THREE-YEAR FOLLOW-UP OF DOSE-DENSE MINI-CVD IN COMBINATION WITH INOTUZUMAB OZOGAMICIN AND BLINATUMOMAB FOR PATIENTS WITH RELAPSED/REFRACTORY B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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INTRODUCTION

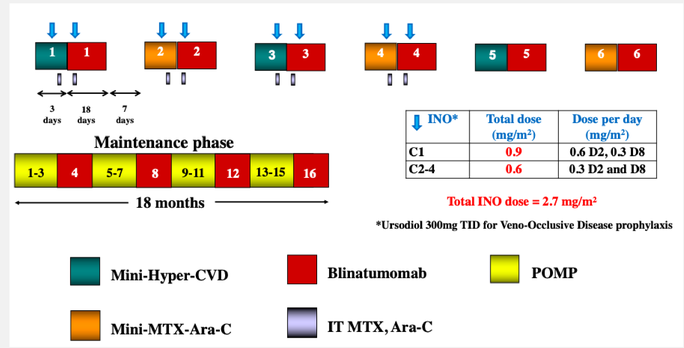
- While inotuzumab ozogamicin and blinatumomab are both superior to standard of care chemotherapy for patients with relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL), the overall survival benefits are modest as single agents[1,2]
- A previous phase 2 study of low-dose chemotherapy with mini-Hyper-CVD alternating with dose-attenuated MTX and Ara-C with inotuzumab and sequential blinatumomab demonstrated an overall response rate of 83% with a 3-year survival rate of 40%[3]
- The achievement of measurable residual disease (MRD) negativity is prognostic in B-ALL[4,5]
- Incorporation of blinatumomab earlier into treatment may increase MRD-negativity rates and improve long-term survival

AIM AND METHODS

- We designed a prospective phase 2 study to evaluate the approach of dose-dense blinatumomab, rituximab, and inotuzumab condensed with chemotherapy (BRICK regimen) in adults with R/R B-ALL
- Adults with R/R B-ALL with an ECOG of ≤3, adequate organ function, defined as a total bilirubin of ≤1.95 mg/dL, a CrCl of ≥50 ml/min, and left ventricular ejection fraction ≥40% were eligible
- Patients with Philadelphia-chromosome positive (Ph+) B-ALL could receive a concomitant tyrosine kinase inhibitor
- The primary endpoint was the overall response rate (CR + CR with incomplete count recovery)
- MRD-negativity was evaluated by both multiparameter flow cytometry (MFC) and next-generation sequencing (NGS, Adaptive ClonoSEQ)

REGIMEN

- The regimen consists of 6 alternating cycles of mini-hyper-CVD and dose reduced MTX and Ara-C
- In Cycle 1, inotuzumab was given at a dose of 0.6 mgm^2 on day 2 and 0.3 mg/m^2 on day 8
- In cycles 2-4, inotuzumab doses were 0.3 mg/m^2 on days 2 and 8, for a total cumulative dose of 2.7mg/m^2
- In cycle 1, blinatumomab 9 mcg/day was given on days 4-5, followed by 28 mcg/day on days 6-21
- In cycles 2-6, blinatumomab 28 mcg/day was given on days 4-21
- Cycles were 28 days in length and Peg-GCSF was given on day 4 of cycles 1-6
- Responding patients could proceed to CAR T-cell therapy, allo-SCT, or maintenance therapy



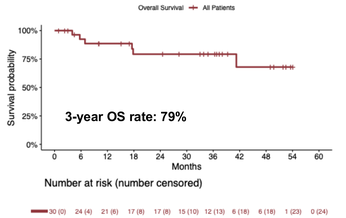
RESULTS

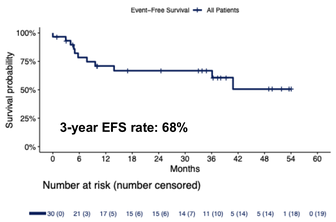
Baseline Characteristics N = 30

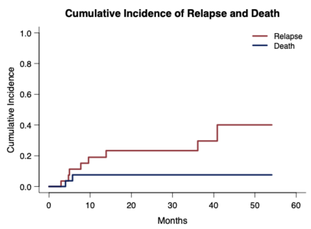
Characteristic	Category	N (%), or Median [range]
Age (years)		39 [19-62]
	≥60 years	4 (13)
Sex	Male	17 (57)
	0	5 (17)
ECOG performance status	1	24 (80)
	2	1 (3)
WBC (x10^9/L)		4.8 [1-94.6]
	≥50	2 (7)
BM blasts (%)		55 [0-94]
	Diploid	9 (30)
	Ho-Tr	2 (7)
	Tetraploid	1 (3)
Karyotype	KMT2A rearranged	1 (3)
	Ph+	3 (10)
	Miscellaneous	9 (30)
	IM/ND	2 (7)
Ph-like ALL		9 (30)
TP53 mutation		6 (20)
CD22 expression (%)		98 [18-99.9]
CD19 expression (%)		99.9 [0-100]
CD20 expression	≥20%	8/17 (47)
Prior blinatumomab		10 (33)
Prior Allo-SCT		3 (10)
	First salvage	26 (87)
	First salvage, primary refractory	7 (27)
Line of therapy	First salvage, CR1 duration <12 months	5 (19)
	Second salvage	3 (10)
	Third salvage	1 (3)

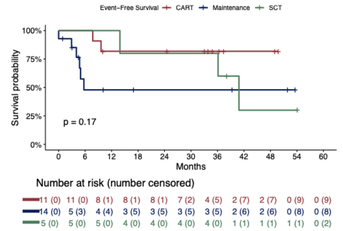
Response rates

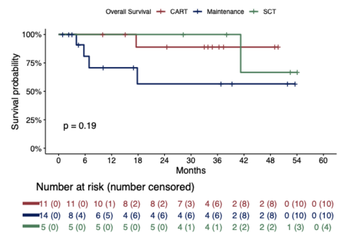
Category	Response, N (%)
Overall response rate	29 (97)
CR rate	23 (77)
MFC MRD-negativity	25/26 (96)
MFC MRD-negativity post C1	20/26 (77)
NGS MRD-negativity	22/25 (88)
NGS MRD-negativity post C1	8/21 (38)



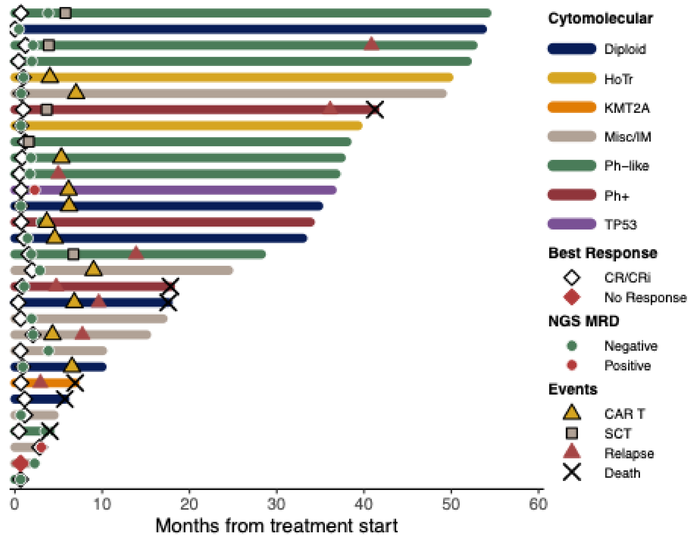








Median follow-up time: 36 months (0.95 CI 28 – 49)



CONCLUSIONS

- Dose-dense mini-CVD in combination with inotuzumab and blinatumomab was safe and effective in R/R B-ALL, leading to very high rates of NGS MRD-negativity and promising survival at 3-years
- Following a response to therapy, a high proportion of patients were able to be bridged to CAR T-cell therapy while in deep NGS MRD-negative remissions, with a resulting 3-year OS rate of close to 90%
- Further follow-up with more patients is needed to establish whether this approach may be curative and can obviate the need for allo-SCT

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