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POSTER ABSTRACTS

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

Mini-Hyper-CVD Plus Venetoclax for Treatment of Older Adults with Newly Diagnosed Ph-Negative B-ALL or T-ALL

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Introduction Treatment of Philadelphia chromosome (Ph)-negative acute lymphoblastic leukemia (ALL) in older patients (pts) is challenging due to poor tolerance of conventional chemotherapy and chemo-resistant disease. Pre-clinical work demonstrates that lymphoblasts are BCL2-dependent and sensitive to the BCL2 inhibitor venetoclax (VEN). We hypothesized that VEN plus dose-reduced hyper-CVD (cyclophosphamide, vincristine, dexamethasone) chemotherapy would be well tolerated and effective in older pts. We previously reported the safety and tolerability of VEN plus hyper-CVD in newly diagnosed and relapsed/refractory (R/R) pts (Jain ASH 2019), with a maximum tolerated dose of VEN 600 mg daily on days 1-21 per 28-day cycle. Preliminarily efficacy was promising in newly diagnosed pts, which prompted study extension to phase (P) 2, enrolling newly diagnosed older pts with Ph-negative (neg) B-ALL and T-ALL.
Methods Pts with Ph-neg B-ALL or T-ALL were enrolled in a multi-center Phase Ib/II study (NCT03319901). In P1, both R/R pts and newly diagnosed pts ≥ 60 years (yrs) were enrolled. In P2, only newly diagnosed pts ≥ 55 yrs old or ≥ 50 yrs old with BMI ≥ 35 kg/m2 were enrolled. Pts began with VEN ramp-up (P1 over 7d; P2 over 3d) to target dose (P1: dose level [DL]1 400 mg/d; DL2 600 mg/d; P2 400 mg/d), **Figure 1**. Hyper-CVD, including central nervous system (CNS) prophylaxis with intrathecal chemotherapy, was then given with VEN per DL for 21/28 days per cycle, for up to 8 cycles. Following completion of hyper-CVD courses, pts received VEN plus POMP maintenance for up to 2 yrs. Pts were recommended to receive fewer than 8 cycles of hyper-CVD in the setting of toxicity or to proceed to allogeneic hematopoietic stem cell transplant (HSCT) per physician discretion. This report updates follow-up of the newly diagnosed pts enrolled in P1 and the P2 cohort. Complete remission (CR) was defined as <5% marrow blasts, no evidence of extramedullary or CNS leukemia, ANC >1.0 K/uL and platelets >100 K/uL. Measurable residual disease (MRD) was evaluated by multicolor flow cytometry (MFC) and negative defined as <0.01%. Survival outcomes are presented via Kaplan Meier.
Results In total, 30 newly diagnosed pts [P1 11 (DL1=3; DL2=8); P2 18] were treated with a median age of 68 yrs (range, 57-81 yrs, n=12 [40%] ≥70 yrs); n=15 (50%) women, n=4 (13%) Hispanic, and n=1 (3%) Black. Twenty-three (77%) pts had B-ALL and 7 (23%) pts had T-ALL (6/7 early T-cell precursor). Two (6%) pts had central nervous system (CNS) involvement at diagnosis (1-CNS3, 1-CNS2). High risk genetics were present in 56% (13/23) of B-ALL pts: *TP53* (n=9 associated with complex [n=3] or hypodiploid [n=5] karyotype), *KMT2A* (n=1), *IKZF1* abnormality (n=2), and Ph-like (n=1). Eight B-ALL pts had received prior chemotherapy for multiple myeloma (n=6; n=4 auto HSCT, n=5 lenalidomide), diffuse large B-cell lymphoma (n=1, RCHOP), and breast cancer (n=1, docetaxel, carboplatin, trastuzumab).
The median number of hyper-CVD cycles received was 4 (range 1-8) among the 27 pts who have completed the hyper-CVD phase of treatment (3 pts are currently receiving consolidation). Mortality within 30 days was 3% (n=1). One patient died in

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CR due to sepsis during cycle 4. Venetoclax did not impair count recovery: median time from C1 to C2 was 34 days (range 27-47). Dose adjustments of VEN occurred in 4 pts (15%).
An MRD-neg CR was achieved in 25/30 (83%) pts. The median cycles to achieve both CR and MRD negativity by MFC was one (range: CR 1-2 cycles; MRD negativity 1-4 cycles). Remaining pts had refractory disease (n=4, 13%), or were not assessed (n=1, 3%) due to early death. Of the 25 pts who achieved CR, 11/25 (44%) received allogeneic HSCT in CR1 after a median of 200 days (range 138 to 347). With a median follow-up of 16.4 months, the estimated 12- and 24-month OS are 82.1% (95% CI 66, 98) and 74.6% (95% CI 54, 95), **Figure 2**; and RFS are 82.9% (95% CI 65, 100.0) and 67.8% (95% CI 44, 92), respectively. At data cut-off, 22 pts (73%) are alive. Death events (n=8, 27%) were due to early mortality (n=1, related to both ALL and infection), post HSCT complications (n=3), refractory ALL (n=1), relapsed ALL (n=1), sepsis in CR (n=1), and complications of cardiac surgery in CR (n=1).
Conclusion In this ongoing study, the addition of VEN to hyper-CVD in newly diagnosed ALL was well tolerated with encouraging responses. A future amendment will incorporate blinatumomab consolidation for pts with B-ALL.

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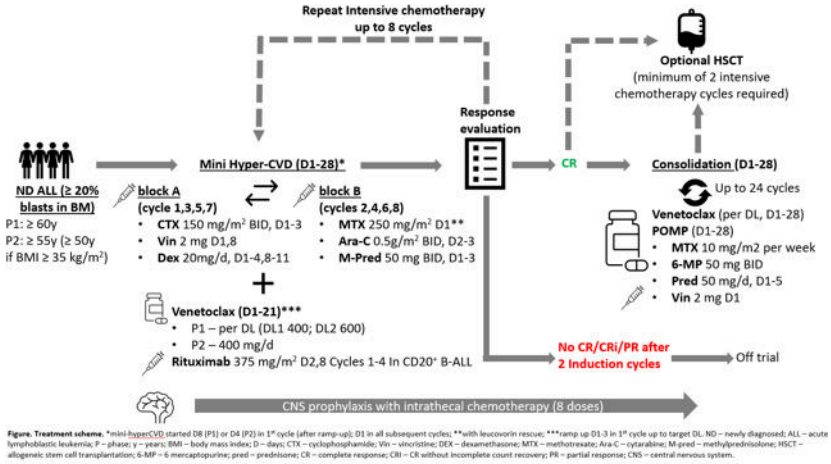

Figure. Treatment scheme. *mini-hyperCVD started D8 (P1) or D4 (P2) in 1st cycle (after ramp-up); D1 in all subsequent cycles; **with leucovorin rescue; ***ramp up D1-3 in 1st cycle up to target DL. ND – newly diagnosed; ALL – acute lymphoblastic leukemia; P – phase; y – years; BMI – body mass index; D – days; CTX – cyclophosphamide; Vin – vincristine; DEX – dexamethasone; MTX – methotrexate; Ara-C – cytarabine; M-pred – methylprednisolone; HSCT – allogeneic stem cell transplantation; 6-MP – 6 mercaptopurine; pred – prednisone; CR – complete response; CRi – CR without incomplete count recovery; PR – partial response; CNS – central nervous system.

Figure 1 Trial Schema

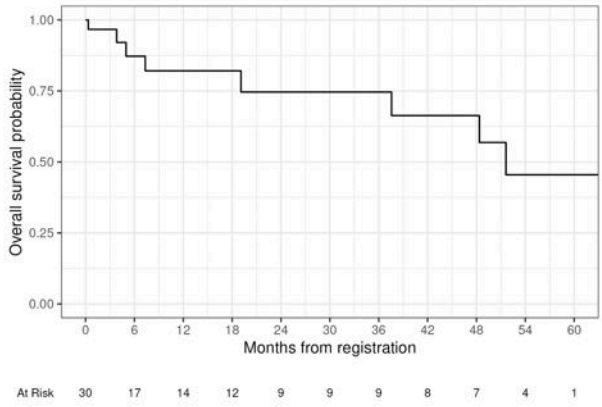

Figure 2 Overall Survival

Figure 1

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