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2016 Mantle Cell Lymphoma Workshop Highlights Advances in Treatment



MCL Consortium Executive Committee members Eduardo Sotomayor, MD of George Washington University, Leo I. Gordon, MD, FACP, of Northwestern University, Brad Kahl, MD of Washington University in St. Louis (Committee Chair), and Martin Dreyling, MD, PhD, Ludwig Maximilian University of Munich.

n April 6 and 7, 2016, more than 80 lymphoma researchers gathered in Atlanta, Georgia for the Lymphoma Research Foundation's 12th Mantle Cell Lymphoma (MCL) Scientific Workshop. This biennial gathering, which includes the Foundation's MCL Consortium members, grantees, and scientists from the United States, Canada, and Europe, provides a unique opportunity for the world's leading MCL researchers to share laboratory research findings, discuss recent and ongoing clinical trials, and strategize on the most important next steps in MCL research.

As one of the world's largest private funders of MCL research, the Lymphoma Research Foundation has funded 50 grants for over \$25 million since inception of the MCL initiative. Foundation grants have led to important developments in the field, including the sequencing of the MCL genome, identification of new molecular targets for therapy, and clinical trials evaluating novel agents, chemotherapy, immunotherapy, radiation therapy, and stem cell transplantation.

The MCL Consortium, established by the Lymphoma Research Foundation in 2005 two years after the first MCL Workshop, includes more than a hundred MCL researchers from North America and Europe. The Consortium aims to accelerate developments in MCL research and treatment by bringing together lead investigators, funding innovative studies, and creating resources. Programmatic efforts have included MCL research grants, the establishment of an MCL Cell Bank, patient education programs, and the biennial MCL Scientific Workshop. This report highlights the themes of LRF's 12th MCL Scientific Workshop and provides a broad overview of each presentation.

"Since the Workshop began in 2003, we've made great strides in understanding and treating mantle cell lymphoma, but there is always more to learn," noted Brad Kahl, MD of Washington University in Saint Louis, Chair of the MCL Consortium. "In assembling researchers from multiple countries on a regular basis to share the latest developments, the MCL Workshop continues to be a valuable resource for clinicians and researchers studying this rare subtype."

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"The MCL Workshop continues to be a valuable resource for clinicians and researchers studying this rare subtype."



FEATURED IN THIS ISSUE: New Scientific Advisory Board Members

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The three newest members of the Foundation's Scientific Advisory Board, including David Weinstock, MD of Dana-Farber Cancer Institute, (pictured, left), discuss their research and goals for their work with the Lymphoma Research Foundation.

LETTER FROM THE CEO



Dear LRF Friends and Supporters,

On July 1, the Foundation welcomed three new members to its Scientific Advisory Board (SAB). This group of world-renowned lymphoma experts evaluates the Foundation's research portfolio, guides the agenda for our scientific and professional programs, and provides their expert knowledge to our patient education initiatives. Our new members' expertise will be a great asset to the SAB; profiles of each new member begin on page 4.

As regular readers of *Research Report* know, the Lymphoma Research Foundation has served as a convener for scientific meetings on unique topics in lymphoma for over a decade. The

Mantle Cell Lymphoma (MCL) Scientific Workshop is a cornerstone of the Foundation's scientific programming, covering a period of significant developments in our understanding of the tumor microenvironment, cellular therapies, and new novel agents, which are proving applicable not just in MCL but across all lymphoma subtypes. I am pleased to bring you highlights of our 2016 Workshop in this issue of *Research Report*, featuring the latest developments in our understanding of the biology and treatment of MCL.

Programs like the MCL Scientific Workshop and the initiatives supported by our SAB would not be possible without your donations and support for lymphoma research. Thank you for your part in supporting the Foundation's efforts to eradicate lymphoma and assist those affected by this disease.



MCL Workshop

[CONTINUED FROM PAGE 1]

The 2016 workshop included 22 original research presentations on topics spanning many aspects of MCL, including recent advances in the understanding of MCL biology, laboratory studies evaluating new potential targets for MCL therapy, preclinical trials of investigational therapies, and recent clinical trials in MCL. The workshop also included two overview presentations on the role of the microenvironment in MCL, a Keynote Address on the use of cellular immunotherapy in lymphoma, and updates on planned and ongoing trials in MCL in both the U.S. and Europe.

Overall, the research presented at the Workshop, both by laboratory scientists and clinical researchers, reflects the continual progress being made toward the Lymphoma Research Foundation's mission to eradicate lymphoma and serve those touched by this disease.

Role of the Microenvironment

Moderator: Brad Kahl, MD – Washington University in St. Louis

Scientists are making progress in understanding how the environment immediately surrounding lymphoma cells can affect lymphoma cell functioning and survival. This information may lead to the identification of new potential therapies.

Opening the session, Stephen Ansell, MD, PhD (Mayo Clinic, Rochester) provided an overview of current scientific understanding on how lymphoma cells interact with the microenvironment in non-Hodgkin lymphoma (NHL). Dr. Ansell pointed out that up to 40 percent of cells in an NHL tumor are not cancer cells; various types of immune cells are present, including cytotoxic T-cells that could potentially destroy tumor cells and regulatory T-cells that prevent those T-cells from attacking the tumor. Thus, it would be advantageous to the tumor to recruit regulatory T-cells that could protect them from the antitumor immune responses. Research suggests that lymphoma cells do attract regulatory T-cells and support their development through a variety of strategies. In NHL, Dr. Ansell explained, "the microenvironment has been fashioned by the tumor

MCL WORKSHOP - PATHOGENESIS

cell into something that favors lymphoma growth."

An understanding of these dynamics has led to the investigation of new potential therapeutic strategies. Although there are efforts to alter the microenvironment, Dr. Ansell explained that these strategies must be targeted, as the wrong approach could lead to a phenomenon called "immune exhaustion," which could render anticancer cells ineffective. However, this line of research is important and Dr. Ansell concluded that "a plethora of tools" are becoming available to skew the microenvironment towards one that is less conducive to tumor cell growth and more conducive to tumor destruction.

In another overview talk, Virginia Amador, PhD (Institute D'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain) reviewed the potential role of SOX11 in MCL biology. SOX11 is a protein that is present in the vast majority of MCLs and has been associated with an aggressive disease course. In contrast, lack of SOX11 expression has been associated with longer survival and stable indolent disease in MCL. Dr. Amador and her colleagues have been working to understand how SOX11 could influence MCL biology. Their laboratory studies suggest that SOX11 regulates new blood vessel development surrounding these tumors as well as MCL homing and invasion. SOX11 may also contribute to drug resistance in MCL through its effects on cell adhesion to adjacent cells of the tumor microenvironments, such as bone marrow stromal cells."Our findings in experimental models and primary human tumors support the oncogenic role of SOX11 in the aggressive behavior of MCL," Dr. Amador explained. She suggested that SOX11 and the SOX11-direct regulated oncogenic proteins and pathways may represent "innovative target strategies" to overcome resistance to chemotherapy in MCL.



Stephen Ansell, MD, PhD of Mayo Clinic, Rochester, delivers his talk on the tumor microenvironment.

Daniel Medina, PhD (Rutgers Cancer Institute of New Jersey) presented results of laboratory studies investigating how MCL cells may interact with surrounding cells to promote an environment that supports further lymphoma growth. Dr. Medina and his colleagues found that MCL cells secrete tumor necrosis factor (TNF) alpha, a protein that promotes inflammation and is well associated with various inflammatory conditions. TNF alpha secreted by MCL cells appears to affect nearby cells called mesenchymal stromal cells. In laboratory studies, stromal cells that have come into contact with TNF alpha appear to form what Dr. Medina called a "sanctuary" that could support the survival and self-renewal of cells that could initiate MCL and possibly protect those cells from the effects of chemotherapy. He suggested that TNF alpha may be a potential therapeutic target in MCL. Multiple TNF inhibitors are commercially available and are used for the treatment of inflammatory conditions.

Nakhle Saba, MD (Tulane University) discussed differences in MCL biology between the lymph nodes, where MCL growth and division commonly occurs, and the bloodstream, where MCL cells can also be found. Dr. Saba and his colleagues compared gene expression levels between MCL cells located in the lymph nodes and those from the blood. The researchers found that certain cellular signaling pathways were activated primarily in lymph node cells, including the B-cell receptor (BCR) pathway (which is targeted by therapies like ibrutinib) and the pathway involving nuclear factor kappa-B (NF-kB). The researchers suggested that these pathways may help support MCL development. They also found that the presence of certain mutations can lead to activation of the BCR and NF-kB pathways in the blood. Finally, by studying outcomes in the patients, the researchers found that an inverse association between the strength of BCR signaling and prognosis after chemotherapy. These findings may provide insight into how MCL may develop resistance to targeted therapies.

Pathogenesis

Moderator: Eric Hsi, MD – Cleveland Clinic

Researchers continue to explore the mechanisms by which MCL develops. A greater understanding of the biology of MCL can lead to better insight into the clinical condition and help improve treatment strategies.

Samir Parekh, MD (Icahn School of Medicine at Mount Sinai) presented the results of studies investigating potential interactions between SOX11 and the gene encoding cyclin D1 (CCND1), which is commonly overexpressed in MCL. In laboratory studies, Dr. Parekh and his colleagues found that overexpression of SOX11 in mice induces a condition that appears identical to MCL at the cellular level. SOX11 overexpression also appears to cause increased signaling through the B-cell receptor. Their studies suggest that SOX11 works in tandem with CCDN1 to contribute to the development of MCL. The researchers used computational and [CONTINUED ON PAGE 6]

NEW SAB PROFILES

Lymphoma Research Foundation Welcomes Three Scientific Advisory Board Members

The Lymphoma Research Foundation is pleased to announce the election of three new members to its Scientific Advisory Board (SAB). The SAB is comprised of 45 world-renowned lymphoma experts who lend their perspective and expertise to evaluating the Foundation's research grants portfolio, providing guidance to scientific, professional, and patient programming, and supporting advocacy efforts to strengthen lymphoma research and patient care.

New general members Ethel Cesarman, MD of Weill Cornell Medicine, Christian Steidl, MD of British Columbia Cancer Agency, and David Weinstock, MD of Dana-Farber Cancer Institute began their five-year terms on July 1. SAB Chair Leo I. Gordon, MD, FACP, of Robert H. Lurie Comprehensive Cancer Center of Northwestern University, said, "I would like to welcome our new SAB board members. This group of new members helps to reinforce the unique nature of the LRF SAB as the leading advisory board in lymphoma research and education in the US and around the world.

"Dr Ethel Cesarman has a distinguished record of research in lymphomas associated with immune deficiency, including AIDS and post transplant lymphomas. Dr Cesarman has been the leader of the Pathology core for the AIDS malignancy consortium and her scholarship and collaboration will be a great asset to the SAB.

"Dr Christian Steidl, from the British Columbia Cancer Agency, is an international leader in the molecular characterization of lymphoid malignancies. He has done seminal work in lymphoma research and is clearly a rising star.

"Dr David Weinstock studies molecular evolution of somatic alteration in lymphoid malignancies and has been a major contributor in this area. Another rising star, Dr Weinstock will be a critical addition to the SAB as an accomplished clinician/scientist."

Meghan Gutierrez, the Foundation's Chief Executive Officer, added "Our Scientific Advisory Board is a crucial component of the Foundation's grantmaking and research programming. With the addition of our new SAB members, we will continue to make strides in our mission of eradicating lymphoma and serving those touched by this disease."



Ethel Cesarman, PhD Weill Cornell Medicine New York, NY

Dr. Cesarman is Professor of Pathology and Laboratory Medicine at Weill Cornell Medicine, where she is the Principal Investigator of the Viral Oncogenesis laboratory. Viral oncogenesis examines how viruses contribute to the formation of cancer, a particularly apt study in lymphoma, where certain subtypes may be caused by the effect of the Epstein-Barr Virus (EBV), Kaposi's sarcoma herpesvirus (KSHV), and HIV/AIDS on the immune system. Dr. Cesarman and her colleagues are performing molecular characterization of AIDS-associated lymphomas and Kaposi's sarcoma (the most common malignancy in AIDS patients). Among other important contributions, Dr. Cesarman's lab has identified that KSHV is linked not only to Kaposi's Sarcoma but is consistently present in a rare subset of non-Hodgkin lymphomas called primary effusion lymphomas. "Our ultimate goal is to understand the role of EBV and KSHV in the development of cancer, in order to find novel targeted therapies," she notes.

Dr. Cesarman's research frequently involves both pediatric and young adult patients – particularly in her work on Burkitt's and classical Hodgkin lymphoma – and patient populations with low resources. A recent research grant focuses on the development of diagnostic tools that can be operated via solar-power and a smartphone for use at clinics in areas without access to a full pathology laboratory. She is also currently working with Ari Melnick, MD of Weill Cornell Medicine (also a Foundation Scientific Advisory Board member) and researchers at Rockefeller University to study the roll of linker histone (H1) mutations in lymphoma pathogenesis.

Dr. Cesarman received her MD from the Autonomous Metropolitan University in Mexico before completing her PhD at New York University and an Anatomic Pathology residency and hematopathology fellowship at Columbia University. In 2014 she became a member of the inaugural steering committee for the Lymphoma Research Foundation's New York Lymphoma Rounds, a professional education program assembling healthcare professionals in six cities across the United States. "It is a great honor to serve on the Lymphoma Research Foundation Scientific Advisory Board," Dr. Cesarman says. "I look forward to collaborating with other SAB members and continuing my work with the Foundation."

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NEW SAB PROFILES



Christian Steidl, MD British Columbia Cancer Agency Vancouver, Canada

Dr. Steidl is Research Director of the Centre for Lymphoid Cancer at the British Columbia Cancer Agency (BCCA) in Vancouver, and an Associate Professor at the University of British Columbia. A physician by training, Dr. Steidl found himself drawn to translational lymphoma research early in his career. "Advancing biomedical science has the enormous potential to improve the lives of patients through discovery," he explains. "I am a strong believer that fundamental research and treating patients should go hand-in hand."

Dr. Steidl's research focuses on the genome mutations that occur in malignant lymphoma cells, using high throughput sequencing to decipher the "spelling errors" in the DNA of tumor cells (somatic mutations). With his colleagues, he has discovered certain mutations that explain why cancer cells are able to escape the human immune system. Dr. Steidl's work has contributed significantly to the discovery of novel somatic gene mutations in B cell lymphomas, as well as establishing tumor-associated macrophages (a type of white blood cell) as a biomarker for outcome prediction in Hodgkin lymphoma. "Moreover, my most recent published work has significantly contributed to the concept that certain types of lymphoma subvert the physiological mechanism of immune privilege for malignant growth advantage ('acquired immune escape' of tumor cells)," he notes.

A native of Germany, Dr. Steidl received his MD from the University of Muenster Medical School and a Doctorate in Pathology from the University of Witten/Herdecke, before joining BCCA. In 2008, Dr. Steidl received a Lymphoma Research Foundation Postdoctoral Fellowship grant, under the sponsorship of Randy Gascoyne, MD (who retired from the Scientific Advisory Board in June). He notes that selecting and supporting "the most promising young scientists" in turn is one of the activities he looks forward to participating in as an SAB member. A presenter at the Foundation's first Adolescent/ Young Adult Lymphoma Symposium in September 2015, Dr. Steidl "strongly supports a focus on the biology of lymphomas affecting adolescents/young adults."

Dr. Steidl cites the increasing data showing that immune therapies, such as checkpoint inhibitors, chimeric antigen receptor (CAR) T cells, and other drugs, are effective treatment strategies in lymphoma, is the most exciting research development. "The precision and comprehensiveness of molecular characterization is unprecedented and will eventually lead to convergence of complex biology and more effective therapies."



David Weinstock, MD Dana-Farber Cancer Institute Boston, MA

Dr. Weinstock is Associate Professor of Medicine at Harvard Medical School/Dana-Farber Cancer Institute. His research utilizes a variety of approaches to identify new prognostic markers and therapeutic targets in lymphoid neoplasms. "My laboratory uses lymphoma specimens from patients to better understand what makes them grow and survive," Dr. Weinstock says. "We then grow these human lymphoma in mice, where we can test new drugs Finally, we work with our clinical lymphoma colleagues to orchestrate trials of the most promising drugs in people, obtain biopsies from those people and use those biopsies to understand why the new drugs did or didn't work."

Dr. Weinstock is most proud of his work characterizing the vulnerabilities of peripheral T cell lymphoma, a subtype that has been resistant to several standard therapies. In addition, as co-Chair of the inaugural American Society of Hematology (ASH) Meeting on Lymphoma Biology in August 2014, Dr. Weinstock led the effort to develop a roadmap for future discovery in lymphoma biology, identifying priority areas of need in both infrastructure and research. He hopes that as a Scientific Advisory Board member he can "participate with other leaders in guiding the direction of lymphoma research ... by pushing a more collaborative, opensource approach."

After receiving his MD from George Washington University School of Medicine, Dr. Weinstock completed his residency at New York Hospital/Cornell (now Weill Cornell Medicine) and a fellowship at Memorial Sloan Kettering Cancer Center. He was drawn to lymphoma research because it was an area where further exploration was needed "especially T-cell lymphomas." He finds the recent growth in the understanding of lymphoma and the development of new therapies a reason for hope. "The trend of success thus far suggests that over the next 10-20 years, we can markedly improve outcomes for the patients who are currently not doing well."

> "Advancing biomedical science has the enormous potential to improve the lives of patients through discovery."

MCL WORKSHOP - NOVEL TARGETS

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laboratory methods to identify molecules that could inhibit interactions between SOX11 and DNA as a potential therapeutic target.

Vu Ngo, PhD (City of Hope) discussed the role of Cyclin D1 mutations in MCL. Dr. Ngo noted that recent published studies have identified recurrent mutations in CCND1 in patients with MCL, although the significance of these is not well understood. In laboratory studies, Dr. Ngo and colleagues found that certain mutations increase CCND1 protein levels in MCL cell lines by deregulating protein degradation. The researchers also found that mutations in CCND1 in MCL cell lines appear to promote resistance to ibrutinib (Imbruvica) and other therapies including PI3K and mTOR (mammalian target of rapamycin) inhibitors. Their findings suggest that increased CCND1 protein levels correlate with ibrutinib resistance. These studies may illuminate a potential cause of ibrutinib insensitivity.

Mitchell R. Smith, MD (Cleveland Clinic) introduced work he and his team have undertaken in collaboration with colleagues to apply mathematical modeling to MCL research. The models analyzed the dynamics of malignant B-cells and subclones and the immune response in order to optimize the development of lymphoma therapy. The mathematical strategy attempts to overcome some of the limitations of other preclinical methods such as cell lines and animal studies to identify the optimal combinations of drugs as well as their dose and scheduling.

David T. Yang, MD (University of Wisconsin) presented results of studies evaluating the protein MUM1 as a biomarker of bortezomib (Velcade) resistance in MCL. Dr. Yang noted in laboratory studies, resistance to the drug bortezomib is associated with expression of MUM1, a plasmacytic marker. Dr. Yang and colleagues therefore correlated MUM1 expression with clinical outcomes in a small group of patients with MCL who had received bortezomib. They found that MUM1 expression was associated with poor responses to therapy. MUM1 may therefore be a potential marker to help guide therapy selection in MCL.

Novel Therapeutic Targets

Moderators: Martin Dreyling, MD – Ludwig Maximilian University of Munich; Michael Williams, MD, ScM – University of Virginia Health System and Cancer Center

Research efforts elucidating the biology of MCL have revealed new potential ways to target lymphoma. A wide variety of novel approaches to MCL therapy have been identified, including ways to enhance existing therapies and possibly overcome drug resistance.

Bijal D. Shah, MD (Moffitt Cancer Center) presented on behalf of his colleague, Jianguo Tao, MD, PhD, the results of studies evaluating the feasibility of individualized drug screens in order to tailor MCL therapy. Dr. Shah noted that ibrutinib is associated with high response rates in B-cell lymphoma but ibrutinib resistance often develops, leading to disease progression. Dr. Shah, Dr. Tao, and their colleagues are using high-throughput screening methods to test the activity of candidate drugs against MCL cells, including those with ibrutinib resistance. Researchers hope to be able to use their technique to predict drug responses in individual patients and tailor therapy as needed to obtain the best responses.



Diagram of how computational/mathematical models can supplement the translational research process. Illustration courtesy Mitchell Smith, MD of Cleveland Clinic.

Shan Zha, MD, PhD (Columbia University Medical Center) discussed a type of mutation that is highly cancer-promoting and that may be targeted by a certain type of therapy. These mutations are found in the ataxia telangiectasia mutated (ATM) gene, which encodes a kinase signaling protein. Dr. Zha explained that mutations in the kinase domain of the ATM gene are common in human cancers, including MCL. Dr. Zha and her colleagues have been conducting experiments to better understand ATM mutations and how their presence may affect sensitivity to cancer therapies. They have found that tumors that express mutated ATM without kinase activity are particularly sensitive to a class of agents called topoisomerase I inhibitors and a class of chemotherapy agents that includes cisplatin. These findings suggest that ATM kinase domain mutations could serve as biomarkers for guiding therapy.

Paul Martin, MD (University of Washington/Fred Hutchinson Cancer Research Center) discussed the potential implications of androgen receptor expression in MCL. Dr. Martin noted that the majority of patients with MCL are male. Research has shown that the androgen

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receptor is expressed in MCL tumors and the predominance of males affected by MCL may be due to differences in androgen receptor activity. In laboratory studies, blocking the androgen receptor with enzalutamide (Xtandi), a hormonal therapy used in prostate cancer, suppressed proliferation of MCL cells, while it had no effect on other lymphoma cells. An ongoing clinical trial is evaluating the potential use of enzalutamide in patients with MCL.

Selina Chen-Kiang, PhD (Cornell-Weill Medical Center) provided an update on Foundation-funded studies investigating mechanisms of ibrutinib resistance and the potential use of the cell cycle (the process by which cells divide) as a target for MCL therapy. Cyclin-dependent kinase 4 (CDK4), an enzyme that promotes cell division, is overactive in lymphomas. Dr. Chen-Kiang and her colleagues are investigating whether administering a CDK4-targeting cell cycle inhibitor may "reprogram" cells for ibrutinib therapy, thus enhancing the efficacy of ibrutinib.

Eric Hsi, MD (Cleveland Clinic) reported on studies evaluating synergistic effects between a new therapy, venetoclax (Venclexta), and a novel cell cycle inhibitor that targets CDK9. Venetoclax is a new drug that targets apoptosis, which is the normal cellular mechanism of self-destruction. Dr. Hsi noted that many cancers become resistant to apoptosis. This process furthers their unregulated growth. Although venetoclax is active against lymphoma, Dr. Hsi noted that there is a potential for venetoclax resistance to develop. Dr. Hsi and his colleagues are assessing possible synergy between venetoclax and a cell cycle inhibitor as a way of overcoming potential resistance.

Kai Fu, MD, PhD (University of Nebraska Medical Center) presented results of studies evaluating the mechanism by which a class of therapies called mTOR inhibitors work to kill cancer cells. The researchers found that second-generation mTOR kinase inhibitors downregulate MCL1, a gene involved in regulating cell survival. Moreover, overexpression of BCL-2, another gene that helps regulate cell survival, induces resistance against these newer mTOR kinase inhibitors. Dr. Fu suggested that combining an mTOR kinase inhibitor with a BCL-2 inhibitor may be an



Diagram of ibrutinib and palbociclib's impact in combination on lymphoma signaling pathways. Illustration courtesy Selina Chen-Kiang, PhD of Weill Cornell Medicine.

active treatment against MCL. Laboratory studies have shown that the combination is effective in an animal model of MCL.

Hilka Rauert-Wunderlich, Dr. rer. nat. (Institute of Pathology, University of Würzburg) discussed the potential for targeting protein kinase C (PKC) in MCL. PKC is a signaling molecule that lies in the same pathway as Bruton's tyrosine kinase (BTK), the target of ibrutinib. Dr. Rauert-Wunderlich and her colleagues have been studying the differential effects of sotrastaurin, an investigational PCK inhibitor, and ibrutinib on MCL cells in the laboratory. They have found that MCL cells differ in their responses to ibrutinib and sotrastaurin, suggesting the importance of individualized treatment approaches. Their studies help elucidate the effects of these compounds on MCL cells. Dr. Rauert-Wunderlich concluded that PKC could be a potential target for MCL treatment, particularly in patients with ibrutinib resistance.

Cellular Therapy

Moderator: Eduardo Sotomayor, MD – The George Washington University School of Medicine and Health Sciences

Scientists reported on several strategies to use cells to fight lymphoma, including novel approaches (CART cells) and existing strategies (stem cell transplantation).

Mariusz Wasik, MD (University of Pennsylvania) discussed his Foundationfunded research investigating the MCL response to the combination of chimeric antigen receptor (CAR) T-cell therapy and ibrutinib. CART-cell therapy is an investigational approach that involves isolating a patient's T-cells, "programming" them to display enhanced antitumor activity, and reintroducing them into the patient. This type of CART-cell therapy is called CART19 because T-cells are engineered to recognize lymphocytes that express CD19, including MCL cells. Dr. Wasik and his colleagues found that in cellular and animal studies, ibrutinib enhanced the efficacy of CART19 treatment. Dr. Wasik concluded that these results support the initiation of clinical trials investigating the combination.

Leslie Popplewell, MD (City of Hope) presented early results of phase 1 studies of CART19 therapy administered after

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MCL WORKSHOP - CLINICAL OUTCOMES



Ashley Staton, MD of Emory University (right) and session moderator Kristie Blum, MD of The Ohio State University, field audience questions.

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autologous stem cell transplant (ASCT) for selected patients with B-lineage NHL. In these studies, Dr. Popplewell and her colleagues are evaluating whether CART19 therapy reduces the risk of relapse after ASCT in patients with aggressive lymphoma, including MCL. One trial enrolled only patients with relapsed NHL and the other allowed patients with high-risk disease in first remission. Thus far, the administration of CART19 therapy after ASCT appears feasible, with 16 patients (five with MCL) having been treated. Dr. Popplewell noted that addition of the CART19 therapy did not appear to increase the toxicity of the high dose chemotherapy and autologous hematopoietic cell transplantation. Longterm results of the studies are awaited to assess the efficacy.

Attaphol Pawarode, MD (University of Michigan) reviewed long-term outcomes after allogeneic hematopoietic cell transplantation (HCT) in patients with advanced aggressive MCL. Allogeneic HCT is associated with increased treatment-related mortality after myeloablative conditioning regimens and increased relapse rate after reduced-intensity conditioning regimens. His presentation included long-term outcomes of 59 patients with advanced or aggressive MCL who underwent allogeneic HCT at the University of Michigan between 1997 and 2016. HCT was a feasible option for patients with aggressive refractory MCL, allowing long-term progression-free survival (PFS) and overall survival (OS) in 35 and 41 percent respectively. Patients with advanced but still chemotherapy-sensitive disease at the time of HCT or those with fewer prior lines of therapy appeared to gain a greater benefit. Reduced-intensity conditioning regimens appeared to yield better outcomes, with 5-year PFS and OS of 42 and 55 percent respectively. Dr. Pawarode also noted that allogeneic HCT could be combined with other therapies to maximize outcomes.

Issa Khouri, MD (MD Anderson Cancer Center) discussed factors associated with outcomes after non-myeloablative allogeneic SCT. Dr. Khouri and colleagues assessed outcomes among 75 patients with relapsed MCL who underwent allogeneic SCT at the MD Anderson Cancer Center between 2005 and 2013. The researchers found that allogeneic SCT appears to overcome the negative prognosis associated with high Ki-67 expression, a genetic marker associated with poor prognosis. Dr. Khouri also noted that the transplant was curative in a substantial proportion of patients, in particular among those with fewer prior lines of therapy. Mixed chimerism—a state in which both recipient and donor blood cells are detectable—is associated with significantly poorer prognosis compared with full donor chimerism, in which only donor-originating cells are detectable.

Clinical Outcomes

Moderator: Kristie Blum, MD – The Ohio State University

In a series of presentations on clinical outcomes, researchers provided updates on new therapeutic approaches, the use of more sensitive methods of assessing responses to therapy, and alternative ways to assess disease risk in newly diagnosed patients. These studies will help inform the knowledge base on how to best care for patients from the time of diagnosis through their treatment experience.

Jonathon Cohen, MD (Emory University), a current LRF Scholar and Career Development Award recipient, discussed results of studies exploring the role of deferred therapy in patients with MCL. Although MCL is typically treated at the time of diagnosis, a subset of patients can safely defer therapy. To better understand which patients may be able to defer therapy, Dr. Cohen and colleagues compared differences between a multicenter cohort of 72 patients who had deferred therapy and 323 patients who had immediate therapy, identifying predictors of overall survival. The researchers found that deferred therapy did not adversely affect survival in this cohort. Moreover, the mantle cell lymphoma International Prognostic Index (MIPI) did not predict selection of deferred therapy. One difference was that patients receiving immediate therapy were more likely to complete aggressive induction therapy and ASCT. Dr. Cohen concluded that additional work was needed to identify patients who may be able to defer therapy.

Ashley Staton, MD (Emory University) presented an analysis of the prognostic role of the MCL International Prognostic Index

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MCL WORKSHOP - KEYNOTE

Stephen Schuster, MD, Delivers MCL Workshop Keynote

The 2016 MCL Workshop's keynote speaker was Stephen Schuster, MD, the Robert and Margarita Louis-Dreyfus Associate Professor in Chronic Lymphocytic Leukemia and Lymphoma Clinical Care and Research at the Perelman Center for Advanced Medicine at the University of Pennsylvania. Dr. Schuster spoke about the cellular immunotherapy of B-cell lymphomas, including the use of chimeric antigen receptor (CAR)-modified T-cells and other approaches. These types of approaches aim to harness the power of the immune system to fight lymphoma.

Dr. Schuster explained the process behind CART-cell (CTL019) therapy, in which T-cells are first isolated from patients through leukapheresis then transduced with a virus that encodes a protein that targets CD19 on the outer surface and induces cytotoxic effects inside the T-cell. The modified T-cells are then expanded in the laboratory and infused back into the patient.

CTL019 therapy is being evaluated in a phase 2 study in 43 patients with advanced CD19-positive B-cell NHL, including three patients with MCL. Thirty patients, including two with MCL, have received the CTL019 cells. The therapy has induced durable responses in patients with diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma and appears to have a tolerable safety profile. Based on these results, a single-arm, open-label, multicenter phase 2 study began in 2015 evaluating CTL019 in adult patients with DLBCL.



Stephen Schuster, MD, of the Perelman Center for Advanced Medicine at the University of Pennsylvania delivers the keynote lecture.

In terms of other cellular immunotherapy approaches, Dr. Schuster noted that two immune checkpoint inhibitors, which "remove the brakes" from T-cells, are being studied in lymphomas. Both nivolumab (Opdivo) and pembrolizumab (Keytruda) are FDA-approved for other cancer types. A combination approach including both CART-cells and a checkpoint inhibitor may yield greater efficacy. This strategy is being tested in clinical trials, including a phase 1/2 study of pembrolizumab in patients with relapsed or refractory CD19-positive lymphoma who have already received anti-CD19-targeted CART-cell therapy.

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(MIPI) in a multicenter cohort of patients with MCL. Dr. Staton and colleagues evaluated outcomes among 228 patients with low-risk (32 percent), intermediate-risk (39 percent) or high-risk (29 percent) MCL based on the MIPI score. After controlling for confounding factors, the MIPI was not significantly associated with survival or progression-free survival at 5 years in this analysis. However, other clinical and biological factors, including complex karyotype, bone marrow involvement, and high Ki-67, were significantly associated with outcomes. Dr. Staton concluded that additional studies were needed to build upon the MIPI with new prognostic indices to better assess disease risk at diagnosis.

Andrew J. Cowan, MD (University of Washington) reported on the impact of remission status and the presence of minimal residual disease in patients with MCL undergoing ASCT. Dr. Cowan explained that the presence of minimal residual disease (MRD) has been shown to correlate with outcomes after ASCT in patients with MCL. To further evaluate the pre-transplant use of MRD assessment in MCL therapy, Dr. Cowan and colleagues conducted MRD assessments prior to ASCT in 142 patients with MCL undergoing ASCT, including 67 with a MRD-negative complete response (indicating no detectable residual disease) and 8 patients with a MRD-positive complete response. The researchers found that MRD status was significantly associated with overall survival and progression-free survival, independent of remission status. There was little added value with the use of MRD testing in patients with a partial response pre-transplant. These findings could help tailor MCL therapy based on the presence of residual disease. Additional studies are needed to further define the role of MRD testing.

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MCL WORKSHOP - CLINICAL TRIALS

MCL Workshop

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Tycel Phillips, MD (University of Michigan), on behalf of the Southwestern Oncology Group (SWOG), presented updated results of the randomized S1106 trial comparing two different initial treatment approaches—R-hyper-CVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone, and rituximab) and bendamustine (Treanda)/rituximab (Rituxan), each followed by ASCT—in 160 patients with MCL. The R-hyper-CVAD arm of the study was closed early due to high rates of adverse events, including severe cytopenias and a high rate of stem cell mobilization failures. Bendamustine and rituximab was found to be a feasible pre-ASCT induction strategy, with a two-year progression-free survival (PFS) rate exceeding 75 percent. Stem cell collection was adequate with bendamustine/rituximab. Another key study point was the evaluation of MRD status in patient pre- and post-therapy. Of the patients with paired samples in the Bendamustine arm, eight of nine patients with detectable MRD at baseline attained MRD-negative status after therapy. Overall most patients attaining MRD negativity (11 of 12) remained free from disease progression at two years. Additional studies are needed to define the role of bendamustine/rituximab in patients undergoing ASCT. Dr. Phillips also concluded that the study raised questions about the role of MRD testing both in clinical trials and in clinical practice.

Ongoing and Planned MCL Clinical Trials

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 ongoing efforts by the U.S. National Clinical Trials Network (NCTN). The E1411 trial is a randomized, phase 2 trial evaluating different approaches to the initial therapy for MCL. Patients are assigned to 6 cycles bendamustine and rituximab, with or without bortezomib, followed by maintenance therapy with rituximab with or without lenalidomide (Revlimid). The trial has enrolled 325 patients. Other trials led by industry are evaluating various combination approaches in older patients; one trial is evaluating bendamustine and rituximab with or without ibrutinib and another is evaluating bendamustine/rituximab plus maintenance rituximab with or without acalabrutinib.

In younger patients, the S1106 trial compared an aggressive induction therapy combination versus bendamustine/ rituximab, each followed by ASCT. The trial showed the aggressive approach was excessively toxic. Researchers are also conducting trials assessing whether all younger patients require frontline ASCT, particularly those with MRD-negative disease. Dr. Kahl noted that it is unknown whether ASCT confers a survival benefit after the highly active induction regimens available today. The role of ASCT in patients with an MRD-negative complete response after induction will be evaluated in a clinical trial under development (EA4151).

Martin Dreyling, MD, spoke on behalf of the European MCL Network, providing an update of trials in MCL being conducted and planned in Europe. For patients younger than age 65, the MCL Younger trial is evaluating R-CHOP and DHAP (dexamethasone, high-dose cytarabine, and cisplatin) with or without ibrutinib, followed by ASCT, ibrutinib maintenance, or a combination of the two. For patients older than 60, the MCL Elderly R2 trial is evaluating R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) with or without cytarabine (Ara-C) followed by rituximab maintenance with or without lenalidomide. For patients older than age 65, the MCL Elderly I trial evaluated bendamustine/ rituximab with or without ibrutinib followed by rituximab maintenance with or without ibrutinib but data are not yet available.

For patients in first relapse, European investigators are evaluating the combination of R-HAD (rituximab, cytarabine, and dexamethasone) with or without bortezomib. Several trials are being conducted in patients in second relapse or those ineligible for R-HAD. One trial had compared ibrutinib versus temsirolimus (Torisel) and another is evaluating the BeRT regimen of bendamustine/rituximab plus temsirolimus. This overview highlighted the range and depth of the clinical trials being conducted in both the U.S. and Europe evaluating new approaches for the treatment of MCL for patients of all agents and at all stages of treatment.

Summary

For more than a decade, the MCL Consortium has served as a valuable resource for MCL investigators by providing research funding and promoting collaborations that increase the impact of individual research efforts. There continues to be great progress in MCL, with the introduction of new therapies and new ways of assessing responses to therapy. Research into the biology of MCL has revealed new possibilities for novel therapies. There is still work to be done, both in the laboratory and in clinical trials, to improve outcomes for patients with MCL. The Lymphoma Research Foundation looks forward to continuing to play a central role in these crucial efforts.

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

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About the Research Report

Research Report is a publication of the Lymphoma Research Foundation, providing the latest updates on our grantees and their progress, as well as on the work of the Foundation. The Lymphoma Research Foundation is the nation's largest non-profit organization devoted to funding innovative lymphoma research and serving the lymphoma community through a comprehensive series of education programs, outreach initiatives, and patient services.

Donor Spotlight

In 2007, **Dr. Bruce and Christine Cheson** founded the Lymphoma Research Ride in Montgomery County, Maryland as a way to give back to Dr. Cheson's patients and medical community in addition to supporting research and raising awareness about lymphoma. 2016 marks the 10th annual Ride, with over \$4 million dollars raised in support of the mission of the Lymphoma Research Foundation. Dr. Cheson, a Scientific Advisory Board member and past SAB Chair, is an annual participant in the Ride; in 2015 his team raised over \$64,000 for a lifetime total of almost \$440,000 through this event.

Riders of all levels are invited to participate in the 2016 Ride on September 25, with the option to choose between routes of 10, 25, 40, or 50 miles. For more information visit lymphoma.org/DCride2016.



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