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Combination low-intensity chemotherapy plus inotuzumab ozogamicin, blinatumomab and rituximab for pediatric patients with relapsed/refractory B-cell acute lymphoblastic leukemia

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The 5-year overall survival (OS) for pediatric patients with relapsed/refractory (R/R) B-cell ALL is <50%[1]. Standard of care re-induction therapy is a 4-drug regimen derived from the mitoxantrone arm of UKALLR3 (R3), which achieves a 3-year OS of 69%[2]. The most recently completed Children's Oncology Group (COG) study for relapsed ALL (AALL1331) utilized this approach with a modified R3 backbone. Although active, this re-induction produced a significant amount of morbidity and treatment-related mortality (TRM), specifically a 39.8% rate of life-threatening infection and a 5% toxic death rate during block 1[2-4]. Promising immunotherapy agents may allow for less cytotoxic chemotherapy with maintained survival. This retrospective chart review identified 10 patients <18 years old with R/R B-cell ALL treated at MD Anderson Cancer Center with an anthracycline-free reduced intensity chemotherapy regimen that consisted of mini-hyper-fractionated cyclophosphamide, vincristine, and dexamethasone alternating with methotrexate and cytarabine cycles (mini-hCVD) plus condensed immunotherapy (inotuzumab-ozogamicin (INO), rituximab and /or blinatumomab), further termed Pedi-cRIB. We report the safety and efficacy in pediatric patients with overall response rate (ORR) of 75%.

Salvage therapy with immunotherapies INO, a CD22-directed humanized monoclonal antibody conjugated to calicheamicin, blinatumomab, a bispecific T-cell engaging antibody with dual affinity for CD19 and CD3, and rituximab a CD20 directed monoclonal antibody, are associated with improved OS compared with conventional chemotherapy in R/R B-cell ALL; but these are often given as monotherapy or after intensive re-induction chemotherapy[5-7]. The combination of INO, +/- blinatumomab and rituximab, with mini-hCVD has been reported in adult patients and produced an ORR of 80% (complete remission (CR) in 57%) with 46% of patients proceeding to hematopoietic stem cell transplantation (HSCT)[8-10].

Here, we report ten pediatric patients with R/R B-cell ALL who received mini-hCVD combined with condensed INO +/- blinatumomab and rituximab (Pedi-cRIB). The chemotherapy schedule (Supplementary Table 1) was administered as described previously with dosing modified for pediatric patients.[11] Baseline characteristics are shown in Table 2. The median age was 8.5 years (range, 2-17 years). Six patients (60%) received Pedi-cRIB in first relapse, 1 (10%) had 2 prior lines of therapy, and 3 (30%) had ≥ 3 prior lines of therapy. Four patients had prior immunotherapy exposure (1 prior blinatumomab, 1 prior CAR-T, 1 prior CAR-T therapy and blinatumomab, and 1 prior CAR-T and INO). No patients had a prior HSCT. Three patients demonstrated CRLF2 rearrangement, 3 with KRAS mutation, 2 with PAX5 mutation, 1 with KMT2A rearrangement and 1 with TCF3-PBX1 fusion.

Patients received a median of 2 cycles (range, 1-4) of therapy. All patients received at least 1 cycle of INO with a median cumulative dose of 1.35 mg/m^2 (range, 0.9-4 mg/m^2). The median time from last INO dose to HSCT was 55 days. Blinatumomab and rituximab were given to 50% and 60% of patients, respectively, both for a median of 1 cycle (range 1-2 cycles).

The most common hematological adverse events were thrombocytopenia, anemia, and neutropenia, as expected in a relapsed ALL population (supplementary table 2). One patient had prolonged thrombocytopenia ≥42 days; attributed to refractory disease rather than therapy. Grade 3 febrile neutropenia occurred in 3 patients (30%) and were effectively managed with antibiotics without complications. No cytokine release syndrome (CRS) or neurotoxicity were seen in patients receiving blinatumomab.

The most notable toxicity was veno-occlusive disease/sinusoidal obstructive syndrome (VOD/SOS) occurring during HSCT. VOD/SOS developed in the first 2 patients who received mini-hCVD + INO without blinatumomab or rituximab. This led to revision of the regimen to include blinatumomab and rituximab to extend time from last INO to HSCT; and the addition of prophylactic defibrotide for high-risk patients[12]. Patient number 1 received an umbilical cord HSCT after a conditioning regimen of total body irradiation, fludarabine, and cyclophosphamide. Grade 3 VOD/SOS developed on day +14, with 1.12 months between HSCT and last INO dose. He received 3 cycles of mini- hCVD + INO with a cumulative INO dose of 2.1mg/m^2. With defibrotide and aggressive diuresis, he recovered and remains alive and in remission with a follow up of 2 years. Patient number 2 received a haploidentical HSCT after a conditioning regimen of busulfan, fludarabine, and thiotepa. On day +9 he developed grade 4 VOD/SOS. There was 1.81 months between HSCT and last INO dose. His therapy cumulative INO dose was 1.5mg/m^2. He required defibrotide, peritoneal drain placement, continuous renal replacement therapy and BiPap. He recovered from this acute event and discharged from the hospital on day +41 from HSCT with only oral furosemide. Subsequently, prophylactic defibrotide was administered during HSCT to all patients who received INO and were high risk for VOD/SOS risk. Of patients who received prophylactic defibrotide, none experienced VOD/SOS. Notably, there were no cases of transplant-related mortality or treatment discontinuations due to toxicity, and there were no new safety concerns observed.

There were 9 evaluable patients (Figure 1), patient 4 was lost to follow up after cycle 1 and therefore not evaluable. The ORR after cycle 1 was 78% (CR=7). Minimal residual disease (MRD) negativity by flow cytometry was achieved in 3 of 7 responders after cycle 1, and all 7 responders after

cycle 2. Three patients had next generation sequencing (NGS) MRD assessment of immunoglobin/T-cell rearrangements; 2 were found to be NGS negative. One patient remained NGS + at 24 cells per million prior to HSCT but has not relapsed 28 months post HSCT. Two patients (patients 6 and 9) had no response and progressed during cycle 1 of therapy. These 2 patients demonstrated high risk cytogenetics that are known to be resistant, one with KMT2A rearrangement and one with TCF3-PBX1 fusion. At a median follow up time of 17.1 months (range, 4.8-39.4 months), 6 (67%) patients remain alive and in remission. It is important to note that 5 of the 6 patients were in first relapse when they received this regimen. The median EFS and OS have not been reached (Figures 2A & 2B). Six of 7 patients with CR proceeded to HSCT. One patient relapsed 5 months post HSCT and died of disease progression. This patient had CRLF2 rearrangement and prior therapy with CAR-T. One patient is still receiving therapy. After a median follow up time of 17 months post-HSCT the median OS had not been reached (Figure 2C). Patients who responded to therapy during cycle 1 showed a better OS than patients who had no response during cycle 1 (Figure 2D).

This series demonstrates the safety and feasibility of giving an anthracycline-free reduced intensity chemotherapy backbone with concurrent CD19, CD20 and CD22 targeted agents, and provides a novel therapy approach for patients who have failed other salvage attempts, have pre-existing cardiotoxicity, or serious infection history. Alternative regimens to the standard of care R3 backbone +/- blinatumomab (COG AALL1331) may produce high response rates with less acute toxicity[7,13-15]. Compared to AALL1331, Pedi-cRIB produced lower rates of infection and no toxic deaths, but there was an increase in manageable immunotherapy-related side effects[2-4].

Despite the lower dosing and cumulative dose of INO administered here in comparison to the current COG trial standards, the most significant toxicity observed in this patient cohort remained VOD/SOS. This is consistent with toxicity data in adult patients that showed mini-hCVD + INO produced a 16% rate of VOD/SOS. In adult patients this was minimized to 3% by decreasing the dose of INO and incorporating blinatumomab to lengthen the time from INO dosing to HSCT[10,11]. Here, two patients developed VOD/SOS between days 9-15 post-HSCT. Interestingly, after the initial two cases, no additional occurrences of VOD/SOS were documented. Several factors may contribute to this phenomenon. First and foremost, the proactive use of defibrotide in VOD/SOS-susceptible patients could have prevented subsequent VOD/SOS. Secondly, taking a broader view, the incorporation of blinatumomab may have played a beneficial role. The incorporation of blinatumomab into the treatment regimen extended the interval between the last dose of INO and the subsequent preparative

HSCT regimens and HSCT itself. This extended timeframe could have facilitated recovery from hepatotoxicity and mitigated the risk of VOD/SOS, as previously postulated in prior studies[16]. This hypothesis requires validation through larger-scale studies to establish conclusive evidence. None of the patients experienced cytokine release syndrome (CRS) as a result of blinatumomab therapy. Rituximab use in this series was variable, making conclusions difficult. There was no cut off value of CD20 expression to give rituximab. Rituximab use was based on data from the adult population indicating that the addition of rituximab to HyperCVAD improved outcomes, and that chemotherapy can increase CD20 expression with rituximab giving a positive effect even among patients with low expression of CD20[6,17]. No patients had infusion reactions to rituximab here. A recent publication by Hoshitsuki et al indicates higher infusion reactions, and no change in MRD at end of induction for patients who received rituximab, so this new data will need to be considered in future upfront trials[18].

This regimen showed notable success, achieving a 75% ORR including some heavily pretreated individuals who had undergone previous CD19 and CD22 directed therapies. Sustained MRD remissions were observed in the majority. While the specific contribution of each component is unclear, the synergistic effect likely reduces tumor burden and targets distinct phenotypes, potentially minimizing the emergence of resistance mechanisms.

Despite the limitations inherent in the study's size, heterogeneity in prior treatment, and retrospective nature, several pivotal insights can be gleaned. Considering relapsed patients frequently present with pre-existing comorbidities and may eventually undergo HSCT, the selection of a lower-intensity chemotherapy approach, when feasible, becomes imperative. This regimen emerges as a compelling candidate within this context, providing a rationale for forthcoming trials to explore the utilization of an anthracycline-free re-induction chemotherapy framework fortified with a combination of targeted immunotherapeutic agents. The use of this regimen must be discussed with each patient individually and the ethics of using a non-standard of care regimen in first relapse but be considered. An ongoing trial is currently underway to evaluate the Pedi-cRIB regimen (NCT05645718).

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of MD Anderson Cancer Center.

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Table 1: Disease characteristics, treatment, and outcomes

	Age/sex /race	Cytogenetic alterations	Molecular alterations	# Prior therapy	Prior immuno therapy received	CD expression/ immunotherapy received	Cycles	Best Response (cycle # achieved)	Lifetime Ino (mg/m2)	HSCT type	Last Ino to HSCT (days)	Preparative Regimen	VOD /SOS	Vital status	Follow up time (months)
1	4/M white	Hyperdiploid , Extra copy of RUNX1	FLT3 mutation	1	none	CD19 99% CD20 30% CD22 97%- INO	3	CR, uMRD, NGS+ (2)	2.1	Cord	34	TBI/cyclo/flu	Yes, grade 3	Alive	31.2
2	16/M Hispanic	CRLF2r by FISH, del (7p)	ASXL1, KRAS	2	CD19 CAR-T	CD19 99% CD20 6% CD22 99%- INO	2	CR, uMRD (2)	1.5	Haplo	55	Bu/Flu/Thio	Yes, grade 4	Deceased (relapsed after 5 months)	13.9
3	17/M Hispanic	CRLF2r by FISH, +X, del (7p)	KRAS, NRAS, PAX5	1	none	CD19 99% CD20 97%- Ritux CD22 99%- INO	4	CR, uMRD, NGS – (2)	4	MUD	59	TBI/etop/ rATG	No	Alive	39.4
4	17/F Hispanic	BCOR/PAX5 fusion, +X, +9, 3 copies CRLF2	CDKN2A	1	none	CD19 99% CD20 95%- Ritux CD22 99%- INO	1	NE	0.9	None	-	-	-	Deceased	11.4
5	5/M Asian	t(6;21), del(9P), Add (17p), CRLF2r by FISH	PAX5, KRAS, TP53, SMC3	4	CD19 CAR-T	CD19 99%- Blina CD20 71%- Ritux CD22 99%- INO	2	CR, uMRD (2)	1.2	MSD	36	TBI/cyclo	No	Alive	16.4
6	2/F Hispanic	t(11;17)(q23 ;p11.2) KMT2Ar	CREBBP	5	CD19 CAR-T, Blina	CD19 98%- Blina CD20 0% CD22 32%- INO	1	PD	1.2	None	-	-	-	Deceased	2.1
7	14/M black	t(5;14) and t(11;19)	None	1	none	CD19 93%- Blina CD20 78%- Ritux CD22 99%- INO	1	CR, uMRD, NGS – (2)	1.2	MSD	82	TBI/etop	No	Alive	22.9
8	8/F	None	None	1	none	CD19 99%- Blina	2	CR, uMRD	1.8	Cord	97	TBI/Flu/Cy	No	Alive	19.5

	black					CD20 10%- Ritux CD22 99%- INO		(2)							
9	9/M white	TCF3-PBX1	None	3	Blina	CD19 99% CD20 14%- Ritux CD22 73%- INO	1	PD	1.2	None	-	-	-	Deceased	5.1
10	7/M Hispanic	Hyperdiploid ; trisomies 4, 17, 21	PTPN11	1	none	CD19 98%- Blina CD20 1% CD22 98%- INO	2	CR, uMRD (1)	1.8	-	-	-	-	Alive	4.8

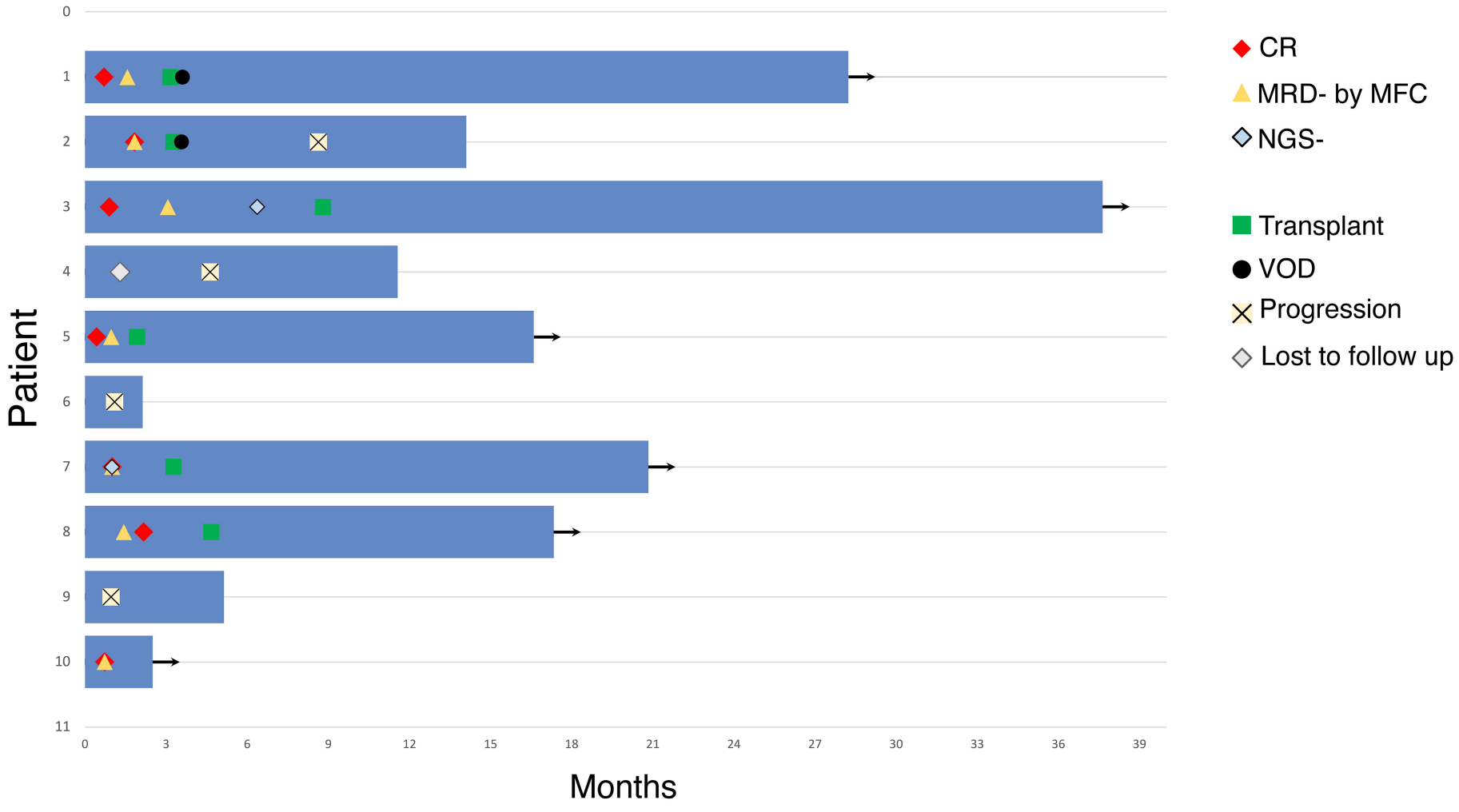
Table 1: Patient baseline characteristics including cytogenetic and molecular alterations, number of prior therapies received, if patient was exposed to prior immunotherapy, which immunotherapy was received with mini-hCVD, the total number of cycles given, best response achieved, lifetime inotuzumab ozogamicin mg/m2 dose, type of HSCT received, HSCT preparative regimen, VOD/SOS status and grade, vital status of patient at last follow up and the total follow up time since receiving mini-hCVD with immunotherapy.

Abbreviations: mini- hCVD – hyper-fractionated cyclophosphamide, vincristine, dexamethasone, methotrexate, cytarabine. FLAG-fludarabine, cytarabine, granulocyte colony stimulating factor. INO-Inotuzumab ozogamicin, Ritux-Rituximab, Blina-blinatumomab, TBI- total body irradiation, rATG- rabbit anti-thymocyte globulin, cyclo-cyclophosphamide, flud-fludarabine, thio-thiotepa, etop-etoposide, cy-cytarabine. CRLF2r- cytokine receptor like factor 2 gene rearrangement, FISH- Fluorescence In Situ Hybridization. CR-complete response; uMRD- undetectable minimal residual disease by multiparameter flow cytometry of bone marrow with less than 0.01% aberrant lymphoblasts; NGS-next generation sequencing by immunoglobin or T-cell receptor gene rearrangements. PD-progressive disease. NE- Not evaluable. HSCT- hematopoietic stem cell transplant, MUD-matched unrelated donor, MSD- matched sibling donor, cord- umbilical cord blood transplant, haplo-haploidentical transplant.

Figure Legends:

Figure 1: Swimmers plot showing outcome of each patient and time points for complete response (CR), minimal residual disease negativity by flow cytometry (MRD- by MFC), next generation sequencing (NGS), transplant, VOD/SOS, progression and lost to follow up.

Figure 2: Survival curves for 9 patients who were evaluable for response. Number at risk is listed below graphs 2a-c. **(A)** Survival proportion graph from start of mini- hCVD + Immunotherapy protocol until death. **(B)** Survival proportion graph from start of mini- hCVD + Immunotherapy until major event, defined as progression, relapse or death. **(C)** Survival proportion graph from transplant until relapse or death for patients who proceeded to HSCT (6 patients total). **(D)** Survival proportion for responders versus non-responders to mini-hCVD + immunotherapy treatment.


Patient
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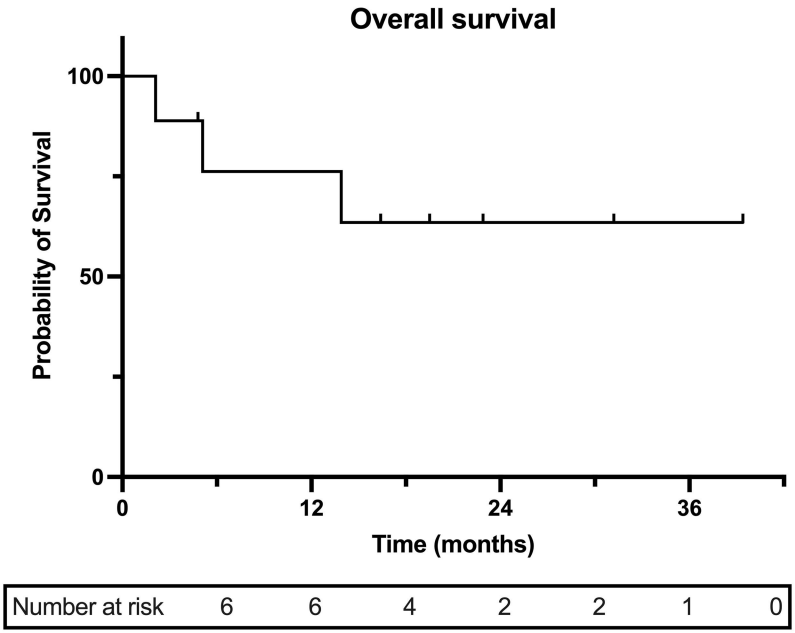
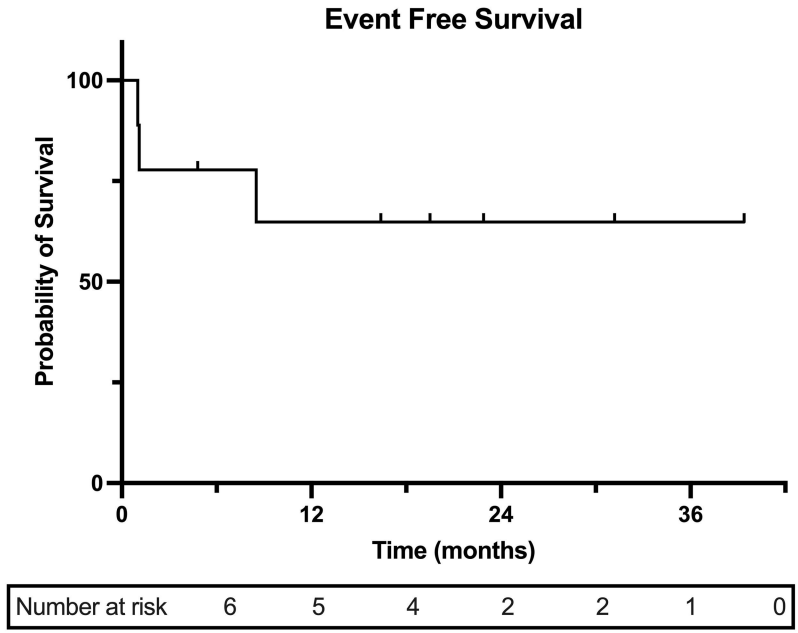
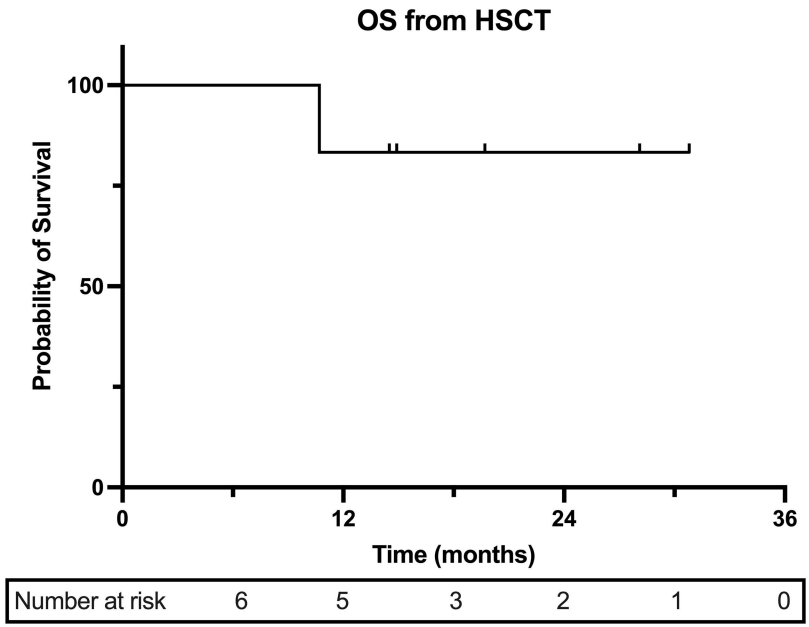
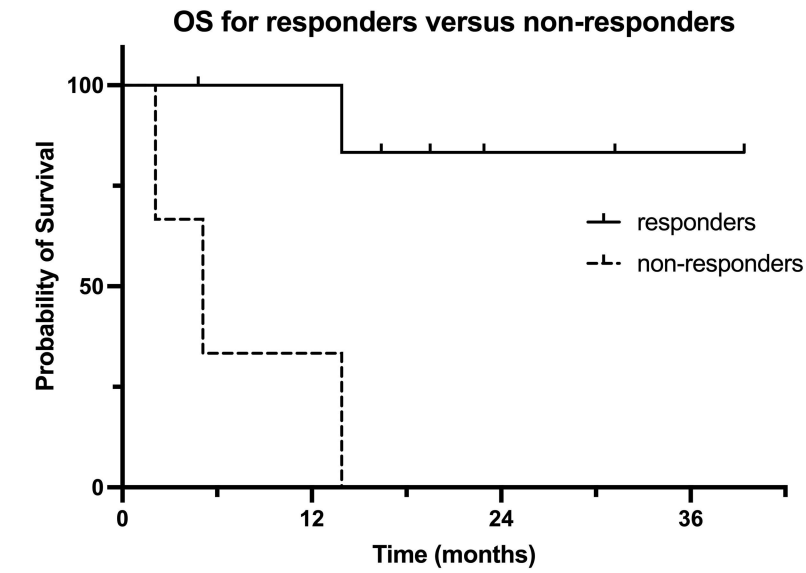
Months
CR
MRD- by MFC
NGS-
Transplant
VOD
Progression
Lost to follow up

Figure 2: Kaplan-Meier Survival Curves









Supplementary Table 1: Mini-Hyper CVD Treatment Schema

Mini-hCVD (odd cycles)	
Cyclophosphamide	150 mg/m^2 IV every 12 hours days 1-3 (6 total doses)
Dexamethasone	10 mg/m^2 IV every 12 hours (max 20 mg/day) days 1-4 and 11-14
Vincristine	1.5 mg/m^2 (max 2 mg/dose) IV days 1 and 8
Peg filgrastim	0.1 mg/kg (max 6 mg) subcutaneous day 4
Intrathecal therapy	Dosing below. Days 1 and 8
Methotrexate/Cytarabine (even cycles)	
Methotrexate	250 mg/m^2 CIV over 24 hours (50 mg/m^2 over 2 hours then 200 mg/m^2 over 22 hours) day 1
Cytarabine[a]	0.5 grams/m^2 IV every 12 hours days 2 and 3 (4 total doses)
Peg filgrastim	0.1 mg/kg (max 6 mg) subcutaneous day 5
Intrathecal therapy	Dosing below. Days 1 and 8
Immunotherapy[b]	
Inotuzumab ozogamicin	Cycle 1: 0.6 mg/m^2 IV day 2 and 0.3 mg/m^2 days 8 and 15 Cycle 2 and after: 0.3 mg/m^2 IV days 2 and 8
Blinatumomab	Cycle 1: 5 mcg/m^2/day (max 9 mcg/day) CIV days 14-17 then 15 mcg/m^2/day (max 28 mcg/day) CIV days 18-29 Cycle 2 and after: 15 mcg/m^2/day (max 28 mcg/day) CIV days 4-28
Rituximab	All Cycles: 375 mg/m^2 IV days 2 and 8

For Leukemia CNS1 or 2: The intrathecal therapies will consist of below:

Methotrexate (MTX)	Age (yrs) 1-1.99 2-2.99 3-8.99 ≥9	Dose MTX:8mg, MTX: 10mg MTX: 12 mg MTX: 15 mg

For Leukemia CNS 3: The intrathecal therapies will consist of triple therapies as listed below:

Methotrexate (MTX) Hydrocortisone (HC) Cytarabine (ARAC)	Age (yrs) 1-1.99 2-2.99 3-8.99 ≥9	Dose MTX:8mg, HC: 8mg, ARAC: 16mg MTX: 10mg HC: 10 mg ARAC: 20 mg MTX: 12 mg HC: 12 mg ARAC: 24 mg MTX: 15 mg HC: 15 mg ARAC: 30 mg

Supplemental Table 1: Abbreviations: mini-hCVD, hyper-fractionated cyclophosphamide, vincristine, and dexamethasone; IV, intravenous; subcutaneous, subcutaneously; CIV, continuous intravenous infusion.

Supportive care: ursodiol 5 mg/kg orally twice daily starting day 1 if inotuzumab administered; urine alkalinization for methotrexate with continuous IV sodium acetate at 2-times maintenance fluid rate to maintain urine pH >7. Leucovorin rescue began 12 hours after end of methotrexate infusion 15 mg/m^2 IV every 6 hours until methotrexate level <0.01 mcmol/L. Methotrexate levels obtained at end of infusion and every 24 hours thereafter until level <0.01 mcmol/L.

[a] Cytarabine delayed until methotrexate level less than 20 mcmol/L if necessary

[b] Immunotherapy administered based on patient expression of CD19 (blinatumomab), CD20 (rituximab), and/or CD22 (inotuzumab ozogamicin)

Supplementary Table 2: Adverse Events per CTCAE v5

Adverse Event, N (%)	Grade 2	Grade 3	Grade 4
VOD/SOS during subsequent HSCT	0	1 (10)	1 (10)
Cytokine release syndrome	0	0	0
Febrile neutropenia	0	3 (30)	0
Sepsis	0	1 (10)	0
INR increase	2 (20)	0	0
ALT increase	2 (20)	1 (10)	0
Hyperglycemia	1 (10)	1 (10)	1 (10)
Neuropathy	1 (10)	0	0
Decreased Fibrinogen	1 (10)	0	0
Constipation	1 (10)	0	0

Supplemental Table 2: Abbreviations: INR- International normalized ratio. ALT- Alanine transaminase. VOD- Veno-Occlusive disease. SOS- Sinusoidal obstructive syndrome. HSCT- hematopoietic stem cell transplant.