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POSTER ABSTRACTS

614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES

A Phase I Study of Venetoclax in Combination with Inotuzumab Ozogamicin for Relapsed or Refractory ALL in Adults

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Introduction Adults with acute lymphoblastic leukemia (ALL), especially those who are older and/or have unfavorable disease biology frequently relapse. Inotuzumab ozogamicin (INO), an anti-CD22 monoclonal antibody covalently linked to calicheamicin, is approved for treatment of relapsed or refractory (R/R) CD22+ ALL. Although INO induces measurable residual disease negative (MRD-neg) complete remission (CR) in >75% of patients (pts), the duration of response (DOR) is limited (<6 months). Pre-clinical work demonstrates that malignant lymphoblasts are BCL2-dependent (Del Gaizo Moore Blood 2008). Initial results of the BCL2 inhibitor venetoclax (VEN) combination therapies for ALL are promising (Jain ASH 2019, Pullarkat Cancer Discov 2021). Due to distinct mechanisms of activity, non-overlapping toxicity, and possible synergy (Kirchhoff Blood 2021), we hypothesized that INO and VEN can be safely and effectively combined.
Study Design and Eligibility This is an investigator-sponsored phase I study (NCT05016947) with a 3+3 dose escalation design. The primary objective is to determine the maximum tolerated dose (MTD) of VEN plus INO at the FDA-approved doses in adults with R/R CD22+ ALL. Secondary objectives assess efficacy (hematologic response, MRD by multi-parametric flow cytometry [MFC] threshold <0.01%, and DOR). A 14 pt expansion cohort is planned. Dose-limiting toxicity (DLT) is defined as treatment-related CTCAE v5 non-heme toxicity grade 3+, sinusoidal obstructive syndrome (SOS) any grade, or liver toxicity during Induction (Ind) Cycle (C) 1 and/or failure of hematologic recovery (ANC ≥500, Plts ≥25 K/mL) by day 42 of Ind C1 in responding pts. Eligibility: ≥18 years (yrs); ALL (≥5% blasts) or LBL (marrow involvement not required); CD22 expression on ≥20% of blasts; R/R to one or more cycles of CC or in the case of Philadelphia-chromosome (Ph)-positive ALL, failed by two or more TKIs, or refractory to/ineligible for ponatinib; ≥60 days from bone marrow transplant (BMT), and off immune suppression ≥2 weeks; adequate liver and kidney function; no history of liver disease including SOS; blast count ≤25 K/mL prior to treatment; no symptomatic central nervous system (CNS) disease. Pts with prior INO or VEN treatment for R/R ALL are excluded.
Regimen Pts are treated with a VEN Ramp-Up over 3 days (DL1: 100/200/200; DL2: 100/200/400) followed by Induction C1: IV INO days 1, 8, 15 (0.8/0.5/0.5 mg/m2) and VEN daily per DL days 1-21. DEX 10 mg/m2 IV/PO is administered during Ramp-Up and Ind C1 days 1-4 (7 days total). Pts with >5% blasts after C1 receive Ind C2 without DEX. Pts with <5% blasts after Ind (1 or 2 cycles) continue with up to four 28-day consolidation cycles (INO 0.5 mg/m2 days 1, 8, 15 plus VEN per DL days 1-21). Pts receive CNS prophylaxis with intrathecal chemotherapy.
Results The 2-level dose-escalation phase has been completed; we enrolled 9 pts (5 female/4 male) with Ph-negative (n=7) or Ph-positive (n=2) ALL. The median age was 45 yrs (range 25 -74). Pts had received 1 (n=5) or 2 (n=4) prior lines of therapy. DL1 enrolled 3 pts without DLT. All DL1 pts achieved an MRD-neg CR and bridged to consolidation: 1 pt XRT to involved disease site (ankle) after 3 cycles and 2 pts to BMT after 2 cycles (Table). Three pts enrolled at DL2; no DLTs were observed. All achieved an MRD-neg CR. Two pts bridged to consolidation (donor lymphocyte infusion after 3 cycles, blinatumomab after 5 cycles) while 1 pt with *KMT2A*-r ALL experienced early relapse with lineage switch during second cycle. A confirmatory cohort of 3 pts enrolled at DL2 without DLT. All achieved a CR (n=2, MRD-neg; n=1, MRD-pos). The pt with MRD-pos CR as best response proceeded to blinatumomab as bridge to BMT after 2 cycles with 2 pts continuing treatment (currently cycle

2). Overall, CR was achieved in 100% (9/9) of pts with 7/8 (87%) achieving MRD-negativity. With median follow-up of 195 days (95% CI 80 - NR), 2 pts have relapsed 48 (on treatment) and 177 (after BMT) days from registration while other pts remain alive in CR. Non-heme grade 3-4 AEs include febrile neutropenia (2), DIC (1), tumor lysis syndrome (1), anxiety (1), hypertension (1), and hypotension (1). There have been no SOS. There were no delays in count recovery during C1, with median time from C1 to C2 being 30 days (range 27-42).
Conclusion VEN 400mg x 21 days in combination with INO at standard doses was well tolerated and declared the recommended phase 2 dose (RP2D) with a CR rate of 100%.

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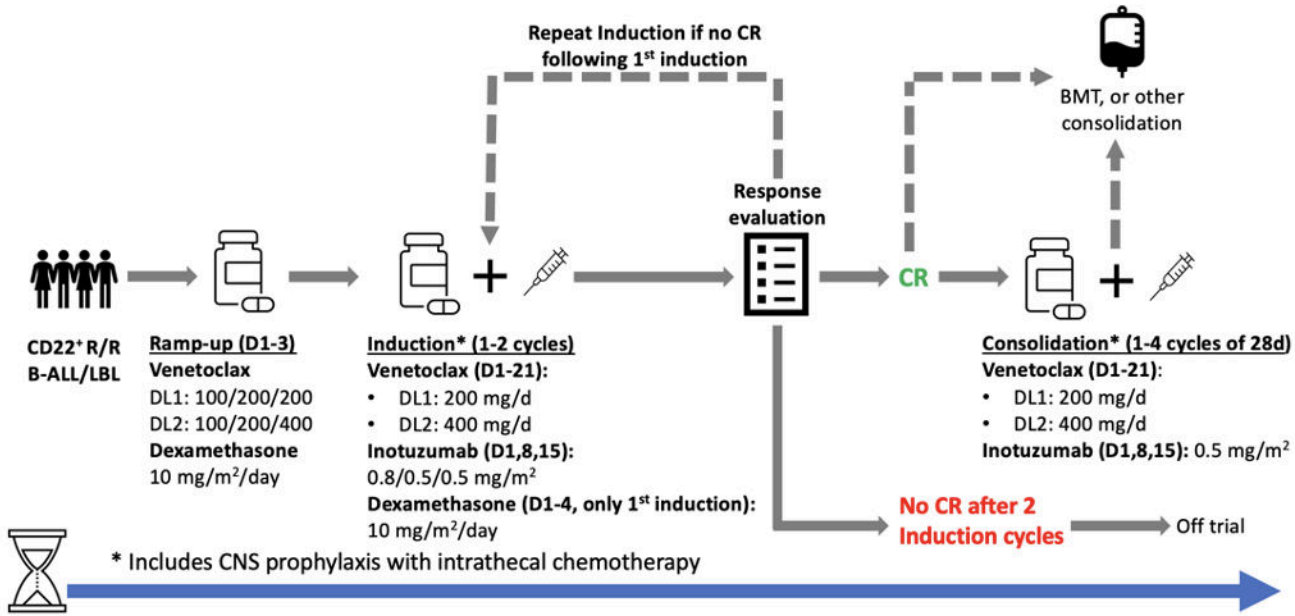

Panel A: Trial Schema

Pt #	DL	Age	Sex	Race/ Ethnicity	Disease	Prior Rx #	Prior BMT	Genetics	CNS	Best Response	C# to Best Response	Best MRD (MPFC), Cycle	Best MRD (Clonoseq), Cycle	Cycles	Consolidation	Relapse status, duration of CR	Alive	OS, days	DLT
1	1	35	F	Other, H	EM, MRD- BM	1	No	NK	Neg	CR	2	N/A	N/A	3	XRT	No, 530	Yes	530	No
2	1	25	F	Other, H	BM	2	No	NK; 2 copy del *CDKN2A, CDKN2B*	Neg	CR	1	Neg, <0.01% (1)	36 (2)	2	BMT	No, 473	Yes	473	No
3	1	45	F	Black, NH	BM	1	No	NK; *TCF3::PBX1*; 2 copy del *CDKN2A/B*	Pos	CR	1	Neg, <0.01% (1)	0 (1)	2	BMT	Yes, 177	No	262	No
4	2	74	F	White, NH	BM	2	Yes	Tetraploid w t(9;22); *ABL1* T315I	Neg	CR	1	Neg, <0.01% (1)	51 (2)	5	Blina	No, 195	Yes	195	No
5	2	59	M	White, NH	EM, MRD+ BM	1	Yes	Hypodiploid, *TP53*	Neg	CR	2	Neg, <0.01% (1)	0 (1)	4	DLI	No, 170	Yes	170	No
6	2	31	M	White, NH	BM	2	No	t(4;11); *KRAS* (p.G12V)	Neg	CR	1	Neg, <0.01% (1)	N/A	2	N/A	Yes, 48	No	155	No
7	2	27	M	White, NH	BM	1	No	NK, *IKFZ1* del, 1 copy del CDKN2A/B	Neg	CR	1	Pos, 0.012% (2)	63 (1)	2	Blina	No, 80	Yes	80	No
8	2	48	F	White, NH	BM	1	No	NK	Neg	CR	1	Neg, <0.01% (1)	9 (1)	2*	N/A	No, 44	Yes	44	No
9	2	62	M	White, NH	BM	2	Yes	*BCR:ABL1* + (FISH)	Neg	CR	1	Neg, <0.01% (1)	5 (1)	2*	N/A	No, 42	Yes	42	No

Data lock – 07/20/23
***Treatment ongoing**
Legend: ALL/LBL (acute lymphoblastic leukemia/lymphoblastic lymphoma); BM, bone marrow; BMT, bone marrow transplant; CNS, central nervous system; CR, complete remission; DL, dose level; DLI, donor lymphocyte infusion; DLT, dose-limiting toxicity; EM, extramedullary; F, female; H, Hispanic; M, male; MPFC, multi-parameter flow cytometry; MRD, measurable residual disease; NH, non-Hispanic; NK, normal karyotype; OS, overall survival; Pt, patient; R/R, relapsed or refractory; XRT, radiation

Panel B: Patient Disposition and Outcome

Figure 1