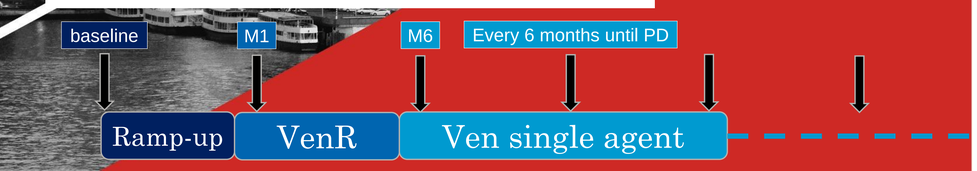
UPDATE FROM THE DEDALO PROTOCOL: AN INTEGRATED APPROACH TO MRD IN CLL PATIENTS RECEIVING VENETOCLAX PLUS RITUXIMAB

F. Mavilia[1], F. Ghio[2], G. Cervetti[2] , C. Baratè[2], G. Tancredi[1], D. Dardanis[1], P. Sammuri[2], V. Guerri[2], C. Bono[1], S. Grassi[1], E. Benedetti[2], S. Galimberti[1]

1. University of Pisa, Pisa, Italy.
2. AOUP, Pisa, Italy.

INTRODUCTION

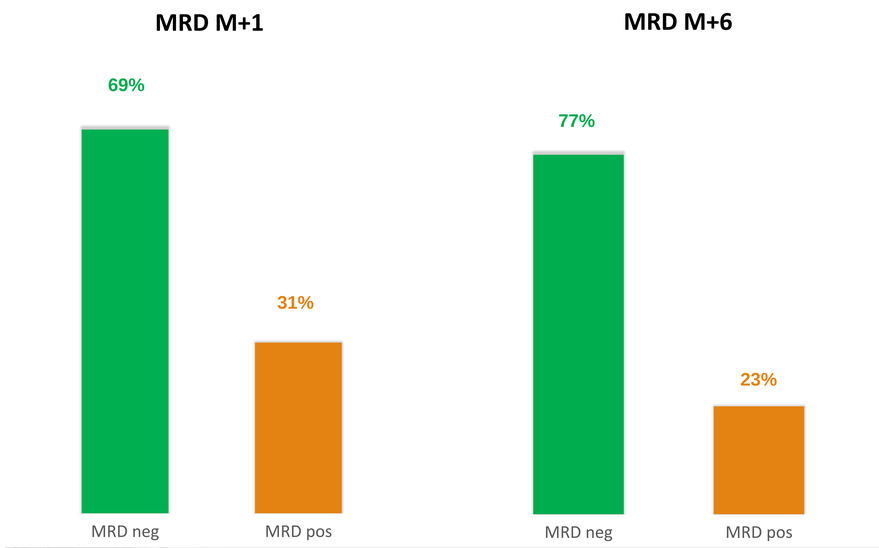
For patients with relapsed/refractory CLL, the MURANO research showed a significant progression-free survival (PFS) and overall survival benefit for fixed-duration venetoclax-rituximab (VR) treatment compared with bendamustine-rituximab. The study also showed that good PFS was associated with profound responses with undetectable minimal residual disease (uMRD). The Dedalo study was designed to test MRD from a multidisciplinary perspective (flow cytometry, molecular biology, and ultrasound), to evaluate MRD's predictive and prognostic value, to analyze the changes and reconstitution of cell-mediated immunity throughout the course of treatment and during the follow-up, and to investigate the significance of partial responses in an MRD negativity status. 19 patients have so far been included in the study; for each, the presence of TP53/del(17p) and the IGHV mutational status were examined. With a sensitivity of 10^{-4}, the MRD status of 13 patients was evaluated by flow cytometry in peripheral blood (PB) after the first cycle (M1) and after the sixth cycle (M6) with VR. Additionally, flow cytometry was used to analyze PB granulocytes, monocytes, T and B lymphocytes, NK cells, CD4+ and CD8+ T naïve, central memory, and terminally differentiated effector memory subsets in all of the patients at each MRD evaluation checkpoint.



RESULTS

Nine patients (47.4%) are under the age of 65, giving the patients' median age of 65.1 years. Ninety-five percent of them, or 17, are men. Five individuals have a TP53 mutation or del(17p) (26.3%), while 63.2% of patients had unmutated IGHV status.

Only one of the 19 patients who were initially recruited has had to stop receiving treatment, and 12 patients have completed their twelveth month of therapy. 13 individuals had their MRD status evaluated after the first cycle, and 69% had PB undetectable MRD (defined as less than 10^{-4}), 31% had low MRD positive (defined as 10^{-4} to 10^{-2}), and 0% had high MRD positivity (defined as more than 10^{-2}). Thirteen individuals had their MRD status evaluated after the sixth cycle, and uMRD was detected in 77% of them. One patient achieved a low MRD positivity after the first cycle, three patients with the TP53 mutation and/or del(17p) reached uMRD after the first cycle, and one patient had MRD positivity after the sixth cycle.



Parameter	Patients
Age, median, y	65.1
Age </= 65 y, N (%)	9 (47.4)
Male sex, N (%)	17 (89.5)
Binet stage N (%)	
B	15 (79)
C	4 (21)
Previous Treatment, N (%)	
1	12 (63.2)
2	2 (10.5)
3	5 (26.3)
IGHV mutational status, N (%)	
Mutated	2 (10.5)
Unmutated	12 (63.5)
Del(17p)/TP53 mut	
Yes	5 (26.3)
No	13 (68.4)

CONCLUSIONS

Favorable MRD kinetics were seen in the VR scenario while all patients were still receiving therapy. After the first cycle of therapy, the majority of patients had PB uMRD, with a higher percentage after the sixth round. Research is still being done on the longevity of uMRD rates, their function in predicting PFS in real-world situations, the impact of genetic factors on the kinetics of MRD, the reconstitution and dynamics of T-cells and cell-mediated immunity, and the relationship between MRD and clinical response.

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CONTACT INFORMATION

fabriziomavilia@gmail.com