

## INNOVATIVE MRD DETECTION AND IMMUNE PROFILING IN RELAPSED CLL TREATED WITH RITUXIMAB-VENETOCLAX: INSIGHTS FROM THE “DEDALUS” PROTOCOL

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**Background:** Fixed-duration Rituximab (R) and Venetoclax (Ven) therapy has improved outcomes in chronic lymphocytic leukemia (CLL), achieving a 7-year overall survival of 69.6% and effective MRD eradication. Accurate minimal residual disease (MRD) assessment is essential to monitor treatment response. The “Dedalus” protocol compared MRD detection by flow cytometry (MFC) and next-generation sequencing (NGS) in relapsed/refractory CLL patients treated with R-Ven and explored correlations with clinical outcomes and immune changes.

**Methods:** Twenty-two patients underwent MRD assessment using ERIC-compliant MFC and Lymphotrack NGS (sensitivity  $10^{-5}$ ). Advanced ultrasound monitored treatment response. MRD and immunological parameters were evaluated at 1, 6, 12, and 18 months or upon treatment discontinuation.

**Results:** Twenty patients achieved complete remission (CR), with MRD undetectable in 15 at first assessment by both methods. In two partial response cases, NGS detected residual IgH clonality ( $3-45$  clonal cells per  $10^6$ ) missed by MFC (Figure 1). Detection thresholds were  $10^{-4}$  (MFC) and  $10^{-5}$  (NGS). Venetoclax caused sustained B cell depletion and reduced CD4+ T cells, altering the CD4/CD8 ratio in 25% of patients. NGS results correlated more closely with clinical outcomes, especially in low-level residual disease.

**Conclusions:** R-Ven is highly effective in achieving durable remissions in relapsed CLL. While MFC is accessible and cost-effective, NGS offers superior sensitivity and better correlation with outcomes. Future studies should evaluate digital PCR for IgH rearrangements as a non-invasive MRD biomarker and further investigate Venetoclax’s immunomodulatory effects.

