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TENTH ANNUAL MEETING

CLL-532

Changes in Proteome of CLL (Chronic Lymphocytic Leukemia) Lymphocytes During Investigator-Initiated Trial of Ibrutinib Alone and in Combination with Venetoclax in Treatment-Naïve Patients with CLL

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CONTEXT

Combined ibrutinib and venetoclax is an effective treatment for CLL.

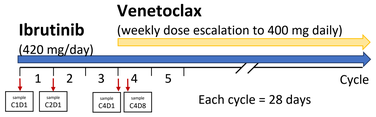
OBJECTIVE

Our investigator-initiated-trial (NCT02756897) combining ibrutinib and venetoclax[1]. demonstrated 72% achieving bone marrow u-MRD (undetectable minimal residual disease) status for patients with treatment-naïve (TN) CLL. These u-MRD status were durable[2]. These results were recapitulated in CAPTIVATE and GLOW trials. Our objective is to elucidate the proteomic landscape during therapy.

PATIENTS

Fourteen TN-CLL patients were selected from NCT02756897 trial.

METHODS



Ibrutinib was administered for 3 28-d-cycles, then venetoclax was initiated at cycle 4. Fifty-six peripheral blood samples from 14 patients were obtained at the baseline (C1D1), after one cycle of ibrutinib (C2D1), after 3 cycles of ibrutinib (C4D1), and in one week after venetoclax addition to ibrutinib (C4D8). Mass-spectrometry-based proteomic profiling was performed on these samples. Tryptic digests were prepared from the cancer cell lysates, and the peptides were fractionated by liquid chromatography and analyzed by untargeted mass spectrometry.

RESULTS

Analysis of proteomic data yielded identification of >1,000 proteins per time-point. K-mean clustering combined with Gap-Statistics identified 8 cluster patterns (Figure 1). Overall, 70 proteins were up-regulated, and 116 proteins were down-regulated (Figure 2). Early changes included upregulation of nuclear pore proteins NUP214, NUP133 and NUP155 at C2D1. PCK2 and PCYT1A were significantly downregulated after ibrutinib treatment. UIMC and SGSH proteins were consistently upregulated throughout all timepoints. Seven selected proteins (AIF1, ARHGAP25, PCK2, PCYT1A, PPBP, PTPN6, S100A11) were further validated using immunoblot analyses (Figure 3).

Figure 1. K-mean longitudinal clustering

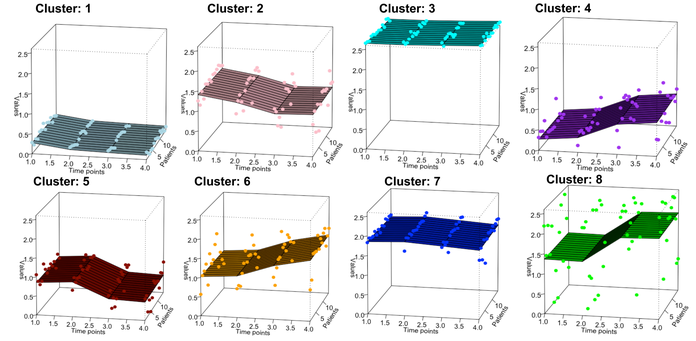


Figure 2. Up-regulated and down-regulated proteins

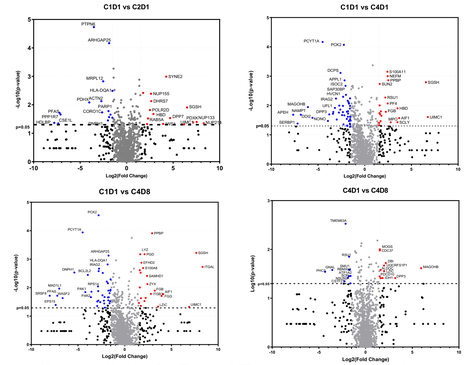


Figure 3. Western Blot data validation

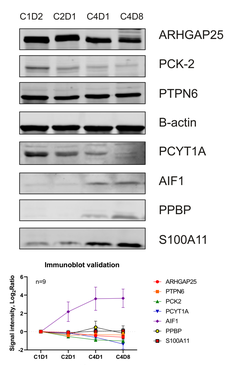
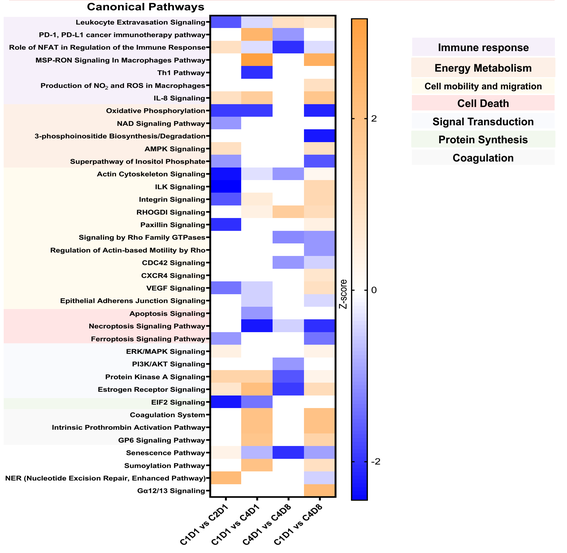
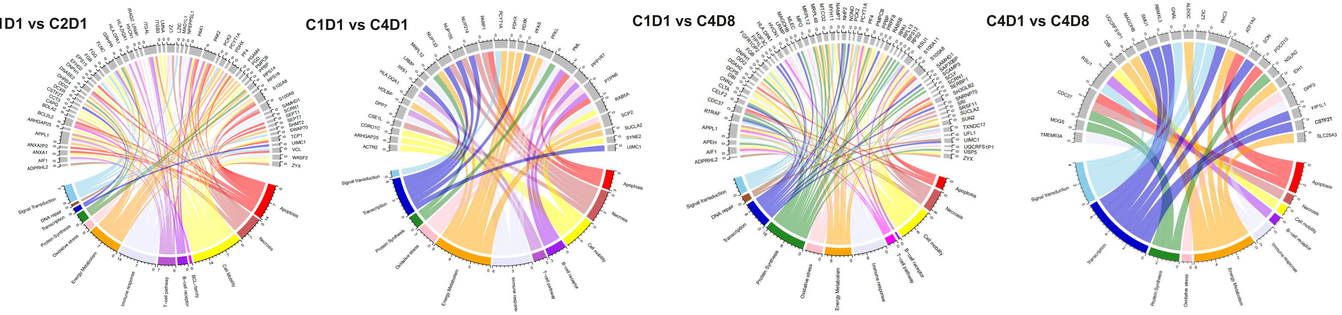


Figure 4. Canonical pathway changes during ibrutinib venetoclax treatment



After 1 cycle of ibrutinib, pathways that dominated maximum changes were energy metabolism, cell death, B- and T-cell signaling, and immune response; these were maintained after 3 cycles of ibrutinib. Impact on transcription and protein synthesis inhibition initiated after first cycle of ibrutinib but dominated after 3 cycles of ibrutinib. After one week of venetoclax, at C4D8 timepoint, the main changes included transcription pathway, signal transduction, and genes responsible for energy metabolism. Cytoskeleton-related pathways are initially downregulated and become upregulated after the addition of venetoclax (Figures 4,5).

Figure 5. Pathways, associated with significantly changed proteins



CONCLUSIONS

The CLL lymphocytes during ibrutinib and venetoclax therapy displayed significant proteome differences compared to baseline. Further validation studies are ongoing to evaluate the roles of these proteins in CLL pathophysiology and therapy response.

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[1]Jain N, Keating M, Thompson P, et al. Ibrutinib and Venetoclax for First-Line Treatment of CLL. New England Journal of Medicine 2019; 380(22): 2095-103.
[2]Jain N, Keating M, Thompson P, et al. Ibrutinib Plus Venetoclax for First-line Treatment of Chronic Lymphocytic Leukemia: A Nonrandomized Phase 2 Trial. JAMA Oncol. 2021;7(8):1213–1219. doi:10.1001/jamaoncol.2021.1649

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