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Leveraging Standardized MRD Assays to Guide CLL Treatment

Investigators from the United Kingdom National Cancer Research Institute published results from FLAIR: Front-Line therapy in Chronic Lymphocytic Leukemia: Assessment of ibrutinib containing regimens: a randomized controlled trial. The investigators found ibrutinib in combination with venetoclax induced significantly higher rates of undetectable measurable residual disease (MRD) compared with fludarabine, cyclophosphamide, and rituximab (FCR) in patients with untreated chronic lymphocytic leukemia (CLL). This abstract was noted in the Best of ASH 2023 presentation and the results were simultaneously published in the New England Journal of Medicine. The study's primary outcome was progression-free survival defined as time from randomization to progressive disease or death from any cause was longer with ibrutinib-venetoclax (I+V) than with FCR in the overall population and in patients with unmutated IGHV. These results should change first line therapy, from chemotherapy with anti-CD20 therapy, to a strategy of combining targeted inhibition of B-cell lymphoma 2 (Bcl-2) and Bruton's tyrosine kinase (BTK) pathways. The four secondary endpoints of the study were: Overall Survival, MRD assessment, Response to therapy (IWCLL criteria), Safety and Toxicity showed either noninferiority or benefit with the I+V arm. The most common grade three to five adverse events occurring within one year after randomization were neutropenia, anemia, and thrombocytopenia with marked lower events in the I+V group compared to the FCR cohort (10.3% vs 47.3%; 0.8% vs 15.5%; 2.0% vs 10.0%.).

Temporary stopping protocols lessen the risk for resistance and adverse events. Stopping interventions were carefully followed with guided MRD results compared to arbitrary time points. MRD was assessed in the peripheral blood (PB) and bone marrow (BM) by highly sensitive multiparameter flow cytometry with a detection limit of 1 CLL cell in 100,000 leukocytes (0.001%, 10^{-5}). Following a standardized harmonized diagnostic strategy all samples from the ninety-six hospitals were sent to a central laboratory (HMDS, Leeds). MRD was deemed to be detectable if CLL-cells represented at least 0.01% of total blood or BM leukocytes and was undetectable-MRD (uMRD) if CLL cells represented less than 0.01% of 12 total blood or BM leukocytes. The first assessment was 9m post-randomization (PB and BM) followed by PB assessment at 12m, then every 6m thereafter in I+V and every 12m in FCR (Figure S2, from supplement).[1]

Most of the patients had durable remission (Figure 1) suggesting cure while five patients (5/260) restarted I+V and were alive and progression free at the last follow up.

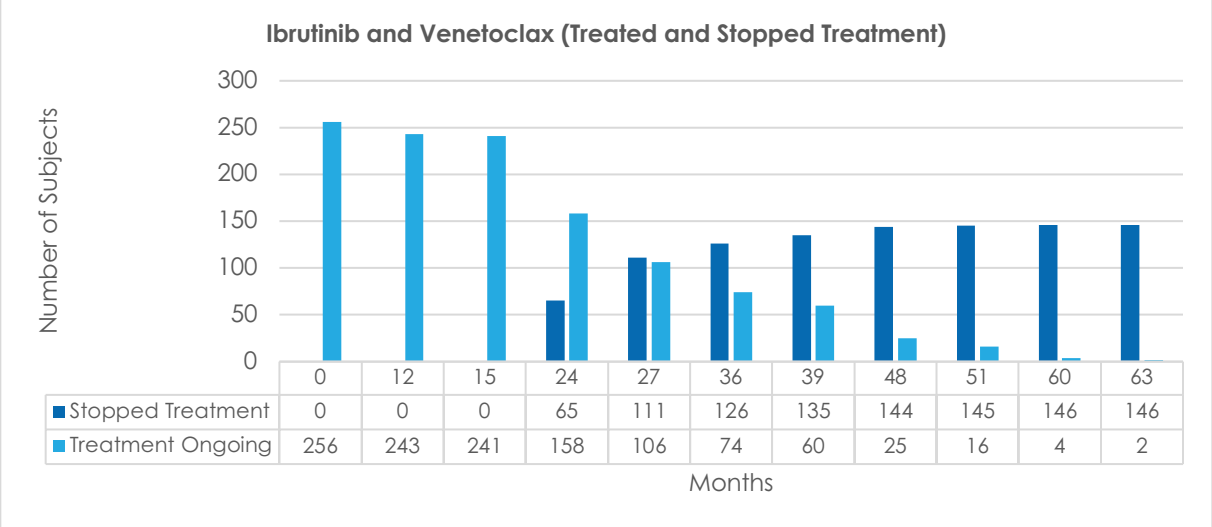

Figure 1: Estimates for I+V treatment stopping for attaining MRD stopping rules up to five years (+3m) post-randomization.[1] This figure was adapted from Table S7 of the Munir T. et al. publication in the New England Journal of Medicine.

What lessons can we take from the investigation?

This trial represents a triumph for individualized medicine based on knowledge of genomic architecture. CLL cells proliferate through dysregulated B-cell receptor signaling and resistance to apoptosis due to increased expression of Bcl-2 leading to accumulation of these cells causing tissue infiltration and resulting immune dysfunction. Using a BTK inhibitor which blocks BCR signaling combined with venetoclax inhibition results in profound CLL-cell apoptosis and potential cure.

Beyond the pharmaceutical breakthroughs the MRD sensitive assay guided rational intervention. Individualized medicine using MRD defined the therapeutic duration which was double the time taken to achieve undetectable MRD.

The investigators followed a wise strategy of bringing all testing of MRD samples to one institution. It speaks to the power of standardization to ensure the same highly sensitive assay is performed for all patient's samples throughout the time of the study. Unlike many trials, ninety-six hospitals and their primary investigators agreed to participate in the trial throughout the UK and to send all the samples to one institution.

Cost Savings

The investigators, like many stakeholders, are keenly aware of the cost of targeted oncologic therapeutics. They assessed cost-effectiveness by means of the Short-Form 12 and EQ-5D to produce quality adjusted life years. Health-related quality of life and cost effectiveness is the subject of separate reports in preparation.

Our Solution

As per the American Cancer Society about 18,740 new cases of chronic lymphocytic leukemia (CLL) are diagnosed each year.[2] Europe and Asia Pacific have similar newly diagnosed CLL patients. Invivoscribe, through its wholly owned subsidiary, LabPMM, offers an ultrasensitive MRD CLL assay with sensitivity and specificity performance comparable to HDMS, Leeds. This assay can be performed throughout the world using an optimized panel with standardized dried down reagents, artificial intelligence assisted interpretation, and final interpretation and reporting by the same group of hematopathologists; the same team that worked with the flow team to develop and validate the assay.

[1]Munir T. et al., *Chronic Lymphocytic Leukemia Therapy Guided by Measurable Residual Disease*. N. Engl. J. Med. 2023. DOI: 10.1056/NEJMoa2310063

[2]https://www.cancer.org/cancer/types/chronic-lymphocytic-leukemia/about/key-statistics.html