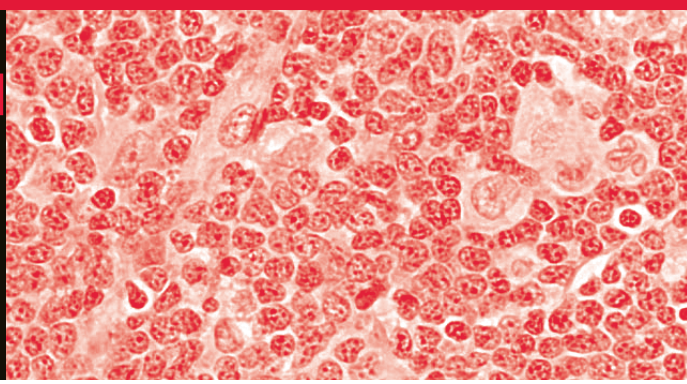
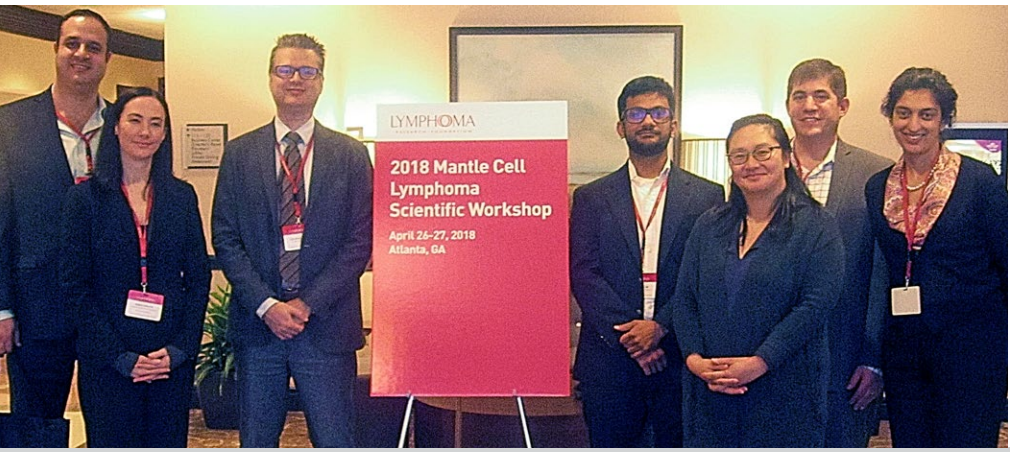
LYMPHOMA RESEARCH • FOUNDATION

Summer 2018

RESEARCH Report



Clinical, Laboratory Advances Highlighted at 2018 Mantle Cell Lymphoma Workshop



LRF Scholars attend the 2018 MCL Workshop (L to R): 2015 Scholar Victor Yazbeck, MD Virginia Commonwealth University, Meghan Gutierrez, LRF CEO, 2016 Scholar Lapo Alinari, MD, PhD, The Ohio State University, 2018 Scholar Shalin Kothari, MD Roswell Park Comprehensive Cancer Center, 2016 Scholar Connie Batlevi, MD, PhD, Memorial Sloan Kettering Cancer Center, and 2014 Scholars Jonathon Cohen, MD, Emory University and Anita Kumar, MD, Memorial Sloan Kettering Cancer Center. The 2018 Scholar class is profiled on pg. 3.

On April 26 and 27, 2018, nearly 100 lymphoma researchers gathered in Atlanta, Georgia, for the Lymphoma Research Foundation's (LRF) 13th Mantle Cell Lymphoma (MCL) Scientific Workshop. This biennial gathering includes LRF MCL Consortium members, MCL grantees, and scientists from the United States, Canada, and Europe, and provides an opportunity for the world's leaders in both laboratory and clinical MCL research to share research findings, discuss recent and ongoing clinical trials, and strategize on the critical next steps to advance MCL research. Concentrated and deliberate communication between scientists and clinicians across this wide scope of research is unique to this forum and the cross-pollination between research fields spanning from the laboratory bench to the patient bedside accelerates the understanding and development of treatment for MCL.

The MCL Consortium (MCLC), established by the LRF in 2005, includes more than 100 MCL researchers from North America and Europe. The Consortium is designed to accelerate developments in the understanding and treatment of MCL by convening leaders in the field across a wide range of research environments, funding innovative studies and creating needed resources. Programmatic efforts of the MCLC include MCL investigator research grants, establishment of an MCL cell bank that contains research tools available for conducting laboratory research, patient education programs and the Focus on Lymphoma app, and the biennial MCL Scientific Workshop. This report provides an overview of each presentation given at the 13th MCL Scientific Workshop and identifies key emergent themes.

"The Lymphoma Research Foundation's MCL Consortium and its Scientific Workshop have been key contributors to the advancement of our understanding of MCL both clinically and biologically," says Thomas M. Habermann, MD, of Mayo Clinic, Chair of the Foundation's Scientific Advisory Board. "It is gratifying that in its 13th incarnation the presentations are as innovative and cutting edge as in the first years of the program."

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"The MCL Consortium and its Scientific Workshop have been key contributors to the advancement of our understanding of MCL both clinically and biologically."

FEATURED IN THIS ISSUE: Profiles of 2018 LCRMP and MCL Grantees Page 3

Recipients of the Foundation's MCL Therapeutic Studies Grant, as well as the 2018 class of the Lymphoma Clinical Research Mentoring Program (including Priyanka Pophali, MD, of Mayo Clinic, pictured left) explain their LRF-funded research.

LETTER FROM THE CEO

Dear LRF Friends and Supporters,

This past April, the Lymphoma Research Foundation (LRF) hosted its 13th Mantle Cell Lymphoma (MCL) Scientific Workshop. In our role as a pivotal convener of events involving key issues in lymphoma research, LRF is proud that this event remains an impactful one for the lymphoma research community, with over thirty presentations on cutting edge basic, translational, and clinical research in MCL presented to nearly 100 researchers from across North America and Europe. In this issue of *Research Report*, we present a summary of the Workshop's proceedings, beginning on page 1.

In this issue, we also conclude our profiles of our 2018 research grantees, with our MCL Therapeutic Grant and Lymphoma Clinical Research Mentoring Program (LCRMP) recipients, beginning on page 3. If you missed coverage of our Clinical Investigator Career Development Award, Postdoctoral Fellowship Grant, and AYA Lymphoma Correlative Grant recipients in the Spring issue, please visit lymphoma.org/researchreport.

Your support of LRF's mission allows us to continue to promote collaboration and innovation in lymphoma research through our grants and scientific workshops. If you are specifically interested in MCL research, please see page 15 for a way to maximize that support. Thank you for your part in helping the Foundation support all those affected by this disease.

Sincerely,

Meghan Gutierrez
Chief Executive Officer

MCL Workshop

[CONTINUED FROM PAGE 1]

The 2018 workshop included 33 original research presentations on a broad range of topics important in the understanding and treatment of MCL, including new findings from research on MCL biology, recent research on novel pathways and potential treatment targets, findings that improve understanding of therapeutic resistance and personalization of therapy, presentation of MCL outcomes research, updates on prognostic and predictive biomarkers, and an update on recent clinical trials. The Keynote Address, on circulating tumor DNA analysis for personalized lymphoma treatment, provided insight into the promise and potential limitations of the technology for non-invasive diagnosis and monitoring of MCL tumor genetics.

The research presented at the Workshop by laboratory scientists and clinical researchers reflects the ongoing progress being made toward the LRF's mission to eradicate lymphoma and serve those touched by this disease. Overall, researchers noted the remarkable improvements in the nature and sensitivity of technologies as well as analytic capabilities as an important contributor to ongoing discovery.

MCL Biology

Moderator: Leticia Quintanilla-Fend, MD, University Tuebingen

Scientists are continuing to develop their understanding of how dysregulation of particular genes or pathways impact overall survival (OS), sensitivity to treatment, and the potential for recurrent disease. This information builds our understanding of the pathways that can be targeted in development of new therapies.

To open the session, Pedro Jares, PhD (Hospital Clinic Barcelona – IDIBAPS) discussed findings from his lab that show new potential roles of cyclin D1, a protein overexpressed in MCL that functions as a regulator of cell growth and division. In addition to its more well-known function as a cell-cycle regulator, cyclin D1 acts through a range of other pathways to control proliferation, cell differentiation, cell migration, and the DNA-damage response, among other functions. When exploring the functional implications of cyclin D1 overexpression in MCL, researchers found that excess cyclin D1 causes an overall decrease in gene expression through inhibition of transcription. As the levels of cyclin D1 increase, overall RNA levels within the

Foundation Announces Research Grants in Mantle Cell Lymphoma, Lymphoma Clinical Research Mentoring Program

In conjunction with the Mantle Cell Lymphoma Scientific Workshop, the Lymphoma Research Foundation announced two MCL Therapeutic Studies Grants, awarded to Sandeep Dave, MD, MS of Duke University and Jianguo Tao, MD of H. Lee Moffitt Cancer Center. As one of the world's largest private funders of MCL research, the Foundation has funded more than 50 grants for over $25 million since inception of the MCL initiative in 2003. LRF grants have led to important developments in the field, including the use of DNA microarray technology to distinguish indolent and aggressive MCL, models to predict prognosis, discoveries that further understanding of treatment resistance in MCL, and the identification of biomarkers that may permit more personalized treatment. This year's funded projects are expected to have an immediate impact on the understanding of MCL's biological mechanisms.

Dr. Dave is a Professor at Duke University and a member of LRF's Scientific Advisory Board. His LRF grant project uses tissue samples collected as part of an NCI-Canada Intergroup Study in patients with previously untreated MCL. He and his colleagues will use the samples to assess biomarkers that can predict the clinical behavior of a patient's disease when given standard therapies, in hopes of identifying biomarkers that can predict whether a patient will respond to or be resistant to current frontline therapies in MCL.

Dr. Tao is Professor at the University of South Florida College of Medicine and Senior Member at H. Lee Moffitt Cancer Center. His project seeks a greater understanding of the biological mechanism behind ibrutinib resistance in MCL, with the goal of designing effective combination therapies to attack the mechanism causing the resistance and prolong ibrutinib's effectiveness. His research on this topic prior to his LRF grant was presented at the 2018 MCL Workshop (see page 11). Both Dr. Dave and Dr. Tao will be profiled in detail on the LRF website this summer.

The Foundation also announced eight LRF Scholars, participants in the Lymphoma Clinical Research Mentoring Program (LCRMP). Founded in 2014, the LCRMP brings fellows and junior faculty pursuing lymphoma clinical research careers together with senior experts in the field. The program begins with a week-long workshop where Scholars work with expert clinicians, statisticians, and translational researchers to improve a clinical trial protocol and participate in discussions particular to a medical research career, such as preparing effective research publications and presentations, working with the NCI cooperative groups, finding (and later becoming) a mentor, and working with LRF education and research programs. Scholars later participate in two follow-up programs, including attending a grant review meeting and presenting their research at the North American Educational Forum on Lymphoma. This year's Scholars are profiled beginning on page 4).

"The Lymphoma Research Foundation's Mantle Cell Initiative and its associated research grants have been a key part of the Foundation's portfolio for fifteen years and we are excited to see that program continue with these two innovative research projects," says Meghan Gutierrez, the Foundation's Chief Executive Officer. "Though the Lymphoma Clinical Research Mentoring Program is our newest addition to the grants program, we are excited to see it continue to grow and attract the brightest early-career clinical researchers in lymphoma in its fifth year."

Applications for the Foundation's 2019 Grants Program, including the LCRMP, are now open. Visit lymphoma.org/grants for more information.

MCL Workshop

[CONTINUED FROM PAGE 2]

cell decrease. To elucidate the mechanism of this down regulation, Dr. Jares' group looked at the regions of the genome where transcription is initiated, and found that cyclin D1 is often bound to these positions, where it physically interacts with the cellular machinery that is responsible for initiating transcription. Importantly, transcription can be repressed to the point of lethality, indicating that cyclin D1 overexpression in MCL may sensitize cells to transcription inhibitors. This "synthetic lethality" is one that may be exploited in the development of future therapeutics.

Maja Milanovic, PhD (Institute for Cancer Genetics, Columbia University Irving Medical Center) presented results of a laboratory study on the role of ATM mutations in MCL pathogenesis. While characteristic of MCL, cyclin D1 overexpression alone does not cause MCL, raising the question of which the additional contributors are to the disease. ATM kinase is a protein that functions as part of the DNA damage response and mutations to its functional kinase domain are present in up to 50 percent of MCLs, indicating that disrupted function is in some way linked to the disease. To better understand the contribution of ATM to the pathogenesis of MCL, a mouse with the most common ATM mutation found in MCL was generated. This particular mutation negatively affects the functional properties of ATM kinase and mice show defects in T- and B- lymphocytes development that are comparable to mice lacking ATM protein. However, mice with the mutated ATM develop lymphomas much later than mice where ATM was missing entirely, indicating that this particular mutation preserves

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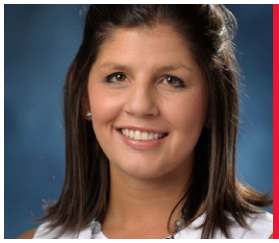
NEW GRANTEE PROFILES



Jennifer Agrusa, MD
Baylor College of Medicine/
Texas Children's Hospital
LCRMP

Investigating the Role of Telomeres in Hodgkin Lymphoma

Telomeres, the DNA-protein structures attached to the ends of chromosomes, play an important role in protecting chromosome integrity. Research suggests that significantly shortened telomeres may indicate an increased risk for developing specific diseases. Dr. Agrusa and her colleagues have hypothesized that patients with Hodgkin lymphoma (HL) may be at risk for shortened telomeres both because of the inflammation caused by HL in the human body and the intensive therapy regimens commonly used to treat HL. Dr. Agrusa's LCRMP project will study the role of short telomeres in HL, identifying how it may affect response to therapy, the development of therapy-related toxicities, and HL pathogenesis. Once these roles are identified, Dr. Agrusa hopes her results will support upfront screening of HL patients to identify those who may need modified treatment regimens or additional supportive care to counter the effects of shortened telomeres.

During Dr. Agrusa's medical studies at New York University, she worked in NYU's Late Effects Clinic, which treated cancer survivors dealing with the long term effects of their cancer diagnosis and treatment. "Because of this experience, it has been my goal to minimize toxicities and develop new ideas and techniques to improve patients' quality of life after treatment of pediatric cancer," she says. After a residency at Children's Hospital of Montefiore in the Bronx, Dr. Agrusa began a fellowship at Texas Children's Hospital/Baylor School of Medicine, where she is now an Instructor. During her fellowship, she studied genetic factors that contributed to pulmonary (lung) dysfunction in survivors of childhood HL. "While performing this research, I realized that there are a number of ways in which genetic biomarkers can improve HL outcomes," she notes, which prompted her LCRMP study and the future trajectory of her research. "The ultimate goal is to develop a strategy for screening HL patients for relevant biological host factors, and to use these results to assist in up-front stratification of patients."

Currently working towards a Masters degree through Baylor's Clinical Scientist Training Program, Dr. Agrusa applied to the LCRMP hoping to further enhance her progression towards a career as an independently-funded translational physician-scientist. She notes that the mentorship aspect of the program is also an important characteristic. "I am extremely appreciative of those who are taking the time to develop a new generation of lymphoma clinical researchers through the LCRMP, and I am looking forward to gaining additional insight from them."

Elizabeth Brem, MD
University of California, Irvine
LCRMP

Breaking New Ground for Elderly Patients with DLBCL

Elderly patients (age 75 and older) with diffuse large B-cell lymphoma (DLBCL) generally receive a lower level of chemotherapy than younger patients, because the intensity of chemotherapy and its side effects can take a greater toll on an elderly patient's body. However, less chemotherapy also leads to poorer outcomes for these patients. Dr. Brem and her colleagues are preparing to conduct the first randomized clinical trial in the U.S. specifically for elderly patients with newly diagnosed DLBCL. They will be testing the addition of an oral therapy called CC-486 to the standard reduced level of chemotherapy and hope this extends patient survival rates without adding significant side effects. "Thirty-three percent of patients 80 or older with DLBCL may not even get chemotherapy for a potentially curable disease," Dr. Brem notes. "In addition to trying to improve outcomes for these older patients, this trial is an opportunity to learn how treatment affects these patients both long-term and short-term."

Dr. Brem received her MD from the State University of New York (SUNY) at Buffalo, before a residency and fellowship at Beth Israel Deaconess Medical Center in Boston. During college and medical school, she was fortunate to work with mentors who ran a translational laboratory specializing in lymphoma research. "Very early in my career, I did some pre-clinical experiments and helped analyze specimens from patients on clinical trials to learn more about the biology of the disease," she says. She was prompted to apply to the LCRMP because of her interest in improving her skills as a clinical researcher. "This is a different skillset than needed in the laboratory. It takes knowledge of trial designs and statistics, succinct but precise writing, leadership, and the ability to give a good presentation, just to name a few skills. [The LCRMP Workshop] is an incredible opportunity to learn from some of the country's best lymphoma investigators and expand and refine my clinical trial skill set."

Dr. Brem hopes to continue her career with further trials like her LCRMP project as well as develop close working relationships with laboratory colleagues to help translate research from the lab to the clinic. She also hopes her success as a researcher ultimately helps her patients. "One of the things that drew me to lymphoma and blood cancers is the depth and intensity of the doctor-patient relationship. I want to continue to have therapies to offer my patients; I don't want to let them down!"

Jennifer Crombie, MD
Dana-Farber Cancer Institute
LCRMP

Investigating A New Combination Therapy for DLBCL and DHL

Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and double-hit lymphoma (DHL) often fail to respond to current therapies, leading to an urgent need for novel therapeutic options. Dr. Crombie's LCRMP project will test the combination of the hypomethylating agent, azacitidine, with venetoclax (Venclexta), an inhibitor of BCL-2, in patients with DLBCL or DHL. "While this combination results in impressive responses in patients with AML [acute myeloid leukemia], the role of these drugs in lymphoma remains unknown," Dr. Crombie says. "Under the mentorship of Dr. Anthony Letai, I have generated data in the laboratory to suggest that azacitidine enhances the activity of venetoclax in DLBCL and DHL cell lines, providing pre-clinical rationale to test this combination in patients." Recent genetic analyses have also revealed that DLBCL is very heterogeneous. Dr. Crombie also plans to test whether genetic profiling can help predict which patients are most likely to respond to this combination as well as other targeted therapies that are likely to be effective in this disease.

Dr. Crombie first became interested in lymphoma research during medical school at the University of Massachusetts while working in the laboratory of Dr. Andrew Evens (now at Rutgers Cancer Institute and a 2018 LCRMP Co-Chair). As a Hematology/Oncology Fellow at Dana-Farber Cancer Institute, she has further developed both her translational research skills under Dr. Letai and Dr. Margaret Shipp, and her skills as a clinical researcher, under Drs. Phillippe Armand, Matthew Davids, and LRF Scientific Advisory Board member Ann LaCasce. "My basic science and clinical research projects are complementary, as I have been identifying optimal combination therapies to use for the treatment of DLBCL, while also developing the framework to translate these treatments to the clinic," she says, adding that she hopes to ultimately become an independent, clinical investigator who also collaborates with laboratory-based investigators.

Dr. Crombie sees her participation in the LCRMP as an "incredible opportunity" to continue her development towards an independent career. "The LCRMP provides additional education in clinical trial development, specifically within the field of lymphoma, and valuable career development support from leaders within the field. This program provides the framework to effectively design and implement both my proposed project and other future clinical trials, and to apply for future grant funding."

Brian Greenwell, MD
Emory University/
Medical University of South Carolina
LCRMP

Testing A New Combination Therapy for Older MCL Patients

Mantle cell lymphoma (MCL) is most commonly diagnosed in patients age 65 and older. As a result, many MCL patients have difficulty tolerating some of the intensive therapies and stem cell transplant that have been responsible for much of the improvement in MCL survival rates. The rise of therapies such as bendamustine and rituximab has helped some patients who need less intensive therapies, but there is still room for improvement. Dr. Greenwell and his colleagues want to combine bendamustine with two newer targeted agents, obinutuzumab (Gazyva) and venetoclax (Venclexta). Dr. Greenwell says, "We want to test this for therapeutic tolerability as well as for efficacy and disease control, including the ability to control minimal residual disease (MRD; small amounts of lymphoma that are not detectable with radiological techniques)."

Dr. Greenwell received his MD from the Medical University of South Carolina (MUSC), before a residency at Washington University in St. Louis /Barnes-Jewish Hospital, and his fellowship at Emory University. He draws inspiration from his own patients as well as his own family. "My mother is a lymphoma survivor, having battled through progression and a bone marrow transplant from her sister. She is now doing well 30 years out from her transplant – and has been an instrumental part of who I am." Dr. Greenwell also notes that the LRF's support for his mentor, Dr. Jonathon Cohen (a participant in the first LCRMP Workshop in 2014, as well as a 2016 Career Development Award recipient) has indirectly provided benefit to his own career. "Dr. Cohen's experience with LRF and subsequent career success have provided a groundwork and road map for my future career success," Dr. Greenwell says. "The LCRMP will now provide me an opportunity for critical review of current research and help to improve my own future clinical research projects."

In July 2018, Dr. Greenwell plans to return to MUSC as a faculty member. "I hope to develop a robust program in clinical investigation at MUSC, building it much as mentors Drs. Christopher Flowers (and LRF Scientific Advisory Board member) and Mary Jo Lechowicz built the program at Emory, and develop collaborations between the clinic and labs based at MUSC's Hollings Cancer Center." Dr. Greenwell further notes that his time at Emory with Dr. Cohen, Dr. Flowers, and Dr. Kristie Blum, all of whom have been LRF Scholars or faculty in the LCRMP helped impress upon him the importance of strong mentors in a medical research career. "I will continue to rely on their mentorship as well as other LRF leaders, and hopefully have the opportunity to 'pass on' the mentorship."

NEW GRANTEE PROFILES

Shalin Kothari, MD
Roswell Park Comprehensive Cancer Center
LCRMP

First-in-class therapy for mantle cell lymphoma

Despite recent advances in available therapies, patients with the aggressive forms of mantle cell lymphoma (MCL) generally survive less than a decade after their diagnosis. Dr. Kothari's LCRMP project is testing the addition of pevonedistat, a first-in-class therapy targeting the enzyme which activated the protein NEDD8. Working as an NEDD8-activating enzyme (NAE) inhibitor, Dr. Kothari believes adding pevonedistat to standard therapies rituximab and ibrutinib will help slow cancer growth. "Cancer cells proliferate with the help of certain cellular proteins. Pevonedistat is a novel drug that triggers a self-killing mode in cancer cells (apoptosis) by paralyzing the processing of such proteins by a proteasome – essentially a cellular internal garbage disposal system," Dr. Kothari explains. Having already published results showing that this combination has been effective and safe in a laboratory setting, Dr. Kothari and his colleagues hope a clinical trial will demonstrate that this combination effectively prolongs survival for MCL patients.

Dr. Kothari received his MD from Gujarat University in his native India before a residency at State University of New York (SUNY) Upstate and his fellowship at Roswell Park Comprehensive Cancer Center, where he is Chief Administrative Oncology Fellow. He credits his mentor at Roswell Park, Dr. Francisco Hernandez-Ilizaliturri with helping him shape and hone his research on this project. Dr. Kothari further notes that in participating in the LCRMP, "the skillset that I acquired will help prevent common errors and challenges faced by young physician-scientists, hindering their success. The opportunity to participate in the multidisciplinary small groups with experts in the field also enhanced my achievement of these skills and milestones."

Dr. Kothari intends to continue his career as an academic researcher, noting that in ten years' time he sees himself leading both clinical and translational projects to support research efforts in lymphoma. He adds that the history of lymphoma treatment – with Hodgkin lymphoma achieving a cure in the 1960s – inspires him to push for further developments. "It was the perseverance of researchers back then that led to the first breakthroughs. Now it is time for the current generation of oncologists to raise that bar, push that envelope, and save more lives."

Ryan Lynch, MD
University of Washington
LCRMP

Improving the efficacy of checkpoint inhibitors in HL

Checkpoint inhibitors such as pembrolizumab (Keytruda) have demonstrated some success in Hodgkin lymphoma (HL) by disrupting a tumor cell's expression of the protein PDL1. Although successful, complete remissions with pembrolizumab alone are rare; Dr. Lynch and his colleagues are testing the combination of pembrolizumab and a PI3K inhibitor, TGR-1202 in patients with relapsed and refractory HL. "Inhibiting the PI3K protein may have a direct effect on the tumor cell as well as augment the immune response against the tumor with pembrolizumab," Dr. Lynch says.

Dr. Lynch received his MD from Boston University before a residency at Washington University in Saint Louis. During his residency, he became interested in lymphoma research through his work with Dr. Kenneth Carson on a project involving diffuse large B cell lymphoma (DLBCL) patients at Veterans Administration hospitals. His experiences on that project led in turn to a hematology/oncology fellowship at Stanford University, where he worked with Drs. Ranjana Advani (a current LRF Scientific Advisory Board member) and Saul Rosenberg (an SAB Member Emeritus), both leaders in the pioneering treatments for Hodgkin lymphoma. His LCRMP project was generated from Dr. Lynch's desire to help HL patients who don't respond to current therapies. "Despite the approval of three new drugs for HL in the past decade, long term cure still eludes many patients who relapse after initial therapy," he notes.

Aiming for a career as an established clinical researcher in lymphoma, Dr. Lynch hopes his participation in the LCRMP will aid him in that goal through the mentorship from the program's expert faculty. "Connections made through LRF will be critical in these early stages of my career as I get involved in multicenter clinical trials and clinical research projects."

Dr. Lynch finds hope in the approval of multiple new targeted therapies and immunotherapies for lymphoma, especially in what it means for patients with relapsed or refractory disease. "The recent approvals have shown that through the work of clinicians and patients on clinical trials, we can make progress in the treatment of lymphoma. For certain patients, particularly those that have failed multiple therapies, even modest improvements can make a huge difference."

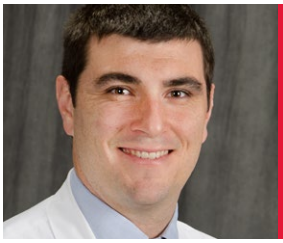
Priyanka Pophali, MD
Mayo Clinic, Rochester
LCRMP

Exploring the effects of exercise on outcomes for survivors

Patients who achieve a complete remission of their lymphoma are still at risk for additional health complications even if they do not relapse. Regular exercise has been demonstrated to reduce fatigue and improve quality of life in cancer survivors, but the exact effects and degree of improvement has not yet been studied in lymphoma survivors specifically. Dr. Pophali's LCRMP project will look at changes in survivor exercise routines and their effect on patient outcomes both through studying data in the Lymphoma Molecular Epidemiology Resource (MER) database, a resource developed by Dr. Pophali's home institution, Mayo Clinic, and through a pilot study testing whether receiving a one-time exercise prescription from their physician will impact survivors' physical activity and, subsequently, their health outcomes. "If we are able to increase a survivor's level of physical activity through a practical, one-time exercise intervention that is tailored to the individual's needs, it will allow lymphoma survivors to play a proactive role in improving their own outcomes," Dr. Pophali notes.

Dr. Pophali's career in medicine was inspired by her father, a hematologist/oncologist in their native India. She received her MBBS (an MD equivalent degree) from Indira Gandhi Government Medical College in her native India before working as a research associate at the National Institutes of Health, where she studied long term complications in survivors of hematopoietic stem cell transplant. Later as a resident at Cleveland Clinic, she began working on outcomes for early stage Hodgkin lymphoma patients. Dr. Pophali continued to pursue her interest in lymphoma outcomes research with her current fellowship at Mayo Clinic. "As I got to know my patients in the continuity clinic, I realized that cancer is a life changing diagnosis and impacts lives even after the disease has been cured," Dr. Pophali says. "Research that understands survivorship issues and attempts to bring survivors' lives closer to normal is a very worthwhile career endeavor for me."

Dr. Pophali's participation in the LCRMP was prompted by a desire to better understand clinical trial design and how to navigate the practical issues around conducting clinical studies. "I enjoyed getting to know colleagues outside my institution who share similar visions for lymphoma patients and exposing myself to new ideas from colleagues who work on different aspects of lymphoma research," she adds. "The skills and experiences I gained through the workshop will help me to further my career goal of contributing meaningfully to the field of hematology, particularly lymphomas."



Patrick Reagan, MD
Wilmot Cancer Institute
University of Rochester
LCRMP

Combating ibrutinib resistance in B-cell NHL and CLL

Patients with B-cell Non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) sometimes have a mutation in a gene called TP53 that has been demonstrated to cause resistance to chemotherapy treatments. "Since lymphomas in which this gene works normally can be treated effectively with chemotherapy, restoring its function could potentially enhance the ability to control these diseases," Dr. Reagan notes. His LCRMP project will study a therapy called APR-246, which binds to TP53 and has been shown in laboratory studies to restore normal function of that gene. Dr. Reagan and his colleagues will test a combination of APR-246 with ibrutinib in B-cell NHL and CLL patients who have mutated TP53, in the hopes that it will allow these patients to experience the full effectiveness of ibrutinib and other standard therapies. "Effective treatments for my patients who have TP53 mutations is a major unmet need and I wanted to pursue a clinical trial concept that could possibly benefit this group," he says.

Dr. Reagan received his MD from State University of New York (SUNY) Upstate Medical University, before a residency at the University of Virginia, where he served as Chief Resident, before a fellowship at Wilmot Cancer Institute of the University of Rochester, where he is currently an Assistant Professor of Medicine. The number of major scientific and therapeutic advances in lymphoma over the past several years prompted Dr. Reagan's interest in lymphoma research. "I think that we are learning more about the biology of lymphomas and the reasons why our current treatments do not currently work well in certain patients," he says. "As we continue to understand this, I think that we will identify more therapies that are more effective and hopefully have fewer side effects."

Dr. Reagan's interest in the LCRMP began as an interest in developing connections with the faculty and his fellow Scholars in the program, as well as an interest in increasing his involvement with the Lymphoma Research Foundation. "Participating in the LCRMP was exciting, and the feedback I received was critical to making my trial as successful as it can be," he says. "I hope to continue designing early phase clinical trials for patients with high risk lymphomas, as well as building collaborations with colleagues at my institution and throughout the country."

Ash A. Alizadeh, MD, PhD, Delivers MCL Workshop Keynote Address

The Workshop's keynote speaker was Ash Alizadeh, MD, PhD, Associate Professor of Oncology at Stanford University. Dr. Alizadeh discussed how MCL tumor DNA circulating in the bloodstream (ctDNA) collected through a "liquid biopsy" blood draw can be used to predict risk during monitoring for individual patients. While tumor biopsies can provide helpful information, they are invasive and are not without risk for the patient. Furthermore, biopsies from a single site may not adequately capture tumor heterogeneity.

Early studies have validated the accuracy of ctDNA testing and its capacity to predict treatment failure following transplant. Dr. Alizadeh provided an overview of how the technology has evolved to its current state, as well as how it can be used for more continuous monitoring of cancer and to predict outcomes of treatments. Dr. Alizadeh and his colleagues at Stanford helped develop one of these advances, called Cancer Personalized Profiling by Deep Sequencing (CAPP-Seq). This technology has helped improve the sensitivity and predictive power of liquid biopsy for lymphomas and other tumors by following many mutations across more than 300 genes.

As technology continues to evolve, Dr. Alizadeh predicts that ctDNA will emerge as a valuable tool for tumor genotyping at diagnosis, treatment selection and predicting response, monitoring, and early detection of relapse through identification of emergent MCL subclones resistant to treatment. At each stage in the process, ctDNA analysis can be used to generate a continuous individualized risk index (CIRI) that will permit a more dynamic patient assessment across tumor types.

Ash Alizadeh, MD, PhD of Stanford University

In addition to the in depth discussion of liquid biopsy, Dr. Alizadeh shared results of a study that used "peptidomic profiling" to identify protein antigens on the surface of MCL cells that may be used to immunize patients during remission so that if the MCL relapses, the cells will be recognized and destroyed by the immune system. Identifying these new antigens paves the way for new immunotherapies.

MCL Workshop

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some ATM protein functions that may play important roles in the late onset of MCL. Further research is underway to understand the role of mutated ATM in mice that overexpress cyclin D1, and to determine if ATM mutation in the MCL setting leads to a favorable response to selective chemotherapy.

Arshia Soleimani, MD (Tulane University) discussed her research on the role of the membrane protein CD5 in MCL. Though up to ten percent of MCLs lack CD5 entirely, the function of this protein in MCL is unknown. In order to understand how the absence of CD5 contributes to clinical outcomes, more than 800 articles were screened and 323 cases of CD5-negtative MCL reported in the literature were analyzed. The primary differences between CD5-negative MCL and conventional MCL were a lower level of expression of SOX11 (44 percent) than in conventional MCL (90 percent), the degree of kappa light chain restriction in CD5-negative MCL was higher, and IGHV mutation was seen in over 40 percent of CD5-negative MCL. Together, these results indicate that CD5-negative MCL may have a unique biology, and that it may be sufficiently different to prompt consideration of a different treatment approach. To assess the importance of CD5 in overall survival (OS), reports from 79 patients were evaluated and the median OS for CD5-negative MCL was found to be greater than 14 years, a substantial difference from the historic OS for conventional MCL of three to five years. Further evaluation of these 79 reports showed that this increase in OS was independent of other prognostic markers SOX11 and Ki-67, raising the question of whether CD5 could be used as an independent biomarker for indolent MCL. While the exact role of CD5 remains unclear, this study highlights the need for additional investigation.

Mariusz Wasik, MD (University of Pennsylvania) presented a case study in which MCL is thought to have mutated and changed into another type of malignancy, sarcoma. While this type of change, called transdifferentiation, has been reported in the past, the conversions described have been limited to those between closely related immune cells. In this report, the conversion is to a much more distantly related cell type. Here, the MCL patient was treated with multiple diverse therapies over the course of twelve years, and eventually developed poorly differentiated sarcoma (PD-Sc). To determine if these two malignancies were related, researchers compared the gene expression profiles, genome sequences, and DNA methylation patterns of the patient's early MCL, late MCL, and PD-Sc cells. The MCL and PD-Sc cells contained several similar genetic abnormalities, indicating that the two cell lines are more closely related than

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expected for cells from malignancies of independent origin. Most dramatic, however, was the change in DNA methylation pattern. DNA methylation represents another layer of control in gene expression, termed epigenetic programming, which can express or silence a particular gene by changing whether the cell's transcription machinery can access it. When comparing the MCL and PD-Sc cells, the patterns of gene methylation was widely variable, supporting the hypothesis that epigenetic reprogramming can permit clonal malignant cells to differentiate into another malignancy. This transdifferentiation permits these cells to escape initial treatments, but can render them vulnerable to a different therapy designed to treat malignancies more closely related to the new lineage.

Birgitta Sander, MD, PhD (Karolinska Institutet) described the clinical and functional impact of S1PR1 mutations in recurrent MCL. S1PR1 is expressed by both normal mantle zone B cells and MCL, and is responsible for controlling the exit of lymphocytes from the marrow to the blood and lymph in response to a chemical gradient of the S1PR1 ligand, SP1. In an initial analysis of 27 samples from 13 patients, eleven of which were relapse biopsies, S1PR1 was found to be one of 25 recurrent mutations. In an expanded study of over 200 samples, paired samples from 17 patients were analyzed, and in eight percent of samples, S1PR1 was found to be mutated; in each case, mutations were such that expression or function of the protein significantly diminished. In an MCL cell line, diminished S1PR1 expression resulted in reduced migration in response to SP1. Researchers hypothesize that this effect is linked to MCL pathology because these S1PR1 mutated cells could be retained in the supportive microenvironment of the tissue where they are less susceptible to chemotherapy. In a recent clinical trial S1PR1 mutations were present in 5.9 percent of diagnostic biopsies and in 14.6 percent of relapse biopsies. Together, these data support the hypothesis that dysfunctional mutations in S1PR1 promotes retention of malignant MCL, thus preserving a "minimal residual disease reservoir" that later may give rise to a relapse.

Thomas Habermann, MD (Mayo Clinic) concluded the first session with a report that identifies mutations within three genes (TNFRSF25, TRAF5 and RELB) as genetic markers associated with overall survival (OS) in MCL. These genes produce proteins that comprise one of two overactive pathways in MCL, the tumor necrosis factor (TNF) and nuclear factor-NF-kB (NF-kB) pathways. In an initial study, researchers analyzed 40 candidate genes in the DNA of 39 MCL patients in the NCI-SEER dataset, and following adjustment for individual patient MIPI and treatment received found that eight genes were associated with differences in OS. To verify these associations, DNA from a larger group of 101 patients from the Molecular Epidemiology Resource (MER) of the University of Iowa and Mayo Clinic Lymphoma Specialized Program of Research Excellence (SPORE) was analyzed, and the association with OS was retained by three of the eight genes from the initial analysis. TNFRSF25 and TRAF5 mutation was found to be associated with inferior survival, while RELB mutation was associated with superior survival. Together, these findings identify three genes that may be further evaluated as drug targets and build understanding of MCL disease progression.

MCL Novel Pathways and Targets

Moderator: Elias Campo, MD, PhD, Hospital Clinic de Barcelona

Researchers continue to identify novel pathways that can be targeted in the treatment of MCL. As new pathways are defined and the nuances of previously recognized pathways are uncovered, strategies for treatment may continue to evolve.

Lalit Sehgal, PhD (University of Texas MD Anderson Cancer Center) shared results from his research on the role of tumor microenvironment on relapsed and refractory MCL. His research used the recently developed system for culturing, or growing, primary MCL cells in the lab. This system requires that MCL cells be co-cultured with mesenchymal stromal cells (hMSC), supportive cells that also reside in the bone marrow. Using this system, Dr. Sehgal's research group showed that in the co-culture system, MCLs were able to survive for four weeks, and that MCL-initiating cells (MCL-ICs) constituted one percent of the MCL population. Using this system, researchers identified the signaling molecule FGFR-1 as important for maintaining growth and survival of MCL in the microenvironment. Importantly, FGFR-1 is known to be associated with poor overall and progression-free survival in R-CHOP-treated MCL. In this study, researchers showed that inhibition of FGFR-1 decreases growth and proliferation and sensitizes MCL cells to chemotherapeutic drugs. Identification of these signals and their role in MCL-IC survival paves the way for design of treatment that disrupt MCL and potentially for curative treatment strategies.

Fengdong Cheng, MD (The George Washington University) discussed research that led to identification of bromodomain (BRD)-specific inhibitors as a novel avenue for targeting MCL. BRDs are architecturally distinct regions of proteins that often have a shared function. BRDs are present in a wide range of proteins that "decode" the pattern of histone acetylation that controls gene expression. This type of epigenetic gene regulation is commonly disrupted in MCL, leading researchers to explore the potential role of BRDs. In the research presented by Dr. Cheng, inhibition of BRD enhances the function of T-cells in the immune system, while leading to a decrease in expression of the protein

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PD-L1, which promotes MCL survival by immunosuppression. In addition, BRD inhibition increases the levels of inflammatory markers. These two activities make MCL treated with BRD inhibitors more susceptible to clearance by the immune system. These features make inhibition of BRD a promising target for MCL therapies.

Elisabeth Silkenstedt, MD (University Hospital Ludwig Maximilian University Munich) presented work on characterization of the impact of NOTCH1 mutations in MCL. In addition to the overexpression of cyclin D1 characteristic of MCL, several secondary genetic alterations are known to contribute to pathogenesis. Among them, NOTCH1 is associated with shorter overall survival (OS) and is present in five to ten percent of MCL. Within this work, researchers identified molecules that activate NOTCH1 in MCL and showed that the NOTCH1-mediated enhancement of tumor angiogenesis as well as several other pathways that contribute to the aggressiveness the disease can be inhibited by antibodies designed to inhibit NOTCH. Together these findings suggest that inhibition of the NOTCH1 signaling pathway may provide effective treatment for a subset of patients with NOTCH1 mutations.

Chengfeng Bi, MD, PhD (University of Nebraska Medical Center) presented the Rac1-PAK axis as a potential novel therapeutic target in MCL. The Rac1 protein is important for a number of cell adhesion pathways and its overexpression in MCL is associated with a poor clinical outcome. Depleting the expression of Rac1 in MCL cells decreased cell proliferation and increased sensitivity to chemotherapy agents. In addition, when two "downstream" proteins in the Rac1 pathway, PAK1 and PAK2, are inhibited, MCL sensitivity to chemotherapy was dramatically increased. Future endeavors will focus on identifying the downstream signaling of Rac1-PAK axis and the potential of PAK inhibition as a promising strategy for enhancing sensitivity to chemotherapy and other targeted therapies in the treatment of MCL.

Jimmy Lee, MD (The University of Chicago) discussed work on identifying the mechanisms of ibrutinib resistance in MCL. In spite of high clinical efficacy, nearly all patients acquire ibrutinib resistance. In this study, comparison of gene profiles in both sensitive and resistant MCL during treatment with ibrutinib confirmed known mechanisms of resistance and also identified another gene, Myc, that fits the pattern of resistance. Researchers found that knocking down Myc expression inhibited MCL growth and induced cell death in ibrutinib-resistant cells. Researchers were able to repeat this outcome when using an antibody to inhibit an upstream protein, HSP90, indirectly inhibiting Myc. This discovery revealed a new target for treatment of ibrutinib-resistant MCL.

Carrie Franzen, PhD (The University of Chicago) described research on the role of Rac2 in cell adhesion and explained how cell adhesion is connected to the constitutively (continuously) active B-cell receptor signaling in MCL. Ibrutinib works by targeting B-cell signaling through Bruton tyrosine kinase (BTK) inhibition and causing a transient increase in the number of cells that move from the lymphoid tissue to the periphery. This shift is thought to be promoted by a reduction in the MCL cells' ability to adhere to the stroma (tissue). In this work, researchers identified the proteins involved in mediating the concomitant reduction in BCR signaling and adhesion. By identifying these proteins and their role in MCL, researchers have provided an additional avenue for therapeutic development.

MCL Therapeutic Resistance and Personalization of Therapy

Moderator: Robert Baiocchi, MD, PhD, The Ohio State University

Research efforts have led to new insights on the drivers of disease heterogeneity in MCL and the events that lead to and maintain ibrutinib resistance. Together these findings support research and clinical trials that lead to more efficient and effective treatment of MCL that is tailored to disease subtypes and eventually to individual patient disease.

Qian Zhang, MD, PhD (University of Pennsylvania) presented a new cultured MCL cell line that maintains key features of primary malignant cells. This finding is of particular importance because when cells are cultured in the lab, they often accumulate mutations or epigenetic changes that render them of little practical use in evaluating treatment efficacy. In this study, concentrations of secreted cytokines, DNA methylation patterns, and gene mutation profile were maintained following extended culture of the cell line in the lab. This cell line, MCL-RL, contains several novel mutations and maintains a relevant sensitivity profile to kinase inhibitors. Together, these findings support the use of MCL-RL cells in research exploring MCL physiology providing another tool for further developing understanding of MCL.

Seung-Cheol Lee, PhD (University of Pennsylvania) discussed a novel method for evaluating patient response to therapy. Currently, response is evaluated by assessing tumor volume using imaging, a method that is somewhat limited given that volume changes occur relatively late after effective inhibition of the targeted kinase. In clinical care, the inability to identify metabolic changes indicating that therapy is effective prevents clinicians from stopping cessation of treatment that is ineffective or making informed, personalized addition of therapies that target alternative pathways. In this study, by examining cell metabolic changes known to contribute to MCL, researchers were able to distinguish ibrutinib-sensitive and ibrutinib-resistant cells. This finding supports the use of imaging that is capable of monitoring cell metab-

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olism, as it may effectively determine the impact of treatment early and has the potential to identify drug-resistant cells and whether or not they may be effectively targeted by alternative therapy.

Selina Chen-Kiang, PhD (Weill Cornell Medicine) provided an update on studies exploring the therapeutic application of inhibiting the cell-cycle regulator cyclin-dependent kinase 4 (CDK4) in resistant MCL. In previous laboratory studies, her team showed that inhibition of CDK4 restored sensitivity of resistant MCL cells to ibrutinib. In this presentation, Dr. Chen-Kiang shared early findings from a phase I clinical trial in patients on the effect of ibrutinib and the CDK4 inhibitor palbociclib (a treatment used in breast cancer). Overall, the response to treatment was rapid and durable and the rate of relapse in patients who received the combination treatment was lower than patients who received ibrutinib or palbociclib alone. To learn more, a larger phase II clinical trial is currently underway.

Jianguo Tao, MD, PhD (H. Lee Moffitt Cancer Center) discussed the outcomes of a study designed to identify the drivers of ibrutinib resistance in MCL. Through analysis of several resistant cell lines and patient samples, researchers determined that there is no single or set of drivers. Rather, resistance arises from a large-scale remodeling of the cellular networks that then lead to aggressive proliferation of MCL. This type of mechanism presents significant challenges for developing individual inhibitor treatments; however, targeting the process of remodeling itself by preventing the global increase in gene expression that precedes the development of resistance has the potential to slow or prevent resistance. Work is currently underway to identify early markers of resistance that can be targeted before the required remodeling occurs.

Bijal Shah, MD, (H. Lee Moffitt Cancer Center) reported on the use of cell-based drug screening to tailor therapy to specific patients. MCL is a complex and heterogeneous disease that has a wide range of genetic mutations that are thought to shape susceptibility to treatment. While work to identify these networks is informative for development of novel therapies, their use in treatment selection is problematic. Instead, MCL cells from patients can be tested for sensitivity to a range of treatments by screening cultured cells prior to treatment. Using a tool called EMMA, Dr. Shah and colleagues can test sensitivity to up to 127 drugs within five days. Sensitivity predicted by EMMA correlates well with observed clinical outcomes in patients, and may be a first step in personalized therapy selection based on cell response to treatments in the lab prior to administration of therapy.

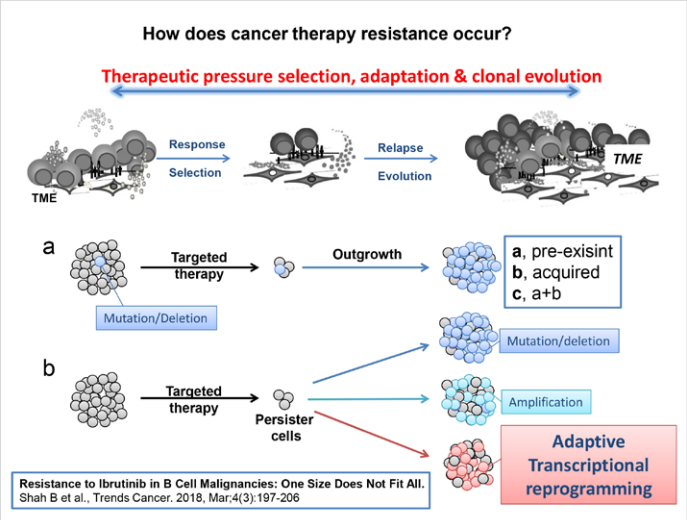

Diagram of the development of cancer therapy resistance. Illustration courtesy Jianguo Tao, MD, PhD, Moffitt Cancer Center.

MCL Outcomes Research

Moderator: Bijal Shah, MD, H.Lee Moffitt Cancer Center

Clinicians reported several population-level analyses that together strengthen understanding of how individual patient characteristics impact MCL treatment outcomes.

Thomas Habermann, MD (Mayo Clinic) reported on studies evaluating the impact of the time from MCL diagnosis to treatment initiation (DTI) on disease outcomes. The study included 271 patients and assessed event free survival (EFS), progression, initiation of another lymphoma therapy, or death from any cause. The study found that a short DTI is strongly associated with poor outcomes and that patients with longer DTI have less aggressive clinical characteristics and better outcomes. Importantly, this pattern persists regardless of therapy. The findings from this study provide a lens through which the results of clinical trials may be viewed and may inform clinical practice.

Dr. Habermann also presented findings from a recent study on the impact of autoimmune diseases such as rheumatoid arthritis or Crohn's disease on treatment outcomes for MCL. Autoimmune conditions are known to be associated with an increased risk of lymphoma, but their impact on disease progression is less clear. In this study, researchers analyzed data from a "natural history" study designed to track variables that may influence disease to uncover any relationship between autoimmune diseases and MCL. Data showed that MCL patients with a history of B-cell-mediated autoimmune disease, primarily rheumatoid arthritis, showed inferior overall and event free survival. These results highlight the need for additional studies to better understand the nature of the impact of these comparatively common autoimmune diseases on MCL natural history so that unique elements of disease management for these patients may be defined.

Max Goldman, BA (Emory University) examined the practice of surveillance imaging in MCL. During remission, the patient is most often placed under "surveil-

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lance" and is periodically evaluated using CT or PET scan to detect relapse. To better understand if there is a role for surveillance imaging in MCL, 801 images for patients in their first remission were collected; of these images, only 3.5 percent led to a diagnosis of relapse. This outcome is consistent with the clinical observation that most relapses are diagnosed when the patient presents with clinical symptoms. This rate of detection is similar for both PET and CT scan, and each modality produced a large number of false positives. This study in MCL mirrors the findings for all non-Hodgkin lymphomas, demonstrating that surveillance imaging does not confer a significant survival benefit to patients. The findings from this study support the most conservative application of surveillance imaging, as there is no significant survival benefit and imaging is associated with high emotional and financial burden as well as unnecessary exposure to radiation.

Andrew Ip, MD (Emory University) discussed the impact of comorbidities on the outcome of autologous stem cell transplant (ASCT). Though the validated Hematopoietic Cell Transplantation Comorbidity Index (HCT-CI) for lymphoma indicates that ASCT is appropriate for many fit patients under 60, the recent emergence of new therapies for this patient group raises the question of whether the impact of comorbidities on ASCT outcomes in MCL remains the same. Researchers analyzed data from Emory Winship Cancer Institute from MCL patients who received ASCT from 2010–2017. Findings indicate that consistent with earlier recommendations, when managed appropriately, comorbidities should not be a barrier to ASCT. One potential exception is obesity, which was associated with inferior survival indicating that additional interventions may be appropriate for these patients.

Krithika Shanmugasundaram, MD (Emory University) discussed the impact of therapy intensity on survival for MCL patients deferring therapy. While there are data showing that patients may safely defer therapy for indolent disease, there is little information surrounding the intensity of therapy once it is initiated. In the work presented by Dr. Shanmugasundaram, outcomes for patients who received intensive therapy (high-dose cytarabine as part of induction regimen or autologous stem cell transplantation in first complete or partial remission) were compared to outcomes for patients who received less intense therapy. This comparison revealed no significant difference in overall or progression free survival based on the intensity of therapy. These findings indicate that less intensive therapy may be appropriate in patients who have deferred treatment for their disease.

Jonathon Cohen, MD (Emory University) presented findings from the first report of the Lymphoma Epidemiology of Outcomes (LEO) Cohort, an observational cohort study that includes eight academic sites throughout the United States. 270 MCL patients enrolled between 2015 and 2018 are included in this report. For each patient, data on tissue samples at baseline and treatment, treatment received, and outcomes were collected. Analysis of collected data reveals heterogeneity in MCL presentation and management in the United States, highlighting a need for stratification criteria to support first-line treatment selection. Strong study accrual is continuing, and this resource can be utilized by interested investigators with clinical, translational, or survivorship questions.

MCL Prognostic and Predictive Biomarkers

Moderator: Brad Kahl, MD, Washington University Medical School in Saint Louis

In a series of presentations on prognostic and predictive biomarkers, clinical scientists provided updates on new approaches to the collection and analysis of patient samples to more accurately stratify patients and predict clinical response.

Hilka Rauert-Wunderlich, Dr. rer. nat. (University of Wuerzburg) discussed results from a study exploring the utility of the MCL35 nanostring assay for stratifying MCL patients into low-, standard-, and high-risk groups. In a study of 169 MCL patients from the European Mantle Cell Lymphoma Network, a set of 35 "proliferation signature" genes was analyzed for each patient and the results were compared to patient prognosis that was generated from two other validated tools, the Mantle Cell Lymphoma International Prognostic Index (MIPI) and Ki-67 proliferation rate. Researchers found that while the MCL35 assay provided a prognosis that was in agreement with other established measures, it also provided additional information that permitted stratification of patients. Stratification is not only important for better understanding prognosis, but for informing the organization of clin-

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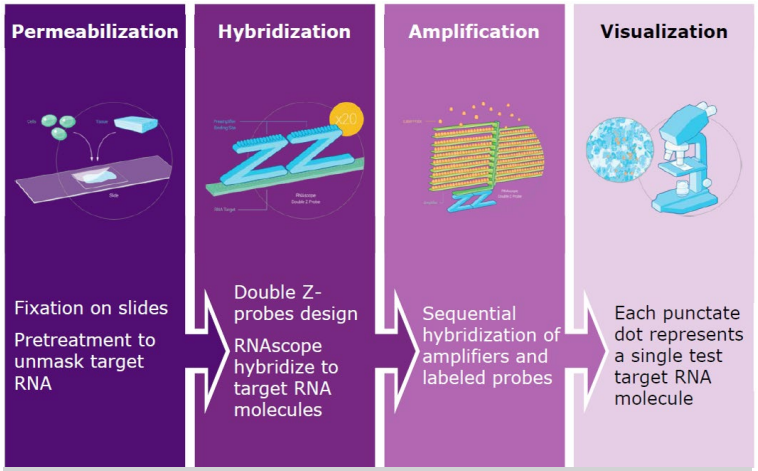

Depiction of the RNA scope process described in Dr. Quintanilla-Fend's presentation. Illustration courtesy Leticia Quintanilla-Fend, MD, University of Tuebingen.

ical trials that assess treatment efficacy for patients with different risk levels.

Leticia Quintanilla-Fend, MD (University of Tuebingen) presented a study aimed at better understanding the prognostic role of the gene SOX11 in MCL. While SOX11 expression in MCL is important for the identification of important subsets of MCL in the clinic, how it is related to disease prognosis is controversial. Perhaps one explanation for the controversy is that methods to measure its level in MCL cells are not quantitative, and thus do not provide specific information about protein levels. Rather, current methods are restricted to simply indicating the presence or absence of the protein. In this study, researchers worked to establish a more sensitive test via the RNAscope process so that SOX11 levels can be measured in tissue sections. Using this test, researchers found that SOX11 expression is variable in MCL, an indicator that levels may be associated with different behavior in malignant cells. Having developed a reliable test to differentiate levels of SOX11 expression, researchers are now able to better evaluate the role of this protein in disease and determine if it is a reliable prognostic marker.

Elias Campo MD, PhD (Hospital Clinic de Barcelona) reported on the development of a molecular test to more reliably identify both conventional MCL (cMCL) and the clinical and biological subtype Leukemic non-nodal MCL (nnMCL). Currently, there is a lack of clinical tools that recognize these two subtypes and little information about genetic drivers of progression and outcomes. In this study, researchers developed and validated a 16-gene assay to differentiate between cMCL and nnMCL. Sequential samples taken from patients over the course of disease were evaluated and the assay was found to make prognostic evaluation achievable with more robust genetic analysis of known genetic alterations (such as TP53 and CDKN2A); with further study, this may aid in treatment decisions. This assay is especially useful in evaluating leukemic samples, where the current proliferation signature used to determine MCL prognosis is not effective. Development of this assay not only improves understanding of disease subtypes and their prognosis, but can differentiate between subtypes in the setting of a clinical trial where different subtypes may respond differently to treatment.

Anita Kumar, MD (Memorial Sloan Kettering Cancer Center) discussed methods for assessing minimal residual disease (MRD) in patients who have received combined immunotherapy and ASCT. Currently, MRD measured using a test called allele-specific oligonucleotide polymerase chain reaction (ASO-PCR) is a strong predictor of relapse, but this test is patient-specific, takes time, and requires a specialized laboratory. Technologies that test for the presence of MRD using deep-sequencing of the B-cell receptor DNA that is circulating in the blood may be potentially more sensitive and easier to implement in the clinical setting. This study evaluated the performance of this DNA-sequencing based MRD assay in a group of uniformly treated MCL patients. A total of 166 patient samples were analyzed using the assay to predict clinical relapse in MCL and found that detection of DNA in lymphocytes and/or circulating in the blood was found to be predictive of relapse. The MRD test was more sensitive using DNA from inside circulating cells versus cell-free DNA circulating in the blood, likely due to the fact that MCL commonly has circulating lymphocytes in the blood. Continued validation of this method may lead to its use for less invasive patient monitoring.

MCL Clinical Trials

Moderator: Martin Dreyling, MD, PhD, University Hospital LMU Munich

In a series of presentations on outcomes of recent clinical trials, researchers shared promising results from early-phase studies and discussed how findings may eventually inform treatment algorithms.

Connie Batlevi, MD, PhD (Memorial Sloan Kettering Cancer Center) discussed results from a phase I/IB study on ibrutinib and buparlisib combination therapy in MCL. In this study, two doses of ibrutinib within the context of combination therapy were tested to determine safety and efficacy. When two drugs are given in combination, it is important to ensure that the any additive side effects are controlled and that there is no synergistic activity that makes the combination unsafe. In addition, the most effective and best-tolerated dose must be determined. Here, 15 patients were evaluated for response to the combination; eleven patients achieved complete response (CR) and four patients achieved a partial response, indicating that the combination of ibrutinib and buparlisib holds promise for MCL treatment.

Anita Kumar, MD (Memorial Sloan Kettering Cancer Center) presented preliminary results from a trial evaluating the use of lenalidomide in combination with cytotoxic induction chemotherapy followed by rituximab and lenalidomide maintenance in the initial treatment of MCL. Of the 20 patients who have completed treatment, 95 percent are PET-negative and have achieved a complete remission. After a median follow-up of 15 months, 18 have evidence of ongoing remission. Early results of this study indicate that lenalidomide and sequential chemotherapy followed by lenalidomide and rituximab maintenance is a promising therapy for MCL. Data analysis from this study is ongoing.

Manali Kamdar, MD, MBBS (University of Colorado) provided an update of results from a study comparing bendamustine-rituximab (BR) to R-HyperCVAD/MTX/ARAC (RH) prior to ASCT. Initial results showed that comparable response rates and MRD negativity could be achieved by either treatment regimen, though RH exhibited more toxicity and inadequate stem cell mobilization, a feature that makes RH less desirable before transplant. This updated analysis includes 4.8 years of follow-up data, and showed a five-year overall survival rate of 79 percent

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for BR and 81 percent for RH. These data indicate that BR is an excellent backbone for induction therapy in transplant eligible patients and needs to be explored further in larger phase III trials.

Brad Kahl, MD (Washington University Medical School in Saint Louis) continued the discussion of induction therapy before transplant by discussing results from a pilot study evaluating the performance of BR when it replaces R-CHOP in an established treatment regimen that includes alternating cycles of R-MaxiCHOP with R-high-dose cytarabine (HiDAC-R). The rationale for this replacement is that BR appears to be superior to R-CHOP in MCL. This study evaluates whether alternating cycles of BR and HiDAC-R outperform the established regimen in patients eligible for transplant. Researchers evaluated stem cell mobilization and response to treatment. The BR and HiDAC-R regimen exhibited effective mobilization and resulted in a complete response rate of 79 percent, an improvement over the 54 percent reported for the R-MaxiCHOP and HiDAC-R regimen. This study provides additional insight into the optimal treatment regimen for MCL before transplant and provides a "backbone" with which other novel therapies may be used to achieve better results for patients.

Update on International Clinical Research Efforts in MCL

To conclude the meeting, two leading MCL investigators, both members of the MCLC Executive Committee, provided updates on planned MCL trials. Brad Kahl, MD, spoke about five National Clinical Trials Network (NCTN) initiatives that mirror those carried out by the European MCL consortium aimed at optimizing treatment approach specifically for older/less fit patients, younger/fit patients and relapsed/refractory disease. In particular, for the older/less fit population, E1141 evaluates bortezomib efficacy when used during BR induction, the efficacy of lenalidomide during rituximab maintenance, and provides additional data on genes, methylation patterns, and gene expression profiles that impact disease response to treatment and progression. Dr. Kahl also noted three additional studies underway in this population, the SHINE trial, Acerta trial, and PrE0404 in relapsed and refractory patients. For younger patients, trials are currently underway comparing autologous hematopoietic stem cell transplantation followed by rituximab maintenance with rituximab maintenance alone in MRD-negative patients during first complete remission (EA4151) and a trial comparing 3 different induction strategies prior to transplantation (EA4181). In addition, PrE0405 assesses the utility of BR plus venetoclax in the relapsed refractory setting. Together, these trials hold promise for determining which treatments are most effective for specific patient groups, improving overall outcomes for patients with MCL.

Martin Dreyling, MD, (University Hospital LMU Munich) spoke about current generation of European MCL Network Studies. In the past two years, progress has been made on several fronts. A recent MCL trial in younger patients showed that the addition of high-dose cytarabine (ARA-C) to R-CHOP results in superior response to therapy. The completed French LyMa trial showed that rituximab following transplant further improves survival. Additionally, rituximab maintenance also demonstrated an improvement in survival in elderly patients. Finally, current treatment guidelines issued by the European Society for Medical Oncology (ESMO) recommend both ibrutinib and lenalidomide-rituximab as first-choice targeted therapies in relapsed MCL. Together, these examples illustrate that optimization of current therapy and utilization of newer therapies in the treatment of MCL continues to improve patient care.

In ongoing trials, a large-scale study evaluates the benefit of ibrutinib in addition to or in place of autologous transplantation in younger patients. The trial has accrued over 200 patients across twelve European countries. In patients over 60 years old, the MCL ELDERLY R2 trial compares an alternating induction R-CHOP/R-HAD to R-CHOP only. Patients who respond to either treatment will then receive either combined rituximab-lenalidomide maintenance or rituximab only for two years. This study has recruited more than 400 patients and is active in seven European countries. In addition, two other trials in elderly patients are evaluating new treatment combinations. Future trials will evaluate non-chemotherapy approaches in first line of elderly patients.

Summary

For over a decade, the Lymphoma Research Foundation MCL Consortium has served as a resource for MCL investigators through research funding, providing a platform for the exchange of scientific ideas to accelerate innovation in MCL, and promoting collaborations that increase the impact of individual research efforts. The progress in MCL is both significant and ongoing, with the continuing development of novel therapies and the introduction of new methodologies for monitoring and understanding patients' response to treatment. Research into the biology of MCL and mechanisms of malignancy and resistance has revealed new avenues for novel therapies. The Lymphoma Research Foundation looks forward to continuing to play a central role in programs aimed at improving treatment and outcomes for MCL patients.

The Foundation extends special thanks to AstraZeneca Pharmaceuticals and Celgene Corporation for supporting the MCL Scientific Workshop through unrestricted educational grants.

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