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POSTER ABSTRACTS

642.CHRONIC LYMPHOCYTIC LEUKEMIA: CLINICAL AND EPIDEMIOLOGICAL

Combined Ibrutinib and Venetoclax for First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL): 5-Year Follow-up Data

Nitin Jain, MD[1], Michael J. Keating, MBBS[1], Philip A. Thompson, MBBS[2], Alessandra Ferrajoli, MD[1], Jayastu Senapati, MDMBBS,DM[1], Jan A. Burger, MD PhD[3], Gautam Borthakur, MD[1], Mahesh Swaminathan, MD[1], Koichi Takahashi, MD PhD[1], Zeev Estrov, MD[1], Marina Y. Konopleva, MD PhD[1], Koji Sasaki, MD[1], Tapan M. Kadia, MD[1], Naveen Pemmaraju, MD[1], Naval Daver, MD[1], Elias Jabbour, MD[1], Courtney D. DiNardo, MD MSc[1], Yesid Alvarado Valero, MD[1], Musa Yilmaz, MD[1], Prithviraj Bose, MD[1], Maro Ohanian, DO[1], Rashmi Kanagal-Shamanna, MD[4], Keyur Patel, MD PhD[4], Jeffrey L. Jorgensen, MD[4], Sa A. Wang[4], Sameh Nassar, MD[5], Naveen Garg, MD[5], Hyunsoo Hwang, MS[6], Xuemei Wang, MS[6], Nichole Cruz, RN[1], Ana Ayala, RN[1], William Plunkett, PhD[7], Hagop M. Kantarjian, MD[1], Varsha Gandhi, PhD[8], William G. Wierda, MD PhD[1]

[1] Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX
[2] Peter MacCallum Cancer Center, Royal Melbourne Hospital and University of Melbourne, Melbourne, Australia
[3] Department of Leukemia, MD Anderson Cancer Center, Houston, TX
[4] Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX
[5] Department of Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX
[6] Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, TX
[7] Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX
[8] Department of Experimental Therapeutics, MD Anderson Cancer Center, Houston, TX

Background: Ibrutinib (IBR) and venetoclax (VEN) combination is an effective therapy for patients (pts) with CLL. We previously reported results of the first-line cohort of a phase II trial of combined IBR and VEN for high-risk pts with CLL (Jain, NEJM 2019, JAMA Oncology 2021). Here we report updated data for 120 pts (80 pts in the original published cohort and 40 pts in an expansion cohort) with a median follow-up of 61.5 months.

Methods: Pts with previously untreated CLL meeting IWCLL treatment criteria were enrolled. All pts had at least one high-risk feature: del(17p), mutated *TP53*, del(11q), unmutated *IGHV*, or age ≥65 years. Pts received IBR 420 mg daily for 3 cycles followed by addition of VEN (weekly dose-escalation to 400mg daily). Combined therapy was given for 24 cycles (28 days/cycle). Pts with bone marrow (BM) undetectable MRD (U-MRD) (flow cytometry; sensitivity 10^{-4}) at 24 cycles of combined therapy discontinued both VEN and IBR; MRD+ pts continued IBR. A trial amendment allowed an additional 12 cycles of combined VEN and IBR for pts who remained BM MRD+ after Cycle 24. Response assessments included BM and CT studies (2008 IWCLL criteria). U-MRD was defined as <0.01%; low MRD+ 0.01% to <1%; high MRD+ ≥1%. Progression-free survival (PFS) was assessed as the time from the start of study drug to CLL progression, Richter transformation, or death from any cause. Blood MRD was monitored every 6 months after active therapy.

Results: Between August 2016 and February 2019, a total of 120 pts were enrolled. Median age was 64.5 years (range, 26-88 years). 86% had *IGHV*-unmutated CLL. 23% had del(17p)/ *TP53* mutation. The median follow-up is 61.5 months.

Six pts came off study during 1 st 3 cycles of IBR monotherapy; 114 pts initiated VEN. After 12 cycles of the combination, 62/120 (52%) achieved BM U-MRD remission; 43/120 (36%) were BM MRD-positive (low MRD+, n=35; high MRD+, n=8). After 24 cycles of the combination, 77/120 (64%) achieved BM U-MRD remission; 24/120 (20%) were BM MRD+ (low MRD+, n=23; high MRD+, n=1). Overall, 86/120 (72%) achieved BM U-MRD as the best response. One pt had DLBCL transformation and 1 pt had CLL progression during the first 2 year of therapy (details below).

The 5-year PFS is 90.1% and 5-year OS is 95.6% (Figure 1). The 5-year PFS for pts with del(17p)/ *TP53* mutation (n=27) is 86.1%. Of the 77 pts who were BM U-MRD at the end of cycle 24 of the combination, 73 discontinued all therapy, 4 pts continued IBR per treating physician discretion. Among these 77 pts, with a median follow-up of 40 months post Cycle 24, 22 pts had recurrence of blood MRD (defined as MRD ≥0.01% in 2 consecutive visits). Of the 22 pts with MRD recurrence, 5 pt had CLL progression at a median of 18 months (range, 6-30 months) from MRD recurrence (details below); 16 are being monitored without any active therapy for CLL and without clinical disease progression; 1 pt died from mesothelioma. Among the 55 pts

who remain in blood U-MRD remission, 53 remain in long-term follow-up in U-MRD remission; 1 pt had B-PLL transformation and 1 patient died (found unresponsive at home; was off therapy for 2 years).
There were 24 pts who were BM MRD+ at the end of cycle 24 of the combination (low MRD+, n=23; high MRD+, n=1). The only pt with high-MRD+ at end of cycle 24 was noted to have Richter transformation at that time. The remaining 23 pts (all low MRD+ in BM, range 0.01-0.95%) continued IBR monotherapy. With a trial amendment, MRD+ pts after Cycle 24 could get 12 additional cycles of VEN; 18/23 pts have resumed VEN. 11/18 (61%) pts achieved U-MRD remission during the third year of combined therapy. Only 2/23 pts are still receiving IBR (remaining pts have d/c IBR; all pts have d/c venetoclax); none of these 23 pts had clinical relapse.
A total of 6 pts had CLL progression (1 during the first 2 yr of therapy; remaining 5 during off-therapy phase). 3/6 had evaluation of BTK, PLGG2 and BCL2 mutations at the time of relapse and none were detected. 5 pts have started subsequent therapy (acalabrutinib, n=4; ibrutinib, n=1; all are clinically responding); 1 pt has not yet started therapy.
Conclusions: We report long term follow-up of combined IBR and VEN in first-line CLL (n=120) with a 5-year PFS of 90.1%. The 5-year PFS for pts with del(17p)/ *TP53* mutation is 86.1%. Retreatment with BTK inhibitor appears effective for pts with disease relapse.

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OffLabel Disclosure: Combination of ibrutinib and venetoclax is not FDA approved

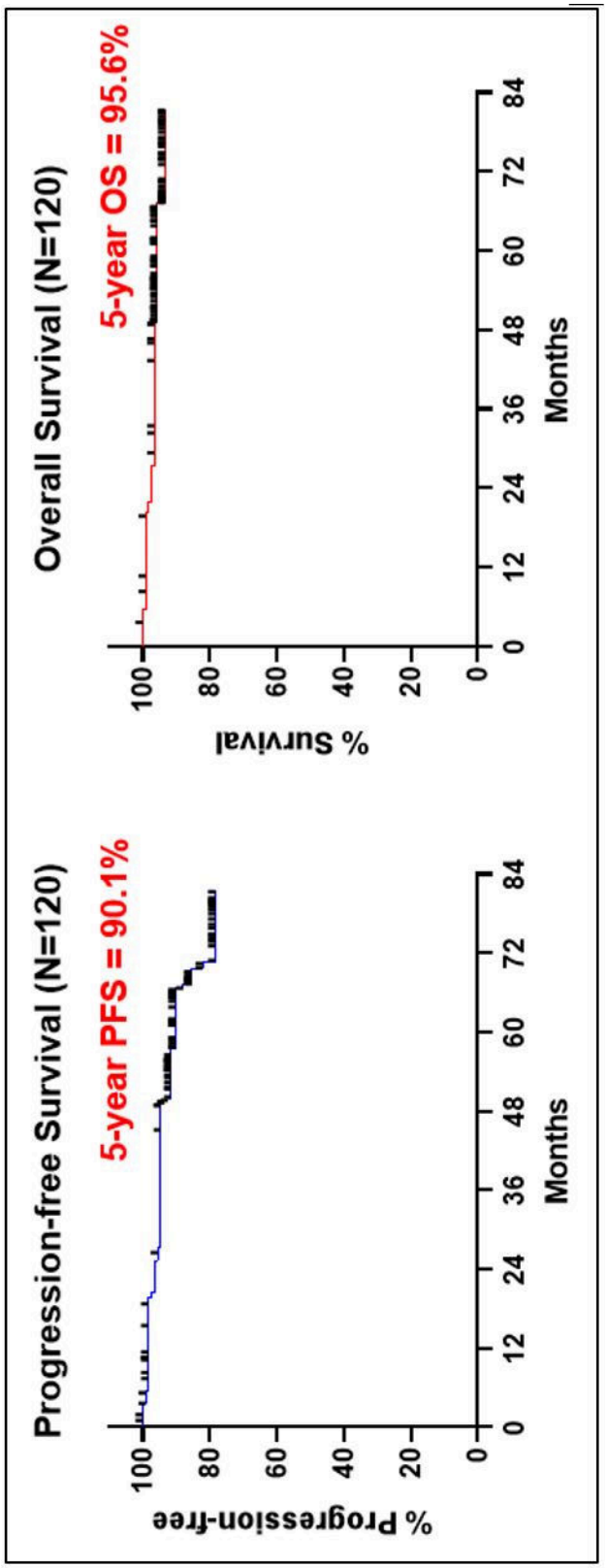

Figure 1

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