (CAR) T-cell was at the discretion of the treating physician after discussion with the patient.

Results

Patient Characteristics

Characteristic	Category	N(%)/Median (range)			
		Overall N=133	Cohort 1 N= 67	Cohort 2 N = 44	Cohort 3 N = 22
Age (years)		37 (17-87)	34 (17-87)	42 (18-79)	41 (19-62)
Gender	Male	66 (50)	31 (46)	21 (48)	14 (64)
ECOG PS	≥2	20 (15)	11 (16)	8 (18)	1 (5)
WBC (x10⁹/L)	Median	3.8 (0.1-194.7)	3.7 (0.1-194.7)	3.3 (0.8-129.9)	5.5 (1.3-94.6)
PB blasts percentage		2.0 (0-97)	3.0 (0-93)	3.0 (0-97)	0.5 (0-87)
BM blasts percentage		66 (0-98)	72 (8-98)	49 (6-96)	51 (0-94)
Karyotype	Diploid	35 (26)	14 (21)	14 (33)	7 (32)
	Other	32 (24)	17 (25)	9 (21)	6 (27)
	Complex	13 (10)	10 (15)	3 (7)	0
	KMT2A rearrangement	11 (8)	8 (12)	2 (5)	1(5)
	Ho-Tr	14 (11)	4 (6)	8 (19)	2(9)
	HeH	3 (2)	3 (4)	0	0
	Tetraploidy	3 (2)	1 (1)	1 (2)	1(5)
	Ph+	4 (3)	0	1 (2)	3(14)
	IM/ND	18 (14)	10 (15)	6 (14)	2(9)
CRLF2		16/87 (18)	6/34 (18)	6/38 (16)	4/15 (27)
TP53 mutation		24/79 (30)	9/24 (38)	10/37 (27)	5/18 (28)
CD22 expression	Median	95.6 (14.3-100)	95.6 (20-100)	94.9 (14.3-99.9)	98.0 (18-99.9)
CD19 expression	Median	99.9 (0.5-100)	99.9 (0.5-100)	99.9 (10.5-100)	99.9 (52.9-100)
CD20 expression	≥20%	37/126 (29)	12/65 (18)	17/44 (39)	8/17 (47)
Prior ASCT		25 (19)	19 (28)	3 (7)	3 (14)
Salvage Status	Salvage 1	98 (74)	38 (57)	41 (95)	19 (86)
	S1, Primary refractory	21 (16)	5 (7)	10 (23)	6 (27)
	S1, CRD1 <12 months	29 (22)	17 (25)	9 (21)	3 (14)
	S1, CRD1 ≥12 months	48 (36)	16 (24)	22 (51)	10 (45)
	Salvage 2	19 (14)	15 (22)	2 (5)	2 (9)
	≥Salvage 3	16 (12)	14 (21)	1 (2)	1 (5)

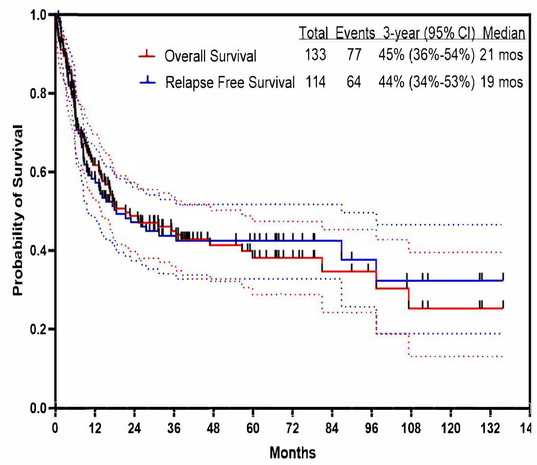
Response Rate

Response	N (%)			
	Overall N=133	Cohort 1 N= 67	Cohort 2 N= 44	Cohort 3 N= 22
Morphologic Response				
ORR	113/132 (86)	51 (76)	41 (93)	21/21 (100)
CR	86/132 (65)	40 (60)	29 (66)	17/21 (81)
CRp	23/132 (17)	10 (15)	10 (23)	3/21 (14)
CRi	4/132 (3)	1 (1)	2 (5)	1/21 (5)
No response	12 (9)	9 (13)	3 (7)	0
Early death	7 (5)	7 (10)	0	0
MRD Negativity by MFC				
After Cycle 1	57/107 (53)	25/49 (51)	18/39 (46)	14/19 (74)
Overall	93/109 (85)	41/50 (82)	34/40 (85)	18/19 (95)
MRD Negativity by NGS				
After Cycle 1	7/29 (24)	1/13 (8)	0/2 (0)	6/14 (43)
Overall	29/47 (62)	8/20 (40)	5/10 (50)	16/17 (94)

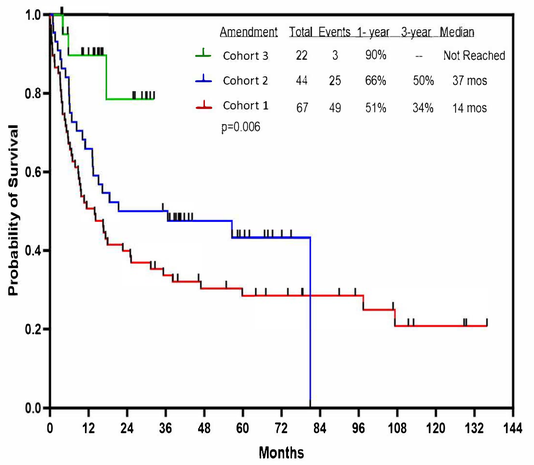
Patient Disposition

Median Follow up	40 mo (range, 3-136)	78 mo (range, 10-136)	44 mo (range, 35-75)	15 mo (range, 3-32)
Event	N (%)			
	Overall N=133	Cohort 1 N= 67	Cohort 2 N= 44	Cohort 3 N= 22
Relapse	41 (31)	25 (37)	13 (30)	3 (14)
ASCT consolidation	57 (43)	29 (43)	24 (55)	4 (18)
CAR-TI consolidation	12 (9)	3 (4)	1 (2)	8 (36)
Veno-Occlusive Disease	10 (8)	9 (13)	1 (2)	0
Death in CR	23 (17)	10 (15)	11 (25)	2 (9)
Death from progressive disease	54 (41)	39 (58)	14 (32)	1 (5)

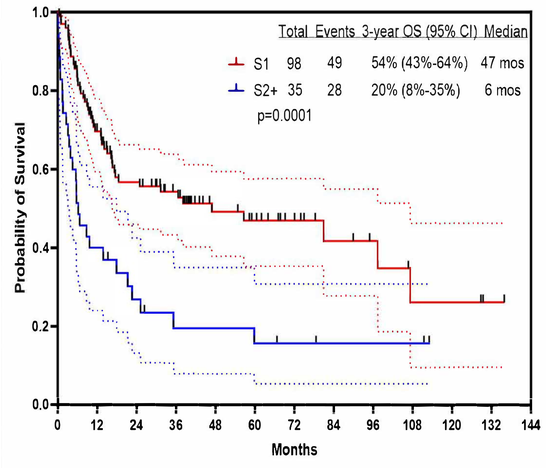
Overall OS and RFS



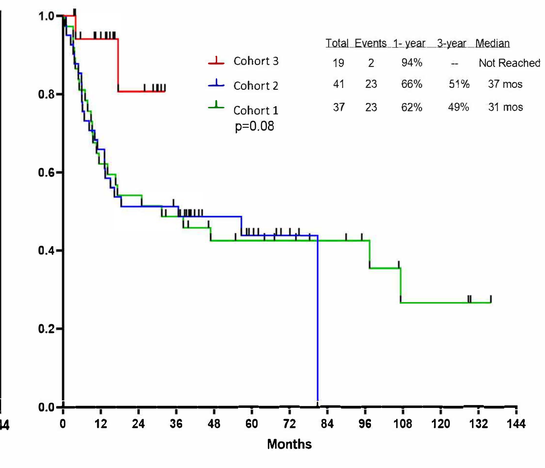
OS per cohort



Overall OS in S1 vs S2+



OS per cohort in S1 vs S2+



Conclusion

- The combination of mini-Hyper- CVD, INO and blina is safe and effective in R/R B-ALL.
- The introduction of blina and the fractionated administration of INO seem to improve the safety and efficacy of this combination.
- The use of a dose-dense approach resulted in high rates of deep and early MRD responses and promising survival outcomes prompting prospective studies in a first line setting.

Updated results from a phase II study of hyper-CVAD, with or without inotuzumab ozogamicin, and sequential blinatumomab in patients with newly diagnosed B-cell acute lymphoblastic leukemia

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Background

- Blinatumomab improves overall survival (OS) in B-ALL when combined with chemotherapy in the frontline setting.
- Inotuzumab ozogamicin (INO) improves OS in the relapsed/refractory setting.
- We hypothesized that the addition of INO to hyper-CVAD plus blinatumomab would lead to deeper and more durable responses, reduce relapses, and improve survival.

Enrollment criteria

Inclusion Criteria

- Newly diagnosed Ph- B-cell ALL
  - Previous therapy with 1 course of chemotherapy was allowed
  - Age ≥ 14 years
- ECOG performance status ≤ 3
- Adequate hepatic and kidney function
  - Bilirubin ≤ 2 mg/dL
  - Creatinine ≤ 2 mg/dL

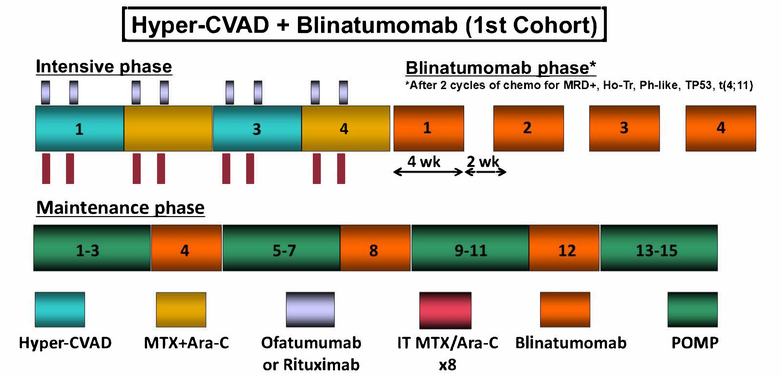
Exclusion Criteria

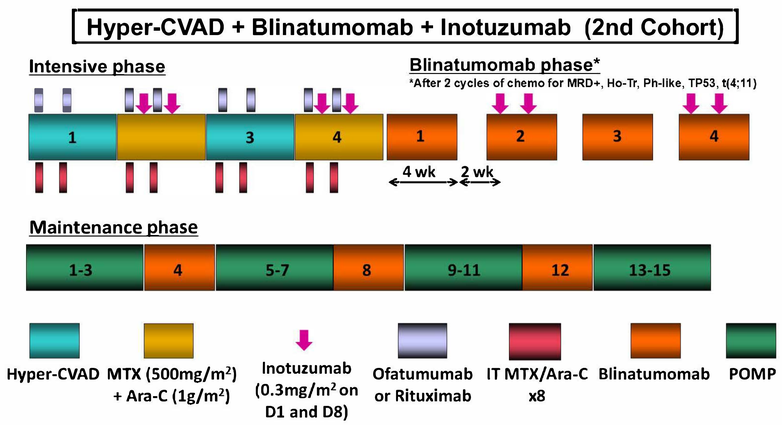
- Ph+ B-cell ALL
- Significant CNS pathology (excluding CNS leukemia)
- No active or co-existing malignancy with life expectancy ≤ 12 months

Methods

- In this phase II study, pts age 14-59 with newly diagnosed Ph-negative B-cell ALL received hyper-CVAD alternating with high dose methotrexate (MTX) and cytarabine (Ara-C) for up to 4 cycles, followed by 4 cycles of blinatumomab.
- Pts with high-risk (HR) cytomolecular features or persistent MRD-positivity started blinatumomab after 2 cycles of hyper-CVAD.
- Pts with CD20+ disease received 8 doses of ofatumumab or rituximab.
- Initially pts received 8 doses of prophylactic IT chemotherapy, but the protocol has been amended to increase IT chemotherapy to 12.
- Maintenance was with alternating blocks of POMP and blinatumomab.
- Beginning with pt #39, INO at a dose of 0.3mg/m^2 on day 1 and 8 was added to the 2 cycles of MTX/Ara-C (which was also dose reduced to 500mg/m^2 and 1g/m^2) and to 2 cycles of blinatumomab consolidation

Study design





Patients

Characteristic N (%) / median [range]	Overall N = 75	Cohort 1 (no INO) N = 38	Cohort 2 (with INO) N = 37
Age	33 [18-59]	37 [18-59]	25 [18-57]
Male	50 (67)	26 (68)	24 (65)
ECOG 0-1	64 (85)	30 (79)	34 (92)
WBC (x10^9/L) at start	4.7 [0.5-553]	3.1 [0.5-360.9]	7.6 [1.0-553]
CD19 expression ≥50%	65/66 (98)	31/32 (97)	34/34 (100)
CD20 expression ≥20%	34/67 (51)	17/33 (52)	17/34 (50)
***TP53* mutation**	14/74 (19)	10/37 (27)	4/37 (11)
CRLF2+ by flow	9/70 (13)	6/33 (18)	3/37 (8)
***JAK2* mutation**	4/74 (5)	2/37 (5)	2/37 (5)
Karyotype			
Diploid	24 (32)	11 (29)	13 (35)
High hyperdiploidy	5 (7)	3 (8)	2 (5)
Low hypodiploidy/Near triploidy	8 (11)	6 (16)	2 (5)
***KMT2A* rearranged**	6 (8)	3 (8)	3 (8)
Complex (≥5 anomalies)	6 (8)	3 (8)	3 (8)
Other	26 (35)	12 (32)	14 (38)
High-risk disease*	36/75 (48)	21/38 (55)	15/37 (41)

*High-risk disease defined as complex, low hypodiploidy, or near triploidy cytogenetics, *KMT2Ar,* Ph-like ALL, or *TP53* mutation

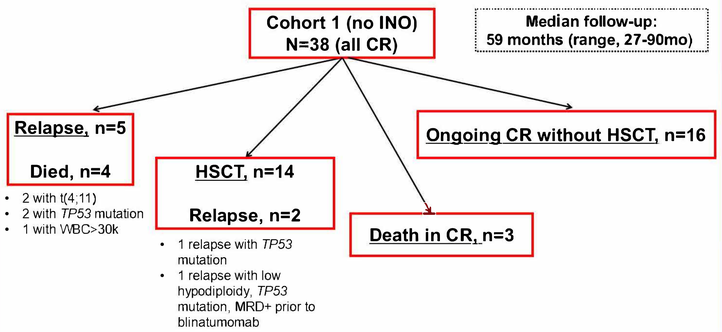
Results

Response rates

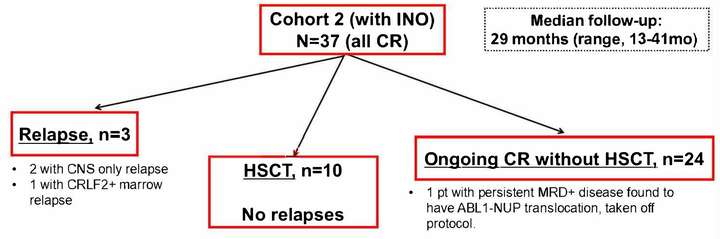
Response N (%)	Overall N = 75	Cohort 1 (no INO) N = 38	Cohort 2 (with INO) N = 37
CR after induction*	50/59 (84)	26/32 (81)	24/27 (89)
CR at any time	59/59 (100)	32/32 (100)	27/27 (100)
Flow MRD negativity after induction**	43/65 (66)	25/33 (76)	18/32 (56)
Flow MRD negativity at any time	62/65 (95)	32/33 (97)	30/32 (94)
NGS MRD negativity at any time	40/56 (71)	14/23 (61)	26/33 (79)
Flow MRD-, standard-risk **Flow MRD-, high-risk**	32/32 (100) 30/33 (91)	14/14 (100) 18/18 (100)	18/18 (100) 12/15 (87)
NGS MRD-, standard-risk **NGS MRD-, high-risk**	23/28 (82) 17/28 (61)	5/8 (63) 9/15 (60)	18/20 (90) 8/13 (62)
Early death (30-day)	0	0	0

*Six pts in Cohort 1 (no INO) and 10 patients in Cohort 2 (with INO) were in CR at start.
**Five pts in Cohort 1 (no INO) and 5 pts in Cohort 2 (with INO) were MRD negative by flow at start.
Abbreviations: CR, complete remission; MRD, measurable residual disease; NGS, next generation sequencing

Disposition of Hyper-CVAD + Blinatumomab (1st Cohort)

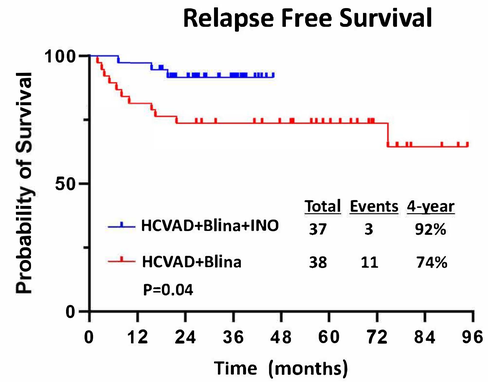


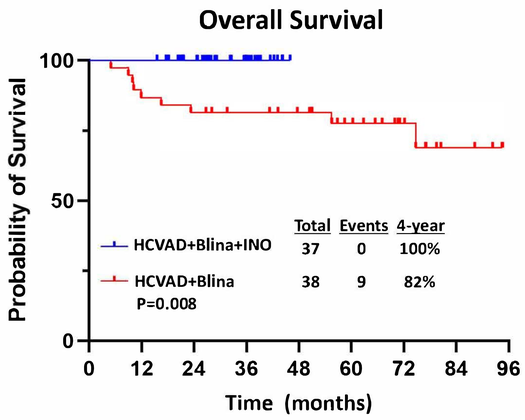
Disposition of Hyper-CVAD + Blinatumomab + INO (2nd Cohort)



Results

Outcomes





Safety (Related Adverse Events)

Blinatumomab
- 1 patient discontinued due to related adverse event (grade 2 encephalopathy and dysphasia)

Inotuzumab
- No patients discontinued due to toxicity
- No cases of veno-occlusive disease

Conclusions

- Hyper-CVAD with sequential blinatumomab +/- INO is highly effective and safe as frontline therapy for Ph-negative B-ALL
- Early data suggest possible benefit of the addition of INO to the chemotherapy + blinatumomab backbone
- Due to CNS relapses, the protocol has been amended to now administer 15 doses of IT chemotherapy

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Clearance of very low levels of measurable residual disease with blinatumomab significantly improves outcomes in B-cell acute lymphoblastic leukemia

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Abstract

Background

- The strongest independent predictor of outcome in B-cell acute lymphoblastic leukemia (B-ALL) is the persistence of minimal residual disease (MRD).
- Blinatumomab, a bispecific CD3-CD19 T-cell engaging antibody, was previously shown to improve outcomes in B-ALL with residual MRD (≥10^{-3}) leading to FDA approval in MRD+ B-ALL in 2018, and more recently approved for consolidation in the frontline setting irrespective of MRD.
- Conventional methods of MRD detection such as multiparameter flow cytometry and qualitative PCR have a sensitivity of 10^{-4}, or 0.01%.
- Next-generation sequencing (NGS)-based MRD assays can detect clinically significant MRD at a sensitivity of 10^{-6}.
- The clinical impact of blinatumomab with low-level MRD detected by NGS and the depth of responses obtained are unknown.

Methods

- We retrospectively analyzed patients with B-ALL in complete remission who received blinatumomab for MRD at any level.
- ClonoSEQ® (Adaptive Biotechnologies) which uses NGS assessment of B-cell and T-cell receptor gene rearrangements was used to quantitate MRD response in both retrospectively banked and prospective clinical samples.
- Patients converted from NGS MRD+ to negative with blinatumomab were considered responders, while patients who remained NGS MRD+ or who relapsed were considered non-responders.

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Patients

Characteristic N (%) / median [range]	Total N = 42
Age (years)	38.5 [19-70]
ECOG 0-1	40 (95)
ECOG ≥2	2 (5)
WBC (x10^9/L) at diagnosis	4.7 [0.4-53.8]
History of CNS / ECM disease	5 (12)
Disease subtype	
Ph+	11 (26)
Ph-	31 (74)
Disease status	
CR1	33 (79)
CR2	7 (17)
CR3+	2 (5)
Karyotype	
Ph+	11 (26)
Diploid	2 (5)
Complex	6 (14)
Low hypodiploidy/near triploidy	2 (5)
KMT2Ar	4 (10)
High hyperdiploidy	3 (7)
Other / Insufficient metaphases	14 (33)
Ph-like ALL	9/31 (29)
TP53 mutation	9 (21)
High-risk disease*	22/42 (52)

*High-risk disease defined as complex, low hypodiploidy, or near triploidy cytogenetics, *KMT2Ar,* Ph-like ALL, or *TP53* mutation
Abbreviations: ECOG, eastern cooperative oncology group; CNS, central nervous system; ECM, extramedullary; CR1, first complete remission

Results

NGS MRD response rates

Response N (%)	Ph- N = 31	Ph+ N = 11	Total cohort N = 42	P
NGS MRD response rate	10/31 (31)	7/11 (64)	17/42 (41)	
MFC+ and/or PCR+	4/19 (21)	5/9 (56)	9/28 (32)	0.2
MFC- and PCR-	6/12 (50)	2/2 (100)	8/14 (57)	
CR1	10/24 (42)	7/9 (78)	17/33 (52)	0.006
CR2+	0/7 (0)	0/2 (0)	0/9 (0)	
Standard-risk disease	5/9 (56)	7/11 (64)	12/20 (60)	0.03
High-risk disease	5/22 (23)	N/A	5/22 (23)	

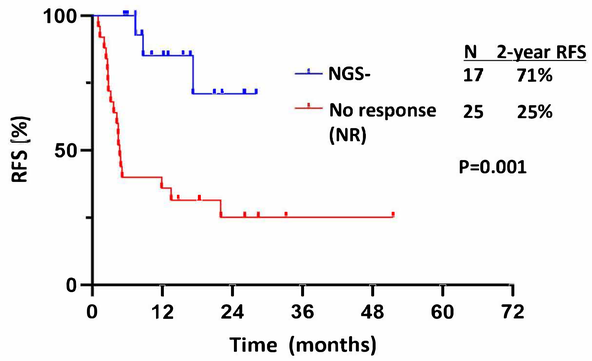
Abbreviations: NGS, next-generation sequencing; MFC, multiparameter flow cytometry

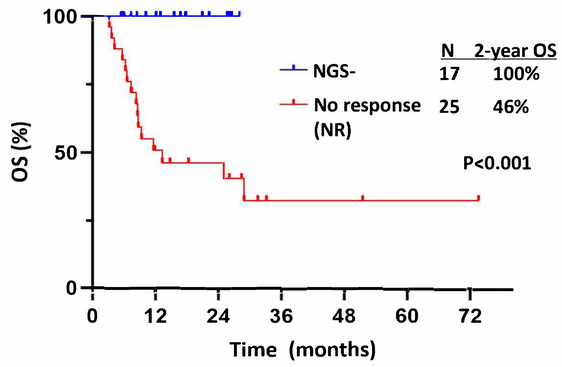
The overall NGS MRD negativity rate with blinatumomab was 41%.

NGS MRD responses were only observed in patients in CR1.

Results

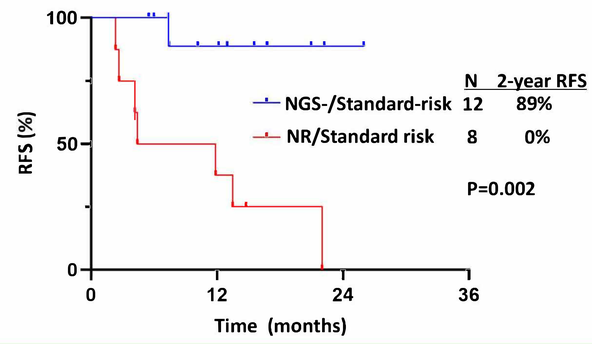
Impact of NGS MRD clearance after blinatumomab (total cohort)

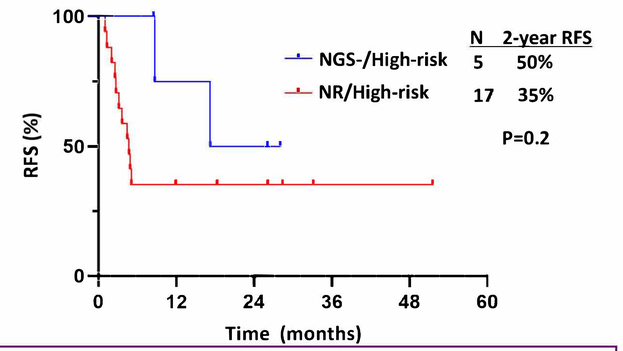




Patients who achieved NGS MRD negativity after blinatumomab had excellent long-term remissions and survival

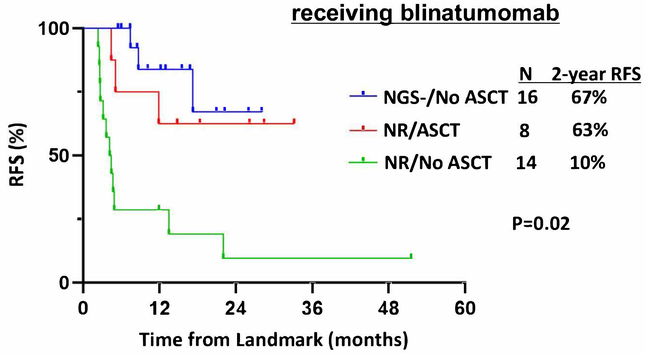
Impact of NGS MRD clearance after blinatumomab, stratified by disease risk





Best long-term outcomes in patients with standard-risk ALL who achieve NGS MRD negativity after blinatumomab

Impact of NGS MRD response and ASCT in patients receiving blinatumomab



ASCT may overcome poor prognosis of NGS MRD non-responders

Conclusions

- Deep responses to blinatumomab as assessed by NGS MRD is associated with superior survival outcomes across clinical contexts and identifies patients who have excellent long-term outcomes
- NGS MRD non-responders to blinatumomab have poor outcomes (2-year RFS: 25%) but may be salvaged by ASCT
- The relatively low rate of NGS MRD negativity with blinatumomab monotherapy (31% in Ph- B-ALL) highlights the need for combination therapies in B-ALL
- Studies evaluating CAR T-cell consolidation in poor NGS MRD responders are needed

Addition of Blinatumomab to Consolidation Therapy Among Older Newly Diagnosed Patients with *BCR::ABL1* Negative B-lineage Acute Lymphoblastic Leukemia (ALL) in the ECOG-ACRIN E1910 Randomized Phase III Trial

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Background

- E1910 patients (pts) with ALL aged 30-70 years who had been measurable residual disease negative (MRD-) in the marrow (MRD <0.01%) after intensification were randomized to conventional chemotherapy (chemo) or chemo with blinatumomab
- Among the entire E1910 cohort, the addition of blinatumomab resulted in improved overall survival (OS)[1] and led to a new standard of care
- Dexamethasone and pegaspargase were reduced for older E1910 pts (aged ≥ 55 years)

Objectives: to compare the OS and relapse free survival (RFS) among older pts aged ≥55 years (pre-specified stratification factor) who received chemo + blinatumomab to that of pts who received chemo alone (step 3 treatment)

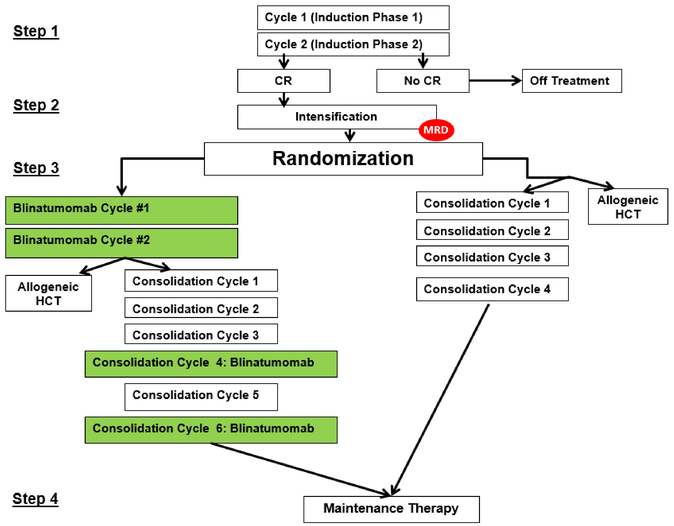
Study design

- Induction (step 1), high dose methotrexate with pegaspargase intensification (step 2), blinatumomab randomization (step 3), maintenance (step 4) or allogeneic transplant (HCT)[1] (**Figure 1**)
- Following approval of blinatumomab in the US for MRD+ disease in 2018, MRD+ pts were assigned to the blinatumomab arm

Statistical Analysis

- Estimates of OS and RFS: Kaplan-Meier method
- Comparison of OS and RFS:
  - Two-sided stratified log-rank test and Cox model (stratification factors: CD20, rituximab, intent for HCT)
  - Stratified multivariate Cox models (adjusted by sex, WBC, platelets, hemoglobin, peripheral blood blasts, marrow blasts, performance status and molecular risk category)

Figure 1. Treatment Schema



Results

- 488 enrolled pts: 211 were ≥55 years; median age of 61
- Median follow-up from step 1 registration: 54.6 months
- Baseline characteristics not significantly different (**Table 1**)
- 174 (82.5%) pts responded: 167 CR, 7 CRi; 93 (44%) MRD-
- HCT: 32 (15.1%) on study and 24 (11.4%) off study
- MRD- pts (n=93): 46 randomized / 45 received blinatumomab

6 (13.3%) – 1; 14 (31.1%) – 2; 2 (4.4%) – 3; 23 (51.1%) had 4 cycles

Conclusions

- Despite evidence of improved outcomes in the whole study cohort, the addition of blinatumomab to consolidation chemo for older pts (age ≥ 55) with ALL was not associated with statistically significant improvement of OS/RFS in exploratory analysis not powered to detect the difference in subgroups
- This is possibly due to sample size but may be due to biologic differences in the older adult population and differences in received treatment
- Further studies are needed to definitively determine tolerance and benefit of blinatumomab addition to consolidation for older pts with ALL

Table 1. Baseline Characteristics of MRD- Patients Age ≥ 55 Years by Treatment Arm

Variable	Blinatumomab (n=46)	Chemo (n=47)	Total (n=93)
Age, median (range), years	62 (55-69)	61 (55-70)	62 (55-70)
Sex, n (%)			
Female	24 (52.2)	26 (55.3)	50 (53.8)
Male	22 (47.8)	21 (44.7)	43 (46.2)
White race, n (%)	36 (78.3)	39 (83.0)	75 (80.6)
WBC ≥ 10.000 /uL, n (%)	8 (17.4)	9 (19.1)	17 (8.1)
Immunophenotype, n (%)			
CD10+ early B-ALL	36 (78.3)	38 (80.9)	74 (79.6)
CD10- B-ALL	10 (21.7)	9 (19.1)	19 (20.4)
Genetic subgroups, n (%)			
Low hypodiploid	14 (30.4)	11 (23.4)	17 (18.3)
BCR::ABL1-like	8 (17.4)	4 (8.5)	12 (12.9)
KMT2A rearranged	5 (10.9)	5 (10.6)	10 (10.8)
Molecular risk, n (%)			
Favorable	5 (10.9)	7 (14.9)	12 (12.9)
Intermediate	5 (10.9)	7 (14.9)	12 (12.9)
Unfavorable	30 (65.2)	21 (44.7)	51 (54.8)
Could not be assigned	6 (13.0)	12 (25.5)	18 (19.4)

Figure 2. OS for MRD- Patients Age ≥55 Years by Treatment Arm

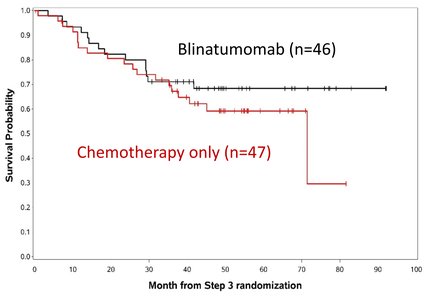


Figure 3. RFS for MRD- Patients Age ≥55 Years by Treatment Arm

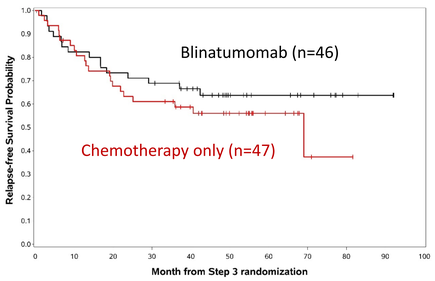


Table 2. OS and PFS Among MRD- Patients (n=93) age ≥ 55 years

	Blinatumomab	Chemo	Univariate model	Multivariate model
3-year OS	71%	67%	HR 0.75, 95% CI: 0.37-1.50	HR 0.56, 95% CI: 0.25-1.27
3-year RFS	69%	59%	HR 0.75, 95% CI: 0.39-1.45	HR 0.67, 95% CI: 0.32-1.42

References

1. M. Litzow et all, NEJM 2024;391:320-333

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ClinicalTrials.gov: NCT02003222

Chemotherapy Free Regimen of Inotuzumab Ozogamicin and Blinatumomab in Frontline Therapy of Older Patients (≥70 years) with Philadelphia Negative B-Cell Acute Lymphoblastic Leukemia

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Background

- Older patients (≥70 years of age) with acute lymphoblastic leukemia (ALL) are particularly vulnerable to chemotherapy. Non relapse mortality (NRM) is an important cause of compromised survival in this age group.
- Low-intensity Mini-HyperCVD-Inotuzumab (InO) ±blinatumomab (Blina) in patients (≥60 years) with Philadelphia negative (Ph-) B-ALL led to 5-year OS of 50%; however, patients ≥70 years of age had high rates of NRM (*Jabbour et al. Lancet Haematology 2023, Senapati et al, ASH 2024*).
- Additionally, chemotherapy exposure can increase the risk of secondary myeloid neoplasms as patients with B-ALL now live longer due to chemoimmunotherapy approaches compared to historical survival outcomes, providing time for evolution of clonal hematopoiesis.
- We report a chemotherapy minimized InO/Blina based treatment approach for frontline therapy in patients ≥70 years of age) with Ph- B-ALL.

Methods

- Phase 2 study (NCT01371630), sub cohort

Patients

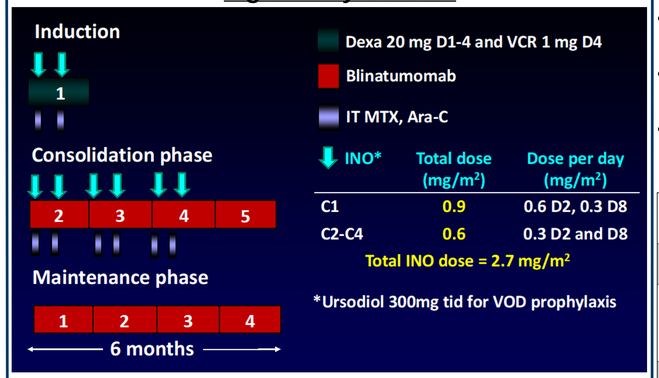
- Adult patients ≥70years of age (or 60-70 years, unfit for any chemotherapy)
- ECOG PS ≤3 with adequate organ function
- Newly diagnosed or <2 cycles of prior therapy (patients in remission at enrollment were eligible for survival assessment)

Treatment

- ***Cycle (C1) 1***: Dexamethasone intravenous (IV) 20 mg (Day) D1-D4 + vincristine 1 mg IV on D4 + fractionated InO 0.6 mg/m2 on D1 and 0.3 mg/m2 on D8. Blina is administered as a continuous IV infusion from D15 for 14 days (9ug/day x 2 days followed by 28 ug/day) (Figure 1)
- ***Consolidation C2-C5***:Blina 28 ug/day x D1-D28/42 days cycle + InO on D1, D8 at 0.6 mg/m2 (only C2-C4; cumulative max dose of InO= 2.7 mg/m2).
- ***Maintenance:*** 4 cycles with single agent Blina continuous IV at 28 ug/day D1-D28/42-day cycles.
- Patients with CD20 positive disease could receive rituximab 375 mg/m2 IV per standard of care on D2 and D9 for C1-4 for a total of 8 doses.

Methods

Fig 1.Study Schema



Study endpoints

Primary:

- **Progression free survival (PFS):** from study therapy initiation to the date of no response (after 2 cycles), relapse (>5% lymphoblasts in a bone marrow aspirate unrelated to recovery, or extramedullary disease), or death from any cause (Intention to treat analysis)

Secondary:

- **Safety** (Intention to treat analysis)

Exploratory:

- **Overall survival (OS)**
- **Continuous remission duration (CRD):** time from response to relapse; censored if death in remission. For patients in remission at enrollment, CRD was calculated from study therapy initiation.

Results

Table 1: Baseline Characteristics (N=14)

Characteristics		N (%), median [range]
Age (years)		76 [65-84]
	≥ 70 years	13 (93)
	≥ 75 years	8 (57)
Gender	Female	7 (50)
ECOG PS	0-1	14 (100)
Karyotype (n=13)	Diploid	2 (15)
[1 patient had	Adverse	6 (46)
inadequate	-Ho-Tr	3 (23)
metaphase]	-Complex	1 (6)
	-*KMT2Ar*	2 (4)
***CRLF2* positive**		1 (8)
***TP53* mutation/s**		7 (50)

•No patient had CNS/ extramedullary disease at diagnosis
•11 patients (79%) received rituximab

Results

- **14 patients enrolled (Apr 2021- May 2024)**
- Median F/U (Oct 31, 2024): 16 months (95% CI 2.3-31.1) (Reverse Kaplan Meier)
- No patient had CNS/ extramedullary disease at diagnosis
- 11 patients (79%) received rituximab

Table 2: Response characteristics

Characteristics		N (%), median [range]
Response evaluable		14
CRc (CR+ CRi)		13 (92)
	CR	12 (86)
	CRi	1 (6)
MRD negative response (MFC)	Best response	13 (100)
	Post C1	11 (85)
MRD negative by NGS (1 in 10^6)	Best response	11/12 (92)
	Post C1	6/8 (75)

Fig 2. PFS and OS

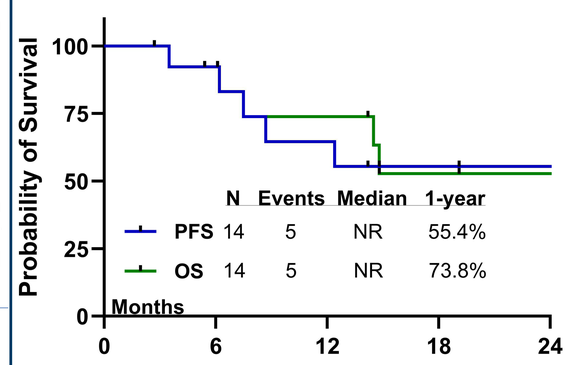
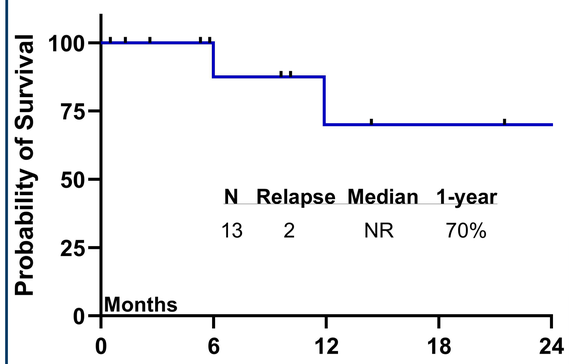
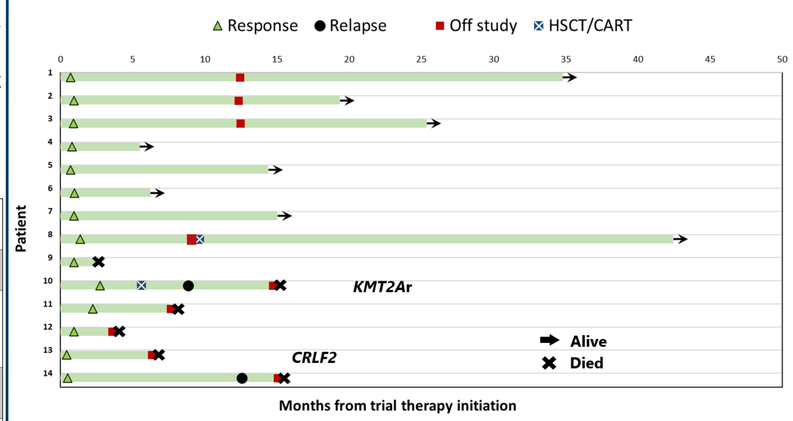


Fig 3. CRD



Results

Fig 4: Swimmer's plot of study patients



Patient disposition

- **At data cutoff: Oct 31, 2024**
  - ➢ HSCT= 1 (Pt #8); CAR T-cell therapy= 1 (Pt #10; *KMT2A* rearranged)
  - ➢ Relapses= 2 (Pt# 10, *KMT2Ar*; Pt #14; Hypoploidy with *TP53* mutation; both patients had achieved NGS MRD negative response))
  - ➢ Died= 6 (1 non-responder, 2 post relapse; 3 NRM).
  - ➢ Causes of NRM: Pneumonia=1, Myocardial infarction=1, non-infectious respiratory failure=1

Safety analysis

- Median time on study= 12.3 months
- Hepatic SOS/VOD= 0; Grade 3 ALT elevation =1 (7%)
- Blina related neurotoxicity:
  - Grade 3 encephalopathy =1 (7%)
  - Grade 1-2 confusion= 5 (36%)
  - Grade 1-2 tremors= 3 (21%)
- Blina related cytokine release syndrome (CRS)= 1 (7%, Grade 2)
- Secondary myeloid neoplasm= 0

Conclusion

- Chemotherapy free combination of InO+ Blina in older (≥ 70 years) patients with Ph- B-ALL is tolerable and efficacious: 1-year OS 74%
- No hepatic SOS event or secondary myeloid neoplasms over limited follow-up

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Low Intensity Mini-HyperCVD, Inotuzumab Ozogamicin, With/Without Blinatumomab In Older Patients with Newly Diagnosed Philadelphia Negative B-Cell Acute Lymphoblastic Leukemia: 10 Years Update

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Background

- Outcomes of older patients with B-cell acute lymphoblastic leukemia (B-ALL) have traditionally been poorer secondary to adverse disease biology and inability to tolerate chemotherapy and Peg-Asparaginase
- Frontline use of targeted immunotherapeutic agents like Inotuzumab ozogamicin (InO) and blinatumomab (Blina) could be more tolerable and improve response and survival outcomes
- MiniHyperCVD (attenuated dose of fractionated cyclophosphamide, vincristine and dexamethasone alternating with attenuated doses of methotrexate and cytarabine) is a low-intensity regimen designed for older (≥60 years) patients with B-ALL
- We report the long-term follow up (F/U) (10 years) of InO with/without Blina added to MiniHyperCVD in the frontline therapy of older patients with Philadelphia negative (Ph-) B-ALL

Methods

- Phase 2 study (NCT01371630)

Patients

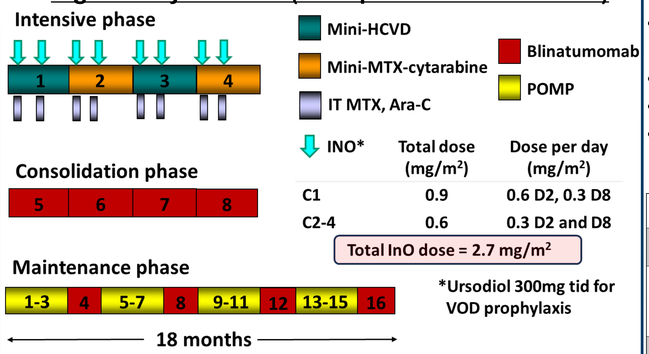
- Adult patients ≥ 60 years of age
- ECOG PS ≤3 with adequate organ function
- Newly diagnosed or <2 cycles of prior therapy (patients in remission at enrollment were eligible for survival assessment)

Treatment

- **Pre amendment:**
  - *Patients 1-49:* InO 1·3 - 1·8 mg/m2 for cycle (C1) followed by 1·0–1·3 mg/m2 in C2–C4. No Blina.
- **Post amendment:**
  - *Patient 50 onwards*: InO was administered at a fractionated lower dose with a max. cumulative dose of 2·7 mg/m2 as follows: 0·9 mg/m2 during C1 fractionated into 0·6 mg/m2 on day 2 and 0·3 mg/m2 on day 8 of C1, and 0·6 mg/m2 in C2–C4 fractionated into 0·3 mg/m2 on day 2 and 0·3 mg/m2 on day 8**. (Study Schema)**
    - 4 cycles of Blina added after 4 cycles of chemotherapy
    - Maintenance: 4 cycles of Blina intercalated with POMP and maintenance reduced to 16 cycles (approx. 18 months)

Methods

Fig 1.Study Schema (Post-protocol amendment)



Study endpoints

Primary:

- **Progression free survival (PFS):** from study therapy initiation to the date of no response (after 2 cycles), relapse (>5% lymphoblasts in a bone marrow aspirate unrelated to recovery, or extramedullary disease), or death from any cause (Intention to treat analysis)

Secondary:

- **Safety** (Intention to treat analysis)

Exploratory:

- **Overall survival (OS)**
- **Continuous remission duration (CRD):** time from response to relapse; censored if death in remission. For patients in remission at enrollment, CRD was calculated from study therapy initiation.

Results

Table 1: Baseline Characteristics (N=83)

Characteristics		N (%), median [range]
Age (years)		67 [60-88]
	≥ 70 years	28 (34)
ECOG PS ≥ 2		11 (13)
WBC (x10⁹ /L)		3.1 [0.3-111.0]
Karyotype (n=67) [excludes patients in remission at enrollment and patients with inadequate metaphases]	Diploid	27 (40)
	Adverse	19 (28)
	-Ho-Tr	12 (18)
	-Complex	4 (6)
	-Tetraploidy	2 (4)
	-KMT2A*r*	1 (1)
	Hyperploidy	6 (9)
CNS disease at diagnosis		4 (5)
CRLF2 positive (n=49)		7 (14)
***TP53* mutation (n=64)**		25 (39)

Results

- **83 patients enrolled (Dec 2011- Aug 2022)**
- Median F/U: 121 months (95% CI 61-129) (Reverse Kaplan Meier)
- 6 patients in remission at enrollment
- 77 eligible for response assessment
- 83 eligible for PFS/CRD/OS and safety assessment

Table 2: Response characteristics

Characteristics		N (%), median [range]
Response evaluable		77
CRc (CR+ CRi)		76 (99)
	CR	69 (90)
	CRi	7 (9)
MRD evaluable		81*
MRD negative response by MFC	Best response	75 (93)
	Post C1	56/75 (75)
MRD negative by NGS (1 in 10^6 sensitivity)	Best response	16/17 (94)

*5 CR-MRD+ve at enrollment + 76 CRc on study)

Fig 2. PFS and OS

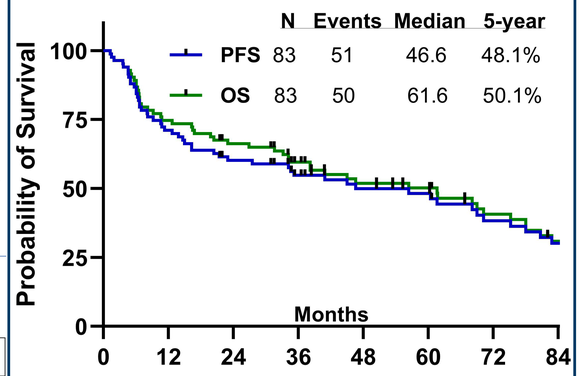
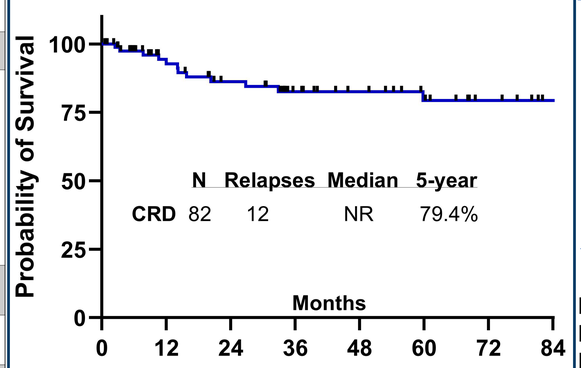


Fig 3. CRD



Results

Fig 4: PFS pre and post amendment

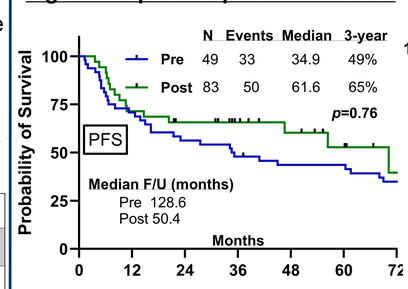
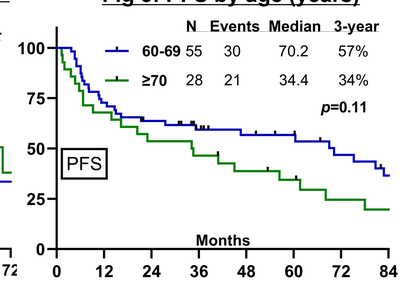


Fig 5: PFS by age (years)



Patient disposition

- **At data cutoff: July 15, 2024**
  - ➢ HSCT= 5 (6%; 4 adverse genomics, 1 persistent MRD+ve)
  - ➢ 33 (39.8%) patients alive
  - ➢ 50 (60.2%) died: 1 non-responder; 11 post-relapse, 38 non-relapse mortality (NRM)
  - ➢ Causes of NRM: secondary myeloid neoplasms=8; infectious complication =9 (6 on study, 3 off study), hepatic sinusoidal obstruction syndrome (SOS)=4; miscellaneous (non-infection/non-leukemia related)=16
  - ➢ Age-wise NRM : 60-69 years=20/55 (36.4%); ≥ 70 years= 18/28 (64.3%)

Safety analysis

- Secondary myeloid neoplasm (SMN)= 8 (9.6%)
  - 6 on therapy, 2 off therapy
  - 5 patients had *TP53* mutation at ALL diagnosis which evolved at diagnosis of myeloid neoplasm
- Hepatic SOS= 6 (7.2%)
  - 4 pre-amendment, 1 post-amendment
  - 1 after HSCT, 4 without HSCT
- Blina neurotoxicity (grade 3)= 7 (8.4%); no seizures

Conclusion

- Low-intensity commination of MiniHyperCVD-InO± Blina was safe and led to 5-year PFS and OS of ≈50% in older adults with Ph- B-ALL
- In patients ≥ 70 years rates of NRM remain high warranting further reduction in chemotherapy and optimizing use of immunotherapy
- In patients with baseline *TP53* mutation/s, reduction in chemotherapy to reduce risks of SMN needs to be studied in future clinical trials

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Baseline Myeloid Type Mutations have No Independent Prognostic Impact in Adult Patients with Philadelphia Negative B-Cell Acute Lymphoblastic Leukemia Treated with Inotuzumab/Blinatumomab Containing Frontline Regimens

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Background

- Myeloid type mutations (MyM) are occasionally detected in patients with B-cell acute lymphoblastic leukemia (B-ALL) with wider use of next generation sequencing (NGS)
- Such mutations are seen more frequently in adults (usually older adults) with B-ALL and can also denote background clonal hematopoiesis.
- Recent data have shown that MyM in B-ALL can be associated with inferior outcomes *(Saygin et al, Blood Cancer Discov 2024)*.
- Targeted therapies like inotuzumab ozogamicin (InO) and blinatumomab (Blina) are now being used in frontline therapy (as consolidation or MRD directed approaches) for B-ALL and prognostic impact of MyM with such agents need further evaluation.

Study Design

Patients

- Adult patients ≥ 18 years of age with Ph-negative B-ALL (Frontline therapy)
- April 2017 – April 2024: 189 patients with Ph negative B-ALL who **received either Ino or Blina or both** in the frontline setting with a chemotherapy backbone of either MiniHyperCVD or HyperCVAD
- All patients ≥60 received MiniHyperCVD
- Baseline bone marrow (BM) cytogenetics and mutation analysis using 81-panel NGS:
  - MyM included ***ASXL1, BCOR/BCORL1, DNMT3A*, cohesin complex genes (*SMC3, SMC1A, STAG1/2, RAD21*), *EZH2, IDH1/2*, splicing factor genes (*SRSF2, SF3B1, U2AF1, ZRSR2*), *RUNX1,* and *TET2*.**
  - **High-risk cytogenetics (HR-CTG):** complex cytogenetics, hypodiploidy/near triploidy, tetraploidy, ***KMT2A*** rearrangement.

Statistical analysis

- Progression free survival (PFS): Frontline therapy initiation to relapse, change in therapy for disease progression, or death
- Overall survival (OS): Frontline therapy initiation to death
- PFS/OS were not censored for allogeneic HSCT
- Cox proportional hazard multivariate (MV) analysis: Forward model selection

Results

Table 1: Baseline Characteristics stratified by the presence of MyM

Parameters	MyM+ (n=28)	MyM- (n=161)	P
	N (%), median [range]		
Age (years)	66 [21-88]	38.1 [18-78]	<0.001
Age ≥ 60 years	18 (64)	38 (24)	<0.001
Gender	12 (43)	69 (43)	
Prior Myeloma	4 (14)	7 (4)	0.06
HR-CTG	5/23 (22)	37/130 (28)	0.61
CRLF2 positive	3 (11)	32 (20)	0.77
Myeloid mutations			
• *ASXL1*	6 (21)	0	
• *BCOR*	0	0	
• *BCORL1*	0	0	
• *CBL*	2 (7)	0	
• *CUX1*	0	0	
• *DNMT3A*	6 (21)	0	
• *EZH2*	2 (7)	0	
• *IDH1/IDH2*	5 (18)	0	
• *RUNX1*	2 (1)	0	
• *Splicing*	4 (14)	0	
• *Cohesin*	5 (18)	0	
Other mutations			
• *FLT3*-ITD/TKD	5 (18)	18 (11)	0.35
• *RAS*	7 (25)	43 (27)	0.99
• *TP53*	6 (21)	38 (24)	0.99

Table 2: Treatment and response parameters stratified by the presence of MyM

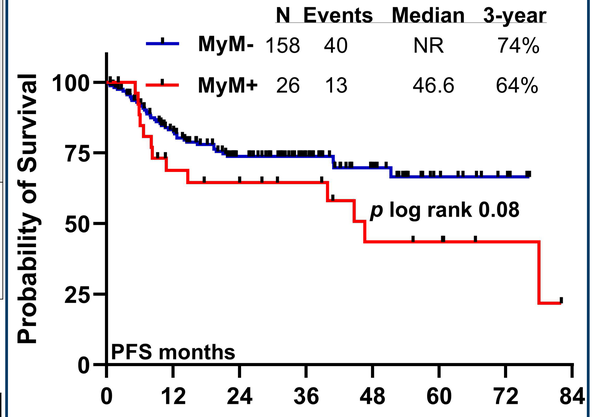
Parameters	MyM+ (n=28)	MyM- (n=161)	P
	N (%), median [range]		
Chemotherapy			
• HyperCVAD	10 (36)	100 (62)	0.01
• MiniHyperCVD	18 (64)	61 (38)	
Immunotherapy			
• InO	2 (7)	11 (7)	
• Blina	6 (21)	38 (24)	
• InO + Blina	20 (71)	112 (70)	0.99
Best Responses			
• CRc (CR+CRi)	26 (93)	158 (98)	0.16
• CR	26 (93)	153 (95)	
• MRD -ve (10^{-4})*	17/26 (65)	102/156 (65)	0.99
HSCT in CR1	3 (11)	38 (24)	0.14

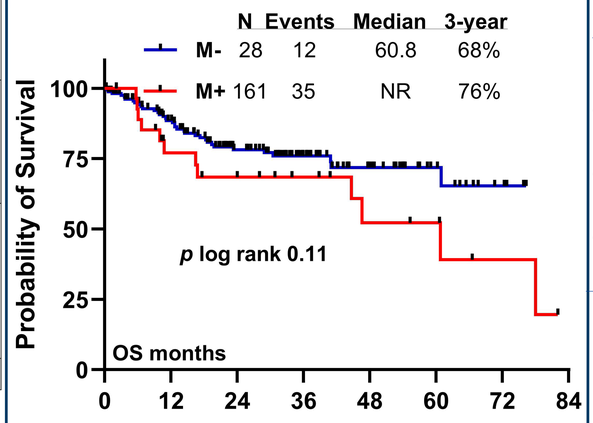
*Amongst patients with CRc and adequate MRD data

Results

- Higher proportion of patients with MyM were ≥ 60 years of age and thus treated with Mini-HyperCVD chemotherapy backbone
- In the MyM+ group more patients had prior multiple myeloma than in the MyM- group
- Equal proportion of patients in both groups received InO or Blina as well as both InO/Blina.
- Frequency of responses and MRD-ve responses were similar between the groups
- Median Follow up (months): MyM 41 vs, MyM 32
- 4 patients developed a secondary myeloid neoplasm, 2 in each cohort and all ≥60 years; one patient had a baseline *TP53* mutation.

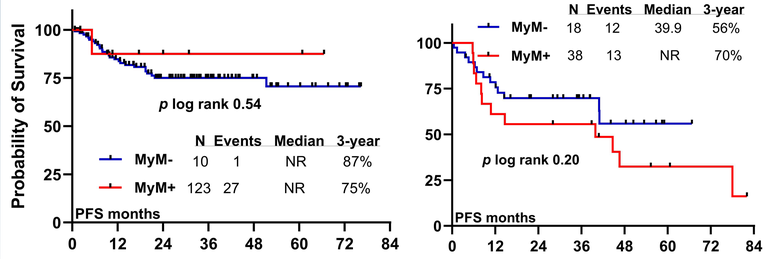
Fig 2. Comparative survival outcomes





Results

Fig 3: Comparison of PFS stratified by age



- 19 patients (11 patients ≥60 years) died in remission at a median of 6 months (1.0-78 months), from therapy initiation without intervening HSCT or a myeloid neoplasm; 6 (21%) MyM+ and 13 (8%) MyM-.

Table 3A: MV Cox for hazards of progression/death

Covariates	HR	HR 95% CI	P-value
Age ≥ 60 years	2.210	1.06-4.57	0.03
CRLF2 +	2.895	1.32-6.19	<0.01
HR-CTG	1.524	0.70-3.30	0.29
***TP53*^{mut}**	2.828	1.27-6.29	0.02
MyM+	1.224	0.54-2.65	0.69
InO + Blina vs. any	0.4552	0.24-0.88	0.02
HSCT-Yes	0.5253	0.23- 1.12	0.11

Table 3B: MV Cox for hazards of death

Covariates	HR	HR 95% CI	P-value
Age ≥ 60 years	2.9	1.37-6.24	<0.01
CRLF2 +	2.6	1.19-6.00	0.02
HR-CTG	1.5	0.66-3.56	0.32
***TP53*^{mut}**	2.6	1.10-6.20	0.03
MyM+	0.84	0.34-1,92	0.83
InO + Blina vs. any	0.51	0.25-1.05	0.06
HSCT-Yes	0.54	0.22-1.22	0.16

Conclusion

- Baseline MyM in patients with B-cell ALL are rare and more common in older patients.
- Though PFS and OS were inferior in MyM+ pts in the whole cohort, there was no significant on age stratified analysis
- On Cox MVA, MyM had no independent impact on hazards of progression or death in InO/Blina treated patients

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