

Celebrating Advances in CLL Research

The last several years have yielded impressive progress in the development of more effective and targeted treatment options for CLL patients. These developments have in turn resulted in improvements in patient survival rates, and these improvements have continued their positive trajectory through 2018. Thanks to a better understanding of the pathophysiology of CLL, including the identification of multiple proteins that are integral to the evolution and survival of CLL cells, we are finally seeing major shifts in therapeutic options that are available to CLL patients, along with a concomitant improvement in patient outcomes. Still described as incurable in medical schools, there is mounting evidence that, for an ever-expanding patient population, long-term remissions in CLL patients are achievable.

The current status of CLL is considered to have commenced in 1983 when fludarabine was found to be effective for the management of relapsed and refractory CLL. The evolution of fludarabine-based treatments inspired the fludarabine-cyclophosphamide-rituximab (FCR) regimen, which has now been approved as the standard of treatment in the United States and around the world for patients younger than 65 years of age and in relatively good physical condition. We now have long-term survival data from patients who received FCR. A review of the original 300 patients treated in the Phase II FCR study shows a high rate (60%) of very long-term (12.8 years) disease-free survival in those patients with mutated immunoglobulin heavy chain variable (IgVH) gene who do not have abnormalities in chromosomes 17 or [11](#) (1). These results support the continued use of chemoimmunotherapy outside of clinical trials in fit patients who meet these criteria.

The next major breakthrough to occur in CLL therapeutics came with the discovery of several proteins integral to CLL development and survival, including Bruton tyrosine kinase (BTK), phosphoinositide 3-kinase delta, and B-cell lymphoma 2 (BCL2). Having identified them, researchers next developed small molecule inhibitors targeting the specific proteins, blocking their actions and inhibiting the disease. These inhibitors include ibrutinib, idelalisib, and venetoclax. Results from a recent Phase II [study](#) in young, fit, high risk CLL patients combining the BTK inhibitor ibrutinib with FCR (iFCR) showed the regimen induced deep responses, with 57% of participants achieving a complete response (CR) with bone marrow minimal residual disease negativity (BM-MED-neg) and 83% achieving BM-MRD-neg (2). These results are significantly higher than the 20% rate seen in this population with FCR alone.

In those patients for whom FCR is not recommended, either based on age, fitness level, or the molecular characteristics of their disease, major therapeutic breakthroughs using small molecule inhibitors including ibrutinib, idelalisib, and venetoclax, and monoclonal antibodies such as rituximab and obinutuzumab, now provide numerous treatment options. Recent updates from multiple trials using these agents in combination are showing response rates as high as 90-100%.

Early results from an investigator-initiated [study](#) combining ibrutinib with venetoclax in previously untreated, high-risk CLL patients revealed promising results, with all patients who completed at least 3 months of the combined therapy showing either a partial or complete response (3). An interim analysis of [results](#) from the randomized, Phase III MURANO trial evaluating the benefits of venetoclax plus rituximab (VR) versus bendamustine plus rituximab (BR) in patients with relapsed or refractory CLL showed a profound improvement in progression free survival at 24 months in the VR treatment group (84.9%) versus the BR group (36.3%) (4). As reported at the 2018 American Society of Hematology meeting in 2018, regimens that combine ibrutinib and venetoclax, with or without a monoclonal antibody, are producing complete response rates of 80% after one year or more of therapy. This is good news for older

patients, as well as for those who have deletions in chromosomes 11 or 17 and/or unmutated IgVH. These findings indicate the doctrine of CLL as an incurable disease may soon be overturned.

The ever-increasing treatment options available to even high-risk and relapsed/refractory patients make this a unique and exciting time in CLL research. Your continued support of our mission to abolish CLL as a threat to the life and health of patients ensures that CLL Global Research Foundation is able to remain at the forefront of supporting many of these activities, translating the optimistic early information into programs that have benefits for present day CLL patients.

1. Thompson, PA, CS Tam, SM O'Brien, et al. Fludarabine, cyclophosphamide, and rituximab treatment achieves long-term disease-free survival in IGHV-mutated CLL. *Blood*. 2016; **127**:303.
2. Davids, Matthew S, HT Kim, DM Brander, et al. A Multicenter, Phase II Study of Ibrutinib Plus FCR (iFCR) as frontline therapy for younger CLL patients. *Blood*. 2017 **130**:496.
3. Jain, Nitin, PA Thompson, A Ferrajoli, et al. Combined venetoclax and ibrutinib for patients with previously untreated high-risk CLL, and relapsed/refractory CLL: A Phase II trial. *Blood*. 2017; **130**:429.
4. John F Seymours, TJ Kipps, BF Eichhorst, et al. 2017. *Blood*. 2017; **130**:LBA-2.

