

Very Promising Results of the Dose Dense (D-D) Mini-Hyper-CVD-Inotuzumab-Blinatumomab Phase 2 Trial in Patients with Relapsed-Refractory Acute Lymphoblastic Leukemia

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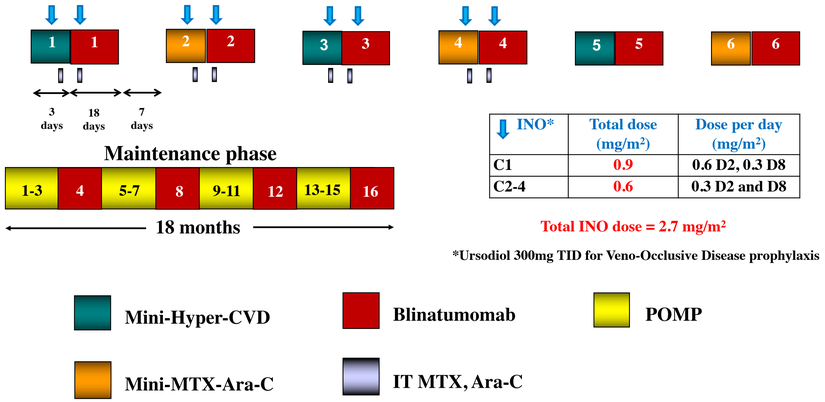
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Background

- Low-intensity mini-Hyper-CVD plus inotuzumab (INO) with or without blinatumomab showed efficacy and safety in patients with newly diagnosed and relapsed-refractory (R/R) B-cell acute lymphoblastic leukemia (ALL).
- The sequential addition of blinatumomab to mini-Hyper-CVD + INO improved the 3-year overall survival (OS): 66% (95%CI 49-79) vs 50% (95%CI 32-65) and the relapse free survival (RFS): 55% (95%CI 38-70) vs 34% (95%CI 19-50).
- We hypothesized that the early incorporation of blina in a D-D fashion would further improve outcomes and may lead to an earlier and deeper measurable residual disease (MRD) response.
- A retrospective review showed that the D-D mini-hyper-CVD, INO, and blina was safe and and effective in R/R setting. In the R/R cohort, all responders achieved MRD negativity by the end of cycle 1.
- We aimed to evaluate this regimen in a prospective clinical trial.

Methods

D-D Cohort Design



INO*	Total dose (mg/m^2)	Dose per day (mg/m^2)
C1	0.9	0.6 D2, 0.3 D8
C2-4	0.6	0.3 D2 and D8

Total INO dose = 2.7 mg/m^2

***Ursodiol 300mg TID for Veno-Occlusive Disease prophylaxis**

Mini-Hyper-CVD | **Blinatumomab** | **POMP** | **Mini-MTX-Ara-C** | **IT MTX, Ara-C**

-The decision to undergo allogeneic stem cell transplantation (ASCT) or chimeric antigen receptor (CAR) T-cell consolidation was based on the discretion of the treating physician after discussion with the patient.

Results

Baseline Patients Characteristics

Characteristic	Category	N(%)/Median (range)
		Dose-Dense (n=22)
Age (years)		41 (19-62)
Gender	Male	14 (64)
ECOG PS	≥2	1 (5)
WBC (x10^9/L)	Median	5.5 (1.3-94.6)
	≥50	2 (9)
PB ABC (x10^9/L)		1.8 (0-5,108)
PB blasts percentage		0.5 (0-87)
BM blasts percentage		51 (0-94)
BM blasts ≥50 %		11 (50)
Karyotype	Diploid	7 (32)
	HeH	0
	Ho-Tr	2 (9)
	Tetraploidy	1 (5)
	KMT2A rearrangement	1 (5)
	Complex	0
	Misc	6 (27)
	IM/ND	2 (9)
	Ph+	3 (14)
CRLF2		4/15 (27)
TP53 mutation		5/18 (28)
CD22 expression	Median	98.0 (18-99.9)
CD19 expression	Median	99.9 (52.9-100)
CD20 expression	≥20%	8/17 (47)
Prior ASCT		3 (14)
Salvage Status	Salvage 1	19 (86)
	Salvage 1, primary refractory	6 (27)
	Salvage 1, CRD1 <12 months	3 (14)
	Salvage 1, CRD1 ≥12 months	10 (45)
	Salvage 2	2 (9)
	≥Salvage 3	1 (5)

Response Rate

Response	N (%)
	Dose-Dense (n=22)
Morphologic Response	
ORR	21/21 (100)
CR	17/21 (81)
CRp	3/21 (14)
CRi	1/21 (5)
No response	0
Early death	0
MRD Negativity by MFC	
After Cycle 1	14/19 (74)
Overall	18/19 (95)
MRD Negativity by NGS	
After Cycle 1	6/14 (43)
Overall	16/17 (94)

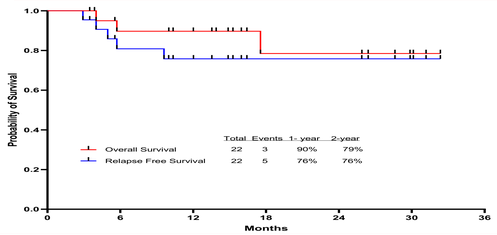
Patient Disposition

Median Follow up of 15 months (3-32 months)

Event	N(%)
	Dose-Dense (n=22)
Relapse*	3 (14)
Death in CR**	2 (10)
Death from progressive disease	1 (5)
ASCT consolidation	4 (18)
Car T-cell consolidation	8 (36)
Veno-Occlusive Disease	0

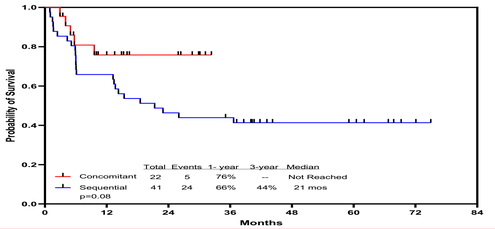
* Ph-like w/ NCOR1-Lyn fusion and MLL
** Sepsis and multiorgan failure

Survival - OS & RFS

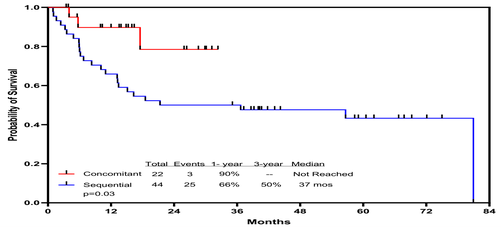


Outcome by Sequential vs Concomitant (D-D) - Overall

RFS

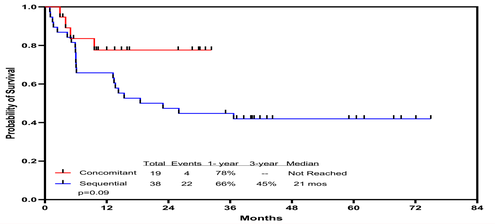


OS

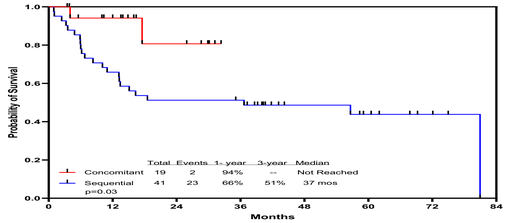


Outcome by Sequential vs Concomitant (D-D) - S1

RFS



OS



Conclusion

- Early and concomitant administration of blina in D-D fashion with Mini-Hyper-CVD + INO is feasible and safe in patients with R/R B-cell ALL.
- D-D approach appears superior to Mini-Hyper-CVD with sequential blinatumomab overall and in S1.
- D-D approach leads to early and high overall rates of deep MRD negativity.
- D-D approach is now being explored in the frontline setting.