

Twenty Years of Advancing Discoveries and Treatment of Mantle Cell Lymphoma: Report of the 2023 Lymphoma Research Foundation's Mantle Cell Lymphoma Consortium Workshop

On May 2nd and 3rd, 2023, in Chicago, IL, the 16th Mantle Cell Lymphoma Consortium (MCLC) workshop was held. Recognizing the need for accelerated MCL research and collaboration between clinical and scientific researchers, The Lymphoma Research Foundation (LRF) has provided MCL-specific research grants and developed MCLC, a working group that includes both basic scientists and clinical researchers from North America and Europe with an interest in mantle cell lymphoma (MCL). Since 2003, the MCLC has convened regularly to allow both clinical and scientific researchers to share their own work and to receive updates on recent scientific and clinical trial findings. The workshop offers a rare opportunity for collaboration between researchers across a wide range of MCL areas of interest and provides a venue for formation of the collaborations needed to conduct leading research. In 2023, the MCLC workshop included sessions on timely MCL topics at the forefront of scientific discovery, treatment development, clinical study, and translation to clinical care. Sessions included MCL genetics, mechanisms of resistance or response to treatment, personalization of therapy and prognostics using biomarkers, the tumor microenvironment (TME), and an international overview of clinical trials.

Mantle cell lymphoma is an aggressive subtype of non-Hodgkin lymphoma (NHL) characterized by the t(11;14) chromosomal translocation, which leads to the dysregulation of the cell cycle through overexpression of cyclin D1. Though advances in treatment have improved outcomes, in particular the introduction of Bruton's tyrosine kinase (BTK) inhibitors to the treatment armamentarium, and more recently CAR-T therapy, MCL often rapidly develops resistance and has a high rate of relapse. In addition, MCL is clinically heterogeneous, and as a result, there is no single therapeutic approach or standard of care. Furthermore, the determinants of varying clinical phenotypes (e.g., indolent disease versus more aggressive disease), are unclear and thus far, there is no way to predict treatment response.

The molecular biology of MCL is of central importance, as it underpins disease severity, treatment response, and outcomes. While advances in our understanding of MCL tumor genetics have shed light on the genetic drivers of disease severity and treatment resistance, multiple genetic changes are involved, as well as epigenetic and transcriptional changes. Additionally, recent research has revealed that it is not just the genetic profile of individual tumor cells which affect treatment response, but also the gene expression and population dynamics of surrounding immune cells within tumor microenvironment (TME). Furthermore, nongenetic metabolic reprogramming could also mediate drug resistance. Within several of the research presentations shared, many of the techniques which have allowed monitoring of MCL tumor genetic and gene expression changes on the single-cell level, were applied to analyze the cross talk between tumor cells and cells within the TME. The further evaluation of both MCL tumor cells and the TME at diagnosis and within the context of response and relapse will yield exciting and likely fruitful findings. During the workshop, several studies indicated that including features of the TME may strengthen existing MCL markers of prognosis and/or treatment response. Furthermore, the TME represents a collection of targetable pathways which may be manipulated to improve treatment outcomes with therapeutics.

Multiple studies that were discussed sought to determine the molecular determinants of treatment response and/or resistance. These studies used an array of advanced computational methods, novel imaging methods, and combinations of molecular tools to not only better understand the drivers of resistance, but also to identify optimal therapeutic sequences, and to uncover pathways required for

development of resistance which may be targeted. Researchers presented several identified vulnerabilities in BTKi-resistant MCL, which may be exploited by novel treatment approaches, even in high-risk patients. Additionally, multiple methodologies for more rapid identification of treatment response were presented, including non-invasive strategies which could indicate response within days. Together, these studies are not only poised to optimize the use of existing agents, but also to support novel combinations of available agents, as well as the *de novo* development of therapies. Importantly, many of the biomarkers of response discussed may be incorporated into clinical trials for validation, or to permit the acceleration of clinical trial read out, thereby reducing the time needed for completion of clinical trials and potentially reducing the number of patients needed. As MCL subtypes are identified or new agents/combinations of agents are developed, this will become increasingly important.

Throughout the workshop, researchers and clinicians were able to participate in an interdisciplinary exchange with other physicians and scientists who share their interest in MCL. By hosting this workshop, LRF provided a venue for the exchange of recent research developments, fostering collaborations and supporting scientists and clinicians in their work improving treatment outcomes in MCL. We are in an important time for MCL in profound basic science discoveries, rapid translation of these into clinical outcomes, and fast FDA approvals of many targeted and immunologic therapies. We are witnessing patients with MCL achieving complete remissions for 15 to 20 years. Cures will be achieved in our time. In addition to doing its important part, LRF is excited to witness this historic time for MCL with all researchers and clinicians around the globe.