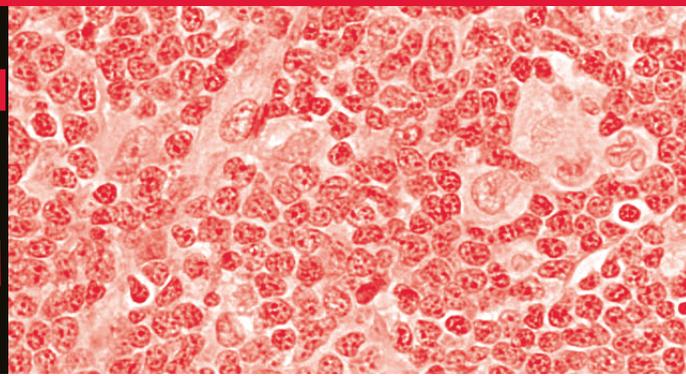


R E S E A R C H
Report



ASH Annual Meeting Highlights Future Lymphoma Treatments

Lymphoma research made tremendous strides in the first years of the 21st century. Researchers have an increasingly detailed understanding of the diverse subtypes of this complex disease, which in turn has allowed treatment to expand, from the “one-size-fits all” approach of chemotherapy and radiation, to new approaches that address the unique nature of specific lymphoma subtypes, and even specific patients. With the first generation of these targeted therapies now well established and the second generation on the immediate horizon, the 2016 Annual Meeting of the

American Society for Hematology (ASH), held in San Diego, California on December 3-6, featured research that acknowledged the long-term efficacy of many current treatments, while providing an exciting glimpse at what future developments may mean for lymphoma patients.

The ASH Annual Meeting, now in its 58th year, is one of the world’s leading conferences for hematologists/ oncologists and researchers across the hematologic malignancies, offering a crucial forum for sharing and discussing new developments. More than 20,000

researchers attend the Annual Meeting each year, among them a number of Lymphoma Research Foundation Scientific Advisory Board members, grantees, and Mantle Cell Lymphoma Consortium members. In 2016, more than 475 lymphoma abstracts presented at ASH featured at least one researcher with ties to the Foundation, with a significant number of the Foundation’s twenty years of grantees still active in lymphoma research [see below infographic].

“The Lymphoma Research Foundation has been investing in the most promising

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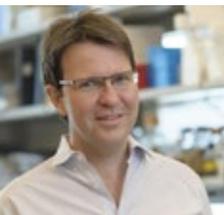
Lymphoma Research Foundation Grantees at ASH 2016

306 LRF grantees (1992-2016)

150 authored at least one ASH 2016 abstract (49%)



66 presented at least one abstract (20%)



FEATURED IN THIS ISSUE: Interview with Dr. H. Guido Wendel

Page 4

Lymphoma Research Foundation grantee H. Guido Wendel, MD of Memorial Sloan Kettering Cancer Center discusses his recently published research outlining exciting new possibilities for CAR T-cell immunotherapy.



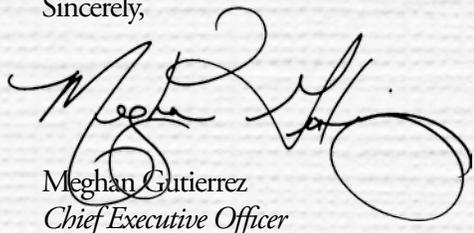
Dear LRF Friends and Supporters,

This past December, I had the opportunity to attend the 58th Annual Meeting of the American Society of Hematology (ASH) in San Diego, California. This meeting and exposition is one of the world's premier events in hematology, offering an opportunity for experts in the field to review thousands of scientific abstracts and research papers highlighting critical updates in the study and treatment of lymphoma. This edition of the Research Report features a sampling of some of the interesting studies discussed at ASH, many of which featured contributions from Foundation grantees, Scientific Advisory Board members, and Mantle Cell Consortium members.

We are proud of the breakthroughs and advancement in lymphoma research that are being made by LRF scientists. While ASH highlights some of these achievements, LRF-associated researchers are making an impact across the field. This issue features an interview with Dr. H. Guido Wendel, a current Foundation grantee who recently published groundbreaking work that demonstrates a new approach for chimeric antigen receptor (CAR) T-cell immunotherapy (see pg 4). On page 8 you will find an overview of our patient education workshops, led by expert lymphoma researchers, most of whom presented research at ASH.

This special edition of Research Report allows us to highlight the results of your donations and support for lymphoma research. Thank you for your part in helping the Foundation advance innovative research and impact the lives of those we exist to serve.

Sincerely,



Meghan Gutierrez
Chief Executive Officer

ASH 2016

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lymphoma research for nearly a quarter century," said SAB Chair Leo I. Gordon, MD, FACP, of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. "The scope of that influence is visible in the number of researchers who have received Foundation grants and are still actively advancing lymphoma research with presentations at ASH."

Current Therapies: Long-term Results and New Combinations

Several practice changing studies published over the last decade were revisited at ASH, as long-term follow-up data demonstrated the effectiveness of the first wave of targeted and novel therapies. Ibrutinib (Imbruvica) was first approved for relapsed/refractory chronic lymphocytic leukemia (CLL) by the U.S. Food and Drug Administration (FDA) in November 2013; former Scientific Advisory Board (SAB) member Susan

O'Brien, MD, of the University of California, Irvine presented the five-year follow-up data from one of the clinical trials which was instrumental in that initial approval. The updated results mark the longest follow-up to date for ibrutinib in CLL. Of 132 patients enrolled (101 relapsed or refractory and 31 untreated CLL), the overall response rate was 86 percent, with 14 percent of patients reporting a complete response. Relapsed/refractory patients had a median duration of response of 45 months (nearly four years); even more encouraging, 92 percent of the patients receiving ibrutinib as their initial treatment have still not seen their disease advance at the five-year mark. Dr. O'Brien and her colleagues also noted that patients with del17p, a complex karyotype (a type of biomarker found in human chromosomes made up of three or more distinct abnormalities) had poor outcomes compared to those patients without del17p. Additionally, nearly half of the patients on this trial

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were over age 70; the strong overall response indicates ibrutinib is effective and safe in older patients who may not be able to tolerate other therapies. The study's results suggest that ibrutinib's FDA approval in CLL had a significant impact in extending and improving survival rates for this subtype.

► *This study also included contributions from Foundation SAB member Kristie Blum, MD, and former SAB member John Byrd, MD, both of The Ohio State University, former LRF Fellowship grantee Danelle James, MD, now with Pharmacyclics, and MCL Consortium member Ian W. Flinn, MD, PhD, of Sarah Cannon Research Institute.*

Additional five year outcomes data was provided by Paul Barr, MD, of the University of Rochester, a 2011 Foundation Career Development Award winner. Dr. Barr presented the long-term follow up for SWOG 0801, a clinical trial for advanced follicular lymphoma (FL) directed by the Southwest Oncology cooperative group (SWOG). The trial, designed to assess the effectiveness of a set four-year treatment plan – chemoimmunotherapy induction followed by radioimmunotherapy, with rituximab (Rituxan) used for maintenance – had 84 patients complete the initial two phases of the plan, with a 99 percent response rate (59 complete responses and 23 partial). Sixty-nine patients continued to the maintenance portion of the plan, and 42 patients completed the entire four years. With a median follow up rate of 5.6 years, only nine patients had seen their FL progress, resulting in a progression free survival rate of 90 percent at three years and 84 percent at five years. Dr. Barr and his colleagues did note that as the majority of patients who discontinued treatment did so during the

maintenance portion, the cumulative toxicity of rituximab may be difficult for some patients to tolerate. However, the overall strong responses to the chemoimmunotherapy and RIT stages suggest this treatment strategy is quite effective in high-risk and advanced FL.

► *This study also included contributions from Foundation FL Pathways grantee Richard Burack, MD, PhD, and SAB member Jonathan Friedberg, MD, both of the University of Rochester; former SAB member and MCL Consortium member Richard I. Fisher, MD of Fox Chase Cancer Center; LRF grantees and MCL Consortium members Ajay K. Gopal, MD and Oliver Press, MD, PhD (also a former SAB member) both of Fred Hutchinson Cancer Research Center; SAB member Sonali M. Smith, MD of The University of Chicago; and Daniel O. Persky, MD of The University of Arizona, Chair of LRF's Arizona Patient Workshop.*

“The scope of LRF's influence is visible in the number of researchers who have received Foundation grants and are still actively advancing lymphoma research”

- Leo I. Gordon, MD, FACP

Proven long-term effectiveness for treatments such as rituximab and ibrutinib has also led to research into expanding the effectiveness of these treatments through different combinations and/or different subtypes. One highly anticipated study looked at preliminary results for a phase II trial of a chemotherapy-free combination therapy for mantle cell lymphoma (MCL) undertaken at MD Anderson Cancer Center in Texas. The trial has enrolled 50 patients with newly diagnosed, untreated MCL. Patients are initially given ibrutinib and rituximab until the best response is reached, followed

by a shortened course of intense chemoimmunotherapy, with the goal of both evaluating both the response rate for ibrutinib plus rituximab alone, as well as the progression free survival for this combination following a shorter chemoimmunotherapy regimen. As presented by LRF MCL Consortium member Michael Wang, MD, the study had 45 evaluable patients, of whom 33 completed both phases of treatment. The chemotherapy-free portion of the treatment led to complete responses in 73 percent of the 45 patients, and partial responses in the other 27 percent, for an unprecedented 100 percent response rate thus far. Dr. Wang noted many patients saw a dramatic reduction in tumor burden after as few as two cycles of ibrutinib plus rituximab. Median duration of response and survival rates had yet to be reached, though no patient has died or yet seen their disease progress. Though long-term follow up results for this study will be needed to assess the full effectiveness of this treatment strategy, the initial results are another promising sign that chemotherapy-free treatments may one day soon be a possibility.

► *This study included contributions from LRF Scholar Jason Westin, MD, and MCL Consortium Member Jorge Romaguera, MD, also of MD Anderson Cancer Center.*

Rare lymphoma subtypes are another area in which existing therapies are being assessed. Central nervous system (CNS) lymphoma is a form of diffuse large b-cell lymphoma (DLBCL) which sometimes occurs on relapse. CNS lymphoma is difficult to treat because therapies must be able to cross the blood-brain barrier to reach the malignant cells, however, lenalidomide (Revlimid)

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Lymphoma Research Foundation Grantee H. Guido Wendel, MD, Discusses His Groundbreaking Work in CAR-T Cell Immunotherapy

Dr. H. Guido Wendel, MD, is a Member at Memorial Sloan Kettering Cancer Center, Associate Professor at Weill Cornell Medicine's Graduate School of Medical Sciences, and a two-time recipient of the Lymphoma Research Foundation's Follicular Pathways Grant. As befits the grant name, Dr. Wendel's research focuses on the microbiology of lymphoma cells, identifying proteins within tumor cells that represent crucial functions for cell growth, or allow a malignant cell to avoid destruction by the immune system. These biomarkers and pathways, once identified, offer avenues along which new therapies can be developed.

In October 2016, Dr. Wendel and his colleagues published a paper in the academic journal *Cell*, in which they posited a new potential use for chimeric antigen receptor (CAR) T-cell therapy, one which may open a number of new possibilities for this type of immunotherapy in general and for lymphoma patients in particular. The following is a brief interview with Dr. Wendel on his research and its implications for lymphoma patients.

How does your work in CAR-T-cells, as published in *Cell*, differ from current research using CD19 CAR-T-cells?

CAR-T-cells have entered the clinic and they work by targeting cells that express the CD19 receptor. These include lymphoma and acute lymphoblastic leukemia (ALL) cells and also normal B lymphocytes. The treatment is highly effective against B-ALL and less so against lymphoma.

We set out to improve the activity against lymphoma. We found that a cell surface receptor HVEM/TNFRSF14 is inactivated by mutations or deletions of the whole gene in some 50 percent of human lymphomas. We further found that this receptor normally binds to another receptor called BTLA (T and T Lymphocyte Attenuator) and represses lymphocyte growth. Hence, lymphoma cells need to inactivate this interaction.

We reasoned that delivering the HVEM receptor protein should re-engage this growth repressive mechanism. The next question then is: How do we deliver HVEM specifically to lymphoma cells? We reasoned that we could use CAR



H. Guido Wendel, MD of Memorial Sloan Kettering Cancer Center, received LRF Follicular Pathways grants in 2013 and 2016.

T-cells that seek out lymphomas to deliver the HVEM protein. Hence, we turned the CAR T-cell into a 'micro-pharmacy' that contains an anti-tumor protein [which it delivers to malignant lymphoma cells].

How is your lab planning to further develop or build on this research?

We are pursuing two directions: 1) Develop CAR/HVEM cells towards clinical application. 2) We realize that the use of CAR T-cells as delivery vehicles is more broadly useful and we are pursuing other "payloads" – other cancer suppressive factors that could be added to CAR-T-cells to inhibit specific cancers.

This is a new strategy aimed at increasing the effectiveness of CAR-T-cell therapy. We hope to bring this procedure to the clinic, but it will take a couple of years before we are ready to do so. Most likely this approach will be used in pre-treated patients whose disease has recurred.

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ASH 2016

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has been shown in recent trials to cross this barrier effectively, though outcomes are still poor. Two trials – one at Mayo Clinic, Rochester, and the other a multi-institution trial in Italy, sought to prevent CNS relapse entirely by combining R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) with lenalidomide (R2CHOP) in patients' initial treatment. 136 DLBCL patients were enrolled in the studies, with a large proportion of patients whose prognostic risk scores indicated they were at intermediate or high risk for a CNS relapse. The researchers, including SAB member Thomas Witzig, MD, of Mayo Clinic, reported only one patient developing isolated CNS relapse (0.7 percent), a far lower rate than the five percent who normally experience CNS relapse when treated with R-CHOP alone. The results suggest R2CHOP may be a successful preventative measure for patients at risk for CNS lymphoma relapse and thus improve outcomes for this patient population.

Epidemiology and Treatment Stratification Optimize Patient Care

As technology has allowed researchers to collect and analyze increasingly detailed patient data and biological samples, large scale studies of epidemiology (the study of incidence, distribution and risk factors for disease) and patient outcomes are improving treatment by identifying subgroups of patients that may need special intervention – and sometimes, demonstrating that certain patients may not need as much therapeutic intervention as previously thought.

MCL and other indolent (slow-growing) lymphoma patients are often put on

a “watch and wait” treatment plan, in which the patient receives regular monitoring of their tumor burden, with no treatment until their disease begins to advance. Though earlier studies have shown watch and wait to be an effective strategy for indolent MCL patients, there is no uniform criteria to identify which patients are most appropriate for initial monitoring over treatment. A study of 404 MCL patients diagnosed between 2000 and 2014 at Memorial Sloan Kettering Cancer Center looked for patterns in both clinical criteria (factors defining the presentation of the disease in the patient) and biologic criteria (biomarkers and other genetic or epigenetic factors expressed by the disease cells). Presenter Anita Kumar, MD, a recipient of multiple LRF early-career scientist grants, noted that she and her colleagues found that various clinical criteria, including the presence of early stage (as opposed to advanced) disease and non-nodal clinical presentation, were associated with superior outcomes for patients who were initially observed rather than treated, and could potentially be used to identify appropriate patients for the watch and wait plan. Dr. Kumar further noted that limited pathologic information for the selected patient group prevented a correlation of biologic criteria to outcomes for the observation group, but that ongoing studies are pursuing those factors.

➤ *This study also featured contributions from current SAB members Anas Younes, MD and Andrew D Zelenetz, MD, PhD, as well as former SAB members Craig Moskowitz, MD and Carol S. Portlock, MD, all of Memorial Sloan Kettering Cancer Center.*

Patients with aggressive lymphomas, such as DLBCL, rarely wait to begin treatment. However, because participating in clinical trials often

requires additional pathology review and genetic testing prior to treatment, researchers have become concerned that DLBCL trials are missing those patients whose disease is aggressive enough that their treatment cannot be delayed for trial enrollment. A study from the University of Iowa/Mayo Clinic SPORE Molecular Epidemiology Resource (MER) sought to identify whether the time from diagnosis to initiation of therapy could be correlated with clinical characteristics (including less aggressive disease) and/or patient outcomes. 720 patients who were enrolled in the MER at diagnosis from 2002-2012 (a process with no additional delay), were tracked throughout their treatment, finding a median time from diagnosis to therapy of 14 days. Patients who had a delay in therapy longer than 14 days were more frequently female and a median age of 63 years vs. 60 years at time of diagnosis; they also had universally less aggressive disease characteristics. Patients with germinal center B-cell (GCB) DLBCL were significantly more likely to delay therapy (64 percent, or 122 patients) than patients with activated B-cell (ABC) DLBCL (28 percent or 91 patients), a subgroup associated with more aggressive disease and poorer outcomes. The researchers further noted that the lower rate of disease progression or other events in the delayed group, due to their less aggressive disease, could result in a study on a delayed group alone having approximately 10 percent less power than a study based on all patients regardless of time from diagnosis to therapy. First author and presenter Matthew Maurer, MS, of Mayo Clinic, a faculty member for the Foundation's upcoming Lymphoma Clinical Research Mentoring Program (LCRMP), concluded that the possibility

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ASH 2016

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of underpowered or biased DLBCL trials due to the delay in enrollment is a valid concern, and that future trials should consider streamlining the enrollment and therapy initiation to avoid these issues.

► *This study included contributions from SAB members Brian K Link, MD, of the University of Iowa; Stephen Ansell, MD, PhD, and Thomas E. Witzig, MD, both of Mayo Clinic, Rochester; and MCL Consortium Member David J. Inwards, MD, also of Mayo Clinic.*

As survival rates continue to improve for non-Hodgkin lymphoma (NHL) patients, epidemiologists have turned their attention to potential health implications for long-term survivors. Foundation Scientific Advisory Board member Lindsay Morton, PhD, of the National Cancer Institute authored two abstracts presented during ASH's poster sessions analyzing the risks of various NHL subtypes for secondary cancers. Dr. Morton was first author and presenter on a study investigating the risk of secondary cutaneous (skin) malignancies, such as melanoma. Lymphoma survivors are known to be at increased risk for melanoma; Dr. Morton and her colleagues sought further details on whether specific NHL subtypes might have differing levels of risk. The study examined data from nearly 130,000 adults diagnosed with lymphoma between 2000 and 2013, using the Surveillances, Epidemiology, and End Results (SEER) database. Chronic lymphocytic leukemia (CLL) survivors were the most closely associated with risk for cutaneous malignancies, with reported melanoma cases in that group occurring at almost twice the rate of occurrence in the general population. Other subtypes

reported elevated risk for specific cutaneous malignancies -- for example DLBCL survivors had strongly elevated risk for sebaceous carcinoma, but not melanoma or other cutaneous malignancies. Dr. Morton and her colleagues noted that NHL survivors should consider the importance of regular skin examinations to aid in detecting cutaneous malignancies as early as possible.

Dr. Morton was also senior author on a poster examining NHL survivor risk for infection-related second cancers, or cancers that commonly develop from an infection in the body, such as lung, stomach, liver, salivary gland, and cervical cancers. Using a similar cohort of lymphoma patients from the SEER database, the National Cancer Institute researchers found that certain infection-related cancers, such as non-small cell lung cancer and salivary gland cancer, had an elevated risk across all NHL subtypes, while certain others, such as stomach and liver cancer, were elevated among DLBCL and marginal zone lymphoma (MZL) survivors. The researchers noted that DLBCL and MZL survivors' increased risk for *H. pylori* and hepatitis C viruses, which are associated with the development of both these lymphomas as well as liver and stomach cancer, likely accounts for this difference. No elevated risk for cervical cancers was seen across the four most common NHL subtypes. The researchers noted that their data could assist in identifying NHL survivors who might benefit from more regular surveillance to guard against the occurrence of specific infection-related malignancies.

The Next Wave of Lymphoma Therapies

Though several significant studies at

ASH examined the effectiveness of current lymphoma therapies, the next generations of both novel targeted agents and immunotherapies also reported encouraging results. The plenary session of ASH included results from the GALLIUM study, an international, randomized study for advanced-stage follicular lymphoma (FL) testing obinutuzumab (Gazyva) plus chemotherapy and maintenance versus the standard rituximab plus chemotherapy and maintenance therapy. Obinutuzumab, an anti-CD20 monoclonal antibody that is currently approved for first line therapy in CLL and second line therapy in FL, was given as first-line treatment to 601 FL patients in the study, most of whom had aggressive disease, with patients receiving some form of chemotherapy and two years of maintenance therapy. At ASH, first author Robert E. Marcus, FRCP, FRCPath from Kings College Hospital in London, noted that the three-year progression free survival (PFS) rate in the obinutuzumab arm was 80 percent, while the 601 patients in the rituximab arm reported a 73.3 percent PFS. Additionally, researchers reported a 34 percent reduction in the risk of progression or death with obinutuzumab, and 92 percent of patients achieved minimal residual disease (lack of malignant cells) in the blood and/or bone marrow, compared with 84.9 percent of the rituximab arm. (A separate presentation on GALLIUM's minimal residual disease (MRD) data was presented by Christiane Pott, MD, of University Hospital Schleswig-Holstein in Germany, a past LRF grantee for an MRD project in MCL.) Dr. Marcus and his colleagues expressed support for obinutuzumab plus chemotherapy becoming the new standard for previously untreated patients with FL.

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Palbociclib, a CDK4/CDK6 inhibitor, currently approved for use in breast cancer, is currently being studied in lymphoma for its potential to alleviate the resistance some lymphoma patients develop to ibrutinib (Imbruvica). The Lymphoma Research Foundation is proud to have been involved with some of the earliest studies of this type through researcher Selina Chen-Kiang, PhD of Weill Cornell Medicine, having supported her work with palbociclib in mantle cell lymphoma through three successive MCL grants. Having developed the initial research through laboratory and translational studies, Dr. Chen-Kiang and her colleagues presented a small scale clinical trial of palbociclib plus ibrutinib in 18 recurrent MCL patients, with separate presentations on the clinical data, presented by Peter Martin, MD of Weill Cornell Medicine, and the genetic and biological data, on which Dr. Chen-Kiang was senior author. The trial, whose primary objective was to evaluate safety and efficacy of the combination therapy, reported a 67 percent response rate (12 patients), including a 44 percent complete response rate (8 patients); no patients who responded to treatment had yet seen their disease progress. Though this is a small cohort, preliminary response rates appear better than those reported in studies of ibrutinib alone; the biological data presented suggested that the presence of palbociclib may aid in blocking key pathways known to contribute to MCL cell growth. A larger, multi-center trial is planned to evaluate the length of time until disease progression.

► In addition to Drs. Martin and Chen-Kiang, both abstracts also included contributions from SAB members Kristie Blum, MD, of The Ohio State University; Nancy Bartlett, MD, of Washington University in Saint Louis, and John P. Leonard, MD of Weill Cornell Medicine; as

well as current LRF Grantee Kami Maddocks, MD of The Ohio State University; and past grantees Stephen I. Park, MD of University of North Carolina, and Jia Ruan, MD, PhD of Weill Cornell Medicine.

Immunotherapies remained a topic of grant interest at ASH, as both chimeric antigen receptor (CAR) T-cells and checkpoint inhibitors presented more extensive clinical data, including data for new combination therapies and subtypes. These two classes of immunotherapies boost the body's natural defenses to fight cancer; in checkpoint inhibitors, this occurs by targeting proteins in cancer cells that can help tumors avoid detection by the immune system, while in CART-cells, actual human immune cells are modified to recognize genetic receptors specific to cancer cells and more directly target the cancer.

With nivolumab's (Opdivo) May 2016 FDA approval in certain relapsed Hodgkin lymphomas opening the door for wider use of this therapy, researchers presented new research into the potential of this therapy and its fellow PD-1 inhibitor, pembrolizumab (Keytruda). A study presented by Catherine Diefenbach, MD, of New York University, a 2014 LRF Career Development Award recipient, examined the combination of nivolumab with brentuximab vedotin (Adcetris) in a small study of 19 patients with Hodgkin lymphoma, who had not responded to initial chemotherapy or stem cell



LRF grantee Catherine Diefenbach, MD of New York University, presents on Hodgkin lymphoma at LRF's 2015 North American Educational Forum on Lymphoma.

transplant. Brentuximab vedotin (BV), a CD30-inhibitor, works by targeting the CD30 protein in lymphoma cells and delivering an attached dose of chemotherapy directly to the cell. Because relapsed and refractory Hodgkin lymphoma can be particularly difficult to treat, Dr. Diefenbach and her colleagues hoped the trial, which was sponsored by the cooperative group ECOG-ACRIN, would show the combination therapy to be more effective than either therapy alone. In preliminary data, they found an overall response rate of 100 percent, with a 62.5 percent complete response, including two patients who had been previously treated with BV alone. The combination was also largely well tolerated with only one adverse event causing a discontinuation of therapy. Dr. Diefenbach noted that these encouraging results, if corroborated in subsequent larger studies, may open a new alternative therapy for Hodgkin lymphoma patients who relapse after standard therapies.

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Lymphoma Research Foundation Patient Education Workshops to Be Led by Foundation Scientific Advisory Board, ASH Researchers

Each year, the Lymphoma Research Foundation hosts patient education programs around the United States, with the goal of providing lymphoma patients and caregivers with accurate, up-to-date information about the diagnosis and treatment of the disease. For more than two decades, the Foundation has presented community-based Ask the Doctor About Lymphoma Programs, regional Lymphoma Workshops, and the nation's largest lymphoma patient conference, the North American Educational Forum on Lymphoma. Members of the Foundation Scientific Advisory Board - among the world's experts in lymphoma and CLL - serve as the speakers for these unique patient programs. Several researchers and presenters who played a prominent role in the ASH proceeding highlighted in this issue of *Research Report* will also serve as program faculty, available to answer patient questions about the latest trends in lymphoma research and treatment.

Several Spring 2017 Lymphoma Workshop faculty contributed research to the 2016 ASH Annual Meeting, including Arizona Workshop Chair Daniel Persky, MD of The University of Arizona Cancer Center (see pg 3). "Lymphoma Research Foundation patient programs offer a unique opportunity to learn about the latest treatments from clinicians who are researchers themselves," says Dr. Persky. "The Arizona Workshop, like other Foundation patient education activities, offers patients the opportunity to learn the latest in available treatments for their specific lymphoma."

The Foundation's spring patient education calendar also includes Lymphoma Workshops in Washington, D.C., and Atlanta, GA, the first patient education workshops in either region. The Chairs of those workshops, Bruce Cheson, MD, FACP, FAAAS of Georgetown University Hospital and Lombardi Comprehensive Cancer Center and Christopher Flowers, MD of Emory University's Winship Cancer Institute, each members of the LRF Scientific Advisory Board, also presented research at ASH, and contributed to several abstracts.



"The Lymphoma Research Foundation is proud to have experts like Dr. Persky, Dr. Cheson, and Dr. Flowers bring their experience with both patient care and lymphoma research to our patient education programs," said Max Mulcahy, the Foundation's Senior Director of Patient and Professional Programs.

In addition to the regional workshops, more than 40 community-based Ask the Doctor About Lymphoma programs will be held throughout the country in 2017 and the annual Educational Forum will be held on October 20-22 in Brooklyn, NY. For additional information for these program, or to register for an education event, visit lymphoma.org/patienteducation or contact the Lymphoma Helpline at (800) 500-9976.

2017 Regional Workshops:

Arizona Lymphoma Workshop (Scottsdale, AZ)
Saturday, February 18

Washington, DC Lymphoma Workshop
Saturday, March 18

Georgia Lymphoma Workshop (Atlanta, GA)
Saturday, April 1

Minnesota Lymphoma Workshop (Bloomington, MN)
Saturday, April 1

Seattle Lymphoma Workshop (Seattle, WA)
Saturday, April 1

North American Educational Forum on Lymphoma:

Brooklyn, NY
October 20-22

ASH 2016

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► Other contributors to this study include SAB members Ranjana Advani, MD, of Stanford University, Stephen Ansell, MD, PhD, of Mayo Clinic, and Brad S. Kahl, MD of Washington University in Saint Louis; current LRF grantee Jonathon Cohen, MD of Emory University; and former SAB member Richard F. Ambinder, MD, PhD of Johns Hopkins.

Pembrolizumab's potential in cutaneous t-cell lymphomas (CTCL) was examined in a multi-center study of relapsed/refractory mycosis fungoides (MF) and Sézary syndrome (SS), two advanced stage forms of the disease. Although treatments are available for these rare lymphomas, the duration of response is often short-lived. Presenter and lead author Michael Khodadoust, MD, of Stanford University, and his colleagues hypothesized that, because the T-cells in which CTCLs occur have high expressions of the programmed death-1 (PD-1) protein that pembrolizumab is designed to inhibit, this type of therapy may prove effective. The study included 24 patients with relapsed MF or SS, most of whom had received a number of previous therapies, with an overall response of 38 percent (one complete response and eight partial responses). Six of the patients who responded had a 90 percent or greater improvement in skin disease, and an additional nine patients had stable disease. Dr. Khodadoust noted that the most encouraging data was the duration of response, with eight of the nine responders, currently still ongoing treatment at a median of 32 weeks (8 months). Median progression free survival had not yet been reached. The researcher concluded that further studies of pembrolizumab and other checkpoint inhibitors in CTCL were

warranted.

► This study also included contributions from SAB member and LRF grantee Ash A. Alizadeh, MD, PhD, of Stanford University; and grantee Steven M. Horwitz, MD, of Memorial Sloan Kettering Cancer Center.

Central nervous system lymphoma (CNSL), in which lymphoma tumors occur in the brain, spinal cord, eye, and or meninges (layers of tissue covering the brain), is a difficult lymphoma to treat due to the difficulty in finding therapies that can cross the blood brain barrier and reach malignant cells. At ASH, two separate studies were presented testing checkpoint inhibitor nivolumab and CD19CAR T-cells, respectively, in this rare subtype. The nivolumab study, which included contributions from SAB members Ann S. LaCasce, MD and Margaret A. Shipp, MD, both of Dana-Farber Cancer Institute, was a pilot study of five patients with primary CNSL (where the tumors start in the CNS) or primary testicular lymphoma (PTL), including one patient with PTL and a CNS relapse (secondary CNSL). All five patients reported a response, including four complete responses, with a median number of three nivolumab treatments needed to achieve a response. All patients were alive and progression free at the time of reporting. The researchers noted plans to open a multi-institutional trial, which is currently recruiting as of January 2017 (NCT02857426).

City of Hope researchers, including LRF grantees Stephen J. Forman, MD (also a former SAB member) and Leslie Popplewell, MD, as well as MCL Consortium member Lihua E. Budde, MD, PhD, presented a poster on CD19CAR T-cells in CNSL. The laboratory in vitro study tested the administration of CART-cells

through three different delivery routes, in an attempt to determine effective methods for targeting these hard to reach tumors; these include intravenous injection (IV, the route used for CART-cells in other lymphomas), intracranial local infusion (IC, directly into the brain as other CNSL drugs are administered), and intracerebroventricular administration (ICV, into the cerebrospinal fluid in an attempt to target the entire CNS). In two separate experiments, the mice models used showed complete eradication of CNS lymphoma by 14 days post-treatment with either a single IC or a single ICV infusion; a single IV infusion induced significant anti-CNSL activity but complete remission did not occur until 21 days post infusion. CAR T-cells were still detectable in peripheral blood in both IV and ICV mice 28 days post treatment, suggesting that the intracerebroventricular system may also play a role in immune surveillance for systemic tumors. The researchers concluded that ICV delivery of CAR T-cells for CNSL is a feasible approach that warrants further study.

Among the many CART-cell studies reported at ASH, one of the most anticipated in lymphoma was the ZUMA-1 study, which reported interim results, expanding on the preliminary data presented in 2015. This multi-center study evaluated the safety and efficacy of the CAR T-cell therapy known as KTE-C19, or axicabtagene ciloleucel, in refractory aggressive B-cell NHL. It is the first multi-center study to evaluate a CART-cell therapy where the patient's cells were sent to a central facility for re-engineering prior to being infused back into the patient. Two separate abstracts covered two cohorts of ZUMA-1, with the first cohort covering DLBCL, and

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ASH 2016

[CONTINUED FROM PAGE 9]

the second covering primary mediastinal B-cell (PMBCL) or transformed follicular lymphoma (TFL). In the smaller PMBCL/TFL cohort, 100 percent of the six evaluable patients at time of reporting had an objective response to treatment, with all patients experiencing ongoing complete remissions. Researchers did report several high grade adverse events of cytopenia (a reduction in the number of blood cells, such as anemia), and low grade neurotoxicities, which were generally reversible. In the DLBCL cohort, 51 evaluable patients reported an overall response rate of 76 percent, with 47 percent complete remission. 92 percent of the responses occurred within the first month, and at three months 39 percent of patients had ongoing responses. The DLBCL cohort reported a lower percentage of high grade adverse events, although one fatal adverse event was reported. Presenters Sattva S. Neelapu, MD of MD Anderson Cancer Center (DLBCL cohort) and Frederick L. Locke, MD, of Moffit Cancer Center (PMBCL/TFL cohort) noted that the trial results included patients from 22 sites, most of whom had no prior experience administering CART-cells, demonstrating

that centrally manufactured CART-cells were a logistically feasible approach to this highly individualized therapy. The results further demonstrated significant clinical benefit for aggressive B-cell lymphomas for whom other therapies fail. As of January 2017, ZUMA-1 is still recruiting participants (NCT02348216).

➤ *These abstracts included contributions from LRF Scholars Alex F. Herrera, MD of City of Hope, and Jason R. Westin, MD of MD Anderson Cancer Center; SAB members and past LRF grantees Nancy L Bartlett, MD of Washington University in Saint Louis, Jonathan Friedberg MD, of the University of Rochester, and Ann S LaCasce, MD of Dana-Farber Cancer Institute; LRF grantees Januario E. Castro, MD of the University of California San Diego and John Timmerman, MD of the University of California Los Angeles; former SAB members Andre Goy, MD of John Theurer Cancer Center and Ronald Levy, MD of Stanford University; and MCL Consortium members Mitchell Smith, MD of Cleveland Clinic, and Ian Flinn, MD of Sarah Cannon Research Institute.*

Summary

The 2016 ASH Annual Meeting represented a trend of analysis and evaluation for lymphoma research. Significant advances over the past several years are now established enough to allow for a thorough, long-

term assessment of the effectiveness of current therapies, while exploring potential new uses. Epidemiological research has provided contextual insight beyond the effectiveness of a particular therapy, allowing researchers to understand potential future risks for lymphoma survivors as well as account for potential bias in their own research. Meanwhile, the next generation of lymphoma therapies, while not yet widely available, are demonstrating promise for those lymphoma patients for whom current therapies are insufficient.

“The Lymphoma Research Foundation is proud to be associated with so many researchers committed not just to developing new therapies, but to ensuring current therapies and treatment strategies are optimized to benefit as many patients as possible,” says Meghan Gutierrez, the Foundation’s Chief Executive Officer. “The Foundation itself remains committed to funding the innovative research that will allow the lymphoma community to continue to build upon this progress and develop the next generation of therapies.”

Interview with Dr. Wendel

[CONTINUED FROM PAGE 4]

Your lab specializes in translational and basic discovery research. Can you explain how these types of research impact the clinical trials that most lay people think of when they think of medical research?

My lab is not involved in clinical trials or accompanying analyses. We try to envision completely new strategies for future therapies. These may be a long way from clinical use and some may never make it there. However, our goal is to invent and begin to explore future therapies.

You have received multiple LRF grants through the Follicular Lymphoma Pathways program. How have those grants aided your research (either this research specifically, or in general)?

Our research is “high-risk and high-gain” and conventional funding agencies (such as the National Institutes of Health) tend to be very conservative and less likely to support innovative and risky studies such as the use of T-cells as cellular pharmacies. We are excited that LRF is supporting our studies, which is absolutely essential to push new ideas like this from the lab towards the clinic.

The Lymphoma Research Foundation's volunteer Scientific Advisory Board, comprised of 45 world-renowned lymphoma experts, guides the Foundation's research activities, seeking out the most innovative and promising lymphoma research projects for support.

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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

John Groskopf of Elm Grove, WI donated nearly \$15,000 in stock to LRF in 2016. John first came to the Foundation in 1997 as a newly diagnosed small lymphocytic lymphoma (SLL) patient. "When you are newly diagnosed you want to understand what is happening to your body and the treatment options available," John says. "I really appreciate the information available through LRF." A long-time member of the Foundation's Lymphoma Support Network, a one-to-one peer support program connecting patients and caregivers with volunteers who have had similar experiences with their subtype and/or treatments, John and his wife continue to donate in multiple ways. "Without the research efforts provided by foundations such as LRF, I would not be around today," he says. "My wife and I want to give back and provide funds for more research and further improvements for others with this disease."



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IN THIS ISSUE:

ASH 2016:

- Introduction** 1
- Current Therapies: Long Term Data and New Indications Epidemiology** 2
- Next Wave Therapies** 5

Features:

- Letter from the CEO** 2
- Interview with Dr. Wendel** 4
- Patient Education Workshops** 8
- Scientific Advisory Board** 11

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